

**Assessment of Omega-3 Carboxylic Acids in Statin Treated Patients
with High Levels of Triglycerides and Low Levels of High Density
Lipoprotein Cholesterol:**

Rationale and Design of the STRENGTH Trial

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Conflicts of Interest

SJN has received research support: AstraZeneca, Amgen, Anthera, Eli Lilly, Esperion, Novartis, Cerenis, The Medicines Company, Resverlogix, InfraRedx, Roche, Sanofi-Regeneron and LipoScience and is a consultant for AstraZeneca, Eli Lilly, Anthera, Omthera, Merck, Takeda, Resverlogix, Sanofi-Regeneron, CSL Behring, Esperion, Boehringer Ingelheim. AML reports receiving grant support, through a research contract with his institution, from Eli Lilly, AstraZeneca, Roche, CSL Behring, Esperion, and AbbVie. CMB received grant/research support (all significant [$>$ \$10,000] and paid to institution, not individual) from: Abbott Diagnostic, Amarin, Amgen Inc, Esperion, Ionis, Novartis, Pfizer, Regeneron, Roche Diagnostic, Sanofi-Synthelabo, NIH, AHA, ADA; and served as a consultant (significant [$>$ \$10,000] denoted by *) for: Abbott Diagnostics, Amarin, Amgen Inc, Astra Zeneca*, Boehringer Ingelheim*, Eli Lilly, Esperion, Ionis, Matinas BioPharma Inc, Merck*, Novartis, Pfizer*, Regeneron, Roche Diagnostic, Sanofi-Synthelabo*. PJB reports Research Grants received from Merck, Pfizer, honoraria received from Amgen, Astra-Zeneca, Merck, Pfizer, Sanofi-Regeneron and is a member of Advisory Boards: Amgen, Merck, Pfizer, Sanofi-Regeneron. MHD has received

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consultant and advisory board fees and honoraria and has participated in speaker's bureaus for AstraZeneca, Sanofi, Regeneron and Amgen. He reports holding equity in Omthera Pharmaceuticals. JPK received personal consulting fees from: Sanofi, Affiris, Akarna Therapeutics, Amgen Inc, CSL Behring, Regeneron, Staten Biotech, Madrigal, The Medicines Company, Kowa, Lilly, Esperion, Gemphire, Ionis Pharmaceuticals, Akcea Pharmaceuticals. WK reports modest consultation fees for advisory board meetings from Novartis, Pfizer, Kowa, Amgen, and AstraZeneca and modest personal fees for lectures from Novartis, Sanofi and Amgen. DKM reports Clinical trial leadership: AstraZeneca, Sanofi Aventis, Janssen, Boehringer Ingelheim, Merck & Co, Novo Nordisk, Lexicon, Eisai, GlaxoSmithKline, Esperion; Consultancy: AstraZeneca, Sanofi Aventis, Lilly US, Boehringer Ingelheim, Merck & Co, Pfizer, Novo Nordisk and Metavant. DM reports personal fees from Acasti Pharma, AstraZeneca, GOED, DSM, Nutrition Impact, Pollock Communications, Bunge, and Indigo Agriculture; royalties from UpToDate for online medical chapters; scientific advisory board, Omada Health and Elysium Health; and research funding from the National Institutes of Health and the Gates Foundation; all outside the present work. TRP reports grants and personal fees from Merck, Pfizer and Amgen. PMK has received research grant support from Kowa, Novartis, and Pfizer and served as a consultant to AstraZeneca during the course of this trial. KKR reports grants and/or personal fees from Pfizer, MSD, Astra Zeneca, Sanofi, Aegerion, Regeneron, Abbvie, Kowa, Cerenis, Medicines Company, Lilly, Esperion, Amgen, Cipla, Algorithm, Takeda, Boehringer Ingelheim and Novo Nordisk within the last 12 months outside of the submitted work. BWK and TL are employees of AstraZeneca Pharmaceuticals. SEN reports that the Cleveland Clinic Center for Clinical Research has received funding to perform clinical trials from Abbvie, AstraZeneca, Amgen Inc, Cerenis, Eli Lilly, Esperion, Pfizer, The Medicines Company, Takeda, and Orexigen. Dr.

Nissen is involved in these clinical trials, but receives no personal remuneration for his participation. Dr. Nissen consults for many pharmaceutical companies, but requires them to donate all honoraria or consulting fees directly to charity so that he receives neither income nor a tax deduction. DB and KW have no industry relationships to disclose.

