IMPLICATIONS OF REDUCE-IT FOR MANAGEMENT OF RESIDUAL RISK IN ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

December 17, 2019

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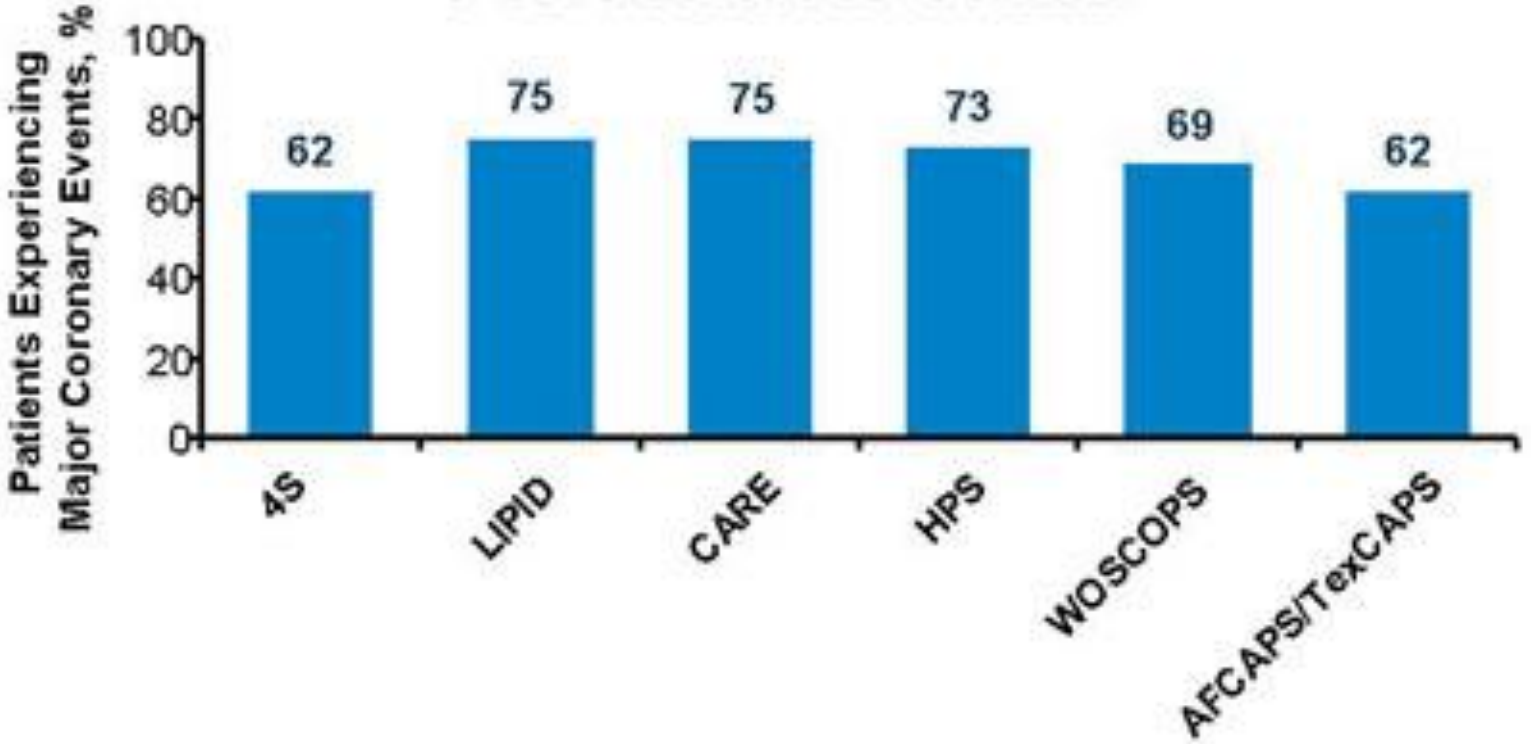
DISCLOSURES

- None

Residual Cardiovascular Risk Despite Intervention in Primary and Secondary Prevention Trials



N	4444	9014	4159	20,536	6595	6605
ΔLDL	−36%	−25%	−28%	−29%	−26%	−27%
	Secondary			High Risk	Primary	

Medscape

RESIDUAL RISK

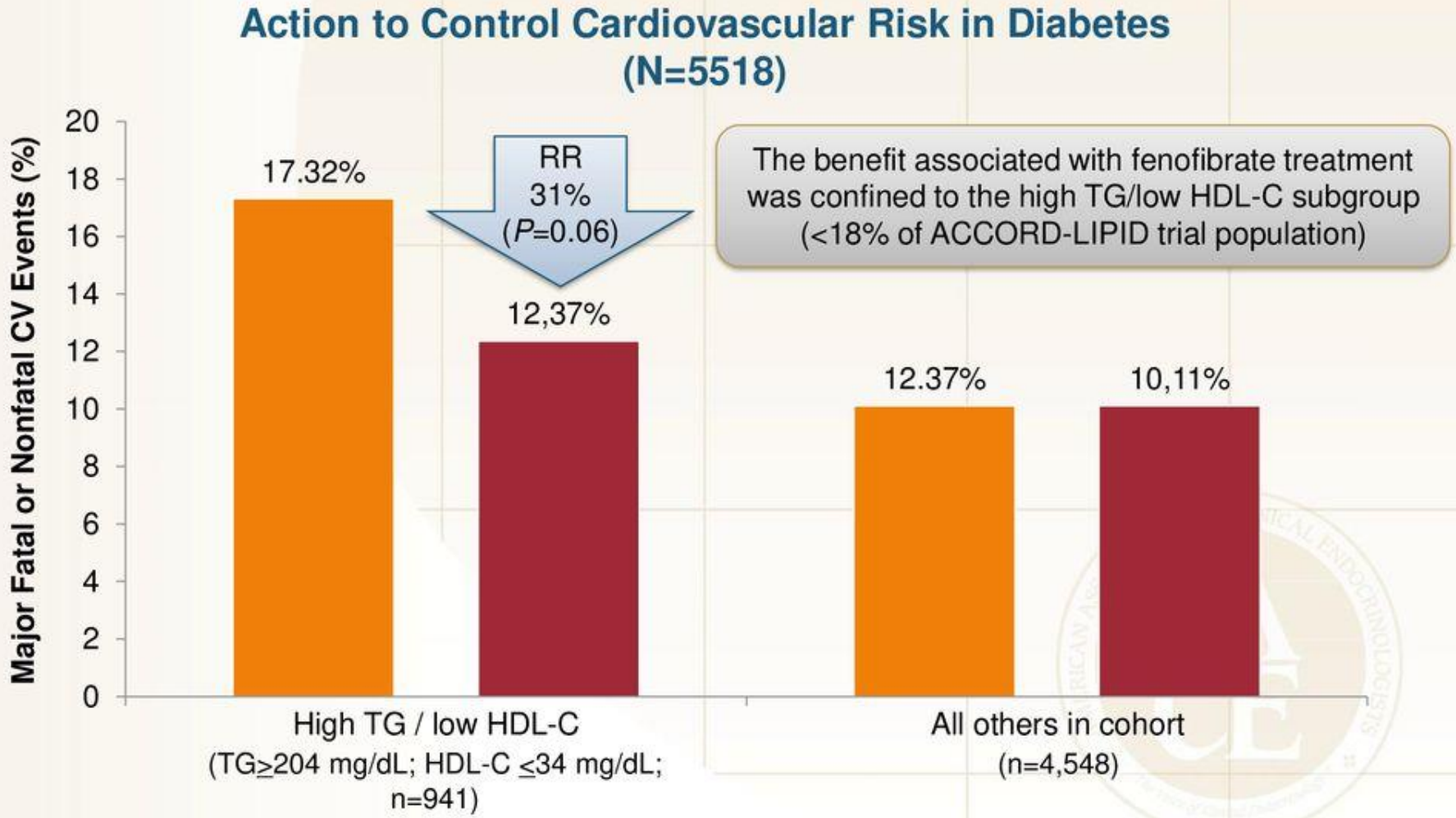
- The majority of statin-treated patients with ASCVD continue to have events
- Ezetimibe (in the IMPROVE IT Study) and the two available PCSK9 Inhibitors (in the FOURIER and ODYSSEY Trials) have been shown to reduce CV events when given on top of statin therapy
- Both of these therapies further lower LDL, but have little effect on other lipids/lipoproteins

RESIDUAL RISK

- Do elevated triglycerides play a role in residual risk ?
- If the answer is yes, do we have proof that adding TG-lowering therapy to statins reduces this risk?
  - Fenofibrate in the ACCORD Trial
  - Extended-release Niacin in the AIM HIGH Trial and Heart Protection Study II

ANSWER: No*

Fenofibrate Benefits Most Likely in Patients with High TG and Low HDL-C



CV, cerebrovascular; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; RR, risk reduction; TG, triglycerides.

Elam M, et al, *Clin Lipidol.* 2011;6:9-20. ACCORD Study Group. NEJM. 2010; 362:1563-1574.

