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Original Article

Combined use of clopidogrel and atorvastatin for angina pectoris caused by coronary heart disease: clinical effectiveness, safety, and contributing factors

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Abstract: Objective: To evaluate the combined use of Clopidogrel (CLO) and Atorvastatin (ATO) in patients with angina pectoris caused by coronary heart disease (CHD-AP), focusing on clinical effectiveness, safety, and contributing factors. Methods: A total of 178 CHD-AP patients admitted to Shaanxi Provincial People's Hospital between October 2022 and October 2025 were retrospectively analyzed. Based on their medication regimens, patients were categorized int an ATO+Acetylsalicylic Acid (ASA) group (n=88), receiving ATO plus ASA therapy, and an ATO+CLO group (n=90), receiving ATO+CLO treatment. Inter-group comparative assessments included clinical efficacy, safety, cardiac function measurements, serum myocardial injury markers, lipid profile (high-/low-density lipoprotein cholesterol [HDL-C/LDL-C], triacylglycerol [TG], total cholesterol [TG]), and hemorheology indices (e.g., plasma viscosity, whole blood viscosity). Factors influencing therapeutic outcomes were further explored using multivariate analysis. Results: The ATO+CLO group demonstrated higher overall clinical efficacy and comparable adverse reaction rates compared to the ATO+ASA group. Moreover, the ATO+CLO group showed greater improvement in cardiac function indices and HDL-C levels after treatment, as well as lower levels of various serum myocardial markers, LDL-C, TG, TC, and hemorheology indices compared to the ATO+ASA group. Multivariate analysis identified Canadian Cardiovascular Society (CCS) angina grading, cardiac index [CI], and medication regimen as independent predictors of therapeutic effects. Conclusion: The combination of CLO and ATO is effective and safe for CHD-AP patients, providing superior clinical benefits without increasing the risk of adverse reactions.

Keywords: Clopidogrel, atorvastatin, coronary heart disease-induced angina pectoris, clinical efficacy, safety, influencing factor

Introduction

Angina pectoris (AP), one of the most common clinical manifestations of coronary heart disease (CHD), affects about 2%-7% of middle-aged individuals in developed countries [1]. It manifests primarily as paroxysmal chest pain or discomfort, often radiating to the neck, jaw, or epigastric region, and can be triggered by physical exertion, emotional distress, cold exposure, or other stimuli [2]. Pathologically, AP is characterized by sudden myocardial ischemia and hypoxia due to coronary insufficiency [3]. The condition can also compromise left ventricular function and increase the risk of acute myocardial infarction (AMI), heart failure, and sudden cardiac death, posing a substantial threat to patient health [4]. Conventional treatments for CHD-AP include anti-platelet therapy, plaque stabilization, anti-angina drugs, risk factor modification, and interventional or surgical revascularization. However, these strategies are often associated with drug resistance and side effects (e.g., renal dysfunction, hepatotoxicity, hematologic abnormalities), along with marked inter-individual variability in therapeutic response, making the need for optimized treatments approaches [5, 6].

Atorvastatin (ATO), a widely used statin, lowers serum cholesterol levels by blocking the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, thus stabilizing atherosclerotic plaques, slowing CHD progression, and improving survival outcomes [7]. Zhang et al. [8] reported that ATO can reduce the frequency and duration of AP episodes and improve cardiac function in CHD patients, especially when used

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in combination with other agents. Furthermore, combination therapy with ATO has been shown to enhance clinical effectiveness while maintaining safety [9]. Clopidogrel (CLO) is an antiplatelet agent indicated for the prevention of myocardial infarction, stroke, and peripheral arterial diseases. In CHD patients, CLO reduces platelet aggregation, thereby lowering the incidence of ischemic events and improving clinical outcomes [10-12]. Randomized controlled trials and meta-analyses have demonstrated that CLO administration in CHD patients, including post-percutaneous coronary intervention, can reduce angina episodes, cardiovascular events, and overall complications [11, 12].

Despite these findings, evidence on the efficacy and safety of combined treatment of CLO and ATO in CHD-AP remains limited. This study aimed to conduct a comprehensive evaluation to verify the therapeutic efficacy and safety of the CLO+ATO regimen and to provide improved treatment options for CHD-AP patients.

