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Original article

# Combination therapy of eicosapentaenoic acid and pitavastatin for coronary plaque regression evaluated by integrated backscatter intravascular ultrasonography (CHERRY study)—Rationale and design

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ABSTRACT

*Background and purpose:* Many clinical trials have shown that 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) can significantly reduce coronary artery disease in both primary and secondary prevention. A recent study showed that aggressive lipid-lowering therapy with strong statins could achieve coronary artery plaque regression, as evaluated with gray-scale intravascular ultrasound (IVUS). However, it is unknown whether coronary plaque regression and stabilization are reinforced when eicosapentaenoic acid (EPA) is used with a strong statin.
*Methods and subjects:* We aim to assess patients with stable angina or acute coronary syndrome who had undergone successful percutaneous coronary intervention (PCI) with integrated backscatter IVUS (IB-IVUS) guidance. They will be randomly allocated to receive pitavastatin (4 mg), or pitavastatin (4 mg) plus EPA (1800 mg), and prospectively followed for 6–8 months.
*Results:* The primary endpoint will be changes in tissue characteristics in coronary plaques, evaluated by IB-IVUS, and secondary endpoints will include absolute changes in coronary plaque volume, serum lipid levels, and inflammatory markers. The safety profile will also be evaluated.
*Conclusions:* The combination therapy of EPA and pitavastatin for regression of coronary plaque evaluated by IB-IVUS (CHERRY) study will be the first multicenter study using IB-IVUS to investigate the effects of combination therapy with pitavastatin and EPA on coronary plaque volume and tissue characteristics.


## Introduction

The clinical benefit of cholesterol-lowering therapy with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) has been conclusively demonstrated by numerous large-scale, multicenter, randomized primary and secondary prevention clinical trials [1–5]. Furthermore, intensive lipid-lowering therapy with strong statins can regress coronary atherosclerosis, as shown with intravascular ultrasound (IVUS) analysis [6–8]. The effects of intensive therapy with pitavastatin (4 mg/day) on coronary plaque regression have been reported to be comparable with those achieved with atorvastatin (20 mg/day) in patients with acute coronary syndrome [9]. However, cardiovascular events cannot be completely prevented by high-dose therapy

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**Table 1**
Inclusion criteria.

- Patients who provide voluntarily written consent after being provided with the details of clinical trial participation
- Patients aged 20 years or older at the time of their consent
- Patients with hypercholesterolemia, as defined by any of the following criteria: (1) TC ≥ 220 mg/dL (2) LDL-C ≥ 140 mg/dl, (3) cholesterol-lowering treatment is necessary in accordance with the investigator's judgment when LDL-C ≥ 100 mg/dL or TC ≥ 180 mg/dL
- Patients with stable angina or acute coronary syndrome who have received successful PCI with IVUS guidance
- Patients with coronary plaques (≥500 μm in thickness or ≥20% plaque coverage) ≥5 mm from the previously treated area in the same coronary artery branch

TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; PCI, percutaneous coronary intervention; IVUS, intravascular ultrasound.

**Table 2**
Exclusion criteria.

- Patients whose target lesion site is a coronary bypass graft
- Patients who have undergone previous PCI on the lesion site where the IB-IVUS evaluation is planned
- Patients who may undergo PCI on the lesion site where the IB-IVUS evaluation is planned
- Patients with familial hypercholesterolemia
- Patients with a past history of allergy to EPA and/or pitavastatin
- Patients with hepatic dysfunction (ALT 100 IU/L or more) and/or biliary obstruction
- Patients with renal dysfunction (serum creatinine 2.0 mg/dL or more) or undergoing dialysis
- Patients deemed ineligible for the study by physicians

PCI, percutaneous coronary intervention; IB-IVUS, integrated backscatter intravascular ultrasound; EPA, eicosapentaenoic acid; ALT, alanine aminotransferase.

with strong statins [10]. This residual risk has gained increasing attention in statin-treated secondary prevention patients [11].

