Effect of Ezetimibe + Pitavastatin on Cardiovascular Outcomes in Patients with ST-Segment Elevation Myocardial Infarction (from the HIJ-PROPER Study)

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Lipid-lowering therapy is necessary to reduce cardiovascular event rates in patients with ST-segment elevation myocardial infarction (STEMI). This study aimed to evaluate the effect of intensive lipid-lowering therapy, which comprised pitavastatin and ezetimibe, on patients with STEMI. We therefore undertook a post hoc subanalysis of the HIJ-PROPER study's data that examined the clinical outcomes of the patients with dyslipidemia and STEMI (n = 880) who received pitavastatin and ezetimibe therapy (intensive lipid-lowering therapy group) or pitavastatin monotherapy (standard lipid-lowering therapy group), and we evaluated their cardiovascular events. The primary end point was a composite of all-cause death, nonfatal myocardial infarction, nonfatal stroke, unstable angina, and ischemia-driven revascularization. During the median 3.4-year follow-up period, the cumulative rates of the primary end point were 31.9% and 39.7% in the intensive lipid-lowering therapy and standard lipid-lowering therapy groups, respectively (hazard ratio [HR], 0.77; 95% confidence interval [CI], 0.62 to 0.97; p = 0.02). Compared with the standard lipid-lowering therapy group, the intensive lipid-lowering therapy group had significantly lower all-cause death (6.9% vs 3.2%; HR, 0.45; 95% CI, 0.23 to 1.84; p = 0.01) and nonfatal stroke (2.9% vs 1.6%; HR, 0.77; 95% CI, 0.62 to 0.97; p = 0.02) rates. Patients with pitavastatin and ezetimibe therapy, as compared with pitavastatin monotherapy, had a lower cardiovascular event in STEMI patients. In conclusion, adding ezetimibe to statin therapy may be beneficial for patients with dyslipidemia and STEMI. **(Am J Cardiol 2020;132:15−21)**

Aggressive lipid-lowering therapy with statins is the generally accepted approach for treating patients with acute coronary syndrome (ACS).[1,2] Recently, the findings from studies of patients with ACS who were administered intensive lipid-lowering therapy involving nonstatin drugs, including ezetimibe and proprotein convertase subtilisin/kexin type 9, that is, PCSK9, inhibitors, showed improved clinical outcomes.[3,4] We published results from the Heart Institute of Japan-PRoper level of lipid lOwering with Pitavastatin and Ezetimibe in acute coRonary syndrome (HIJ-PROPER) study, a randomized controlled trial which tested the efficacy of intensive lipid-lowering therapy by statin and ezetimibe and compared it with standard lipid-lowering therapy by statin monotherapy in ACS patients[5]. Although most ST-segment elevation myocardial infarction (STEMI) derive from coronary occlusions caused by thrombi that develop after lipid-rich, vulnerable plaques rupture,[6] a variety of factors can cause other types of ACS, namely, non-STEMI (NSTEMI), and unstable angina (UA).[7] Hence, patients with STEMI should be evaluated as a separate ACS subset. This study aimed to undertake a subgroup analysis of the HIJ-PROPER study's data to evaluate the effects of intensive lipid-lowering therapy, which comprised pitavastatin and ezetimibe, on patients with STEMI.

Methods

This study comprised a subanalysis of data from the HIJ-PROPER study, which was a multicenter, prospective, randomized, open-label, blinded end point trial with an active-control design that compared 2 lipid-lowering treatment strategies in 19 Japanese hospitals.[8] A total of 1,734 patients with ACS were randomized to receive intensive lipid-lowering therapy (pitavastatin and ezetimibe) or standard lipid-lowering therapy (pitavastatin monotherapy) between January 2010 and April 2013. During the original HIJ-PROPER study, 13 patients were lost to follow-up and 1,721 patients were analyzed.

