Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial

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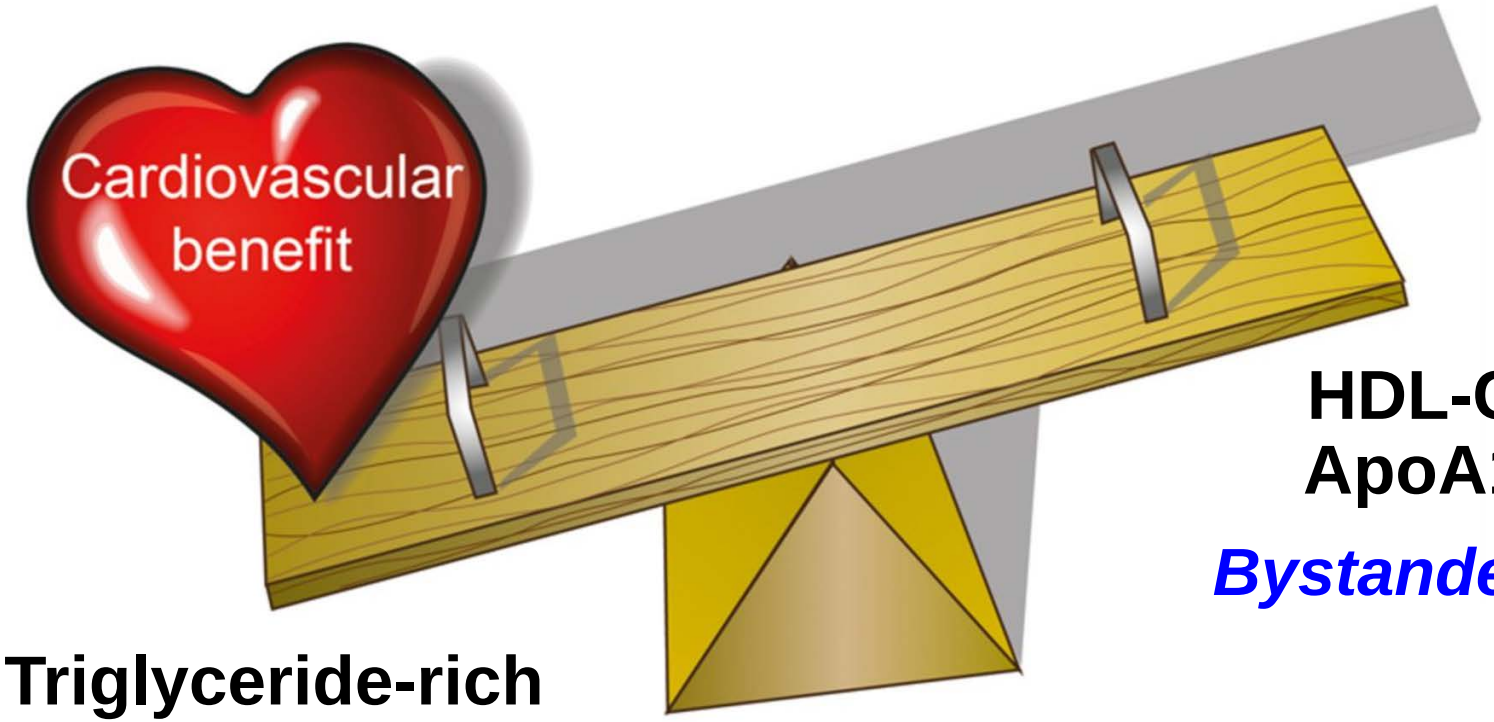
Disclosures

Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic, Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); **Research Funding**: Abbott, **Amarin**, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, PhaseBio, Pfizer, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Novo Nordisk, PLx Pharma, Takeda.

This presentation includes off-label and/or investigational uses of drugs.

REDUCE-IT was sponsored by Amarin Pharma, Inc.

Triglycerides a Causal Risk Factor?



HDL-C
ApoA1

Bystanders?

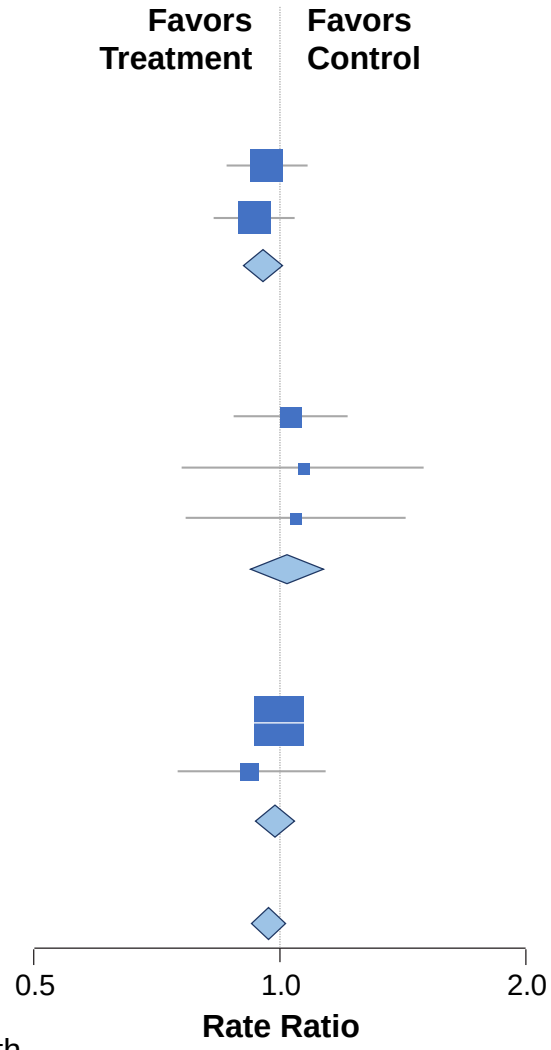
Triglyceride-rich lipoproteins
ApoC3

Causal risk factors?

Adapted with permission from Libby P. Triglycerides on the rise: should we swap seats on the seesaw? *Eur Heart J*. 2015;36:774-776.

Low Dose Omega-3 Mixtures Show No Significant Cardiovascular Benefit

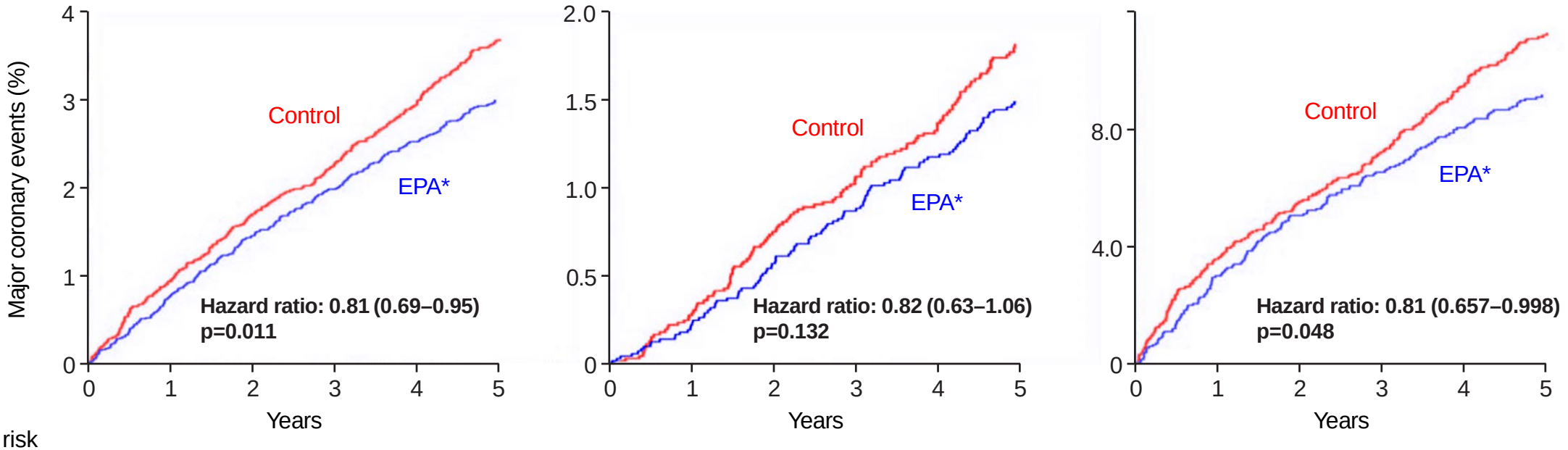
Source	No. of Events (%)		Rate Ratios (CI)
	Treatment	Control	
Coronary heart disease			
Nonfatal myocardial infarction	1121 (2.9)	1155 (3.0)	0.97 (0.87–1.08)
Coronary heart disease	1301 (3.3)	1394 (3.6)	0.93 (0.83–1.03)
Any	3085 (7.9)	3188 (8.2)	0.96 (0.90–1.01)
			P=.12
Stroke			
Ischemic	574 (1.9)	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



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 Suggests CV Risk Reduction with EPA in Japanese Hypercholesterolemic Patients

Kaplan-Meier Estimates of Incidence of Coronary Events



Numbers at risk						
Control group	9319	8931	8671	8433	8192	7958
Treatment group	9326	8929	8658	8389	8153	7924

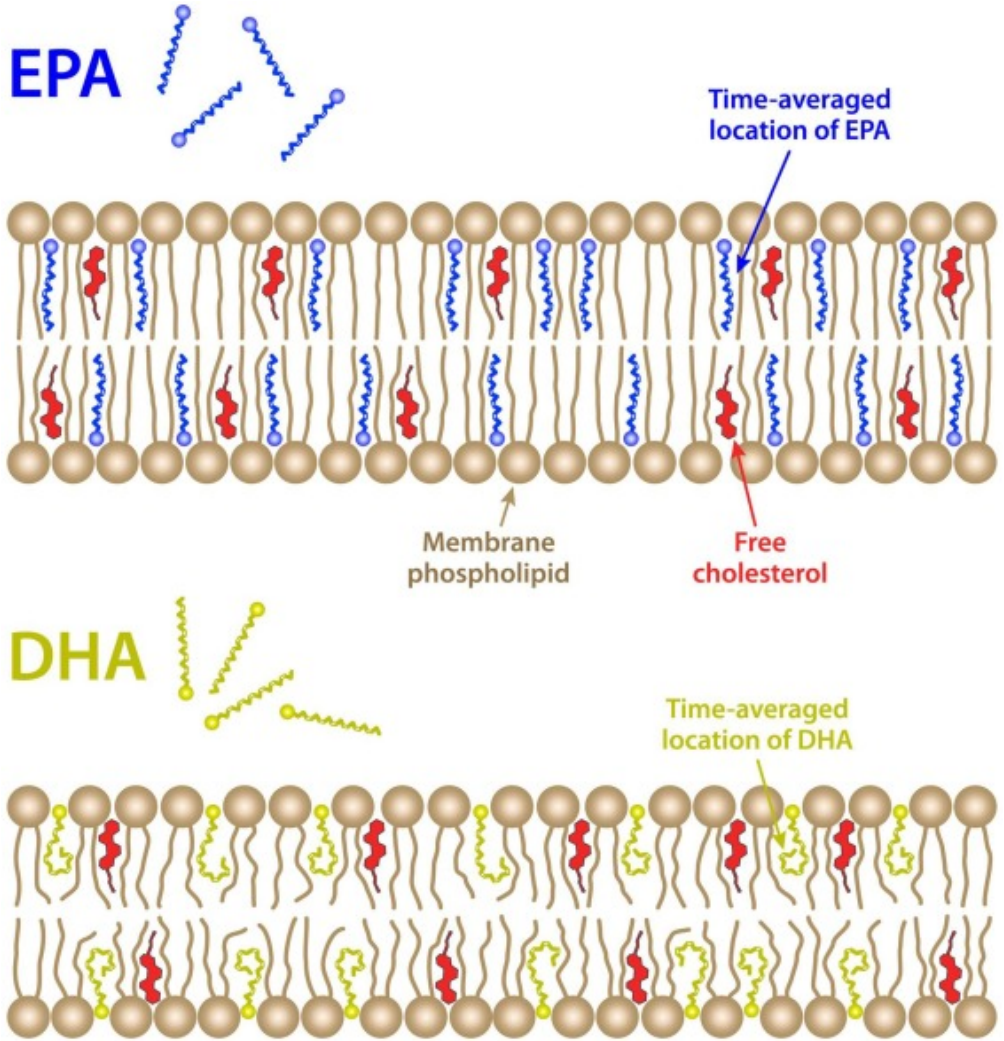
7478	7204	7103	6841	6678	6508
7503	7210	7020	6823	6649	6482

1841	1727	1658	1592	1514	1450
1823	1719	1638	1566	1504	1442

*1.8 g/day

Adapted with permission from Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet.* 2007;369:1090-1098.

EPA and DHA Have Differing Effects on Cellular Membranes



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Key Inclusion Criteria – REDUCE-IT

1. Age ≥45 years with established CVD (Secondary Prevention Cohort) *or* ≥50 years with diabetes with ≥1 additional risk factor for CVD (Primary Prevention Cohort)

2. Fasting TG levels ≥150 mg/dL and <500 mg/dL*

3. LDL-C >40 mg/dL and ≤100 mg/dL and on stable statin therapy (± ezetimibe) for ≥4 weeks prior to qualifying measurements for randomization

*Due to the variability of triglycerides, a 10% allowance existing in the initial protocol, which permitted patients to be enrolled with qualifying triglycerides ≥135 mg/dL. protocol amendment 1 (May 2013) changed the lower limit of acceptable triglycerides from 150 mg/dL to 200 mg/dL, with no variability allowance.

