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Early initiation of eicosapentaenoic acid and statin treatment is associated with better clinical outcomes than statin alone in patients with acute coronary syndromes: 1-year outcomes of a randomized controlled study☆

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ABSTRACT

Background: Early initiation of EPA treatment in combination with a statin within 24 h after percutaneous coronary intervention (PCI) in patients with acute myocardial infarction (MI) reduces inflammation and ventricular arrhythmia compared with statin monotherapy; however, the impact of early initiation of EPA treatment on cardiovascular events is unclear. We determined whether early eicosapentaenoic acid (EPA) treatment in patients with acute coronary syndrome (ACS) reduces adverse cardiovascular events.

Methods: This prospective, open-label, blind end point–randomized trial consisted of 241 patients with ACS. Patients were randomly assigned to receive pitavastatin (2 mg/day) with or without 1800 mg/day of EPA initiated within 24 h after PCI. The primary endpoint was defined as cardiovascular events occurring within 1 year, including death from a cardiovascular cause, nonfatal stroke, nonfatal MI and revascularization.

Results: The mean EPA/arachidonic acid ratio at follow-up was 0.40 in the control group and 1.15 in the EPA group. A primary endpoint event occurred in 11 patients (9.2%) in the EPA group and 24 patients (20.2%) in the control group (absolute risk reduction, 11.0%; hazard ratio, 0.42; 95% confidence interval, 0.21 to 0.87; P = 0.02). Notably, death from a cardiovascular cause at 1 year was significantly lower in the EPA group than in the control group (0.8% vs. 4.2%, P = 0.04).

Conclusions: Early initiation of treatment with EPA combined with statin after successful primary PCI reduced cardiovascular events after ACS.

Clinical Trial Registration: UMIN Clinical Trials Registry (UMIN-CTR); Registry Number, UMIN000016723; URL, http://www.umin.ac.jp/ctr/index-j.htm

Abbreviations: 18R-HPEPE, 18R-hydroperoxyeicosapentaenoic acid; AA, arachidonic acid; ACS, acute coronary syndrome; AMI, acute myocardial infarction; ANOVA, analysis of variance; CABG, coronary artery bypass graft; CAG, coronary angiography; CI, confidence interval; COX2, cyclooxygenase-2; CRP, C-reactive protein; DHA, docosahexaenoic acid; ECG, electrocardiogram; EPA, eicosapentaenoic acid; LAD, left anterior descending artery; GISSI, Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico; HDL, high-density lipoprotein; HDL-C, HDL-cholesterol; HR, hazard ratio; IMT, intima-media thickness; JELIS, Japan EPA Lipid Intervention Study; LDL, low-density lipoprotein; LDL-C, LDL-cholesterol; MI, myocardial infarction; MIRACL, Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering; PUFA, polyunsaturated fatty acid; PCI, percutaneous coronary intervention; RLP-C, remnant-like lipoparticle cholesterol; TIMI, thrombolysis in MI.

☆ These author take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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1. Introduction

Lowering low-density lipoprotein cholesterol (LDL-C) levels by statins reduces cardiovascular events after acute coronary syndrome (ACS) [1–3]. In addition, the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study demonstrated that early treatment with atorvastatin initiated 24–96 h after ACS reduced recurrent ischemic events [4]. Thus, early initiation of treatment with statins after ACS is commonly accepted in clinical practice. Although aggressive treatment with statins enables attainment of targeted LDL-C levels, cardiovascular events after ACS is still prevalent [5,6]. Among putative clinical therapies guarding against residual cardiovascular risks, an increased intake of omega-3 polyunsaturated fatty acids (PUFAs) including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) has been reported to protect against mortality after acute myocardial infarction (MI) [7–9].

Ingestion of omega-3 PUFAs including EPA and DHA may attenuate the inflammatory response after MI through multiple mechanisms. Omega-3 PUFAs are readily incorporated into lipid membranes and modify cellular signaling, leading to the disruption of lipid raft–related pro-inflammatory signaling [10]. In addition, the conversion of omega-3 PUFAs into oxygenated bioactive derivatives such as resolvins and protectins promotes the resolution of inflammation [11–14]. Recent preclinical data have indicated that an acute inflammatory response after MI accelerates systemic atherosclerosis [15–17]. These results suggest that omega-3 PUFAs could reduce the intensity of the inflammatory response, which then influences clinical outcome after ACS.

