CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

ICOSAPENT ETHYL (VASCEPA)

(HLS Therapeutics Inc.)

Indication: Prevention of cardiovascular events in statin-treated patients

Service Line:	CADTH Common Drug Review
Version:	Final
Publication Date:	August 2020
Report Length:	56 Pages

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

CDR	CADTH Common Drug Review
CI	confidence interval
CV	cardiovascular
CVD	cardiovascular disease
DHA	docosahexaenoic acid
EPA	eicosapentaenoic acid
HDL-c	high-density lipoprotein cholesterol
HR	hazard ratio
hsCRP	high-sensitivity C-reactive protein
ITT	intention-to-treat population
LDL-c	low-density lipoprotein cholesterol
MACE	major adverse cardiovascular event
MI	myocardial infarction
SD	standard deviation
TG	triglyceride
VLDL-c	very low-density lipoprotein cholesterol

Drug	Icosapent ethyl (Vascepa)
Indication	To reduce the risk of cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, or hospitalization for unstable angina) in statin-treated patients with elevated triglycerides, who are at high risk of cardiovascular events due to: • established cardiovascular disease, or • diabetes, and at least one other cardiovascular risk factor
Reimbursement request	As per indication
Dosage form(s) and route of administration)/strength(s)	1 g capsules for oral administration
NOC date	December 30, 2019
Sponsor	HLS Therapeutics Inc.

Executive Summary

Introduction

Hypertriglyceridemia is causally linked to the development of atherosclerosis and eventually to an increased risk of ischemic cardiovascular (CV) events. High blood cholesterol levels (in particular, low- and very low-density lipoprotein cholesterol [LDL-c and VLDL-c]) is a common lipid abnormality, and reducing levels can lead to a reduced risk of CV events (CV death, non-fatal myocardial infarction [MI], and ischemic stroke). Current treatments include fibrates, niacin, or statins, among others, as well as lifestyle modifications.

Despite the use of interventions to reduce blood lipid levels, a significant proportion of patients can still be at risk of CV events due to persistent high lipid levels (residual risk for cardiovascular disease [CVD]). These patients can be classified as having an established risk of CVD if they have had a previous CV event — such as coronary heart disease, cerebrovascular disease, or peripheral artery disease; or they can be considered *at high risk* for future CV events if they are older than 50 years of age, have diabetes, and have more than one CV risk factor such as smoking, hypertension, or low high-density lipoprotein cholesterol (HDL-c) levels. Initial studies and empirical observations have put omega-3 fatty acids (essentially, eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) in the spotlight of treatments that could help reduce the risk of CV events, especially if added to existing treatments in this group of patients with residual risk.

Icosapent ethyl is a highly purified version of EPA that is currently being reviewed by Health Canada for the following indication: to reduce the risk of CV events (CV death, non-fatal MI, non-fatal stroke, coronary revascularization, or hospitalization for unstable angina) in statin-treated patients with elevated triglyceride (TG) levels who are at high risk of CV events due to established CVD, or diabetes and at least one other CV risk factor. It is supplied as 1 g capsules and administered in a dosage of 4 g per day.

The objective of the current review is to perform a systematic review of the beneficial and harmful effects of icosapent ethyl for the indication.

Stakeholder Engagement

Patient Input

No patients were available to provide input for this review.

Clinician Input

The following input is a summary of information provided by clinical specialists with expertise in the diagnosis and management of hypertriglyceridemia and CV risk.

Patients with established CVD (defined as the *secondary prevention* group) and patients with diabetes and one or more CV risk factors (the *primary prevention* or *at high risk* group) can remain at high risk for a major adverse CV event (MACE) due to persistent high levels of TGs, even after treatment with statins. Studies of added therapies to reduce these persistent levels of TG, such as fibrates or niacin, have demonstrated little to no effect for decreasing the risk of CV events. Fish oil supplements containing omega-3 fatty acids EPA and DHA have been tested as well, with no difference in the reduction of risk for further MACE. This group of patients, often referred to as patients with residual risk, are a subgroup of interest for whom there is an unmet need for effective and safe treatments. The main goal of treatment in this specific group of patients is the achievement of a reduced risk in CV events, including CV death, MI infarction, stroke, and need for urgent revascularization. Currently available treatments are not meeting the goals and needs of patients. These patients remain at higher risk of CV events when compared to those whose values have been normalized after therapy and lifestyle modifications. Current research has not identified definite subgroups in whom an intervention will have increased efficacy.

Although the exact mechanism of action of icosapent ethyl is not yet fully understood, previous studies have shown a reduction in TG levels, probably involving complex anti-inflammatory, antithrombotic, and TG metabolism effects. Icosapent ethyl could be used when TG levels remain elevated despite stable use of statin therapy (i.e., for more than four weeks). Icosapent ethyl's main use will be as a complementary intervention. It is not expected to be used as first-line therapy.

Patients meeting the criteria of established CV risk or at high risk for CV, identified by primary care physicians and eventually assessed, when needed, by cardiologists or endocrinologists, will be eligible for treatment with icosapent ethyl. They will have to be receiving treatment with stable statin dosages.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

Two randomized double-blind placebo-controlled studies were included in this review.

The first study is the REDUCE-IT trial, conducted in 11 countries, with a median follow-up of 4.9 years (up to 6.2 years). This trial included 8,179 patients older than 45 years of age with established CV risk, or older than 50 years of age with diabetes in combination with one additional risk factor for CVD. Patients had to have elevated TG levels (≥ 1.7 mmol/L and < 5.6 mmol/L) and to be receiving stable dosages of statins. This study evaluated 4 g

daily of icosapent ethyl versus placebo. The primary end point assessed was the time from randomization to the first occurrence of any of the composite outcome events of CV death, non-fatal MI infarction, non-fatal stroke, coronary revascularization, and unstable angina requiring hospitalization. Secondary end points were evaluated in a hierarchical fashion and included a key secondary composite end point of time from randomization to any of CV death, non-fatal MI, or non-fatal stroke; a composite of CV death or non-fatal MI; fatal or non-fatal MI; emergency or urgent revascularization; CV death; hospitalization for unstable angina; fatal or non-fatal stroke; a composite of total mortality, non-fatal MI (including silent MI), or non-fatal stroke; and total mortality.

The second study is the ANCHOR trial, with 12 weeks of follow-up, conducted in 97 centres across the US. The study included 702 patients aged 18 years and older with fasting TG levels 2.3 mmol/L or greater and less than or equal to 5.6 mmol/L, receiving a stable dose of statin therapy (with or without ezetimibe), and at high risk for CVD. This study included three arms: placebo and icosapent ethyl 2 g daily and 4 g daily, of which only the icosapent ethyl 4 g daily dosage arm was included because this is the dosage submitted for the application to Health Canada. The study evaluated the percent change in TG blood levels from baseline to week 12 as the primary outcome; CV events or other clinically important end points were not assessed. Secondary end points included the percent change in non-HDL-c, LDL-c, apolipoprotein B, VLDL-c, and lipoprotein-associated phospholipase A2 from baseline to week 12.

Efficacy Results

Based on data from the REDUCE-IT study (Table 1), 17% of patients treated with icosapent ethyl 4 g daily versus 22% of patients in the placebo group had at least one of the events of the composite outcome of CV death, non-fatal MI, non-fatal stroke, coronary revascularization, and unstable angina (hazard ratio [HR] 0.75; 95% confidence interval [CI], 0.68 to 0.83). Icosapent ethyl 4 g also reduced CV mortality (HR 0.80; 95% CI, 0.65 to 0.98), non-fatal MI (HR 0.69; 95%CI, 0.59 to 0.82), non-fatal stroke (HR 0.70; 95%CI, 0.53 to 0.93), hospitalizations due to unstable angina (HR 0.67; 95% CI, 0.53 to 0.86), and need for coronary revascularization (HR 0.66; 95% CI, 0.58 to 0.75) compared with placebo. Icosapent ethyl did not demonstrate benefit versus placebo on overall mortality (HR 0.87; 95% CI, 0.74 to 1.02), hospitalization due to heart failure (HR 0.97; 95% CI, 0.77 to 1.22), or arrhythmia (HR 1.21; 95% CI, 0.97 to 1.49).

Subgroups of interest for the review were baseline CVD risk (established CVD or at high risk for CVD) and baseline diabetes (diabetes or no diabetes). The results of the pre-specified subgroup analyses of the primary outcome in REDUCE-IT were similar to those for the full population: icosapent ethyl reduced the risk of the composite outcome relative to placebo. The subgroup analyses suggested a different magnitude of effect in the subgroups stratified according to the CV risk of patients (at high risk for CVD [primary prevention] or established CVD [secondary prevention]). The results for patients in the secondary prevention subgroup indicated a statistically significant effect on the primary outcome with icosapent ethyl (559/2,892 events [19.3%]) versus placebo (738/2,893 events [25.5%]; HR 0.726; 95% CI, 0.650 to 0.810), similar to that observed in the total population. However, the results in the primary prevention subgroup were not statistically significant because the upper confidence interval for the HR goes beyond 1.00 (146/1,197 [12.2%] events with icosapent ethyl; 163/1,197 [13.6%] events with placebo; HR 0.876; 95% CI, 0.700 to 1.095]). The absolute risk difference between the two groups in this subgroup was 1.4%, which is unlikely to be clinically significant. The test for interaction was statistically significant (P = 0.14; significance level pre-specified at < 0.15), which indicates that the

effect of icosapent ethyl differs depending on the CV risk category. This difference is at least partly explained by the imbalance in sample size between the CV risk category subgroups. The results did not find statistically significant differential effects between diabetes subgroup categories.

Data from the REDUCE-IT and ANCHOR trials indicated that icosapent reduced the levels of TGs, LDL-c, HDL-c, and high-sensitivity C-reactive protein (hsCRP) from baseline when compared to placebo.

Harms Results

Adverse events, serious adverse events, and withdrawals due to adverse events occurred at similar frequencies between icosapent ethyl and placebo in both studies. Atrial fibrillation occurred more frequently in the icosapent ethyl arm compared to the placebo arm (5.3% versus 3.9%, respectively) in the REDUCE-IT study but not in the ANCHOR study (0% versus less than 1%, respectively). Peripheral edema occurred more frequently in the icosapent ethyl group than in the placebo group in both REDUCE-IT (6.5% versus 5.0%, respectively) and in the ANCHOR study (1.3% versus 0.9%, respectively). Serious adverse bleeding events occurred in 2.7% in the icosapent ethyl group and 2.1% in the placebo group in REDUCE-IT; there were no fatal bleeding events in either group. There were no differences between the icosapent ethyl group and the placebo group in the proportion of adjudicated hemorrhagic stroke. Also, a higher percentage of patients in the icosapent ethyl group reported constipation compared with those in the placebo group (5.4% versus 3.6%, respectively).

Of all notable harms, only diarrhea was slightly increased in the placebo arm (11%) versus the intervention group (9%), although this was only present in the REDUCE-IT study. The rest of adverse events reported in both studies were rare (less than 3% prevalence) and similar between groups.

Table 1: Summary of Key Results From Pivotal and Protocol Selected Studies (ITT Population, REDUCE-IT)

	Icosapent ethyl, n (%) N = 4,089	Placebo, n (%) N = 4,090	Hazard ratio (95% CI)[a]
Composite of CV death, non-fatal MI (including silent MI), non-fatal stroke, coronary revascularization, and unstable angina requiring hospitalization	705 (17.2)	901 (22.0)	0.752 (0.682 to 0.830)
CV mortality (adjudicated CV deaths and deaths of undetermined causality)	174 (4.3)	213 (5.2)	0.803 (0.657 to 0.981)
All-cause mortality (includes CV death, non-CV death, undetermined, and total mortality)	274 (6.7)	310 (7.6)	0.870 (0739 to 1.023)
Non-fatal MI	237 (5.8)	332 (8.1)	0.697 (0.590 to 0.823)
Non-fatal stroke	85 (2.1)	118 (2.9)	0.708 (0.536 to 0.936)
Coronary revascularization	376 (9.2)	544 (13.3)	0.664 (0.583 to 0.758)
Hospitalization for unstable angina	108 (2.6)	157 (3.8)	0.679 (0.531 to 0.868)
Hospitalization for arrhythmias	188 (4.6)	154 (3.8)	1.21 (0.97 to 1.49)
Hospitalization for congestive heart failure	141 (3.4)	144 (3.5)	0.97 (0.77 to 1.22)
Serious adverse events	1,252 (30.6)	1,254 (30.7)	–
TEAEs	3,343 (81.8)	3,326 (81.3)	–
Serious TEAEs leading to discontinuations	321 (7.9)	335 (8.2)	–

CI = confidence interval; CV = cardiovascular; ITT = intention-to-treat; MI = myocardial infarction; TEAE = treatment-emergent adverse event.

[a] A Cox proportional hazards model stratified by geographic region, CV risk category, and use of ezetimibe was used for the HR and 95% CI, and P values were determined by the log-rank test using the same stratification factors. Median follow-up time was 4.9 years in both treatment groups.

Source: Clinical Study Reports for REDUCE IT[1] and ANCHOR.[2]

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Critical Appraisal

Both studies were at low risk of bias regarding randomization schedules, concealment of random allocation sequences, and blinded measurements. Approximately 10% of patients in both studies were lost to follow-up, and 30% had a drug interruption for more than 30 days, but there were no differences between groups in these numbers. Hence, the risk of bias was judged as moderate. Follow-up and management of study discontinuations were appropriate, and both intention-to-treat (ITT) and per-protocol analyses presented consistent results. The ANCHOR trial did not analyze subgroups. The REDUCE-IT study was considered underpowered to obtain appropriate subgroup analyses. Generalizability of the results from REDUCE-IT is a concern, given that the benefits and harms were derived from a single, albeit large, randomized controlled trial, and only 43% of patients who underwent screening were randomized to treatment groups in the study. There is also

uncertainty regarding the generalizability of the distribution of statin intensity at baseline in REDUCE-IT, although, regardless of statin intensity distribution, the median baseline LDL-c was within the target range at approximately 1.94 mmol/L (75 mg/dL) across the studied population. ANCHOR was a relatively small, short-term study that focused on evaluating changes in blood lipid profiles instead of clinical outcomes; therefore, this study is supportive in demonstrating the mechanism of action of icosapent ethyl but it does little to elucidate the clinical added value of the drug in the target population.

