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Short communication

Impact of statin-ezetimibe combination on coronary atheroma plaque in patients with and without chronic kidney disease — Sub-analysis of PRECISE-IVUS trial

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ABSTRACT

Background: Chronic kidney disease (CKD) deteriorates the prognosis of patients undergoing percutaneous coronary intervention (PCI). Because coronary artery disease (CAD) is the major cause of death in CKD patients, cardiovascular risk reduction has been clinically important in CKD. We hypothesized intensive lipid-lowering with statin/ezetimibe attenuated coronary atherosclerotic development even in patients with CKD.

Methods: In the prospective, randomized, controlled, multicenter PRECISE-IVUS trial, 246 patients undergoing intravascular ultrasound (IVUS)-guided PCI were randomly assigned to receive atorvastatin/ezetimibe combination or atorvastatin alone (the dosage of atorvastatin was up-titrated to achieve the level of low-density lipoprotein cholesterol < 70 mg/dL). Serial volumetric IVUS findings obtained at baseline and 9–12 month follow-up to quantify the coronary plaque response in 202 patients were compared stratified by the presence or absence of CKD.

Results: CKD was observed in 52 patients (26%) among 202 enrolled patients. Compared with the non-CKD group, the CKD group was significantly older (71.5 ± 8.6 years vs. 64.4 ± 9.6 years, P < 0.001) with similar prevalence of comorbid coronary risk factors and lipid profiles. Similar to the non-CKD group (−1.4 [−2.8 to −0.1]% vs. −0.2 [−1.7 to 1.0]%, P = 0.002), the atorvastatin/ezetimibe combination significantly reduced ΔPAV compared with atorvastatin alone even in the CKD group (−2.6 [−5.6 to −0.4]% vs. −0.9 [−2.4 to 0.2]%, P = 0.04).

Conclusions: As with non-CKD, intensive lipid-lowering therapy with atorvastatin/ezetimibe demonstrated stronger coronary plaque regression effect even in patients with CKD compared with atorvastatin monotherapy.

Trial registration: NCT01043380 (ClinicalTrials.gov).

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1. Introduction

A recent study demonstrated dual lipid-lowering therapy (DLLT) with a combination of statin and ezetimibe successfully reduce cardiovascular events [1]. Furthermore, the benefit of DLLT on coronary plaque regression has been shown in PRECISE-IVUS (Plaque REgression with Cholesterol absorption Inhibition or Synthesis inhibitor Evaluated by IntraVascular UltraSound) trial we previously reported [2]. In these studies, the achieved levels of low-density lipoprotein cholesterol (LDL-C) were also correlated with reduction of cardiovascular events, or the change of coronary plaque atheroma volume, successfully demonstrating "the lower, the better" concept by DLLT with a combination of statins and ezetimibe.

Chronic kidney disease (CKD) impairs the prognosis of patients undergoing percutaneous coronary intervention (PCI). Because coronary artery disease (CAD) is the major cause of death in patients with CKD, cardiovascular risk reduction has been clinically important in CKD. We hypothesized that the intensive DLLT with the combination of statin and ezetimibe could attenuate coronary atherosclerotic development even in patients with CKD.

2. Methods

2.1. Study protocol of PRECISE-IVUS trial

In the prospective, randomized, controlled, multicenter PRECISE-IVUS trial, 246 patients undergoing intravascular ultrasound (IVUS)-guided PCI were randomly assigned to receive atorvastatin/ezetimibe combination or atorvastatin alone (the dosage of atorvastatin was up-titrated to achieve the level of LDL-C < 70 mg/dL) [2]. Serial volumetric IVUS findings obtained at baseline and 9–12 month follow-up to quantify the coronary plaque response in 202 patients were compared stratified by the presence or absence of CKD. Patients were classified into 2 groups based on the presence of CKD (Fig. 1A). We analyzed laboratory and IVUS data of each group.

The study complied with the Declaration of the Helsinki with respect to investigation in humans had been approved by institutional review committees, and conducted in accordance with the guidelines of the ethics committee at participating institutions. Written informed consent was obtained from all patients.

2.2. IVUS imaging for analysis of coronary plaque

Detailed methods of IVUS image recording was described previously [2]. Based on an expert consensus document paper, the primary endpoint was the absolute change in percent atheroma volume (ΔPAV) [3].

