Usefulness of Icosapent Ethyl (Eicosapentaenoic Acid Ethyl Ester) in Women to Lower Triglyceride Levels (Results from the MARINE and ANCHOR Trials)

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There are limited data on the efficacy and safety of triglyceride (TG)-lowering agents in women. We conducted subgroup analyses of the effects of icosapent ethyl (a high-purity prescription form of the ethyl ester of the omega-3 fatty acid, eicosapentaenoic acid) on TG levels (primary efficacy variable) and other atherogenic and inflammatory parameters in a total of 215 women with a broad range of TG levels (200−2000 mg/dl) enrolled in two 12-week placebo-controlled trials: MARINE (n = 18; placebo, n = 18) and ANCHOR (n = 91; placebo, n = 88). Icosapent ethyl 4 g/day significantly reduced TG levels from baseline to week 12 versus placebo in both MARINE (−22.7%; p = 0.0327) and ANCHOR (−21.5%; p <0.0001) without increasing low-density lipoprotein cholesterol levels. Significant improvements were also observed in non−high-density lipoprotein cholesterol levels in MARINE (−15.7%; p = 0.0082) and ANCHOR (−14.2%; p <0.0001) and total cholesterol levels in MARINE (−14.9%; p = 0.0023) and ANCHOR (−12.1%; p <0.0001), along with significant increases of >500% in eicosapentaenoic acid levels in plasma and red blood cells (all p <0.001). Icosapent ethyl was well tolerated, with adverse-event profiles comparable with findings in the overall studies. In conclusion, icosapent ethyl 4 g/day significantly reduced TG levels and other atherogenic parameters in women without increasing low-density lipoprotein cholesterol levels compared with placebo; the clinical implications of these findings are being evaluated in the REDUCtion of Cardiovascular Events With Eicosapentaenoic Acid [EPA]−Intervention Trial (REDUCE-IT) cardiovascular outcomes study. **(Am J Cardiol 2017;119:397−403)**

Management of triglycerides (TGs) represents a clinical challenge and may be particularly important among women, given that TG levels are a stronger predictor of cardiovascular disease (CVD) in women than in men.[1−5] Recommendations from the American Heart Association and the Institute of Medicine's Committee of Women's Health Research support reporting of gender-specific analyses for both the efficacy and adverse effects of preventative interventions in CVD.[6,7] Icosapent ethyl (Vascepa; Amarin Pharma Inc., Bedminster, NJ) is a high-purity prescription form of the ethyl ester of the omega-3 fatty acid, eicosapentaenoic acid (EPA).[8] In the MARINE and ANCHOR (also placebo-controlled, randomized, double-blind, and 12 weeks long) trials, icosapent ethyl significantly lowered levels of TGs and other atherogenic parameters without raising low-density lipoprotein cholesterol (LDL-C) levels in patients with very high TG levels in MARINE (TGs ≥500 and ≤2000 mg/dl) and high TG levels and on statin therapy in ANCHOR (TGs ≥200 and <500 mg/dl) compared with placebo.[9,10] As there are limited clinical trial data on TG-lowering agents in women, we evaluated subgroup data from MARINE and ANCHOR to provide robust information on the efficacy and safety of icosapent ethyl at the Food and Drug Administration−approved dose of 4 g/day among women who participated in these studies.

Methods

Details of the MARINE and ANCHOR study designs and participants were previously reported.[9,10] Briefly, patients were randomized to icosapent ethyl 4 g/day, 2 g/day, or placebo.[9,10] Both studies were conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki with protocol approval by the appropriate institutional review boards and written informed consent provided by all participants. In MARINE, patients were required to have very high TG levels (≥500 and ≤2000 mg/dl) and were allowed, but not required, to be on stable statin therapy with or without ezetimibe.[9] ANCHOR included patients with

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elevated TG levels (≥200 and <500 mg/dl) at high risk for CVD; patients were also required to be on a stable statin therapy with or without ezetimibe.[10]

