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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

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Aims To elucidate the effects of intensive LDL-C lowering treatment with a standard dose of statin and ezetimibe in patients with dyslipidaemia and high risk of coronary events, targeting LDL-C less than 70 mg/dL (1.8 mmol/L), compared with standard LDL-C lowering lipid monotherapy targeting less than 100 mg/dL (2.6 mmol/L).

Methods and results The HIJ-PROPER study is a prospective, randomized, open-label trial to assess whether intensive LDL-C lowering with standard-dose pitavastatin plus ezetimibe reduces cardiovascular events more than standard LDL-C lowering with pitavastatin monotherapy in patients with acute coronary syndrome (ACS) and dyslipidaemia. Patients were randomized to intensive lowering (target LDL-C < 70 mg/dL [1.8 mmol/L]; pitavastatin plus ezetimibe) or standard lowering (target LDL-C 90 mg/dL to 100 mg/dL [2.3–2.6 mmol/L]; pitavastatin monotherapy). The primary endpoint was a composite of all-cause death, non-fatal myocardial infarction, non-fatal stroke, unstable angina, and ischaemia-driven revascularization. Between January 2010 and April 2013, 1734 patients were enroled at 19 hospitals in Japan. Patients were followed for at least 36 months. Median follow-up was 3.86 years. Mean follow-up LDL-C was 65.1 mg/dL (1.68 mmol/L) for pitavastatin plus ezetimibe and 84.6 mg/dL (2.19 mmol/L) for pitavastatin monotherapy. LDL-C lowering with statin plus ezetimibe did not reduce primary endpoint occurrence in comparison with standard statin monotherapy (283/864, 32.8% vs. 316/857, 36.9%; HR 0.89, 95% CI 0.76–1.04, $P = 0.152$). In, ACS patients with higher cholesterol absorption, represented by elevated pre-treatment sitosterol, was associated with significantly lower incidence of the primary endpoint in the statin plus ezetimibe group (HR 0.71, 95% CI 0.56–0.91).

Conclusion Although intensive lowering with standard pitavastatin plus ezetimibe showed no more cardiovascular benefit than standard pitavastatin monotherapy in ACS patients with dyslipidaemia, statin plus ezetimibe may be more

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effective than statin monotherapy in patients with higher cholesterol absorption; further confirmation is needed.

Trial No UMIN000002742, registered as an International Standard Randomized Controlled Trial.

Keywords Clinical trial • Ezetimibe • Pitavastatin • Combination therapy • Lipid-lowering • Acute coronary syndrome

Introduction

Today the development of atherosclerotic cardiovascular disease has been clearly linked to elevated concentrations of low-density lipoprotein cholesterol (LDL-C), and research on LDL-C lowering therapy has built a widely accepted consensus that lowering cholesterol levels can reduce cardiovascular events to some extent.[1,2] Some findings have even suggested 'the lower, the better' for the management of dyslipidaemia, at least in patients at high risk; the American National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) recommends target LDL-C of less than 70 mg/dL (1.8 mmol/L) in patients with diabetes mellitus, chronic kidney disease, or recent acute coronary syndrome (ACS).[3] This position has been substantiated by cholesterol treatment trialists' (CTT) collaborators, who have reported a strong association between lower LDL-C (reduced by 38.7 mg/dL, 1.0 mmol/L) and lower 5-year risk of major events (reduced by 23%),[2] and supported by recommendations from the American Diabetes Association and the American College of Cardiology Foundation (LDL-C below 70 mg/dL [1.8 mmol/L]) in any patient with known coronary artery disease (CAD).[4] However, these recommendations have not yet been supported with data-driven evidence for the benefits of such reduction.

One roadblock has been the difficulty of achieving these very low levels of LDL-C with conventional pharmacotherapy in real-world clinical practice. This may be due in part to the mechanism of action of the statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors), which target cholesterol synthesis in the liver. Although the statins are clearly effective in reducing the risk of coronary events in high-risk populations,[5] it is difficult to reach the recommended aggressive targets with the use of statin alone. Even in the Lipid Treatment Assessment Project 2,[6] for example, only 30% of the very high-risk patients reached the optional goal of LDL-C less than 70 mg/dL (1.8 mmol/L). And in a real-world setting among high-risk patients treated with statin monotherapy for >90 days, 67–77% achieved LDL-C <100 mg/dL (2.6 mmol/L), but only 20–26% reached the optional goal of LDL-C < 70 mg/dL (1.8 mmol/L).

Recently a new paradigm has emerged for the treatment of hyperlipidaemic patients who are at risk for cardiovascular events: high-intensity statin therapy for high-risk patients in the absence of safety concerns, and moderate-intensity statin therapy for lower-risk primary prevention and for high-risk patients if safety concerns are present (introduced in the 2013 American College of Cardiology [ACC]/American Heart Association [AHA] Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults).[7] The European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) also updated their therapeutic guidelines for health professionals, based on accumulating evidence.[8]

Pitavastatin is a new member of the statin family that shows considerable promise. Its unique chemical structure provides potent efficacy against dyslipidaemia, high systemic bioavailability, and favourable oral absorption.[9] It offers potent anti-inflammatory effects,[10] and provides equivalent regression of plaque volume at lower doses than conventional statins in ACS patients.[11]

Initial statin therapy tends to significantly reduce LDL-C, but further reductions can be challenging. Generally, after the initial reduction, a doubling of the statin dose is required for each additional reduction of 5–6% in LDL-C treatment.[12] (This occurs because cholesterol uptake from the gastrointestinal tract is accelerated, in response to statin-induced reduction in serum cholesterol.) Since statin-related adverse effects are dose-dependent and occur more commonly at higher doses,[13] massive doses of statin monotherapy are clearly not the answer for lipid management. High-dose statin therapy increases proprotein convertase subtilisin kexin type 9 (PCSK9) levels, which impairs LDL-C clearance from the plasma. This limits the effectiveness of statin therapy.[14] In addition, most hyperlipidaemic patients will remain under treatment for years, and although lipids should be measured regularly to assess therapeutic response, such assessment is not always continued over the long term. This is unfortunate, since patients with atherosclerotic disease need ongoing lipid assessment to ensure that their treatment regimen is actually providing the desired results.