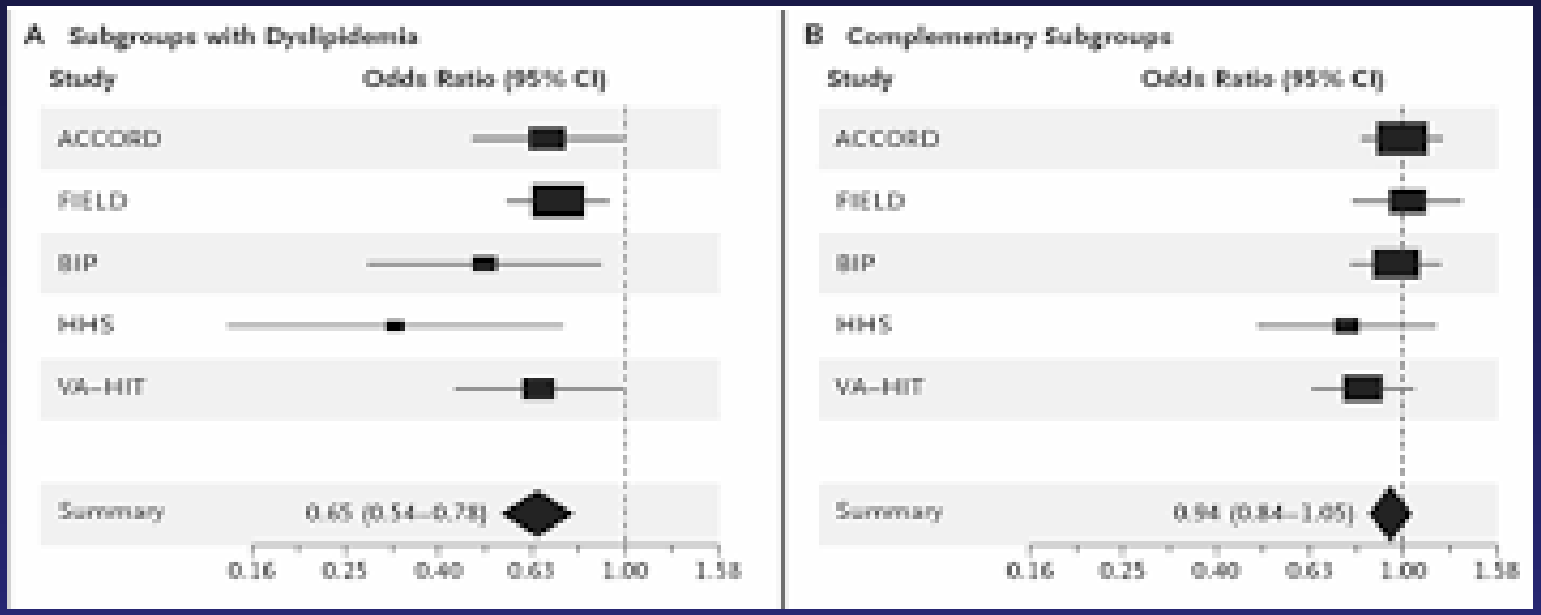
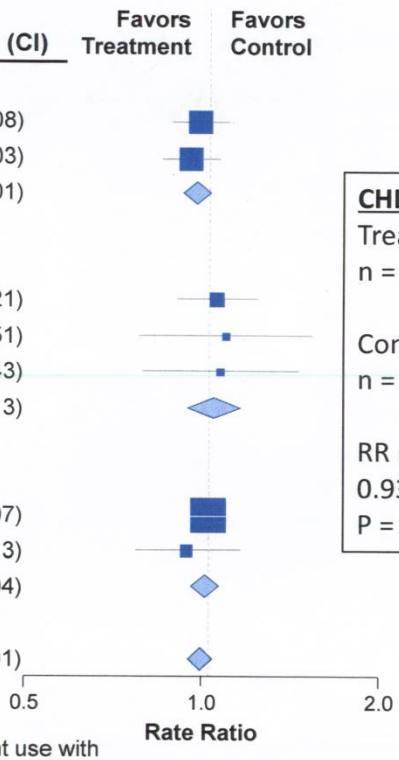


Figure 1. Forest Plot of the Treatment Effect in Subgroups. Data from a meta-analysis of randomized trials of fibrate drugs are shown; an odds ratio of less than unity indicates a beneficial therapeutic effect. Panel A shows data from subgroups of patients with dyslipidemia (i.e., high levels of triglycerides and low levels of high-density lipoprotein [HDL] cholesterol), and Panel B shows data from the complementary subgroups without this type of dyslipidemia. **The subgroup with dyslipidemia defined according to criteria prespecified in the ACCORD Lipid trial (a triglyceride level of ≥ 204 mg per deciliter and an HDL cholesterol level of ≤ 34 mg per deciliter)** and the subgroup with levels closest to these lipid criteria in each of the other trials were used.

(NEJM 2010; 363: 692-94).

Long Chain Omega-3 Interventions and CV Events

Source	No. of Events (%) Treatment	Control	Rate Ratios (CI)
Coronary heart disease			
Nonfatal myocardial infarction	1121 (2.9)	1155 (3.0)	0.97 (0.87–1.08)
Coronary heart disease	1301 (3.3)	1394 (3.6)	0.93 (0.83–1.03)
Any	3085 (7.9)	3188 (8.2)	0.96 (0.90–1.01)
			P=.12
Stroke			
Ischemic	574 (1.9)	554 (1.8)	1.03 (0.88–1.21)
Hemorrhagic	117 (0.4)	109 (0.4)	1.07 (0.76–1.51)
Unclassified/other	142 (0.4)	135 (0.3)	1.05 (0.77–1.43)
Any	870 (2.2)	843 (2.2)	1.03 (0.93–1.13)
			P=.60
Revascularization			
Coronary	3044 (9.3)	3040 (9.3)	1.00 (0.93–1.07)
Noncoronary	305 (2.7)	330 (2.9)	0.92 (0.75–1.13)
Any	3290 (10.0)	3313 (10.2)	0.99 (0.94–1.04)
			P=.60
Any major vascular event	5930 (15.2)	6071 (15.6)	0.97 (0.93–1.01)
			P=.10



CHD Death Events
Treatment
n = 1301 (3.3%)

Control
n = 1394 (3.6%)

RR (95% CI)
0.93 (0.85-1.00)
P = 0.05

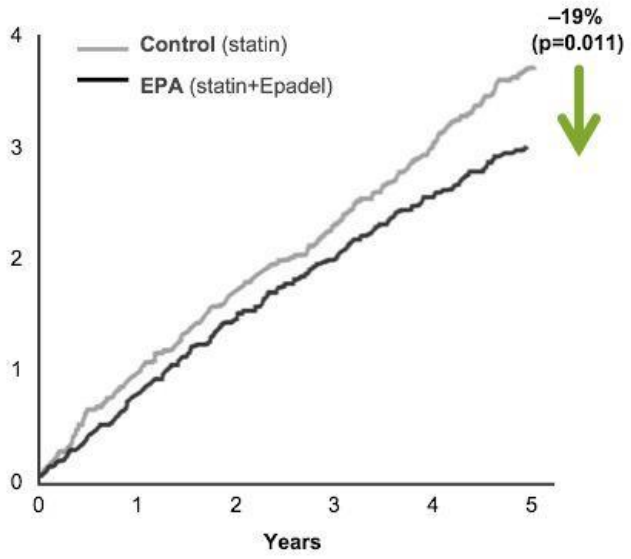
Adapted with permission* from Aung T, Halsey J, Kromhout D, et al. Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: Meta-analysis of 10 trials involving 77917 individuals. *JAMA Cardiol.* 2018;3:225-234. [*https://creativecommons.org/licenses.org/by-nc/4.0/]

JELIS TRIAL

18,645 Japanese Men and Women Randomized to Statin Alone or Statin + Ethyl-EPA (Epadel) and Followed for 5 Years

TOTAL COHORT

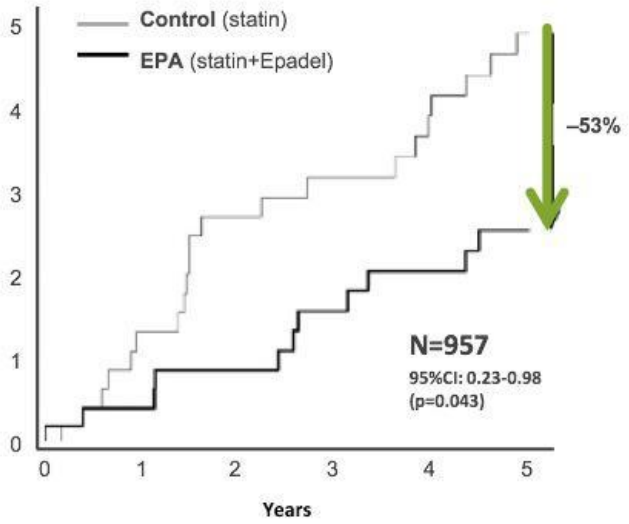
(No Pre-specified Minimum TG level)
Cumulative Incidence of Major Coronary Events (%)



Source: Yokoyama M. *The Lancet 2007*

SUB GROUP

(TG>150 mg/dL and HDL < 40 mg/dL)
Cumulative Incidence of Major Coronary Events (%)



P value adjusted for age, gender, smoking, diabetes, and hypertension.
CI=confidence interval.

Source: Saito et al, 2008 *Atherosclerosis*


MOUSE TRAP
AGE 6+
A GAME OF TASTY ACTION ON A CRAZY CONTRAPTION!
WARNING:
MB
START
TURN CRANK
SAFE

Original Article

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D., Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D., Lixia Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators

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REDUCE-IT

- A randomized, double-blind, placebo-controlled trial comparing Icosapent Ethyl (IPE) 2 g BID with placebo (mineral oil)
- Randomization was stratified according to CV risk stratum: secondary prevention or primary prevention (capped at 30%of enrollees)
- ≥ 45 yo with established CVD or ≥ 50 yo with diabetes + 1 additional risk factor
- Fasting TG = 150 - 499 mg/dl and LDL-C = 41-100 mg/dl on a stable dose of statin

REDUCE-IT

- The lower limit for acceptable TGs was later increased to 200 mg/dl
- Primary End Point: CV death, nonfatal MI, nonfatal CVA, coronary revascularization, or unstable angina
- Secondary End Point: CV death, nonfatal MI, or nonfatal CVA
- 8179 patients underwent randomization; 70.7% were secondary prevention/29.3% were primary prevention
- Median duration of follow up was 4.9 years

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Icosapent Ethyl (N = 4089)	Placebo (N = 4090)
Age		
Median (IQR) — yr	64.0 (57.0–69.0)	64.0 (57.0–69.0)
≥65 yr — no. (%)	1857 (45.4)	1906 (46.6)
Male sex — no. (%)	2927 (71.6)	2895 (70.8)
White race — no. (%)†	3691 (90.3)	3688 (90.2)
Body-mass index‡		
Median (IQR)	30.8 (27.8–34.5)	30.8 (27.9–34.7)
≥30 — no. (%)	2331 (57.0)	2362 (57.8)
Geographic region — no. (%)§		
United States, Canada, the Netherlands, Australia, New Zealand, and South Africa	2906 (71.1)	2905 (71.0)
Eastern European	1053 (25.8)	1053 (25.7)
Asia–Pacific	130 (3.2)	132 (3.2)
Cardiovascular risk stratum — no. (%)		
Secondary-prevention cohort	2892 (70.7)	2893 (70.7)
Primary-prevention cohort	1197 (29.3)	1197 (29.3)
Ezetimibe use — no. (%)	262 (6.4)	262 (6.4)
Statin intensity — no. (%)		
Low	254 (6.2)	267 (6.5)
Moderate	2533 (61.9)	2575 (63.0)
High	1290 (31.5)	1226 (30.0)
Data missing	12 (0.3)	22 (0.5)
Diabetes — no. (%)		
Type 1	27 (0.7)	30 (0.7)
Type 2	2367 (57.9)	2363 (57.8)
No diabetes at baseline	1695 (41.5)	1694 (41.4)
Data missing	0	3 (0.1)
Median high-sensitivity CRP level (IQR) — mg/liter	2.2 (1.1–4.5)	2.1 (1.1–4.5)
Median triglyceride level (IQR) — mg/dl	216.5 (176.5–272.0)	216.0 (175.5–274.0)
Median HDL cholesterol level (IQR) — mg/dl	40.0 (34.5–46.0)	40.0 (35.0–46.0)
Median LDL cholesterol level (IQR) — mg/dl	74.0 (61.5–88.0)	76.0 (63.0–89.0)
Distribution of triglyceride levels — no./total no. (%)		
<150 mg/dl	412/4086 (10.1)	429/4089 (10.5)
≥150 to <200 mg/dl	1193/4086 (29.2)	1191/4089 (29.1)
≥200 mg/dl	2481/4086 (60.7)	2469/4089 (60.4)
Triglyceride level ≥200 mg/dl and HDL cholesterol level ≤35 mg/dl — no. (%)	823 (20.1)	794 (19.4)
Median eicosapentaenoic acid level (IQR) — μg/ml	26.1 (17.1–40.1)	26.1 (17.1–39.9)