In both studies, the primary efficacy variable was the median percent change in plasma TG levels from baseline to week 12 versus placebo. Additional efficacy assessments included the median percent change from baseline to week 12 versus placebo in plasma levels of other lipid parameters (LDL-C, high-density lipoprotein cholesterol [HDL-C], non-HDL-C, total cholesterol, very low−density lipoprotein cholesterol [VLDL-C], VLDL-TGs, and remnant lipoprotein cholesterol), apolipoproteins (apolipoprotein B and apolipoprotein C-III), inflammatory markers (oxidized LDL, lipoprotein-associated phospholipase A_2, and high-sensitivity C-reactive protein), and plasma and red blood cell (RBC) levels of EPA. Measurement methods for these parameters have previously been described.[9,11−16]

Safety assessments included and treatment-emergent adverse events (TEAEs), which were defined as any adverse event (AE) that began after the first dose or occurred before the first dose and worsened in severity during the double-blind treatment period.

For the primary efficacy variable, subgroup analysis by gender was prespecified in MARINE and ANCHOR (patients were stratified by gender at randomization). The analyses were based on the intent-to-treat population, defined as all randomized patients who had a baseline TG measurement, received ≥1 dose of study drug, and had ≥1 post-randomization efficacy measurement. For missing week 12 measurements, the last post-baseline measurement was carried forward as the end point measurement (last observation carried forward). The Hodges-Lehmann method was used to estimate median percent changes from baseline in differences between the icosapent ethyl 4 g/day and placebo groups. The Wilcoxon rank-sum test was used to calculate p values. MARINE and ANCHOR were powered to examine the change from baseline in fasting TG levels. For all prespecified subgroup analyses in MARINE and ANCHOR, 0.05 was the prespecified alpha for significance, which was also used in all post hoc analyses, including those reported here, which were exploratory in nature.

Results

Baseline characteristics of women in this subgroup analysis are provided in Table 1. In MARINE, 2 women discontinued treatment: in the icosapent ethyl 4 g/day group, 1 withdrew consent; in the placebo group, 1 discontinued due to an AE. A total of 8 women receiving icosapent ethyl 4 g/day and 9 women receiving placebo discontinued treatment in ANCHOR: in the icosapent ethyl 4 g/day group, 4 discontinued due to AEs, 2 withdrew consent, 1 was lost to follow-up, and 1 discontinued for other reasons; in the placebo group, 4 discontinued due to AEs, 4 withdrew consent, and 1 discontinued for other reasons.

For the primary end point, significant median percent reductions in TG levels from baseline to week 12 versus placebo were demonstrated in women treated with icosapent ethyl 4 g/day in both MARINE (−22.7%; p = 0.0327) and ANCHOR (−21.5%; p <0.0001) (Table 2; Figure 1). Reductions in TG levels versus placebo in women were comparable with those observed in men. In men treated with icosapent ethyl 4 g/day from MARINE and ANCHOR, respectively, TG levels were reduced by −36.1% and −21.4% versus placebo (both p <0.0001); it may be worth noting the sample size was smaller in MARINE than ANCHOR. For both studies, there was no significant interaction between gender as a baseline characteristic and treatment with respect to the percent change in TG levels from baseline versus placebo (both p = not significant for interaction; data not shown). In MARINE, among women receiving icosapent ethyl 4 g/day, there was a trend toward greater TG-lowering efficacy versus placebo in women on statin therapy than women not on statin therapy, although the sample size was small.

Table 1
Baseline characteristics (women randomized to icosapent ethyl 4 g/day or placebo in MARINE and ANCHOR)

Variable	MARINE		ANCHOR	
	Icosapent Ethyl 4 g/day (n = 18)	Placebo (n = 18)	Icosapent Ethyl 4 g/day (n = 91)	Placebo (n = 88)
Age, mean (SD) (years)	58 ± 9	60 ± 7	61 ± 10	63 ± 10
Body mass index, mean (SD) (kg/m^2)	31 ± 4	31 ± 4	32 ± 5	33 ± 5
White, n (%)	16 (89%)	17 (94%)	89 (98%)	85 (97%)
Statin use, n (%)	6 (33%)	3 (17%)	All	All

Median percent changes in the levels of other lipids, lipoproteins, and additional parameters from baseline to week 12 versus placebo are summarized in Table 2 and Figure 1. Significant reductions in non-HDL-C and total cholesterol with icosapent ethyl 4 g/day versus placebo were observed in women in both studies. VLDL-C, VLDL-TG, remnant lipoprotein cholesterol, apolipoprotein B, and ApoC-III were significantly reduced in ANCHOR. Changes in LDL-C and HDL-C were not significant among women in either study versus placebo. Median percent changes from baseline to week 12 versus placebo in the inflammatory markers oxidized LDL, lipoprotein-associated phospholipase A_2, and high-sensitivity C-reactive protein showed significant reductions among women in ANCHOR.