Abstract

Background: It is uncertain whether omega-3 fatty acids are beneficial in statin-treated patients. Epanova is a mix of omega-3 free fatty acids, not requiring co-ingestion with food, which can lower triglycerides by up to 31%. STRENGTH will examine whether Epanova 4 g daily reduces the rate of cardiovascular events in statin-treated patients with hypertriglyceridemia and low levels of HDL-C at high risk for developing cardiovascular events.

Study design: STRENGTH is a randomized, double-blind, placebo-controlled trial.

Patients had a triglyceride level ≥ 180 to < 500 mg/dL and HDL-C < 42 mg/dL (men) or < 47 mg/dL (women) in the presence of either (i) established atherosclerotic cardiovascular disease, (ii) diabetes with one additional risk factor or (iii) were other high risk primary prevention patients, based on age and risk factor assessment. Patients should be treated with a statin, for > 4 weeks, and have LDL-C < 100 mg/dL, but were also eligible if LDL-C was ≥ 100 mg/dL while on maximum tolerated statin therapy. The study will extend from October 30, 2014 to October 30, 2019. 13,086 patients were randomized to Epanova 4 g or placebo daily in addition to standard medical therapy. The primary efficacy outcome is time to first event of cardiovascular death, myocardial infarction, stroke, coronary revascularization or hospitalization for unstable angina. The trial will continue until 1600 patients reach the primary endpoint, with a median duration of therapy of 3 years.

Conclusions: STRENGTH will determine whether Epanova 4 gm daily will reduce cardiovascular events in statin-treated high-risk patients with hypertriglyceridemia and low HDL-C levels.

Key words

Omega-3 fatty acids; cardiovascular risk; clinical trials; triglycerides; non-HDL
cholesterol

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Introduction

Randomized controlled trials consistently demonstrate that lowering levels of low-density lipoprotein cholesterol (LDL-C) with statins reduce cardiovascular events in high-risk patients.(1) Accordingly, statins have become a cornerstone in treatment guidelines for prevention of atherosclerotic cardiovascular events. Despite widespread statin use, many patients continue to experience cardiovascular events,(2) emphasizing the need to identify additional therapeutic targets.

Triglycerides and non-HDL cholesterol as cardiovascular targets

Evidence accumulated over many decades implicates triglyceride-rich lipoproteins in the pathogenesis of atherosclerotic disease.(3) Population studies report that triglyceride levels associate with cardiovascular risk.(4) Post-hoc analyses of statin trials demonstrate that on-treatment triglyceride levels associate with cardiovascular event rates and progression of coronary atherosclerosis, regardless of achieved LDL-C levels.(5) Hypertriglyceridemia accompanies insulin resistance and associated risk factors including hypertension, hyperglycemia, hypercoagulable state and other features of atherogenic dyslipidemia (preponderance of small, dense LDL particles and low levels of HDL-C), which may contribute to this heightened cardiovascular risk.(6) Triglyceride rich lipoproteins may directly influence the artery wall. Genetic studies have reported that polymorphisms in factors regulating triglyceride levels,(7) including loss of function of apolipoprotein C-III(8) and angiopoietin like protein (ANGPLT) (9), associate with higher levels of triglyceride and cardiovascular risk. Preclinical studies have demonstrated that triglyceride-rich lipoproteins stimulate inflammatory, oxidative and thrombotic factors implicated in atherosclerosis.(10) This is evidenced by animal

studies in which genetic manipulation resulting in higher triglyceride levels results in accelerated atherosclerosis.(11)

Increasing attention has focused on the ability to measure and target the full atherogenic lipoprotein burden. While evidence implicates triglyceride-rich lipoproteins in atherosclerosis formation and progression, their atherogenicity may result from their ability to deliver cholesterol to the artery wall. Calculation of non-HDL-C permits determination of the cholesterol content of all lipoproteins considered to promote atherosclerosis. Reports from population, genetic and clinical trials confirm the association between non-HDL-C and cardiovascular risk and a direct relationship between non-HDL-C lowering and cardiovascular benefit.(12) Given its ability to identify some of the residual risk in statin-treated patients, non-HDL-C has become increasingly integrated into treatment guidelines as both a treatment target and to identify patients who require more aggressive lipid lowering.(13) However, studies have demonstrated that only 4% of patients with triglyceride levels greater than 200 mg/dL and at very high risk had an optimal non-HDL-C level <100 mg/dL.(14) Since statins produce limited triglyceride lowering, it is likely that many patients will require additional lipid modifying agents to achieve their non-HDL-C goal.