Epidemiological and clinical evidence suggest a significant inverse association between long-term intake of long-chain n-3 polyunsaturated fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and mortality due to coronary artery disease [12–18]. In JELIS (Japan eicosapentaenoic acid lipid intervention study), EPA significantly reduced coronary events in patients with hypercholesterolemia under statin treatment [19]. EPA is especially effective for secondary prevention of coronary artery disease [20]. Because standard statins, such as pravastatin or simvastatin, were used in the JELIS trial, it is unclear whether there are additional effects of EPA in coronary artery disease patients undergoing treatment with high-doses of strong statins.

The evaluation of coronary atherosclerosis progression-regression by IVUS is reported to be a feasible surrogate endpoint to predict future cardiovascular events [21,22]. Although coronary plaque has been evaluated by gray-scale IVUS, it remains unclear whether coronary plaque tissue characteristics change over time. Integrated backscatter IVUS (IB-IVUS) has recently been developed and allows analysis of specific tissue components (calcification, dense fibrosis, fibrosis, lipid pool) of coronary plaques *in vivo* [23–25]. IB-IVUS has also proved useful for assessing the prognosis of patients with coronary atherosclerosis and the risk of experiencing a coronary event [26–28].

The present study was designed to evaluate the effects of combination therapy consisting of high-dose pitavastatin and EPA on coronary plaque tissue characteristics using IB-IVUS.

## Materials and methods

### *Study design*

All procedures will be in accordance with the principles described in the Declaration of Helsinki. The CHERRY study will be a randomized, non-blinded, parallel group study. Patients who satisfy all inclusion criteria will be enrolled after undergoing successful percutaneous coronary intervention (PCI) under IVUS guidance to treat stable angina or an episode of acute coronary syndrome (Table 1). Patients with any of the exclusion criteria (Table 2) will not be enrolled. Included patients will provide written informed consent before they are randomly allocated to receive either pitavastatin (4 mg daily) or pitavastatin and EPA (4 mg and 1800 mg daily, respectively) (Fig. 1). The supervising physician will administer the allocated drugs within one week of successful PCI. The participants will continue taking the allocated drugs until the end of study or when certain endpoints are met, including death, any cardiovascular event, any adverse event, or discontinued participation in the study. Administration of cholesterol-lowering drugs such as other statins, fibrates, probucol, niacin, colestimide, and ezetimibe, and supplementation of n-3 polyunsaturated fatty acids are prohibited during the present study. Investigators will follow up the participants for 6–8 months at six centers and will conduct medical examinations, blood testing, IVUS, and coronary angiography (CAG). Patient enrollment is planned for between September 2009 and April 2014 and may be extended if necessary. The study has been registered at University Hospital Medical Information Network (UMIN) (UMIN ID: 000002815).

### *Endpoints*

The primary endpoint will be the change of coronary plaque tissue characteristics as evaluated by IB-IVUS. Secondary endpoints include: (1) changes in the volume and minimum intravascular lumen diameter of target coronary plaques; (2) changes in total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), triglyceride (TG), high-density lipoprotein-cholesterol (HDL-C), malonyldialdehyde LDL (MDA-LDL), remnant-like particle-cholesterol (RLP-C), lipoprotein (a), and apoliproteins (Apo A-I, Apo B, Apo E); (3) changes in EPA/arachidonic acid levels; (4) changes in high sensitivity C-reactive protein (hs-CRP); (5) changes in coronary plaque volume, minimum intravascular lumen diameter, and % stenosis at the site of the lesion where the coronary plaque is evaluated; and (6) the incidence of major adverse cardiovascular events (MACE) defined as cardiac death, nonfatal myocardial infarction, PCI, or coronary artery bypass grafting.

### *Safety monitoring*

Safety will be evaluated by regular medical examinations and laboratory tests at 1, 3, and 6–8 months after enrollment. The Assessment Committee will evaluate MACE and any other adverse events.