In this analysis, we focused on patients with STEMI. The original HIJ-PROPER study defined STEMI as patients who had electrocardiographic changes, comprising persistent ST-segment elevations ≥0.1 mV, new Q waves, or new left bundle-branch blocks, as well as elevated cardiac enzyme levels, namely, troponin or creatinine kinase-MB.[5] After excluding the patients with NSTEMI and UA from the original study population, 880 patients who were

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See page 20 for disclosure information.

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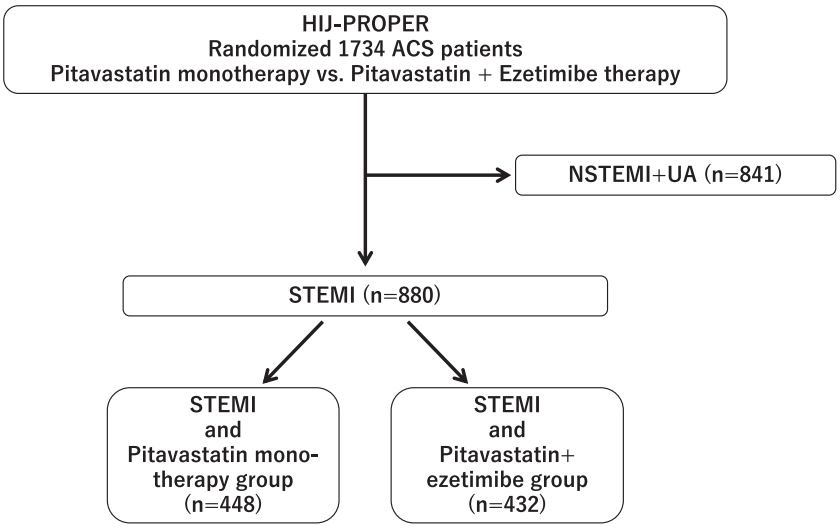

Figure 1. Patient enrollment in this study. ACS = acute coronary syndrome; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina.

diagnosed with STEMI were ultimately analyzed, of whom, 448 received pitavastatin monotherapy (standard lipid-lowering therapy group) and 432 received pitavastatin and ezetimibe (intensive lipid-lowering therapy group; Figure 1).

The groups were compared in relation to their characteristics and cardiovascular events. The study's primary end point was the same as that in the original HIJ-PROPER study, namely, a composite of all-cause death or the first occurrence of a nonfatal myocardial infarction, nonfatal stroke, UA, or ischemia-driven revascularization that comprised either percutaneous coronary intervention or coronary artery bypass grafting. Moreover, in this study, we evaluated a secondary end point that consisted of a composite of all-cause death or the first occurrence of a nonfatal myocardial infarction or nonfatal stroke. The participants were followed by hospital doctors or other nonspecialist practitioners. We determined the incidence of the end points during scheduled visits at 3, 6, 12, 24, and 36 months.

The study's protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, which was reflected by its a priori approval by each participating medical center's institutional review board or relevant ethics committee. Written informed consent for trial enrollment was obtained from all of the patients.

The patients' baseline characteristics are presented according to the lipid-lowering treatment received. The continuous variables are expressed as the means and the standard deviations, and the categorical variables are expressed as absolute values and percentages. Welch's *t* test was used to compare the normally distributed continuous variables, the Mann-Whitney U test was used to compare the non-normally distributed continuous variables, and Pearson's chi-squared test was used to compare the categorical variables. The times to death or the first occurrence of events were analyzed using the Kaplan-Meier method with the log-rank test. To assess the effects of the lipid-lowering treatments on the end points, a standard Cox proportional hazards regression model was used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs). Variables were included in the multivariate model if they had values of $p < 0.10$ after the univariate analysis, and independent risk factors associated with the primary end point were identified in the patients with STEMI. A value of $p < 0.05$ was considered to indicate statistical significance, unless stated otherwise. All of the statistical analyses were performed using JMP Pro 14 software (SAS Institute Inc., Cary, NC).