* Median low-density lipoprotein (LDL) cholesterol level at baseline differed significantly between the trial groups (P=0.03); there were no other significant between-group differences in baseline characteristics. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. In general, the baseline value was defined as the last nonmissing measurement obtained before randomization. The baseline LDL cholesterol value as measured by means of preparative ultracentrifugation was used in our analyses; however, if the preparative ultracentrifugation value was missing, the LDL cholesterol value measured by another method was used in the following order of priority: the value obtained by means of direct measurement of LDL cholesterol, the value derived with the use of the Friedewald equation (only for patients with a triglyceride level <400 mg per deciliter), and the value derived with the use of the calculation published by Johns Hopkins University investigators.[22] At the first and second screening visits, the LDL cholesterol value obtained by direct measurement was used if at the same visit the triglyceride level was higher than 400 mg per deciliter. At all remaining visits, the LDL cholesterol value was obtained by means of direct measurement or preparative ultracentrifugation if at the same visit the triglyceride level was higher than 400 mg per deciliter. For all other measures of lipid and lipoprotein markers, whenever possible, the baseline value was derived as the arithmetic mean of the value obtained at visit 2 (day 0) and the value obtained at the preceding screening visit. If only one of these values was available, that single value was used as the baseline value. CRP denotes C-reactive protein, HDL high-density lipoprotein, and IQR interquartile range. Percentages may not total 100 because of rounding.

† Race was reported by the investigators.

‡ Body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Eastern European region includes Poland, Romania, Russia, and Ukraine, and Asia–Pacific region includes India.

Effects on Biomarkers from Baseline to Year 1

	Icosapent Ethyl (n=4089) Median		Placebo (n=4090) Median		Median Between Group Difference at Year 1		
Biomarker*	**Baseline**	**Year 1**	**Baseline**	**Year 1**	**Absolute Change from Baseline**	**% Change from Baseline**	**% Change P-value**
Triglycerides (mg/dL)	216.5	175.0	216.0	221.0	-44.5	-19.7	<0.0001
Non-HDL-C (mg/dL)	118.0	113.0	118.5	130.0	-15.5	-13.1	<0.0001
LDL-C (mg/dL)	74.0	77.0	76.0	84.0	-5.0	-6.6	<0.0001
HDL-C (mg/dL)	40.0	39.0	40.0	42.0	-2.5	-6.3	<0.0001
Apo B (mg/dL)	82.0	80.0	83.0	89.0	-8.0	-9.7	<0.0001
hsCRP (mg/L)	2.2	1.8	2.1	2.8	-0.9	-39.9	<0.0001
Log hsCRP (mg/L)	0.8	0.6	0.8	1.0	-0.4	-22.5	<0.0001
EPA (µg/mL)	26.1	144.0	26.1	23.3	+114.9	+358.8	<0.0001

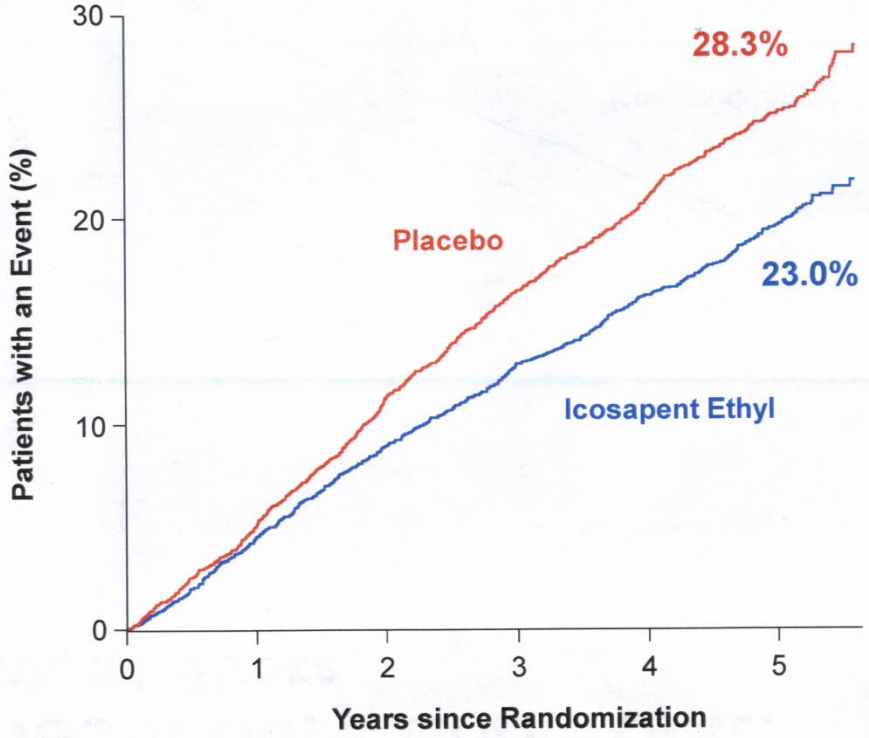
*Apo B and hsCRP were measured at Year 2.

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019; 380:11-22.

REDUCE-IT

- Primary End Point (1606 events): 17.2% w/IPE vs 22% w/PBO (HR 0.75, p<0.001)
- Secondary End Point: 11.2% w/IPE vs 14.8% w/PBO (HR 0.74, p<0.001)
- Among prespecified tertiary endpoints, the rates of adjudicated sudden cardiac death were 1.5% w/IPE and 2.1% w/PBO (HR 0.69)

Primary End Point:
CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



Hazard Ratio, 0.75
(95% CI, 0.68–0.83)

RRR = 24.8%

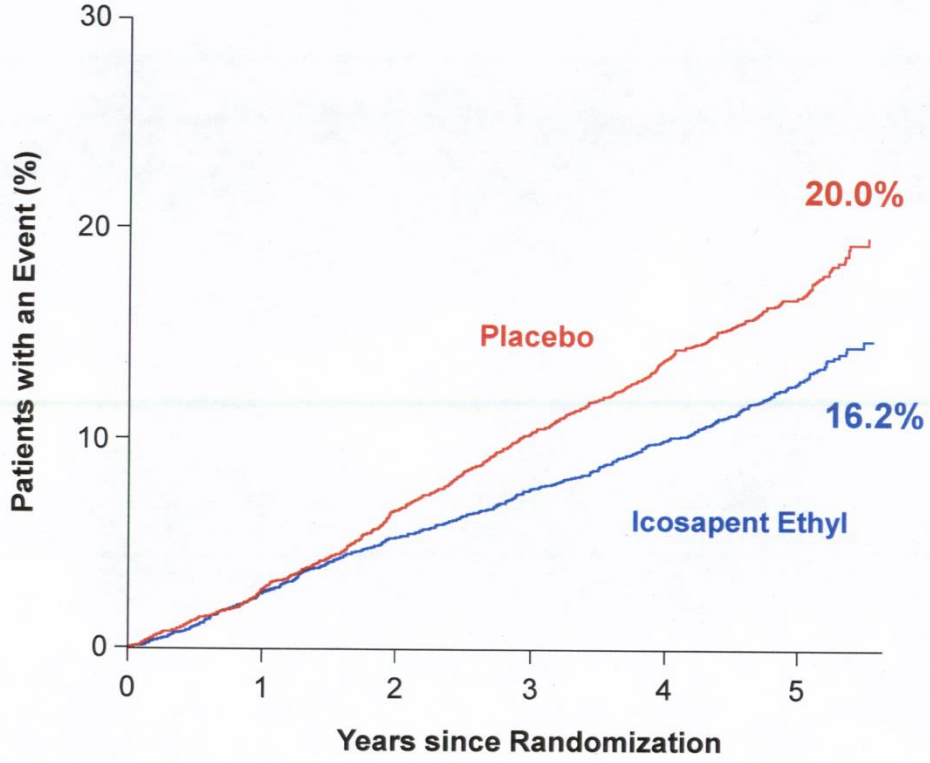
ARR = 4.8%

NNT = 21 (95% CI, 15–33)

P=0.00000001

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019. Bhatt DL. AHA 2018, Chicago.

Key Secondary End Point:
CV Death, MI, Stroke



Hazard Ratio, 0.74
(95% CI, 0.65–0.83)

RRR = 26.5%

ARR = 3.6%

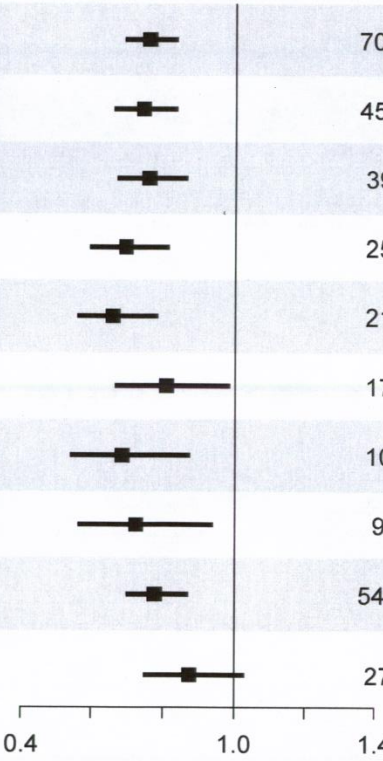
NNT = 28 (95% CI, 20–47)

P=0.0000006

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019. Bhatt DL. AHA 2018, Chicago.

