Q: What is Amarin's perspective on analyses of the elevated TG subgroups in the previously reported ACCORD-Lipid, AIM-HIGH, HPS2-THRIVE, and JELIS cardiovascular outcome studies?

A: Epidemiological studies suggest that elevations in cardiovascular (CV) risk begin to emerge in patients with triglyceride (TG) levels of approximately 150 mg/dL, and increase more significantly by the time TG levels reach approximately 200 mg/dL.[1] In addition, and in accord with the epidemiological data, clinical studies have suggested a reduction in CV risk when TG levels are reduced in patients with elevated baseline TG levels above approximately 150 to 200 mg/dL.[2] Therefore in contrast to patients with normal TG levels, this would suggest that patients with elevated TG levels are more likely to experience a manifest reduction in CV risk due to TG-lowering therapies. In addition, recent genetic studies centering on the metabolism of TG-rich lipoproteins have consistently put TG-rich lipoproteins within the causative pathway of CV disease, similar to low density lipoprotein cholesterol (LDL-C). Of note, the same genetic correlation between high density lipoprotein cholesterol (HDL-C) and CV disease was not found.[3,4]

Despite the evidence noted above, and other supportive data, no completed outcomes study to date has prospectively asked if TG-lowering in a patient population with elevated TG levels despite statin therapy results in a reduction in CV risk. Nonetheless, and in agreement with the data mentioned above, in the cardiovascular outcome studies (CVOTs) ACCORD-Lipid, AIM-HIGH, and JELIS, the subsets of patients with elevated baseline TG and low baseline HDL-C suggest cardiovascular outcome benefit to TG-lowering therapies in these subgroups. While low HDL-C is not an inclusion criterion for REDUCE-IT, and high TG levels can occur in isolation of low HDL-C, high TG and low HDL-C are metabolically linked and many patients with elevated TG levels present with concomitantly low HDL-C.[5] Therefore although the patient populations are not identical, the high TG and low HDL-C subgroups within the above studies most closely approximate the ANCHOR[6] and REDUCE-IT[7] patient populations and are therefore presented in more detail below (within the text and summary Table). Finally, within the full cohort of the JELIS study, a 19% reduction in the relative risk of major coronary events was observed with eicosapentaenoic acid (EPA) and statin co-administration over statin monotherapy; this distinction of JELIS and EPA therapy from CVOTs utilizing other TG-lowering therapies is also explored.

FDA's perspective on ACCORD-Lipid, AIM-HIGH, and HPS2-THRIVE

As discussed in connection with the public October 2013 ANCHOR study FDA advisory committee meeting and expressed to Amarin in subsequent regulatory dialogue, FDA's view on analyses of the elevated TG subgroups in ACCORD-Lipid, AIM-HIGH, and HPS2-THRIVE is summarized as follows:

- Instead of confirming that raising HDL-C or that further lowering of TG or baseline non-high density lipoprotein cholesterol (non-HDL-C) in statin-treated patients reduces residual CV risk, these trials failed in the overall trial populations to demonstrate additional benefit of lipid-altering drugs.

- Although post hoc subgroup analyses have suggested that patients with both high TG and low HDL-C (defined in various ways) may benefit from the lipid-altering drugs that were studied, this remains to be confirmed in an appropriately designed prospective trial.
- There was no suggestion of benefit in any of these trials for the subgroup of patients selected based on high TG alone (i.e., regardless of HDL-C).

As previously disclosed, given the current level of uncertainty at FDA regarding the benefits of drug-induced changes in lipid/lipoprotein parameters on CV risk among statin-treated patients with residually high TG (200-499 mg/dL), FDA informed Amarin it will need to provide evidence that Vascepa reduces the risk of major adverse CV events in patients at high risk for cardiovascular disease, at LDL-C goal on statin therapy, with residually high TG levels. FDA informed Amarin that it anticipates that the final results from the REDUCE-IT trial could be submitted to satisfy this deficiency and FDA has urged Amarin to complete the REDUCE-IT trial.

Amarin's perspective on ACCORD-Lipid, AIM-HIGH, and HPS2-THRIVE

As discussed in more detail below, these three studies did not prospectively enroll patient populations based on high TG levels, nor did these trials involve the use of Vascepa or other drugs with profiles directly comparable to Vascepa. A commonly stated goal of each of these studies was to demonstrate improved cardiovascular outcomes from increasing HDL-C ("good cholesterol"), with only ACCORD-Lipid also explicitly including TG reduction as an additional primary goal of therapy. Regardless of the stated goals of each trial, any TG reductions that occurred in these CVOTs may have been of limited value in a patient population that was not at risk due to elevated TG levels. These CVOTs did not achieve their primary endpoint within their full study populations, but some subgroup analyses suggest that certain patients may benefit from TG-lowering therapy. Each study design is explored in more detail below, in particular as to how that design might have affected results of the full cohort and subgroup analyses.