We have reported that early initiation of EPA treatment in patients with acute MI reduced the inflammatory response as assayed by high-sensitivity C-reactive protein (CRP) on days 3 and 4 [18]. However, the impact of early EPA treatment after ACS on remote-stage clinical outcomes remains unknown. The aim of this study was to investigate whether early initiation of EPA treatment combined with a statin started within 24 h after successful primary percutaneous coronary intervention (PCI) reduced cardiovascular events compared with statin monotherapy in patients after ACS.

2. Methods

2.1. Study design

This study consisted of a prospective, single-center randomized open-labeled trial (Fig. 1). The study protocol was approved by the ethics committee of Kagawa Prefectural Central Hospital, and written informed consent was obtained from all patients.

2.2. Study population

Between November 2010 and March 2014, 329 consecutive ACS patients treated with PCI were eligible to participate as part of the study population (Fig. 2). ACS was diagnosed according to the American College of Cardiology/American Heart Association 2007 guideline; recent-onset chest pain, associated with ST segment and/or negative T wave electrocardiogram (ECG) changes and/or positive cardiac enzymes (creatine kinase or troponin T) [19]. Key exclusion criteria were cardiogenic shock, severe renal insufficiency requiring dialysis, cardiopulmonary arrest, emergent coronary artery bypass, failure of PCI, and expected prognosis less than 1 year because of cancer. Among ACS patients who enrolled in this study, 115 patients with acute myocardial patients were overlapped with our previous study, which evaluated composite events, including cardiac death, stroke, re-infarction, ventricular arrhythmias, and paroxysmal atrial fibrillation within 1 month after PCI. [18]

2.3. Acute-stage treatment and study protocol

Before PCI, patients received 200 mg aspirin and 300 mg clopidogrel. PCI was performed with conventional techniques by the femoral or radial approach. Intravenous heparin (10,000 IU) was administered after arterial access was obtained to achieve an activated clotting time of >200 s. Intravenous heparin was continued for 48 h after angioplasty, followed by stent deployment. Post-procedural antithrombotic therapy consisted of 100 mg aspirin daily and 75 mg clopidogrel daily. No patients received glycoprotein inhibitors during the study period.

After PCI, the patients were randomly assigned at a 1:1 ratio to two groups: patients in one group received pitavastatin at a dose of 2 mg plus EPA, which is highly (>98%) purified EPA ethyl ester (ethyl all-cis-5,8,11,14,17-icosapentaenoate), at a dose of 1800 mg (EPA group); those in the other received pitavastatin alone at a dose of 2 mg (control group). Group placement was determined by a research technician according to a computer-generated randomization plan that included stratification by gender and acute MI or unstable angina pectoris. Drugs were started within 24 h after PCI and were continued for at least 52 weeks. We checked the condition of each patient at 1, 3, 6, 9, and 12 months after the initiation of therapy. Laboratory examinations were performed for each patient at admission and 6–9 months after the initiation of therapy.

2.4. End points

The primary composite end point consisted of death from a cardiovascular cause, or nonfatal MI, nonfatal stroke, coronary revascularization for new lesions with either PCI or coronary artery bypass graft (CABG). We assessed the first occurrence of one of these events starting from the time of randomization. The secondary composite end point consisted of either a primary end point or hospitalization for heart failure after starting study drugs. Non-fatal acute MI was defined as having at least two of the following: chest pain of typical intensity and duration; ST segment elevation or depression of ≥1 mm in any limb lead of

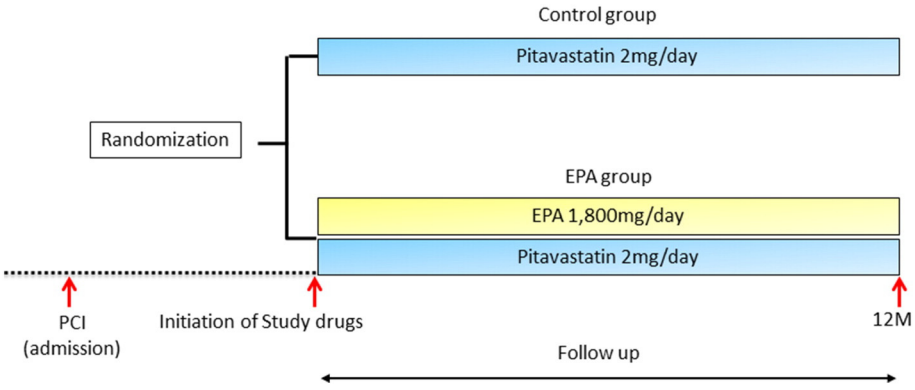

Fig. 1. Study protocol.