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Clinically evident polyvascular disease and regression of coronary atherosclerosis after intensive statin therapy in patients with acute coronary syndrome: Serial intravascular ultrasound from the Japanese assessment of pitavastatin and atorvastatin in acute coronary syndrome (JAPAN-ACS) trial

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ABSTRACT

Aim: To clarify whether the effects of statin treatment on plaque regression vary according to the presence or absence of polyvascular disease (PVD) in patients with acute coronary syndrome (ACS).
Methods: 307 patients with ACS who underwent percutaneous coronary intervention for the culprit lesion at 33 centers were treated with atorvastatin or pitavastatin. Noncoronary atherosclerosis was defined as coexistent, clinically recognized arterial disease other than coronary artery disease (CAD) (cerebral, aortic, or lower extremity). Intravascular ultrasound (IVUS) was performed to assess non-culprit coronary atherosclerosis at baseline and at 8–12 months follow-up. Serial IVUS examinations were obtained in 252 patients. Atheroma volume and percent change in atheroma volume of the target plaque was assessed.
Results: Patients of the CAD + PVD ($n = 19$) were older (68 vs. 62 years, $p = 0.02$), had lower low-density lipoprotein cholesterol (LDL-C) levels at baseline (116 vs. 134 mg/dL, $p = 0.03$) than those of the CAD-only group ($n = 233$), whereas LDL-C levels at follow-up were similar (81 vs. 83 mg/dL). Although the baseline plaque volume was similar in the two groups (59 vs. 57 mm^3), patients of the CAD + PVD group showed milder regression of atherosclerosis than those of the CAD-only group (−8.9% vs. −18.2%, $p = 0.005$). This difference remained significant even after adjustment for coronary risk factors including age and serum LDL-C ($p = 0.047$).
Conclusions: Statin treatment results in milder regression of coronary atherosclerosis in CAD patients with polyvascular disease compared to those with CAD only.

1. Introduction

Atherosclerosis is a systemic and generalized disease. Previous reports indicated that 10–64% of patients with coronary artery disease (CAD) were found coincidentally to have atherosclerotic disease in other vascular territories [1–4]. Recently published results of Reduction of Atherothrombosis of Continued Health (REACH) registry showed that patients with atherosclerotic

Abbreviations: ABPI, ankle–brachial pressure index; ACS, acute coronary syndrome; CAD, coronary artery disease; CSA, cross-sectional area; EEM, external elastic membrane; HDL-C, high density lipoprotein cholesterol; IVUS, intravascular ultrasound; LDL-C, low density lipoprotein cholesterol; PCI, percutaneous coronary intervention; PV, plaque volume; PVD, polyvascular disease.

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disease in more than one vascular territories have worse long-term outcome irrespective of their baseline cardiovascular disease [5]. Large-scale randomized trials have also shown that patients with combined coronary and clinically evident noncoronary atherosclerosis in systemic arteries (polyvascular disease; PVD) had higher incidence of subsequent cardiovascular and total mortality compared to those with isolated coronary disease [4,6]. Therefore, patients with PVD seem to have greater propensity toward accelerated progression of atherosclerosis, although no previous data examined the impact of noncoronary vascular disease on the progression/regression of coronary atherosclerotic plaque in patients with CAD.

Intravascular ultrasound (IVUS) allows precise measurement of atheroma burden at baseline and follow-up, enabling calculation of progression/regression of atherosclerosis. The JAPAN-ACS (Japan assessment of pitavastatin and atorvastatin in acute coronary syndrome) study enrolled patients with acute coronary syndrome (ACS) who underwent IVUS at baseline and 8–12 months follow-up. The aim of the present study was to compare the effects of treatment with lipid-lowering agents on plaque regression between patients with CAD only and those with CAD and PVD (CAD + PVD).

2. Subjects, materials and methods

2.1. Study patients

The JAPAN-ACS is a prospective, randomized open-label parallel group study with blind endpoint evaluation at 33 centers to compare the effects of 8–12 months treatment with pitavastatin versus atorvastatin on coronary plaque regression in non-percutaneous coronary intervention (PCI) sites of the culprit vessel in patients with ACS [7]. An outline of the design of the present study was published before the dataset was locked. Briefly, all subjects were diagnosed as having ACS and received successful PCI to the culprit lesion under IVUS guidance. We defined ACS as an unstable angina pectoris, non-ST-segment elevation myocardial infarction or ST-segment elevation myocardial infarction. Patients who had been treated with lipid lowering agents were excluded. Patients had to have coronary plaques (>500 μm in thickness, or percent plaque area ≥ 20%) in the culprit vessel at least 5 mm apart from the PCI-treated lesions. The JAPAN-ACS study showed that intensive statin therapy with 4 mg/day of pitavastatin or 20 mg/day of atorvastatin in patients with ACS resulted in a significant regression of atheroma burden with negative vessel remodeling in a large-scale, multi-center trial using central IVUS core-laboratory. In addition, the study confirmed that the effects of pitavastatin were similar to those of atorvastatin.