Conclusions

Icosapent ethyl reduced the occurrence of events included in the composite outcome of CV death, non-fatal MI, non-fatal stroke, coronary revascularization, and hospitalization for unstable angina in patients treated with statins and with residual CV risk (i.e., those with increased TG levels despite treatment and with established CVD or at high risk of CV events). The key secondary end points, a composite of CV death, MI, or stroke, were also fewer in those treated with icosapent ethyl when compared to placebo. Icosapent ethyl also had a beneficial effect when the components of the composite outcome CV mortality, non-fatal CV events, and coronary revascularization were evaluated individually, although there was no difference in all-cause mortality or in hospitalizations due to heart failure and arrhythmia. These effects of icosapent ethyl, however, might include an increase the number of adverse events such as serious bleeding, peripheral edema, and hospitalization due to atrial fibrillation. The results may not be generalizable and may be restricted to the specific population enrolled in the REDUCE-IT study.

Introduction

Disease Background

CVD is the leading cause of death in the adult population globally and an economic burden for health care systems, affecting the majority of people older than 60 years and accounting for half of all non-communicable diseases worldwide.[3] In Canada, CVD is the second leading cause of death (after cancer) and the leading cause of hospitalization. It is also the leading cause of years of life lost, and the second leading cause of disability-adjusted life-years lost (the number of years lost due to ill health, disability, or early death).[4] Approximately 2.4 million Canadians over the age of 20 live with a diagnosed heart condition.

Atherosclerosis is accepted as the main underlying condition leading to CV events.[5,6] Dyslipidemia, particularly hypercholesterolemia involving LDL-c and VLDL-c as well as hypertriglyceridemia, is causally linked to atherosclerosis.[7,8]

Hypertriglyceridemia is a frequent lipid abnormality usually appearing in persons who are obese (with or without insulin resistance), and in those who have type 2 diabetes mellitus or metabolic syndrome. It is defined as mild hypertriglyceridemia when fasting TG levels are 1.7 to 5.6 mmol/L (150 to 499 mg/dL), moderate when levels fall between 5.6 to 10.0 mmol/L (500 to 886 mg/dL), and very high or severe when levels are higher than 10.0 mmol/L (886 mg/dL).[9] According to the Canadian Health Measures Survey (2007–2009), the prevalence of dyslipidemia is 23% for those aged 18 to 39, 40% in those aged 40 to 59, and 59% in those 60 to 79 years old.[10]

Current evidence syntheses and individual studies have demonstrated a 20% to 22% relative risk reduction in CV events for each 1 mmol/L reduction in LDL-c.[11] Hence, reducing dyslipidemia has been a cornerstone approach of clinicians and a main goal specified in clinical guidelines and recommendations around the world.

Standards of Therapy

The main goal of treating lipid disorders is to prevent and/or reduce CV mortality and morbidity — mainly MI, stroke, and need for revascularization — associated with high lipid levels. The therapeutic options for lowering TGs include lifestyle modifications (such as weight control, avoiding smoking and alcohol overuse, and diet management) and medications.

Systematic reviews of randomized trials have shown that LDL-lowering therapy with beta-hydroxy beta-methylglutaryl-CoA (HMG-CoA) reductase inhibitors (statins) reduces the risk of CV events (including stroke) and overall mortality in patients with CV risk factors.[12] Together with other therapies and lifestyle modifications, these are considered first-line medications in most guidelines.[11] Further treatment with niacin, fibrates, or fish oils is available; however, adding these drugs to statin treatment has not demonstrated CV benefits in high-risk patients with persisting dyslipidemia. This subgroup of patients may still present with CV events (8.5% in 3.8 years).[13,14]

Evidence from observational studies in Western and Asian populations have shown an association between regular fish consumption and lower rates of coronary heart disease.[15,16] These findings stemmed from initial observations in populations that consumed high amounts of foods rich in very-long-chain polyunsaturated fatty acids containing omega-3 fatty acids, including EPA and DHA, usually found in fish and other seafood. However, a recent systematic review including 10 randomized controlled trials found little to no effect of omega-3 fatty acid supplements on fatal or non-fatal coronary heart disease or any MACE.[17] All included randomized trials, however, used combinations of DHA and EPA in different proportions and doses. Based on recent evidence, some have proposed that DHA and EPA might have different effects and impact on patients at high risk of CVD or with established CVD who are already on statins.[18,19]

Drug

Icosapent ethyl (Vascepa) is an ethyl ester — a highly purified version — of EPA currently pending approval from Health Canada at the time of drafting this report. The indication is to reduce the risk of CV events (CV death, non-fatal MI, non-fatal stroke, coronary revascularization, or hospitalization for unstable angina) in statin-treated patients with elevated TG levels who are at high risk of CV events due to established CVD, or diabetes and at least one other CV risk factor. The drug is undergoing an expedited (priority) review with Health Canada. The sponsor's reimbursement request is as per the anticipated indication. Icosapent ethyl is supplied as a 1 g liquid-filled soft gelatin capsule for oral administration with a recommended dose of 4 g per day, as two 1 g capsules twice a day. This product has not been previously evaluated by CADTH.

The mechanism of action of icosapent ethyl is still not completely understood. It has been suggested that anti-oxidant and anti-inflammatory properties of icosapent ethyl result in reduced or slowed progression of the atherosclerotic process.[20] Non-conclusive reproductive and developmental studies suggest potential for direct harm to fetal development and reproductive maturation; therefore, icosapent ethyl should be avoided during pregnancy and during lactation, as specified in the product monograph. Table 2 presents the characteristics of icosapent ethyl and its main comparators for the purpose of this review.

Table 2: Key Characteristics of Icosapent Ethyl and Main Comparators — Fish Oil, Niacin, Ezetimibe, and Fibrates

	Icosapent ethyl	Fish oil	Niacin	Ezetimibe	Fibrates
Mechanism of action	Decreases the production and accelerates clearance of TGs plus slows production of VLDL	Mediates anti-inflammatory effects and increases levels of EPA/DHA	Unknown	Inhibits cholesterol absorption	Enhances catabolism of TG-rich particles and reduces secretion of VLDL
Indication [a]	To reduce the risk of cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, and hospitalization for unstable angina) in statin-treated patients with elevated TGs who are at high risk of cardiovascular events due to established cardiovascular disease, or diabetes and at least one other cardiovascular risk factor	No specific official indication; commonly used as supplement for lowering blood lipid levels	No indication	To reduce elevated lipid levels — alone or in combination with a statin — in patients with primary hyperlipidemia, mixed hyperlipidemia (in combination with fenofibrate), homozygous familial hypercholesterolemia, and homozygous sitosterolemia (phytosterolemia)	As an adjunctive therapy to diet to (a) reduce TG levels in adult patients with severe high TGs, and (b) reduce elevated total cholesterol, LDL-c, TGs, and apolipoprotein B, and to increase HDL-c in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson types IIa and IIb)
Route of administration	Oral	Oral	Oral	Oral	Oral
Recommended dose	4 g per day (two 1 g capsules twice a day)	No official standard dose; usually 200 to 500 mg of combined EPA and DHA are used per day	250 mg twice a day to 500 mg three times a day	10 mg daily	Fenofibrate dose: 1 capsule (160 mg) once a day
Serious adverse effects or safety issues	Edema, bleeding, and atrial fibrillation have been reported	Increase risk of bleeding and anaphylactic reactions in susceptible people	No serious adverse events; people sensitive to nicotinic acid may experience flushing of the skin that is generally mild and transient	Hepatitis/liver function test abnormalities, hypersensitivity, erythema multiforme, myopathy, thrombocytopenia, paresthesia	Increased risk of myopathies/rhabdomyolysis when used in combination with some statins

	Icosapent ethyl	Fish oil	Niacin	Ezetimibe	Fibrates
Other	Any other notable issue that is relevant	Used commonly as supplement with no standards of dosage	Used commonly as part of multivitamin supplements	None	None

DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; HDL-c = high-density lipoprotein cholesterol; LDL-c = low-density lipoprotein cholesterol; TG = triglyceride; VLDL = very low-density lipoprotein.

[a] Health Canada–approved indication. Fish oils and niacin are Schedule 1 Natural Health Products.

Source: Product monographs of icosapent ethyl,[20] ezetimibe,[21] and fenofibrate;[22] as well as electronic sources of information for fish oil[23] and niacin.[24]

Stakeholder Engagement

Patient-Group Input

No patient-group input was received for this review.

Clinician Input

All CADTH review teams include at least one clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by clinical specialists with expertise in the diagnosis and management of CVD and dyslipidemia.

Description of the Current Treatment Paradigm for the Disease

Patients with established CVD (defined as the *secondary prevention* group) and patients with diabetes and one or more CV risk factor(s) (the *primary prevention* or *at high risk* group) can remain at high risk for a MACE due to persistent high levels of TGs, even after treatment with statins. Studies of added therapies to reduce these persistent levels of TGs, such as fibrates or niacin, have demonstrated little to no effect for decreasing the risk of CV events. Fish oil supplements containing omega-3 fatty acids EPA and DHA have been tested as well, with no difference in the risk reduction for further MACE. This group of patients with residual risk despite optimized statin therapy is an important subgroup of patients with a need for treatments to reduce the risk of CV events.

Treatment Goals

The main goal of treatment in this specific group of patients is the achievement of a reduced risk of CV events, including CV death, MI, stroke, and need for urgent revascularization.

Unmet Needs

Currently, available treatments are not meeting the goals and needs of patients who have persistent elevated levels of TGs and low HDL-c. These patients remain at higher risk of CV events when compared to those whose values have been normalized after therapy and lifestyle modifications. Treatments are needed to reduce high TG levels in this group of patients with residual risk. Furthermore, current research has not identified definite subgroups in whom an intervention will have increased efficacy.

Place in Therapy

Although the exact mechanism of action of icosapent ethyl is not yet fully understood, previous studies have shown a reduction in TG levels, probably involving complex anti-inflammatory, antithrombotic, and TG metabolism effects. Icosapent ethyl could be used when TG levels remain elevated despite stable use of statin therapy (i.e., for more than four weeks). Currently, no other medication has clear and consistent evidence for reducing elevated TG levels in patients with established arteriosclerotic CVD and in patients with diabetes and other high-risk features. Although icosapent ethyl may reduce the use of niacin and fibrates, as well as omega-3 fatty acid supplements (non-prescription), its main use will be as a complementary intervention to treat and prevent atherosclerosis in this

group of patients. It is not expected to be used as first-line therapy and is therefore unlikely to cause a clinical paradigm shift.

Patient Population

Patients with established CVD or with diabetes and with elevated levels of TGs (i.e., those meeting the inclusion criteria from the included studies and the indication for this review) will be the target population for treatment with icosapent ethyl in clinical settings. Only one study has been able to confirm these conditions,[25] and, as expected, we do not know the effect on those patients outside the inclusion criteria.

Patients to be treated with icosapent ethyl would have to be receiving treatment — and on stable dosages — with statins that is maximally tolerated, as well as receiving treatment with other guideline-recommended therapies. These patients would ideally be identified and assessed by primary care physicians or specialists in cardiology or endocrinology who have full access to the patients' family and medical history, with information about their lipid profile and other pertinent tests (e.g., to confirm the diagnosis of diabetes), as well as detection of other risk factors. Within these patients, no specific subgroups of patients have been identified so far in whom icosapent ethyl would have greater efficacy.

Assessing Response to Treatment

The benefits from the intervention are expected to have clear and objective outcomes, as stated in this review and the included trials. These outcomes are a reduction in CV death, MACEs (MI and stroke), and need for revascularization. Measuring response to treatment in individual patients might be difficult, as the most appropriate way would be by measuring TG levels; however, there has been no relationship found between levels of TGs and clinical response according to the currently available evidence.

Discontinuing Treatment

The intervention might be discontinued if intolerance develops (adverse effects). However, in the current literature, there are no specific data on harms that would drive this decision, so the decision to discontinue would most likely be made based on purely empirical and clinical observations and the physician's judgment.

Prescribing Conditions

The appropriate and most likely setting for the prescription of icosapent ethyl will be primary care (outpatient clinics and family physicians), followed by specialty and sub-specialty programs, supporting primary care. Guideline adherence and implementation will play an important role in attaining the maximum possible and appropriate use of the drug.

Clinical Evidence

The clinical evidence included in this review of icosapent ethyl is presented in three sections. Section 1, the systematic review, includes pivotal studies provided in the sponsor's submission to CADTH Common Drug Review (CDR) and Health Canada, as well as those studies that were selected according to an a priori protocol. Section 2 includes indirect evidence from the sponsor (if submitted) and indirect evidence selected from the literature that met the selection criteria specified in the review. Section 3 includes sponsor-submitted long-term extension studies and additional relevant studies that were considered to address important gaps in the evidence included in the systematic review.

Systematic Review (Pivotal and Protocol Selected Studies)

Objective

To perform a systematic review of the beneficial and harmful effects of icosapent ethyl for reducing the risk of ischemic CV events (death due to CV event, non-fatal MI, non-fatal stroke, coronary revascularization, and unstable angina) in adult patients treated with statins and with elevated TGs and other risk factors such as established CVD or being at high risk for CVD.