Materials and methods

General information

This retrospective study included 178 CHD-AP patients treated at Shaanxi Provincial People's Hospital between October 2022 and October 2025. Patients were retrospectively grouped according to their medication regimens: 88 cases receiving ATO and Acetylsalicylic Acid (ASA) formed the ATO+ASA group, and 90 cases receiving ATO and CLO formed the ATO+CLO group. This study was approved by the Ethics Committee of Shaanxi Provincial People's Hospital.

Inclusion and exclusion criteria

Inclusion criteria: A diagnosis of CHD-AP based on laboratory and imaging examinations [13]; treatment-naive for CHD-AP therapy; no recent surgery or injury; normal communication and cognitive abilities; and complete medical record available.

Exclusion criteria: Allergies to study medications; acute myocardial infarction or cerebrovascular disease; a history of coronary artery bypass grafting or myocardial infarction; other malignancies; severe dysfunction of the heart, lung, or kidney; severe liver injury; autoimmune deficiency, coagulation dysfunction, or chronic infection; or in pregnancy or lactation.

Treatment methods

In the ATO+ASA group, patients received Atorvastatin Calcium Tablets (20 mg once daily before bedtime) plus Aspirin Enteric-Coated Tablets (100 mg once daily after breakfast).

In the ATO+CLO group, ATO was administered in the same regimen as in the ATO+ASA group, and CLO Tablets (75 mg/d) were additionally administered after dinner. The treatment duration was 4 weeks for both groups.

Treatment regimens were individualized based on patients' indications, with CLO prescribed to those requiring long-term prevention of ischemic events.

Detection indicators

Clinical efficacy [14]: Markedly effective: Complete resolution of AP-associated symptoms after medication, with ≥70% reduction in angina attacks and normalization of electrocardiogram (ECG) findings; Effective: Significant improvement in AP-associated symptoms after medication, 40%-69% reduction in AP attack frequency, and essentially normal or near-normal ECG results; Ineffective: persistent symptoms with no reduction in attack frequency and no ECG improvement. The total effective rate (%) = (Number of markedly effective + effective cases)/Total cases * 100%.

Safety: Adverse events were recorded for all patients, including bleeding events, transient elevation of serum transaminase (ALT/AST), myalgia or fatigue, gastrointestinal reactions, and headache or dizziness. The incidence of adverse events was calculated.

Cardiac function: Cardiac function indices, including cardiac index (CI), cardiac output (CO), and left ventricular ejection fraction (LVEF), were measured before and after treatment.

Serum myocardial markers: Serum levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), cardiac troponin (cTnI), and creatine kinase-myocardial band (CK-MB) were quantified using chemiluminescence microparticle immunoassay (CMIA) before and after treatment.

Table 1. Comparison of baseline characteristics between the two groups

Data	ATO+ASA group (n=88)	ATO+CLO group (n=90)	χ^2/Z/t	P
Sex			0.020	0.887
Male	46 (52.27)	48 (53.33)		
Female	42 (47.73)	42 (46.67)		
Age (years)	62.42±6.67	61.96±6.17	0.478	0.633
Disease duration (years)	5.00 (3.00, 6.00)	4.00 (3.00, 5.00)	-1.865	0.062
Body mass index (kg/m^2)	22.80±2.36	22.99±2.16	0.561	0.576
Comorbid hyperlipidemia	27 (30.68)	29 (32.22)	0.049	0.825
Comorbid hypertension	31 (35.23)	30 (33.33)	0.071	0.790
Comorbid diabetes	33 (37.50)	37 (41.11)	0.243	0.622
Angina pectoris type			0.371	0.831
Spontaneous	12 (13.64)	15 (16.67)		
Worsening exertional	26 (29.55)	27 (30.00)		
Initial exertional	50 (56.82)	48 (53.33)		
Canadian Cardiovascular Society (CCS) grading of angina pectoris			0.491	0.484
Grade I-II	62 (70.45)	59 (65.56)		
Grade III-IV	26 (29.55)	31 (34.44)		
New York Heart Association (NYHA) classification			0.227	0.634
Grade I	36 (40.91)	40 (44.44)		
Grade II	52 (59.09)	50 (55.56)		

Note: ATO, Atorvastatin; CLO, Clopidogrel; ASA, Acetylsalicylic Acid.

