The National Lipid Association has created this educational guide to assist clinicians in the management of residual cardiovascular risk with triglyceride-lowering therapies in their high-risk patients.

### On Triglyceride Lowering...
Evidence from epidemiologic and Mendelian randomization studies supports an association between triglyceride (TG) elevation and cardiovascular (CV) risk.

**Clinical Trial Results**
Clinical trial results have been mixed, but there are data to support a role of TG lowering for reducing adverse CV events in patients with elevated TGs.

**Primary Sources**
Primary and secondary prevention data in subgroups with elevated TGs from studies with fibrates. Japanese EPA Lipid Intervention Study (JELIS): Japanese population with and without cardiovascular disease (CVD) given eicosapentaenoic acid (EPA) —> reduced events (no placebo control) Reduction of Cardiovascular Events with EPA - Intervention Trial (REDUCE-IT)

### Omega-3 Fatty Acids in ASCVD Risk Reduction
There are biologically plausible mechanisms for atherosclerotic cardiovascular disease (ASCVD) risk reduction with therapeutic application of omega-3 fatty acids.

**Results from REDUCE-IT**
Results from REDUCE-IT provide strong evidence for reduced CV events with 4 g/day icosapent ethyl (IPE; EPA ethyl esters) when added to statin therapy in patients with high or very high ASCVD risk.

**About STRENGTH...**
An outcomes study on omega-3 carboxylic acids, “Outcomes Study to Assess Statin Residual Risk Reduction With EpaNova in High CV Risk PatienTs With Hypertriglyceridemia (STRENGTH)” was stopped in February 2020 due to futility.

EPA + DHA
There are questions remaining about the efficacy of EPA compared to EPA + docosahexaenoic acid (DHA).

### REDUCE-IT: Study Design

#### Screening Period
- **Key Inclusion Criteria**
  - Statin treated men & women ≥ 45 yrs
  - Established CVD (e.g., patient) or T2DM + ≥1 risk factor
  - TG ≥150 mg/dL and <500 mg/dL
  - LDL-C >40 mg/dL and <100 mg/dL

- **Lead-In**
  - Statin stabilization
  - Medication washout
  - TG qualification

#### Double-Blind Treatment/Follow-up Period
- **Randomization**
  - 1:1 Randomization with continuation of statin therapy (N=4000)

- **Follow-up (up to =6.5 years)**
  - 4 months, 12 months, Annually

- **End-of-Study Follow-up Visit**

#### Primary Endpoint
Time to the first occurrence of composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, unstable angina

#### Results from REDUCE-IT: Cardiovascular Endpoints

### Data Summary
- **N = 8179; mean age 64 years**
- High or very high ASCVD risk with TG 135-499 mg/dL while on a statin
- Median follow-up 4.9 years

**Primary Composite**
CV death, MI, stroke, coronary revascularization, and unstable angina

**Key Secondary Composite**
CV death, MI and stroke
established cardiovascular disease or diabetes mellitus and 2 or more risk factors were mixed. The reasons for the mixed results in prior studies include 3 main issues:

1. The use of long-chain omega-3 fatty acids, results from clinical trials prior to REDUCE-IT

2. An old fisherman’s tale or a great catch?

3. Omega-3 fatty acids in ASCVD risk reduction: An old fisherman’s tale or a great catch?

The 2 large-scale studies (JELIS and REDUCE-IT) that have used dosages ≥1.8 g/day of EPA alone have shown statistically significant reductions in major adverse cardiac or CV events.

Based on results from studies of statins and fibrates...

The predicted risk reduction based on differences in non-HDL-C is closer to 10%

Other mechanisms are hypothesized to account for the further risk reduction...

(e.g., reductions in inflammation, oxidation, platelet activation, vascular dysfunction, blood pressure, cardiac fibrosis, etc.)

Omega-3 fatty acids in ASCVD risk reduction:

A great catch! Although there are biologically plausible mechanisms for CV risk reduction with the use of long-chain omega-3 fatty acids, results from clinical trials prior to REDUCE-IT were mixed. The reasons for the mixed results in prior studies include 3 main issues:

1. Low dosages of omega-3 fatty acids in most trials (<1 g/day EPA + DHA);
2. No targeted level of biomarker status; because omega-3 fatty acids are also in food and baseline tissue levels vary between individuals;
3. Subjects were generallynot selected to have a metabolic or other disorder that would be addressed by increasing omega-3 fatty acids (i.e., hypertriglyceridemia, inflammation, increased platelet activation).

In REDUCE-IT, the NLA Scientific Statement describes the following patients for which treatment with IPE is recommended:

- Patients ≥45 years of age with clinical ASCVD, or ≥50 years of age with diabetes mellitus requiring medication plus ≥1 additional risk factor, with fasting TGs 135-499 mg/dL on high-intensity or maximally tolerated statin therapy (ezetimibe);
- Subjects were generally not selected to have a metabolic or other disorder that would be addressed by increasing omega-3 fatty acids (i.e., hypertriglyceridemia, inflammation, increased platelet activation).

Additional research is needed to define the mechanisms responsible for the CV benefits given the out-of-proportion CV event reduction compared to non-HDL-C lowering noted in REDUCE-IT.