ACCORD-Lipid

Key Points:

- The ACCORD-Lipid study did not prospectively enroll patients at risk due to elevated TG levels and therefore was not designed to study of the benefits of TG-lowering in subjects with high TGs.
- Overall, in ACCORD-Lipid co-administering the HDL-C raising and TG-lowering therapy of fenofibrate with statin did not demonstrate a benefit of fenofibrate therapy added to statin compared with statin alone within the full study population.
- Assessment of the TG-lowering benefit of fenofibrate in ACCORD-Lipid is complicated by
    - the relatively small number of study subjects with elevated TG at baseline prior to statin stabilization of the full study population and
    - the likely mitigation of potential CV benefits of TG-lowering in the 40% of subjects expected to have benefited from initiation of statin therapy (including TG-lowering) at baseline.

- Despite the study limitations,
    - the nominally fewer events with fenofibrate therapy in patients with high TGs, although not statistically significant, is consistent with the correlation of high TG levels and increased CV risk, as is the fact that event rates within each treatment arm generally increased with increasing TG levels, and
    - a prespecified subgroup analysis of patients with dyslipidemia evident by high TGs and low HDL-C suggests a CV benefit to lowering TG in this patient population.

Overview

ACCORD-Lipid was a sub-study within the larger ACCORD (Action to Control Cardiovascular Risk in Diabetes) CVOT and was designed to test the effects of fenofibrate plus statin on a composite of major cardiovascular events in 5,518 patients with type 2 diabetes at high risk for CVD.[8] The primary endpoint was the first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from CV causes, and the mean follow-up was 4.7 years. Fenofibrate therapy did not result in a change in the primary endpoint within the full patient cohort (HR=0.92; 95% confidence interval [CI] = 0.79-1.08, p=0.33).

Importantly, the ACCORD-Lipid study was not designed to answer the question of whether TG reduction in patients with elevated TG levels despite statin therapy (with or without low HDL-C) results in a reduction of cardiovascular risk. As acknowledged by the ACCORD-Lipid investigators, because ACCORD-Lipid was a sub-study of the larger ACCORD study, they "used broader inclusion criteria for plasma lipid levels than might have been used if the lipid trial had been an independent study." In this regard, there are two relevant design constraints in ACCORD-Lipid that limit the reliability of the study's data when discussing the effect of TG-lowering on CV risk reduction. First, ACCORD-Lipid had no enrollment criteria specifying a lower limit for TG levels. Second, patients were not required to be on statin therapy at baseline; resulting in approximately 40% of patients being statin-naïve at baseline. As such, the median baseline (pre-statin stabilization) TG value for the full study cohort was 162 mg/dL, with an interquartile range of 113-229 mg/dL. This interquartile range is reflected in the fact that only about a third of patients (33.2%, or 1822 of 5489 subjects) in the ACCORD-Lipid trial had TG values at or above 204 mg/dL prior to the statin stabilization phase; the number of patients with TG ≥200 mg/dL once statin stabilization occurred is unknown. We do know that at Month 4 the median TG level dropped from 164 mg/dL to 152 mg/dL with placebo plus statin therapy, and continued to drop to 144 mg/dL at the end of the study, and therefore the number of statin-stabilized patients in ACCORD-Lipid with TG levels above 200 mg/dL surely also dropped to well below one third. Thus, while in the ACCORD-Lipid trial the median baseline for the full study cohort was 162 mg/dL and at baseline about a third of patients had TG values at or above 204 mg/dL, statin therapy introduced at baseline in 40% of patients likely resulted in a decline in TG levels in the active as well as the placebo group, and thereby reduced the potential for additional benefit from TG-focused therapy, thus complicating conclusions that could be drawn from the cardiovascular risk reduction effects of fenofibrate that may have resulted from TG-lowering in the subset of patients that had high TG levels despite statin stabilization.

Although the full ACCORD-Lipid study did not ask if lowering TG in patients at risk due to elevated TG levels despite statin therapy results in a CV benefit, a prespecified subgroup analysis of subjects with both high baseline TG (≥204 mg/dL) and low baseline HDL-C (≤34 mg/dL) suggested a benefit to fenofibrate therapy in this subgroup, with a 31% reduction in the primary endpoint (p=0.057). An additional prespecified subgroup analysis by baseline TG tertile did not demonstrate a benefit across the tertiles (p=0.64 for the interaction), but since two of the three tertiles fell below approximately 200 mg/dL (i.e. two of the three groups of patients were not likely at risk due to TG elevations and not likely to benefit from TG-lowering therapy), and since the actual statin-stabilized TG levels were lower than the reported baseline values (due to statin initiation in 40% of patients at baseline), it is difficult to interpret a lack of a trend across these tertiles. The studied cardiovascular event rate for the highest baseline TG tertile (pre-statin stabilization median = 269 mg/dL) did decrease with fenofibrate therapy (from 12.84% to 11.13%), but due to powering of the study, it is not expected (nor reported) that this difference would reach statistical significance. The nominally fewer events with fenofibrate therapy, although not statistically significant, is consistent with the correlation of high TG levels and increased CV risk, as is the fact that event rates within each treatment arm generally increased with increasing TG levels, especially once TG levels were above approximately 200 mg/dL (i.e. within the fenofibrate arm the event rate was 9.88% for TG ≤ 128 mg/dL, 10.50% for TG 129–203 mg/dL, and 11.13% for TG ≥ 204 mg/dL and in the placebo arm event rates were 11.29% for TG ≤ 128 mg/dL and 9.86% for TG 129–203 mg/dL, but 12.84% for TG ≥ 204 mg/dL).