Lipid profiles: Fasting venous blood (5 mL) was collected before and after treatment. Serum was separated by centrifugation and analyzed for high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triacylglycerol (TG), and total cholesterol (TC) using a dual-reagent enzymatic method.

Hematologic indices: Platelet hematocrit (PCT), hematocrit (HCT), mean corpuscular volume (MCV), and hemoglobin (Hb) levels were measured using enzyme-linked immunosorbent assays (ELISAs).

Statistical analyses

Statistical analyses were performed using SPSS 22.0 software. Normally distributed continuous data were expressed as mean ± standard deviation (SD), and inter-group comparisons were conducted using independent t-tests and within-group comparisons before and after medication using paired t-tests. Non-normally distributed data were expressed as median (interquartile range) [M (Q1, Q3)], with differences between groups compared using the Mann-Whitney U test. Categorical data were expressed as n(%) and analyzed using the Pearson chi-square test. A *P* value <0.05 was considered significant.

Results

Patient baseline information

No significant differences were observed between the ATO+ASA and ATO+CLO groups in terms of sex, age, disease duration, body mass index (BMI), comorbidities (e.g., hyperlipidemia, hypertension, diabetes), AP type, Canadian Cardiovascular Society (CCS) angina grading, or New York Heart Association (NYHA) classification (all P>0.05; **Table 1**), confirming the comparability of the cohorts.

Clinical efficacy

As shown in **Table 2**, in the ATO+ASA group, 28, 43, and 17 cases were classified as markedly effective, effective, and ineffective, respectively; in the ATO+CLO group, the corresponding numbers were 35, 47, and 8. The overall treatment efficacy of the ATO+CLO group was significantly higher than that of the ATO+ASA group (P=0.045).

Safety profile

As shown in **Table 3**, the incidence of bleeding, transient ALT/AST elevation, myalgia or fatigue, gastrointestinal reactions, and head-

Table 2. Comparison of therapeutic efficacy between the two groups

Efficacy	ATO+ASA group (n=88)	ATO+CLO group (n=90)	χ^2	P
Marked effectiveness	28 (31.82)	35 (38.89)		
Effectiveness	43 (48.86)	47 (52.22)		
Ineffectiveness	17 (19.32)	8 (8.89)		
Overall effectiveness	71 (80.68)	82 (91.11)	4.009	0.045

Note: ATO, Atorvastatin; CLO, Clopidogrel; ASA, Acetylsalicylic Acid.

Table 3. Comparison of safety profiles between the two groups

Safety	ATO+ASA group (n=88)	ATO+CLO group (n=90)	χ^2	P
Bleeding events	1 (1.14)	3 (3.33)		
Transient ALT/AST elevation	3 (3.41)	4 (4.44)		
Myalgia or debilitation	1 (1.14)	2 (2.22)		
Gastrointestinal reaction	4 (4.55)	5 (5.56)		
Headache or dizziness	2 (2.27)	3 (3.33)		
Total	11 (12.50)	17 (18.89)	1.370	0.242

Note: ATO, Atorvastatin; CLO, Clopidogrel; ASA, Acetylsalicylic Acid; ALT/AST, Alanine Aminotransferase/Aspartate Aminotransferase.