Results

Between January 2010 and April 2013, 1,734 patients participated in the HIJ-PROPER study, and the present analysis was limited to the patients with STEMI; therefore, a total of 880 patients were included in this study (Figure 1). Supplementary Table 1 and Supplementary Table 2 summarize the characteristics of the patients who were included in and excluded from this analysis, together with the absolute changes in the excluded patients' lipid profiles.

Table 1 shows the patients' baseline clinical characteristics. The 2 treatment groups were well balanced, and there were no significant differences between the groups regarding the patients' backgrounds, medications, and cholesterol metabolism.

The patients' mean age was 64 years, and 75.7% of the patients were men. About 31.8% of the patients had diabetes mellitus, and 87.1% of the patients were statin-naive. The baseline mean low-density lipoprotein cholesterol (LDL-C) levels were 137.4 (±29.2) mg/dl in the standard lipid-lowering therapy group and 136.6 (±31.2) mg/dl in the intensive lipid-lowering therapy group, and these values declined to 85.1 (±23.1) mg/dl and 66.4 (± 21.7) mg/dl, respectively, after 3 months of treatment ($p < 0.0001$; Table 2). The LDL-C level reductions were maintained over time (Figure 2). Table 2 presents the absolute changes in the profiles of all of the lipid parameters and the high-sensitivity C-reactive protein (hs-CRP) levels.

During follow-up, the cumulative incidence of the primary end point was significantly lower in intensive lipid-lowering therapy group than in standard lipid-lowering

Table 1
Baseline characteristics of the study population

Variable	Pitavastatin monotherapy (n = 448)	Pitavastatin + ezetimibe (n = 432)	p value
Age (years)	64.5 ± 12.0	64.1 ± 12.1	0.59
Men	344 (76.8%)	323 (74.8%)	0.53
BMI (kg/m^2)	24.3 ± 3.8	24.3 ± 3.4	0.81
GFR (ml/min/1.73 m^2)	75.1 ± 37.4	73.8 ± 18.8	0.51
Statin naive	396 (88.4 %)	371 (86.1%)	0.31
Hypertension	286 (63.8 %)	286 (66.2%)	0.48
Diabetes mellitus	150 (33.5%)	130 (30.1%)	0.31
Current smoker	171 (38.2 %)	171 (40.0%)	0.68
Previous myocardial infarction	23 (5.1%)	24 (5.6%)	0.88
Previous revascularization	16 (3.6%)	26 (6.0%)	0.11
Previous heart failure	8 (1.8%)	10 (2.3%)	0.64
Medication			
Beta blocker	27 (6.0%)	30 (6.9%)	0.59
ACEIs/ARBs	116 (25.9 %)	108 (25.0%)	0.82
Calcium channel blocker	115 (25.7 %)	112 (25.9%)	0.94
Aspirin	33 (7.4 %)	46 (10.7%)	0.10
Lipids			
Total cholesterol (md/dl)	211 ± 35.7	210 ± 36.2	0.81
HDL-cholesterol (md/dl)	47.5 ± 12.3	48.6 ± 12.2	0.19
LDL-cholesterol (md/dl)	137 ± 29.2	137 ± 31.2	0.68
Triglyceride (md/dl)	127 ± 73.6	123 ± 66.3	0.38
EPA/AA ratio	0.36 ± 0.25	0.36 ± 0.21	0.87
High-sensitivity CRP (mg/L)	27.3 ± 35.5	26.6 ± 33.7	0.75

AA = arachidonic acid; ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor blockers; BMI = body mass index; CRP = C-reactive protein; EPA = eicosapentaenoic acid; GFR = glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

*Data are expressed as mean ± SD or as number (percentage).