Pre-specified Hierarchical Testing

Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	RRR	P-value
Primary Composite (ITT)	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	25%▼	<0.001
Key Secondary Composite (ITT)	459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65–0.83)	26%▼	<0.001
Cardiovascular Death or Nonfatal Myocardial Infarction	392/4089 (9.6%)	507/4090 (12.4%)	0.75 (0.66–0.86)	25%▼	<0.001
Fatal or Nonfatal Myocardial Infarction	250/4089 (6.1%)	355/4090 (8.7%)	0.69 (0.58–0.81)	31%▼	<0.001
Urgent or Emergent Revascularization	216/4089 (5.3%)	321/4090 (7.8%)	0.65 (0.55–0.78)	35%▼	<0.001
Cardiovascular Death	174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66–0.98)	20%▼	0.03
Hospitalization for Unstable Angina	108/4089 (2.6%)	157/4090 (3.8%)	0.68 (0.53–0.87)	32%▼	0.002
Fatal or Nonfatal Stroke	98/4089 (2.4%)	134/4090 (3.3%)	0.72 (0.55–0.93)	28%▼	0.01
Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke	549/4089 (13.4%)	690/4090 (16.9%)	0.77 (0.69–0.86)	23%▼	<0.001
Total Mortality	274/4089 (6.7%)	310/4090 (7.6%)	0.87 (0.74–1.02)	13%▼	0.09

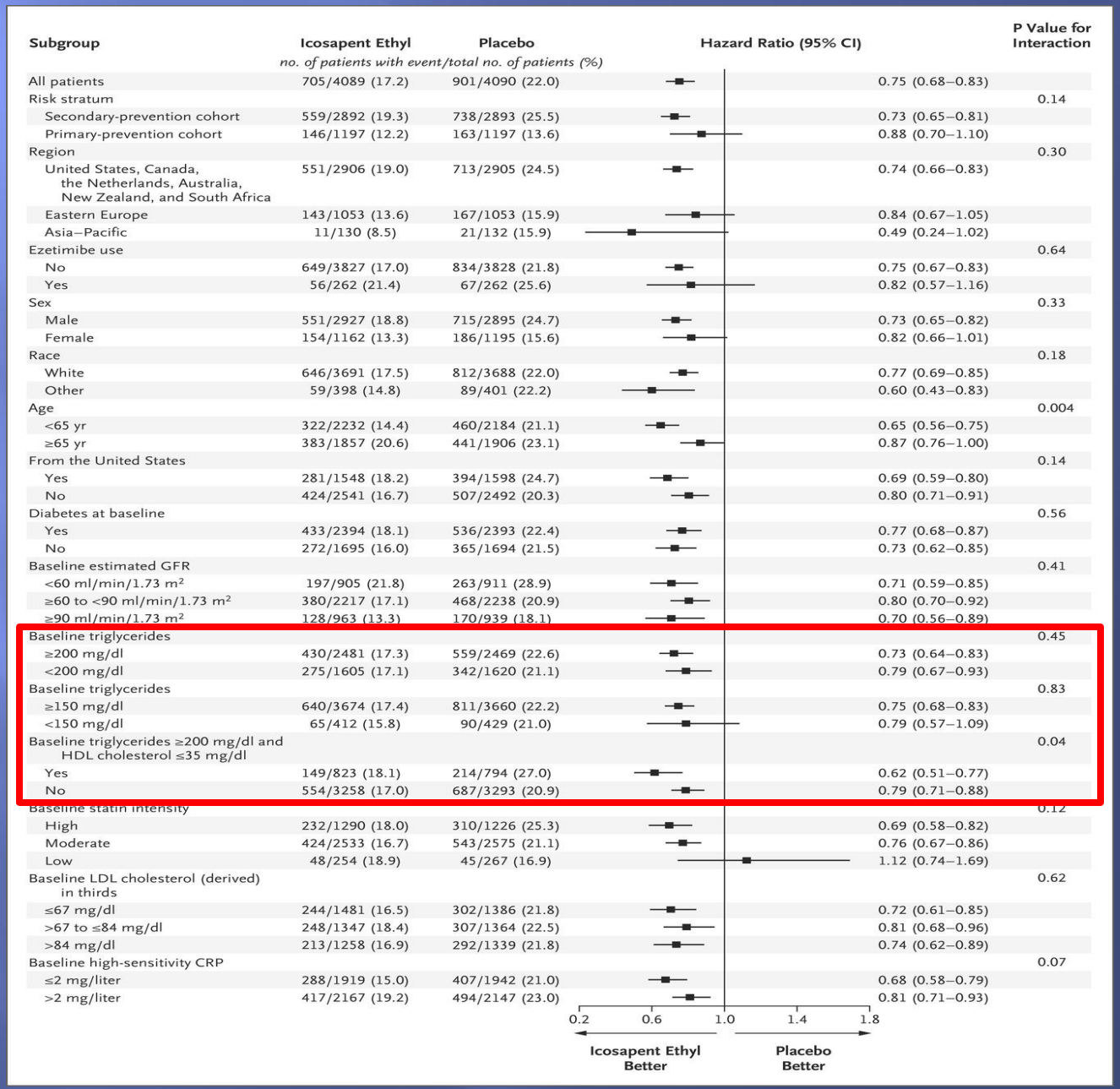


RRR denotes relative risk reduction

Bhatt DL. AHA 2018, Chicago.

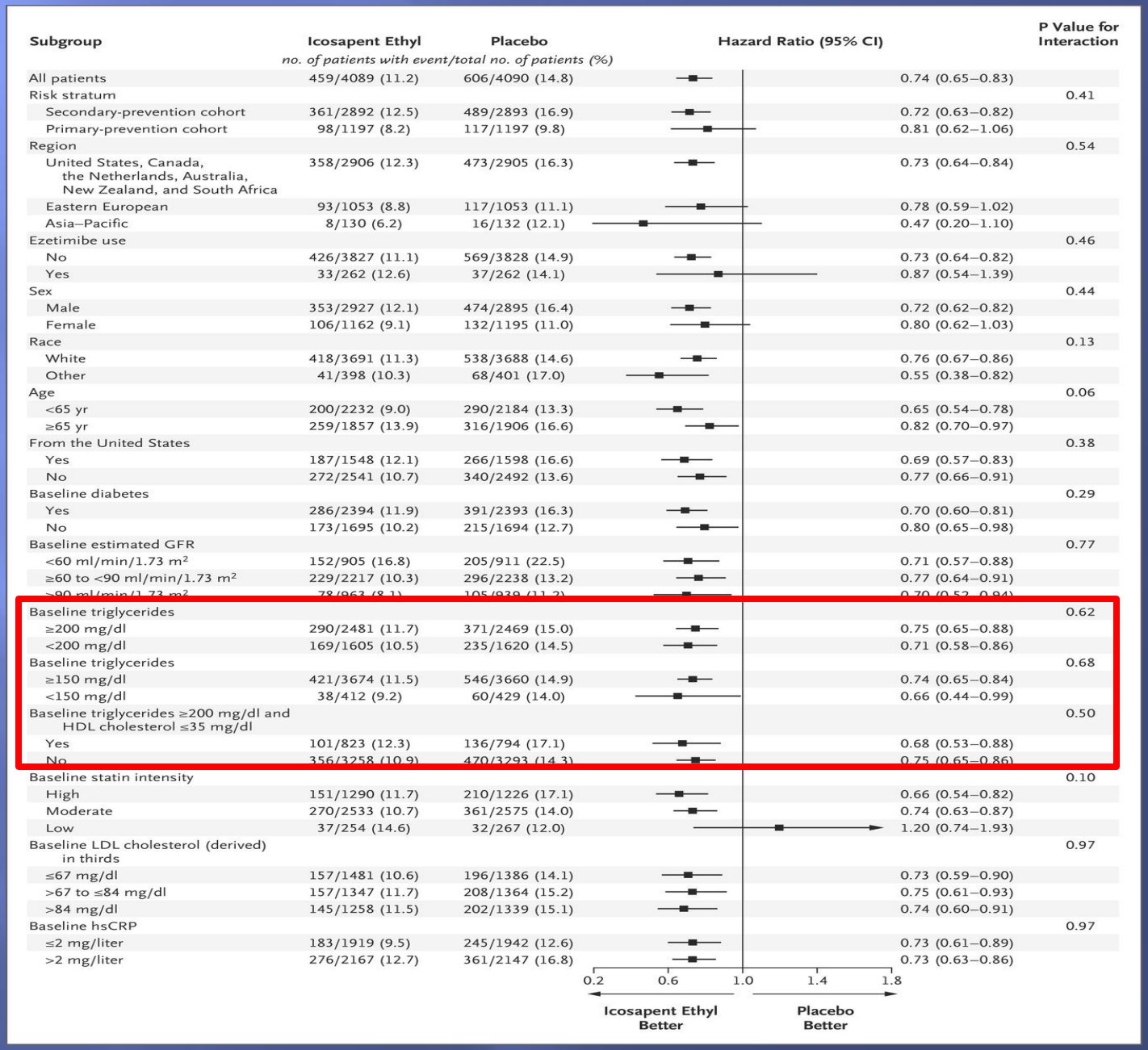
Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019.

