Circulation Reports
Circ Rep 2020; 2: 128–134
doi:10.1253/circrep.CR-19-0118

ORIGINAL ARTICLE
Preventive Medicine

Effect of Aggressive Lipid-Lowering Therapy in Single-Vessel vs. Multivessel Coronary Artery Disease Patients With Acute Coronary Syndrome

— Heart Institute of Japan-Proper Level of Lipid Lowering With Pitavastatin and Ezetimibe in Acute Coronary Syndrome (HIJ-PROPER) Substudy —

Masataka Ogiso, MD, PhD; Junichi Yamaguchi, MD, PhD; Erisa Kawada-Watanabe, MD, PhD; Ryo Koyanagi, MD, PhD; Haruki Sekiguchi, MD, PhD; Tomohiro Sakamoto, MD, PhD; Nobuo Iguchi, MD, PhD; Hiroyuki Tanaka, MD, PhD; Hisayuki Okada, MD, PhD; Yoshimi Ota, MD, PhD; Kentaro Jujo, MD, PhD; Shinya Fujii, MD, PhD; Hiroshi Ogawa, MD, PhD; Nobuhisa Hagiwara, MD, PhD

Background: The effects of aggressive lipid-lowering therapy according to the number of diseased coronary arteries in acute coronary syndrome (ACS) are still controversial. This study investigated the efficacy of this therapy in ACS patients with multivessel disease (MVD) and single-vessel disease (SVD).

Methods and Results: The subjects were derived from the HIJ-PROPER study, in which ACS patients with dyslipidemia were randomized to receive either pitavastatin+ezetimibe (targeting low-density lipoprotein cholesterol [LDL-C] <70 mg/dL) or pitavastatin monotherapy (targeting LDL-C <90 mg/dL). In this study, treatment efficacy was compared between patients with MVD and SVD. The primary endpoint was a composite of major advanced cardiovascular events (MACE; all-cause death, non-fatal myocardial infarction, non-fatal stroke, and ischemia-driven revascularization). We identified 1,702 eligible patients (MVD, n=869; SVD, n=833; mean age, 65.6 years; male, 75.6%; acute revascularization, 96.2%). MACE incidence was significantly higher in the MVD group than in the SVD group (43.7% vs. 25.9%, HR, 1.95; 95% CI: 1.65–2.31, P<0.001). In the SVD group, pitavastatin+ezetimibe had significantly fewer MACE than pitavastatin monotherapy (34.6% vs. 47.4%, HR, 0.72; 95% CI: 0.55–0.94, P=0.02).

Conclusions: The benefits of aggressive lipid-lowering therapy, with the addition of ezetimibe to statins, were enhanced in ACS patients with SVD, but not with MVD, in the early invasive strategy era.

Key Words: Acute coronary syndrome; Lipid-lowering therapy; Multivessel disease; Single-vessel disease

Acute coronary syndrome (ACS) with multivessel coronary artery disease (MVD) is highly correlated with poor prognosis in terms of both worse mortality and major adversed cardiac events (MACE) compared with single-vessel coronary artery disease (SVD).[1,2] More MVD patients have been found to have higher risk factors for coronary artery disease (CAD), such as diabetes mellitus (DM) and dyslipidemia,[3] and complete coronary revascularization is also more difficult in patients with MVD compared with those with SVD,[4] resulting in a poorer prognosis.

The concept of aggressive lipid-lowering therapy for patients with a high risk of CAD is now generally accepted: the lower the low-density lipoprotein cholesterol (LDL-C)

Received November 14, 2019; revised manuscript received December 17, 2019; accepted December 18, 2019; J-STAGE Advance Publication released online January 28, 2020 Time for primary review: 1 day

Department of Cardiology, The Heart Institute of Japan, Tokyo Women's Medical University, Tokyo (M.O., J.Y., E.K.-W., R.K., H.S., K.J., H. Ogawa, N.H.); Division of Cardiology, Cardiovascular Center, Saisei-Kai Kumamoto Hospital, Kumamoto (T.S.); Department of Cardiology, Sakakibara Heart Institute, Fuchu (N.I.); Division of Cardiology, Tokyo Metropolitan Tama Medical Center, Fuchu (H.T.); Department of Cardiology, Seirei Hamamatsu General Hospital, Hamamatsu (H. Okada); Department of Cardiology, Saisei-Kai Kurihashi Hospital, Kuki (Y.O.); and Department of Cardiology, Cardiovascular Center of Sendai, Sendai (S.F.), Japan

N.H. is a member of *Circulation Reports*' Editorial Team.