Clinical Trials Targeting Triglyceride-Rich Lipoproteins

While clinical trials of LDL-C lowering agents have consistently produced clinical benefit, agents targeting additional lipid parameters have produced variable results. Fibrates are pharmacological agonists of peroxisome proliferator activated receptor (PPAR- α) that lower triglycerides by up to 25%, modestly raise HDL-C and reduce small, dense LDL particle levels.(15) Cardiovascular outcomes trials of these agents have shown mixed results with evidence of benefit with gemfibrozil,(16,17) but not

other agents.(18,19) While triglyceride lowering was not associated with the clinical benefit observed with gemfibrozil, subgroup analyses of all fibrate trials have demonstrated clinical benefit in the subsets of patients with hypertriglyceridemia and low HDL-C levels at baseline.(20) These observations suggest that such patients have potentially modifiable risk and are more likely to benefit from targeted additional therapy. While PPAR- γ agonists have primarily been used to treat hyperglycemia by improving insulin sensitivity in patients with type 2 diabetes mellitus, these agents similarly demonstrate modest triglyceride lowering, with evidence that lowering the triglyceride/HDL-C ratio with pioglitazone is independently associated with its ability to slow progression of coronary atherosclerosis.(21)

Attention has focused on development of novel PPAR agonists, in an attempt to deliver more potent receptor agonism or activate multiple receptor subclasses. This has proven to be disappointing, due to either evidence of toxicity or clinical futility with PPAR- γ agonists, novel potent PPAR- α agents and dual PPAR- α/γ agonists in large outcomes trials.(22) An ongoing trial of the PPAR- α agonist, pemafibrate, is evaluating the impact on cardiovascular events in high-risk patients with concomitant hypertriglyceridemia.(23) This study has drawn on prior observations of potentially greater modification of cardiovascular risk in patients with evidence of atherogenic dyslipidemia at baseline. This represents the ability to identify a patient subgroup, which may be more likely to derive clinical benefit from therapy targeting this lipid phenotype. (Figure 1)

Niacin is a longstanding lipid modifying strategy with a multitude of effects including lowering levels of triglycerides, LDL-C and lipoprotein (a), in addition to raising HDL-C. While early trials, prior to the statin era, demonstrated clinical benefit with immediate release formulations,(24) niacin has proven challenging to use in

clinical practice due to adverse events and a lack of contemporary evidence of benefit in statin-treated patients.(25) Two large trials of niacin, delivered in either an extended release formulation or in combination with a prostanoid receptor antagonist, both delivery methods intended to improve tolerance, failed to reduce cardiovascular events in statin-treated patients.(26,27)

Omega-3 fatty acids

Considerable evidence has supported a potential role for the polyunsaturated omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), in protection from cardiovascular disease. Population studies have reported that greater dietary consumption of either fatty fish(28) or omega-3 fatty acids(29) are associated with lower rates of cardiovascular events. This observation is further supported by reports that red blood cell levels of EPA and DHA inversely correlate with cardiovascular risk.(30) The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI)-Prevenzione study provided some data suggesting that administration of low dose of prescription omega-3 fatty acids was associated with cardiovascular benefit, in the era prior to widespread use of statins.(31) In addition to lowering triglyceride and non-HDL-C levels, potential cardioprotective effects of omega-3 fatty acids may derive from favorable effects on inflammation, oxidation, thrombosis, endothelial function and cardiac arrhythmias.(32) A large number of studies have been performed to evaluate the impact of omega-3 fatty acids on a range of surrogate and clinical cardiovascular measures. These studies have failed to demonstrate consistent evidence of benefit, a conclusion confirmed by recent meta-analyses of these investigations.(33) However, many of these trials involved empirical administration of low doses (eg. 1 gm daily) of omega-3 fatty acids using formulations with variable bioavailability and no real effect

on triglycerides, tested in patients regardless of baseline triglyceride levels, and with no evidence that tissue omega-3 fatty acid content was modified. Average baseline triglyceride levels across these trials were usually around the upper limit of the normal range, and only modestly reduced by treatment. Higher doses of omega-3 fatty acids have greater lipid effects, whether this translates to an impact on cardiovascular events remains uncertain. Accordingly, the optimal dose and patient subgroup most likely to derive clinical benefit from omega-3 fatty acids remain uncertain.

