LIPID/METABOLIC

# MARINE: Ethyl-EPA reduces triglyceride levels without raising LDL cholesterol

NOVEMBER 30, 2010 | Michael O'Riordan

Dublin, Ireland and Mystic, CT - Ethyl eicosapentaenoic acid (EPA), a semisynthetic derivative of omega-3 fatty acids, significantly lowers triglyceride levels in patients with very high triglyceride levels without significantly increasing LDL-cholesterol levels.

Top-line results of the MARINE trial, a randomized, placebo-controlled trial testing ethyl-EPA in 229 patients with triglyceride levels ≥500 mg/dL, were announced today by Amarin Corporation. During a conference call to analysts, investors, and media, the company reported that the 2-g and 4-g dose of AMR101, as the ethyl-EPA is currently known, reduced triglyceride levels 20% and 33%, respectively, all without a significant increase in LDL-cholesterol levels.

"This is the only triglyceride-lowering therapy studied in this population with very high triglycerides to show a lack of elevation in LDL cholesterol," said Dr Paresh Soni, senior vice president and head of drug development at Amarin.

Speaking with heartwire about the study, which hasn't yet been published or peer reviewed, Dr Darren McGuire (University of Texas Southwestern, Dallas) was cautious in interpreting the results, pointing out the trial was small and short in duration. He noted that researchers have not yet proven that lowering triglyceride levels reduces cardiovascular risk, and coupled with the increase in LDL-cholesterol levels, this remains a concern of all triglyceride-lowering therapies. That said, trials such as Japan EPA Lipid Intervention Study (JELIS) and GISSI-Prevenzione showed a favorable signal of reduced cardiovascular events among patients treated with fish oil.

"At the end of the day, if you can have favorable cardiovascular effects without raising LDL cholesterol, that's going to be an advantage," said McGuire. "There is a lot of enthusiasm for this compound, but this is really early in development, and I would insert a dose of caution here. The early results are intriguing."

## The MARINE trial

Briefly, the investigators enrolled 229 patients with very high triglyceride levels—the median baseline triglyceride level in the 2-g and 4-g dose arms was 681 mg/dL and 657 mg/dL, respectively—and compared the change in triglyceride levels at 12 weeks.

As noted, both doses significantly reduced triglyceride levels, but they also decreased non-HDL cholesterol, apolipoprotein B, lipoprotein-phospholipase A2, VLDL cholesterol, and total cholesterol. In a subgroup analysis evaluating patients with the highest triglyceride levels, ≥750 mg/dL, treatment with the 2-g and 4-g doses of ethyl-EPA resulted in 33% and 45% reductions in triglyceride levels, respectively, again without an increase in LDL-cholesterol levels.

Speaking to the results, lead MARINE investigator Dr Harold Bays (Louisville Metabolic and Atherosclerosis Research Center, KY) said the findings are good news given that increases in LDL-cholesterol levels are a problematic side effect of therapies that lower triglyceride levels, especially in patients with very high triglyceride levels. In some instances, these therapies, including fibrates and prescription omega-3 fatty acids, can increase LDL-cholesterol levels 40% to 50%.

"The findings are clinically important because elevated triglyceride levels are an important modifiable atherosclerotic coronary heart disease risk factor, and lowering triglycerides in patients with very high triglyceride levels has health benefits such as potentially reducing the risk of triglyceride-induced pancreatitis and other complications, as well as improving atherosclerotic coronary heart disease risk factors," said Bays.

To heart*wire*, McGuire said that he has seen LDL-cholesterol increases of 20 mg/dL, or 10% to 20%, in some patients treated with prescription fish oil, and while this might be managed with a statin, he said clinicians are reluctant to treat one drug's side effect with another drug. He said that patients with hypertriglyceridemia typically receive statins based on their background risk of cardiovascular disease, whereas lowering triglycerides is done mainly to prevent hyperviscosity complications, such as pancreatitis and other abnormalities.

Also commenting on the MARINE findings, Dr Roger Blumenthal (Johns Hopkins University Medical Institute, Baltimore, MD) said that while LDL increases can occur with prescription fish oil or fibrates, the increase is "modest" and "not that big an issue." Moreover, he said that while these drugs can raise LDL cholesterol, they do not affect levels of apolipoprotein B, a better measure of the atherogenic particles. Overall, he was skeptical of the findings, pointing out that the available prescription omega-3 fatty acid is effective in reducing triglycerides, is well tolerated, and works well

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with statin therapy. Most patients with high triglycerides have mixed dyslipidemia and would likely be treated with background statin therapy, he added.

Dr Steven Nissen (Cleveland Clinic, OH), on the other hand, was impressed with the MARINE data, although he expressed the same caveats about trial size, duration, and lack of peer review. The semisynthetic ethyl-EPA, which does not include docosahexaenoic acid (DHA) in the formulation and has no effect on LDL-cholesterol levels, is a real advance in the treatment of elevated triglycerides, he told heart*wire*.

"It gives you all the benefit without the downside," said Nissen. "It's an interesting wrinkle. There's still room for small companies to do innovative things in this field."

