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Serum Levels of PCSK9 Are Associated with Coronary Angiographic Severity in Patients with Acute Coronary Syndrome (*Diabetes Metab J* 2018;42:207-14)

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We appreciate Dr. Kim expressing interest and giving a valuable comments on our article entitled "Serum levels of PCSK9 are associated with coronary angiographic severity in patients with acute coronary syndrome" which was published in *Diabetes & Metabolism Journal* [1].

Proprotein convertase subtilisin/kexin type 9 (PCSK9) has an important role in homeostasis of low density lipoprotein cholesterol (LDL-C). A high level of LDL-C is a major risk factor for cardiovascular diseases, and several studies have shown that PCSK9 levels are associated with the incidence of coronary artery disease (CAD) [2]. Moreover, considering only a few patients who are taking high intensity statin due to acute coronary syndrome (ACS) reach the long-term target goal of LDL-C [3,4], up-regulation of PCSK9 levels is one alternative option for the patients who have statin resistance [5]. Therefore, these evidences suggest that PCSK9 has an important prognostic value of ACS. However, the results of studies that investigated the prognostic value of PCSK9 for ACS have not been consistent. One study reported that high plasma levels of PCSK9 were associated with poor controlled LDL-C 1 year after ACS, but did not predict mortality [6]. Another study reported that PCSK9 concentrations predict cardiovascular events in patients with CAD for up to 4 years follow-up [7].

Furthermore, the effects of PCSK9 on vascular cells and cardiomyocytes have not been extensively studied. PCSK9 may affect atherosclerosis via regulation of LDL-C and oxidized LDL plasma concentrations [8,9]. The increased vascular expression of PCSK9 may correlate with high levels of reactive oxygen species and inflammation [6]. PCSK9 exerts direct effects on plaque composition, and this is independent from LDL-C but related to LDL-receptor expression [10,11]. However, a role of PCSK9 on cardiomyocytes has not been clearly established. Experimental study reported that PCSK9 increased levels of oxidized LDL, and induced the expression of brain natriuretic peptide (BNP) on HL1 cells [12]. One recent study reported that levels of PCSK9 and LDL-receptor was associated with outcomes in patients with heart failure [13]. In our study, levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) was positively associated with PCSK9 levels (Fig. 1A, unpublished data). Although there was no statistical significance in the association between ejection fraction on echocardiography and levels of PCSK9, NT-proBNP was still significantly associated with PCSK9 after adjusting multiple confounding factors (Fig. 1B, unpublished data). Though, it is difficult to interpret this result with our own investigation, it may be helpful to investigate the effect of PCSK9 on vascular cells and cardiomyocytes in the future.

We totally agree with Dr. Kim's suggestion to perform multicenter cohort study involving female subjects considering menopause. In several studies, levels of PCSK9 were higher in women than in men, and in postmenopausal women than in premenopausal women [14,15]. Therefore, it is necessary to

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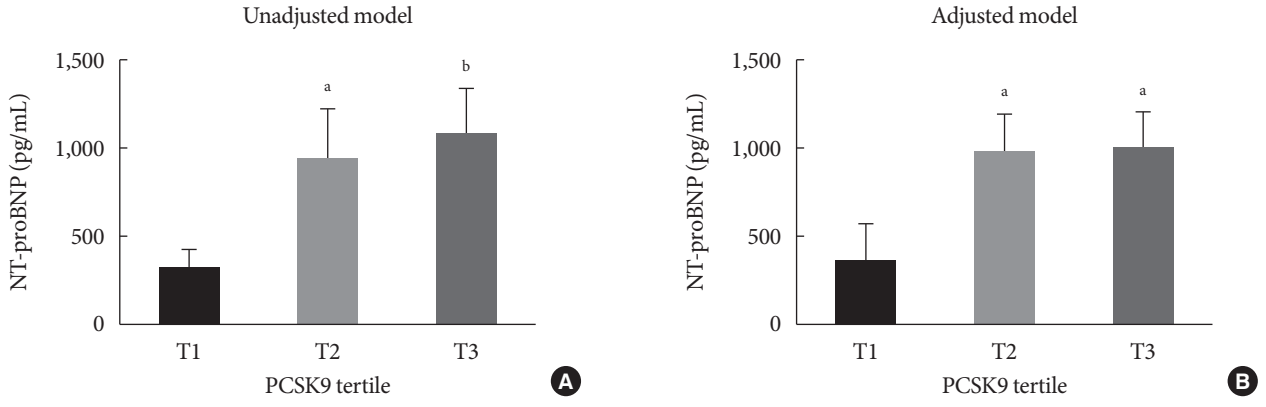

Fig. 1. Levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) according to serum proprotein convertase subtilisin/kexin type 9 (PCSK9) tertiles. Unadjusted model (A) and adjusted model (B). Model is adjusted for age, body mass index, past history of hypertension and diabetes mellitus, familial history of ischemic heart disease, and smoking. [a]$P<0.05$, [b]$P<0.01$.

consider the differences of PCSK9 levels according to gender and menopause status. As mentioned before, since the prognostic value of circulating PCSK9 levels has not been established yet, multicenter prospective cohort study is needed to elucidate the relevance of PCSK9 levels in recurrence rate after coronary intervention. Since the use of statins has a preventive effect on CAD but increases serum PCSK9 levels, making it difficult to assess the CAD predict value of PCSK9 in patients using statins. In line with, given that statin also influences on other circulating biomarker levels in high risk patients for ACS, there may be adversity to investigate the relevance of circulating PCSK9 to other biomarkers. Nevertheless, it might be interesting study to investigate the association of circulating PCSK9 levels to other biomarkers of ACS.

Thank you for your interests in our study and thoughtful comments.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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