Inclusion Criteria for Secondary Prevention Cohort

One or more of the following:

1. Documented coronary artery disease
   - Multi vessel CAD (≥50% stenosis in ≥2 major epicardial coronary arteries – with or without antecedent revascularization
   - Prior MI
   - Hospitalization for high-risk non-ST-segment elevation acute coronary syndrome with ST-segment deviation or biomarker positivity

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   - Prior MI
   - Hospitalization for high-risk non-ST-segment elevation acute coronary syndrome with ST-segment deviation or biomarker positivity
2. Documented cerebrovascular or carotid disease
   - Prior ischemic stroke
   - Symptomatic carotid artery disease with ≥50% carotid arterial stenosis
   - Asymptomatic carotid artery disease with ≥70% carotid arterial stenosis
   - History of carotid revascularization

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   - Prior ischemic stroke
   - Symptomatic carotid artery disease with ≥50% carotid arterial stenosis
   - Asymptomatic carotid artery disease with ≥70% carotid arterial stenosis
   - History of carotid revascularization
3. Documented peripheral artery disease
   - Ankle-brachial index <0.9 with symptoms of intermittent claudication
   - History of aorto-iliac or peripheral artery intervention

Adapted with permission[‡] from: Bhatt DL, Steg PG, Brinton EA, et al; on behalf of the REDUCE-IT Investigators. Rationale and design of REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial. *Clin Cardiol*. 2017;40:138-148. [‡https://creativecommons.org/licenses/by-nc/4.0/]

Inclusion Criteria for Primary Prevention Cohort

1. Diabetes mellitus requiring medication AND

Patients with diabetes and CVD are counted under Secondary Prevention Cohort

Inclusion Criteria for Primary Prevention Cohort

1. Diabetes mellitus requiring medication AND
2. ≥50 years of age AND

Patients with diabetes and CVD are counted under Secondary Prevention Cohort

Inclusion Criteria for Primary Prevention Cohort

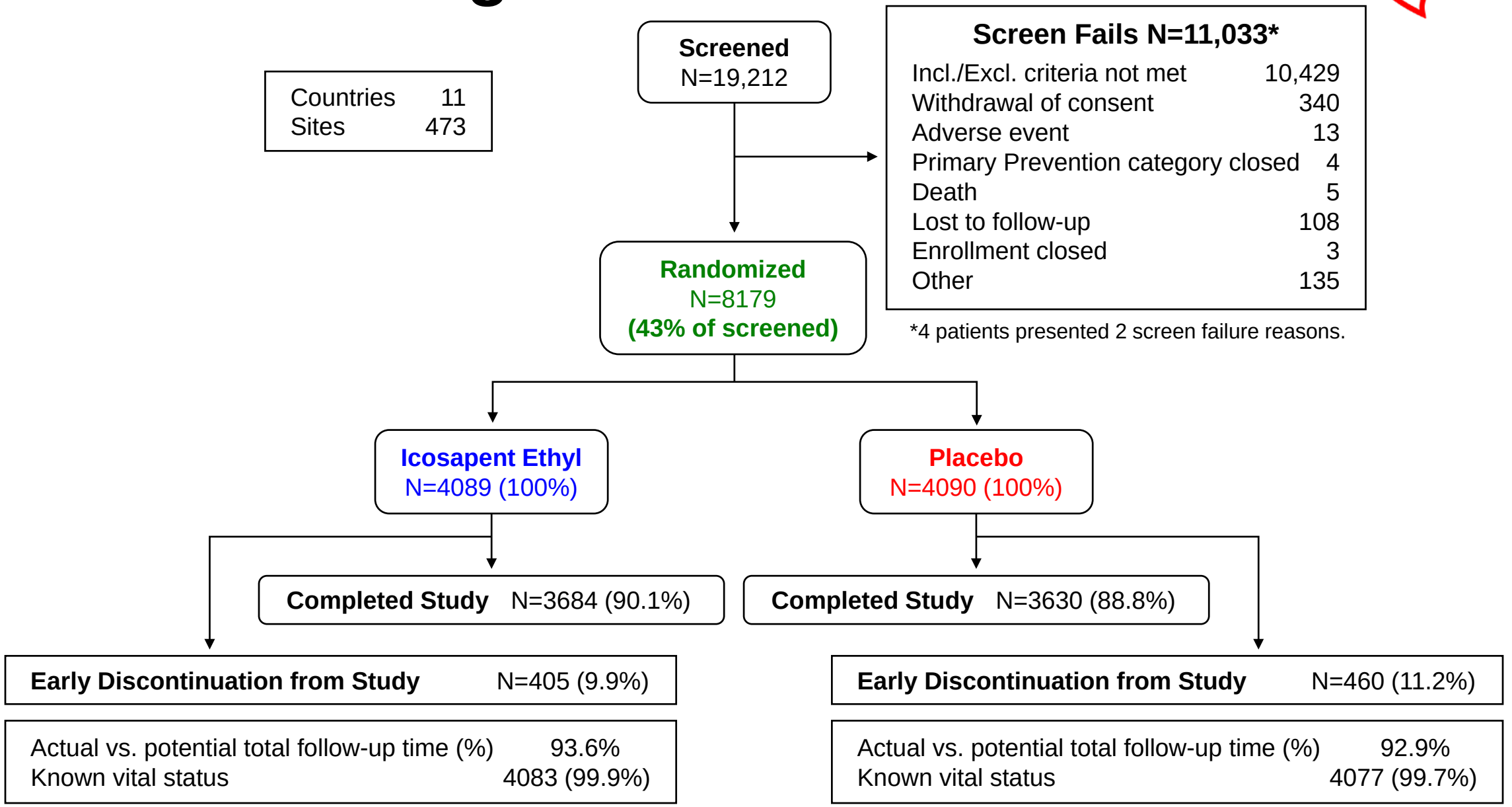
1. Diabetes mellitus requiring medication AND
2. ≥50 years of age AND
3. ≥1 additional risk factor for CVD
   - Men ≥55 years and women ≥65 years
   - Cigarette smoker or stopped smoking within 3 months
   - Hypertension (≥140 mmHg systolic OR ≥90 mmHg diastolic) or on antihypertensive medication;
   - HDL-C ≤40 mg/dL for men or ≤50 mg/dL for women
   - hsCRP >3.0 mg/L
   - Renal dysfunction: Creatinine clearance >30 and <60 mL/min
   - Retinopathy
   - Micro- or macroalbuminuria
   - ABI <0.9 without symptoms of intermittent claudication

Patients with diabetes and CVD are counted under Secondary Prevention Cohort

Key Exclusion Criteria

1. Severe (NYHA class IV) heart failure
2. Severe liver disease
3. History of pancreatitis
4. Hypersensitivity to fish and/or shellfish

CONSORT Diagram



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

Median trial follow up duration was 4.9 years.

REDUCE-IT Study PI and Committees

Global Principal Investigator and Steering Committee Chair

Deepak L. Bhatt MD, MPH, Professor of Medicine at Harvard Medical School, Executive Director of Interventional Cardiovascular Programs at Brigham and Women's Hospital Heart & Vascular Center, and the Global Principal Investigator and Steering Committee Chair of REDUCE-IT

Steering Committee

Deepak L. Bhatt MD, MPH (Chair and Global Principal Investigator), Christie M. Ballantyne MD, Eliot A. Brinton MD, Terry A. Jacobson MD, Michael Miller MD, Ph. Gabriel Steg MD, Jean-Claude Tardif MD

Data Monitoring Committee

Brian Olshansky MD (Chair), Mina Chung MD, Al Hallstrom PhD, Lesly A. Pearce MS (non-voting independent statistician)
Independent Statistical Center Support for Data Monitoring Committee: Cyrus Mehta PhD, Rajat Mukherjee PhD

Clinical Endpoint Committee

C. Michael Gibson MD, MS (Chair), Anjan K. Chakrabarti MD, MPH, Eli V. Gelfand MD, Robert P. Giugliano MD, SM, Megan Carroll Leary MD, Duane S. Pinto MD, MPH, Yuri B. Pride MD

Key Baseline Characteristics

	Icosapent Ethyl (N=4089)	Placebo (N=4090)
Age (years), Median (Q1-Q3)	64.0 (57.0 - 69.0)	64.0 (57.0 - 69.0)
Female, n (%)	1162 (28.4%)	1195 (29.2%)
Non-White, n (%)	398 (9.7%)	401 (9.8%)
Westernized Region, n (%)	2906 (71.1%)	2905 (71.0%)
CV Risk Category, n (%)		
Secondary Prevention Cohort	2892 (70.7%)	2893 (70.7%)
Primary Prevention Cohort	1197 (29.3%)	1197 (29.3%)
Ezetimibe Use, n (%)	262 (6.4%)	262 (6.4%)
Statin Intensity, n (%)		
Low	254 (6.2%)	267 (6.5%)
Moderate	2533 (61.9%)	2575 (63.0%)
High	1290 (31.5%)	1226 (30.0%)
Type 2 Diabetes, n (%)	2367 (57.9%)	2363 (57.8%)
Triglycerides (mg/dL), Median (Q1-Q3)	216.5 (176.5 - 272.0)	216.0 (175.5 - 274.0)
HDL-C (mg/dL), Median (Q1-Q3)	40.0 (34.5 - 46.0)	40.0 (35.0 - 46.0)
LDL-C (mg/dL), Median (Q1-Q3)	74.0 (61.5 - 88.0)	76.0 (63.0 - 89.0)
Triglycerides Category		
<150 mg/dL	412 (10.1%)	429 (10.5%)
150 to <200 mg/dL	1193 (29.2%)	1191 (29.1%)
≥200 mg/dL	2481 (60.7%)	2469 (60.4%)

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

Effects on Biomarkers from Baseline to Year 1

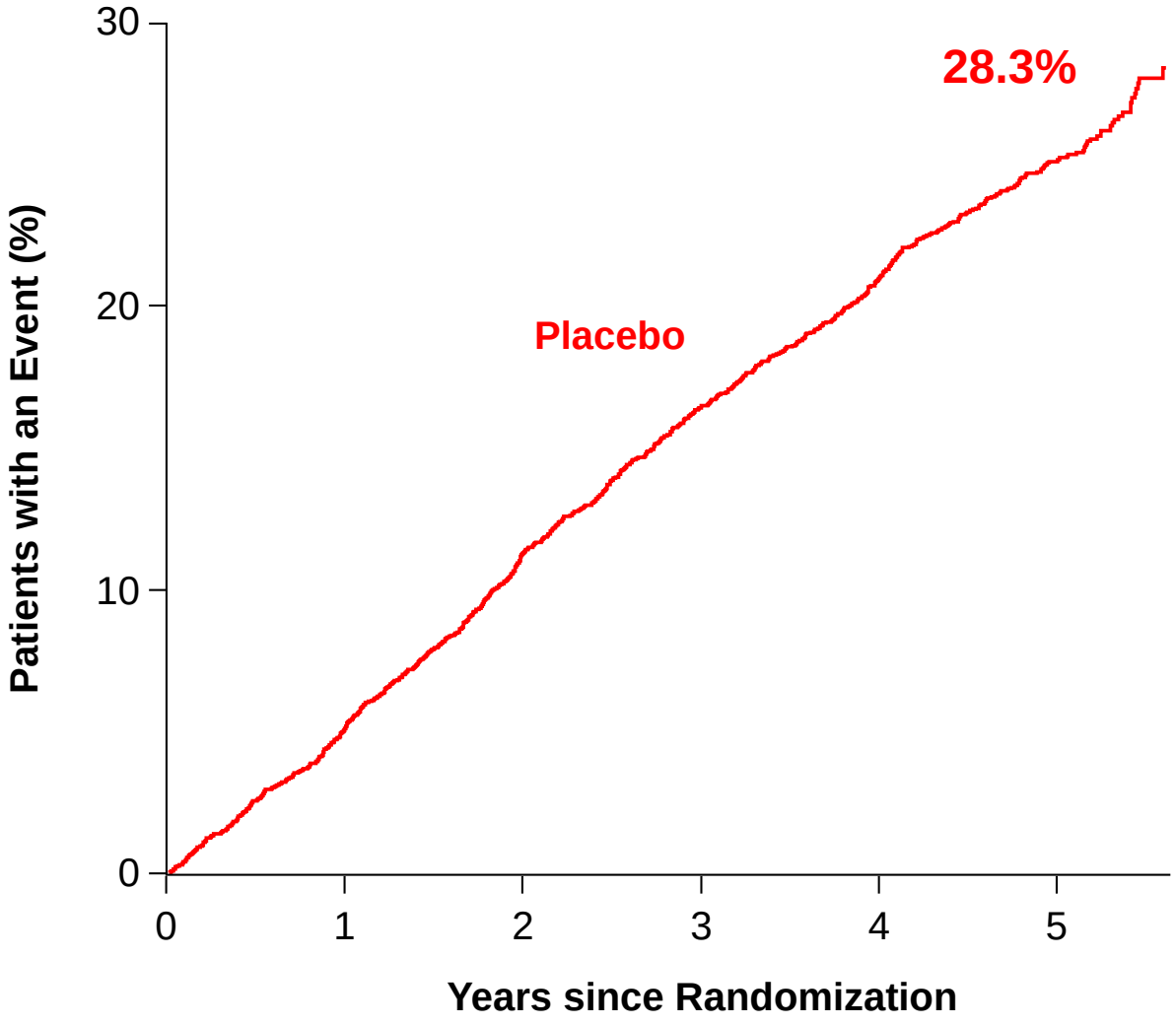
Biomarker*	Icosapent Ethyl (N=4089) Median		Placebo (N=4090) Median		Median Between Group Difference at Year 1		
	Baseline	Year 1	Baseline	Year 1	Absolute Change from Baseline	% Change from Baseline	% Change P-value
Triglycerides (mg/dL)	216.5	175.0	216.0	221.0	-44.5	-19.7	<0.0001
Non-HDL-C (mg/dL)	118.0	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.* 2018.

Primary End Point:

CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



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

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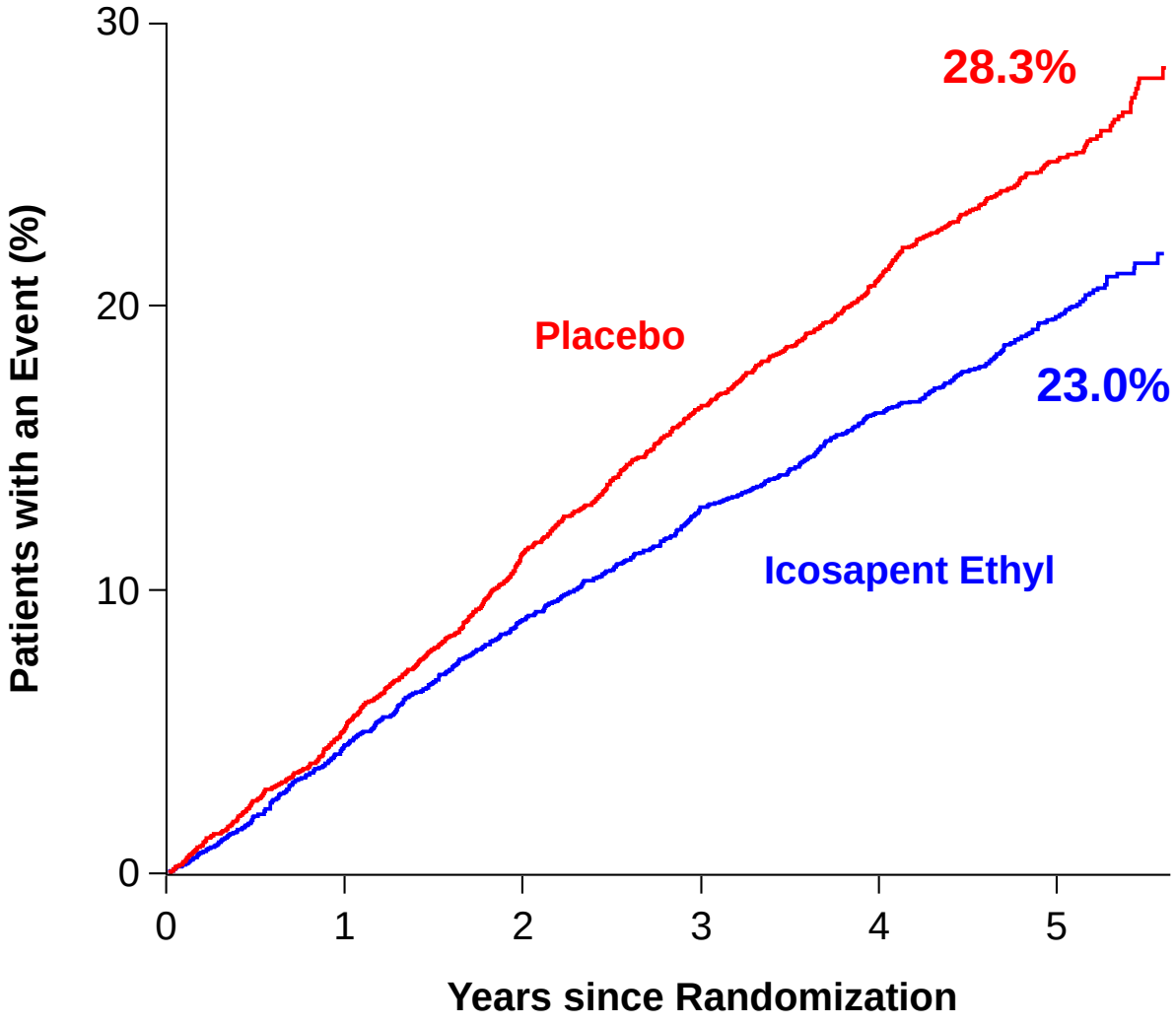

