Trials

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Comparison of ezetimibe and atorvastatin versus atorvastatin alone on short-term major adverse cardiac events after percutaneous coronary intervention, a double-blind placebo-controlled randomized clinical trial

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Abstract

Background Major cardiovascular events (MACE) after percutaneous coronary intervention (PCI) are among the most common causes of death in patients. Lipid-lowering strategies seem to affect these events. Reaching the best regimen for controlling lipid abnormalities is important. This study aimed to compare the effect of ezetimibe and atorvastatin versus atorvastatin alone in short-term major cardiovascular events in patients after PCI in Bandar Abbas in 2018.

Methods This double-blinded randomized controlled trial was done in Bandar Abbas in 2018 on 224 patients. Patients were randomly divided into two groups either to receive ezetimibe and atorvastatin (group A) or atorvastatin alone (group B). Patients were followed for 1 month for major cardiovascular events and drug side effects. Data was analyzed using SPSS software.

Results Patients in the two groups had similar baseline characteristics. The mean low-density lipoproteins (LDL) level was 69.83 ± 28.8 in group A and 82.45 ± 29.9 in group B ($P = 0.014$). At the end of the study, high-sensitivity C-reactive protein (hs-CRP) values were notably lower in group A (P value = 0.005). Three (2.7%) patients in group A and 1 patient (0.9%) in group B had a myocardial infarction (P value = 0.313). Also, 11 patients (9.8%) in group A and 13 patients (11.6%) in group B had unstable angina (P value = 0.666). No patients had death, cerebrovascular event, or stent thrombosis in the two groups.

Conclusion Although adding ezetimibe to atorvastatin can decrease LDL and hs-CRP levels in short-term follow-up; it is not effective in lowering short-term major cardiovascular events in patients after PCI. Studies with longer-term follow-up are recommended.

Trial registration IRCT, IRCT20171028037047N1. Registered on 22 June 2018, https://irct.behdasht.gov.ir/trial/28808.

Keywords Ezetimibe, Atorvastatin, Major adverse cardiovascular events, Coronary intervention

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Introduction

Statins are a class of lipid-lowering drugs known for their beneficial effects in patients undergoing coronary artery angiography. These drugs have been found to reduce the risk of cardiovascular diseases. One mechanism through which statins exert their benefits is by reducing inflammation [1, 2]. C-reactive protein (CRP) is a marker associated with the prediction of mortality from acute coronary artery disease, as its levels rise during inflammation. Elevated CRP levels have been linked to cardiovascular events in patients, highlighting the role of inflammation in the development of cardiovascular diseases [3–5]. Ezetimibe is another medication with a lipid-lowering ability that inhibits intestinal cholesterol absorption and is used to lower lipid levels in patients with hyperlipidemia. In addition to its lipid-lowering effects, ezetimibe has been found to have anti-inflammatory properties that reduce the risk of heart disease [3, 6, 7]. Combining ezetimibe with statins in patients with hypercholesterolemia has been shown to decrease levels of hs-CRP, indicating additional anti-inflammatory mechanisms of ezetimibe [8, 9]. Statins also possess anti-inflammatory properties and have been proven to reduce the risk of cardiovascular disease [5]. Hence, the combination of ezetimibe with statins could potentially decrease cardiovascular events by lowering inflammation and hs-CRP levels in high-risk patients [9].

Despite the current lipid-lowering therapies available, a significant number of patients still experience cardiovascular events. Therefore, ongoing studies aim to develop more effective drug therapies. Many patients undergoing PCI have atherosclerotic plaques in their coronary arteries that are prone to rupture and cause thrombosis. Studies have shown that statins can help stabilize atherosclerotic plaques [10], and they can also slow the progression and reduce the size of these plaques. Intensive lipid-lowering strategies, defined as a more than 50% reduction in LDL cholesterol, have been studied by adding ezetimibe to statins in patients undergoing angiography. This strategy has been found to reduce atherosclerotic plaque buildup and decrease the risk of plaque rupture and thrombosis [4]. Implementing this approach in patients undergoing PCI has been linked to a reduction in major cardiovascular events. The anti-inflammatory effects of ezetimibe may be particularly impactful in patients with positive inflammatory markers, such as CRP positivity [11–14]. Cardiovascular events following PCI are significant contributors to patient mortality, underscoring the importance of effective lipid-lowering strategies in reducing these events. Therefore, optimizing lipid control regimens in these patients is crucial. The objective of this study is to compare the impact of combining ezetimibe with atorvastatin versus atorvastatin alone on short-term major cardiovascular events in patients following elective coronary angioplasty.