Methods

Studies selected for inclusion in the systematic review include pivotal studies provided in the sponsor's submission to CDR and Health Canada, as well as those meeting the selection criteria presented in Table 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient population	Adults treated with statins and with elevated levels of triglycerides and other risk factors such as established CVD or being at high risk for CVD.
	Subgroups:
	• diabetes mellitus
	• risk for CVD
	  ○ established CVD
	  ○ high risk for CVD

Intervention	Icosapent ethyl, 1 g capsules, 4 g per day (two 1 g capsules twice a day)
Comparators	• placebo • omega-3 preparations (EPA- or DHA-containing products) • niacin • ezetimibe • fibrates

Outcomes	**Efficacy outcomes:**
	• mortality
	  ○ cardiovascular mortality
	  ○ all-cause mortality
	• morbidity
	  ○ non-fatal CV events
	  ○ hospitalizations due to heart failure, arrhythmia, or unstable angina
	  ○ any revascularization

	• health-related quality of life
	• blood levels change in:
	  ○ triglycerides
	  ○ LDL-c
	  ○ HDL-c
	  ○ C-reactive protein
	
	Harms outcomes:
	• AEs, SAEs, WDAEs
	• Notable harms: bleeding leading to transfusion or hospitalization (including visits to the emergency department), edema, atrial fibrillation, constipation, gout, musculoskeletal pain, arthralgia, and diarrhea

Study Design	Published and unpublished phase III and IV RCTs

AE = adverse event; CV = cardiovascular; CVD = cardiovascular disease; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; HDL-c = high-density lipoprotein cholesterol; LDL-c = low-density lipoprotein cholesterol; RCT = randomized controlled trial; SAE = serious adverse events; WDAE = withdrawal due to adverse events.

The literature search was performed by an information specialist using a peer-reviewed search strategy (Appendix 1).

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Findings From the Literature

A total of two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4. A list of excluded studies is presented in Appendix 2.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

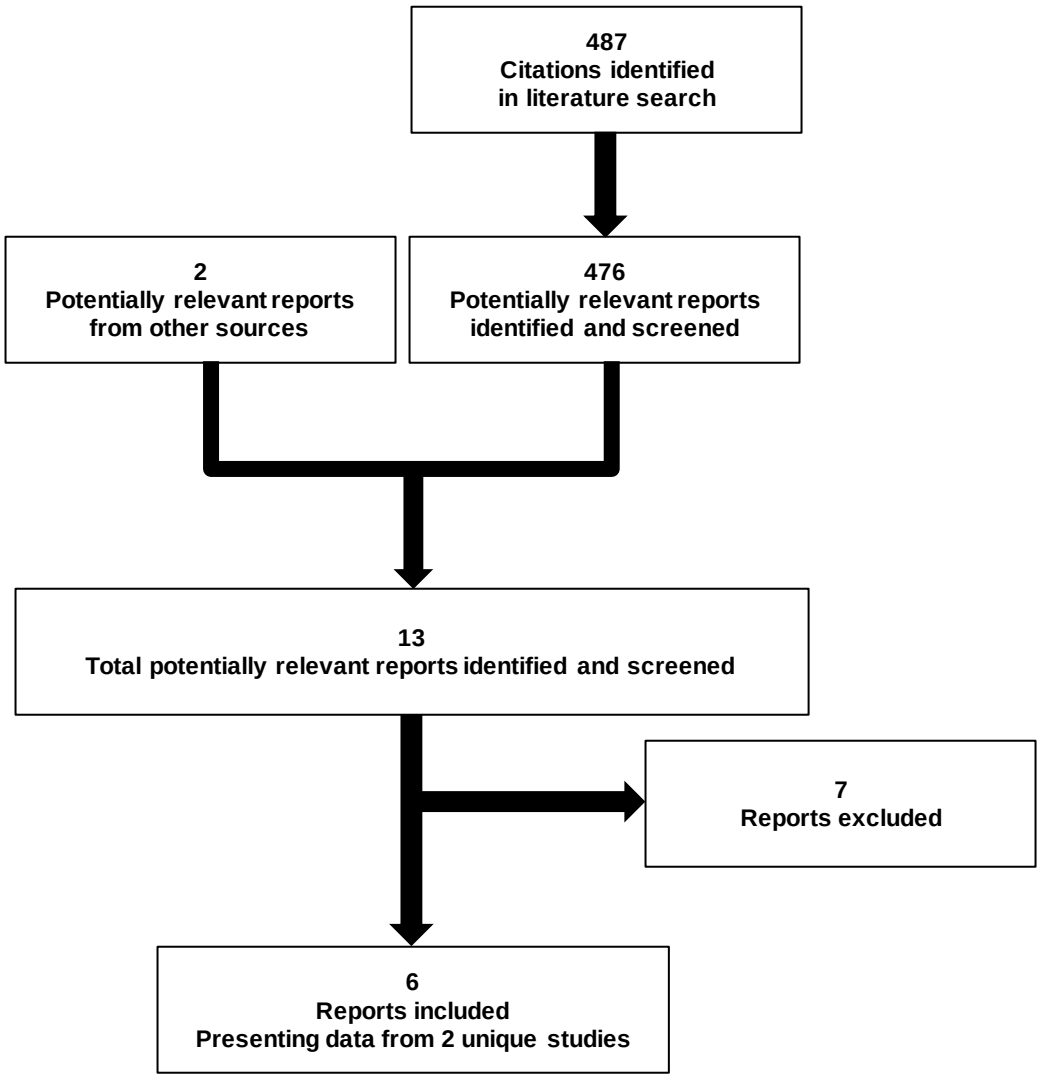


Table 4: Details of Included Studies

		REDUCE-IT[25]	ANCHOR[26]
DESIGNS AND POPULATIONS	**Study design**	DB placebo-controlled RCT	DB placebo-controlled RCT
	Locations	US, Netherlands, Ukraine, Russian Federation, South Africa, Poland, India, Canada, Romania, Australia, and New Zealand	US (97 sites)
	Randomized (N)	8,179	702
	Inclusion criteria	• Men or women ≥ 45 years old with established CVD or age ≥ 50 years with DM in combination with 1 additional risk factor for CVD • Fasting TG ≥ 1.7 mmol/L (150 mg/dL) and < 5.6 mmol/L (500 mg/dL) • LDL-c > 1.0 mmol/L (40 mg/dL) and < 2.6 mmol/L (100 mg/dL) and on stable statin therapy	• Men or women > 18 years of age with BMI ≤ 45 kg/m^2 with high fasting TG levels (≥ 2.3 mmol/L [200 mg/dL] and < 5.6 mmol/L [500 mg/dL]), a stable dose of statin therapy (with or without ezetimibe), and at high risk for CVD. High risk for CVD was defined as clinical CHD or clinical CHD risk equivalents (10-year risk ≥ 20%), as defined in the NCEP ATP III guidelines; i.e., when one of the following were present: history of coronary artery disease (MI, angina, coronary procedure), atherosclerotic disease (e.g., PAD, TIA, carotid obstruction) • Using atorvastatin, rosuvastatin, or simvastatin at optimal doses; patients had an LDL-c ≥ 1.0 mmol/L (40 mg/dL) and ≤ 3.0 mmol/L (115 mg/dL)
	Exclusion criteria	• Severe heart failure • Active liver disease • Pregnant, breastfeeding, or plans for pregnancy • Planned coronary intervention	• BMI > 45 kg/m^2 or weight change > 3 kg from the first visit to the end of the qualifying period • Use of other non-study, lipid-altering medication, or other statin not stated in the protocol • Hemoglobin A1C > 9.5% after visit 1 • Percutaneous coronary intervention within 4 weeks before screening • Hospitalization within 4 weeks before screening • Known nephrotic proteinuria • Other major conditions (e.g., liver failure)
DRUGS	**Intervention**	Icosapent ethyl: 2 capsules of 1 g twice a day (4 g per day) p.o.	Icosapent ethyl (2 g per day): 1 g capsule (plus 1 placebo capsule) twice a day p.o. Icosapent ethyl (4 g per day): 2 capsules of 1 g twice a day p.o.
	Comparator(s)	Placebo twice a day (4 capsules daily p.o.)	Placebo twice a day (4 capsules daily p.o.)
DURATION	**Phase**		
	Run-in	Approximately 40 days	6 to 9 weeks
	Double-blind	Up to 6.2 years	Through follow-up (12 weeks)
	Follow-up	Up to 6.2 (median 4.9) years	12 weeks
OUTCOMES	**Primary end points**	First time to occurrence of any component of the composite of the following major adverse CV events: • CV death • non-fatal MI (including silent MI) • non-fatal stroke • coronary revascularization	Percent change in TG levels from baseline to week 12

		REDUCE-IT[25]	ANCHOR[26]
		• unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization	
	Secondary and exploratory end points	• Composite of CV death or non-fatal MI (including silent MI) • Fatal or non-fatal MI (including silent MI) • Non-elective coronary revascularization represented as the composite of emergent or urgent classifications • CV death • Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization • Fatal or non-fatal stroke • Composite of total mortality, non-fatal MI (including silent MI), or non-fatal stroke • Total mortality	• Percent changes in LDL-c, non-HDL-c, VLDL-c, Lp-PLA2, and apo B from baseline to week 12 end point • Safety assessments included adverse events, clinical laboratory measurements (chemistry, hematology, and urinalysis), 12-lead electrocardiograms, weight, and BMI, vital signs, and physical examinations *Exploratory efficacy variables:* • Percent changes in total cholesterol and HDL-c, VLDL-c, and high-sensitivity C-reactive protein
NOTES	**Publications**	Bhatt et al. (2019)[25]	Ballantyne et al. (2012)[26] Bays et al. (2013)[27] Ballantyne et al. (2015)[28]

apo B = apolipoprotein B; BMI = body mass index; CHD = coronary heart disease; CV = cardiovascular; CVD = cardiovascular disease; DB = double-blind; DM = diabetes mellitus; LDL-c = low-density lipoprotein cholesterol; Lp-PLA2 = lipoprotein-associated lipase A2; HDL = high-density lipoprotein cholesterol; MI = myocardial infarction; NCEP ATP = National Cholesterol Education Program Adult Treatment Panel; PAD = peripheral artery disease; p.o. = by mouth; RCT = randomized controlled trial; TIA = transient ischemic attack; TG = triglyceride; `VLDL-c = very low-density lipoprotein cholesterol.

Note: Two additional reports were included (Clinical Study Reports for REDUCE IT[1] and ANCHOR[2]).

Source: Clinical Study Reports for REDUCE IT[1] and ANCHOR.[2]

Description of Studies

Two double-blind, randomized, placebo-controlled trials met the inclusion criteria for the review: the ANCHOR[26] and the REDUCE-IT[25] studies.

The ANCHOR trial was conducted from December 2009 to February 2011 across 97 centres in the US. The study aimed to evaluate the difference in the percent change in TG levels from baseline to week 12 for icosapent ethyl (2 g and 4 g) compared to placebo in patients with high risk for CVD and with TG levels ≥ 2.3 mmol/L (200 mg/dL) and < 5.6 mmol/L (500 mg/dL). The investigators screened 2,309 patients for eligibility, of which 1,602 patients were considered screening failures, mainly because they did not satisfy the inclusion criteria (n = 1,461) or because they withdrew consent (n = 102). The screening period consisted of four to six weeks with diet and lifestyle stabilization, after which a 12-week double-blind period ensued. After randomization procedures, investigators distributed 702 patients to three arms of study: an intervention arm with icosapent ethyl at 4 g per day (n = 233), a second intervention arm using icosapent ethyl at 2 g per day (n = 236), and a placebo group (n = 233). The 2 g per day regimen is not included in this review because it was not a dosage submitted to Health Canada. The randomization list was stratified according to the type of statin (atorvastatin, rosuvastatin, or simvastatin), presence of diabetes, and gender.

The REDUCE-IT study was a larger randomized trial evaluating clinical outcomes in addition to TG blood levels and harms. It was conducted between November 2011 to August 2016 in 473 centres from 11 countries. The screening (run-in) period consisted of one month of assessment for eligibility, after which patients were randomized 1:1 to 4 g per day of icosapent ethyl or placebo. Randomization was stratified by CV risk category, use of ezetimibe, and geographical region (a group of western countries, Eastern European countries, and the Asia–Pacific region). Of 19,212 screened patients, 8,179 were randomized to intervention or control groups. Most of the screening failures were because the patients did not meet the inclusion criteria (n = 10,429), withdrew consent (n = 340), or were lost to follow-up during this period (n = 108). The median follow-up time was 4.9 years and up to 6.2 years.

Populations

Inclusion and Exclusion Criteria

The ANCHOR study included patients older than 18 years of age with BMI 45 kg/m^2 or lower, fasting TG levels of 2.3 mmol/L (200 mg/dL) or higher and less than 5.6 mmol/L (500 mg/dL), a stable dose of statin therapy (with or without ezetimibe), and at high risk for CVD. Patients at high risk for CVD were defined as having clinical coronary heart disease or clinical coronary heart disease risk equivalents (10-year risk ≥ 20%), as delineated in the National Cholesterol Education Program Adult Treatment Panel III guidelines; i.e., when one of the following were present: history of coronary artery disease (MI, angina, coronary procedure), or atherosclerotic disease (e.g., peripheral artery disease, transient ischemic attack, carotid obstruction). Patients were excluded if they were receiving non-study lipid-altering medications or other statins not stated in the protocol; if they had hemoglobin A1C greater than 9.5%; or if they had had percutaneous coronary intervention within four weeks before screening, hospitalization within four weeks before screening, known nephrotic proteinuria, or other major conditions.

The REDUCE-IT trial included patients who were 45 years of age and older and had established risk for CVD (secondary prevention), or who were 50 years of age and older and were considered at high risk (primary prevention), defined as having diabetes plus one additional risk factor for CVD. Both groups also had to have a fasting TG level of 1.7 mmol/L (150 mg/dL) or greater and less than 5.6 mmol/L (500 mg/dL), and LDL-c greater than 1.0 mmol/L (40 mg/dL) and less than 2.6 mmol/L (100 mg/dL) and had to be on stable statin therapy.