As noted previously, even in the current era of intensive statin therapy, ACS patients with dyslipidaemia may not reach their targeted LDL-C or obtain improved clinical outcomes. These challenges are now being considered in a number of clinical trials. Although no data are yet available on cardiovascular outcomes, it seems feasible that statins in combination with non-statin drugs might provide greater lipid lowering and thus prove more effective in the prevention of cardiovascular events than statins alone, particularly in high-risk populations. However, to the best of our knowledge, no prospective clinical trials have yet evaluated the effects of LDL-C targeting therapy on subsequent cardiovascular outcomes in ACS patients.

To explore this question, we needed a drug regimen that would reliably reduce LDL-C to the aggressive target level of < 70 mg/dL (1.8 mmol/L). We decided to combine a statin with ezetimibe, an intestinal cholesterol transporter inhibitor that selectively inhibits cholesterol absorption by blocking the Niemann-Pick C1-like 1 receptor.[15] Two recent studies that demonstrated the benefits of a combination of statin plus ezetimibe in patients with CAD support our choice of ezetimibe.[16,17]

We hypothesized that we could achieve intensive LDL-C lowering by administering ezetimibe in conjunction with a standard dose of statin, and that this treatment would be more beneficial for secondary prevention than statin monotherapy in ACS patients with dyslipidaemia.

The Heart Institute of Japan, Department of Cardiology (HIJC) Investigators' project is an ongoing collaborative effort designed to develop a contemporary epidemiologic database and to improve the quality of care for patients with cardiovascular disease in Japan.[18–20] One project of HIJC is the Heart Institute of Japan PRoper level of lipid lOwering with Pitavastatin and Ezetimibe in acute coRonary syndrome (HIJ-PROPER) trial, which was designed to investigate whether such combined treatment would positively affect secondary prevention in ACS patients with dyslipidaemia. The study investigated the effect in patients with ACS of intensive LDL-C lowering treatment with a standard dose of statin and ezetimibe, targeting less than 70 mg/dL (1.8 mmol/L), compared with standard LDL-C lowering lipid monotherapy targeting less than 100 mg/dL (2.6 mmol/L).

Methods

Study design

The HIJ-PROPER study[21] is a multicentre, prospective, randomized, open-label, blinded-endpoint trial with an active-control design comparing two 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 centre approved the protocol, and all patients provided 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.

Inclusion criteria

Heart Institute of Japan PRoper level of lipid lOwering with Pitavastatin and Ezetimibe in acute coRonary syndrome enroled specifically targeted hospitalized patients with ACS and dyslipidaemia. All participants had been hospitalized for ST-segment elevation myocardial infarction (STEMI) or for non-ST-segment elevation myocardial infarction (NSTEMI) or unstable angina (UA) within 72 h before randomization. All participants were at least 20 years of age. Participants with STEMI had electrocardiographic changes (persistent ST-segment elevation ≥ 0.1 mV, new Q waves, or new left bundle-branch block), and elevated troponin or creatine kinase (CK)–MB. Participants presenting with UA/NSTEMI had ischaemic discomfort at rest, lasting at least 10 min, and at least one of the following: new ST-segment deviation of at least 1 mV, elevated troponin or CK-MB, a history of prior MI, peripheral arterial disease, a history of coronary artery bypass grafting (CABG) at least 3 years previously, or known multivessel CAD including at least two major coronary arteries with stenosis of >50%.

Low-density lipoprotein cholesterol, measured within 24 h of hospitalization for the ACS event, was at least 100 mg/dL (2.6 mmol/L). Fasting plasma triglyceride level was at least 400 mg/dL (4.5 mmol/L) (Friedewald equation). Levels of the cholesterol absorption markers sitosterol and campesterol and the cholesterol synthesis intermediate lathosterol were also measured at enrolment and 12 weeks after randomization. All laboratory analyses were performed at SRL Inc. (Tokyo, Japan).

Major exclusion criteria were the occurrence within 24 hours before enrolment of (i) hemodynamic instabilities such as hypotension, pulmonary oedema, congestive heart failure, acute mitral regurgitation, or ventricular rupture; (ii) ischaemic events (stroke, recurrent symptoms of cardiac ischaemia, acute occlusion of target vessel); and (iii) arrhythmic events (ventricular fibrillation, sustained ventricular tachycardia, advanced heart block). Patients in whom CABG was planned for the treatment of an ACS event were excluded. Other exclusion criteria included pregnancy; active liver disease or persistent unexplained serum transaminase elevations (≥3 × the upper limit of normal), current treatment with immunosuppressants such as cyclosporine, tacrolimus, azathioprine, or long-term oral glucocorticoids; any other condition that would substantially reduce life expectancy or limit compliance with the protocol; history of alcohol or drug abuse; or allergy or sensitivity to any statin, ezetimibe, or their excipients.

Randomization and masking

After patient eligibility was confirmed, patients were randomized either to the pitavastatin plus ezetimibe group or to the pitavastatin monotherapy group. Randomization was by the minimization method, based on the five factors of age, LDL-C level on randomization, history of statin treatment, history of diabetes mellitus, and clinical site. Although treatment was not masked for patients and physicians, these events and pertinent patient documents were reviewed by an Endpoint Committee masked to treatment assignment (Appendix).

Procedures

The starting dose for pitavastatin plus ezetimibe was 2 mg of pitavastatin and 10 mg of ezetimibe, targeting LDL-C of 70 mg/dL (1.8 mmol/L). Participants already receiving statins other than pitavastatin discontinued the previous agents and started receiving pitavastatin 2 mg/day under the Japanese regulations related to pharmacotherapies. In the pitavastatin monotherapy arm, patients discontinued their previous statin, if any, and began taking 2 mg of pitavastatin, targeting LDL-C of between 90 mg/dL (2.3 mmol/L) and 100 mg/dL (2.6 mmol/L). During the entire study period, the pitavastatin dose (1–4 mg/day) was adjusted to provide the LDL-C level targeted for each specific group. During the study period, combined lipid-lowering medications other than statins and ezetimibe were also allowed in order to achieve the target level of LDL-C in each group.

Participants were followed by hospital doctors or other general practitioners. The incidence of endpoint events in addition to drug safety information was determined during the scheduled visits at 3, 6, 12, 24, and 36 months, through contact with each patient, or via access to certificates issued by administrative authorities if necessary. All patients were followed for at least 36 months. Pre-specified measurements, prescribed medications, and clinical events were reported to the Data Management Center every 6 months. Trained clinical research coordinators (CRC) visited the study centres regularly to collect and reconfirm the reported data. If a patient stopped coming to their institution, CRC personnel confirmed the patient's health status by letter or phone call.