Method

This is a double-blind randomized clinical trial study in patients referring to the Jorjani Angiographic Center of Shahid Mohammadi Hospital in Bandar Abbas and has been registered in the Iranian Registry of Clinical Trials (IRCT registration number: IRCT20171028037047N1, https://irct.behdasht.gov.ir/trial/28808). The ethics committee of Hormozgan University of Medical Sciences (ethic number: IR.HUMS.REC.1396.133) has also approved the study. Considering the 8.2% incidence of cardiovascular events in the ezetimibe and atorvastatin groups with 95% confidence intervals and 80% strength, to detect at least 10% differences in the incidence of cardiovascular events in the two groups, the minimum sample size of 112 patients in each group were calculated. In a randomized manner, every patient who was referred to PCI who had all the inclusion criteria and none of the exclusion criteria was included in the study and then put into group A or B. The criteria for entering the study include patients who are candidates for elective PCI, have normal hepatic enzymes, and negative baseline troponin levels. The exclusion criteria include individuals with any inflammatory and rheumatologic diseases, concurrent infectious diseases, high creatinine levels or abnormal baseline liver enzymes, pregnant and lactating women, and history of recent nonsteroidal anti-inflammatory drugs (NSAIDs) use, patients' dissatisfaction with participating in the study, left ventricular ejection fraction (LVEF) below 30% in echocardiographic examination, and history of recent myocardial infarction in the last month or the increase in troponin after PCI more than 5 times higher than the normal maximum of 99 percentile.

After determining eligibility, patients were randomly assigned to two groups, A and B. Random assignment was performed using a coin toss method, which effectively facilitated random distribution. In group A, patients received 40 mg of atorvastatin and 10 mg of ezetimibe daily, while in group B, patients received 40 mg of atorvastatin and a placebo. The placebo was in the same package as the original drug, with the same shape, color, and size in a way that was not differentiated from the original drug. Medications were given to patients in pre-prepared packages, and the patients as well as those who recorded the results of the study were unaware of how the patients were grouped. The secretary of the angiography department was responsible for generating the random allocation sequence, enrolling participants, and assigning them to their respective interventions. Since both the participants and personnel involved in assessing outcomes were unaware of the group allocations, the

study's integrity was maintained. The blinded groups in this study included participants, care providers, outcome assessors, and data analysts. CRP values were checked for all patients at the beginning of the study, after 24 h, and at the end of the study. Patients were followed for 1 month to monitor for clinical adverse events such as unstable angina, decompensated heart failure, myocardial infarction, stroke, and stent thrombosis using various methods including electrocardiogram (ECG), hospital records, blood tests, and imaging. Furthermore, patients were observed for possible adverse reactions to medication and instructed to report any myalgia, with creatine phosphokinase (CPK) levels being evaluated if patients experience any notable musculoskeletal symptoms. The follow-up of patients included the following assessments: before angiography, a comprehensive checklist of factors such as age, sex, number of vessels involved, type of stent, levels of CRP, troponin, creatinine, systolic and diastolic blood pressure, high-density lipoprotein (HDL) and LDL levels, liver function tests, and body mass index (BMI) were recorded. Patients were then compared 24 h after PCI and 1 month after PCI for MACE, as well as for hs-CRP levels, lipid profiles, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels, any drug side effects including myalgia.

Data analysis

After data collection, the information was entered into IBM SPSS Statistics version 23.0 for analysis. For quantitative data, mean and standard deviation were used, while for qualitative data, percentage and frequency were utilized. The normality of the data was assessed using the Kolmogorov-Smirnov test. For comparing quantitative variables, independent sample *t*-tests were used for normally distributed data, while the Mann-Whitney test was applied to non-normally distributed data. Additionally, the chi-square test was performed to compare qualitative variables between the two groups.