PRIMARY END POINT IN PRESPECIFIED SUBGROUPS



Subgroup	Icosapent Ethyl	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients with event/total no. of patients (%)			
All patients	705/4089 (17.2)	901/4090 (22.0)	0.75 (0.68–0.83)	
Risk stratum				0.14
Secondary-prevention cohort	559/2892 (19.3)	738/2893 (25.5)	0.73 (0.65–0.81)	
Primary-prevention cohort	146/1197 (12.2)	163/1197 (13.6)	0.88 (0.70–1.10)	
Region				0.30
United States, Canada, the Netherlands, Australia, New Zealand, and South Africa	551/2906 (19.0)	713/2905 (24.5)	0.74 (0.66–0.83)	
Eastern Europe	143/1053 (13.6)	167/1053 (15.9)	0.84 (0.67–1.05)	
Asia–Pacific	11/130 (8.5)	21/132 (15.9)	0.49 (0.24–1.02)	
Ezetimibe use				0.64
No	649/3827 (17.0)	834/3828 (21.8)	0.75 (0.67–0.83)	
Yes	56/262 (21.4)	67/262 (25.6)	0.82 (0.57–1.16)	
Sex				0.33
Male	551/2927 (18.8)	715/2895 (24.7)	0.73 (0.65–0.82)	
Female	154/1162 (13.3)	186/1195 (15.6)	0.82 (0.66–1.01)	
Race				0.18
White	646/3691 (17.5)	812/3688 (22.0)	0.77 (0.69–0.85)	
Other	59/398 (14.8)	89/401 (22.2)	0.60 (0.43–0.83)	
Age				0.004
<65 yr	322/2232 (14.4)	460/2184 (21.1)	0.65 (0.56–0.75)	
≥65 yr	383/1857 (20.6)	441/1906 (23.1)	0.87 (0.76–1.00)	
From the United States				0.14
Yes	281/1548 (18.2)	394/1598 (24.7)	0.69 (0.59–0.80)	
No	424/2541 (16.7)	507/2492 (20.3)	0.80 (0.71–0.91)	
Diabetes at baseline				0.56
Yes	433/2394 (18.1)	536/2393 (22.4)	0.77 (0.68–0.87)	
No	272/1695 (16.0)	365/1694 (21.5)	0.73 (0.62–0.85)	
Baseline estimated GFR				0.41
<60 ml/min/1.73 m²	197/905 (21.8)	263/911 (28.9)	0.71 (0.59–0.85)	
≥60 to <90 ml/min/1.73 m²	380/2217 (17.1)	468/2238 (20.9)	0.80 (0.70–0.92)	
≥90 ml/min/1.73 m²	128/963 (13.3)	170/939 (18.1)	0.70 (0.56–0.89)	
Baseline triglycerides				0.45
≥200 mg/dl	430/2481 (17.3)	559/2469 (22.6)	0.73 (0.64–0.83)	
<200 mg/dl	275/1605 (17.1)	342/1620 (21.1)	0.79 (0.67–0.93)	
Baseline triglycerides				0.83
≥150 mg/dl	640/3674 (17.4)	811/3660 (22.2)	0.75 (0.68–0.83)	
<150 mg/dl	65/412 (15.8)	90/429 (21.0)	0.79 (0.57–1.09)	
Baseline triglycerides ≥200 mg/dl and HDL cholesterol ≤35 mg/dl				0.04
Yes	149/823 (18.1)	214/794 (27.0)	0.62 (0.51–0.77)	
No	554/3258 (17.0)	687/3293 (20.9)	0.79 (0.71–0.88)	
Baseline statin intensity				0.12
High	232/1290 (18.0)	310/1226 (25.3)	0.69 (0.58–0.82)	
Moderate	424/2533 (16.7)	543/2575 (21.1)	0.76 (0.67–0.86)	
Low	48/254 (18.9)	45/267 (16.9)	1.12 (0.74–1.69)	
Baseline LDL cholesterol (derived) in thirds				0.62
≤67 mg/dl	244/1481 (16.5)	302/1386 (21.8)	0.72 (0.61–0.85)	
>67 to ≤84 mg/dl	248/1347 (18.4)	307/1364 (22.5)	0.81 (0.68–0.96)	
>84 mg/dl	213/1258 (16.9)	292/1339 (21.8)	0.74 (0.62–0.89)	
Baseline high-sensitivity CRP				0.07
≤2 mg/liter	288/1919 (15.0)	407/1942 (21.0)	0.68 (0.58–0.79)	
>2 mg/liter	417/2167 (19.2)	494/2147 (23.0)	0.81 (0.71–0.93)	

SECONDARY END POINT IN PRESPECIFIED SUBGROUPS



Subgroup	Icosapent Ethyl	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients with event/total no. of patients (%)			
All patients	459/4089 (11.2)	606/4090 (14.8)	0.74 (0.65–0.83)	
Risk stratum				0.41
Secondary-prevention cohort	361/2892 (12.5)	489/2893 (16.9)	0.72 (0.63–0.82)	
Primary-prevention cohort	98/1197 (8.2)	117/1197 (9.8)	0.81 (0.62–1.06)	
Region				0.54
United States, Canada, the Netherlands, Australia, New Zealand, and South Africa	358/2906 (12.3)	473/2905 (16.3)	0.73 (0.64–0.84)	
Eastern European	93/1053 (8.8)	117/1053 (11.1)	0.78 (0.59–1.02)	
Asia–Pacific	8/130 (6.2)	16/132 (12.1)	0.47 (0.20–1.10)	
Ezetimibe use				0.46
No	426/3827 (11.1)	569/3828 (14.9)	0.73 (0.64–0.82)	
Yes	33/262 (12.6)	37/262 (14.1)	0.87 (0.54–1.39)	
Sex				0.44
Male	353/2927 (12.1)	474/2895 (16.4)	0.72 (0.62–0.82)	
Female	106/1162 (9.1)	132/1195 (11.0)	0.80 (0.62–1.03)	
Race				0.13
White	418/3691 (11.3)	538/3688 (14.6)	0.76 (0.67–0.86)	
Other	41/398 (10.3)	68/401 (17.0)	0.55 (0.38–0.82)	
Age				0.06
<65 yr	200/2232 (9.0)	290/2184 (13.3)	0.65 (0.54–0.78)	
≥65 yr	259/1857 (13.9)	316/1906 (16.6)	0.82 (0.70–0.97)	
From the United States				0.38
Yes	187/1548 (12.1)	266/1598 (16.6)	0.69 (0.57–0.83)	
No	272/2541 (10.7)	340/2492 (13.6)	0.77 (0.66–0.91)	
Baseline diabetes				0.29
Yes	286/2394 (11.9)	391/2393 (16.3)	0.70 (0.60–0.81)	
No	173/1695 (10.2)	215/1694 (12.7)	0.80 (0.65–0.98)	
Baseline estimated GFR				0.77
<60 ml/min/1.73 m²	152/905 (16.8)	205/911 (22.5)	0.71 (0.57–0.88)	
≥60 to <90 ml/min/1.73 m²	229/2217 (10.3)	296/2238 (13.2)	0.77 (0.64–0.91)	
≥90 ml/min/1.73 m²	78/963 (8.1)	105/939 (11.2)	0.70 (0.52–0.94)	
Baseline triglycerides				0.62
≥200 mg/dl	290/2481 (11.7)	371/2469 (15.0)	0.75 (0.65–0.88)	
<200 mg/dl	169/1605 (10.5)	235/1620 (14.5)	0.71 (0.58–0.86)	
Baseline triglycerides				0.68
≥150 mg/dl	421/3674 (11.5)	546/3660 (14.9)	0.74 (0.65–0.84)	
<150 mg/dl	38/412 (9.2)	60/429 (14.0)	0.66 (0.44–0.99)	
Baseline triglycerides ≥200 mg/dl and HDL cholesterol ≤35 mg/dl				0.50
Yes	101/823 (12.3)	136/794 (17.1)	0.68 (0.53–0.88)	
No	356/3258 (10.9)	470/3293 (14.3)	0.75 (0.65–0.86)	
Baseline statin intensity				0.10
High	151/1290 (11.7)	210/1226 (17.1)	0.66 (0.54–0.82)	
Moderate	270/2533 (10.7)	361/2575 (14.0)	0.74 (0.63–0.87)	
Low	37/254 (14.6)	32/267 (12.0)	1.20 (0.74–1.93)	
Baseline LDL cholesterol (derived) in thirds				0.97
≤67 mg/dl	157/1481 (10.6)	196/1386 (14.1)	0.73 (0.59–0.90)	
>67 to ≤84 mg/dl	157/1347 (11.7)	208/1364 (15.2)	0.75 (0.61–0.93)	
>84 mg/dl	145/1258 (11.5)	202/1339 (15.1)	0.74 (0.60–0.91)	
Baseline hsCRP				0.97
≤2 mg/liter	183/1919 (9.5)	245/1942 (12.6)	0.73 (0.61–0.89)	
>2 mg/liter	276/2167 (12.7)	361/2147 (16.8)	0.73 (0.63–0.86)	

REDUCE-IT

- Attainment of TGs < 150 mg/dl at 1 year did not influence the primary or secondary end points
- However, there was a significantly larger risk reduction among those subjects with TGs > 200 mg/dl and HDL-C < 35 mg/dl versus those w/o this phenotype (38% vs 21%, P for heterogeneity = 0.04)

SAFETY AND ADVERSE EVENTS

- The rate of AF was significantly higher in the IPE group (5.3%) vs the PBO group (3.9%) (P = 0.003)
- The rate of hospitalization for AF/Flutter was significantly higher in the IPE group than in the PBO group (3.1% vs 2.1%, P = 0.004)
- Overall rates of serious adverse bleeding events were 2.7% in the IPE group and 2.1% in the PBO group (P = 0.06), and no fatal bleeding events in either group
- No significant differences in the rates of hemorrhagic CVA, serious CNS bleeding, or GI bleeding

REDUCE-IT CONCLUSIONS

- **25% reduction** in the 1º Composite End Point (NNT = 21)
- **26% reduction** in the 2º Composite End Point (NNT = 28)
- **20% lower risk of CV death** in statin-treated patients with a baseline LDL-C = 75 mg/dl
- More bleeding events with IPE, but the overall rates were low, and there were no fatal bleeding events
- Significantly more IPE patients hospitalized for AF/Flutter, but the rates were low