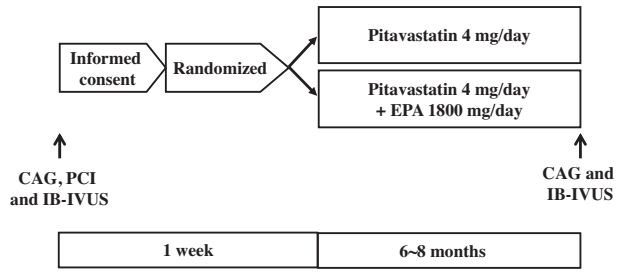


**Fig. 1.** Flow chart of the study timeline. EPA, eicosapentaenoic acid; IB-IVUS, integrated backscatter intravascular ultrasound; CAG, coronary angiography; PCI, percutaneous coronary intervention.

*Sample size calculation*

The aim of this study is to investigate differences between patients treated with pitavastatin and pitavastatin supplemented with EPA in terms of changes in coronary artery plaque composition as measured by IB-IVUS. There is currently no information in the literature regarding the effects of pitavastatin supplemented with EPA on coronary artery plaque. The study group estimated the necessary sample size based on the effect of EPA or fish oil supplementation on carotid plaque regression [29,30], and 100 patients in each group are necessary to achieve 80% power by a two-sided, two-sample t-test at a significance level of 5%. Assuming a 10% drop-out rate, the desired sample size per group is 110 patients.

*Data management*

Patient information, blood samples, and IB-IVUS images will be coded with a study identification number, and the key code for individual identity will remain blinded. Serum lipids, RLP-C, apolipoproteins, and hs-CRP will be measured using routine laboratory methods. MDA-LDL and fatty acid fraction will be measured at SRL Co., Ltd. (Tokyo, Japan). IB-IVUS and CAG images will be quantitatively analyzed at the core laboratory by an independent experienced investigator who is unaware of the patient groups. Baseline and follow-up IVUS images will be reviewed together on a display, and target segments will be selected. One target segment will be determined at a non-PCI site (>5 mm proximal or distal to the PCI site) with a reproducible index side branch on the PCI vessel.

*Statistical analysis*

Continuous variables, such as laboratory data, are expressed as the mean ± standard deviation (SD) for each period. Group comparisons between the pitavastatin and pitavastatin and EPA group will be calculated by Student's *t*-tests, analyses of variance (ANOVAs), chi-square tests, Fisher's exact tests, or Mann–Whitney *U*-tests, as appropriate. When an adjustment for multiplicity of testing is necessary, a closed testing procedure in which the test for each component is performed in the order of calcification, dense fibrosis, fibrosis, and lipid pool; the significance level will be 5%. Statistical analyses are performed using a standard software package (JMP version 8; SAS Institute Inc., Cary, NC, USA).

*Study organization*

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## Discussion

Recent large-scale clinical trials such as ORIGIN and OMEGA revealed that supplementation with n-3 polyunsaturated fatty acids containing EPA and DHA did not show additional effects for primary and secondary prevention of coronary artery disease [31,32]. However, clinical and experimental studies showed that EPA potentially reduces and stabilize atherosclerosis [19,33]. The CHERRY study will be the first multicenter study employing IB-IVUS to evaluate the effects of EPA and pitavastatin on coronary artery plaque composition. The study group will investigate the relationship between changes in plaque composition and lipid levels in patients with stable angina or acute coronary syndrome receiving EPA and pitavastatin. Furthermore, the study group hopes to demonstrate the process of coronary artery plaque stabilization and determine whether EPA reduces residual risk in patients treated with high-dose strong statin for secondary prevention.