Mailing address: Junichi Yamaguchi, MD, PhD, Department of Cardiology, The Heart Institute of Japan, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan. E-mail: j.yamaguchi0110@gmail.com

ISSN-2434-0790

Table 1. Baseline Characteristics vs. No. Diseased Vessels

Variable	MVD (n=870)	SVD (n=832)	All patients (n=1,702)	P-value
Age (years)	67.5±11.1	63.7±12.2	65.6±11.8	<0.001
Male	654 (75.2)	632 (75.9)	1,286 (75.6)	0.74
BMI (kg/m^2)	24.2±3.5	24.4±3.6	24.3±3.6	0.50
eGFR (mL/min/1.73 m^2)	71.9±30.4	74.2±18.0	73.0±25.2	0.06
Hypertension	624 (71.7)	541 (65.0)	1,165 (68.4)	0.004
DM	325 (37.4)	194 (23.3)	519 (30.5)	<0.001
Smoking	529 (60.8)	523 (62.9)	1,052 (61.8)	0.39
Previous MI	90 (10.3)	40 (4.8)	130 (7.6)	<0.001
Previous HF	24 (2.8)	12 (1.4)	36 (2.1)	0.06
Diagnosis on admission				0.14
STEMI	433 (49.8)	445 (53.5)	878 (51.6)	
Non-STEMI	102 (11.7)	76 (9.1)	178 (10.5)	
UA	335 (38.5)	311 (37.4)	646 (37.9)	
ACS intervention				
PCI	836 (96.1)	802 (96.4)	1,638 (96.2)	0.79
LVEF				
≥35%	834 (95.9)	813 (97.7)	1,647 (96.8)	0.039
Lipid on admission				
LDL-C (mg/dL)	135.7±30.4	134.9±28.9	135.3±29.7	0.63
TC (mg/dL)	209.9±36.0	211.1±34.5	210.5±35.3	0.51
HDL-C (mg/dL)	47.7±11.9	49.6±12.8	48.6±12.4	0.002
TG (mg/dL)	131.1±71.1	130.6±70.7	130.8±70.9	0.88
Medication at randomization				
β-blockers	621 (71.5)	516 (61.9)	1,137 (66.8)	<0.001
ACEI/ARB	685 (78.8)	631 (75.8)	1,316 (77.3)	0.13
CCB	208 (23.9)	174 (20.9)	382 (22.4)	0.13
Nitrates	199 (22.9)	121 (14.5)	320 (18.8)	<0.001
Aspirin	852 (98.0)	820 (98.4)	1,672 (98.2)	0.54
Thienopyridines	802 (92.2)	772 (92.7)	1,574 (92.5)	0.78
Statin use on admission	166 (19.1)	123 (14.8)	289 (16.9)	0.02
Ezetimibe use on admission	10 (1.2)	9 (1.1)	19 (1.1)	0.89

Data given as mean±SD or n (%). ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin II receptor blocker; BMI, body mass index; CCB, calcium-channel blocker; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MVD, multivessel disease; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; Pitava+Eze, pitavastatin+ezetimibe; STEMI, ST-segment elevation myocardial infarction; SVD, single-vessel disease; TC, total cholesterol; TG, triglyceride; UA, unstable angina.

level, the greater the clinical benefit.[5] Recently, aggressive lipid-lowering therapy using non-statin agents, such as ezetimibe or proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors, was shown to produce a great improvement in the clinical outcome of patients at a high risk of CAD.[6–8]

According to a subanalysis of the FOURIER trial, aggressive lipid-lowering therapy was more effective in MVD patients than in SVD patients with stable atherosclerotic cardiac disease,[9] in whom the revascularization rate was uncertain. However, to date there have been no studies on the differences in the effect of aggressive lipid-lowering treatment in ACS patients in the early invasive strategy cohort according to the number of diseased coronary arteries; thus, this aspect remains to be fully elucidated. Accordingly, in this subanalysis, we evaluated the benefits of aggressive lipid-lowering treatment with pitavastatin+ezetimibe in MVD and SVD patients in the modern early invasive strategy era using the study population derived from the Heart Institute of Japan-PRoper level of lipid lOwering with Pitavastatin and Ezetimibe in acute coRonary syndrome (HIJ-PROPER) study, which investigated aggressive lipid-lowering treatment with pitavastatin+ezetimibe in ACS patients.[10]

Methods

This is a post-hoc study of the HIJ-PROPER study. The design, treatment, algorithms, and results of the HIJ-PROPER study have been reported previously.[10,11] In brief, the HIJ-PROPER study was a multicenter, prospective, randomized, open-labeled, blinded endpoint trial with an active control design comparing 2 lipid-lowering treatment strategies. The study involved 19 hospitals in Japan and was conducted in accordance with the principles of the Declaration of Helsinki. The institutional review board or relevant ethics committee of each participating medical center approved the protocol, and all patients provided

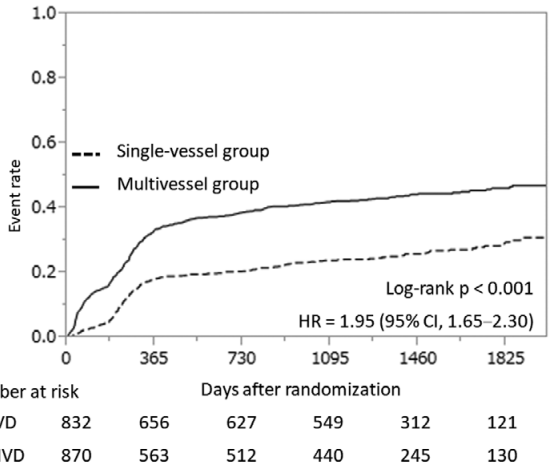

Figure 1. Kaplan-Meier curves for the primary endpoint (a composite of all-cause death, non-fatal myocardial infarction, non-fatal stroke, and ischemia-driven revascularization) in patients with multivessel disease (MVD) and single-vessel disease (SVD).

written informed consent for trial enrolment. A steering committee was responsible for scientific conduct and publication of the results of the trial, and a working group was responsible for daily administration.