Table 2
Absolute change of each lipid profiles in STEMI patients

Variable	Baseline	3-month follow-up	p value*
Total cholesterol (mg/dl)			
Pitavastatin monotherapy	211±36	162±30	<0.0001
Pitavastatin + ezetimibe	210±36	141±26†	<0.0001
HDL cholesterol (mg/dl)			
Pitavastatin monotherapy	47.5±12.3	47.1±12.0	0.48
Pitavastatin + ezetimibe	48.6±12.2	48.4±11.5	0.72
LDL cholesterol (mg/dl)			
Pitavastatin monotherapy	137±29.2	85.1±23.1	<0.0001
Pitavastatin + ezetimibe	137±31.2	66.4±21.7†	<0.0001
Triglyceride (mg/dl)			
Pitavastatin monotherapy	127±73.6	155±98.1	<0.0001
Pitavastatin + ezetimibe	123±66.3	134±76.7†	0.008
EPA/AA ratio			
Pitavastatin monotherapy	0.36±0.25	0.44±0.32	<0.0001
Pitavastatin + ezetimibe	0.36±0.21	0.39±0.26‡	0.11
High-sensitivity CRP (mg/L)			
Pitavastatin monotherapy	27.3±35.5	2.45±8.18	<0.0001
Pitavastatin + ezetimibe	26.6±33.7	1.52±3.28‡	<0.0001

AA, arachidonic acid; CRP, C-reactive protein; EPA, eicosapentaenoic acid; HDL, high-density lipoprotein; LDL, low-density lipoprotein; STEMI, ST-segment elevation myocardial infarction.

Data are expressed as mean ± SD.

* p value refers to the difference between baseline and 3-month follow-up by a paired *t* test.

† Data in pitavastatin + ezetimibe therapy are lower than those in pitavastatin monotherapy (p <0.001).

‡ Data in pitavastatin + ezetimibe therapy are lower than those in pitavastatin monotherapy (p <0.05).

therapy group (Figure 3). With respect to the individual component of primary end point, the all-cause death and nonfatal stroke were significantly lower in the patients with intensive lipid-lowering therapy, compared with those in the patients with standard lipid-lowering therapy. The cumulative incidence of the secondary end point, a composite of all-cause death/nonfatal myocardial infarction /nonfatal stroke, was also significantly lower in intensive lipid-lowering therapy group than in standard lipid-lowering therapy group (Table 3).

The univariate analyses indicated that age, the body mass index, the presence of diabetes mellitus, and using ezetimibe tended to be associated with the occurrence of the primary end point (Table 4). The multivariate analyses revealed that the presence of diabetes mellitus (HR, 1.49; 95% CI, 1.17 to 1.89; p = 0.001) and using ezetimibe (HR, 0.79; 95% CI, 0.63 to 0.99; p = 0.04) independently predicted the primary end point.

The adverse events requiring study drug discontinuation in both groups were shown in Supplementary Table 3.

Discussion

This study's key findings showed that compared with pitavastatin monotherapy, pitavastatin combined with ezetimibe significantly lowered the LDL-C level for the duration of the observation period, which resulted in significantly lower cardiovascular event rates. Furthermore, the findings showed that the benefits of treatment were mainly driven by reduced mortality and nonfatal stroke rates, and that