Patients that investigators categorized as high risk in the ANCHOR study would have been classified as in the established-risk (secondary prevention) group in the REDUCE-IT trial. For this reason, we did not consider the ANCHOR trial to have high-risk patients, but rather all were managed as established CVD (secondary prevention) patients (Table 6).

Baseline Characteristics

Baseline characteristics were considered similar between the intervention and placebo groups in both studies, denoting a randomization process that produced an appropriate balance of known or unknown prognostic factors, baseline conditions, medications, or prior treatments (Table 5 and Table 6). Statin intensity was defined according to the American College of Cardiology/American Heart Association (ACC/AHA) Blood Cholesterol Guidelines (Appendix 4).

Table 5: Summary of Baseline Characteristics — REDUCE-IT Study

Baseline characteristic	REDUCE-IT	
	Icosapent ethyl 4 g (N = 4,089)	Placebo (N = 4,090)
Age (years), mean (SD)	63.4 (8.4)	63.4 (8.43)
Male sex, n (%)	2,927 (71.6)	2,895 (70.8)
Body mass index (kg/m^2), median (IQR)	30.8 (27.8 to 34.5)	30.8 (27.9 to 34.7)
Region, n (%)		
Group of western countries	2,906 (71.1)	2,905 (71.0)
Eastern European countries	1,053 (25.8)	1,053 (25.7)
Asia–Pacific region	130 (3.2)	132 (3.2)
CV risk stratum, n (%)		
Established CV risk (secondary prevention)	2,892 (70.7)	2,893 (70.7)
At high CV risk (primary prevention)	1,197 (29.3)	1,197 (29.3)
Diabetes, n (%)		
Type 1	27 (0.7)	30 (0.7)
Type 2	2,367 (57.9)	2,363 (57.8)
No diabetes	1,695 (41.5)	1,694 (41.4)
Prior atherosclerotic CVD, n (%)	2,816 (68.9)	2,835 (69.3)
Prior non-atherosclerotic CVD (including CHF), n (%)	3,649 (89.2)	3,645 (89.1)
Statin intensity/regimen,[a] n (%)		
Low	254 (6.2)	267 (6.5)
Moderate	2,533 (61.9)	2,575 (63.0)
High	1,290 (31.5)	1,226 (30.0)
Baseline ezetimibe use	262 (6.4)	262 (6.4)
TG levels, n/N (%)		
< 1.7 mmol/L (150 mg/dL)	412/4,086 (10.1)	429/4,089 (10.5)
≥ 1.7 mmol/L (150 mg/dL) to < 2.3 mmol/L (200 mg/dL)	1,193/4,086 (29.2)	1,191/4,089 (29.1)
≥ 2.3 mmol/L (200 mg/dL) to < 5.6 mmol/L (500 mg/dL)	2,481/4,086 (60.7)	2,469/4,089 (60.4)
≥ 5.6 mmol/L (500 mg/dL)	0	0
TG levels (mg/dL), median (IQR)	216.5 (176.5 to 272)	216.0 (175.5 to 274)
Renal impairment,[b] n (%)	905 (22.1)	911 (22.3)
Hypertension, n (%)	3,541 (86.6)	3,543 (86.6)
Abnormal lipids	1,496 (36.6)	1,419 (34.7)
High HDL-c (≥ 1.6 mmol/L [60 mg/dL])	187 (4.6)	187 (4.6)
Low HDL-c (< 1.0 mmol/L [40 mg/dL])	1,327 (32.5)	1,259 (30.8)
TGs > 11.3 mmol/L (1,000 mg/dL)	76 (1.9)	72 (1.8)

CV = cardiovascular; CVD = cardiovascular disease; CHF = congestive hearth failure; HDL-c = high-density lipoprotein cholesterol; IQR = interquartile range; TG = triglyceride; SD = standard deviation.

[a] Statin intensity, as defined in the American College of Cardiology/American Heart Association cholesterol guidelines (Appendix 4).[29]

[b] Defined as estimated glomerular filtration rate < 60 mL/min/1.73 m^2.

Source: Clinical Study Report for the REDUCE-IT[1] and ANCHOR[2] studies.

Table 6: Summary of Baseline Characteristics — ANCHOR Study

	Icosapent ethyl 4 g (N = 233)	Placebo (N = 233)
Age (years), mean (SD)	61.1 (10.03)	61.2 (10.05)
Male sex, n (%)	142 (61)	145 (62)
Body mass index (kg/m^2), mean (SD)	32.7 (4.99)	33.0 (5.04)
Ethnic background, n (%)		
White	218 (96.0)	219 (96.9)
Black or African-American	4 (1.8)	2 (0.9)
Asian	3 (1.3)	3 (1.3)
American Indian or Alaskan Native	1 (0.4)	0
Other	1 (0.4)	2 (0.9)
CV risk stratum, n (%)		
Established CV risk (secondary prevention) [a]	233 (100)	233 (100)
At high CV risk (primary prevention)	0	0
Diabetes, n (%)		
Type 1	1 (0.4)	0
Type 2	170 (72.9)	171 (73.3)
No diabetes	62 (26.6)	62 (26.6)
History of CVD, n (%)		
Myocardial infarction	46 (19.7)	31 (13.3)
Unstable angina	32 (13.7)	18 (7.8)
Stable angina	26 (11.1)	28 (12.0)
Angioplasty	55 (23.6)	40 (17.2)
Bypass surgery	21 (9.0)	21 (9.0)
Myocardial ischemia	15 (6.4)	9 (3.9)
Peripheral artery disease	8 (3.4)	10 (4.3)
Abdominal aortic aneurysm	7 (3.0)	3 (1.3)
Transient ischemic attack	9 (3.8)	10 (4.3)
Stroke of carotid origin	6 (2.6)	7 (3.0)
Obstruction of carotid artery (> 50%)	15 (6.4)	11 (4.7)
Statin intensity/regimen, n (%) [b]		
Low	16 (6.9)	15 (6.4)
Moderate	148 (63.5)	144 (61.8)
High	69 (29.6)	74 (31.8)
Baseline ezetimibe use	15 (6.43)	18 (7.72)
TG levels (mg/dL), mean (SD)	281.1 (82.88)	270.6 (75.02)
Abnormal lipids, n (%)	111 (47.6)	97 (41.6)

	Icosapent ethyl 4 g (N = 233)	Placebo (N = 233)
High HDL-c (≥ 1.6 mmol/L [60 mg/dL])	12 (5.1)	14 (6.0)
Low HDL-c (< 1.0 mmol/L [40 mg/dL])	99 (42.4)	83 (35.6)
TGs > 11.3 mmol/L (1,000 mg/dL)	NA	NA
Renal impairment,[c] n (%)	NA	NA
Hypertension, n (%)	193 (82.8)	195 (83.7)

IQR = interquartile range; CV = cardiovascular; CVD = cardiovascular disease; HDL-c = high-density lipoprotein cholesterol; TG = triglycerides; SD = standard deviation; NA = not available.

[a] In this trial, patients included are categorized as high risk for CVD, yet, for the REDUCE-IT study, these would be equivalent to the secondary prevention or established CVD (Table 4).

[b] Statin intensity, as defined in the American College of Cardiology/American Heart Association cholesterol guidelines (Appendix 4).[29]

[c] Defined as estimated glomerular filtration rate < 60 mL/min/1.73 m^2.

Source: Clinical Study Report for the REDUCE-IT[1] and ANCHOR[2] studies.

Interventions

In both studies, the intervention groups received icosapent ethyl as 1 g liquid-filled, oblong, gelatin capsules, at a dosage of 4 g per day. The placebo groups differed between these two studies. In the REDUCE-IT study, the placebo used was mineral oil in 1 g capsules administered as two capsules twice daily taken with food or about 4 mL per day (4 g per day). The ANCHOR study had a different approach by using a three-arm design: the control group, using four capsules filled with liquid paraffin as placebo administered twice a day orally, an icosapent ethyl 4 g daily group and an icosapent ethyl 2 g daily group.

Certain concurrent medications were permitted in both studies. Because both studies included patients with persistent hypertriglyceridemia, clinicians were allowed to administer statins as long as they were used according to the protocol. In the ANCHOR study, for instance, investigators were allowed to change patients from a non-study statin to one allowed by the protocol, such as atorvastatin, rosuvastatin, or simvastatin. The choice of statin was left to the discretion of the investigator/clinician. Other non-statin lipid-altering medications, as well as corticosteroids, weight-reduction agents, protease inhibitors to treat HIV, cyclophosphamide, or isotretinoin, were not permitted. No difference was noted between groups in the proportion of patients that used antihypertensive drugs, antidiabetic medications, statins, or other co-interventions.

Meanwhile, in the REDUCE-IT trial, non-statin lipid-altering medications or supplements were prohibited during the duration of the study, including niacin, fibrates, prescription omega-3 fatty acid medications, dietary supplements having omega-3 fatty acids (e.g., flaxseed, fish, krill, or algal oils), bile acid sequestrants, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, cyclophosphamide, and systemic retinoids. Use of any of these products during the study had to be "for compelling medical reasons" and documented. Statins, ezetimibe, herbal products, and dietary supplements not containing omega-3 fatty acids were allowed and were balanced between study groups. Modifications in drug choice and dosages on these co-interventions or additions of other medications were allowed "for compelling medical reasons" and left to the discretion of the investigator/physician.

Outcomes

The primary efficacy outcome in the ANCHOR trial was the percent change in TG level from baseline to 12 weeks. The pre-specified secondary efficacy outcomes were the percent change in LDL-c, non-HDL-c, VLDL-c, lipoprotein-associated lipase A2 (Lp-PLA2), and apolipoprotein B from baseline to 12 weeks. Laboratory measurements were analyzed by a central laboratory.

In the REDUCE-IT trial, the primary efficacy outcome was the time from randomization to the first occurrence of any of the composite outcome — blindly adjudicated by an independent committee — that incorporated the following: CV death, non-fatal MI, non-fatal stroke, coronary revascularization, and hospitalization for unstable angina. Researchers assessed the time from randomization to the first occurrence of any component of the composite outcome. All observed data that were positively adjudicated by the committee, including data from patients with premature discontinuation of study drug, were included in the primary analysis. All components of the composite outcome were evaluated for up to 6.2 (median 4.9) years. The key secondary outcome was the time from randomization to the first occurrence of a composite of CV death, non-fatal MI (including silent MI), or non-fatal stroke. Other secondary outcomes were the time from randomization to the first occurrence of the individual or composite of CV death or non-fatal MI; fatal or non-fatal MI; non-elective coronary revascularization; CV death; unstable angina; fatal or non-fatal stroke; composite of total mortality, non-fatal MI, or non-fatal stroke; and total mortality. Morbidity events related to heart failure and cardiac arrhythmias were pre-specified as important outcomes for this review. Time from randomization to the first occurrence of these were tertiary outcomes in REDUCE-IT.

Adverse events were assessed in both studies using accepted definitions and approaches. No minimally important difference was set for any of the continuous outcomes in both studies.

Statistical Analysis

The primary efficacy variable in the ANCHOR trial was the percent change in fasting TG levels from baseline to week 12. A sample size of 194 patients per treatment group provided 90.6% or greater power to detect a difference of 15% between icosapent ethyl 4 g daily and placebo in percent change from baseline in fasting TG levels, assuming a standard deviation (SD) of 45% in TG measurements and a significance level of $P < 0.05$. To account for a 10% dropout rate, a total of 216 patients per treatment group were needed. For efficacy parameters, baseline (visit 4 [week 0]) measurement and week 12 (visit 7) differences were compared between groups. The primary efficacy (ITT) analysis was performed using an analysis of covariance (ANCOVA) model with treatment, sex, type of statin, and presence of diabetes as factors, and baseline TG value as a covariate. The Wilcoxon rank sum test was used as an alternative non-parametric analysis for the treatment comparisons, and medians and quartiles were provided for each treatment group. Estimates for the median of the treatment differences and 95% CI were provided for each treatment comparison. Authors used the Hommel's procedure to test the adequate control for type I error for multiple comparisons for secondary end points.

In the REDUCE-IT trial, sample size was determined by estimating the adjudicated primary end point events. With 90% power to detect a 15% lower relative risk reduction of the primary composite end point in the icosapent ethyl group than in the placebo group,

approximately 1,612 events would be required, and the sample size needed to reach this number of events was approximately 7,990 patients.

The REDUCE-IT study assessed the primary outcome by counts and Kaplan–Meier estimates of the percentage of patients experiencing each type of event by study completion per treatment arm. HRs and 95% CIs were generated with the use of a Cox proportional hazards model that included trial-group assignment as a covariate, stratified according to CV risk category, geographic region, and use of ezetimibe. The two-sided alpha level for the primary analysis was adjusted to 0.0437 from 0.05 to account for the two interim analyses based on a group sequential design with O'Brien–Fleming boundaries generated using the Lan-DeMets alpha-spending function. Log-rank P values from the Kaplan–Meier analysis (stratified based on the three randomization factors) are reported. Subgroup analysis was performed using Kaplan–Meier estimates and the log-rank test stratified by stratification factors used at randomization (except where the subgroup was a stratification factor). The subgroups of interest for this review were pre-specified subgroups in REDUCE-IT: baseline CV risk category (primary versus secondary prevention) and presence or absence of diabetes at baseline. Tests for interaction between subgroup categories were performed and considered a P value of less than 0.15 to be statistically significant. The sponsor noted that subgroup analyses were not powered to detect statistically significant differences between treatment groups within each individual subgroup, "particularly when a subgroup represents less than 50% of the enrolled population, and when a subgroup has low event rates."