Plasma and RBC EPA levels were measured and/or available for a subset of women in MARINE and ANCHOR (Table 3). In the MARINE study, there were significant increases in mean (standard error) EPA levels from baseline to 12 weeks versus placebo in both plasma EPA (583.4% [143.0%]; p = 0.0002) and RBC EPA (532.6% [85.1%]; p <0.0001). Similarly, in the ANCHOR study, there were significant increases from baseline to 12 weeks versus placebo in both plasma and RBC mean (standard error) EPA levels of 667.2% (57.4%) and 618.7% (64.6%), respectively (both p <0.0001).

TEAEs were reported in 5 (27.8%) and 11 (61.1%) women treated with icosapent ethyl 4 g/day and placebo, respectively, in MARINE. TEAEs were reported in 46 (50.5%) and 42 women (47.7%) treated with icosapent ethyl 4 g/day and placebo, respectively, in ANCHOR. Arthralgia

Table 2
Median percent change in lipid and lipoprotein parameters and inflammatory markers from baseline to week 12 (women from intent-to-treat populations randomized to icosapent ethyl 4 g/day or placebo in the MARINE and ANCHOR studies)

Parameter	Icosapent Ethyl 4 g/day			Placebo			Median Change From Baseline
	Baseline	End of Treatment	Change From Baseline, %	Baseline	End of Treatment	Change From Baseline, %	Icosapent Ethyl 4 g/day vs Placebo, %, *P*
Lipid Parameters							
Triglycerides (mg/dl) (primary efficacy variable)							
MARINE	733 (257)	433 (303)	−27 (39)	550 (148)	585 (252)	−8.6 (54)	−23
n = 18, 18							0.0327
ANCHOR	267 (93)	215 (78)	−20 (25)	258 (78)	269 (117)	4.5 (40)	−22
n = 87, 86							<0.0001
Low-density lipoprotein cholesterol (mg/dl)							
MARINE	98 (40)	95 (69)	−2.7 (19)	113 (83)	121 (102)	11 (55)	−12
n = 18, 18							0.2114
ANCHOR	87 (29)	88 (30)	0 (25)	83 (28)	86 (34)	9.5 (32)	−5.8
n = 87, 86							0.1454
Non-high-density lipoprotein cholesterol (mg/dl)							
MARINE	228 (141)	219 (101)	−14 (20)	230 (88)	249 (79)	2.7 (17)	−16
n = 18, 18							0.0082
ANCHOR	132 (30)	123 (35)	−5.6 (19)	128 (36)	135 (40)	8.9 (31)	−14
n = 87, 86							<0.0001
Total cholesterol (mg/dl)							
MARINE	258 (143)	248 (125)	−11 (15)	260 (79)	285 (80)	1.9 (14)	−15
n = 18, 18							0.0023
ANCHOR	178 (37)	170 (44)	−4.6 (17)	171 (32)	184 (42)	8.1 (19)	−12
n = 87, 86							<0.0001
High-density lipoprotein cholesterol (mg/dl)							
MARINE	32 (14)	32 (16)	−1.9 (30)	30 (8)	32 (14)	11 (30)	−9.3
n = 18, 18							0.1591
ANCHOR	42 (15)	41 (13)	0 (22)	43 (14)	46 (19)	6.2 (22)	−3.9
n = 87, 86							0.0940
Very-low-density lipoprotein cholesterol (mg/dl)							
MARINE	123 (133)	122 (102)	−20 (39)	114 (93)	115 (83)	9.1 (71)	−22
n = 18, 18							0.1173
ANCHOR	43 (20)	36 (22)	−20 (43)	42 (21)	47 (30)	10 (58)	−25
n = 87, 86							<0.0001
Very-low-density lipoprotein triglycerides (mg/dl)							
MARINE	485 (372)	330 (333)	−25 (49)	411 (251)	400 (354)	−9.2 (79)	−18
n = 18, 18							0.2114
ANCHOR	186 (77)	142 (77)	−25 (34)	182 (100)	186 (117)	2.3 (69)	−28
n = 87, 86							<0.0001
Remnant lipoprotein cholesterol (mg/dl)							
MARINE	41 (68)	32 (42)	−15 (59)	33 (39)	31 (50)	5.3 (113)	−20
n = 18, 17							0.2760
ANCHOR*	14 (5.0)	9.0 (6.0)	−29 (38)	15 (8.0)	14 (8.0)	13 (74)	−34
n = 30, 33							0.0014
Lipoprotein Parameters							
Apolipoprotein B (mg/dl)							
MARINE	138 (29)	136 (31)	−5.1 (21)	132 (37)	140 (42)	3.1 (7.2)	−9.1
n = 18, 17							0.1131
ANCHOR	97 (20)	93 (27)	−4.2 (15)	92 (22)	98 (27)	7.0 (23)	−10
n = 82, 81							0.0003
Apolipoprotein C-III (mg/dl)							
MARINE†	26 (15)	19 (11)	−15 (26)	24 (12)	26 (13)	6.7 (43)	−20
n = 11, 10							0.0620
ANCHOR†	16 (4.5)	14 (4.2)	−11 (26)	15 (4.1)	16 (4.2)	5.5 (26)	−19
n = 80, 74							<0.0001
Inflammatory Markers							
Oxidized low-density lipoprotein (U/l)							
MARINE	91 (24)	81 (30)	−7.8 (27)	82 (26)	81 (43)	2.1 (25)	−8.2
n = 17, 17							0.4282