Hazard Ratio, 0.75

(95% CI, 0.68–0.83)

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

Primary End Point:

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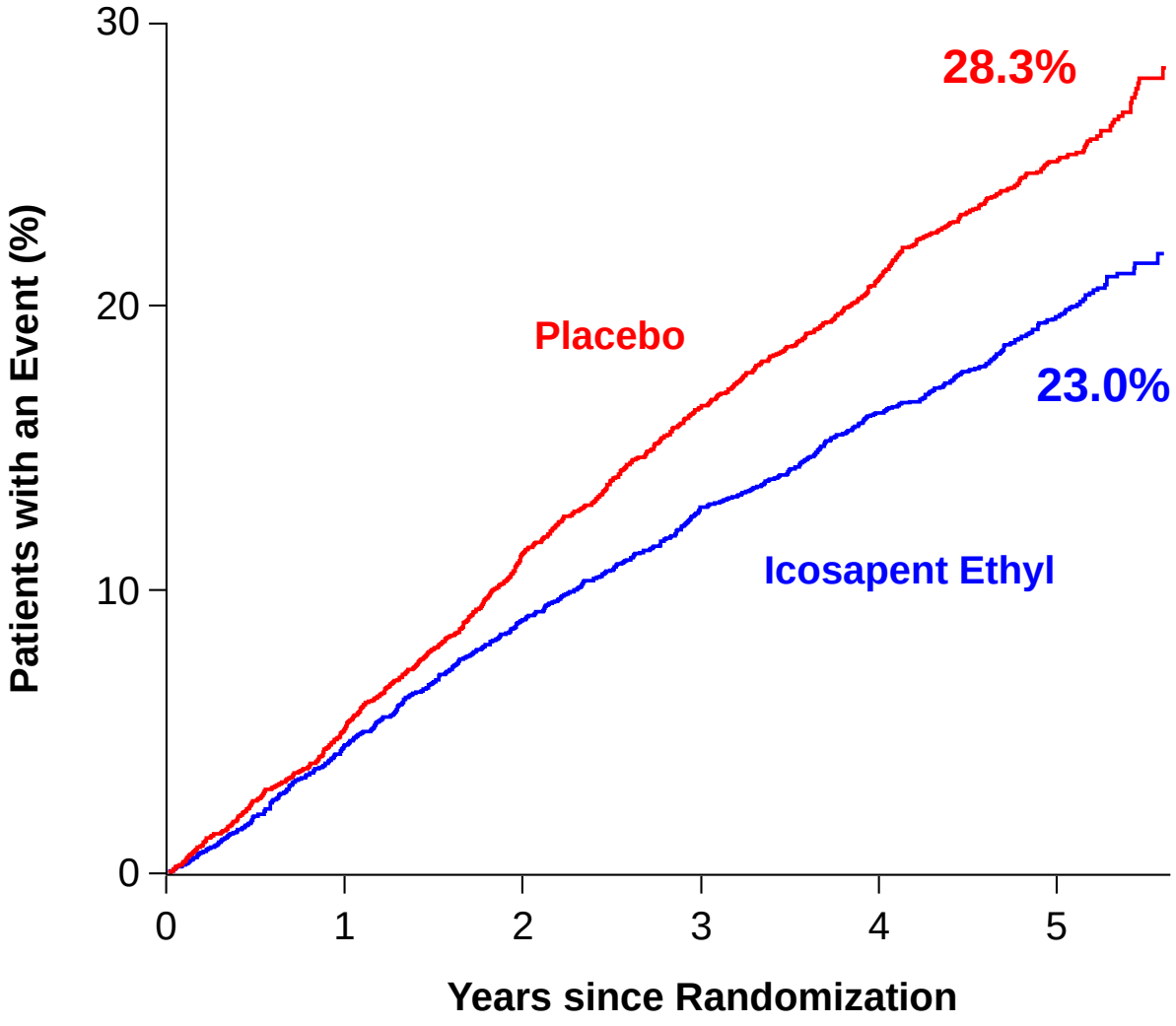


Hazard Ratio, 0.75
(95% CI, 0.68–0.83)

RRR = 24.8%

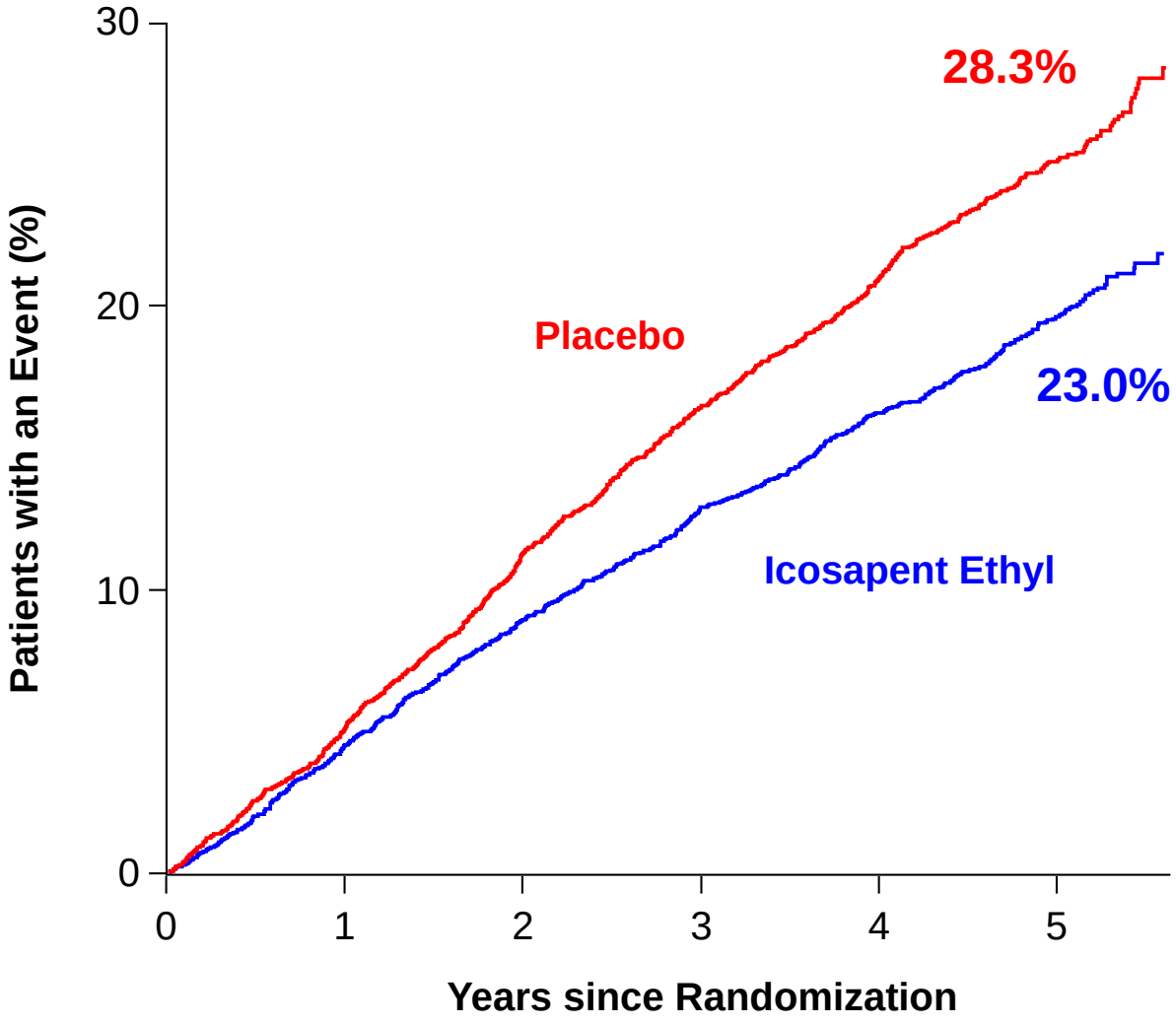
ARR = 4.8%

NNT = 21 (95% CI, 15–33)

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

Primary End Point:

CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



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

RRR = 24.8%

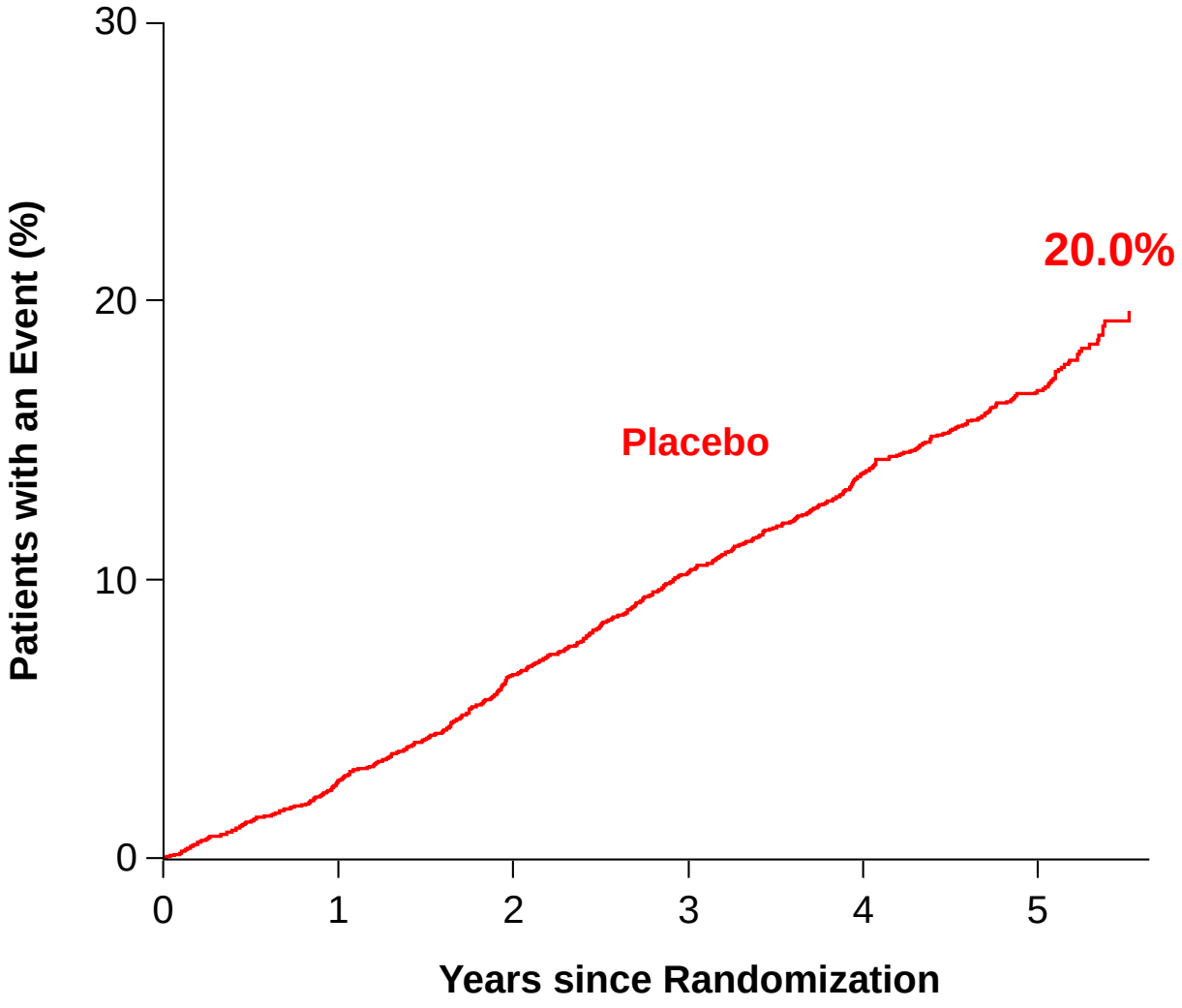
ARR = 4.8%

NNT = 21 (95% CI, 15–33)

P=0.00000001

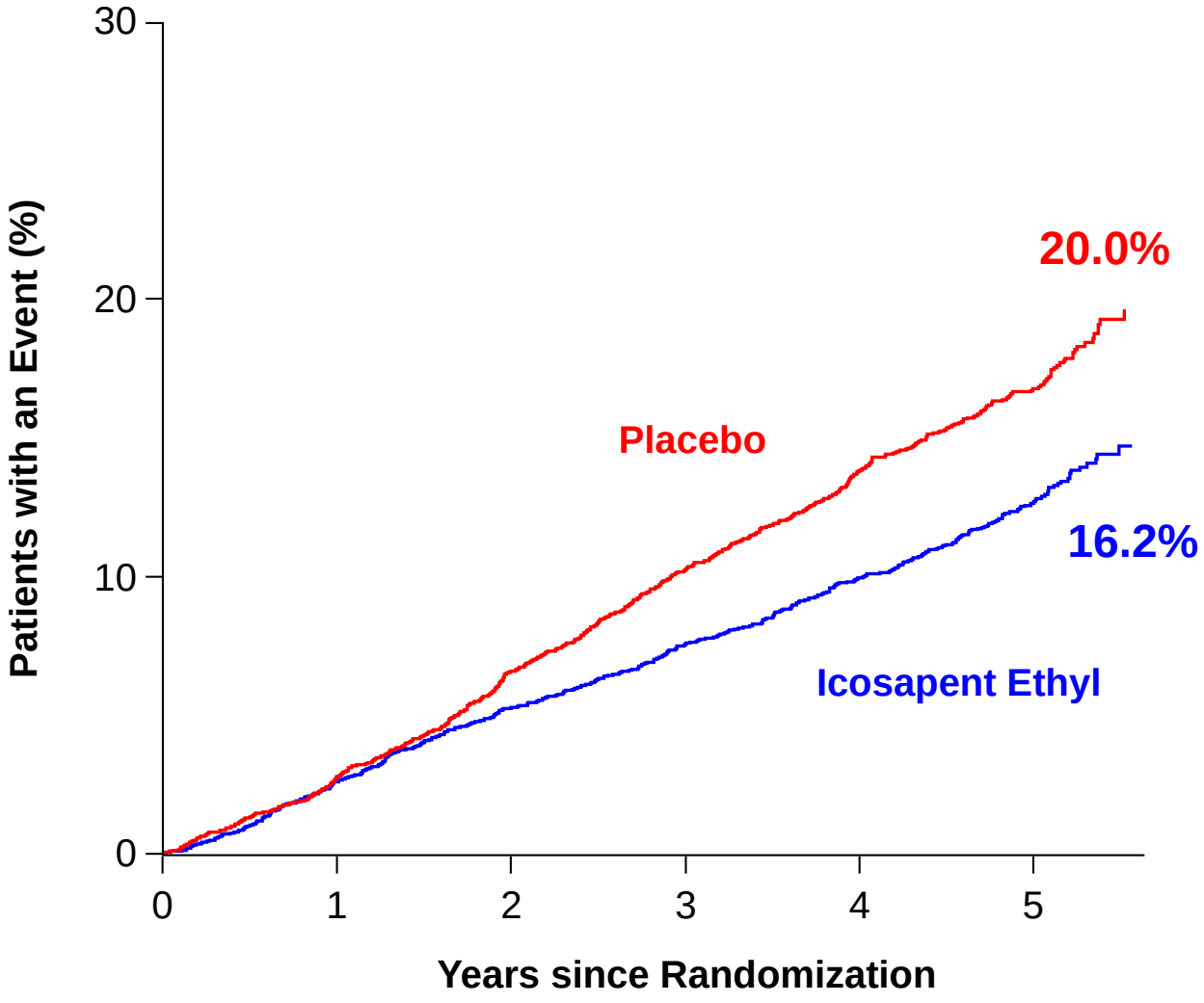
Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018. Bhatt DL. AHA 2018, Chicago.

