

# Effectiveness and safety of combinational therapy compared with intensified statin monotherapy in patients with coronary heart disease

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**Abstract.** Reducing the plasma levels of low-density lipoprotein-cholesterol (LDL-C) is critical for patients with coronary heart disease (CHD). Conventional treatment with statins alone may not achieve the goal of lowering LDL-C due to drug intolerance or resistance. The present study evaluated the effectiveness and safety of combining statin with another lipid-lowering agent in the management of dyslipidemia in CHD patients. A total of 180 patients with CHD were divided into three therapeutic groups (n=60 in each): Statin/colesevelam group (20 mg atorvastatin and 10 mg colesevelam daily), statin/ezetimibe group (20 mg atorvastatin and 10 mg ezetimibe daily) and high-intensity statin monotherapy group (30 mg atorvastatin daily). The baseline plasma lipid levels were measured. The duration of the treatment was eight weeks and the side effects were noted at one year's follow-up. After eight weeks' treatment, the mean plasma level of LDL-C was reduced by 45.2, 44.8 and 30.0% in the statin/colesevelam, statin/ezetimibe and statin monotherapy group, respectively. The reduction of LDL-C in the combinational therapy groups was greater than that in the statin monotherapy group (P<0.05). The proportion of patients achieving the goal of lowering LDL-C in the combinational therapy groups was higher than that in the statin monotherapy group. The effectiveness of reducing lipids was similar in the two combinational statin/colesevelam and statin/ezetimibe groups. Rates of adverse events were not significantly different among the three groups. In conclusion, statins combined with colesevelam or ezetimibe were more effective in reducing plasma LDL-C levels than high-intensity statin monotherapy. This combinational therapeutic strategy may be an alternative for patients that are resistant or intolerant to statins.

## Introduction

It is well established that dyslipidemia is one of the most important risk factors for coronary heart disease (CHD) (1,2). For patients with established CHD, the use of lipid-lowering drugs is important in order to reduce the risk of recurrent cardiovascular events (3). Based on a series of clinical trials over the last two decades, statins block the rate-limiting step in the biosynthesis of cholesterol and are the first-line treatments used to decrease low-density lipoprotein-cholesterol (LDL-C) levels (4,5). The United States guidelines recommend using high-intensity statin therapy in coronary patients in order to achieve a lowering of LDL-C by at least 50% (6). European guidelines recommend an LDL-C goal of <1.8 mmol/l (70 mg/dl) or at least a 50% reduction of LDL-C in patients with established CHD (2,7).

Certain patients are resistant or poorly tolerant to statin treatment. Other lipid-lowering agents may be combined with statins to reduce lipid levels. Ezetimibe and colesevelam hydrochloride are two cholesterol-lowering agents often used as add-on therapy to statins to further lower LDL-C levels when therapeutic goals are not achieved with statins alone. Colesevelam is the second-generation medication of bile acid sequestrant, which has a high binding affinity for specific bile acids (8,9). Studies have demonstrated that colesevelam in combination with other lipid-lowering drugs effectively lowers plasma lipid levels (10,11). By contrast, ezetimibe lowers LDL-C levels by inhibiting intestinal cholesterol absorption when used alone or with statin therapy (12,13). The results of the IMPROVED Reduction of Outcomes: Vytorin Efficacy International Trial indicated that significantly more CHD patients treated with a combination of a statin and ezetimibe met LDL-C goals than patients treated with statin alone (14,15). Ezetimibe-statin combination therapy reduces cardiovascular outcomes in patients following vascular surgery or acute coronary syndrome (16). The effectiveness and safety of combined therapy with statins and other lipid-lowering agents is worthy of further investigation.

Given the importance of LDL-C reduction in influencing long-term risks of cardiovascular events, it's important to investigate the clinical effectiveness of cholesterol-targeted agents (17). Only few studies have been performed to investigate the use combinational therapy in CHD patients. The present study investigated the effectiveness and safety of

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statin/colesevelam combination therapy, statin/ezetimibe combination therapy and high-intensity statin monotherapy in patients with CHD. The present study may provide guidance for the management of dyslipidemia in CHD patients.