Therefore, although administering the TG-lowering therapy of fenofibrate added to statin, the ACCORD-Lipid study did not prospectively enroll patients at risk due to elevated TG levels and did not show a CV benefit to fenofibrate therapy added to statin. Nonetheless, a subgroup analysis of patients with both elevated TG and low HDL-C levels suggests a CV benefit to TG-lowering therapy in this patient population.

AIM-HIGH

Key Points:

- The AIM-HIGH study did not prospectively enroll patients at risk due to elevated TG levels and therefore was not designed to study the benefits of TG-lowering in subjects with high TG.
- Overall, co-administering the HDL-C raising and TG-lowering therapy of niacin with statin did not demonstrate a benefit of niacin therapy added to statin compared with statin alone within the full study population.
- Assessment of the TG-lowering benefits of niacin therapy in AIM-HIGH is complicated by the relatively small number of study subjects with elevated TG at baseline.
- Despite the study limitations,
    - the nominally fewer events with niacin therapy in patients with high TG, although not significantly different, is consistent with the correlation of high TG levels and increased CV risk, as is the fact that event rates within each treatment arm increased with increasing TG levels, and
    - a prespecified subgroup analysis of patients with dyslipidemia evident by high TG and low HDL-C suggests a CV benefit to lowering TG in this patient population.

Overview

AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes) was a CVOT designed to test the effect of extended release niacin plus statin on a primary composite endpoint of CV events in 3,414 patients with established CVD.[9] The primary endpoint of AIM-HIGH was a composite of the first event of death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization (for >23 hours) from an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization. AIM-HIGH was stopped prematurely due to futility and safety concerns, which subsequently were determined not to be drug related. The resulting mean follow-up was three years and with a hazard ratio of 1.02 for the primary endpoint (95% CI = 0.87-1.21, p=0.79).

As presented by the authors, the AIM-HIGH study was designed primarily to test the high density lipoprotein (HDL) hypothesis; the full study was not designed to test the CV benefit of TG-lowering in patients with persistent hypertriglyceridemia despite statin therapy, or to ask this question within a well-powered subgroup analysis. The lower limit entry criterion for statin-stabilized TG was 100 mg/dL, which resulted in similar (and relatively normal) median baseline TG values for both treatment groups, being 164 mg/dL for the niacin group, with an interquartile range of 127-218 mg/dL. As with ACCORD-Lipid, this interquartile range is reflected in the fact that only a third of patients (33.3%, or 1136 of 3414 subjects) in the AIM-HIGH trial had TG values at or above 198 mg/dL.

Much like the ACCORD-Lipid, AIM-HIGH did not ask if lowering TG in patients with elevated TG levels despite statin therapy results in a CV benefit, but a subgroup analysis of subjects with both high baseline TG (≥200 mg/dL) and low baseline HDL-C (≤32 mg/dL) suggested a benefit to niacin therapy, with a 36% reduction in the primary endpoint (p=0.032).[10] An additional subgroup analysis by baseline TG tertile did not demonstrate a benefit in the highest TG tertile (HR=0.96; 95% CI = 0.73-1.27), but it is important to remember that this study was not powered to observe differences in this post-hoc subgroup analysis. Nonetheless, in patients within the highest tertile, nominally fewer events did occur with niacin therapy (17.5% for placebo vs. 17.0% for niacin), which was not the case for patients in the two lower TG tertiles. Although not statistically significant, this is consistent with the correlation of high TG levels and increased CV risk, as is the fact that event rates within each treatment arm increased with increasing TG levels (e.g. within the placebo arm the event rate was 14.9% for TG of 93-142 mg/dL, 16.1% for TG 143-197 mg/dL, and 17.5% for TG 198-400 mg/dL).

Therefore, much like ACCORD-Lipid, although administering the TG-lowering therapy of niacin added to statin, the AIM-HIGH study did not prospectively enroll patients at risk due to elevated TG levels and did not show a CV benefit to niacin therapy added to statin. Nonetheless, a subgroup analysis of patients with both elevated TG and low HDL-C levels suggests a CV benefit to TG-lowering therapy in this patient population.