The key and other secondary outcomes and tertiary outcomes, as well as the components of the composite outcomes, were analyzed using the same methods as the primary outcome analysis. Statistical analyses of secondary outcomes followed a hierarchical sequential approach to control for inflated type I error. Specifically, the key secondary end point (the time from randomization to the first occurrence of the composite of CV death, non-fatal MI [including silent MI], or non-fatal stroke) was tested only if the primary analysis was statistically significant. Other secondary end points were the time from randomization to the first occurrence of the individual or composite end points, as follows (statistically tested in the order listed):

- composite of CV death or non-fatal MI (including silent MI)
- fatal or non-fatal MI (including silent MI)
- non-elective coronary revascularization
- CV death
- unstable angina requiring emergent hospitalization
- fatal or non-fatal stroke
- composite of total mortality, non-fatal MI (including silent MI), or non-fatal stroke
- total mortality.

Testing was done at a significance level of 0.0437 and ceased when a comparison for a secondary end point was greater than this threshold. All analyses beyond the primary or the last end point meeting statistical significance in this hierarchical order at this alpha level were exploratory, per the analysis plan.

Analysis Populations

For the ANCHOR study, the following analysis populations were defined:

- The ITT population included all randomized patients who took at least one dose of any study drug, had a valid baseline laboratory efficacy measurement, and had at least one valid post-randomization laboratory efficacy measurement of any type. The ITT population was the primary analysis population for the efficacy analyses.
- The per-protocol population included all ITT patients without any major protocol deviations. The per-protocol population was used to assess robustness of the primary analysis results.
- The safety population included all randomized patients who received at least one dose of any study drug.

For the REDUCE-IT study, the following analysis populations were defined:

- The ITT population was defined as all patients who were randomized. All efficacy analyses, including the primary analysis, were performed on the ITT population.
- The modified ITT population was defined as all randomized patients who had study drug dispensed after randomization. Patients were analyzed according to the randomized treatment.
- The per-protocol population included all modified ITT patients without any major protocol deviations who had 80% or greater adherence while on treatment. To be included in the per-protocol population, the minimum time on therapy was 90 days.
- The safety population was defined as all randomized patients, and was the same as the ITT population. Patients were analyzed for safety according to treatment received.

Results

Patient Disposition

In the ANCHOR study, 2,309 patients were screened and 702 were eligible for randomization (30.4%), of which 233 patients were randomized to the icosapent ethyl 4 g daily group, 236 to icosapent ethyl 2 g daily group, and 233 to the control (placebo) group. No major differential dropouts were noticed during the analysis of the disposition of patients (5.2% versus 6.9%, respectively; Table 7).

In the REDUCE-IT study, there was a large number of screening failures. From 19,212 screened patients, 11,033 (57.4%) were not included in the randomization schedule, mostly due to not meeting inclusion criteria, withdrawal of consent, adverse events before randomization, and loss to follow-up. Of the patients eligible for randomization, 4,089 were assigned to the icosapent ethyl group and 4,090 to the control group. Also, little to no difference in the number of patients who discontinued medications between groups was found (9.9% versus 11.2%, respectively, Table 7).

Table 7: Patient Disposition

	REDUCE-IT		ANCHOR	
	Icosapent ethyl 4 g (N = 4,089)	Placebo (N = 4,090)	Icosapent ethyl 4 g (N = 233)	Placebo (N = 233)
Screened, N	19,212		2,309	
Randomized, N	8,179		702	
Randomized to each group, N (%)	4,089	4,090	233	233
Discontinued, N (%)	405 (9.9)	460 (11.2)	12 (5.2)	16 (6.9)
Reason for discontinuation, N (%)				
Adverse events	0	0	5 (2.1)	7 (3.0)
Lost to follow-up	63 (1.5)	89 (2.2)	1 (0.4)	0 (0)
Withdrew consent	281 (6.9)	297 (7.3)	4 (1.7)	6 (2.6)
Investigator judgment	12 (0.29)	12 (0.29)	1 (0.4)	0 (0)
Death before final visit	265 (6.4)[a]	295 (7.2)[a]	0 (0)	1 (0.4)
Other	49 (1.2)	62 (1.5)	1 (0.4)	2 (0.9)
ITT, N	4,089	4,090	226	227
PP, N	3,360	3,299	215	205
Safety, N	4,089	4,090	233	233

ITT = intention-to-treat; PP = per-protocol.

[a] Deaths before final visit are part of the evaluated outcomes, therefore, authors did not count them as discontinuations.

Source: Clinical Study Report for the REDUCE-IT[1] and ANCHOR[2] studies.

Exposure to Study Treatments

In the ANCHOR study, drug adherence (exposure) or days of possible exposure was defined as the date of last dose of study drug: date of first dose + 1 during the double-blind treatment period. Numbers were also presented as percentages. Overall, 88.2% of patients reached more than 90% of exposure, with 88.2% in the icosapent ethyl group and 89.7% in the control group reaching this exposure (Table 8). Approximately 85% of patients were adherent to statin therapy, and 83% remained on the same statin dose throughout the study; there were no differences between treatment groups related to statin use.

In the REDUCE-IT study, drug exposure was calculated as the number of doses assumed to be taken relative to documented dosing period — from randomization to the patient's final date in the study. Overall, 91.9% of patients in the icosapent ethyl group and 91.2% in the placebo group were at least 80% compliant with study drug (i.e., took at least 80% of their prescribed study drug capsules during the study). Table 9 shows the treatment exposure for the REDUCE-IT study. Approximately 3% of patients in both treatment groups were not adherent with study statin use (i.e., took less than 80% of their prescribed statin during the study), and approximately 0.1% of patients in both groups were not on a stable statin regimen during the study. Less than 4% of patients in each treatment group used fibrates, niacin, bile acid sequestrants, PCSK9 inhibitors, or omega-3 fatty acid compounds after randomization during the study.

Table 8: Overall Study Treatment Exposure (ANCHOR Study)

		Icosapent ethyl 4 g (N = 233)	Placebo (N = 233)	Overall (N = 702)
Exposure (days)	Mean	82.1	81.3	81.8
	SD	14.29	14.05	13.23
Exposure categories, n (%)	1 to 28 days	7 (3.0)	6 (2.6)	17 (2.4)
	29 to 42 days	1 (0.4)	6 (2.6)	10 (1.4)
	43 to 84 days	137 (58.8)	140 (60.1)	436 (62.1)
	> 84 days	88 (37.8)	81 (34.8)	239 (34.0)
Adherence (%)	Mean (SD)	95.7 (22.2)	94.6 (12.03)	95.4 (15.47)
Adherence ≥ 90%	n (%)	209 (89.7)	200 (85.8)	619 (88.2)

SD = standard deviation.

Note: Exposure is the date of the last dose of study drug: date of first dose + 1 during double-blind period. When the last dose of study drug is missing, the date of the last known visit is used. Adherence = 100 × (total number of capsules dispensed – total number of capsules returned) / (4 × [last visit date – first dose date]).

Source: Clinical Study Report for the REDUCE-IT[1] and ANCHOR[2] studies.

Table 9: Overall Study Treatment Exposure (REDUCE-IT Study — Safety Population)

	Icosapent ethyl 4 g (N = 4,089)	Placebo (N = 4,090)	Overall (N = 8,179)
Number of capsules per day [a]			
N	3,976	3,980	7,956
Mean (SD)	3.9 (1.12)	4.0 (1.62)	3.9 (1.39)
Overall adherence [b]			
N	3,976	3,980	7,956
Mean % (SD)	98.3 (28.12)	99.2 (40.43)	98.7 (34.83)
Overall adherence categorized [c]			
< 80%, n (%)	322 (8.1)	350 (8.8)	672 (8.4)
≥ 80%, n (%)	3,654 (91.9)	3,630 (91.2)	7,284 (91.6)

SD = standard deviation.

Note: Based on the number of subjects randomized to each treatment group in the safety population (N).

[a] The total number of capsules taken is derived as the total number of capsules dispensed – total number of capsules returned; 1 capsule = 1 g.

[b] Overall adherence (%) = (total number of capsules taken / overall treatment duration × 4 capsules per day) × 100.

[c] Percentage based on number of subjects with overall adherence.

Source: Clinical Study Report for the REDUCE-IT[1] and ANCHOR[2] studies.

Efficacy Outcomes

All-Cause Mortality

Based on the REDUCE-IT study, icosapent ethyl did not statistically significantly reduce overall mortality. The event rates were 6.7% in the icosapent ethyl group versus 7.6% in the control group (HR 0.87; 95% CI, 0.74 to 1.02). The ANCHOR study did not evaluate this outcome.

Cardiovascular Mortality

Based on the REDUCE-IT study, a reduction in the rate of CV mortality (includes adjudicated CV deaths and deaths of undetermined causality) was observed, with a 4.3% event rate in the icosapent ethyl group versus 5.2% in the control group (HR 0.80; 95% CI, 0.65 to 0.98).

Non-Fatal Cardiovascular Events

Non-fatal CV events included non-fatal MI (including silent MI) and non-fatal stroke. The REDUCE-IT study showed that using icosapent ethyl results in a reduction in MI, with an event rate of 5.8% in the icosapent ethyl group versus 8.1% in the placebo group (HR 0.69; 95% CI, 0.59 to 0.83). Also based on this study, icosapent ethyl probably reduces the rate of non-fatal strokes (2.1% events in the intervention group versus 2.9% in the placebo group; HR 0.70; 95% CI, 0.53 to 0.93).

Hospitalizations Due to Unstable Angina, Heart Failure, and Arrhythmia

Icosapent ethyl reduced the occurrence of hospitalizations due to unstable angina (2.6% versus 3.8% event rate in the intervention versus placebo groups, respectively; HR 0.67; 95% CI, 0.53 to 0.86) in REDUCE-IT.

Icosapent ethyl was not found to be different from placebo for the risk in hospitalizations due to congestive heart failure (3.4% versus 3.5% event rate in the intervention and placebo groups, respectively; HR 0.97; 95% CI, 0.77 to 1.22) or cardiac arrhythmias (4.6% versus 3.8% event rate in the intervention and placebo groups, respectively; HR 1.21; 95% CI, 0.97 to 1.49).

Revascularization

Total coronary revascularizations were reduced with the use of icosapent ethyl (event rate of 9.2%) versus placebo (13.3%) (HR 0.66; 95% CI, 0.58 to 0.75). Total revascularization was not part of the hierarchical analysis plan and therefore not adjusted for inflated type I error.

Health-Related Quality of Life

Neither study evaluated the effects of icosapent ethyl on health-related quality of life.

Lipid Blood Levels and hsCRP

Both studies assessed blood concentrations of lipids and hsCRP. From the REDUCE-IT study, icosapent ethyl reduced TG levels, LDL-c, HDL-c, and hsCRP (). When comparing these changes between intervention and placebo groups, the icosapent ethyl group showed larger differences.

The ANCHOR study's main efficacy outcome was the mean change from baseline in TG and other lipids. The icosapent ethyl group had a larger reduction in total TG levels from baseline values (measured at 12 weeks of follow-up) than the placebo group (21.5% median difference between groups). The same was observed with levels of LDL-c, HDL-c, and hsCRP; these changes from baseline were statistically significant (Table 12).

Composite Outcomes

The primary and key secondary composite outcomes used in the REDUCE-IT study were not pre-specified outcomes in the protocol for this review. The outcomes, however, consist of individual outcomes that were identified as relevant, the results for which have already been presented.

Table 10 shows the results for the primary and key secondary composite outcomes. Icosapent ethyl reduced the risk of both outcomes versus placebo. The Kaplan–Meier curve for the primary outcome is presented in Figure 2. Sensitivity analyses confirmed the primary outcome results (Appendix 3, Table 16).

The occurrence of the primary outcome was lower with icosapent ethyl than with placebo in the established CVD (secondary prevention) subgroup, but there was no statistically significant difference between groups in the subgroup at risk for CVD (primary prevention) (Appendix 3, Table 16). The test for interaction between these subgroups was statistically significant (P = 0.1388). In the subgroup of patients with diabetes at baseline and in those without diabetes at baseline, icosapent ethyl reduced the occurrence of the composite primary outcome relative to placebo to a similar magnitude (P value for interaction = 0.5598).

Results from the analyses of the individual components of the primary and key secondary outcomes, each analyzed as an independent outcome (e.g., time to first occurrence of non-fatal MI, regardless of the time to first occurrence of any other end points for the same patient), is presented in Figure 3 (Appendix 3).