REDUCE-IT CONCLUSIONS

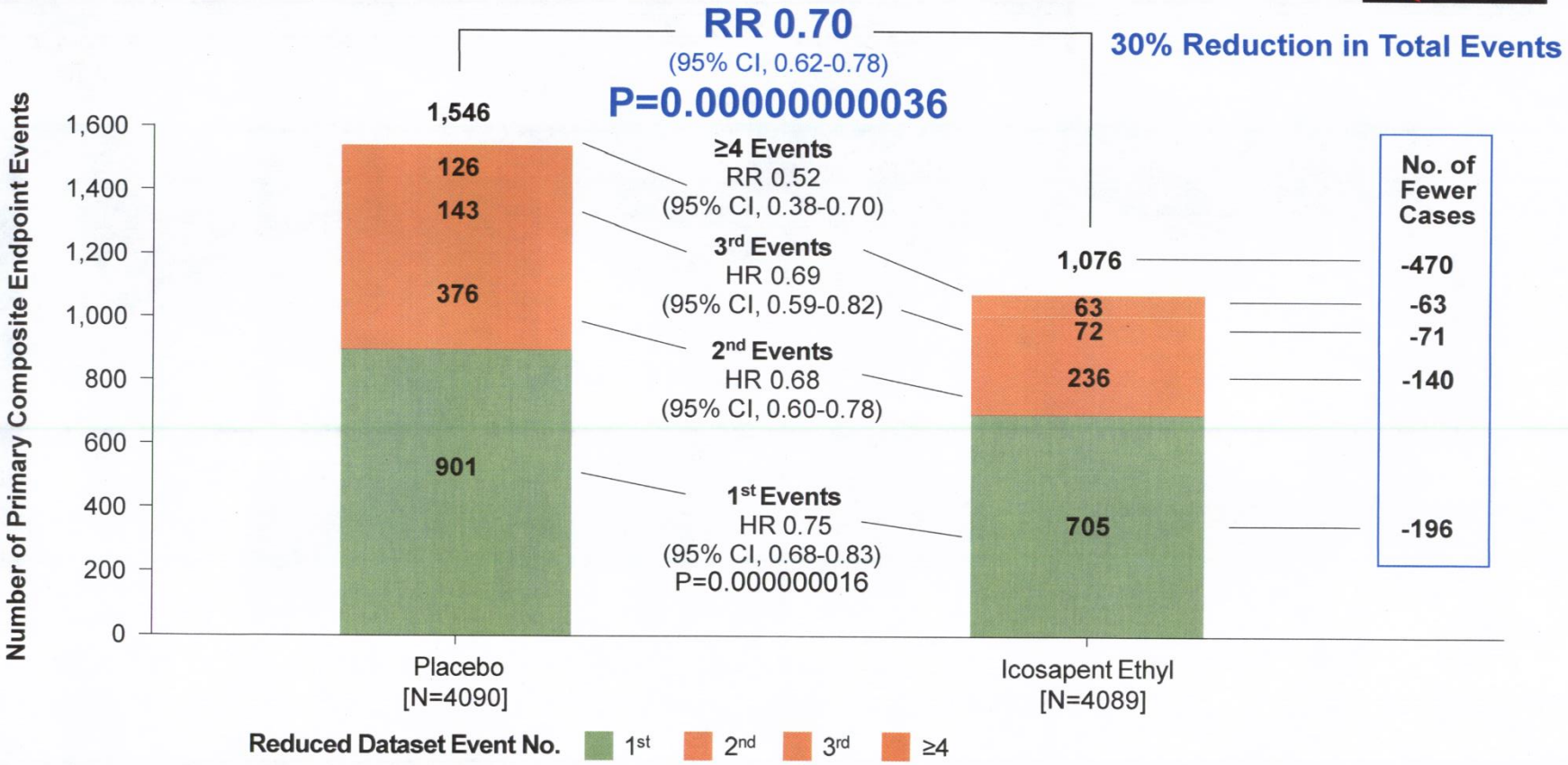
- CV benefits were similar across baseline TG levels (< 150, ≥ 150 to < 200, and ≥ 200 mg/dl)
- Benefits also occurred irrespective of TG levels attained at 1 year (≥ 150 or < 150 mg/dl)
- A post hoc analysis showed no substantial difference in the primary end point in PBO-treated patients with an increase in LDL-C at 1 year vs those with no change or a decrease in LDL-C
- Mineral oil placebo raised hs-CRP levels by 32.3% from baseline, resulting in a significant difference compared to the IPE group at 2 years

EFFECTS OF ICOSAPENT ETHYL ON TOTAL ISCHEMIC EVENTS FROM REDUCE-IT

DEEPAK L. BHATT, MD, MPH, PH. GABRIEL STEG, MD, MICHAEL MILLER, MD, ELIOT A. BRINTON, MD, TERRY A. JACOBSON, MD, STEVEN B. KETCHUM, PHD, RALPH T. DOYLE, JR, BA, REBECCA A. JULIANO, PHD, LIXIA JIAO, PHD, CRAIG GRANOWITZ, MD, PHD, JEAN-CLAUDE TARDIF, MD, JOHN GREGSON, PHD, STUART J. POCOCK, PHD, CHRISTIE M. BALLANTYNE, MD, ON BEHALF OF THE REDUCE-IT INVESTIGATORS*

J Am Coll Cardiol 2019; 73: 2791 - 2802

First and Subsequent Events

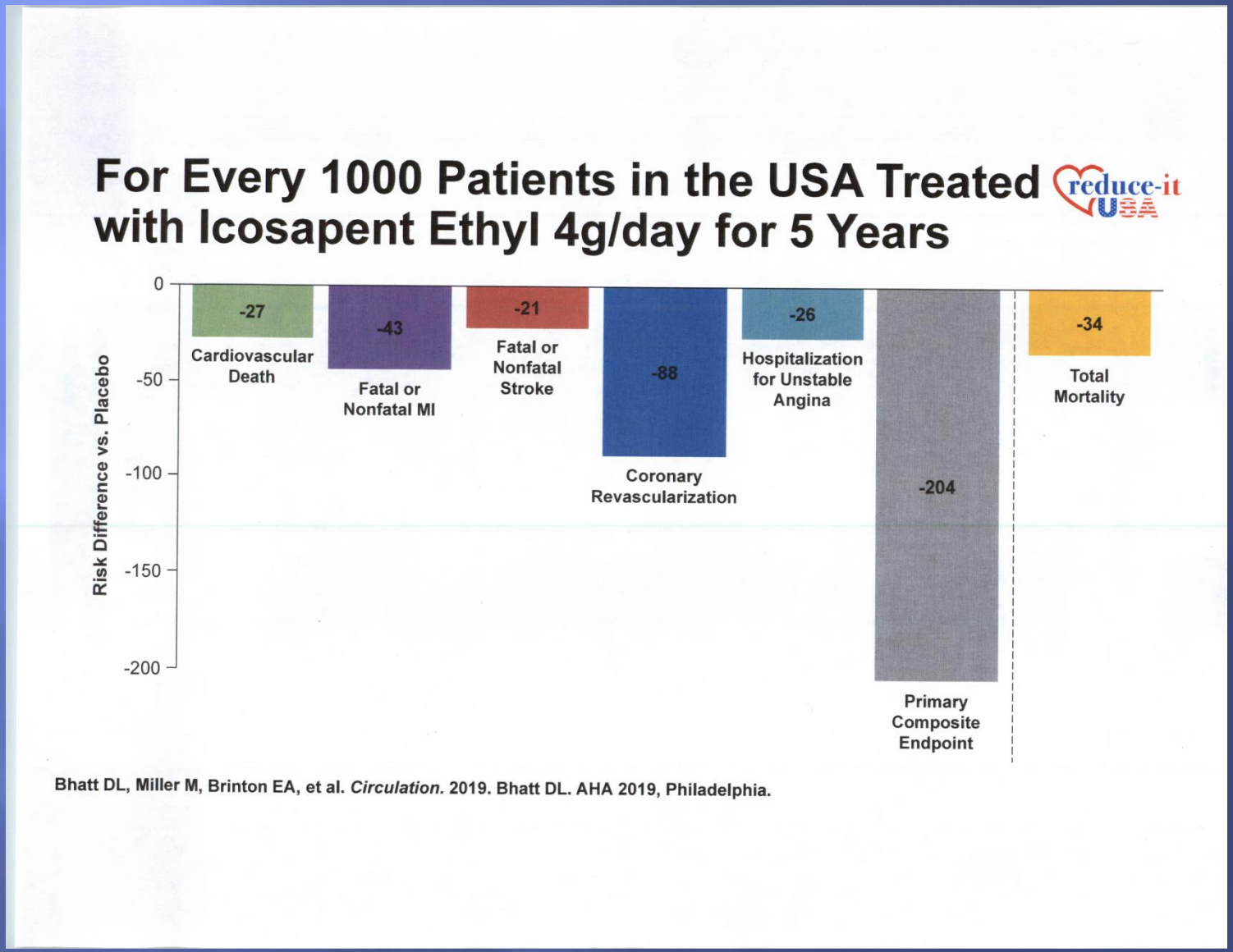


Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019.

Note: WLW method for the 1st events, 2nd events, and 3rd events categories; Negative binomial model for ≥4th events and overall treatment comparison.

REDUCE-IT USA

(10.1161/CIRCULATIONAHA.119.044440)



ASSOCIATION BETWEEN TRIGLYCERIDE LOWERING AND REDUCTION OF CARDIOVASCULAR RISK ACROSS MULTIPLE LIPID-LOWERING THERAPEUTIC CLASSES

Nicholas A. Marston, MD, Robert P. Giugliano, MD, SM, KyungAh Im, PhD, Michael G. Silverman, MD, MPH, Michelle L. O'Donoghue, MD, MPH, Stephen D. Wiviott, MD, Brian A. Ference, MD, Mphil, MSc, Marc S. Sabatatine, MD, MPH

Circulation 2019; 140: 1308 - 1317

ASSOCIATION BETWEEN TRIGLYCERIDE LOWERING AND REDUCTION OF CARDIOVASCULAR RISK ACROSS MULTIPLE LIPID-LOWERING THERAPEUTIC CLASSES

- A meta-regression analysis examining the association between the magnitude of Non-HDL-C, LDL-C, and TG-lowering and the reduction in major vascular events across trials of fibrates, niacin, and O-3 fatty acids, as well as statins (as an established reference)
- For the O-3 fatty acid trials, an additional meta-regression analysis was performed to evaluate the association between EPA and DHA dosage and the RR for major CV events

ASSOCIATION BETWEEN TRIGLYCERIDE LOWERING AND REDUCTION OF CARDIOVASCULAR RISK ACROSS MULTIPLE LIPID-LOWERING THERAPEUTIC CLASSES

- 24 TG-lowering trials (9 fibrate trials, 3 niacin trials, and 13 O-3 fatty acid trials)
- 197,270 patients with a mean baseline TG level of 163 mg/dl
- Average median trial follow up was 4.8 years, during which there were 25,218 major CVE
- Data from an additional 25 statin trials, including an additional 177,088 patients and 20,962 major CVE