Outcomes

The primary endpoint was a composite of the first occurrence of a component of the primary endpoint: all-cause death, non-fatal myocardial infarction, non-fatal stroke, UA, or revascularization with either percutaneous coronary intervention (PCI) or CABG. The secondary endpoints included (i) cardiovascular event (non-fatal myocardial infarction, non-fatal stroke, UA, ischaemia-driven revascularization with either PCI or CABG), (ii) all-cause death, (iii) heart failure, (iv) inflammatory markers, and (v) adverse events (including new occurrence of malignant tumour).

Statistical analysis

The prespecified number of events required to provide meaningful data was estimated for an α level of 5%, 80% power, and a dropout rate of 2% during a follow-up period of three years. The expected occurrence of a primary endpoint in the statin-monotherapy group was 10%, based on data from contemporary studies of UA pectoris and AMI with comparable follow-up time.[5,20,22] An initial sample size of 3000 patients was selected to afford 80% power to detect relative risk reduction of 20% in the

primary endpoint by a two-sample *t*-test at a significance level of 0.05. The sample size was based on anticipated event rates at one year (100 events/1000 patients/year).

Patient enrolment began in January 2010 on the assumption that 1500 patients for each group would be enroled by the end of 2012. The enrolment period was extended to the end of April 2013, by which point we had recruited a total of 1734 patients. The Data and Safety Monitoring Board then suggested stopping recruitment, since a recruitment period long enough to complete the enroled might contribute to critical differences in follow-up periods between patients.

Accordingly, we re-calculated the sample size on the basis of previous domestic data.[20,22] We estimated relative risk reduction as 25%, the primary endpoint event rate of approximately 100 events/1000 person-years in the control group, and then concluded that 814 patients per group, or 1628 in total, were required during a two-year enrolment period and at least three years of follow-up to detect this difference in effects at the two-tailed 5% level of significance with 80% power.

The intention-to-treat approach was used for efficacy and safety analyses, and all randomized patients were included in all analyses, regardless of protocol violations. Time-to-first-occurrence of events was analysed using the Kaplan–Meier method with log-rank test and conventional Cox proportional hazards model. Treatment effects on the primary endpoints in subgroups, were analysed by the Cox regression model, using tests for interaction to examine consistency of the results. The subgroups were gender, age (<65 years vs. ≥65 years), type of index ACS event, number of diseased vessels, history of hypertension, history of diabetes mellitus, smoking habit, body mass index, history of statin treatment, baseline lipid profile including cholesterol absorption and synthesis markers, and baseline renal function (30>, 30 ≤ <60, 60≤ mL/min./1.73 m^2). To assess renal function, creatinine clearance was calculated using the Cockcroft-Gault formula. Categorical data are expressed as frequencies. For continuous variables with a normal distribution, means ± standard deviation (SD) are reported. For LDL-C during the treatment period, the geometric means and interquartile ranges are reported. An independent statistical data centre (Data Research Section, Kondo P.P. Inc., Osaka, Japan) analysed data using SAS ver. 9.1 software (SAS Institute, Cary, NC, USA).

Role of the funding source

This trial was funded by the Japan Research Promotion Society for Cardiovascular Diseases, which had no role in conducting the study. 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.

Results

Between January 2010 and April 2013, 1734 patients were enroled and randomized to either pitavastatin plus ezetimibe or pitavastatin monotherapy (*Figure 1*). Final follow-up assessment was performed in March 2016 and the trial database was locked on 31 March 2016. Baseline clinical characteristics of the randomized population are shown in *Table 1*. The two treatment groups were well balanced with respect to baseline characteristics. Mean age (±SD) was 65.6 ± 11.8 years. PCI for acute revascularization had been performed successfully in 94.6% of patients. Before randomization, 83.0% of the patients were statin-naïve. Prior to enrolment, ACEIs had been prescribed for 27.4% of patients, calcium channel blockers for 23.2%, β-blockers for 66.4%, aspirin for 97.4%, and ARBs for 49.7%.

Table 2 shows mean LDL-C for the two groups: 135.6 ± 30.0 mg/dL (3.51 ± 0.78 mmol/L) in the standard treatment group and

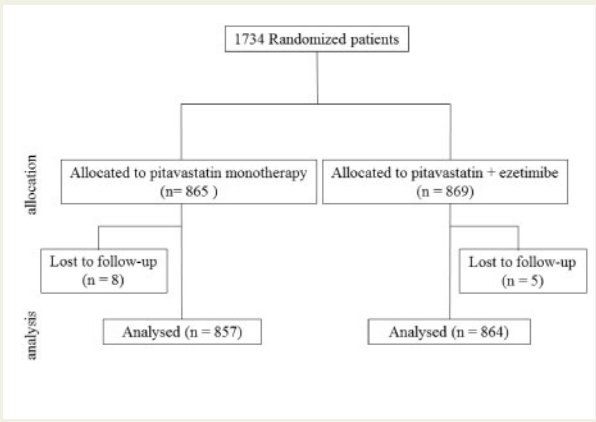

Figure 1 Study flow chart.

134.8 ± 29.3 mg/dL (3.49 ± 0.76 mmol/L) in the intensive treatment group at baseline and 84.6 mg/dL (2.19 mmol/L) in the standard treatment group and 65.1 mg/dL (1.68 mmol/L) in the intensive treatment group at follow-up. Reduction from baseline was 37.6% for standard treatment and 51.7% for intensive treatment. LDL-C differed significantly between the two groups throughout the trial (ΔLDL-C = 19.5 mg/dL, (0.50 mmol/L) $P < 0.001$).

During a median observation period of 3.86 years, a total of 2004 events were reported. Incidence of the primary endpoint was 36.9% for standard treatment (128.1/1000 patient-years) and 32.8% for intensive treatment (111.6/1000 patient-years). The reduction in the incidence of major adverse cardiac events did not achieve statistical significance [Hazard ratio (HR) 0.89; 95% confidence interval (CI), 0.76–1.04; $P = 0.152$; *Figure 2A*]. No significant differences were noted between standard and intensive treatment in terms of all cause of death (7.0% vs. 4.9%; HR, 0.70; 95% CI, 0.47–1.04; $P = 0.075$); non-fatal myocardial infarction (1.2% vs. 1.3%; HR, 1.10; 95% CI, 0.47–2.58; $P = 0.834$); non-fatal stroke (2.1% vs. 2.0%; HR, 0.94; 95% CI, 0.49–1.83; $P = 0.866$); or UA (3.9% vs. 4.3%, HR, 1.13; 95% CI, 0.70–1.80; $P = 0.623$) (*Table 3*). A composite of hard endpoints of any cause of death, non-fatal MI, and non-fatal-stroke showed no significant difference between the two groups (*Figure 2B*). Ischaemia-driven coronary revascularization, a soft endpoint, also showed no significant difference between two treatment groups (*Figure 2C*).