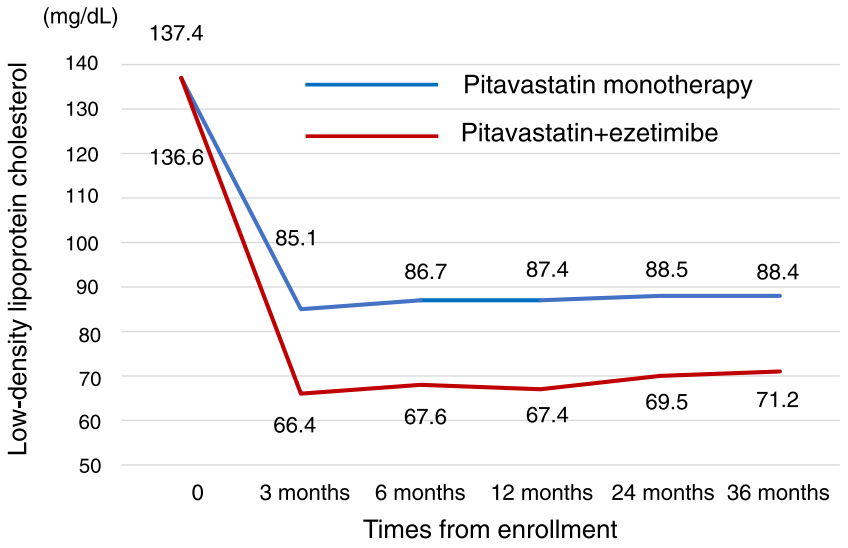

Figure 2. Changes in LDL-C in pitavastatin monotherapy group and pitavastatin plus ezetimibe group. The baseline mean LDL-C levels were comparable. The value was significantly lower in pitavastatin plus ezetimibe group after 3 months of treatment ($p < 0.0001$) and the LDL-C level reductions were maintained over time. LDL-C = low-density lipoprotein cholesterol.

ezetimibe use and diabetes mellitus were independent predictors of cardiovascular events.

STEMI is a type of ACS that is characterized by the findings from ECGs, and most patients have acute total coronary occlusions that require immediate reperfusion. Although the clinical and pathophysiological features of STEMI differ from other types of ACS, few trials have examined the impact of intensive lipid-lowering therapy administered specifically to patients with STEMI.

The findings from the landmark IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) in which 29% of the patients had STEMI, demonstrated the efficacy of statin and ezetimibe therapy, compared with statin monotherapy administered to patients

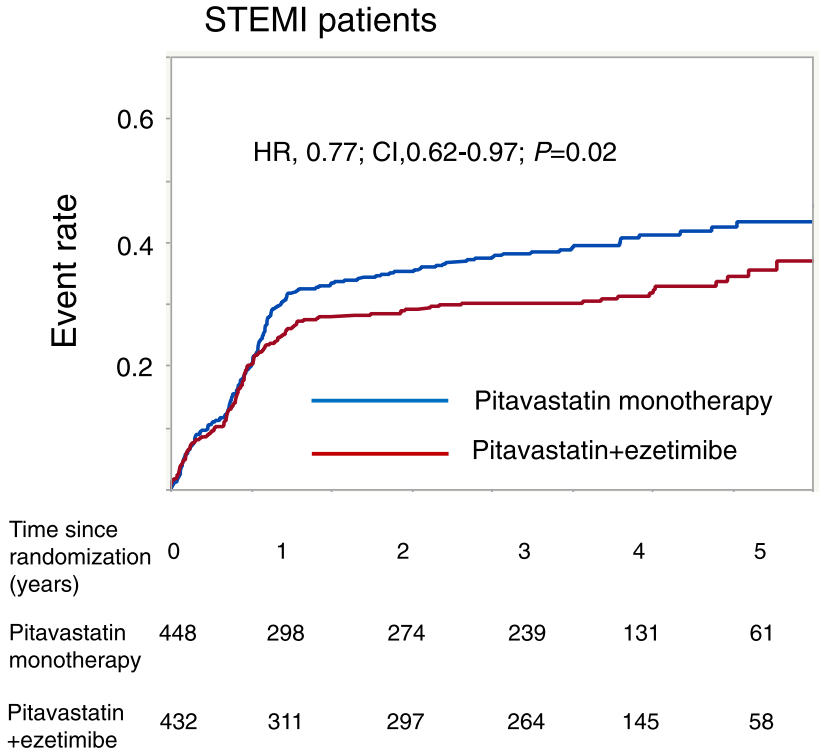

Figure 3. Kaplan−Meier curve for the primary end point. Primary end point was a composite of all-cause death, nonfatal myocardial infarction, nonfatal stroke, unstable angina, and ischemia-driven revascularization. CI = confidence interval; HR = hazard ratio; STEMI = ST-segment elevation myocardial infarction.