Recent cardiovascular outcomes trials have evaluated the impact of omega-3 fatty acids in the setting of contemporary therapy for high risk patients. Results from the Japan Eicosapentanoic acid Lipid Intervention Study (JELIS) showed that administration of EPA 1.8 g/day resulted in a 19% reduction in cardiovascular events in statin-treated patients. This benefit was observed in patients with relatively normal triglyceride levels. However, the subgroup of patients with baseline triglyceride levels greater than 150 mg/dL and HDL-C <40 mg/dL achieved a 53% reduction in cardiovascular events with EPA.(34) Subsequent investigation demonstrated lower cardiovascular event rates in those patients with higher plasma EPA concentrations.(35)

A number of ongoing studies are attempting to evaluate the impact of omega-3 fatty acids on cardiovascular events. The Vitamin D and Omega-3 Trial (VITAL) is evaluating the impact of omega-3 fatty acids on cardiovascular events and cancer in a general population of more than 25,000 individuals,(36) while A Study of Cardiovascular Events in Diabetes (ASCEND) is comparing administration of omega-3 fatty acids or placebo in patients with diabetes without clinically manifest cardiovascular disease.(37) Both of these studies involve administration of a relatively low dose (1 gram per day) of omega-3 fatty acids. Icosapent ethyl is a purified ethyl

ester of EPA, shown to have favorable effects on triglycerides and associated lipid parameters. The Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) is currently investigating the impact of icosapent 4 g/day compared with mineral oil control on cardiovascular events in high risk, statin-treated patients with triglyceride levels between 200 and <500 mg/dL.(38)

Epanova

Epanova is a formulation of omega-3 fatty acid that has undergone an additional manufacturing step to hydrolyze and distill the ethyl esters into omega-3 free fatty acids (omega-3 carboxylic acids) with a final concentration of 75% EPA and DHA. Given the free fatty acid formulation, Epanova does not require hydrolysis by pancreatic lipase that conventional omega-3 ethyl ester do to maximize intestinal absorption. This greater bioavailability is supported by a lack of dependency on meal fat content. Accordingly, studies of this agent have the opportunity to provide a major change from prior studies of omega-3 fatty acid preparations in patients at high risk of cardiovascular events. This may be particularly important in patients with severe hypertriglyceridemia, in whom fat intake restriction is often employed, with potential implications for absorption of omega-3 ethyl ester formulations. The ability to administer Epanova with greater bioavailability than many prior omega-3 formulations has the potential to result in higher plasma EPA/DHA concentrations.

Open label administration of Epanova increased trough plasma EPA levels by 351% compared with baseline. The Epanova for Lowering Very High Triglycerides (EVOLVE) study compared the effects of treatment with Epanova 2-4 g/day with olive oil control for 12 weeks in patients with triglyceride levels between 500 and 2000 mg/dL. Plasma levels of EPA increased by 267-406% and DHA by 57-72% with Epanova

and were associated with lowering of triglycerides by 26-31% and non-HDL-C by 7.6-9.6%.⁽³⁹⁾ Epanova combined with a Statin in Patients with Hypertriglyceridemia to Reduce Non-HDL Cholesterol (ESPRIT) evaluated the impact of Epanova 2-4 g/day compared with olive oil for 6 weeks in high cardiovascular risk patients with baseline fasting triglyceride levels between 200 and 500 mg/dL. In this study, Epanova reduced triglyceride levels by 15-21% and non-HDL-C by up to 6.9%.⁽⁴⁰⁾ Any increase in LDL-C with omega-3 fatty acids is modest and not thought to adversely impact cardiovascular risk, particularly in the setting of triglyceride and non-HDL-C lowering. These trials demonstrated that Epanova administration was well tolerated without any observed concerning side effects, with the most common adverse event being higher incidences of diarrhea, nausea and eructation.