Results

In this study, a total of 224 patients were included, with 112 patients (50%) in the atorvastatin + ezetimibe group (group A) and 112 patients (50%) in the atorvastatin only group (group B). Among the participants, 115 (51.3%) were male and 109 (48.7%) were female, with a mean age of 60.08 ± 10.18 years. The average BMI was 25.41 ± 4.14 kg/m^2, while the mean systolic blood pressure was 134.13 ± 13.86 mmHg and the mean diastolic blood pressure was 84.87 ± 13.02 mmHg. Radial angiography was performed on 10 patients (4.5%), while femoral angiography was done on 214 patients (95.5%). Among the procedures conducted, angioplasty was performed in various coronary arteries: 79 patients (35.3%) in RCA, 27 (12.1%) in LCX, 2 (0.9%) in RAMUS, 95 (42.4%) in LAD, 2 (0.9%) in LM, 2 (0.9%) in PLV, 3 (1.2%) in PDA, 2 (0.9%) in D1, and 18 (8%) in OM. Additionally, eptifibatide was administered to 12 patients (4.5%) after stenting. The individuals in both groups did not significantly differ in angiographic access, target vessel PCI, and eptifibatide use during the procedure. It is important to highlight that all subjects in the study received a drug-eluting stent. Furthermore, the baseline characteristics of the subjects were comparable between the two groups, as indicated in Table 1.

In the follow-up study, we observed that three patients (2.7%) in group A and one patient (0.9%) in group B experienced a myocardial infarction. However, the difference in myocardial infarction rates between the two groups was not statistically significant ($P=0.331$). During the follow-up period, 11 patients (9.8%) in group A and 13 patients (11.6%) in group B developed unstable angina, with no statistically significant difference in incidence ($P=0.666$). Fortunately, there were no reported deaths due to heart disease in either group throughout the study. Furthermore, none of the participants in either group experienced new strokes (cerebrovascular accidents) or stent thrombosis during the follow-up period. Table 2 compares the levels of hs-CRP, triglycerides (TG), total cholesterol (Chol), LDL, and HDL between the two groups after 24 h and at the end of the study. As shown in Table 2, the analysis demonstrates significant differences in hs-CRP values between the two groups at the study's conclusion ($P=0.005$). Additionally, the LDL values at the end of the study were significantly lower

Table 1 Comparison of baseline characteristics between group A and group B in coronary artery disease patients undergoing PCI

	Group A	Group B	*P* value
Age (year)	60.68 ± 10.65	59.48 ± 9.69	0.380[a]
Height (cm)	161.95 ± 9.31	164.13 ± 8.19	0.053[b]
Weight (kg)	66.75 ± 10.95	68.52 ± 13.86	0.347[b]
Systolic blood pressure (mmHg)	134.96 ± 16.52	133.29 ± 17.22	0.367[b]
Diastolic blood pressure (mmHg)	84.83 ± 12.49	84.58 ± 13.58	0.821[b]
BMI (kg/m^2)	25.49 ± 4.01	25.33 ± 4.30	0.784[a]
Male	52 (46.4%)	63 (56.3%)	0.141[c]
Smoking	37 (33%)	46 (41.1%)	0.213[c]
Diabetes	49 (43.8%)	63 (56.3%)	0.061[c]
Hypertension	80 (71.4%)	79 (70.5%)	0.883[c]

BMI Body mass index

[a] *P* value obtained from independent sample *t*-test

[b] *P* value obtained from the Mann–Whitney *U* test

[c] *P* value obtained from chi-square test

Table 2 Comparison of hs-CRP, lipid profile, CPK, and liver enzyme levels in coronary artery disease patients undergoing PCI

