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Impact of combination therapy with statin and ezetimibe on secondary prevention for post-acute myocardial infarction patients in the statin era

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ABSTRACT

Background: Little is known concerning the effect of ezetimibe for secondary prevention in post-myocardial infarction (MI) patients. In this study, we investigated the secondary prevention effect of ezetimibe for post-MI patients.

Methods: This study is a retrospective analysis of Assessing Lipophilic vs. hydrophilic Statin therapy for Acute MI (ALPS-AMI study). The patients were divided into two groups: those administered a statin to control low density lipoprotein-cholesterol (LDL-C), the ezetimibe(−) group, and those administered ezetimibe in addition to a statin to control LDL-C, the ezetimibe(+) group. The endpoints were Major Adverse Cardiac and Cerebrovascular Event (MACCE), including all-cause death, recurrence of MI, stroke, and heart failure requiring hospitalization, and MACCE with revascularization.

Results: The ezetimibe(+) and ezetimibe(−) groups contained 113 and 337 patients, respectively. Incidences of MACCE and MACCE with revascularization were lower in the ezetimibe(+) group than in the ezetimibe(−) group (2.6% vs. 11.5%, $p = 0.002$; 23.0% vs. 36.7%, $p = 0.014$, respectively). Moreover, logistic regression analysis revealed ezetimibe(+) was a significant negative predictor of MACCE (OR 0.208, 95% CI 0.048 to 0.903, $p = 0.047$) and MACCE with revascularization (OR 0.463, 95% CI 0.258 to 0.831, $p = 0.008$). The preventive effect of ezetimibe against MACCE was observed in both moderate- and high-intensity lipid lowering treatment groups (0% vs. 17%; $p = 0.077$, 3.1% vs. 9.4%; $p = 0.033$).

Conclusions: In lipid-lowering therapy post-MI, ezetimibe and statin combination therapy improved MACCE with or without revascularization compared with statin monotherapy. These findings suggest that post-MI secondary prevention should be more intensive.

1. Introduction

Low-density lipoprotein cholesterol (LDL-C) is considered an important target for the prevention of atherosclerotic events [1–3]. Insufficient control over LDL-C increases the atherosclerotic plaque burden and worsens plaque vulnerability [4–6]. Previous ACC/AHA guidelines recommended an absolute decrease in LDL-C levels below 100 mg/dl, while the current guideline recommends a 30–50% decrease or more from baseline levels to prevent secondary atherosclerotic events. Moreover, the new ACC/AHA guideline recommends statins as the only agents to reduce LDL-C and improve lipid metabolism, and thus prognosis, for post-MI patients [7]. In many investigations, statin use was reported to improve plaque burden and vulnerability [4–6] and the prognosis of atherosclerotic disease patients. However, although in the modern era statins are considered a necessary agent to improve atherosclerotic disease, statin monotherapy does not sufficiently prevent atherosclerotic disease [8]. Strict lipid-lowering therapy with another agent combined with a statin may be required to prevent secondary atherosclerotic events. Ezetimibe, a selective Niemann–Pick C1-like protein (NPC1L1) inhibitor, employs a different mechanism from statins to improve cholesterol metabolism by inhibiting intestinal cholesterol absorption [9]. Many investigations have reported favorable effects of ezetimibe for atherosclerosis [10]. Thus, we investigated the impact of combination therapy with ezetimibe and statin for secondary prevention of MI.

2. Materials and methods

This study is a retrospective analysis of prospectively collected data assessing lipophilic vs. hydrophilic statin therapy for acute MI (ALPS-

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AMI study) with a head-to-head comparison of the efficacy of lipophilic atorvastatin vs. hydrophilic pravastatin [11,12]. This study was a prospective, randomized, open-labeled, blinded endpoint study that required patients at 20 participating sites in Nagano and Niigata prefectures of Japan. The inclusion criteria included: male or female, aged >20 years, written informed consent, and percutaneous coronary intervention (PCI) to treat either ST-segment elevation or non-ST-segment elevation acute MI done within 96 h. Exclusion criteria included planned surgery for coronary artery bypass grafting, pregnancy, active liver or renal disease, malignant disease, withdrawal of informed consent, and serious arrhythmic events or the presence of hemodynamic instability (hypotension, congestive heart failure, or mechanical complication following acute MI). Patients were randomly allocated to receive 10 mg of either atorvastatin or pravastatin once daily, with the treatment goal to reduce the LDL-C level below 100 mg/dl. If necessary, the dose was increased to 20 mg in one month after admission of statin. If the treatment goal still was not achieved with statin monotherapy, then 10 mg ezetimibe was added in one month after increasing each statin dose up to 20 mg. Patients were enrolled from June 2008 to December 2010 and followed for at least 24 months. The study was performed in accordance with the Declaration of Helsinki ant the Good Clinical Practice Guidelines. The protocol was approved by each participating site's ethics committee, and was registered at the University Hospital Medical Information Network (UMIN000001521).

2.1. Patient population

According to ALP-AMI study criteria, we screened 450 patients. The patients were divided into two groups: those administered only a statin to control LDL-C level, the ezetimibe(−) group, and those administered ezetimibe in addition to a statin to control LDL-C level, the ezetimibe(+) group. The endpoints were major adverse cardiac and cerebrovascular events (MACCE), including all-cause death, cardiovascular death, recurrence of myocardial infarction, stroke, and heart failure requiring hospitalization, and MACCE with revascularization.