(*continued*)

Table 2
(*continued*)

Parameter	Icosapent Ethyl 4 g/day			Placebo			Median Change From Baseline
	Baseline	End of Treatment	Change From Baseline, %	Baseline	End of Treatment	Change From Baseline, %	Icosapent Ethyl 4 g/day vs Placebo, %, *P*
ANCHOR‡	56 (16)	52 (14)	−9.6 (23)	54 (17)	65 (18)	16 (26)	−23
n = 31, 32							0.0002
Lipoprotein-associated phospholipase A_2 (ng/ml)							
MARINE	234 (177)	201 (88)	−13 (34)	230 (116)	226 (86)	−1.6 (27)	−3.3
n = 17, 16							0.6525
ANCHOR	177 (53)	154 (44)	−15 (19)	182 (62)	193 (61)	3.9 (23)	−18
n = 82, 77							<0.0001
High-sensitivity C-reactive protein (mg/l)							
MARINE	3.4 (4.2)	3.5 (5.4)	−0.5 (116)	2.2 (3.0)	2.9 (2.8)	32 (66)	−13
n = 18, 17							0.7165
ANCHOR	2.9 (3.6)	2.9 (4.3)	1.4 (82)	3.4 (4.1)	3.9 (6.6)	20 (109)	−24
n = 82, 81							0.0238

Data are presented as median (interquartile range) for endpoint values. Median percent changes versus placebo are Hodges-Lehmann medians. Patient numbers are presented as icosapent ethyl 4 g/day and placebo, respectively.

* Remnant lipoprotein cholesterol was only measured in approximately the first 35% of patients randomized in ANCHOR.

† Apolipoprotein C-III levels were measured in the subset of all patients with available archived plasma samples from MARINE and ANCHOR.

‡ Oxidized low-density lipoprotein was only measured in approximately the first 35% of patients randomized in ANCHOR.

