学 位 論 文 の 要 旨

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学　位　論　文　名　Prognostic Role of Apolipoproteins on Long-term Major Adverse Cardiac Events After Percutaneous Coronary Intervention

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論 文 内 容 の 要 旨

INTRODUCTION

Elevated low-density lipoprotein cholesterol (LDL-C) levels are associated with atherosclerotic cardiovascular disease (ASCVD). Although statin therapy is a well-established approach for the secondary prevention of ASCVD, it cannot completely prevent cardiovascular events after percutaneous coronary intervention (PCI). Apolipoprotein B (apo B) and apo A1 levels and the apo B/apo A1 ratio are markers for coronary risk even in patients receiving lipid-lowering therapy. A meta-analysis of combined primary and secondary prevention reported that lowering apo B levels with statins reduces the risk of cardiovascular events, independent of the reduction in LDL-C levels. However, the relationship between apo levels and ASCVD among patients undergoing PCI remains unclear. The apo B/apo A1 ratio during follow-up has been reported to have better predictive accuracy than the total cholesterol (T-Cho)/high-density lipoprotein cholesterol (HDL-C) ratio or lipoprotein (a) in the mid-term clinical outcomes of patients with LDL-C levels <70 mg/dL after PCI.

Therefore, this study aimed to investigate whether apo levels are more closely associated with long-term major adverse cardiac events (MACEs) than conventional lipid levels in patients undergoing PCI.

MATERIALS AND METHODS

This was a single-center, prospective, observational study. It used the clinical records of patients who underwent PCI between January 2004 and August 2008 at Masuda Red Cross Hospital. If the patient had undergone more than one PCI during the study period, the first PCI was considered as index PCI. We excluded patients; 1) who did not have all background data available, 2) who could not be followed for at least 5 years in spite of no events having occurred,

3) who had no follow-up coronary angiography (CAG), 4) who were scheduled for cardiac surgery, and 5) who did not consent to this study. The primary endpoint was MACE, which was defined as cardiac death, acute coronary syndrome, or coronary revascularization for new lesions. Scheduled PCI at the time of enrolment was not considered as a MACE. Target lesion revascularization for stable angina was also not included. The secondary endpoint was composite of cardiac death and acute coronary syndrome. Medical condition data from patients who did not visit our hospital were collected by letter or phone. Data for age, gender, height, weight, body mass index, smoking habits, risk factors for coronary artery disease, laboratory parameters, and cardiovascular medications at the time of follow-up CAG or MACE were obtained by checking hospital records.

The ethics committee of Masuda Red Cross Hospital approved this study (No. 39), which was conducted in accordance with the directives of the Helsinki Declaration. All patients provided informed consent before participation in this study. In all analyses, statistical significance was set at a P value of <0.05.

RESULTS AND DISCUSSION

During the follow-up period of the study, 458 patients underwent PCI, and 217 patients were excluded owing to lack of follow-up CAG, incomplete data, or lack of follow-up for at least 5 years if no MACE occurred. Twenty-five patients were not eligible because of the following reasons: 13 passed away on admission for initial PCI, 8 were distant residents, and 4 were scheduled for cardiac surgery after initial PCI. The remaining 192 patients were not included for the following reasons: 106 had incomplete apo or other data, 38 had no follow-up CAG because of advanced age or renal dysfunction, 28 had no data because of noncardiovascular death before follow-up CAG or MACE, 16 had unknown outcome within 5 years, 1 was suspected of AMI with CAG declined, 1 was recommended for CABG with refusal, and 2 had other reasons. As a result, we analyzed 241 patients in this study. The reasons for index PCI were as follows: 72 cases of acute myocardial infarction, 25 cases of unstable angina, and 144 cases of stable angina. The average follow-up is 2079 days from the date of index PCI. MACE occurred in 78 patients: 1 cardiac death, 10 non-fatal acute myocardial infarction, and 67 coronary revascularizations for new lesions. There were significant differences in age (P=0.009), female sex (P=0.009), height (P=0.03), weight (P=0.04), follow-up period (P<0.001), HDL-C (P=0.02), apo B (P=0.005), apo B/A1 ratio (P=0.003), LDL-C/HDL-C ratio (P=0.005), and non-HDL-C (P=0.02) between patients with and without MACE.

For the primary endpoint, age (P=0.03), female sex (P=0.02), HDL-C (P=0.04), apo B (P=0.006), apo B/apo A1 ratio (P=0.02), and non-HDL-C (P=0.03) were detected as predictors of long-term MACE after PCI in Cox proportional hazard models with univariate analysis.

Multivariate analysis with the addition of variables related to cardiovascular events showed that apo B was an independent prognostic factor (HR: 1.11, 95% CI: 1.03 to 1.20; P=0.009).

The Kaplan–Meier estimation with log-rank test showed that there was a significant difference in the incidence of MACEs between the two groups for apo B and apo B/apo A1 ratio (P=0.04 and P=0.004, respectively), whereas no significant difference was found for LDL-C and LDL-C/HDL-C ratio (P=0.07 and P=0.08, respectively).

In terms of secondary endpoints, the Cox proportional hazard models using univariate analysis revealed statistical disparities in HbA1c (P=0.03), hypertension (P=0.02), antiplatelet therapy (P=0.01), and the apo B/apo A1 ratio (P=0.02). The significant results of multivariate analysis were hypertension (HR: 0.27, 95% CI: 0.09 to 0.81; P=0.02), antiplatelet therapy (HR: 0.02, 95% CI: 0.002 to 0.16; P<0.001), and apo B/apo A1 ratio (HR: 13.66, 95% CI: 1.38 to 134.87; P=0.03). Although the difference between the two groups disappeared for apo B (P=0.206), the event rate was higher in the high apo B/apo A1 ratio group (P=0.007) in the Kaplan–Meier estimation with log-rank test. LDL-C and LDL-C/HDL-C ratio remained not significantly different (P=0.170, P=0.091, respectively).

This study found that long-term recurrence of cardiovascular events after PCI was closely associated with apo B and apo B/apo A1 ratio rather than with LDL-C and LDL-C/HDL-C ratio. High LDL-C and low HDL-C levels are associated with ASCVD. Apo A1, apo B, and apo B/apo A1 ratio have been suggested to be more useful predictors of ischemic heart disease than HDL-C, LDL-C, and LDL-C/HDL-C ratio. Meanwhile, there is little information on post-PCI patients. The apo B/apo A1 ratio was shown to be a better prognostic factor than the T-Cho/HDL-C ratio and lipoprotein (a) only in the mid-term follow-up of patients achieving LDL levels <70 mg/dL after PCI. We found an association between cardiovascular events and apos in this study, without limiting the patients with LDL-C levels <70 mg/dL and in the long-term, instead of in the mid-term after PCI.

There are several issues with apolipoproteins. There is insufficient information on the efficacy of treatment targeting apo B lowering, and even less information on apo A1 and apo B/apo A1 targeted interventions. In addition, therapeutic target values are not totally defined. Future studies are needed to resolve these issues.

Several limitations associated with the present study warrant mention. This study was a single-center prospective observational study with a small sample size. Medical therapy and indications for PCI would differ from the current situation.

CONCLUSION

Apo B and apo B/apo A1 ratio were found to be better prognostic predictors of long-term MACEs than LDL-C and LDL-C/HDL-C ratio in patients who have undergone PCI. The use of

apos in addition to conventional lipid markers could lead to better medical therapy, resulting in prevention of recurrent ischemic heart disease.