HPS2-THRIVE

Key Points:

- The HPS2-THRIVE study did not prospectively enroll patients at risk due to elevated TG levels and therefore was not designed to study of the benefits of TG-lowering in subjects with high TGs. On the contrary, HPS2-THRIVE was designed to study subjects of varying lipid profiles.
- Overall, co-administering the HDL-C raising and TG-lowering therapy of niacin and laropiprant (for purposes of discussion of HPS2-THRIVE in this document, niacin refers to the co-administration of niacin and laropiprant) with statin did not demonstrate a benefit of niacin therapy added to statin compared with statin alone within the full study population.
- Assessment of the TG-lowering benefits of niacin therapy in HPS2-THRIVE is complicated by the relatively small number of study subjects with elevated TG at baseline, and in particular by the lack of essentially any subjects with high TG (≥ 200 mg/dL).
- Despite the study limitations, the occurrence of nominally fewer events with niacin therapy in patients with elevated TG (>150 mg/dL), although not statistically significant, is consistent with the correlation of high TG levels and increased CV risk, as is the fact that event rates within each treatment arm increased with TG levels above 150 mg/dL.

Overview

HPS2-THRIVE (Heart Protection Study 2: Treatment of HDL to Reduce the Incidence of Vascular Events) was a randomized, double-blind, multicenter, placebo-controlled study conducted at sites in Europe and China.[11,12] The HPS2-THRIVE study enrolled 25,673 high risk patients with pre-existing occlusive arterial disease, and was designed to test the effect of extended release niacin (2,000 mg/d) plus the anti-flushing agent laropiprant (40 mg/d), as add-on to statin therapy, on major vascular outcomes. The primary endpoint of HPS2-THRIVE was a composite of the first major vascular event; including nonfatal myocardial infarction, coronary death, non-fatal or fatal stroke, or coronary or non-coronary artery surgery or angioplasty (including amputation), and the mean follow-up was 3.9 years. HPS2-THRIVE did not meet the primary endpoint within the full patient cohort (HR=0.96; 95% CI = 0.90-1.03, p=0.29).

Importantly, there were no lipid inclusion criteria in this study; according to the authors "HPS2-THRIVE aims to examine the effects on [major vascular events] among participants with various lipid profiles." As a result, the median baseline TG values were 108 mg/dL with a full interquartile range of 73 mg/dL (mean TG ± standard deviation was 125 ± 74 mg/dL).[11] Markedly lower than the median baseline TG values in ACCORD-Lipid and AIM-HIGH, this interquartile range is reflected in the fact that only 26% of patients in the HPS2-THRIVE trial had TG values at or above 151 mg/dL. In other words, approximately 74% of patients in the HPS2-THRIVE trial had normal TG levels and from the median and interquartile range values, it appears that very few – if any – patients had TG levels above 200 mg/dL.

A prespecified subgroup analysis of patients with elevated TG (≥151 mg/dL) and low HDL-C (<35 mg/dL) did not demonstrate any additional CV benefit (p=0.95 for the trend), but since this subgroup only represented approximately 17% of patients in the study, and since the vast

majority (if not all) of these patients had TG levels well below 200 mg/dL (i.e. none of the patients were likely at high risk due to TG elevations, nor were they expected to benefit from TG-lowering), it is difficult to interpret a lack of a trend in this analysis. Similarly, an additional pre-specified subgroup analysis across baseline TG cuts (not by tertile; <89 , 89 - <151, and ≥151 mg/dL) also did not demonstrate a benefit (p=0.66 for the trend), but since two of the three cuts fell below 151 mg/dL, all three cuts fell well below 200 mg/dL, and the HPS2-THRIVE study was not powered to detect differences in this subgroup analysis, it is difficult to interpret a lack of a trend across these low TG cuts. The event rate for the highest baseline TG cut did nominally decrease with niacin therapy (from 14.8% to 13.9%), which was more pronounced than for patients in the two lower TG cuts, but it is not expected (nor reported) that this difference would reach statistical significance. Although not statistically significant, this is consistent with the correlation of high TG levels and increased CV risk, as is the fact that event rates within each treatment arm increased once TG levels were above 150 mg/dL (e.g. within the placebo arm the event rates were 13.4% for TG < 89 mg/dL and 13.2% for TG ≥89 to <151 mg/dL, but 14.8% for TG ≥ 151 mg/dL).

Therefore, much like ACCORD-Lipid and AIM-HIGH, although administering the TG-lowering therapy of niacin added to statin, the HPS2-THRIVE study did not prospectively enroll patients at risk due to elevated TG levels and did not show a CV benefit to niacin therapy added to statin.