## References

[1] Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383–9.
[2] Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto Jr AM, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195–207.
[3] Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med 1996;335:1001–9.
[4] Streja L, Packard CJ, Shepherd J, Cobbe S, Ford I. Factors affecting low-density lipoprotein and high-density lipoprotein cholesterol response to pravastatin in the West Of Scotland Coronary Prevention Study (WOSCOPS). Am J Cardiol 2002;90:731–6.
[5] Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350:1495–504.
[6] Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, Davignon J, Erbel R, Fruchart JC, Tardif JC, Schoenhagen P, Crowe T, Cain V, Wolski K, Goormastic M, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. J Am Med Assoc 2006;295:1556–65.
[7] Okazaki S, Yokoyama T, Miyauchi K, Shimada K, Kurata T, Sato H, Daida H. Early statin treatment in patients with acute coronary syndrome: demonstration of the beneficial effect on atherosclerotic lesions by serial volumetric intravascular ultrasound analysis during half a year after coronary event: the ESTABLISH Study. Circulation 2004;110:1061–8.
[8] Takayama T, Hiro T, Ueda Y, Honye J, Komatsu S, Yamaguchi O, Li Y, Yajima J, Takazawa K, Nanto S, Saito S, Hirayama A, Kodama K. Plaque stabilization by intensive LDL-cholesterol lowering therapy with atorvastatin is delayed in type 2 diabetic patients with coronary artery disease—serial angioscopic and intravascular ultrasound analysis. J Cardiol 2013;61:381–6.
[9] Hiro T, Kimura T, Morimoto T, Miyauchi K, Nakagawa Y, Yamagishi M, Ozaki Y, Kimura K, Saito S, Yamaguchi T, Daida H, Matsuzaki M. Effect of intensive statin therapy on regression of coronary atherosclerosis in patients with acute coronary syndrome: a multicenter randomized trial evaluated by volumetric intravascular ultrasound using pitavastatin versus atorvastatin (JAPAN-ACS [Japan assessment of pitavastatin and atorvastatin in acute coronary syndrome] study). J Am Coll Cardiol 2009;54:293–302.
[10] LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein JJ, Shepherd J, Wenger NK. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005;352:1425–35.
[11] Mora S, Wenger NK, Demicco DA, Breazna A, Boekholdt SM, Arsenault BJ, Deedwania P, Kastelein JJ, Waters DD. Determinants of residual risk in secondary prevention patients treated with high- versus low-dose statin therapy: the Treating to New Targets (TNT) study. Circulation 2012;125:1979–87.
[12] Albert CM, Campos H, Stampfer MJ, Ridker PM, Manson JE, Willett WC, Ma J. Blood levels of long-chain n-3 fatty acids and the risk of sudden death. N Engl J Med 2002;346:1113–8.
[13] Albert CM, Hennekens CH, O'Donnell CJ, Ajani UA, Carey VJ, Willett WC, Ruskin JN, Manson JE. Fish consumption and risk of sudden cardiac death. J Am Med Assoc 1998;279:23–8.
[14] Daviglus ML, Stamler J, Orencia AJ, Dyer AR, Liu K, Greenland P, Walsh MK, Morris D, Shekelle RB. Fish consumption and the 30-year risk of fatal myocardial infarction. N Engl J Med 1997;336:1046–53.
[15] Hu FB, Bronner L, Willett WC, Stampfer MJ, Rexrode KM, Albert CM, Hunter D, Manson JE. Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. J Am Med Assoc 2002;287:1815–21.
[16] Kromhout D, Bosschieter EB, de Lezenne Coulander C. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. N Engl J Med 1985;312:1205–9.
[17] Lemaitre RN, King IB, Mozaffarian D, Kuller LH, Tracy RP, Siscovick DS. n-3 polyunsaturated fatty acids, fatal ischemic heart disease, and nonfatal myocardial infarction in older adults: the Cardiovascular Health Study. Am J Clin Nutr 2003;77:319–25.
[18] Siscovick DS, Raghunathan TE, King I, Weinmann S, Wicklund KG, Albright J, Bovbjerg V, Arbogast P, Smith H, Kushi LH, et al. Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. J Am Med Assoc 1995;274:1363–7.