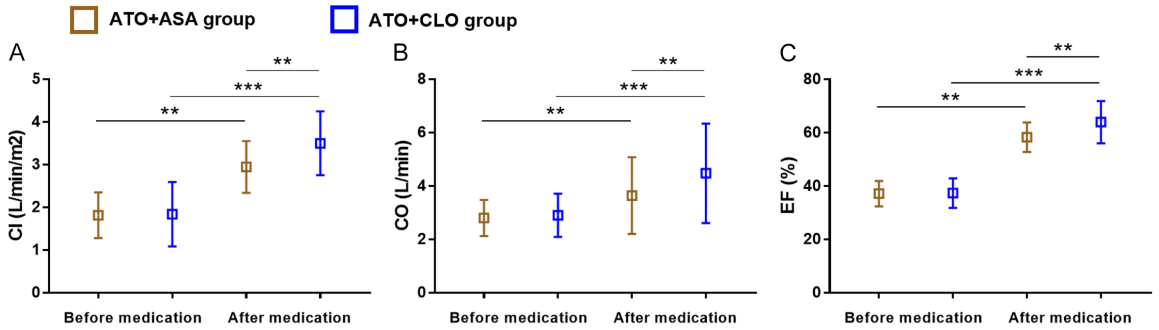

Figure 1. Comparison of cardiac function indices between the two groups before and after treatment. A. CI; B. CO; C. LVEF. Note: **P<0.01; ***P<0.001. CI, Cardiac Index; CO, cardiac output; LVEF, left ventricular ejection fraction; ATO, Atorvastatin; CLO, Clopidogrel; ASA, Acetylsalicylic Acid.

ache or dizziness were comparable between groups (P>0.05). Specifically, the number of cases experiencing the above events were 3, 4, 2, 5, and 3 in the ATO+CLO group, respectively, showing no notable differences compared to 1, 3, 1, 4, and 2 cases in the ATO+ASA group, respectively.

Cardiac function evaluation

As depicted in **Figure 1**, baseline cardiac function parameters (CI, CO, and LVEF) were similar between groups (P>0.05). Post-treatment, these indices increased statistically in both (P<0.01), with greater improvements observed in the ATO+CLO group (P<0.01).

Serum myocardial markers

Baseline serum NT-proBNP, cTnI, and CK-MB levels were comparable between the two groups (all P>0.05). After treatment, all these indices decreased significantly in both groups (P<0.01), with the ATO+CLO group demonstrating a greater reduction compared to the ATO+ASA group (all P<0.01; **Figure 2**).

Lipid profile

Pre-treatment HDL-C, LDL-C, TG, and TC levels were comparable between groups (P>0.05). After treatment, HDL-C increased while LDL-C, TG, and TC decreased significantly in both groups (P<0.05), with magnitude of change being

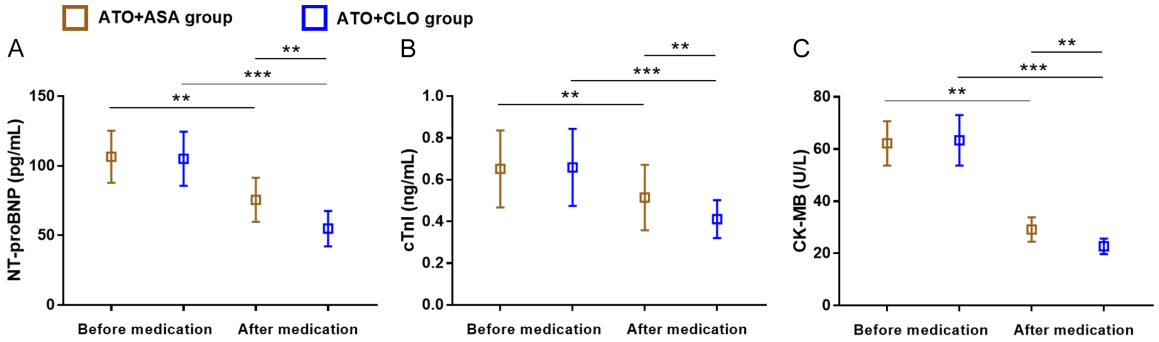

Figure 2. Comparison of serum myocardial markers between the two groups before and after treatment. A. NT-proBNP; B. cTnI; C. CK-MB. Note: **P<0.01; ***P<0.001. NT-proBNP, N-terminal pro-B-type natriuretic peptide; cTnI, cardiac troponin; CK-MB, creatine kinase-myocardial band; ATO, Atorvastatin; CLO, Clopidogrel; ASA, Acetylsalicylic Acid.