Nissen would like to eventually see a head-to-head comparison between Lovaza, the prescription omega-3 fatty acid made by GlaxoSmithKline, and AMR101. Although it is difficult to compare the amount of triglyceride lowering across different trials, the amount of reduction appears similar with both drugs, he said.

### Background of statin therapy

In MARINE, approximately 25% of patients were concomitantly treated with statin therapy, and in this cohort AMR101 also significantly reduced triglyceride levels, even more so than in those who were not taking statins. During the presentation, company officials said these results are line with the JELIS, the large trial showing the benefit of adding EPA to statin therapy for primary and secondary coronary heart disease prevention. Triglyceride-lowering therapies can raise LDL-cholesterol levels even in patients treated with statins, although this is mitigated by the lipid-lowering drugs.

In contrast, an analysis of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial recently showed that combination therapy with fenofibrate and simvastatin failed to reduce the risk of fatal cardiovascular events, nonfatal MI, or nonfatal stroke in diabetic patients. The most recent trial of prescription omega-3 fatty acids occurred in patients with symptomatic paroxysmal AF, and that study, reported by heart*wire*, showed that Lovaza capsules, even at the fairly high dose of 4 g/day for six months, failed to reduce the risk of atrial-fibrillation recurrence.

The company said it plans to file a new drug application with the Food and Drug Administration (FDA) in 2011, saying it believes the drug might prove to be a "first-in-class" EPA triglyceride-lowering agent. It is currently testing the drug in the ANCHOR trial, a study of approximately 650 patients with mixed dyslipidemia, including triglyceride levels between 200 mg/dL and 500 mg/dL, or ≤500 mg/dL on statin therapy. Like MARINE, the ANCHOR trial is 12 weeks in duration, with the primary end point being change in triglyceride levels from baseline. Results of the trial are expected in 2011.

During the conference call, the company officials, including Soni and chief executive officer Joseph Zakrzewski, were extremely excited about the findings, telling investors and analysts they believe the drug represents a potential "blockbuster." They pointed out that the first indication they are seeking with the FDA is for reducing hypertriglyceridemia, similar to Lovaza, a drug that has approximately $1 billion in revenues. ANCHOR, with its mixed-dyslipidemia population and the second sought-after indication, will represent a real-world cohort, as statin therapy currently represents the backbone of therapy for lipid disorders.

A public relations official acting on behalf of Amarin said the company plans to present the MARINE data at a meeting and publish the results in a medical journal, but final details have not yet been arranged.

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## Your comments

MARINE: Ethyl-EPA reduces triglyceride levels without raising LDL cholesterol

# 1 of 13 December 1, 2010 08:18 (EST)

James DiNicolantonio

Dr. Nissen Dr. Bays Mcguire
We all know how bad LDL-C predicts events...so what if fish oil raises LDL-C...it increases its buoyancy...ie it decreases the amount of small dense LDL particles and makes them larger and less likely to penetrate endothelium oxidize and form plaques

So for Dr. Nissen to say this is "real advancement" doesn't make sense...its not just about LDL-C...fish oil gets into plaques and stabilizes them - OCEAN TRIAL - less foam cells, less Matrix metalloproteinases, less ICAM and IL-6

Fish oil lowers non-hdl and apoB much better predictors of heart disease than LDL-C....if the raising of LDL-C was a problem we would have seen it in the trials...DART...JELIS, GISSI-P, GISSI-HF...so why are we concerned with a surrogate like LDL-C

zetia lowers LDL-C does nothing to stop progression of plaques, may increase cancer SHARP...so who cares of a 20% increase in LDL-C with fish oil?

# 2 of 13 December 1, 2010 08:46 (EST)

Jodi Godfrey

All Patients Are Not Created Equal
From this report, we know only that there are 229 patients in the study. While it is well understood that CVD is sex specific, here again is a report that does not indicate how many participants if any are women, and if the findings reflect differences based on the sex of the subjects. It is critical that all studies indicate the sex of the subjects and what if any results differ based on sex. Only then can we stuly provide evidence based and informed care.

# 3 of 13 December 1, 2010 09:19 (EST)

David Brown

How about reducing omega-6
Why is there so little interest in reducing omega-6s to improve the effectiveness of increased omega-3s intake?

Here's an excerpt from an article entitled "Workshop on the Essentiality of and Recommended Dietary Intakes for Omega-6 and Omega-3 Fatty Acids" which was published in Journal of the American College of Nutrition, Vol. 18, No. 5, 487-489 (1999)

"One recommendation deserves explanation here. After much discussion consensus was reached on the importance of reducing the omega-6 polyunsaturated fatty acids (PUFAs) even as the omega-3 PUFAs are increased in the diet of adults and newborns for optimal brain and cardiovascular health and function. This is necessary to reduce adverse effects of excesses of arachidonic acid and its eicosanoid products. Such excesses can occur when too much LA and AA are present in the diet and an adequate supply of dietary omega-3 fatty acids is not available. The adverse effects of too much arachidonic acid and its eicosanoids can be avoided by two interdependent dietary changes. First, the amount of plant oils rich in LA, the parent compound of the omega-6 class, which is converted to AA, needs to be reduced. Second, simultaneously the omega-3 PUFAs need to be increased in the diet. LA can be converted to arachidonic acid and the enzyme, {Delta}-6 desaturase, necessary to desaturate it, is the same one necessary to desaturate LNA, the parent compound of the omega-3 class; each competes with the other for this desaturase. The presence of LNA in the diet can inhibit the conversion of the large amounts of LA in the diets of Western industrialized countries which contain too much dietary plant oils rich in omega-6 PUFAs (e.g. corn, safflower, and soybean oils). The increase of LNA, together with EPA and DHA, and reduction of vegetable oils with high LA content, are necessary to achieve a healthier diet in these countries."