STRENGTH Trial Objectives and Design

A Long-Term Outcomes Study to Assess Statin Residual Risk Reduction with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia (STRENGTH: [clinicaltrials.gov NCT02104817](https://clinicaltrials.gov/ct2/show/study/NCT02104817)) tests the hypothesis that administration of EPA/DHA at a higher dose than typically employed in clinical trials in addition to conventional medical therapy affects risk for cardiovascular events in patients with high vascular risk (Figure 2). This is a randomized, double-blind, placebo-controlled, event-driven trial. Patients are treated with Epanova 4 g or matching corn oil placebo capsules once daily. Corn oil, rather than liquid paraffin or mineral oil, was chosen due to a lower incidence of gastrointestinal side effects, and to provide appropriate caloric control. Corn oil may slightly modify lipid levels, including small reductions in non-HDL-C.^(41,42) The trial will continue until 1,600 primary endpoints are positively adjudicated. The expected median duration of the trial is 3 years with a maximum duration of 5 years.

Study Organization

The trial is funded by AstraZeneca Pharmaceuticals AB (Sodertalje, Sweden) and coordinated by the Cleveland Clinic Coordinating Center for Clinical Research (C5 Research, Cleveland, OH). IQVIA (Durham, NC) serves as the contract research organization and provides data and site management. Academic members of the Executive Committee designed the trial in collaboration with the sponsor. The Steering Committee, consisting of the Executive Steering Committee and physician National Coordinators from each country, is responsible for scientific and medical conduct of the study and presentation and publication of the trial results. A copy of the complete final locked database will be transferred to the Executive Steering Committee for independent statistical analyses of study results for the purpose of scientific presentation and publication. An independent Data Monitoring Committee (DMC), supported by an independent data analysis center at Statistics Collaborative, Inc. (Washington DC) monitors the safety of the study and has access to unblinded data. The appropriate national and institutional regulatory and ethical boards approved the protocol, and all patients provided written informed consent. The authors are responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Patient Population

A total of 13,086 patients have been enrolled at 675 sites in 22 countries. The study population (Table 1 and 2) consists of patients ≥ 18 years of age on a stable diet and treated with a statin for at least 4 weeks prior to randomization with evidence of:

- LDL-C <100 mg/dL, but subjects were also eligible if LDL-C was \geq 100 mg/dL if they were being treated with high-intensity or maximally tolerated statin doses, with or without ezetimibe.
- Atherogenic dyslipidemia, defined as triglyceride levels \geq 180 mg/dL and <500 mg/dL and HDL-C <42 mg/dL for men or <47 mg/dL for women, measured after an overnight fast.
- Considered to be at high risk for a future cardiovascular event, defined by the presence of:
 - Established atherosclerotic cardiovascular disease involving the coronary, peripheral, carotid or aortic vascular territories (secondary prevention).
 - Type 1 or 2 diabetes mellitus with age \geq 40 years for men and \geq 50 years for women with at least one of the additional following risk factors: chronic cigarette smoking, hypertension, high C-reactive protein (hs-CRP) \geq 2 mg/L, or micro-albuminuria (urinary albumin:creatinine ratio >30 mg/g).
 - High-risk primary prevention defined as age >50 years for men >60 years for women with at least one of the additional following risk factors: family history of premature CAD, chronic cigarette smoking, hs-CRP >2.0 mg/L, impaired renal function, or coronary calcium score >300 Agatston units.

At least 50% of randomized patients were required to satisfy criteria for secondary prevention. Patients were permitted to undergo rescreening of lipid parameters on two occasions to evaluate the impact of adjustment of lipid modifying therapy or to discontinue excluded agents. Once patients met all inclusion criteria and

no exclusion criteria and agreed to volunteer for trial participation, they were randomized to study treatment within 14 days. The study was executed in accordance with the Declaration of Helsinki, all patients provided written informed consent and the protocol was approved by ethics or institutional review boards for each site.

Treatment Regimen and Follow-up

Patients were randomized to treatment using an interactive voice response system to treatment with Epanova 4 g orally once daily or matching placebo, in a 1:1 fashion, in addition to background therapy that adhered to national treatment guidelines for patients at high risk of a cardiovascular event. Given the free fatty acid formulation, Epanova does not require stringent co-administration with food, unlike prior studies of alternative fish oil preparations. Following dispensing of study drug, patients were to be seen at clinic visits at 3, 6 and 12 months following randomization and then every 6 months thereafter. A safety visit will be performed approximately three weeks after the last dose of study medication. Additional telephone calls to patients will be made on a 3-month basis commencing at month 9, in order to query about adverse events, clinical endpoints, changes in medications and any issues with study drug.