Key Secondary End Point:
CV Death, MI, Stroke



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

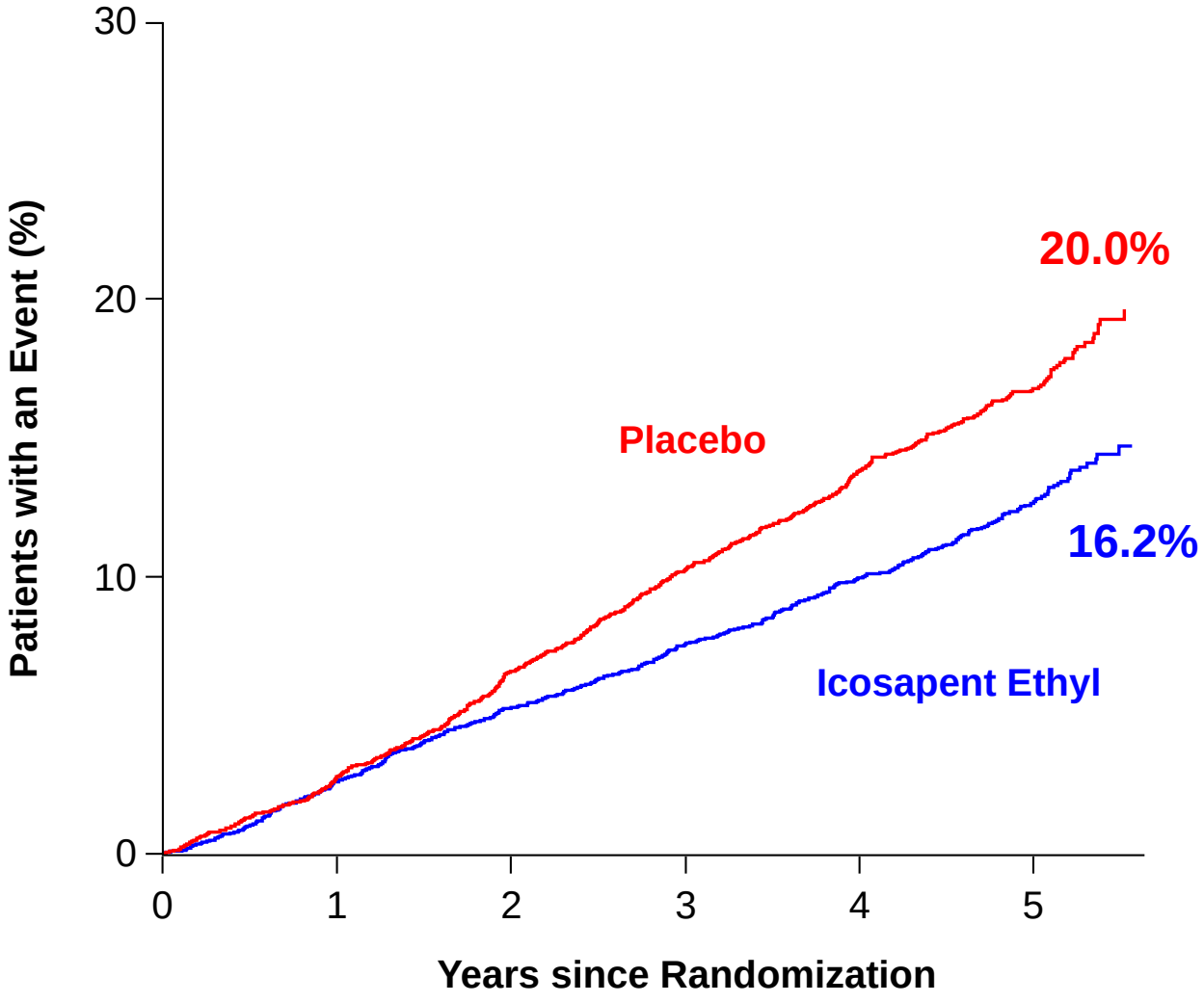
Key Secondary End Point:
CV Death, MI, Stroke



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

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

Key Secondary End Point:
CV Death, MI, Stroke



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

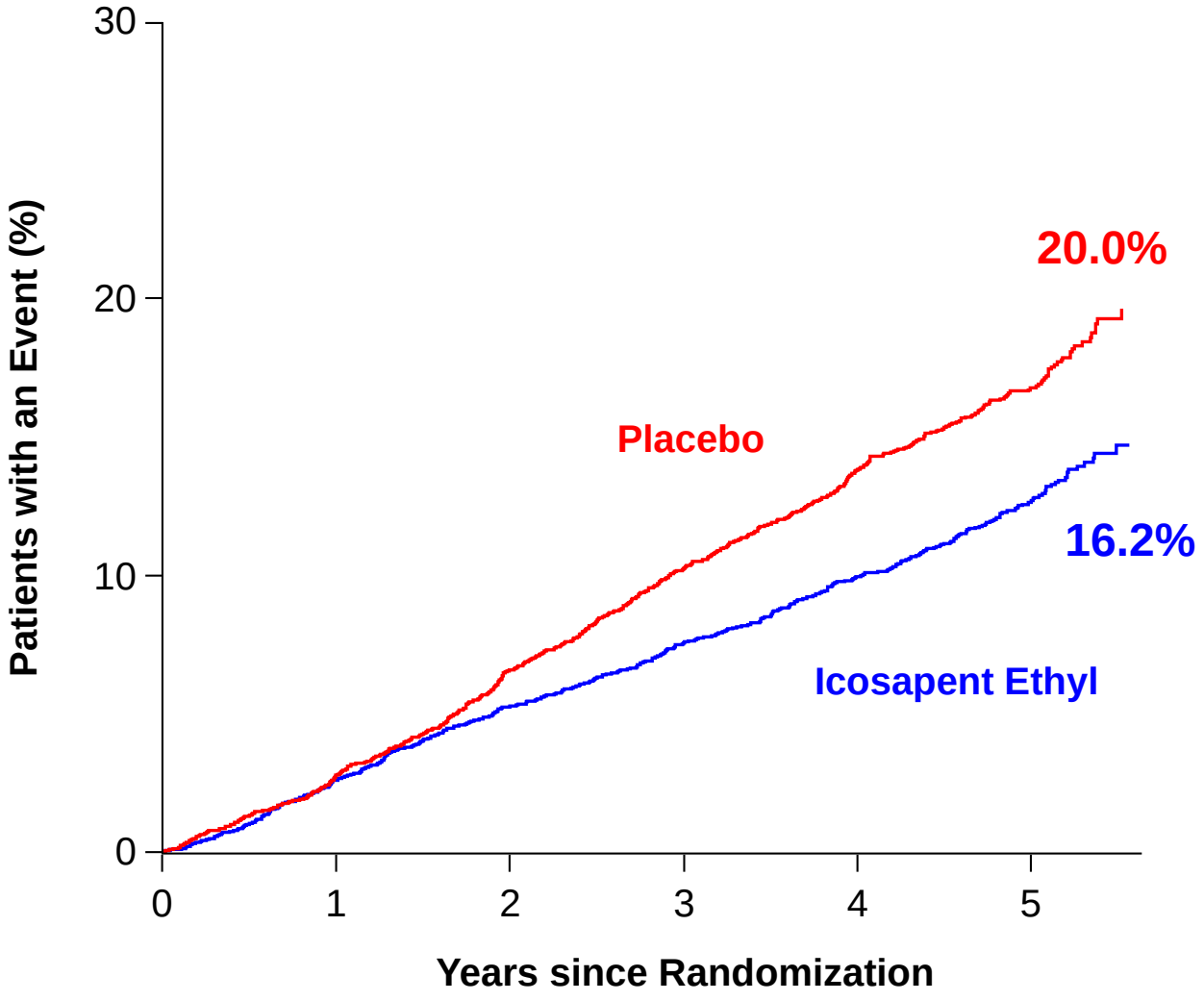
RRR = 26.5%

ARR = 3.6%

NNT = 28 (95% CI, 20–47)

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

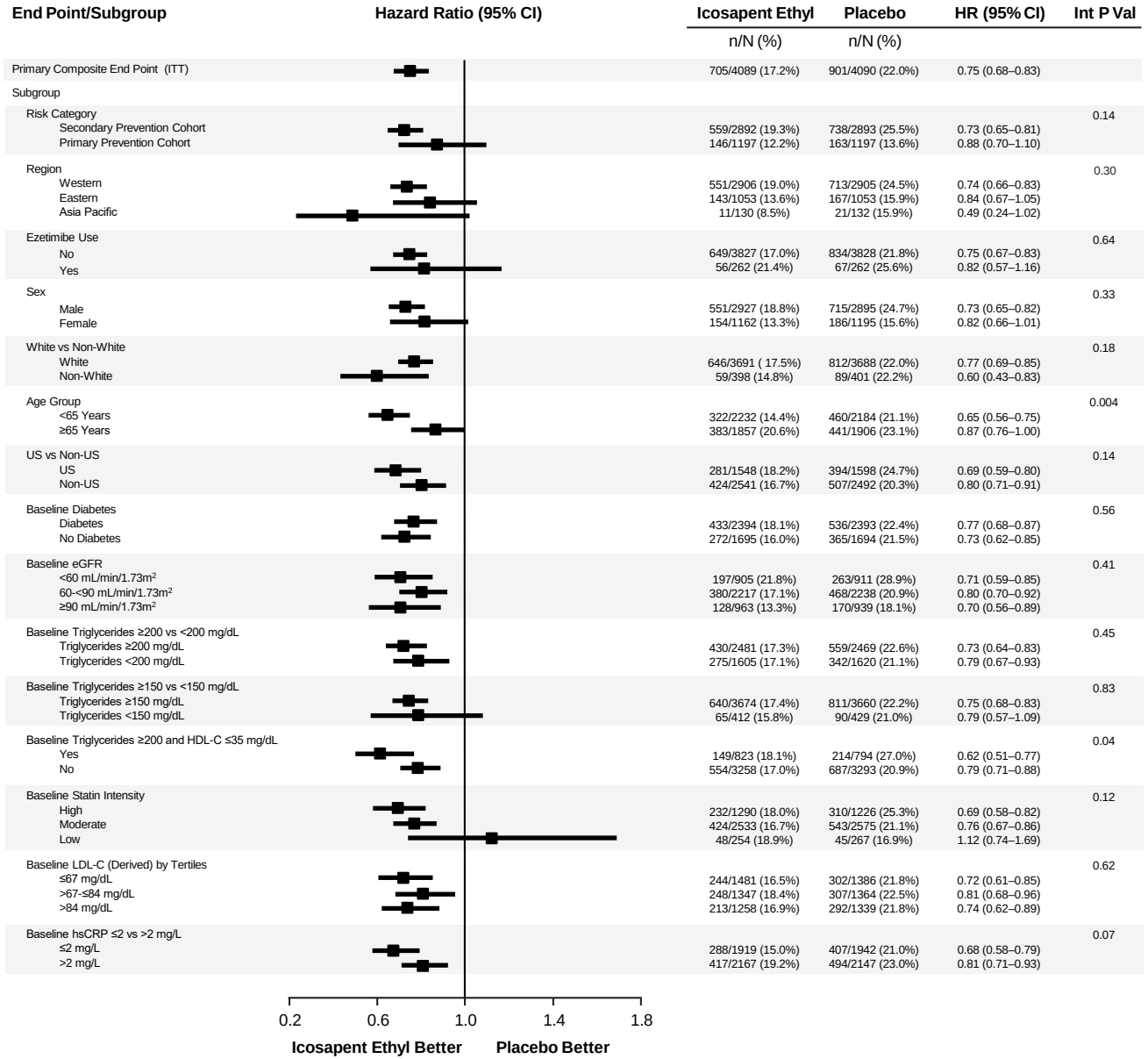
ARR = 3.6%

NNT = 28 (95% CI, 20–47)