Table 3
Individual components of primary end point

Variable	Pitavastatin monotherapy (n = 448)	Pitavastatin + ezetimibe (n = 432)	HR	95% CI	p value
Primary end point	178 (39.7 %)	138 (31.9 %)	0.77	0.62-0.97	0.02
All-cause death	31 (6.9 %)	14 (3.2 %)	0.45	0.23-0.84	0.01
Nonfatal myocardial infarction	3 (0.6 %)	7 (1.6 %)	2.36	0.66-10.9	0.19
Nonfatal stroke	13 (2.9 %)	7 (1.6 %)	0.77	0.62-0.97	0.02
Unstable angina	12 (2.7 %)	15 (3.5 %)	1.27	0.60-2.77	0.53
Ischemia-driven coronary revascularization	147 (32.8 %)	118 (27.3 %)	0.80	0.63-1.02	0.07
All-cause death/nonfatal MI/nonfatal stroke	45 (10.0 %)	27 (6.3 %)	0.60	0.37-0.97	0.04
Cardiovascular death	14 (3.1 %)	12 (2.8 %)	0.86	0.39-1.87	0.71

CI = confidence interval; HR = hazard ratio.
*Data are expressed as number (percentage).

with ACS.[3] Indeed, over 7 years, the cardiovascular events were significantly lower in the intensive lipid-lowering therapy group compared with that in the standard lipid-lowering therapy group. In contrast, an initial analysis of the data from the HIJ-PROPER trial in which 51% of the patients had STEMI, showed that compared with statin monotherapy, statin and ezetimibe therapy was not associated with better cardiovascular benefits. Given the differences between the patients regarding their race and characteristics, direct comparisons between the IMPROVE-IT and HIJ-PROPER trial are difficult, but the inconsistent results might derive from the small sample sizes, the studies' durations, and the low event rates. The findings from a subanalysis of the data from the IMPROVE-IT showed that the benefits of therapy with a statin and ezetimibe were enhanced in the high-risk patient subsets that included patients with diabetes,[9] a history of coronary artery bypass graft surgery,[10] and a high Thrombolysis In Myocardial Infarction Risk Score for Secondary Prevention.[11] Recent guidelines recommend risk assessments of the patients with atherosclerotic cardiovascular disease and the initiation of ezetimibe therapy for very high-risk patients.[12] The present study's findings also revealed that patients with STEMI were potential candidates for intensive lipid-lowering therapy given the enhanced benefits associated with administering a statin and ezetimibe to them.

Table 4
Independent predictor associated for primary end point in STEMI

Variable	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	p value	Hazard ratio	95% CI	p value
Age*	1.01	0.99-1.02	0.053	1.00	0.99-1.01	0.50
Men	1.08	0.83-1.41	0.59			
Body mass index*	0.97	0.94-1.00	0.09	0.97	0.93-1.00	0.07
Glomerular filtration rate**	0.98	0.93-1.02	0.32			
Hypertension	1.01	0.80-1.28	0.91			
Diabetes mellitus	1.51	1.21-1.89	0.0004	1.49	1.17-1.89	0.001
Current smoker	1.13	0.90-1.41	0.30			
Previous myocardial infarction	1.11	0.66-1.73	0.68			
Previous revascularization	1.11	0.65-1.78	0.68			
Use of Beta blocker	1.01	0.63-1.54	0.95			
Use of ACEIs/ARBs	0.92	0.71-1.18	0.52			
Use of calcium channel blocker	1.11	0.86-1.41	0.86			
Use of aspirin	0.92	0.60-1.35	0.69			
Use of ezetimibe	0.77	0.62-0.97	0.02	0.79	0.63-0.99	0.049
HDL-C**	0.93	0.84-1.02	0.11			
LDL-C**	1.01	0.97-1.04	0.59			
Triglyceride**	0.99	0.98-1.01	0.37			
EPA/AA ratio*	1.00	0.52-1.80	0.99			
High-sensitivity CRP**	1.03	0.99-1.06	0.07	1.03	0.99-1.06	0.057