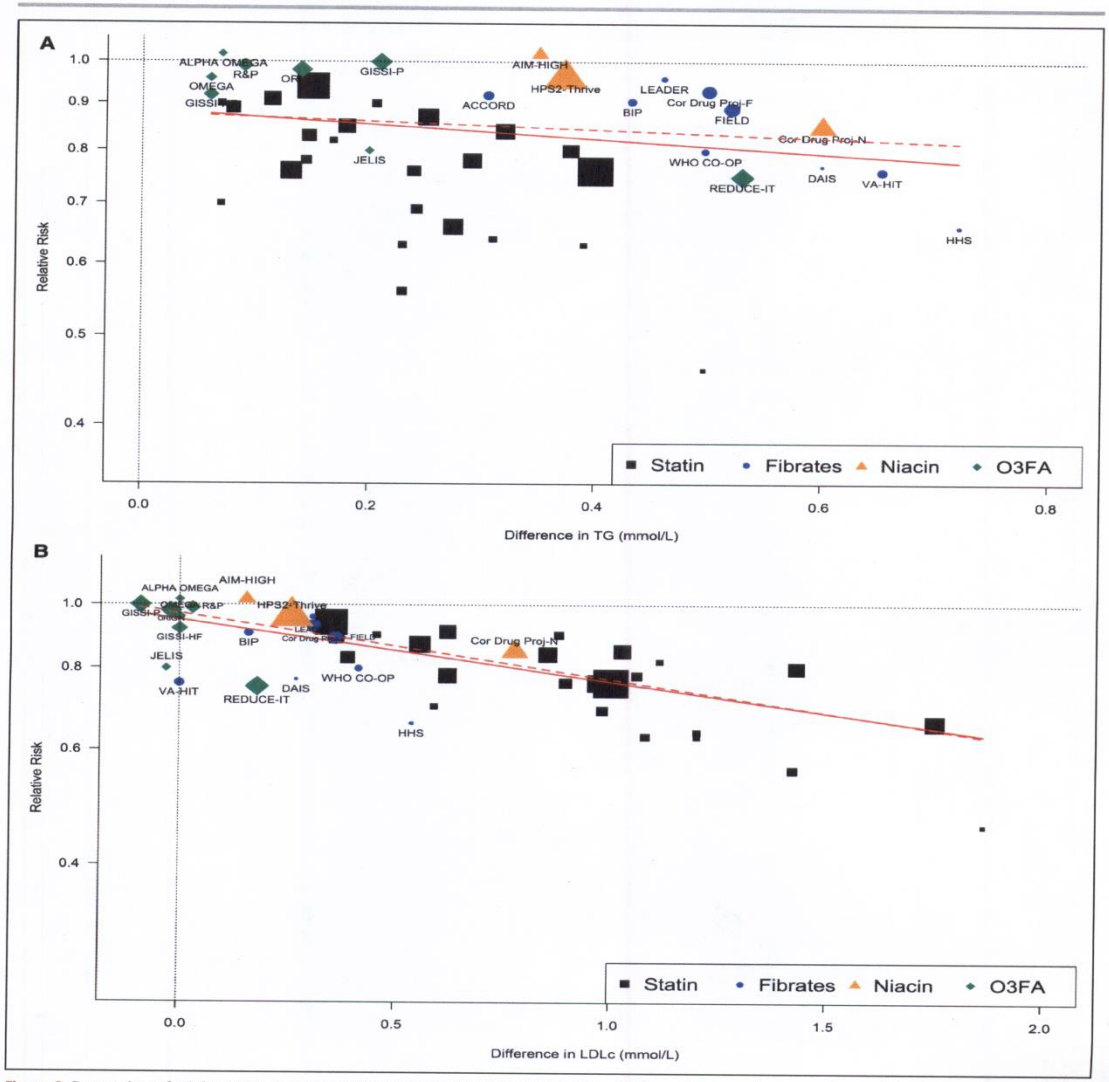
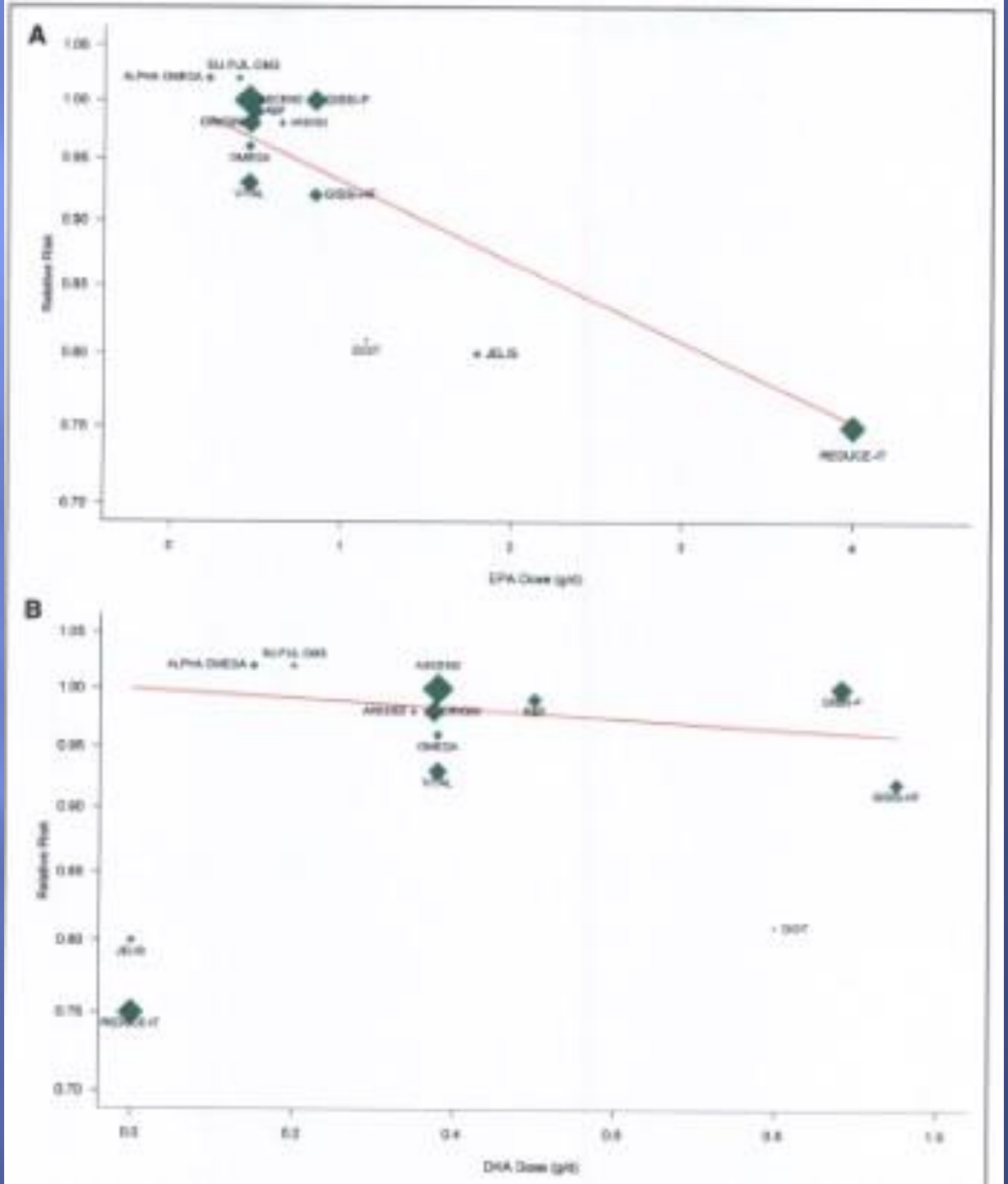


Figure 2. Regression of triglycerides, low-density lipoprotein cholesterol and risk ratio for major vascular events in 44 trials of statins, fibrates, niacin, and omega-3 fatty acids (O3FAs).

Effect of 1-mmol/L difference in (**A**) achieved triglycerides (TG) on the risk ratio (RR) for major vascular events (all trials [solid regression line]: RR, 0.84 [95% CI, 0.75–0.94]; P=0.0026; without REDUCE-IT [Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial; dashed regression line]: RR, 0.91 [95% CI, 0.81–1.006]; P=0.06) at mean weighted low-density lipoprotein cholesterol (LDL-C) (0.5586 mmol/L) and (**B**) achieved low-density lipoprotein cholesterol on the RR for major vascular events (all trials [solid regression line]: RR, 0.80 [95% CI, 0.76–0.85]; P<0.0001; without REDUCE-IT [dashed regression line]: RR, 0.79 [95% CI, 0.76–0.83]; P<0.0001) at mean weighted achieved triglycerides (0.2918 mmol/L). ACCORD indicates Action to Control Cardiovascular Risk in Diabetes; AIM-HIGH, Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes; (*Continued*)

ASSOCIATION BETWEEN TRIGLYCERIDE LOWERING AND REDUCTION OF CARDIOVASCULAR RISK ACROSS MULTIPLE LIPID-LOWERING THERAPEUTIC CLASSES

- 11/13 O-3 fatty acid trials used EPA + DHA
- Total O-3 dose ranged from 376 – 4000 mg/d, with a mean of 1355 mg
- EPA dose ranged from 226 – 4000 mg/d, with a mean of 944 mg
- DHA dose ranged from 0 – 950 mg/d, with a mean of 411 mg


A
B
EPA Dose (g/d)
DHA Dose (g/d)

ASSOCIATION BETWEEN TRIGLYCERIDE LOWERING AND REDUCTION OF CARDIOVASCULAR RISK ACROSS MULTIPLE LIPID-LOWERING THERAPEUTIC CLASSES

- A reduction in Non-HDL-C is strongly associated with a lower risk of major CVE regardless of the lipid-lowering drug class
- TG-lowering is associated with a lower risk of major CVE but to a lesser extent per absolute amount of reduction than with LDL-C
- Nearly all non-statin trials focusing on TG-lowering have been under-powered with respect to Non-HDL-C lowering to detect a clinical difference in major CVE

ASSOCIATION BETWEEN TRIGLYCERIDE LOWERING AND REDUCTION OF CARDIOVASCULAR RISK ACROSS MULTIPLE LIPID-LOWERING THERAPEUTIC CLASSES

- REDUCE-IT was the most significant outlier and influencer of the meta-regression, and removing it attenuated the effect estimate for TG-lowering
- REDUCE-IT may have been an outlier because of the type of O-3 fatty acid and/or the dose that was used
- The mineral oil placebo raised hs-CRP levels , resulting in a between-group difference at 2 years of 0.9 mg/dl

Non-Lipid CV Benefits of Omega-3 Fatty Acids

- Anti-thrombotic
- Anti-inflammatory
- Anti-arrhythmic
- Anti-oxidative
- Vasodilatory/BP-lowering
- Membrane-stabilizing
- Reduced development, slowed progression, and increased stabilization of atherosclerotic plaque

EVAPORATE: Effect of EPA on Improving Coronary Atherosclerosis in People With High Triglycerides Taking Statin Therapy

Randomized, Double-Blind, Placebo-Controlled Trial

Patient Population (N=~80)

- 30–85 years of age
- TG: 135–499 mg/dL
- LDL-C >40 mg/dL and ≤115 mg/dL (on statin)
- ≥1 angiographic stenosis with ≥20% narrowing by CTA
- No history of MI, stroke, or life-threatening arrhythmia within the prior 6 months and no history of CABG

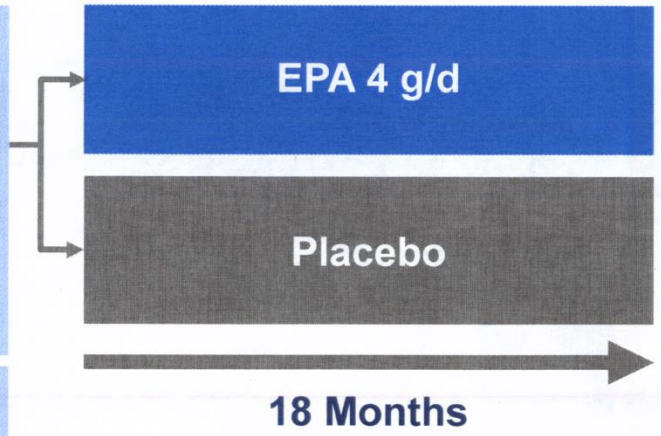
Primary endpoint

- Progression rates of low attenuation plaque

Secondary endpoints include

- Plaque morphology and composition
- Markers of inflammation (Lp-PLA_2)
- LDL-C and HDL-C

Estimated Study Completion Date: September 2019



The EVAPORATE study seeks to determine whether IPE 4g/d will result in a greater change from baseline in plaque volume measured by serial multidetector computed tomography (MDCT) than placebo in statin-treated patients

CABG=coronary artery bypass graft; CTA=computed tomography angiography.