Values	Time	Group A	Group B	*P* value
AST (U/L)	Post-24 h	19.31 ± 9.77	20.52 ± 8.54	0.156[a]
	At the end	21.32 ± 8.19	21.72 ± 7.63	0.887[a]
ALT (U/L)	Post-24 h	21.87 ± 15.05	24.72 ± 16.42	0.188[a]
	At the end	32.24 ± 23.91	26.53 ± 14.24	0.391[a]
hs-CRP (mg/l)	Post-24 h	5.50 ± 8.49	4.38 ± 5.40	0.655[a]
	At the end	3.31 ± 7.98	2.63 ± 3.32	0.005[a]
TG (mg/dl)	Post-24 h	147.5 ± 129.2	152.1 ± 108.3	0.545[a]
	At the end	120.8 ± 51.4	133.1 ± 62.6	0.330[b]
Chol (mg/dl)	Post-24 h	155.4 ± 45.4	165.5 ± 47.8	0.039[a]
	At the end	135.9 ± 38.7	140.1 ± 46.2	0.239[b]
HDL (mg/dl)	Post-24 h	37.69 ± 10.16	41.25 ± 19.97	0.191[a]
	At the end	41.87 ± 19.82	40.56 ± 19.7	0.810[a]
LDL (mg/dl)	Post-24 h	89.48 ± 35.61	96.28 ± 32.42	0.132[b]
	At the end	69.83 ± 28.82	82.45 ± 29.90	0.014[a]
CPK (U/L)	During study	58.28 ± 17.51	58.88 ± 10.04	0.259

hs-CRP High-sensitivity C-reactive protein, *TG* Triglycerides, *Chol* Total cholesterol, *HDL* High-density lipoprotein, *LDL* Low-density lipoprotein, *AST* Aspartate aminotransferase, *ALT* Alanine aminotransferase, *CPK* Creatine phosphokinase

[a] *P* value obtained from the Mann–Whitney *U* test

[b] *P* value obtained from independent sample *t*-test

in group A than in group B ($P=0.014$). The results presented in Fig. 1 illustrate a significant reduction in both LDL levels and hs-CRP comparing groups A and B. The study findings also revealed that none of the participants reported drug side effects or myalgia. Although the average cholesterol level was higher in group B 24 h after PCI, this result was not consistent until the end of the study. Among those who underwent assessments of CPK levels, the mean CPK level in group A was 58.28 ± 17.51, while in group B, it was 58.88 ± 10.04. The difference in CPK levels between the two groups was not statistically significant ($P=0.259$).

Discussion

In our double-blind, placebo-controlled randomized clinical trial, we investigated the efficacy of a combination therapy involving ezetimibe and atorvastatin compared to atorvastatin alone, specifically focusing on short-term MACEs following PCI. Our findings indicate that the combination therapy not only significantly reduced LDL cholesterol levels but also led to a notable decrease in hs-CRP levels in the study population. These results highlight the potential advantages of this combined therapeutic strategy in optimizing LDL control and alleviating the inflammatory burden in patients following PCI.

LDL cholesterol reduction

The reduction in LDL levels observed with the combined use of ezetimibe and atorvastatin in our study aligns with findings from previous research and is further supported by a meta-analysis [15, 16]. Ezetimibe, a cholesterol absorption inhibitor, can provide additive cholesterol-lowering benefits when used in conjunction with statins [17]. Statins, such as atorvastatin, primarily function by inhibiting HMG-CoA reductase, leading to reduced cholesterol synthesis [18]. Ezetimibe complements this mechanism by limiting intestinal cholesterol absorption, which ultimately results in a more pronounced LDL reduction [19]. The study by Tsujita et al., which also analyzed the combined effects of atorvastatin and ezetimibe, reported a significant reduction in LDL levels and observed a regression of atherosclerotic plaques, in

