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Editorial

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Optimal Cut-off Points of Triglycerides for Cardiovascular Disease Prediction in Japanese Population

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Previous studies have suggested that elevated triglyceride (TG) levels in fasting and nonfasting state were risk factors for cardiovascular disease (CVD). Elevated TG levels are caused by an increase in TG-rich lipoproteins, such as remnant lipoproteins and small dense low-density lipoprotein (LDL) of which particles are small enough to penetrate the arterial intima, and the contained cholesterol is easily accumulated in the arterial wall. TG levels gradually increase after a meal, reaching a peak 4–6 hours later and decreasing to the nonfasting TG levels 8–10 hours after a meal. Elevated levels of nonfasting TG strongly reflect the increase in remnant lipoprotein. Accordingly, nonfasting TG could be a better predictor of CVD.

Nowadays, some guidelines recommend cut-off points of TG for CVD risk prediction, and fasting TG cut-off points of 150 mg/dL or higher are proposed widely by guidelines, including the Japan Atherosclerosis Society (JAS) Guidelines[1]. Nonfasting TG cut-off points of 200 mg/dL or higher are proposed by a scientific statement from the American Heart Association[2] and 175 mg/dL or higher by the European Atherosclerosis Society and the European Federation of Clinical Chemistry and Laboratory Medicine[3]. However, unfortunately, the rationale for these cut-off points is insufficient, particularly in Japan, where a few studies have examined the impact of TG fasting and nonfasting, respectively, on CVD events in the general population.

Imano H, *et al.* explored the cut-off points of fasting and nonfasting TG, respectively, for ischemic heart disease prediction in the Circulatory Risk in Communities Study (CIRCS) in a general Japanese population[4]. They determined a cut-off point of 110mg/dL for fasting TG and 145 mg/dL for nonfasting TG with a C-statistic of 0.594 and 0.626, respectively, and confirmed the optimal cut-off points by estimating multivariable hazard ratios and population attributable fractions. These cut-off points were lower than those recommended using current guidelines. The Women's Health Study in the United States (US) using a similar method has reported that the optimal cut-off point of nonfasting TG for predicting cardiovascular disease was 175 mg/dL with a C-statistic of 0.656 [5]. The fasting TG cut-off point of 150 mg/dL or higher in Japan was originally defined from the findings of the Framingham study in the US, and it was established owing to the fact that some studies from Japan also showed that fasting TG of 150 mg/dL or higher increased the risk of coronary artery disease. Meanwhile, CIRCS has shown a positive linear association between fasting and nonfasting TG levels and ischemic CVD in a general Japanese population, which suggests that fasting and nonfasting TG levels, respectively, at risk are lower than those levels in other countries[6]. This means that the higher the TG level, the higher the potential risk of developing ischemic CVD in the general Japanese population, regardless of the cut-off point.

Meanwhile, the C-statistic from these two studies was around 0.60, which is not designated as a high prediction. This may reflect the fact that lipids beyond TG, such as LDL-C or nonhigh-density cholesterol lipoprotein (non-HDL-C), and other strong risk factors, such as hypertension, affect the increased risk of CVD. Indeed, LDL-C or non-HDL-C is recommended as the primary target of dyslipidemia management for CVD prevention based on evidence from previous studies. Additionally, as mentioned earlier, the contained cholesterol in TG-rich lipoprotein, rather than elevated TG per se, could be a direct cause of atherosclerosis. Considering these

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findings, the impact of TG on cardiovascular disease could be easily affected by factors other than TG per se, such as the metabolism or CVD risks related to the background characteristics (e.g., age and nutritional status).

The findings of Imano H, *et al.* differed from those from other countries and even from Japan. Previous studies from Japan have shown that a fasting TG of 155 mg/dL or higher was significantly associated with ischemic CVD events compared to 87–112 mg/dL of fasting TG in urban residents[7], and a fasting TG of 200 mg/dL or higher was significantly associated with myocardial infarction compared with a fasting TG of 100 mg/dL among workers[8]. Another study from Japan has reported a positive association between nonfasting TG and cardiovascular disease mortality risk in the population aged under 65 years, with increased risk at nonfasting TG of 210 mg/dL or higher, but a negative association between nonfasting TG and the risk in those aged 65 years or older[9]. These findings suggest that the impact of TG on CVD varies depending on several factors including unmeasured factors. Additionally, it means that TG values need to be managed with appropriate cut-off points for different characteristics. Furthermore, if the cut-off points proposed by Imano H, *et al.* are used, numerous people will require medical care or health guidance, which directly affect medical resources and increase additional costs for this purpose. There are few findings in Japan, particularly on nonfasting TG, thus further studies are warranted.

Conflicts of Interest

None.

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