# 4 of 13 December 1, 2010 09:59 (EST)

Cathy leet

Natural stable ratio fish oil- Cardinova
Natural stable ratio fish oil reduced triglycerides 64%, raised HDL 20%, reduced plasma fibrinogen by up to 23%, reduced lp(a) 19%, and did not raise LDL. Why does this fish oil raise LDL and it doesn't. Cardinova has over 120 clinical studies and is used by most Integrative Medicine doctors in the US. Do your homework there is a fish oil that does not raise LDL but effects TG and HDL. But it is not a prescription in US and therefore you are not aware of it. Cardinova did the research, they are in Sweden.

# 5 of 13 December 1, 2010 10:06 (EST)

James DiNicolantonio

omega-6 are the major constituents of lipoproteins
Omega 6 are very important...they are the main components of lipoproteins and are at a much higher ratio in lipoprotiens compared to omega-3 I want to say on the order of 100:1...the problem is we get all our omega-6 from oxidized processed foods...so the problem wouldn't be necessarily to decrease omega-6,,,, but to get better QUALITY omega-6 as well as increasing omega-3

# 6 of 13 December 1, 2010 02:10 (EST)

Carol Anaski Figurski

RN BSN
Great article, I have seen first hand the results of chemical therapy to reduce ldl and it works. I have also seen Rush University physicans such as Dr. Olivia Floiran use ETOH, a glass a day for women and 2 for men as a natural way of lovering heart disease. We are living in exciting times where a person can now go to heart check of america using EBT technologies and have a coronary artery scan done, for purpose and prevention. Mine was zero.

# 7 of 13 December 2, 2010 08:15 (EST)

James J. King

Krill oil (NKO) is a phospholipid based oil and has different results than the MARINE trial
Krill oil has been being studied as a natural remedy for high cholesterol. In one study, 120 people were given krill oil, fish oil or a placebo. Krill oil reduced LDL (commonly referred to as "bad") cholesterol by 34% and increased HDL ("good") cholesterol by 43.5% compared to the placebo. In comparison, fish oil reduced LDL cholesterol by 4.6% and increased HDL cholesterol by 4.2%. Krill also lowered triglycerides.

# 8 of 13 December 2, 2010 12:06 (EST)

Woody Johnson

LDL-P not LDL-C
The commentary in this article is truely sad. LDL-P is the driver of athrosclerosis not the cholesterol content of LDL. Omega-3's increase the cholesterol content of LDL but reduce the LDL particle number. Isn't it time we have lipidologist comment on these studies and not cardiologist who haven't a clue about lipoprotein metabolism

# 9 of 13 December 2, 2010 11:00 (EST)

Wiliam Blanchet

Golden hood
I think that Nissen is angling for an IVUS trial.

We are not utilizing Lovaza to its potential and we are not recommending supplemental fish oil nearly enough based on current DATA.

# 10 of 13 December 3, 2010 12:49 (EST)

James DiNicolantonio

Precisely
Fish oil (a good one) like from Nordic Naturals , ortho molecular etc that third party tests their products or LOVAZA should be given in HF patients GISSI-HF and anyone with fasting triglycerides over 100... epidemiological studies show CV risk increases at fasting TG level of 90 or higher...usually signifies HDL has more TG content theirfore it gets acted upon by lipoprotein lipase and is excreted more readily, is more dysfunctional etc...lovaza should help this

# 11 of 13 December 5, 2010 04:03 (EST)

James ehrlich

LDL-C elevation is of little significance with omegas
As an extension of Dr. Woody Johnson's remarks, Apo B (or LDL-P) is decreased after omega 3 supplementation. Even if LDL-C is elevated, it has been "remodeled". The LDL is more buoyant and is in an environment of lower remnant lipoproteins (lower VLDL3 and IDL). So, this concern about LDL-C elevation reflects a lack of understanding of the total atherogenic particle burden (Apo B or LDL-P).

# 12 of 13 December 5, 2010 04:06 (EST)

James ehrlich

agree with comments by James DiNicolantonio and Woody Johnson
I see that Dr. James DiNicolantonio started out with similar sentiment as mine---so need to give him credit for his clear understanding as well as Dr. Johnson.

# 13 of 13 December 6, 2010 05:54 (EST)

James DiNicolantonio

James ehrlich
Thank you James Ehrlich...what is your email address??

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