## Patients and methods

**Enrollment of participants.** The enrolled CHD patients with hypercholesterolemia were hospitalized and received percutaneous coronary intervention (PCI) at the Department of Cardiovascular Medicine of Linyi Central Hospital (Linyi, China) between January 2016 and June 2016. All of the participants were Chinese. The study was approved by the Ethics Committee of Linyi Central Hospital (Linyi, China). Patients provided written informed consent prior to the study commencing. None of the patients took any lipid-lowering agents within one month prior to admission and those with plasma LDL-C levels of >100 mg/dl were eligible for inclusion. Patients were required to have liver alanine aminotransferase (ALT) or aspartate aminotransferase (AST) and creatine phosphokinase (CK) of <50% above the upper limit of normal (ULN). Pregnant or lactating patients, patients with kidney or liver diseases, and patients with malignant tumors, autoimmune diseases or hypothyroidism were excluded from the study. In total, 180 patients were enrolled in the study.

**Patient grouping.** After receiving standard treatments for CHD, patients were randomly divided into three groups that received different lipid-lowering therapies: Statin/colesevelam combined therapy (statin/col; 20 mg atorvastatin and 10 mg colesevelam daily), statin/ezetimibe combined therapy (statin/eze; 20 mg atorvastatin and 10 mg ezetimibe daily) and high-intensity statin monotherapy (statin mono; 30 mg atorvastatin daily). The drugs were taken once a day. Plasma levels of lipids and enzymes were measured on admission and eight weeks after lipid-lowering therapy. Patients were followed up for one year after treatment for monitoring of adverse events.

No differences in the demographic data were noted among the three groups of patients. The baseline characteristics of the patients are summarized in Table I. The majority of the patients were male. The age (mean  $\pm$  standard deviation) was 61 $\pm$ 9.1 years in the statin/col group, 60 $\pm$ 8.7 years in the statin/eze group and 60 $\pm$ 8.5 years in the statin monotherapy group.

**Effectiveness and safety measurements.** Treatments were considered as effective when the LDL-C-lowering goals were achieved. The goal was defined as LDL-C <70 mg/dl (1.8 mmol/l) or a reduction of LDL-C by at least 50%. The effectiveness rates in the three groups of patients were compared. The percentage changes of LDL-C from baseline after eight weeks of treatment were recorded and compared. Plasma lipid levels were measured. Safety was assessed by recording the occurrence of adverse cardiovascular events, including all-cause death, recurrence of myocardial infarction, coronary revascularization and stroke. Adverse cardiovascular events were measured at one year after treatment of CHD.

**Statistical analyses.** Categorical variables were presented as absolute values or percentages. The Chi-square test was used

for comparisons among three groups of patients. Continuous variables were described as the mean  $\pm$  standard deviation and differences between groups were assessed by one-way analysis of variance followed by a Least Significant Difference test.  $P < 0.05$  was considered to indicate a statistically significant difference. All statistical analyses were performed with SPSS 20 (IBM Corp., Armonk, NY, USA) or GraphPad prism 5 software (GraphPad, Inc., La Jolla, CA, USA).

## Results

**Baseline information of patients.** The mean baseline LDL-C was 3.1 $\pm$ 0.6, 2.9 $\pm$ 0.4 and 3.0 $\pm$ 0.6 mmol/l in the statin/col, statin/eze and statin mono group, respectively. Baseline values of plasma lipids and safety parameters were similar among the three groups (Table II).

**Effectiveness of the three therapeutic strategies.** After eight weeks of treatment, the levels of LDL-C in the three groups of participants were all reduced (Table III). Combinational treatments resulted in significantly greater reductions in mean LDL-C levels as compared with those achieved by high-intensity statin monotherapy (Fig. 1). The reductions of the mean LDL-C values in the two combinational treatment groups were not significantly different (Fig. 1). The proportions of patients achieving the LDL-C-lowering goal were 68, 72 and 50% in the statin/col, statin/eze and statin monotherapy group, respectively (data not shown). In the combinational treatment groups, a higher percentage of patients achieved the LDL-C goals.