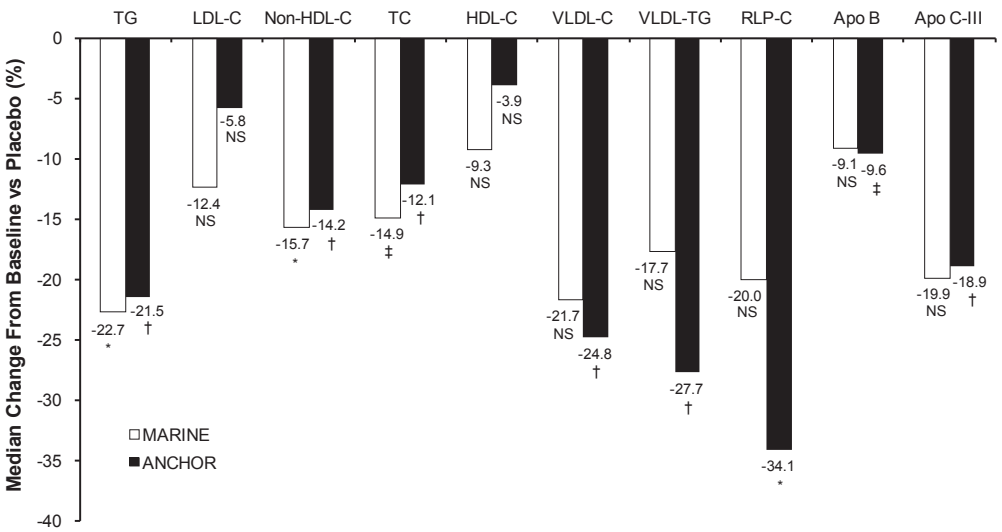

Figure 1. Median percent change in lipid and lipoprotein parameters from baseline to week 12 for icosapent ethyl 4 g/day versus placebo (women from the intent-to-treat populations in the MARINE and ANCHOR studies). Lipid parameters: TGs (primary end point), LDL-C, non-HDL-C, TC, HDL-C, VLDL-C, VLDL-TG, and RLP-C. Lipoprotein parameters: Apo B, Apo C-III. *p <0.05; †p <0.0001; ‡p <0.005. Apo C-III = apolipoprotein C-III; Apo B = apolipoprotein B; NS = nonsignificant; RLP-C = remnant lipoprotein cholesterol.

is the most commonly reported adverse reaction listed in the icosapent ethyl prescribing information[8]; myalgia is an adverse reaction of particular interest for icosapent ethyl use in addition to a statin given the safety profile of statins with respect to this symptom. In the original MARINE study, TEAEs occurring in >3% of patients in any group included nausea, diarrhea, and eructation; none of these TEAEs occurred with greater frequency in the icosapent ethyl 4 g/day group than in the placebo group.[9] In the subgroup of women from MARINE, no patients in the icosapent ethyl 4 g/day group experienced any of these TEAEs, arthralgia, or myalgia. In the original ANCHOR study, TEAEs occurring in >3% of patients in any group included nausea, diarrhea, nasopharyngitis, and arthralgia and only arthralgia occurred with greater frequency in the icosapent ethyl 4 g/day group than in the placebo group.[10] In the subgroup of women from ANCHOR (placebo and icosapent ethyl 4 g/day groups, respectively), 2 (2.3%) and 3 (3.3%) experienced nausea, 7 (8.0%) and 5 (5.5%) experienced diarrhea, 2 (2.3%) and 1 (1.1%) experienced nasopharyngitis, and 0 and 2 (2.2%) experienced arthralgia.

Discussion

Among women with TGs ≥500 mg/dl at risk for pancreatitis (MARINE study) and women on stable statin

Table 3
Change in plasma and red blood cell eicosapentaenoic acid levels from baseline to week 12 (women from intent-to-treat populations randomized to icosapent ethyl 4 g/day or placebo in the MARINE and ANCHOR studies)