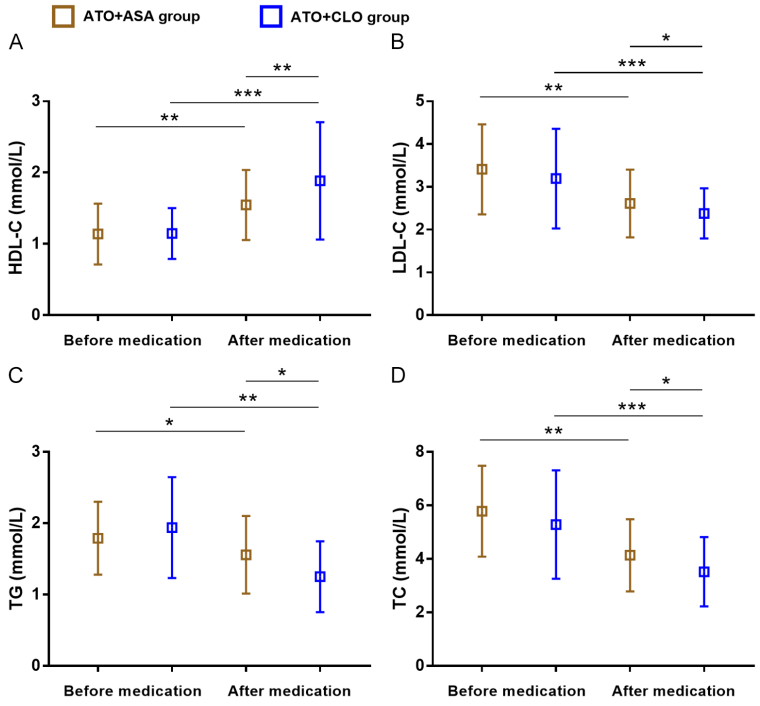

Figure 3. Comparison of lipid profiles between the two groups before and after treatment. A. HDL-C; B. LDL-C; C. TG; D. TC. Note: *P<0.05, **P<0.01; ***P<0.001. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triacylglycerol; TC, total cholesterol; ATO, Atorvastatin; CLO, Clopidogrel; ASA, Acetylsalicylic Acid.

more pronounced in the ATO+CLO group (all P<0.05, **Figure 3**).

Hematologic changes

Baseline levels of PCT, HCT, and MCV were comparable between the two groups (all P> 0.05). After treatment, all these hematologic indices decreased notably in both groups (all P<0.01), and the ATO+CLO group demonstrated greater reductions compared to the ATO+ASA group (P<0.01, **Figure 4**).

Analysis of factors influencing therapeutic efficacy

Univariate analysis revealed that gender, disease duration, BMI, comorbidities (hyperlipidemia, hypertension), AP type, NYHA grade, CO, NT-proBNP, cTnI, CK-MB, HDL-C, TG, TC, PCT, and MCV, were not statistically associated with therapeutic efficacy (all P>0.05). Conversely, age, comorbid diabetes, CCS grading of AP, CI, LVEF, LDL-C, HCT, and medication regimen were significantly correlated with clinical efficacy (all P<0.05). Further multivariate analysis identified CCS angina grading as an independent risk factor (P=0.034) while CI (P=0.003) and medication regimen (P=0.007) were identified as independent protective factors (**Tables 4**, **5**). However, age, comorbid diabetes, LVEF, LDL-C, and HCT were no longer significant in the multivariate analysis.

Discussion

In this study, the clinical efficacy and safety of CLO-ATO co-medication versus ATO alone in patients with CHD-AP were comparatively analyzed. Our findings revealed that co-administra-