P=0.0000006

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

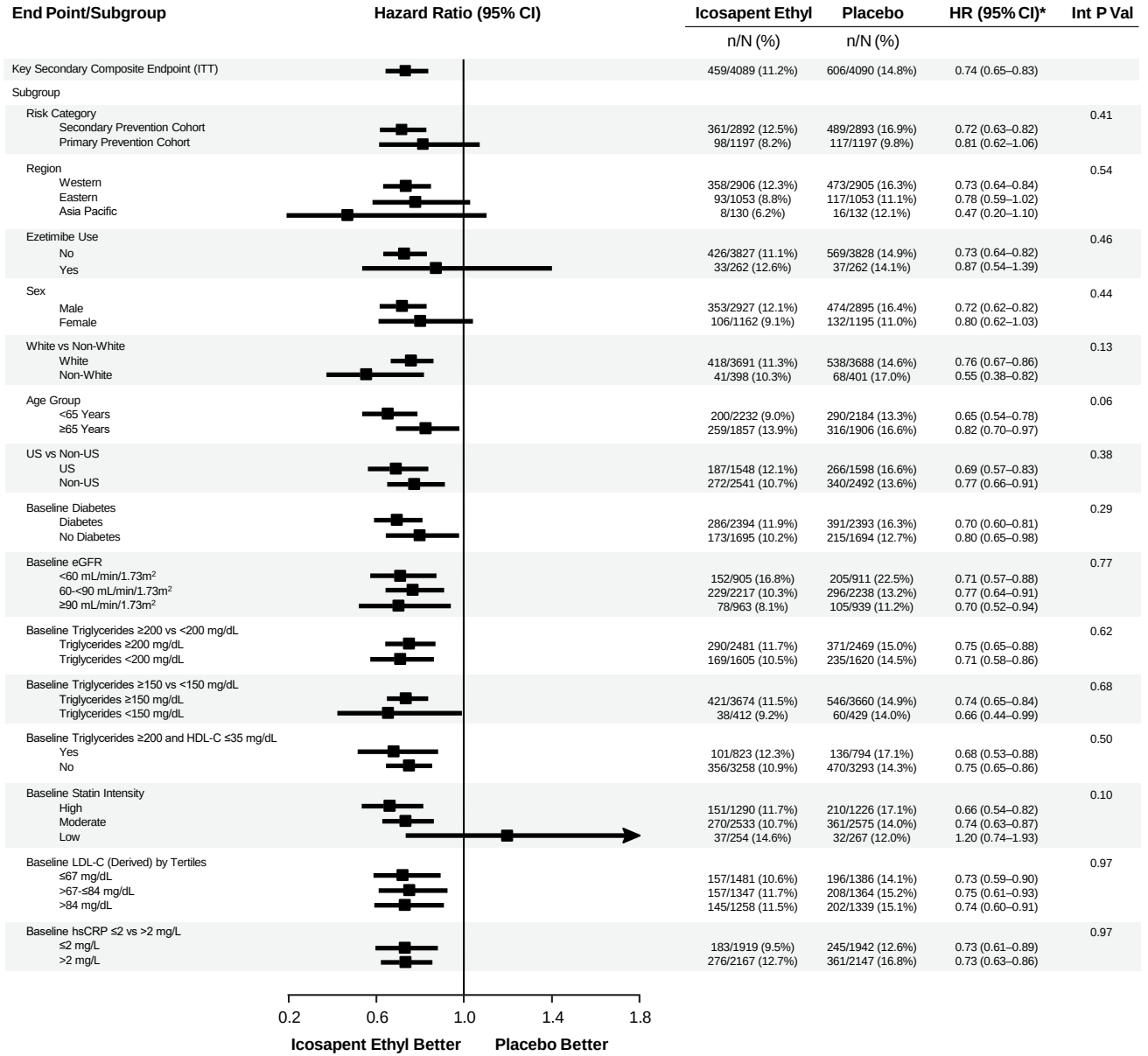
Primary End Point in Subgroups



End Point/Subgroup	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Primary Composite End Point (ITT)	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	
Subgroup				
Risk Category				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
Western	551/2906 (19.0%)	713/2905 (24.5%)	0.74 (0.66–0.83)	
Eastern	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)	
White vs Non-White				0.18
White	646/3691 (17.5%)	812/3688 (22.0%)	0.77 (0.69–0.85)	
Non-White	59/398 (14.8%)	89/401 (22.2%)	0.60 (0.43–0.83)	
Age Group				0.004
<65 Years	322/2232 (14.4%)	460/2184 (21.1%)	0.65 (0.56–0.75)	
≥65 Years	383/1857 (20.6%)	441/1906 (23.1%)	0.87 (0.76–1.00)	
US vs Non-US				0.14
US	281/1548 (18.2%)	394/1598 (24.7%)	0.69 (0.59–0.80)	
Non-US	424/2541 (16.7%)	507/2492 (20.3%)	0.80 (0.71–0.91)	
Baseline Diabetes				0.56
Diabetes	433/2394 (18.1%)	536/2393 (22.4%)	0.77 (0.68–0.87)	
No Diabetes	272/1695 (16.0%)	365/1694 (21.5%)	0.73 (0.62–0.85)	
Baseline eGFR				0.41
<60 mL/min/1.73m^2	197/905 (21.8%)	263/911 (28.9%)	0.71 (0.59–0.85)	
60-<90 mL/min/1.73m^2	380/2217 (17.1%)	468/2238 (20.9%)	0.80 (0.70–0.92)	
≥90 mL/min/1.73m^2	128/963 (13.3%)	170/939 (18.1%)	0.70 (0.56–0.89)	
Baseline Triglycerides ≥200 vs <200 mg/dL				0.45
Triglycerides ≥200 mg/dL	430/2481 (17.3%)	559/2469 (22.6%)	0.73 (0.64–0.83)	
Triglycerides <200 mg/dL	275/1605 (17.1%)	342/1620 (21.1%)	0.79 (0.67–0.93)	
Baseline Triglycerides ≥150 vs <150 mg/dL				0.83
Triglycerides ≥150 mg/dL	640/3674 (17.4%)	811/3660 (22.2%)	0.75 (0.68–0.83)	
Triglycerides <150 mg/dL	65/412 (15.8%)	90/429 (21.0%)	0.79 (0.57–1.09)	
Baseline Triglycerides ≥200 and HDL-C ≤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-C (Derived) by Tertiles				0.62
≤67 mg/dL	244/1481 (16.5%)	302/1386 (21.8%)	0.72 (0.61–0.85)	
>67-≤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 hsCRP ≤2 vs >2 mg/L				0.07
≤2 mg/L	288/1919 (15.0%)	407/1942 (21.0%)	0.68 (0.58–0.79)	
>2 mg/L	417/2167 (19.2%)	494/2147 (23.0%)	0.81 (0.71–0.93)	

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

Key Secondary End Point in Subgroups



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

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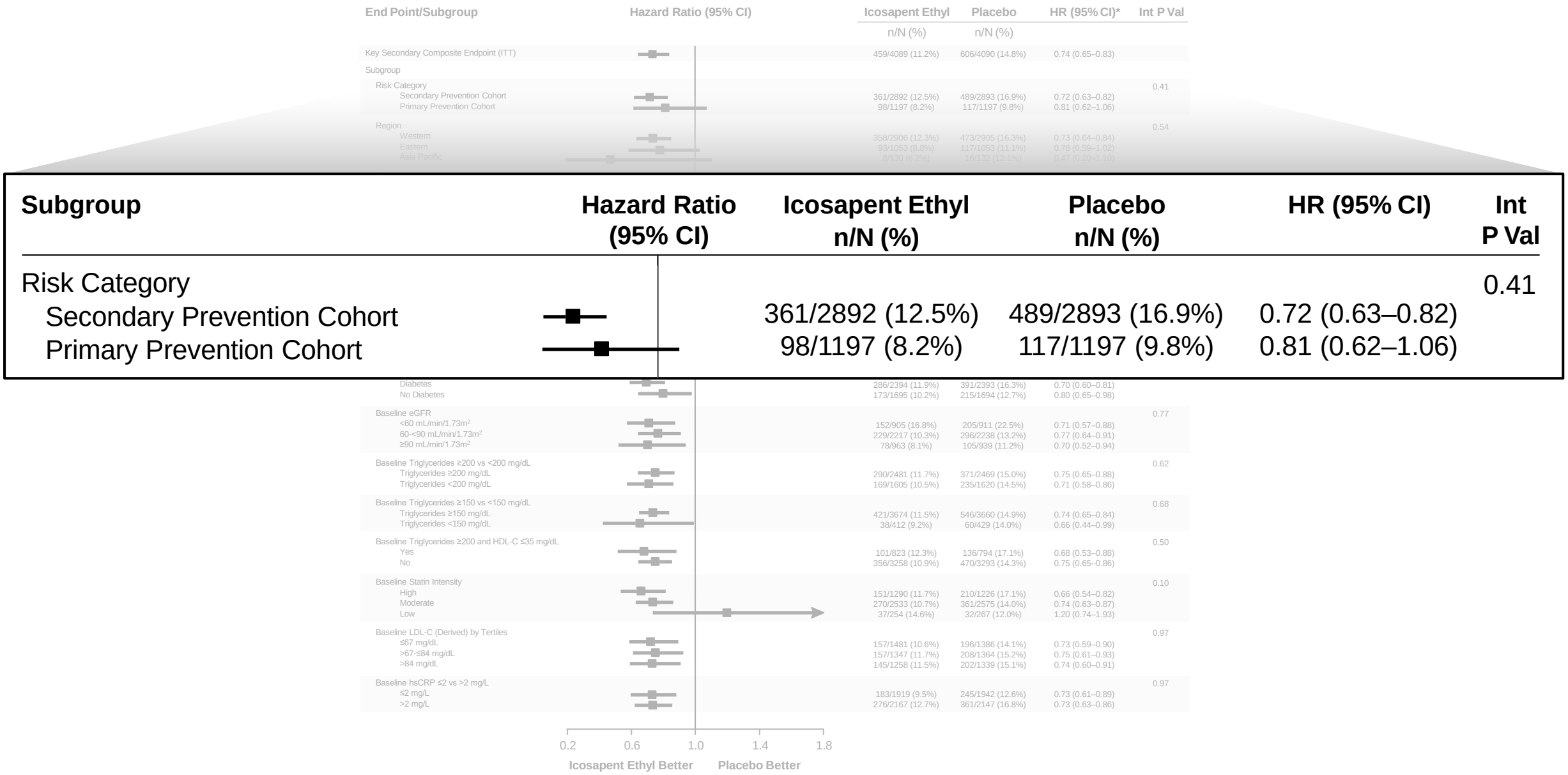
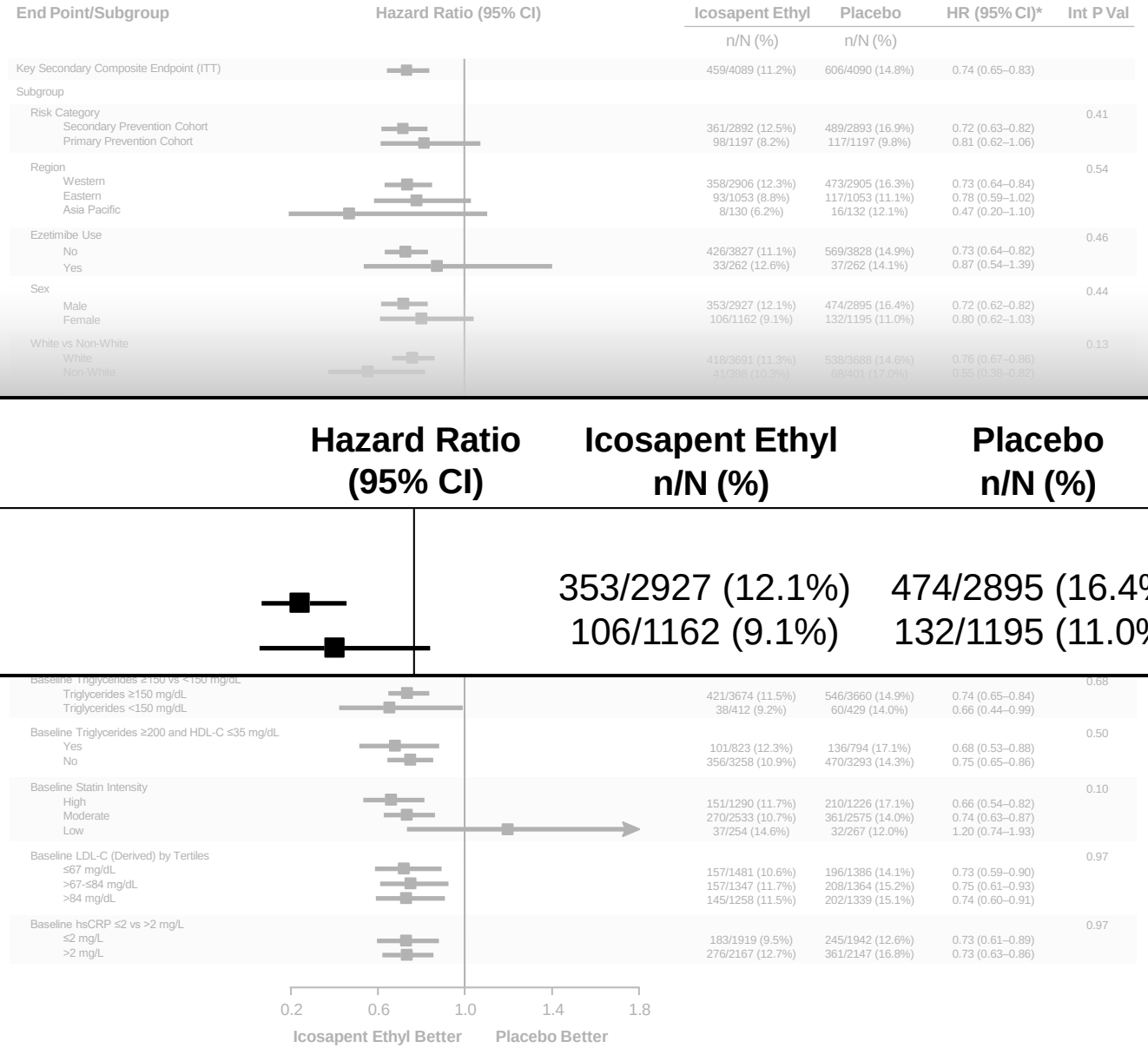


Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Risk Category					0.41
Secondary Prevention Cohort		361/2892 (12.5%)	489/2893 (16.9%)	0.72 (0.63–0.82)	
Primary Prevention Cohort		98/1197 (8.2%)	117/1197 (9.8%)	0.81 (0.62–1.06)	

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

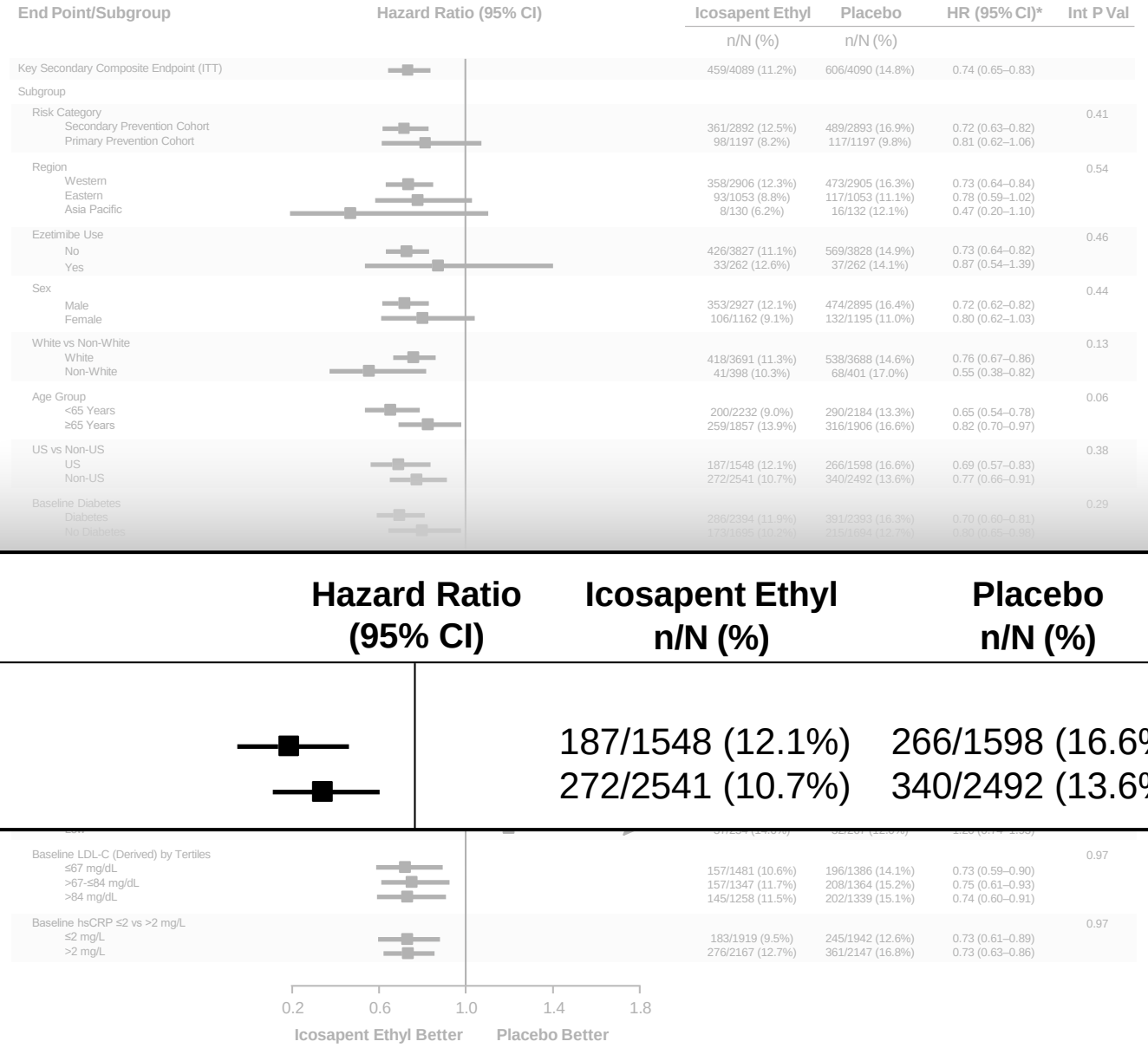
Key Secondary End Point in Subgroups



Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
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)	