The percentage reductions of total cholesterol were 34.0, 34.8 and 25.5% in the statin/col, statin/eze and statin mono group, respectively. Combinational treatments achieved higher effectiveness in reducing total cholesterol (Fig. 2). Changes in triglycerides were similar among the three treatment groups. Levels of HDL-C were increased in the statin/col group and decreased in statin/eze and statin mono groups compared with the baseline levels. The difference was not significant among the three groups.

**Safety assessment.** The proportion of patients reporting serious adverse events, including strokes, coronary artery diseases and mortalities, was similar among the three treatment groups. During the 12-month follow-up, one case of stroke was reported in the statin mono group, one coronary artery bypass grafting in the statin/col group and one transient ischemic attack in the statin/eze group. These serious events were considered not to be associated with the drugs. The number and rate of other observed drug-associated events, which were mainly muscle-associated adverse events, were similar among the three groups ( $P = 0.73$ ). No patient was reported to have increased ALT or AST  $\geq 3$ X ULN. Two patients had CK  $\geq 5$ X ULN. These two patients also had symptoms of myalgia. A summary of the safety assessment is presented in Table IV.

## Discussion

The importance of reducing the levels of LDL-C in CHD patients has been well recognized. When the first-line statin medication is insufficient or poorly tolerated, a second-line treatment option, including ezetimibe or colesevelam, may be

Table I. Baseline characteristics of patients.

Characteristics	Statin/col (n=60)	Statin/eze (n=60)	Statin mono (n=60)
Demographic data			
Age (years)	61±9.1	60±8.7	60±8.5
Males	38 (63.3)	40 (66.7)	37 (61.7)
Hypertension	34 (56.7)	33 (55)	35 (58.3)
Smoking history	27 (45)	29 (48.3)	28 (46.7)
Clinical presentation			
STEMI	19 (31.7)	20 (33.3)	17 (28.3)
NSTE-ACS	41 (68.3)	40 (66.7)	43 (71.7)

Values are expressed as the mean ± standard deviation or as n (%). STEMI, ST-elevation myocardial infarction; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; col, colesevelam; eze, ezetimibe; mono, monotherapy.

Table II. Baseline levels of plasma lipids and enzymes of patients in the three groups.

Items	Statin/col (n=60)	Statin/eze (n=60)	Statin mono (n=60)
Baseline plasma lipid values (mmol/l)			
LDL-C	3.1±0.6	2.9±0.4	3.0±0.6
Total C	4.7±0.7	4.6±0.5	4.7±0.7
HDL-C	1.2±0.3	1.2±0.2	1.3±0.3
Triglycerides	1.8±0.5	1.9±0.5	1.9±0.6
Baseline plasma enzyme levels (U/l)			
AST	25.6±6.2	26.3±5.7	27.1±6.9
ALT	26.1±7.8	27.0±8.1	25.3±8.4
CK	105.1±40.0	117.2±45.3	110.4±39.5

Values are expressed as the mean ± standard deviation. No significant differences were present between the groups for all parameters. LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CK, creatine phosphokinase; col, colesevelam; eze, ezetimibe; mono, monotherapy.

Table III. Plasma lipid levels (mmol/l) after eight weeks of treatment.

Plasma lipid	Statin/col (n=60)	Statin/eze (n=60)	Statin mono (n=60)
LDL-C	1.7±0.4 <sup>a</sup>	1.9±0.3 <sup>a</sup>	2.1±0.4
Total C	3.1±0.6	3.3±0.4	3.5±0.6
HDL-C	1.3±0.3	1.1±0.3	1.2±0.3
Triglycerides	1.4±0.4	1.4±0.4	1.5±0.5

The plasma levels of LDL-C, total C and triglycerides were reduced by the three treatments. The plasma levels of HDL-C were increased by statin/col treatment and were reduced by statin/eze and statin monotherapy. Values are expressed as the mean ± standard deviation. <sup>a</sup>P<0.05 vs. the statin mono group. col, colesevelam; eze, ezetimibe; mono, monotherapy; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

considered. These second-line treatments are known to reduce LDL-C levels. However, studies investigating the effectiveness

and side effects of combinational treatment in CHD patients, particularly in Asian populations, are currently lacking. The present study compared the effectiveness of statin/ezetimibe, statin/colesevelam and high-intensity statin monotherapy in the management of plasma lipids in CHD patients, and the side effects were also observed. The present study indicated that the combined therapies were more effective in reducing LDL-C than high-dose statin monotherapy in CHD patients. Furthermore, a larger percentage of patients achieved lowering LDL-C goals in the combined therapy groups than in the statin monotherapy group. The safety was similar among the three therapeutic methods.