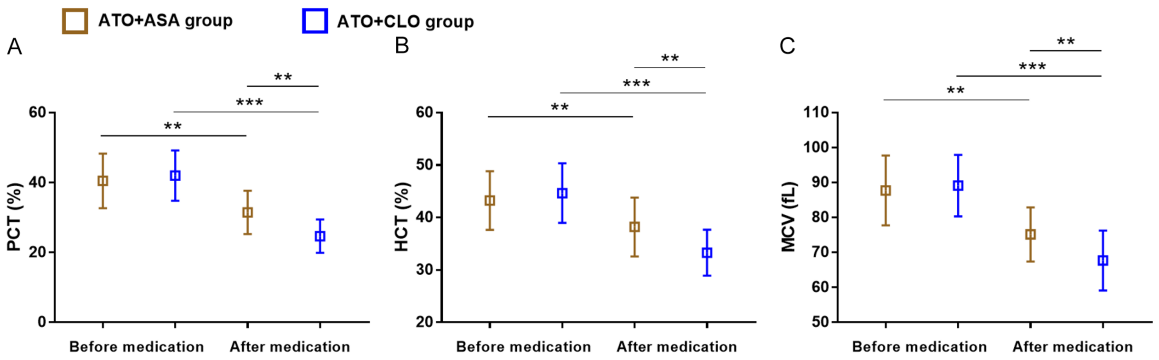

Figure 4. Comparison of hematologic indices between the two groups before and after treatment. A. PCT; B. HCT; C. MCV. Note: **P<0.01; ***P<0.001. PCT, Platelet hematocrit; HCT, hematocrit; MCV, mean corpuscular volume; ATO, Atorvastatin; CLO, Clopidogrel; ASA, Acetylsalicylic Acid.

Table 4. Univariate analysis of factors associated with therapeutic efficacy

Variable	Ineffective group (n=25)	Effective group (n=153)	χ^2	P
Sex			0.008	0.930
Male (n=94)	13 (52.00)	81 (52.94)		
Female (n=84)	12 (48.00)	72 (47.06)		
Age (years)			6.886	0.009
<62 (n=86)	8 (32.00)	78 (50.98)		
≥62 (n=92)	17 (68.00)	75 (49.02)		
Disease duration (years)			0.597	0.440
<4 (n=66)	11 (44.00)	55 (35.95)		
≥4 (n=112)	14 (56.00)	98 (64.05)		
Body mass index (kg/m^2)			0.047	0.829
<23 (n=89)	12 (48.00)	77 (50.33)		
≥23 (n=89)	13 (52.00)	76 (49.67)		
Comorbid hyperlipidaemia (n=56)	10 (40.00)	46 (30.07)	0.984	0.321
Comorbid hypertension (n=61)	5 (20.00)	56 (36.60)	2.629	0.105
Comorbid diabetes (n=70)	16 (64.00)	54 (35.29)	7.421	0.006
Types of angina pectoris			0.778	0.678
Spontaneous (n=27)	5 (20.00)	22 (14.38)		
Worsening exertional (n=53)	6 (24.00)	47 (30.72)		
Initial exertional (n=98)	14 (56.00)	84 (54.90)		
CCS grading of angina pectoris			5.333	0.021
Grade I-II (n=121)	12 (48.00)	109 (71.24)		
Grade III-IV (n=57)	13 (52.00)	44 (28.76)		
NYHA classification			0.020	0.887
Grade I (n=76)	11 (44.00)	65 (42.48)		
Grade II (n=102)	14 (56.00)	88 (57.52)		
CI (L/min/m^2)			5.631	0.018
<1.82 (n=89)	18 (72.00)	71 (46.41)		
≥1.82 (n=89)	7 (28.00)	82 (53.59)		
CO (L/min)			0.114	0.736
<2.82 (n=87)	13 (52.00)	74 (48.37)		
≥2.82 (n=91)	12 (48.00)	79 (51.63)		

LVEF (%)			4.811	0.028
<37.00 (n=78)	14 (56.00)	64 (41.83)		
≥37.00 (n=100)	11 (44.00)	89 (58.17)		
NT-proBNP (pg/mL)			0.024	0.877
<108 (n=88)	12 (48.00)	76 (49.67)		
≥108 (n=90)	13 (52.00)	77 (50.33)		
cTnI (ng/mL)			0.419	0.518
<0.65 (n=89)	11 (44.00)	78 (50.98)		
≥0.65 (n=89)	14 (56.00)	75 (49.02)		
CK-MB (U/L)			2.280	0.131
<62.50 (n=89)	9 (36.00)	80 (52.29)		
≥62.50 (n=89)	16 (64.00)	73 (47.71)		
HDL-C (mmol/L)			0.076	0.782
<1.15 (n=88)	13 (52.00)	75 (49.02)		
≥1.15 (n=90)	12 (48.00)	78 (50.98)		
LDL-C (mmol/L)			5.073	0.024
<3.26 (n=87)	9 (36.00)	78 (50.98)		
≥3.26 (n=91)	16 (64.00)	75 (49.02)		
TG (mmol/L)			0.076	0.782
<1.81 (n=88)	13 (52.00)	75 (49.02)		
≥1.81 (n=90)	12 (48.00)	78 (50.98)		
TC (mmol/L)			0.419	0.518
<5.51 (n=89)	11 (44.00)	78 (50.98)		
≥5.51 (n=89)	14 (56.00)	75 (49.02)		
PCT (%)			0.047	0.829
<41.50 (n=89)	12 (48.00)	77 (50.33)		
≥41.50 (n=89)	13 (52.00)	76 (49.67)		
HCT (%)			5.701	0.017
<44.00 (n=82)	6 (24.00)	76 (49.67)		
≥44.00 (n=96)	19 (76.00)	77 (50.33)		
MCV (fL)			1.163	0.281
<89.50 (n=89)	10 (40.00)	79 (51.63)		
≥89.50 (n=89)	15 (60.00)	74 (48.37)		
Medication regimen			4.009	0.045
Monotherapy (n=88)	17 (68.00)	71 (46.41)		
Combined medication (n=90)	8 (32.00)	82 (53.59)		