In addition to evaluation of patients for the incidence of cardiovascular events and adverse events, blood is collected at baseline, during the treatment period and at the end of treatment for assessment of lipids, biochemistry, hsCRP, glycemic control and fatty acid content within both plasma and red blood cells. Blood samples are also collected on a limited number of patients at sites within the United States for examination of exploratory lipid (apoB, apoC-III) and inflammatory biomarkers, in addition to genetic analyses. Patients who declined to participate in the genetic substudy were not prevented from participation in the overall trial.

While temporary discontinuation of study drug is permitted, every effort is made to recommence therapy as soon as possible. If patients discontinue study drug permanently, they continue to be followed in the trial for all efficacy and safety evaluations, where possible, given the intent to treat design of the study. For patients who are either unable or unwilling to return to the study site for follow up, every effort will be undertaken to use alternative approaches to review, including telephone calls or medical record review, in order to promote retention of patients in the study.

Endpoints

An independent clinical events committee, blinded to treatment allocation, will adjudicate all reported clinical events. The primary efficacy measure is the time to first occurrence of any component of the composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization and hospitalization for unstable angina. Death is defined as cardiovascular unless there is a documented identifiable non-vascular cause. Myocardial infarction includes types 1-5 of the Universal Definition. Stroke is defined as an acute episode of neurological dysfunction caused by vascular injury lasting longer than 24 hours. Elective and emergent coronary revascularization includes both percutaneous and surgical procedures. Hospitalization for unstable angina is defined by symptoms of myocardial ischemia at rest or with increasing frequency without evidence of acute myocardial infarction, but with evidence of either myocardial ischemia on non-invasive imaging or the presence of severe stenotic disease or thrombus on coronary angiography that is considered to underpin the clinical presentation.

Key secondary endpoints, tested hierarchically, include (i) cardiovascular events (cardiovascular death, non-fatal myocardial infarction and non-fatal stroke), (ii)

coronary events (cardiac death, non-fatal myocardial infarction, coronary revascularization and hospitalization for unstable angina) and (iii) time to cardiovascular death. Other secondary endpoints include each of the individual components of the primary endpoint and all-cause death. Tertiary endpoints include (i) new onset atrial fibrillation, (ii) total thrombotic events (coronary stent thrombosis and any systemic thromboembolism) and (iii) new onset heart failure events. Changes in lipid parameters and standard safety assessments will be performed. There are currently no planned substudies.

Statistical Considerations

STRENGTH is an event-driven clinical trial. The targeted minimum number of primary endpoints is 1,600, with patients treated for a projected median of 3 years. With a total of 13,000 patients randomized to Epanova or corn oil placebo, the study has 90% power to detect a 15% or greater relative reduction in hazard for the primary endpoint using log-ranked test at a two-sided alpha of 0.05. An annual incidence of the primary composite outcome of 4% per year is assumed, leading to an assumed total study duration of 4.5 years. The enrolment of patients with clinically manifest atherosclerotic cardiovascular disease was specified to comprise at least 50% of the entire study cohort. Sequential efficacy and futility assessments by the unblinded DMC will be performed following positive adjudication of approximately 50% and 75% of the targeted composite primary endpoint events. A group-sequential design will be used to preserve the overall type 1 error probability of 0.05.

The efficacy analysis data set will be based on the intent-to-treat population including all randomized patients. The safety analysis set will include all randomized patients who have received at least one dose of study drug. Patients lost to follow-up

will be censored at the time that they are last known to be event free and those who withdraw consent will be censored at the time of withdrawal. For the primary endpoint, the test of the null hypothesis will be based on the log-rank test. Contingent on Epanova favorably reducing the primary endpoint, key secondary endpoints will be evaluated in a hierarchical fashion.

Trial Progress

Enrolment started in October 2014 and was completed on July 12, 2017 when 13,086 patients had been randomized. The DMC has reviewed patient safety and trial conduct during 7 meetings through March 2018 and recommended continuation of the trial without modification after each of these reviews.

Summary

Greater triglyceride and non-HDL-C levels identify statin-treated patients at higher residual cardiovascular risk. While omega-3 fatty acids are of interest as a potential preventive therapy, most studies have used suboptimal doses and formulations with variable bioavailability for non-HDL-C reduction and failed to evaluate their impact in patients who are most likely to derive potential benefit. STRENGTH will permit the opportunity to determine the effects of administration of Epanova 4 gm daily, a much higher dose than evaluated in many studies and with a preparation that does not require co-administration with food, on atherosclerotic cardiovascular risk in patients with atherogenic dyslipidemia, considered to identify patients with high modifiable risk.