It has been reported that in patients with hypercholesterolemia and CHD, achieving LDL-C targets often fails (18). Moderate dosages of statin therapy may not be sufficient for achieving the LDL-C treatment goals (19). Physicians often prescribe low or moderate doses of statins instead of high-intensity statins in order to reduce adverse effects (20,21). Indeed, certain patients are intolerant or resistant to high doses of statin therapy. Statins combined with other lipid-lowering agents may be a choice for those patients. Several studies have investigated the effects of statin/eze as

Table IV. Summary of safety data.

Item	Statin/col (n=60)	Statin/eze (n=60)	Statin mono (n=60)
Serious adverse events	1 (1.7)	1 (1.7)	1 (1.7)
Drug-associated adverse events	4 (6.7)	3 (5)	3 (5)
Serious drug-associated adverse events	0	0	0
ALT/AST $\geq$ 3X ULN	0	0	0
CK $\geq$ 5X ULN	1 (1.7)	0	1 (1.7)

Values are expressed as n (%). One serious adverse events, including strokes, coronary artery diseases and mortalities, was reported in each of the three groups. Drug-associated adverse events were similar in the three groups. No significant differences were present among the three groups. ALT, AST and CK levels were not significantly different among the three groups. AST, aspartate aminotransferase; ALT, alanine aminotransferase; CK, creatine phosphokinase; ULN, upper limit of normal; col, colesvelam; eze, ezetimibe; mono, monotherapy.

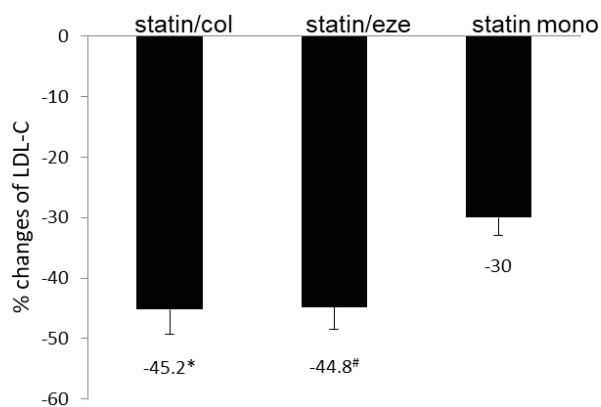


Figure 1. Percentage changes of LDL-C from baseline in the three groups after eight weeks of treatment. Patients in the statin/col and statin/eze groups achieved higher percentages of LDL-C reductions compared with those in the statin monotherapy group. Values are expressed as the  $\pm$  standard error of the mean (n=60). \*P=0.03 and #P=0.04 vs. the statin mono group. LDL-C, low-density lipoprotein cholesterol; col, colesvelam; eze, ezetimibe; mono, monotherapy.

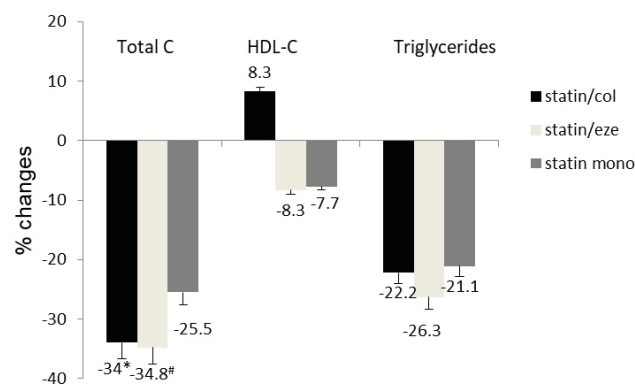


Figure 2. Percentage changes of total C, HDL-C and triglycerides from baseline after eight weeks of treatment. Patients in the statin/col and statin/eze groups achieved higher percentages of total C reduction compared with those in the statin monotherapy group. Reductions of HDL-C and triglycerides were similar among the three groups. Values are expressed as the  $\pm$  standard error of the mean (n=60). \*P=0.043 and #P=0.035 vs. statin mono group. total C, total cholesterol; HDL-C, high-density lipoprotein cholesterol; col, colesvelam; eze, ezetimibe; mono, monotherapy.