2.2. Guideline of lipid lowering therapy for secondary prevention of post-myocardial infarction patient

In the 2013 ACC AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults, patients with a history of clinical atherosclerotic systemic cardiovascular disease including myocardial infarction were divided into 2 groups; patients ≤75 years old received high-intensity lipid lowering therapy, while those >75 years old were assigned to moderate-intensity lipid lowering therapy. In the guideline, the target level of LDL-C was not set, and statin titration was not recommended. Furthermore, statin was only the recommended agent for lipid lowering therapy, and other agents including ezetimibe were not recommended. However, we consider that the effect of ezetimibe and statin combination therapy should be examined in each therapy intensity group.

2.3. Statistical analysis

Continuous variables are presented as mean ± standard deviation, and categorical variables are expressed as a number and percentage. Continuous variables were compared using the two-sided paired t-test, and categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. All p values are two-sided, and results with $p < 0.05$ were considered statistically significant. A logistic regression model was subsequently used to analyze the incidence of MACCE and MACCE with revascularization. As the first step, potential predictors of MACCE and MACCE with revascularization incidence were separately assessed in logistic regression analyses. Then multiple logistic regression analysis was conducted for covariates that demonstrated an association with the incidence of MACCE and MACCE with revascularization ($p \leq 0.10$). Results are expressed as odds ratios with 95% confidence intervals (95% CI). All analyses were performed using SPSS statistical software, version 13.0 (SPSS Inc., Chicago, Illinois).

Table 1
Comparison of characteristics at baseline and 24 months between the ezetimibe(+) and ezetimibe(−) groups. Baseline characteristics.

	Ezetimibe(+)	Ezetimibe(−)	p value
	n = 113	n = 337	
Female sex n = 450 (%)	23 (20.3)	61 (18.1)	0.343
Age (years)	62.13 ± 11.5	67.1 ± 10.9	<0.0001
BMI (kg/m^2)	24.17 ± 3.79	23.6 ± 3.7	0.303
Hypertension n = 449 (%)	55 (48.6)	146 (43.3)	0.205
Diabetes mellitus n = 450 (%)	31 (27.4)	126 (37.3)	0.034
Smoking n = 450 (%)	76 (67.2)	212 (62.9)	0.237
Familial history n = 450 (%)	31 (27.4)	67 (19.8)	0.062
Hemoglobin (g/dl)	14.56 ± 1.9	14.4 ± 2.4	0.69
Creatinine (mg/dl)	0.82 ± 0.24	0.89 ± 0.64	0.288
eGFR (ml/min/1.73 m^2)	73.88 ± 17.5	71.03 ± 20.09	0.179
T-chol (mg/dl)	228 ± 39.1	194.7 ± 35.6	<0.0001
HDL-C (mg/dl)	47.1 ± 10.9	47.7 ± 11.8	0.666
LDL-C (mg/dl)	153 ± 34.2	123.6 ± 29.6	<0.0001
TG (mg/dl)	167.7 ± 142.3	126.3 ± 88.1	<0.0001
Non-HDL (mg/dl)	184 ± 40.2	148.7 ± 35.1	<0.0001
HbA1c (%)	5.79 ± 1.1	5.97 ± 1.17	0.164
STEMI	84 (74.3)	246 (72.9)	0.32
pAf n = 433 (%)	3 (2.6)	12 (3.5)	0.436
NSVT n = 433 (%)	31 (27.4)	23 (6.8)	0.003
Killip class ≥ 2	9 (7.9)	43 (12.7)	0.107
BNP (pg/ml)	101.8 ± 160.1	134.7 ± 179.9	0.125
LVEF (%)	55 ± 10.7	54.8 ± 12.2	0.87
Triple vessel disease (%)	9 (7.9)	21 (6.2)	0.296

Abbreviations. BMI: body mass index, eGFR: estimated glomerular filtrated rate, T-chol: total cholesterol, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, TG: triglyceride, STEMI: ST-elevated myocardial infarction, pAf: paroxysmal atrial fibrillation, NSVT: non-sustained ventricular tachycardia, BNP: brain natriuretic peptide, LVEF: left ventricular ejection fraction.

3. Results

3.1. Baseline characteristics

Baseline clinical characteristics of the ezetimibe(+) and ezetimibe(−) groups are compared in Table 1. The ezetimibe(+) and ezetimibe(−) groups contained 113 and 337 patients, respectively. The ezetimibe(−) group was significantly older than the ezetimibe(+) group (62.1 ± 11.5 vs. 67.1 ± 10.9 years, $p < 0.0001$). There were no significant differences in history of hypertension or smoking. Diabetes mellitus was observed in 31 patients in the ezetimibe(+) group (27.4%) and 126 (37.3%) in the ezetimibe(−) group ($p = 0.034$). Total cholesterol and LDL-C

Table 2
Lipid parameter at 24 months and differences between values at baseline and 24 months.

	Ezetimibe(+)	Ezetimibe(−)	p value
	n = 108	n = 311	
24 M T-chol (mg/dl)	167.1 ± 29.5	155.2 ± 24.1	0.001
24 M HDL-C (mg/dl)	49.2 ± 11.3	49.5 ± 11.8	0.865
24 M LDL-C (mg/dl)	94.6 ± 24.7	83.7 ± 17.8	<0.0001
24 M TG (mg/dl)	163.8 ± 97.6	132.9 ± 75.7	0.004
ΔT-chol (mg/dl)	−73.1 ± 36.8	−56.9 ± 31.2	<0.0001
ΔLDL-C (mg/dl)	−69.8 ± 32.1	−51.7 ± 26.3	<0.0001
ΔHDL-C (mg/dl)	12.9 ± 7.1	13.8 ± 9.2	0.345
ΔTG (mg/dl)	−73.1 ± 36.8	−56.9 ± 31.2	<0.0001

Abbreviations. Same as in Table 1. 24 M: 24 months.
Δ indicates the difference between values at baseline and 24 months.