Table 10: Mortality and Non-Fatal Events — ITT Population

Outcomes[a]	REDUCE-IT	
	Icosapent ethyl N = 4,089	Placebo N = 4,090
Primary composite outcome (composite of CV death, non-fatal MI [including silent MI], non-fatal stroke, coronary revascularization, and unstable angina requiring hospitalization)		
n (%)	705 (17.2)	901 (22.0)
HR (95% CI)	0.752 (0.682 to 0.830)	
P value	0.00000001	
Components contributing to composite outcome, n (%)[b]		
CV death[c]	137 (3.4)	149 (3.6)
Non-fatal MI[d]	205 (5.0)	280 (6.8)
Non-fatal stroke	80 (2.0)	105 (2.6)
Coronary revascularization	189 (4.6)	244 (6.0)
Hospitalization for unstable angina	94 (2.3)	123 (3.0)
Key secondary composite outcome (composite of CV death, non-fatal MI [including silent MI], and non-fatal stroke)		
n (%)	459 (11.2)	606 (14.8)
HR (95% CI)	0.735 (0.651 to 0.830)	
P value	0.0000006	
Components contributing to composite outcome, n (%)[b]		

Outcomes[a]	REDUCE-IT	
	Icosapent ethyl N = 4,089	Placebo N = 4,090
CV death[c]	149 (3.6)	167 (4.1)
Non-fatal MI[d]	230 (5.6)	325 (7.9)
Non-fatal stroke	80 (2.0)	114 (2.8)
CV death or non-fatal MI		
n (%)	392 (9.6)	507 (12.4)
HR (95% CI)	0.753 (0.660 to 0.859)	
P value	< 0.001	
Fatal or non-fatal MI		
n (%)	250 (6.1)	355 (8.7)
HR (95% CI)	0.688 (0.585 to 0.808)	
P value	< 0.001	
Fatal MI, n (%)	16 (0.4)	29 (0.7)
HR (95% CI)	0.546 (0.297 to 1.005)	
P value	0.0484	
Non-fatal MI, n (%)	237 (5.8)	332 (8.1)
HR (95% CI)	0.697 (0.590 to 0.823)	
P value	< 0.0001	
Urgent or emergency revascularization		
n (%)	216 (5.3)	321 (7.8)
HR (95% CI)	0.653 (0.550 to 0.776)	
P value	< 0.001	
CV death		
n (%)	174 (4.3)	213 (5.2)
HR (95% CI)	0.803 (0.657 to 0.981)	
P value	0.0315	
Hospitalization for unstable angina		
n (%)	108 (2.6)	157 (3.8)
HR (95% CI)	0.679 (0.531 to 0.868)	
P value	0.0018	
Fatal or non-fatal stroke		
n (%)	98 (2.4)	134 (3.3)
HR (95% CI)	0.720 (0.555 to 0.934)	
P value	0.0129	
Fatal stroke, n (%)	14 (0.3)	18 (0.4)
HR (95% CI)	0.767 (0.382 to 1.543)	
P value	0.4564	

Outcomes[a]	REDUCE-IT	
	Icosapent ethyl N = 4,089	Placebo N = 4,090
Non-fatal stroke, n (%)	85 (2.1)	118 (2.9)
HR (95% CI)	0.708 (0.536 to 0.936)	
P value	0.0149	
Death from any cause, non-fatal MI, or non-fatal stroke		
n (%)	549 (13.4)	690 (16.9)
HR (95% CI)	0.772 (0.690 to 0.864)	
P value	< 0.001	
Death from any cause		
n (%)	274 (6.7)	310 (7.6)
HR (95% CI)	0.870 (0.739 to 1.023)	
P value	0.0915[e]	
Outcomes outside the hierarchy		
Coronary revascularization		
n (%)	376 (9.2)	544 (13.3)
HR (95% CI)	0.664 (0.583 to 0.758)	
P value	0.0013	
Hospitalization for arrhythmias		
n (%)	188 (4.6)	154 (3.8)
HR (95% CI)	1.21 (0.97 to 1.49)	
P value	0.0856	
Hospitalization for congestive heart failure		
n (%)	141 (3.4)	144 (3.5)
HR (95% CI)	0.97 (0.77 to 1.22)	
P value	0.781	

CI = confidence interval; CV = cardiovascular; HR = hazard ratio; ITT = intention-to-treat; MI = myocardial infarction.

[a] Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

[b] Based on a patient's first post-randomization occurrence of the event contributing to the primary end point.

[c] CV death includes adjudicated CV deaths and deaths of undetermined causality.

[d] Non-fatal MI includes silent MI, which was assumed to occur on the date of the first post-randomization electrocardiogram tracing indicative of a silent MI.

[e] Death from any cause was the only comparison not meeting statistical significance during the hierarchical evaluation. After this, all tertiary outcomes, such as heart failure and arrhythmias, were considered exploratory.

Source: Clinical Study Report for the REDUCE-IT[1] study.

Table 11: Efficacy Outcomes — Lipids and hsCRP (REDUCE-IT Trial), ITT Population

	Icosapent ethyl 4 g (N = 4,089)				Placebo (N = 4,090)				Treatment difference between intervention and placebo		
	Baseline (N = 4,086)	Day 360 (N = 3,689)	Change from baseline	% change from baseline	Baseline (N = 4,089)	Day 360 (N = 3,633)	Change from baseline (N = 3,883)	% change from baseline	Change from baseline [a]	% change from baseline [a]	P value
Median TG, mg/dL, (IQR)	216.5 (176.5 to 272.0)	175.0 (132.0 to 238.0)	–39.0 (–82.0 to 7.0)	–18.3 (–36.4 to 3.2)	216.0 (175.5 to 274.0)	221.0 (164.0 to 298.0)	4.5 (–44.0 to 57.5)	2.2 (–20.3 to 27.5)	–44.5 (–48.0 to –40.5)	–19.7 (–21.3 to –18.2)	< 0.001
Median LDL-c, mg/dL (IQR)	74.0 (61.5 to 88.0)	77.0 (63.0 to 94.0)	2.0 (–9.0 to 15.0)	3.1 (–11.6 to 23.0)	76.0 (63.0 to 89.0)	84.0 (69.0 to 100.0)	7.0 (–5.0 to 21.0)	10.2 (–5.9 to 31.3)	–5.0 (–6.0 to –4.0)	–6.6 (–7.9 to –5.3)	< 0.001
Median HDL-c, mg/dL (IQR)	40.0 [b] (34.5 to 46.0)	39.0 [c] (33.0 to 45.0)	–1.0 (–4.0 to 2.5)	–2.6 (–10.3 to 6.0)	40.0 [d] (35.0 to 46.0)	42.0 [e] (36.0 to 48.0)	1.5 (–2.0 to 5.0)	3.8 (–4.9 to 13.5)	–2.5 (–2.5 to –2.0)	–6.3 (–6.9 to –5.6)	< 0.001
Median hsCRP, mg/L (IQR)	0.8 (0.1 to 1.5)	0.6 [f] (–0.2 to 1.4)	–0.1 (–0.7 to 0.4)	–21 (–82.3 to 34.1)	0.8 (0.1 to 1.5)	1.0 [g] (0.3 to 1.8)	0.3 (–0.2 to 0.8)	0.0 (–65.6 to 65.8)	–0.4 (–0.5 to –0.4)	–22.5 (–27.9 to –17.0)	< 0.001

TG = triglyceride; LDL-c = low-density lipoprotein cholesterol; HDL-c = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; IQR = interquartile range.

[a] Values in parentheses indicate the 95% CI.

[b] N = 4,077

[c] N = 3,676

[d] N = 4,090

[e] N = 3,619

[f] N = 3,322; this outcome was evaluated at day 720.

[g] N = 3,229; this outcome was evaluated at day 720.

Source: Clinical Study Report for the REDUCE-IT[1] study.

Table 12: Efficacy Outcomes — Lipids and hsCRP (ANCHOR Trial)

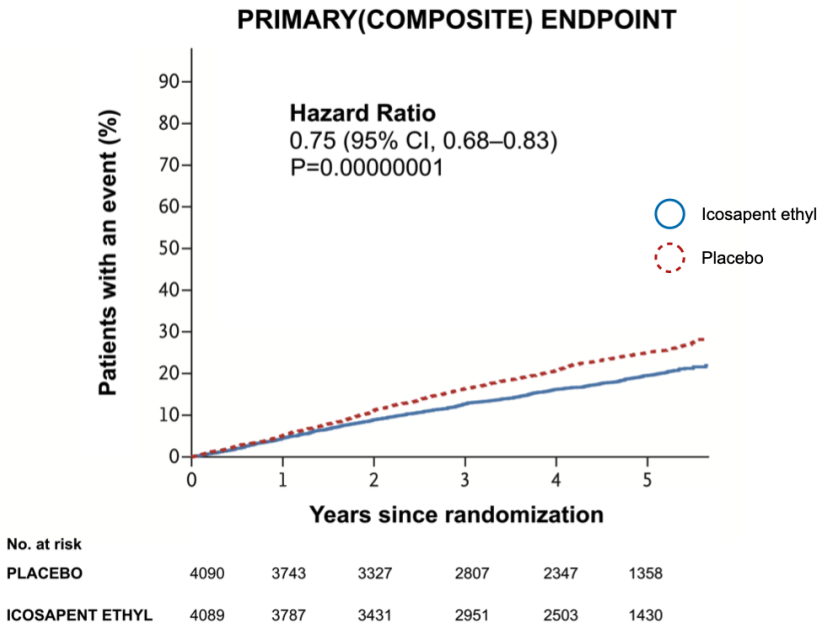
Biomarker	Icosapent ethyl 4 g (N = 4,089)			Placebo (N = 4,090)			Treatment difference		
	Baseline (N = 226)	Week 12 (N = 226)	% change from baseline	Baseline (N = 227)	Week 12 (N = 227)	% change from baseline	Median difference	95% CI	P value
Median TG, mg/dL, (IQR)	264.8 (93.0)	220.8 (92.0)	–17.5 (31.0)	259.0 (81.0)	269.5 (149.5)	5.9 (44.9)	–21.5	–26.7 to –16.2	< 0.001
Median LDL-c, mg/dL (IQR)	82.0 (25.0)	83.0 (31.0)	1.5 (26.6)	84.0 (27.0)	88.5 (31.0)	8.8 (31.0)	–6.2	–10.5 to –1.7	0.0067
Median HDL-c, mg/dL (IQR)	37.0 (12.0)	37.0 (13.0)	–1.0 (18.2)	39.0 (12.0)	40.0 (14.0)	4.8 (22.0)	–4.5	–7.4 to –1.8	0.0013
Median hsCRP, mg/L (IQR)[a]	2.2 (2.7)	2.0 (3.0)	–0.1 (1.4)	2.2 (4.0)	2.6 (4.7)	0.3 (1.8)	–0.5	–0.8 to –0.2	< 0.001

CI = confidence interval; TG = triglyceride; LDL-c = low-density lipoprotein cholesterol; HDL-c = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; IQR = interquartile range.

[a] Change from baseline measured in mg/dL, in 217 patients in the intervention group and 219 in the placebo group.

Source: Clinical Study Report for the ANCHOR[2] study.

Figure 2: Kaplan–Meier Curve of Time to Primary Composite End Point From Date of Randomization (REDUCE-IT Trial)[1]



CI = confidence interval.

Source: Clinical Study Report for REDUCE-IT[1].

Harms

Adverse Events

The percentage of patients experiencing AEs was similar in the icosapent ethyl and placebo groups in REDUCE-IT (82% and 81%, respectively) and in ANCHOR (45% and 48%, respectively). The most common adverse events reported in both studies (with prevalence above 3%) were also similar between groups. Among these, the most commonly reported were diarrhea, nausea, back pain, nasopharyngitis, and arthralgia (Table 13 and Table 14).

Serious Adverse Events

The REDUCE-IT study reported that 31% of patients in each group had a serious adverse event. In the ANCHOR trial, 3% of patients in the icosapent ethyl group and 2.1% in the placebo group had a serious adverse event. Individual types of serious adverse events occurred at a frequency of less than 3% in REDUCE-IT.

Withdrawals Due to Adverse Events

There was no difference between the icosapent ethyl and placebo groups (8% in each group) in the number of patients who withdrew due to adverse events in the REDUCE-IT study. Fewer patients in the ANCHOR study withdrew due to adverse events (2.1% with icosapent ethyl and 3.0% with placebo).

Notable Harms

Potential adverse events of particular interest were identified for the review based on feedback from clinical experts, the draft product monograph for icosapent ethyl, and notable harms pre-specified in the protocol. These notable harms included bleeding leading to transfusion or hospitalization (including visits to the emergency department), edema, atrial fibrillation, constipation, gout, musculoskeletal pain, arthralgia, and diarrhea (Table 13 and Table 14).

In the REDUCE-IT study, a larger percentage of patients treated with icosapent ethyl had atrial fibrillation than in the placebo arm (5.3% versus 3.9%, respectively). Only one patient with atrial fibrillation was reported in the ANCHOR study, in a person randomized to placebo. Peripheral edema was also observed more frequently in the icosapent ethyl group than in the placebo group in REDUCE-IT (6.5% versus 5.0%, respectively) and in the ANCHOR study (1.3% versus 0.9%, respectively). Rates of serious adverse bleeding events were 2.7% in the icosapent ethyl group and 2.1% in the placebo group in REDUCE-IT; there were no fatal bleeding events in either group. There were no differences in the rates of adjudicated hemorrhagic stroke between the icosapent ethyl group and the placebo group.

A higher frequency of constipation was reported for icosapent ethyl versus placebo (5.4% versus 3.6%, respectively) in REDUCE-IT. Diarrhea was the most commonly occurring AE in both trials but occurred more frequently in the placebo arm than in the icosapent ethyl group. Musculoskeletal pain (back pain and arthralgia) occurred more frequently with icosapent ethyl than placebo in the trials. Finally, gout was observed in more patients treated with icosapent ethyl than placebo in REDUCE-IT; however, in ANCHOR, two patients in the placebo group had gout, whereas no patients treated with icosapent ethyl had gout.