For secondary endpoints, ischaemia-driven coronary revascularization was performed in 257 patients (30.0%) in the standard treatment group and in 225 patients (26.0%) in the intensive treatment group (HR, 0.87; 95% CI, 0.72–1.04; $P = 0.115$). Heart failure hospitalization occurred in 40 patients (4.7%) in the standard treatment group and in 19 patients (2.2%) in the intensive treatment group (HR, 0.47; 95% CI, 0.27–0.81, $P = 0.006$). (*Table 3*)

Table 4 shows relative risk and 95% CI for the primary endpoint by selected demographics and background treatment. Most point estimates demonstrated similar HRs, and no statistical heterogeneity was identified among subgroups. Hypertension significantly modified the effect of intensive lipid lowering treatment (*P*-value for interaction = 0.017). Specifically, in non-hypertensive patients, intensive therapy significantly reduced the risk of the primary

Table 1 Baseline characteristics of randomized population

Variable	Pitavastatin monotherapy (*n* = 857)	Pitavastatin + ezetimibe (*n* = 864)
Age, y, mean ± SD	65.5 ± 11.9	65.7 ± 11.7
Male (%)	661 (77.1%)	639 (74.0%)
BMI, kg/m^2, mean ± SD	24.3 ± 3.6	24.3 ± 3.5
Qualifying ACS event		
STEMI	448 (52.3%)	432 (50.0%)
Non-STEMI	88 (10.3%)	92 (10.6%)
UA	321 (37.5%)	340 (39.4%)
ACS intervention		
Percutaneous coronary intervention	817 (95.3%)	821 (95.0%)
Left ventricular ejection fraction		
≥35%	829 (96.7%)	837 (96.9%)
Narrowed vessels[a]		
Right coronary artery	420 (49.0%)	414 (47.9%)
Left main trunk	42 (4.9%)	33 (3.8%)
Left anterior descending artery	642 (74.9%)	634 (73.4%)
Circumflex artery	396 (46.2%)	382 (44.2%)
Bypass graft	7 (0.8%)	6 (0.7%)
Cholesterol, mg/dL (mmol/L), mean ± SD		
Total	210.8 ± 36.1	210.0 ± 34.4
	(5.45 ± 0.93)	(5.43 ± 0.89)
Triglycerides	132.5 ± 72.8	129.1 ± 69.3
	(1.50 ± 0.82)	(1.46 ± 0.78)
High-density lipoprotein cholesterol	48.3 ± 12.3	49.0 ± 12.5
	(1.25 ± 0.32)	(1.27 ± 0.32)
Low-density lipoprotein cholesterol	135.6 ± 30.0	134.8 ± 29.3
	(3.51 ± 0.78)	(3.49 ± 0.76)
Fasting plasma glucose, mg/dL, mean ± SD	142.5 ± 60.6	140.8 ± 58.8
HbA1c, %, mean ± SD	6.07 ± 1.36	6.06 ± 1.31
Sitosterol, μg/mL, mean ± SD	2.51 ± 1.47	2.49 ± 1.63
Campesterol, μg/mL, mean ± SD	4.76 ± 2.38	4.66 ± 2.40
Lathosterol, μg/mL, mean ± SD	1.89 ± 1.32	1.84 ± 1.24
Eicosapentaenoic acid/arachidonic acid ratio, mean ± SD	0.40 ± 0.26	0.38 ± 0.22
hs-CRP, ng/mL, mean ± SD	20960 ± 30510	21212 ± 30731
Heart rate, beats/min.	76.8 ± 17.5	74.9 ± 15.8
Systolic blood pressure, mmHg	138.3 ± 26.5	137.4 ± 25.6
Diastolic blood pressure, mmHg	80.2 ± 17.3	79.7 ± 17.9
CV history		
Stable angina pectoris	100 (11.7%)	98 (11.3%)
Previous MI	68 (7.9%)	62 (7.2%)
Percutaneous coronary intervention	75 (8.8%)	71 (8.2%)
Coronary artery bypass graft	8 (0.9%)	10 (1.2%)
Chronic HF	15 (1.8%)	21 (2.4%)
Cerebrovascular disease	49 (5.7%)	56 (6.5%)
Peripheral artery disease	17 (2.0%)	15 (1.7%)
Hypertension	576 (67.2%)	599 (69.3%)
Diabetes mellitus	260 (30.3%)	260 (30.1%)
Smoker		
Current	300 (35.0%)	294 (34.0%)
Former	248 (28.9%)	219 (25.3%)

Continued

Table 1 *Continued*

Variable	Pitavastatin monotherapy ($n = 857$)	Pitavastatin + ezetimibe ($n = 864$)
Estimated glomerular filtration rate, mL/min/1.73 m^2		
30>	5 (0.6%)	8 (0.9%)
30≤, <60	213 (24.9%)	198 (22.9%)
60≤, <90	503 (58.7%)	522 (60.4%)
90≤	136 (15.9%)	136 (15.7%)
CV medications at randomization		
ACEI	230 (26.8%)	241 (27.9%)
ARB	417 (48.7%)	438 (50.7%)
β-Blocker	585 (68.3%)	558 (64.6%)
Calcium-channel blocker	211 (24.6%)	189 (21.9%)
Nitrates	176 (20.5%)	157 (18.2%)
Aspirin	841 (98.1%)	835 (96.6%)
Thienopyridines	790 (92.2%)	797 (92.2%)
Statin use on admission	149 (17.4%)	143 (16.6%)
Ezetimibe use on admission	7 (0.8%)	12 (1.4%)

Data presented are number (percentages) unless otherwise indicated. Percentages are calculated based on the number of patients with available data.
ACEI, Angiotensin-converting enzyme inhibitor; ACS, Acute coronary syndrome; ARB, angiotensin receptor blocker; BMI, Body mass index; CV, Cardiovascular; HF, Heart failure; hs-CRP, high-sensitivity C-reactive protein; MI, Myocardial infarction; STEMI, ST-elevation myocardial infarction; UA, Unstable angina.
[a]A narrowing of the lumen by more than 75% of the prestenotic diameter was considered to indicate clinically significant stenosis, except for the left main artery, in which a narrowing of more than 50% was considered clinically significant.