[19] Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet 2007;369:1090–8.
[20] Matsuzaki M, Yokoyama M, Saito Y, Origasa H, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K, et al. Incremental effects of eicosapentaenoic acid on cardiovascular events in statin-treated patients with coronary artery disease. Circ J 2009;73:1283–90.
[21] Dohi T, Miyauchi K, Okazaki S, Yokoyama T, Yanagisawa N, Tamura H, Kojima T, Yokoyama K, Kurata T, Daida H. Plaque regression determined by intravascular ultrasound predicts long-term outcomes of patients with acute coronary syndrome. J Atheroscler Thromb 2011;18:231–9.
[22] Miyauchi K, Daida H, Morimoto T, Hiro T, Kimura T, Nakagawa Y, Yamagishi M, Ozaki Y, Kadota K, Kimura K, Hirayama A, Hasegawa Y, Uchiyama S, Matsuzaki M. Reverse vessel remodeling but not coronary plaque regression could predict future cardiovascular events in ACS patients with intensive statin therapy—the extended JAPAN-ACS study. Circ J 2012;76:825–32.
[23] Amano T, Matsubara T, Uetani T, Nanki M, Marui N, Kato M, Arai K, Yokoi K, Ando H, Ishii H, Izawa H, Murohara T. Impact of metabolic syndrome on tissue characteristics of angiographically mild to moderate coronary lesions integrated backscatter intravascular ultrasound study. J Am Coll Cardiol 2007;49: 1149–56.
[24] Kawasaki M, Takatsu H, Noda T, Sano K, Ito Y, Hayakawa K, Tsuchiya K, Arai M, Nishigaki K, Takemura G, Minatoguchi S, Fujiwara T, Fujiwara H. In vivo quantitative tissue characterization of human coronary arterial plaques by use of integrated backscatter intravascular ultrasound and comparison with angioscopic findings. Circulation 2002;105:2487–92.
[25] Okubo M, Kawasaki M, Ishihara Y, Takeyama U, Yasuda S, Kubota T, Tanaka S, Yamaki T, Ojio S, Nishigaki K, Takemura G, Saio M, Takami T, Fujiwara H, Minatoguchi S. Tissue characterization of coronary plaques: comparison of integrated backscatter intravascular ultrasound with virtual histology intravascular ultrasound. Circ J 2008;72:1631–9.
[26] Amano T, Matsubara T, Uetani T, Kato M, Kato B, Yoshida T, Harada K, Kumagai S, Kunimura A, Shinbo Y, Ishii H, Murohara T. Lipid-rich plaques predict non-target-lesion ischemic events in patients undergoing percutaneous coronary intervention. Circ J 2011;75:157–66.
[27] Sano K, Kawasaki M, Ishihara Y, Okubo M, Tsuchiya K, Nishigaki K, Zhou X, Minatoguchi S, Fujita H, Fujiwara H. Assessment of vulnerable plaques causing acute coronary syndrome using integrated backscatter intravascular ultrasound. J Am Coll Cardiol 2006;47:734–41.
[28] Kunimura A, Amano T, Uetani T, Harada K, Yoshida T, Suzuki A, Shimbo Y, Kitagawa K, Kato B, Kato M, Takashima H, Ando H, Matsubara T, Ishii H, Murohara T. Prognostic impact of concurrence of metabolic syndrome and chronic kidney disease in patients undergoing coronary intervention: involvement of coronary plaque composition. J Cardiol 2013;61:189–95.
[29] Thies F, Garry JM, Yaqoob P, Rerkasem K, Williams J, Shearman CP, Gallagher PJ, Calder PC, Grimble RF. Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomised controlled trial. Lancet 2003;361:477–85.
[30] Mita T, Watada H, Ogihara T, Nomiyama T, Ogawa O, Kinoshita J, Shimizu T, Hirose T, Tanaka Y, Kawamori R. Eicosapentaenoic acid reduces the progression of carotid intima-media thickness in patients with type 2 diabetes. Atherosclerosis 2007;191:162–7.
[31] Bosch J, Gerstein HC, Dagenais GR, Diaz R, Dyal L, Jung H, Maggiono AP, Probstfield J, Ramachandran A, Riddle MC, Ryden LE, Yusuf S. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. N Engl J Med 2012;367:309–18.
[32] Rauch B, Schiele R, Schneider S, Diller F, Victor N, Gohlke H, Gottwik M, Steinbeck G, Del Castillo U, Sack R, Worth H, Katus H, Spitzer W, Sabin G, Senges J. OMEGA, a randomized, placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction. Circulation 2010;122:2152–9.
[33] Matsumoto M, Sata M, Fukuda D, Tanaka K, Soma M, Hirata Y, Nagai R. Orally administered eicosapentaenoic acid reduces and stabilizes atherosclerotic lesions in ApoE-deficient mice. Atherosclerosis 2008;197:524–33.