Table 13: Summary of Harms — REDUCE-IT Study

	Icosapent ethyl N = 4,089	Placebo N = 4,090
Patients with at least one TEAE,[a] n (%)	3,343 (81.8)	3,326 (81.3)
Serious AE	1,252 (30.6)	1,254 (30.7)
TEAE leading to withdrawal of study drug [b]	321 (7.9)	335 (8.2)
Serious TEAE leading to withdrawal of study drug [b]	88 (2.2)	88 (2.2)
Serious TEAE leading to death	94 (2.3)	102 (2.5)
Most common AEs with > 3% prevalence, n (%)		
Diarrhea [c]	367 (9.0)	453 (11.1)
Back pain	335 (8.2)	309 (7.6)
Hypertension	320 (7.8)	344 (8.4)
Nasopharyngitis	314 (7.7)	300 (7.3)
Arthralgia	313 (7.7)	310 (7.6)
Upper respiratory tract infection	312 (7.6)	320 (7.8)
Bronchitis	306 (7.5)	300 (7.3)
Chest pain	273 (6.7)	290 (7.1)
Peripheral edema [c]	267 (6.5)	203 (5.0)
Pneumonia	263 (6.4)	277 (6.8)

	Icosapent ethyl N = 4,089	Placebo N = 4,090
Influenza	263 (6.4)	271 (6.6)
Dyspnea	254 (6.2)	240 (5.9)
Urinary tract infection	253 (6.2)	261 (6.4)
Cough	241 (5.9)	241 (5.9)
Osteoarthritis	241 (5.9)	218 (5.3)
Dizziness	235 (5.7)	246 (6.0)
Pain in extremity	235 (5.7)	241 (5.9)
Cataract	233 (5.7)	208 (5.1)
Fatigue	228 (5.6)	196 (4.8)
Constipation [c]	221 (5.4)	149 (3.6)
Atrial fibrillation [c]	215 (5.3)	159 (3.9)
Requiring hospitalization > 24 h	127 (3.1)	84 (2.1)
Angina pectoris	200 (4.9)	205 (5.0)
Anemia	191 (4.7)	236 (5.8)
Gout [c]	171 (4.2)	127 (3.1)
Bleeding related disorders [c]	111 (2.7)	85 (2.1)
GI bleeding	62 (1.5)	47 (1.1)
CNS bleeding	14 (0.3)	10 (0.2)
Most common serious AEs with > 2% prevalence, n (%)		
Pneumonia	105 (2.6)	118 (2.9)

AE = adverse event; CNS = central nervous system; GI = gastrointestinal; TEAE = treatment-emergent adverse event.

Note: A treatment-emergent adverse event (TEAE) is defined as an event that first occurs or worsens in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. Percentages are based on the number of subjects randomized to each treatment group in the safety population (N). Events that were positively adjudicated as clinical end points are not included.

[a] Drug-related TEAEs include those characterized as related, probably related, or possibly related.

[b] Withdrawal of study drug excludes subjects who were off drug in study for 30 days or more, then restarted study drug.

[c] Notable harms as detailed in this review protocol (Table 4).

Source: Clinical Study Report for the REDUCE-IT[1] study.

Table 14: Summary of Harms — ANCHOR Study

Category, n (%)	Icosapent ethyl N = 233	Placebo N = 233
Patients with at least 1 TEAE	106 (45.5)	112 (48.1)
Patients with SAEs	7 (3.0)	5 (2.1)
Deaths	0 (0.0)	1 (0.4)
Patients with an adverse event leading to discontinuation from the study	5 (2.1)	7 (3.0)
Patients with an SAE leading to discontinuation	1 (0.4)	2 (0.9)
Most common AEs with > 3% prevalence, n (%)		
Diarrhea [a]	8 (3.4)	10 (4.3)
Nausea	5 (2.1)	7 (3.0)
Nasopharyngitis	1 (0.4)	7 (3.0)

Category, n (%)	Icosapent ethyl N = 233	Placebo N = 233
Arthralgia	4 (1.7)	1 (0.4)
GI bleeding [a]	1 (0.4)	1 (0.4)
CNS bleeding [a]	1 (0.4)	0 (0)
Atrial fibrillation [a]	0 (0)	1 (0.4)
Peripheral edema [a]	3 (1.3)	1 (0.4)
Musculoskeletal pain [a]	3 (1.3)	2 (0.9)
Constipation [a]	2 (0.9)	4 (1.7)
Gout [a]	0 (0)	2 (0.9)

AE = adverse event; CNS = central nervous system; GI = gastrointestinal; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Note: A TEAE was defined as an adverse event that started after the first dose of double-blind study drug or occurred before the first dose and worsened in severity during the double-blind treatment period. % = n/N, where n is the number of patients with at least 1 TEAE for the specified category and N is the number of patients for the treatment group. For maximum severity summary, only the worst severity for each patient was used. Each patient was counted only once.

[a] Notable harm as stated in this review protocol (Table 4).

Source: Clinical Study Report for the ANCHOR[2] study.

Critical Appraisal

Internal Validity

Both studies had a proper randomization process. The generation of the randomization sequence was adequate, and the concealment of the allocation sequence was concealed until participants were enrolled and assigned to the interventions. Furthermore, no differences were noted in baseline characteristics, suggesting that the randomization process was successful.

The blinding of participants, clinicians, and researchers was achieved through identical placebo capsules, which avoided important and unbalanced deviations from the intended interventions. There is no clear evidence that participants were aware of their assigned intervention during the trial. Additionally, patients who discontinued or deviated from the interventions were properly analyzed in both ITT and per-protocol principles. Certain scenarios related to censoring in the primary time-to-event analysis were modelled appropriately in REDUCE-IT.

Overall, follow-up was relatively complete for the primary end point, with more than 95% of patients accounted for in the ITT analysis. Missing data were handled by evaluating both ITT and per-protocol analyses. Differences in missing data between study groups were unlikely to affect the final results.

The ANCHOR trial was short-term, and long-term effects could not be evaluated. However, outcomes were objectively obtained, and the processes to accomplish outcome measurements were well described. In the REDUCE-IT trial, the components of the composite outcome were objectively assessed in a blinded fashion by an appropriate adjudication committee to minimize bias. These measurements were similar among intervention and placebo groups.

There is a low risk of bias due to selection of the reported results. A protocol is well described for both studies, and the results analyzed are in accordance with the pre-specified analysis plan, even after considering the amendment in the protocol of the

REDUCE-IT study to designate a key secondary composite outcome. This amendment was performed before the study's conclusion and data evaluation.

Subgroup analyses were set a priori and properly conducted. However, all were underpowered to detect a significant effect from modifiers. Multiplicity was assessed by using a hierarchical model; however, it was not accounted for in the subgroup analysis.

The placebo used in the REDUCE-IT study was composed of mineral oil to mimic the active intervention. An increase in LDL-c levels at year one was observed in the placebo group when compared to the icosapent ethyl–treated arm (an increase of 10.2% and 3.1% in the placebo and intervention groups, respectively; Table 11). Also, an increase in hsCRP at year two was reported (32.9% versus –13.9% in the placebo versus intervention groups, respectively) suggesting a possible biological effect of the mineral oil contained in the placebo, potentially inhibiting the gastrointestinal absorption of statins. These increases were not substantial, and a post hoc analysis by the sponsor suggests a similarly lower risk of events with icosapent ethyl and placebo, regardless of whether there was an increase in LDL-c in the placebo arm. However, the clinical experts consulted by CADTH indicated that this was notable.

External Validity

Patients included in the ANCHOR study were only from the US, while those from the REDUCE-IT trial were distributed worldwide. Results from the primary outcome by region subgroup analysis (categorized as a group of western countries, Eastern European countries, and Asia–Pacific) in REDUCE-IT suggested potential differences in the magnitude of treatment effects by region (HR 0.491 for Asia–Pacific region, 0.740 for western countries, and 0.842 for Eastern European countries); however, the numbers of patients in the Eastern European and Asia–Pacific subgroups were relatively small, with imprecise estimates (very wide confidence intervals), and the test for interaction was not statistically significant (P = 0.3046). The clinical experts consulted by CADTH indicated that, despite some potential differences, the populations are likely similar to the target population in Canada in which icosapent ethyl would be used.

As in many clinical trials, the patients included could be considered highly selected, as the studies excluded a large number of patients (screening failures) who could be encountered in real clinical practice, such as those with TG below 2.3 mmol/L (200 mg/dL) or above 5.6 mmol/L (500 mg/dL), with congestive heart failure, active liver disease, or a planned coronary surgery or intervention. The mean (SD) ages in both studies were approximately 61 (9.8) and 63 (8.4) years; the clinical experts noted that the studies provide limited evidence on patients younger than 50 years and older than 70 years, which are patients seen in clinical settings.

The distribution of the baseline statin intensity may not reflect clinical practice. The clinical experts consulted by CADTH indicated that the distribution of patients receiving moderate- and high-intensity statin therapy is reversed from what clinical practice guidelines would recommend in this population of patients. The goal should be to first ensure optimal treatment with a statin before adding another therapy: the highest tolerated intensity of statin therapy is used to bring the lipid profile to the target range. The experts acknowledged that the distribution in the studies may reflect what is observed in registry data, because there is suboptimal adherence to practice guidelines in clinical practice settings. The distribution of baseline statin intensity was balanced between treatment groups in both studies and was unlikely to influence the results; furthermore, regardless of

statin intensity distribution, the median baseline LDL-c level was within target levels at approximately 1.94 mmol/L (75 mg/dL) across the studied population.

Other Relevant Studies

At the time of writing this report, no other relevant studies have been published from the REDUCE-IT study. Regarding the ANCHOR study, one report pertinent to this review is described below.

Ballantyne et al.[28] is an exploratory analysis pre-specified from the ANCHOR study. It assesses patients in the same group with TG levels between 2.3 and 5.6 mmol/L (200 and 500 mg/dL) despite statin treatment. However, the aim of the study was to assess the effects of icosapent ethyl on lipoprotein particle concentration and size as the main outcome, and the correlations of atherogenic particles with apolipoprotein B. Nuclear magnetic resonance spectroscopy was used to measure lipoprotein particle concentration and size. It was reported that, compared with placebo, icosapent ethyl 4 g per day significantly reduced VLDL-c (7.7%, P = 0.0001) and HDL-c (1.2%, P = 0.0014) particle sizes, with a modest but significant increase in LDL-c particle size (0.5%, P 0.0031). This is a descriptive study with indirect outcomes that are not directly applicable to clinical practice.

Discussion

Summary of Available Evidence

Two randomized, double-blind, placebo-controlled studies met the inclusion criteria for this review comparing the recommended dose of icosapent ethyl (4 g daily) to placebo in patients with persistent elevated blood levels of TG despite treatment with statins and either established CVD or considered at high risk for CVD. The ANCHOR study was a 12-week trial including 702 participants in the US, and the REDUCE-IT study was multinational and included 8,179 patients who were followed for a median of 4.9 years. The ANCHOR study evaluated changes from baseline in blood levels of TG, as well as LDL-c, HDL-c, and hsCRP. The REDUCE-IT study, on the other hand, focused on clinically important outcomes, of which the main was a composite of CV death, non-fatal MI, non-fatal stroke, coronary revascularization, and hospitalization due to unstable angina.

Interpretation of Results

Efficacy

Based on the REDUCE-IT study, icosapent ethyl resulted in a reduction in the composite outcome of CV death, non-fatal MI, non-fatal stroke, coronary revascularization, and hospitalization for unstable angina. Overall, 22% of patients in the placebo group and 17.2% of those taking icosapent ethyl (absolute difference of 4.8%) experienced at least one component of the composite outcome. Icosapent ethyl was associated with a 24.8% relative risk reduction, which the clinical experts consulted by CADTH indicated is clinically meaningful. The clinical experts noted, however, that the magnitude of benefit with icosapent ethyl may vary in clinical practice settings outside of the controlled trial with greater variation in treatment adherence and statin dosage, and a more heterogeneous population than that in the trials, as examples. Results for the individual components of the composite primary outcome did not clearly suggest that one component dominated in driving the treatment effect of icosapent ethyl.

Subgroup analyses in REDUCE-IT suggested a potential difference in risk reduction for the composite primary outcome with icosapent ethyl in patients with established CVD (HR versus placebo 0.726; 95% CI, 0.650 to 0.810) and those at high risk for CVD (HR versus placebo 0.876; 95% CI, 0.700 to 1.095). The test for interaction was statistically significant at the pre-specified alpha level. The imbalance in the percentage of patients categorized as having established CVD (70%) versus those at risk (30%) may, in part, explain this result.

Although icosapent ethyl reduced CV mortality events (4.3% event rate in the icosapent ethyl group versus 5.2% in the placebo group), non-fatal CV events, and coronary revascularization, the study revealed no significant difference in all-cause mortality, or hospitalizations due to arrhythmia or congestive heart failure. The lack of a statistically significant effect on all-cause mortality is not surprising, at least in part because of the sample size and the duration of REDUCE-IT, both of which were likely insufficient to evaluate this outcome.

In both studies, blood levels of TG, LDL-c, HDL-c, and hsCRP changed from baseline in the intervention group, and this change was larger in the icosapent ethyl group than in the placebo group. The complete mechanism of action of icosapent ethyl in the studied populations remains unclear, but it appears, in part, to positively impact blood lipid profiles.

The clinical significance of this treatment effect still needs to be evaluated to understand its relationship to clinically important outcomes.

It is difficult to determine the clinical value added of icosapent ethyl, given that the primary efficacy data comes from a single — albeit relatively large — randomized controlled trial versus placebo. No studies were available comparing icosapent ethyl with relevant comparators considered for this review: fibrates, ezetimibe, niacin, and omega-3 fatty acid preparations. Studies with these other drugs that also lower TG levels have not demonstrated a benefit as add-on treatment in the patient population with residual risk and in other groups of patients.[17,30-32] The low dose or the low ratio of EPA to DHA in some of the omega-3 fatty acids studied may be the reason previous studies showed no effect. Yet, the absence of head-to-head or indirect comparisons between icosapent ethyl and comparators of interest for this review means the comparative effects are unknown.

Furthermore, the results for efficacy may not be applicable to patients with characteristics outside the inclusion criteria of the REDUCE-IT trial. Indeed, the clinical experts consulted by CADTH noted that use of icosapent ethyl will be targeted to the studied population as add-on to optimized statin treatment. The real-world benefit of icosapent ethyl may be less than observed in the seemingly selected population of REDUCE-IT (which is a common trait of randomized controlled trials of drugs for CV conditions). It is important to note the concern generated by the increased levels of TG and hsCRP observed in the placebo arm of the REDUCE-IT trial. Although the effect of this increase on the results of REDUCE-IT is still uncertain, as no effects of this difference were observed in post hoc analyses, it is worth considering when the drug is used in clinical settings and when adherence to treatment may not be complete.