Patients were randomized to an aggressive lipid-lowering group (pitavastatin+ezetimibe group: pitavastatin+ezetimibe 10 mg/day, with a treatment goal of LDL-C <70 mg/dL [1.81 mmol/L]) or a conventional lipid-lowering therapy group (pitavastatin monotherapy group: pitavastatin only, with a treatment goal of 90 mg/dL [2.33 mmol/L] <LDL-C ≤100 mg/dL [2.59 mmol/L]). During the study period, the use of non-study anti-dyslipidemia agents was prohibited. Between January 2010 and April 2013, 1,734 patients were enrolled. Participants were followed by hospital doctors or other general practitioners. The incidence of endpoint events in addition to drug safety information was determined during scheduled follow-up visits at 3, 6, 12, 24, and 36 months. All patients were followed for at least 36 months.

In the present study, patients were divided into 2 groups according to the number of diseased vessels. The number of diseased vessels with ≥50% stenosis was categorized at baseline coronary angiography (CAG) for each patient. Patients with 1 vessel with ≥50% stenosis were categorized as having SVD, and patients with >1 vessel with ≥50% stenosis or stenosis in the left main artery, as having MVD. The long-term clinical outcomes were compared between pitavastatin+ezetimibe therapy and pitavastatin monotherapy in both the MVD and SVD groups.

The primary endpoint was a composite of the first occurrence of MACE, that is, all-cause death, non-fatal myocardial infarction (MI), non-fatal stroke, or ischemia-driven revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting.

Statistical Analysis

Continuous variables were compared using Student's t-test or Wilcoxon's rank-sum test as appropriate. Categorical variables were compared using Fisher's exact test. Time to first occurrence of events was analyzed using the Kaplan-Meier method with the log-rank test and conventional Cox proportional hazards models.

P<0.05 was considered to indicate a statistically significant difference. All statistical analysis was performed with JMP Pro version 12.1.0 (SAS Institute, Cary, NC, USA).

Results

MVD vs. SVD

In the present analysis, 32 patients were excluded from the full cohort of HIJ-PROPER due to lack of detailed angiography data. Therefore, 1,702 patients were finally evaluated. The median follow-up period was 3.86 years. **Table 1** lists the baseline characteristics of MVD (n=870) and SVD patients (n=832). MVD patients were older and had higher rates of hypertension, DM, prior MI, and of low left ventricular ejection fraction (<35%) than SVD patients. PCI as an acute revascularization strategy was performed successfully in 96.2% of all patients, with no significant difference between the 2 groups.

The incidence of the primary endpoint was 43.7% in the MVD group and 25.9% in the SVD group. Kaplan-Meier event rate curves for the primary endpoint are shown in **Figure 1** (hazard ratio [HR], 1.95; 95% CI: 1.65–2.30; P<0.001). With regards to components of the primary endpoint, significant differences were noted between the MVD group and SVD group in terms of all-cause death (HR, 2.08; 95% CI: 1.38–3.21, P<0.001) and ischemia-driven coronary revascularization (HR, 2.09; 95% CI: 1.74–2.53; P<0.001), although non-fatal MI and non-fatal stroke were not significantly different between the 2 groups (**Supplementary Figure 1**).

Efficacy Outcomes of Ezetimibe

In both the MVD and SVD groups, patients assigned to the pitavastatin+ezetimibe or pitavastatin monotherapy arms had similar baseline characteristics (**Table 2**). **Figure 2** shows the change in mean LDL-C in each treatment group. In the MVD group, LDL-C reduction from baseline was 46.9% for the pitavastatin+ezetimibe group and 34.9% for the pitavastatin monotherapy group. In the SVD group, the reduction from baseline was 47.4% in the pitavastatin+ezetimibe group and 34.6% in the pitavastatin monotherapy group.