Note: CCS, Canadian Cardiovascular Society; NYHA, New York Heart Association; CI, cardiac index; CO, cardiac output; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; cTnI, cardiac troponin; CK-MB, creatine kinase-myocardial band; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triacylglycerol; TC, total cholesterol alcohol; PCT, platelet hematocrit; HCT, hematocrit; MCV, mean corpuscular volume.

tion of CLO and ATO provided superior therapeutic efficacy in treating CHD-AP.

Mechanistically, ATO possibly exerts its effects by modulating the C-C motif chemokine ligand 2 (CCL2)/C-C motif chemokine receptor 2 (CCR2) axis, thereby inhibiting inflammatory cascades, preventing atherosclerosis progression, and facilitating cardiac remodeling [15]. The therapeutic mechanism of CLO may be related to its down-regulation of soluble cluster of differentiation 40 (CD40) ligand levels, which aids in suppressing thrombosis and ameliorating the inflammatory microenvironment in CHD-AP patients [16]. Consequently, the combination of CLO and ATO may enhance curative effects through complementary pathways.

High-dose ATO has been indicated to significantly enhance the antiplatelet effect of CLO,

Table 5. Multivariate analysis of independent factors for therapeutic efficacy

Variable	B	SE	WALD	P	OR	95% CI
Age (years)	0.887	0.547	2.628	0.105	2.427	0.831-7.091
Diabetes	0.961	0.512	3.527	0.060	2.615	0.959-7.130
Canadian Cardiovascular Society grading of angina pectoris	1.091	0.516	4.476	0.034	2.978	1.084-8.186
CI (L/min/m^2)	-1.750	0.589	8.823	0.003	0.174	0.055-0.551
LVEF (%)	-1.020	0.523	3.799	0.051	0.361	0.129-1.006
LDL-C (mmol/L)	0.749	0.531	1.987	0.159	2.115	0.746-5.991
HCT (%)	0.732	0.529	1.914	0.166	2.080	0.737-5.866
Medication regimen	-1.552	0.564	7.282	0.007	0.218	0.072-0.659

Note: CI, cardiac index; LVEF, left ventricular ejection fraction; LDL-C, low-density lipoprotein cholesterol; HCT, hematocrit; SE, Standard Error; OR, Odds Ratio; CI, Confidence Interval.

further supporting possible pharmacodynamic synergy [17]. Lee et al. [18] demonstrated that administration of ATO and rosuvastatin prevented, to a certain extent, the occurrence of new-onset diabetes in adult CHD patients requiring antidiabetics and cataract surgery. As indicated by Wang et al. [19], CLO intervention in acute coronary syndrome has the same efficacy and safety as ticagrelor, and can reduce the risk of dyspnea. Kim et al. [20] reported that CLO-ATO co-administration in stable AP patients after coronary stenting did not impair the antiplatelet activity of CLO, offering long-term clinical benefits without serious drug interactions, which is similar to our findings. As reported by Valgimigli et al. [21], CLO alone was more effective than ASA monotherapy in preventing major adverse cardiovascular or cerebrovascular events, suggesting greater potential clinical benefits for CHD-AP patients. Previous reports have also pointed out that CLO is more cost-effective than ASA in preventing atherothrombosis in the Greek setting [22]. Concerning safety, the two treatment schemes did not exhibit notable differences in clinical safety, supporting the certain tolerability of the CLO-ATO co-medication. Similar observations were reported in a meta-analysis by Lv et al. [23], where combination therapy with amlodipine and an ACEI resulted in a significantly lower overall rate of adverse events and a marked reduction in edema compared to amlodipine monotherapy, although cough was more frequent in the combination group due to the known properties of ACEIs. In the study of Song et al. [24], ATO applied to AP patients has the same efficacy and exercise tolerance as doxycycline. As reported by Isshiki et al. [25], CLO is relatively safer than ticlopidine in patients with stable AP and old myocardial infarction, mainly reflected in the lower cumulative incidence of safety events.