Table 2 Changes in low-density lipoprotein cholesterol (mean ± SD)

Months after randomization		Pitavastatin monotherapy	(Number)	Pitavastatin + ezetimibe	(Number)	*P*-value
0	(mg/dL)	135.6 ± 30.0	(857)	134.8 ± 29.3	(864)	1.00
	(mmol/L)	3.51 ± 0.78		3.49 ± 0.76		
3	(mg/dL)	85.7 ± 23.0	(794)	66.1 ± 22.2	(799)	<0.001
	(mmol/L)	2.22 ± 0.59		1.71 ± 0.57		
6	(mg/dL)	87.6 ± 22.5	(788)	66.7 ± 22.9	(775)	<0.001
	(mmol/L)	2.27 ± 0.58		1.72 ± 0.59		
12	(mg/dL)	87.2 ± 21.7	(763)	67.5 ± 20.8	(754)	<0.001
	(mmol/L)	2.25 ± 0.56		1.75 ± 0.54		
24	(mg/dL)	87.7 ± 22.9	(696)	68.8 ± 22.3	(693)	<0.001
	(mmol/L)	2.27 ± 0.59		1.78 ± 0.58		
36	(mg/dL)	88.5 ± 21.6	(642)	71.3 ± 24.8	(647)	<0.001
	(mmol/L)	2.29 ± 0.56		1.84 ± 0.64		
During treatment period[a]	(mg/dL)	84.6 [83.3–86.0]		65.1 [64.0–66.1]		<0.001
	(mmol/L)	2.19 [2.15–2.22]		1.68 [1.66–1.71]		
Mean dose of study drug during follow-up period						
Pitavastatin, mg/day (mean ± SD)		2.02 ± 0.91	(817)	2.36 ± 0.90	(813)	
Ezetimibe, mg/day (mean ± SD)		–		10.0 ± 0.61	(787)	

[a]Expressed as geometric mean [95% CI] because of its non-normal distribution.

endpoint (HR, 0.65; 95% CI, 0.48–0.88), but there was no significant reduction in the hypertensive group when compared with patients on monotherapy (HR, 1.01; 95% CI, 0.83–1.22). Increased cholesterol absorption, represented by comparatively high values for the predetermined variable of baseline sitosterol, significantly modified the effect of intensive lipid lowering treatment (*P*-value for interaction = 0.010). In patients with elevated sitosterol, intensive therapy significantly reduced the risk of the primary endpoint

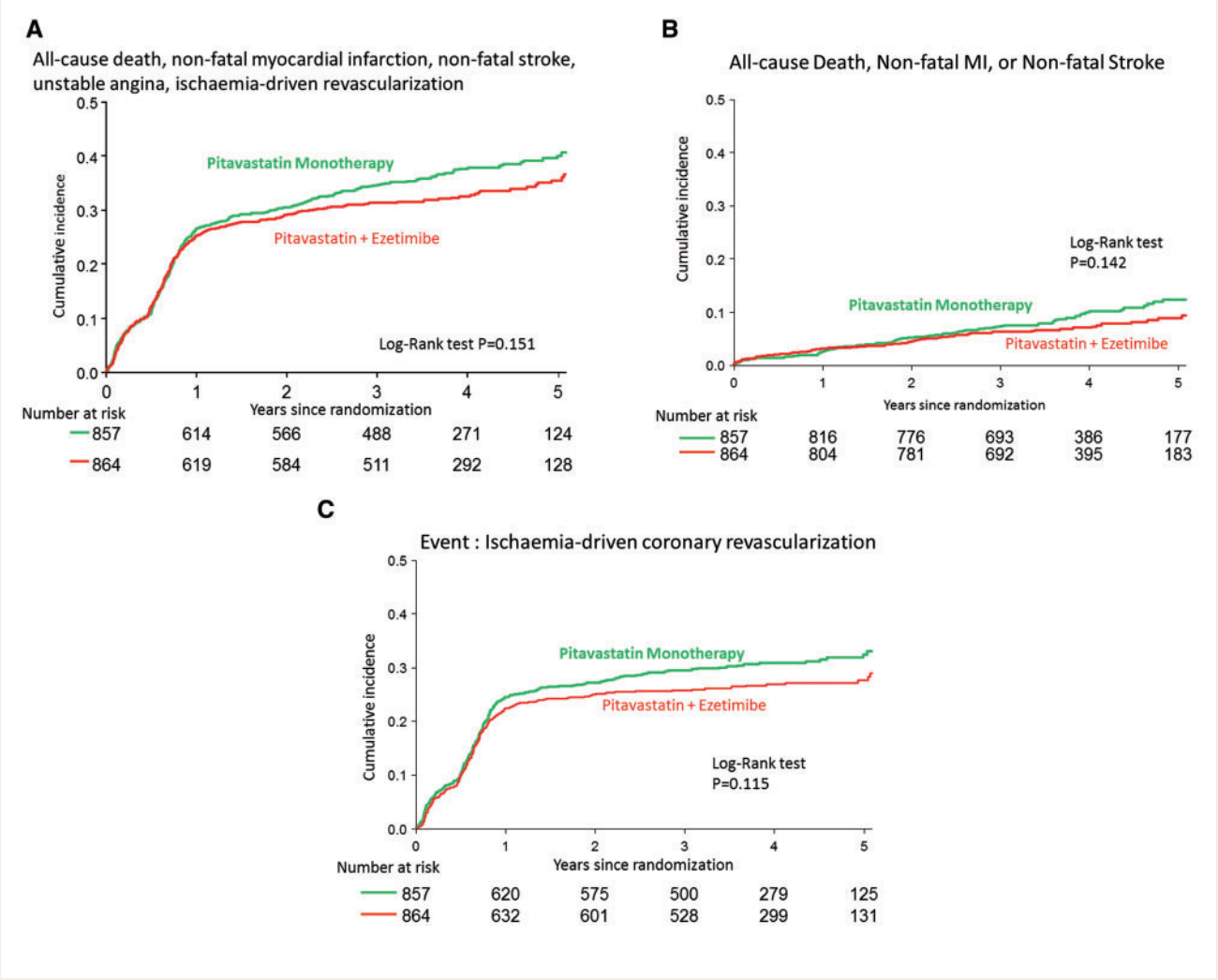

Figure 2 Kaplan–Meier curves for the primary efficacy endpoint and composite of several hard endpoints. (*A*) Primary endpoint, (*B*) All-cause death, non-fatal MI, or non-fatal stroke (*C*) Ischaemia-driven coronary revascularization. MI, myocardial infarction.