Legends for figures

Figure 1. Percentage change in major adverse cardiovascular events (MACE) with therapeutic interventions in both the whole study cohort and patient subgroups with hypertriglyceridemia and low levels of high-density lipoprotein cholesterol (HDL-C) at baseline.

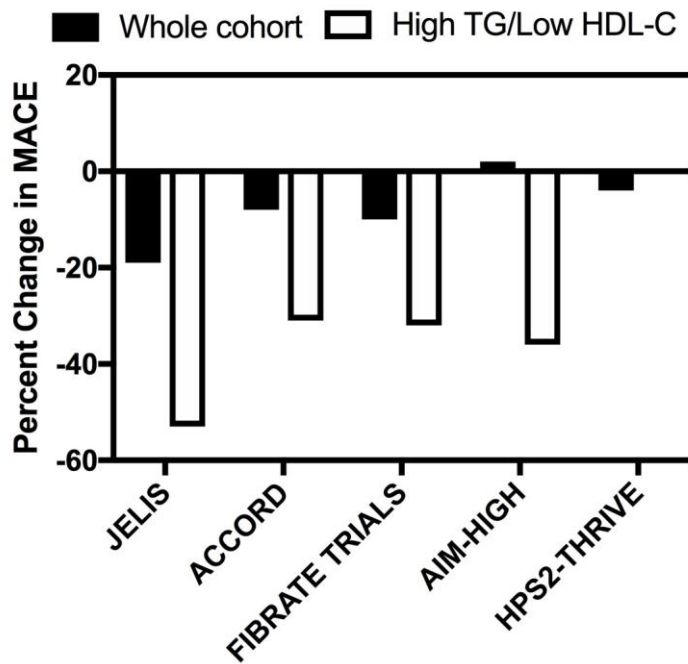
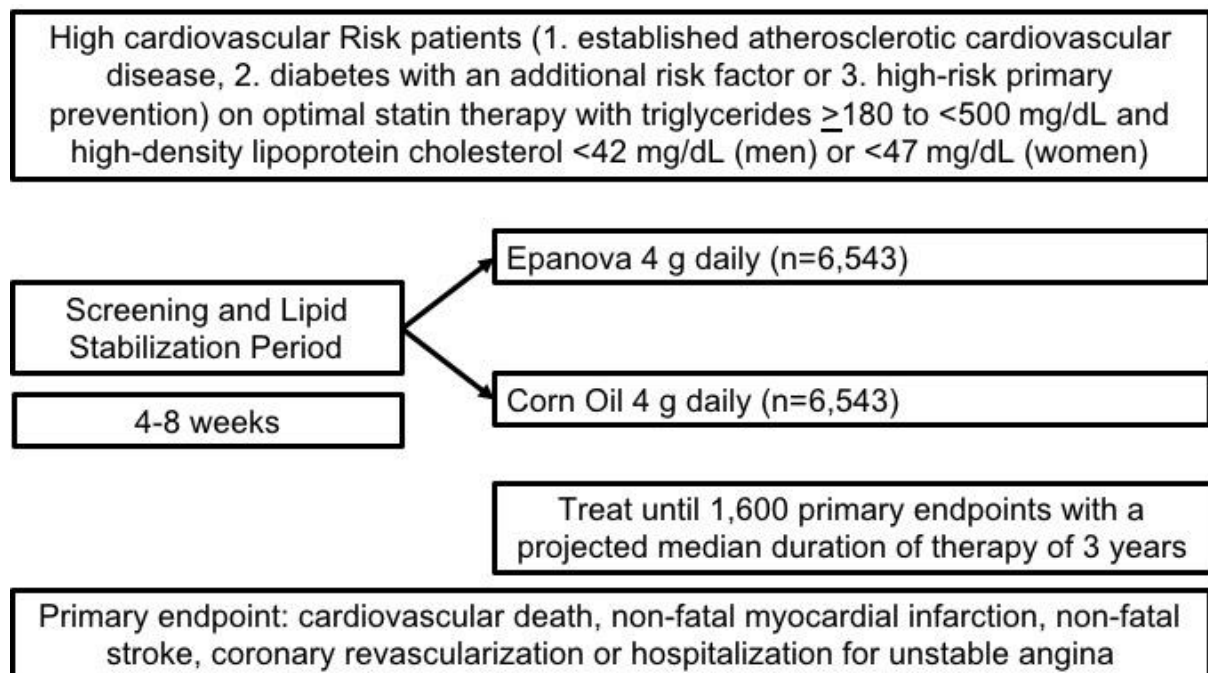


Figure 2. Study design features of the STRENGTH trial.



