

## Triglycerides on the Rise!

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### Triglycerides on the Rise!

We already know that LDL cholesterol is one of the causal factors for cardiovascular disease (CVD)<sup>1)</sup>. In fact, we are using statins, ezetimibe, and a PCSK9 inhibitor to achieve further reduction in LDL cholesterol, more than ever<sup>1)</sup>. On the other hand, serum triglycerides have also been suggested to be an important causal factor for CVD<sup>2)</sup>; however, awareness regarding this issue is still inadequate in local communities and in hospital settings<sup>3)</sup>. According to a national survey published by the Ministry of Health, Labor, and Welfare of Japan, serum triglyceride levels in the general population have increased, especially in the elderly population in the last decade under suboptimal treatments; whereas the LDL cholesterol levels have remain unchanged under more frequent treatments<sup>4)</sup> (Fig. 1).

Under these circumstances, we now have several options to effectively reduce serum triglycerides, such as polyunsaturated fatty acid (PUFA) and selective peroxisome proliferator-activated receptor  $\alpha$  modulator (SPPARM $\alpha$ ) in addition to statin therapy<sup>5)</sup>. Moreover, several other treatments targeting particular molecules, such as angiopoietin-like 3 (ANGPTL3) inhibitor and apolipoprotein C3 (APOC3) inhibitor, are now being developed. In that sense, the current situation should be considered as both the interest in treatments as well as serum triglyceride levels in the general population are on the rise. In this article, Higashiyama, *et al.* showed an important evidence that fasting triglycerides are associated with CVD events among Japanese population, based on a cohort study in urban areas<sup>6)</sup>. In the past, there have been a

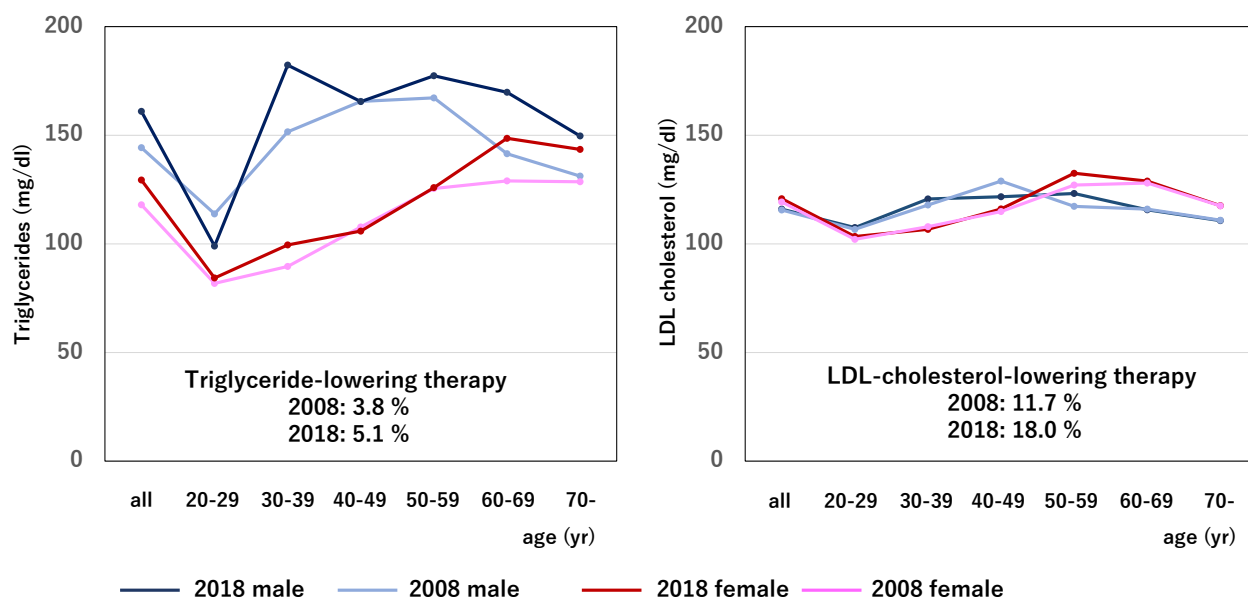
few epidemiological studies to clarify this issue, such as the Circulatory Risk in Communities Study (CIRCS)<sup>7)</sup>, and the Japan Diabetes Complications Study (JDCS)<sup>8)</sup>. Now, we are quite confident that triglycerides levels are associated with CVD events among Japanese population. What else do we need to know? There are a couple of issues that need to be clarified: 1) fasting or non-fasting, 2) threshold, 3) how do we treat, and 4) lower the better.

### Fasting or Non-Fasting?

Given that serum triglycerides are associated with CVD, there have been many debates and discussions about which is better, fasting or non-fasting. In this regard, it has been shown that fasting and non-fasting triglycerides are associated with CVD events among Japanese<sup>9)</sup>. Accordingly, both indices are good enough to assess the risk for CVD.

### Threshold

Currently, we are using a threshold of <150 mg/dL triglycerides in fasting state, regardless of their other state of risk. However, some people argue that the measurements of triglycerides for most of the patients are performed in the non-fasting state, lowering our motivation to reduce, or even assess their triglycerides. It is difficult to set a clear threshold of triglycerides, especially, in the non-fasting state, because they usually fluctuate after the meal. At present, the European Atherosclerosis Society (EAS) provides a good example in this matter, suggesting that 175 mg/dL in the non-fasting state would be a useful threshold for hypertriglyceridemia<sup>10)</sup>.



**Fig. 1.** Changes in serum triglycerides and LDL cholesterol among general population

X-axis represents age. Y-axis represents triglycerides (left), and LDL cholesterol (right).

Dark blue indicates male (2018)

Light blue indicates male (2008)

Red indicates female (2018)

Pink indicates female (2008)

### How do We Treat?

Based on the notion that triglycerides appear to be causally associated with CVD, this should also be considered to combat the residual risk. Currently, there are many agents to lower triglycerides besides statins, including PUFA and SPPARM $\alpha$ . Several more, such as ANGPTL3 inhibitor and APOC3 inhibitor will be coming soon. We need more detailed data to determine which agents are better for whom and for what reasons. Those pieces of information should collectively lead to the development of more advanced personalized medicine to combat the residual risk of CVD.

### Lower the Better?

Finally, we come up with the simple question of whether lower triglycerides are better. We believe the answer is yes, because of the fact that we have never encountered a case of CVD because the serum triglycerides were too low.

### Conclusion

Thus, the epidemiological evidence has consistently assured that triglycerides in fasting and

non-fasting state are associated with CVD among Japanese populations. However, serum triglyceride levels exhibit a rising trend, in contrast to LDL cholesterol, suggesting that serum triglyceride level is becoming much more important as a residual risk factor for CVD in the Japanese population.

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