Figure 3 shows the results of the Kaplan-Meier analysis for the primary endpoint in each group. In the MVD group, the event rate during the entire study period was 43.5% in the pitavastatin+ezetimibe group and 43.9% in the pitavastatin monotherapy group. Aggressive lipid-lowering treatment with ezetimibe did not significantly reduce MACE (HR, 1.0; 95% CI: 0.83–1.23; P=0.92; **Figure 3A**). In the SVD group, the event rate during the entire study period was significantly lower in the pitavastatin+ezetimibe group than in the pitavastatin monotherapy group (22.1% vs. 30.0%, HR, 0.72; 95% CI: 0.55–0.94; P=0.016; **Figure 3B**). The 1-year landmark analysis also showed that the combination therapy with ezetimibe significantly reduced MACE (HR, 0.51; 95% CI: 0.31–0.84; P=0.0074). In contrast, in the MVD group, 1-year landmark analysis did not show significant reduction of MACE (HR, 0.94; 95% CI: 0.63–1.41; P=0.77; **Supplementary Figure 2**). According to the Kaplan-Meier analysis of the components of MACE between the 2 treatment groups, a significant difference was observed only in ischemia-driven coronary revascularization in the

Table 2. Baseline Characteristics at Admission vs. No. Diseased Vessels and Treatment

Variable	MVD			SVD		
	Pitavastatin (n=445)	Pitava+Eze (n=425)	P-value	Pitavastatin (n=402)	Pitava+Eze (n=430)	P-value
Age (years)	67.5±11.1	67.5±11.1	0.98	63.4±12.3	64.0±12.0	0.53
Male	339 (76.2)	315 (74.1)	0.53	314 (78.1)	318 (74.0)	0.17
BMI (kg/m^2)	24.2±3.6	24.3±3.5	0.74	24.3±3.6	24.4±3.6	0.86
eGFR (mL/min/1.73 m^2)	72.9±38.2	70.9±19.2	0.34	74.2±17.8	74.2±18.3	0.96
Hypertension	308 (69.2)	316 (74.4)	0.10	263 (65.4)	278 (64.7)	0.83
DM	167 (37.5)	158 (37.2)	0.94	93 (23.1)	101 (23.5)	0.93
Smoking	282 (63.4)	247 (58.1)	0.13	261 (64.9)	262 (60.9)	0.25
Previous MI	48 (10.8)	42 (9.9)	0.74	20 (4.9)	20 (4.7)	0.87
Previous HF	12 (2.7)	12 (2.8)	0.91	3 (0.8)	9 (2.1)	0.15
Diagnosis on admission			0.44			0.98
STEMI	231 (51.9)	202 (47.5)		216 (53.7)	229 (53.3)	
Non-STEMI	50 (11.2)	52 (12.2)		37 (9.2)	39 (9.1)	
UA	164 (36.9)	171 (40.2)		149 (37.1)	162 (37.7)	
ACS intervention						
PCI	426 (95.7)	410 (96.5)	0.60	391 (97.3)	411 (95.6)	0.26
Lesion						
LMT	42 (9.4)	33 (7.8)	0.40	0 (0)	0 (0)	NA
LAD	389 (87.4)	371 (87.3)	0.96	253 (62.9)	263 (61.2)	0.67
RCA	330 (74.2)	306 (72.0)	0.49	90 (22.4)	108 (25.1)	0.37
LCX	337 (75.7)	323 (76.0)	0.94	59 (14.7)	59 (13.7)	0.77
Graft	7 (1.6)	6 (1.4)	0.84	0 (0)	0 (0)	NA
Lipid on admission						
LDL-C (mg/dL)	136.1±30.3	135.2±30.6	0.65	135.1±29.8	134.8±28.2	0.87
TC (mg/dL)	210.2±36.7	209.8±35.4	0.87	211.6±35.7	210.7±33.3	0.71
HDL-C (mg/dL)	47.4±11.7	48.0±12.0	0.40	49.3±12.8	49.9±12.9	0.44
TG (mg/dL)	131.3±71.2	130.8±71.1	0.93	133.8±74.8	127.6±66.6	0.21
Medication at randomization						
β-blocker	436 (98.2)	416 (97.9)	0.30	256 (63.5)	260 (60.5)	0.39
ACEI/ARB	347 (78.2)	338 (79.5)	0.68	297 (73.7)	334 (77.7)	0.19
CCB	137 (30.9)	153 (36.0)	0.11	85 (21.1)	89 (20.7)	0.93
Nitrates	87 (19.6)	79 (18.6)	0.73	56 (13.9)	65 (15.1)	0.62
Aspirin	375 (93.1)	397 (92.3)	0.79	398 (98.8)	422 (98.1)	0.58
Thienopyridines	407 (91.7)	395 (92.9)	0.53	375 (93.1)	397 (92.3)	0.79
Statin use on admission	87 (19.6)	79 (18.6)	0.73	61 (15.2)	62 (14.4)	0.76
Ezetimibe use on admission	3 (0.7)	7 (1.7)	0.21	4 (1.0)	5 (1.2)	0.82

Data given as mean±SD or n (%). LMT, left main trunk; MI, myocardial infarction; RCA, right coronary artery. Other abbreviations as in Table 1.

SVD group. The incidence of ischemia-driven coronary revascularization in the pitavastatin+ezetimibe group was 16.5% compared with 23.6% in the pitavastatin monotherapy group (HR, 0.69; 95% CI: 0.50–0.93; P=0.017; **Supplementary Figure 3**). Kaplan-Meier analysis for the components of MACE in each group is summarized in **Table 3**.