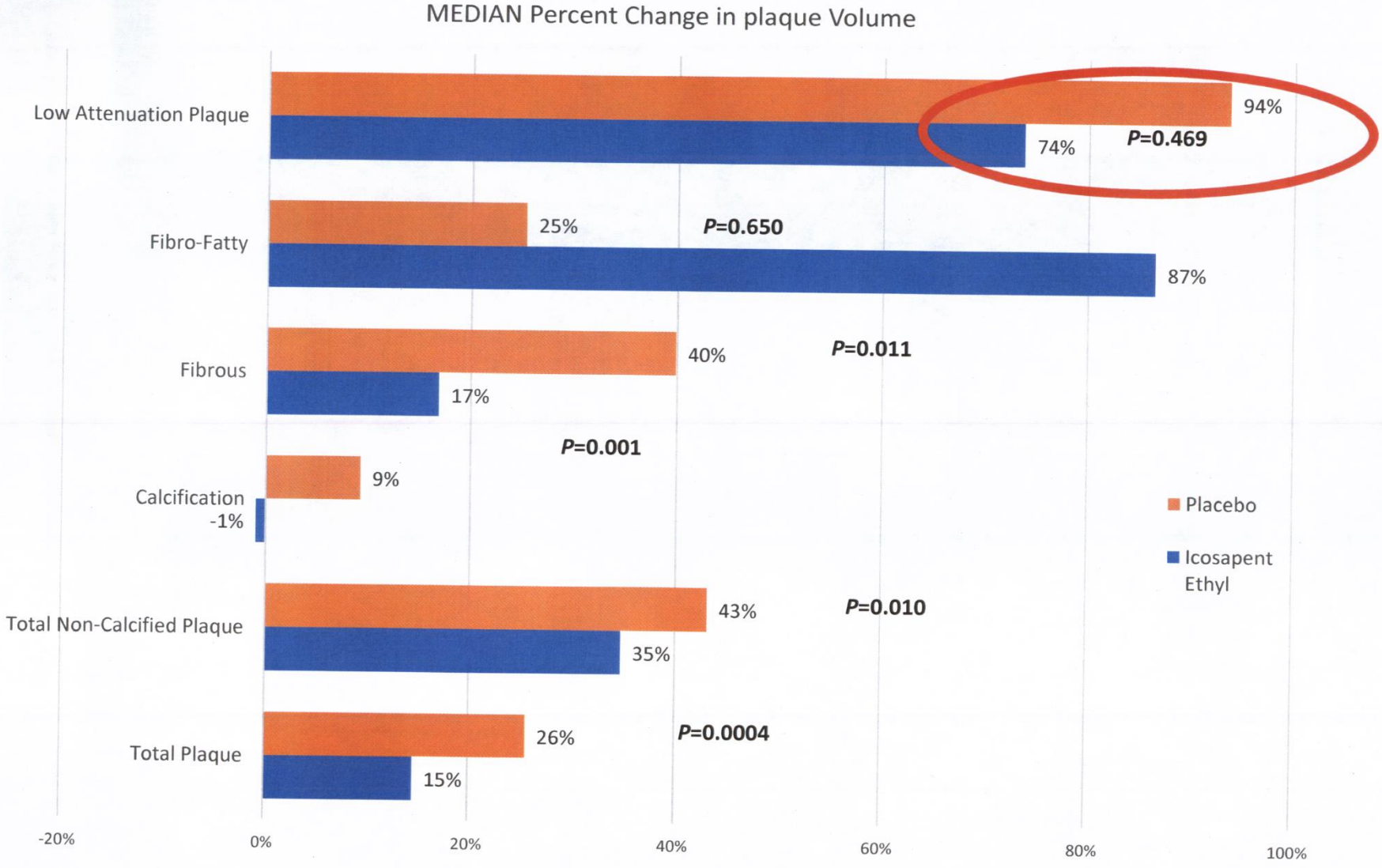
EVAPORATE Clinical Trial. https://clinicaltrials.gov/ct2/show/NCT02926027. Updated February 08, 2018. Accessed June 19, 2018.

TABLE 2 EVAPORATE study endpoints

Primary endpoint
Change in low-attenuation plaque volume as measured by MDCTA and defined as −50 to 50 HU
Secondary endpoints
Incident plaque rates; quantitative changes in different plaque types and morphology
Changes in markers of inflammation including Lp-PLA_2 and hsCRP
Changes in lipids and lipoproteins including standard lipid panel, lipoproteins, remnants, Apo-A1/remnant ratio, EPA, AA, and EPA/AA ratio
Relationship between changes in the above with noncalcified coronary plaque burden and/or plaque-vulnerability features

Abbreviations: AA, arachidonic acid; Apo-A1, apolipoprotein A1; EPA, eicosapentaenoic acid; EVAPORATE, Effect of Vascepa on Improving Coronary Atherosclerosis in People With High Triglycerides Taking Statin Therapy study; hsCRP, high-sensitivity C-reactive protein; HU, Hounsfield

Fully adjusted median Plaque Progression at 9 months



RESULTS

- At 9 Month Prespecified Timepoint, compared with placebo, icosapent ethyl slowed progression by:
- **21%** for low attenuation plaque (p=0.469)
- **42%** for total plaque (p=0.0004)
- **19%** for total non-calcified plaque (p=0.010)
- **57%** for fibrous plaque (p=0.011)
- **89%** for calcified plaque (p=0.001)
- No Effect on Fibrofatty plaque (p=0.650)

- Consistent efficacy across multiple subgroups
- Including baseline triglycerides from 135-500 mg/dL

POSITIONS OF OTHER ORGANIZATIONS

- Based on the results of REDUCE-IT, the use of IPE in appropriate patients is supported by:
  - AHA
  - ADA Standards of Care (3/27/19)
  - EAS/ESC 2019 Guidelines
  - NLA

Circulation

AHA SCIENCE ADVISORY

Omega-3 Fatty Acids for the Management of Hypertriglyceridemia

A Science Advisory From the American Heart Association

Circulation. 2019;140:e673–e691

ABSTRACT: Hypertriglyceridemia (triglycerides 200–499 mg/dL) is relatively common in the United States, whereas more severe triglyceride elevations (very high triglycerides, ≥500 mg/dL) are far less frequently observed. Both are becoming increasingly prevalent in the United States and elsewhere, likely driven in large part by growing rates of obesity and diabetes mellitus. In a 2002 American Heart Association scientific statement, the omega-3 fatty acids (n-3 FAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were recommended (at a dose of 2–4 g/d) for reducing triglycerides in patients with elevated triglycerides. Since 2002, prescription agents containing EPA+DHA or EPA alone have been approved by the US Food and Drug Administration for treating very high triglycerides; these agents are also widely used for hypertriglyceridemia. The purpose of this advisory is to summarize the lipid and lipoprotein effects resulting from pharmacological doses of n-3 FAs (>3 g/d total EPA+DHA) on the basis of new scientific data and availability of n-3 FA agents. In treatment of very high triglycerides with 4 g/d, EPA+DHA agents reduce triglycerides by ≥30% with concurrent increases in low-density lipoprotein cholesterol, whereas EPA-only did not raise low-density lipoprotein cholesterol in very high triglycerides. When used to treat hypertriglyceridemia, n-3 FAs with EPA+DHA or with EPA-only appear roughly comparable for triglyceride lowering and do not increase low-density lipoprotein cholesterol when used as monotherapy or in combination with a statin. In the largest trials of 4 g/d prescription n-3 FA, non–high-density lipoprotein cholesterol and apolipoprotein B were modestly decreased, indicating reductions in total atherogenic lipoproteins. The use of n-3 FA (4 g/d) for improving atherosclerotic cardiovascular disease risk in patients with hypertriglyceridemia is supported by a 25% reduction in major adverse cardiovascular events in REDUCE-IT (Reduction of Cardiovascular Events With EPA Intervention Trial), a randomized placebo-controlled trial of EPA-only in high-risk patients treated with a statin. The results of a trial of 4 g/d prescription EPA+DHA in hypertriglyceridemia are anticipated in 2020. We conclude that prescription n-3 FAs (EPA+DHA or EPA-only) at a dose of 4 g/d (>3 g/d total EPA+DHA) are an effective and safe option for reducing triglycerides as monotherapy or as an adjunct to other lipid-lowering agents.

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On behalf of the American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; and Council on Clinical Cardiology

*This update was prepared in part by Dr Engler in her personal capacity. The opinions expressed in this article are the author's own and do not reflect the view of the National Institutes of Health, the US Department of Health and Human Services, the US Department of Defense, the US government, or the Uniformed Services University of the Health Sciences.

Key Words: AHA Scientific Statements ■ docosahexaenoic acid ■ eicosapentaenoic acid ■ fatty acids, omega-3 ■ hypertriglyceridemia ■ hypolipidemic agents ■ lipoproteins ■ triglycerides

https://www.ahajournals.org/journal/circ

Differing Effects on LDL-C?

- "In conclusion, there is no strong evidence that DHA-containing prescription n-3 FA agents used as monotherapy or in combination with statins raise LDL-C in patients with HTG." (Skulas-Ray, et. al. *Omega-3 Fatty Acids for the Management of Hypertriglyceridemia: A Science Advisory from the AHA*. Circ 2019; 140: page e9)
- Dependent on level of TGs and % reduction (increase in LDL-C from increased conversion and/or increase in size of LDL particles, but decreases in Non-HDL-C and Apo B

Differing Effects on LDL-C?

- "The increase in LDL-C levels is typically less than 5% to 10%, but in patients with severe hypertriglyceridemia, an increase of up to 30% can occur. In such cases, however, levels are depressed at baseline and usually do not increase above 130 mg/dl." (O'Keefe, Jr, JH and Harris WS. *From Inuit to Implementation: Omega-3 Fatty Acids Come of Age.* Mayo Clin Proc. 2000; 75: page 611)
- This is not an issue when combined with a statin