(HR, 0.71; 95% CI, 0.56–0.91), there was no significant reduction in patients without enhanced cholesterol absorption when compared with patients on monotherapy (HR, 1.11; 95% CI, 0.88–1.39) (*Table 5*).

Table 6 shows the occurrence of pre-specified adverse events. No significant between-group differences were seen in the percentage of patients whose alanine aminotransferase levels exceeded three times the upper limit of the normal range or in the rates of gallbladder-related adverse events, muscle-related adverse events, or incidence of cancer. The attending physician decided to discontinue the study drug because of an adverse event in 8.52% of pitavastatin monotherapy patients and in 6.37% of pitavastatin + ezetimibe patients.

Discussion

The present study demonstrates that, in ACS patients with dyslipidaemia under contemporary aggressive coronary revascularization and optimal medical therapy, LDL-C lowering to a target of <70 mg/dL (1.8 mmol/L) with a standard dose of pitavastatin plus ezetimibe provided no greater reduction of subsequent cardiovascular events than standard pitavastatin monotherapy. In ACS patients who showed elevated cholesterol absorption at baseline, however, statin plus ezetimibe treatment reduced such cardiovascular events more than standard statin monotherapy.

Dyslipidaemia is a risk factor for patients with CAD, which means that lipid management, and especially LDL-C lowering, can be especially valuable in these patients. But how low is 'low enough'? Previous guidelines from NCEP ATP III recommend lipid-lowering therapy to bring LDL-cholesterol below 70 mg/dL (1.8 mmol/L) in patients with coronary artery disease.[23] Similarly, a recent European guideline[24] encourages lowering LDL-C to less than 70 mg/dL (1.8 mmol/L) or by at least 50% for baseline between 70 mg/dL (1.8 mmol/L) and 135 mg/dL (3.5 mmol/L) in very high-risk patients, and lowering to less than 100 mg/dL (2.6 mmol/L) or by at least 50% for baseline between 100 mg/dL (2.6 mmol/L) and 200 mg/dL

Table 3 Primary, secondary, and individual endpoints

Outcome	Pitavastatin monotherapy (n = 857) Number of events (%)	Rate per 1000 patient-year	Pitavastatin + ezetimibe (n = 864) Number of events (%)	Rate per 1000 patient-year	Hazard Ratio (95% CI)	P-value
Primary endpoint: any cause of death, major coronary event, or non-fatal stroke	316 (36.9%)	128.1	283 (32.8%)	111.6	0.89 (0.76–1.04)	0.152
Secondary endpoints						
Non-fatal myocardial infarction	10 (1.2%)	3.0	11 (1.3%)	3.3	1.10 (0.47–2.58)	0.834
Non-fatal stroke	18 (2.1%)	5.5	17 (2.0%)	5.2	0.94 (0.49–1.83)	0.866
Unstable angina	33 (3.9%)	10.2	37 (4.3%)	11.5	1.13 (0.70–1.80)	0.623
Ischaemia-driven coronary revascularization	257 (30.0%)	102.8	225 (26.0%)	86.7	0.87 (0.72–1.04)	0.115
All-cause death	60 (7.0%)	18.1	42 (4.9%)	12.6	0.70 (0.47–1.04)	0.075
Heart failure hospitalization	40 (4.7%)	12.5	19 (2.2%)	5.8	0.47 (0.27–0.81)	0.006

(5.2 mmol/L) in high-risk patients. However, the medical community has not yet reached consensus on the appropriate statin dose, or on whether LDL-C should be a factor in determining that dose.[7,25,26]

The initial statin dose is generally quite effective in reducing LDL-C, but further reductions require disproportionately large dose increases,[12] as statin-induced reductions in serum cholesterol trigger increased cholesterol uptake from the gastrointestinal tract. This is of particular importance because statin-related adverse effects are dose-dependent and occur more commonly at the highest doses.[13]

After statin therapy has been initiated, the patient should be assessed every 3–12 months as clinically indicated, since adherence to both medication and lifestyle regimens are required for cardiovascular risk reduction. Statins may affect the incidence of muscle injury, and the incidence of rhabdomyolysis increases dose-dependently with statin use.[27] Statins may also impact glucose metabolism and influence the development of diabetes.[28] Previous studies have demonstrated increased risk of new-onset diabetes with intensive statin therapy in comparison to standard statin therapy.[29] All of these factors suggest that a combined drug regimen, which would allow the targeting of lower LDL-C levels without the risk of high-dose statin therapy, might be beneficial particularly in improving cardiovascular outcomes in high-risk patients.

The present study shows some inconsistencies with the results of the IMPROVE-IT trial,[16] a landmark study in this area. The investigators of the IMPROVE-IT trial clearly demonstrated the usefulness of intensive lipid lowering with statin + ezetimibe compared with statin monotherapy, but the results of our study do not support the IMPROVE-IT findings of beneficial effects on the primary outcome. To interpret the differences between these two trials, it is useful to compare the characteristics of participants and the resulting individual event rates.

Although participants in both trials received contemporary optimal medical therapy at baseline, the rates of acute revascularization differed substantially (70% in IMPROVE-IT vs. 95% in HIJ-PROPER). Previous studies[30,31] demonstrated that primary coronary intervention improved both short-term and long-term clinical outcomes in ACS patients. With the introduction of second-generation drug-eluting coronary stents (DES) into clinical practice in this decade, PCI now shows long-term beneficial effects comparable to coronary artery bypass surgery in high-risk CAD patients.[32] Indeed, we found a very low incidence of hard endpoints in HIJ-PROPER (6% for total death, 3% for cardiac death, and 1% for non-fatal MI in the entire HIJ-PROPER cohort). The respective findings in the IMPROVE-IT study were 15.3% for any cause of death, 6.8% for cardiovascular death, and 11.2% for non-fatal MI. The low incidence of hard endpoints in our study could have resulted in insufficient power to detect significant differences in primary composite outcomes. We postulate that the effects of sample size and duration of the study period in combination with the low event rates may explain why the primary outcome was not significantly reduced in the intensive lipid lowering arm of HIJ-PROPER, as was seen in the IMPROVE-IT study.

