**What is the difference between using TG levels as an identifier of CV risk and correlating lowering TG levels and lowering CV risk?**

There are substantial data linking elevated TG levels to increased cardiovascular risk. See the publications section of this website for a chart which lists published references supporting this correlation between increased TG levels and increased CV risk.

However, excluding the results of the REDUCE-IT and JELIS studies, cardiovascular outcomes studies of therapies which lowered TG levels have not demonstrated CV benefit.

In REDUCE-IT, TG levels were used to identify patients with elevated CV risk. Treating such patients with Vascepa lowered their TG levels. However, the level of CV benefit was disproportionately larger than the level of TG reduction. There was a similar finding in the JELIS study. And, interestingly in REDUCE-IT, as noted in *NEJM*:

> "The observed cardiovascular benefits were similar across baseline levels of triglycerides (<150, ≥150 to <200, and ≥200 mg per deciliter). In addition, the significantly lower risk of major adverse cardiovascular events with icosapent ethyl than with placebo appeared to occur irrespective of the attained triglyceride level at 1 year (≥150 or <150 mg per deciliter), which suggests that the cardiovascular risk reduction was not associated with attainment of a more normal triglyceride level. These observations suggest that at least some of the effect of icosapent ethyl that resulted in a lower risk of ischemic events than that with placebo may be explained by metabolic effects other than a reduction of triglyceride levels."[1]

The degree to which lowering TG levels, as demonstrated by Vascepa, contributed to the successful REDUCE-IT outcomes study results is unknown. Mechanisms responsible for Vascepa's effects in the REDUCE-IT study were not directly evaluated in the outcomes study. Independent of REDUCE-IT, Amarin has worked to further support the REDUCE-IT thesis with published scientific findings based on various degrees of evidence that show that icosapent ethyl may interrupt the atherosclerotic processes (e.g., plaque formation and instability) by beneficially affecting cellular functions thought to contribute to atherosclerosis and cardiovascular events and by beneficially affecting lipid, lipoprotein and inflammation biomarkers.[1]

[1] Bhatt DL, Steg PG, Miller M, et al. Cardiovascular Risk Reduction with Icosapent Ethyl in Hypertriglyceridemia. N Engl J Med. 2018. Nejm.org/doi/full/10.1056/NEJMoa1812792