Amarin's perspective on JELIS

In contrast to the three CVOTs discussed above, JELIS explored the CV benefit of EPA therapy added to a statin over statin monotherapy and demonstrated a 19% relative reduction in its primary endpoint of major coronary events.[13] Similar to the CVOTs discussed above, JELIS did not prospectively enroll subjects with elevated TG levels, but did demonstrate additional CV benefit in subjects with both elevated TG levels and low HDL-C, demonstrating a 53% relative risk reduction in this subgroup.[15] As the JELIS study best approximates the therapy utilized in REDUCE-IT, some relevant details regarding trial design and study results are discussed below.

Key Points:

- The JELIS study met its primary endpoint with a 19% relative reduction in major coronary events.
    - JELIS met its primary endpoint despite the fact that it did not prospectively enroll patients at risk due to elevated TG levels and therefore was not designed to study of the benefits of TG-lowering in subjects with high TG;
    - this distinguishes JELIS from CVOTs of other TG-lowering therapies.
- Assessment of the TG-lowering benefits of EPA therapy in JELIS is complicated by
    - the relatively small number of study subjects with elevated TG at baseline prior to statin stabilization, and
    - the likely mitigation of potential CV benefits due to the initiation of statin therapy (including TG-lowering) at baseline.

- Despite the study limitations,
    - the decrease in events with EPA therapy in patients with high TG, although not significantly different from the decrease in events within patients with normal TG levels, is consistent with the correlation of high TG levels and increased CV risk, as is the fact that event rates within each treatment arm increased with increasing TG levels, and
    - a subgroup analysis of patients with dyslipidemia evident by elevated TG and low HDL-C suggests a CV benefit to lowering TG in this patient population.

Overview

While no outcome study to date has specifically tested the benefit of lowering TG in a statin-treated population with persistent hypertriglyceridemia, JELIS (Japan EPA Lipid Intervention Study) has demonstrated the cardiovascular benefit of 1.8 g/day EPA added to a statin in 18,645 patients with elevated cholesterol.[13] JELIS is the only completed CVOT that has looked specifically at the effects of EPA therapy – without DHA and other omega-3 fatty acids – on CV risk reduction. The primary endpoint in JELIS was the occurrence of major coronary events, including sudden cardiac death, fatal and non-fatal myocardial infarction, unstable angina pectoris, angioplasty, stenting, and coronary artery bypass grafting, and the mean follow-up was 4.6 years. Compared to statin therapy alone (control), statin plus EPA treatment resulted in a significant 19% relative risk reduction in the primary endpoint (HR = 0.81, 95% CI = 0.69 to 0.95).

It is worthwhile to note some details of JELIS design and the resulting data. First, the baseline TG levels in JELIS were fairly low (153-154 mg/dL). Also of note, the Japanese population is generally found to have higher baseline EPA levels in comparison to Western populations, which is believed to be due to higher dietary intake. This was true in JELIS, and yet despite the differences in EPA baseline levels, dose and duration of treatment between JELIS (1.8 g/day in a Japanese population for a median follow-up of 4.6 years) and the ANCHOR study (4 g/day in a more diverse and Westernize population for 12 weeks),[6] the final plasma EPA levels were similar between studies. In addition, there are some aspects of the JELIS study that might limit its applicability to broader patient populations. The patients enrolled in JELIS were exclusively Japanese and the majority were women. In addition, treatment in JELIS was open label (although endpoint adjudication was blinded), which could influence patient and physician behavior and reporting of symptoms, decisions regarding hospitalization, and referral of events for adjudication. This may be particularly relevant since hospitalizations for unstable angina was a primary contributor of the overall positive result, and is considered a softer endpoint than fatal cardiovascular events. Finally, at baseline statin-naïve patients had a high LDL-C and a low dose of statins was administered, potentially limiting the generalizability of the JELIS study results to a broader, more aggressively treated population. Therefore, overall it is unknown whether the positive treatment effects observed in JELIS would have persisted if these patients had been more optimally treated with statins using contemporary LDL-C targets in the United States. Nonetheless, 80% of JELIS patients were primary prevention and the mean baseline LDL-C of 182 mg/dL was reduced by 25% with statin therapy, therefore to approximately 136 mg/dL. For primary prevention Japanese patients at low risk for coronary artery disease death,

an LDL-C <160 mg/dL would meet LDL-C treatment goals according to the Japanese Atherosclerosis Society (JAS) guidelines, and an LDL-C <140 mg/dL would meet treatment goals for primary prevention Japanese patients at moderate risk.[14] Therefore, while some higher risk JELIS subjects may not have been treated as aggressively as guidelines for a United States-based population would recommend, the mean LDL-C data and the patient distribution from JELIS would suggest that many of the low-to-moderate risk primary prevention subjects were treated to Japanese guidelines.