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

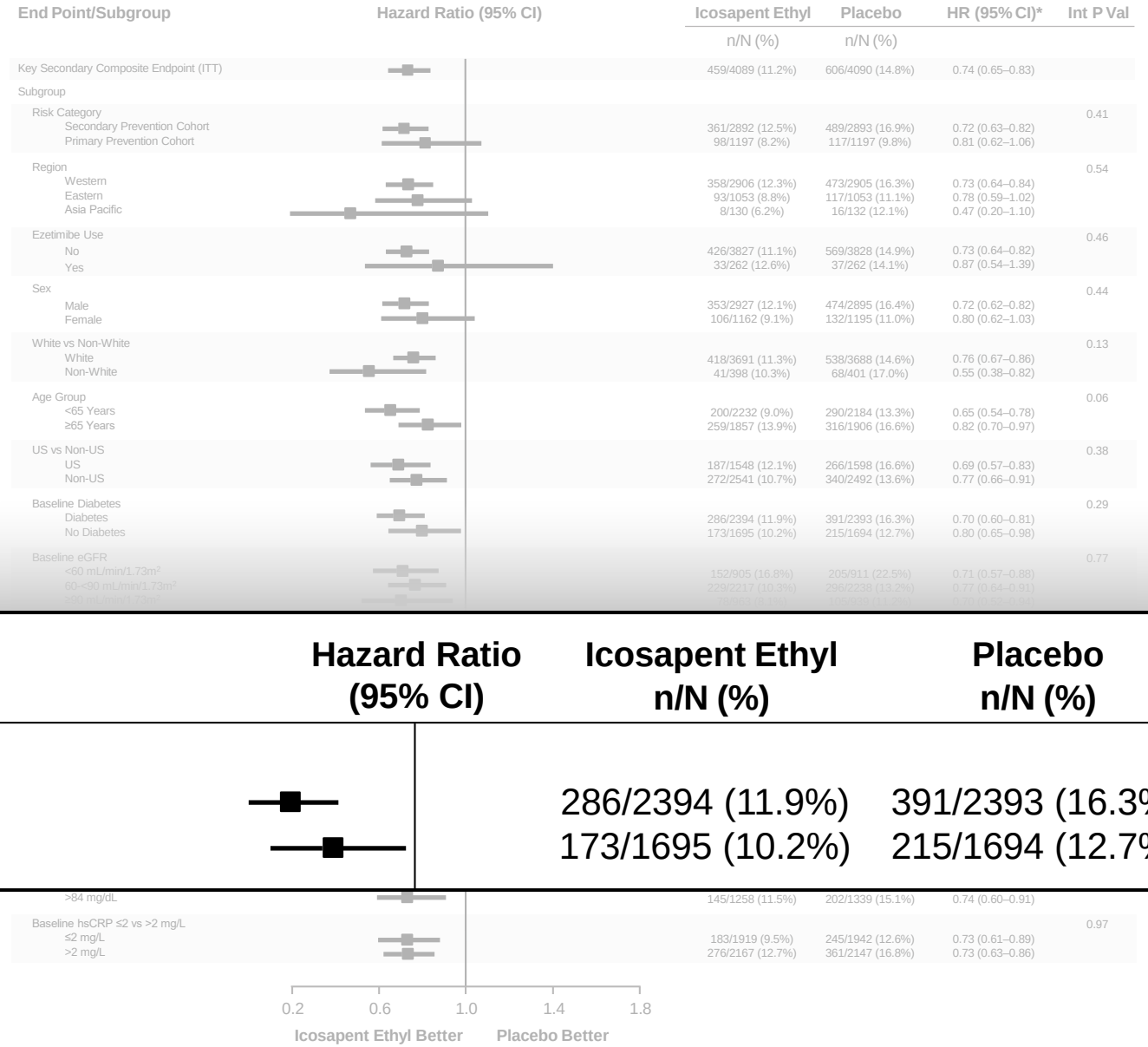
Key Secondary End Point in Subgroups



Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
US vs Non-US					0.38
US		187/1548 (12.1%)	266/1598 (16.6%)	0.69 (0.57–0.83)	
Non-US		272/2541 (10.7%)	340/2492 (13.6%)	0.77 (0.66–0.91)	

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

Key Secondary End Point in Subgroups



Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Baseline Diabetes					0.29
Diabetes		286/2394 (11.9%)	391/2393 (16.3%)	0.70 (0.60–0.81)	
No Diabetes		173/1695 (10.2%)	215/1694 (12.7%)	0.80 (0.65–0.98)	

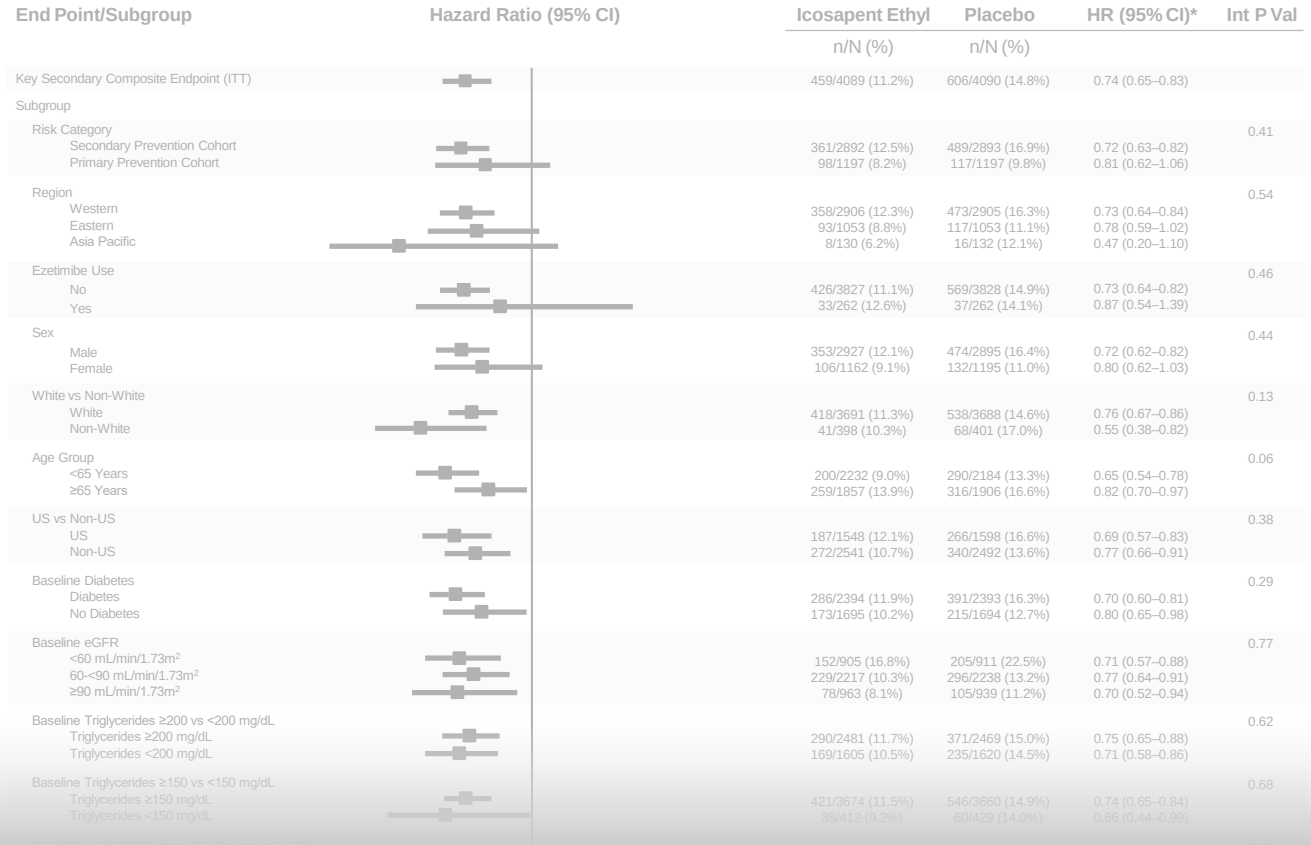
Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

Key Secondary End Point in Subgroups

Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Baseline Triglycerides ≥200 vs <200 mg/dL					0.62
Triglycerides ≥200 mg/dL		290/2481 (11.7%)	371/2469 (15.0%)	0.75 (0.65–0.88)	
Triglycerides <200 mg/dL		169/1605 (10.5%)	235/1620 (14.5%)	0.71 (0.58–0.86)	

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

Key Secondary End Point in Subgroups



Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Baseline Triglycerides ≥150 vs <150 mg/dL					0.68
Triglycerides ≥150 mg/dL		421/3674 (11.5%)	546/3660 (14.9%)	0.74 (0.65–0.84)	
Triglycerides <150 mg/dL		38/412 (9.2%)	60/429 (14.0%)	0.66 (0.44–0.99)	

Icosapent Ethyl Better Placebo Better

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Prespecified Hierarchical Testing

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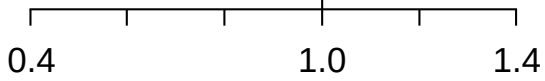

RRR denotes relative risk reduction

Bhatt DL. AHA 2018, Chicago.

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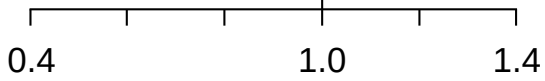

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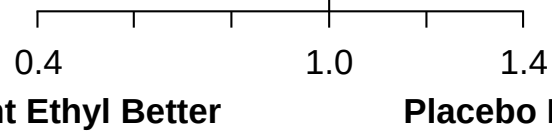

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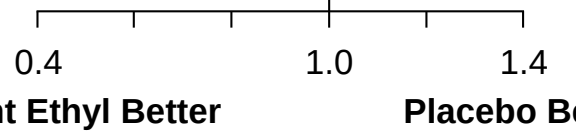

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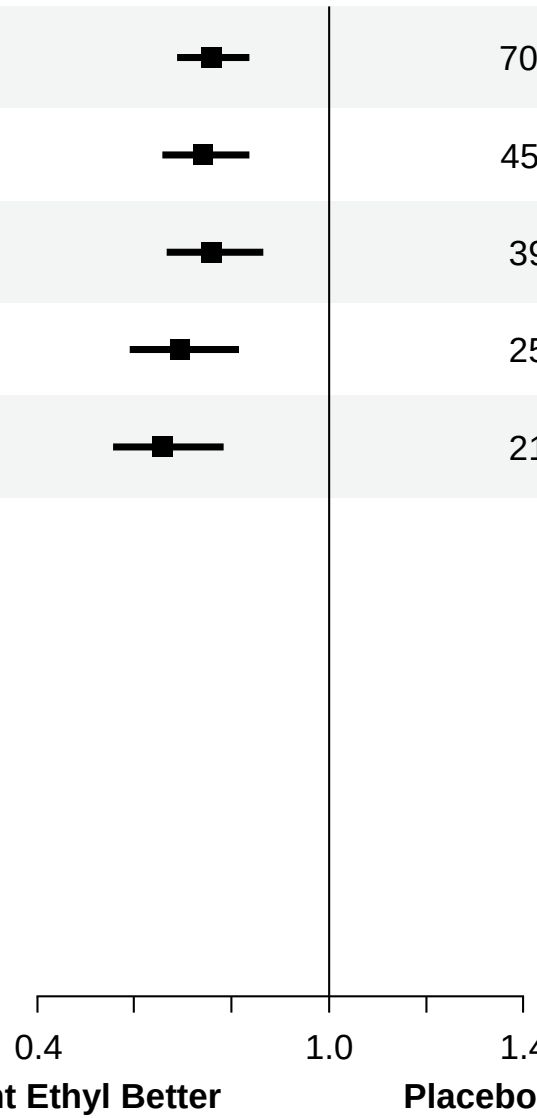

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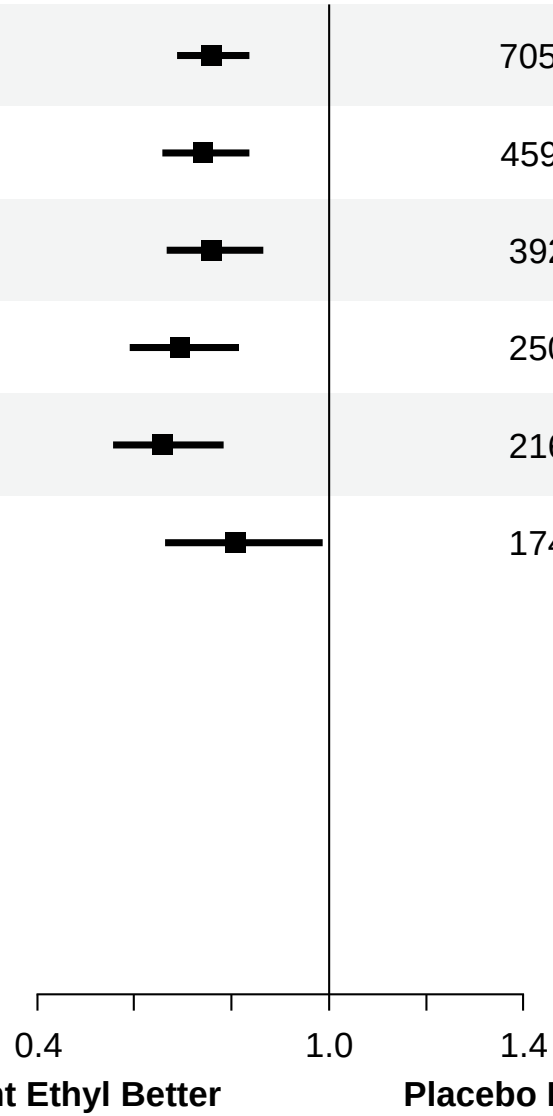