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Table 1. STRENGTH Inclusion Criteria

- ≥ 18 years of age
- Stable diet and treated with a statin for at least 4 weeks prior to randomization
- LDL-C < 100 mg/dL or ≥ 100 mg/dL provided they are treated with maximally tolerated statin doses, with or without ezetimibe
- Atherogenic dyslipidemia, defined as triglyceride levels ≥ 180 mg/dL and < 500 mg/dL and HDL-C < 42 mg/dL for men or < 47 mg/dL for women
- High risk for a future cardiovascular event:
 - Established atherosclerotic cardiovascular disease (any or more of the following)
 - myocardial infarction ≥ 30 days prior to randomization
 - percutaneous coronary intervention ≥ 6 months prior to randomization
 - coronary artery bypass grafting ≥ 30 days prior to randomization
 - invasive or computed tomography coronary angiography demonstrating $\geq 50\%$ stenosis in a native or grafted vessel
 - angina with evidence of perfusion defect or wall motion abnormality on non-invasive imaging
 - asymptomatic coronary ischemia on stress imaging
 - peripheral vascular disease with symptoms of claudication and either an ankle brachial index < 0.9 or angiographic evidence of stenosis $\geq 50\%$
 - peripheral arterial revascularization ≥ 30 days prior to randomization
 - carotid endarterectomy, carotid stenting or stenosis $\geq 50\%$
 - abdominal aortic aneurysm diagnosed ≥ 30 days prior to randomization
 - ischemic stroke ≥ 30 days prior to randomization
 - Type 1 or 2 diabetes mellitus and ≥ 40 years of age for men and ≥ 50 years for women, with at least one additional risk factor
 - chronic smoking
 - history of hypertension (blood pressure $> 140/90$ mmHg) or taking antihypertensive medication
 - hsCRP > 2 mg/L
 - urinary albumin:creatinine ratio > 30 mg/g
 - High risk primary prevention defined as age > 50 years for men or > 60 years for women with at least one additional risk factor
 - family history of premature coronary heart disease
 - chronic smoking
 - hsCRP > 2 mg/L
 - estimated glomerular filtration rate < 45 mL/min per 1.73 m² determined by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula
 - coronary calcium score > 300 Agatston units

Table 2. STRENGTH Exclusion Criteria

- allergy or intolerance to omega-3 carboxylic acids, omega-3 fatty acids, omega-3 acid ethyl esters or corn oil
- known hypersensitivity to fish and/or shellfish
- use of fibrates, bile acid sequestrants or niacin or its analogues >250 mg/day
- statin naïve at visit 1
- use of simvastatin 80 mg within 4 weeks prior to visit 2
- use of any prescription medications containing EPA and/or DHA
- more than one capsule/day of omega-3 dietary supplements
- use of weight loss drugs
- chronic use of oral corticosteroids
- known lipoprotein lipase impairment/deficiency or apoC-II deficiency
- HbA1c >12%
- Poorly controlled hypertension (blood pressure \geq 180 mmHg systolic and/or \geq 100 mmHg diastolic)
- Uncontrolled hypothyroidism
- History of cancer except non-melanoma skin cancer or carcinoma in situ of cervix in the last two years
- Patients on dialysis
- Females who are pregnant, planning to be pregnant, lactating or women of child bearing potential who are not using an acceptable method of contraception
- Creatinine kinase >5 times the upper limit of normal (ULN), aspartate aminotransferase or alanine aminotransferase >3 times ULN or total bilirubin >2 times ULN in the absence of a confirmed diagnosis of Gilbert's disease
- Excessive use of alcohol or other substance abuse that would jeopardize the patient's participation in the study
- Exposure to any investigational agent in the prior 4 weeks
- Prior myocardial infarction or stroke within the prior 30 days, coronary bypass grafting, peripheral or carotid revascularization or diagnosis of abdominal aortic aneurysm within the prior 30 days or percutaneous coronary intervention within the prior 6 months
- Any other condition the investigator believes would interfere with the patient's ability to provide informed consent and comply with study procedures