Since there was no significant difference in percent change in plaque volume between the two statin groups, the following analyses were conducted using data of the entire group of patients. Patients were classified according to the presence or absence of PVD. Noncoronary atherosclerosis was defined as claudication, peripheral vascular surgery, thoracic/abdominal aortic aneurysm, history of cerebral ischemia, or carotid disease. Among 252 patients in whom serial IVUS examinations could be evaluated, 7 (2.8%) patients had previous cerebral infarction, 5 (2.0%) had aortic aneurysm and 10 (4.0%) had lower extremity disease. Three patients had atherosclerotic disease involving two peripheral vascular territories. Thus, 19 patients with history of preexisting noncoronary disease formed the CAD + PVD group, representing 7.5% of the study population. The remaining 233 patients formed the CAD-only group.

This study was conducted according to the 'Declaration of Helsinki', and with the approval of the institutional review boards of all 33 participating institutions. Written informed consent was obtained from each of the 19 and 233 patients.

2.2. IVUS study protocol

Intracoronary nitroglycerin (200 μg) was administered before angiography to prevent coronary artery spasm. The PCI strategy used was left to the discretion of the individual operator. All IVUS studies were performed with a commercially available system (Boston Scientific, Natick, MA) before any intervention. After intracoronary administration of another 200 μg of nitroglycerin, a 40-MHz IVUS catheter (Atlantis SR Pro2, Boston Scientific) was advanced as far distally as could be safely reached, and imaging was performed in a retrograde fashion to the aorto-ostial junction at an automatic pullback speed of 0.5 mm/s, facilitating observation of the lesion. IVUS examinations were performed at 8- to 12-month follow-up. The same imaging system with the same type of IVUS catheter was used for both the baseline and follow-up examinations.

Two independent experienced investigators analysed the IVUS quantitatively at the central core-laboratory. The target segment for analysis was a non-PCI site of the culprit vessel (>5 mm proximal or distal to the PCI site) based on some reproducible indices. Spotty calcification, side branch, and stent edge were used as the reproducible landmarks to synchronize the target plaque at baseline and at follow-up.

For each patient, the cross-sectional areas (CSA) of the external elastic membrane (EEM) and intravascular lumen were measured in accordance with the standards of the American College of Cardiology [8]. The luminal/intimal borders were traced manually to determine the lumen CSA. The EEM CSA, representing the area encompassed by the medial/adventitial border, was measured by tracing the leading edge of the adventitia to determine the CSA of the vessel. We traced every 6th image (0.1 mm apart) manually using a commercially available IVUS measurement software (echoPlaque2, INDEC systems Inc., Santa Clara, CA). This software automatically interpolated the tracings of 5 cross-sections between two manually traced images. Therefore, the volume was calculated from each of the 0.017 mm apart segments. Vessel volume and lumen volume were calculated using Simpson's rule. Plaque volume (PV) was calculated as vessel volume minus lumen volume.

2.3. Calculation of endpoints

The primary endpoint was the percent change in coronary PV during the follow-up period, calculated as:

$$\frac{\text{PV (follow up)} - \text{(baseline)}}{\text{PV (baseline)}} \times 100$$

The secondary endpoints were the nominal change in the percent PV (%PV) and nominal change of the normalized plaque volume (NPV), which compensated for the pullbacks of differing lengths. The %PV was calculated using the following formula:

$$\%\text{PV} = \frac{\Sigma(\text{EEM}_{\text{CSA}} - \text{LUMEN}_{\text{CSA}})}{\Sigma(\text{EEM}_{\text{CSA}})} \times 100$$

NPV was calculated as:

$$\text{NPV} = \text{PV} \times \frac{L_{\text{MED}}}{L_{\text{MEASURED}}}$$

where L_{MED} = the median value of the observed length in all subjects and L_{MEAURED} = the observed length for each plaque.