As performed in the ACCORD-Lipid, AIM-HIGH, and HPS2-THRIVE trials, the JELIS investigators conducted a sub-analysis of patients with abnormal lipid levels (within the primary prevention cohort), defined as baseline (statin-naïve) TG ≥150 mg/dL and HDL-C <40 mg/dL.[15] Compared to patients with normal baseline serum TG and HDL-C levels, those with abnormal levels had a significantly higher risk of coronary artery disease, and EPA treatment suppressed the risk of coronary artery disease by 53% in this higher risk population (HR = 0.47; 95% CI = 0.23–0.98; p=0.043). An additional subgroup analysis by baseline (statin naïve) TG (<151 versus ≥151 mg/dL) did not detect a difference in benefit to subjects above or below the TG cut (p=0.75 for the interaction), but it is important to remember that this study was not powered to observe differences in this subgroup analysis. The event rate for the highest baseline TG cut did nominally decrease with EPA therapy (from 4.0% to 3.4%; hazard ratio = 0.84; interquartile range = 0.68–1.04), but was not greater than the reduction with EPA therapy observed for subjects in the lower TG cut (from 2.9% to 2.3%; hazard ratio = 0.79; interquartile range = 0.61–1.02). Although not statistically significant, the drop in event rate with EPA therapy, and the increase in event rates with increasing TG levels within each treatment arm, are consistent with the correlation of high TG levels and increased CV risk (i.e. within the EPA arm the event rate was 2.3% for TG < 151 mg/dL and 3.4% for TG ≥ 151 mg/dL, and in the placebo arm the event rate was 2.9% for TG < 151 mg/dL and 4.0% for TG ≥ 151 mg/dL). Finally, subjects were statin naïve at baseline, so the cut between the statin treated levels of this subgroup analysis would be expected to fall well below 151 mg/dL, which would likely translate to a large proportion of subjects who, although above the median, had statin-treated TG levels below 150 mg/dL, and therefore not representing a patient population at risk due to elevated TG levels.

Overall, in the JELIS study EPA-only therapy added to statin therapy resulted in a coronary benefit beyond statin monotherapy in both the full cohort of patients with relatively normal TG levels (19% reduction) and a more dramatic benefit within a subgroup of higher risk patients with dyslipidemia (53% reduction).

Differing Mechanisms of Action for Various TG-Lowering Therapies

Key Points:

- EPA has been shown to alter lipid metabolism through a multitude of biophysical, biochemical, and transcriptional pathways.
- EPA is incorporated into lipids and tissues throughout the body and is postulated to have far reaching benefits within cardiovascular disease beyond lipid lowering such as improvements in inflammation, oxidative stress, and plaque stabilization, as well as

arterial function, heart rate and blood pressure, blood-clotting, and cardiac function and rhythm.

- No head-to-head outcomes or lipid lowering studies have been performed between EPA therapy and fibrates or niacin. However, the FDA-approved labels for such therapies describe varied efficacy, safety, and tolerability profiles based on the results of the respective lipid-modifying clinical studies of these therapies
    - For example, EPA therapy in studies of patients with high TG (ANCHOR study) or very high TG (MARINE study) levels does not increase LDL-C compared to placebo, whereas FDA-approved labels for fenofibrates demonstrate that they may increase LDL-C levels in patients with very high TG levels.
- The diversity and mechanisms of the putative cardioprotective effects of EPA therapy, and the persistence of benefits when added to statin therapy, are unique in comparison to other TG-lowering therapies, especially fibrates and niacin.

Overview

EPA has many lipid and non-lipid mechanisms of action that differ from those of fibrate or niacin studied in ACCORD-Lipid, AIM-HIGH, and HPS2-THRIVE. Postulated mechanisms of action for fibrates have been rather well studied and stem from fibrates being strong agonists of the peroxisome proliferator-activated receptor α (PPARα).[16-20] The mechanisms of action for niacin are not clearly elucidated, but overall, the better characterized effects of niacin therapy are the result of niacin high-affinity binding to a G-protein coupled receptor (GRP109A or HCA_2), [21,22] which is distinct from the lipid and vascular effects of omega-3 fatty acids, and little is known about how niacin may/may not exert effects outside of this binding. In stark contrast to the lipid-altering mechanisms of fibrate or niacin that primarily appear to work through a single key gateway, EPA has been shown to alter lipid metabolism through a multitude of biophysical, biochemical, and transcriptional pathways.[23] For example, even where there is apparent overlap, such as both EPA and fibrates being agonists of PPARs, fibrates are only agonists for PPARα, while EPA is an agonist for all three PPARs and also modulates the levels/function of multiple transcription factors beyond PPARs (e.g. Marx[19], Lu[20]).