Serum cholesterol concentration is determined both by endogenous cholesterol from hepatic and extrahepatic synthesis and by exogenous cholesterol from intestinal absorption of dietary and biliary cholesterol.[33] Statins produce beneficial effects by inhibiting hepatic cholesterol synthesis but do not directly affect intestinal absorption. Subgroup analysis in a Scandinavian simvastatin survival study (4S)[34] suggested that patients with high baseline synthesis of cholesterol seemed to respond to statin treatment, while those with low cholesterol synthesis were non-responders. In the present study, intensive lipid lowering with ezetimibe was associated with a significant reduction of primary endpoint events in patients with increased cholesterol absorption as expressed through higher baseline sitosterol. Further investigation is needed to elucidate the mechanisms underlying the beneficial effects of statin plus ezetimibe in ACS patients with high baseline cholesterol absorption.

Table 4 Subgroup analyses for primary endpoint

Subgroup	Pitavastatin monotherapy Number of patients	Number of events	Pitavastatin + ezetimibe Number of patients	Number of events	Hazard ratio (95% CI)	*P*-value for interaction
Gender						0.473
Women	196	64	225	71	1.00 (0.71–1.40)	
Men	661	252	639	212	0.86 (0.72–1.04)	
Age (years)						0.992
<65	381	118	379	104	0.89 (0.69–1.16)	
≥65	476	198	485	179	0.89 (0.72–1.08)	
Type of Index ACS event						0.162
STEMI	448	178	432	138	0.77 (0.62–0.97)	
Non-STEMI	88	26	92	34	1.36 (0.82–2.27)	
Unstable angina	321	112	340	111	0.97 (0.75–1.26)	
Number of Diseased vessels						0.118
1	402	121	430	95	0.72 (0.55–0.94)	
2	247	96	246	98	1.07 (0.81–1.41)	
3	156	78	146	72	0.98 (0.71–1.35)	
Hypertension						0.017
No	281	107	265	70	0.65 (0.48–0.88)	
Yes	576	209	599	213	1.01 (0.83–1.22)	
Diabetes						0.482
No	597	203	604	176	0.85 (0.70–1.04)	
Yes	260	113	260	107	0.96 (0.74–1.26)	
Smoker						0.529
No	557	201	570	187	0.92 (0.76–1.13)	
Yes	300	115	294	96	0.83 (0.63–1.09)	
Body Mass Index, kg/m^2						0.965
<25	551	209	541	184	0.91 (0.74–1.10)	
25≤, <30	250	88	248	74	0.83 (0.61–1.13)	
30≤	49	16	55	19	1.02 (0.52–2.01)	
Statin use before randomization						0.911
No	708	259	721	234	0.89 (0.74–1.06)	
Yes	149	57	143	49	0.90 (0.61–1.32)	
Estimated GFR, mL/min/1.73 m^2						0.586
30>	5	3	8	4	1.12 (0.24–5.28)	
30≤, <60	213	89	198	69	0.82 (0.60–1.12)	
60≤	639	224	658	210	0.92 (0.76–1.11)	

ACS, acute coronary syndrome; GFR, glomerular filtration rate; STEMI, ST-elevation myocardial infarction.

A recently published analysis and meta-analysis of data from the Minnesota Coronary Experiment indicate that drastic changes in eating habits led to significant lowering of serum cholesterol. However, these cholesterol-lowering interventions were not associated with benefits in mortality from coronary heart disease or in all-cause mortality.[35] A recent cohort study also demonstrated that statin-taking coronary heart disease patients with LDL-C 70 mg/dL (1.8 mmol/L)–100 mg/dL (2.6 mmol/L) had a lower risk of adverse cardiac outcomes than those with LDL-C between 100 mg/dL (2.6 mmol/L) and 130 mg/dL (3.4 mmol/L), but no additional benefit was gained by achieving LDL-C of 70 mg/dL (1.8 mmol/L) or less.[36] Although the results of the present study are consistent with these two studies, expectations based on CTT analysis[2] continue to be widely emphasized. PCSK9 inhibitors induce a marked lowering of LDL-C,[37] but no data are yet available on their effects on cardiovascular morbidity and mortality. Data from an ongoing trial[38] to evaluate the effects of PCSK9 inhibitors on cardiovascular outcomes may provide a breakthrough in the therapeutic limits for high-risk patients with atherosclerotic disease.

At this point, the impact of statin therapy remains controversial in reducing hospitalization for heart failure.[39–41] Findings from the present study suggest that heart failure hospitalization decreased in the intensive lipid lowering arm in comparison with standard statin monotherapy. However, further investigation is needed to determine the precise mechanisms for potential prevention of heart failure with statin plus ezetimibe as suggested in the present study.

Table 5 Baseline lipid profiles and subgroup analyses for primary endpoint

Subgroup	Pitavastatin monotherapy (n = 857) Number of patients	Number of events	Pitavastatin + ezetimibe (n = 864) Number of patients	Number of events	Hazard Ratio (95% CI)	P-value for interaction
Low density lipoprotein cholesterol, mg/dL (mmol/L)						0.140
<129 (3.3)[a]	414	141	415	140	1.01 (0.80–1.28)	
≥129 (3.3)	443	175	449	143	0.79 (0.64–0.99)	
High density lipoprotein cholesterol, mg/dL (mmol/L)						0.179
<47 (1.2)[a]	418	170	401	136	0.80 (0.64–1.00)	
≥47 (1.2)	439	146	463	147	0.99 (0.79–1.25)	
Triglycerides, mg/dL (mmol/L)						0.542
<114 (1.3)[a]	423	161	434	139	0.84 (0.67–1.06)	
≥114 (1.3)	434	155	430	144	0.94 (0.75–1.17)	
Eicosapentaenoic acid/Arachidonic acid ratio						0.161
<0.34[a]	271	99	299	82	0.70 (0.52–0.94)	
≥0.34	299	109	285	95	0.93 (0.71–1.23)	
Sitosterol (μg/mL)						0.010
<2.2[a]	398	142	411	157	1.11 (0.88–1.39)	
≥2.2	416	156	399	111	0.71 (0.56–0.91)	
Campesterol (μg/mL)						0.094
<4.2[a]	395	143	404	147	1.03 (0.82–1.30)	
≥4.2	419	155	408	121	0.78 (0.61–0.99)	
Lathosterol (μg/mL)						0.299
<1.6[a]	384	143	391	123	0.82 (0.64–1.04)	
≥1.6	429	155	420	145	0.98 (0.78–1.23)	

[a]median.