Vascepa® is an ethyl ester of eicosapentaenoic acid (EPA) indicated as:

- An adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated TG levels (≥150 mg/dL) and disorders characterized by increased cardiovascular risk;
- An adjunct to diet to reduce TG levels in adult patients with severe hypertriglyceridemia (TGs ≥ 500 mg/dL).

Who is the right patient?

The European Society of Cardiology/European Atherosclerosis Society, American Diabetes Association, and the National Lipid Association (NLA) have all released statements regarding treating patients with high risk of ASCVD for the reduction of CV events. Based primarily on results from REDUCE-IT, the NLA Scientific Statement describes the following patients for which treatment with IPE is recommended:

Patients ≥45 years of age with clinical ASCVD, or ≥50 years of age with diabetes mellitus requiring medication plus ≥1 additional risk factor, with fasting TGs 135-499 mg/dL on high-intensity or maximally tolerated statin therapy (ezetimibe).

Caution should be considered in patients prone to:

- Peripheral edema
- Atrial fibrillation
- Bleeding

Meet Catherine, a patient with known atherosclerotic cardiovascular disease (ASCVD).

Patient Case Questions

1. According to the 2018 American Heart Association/American College of Cardiology/Multisociety Guideline on the Management of Blood Cholesterol, what would be the best next step to consider in Catherine’s lipid management?
   a. Stop; She’s at Goal
   b. Colesevelam 625 mg 6 times per day
   c. Evolocumab 140 mg every 2 weeks subs敢antaneous
   d. Aspirin 81 mg daily

2. Based on Catherine’s current lipid profile and very high ASCVD risk, what would be an appropriate alternative or supplemental step to manage her dyslipidemia and ASCVD risk?
   a. Fenofibrate 120 mg daily
   b. Icosapent Ethyl 2 g BID
   c. Omega-3-Acid Ethyl Esters 4 g daily
   d. Fish oil supplement 1000 mg daily

ANSWERS
Frequently Asked Questions

**Q** How high does the TG level need to be for IPE to produce a benefit?

**A** REDUCE-IT showed CV event reduction in patients with TG 135 mg/dL to 499 mg/dL.

**Q** Is the other currently available prescription omega-3 product containing EPA + DHA also effective for reducing MACE risk?

**A** While there is suggestive evidence of benefit of reducing MACE risk in some trials with lower dosages (1 g/day) of EPA + DHA ethyl esters, the best evidence available to date is for EPA alone at a dosage of 4 g/d of IPE.

**Q** If a patient has a difficult time taking 4 capsules per day of IPE, could 2 capsules per day be used?

**A** The strongest evidence for benefit of IPE was from REDUCE-IT with 4 capsules/day. In a different population, JELIS demonstrated a 19% MACE risk reduction with a similar product containing an amount of EPA similar to that delivered in 2 capsules/day of IPE, albeit on top of a baseline diet rich in dietary omega-3 fatty acids in Japan. Thus, while 4 g/day of IPE is recommended, there may be benefit with 2 capsules per day for patients who are unable to take the full dosage.

**Q** How important is TG-lowering for MACE risk reduction with IPE?

**A** It is likely that TG lowering contributed to the MACE risk reduction in REDUCE-IT, but TG lowering alone does not appear likely to explain the full benefit. Additional mechanisms that could be contributing include effects on platelet action, inflammation, oxidation, blood pressure and endothelial function.

**Q** Would IPE be effective for lowering MACE risk in a patient who is statin-intolerant?

**A** At present it is unknown whether IPE will be effective for lowering MACE risk in patients who are not taking a statin (e.g., due to statin intolerance). Data from trials of lower dosages of omega-3 fatty acids suggest a potential benefit in people who are not taking statins, but this will need to be explored further in additional clinical trials. It is important to remember that regardless of TG levels, statins are indicated as the first-line drug therapy for primary and secondary prevention of ASCVD.

**Q** Should I be worried about IPE-induced increased bleeding risk, especially in my patients already on aspirin and/or clopidogrel etc.?

**A** High doses (3-15 g/day) of fish oil supplements are known to increase bleeding times via omega-3 polyunsaturated fatty acids’ suppression of platelet activation. However, recent meta-analyses of primary and secondary CV prevention trials of over 45,000 subjects have not demonstrated an increased risk for major bleeding events with omega-3 fatty acid supplementation. REDUCE-IT, which did not exclude patients taking anticoagulant medications, showed a near significant increase in non-serious bleeding events (IPE, 2.7% and placebo, 2.1%; p = 0.06).

**Q** Is IPE covered by insurance?

**A** IPE is covered by some Medicare and insurance plans. Co-pay may vary from approximately $25 to $328 per month if deductibles are met. There are also assistance programs such as co-pay cards and need-based programs. Without insurance, 1-g liquid-filled capsules (#120) are approximately $378 estimated retail price.

**Q** What are possible side-effects of icosapent ethyl? Does it have a fishy after-taste?

**A** All medications can have possible side effects. The dosing suggested is 2 capsules, twice daily. Clinicians should suggest patients take IPE with food, such as breakfast and dinner, to help reduce fishy after-taste, increase absorption and maximize bioavailability. A rare side effect that has been reported, but not in REDUCE-IT, is joint pain (arthralgia). Patients should contact their healthcare provider immediately if this is noted.