Discussion

The primary findings of the present study are as follows: (1) ACS patients with MVD were still at significantly higher risk of MACE than those with SVD, even when undergoing contemporary aggressive lipid-lowering therapy and with a high rate of revascularization in the acute phase; and (2) ACS patients with SVD derived significantly greater benefits from pitavastatin+ezetimibe therapy than from pitavastatin monotherapy, but MVD patients did not, which was different from previous reports in patients with stable atherosclerotic CAD.[9]

Influence of MVD in Aggressive Lipid-Lowering Therapy

MVD is present in 40–70% of ACS patients.[12–15] The subanalysis of Controlled Abciximab and Device Investigation to Lower Later Angioplasty Complications trial reported that MVD patients have a greater incidence of comorbid high-risk baseline features that may contribute to less favorable prognoses, and the presence of MVD was a powerful independent predictor of mortality, even after adjustment for differences in baseline clinical and angiographic variables.[3] Similar to that report, the present MVD patients had more coronary risk factors and poorer clinical outcomes than SVD patients.

Patient Background and Achieved LDL-C Level

In the present study intensive LDL-C-lowering therapy

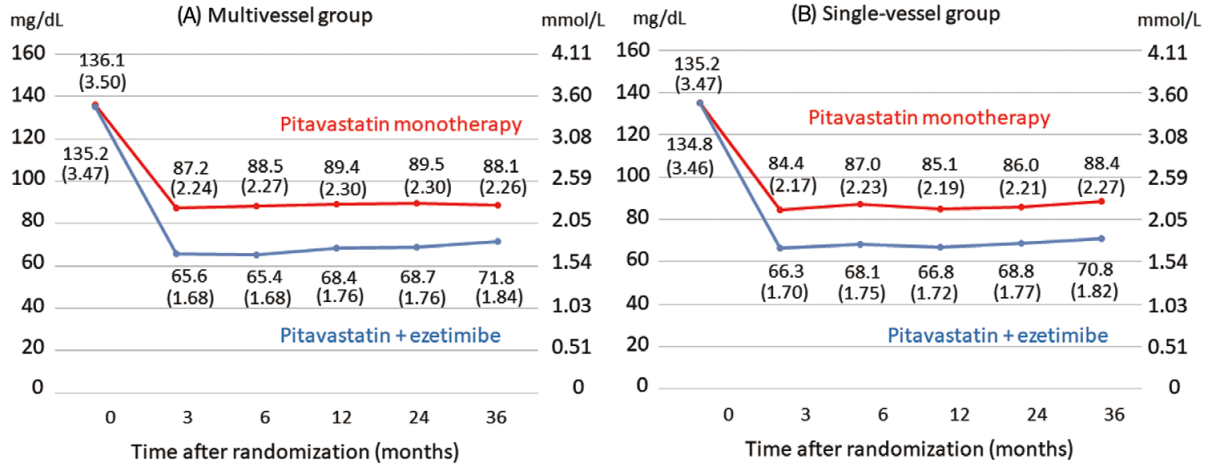

Figure 2. Change in mean low-density lipoprotein cholesterol in the (**A**) multivessel disease and (**B**) single-vessel disease treatment groups.