Parameter	Icosapent Ethyl 4 g/day			Placebo			Change From Baseline
	Baseline	End of Treatment	Change From Baseline	Baseline	End of Treatment	Change From Baseline	Icosapent Ethyl 4 g/day vs Placebo, %, *P*
Plasma eicosapentaenoic acid (μg/mL; active ingredient of icosapent ethyl)							
MARINE*	59 (51)	315 (233)	239 (39)	65 (34)	67 (38)	−33 (45)	583 (143) 0.0002
ANCHOR†	29 (16)	207 (86)	187 (14)	27 (11)	31 (13)	13 (13)	667 (57) <0.0001
Red blood cell eicosapentaenoic acid, μg/mL (active ingredient of icosapent ethyl)							
MARINE‡	16 (8.9)	76 (35)	60 (5.7)	18 (11)	15 (12)	−6.0 (6.3)	533 (85) <0.0001
ANCHOR§	12 (6.3)	74 (38)	66 (4.6)	11 (6.5)	10 (4.3)	2.5 (4.2)	619 (65) <0.0001

Eicosapentaenoic acid levels are presented as mean (standard deviation). Change from baseline values are least squares mean (standard error).
* n = 15 icosapent ethyl; n = 13 placebo.
† n = 29 icosapent ethyl; n = 32 placebo.
‡ n = 15 icosapent ethyl; n = 14 placebo.
§ n = 27 icosapent ethyl; n = 31 placebo.

therapy with TGs ≥200 and <500 mg/dl at elevated risk of CVD (ANCHOR study), icosapent ethyl 4 g/day was shown to significantly reduce TG levels without a subsequent increase in LDL-C levels. Icosapent ethyl 4 g/day produced generally favorable effects on the other atherogenic lipid, lipoprotein, and inflammatory parameters in women in both studies and was well tolerated.

The reductions in lipid and lipoprotein parameters in these subgroups of women from the MARINE and ANCHOR studies were generally comparable with those observed in the overall study populations.[9,10,15,16] The reductions in inflammatory parameters in women were also generally comparable with those observed in the overall populations in the MARINE and ANCHOR studies.[11] The observed reductions in levels of TG and other atherogenic parameters, along with the known beneficial effects of EPA on multiple cellular and molecular mechanisms involved in the development and progression of atherosclerosis,[17] support the biologic plausibility of EPA as a treatment that may have cardiovascular benefits in women. The Japan EPA Lipid Intervention Study conducted among 18,645 statin-treated patients demonstrated a 19% relative reduction in major coronary events ($p = 0.011$) in patients taking 1.8 g/day EPA ethyl esters compared with controls.[18] Effects in women (69% of total group) and men (31%) were comparable ($p = 0.43$ for interaction).[18]

Icosapent ethyl is a high-concentration EPA prescription product and its biologic effects may differ from dietary supplements and other prescription omega-3 fatty acid products that contain variable amounts of EPA and the omega-3 fatty acid docosahexaenoic acid (DHA), which may increase LDL-C levels in some patients.[19–21] Potential mechanisms for the LDL-C increase observed with DHA, but not EPA, include differences in how EPA and DHA affect LDL clearance (DHA has been found to increase cholesteryl ester transfer protein activity and decrease LDL receptor expression in an animal model[22] and to downregulate the LDL receptor gene in humans[23]), DHA-mediated increased conversion of VLDL to LDL, and DHA-mediated increased LDL particle size.[24] Omega-3 fatty acid dietary supplements have been documented to not only have variable/inconsistent amounts of omega 3 fatty acids but also high saturated fat content and oxidation products.[19–21]

As expected, the significant increase in plasma and RBC EPA levels observed with icosapent ethyl treatment among women in these subgroup analyses was comparable with previous reports[13,14,25] and is consistent with the observed therapeutic effects.

The safety profile of icosapent ethyl observed among women in these subanalyses was similar to that in the overall MARINE and ANCHOR study populations.[9,10] As there are very little data available regarding the safety and lipid-lowering efficacy of prescription omega-3 fatty acid therapies in women, this analysis helps to address this gap.

An important limitation of the current subgroup analyses is that differences in the MARINE and ANCHOR study populations precluded pooling of data. Thus, the findings are based on relatively small samples of women. The clinical implications of lowering TG levels with icosapent ethyl 4 g/day need confirmation. The large ongoing cardiovascular outcomes trial, REDUCtion of Cardiovascular Events With Eicosapentaenoic Acid [EPA]—Intervention Trial (REDUCE-IT), should help to address this; notably, subanalyses in women will be needed.[26]

Disclosures

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