This study had some limitations. First, the prospective, randomized, open-label, controlled trial with blinded end-point assessment (PROBE) design is potentially less reliable than a double-blind randomized trial. Although endpoint classification was conducted by a blinded independent committee on validation of data and events, and committee members were unaware of group assignment, participants who knew that they were assigned to standard statin monotherapy might work harder on life-style modification. In addition, treatment strategies such as requiring hospitalization and revascularization treatment were used at the discretion of the responsible physician at each hospital, although all potential endpoints were adjudicated by an endpoint committee whose members were blinded to treatment group assignment. Second, a total of 8538 consecutive patients with ACS were screened at 19 clinical centers in Japan between January 2010 and April 2013. Of those, 1734 were considered eligible for study participation, based on the evaluation of the attending physicians, and also agreed to participate in the study. Unfortunately, the individual reasons for exclusion of each non-eligible patient were not consistently recorded, and thus could not be fully reported here. Consequently, we cannot exclude the possibility of selection bias. Third, the actual event rate was much lower than expected. Given the low event rate in HIJ-PROPER, our study was underpowered for demonstrating that intensive lipid lowering with pitavastatin + ezetimibe had a significant effect on reducing total adverse cardiovascular events. The small difference between the two groups (65.1 mg/dL vs. 84.6 mg/dL, i.e. 1.68 mmol/L vs 2.19 mmol/L), may have led to this lack of statistical power.

Our study consisted entirely of Japanese patients with ACS, which could affect the generalizability of our findings to patients in the rest of the world. Extrapolation of our results to non-Japanese patients with stable CAD might lead to incorrect conclusions; results should be validated in other cohorts. Among the 19 participating hospitals, 16 had a catheter laboratory and were ready on a 24-h basis to conduct primary PCI, which may explain the higher rate of PCI in the present study than in the previous report.[42] Additionally, the Norwegian Coronary Stent Trial (NORSTENT)[43] has provided recent evidence that the use of newer-generation DES decreases the rate of subsequent revascularization in comparison with contemporary bare-metal coronary stents. The frequent use of newer-generation DES would reduce the event rate, and may have caused this study to be underpowered.

Another is the relatively short duration (median of 3.86 years) of clinical follow-up. The time required for lipid-lowering therapy to affect cardiovascular events is not well defined, and this could have

Table 6 Adverse events and study drug discontinuation

	Pitavastatin monotherapy (n = 857) Number of events (%)	Pitavastatin + ezetimibe (n = 864) Number of events (%)	P-value
Incidence of cancer	42 (4.90)	33 (3.82)	0.27
Rhabdomyolysis	1 (0.12)	2 (0.23)	0.57
Myopathy[a]	8 (0.93)	8 (0.93)	0.99
Hepatobiliary system			
ALT and/or AST≥3 × ULN	15 (1.75)	28 (3.24)	0.05
γ-GTP ≥3 × ULN	5 (0.58)	5 (0.58)	0.99
Gallbladder-related	11 (1.28)	10 (1.16)	0.81
Creatine kinase elevation ≥5 × ULN	4 (0.47)	2 (0.23)	0.41
Doubling of serum creatinine	3 (0.35)	2 (0.23)	0.65
Study drug discontinuation			
Pitavastatin	73 (8.52)	19 (2.20)	
Ezetimibe	—	46 (5.32)	
Both	—	55 (6.37)	

ALT, alanine amino transferase; AST, aspartate aminotransferase; GTP, glutamly transpeptidase; ULN, upper limit of the normal range.
[a]Defined as new muscle pain, tenderness, or weakness without another obvious cause that was associated with an elevation of creatine kinase (CK) ≥ 10 × ULN.

influenced differences in the main outcomes between the IMPROVE-IT and HIJ-PROPER trials.

Although our results provide no evidence of superiority for intensive lipid lowering over standard statin therapy in all patients, analysis of several subgroups yielded findings that are potentially hypothesis-generating. Caution is needed in their interpretation, but our results suggest the possible superiority of concomitant ezetimibe over standard statin monotherapy for secondary prevention in CAD patients with dyslipidaemia due to increased cholesterol absorption.

In conclusion, within the modern context of aggressive coronary revascularization and optimal medical therapy, LDL-C lowering to a target of <70 mg/dL (1.8 mmol/L) with a standard dose of pitavastatin plus ezetimibe showed no more cardiovascular benefit than standard pitavastatin monotherapy in ACS patients with dyslipidaemia. In ACS patients with increased cholesterol absorption, statin plus ezetimibe treatment may be more effective than standard statin monotherapy for reducing subsequent cardiovascular events. We consider this subanalysis outcome to be of considerable interest and to warrant further investigation.

Contributions

Nobuhisa Hagiwara: Chair of the HIJ-PROPER Investigators and a member of the writing committee. Erisa Kawada-Watanabe: Clinical follow-up of patients. Ryo Koyanagi: A member of the executive committee, Design of the study. Hiroyuki Arashi: Clinical follow-up of patients. Junichi Yamaguchi: A member of the executive committee, Design of the study. Koichi Nakao: Clinical follow-up of patients. Tetsuya Tobaru: Enrolment of patients. Hiroyuki Tanaka: Clinical follow-up of patients. Toshiaki Oka: Enrolment of patients. Yasuhiro Endoh: Clinical follow-up of patients. Katsumi Saito: Enrolment of patients. Tatsuro Uchida: Enrolment of patients. Kunihiko Matsui: Statistical analysis. Hiroshi Ogawa: A member of the executive committee and the writing committee.

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Conflict of interest: The authors have the following disclosures: All members of the HIJ-PROPER study group report having received research support to perform clinical trials through the Japan Research Promotion Society for Cardiovascular Diseases, which is sponsored by Abbott Vascular Japan Co., Ltd., AstraZeneca K.K., Bayer Yakuhin, Ltd., Boston Scientific Corporation, Bristol-Myers K.K., Daiichi Sankyo Company, Limited, Kowa Pharmaceutical Co., Ltd., Mochida Pharmaceutical Co., Ltd., MSD K.K., Nippon Boehringer Ingelheim Co., Ltd., Novartis Pharma K.K., Pfizer Japan Inc., Sanofi K.K., and Takeda Pharmaceutical Company Limited. N. Hagiwara reports that he has received honoraria from Bristol-Myers K.K., and Nippon Boehringer Ingelheim Co., Ltd., and grants from Astellas Pharma Inc., Daiichi Sankyo Company, Limited, Eisai Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Otsuka Pharmaceutical Co., Ltd., Shionogi & Co., Ltd., and Takeda Pharmaceutical Company Limited. J. Yamaguchi reports that he has received honoraria from Abbott Vascular Japan Co., Ltd., and grants from Daiichi Sankyo Company, Limited. 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.

Appendix

Study organization

Executive Committee: Nobuhisa Hagiwara (Chair), Hiroshi Ogawa.

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