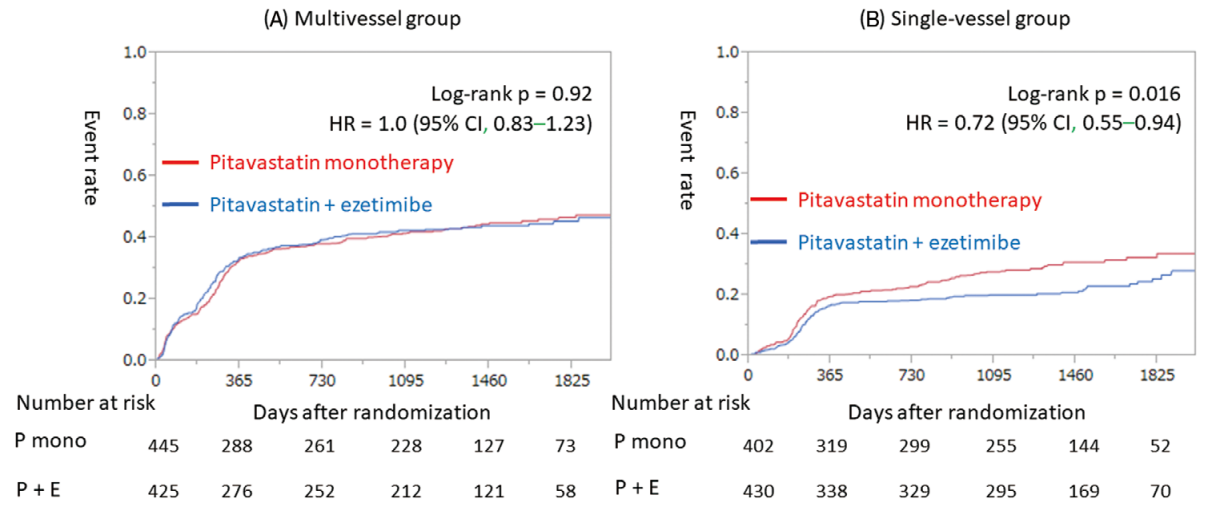

Figure 3. Kaplan-Meier curves for the efficacy of ezetimibe in preventing the primary endpoint (a composite of all-cause death, non-fatal myocardial infarction, non-fatal stroke, and ischemia-driven revascularization) in the (**A**) multivessel disease group and (**B**) single-vessel disease groups. P mono, pitavastatin monotherapy; P+E, pitavastatin+ezetimibe.

consisting of ezetimibe added to pitavastatin reduced the incidence of MACE in patients with SVD. Of the components of the primary endpoint, only the ischemia-driven revascularization rate was significantly reduced in SVD compared with MVD. The IMPROVE-IT trial and ODYSSEY OUTCOMES clearly demonstrated the usefulness of intensive lipid-lowering with statin+ezetimibe or statin+alirocumab compared with statin monotherapy for ACS patients.[6,8] Those studies, however, did not describe the number of diseased vessels, and acute revascularization rates were lower in those studies than in HIJ-PROPER. The FOURIER trial reported that the PCSK9 inhibitor evolocumab lowered LDL-C more aggressively and significantly reduced cardiovascular events.[7] A subanalysis of the FOURIER trial found that aggressive lipid-lowering therapy was more effective in MVD patients than in SVD patients,[9] in contrast to the present study. There are some possible explanations for the differences between these 2 sub-analyses. The FOURIER trial included only patients with stable atherosclerotic cardiovascular disease, whereas the HIJ-PROPER study enrolled only ACS patients. One observational study showed that ACS patients with MVD presented with simultaneous rupture of multiple atherosclerotic plaques and were at significantly increased risk of late death and revascularization.[1] Some studies demonstrated that aggressive lipid-lowering therapy has important roles in the regression of atherosclerotic plaques and the reduction of plaque instability.[16–18] Because the character-

Table 3. Components of the Primary Endpoint vs. No. Diseased Vessels

	Pitavastatin+ ezetimibe (n=425)	Pitavastatin monotherapy (n=445)	HR	95% CI	P-value
Multivessel group (n=870)					
Composite outcome	185 (43.5)	195 (43.8)	1.0	0.83–1.23	0.92
All-cause death	26 (6.1)	42 (9.4)	0.65	0.39–1.05	0.08
Non-fatal MI	6 (1.4)	4 (0.9)	0.64	0.16–2.25	0.49
Non-fatal stroke	8 (1.9)	8 (1.8)	1.06	0.39–2.87	0.91
Ischemia-driven revascularization	154 (36.2)	162 (36.5)	0.99	0.80–1.25	0.98
	Pitavastatin+ ezetimibe (n=430)	**Pitavastatin monotherapy (n=402)**	**HR**	**95% CI**	**P-value**
Single-vessel group (n=832)					
Composite outcome	95 (22.1)	121 (30.1)	0.72	0.55–0.94	0.016
All-cause death	14 (3.3)	18 (4.5)	0.73	0.36–1.47	0.39
Non-fatal MI	5 (1.2)	6 (1.5)	0.77	0.22–2.57	0.67
Non-fatal stroke	9 (2.1)	10 (2.5)	0.84	0.33–2.09	0.71
Ischemia-driven revascularization	71 (16.5)	95 (23.6)	0.69	0.5–0.93	0.017

MI, myocardial infarction.

istics of enrolled patients were completely different, the stability of coronary plaque might have been different between the 2 trials, which may have affected the results. Indeed, in the aggressive treatment arm of the FOURIER trial, the median achieved LDL-C level was 30 mg/dL, but in HIJ-PROPER, the median level was 71 mg/dL in the pitavastatin+ezetimibe group. Although the effect of atorvastatin therapy on fibrous cap thickness in coronary atherosclerotic plaque, as assessed using optical coherence tomography, suggested that LDL-C <70 mg/dL using high-dose statin more reliably stabilizes coronary atherosclerotic plaques than standard therapy,[19] the present results suggest that an LDL-C level of 71 mg/dL might not be enough to reduce MACE in ACS patients with MVD, who would have multiple unstable plaques. More aggressive lipid-lowering therapy would be necessary to stabilize atherosclerotic plaques in patients with MVD.

Influence of Early Invasive Strategy in ACS Patients

The revascularization rate in the HIJ-PROPER study during the acute phase of ACS was significantly higher than that in previous studies examining the effect of aggressive lipid-lowering therapy on ACS patients.[10] In previous studies, early revascularization improved prognosis in ACS patients.[12,20] The effect might be greater in SVD patients because it would reflect complete coronary revascularization. Complete revascularization has been shown to improve the long-term outcome of CAD patients, while incomplete revascularization is known to have detrimental effects on mortality.[4,21] Based on the higher baseline risk and increased procedural complexity of revascularization, a retrospective cohort study showed that complete revascularization success rates were lower in MVD patients than in SVD patients.[22] According to the present study, an achieved LDL-C level of 71 mg/dL (absolute reduction of 47%) might be effective in improving clinical outcomes in ACS patients with a high rate of complete revascularization.