2.3. Definition of CKD

Definition of CKD is described in the Supplementary material.

2.4. Statistical analysis

Data are expressed as mean ± standard deviation for normally distributed variables, and those with non-normally skewed distributions are expressed as the medians with interquartile ranges. Continuous variables among groups were compared using the unpaired Student *t*-test or the Mann-Whitney *U* test, as appropriate. Categorical variables were compared using chi-square statistics or the Fisher's exact test. A P value < 0.05 was considered significant. Statistical analysis was performed using SPSS 23 for Macintosh (SPSS Inc., Tokyo, Japan). An expended method is available in the Supplementary material.

3. Results

Among the PRECISE-IVUS trial cohort, CKD was observed in 52 patients (26%) among 202 enrolled patients (Fig. 1A). There were no patients with end-stage kidney disease corresponding to CKD stage 5, because of exclusion criteria of the original PRECISE-IVUS study. The median follow-up periods of the CKD group and the non-CKD group were 284 [274 to 308] days and 285 [273 to 310] days, respectively. There was no significant difference in follow-up period between both groups. Compared with the non-CKD group, the CKD group was significantly older (71.5 ± 8.6 years vs. 64.4 ± 9.6 years, P < 0.001), and had higher ratio of using insulin (12% vs. 1%, P = 0.001) with similar prevalence of comorbid coronary risk factors (Supplementary Table 1). Paradoxically, the baseline levels of triglyceride, remnant like particle cholesterol, small dense LDL, and campesterol were significantly lower, and total adiponectin was significantly higher in the CKD group (Supplementary Table 1). In the baseline of patients with CKD, the DLLT group had similar backgrounds in age, the prevalence of

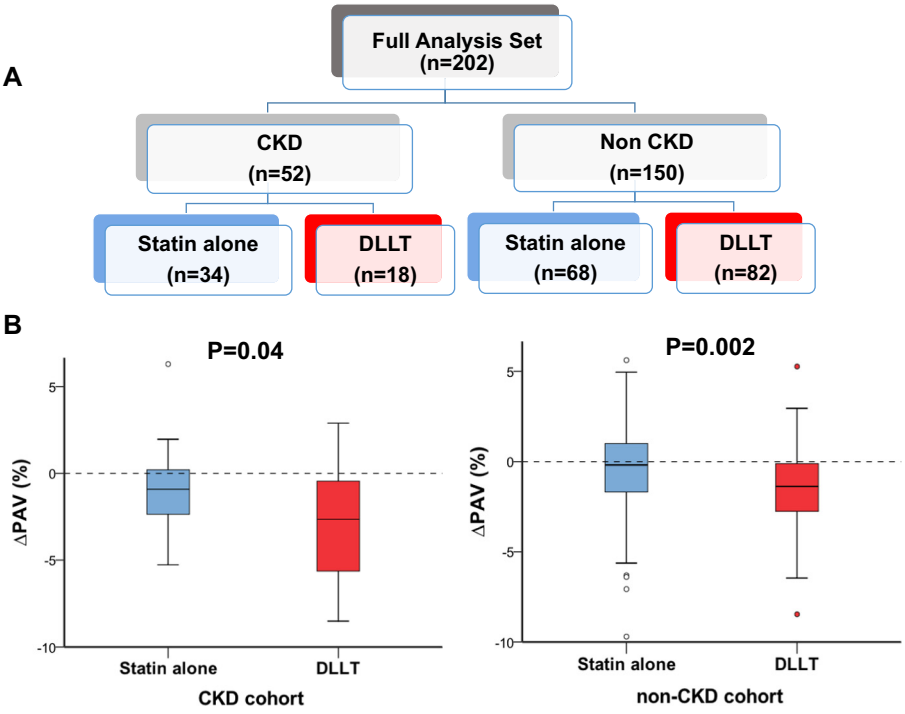

Fig. 1. Study flow chart and the rate of coronary plaque regression in patients with CKD and non-CKD. CKD, chronic kidney disease; DLLT, dual lipid lowering therapy with atorvastatin and ezetimibe; and PAV, percent atheroma volume. Data are median and interquartile range.

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