Effect of eicosapentaenoic acid/docosahexaenoic acid on coronary high-intensity plaques detected with non-contrast T1-weighted imaging: subgroup analysis of the AQUAMARINE EPA/DHA study

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Background: In the recent the Reduction of Cardiovascular Events with EPA-Intervention Trial (REDUCE-IT), statin therapy plus high-dose eicosapentaenoic acid (EPA) significantly reduced the risk of cardiovascular death in patients with coronary artery disease (CAD) with elevated triglyceride (TG) levels. An epidemiologic study has shown that increasing the intake of long-chain n-3 polyunsaturated fatty acids, especially EPA and docosahexaenoic acid (DHA), are associated with a lower risk of fatal CAD. However, the anti-atherosclerotic effect of high-dose EPA/DHA has not be clarified.

We reported that coronary high-intensity plaques (HIPs) detected with non-contrast T1-weighted imaging (T1WI) on cardiac magnetic resonance (CMR), which can be uniquely quantitative assessed using the plaque-to-myocardium signal intensity ratio (PMR) of $\geq$1.4, are significantly associated with future coronary events. Moreover, we demonstrated that intensive statin therapy reduces the PMR of coronary HIPs by 19% but is unlikely to completely resolve HIP (PMR$<$1.0).

In the AQUAMARINE EPA/DHA study, our goal was to assess the anti-atherogenic effect of EPA/DHA in an exploratory manner by examining the change in PMR of coronary HIPs after 12 months of EPA/DHA therapy in patients with CAD on statin therapy.

Methods: This study was designed as a single-center, triple-arm, parallel-group, randomized controlled, open-label, superiority trial examining the effect of 12 months of additional EPA/DHA therapy on coronary HIPs in patients with CAD who receiving statin therapy. Eligible subjects are randomly assigned to the 2 g/day EPA/DHA group (n=26), the 4 g/day group (n=23), or the no EPA/DHA (statin-only) group (n=24) between May 2014 and December 2017. The PMR was defined as the signal intensity of the coronary plaque divided by that of nearby left ventricular myocardium. The primary endpoint is the change in PMR after EPA/DHA treatment.

Results: These 3 groups were well matched at baseline, with no statistically significant differences in age, male sex, conventional coronary risk factors, TG level, medications, and PMR. Figure 1 shows subgroup analysis of patients with high triglyceride levels ($>$150mg/dl). In the patient-based analysis (A), 12 months of EPA/DHA therapy significantly reduced the PMR of primary lesions. In the segment-based analysis (B), additional reduction of PMR was observed in the high-dose EPA/DHA group compared with the no EPA/DHA treatment group.

Discussion: The present study of patients with high triglyceride levels demonstrated that EPA/DHA had a dose-dependent anti-atherosclerotic effect. This finding may provide additional information of EPA/DHA for lowering the residual risk in patients with CAD on statin therapy.

Figure 1: % change in PMR of coronary high risk plaques detected by CMR after 12 month of EPA/DHA therapy :Sub group analysis in patients with high triglyceride levels(>150mg/dl)