Study Limitations

The present study had several limitations. First, it was a post-hoc analysis of a prospective study, and the sample size may have been too small to analyze the differences in the usefulness of aggressive lipid-lowering therapy between SVD and MVD patients. Second, further treatment for the non-culprit lesion was performed at the discretion of attending physicians in the collaborating centers, but details of those additional treatments were not investigated. Third, the target LDL-C reduction level was modest when compared with that in recent clinical trials. Finally, the present results may not be generalizable to non-Japanese individuals because this study included only Japanese patients with ACS. A study that includes patients from several countries and evaluates the difference in the usefulness of aggressive lipid-lowering therapy between ACS patients with SVD and MVD might be necessary. Thus, the present results must be interpreted with caution.

Conclusions

In this sub-analysis of the HIJ-PROPER study, the benefits of aggressive lipid-lowering therapy, with the addition of ezetimibe to statins, were enhanced in ACS patients with SVD, but not in those with MVD, in the modern early invasive strategy era. Further studies are warranted to establish different treatment approaches, including more intensive lipid-lowering far below the LDL-C level of 70 mg/dL, to improve the prognosis of ACS patients with MVD.

Acknowledgments

We thank the HIJ-PROPER participants as well as the staff and investigators of the HIJ-PROPER study for their contributions and the participating centers: Ebara Metropolitan Hospital (Tokyo), Tokyo Metropolitan Tama Medical Center Hospital (Tokyo), Tokyo Metropolitan Tama-Hokubu Medical Center Hospital (Tokyo), Kosei General Hospital (Tokyo), Nishiarai Hospital (Tokyo), Kanto Medical Center NTT East (Tokyo), Saiseikai Kurihashi Hospital (Saitama), Saiseikai Kumamoto Hospital (Kumamoto), Seirei Hamamatsu Hospital (Shizuoka), Sendai Cardiovascular Center (Miyagi), Shin-Matsudo-Chuo General Hospital (Chiba), Shiseikai Second Hospital (Tokyo), The Sakakibara Heart Institute (Tokyo), Yokohama Medical Center (Kanagawa), Tokyo Women's Medical

University Medical Center East (Tokyo), and Tokyo Women's Medical University (Tokyo). We would also like to thank Editage (www.editage.com) for English language editing and publication support.

Disclosures

All members of the HIJ-PROPER study group have received research support to perform clinical trials through the Japan Research Promotion Society for Cardiovascular Diseases, which is sponsored by Abbott Vascular Japan, AstraZeneca, Bayer Yakuhin, Boston Scientific Corporation, Bristol-Myers, Daiichi Sankyo, Kowa Pharmaceutical, Mochida Pharmaceutical, MSD, Nippon Boehringer Ingelheim, Novartis Pharma, Pfizer Japan, Sanofi, and Takeda Pharmaceutical. N. Hagiwara has received honoraria from Bristol-Myers and Nippon Boehringer Ingelheim, and grants from Astellas Pharma, Daiichi Sankyo, Eisai, Mitsubishi Tanabe Pharma Corporation, Otsuka Pharmaceutical, Shionogi, and Takeda Pharmaceutical. J.Y. belongs to a division (Clinical Research division for Cardiovascular Catheter Intervention) financially maintained by donation from Abbott Vascular, Boston Scientific, Medtronic, and Terumo. All authors have no relationships relevant to the contents of this paper to disclose. The HIJ-PROPER Steering Committee had full access to all data in the study and had final responsibility for the decision to submit for publication. N.H. is a member of *Circulation Reports*' Editorial Team.

Funding

This study was funded by the Japan Research Promotion Society for Cardiovascular Diseases, which had no role in the conduction of the study (Tokyo, Japan).