compared with high-intensity statin monotherapy (22-25). Although the dosages of agents used may differ between various studies, the present results were consistent or similar to those of previous studies. As atorvastatin is usually prescribed at a daily dosage of 20 mg in China, patients in the high-intensity statin group received 30 mg atorvastatin daily and patients in the combined therapy groups received 20 mg atorvastatin plus 10 mg ezetimibe or colesvelam. A review estimated that compared with high-intensity statin monotherapy, mid-intensity statin combined with ezetimibe may achieve a further decrease of LDL-C by 5-15% (26). The results of the present study indicated that statin combined with ezetimibe reduced LDL-C by 44.8% as compared with 30% by statin alone. The proportion of patients reaching the LDL-C-lowering goal was also higher in the statin/eze group, indicating that combining ezetimibe with a moderate dose of statin is more effective in reducing LDL-C than high-intensity statin therapy alone. Statins inhibit the production of cholesterol, which in turn may upregulate the absorption of cholesterol, whereas ezetimibe reduces the absorption of cholesterol by inhibiting the Niemann-Pick C1-like 1 protein. This may reflect that the two agents have different

mechanisms by which they reduce LDL. Colesevelam is another type of lipid-lowering agent, which acts as a bile acid sequestrant (27,28). Combining colesvelam with statins is an alternative to high-intensity statin therapy. Several trials compared the effect of statin monotherapy to combination therapy with bile acid sequestrant in patients with hyperlipidemia (10,29-32). In high-risk hyperlipidemic patients, low-intensity statin combined with bile acid sequestrant decreased LDL-C levels 0-14% more than moderate-intensity statin monotherapy (26). However, there is currently a lack of studies investigating the lipid-lowering effects of colesvelam plus statin in CHD patients. The results of the present study indicated that colesvelam combined with moderate-intensity statin therapy was more effective in lowering LDL-C than high-intensity statin monotherapy. Colesevelam has been reported to improve the lipoprotein particles; in the present study, HDL was increased by colesvelam, which was consistent with the results of previous studies (33,34). The proportion of patients achieving the LDL-C lowering goal was 68% in the statin/col group as compared with 50% in the statin monotherapy group. The effects of the two combinational treatment methods were similar, suggesting



that administration of colessevelam or ezetimibe combined with moderate-dose statin may be an alternative method for the management of hyperlipidemia.

The safeties and tolerability of the three treatment methods were studied and compared. There was no report of drug-associated serious side effects. A total of 10 patients (5.6%) developed musculoskeletal side effects and the symptoms were mainly myalgia. The rate is consistent with that reported in a previous study (35). None of the patients had any increased ALT or AST by  $\geq 3X$  ULN; however, two patients had CK  $\geq 5X$  ULN. The incidence of side effects was similar among the three groups of patients. The major side effects of colessevelam are reported to be gastrointestinal discomfort, including nausea, abdominal cramps and impaired absorption of other medications (8,36). None of these side effects were observed in the present study. The treatments were generally well tolerated and safe in the whole population of participants.

In conclusion, atorvastatin combined with colessevelam or ezetimibe was more effective than high-intensity statin monotherapy in reducing plasma LDL-C levels in patients with CHD. The combined therapies are safe and well-tolerated. The combinational therapeutic strategy may be an alternative to high-intensity statin monotherapy for patients that are resistant or intolerant to statins. One limitation of the present study is that the number of patients is moderate. Multi-centered, large-scale and randomized clinical trials are warranted to confirm the results of the present study.

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#### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

#### Authors' contributions

CHL gathered the patients' clinical information, and analyzed and interpreted the patient data. QWL helped to design the study and was a major contributor in writing the study. XHX designed the study and carried out the statistical analysis. All authors read and approved the final study.

#### Ethics approval and consent to participate

The study was approved by the Ethics Committee of Linyi Central Hospital (Linyi, China). Patients provided written informed consent prior to the study commencing.

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare that they have no competing interests.

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