Therefore, although TG-lowering therapies are often considered collectively, scientific studies define some EPA mechanisms of action that overlap with those of other TG-lowering therapies, but also define some mechanisms that are distinct, and these distinctions are supported within the results of clinical studies utilizing various TG-lowering therapies. For example, while no direct head-to-head studies have been conducted with EPA and either fibrates or niacin, their FDA-approved labels suggest some similar and some differential effects on lipids and lipoproteins within similar patient populations.[16,21,24,] For instance, and of particular note, fibrates have been shown to increase LDL-C in some subjects with very high TG levels, demonstrating a median increase in LDL-C of 45% ($p < 0.05$ versus placebo) in subjects with baseline TG levels of 500 to 1500 mg/dL,[16]while Vascepa had no significant effect on LDL-C (-2% versus placebo, with a 95% confidence interval of -13 to +8) in a similar patient population with baseline TG levels of 500 to 2000 mg/dL.[24] It is interesting to note that omega-3 fatty acid-containing therapies that include a combination of both EPA and docosahexaenoic (DHA) also demonstrate a median increase in LDL-C in a study population with very high TG levels, showing

an increase in LDL-C of 49.3% in subjects with baseline TG levels of 500 to 2000 mg/dL.[25] Such a comparison of the EPA and EPA+DHA labels suggests that some of the mechanisms of action of EPA are distinct even from those of DHA, and while a further discussion of the differences between EPA and DHA is beyond the scope of this current document, the above comparisons highlight the uniqueness of EPA therapy relative to other TG-lowering therapies, and the limitations of assuming that all therapies that lower TG levels will have the same clinical manifestations.

Beyond lipid lowering, it is also postulated that EPA therapy could have additional and far reaching cardiovascular benefits. This is because EPA has been shown to be incorporated into lipids and membranes throughout lipoproteins and cells (in tissues throughout the body) having a multitude of effects mediated by a variety of biochemical and biophysical effects (e.g. alterations in membrane structure/function and cell signaling).[21,26,27] As an example, hardening of the arteries, or atherosclerosis, is a primary underlying process of cardiovascular disease involving oxidative stress, inflammation, cell dysfunction, and cholesterol accumulation within the arterial wall, followed by the formation and progression of plaque, which can eventually become unstable and rupture, leading to heart attack and stroke. EPA therapy may reduce atherosclerotic burden both by improving many aspects of the lipid profile and by improving various parameters within the arterial wall. Atherosclerotic plaques readily incorporate EPA and DHA, and higher EPA plaque content is associated with decreased inflammation and increased plaque stability.[28] In addition, intervention with EPA-only therapy in combination with statin therapy may reduce markers of oxidative stress and inflammation in plasma and in plaque and may stabilize vulnerable plaques better than statin alone.[29-33] Beyond the atherosclerotic processes discussed above, studies have also suggested that EPA may have beneficial effects on arterial function, heart rate and blood pressure, blood-clotting, and cardiac function and rhythm.[21-23]

The diversity of the putative cardioprotective effects of EPA therapy alone or in addition to statin is unique in comparison to other TG-lowering therapies. For example, there have been limited fibrate and niacin monotherapy studies that have demonstrated some anti-inflammatory effects and current data continue to support these effects being mediated through their respective, single key mediators (PPARα for fibrates, GRP109A/HCA_2 receptors for niacin). In contrast, EPA-mediated anti-inflammatory effects appear to be modulated through multiple pathways, from transcriptional regulation to antioxidant effects and changes in membrane function. This distinction is supported by recent studies in model membranes that found EPA to have antioxidant effects as monotherapy and in addition to statins,[34] while similar monotherapy studies did not demonstrate antioxidant effects of niacin or fibrate.[35]

Overall Summary

- Epidemiological, clinical, and genetic data support an increase in CV risk with high TG levels above at least 150 mg/dL (greater evidence above 200 mg/dL), and also support a reduction in CV risk with TG lowering.
    - Recent genetic studies in particular have consistently put the metabolism of TG-rich lipoproteins within the causative pathway of cardiovascular disease.
- No completed outcome study to date has prospectively addressed the CV benefit of TG-lowering in statin treated patients with persistent hypertriglyceridemia.
    - Support for an increase in risk along with a benefit to TG-lowering therapies in patients with dyslipidemia arise from subgroup analyses of patients, in particular with elevated TG and low HDL-C, in CVOTs that utilized TG-lowering therapies, such as ACCORD-Lipid, AIM-HIGH, and JELIS.
    - While not powered to observe differences and not reaching statistical significance in any of the studies discussed herein, there is also a consistent trend in the subgroups of subjects with elevated TG levels, in that each study demonstrated a nominal increase in event rate with elevated TG levels (above approximately 150 or 200 mg/dL) and a nominal decrease in event rate with TG-lowering therapy within the groups with the highest TG levels.
- A substantial CV risk reduction was observed with EPA therapy in the full JELIS cohort, despite baseline TG levels being relatively normal.
    - In contrast, the full cohorts of the ACCORD-Lipid, AIM-HIGH, and HPS2-THRIVE studies did not show a CV benefit to niacin or fibrate add-on therapy.
- Taken together, the above points suggest that the CV risk reduction observed in JELIS was due in part to TG-lowering in patients with dyslipidemia, but that EPA therapy may have additional benefits that go beyond TG-lowering and may be of relevance to a broader patient population.
- These data inform our perspectives on REDUCE-IT, which is designed to test the CV benefit of EPA-only therapy in patients with elevated TG levels despite statin therapy.
    - The REDUCE-IT study is an event-driven trial that is expected to reach the final event within 2017 with results made public in 2018.
    - The REDUCE-IT study will fill important gaps in our understanding of the role that TG levels play in CV risk and the putative CV benefits of EPA-only therapy in statin-treated patients at high risk for cardiovascular disease.