AA = arachidonic acid; ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor blockers; CI = confidence interval; CRP = C-reactive protein; EPA = eicosapentaenoic acid; HDL = high-density lipoprotein; LDL = low-density lipoprotein; STEMI = ST-segment elevation myocardial infarction.
* Per 1 increase.
** Per 10 increase.

The administration of ezetimibe and pitavastatin to the patients with STEMI was associated with a significant 23% reduction in the relative risk of the primary end point. Of the primary end point's components, the all-cause death and nonfatal stroke rates were significantly lower in the intensive lipid-lowering therapy group. In contrast, there was no significant difference in cardiovascular death. Although there are no specific reasons that can explain these findings, the results from the IMPROVE-IT revealed that the patients who achieved a combined target of an LDL-C level <70 mg/dl and a hs-CRP level <2 mg/L experienced fewer cardiovascular events, including mortality.[13] Likewise, we published subgroup analyses of the data from the HIJ-PROPER trial and showed that the patients with elevated hs-CRP levels had a high risk of cardiovascular events.[14] The patients with STEMI who received intensive lipid-lowering therapy had significantly lower hs-CRP levels after 3 months compared with those in the patients who received standard lipid-lowering therapy (Table 2); these findings were not apparent in the patients with NSTEMI and UA (Supplementary Table 2). Inflammation plays a crucial role during myocardial infarction,[15] and excessive inflammation is associated with adverse outcomes in patients with ACS.[16] Notably, enhanced inflammation is involved in plaque rupture, which is the most common cause of coronary thrombosis in patients with STEMI, and this may underlie the enhanced clinical benefits associated with intensive lipid-lowering therapy administered to patients with STEMI.

Regarding the baseline lipid profiles, the eicosapentaenoic (EPA)/arachidonic acid (AA) ratio was significantly lower in the patients with STEMI compared with that in the patients with NSTEMI and UA (Supplementary Table 1). Adding ezetimibe to statin therapy reduces the risk of cardiovascular events after ACS compared with statin monotherapy in patients with lower EPA/AA ratios.[17] Although few reports describe the EPA/AA ratios in patients with STEMI, low EPA/AA ratios in these patients could explain this study's results.

The present study has several limitations. First, this was a post hoc subgroup analysis of data from a prospective randomized controlled trial, and the results must be interpreted with caution. Second, there were no detailed data that described noncardiovascular deaths; therefore, we were unable to examine differences between intensive and standard lipid-lowering therapy in relation to mortality in detail. Third, our study comprised Japanese patients with ACS only, which could affect the generalizability of our data to non-Japanese patients.

In conclusion, compared with pitavastatin monotherapy, pitavastatin combined with ezetimibe was associated with a lower cardiovascular event rate in the patients with STEMI. Hence, adding ezetimibe to a statin may be beneficial for patients with dyslipidemia and STEMI.

Authors' Contributions

Dr. Arashi, Dr. Yamaguchi, Dr. Ogawa, and Dr. Hagiwara conceptualized and designed the original study. Dr. Otsuki, Dr. Arashi, and Dr. Yamaguchi analyzed and interpreted the data. Dr. Otsuki, Dr. Arashi, and Dr. Yamaguchi drafted and wrote the manuscript. Dr. Ogawa and Dr. Hagiwara reviewed the manuscript. All authors, both external and internal, had full access to all of the data, including the statistical reports and tables, from the study and are responsible for the integrity of the data and the accuracy of the analyses.

Disclosures

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Supplementary materials

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