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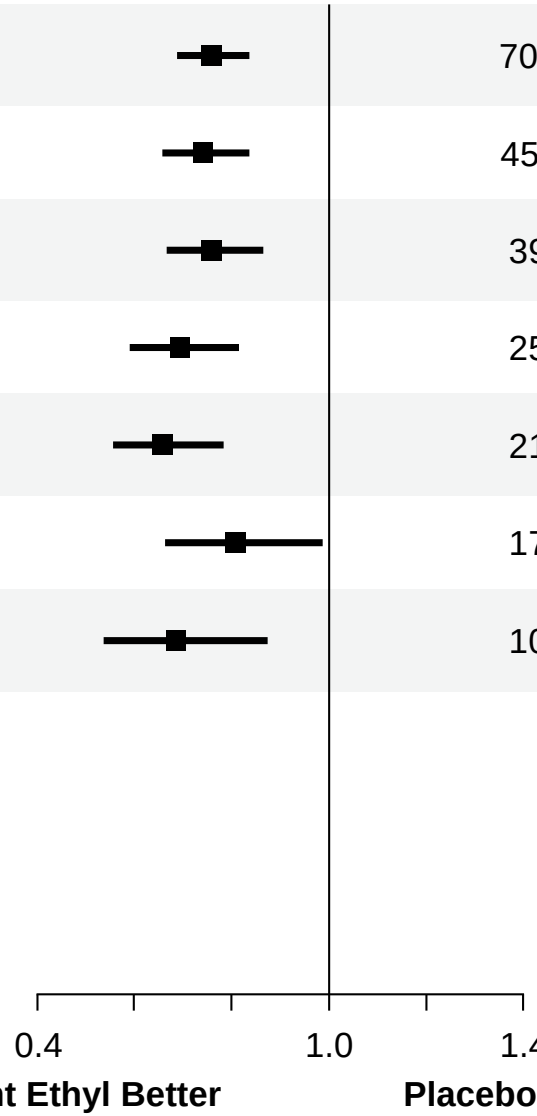

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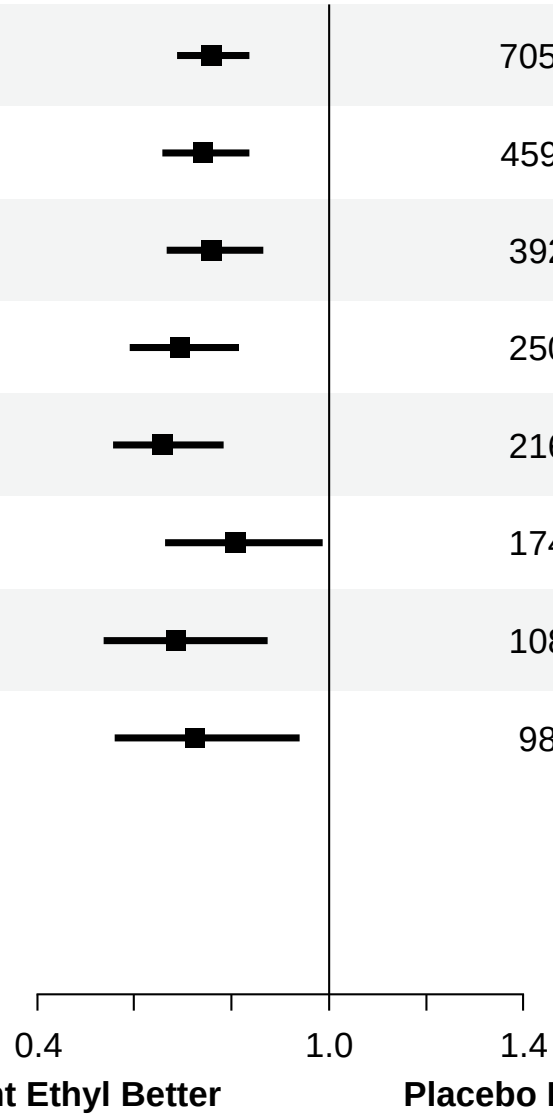

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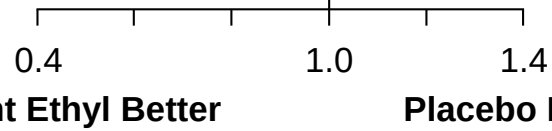

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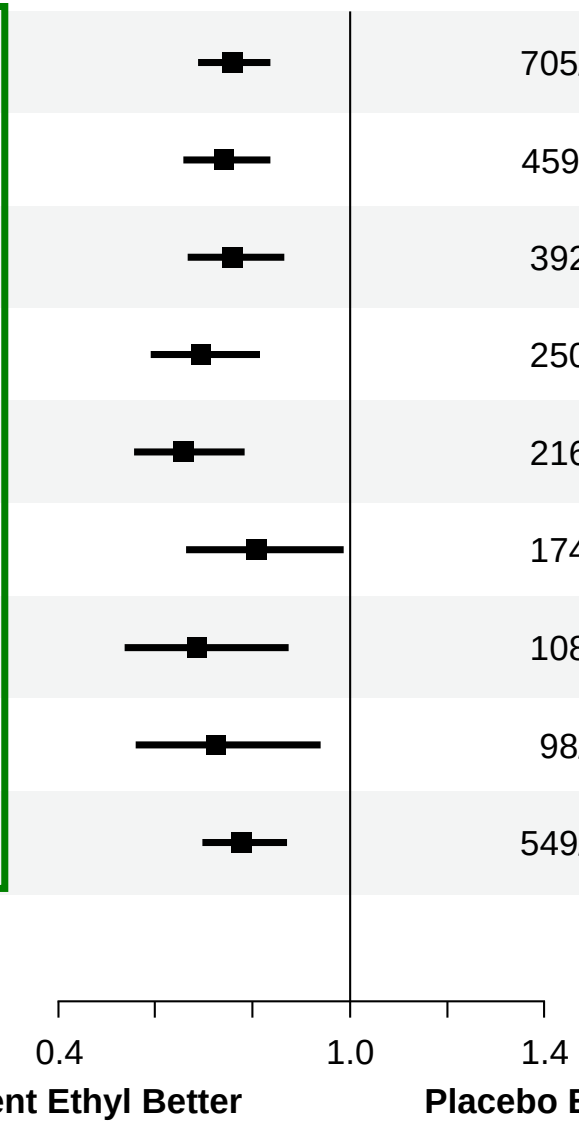

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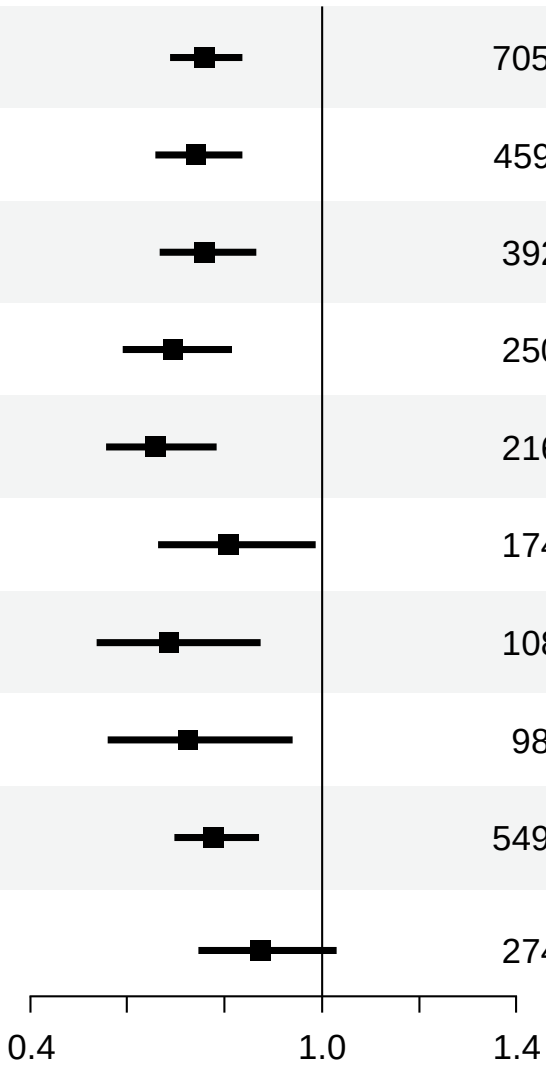
Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke	549/4089 (13.4%)	690/4090 (16.9%)	0.77 (0.69–0.86)	23%▼	<0.001
Total Mortality	274/4089 (6.7%)	310/4090 (7.6%)	0.87 (0.74–1.02)	13%▼	0.09



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Treatment-Emergent Adverse Events

	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P-value
Subjects with at Least One TEAE, n (%)	3343 (81.8%)	3326 (81.3%)	0.63
Serious TEAE	1252 (30.6%)	1254 (30.7%)	0.98
TEAE Leading to Withdrawal of Study Drug	321 (7.9%)	335 (8.2%)	0.60
Serious TEAE Leading to Withdrawal of Study Drug	88 (2.2%)	88 (2.2%)	1.00
Serious TEAE Leading to Death	94 (2.3%)	102 (2.5%)	0.61

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

Treatment-Emergent Adverse Event of Interest: Serious Bleeding

	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P-value
Bleeding related disorders	111 (2.7%)	85 (2.1%)	0.06
Gastrointestinal bleeding	62 (1.5%)	47 (1.1%)	0.15
Central nervous system bleeding	14 (0.3%)	10 (0.2%)	0.42
Other bleeding	41 (1.0%)	30 (0.7%)	0.19

- No fatal bleeding events in either group
- Adjudicated hemorrhagic stroke - no significant difference between treatments (13 icosapent ethyl versus 10 placebo; P=0.55)

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

Most Frequent Treatment-Emergent Adverse Events: ≥5% in Either Treatment Group and Significantly Different

Preferred Term	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P-value
Diarrhea	367 (9.0%)	453 (11.1%)	0.002
Peripheral edema	267 (6.5%)	203 (5.0%)	0.002
Constipation	221 (5.4%)	149 (3.6%)	<0.001
Atrial fibrillation	215 (5.3%)	159 (3.9%)	0.003
Anemia	191 (4.7%)	236 (5.8%)	0.03

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

Limitations

Few patients on ezetimibe

- Though data appeared consistent in that subgroup

Concomitant PCSK9 inhibitors prohibited

- Though no reason to think they are not additive

Small difference (5 mg/dL) in LDL-C between groups

- Cannot tell from this study if due to drug or placebo
- Would not account for 25% RRR
- JELIS saw 19% RRR in open label design, no placebo
- Consistent benefit in patients with LDL-C ↑ vs no LDL-C ↑

Pending Questions

Cannot comment on mechanisms of benefit from this study

- Consistent reduction across triglyceride range (135-500)
- Similar benefit by 1-year triglycerides < or > 150 mg/dL
- Detailed biomarker and genetic analyses are planned

Cannot comment on cost-effectiveness

- Though with NNT of 21, likely cost-effective
- Formal cost-effectiveness analyses planned
- Full benefits not captured with only first events, await recurrent and total events analyses

Conclusions

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- Non-statistically significant increase in serious bleeding

Consistent efficacy across multiple subgroups

- Including baseline triglycerides from 135-500 mg/dL
- Including secondary and primary prevention cohorts

We thank the investigators, the study coordinators, and especially the 8,179 patients in REDUCE-IT!

The NEW ENGLAND JOURNAL of MEDICINE

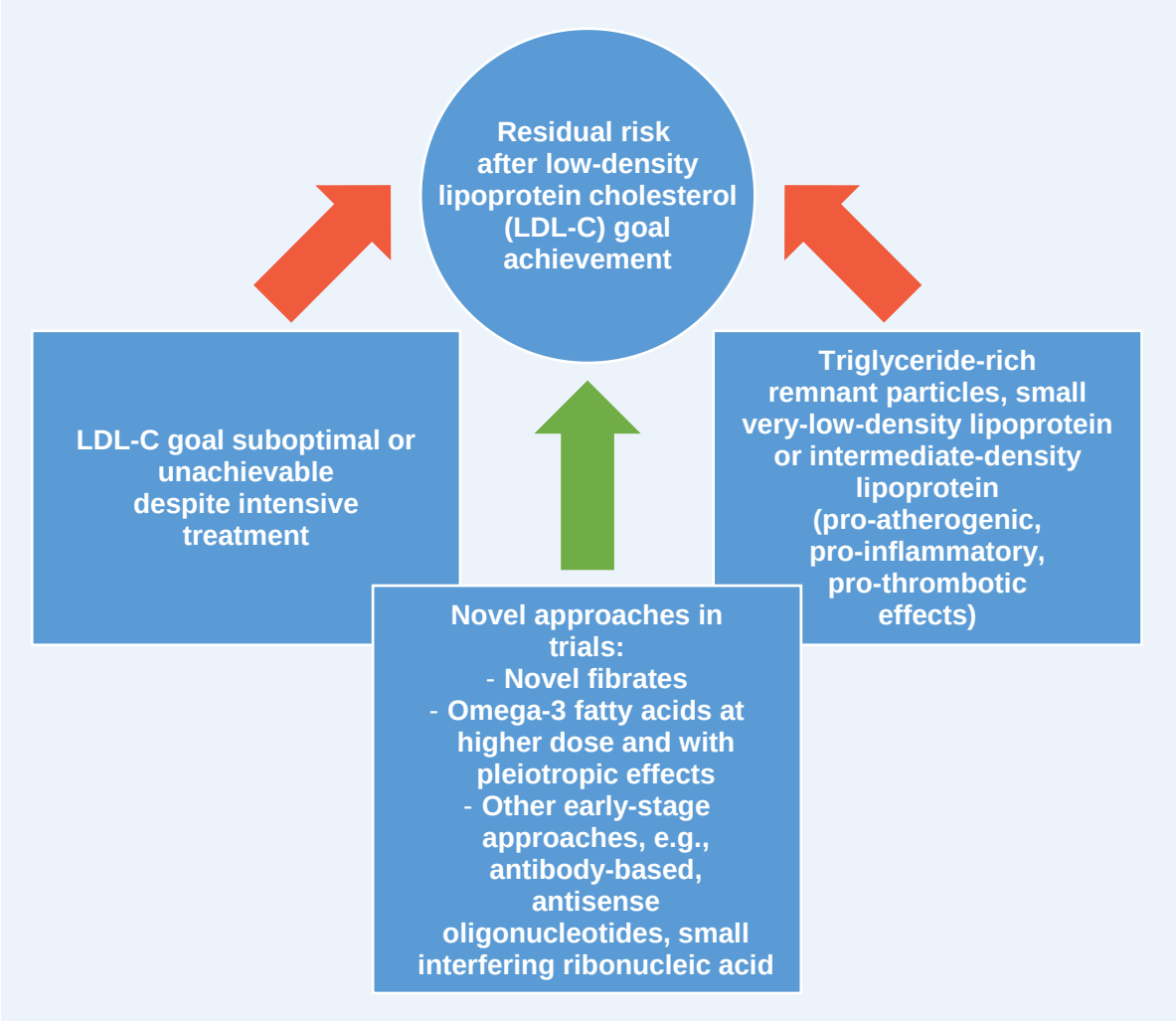
ORIGINAL ARTICLE

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., and Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators*