Table. CVOTs utilizing TG-lowering therapies as add-on to statin; analyses of the full cohorts and subgroups with dyslipidemia.

Trial Pub. Year	CV Risk Profile (therapy) N	Stated Goal (as statin add-on)	Statin-treated TG Lower Limit? (Upper Limit) (mg/dL)	Median Baseline TG (mg/dL) (IQR)	Primary Endpoint (*p*-value)	TG + HDL-C Subgroup Baseline Criterion (mg/dL) N (% full cohort)	TG + HDL-C Subgroup Endpoint (*p*-value)
ACCORD-Lipid 2010	Type II DM 1° & 2° Prevention (fenofibrate) N = 5,518	CV benefit of raising HDL-C & lowering TG	None (<400)	162 (113, 229) *Note: At BL ~40% of patients were statin-naive*	MACE OR 0.92 (0.32)	TG ≥ 204 HDL-C ≤ 34 N = 941 (17%)	-31% (0.0567)
AIM-HIGH 2011	CVD 2° Prevention (ER Niacin) N = 3,414	CV benefit of raising HDL-C	≥ 100 (≤400)	163 (127, 218)	Expanded MACE HR 1.02 (0.79)	TG ≥ 198 HDL-C < 33 N = 523 (15%)	-36% (0.032)
HPS2-THRIVE 2013	CVD 2° Prevention (Niacin + Lp) N = 25,673	CV benefit of raising HDL-C	None (None)	108 (Full IQR = 73)	MVE HR 0.96 (0.29)	TG ≥ 151 HDL-C: < 40 (men) < 51 (women) N = 4,362 (17%)	No significant difference between groups*
JELIS 2007	High Cholesterol 1° & 2° Prevention (EPA) N = 18,645	CV benefit of EPA therapy in Japanese with high cholesterol	None (None)	153 (109, 220)	Expanded MACE HR 0.85 (<0.05)	TG ≥ 150 HDL-C ≤ 40 N = 957 (5%) *Note: Only 1° Prevention patients were analyzed*	-53% (0.043)

Endpoints that reached or neared statistical significance are shaded. *Heterogeneity test =0% (p=0.95). 1°=primary; 2°=secondary; BL=baseline; CV=cardiovascular; CVD=CV disease; CVOT=cardiovascular outcomes trial; DM=diabetes mellitus; ER=extended release; HDL-C=high-density lipoprotein cholesterol; HR=hazard ratio; IQR=interquartile range; Lp= laropiprant; MACE= major adverse coronary events; MVE=major vascular events; OR=odds ratio; TG=triglyceride.

Vascepa has been approved for use by the FDA as an adjunct to diet to reduce triglyceride levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia. Vascepa is under various stages of development for potential use in other indications that have not been approved by the FDA. Nothing in this update should be construed as marketing the use of Vascepa in any indication that has not been approved by the FDA.

About Vascepa® (icosapent ethyl) capsules

Vascepa® (icosapent ethyl) capsules, known in scientific literature as AMR101, is a highly-pure EPA omega-3 prescription product in a 1 gram capsule.

Indications and Usage

Vascepa (icosapent ethyl) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia.

The effect of Vascepa on the risk for pancreatitis and cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined.

Important Safety Information for Vascepa

Vascepa is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to Vascepa or any of its components and should be used with caution in patients with known hypersensitivity to fish and/or shellfish.

The most common reported adverse reaction (incidence > 2% and greater than placebo) was arthralgia (2.3% for Vascepa, 1.0% for placebo). There was no reported adverse reaction > 3% and greater than placebo.

FULL VASCEPA PRESCRIBING INFORMATION CAN BE FOUND AT WWW.VASCEPA.COM.

VASCEPA® is a registered trademark of the Amarin group of companies

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2. For references regarding clinical data that support a CV benefit to TG reduction in patients with elevated TG levels, please see the prior FAQ entitled "What is the clinical need and scientific rationale for the REDUCE-IT study?" which can be found on the Amarin investor website at http://investor.amarincorp.com/faq.cfm.
3. For references regarding genetic data that support TG-rich lipoproteins being in the causative pathway of CV disease, please see the prior FAQ entitled "What is the clinical need and scientific rationale for the REDUCE-IT study?" which can be found on the Amarin investor website at http://investor.amarincorp.com/faq.cfm.
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