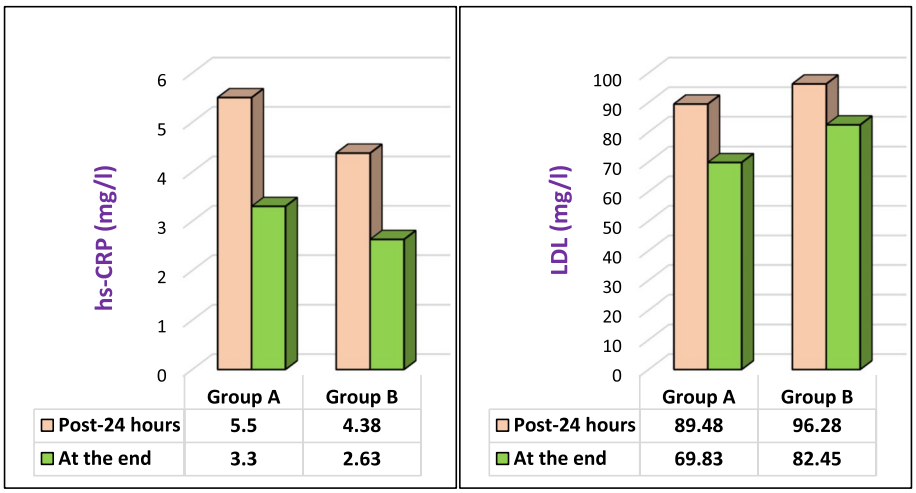

Fig. 1 Comparison of therapy effects on LDL cholesterol and hs-CRP levels

contrast to our findings. Their follow-up periods of 9 and 12 months may have played a crucial role in their outcomes [16].

Elevated LDL cholesterol is a recognized risk factor for cardiovascular disease. Research indicates that a reduction of 1 mmol/L in LDL cholesterol corresponds to a 20–25% decrease in the risk of major vascular events [20]. Consequently, the LDL-lowering effect achieved through the combination of ezetimibe and atorvastatin could significantly decrease the incidence of cardiovascular complications and long-term mortality in patients undergoing percutaneous coronary intervention (PCI).

Inflammation and hs-CRP reduction

hs-CRP as a sensitive indicator of inflammation is closely linked to the pathophysiology of atherosclerosis and acute coronary syndromes [21, 22]. The reduction in hs-CRP levels observed in our study parallels the findings related to LDL cholesterol, underscoring ezetimibe's potential impact on inflammatory pathways while effectively managing lipid levels. Sager et al. have reported comparable effects regarding the impact of ezetimibe and simvastatin on reducing hs-CRP levels [9].

The interaction between LDL cholesterol and inflammation is significant; elevated LDL levels can trigger inflammation in arterial walls, and persistent inflammation can exacerbate lipid accumulation, creating a harmful cycle that increases the risk of plaque rupture and subsequent cardiac events [23]. Thus, simultaneously targeting both LDL and hs-CRP levels may offer a more holistic approach to reducing cardiovascular risk in patients following PCI [24]. Given the austere cardiovascular landscape that follows PCI, optimizing therapy to minimize MACE is paramount. Incorporating ezetimibe into the standard atorvastatin regimen presents a promising strategy to improve lipid profiles and concurrently target inflammatory markers. While our study focused on short-term outcomes, further investigations are warranted to observe the long-term effects of this combination therapy on clinical endpoints, including overall mortality and the incidence of recurrent cardiac events.

Limitations and future directions

While our study provides compelling evidence for the combination of ezetimibe and atorvastatin, it is important to acknowledge its limitations. The sample size might restrict the generalizability of the findings, and the follow-up period for MACE was relatively short. Future research should involve larger groups of patients and longer follow-up times to better understand this treatment's long-term effects. Additionally, exploring how ezetimibe influences hs-CRP levels could shed light on its benefits beyond managing cholesterol.

Conclusion

The results of our study indicate that the combination of ezetimibe and atorvastatin after PCI leads to significant reductions in LDL cholesterol and hs-CRP levels, suggesting potential benefits in lowering short-term major adverse cardiac events. This highlights the importance of a comprehensive strategy for managing cardiovascular health.

Abbreviations

MACE	Major adverse cardiovascular events
PCI	Percutaneous coronary intervention
LDL	Low-density lipoproteins
hs-CRP	High-sensitivity C-reactive protein
NSAIDs	Nonsteroidal anti-inflammatory drugs
LVEF	Left ventricular ejection fraction
ECG	Electrocardiogram
CPK	Creatine phosphokinase
HDL	High-density lipoprotein
BMI	Body mass index
AST	Aminotransferase
ALT	Alanine aminotransferase
TG	Triglycerides
Chol	Total cholesterol

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Authors' contributions

SH.A, B.B, and H.F contributed to the study design and supervision. SH.A, B.B, H.F, A.S, and A.GH wrote the manuscript. A.S and SH.A revised manuscript. All authors read and approved the final manuscript.

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Data availability

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

Declarations

Ethics approval and consent to participate

The study received ethics approval from the Ethics Committee of Hormozgan University of Medical Sciences (IR.HUMS.REC.1396.133). Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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