No input from patient groups was received for this review. However, based on input provided for previous CADTH CDR reviews on drugs for the prevention or treatment of CVD, it is likely that outcomes of interest to patients (with exception of health-related quality of life) were evaluated in REDUCE-IT. Past patient-group input, as well as input from the clinical experts consultations, suggests that the efficacy results of REDUCE-IT would fill some of the unmet needs for an effective therapy in patients with residual CV risk despite statin therapy.

Harms

The rates of adverse events were low and generally similar between the trial groups. Some differences, however, are important to mention.

Atrial fibrillation, constipation, peripheral edema, and serious adverse bleeding were more frequent in the icosapent ethyl group than in the placebo group. The higher frequencies of bleeding and of hospitalization for atrial fibrillation or flutter in the icosapent ethyl group versus placebo were considered important by the clinical experts participating in this review. This was considered a safety signal that should be monitored in clinical practice. The incidence of bleeding was greater in patients receiving concomitant antithrombotic medications, such as Aspirin, clopidogrel, or warfarin. However, even with these increased risks of bleeding and atrial fibrillation, the undesirable events are likely outweighed by the reduction of CV risk in high-risk patients with elevated serum TG levels despite treatment with a statin.

Conclusions

Icosapent ethyl reduced the occurrence of events included in the composite outcome of CV death, non-fatal MI, non-fatal stroke, coronary revascularization, and hospitalization for unstable angina in patients treated with statins and with residual CV risk (i.e., those with increased TG levels despite treatment and with established CVD or at high risk of CV events). The key secondary end points — a composite of CV death, MI, or stroke — were also fewer in those treated with icosapent ethyl than in the placebo group. Icosapent ethyl also had a beneficial effect when the components of the composite outcome CV mortality, non-fatal CV events, and coronary revascularization were evaluated individually, although there was no difference in all-cause mortality or hospitalizations due to heart failure and arrhythmia. The effects of icosapent ethyl, however, might include an increase in the number of adverse events such as serious bleeding, peripheral edema, and hospitalization due to atrial fibrillation. The results may not be generalizable; they may be restricted to the specific population enrolled in the REDUCE-IT study.

Appendix 1: Literature Search Strategy

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946–present) Embase (1974–present) Cochrane Central Register of Controlled Trials (CCTR) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	July 16, 2019
Alerts:	Bi-weekly search updates until project completion
Study Types:	No filters were applied to limit retrieval by study type
Limits:	Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.mp	Mapped term
.rn	Registry number
.nm	Name of substance word
.ot	Original title
.go	Grant organization
.pb	Publisher
.ir	Investigator
.ia	Investigator affiliation

SYNTAX GUIDE	
.dq	Candidate term word (Embase)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily
cctr	Ovid database code; Cochrane Central Register of Controlled Trials

MULTI-DATABASE STRATEGY	
1	(vascepa* or AMR101* or AMR 101* or epadel* or 6GC8A4PAYH* or UNII6GC8A4PAYH* or vp-pnv-dha* or vp pnv dha* or ethyl-EPA* or ethyl EPA* or EPA ethyl ester* or K85 or miraxion* or mnd 21* or mnd21* or lax 101* or lax101*).ti,ab,kf,ot,hw,rn,nm.
2	((icosapen* or eicosapent* or timnodon*) adj4 ethyl).ti,ab,kf,ot,hw,rn,nm.
3	exp Eicosapentaenoic Acid/ or (eicosapentaenoic acid or icosapentaenoic acid).ti,ab.
4	(HLS or Amarin).ti,ab,kf,ot,hw,go,pb,ir,ia.
5	3 and 4
6	1 or 2 or 5
7	6 use medall
8	*icosapentaenoic acid ethyl ester/
9	(vascepa* or AMR101* or AMR 101* or epadel* or vp-pnv-dha* or vp pnv dha* or ethyl-EPA* or ethyl EPA* or EPA ethyl ester* or K85 or miraxion* or mnd 21* or mnd21* or lax 101* or lax101*).ti,ab,kw,dq.
10	((icosapen* or eicosapent* or timnodon*) adj4 ethyl).ti,ab,kw,dq.
11	icosapentaenoic acid/ or (eicosapentaenoic acid or icosapentaenoic acid).ti,ab.
12	(HLS or Amarin).ti,ab,kf,ot,hw,go,pb,ir,ia.
13	11 and 12
14	8 or 9 or 10 or 13
15	14 use oemezd
16	(conference abstract or conference review).pt.
17	15 not 16
18	7 or 17
19	exp animals/
20	exp animal experimentation/ or exp animal experiment/
21	exp models animal/
22	nonhuman/
23	exp vertebrate/ or exp vertebrates/
24	or/19-23
25	exp humans/
26	exp human experimentation/ or exp human experiment/
27	or/25-26
28	24 not 27
29	18 not 28
30	remove duplicates from 29

CLINICAL TRIAL REGISTRIES		
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. Search terms: Vascepa, Epadel, icosapent ethyl, AMR101	
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. Search terms: Vascepa, Epadel, icosapent ethyl, AMR101	

OTHER DATABASES		
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	

Grey Literature

Dates for Search:	July 6–10, 2019
Keywords:	Vascepa, Epadel, icosapent ethyl, eicosapentaenoic ethyl, icosapentaenoic ethyl, ethyl -EPA
Limits:	None

Relevant websites from the following sections of the CADTH grey literature checklist Grey Matters: a practical tool for searching health-related grey literature (https://www.cadth.ca/grey-matters) were searched:

- health technology assessment agencies
- health economics
- clinical practice guidelines
- drug and device regulatory approvals
- advisories and warnings
- drug class reviews
- clinical trial registries
- databases (free)
- health statistics
- internet search.

Appendix 2: Excluded Studies

Table 15: Excluded Studies

Reference	Reason for Exclusion
Maki et al. (2017) [33]	Intervention: Vascepa is the comparator against an EPA/DHA combination (MAT9001); small open-label trial crossover; outcomes were TG levels and adverse events related to the drugs
Bhatt et al. (2019) [34]	Study design: Post hoc analysis of REDUCE-IT of subsequent ischemic events (first, subsequent, and total ischemic events)
Bays et al. (2011) [35]	Study population: The MARINE study; population did not meet inclusion criteria for our protocol
Mosca et al. (2017) [36]	Post hoc report of the MARINE and ANCHOR trials
Budoff et al. (2018) [37]	Protocol of the EVAPORATE study: no results yet; it assesses Vascepa
Bays et al. (2012) [38]	Design: MARINE trial exploratory analysis on lipoprotein particle concentrations and sizes
Bhatt et al. (2017) [39]	Design: Narrative analysis of the REDUCE-IT study

Appendix 3: Detailed Outcome Data

Table 16: Stratified Analysis of Time to the Primary Composite End Point From Date of Randomization: Sensitivity Analyses — ITT Population

End point, n (%)	Icosapent ethyl N = 4,089	Placebo N = 4,090	HR (95% CI)	P value
Primary composite – excluding undetermined death	673 (16.5)	878 (21.5)	0.737 (0.667 to 0.815)	< 0.0001
Primary censored at drug discontinuation	577 (14.1)	732 (17.9)	0.739 (0.662 to 0.824)	< 0.0001
Primary censored at drug discontinuation + 30 days	596 (14.6)	776 (19.0)	0.721 (0.648 to 0.802)	< 0.0001
Primary with silent MI censored at last normal	705 (17.2)	901 (22.0)	0.752 (0.682 to 0.830)	< 0.0001
Primary with silent MI censored at mid-point	705 (17.2)	901 (22.0)	0.752 (0.682 to 0.830)	< 0.0001

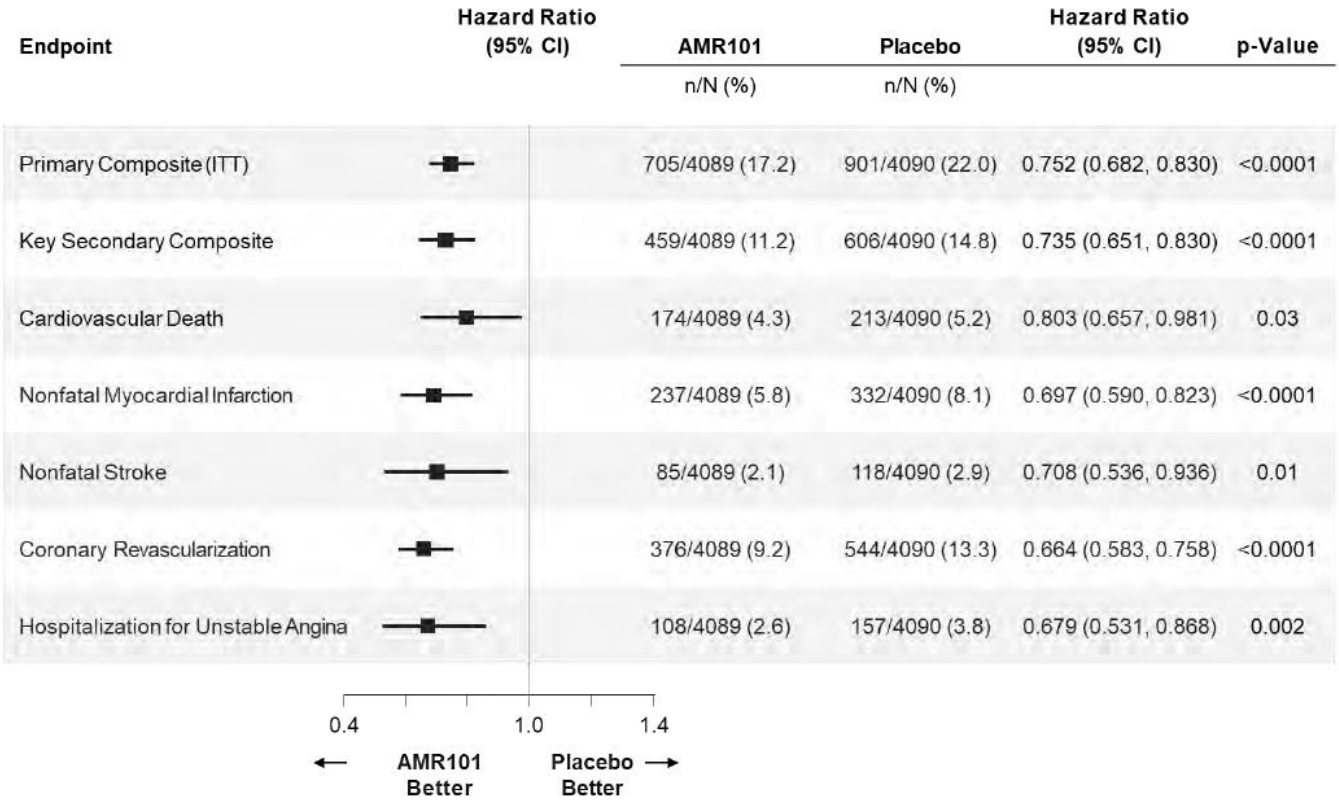
CI = confidence interval; HR = hazard ratio; MI = myocardial infarction.

Table 17: Subgroup Analysis Hazard Ratios (95% CI) for Primary Composite End Point by Subgroups — ITT Population

	Icosapent ethyl, n/N (%)	Placebo n/N (%)	HR (95% CI)	Interaction P value
Primary composite (ITT)	705/4,089 (17.2)	901/4,090 (22.0)	0.752 (0.682 to 0.830)	
Risk Category				0.1388
Established CVD (secondary prevention)	559/2,892 (19.3)	738/2,893 (25.5)	0.726 (0.650 to 0.810)	
At high risk for CVD (primary prevention)	146/1,197 (12.2)	163/1,197 (13.6)	0.876 (0.700 to 1.095)	
Baseline diabetes				0.5598
Diabetes	433/2,394 (18.1)	536/2,393 (22.4)	0.769 (0.678 to 0.873)	
No diabetes	272/1,695 (18.0)	365/1,694 (21.5)	0.726 (0.620 to 0.849)	

CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio; ITT = intention-to-treat.

Figure 3: Forest Plot of Analyses of Individual Components of the Primary and Key Secondary Outcomes (ITT Population, REDUCE-IT)



AMR101 = icosapent ethyl; CI = confidence interval; ITT = intention-to-treat.

Source: Clinical Study Report for REDUCE-IT[1].

Appendix 4: Definition of Statin Intensity

High-intensity statin therapy	Moderate-intensity statin therapy	Low-intensity statin therapy
Daily dose lowers LDL-c, on average, by approximately > 50%	Daily dose lowers LDL-c, on average, by approximately 30% to < 50%	Daily dose lowers LDL-c, on average, by < 30%
Atorvastatin 40 mg to 80 mg daily Rosuvastatin 20 mg to 40 mg daily	Atorvastatin 10 mg to 20 mg daily Rosuvastatin 5 to 10 mg daily Simvastatin 20 mg to 40 mg daily Pravastatin 40 mg to 80 mg daily Lovastatin 40 mg daily Fluvastatin XL 80 mg daily Fluvastatin 40 mg b.i.d. Pitavastatin 2 mg to 4 mg daily	Simvastatin 10 mg daily Pravastatin 10 mg to 20 mg daily Lovastatin 20 mg daily Fluvastatin 20 mg to 40 mg daily Pitavastatin 1 mg daily

Source: 2013 American College of Cardiology/American Heart Association Blood Cholesterol Guideline.[29]
b.i.d. = twice daily; LDL-c = low-density lipoprotein cholesterol.

Appendix 5: Description and Appraisal of Outcome Measures

Outcomes measured in the REDUCE-IT and ANCHOR trials were objective and clinically oriented. No health-related quality of life outcomes were measured, nor were other types of exploratory outcomes that would require assessment of their validity and reliability.

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