References

1. Goldstein JA, Demetriou D, Grines CL, Pica M, Shoukfeh M, O'Neill WW. Multiple complex coronary plaques in patients with acute myocardial infarction. *N Engl J Med* 2000; **343:** 915–922.
2. Jaski BE, Cohen JD, Trausch J, Marsh DG, Bail GR, Overlie PA, et al. Outcome of urgent percutaneous transluminal coronary angioplasty in acute myocardial infarction: Comparison of single-vessel versus multivessel coronary artery disease. *Am Heart J* 1992; **124:** 1427–1433.
3. Sorajja P, Gersh BJ, Cox DA, McLaughlin MG, Zimetbaum P, Costantini C, et al. Impact of multivessel disease on reperfusion success and clinical outcomes in patients undergoing primary percutaneous coronary intervention for acute myocardial infarction. *Eur Heart J* 2007; **28:** 1709–1716.
4. Arora S, Panaich SS, Patel NJ, Patel N, Solanki S, Deshmukh A, et al. Multivessel percutaneous coronary interventions in the United States: Insights from the nationwide inpatient sample. *Angiology* 2016; **67:** 326–335.
5. Davidson MH, McGarry T, Bettis R, Melani L, Lipka LJ, LeBeaut AP, et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. *J Am Coll Cardiol* 2002; **40:** 2125–2134.
6. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015; **372:** 2387–2397.
7. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017; **376:** 1713–1722.
8. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med* 2018; **379:** 2097–2107.
9. Sabatine MS, De Ferrari GM, Giugliano RP, Huber K, Lewis BS, Ferreira J, et al. Clinical benefit of evolocumab by severity and extent of coronary artery disease. *Circulation* 2018; **138:** 756–766.
10. Hagiwara N, Kawada-Watanabe E, Koyanagi R, Arashi H, Yamaguchi J, Nakao K, et al. Low-density lipoprotein cholesterol targeting with pitavastatin+ezetimibe for patients with acute coronary syndrome and dyslipidaemia: The HIJ-PROPER study, a prospective, open-label, randomized trial. *Eur Heart J* 2017; **38:** 1–13.
11. Kawada-Watanabe E, Ogawa H, Koyanagi R, Arashi H, Yamaguchi J, Matsui K, et al. Rationale, design features, and baseline characteristics: The Heart Institute of Japan-PRoper level of lipid lOwering with Pitavastatin and Ezetimibe in acute coRonary syndrome (HIJ-PROPER). *J Cardiol* 2017; **69:** 536–541.
12. Gregg WS, Akiko M, Alexandra JL, de Bruyne B, Cristea E, Mintz GS, et al. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011; **364:** 226–235.
13. Kasanuki H, Honda T, Haze K, Sumiyoshi T, Horie T, Yagi M, et al. A large-scale prospective cohort study on the current status of therapeutic modalities for acute myocardial infarction in Japan: Rationale and initial results of the HIJAMI Registry. *Am Heart J* 2005; **150:** 411–418.
14. O'Keefe JH Jr, Rutherford BD, McConahay DR, Ligon RW, Johnson WL Jr, Giorgi LV, et al. Early and late results of coronary angioplasty without antecedent thrombolytic therapy for acute myocardial infarction. *Am J Cardiol* 1989; **64:** 1221–1230.
15. Panaich SS, Arora S, Patel N, Schreiber T, Patel NJ, Pandya B, et al. Comparison of in-hospital mortality, length of stay, postprocedural complications, and cost of single-vessel versus multivessel percutaneous coronary intervention in hemodynamically stable patients with ST-segment elevation myocardial infarction (from nationwide inpatient sample [2006 to 2012]). *Am J Cardiol* 2016; **118:** 950–958.
16. Tsujita K, Sugiyama S, Sumida H, Shimomura H, Yamashita T, Yamanaga K, et al. Impact of dual lipid-lowering strategy with ezetimibe and atorvastatin on coronary plaque regression in patients with percutaneous coronary intervention: The multicenter randomized controlled PRECISE-IVUS trial. *J Am Coll Cardiol* 2015; **66:** 495–507.
17. Kataoka Y, Puri R, Hammadah M, Duggal B, Uno K, Kapadia SR, et al. Cholesterol crystals associate with coronary plaque vulnerability in vivo. *J Am Coll Cardiol* 2015; **65:** 630–632.
18. Habara M, Nasu K, Terashima M, Ko E, Yokota D, Ito T, et al. Impact on optical coherence tomographic coronary findings of fluvastatin alone versus fluvastatin+ezetimibe. *Am J Cardiol* 2014; **113:** 580–587.
19. Komukai K, Kubo T, Kitabata H, Matsuo Y, Ozaki Y, Takarada S, et al. Effect of atorvastatin therapy on fibrous cap thickness in coronary atherosclerotic plaque as assessed by optical coherence tomography: The EASY-FIT study. *J Am Coll Cardiol* 2014; **64:** 2207–2217.
20. Fox KA, Steg PG, Eagle KA, Goodman SG, Anderson FA Jr, Granger CB, et al. Decline in rates of death and heart failure in acute coronary syndromes, 1999–2006. *JAMA* 2007; **297:** 1892–1900.
21. Aggarwal V, Rajpathak S, Singh M, Romick B, Srinivas VS. Clinical outcomes based on completeness of revascularisation in patients undergoing percutaneous coronary intervention: A meta-analysis of multivessel coronary artery disease studies. *EuroIntervention* 2012; **7:** 1095–1102.
22. Toma A, Stahli BE, Gick M, Gebhard C, Nührenberg T, Mashayekhi K, et al. Impact of multi-vessel versus single-vessel disease on outcomes after percutaneous coronary interventions for chronic total occlusions. *Clin Res Cardiol* 2017; **106:** 428–435.

Supplementary Files

Please find supplementary file(s);
http://dx.doi.org/10.1253/circrep.CR-19-0118