Article available at https://www.nejm.org
Slides available for download at https://professional.heart.org
or at https://www.ACC.org

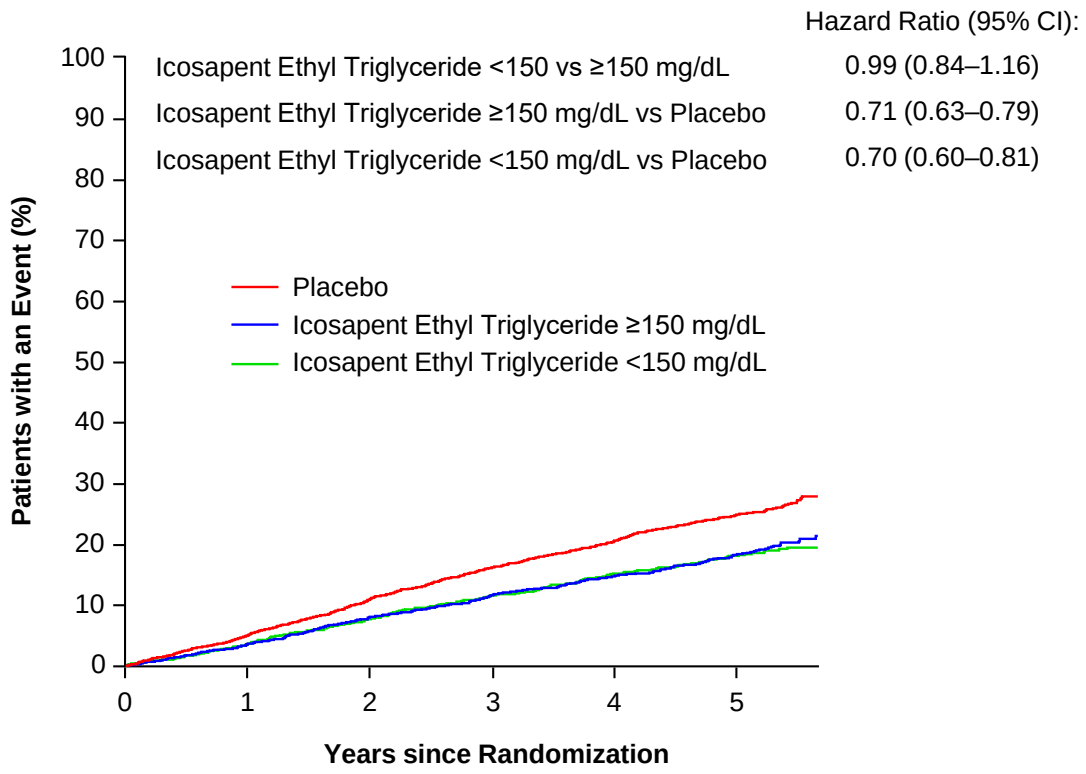
Promising Therapies for Hypertriglyceridemia



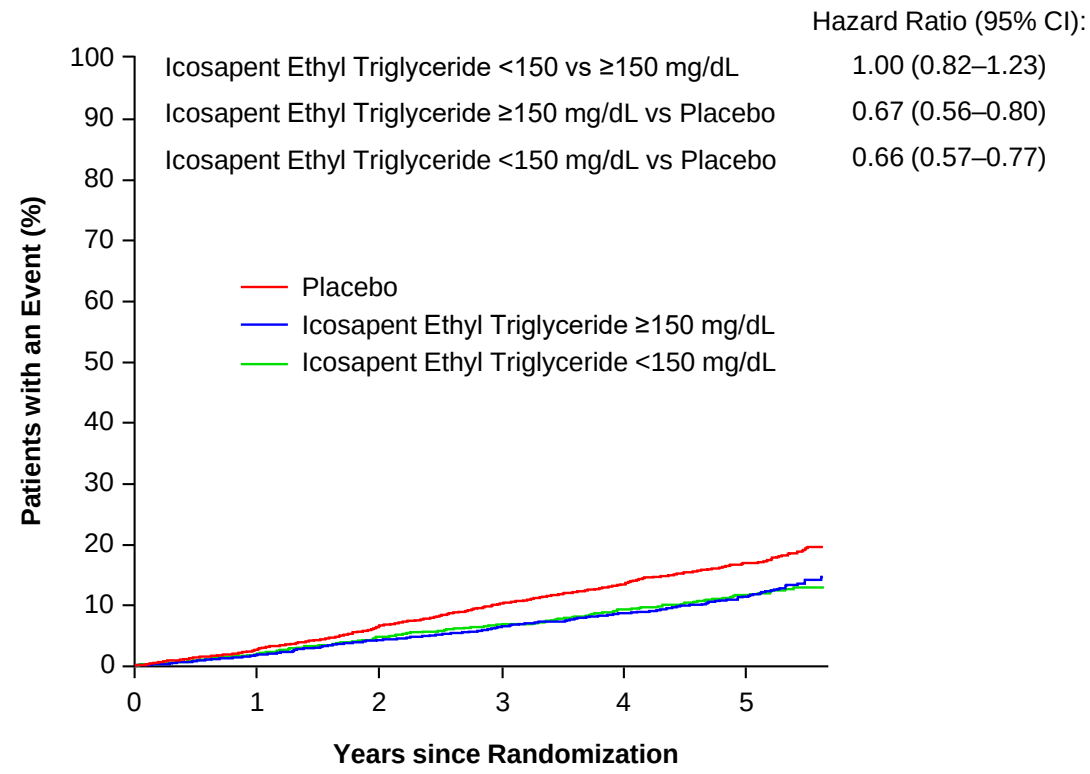
Adapted with permission* from Ganda OP, Bhatt DL, Mason RP, Miller M, Boden WE. Unmet need for adjunctive dyslipidemia therapy in hypertriglyderidemia management. *J Am Coll Cardiol*. 2018;72:330-343. [*https://creativecommons.org/licenses.org/by-nc/4.0/]

Achieved Triglyceride Levels: <150 mg/dL and ≥150 mg/dL

A Primary End Point by Achieved Triglyceride Level at 1 Year

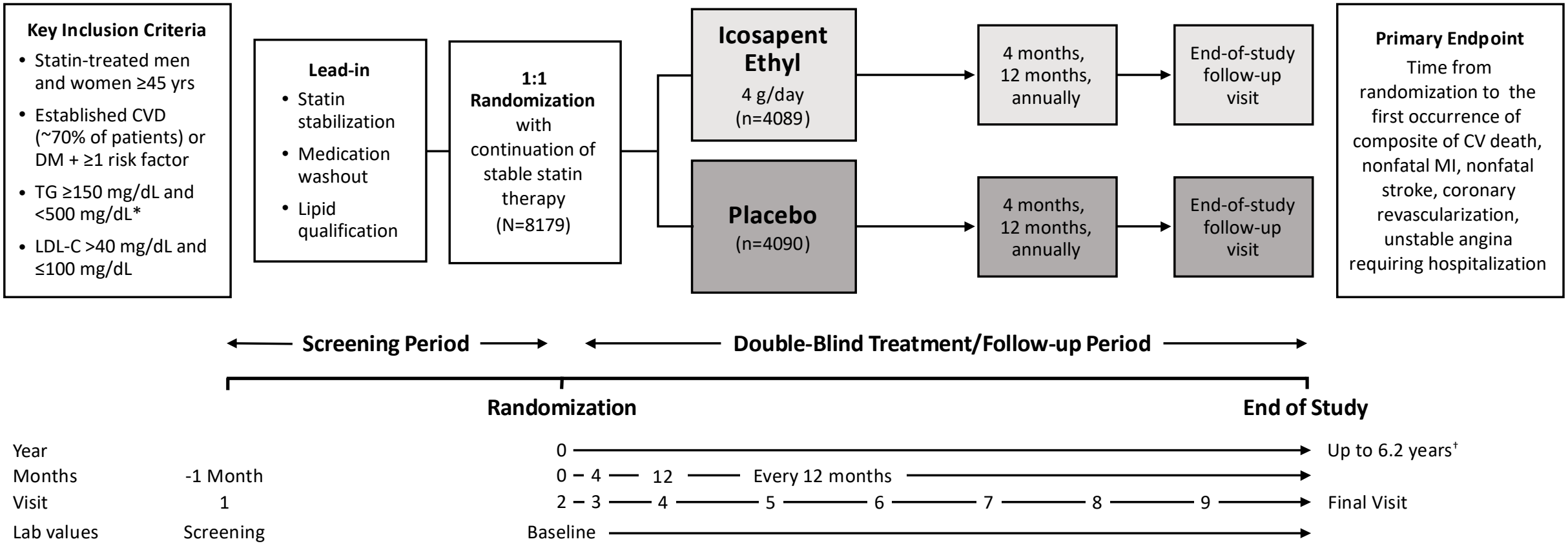


B Key Secondary End Point by Achieved Triglyceride Level at 1 Year



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

REDUCE-IT Design



* Due to the variability of triglycerides, a 10% allowance existed in the initial protocol, which permitted patients to be enrolled with qualifying triglycerides ≥135 mg/dL. Protocol amendment 1 (May 2013) changed the lower limit of acceptable triglycerides from 150 mg/dL to 200 mg/dL, with no variability allowance.

† Median trial follow-up duration was 4.9 years (minimum 0.0, maximum 6.2 years).

Adapted with permission‡ from Bhatt DL, Steg PG, Brinton EA, et al; on behalf of the REDUCE-IT Investigators. Rationale and design of REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial. *Clin Cardiol*. 2017;40:138-148. REDUCE-IT ClinicalTrials.gov number, NCT01492361.

Key Inclusion Criteria

1. Men or women ≥45 years with established CVD (Secondary Prevention Cohort) *or* ≥50 years with diabetes with ≥1 additional risk factor for CVD (Primary Prevention Cohort)
2. Fasting TG levels ≥150 mg/dL and <500 mg/dL*
3. LDL-C >40 mg/dL and ≤100 mg/dL and on stable statin therapy (± ezetimibe) for ≥4 weeks prior to qualifying measurements for randomization
4. Women who are not pregnant, not breastfeeding
5. Provide informed consent
6. Maintain a physician-recommended diet during the study

*A study amendment (May 2013) increased minimum fasting TG level from ≥150 mg/dL to ≥200 mg/dL

Adapted from: Bhatt DL, Steg PG, Brinton EA, et al; on behalf of the REDUCE-IT Investigators. Rationale and design of REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial. *Clin Cardiol*. 2017;40:138-148.

Key Inclusion Criteria by Risk Category

Inclusion Criteria for Secondary Prevention Cohort.

One or more of the following:

1. Documented coronary artery disease (one or more of the following)
   - Multi vessel CAD (≥50% stenosis in ≥2 major epicardial coronary arteries – with or without antecedent revascularization
   - Prior MI;
   - Hospitalization for high-risk non-ST-segment elevation acute coronary syndrome with ST-segment deviation or biomarker positivity
2. Documented cerebrovascular or carotid disease
   - Prior ischemic stroke
   - Symptomatic carotid artery disease with ≥50% carotid arterial stenosis
   - Asymptomatic carotid artery disease with ≥70% carotid arterial stenosis
   - History of carotid revascularization
3. Documented peripheral arterial disease
   - Ankle-brachial index <0.9 with symptoms of intermittent claudication
   - History of aorto-iliac or peripheral arterial intervention

Inclusion Criteria for Primary Prevention Cohort.

1. Diabetes mellitus requiring medication AND
2. ≥50 years of age AND
3. ≥1 additional risk factor for CVD
   - Men ≥55 years and Women ≥65 years
   - Cigarette smoker or stopped smoking within 3 months
   - Hypertension (≥140 mmHg systolic OR ≥90 mmHg diastolic) or on antihypertensive medication;
   - HDL-C ≤40 mg/dL for men or ≤50 mg/dL for women
   - Hs-CRP >3.00 mg/L
   - Renal dysfunction: Creatinine clearance >30 and <60 mL/min
   - Retinopathy
   - Micro- or macroalbuminuria
   - ABI <0.9 without symptoms of intermittent claudication

Patients with diabetes and CVD are counted under Secondary Prevention Cohort

Adapted from: Bhatt DL, Steg PG, Brinton EA, et al; on behalf of the REDUCE-IT Investigators. Rationale and design of REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial. *Clin Cardiol*. 2017;40:138-148.

Key Exclusion Criteria

1. Severe (NYHA class IV) heart failure
2. Life-threatening disease (other than CVD)
3. Severe liver disease
4. Hemoglobin A_{1c} >10.0%
5. Poorly controlled hypertension
6. Planned coronary intervention or major surgical procedure
7. Familial lipoprotein lipase deficiency, apolipoprotein C-II deficiency, or familial dysbetalipoproteinemia
8. Participation in another clinical trial involving an investigational agent within 90 days prior
9. Intolerance or hypersensitivity to statins
10. Hypersensitivity to fish and/or shellfish
11. History of pancreatitis
12. Malabsorption syndrome or chronic diarrhea
13. Non-statin, lipid-altering medications, dietary supplements
14. Other medications with lipid-altering potential
    a. Not stable for ≥28 days prior to qualifying
15. Known AIDS
16. Peritoneal dialysis or hemodialysis
17. Creatine kinase concentration >5 × ULN
18. Drug or alcohol abuse within the past 6 months

Adapted from: Bhatt DL, Steg PG, Brinton EA, et al; on behalf of the REDUCE-IT Investigators. Rationale and design of REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial. *Clin Cardiol*. 2017;40:138-148.

Serious Treatment-Emergent Adverse Events Occurring at ≥2% in Either Treatment Group

Preferred Term	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P-value[1]
Pneumonia	105 (2.6%)	118 (2.9%)	0.42

Note: A treatment-emergent adverse event (TEAE) is defined as an event that first occurs or worsens in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. Percentages are based on the number of subjects randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints are not included.
All adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1).
[1] Fisher's Exact test.

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

Adjudicated Events: Hospitalization for Atrial Fibrillation or Atrial Flutter

Primary System Organ Class Preferred Term	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P-value
Positively Adjudicated Atrial Fibrillation/Flutter[1]	127 (3.1%)	84 (2.1%)	0.004

Note: Percentages are based on the number of subjects randomized to each treatment group in the Safety population (N).
All adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1).
[1] Includes positively adjudicated Atrial Fibrillation/Flutter clinical events by the Clinical Endpoint Committee (CEC). P value was based on stratified log-rank test.

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

Tolerability: GI TEAEs >3% in Either Treatment Arm

Primary System Organ Class Preferred Term	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P-value[1]
Gastrointestinal disorders	1350 (33.0%)	1437 (35.1%)	0.04
Diarrhea	367 (9.0%)	453 (11.1%)	0.002
Constipation	221 (5.4%)	149 (3.6%)	<0.001
Nausea	190 (4.6%)	197 (4.8%)	0.75
Gastroesophageal Reflux Disease	124 (3.0%)	118 (2.9%)	0.70

Note: Percentages are based on the number of randomized subjects within each treatment group (N).
[1] Fisher's Exact test

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