When evaluating cardiac function parameters, we observed a superiority of CLO-ATO co-medication in terms of cardiac function enhancement in CHD-AP cases. In the research of Gao et al. [26], CLO+rosuvastatin contributed to greater cardiac function improvement and blood lipid reduction in elderly CHD patients, similar to our results. The cardioprotective mechanism of CLO may be related to its protective effect on the vascular endothelium, as well as its ability to effectively resist platelet aggregation and stabilize vulnerable plaques [27]. As to ATO, it possibly protects cardiac function through its regulation of the microRNA-139-3P/signal transduction and activator of transcription 1 (Stat1) pathway, which is helpful for strengthening cardiac repair through macrophage polarization [28]. The dual-drug combination helps mediate the above mechanisms to further protect the cardiac function of CHD-AP patients. ATO and CLO co-administration for CHD-AP contributed to greater inhibition of the abnormally high-level serum myocardial markers, suggesting the effectiveness of the combined scheme in alleviating myocardial injury. In terms of lipid profile, combined administration of CLO and ATO for CHD-AP improved blood lipid metabolism. Dyslipidaemia may induce coronary artery stenosis and myocardial ischemia by aggravating the progression of atherosclerosis, thus leading to AP [29]. ATO has been shown to significantly down-regulate plasma LDL-C and TC levels in CHD patients, consistent with our observations [30]. In the report of Bian et al. [31], CLO-ATO regimen exerts a more significant positive effect on blood lipid regulation in patients with transient ischemic attacks,

supporting our results. The assessment of hemorheology indices showed that CLO+ATO treatment for CHD-AP was more conducive to improving hemorheology. Univariate and multivariate analyses further identified CCS grading as an independent risk factor for treatment efficacy, and CI and medication regimen as independent protective factors. Specifically, patients with CCS grade III-IV AP, CI<1.82 L/min/m^2, or treated with ATO alone were at higher risk of reduced therapeutic efficacy.

The main innovations and highlights of this study are as follows: (1) The clinical benefits of ATO+CLO co- administration were confirmed through comprehensive assessments of therapeutic efficacy and safety; (2) The advantages of the combined medication were further explored across multiple dimensions, including cardiac function, myocardial injury, lipid metabolism, and hemorheological indices; (3) Determinants of therapeutic efficacy in this cohort were systematically investigated, enabling identification of CHD-AP patients at high risk of reduced treatment response, which may inform clinical decision-making.

Nevertheless, some limitations should be acknowledged: (1) The representativeness of the sample may have been insufficient, as all participants were enrolled from a single region. Future studies with larger sample size and diverse populations to are warranted to enhance the generalizability of these conclusions; (2) The precise mechanism by which ATO modulates the CCL2/CCR2 axis remains unclear and requires further *in vivo* and *in vitro* studies for elucidation; (3) The interaction between CLO-mediated CD40 down-regulation and the therapeutic effects of ATO is not fully understood, and basic research is warranted to explore the potential synergistic mechanisms.

Conclusion

CLO-ATO co-administration improveed therapeutic efficacy in CHD-AP patients, while maintaining clinical safety. It effectively alleviated myocardial injury, enhanced cardiac function, and improved lipid metabolism and hematologic indices. AP patients with CCS grade III-IV angina, CI<1.82 L/min/m^2, or receiving ATO treatment alone were at an increased risk of reduced therapeutic efficacy.

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Disclosure of conflict of interest

None.

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