



Reduction of Cardiovascular Events with Icosapent Ethyl—Intervention Trial

Deepak L. Bhatt, MD, MPH, Michael Miller, MD, Eliot A. Brinton, MD,
 Terry A. Jacobson, MD, Ph. Gabriel Steg, 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, Brian Olshansky, MD,
 Mina K. Chung, MD, C. Michael Gibson, MS, MD, Robert P. Giugliano, MD, SM,
 Matthew J. Budoff, MD, Christie M. Ballantyne, MD,
 on Behalf of the **REDUCE-IT** Investigators



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Disclosures



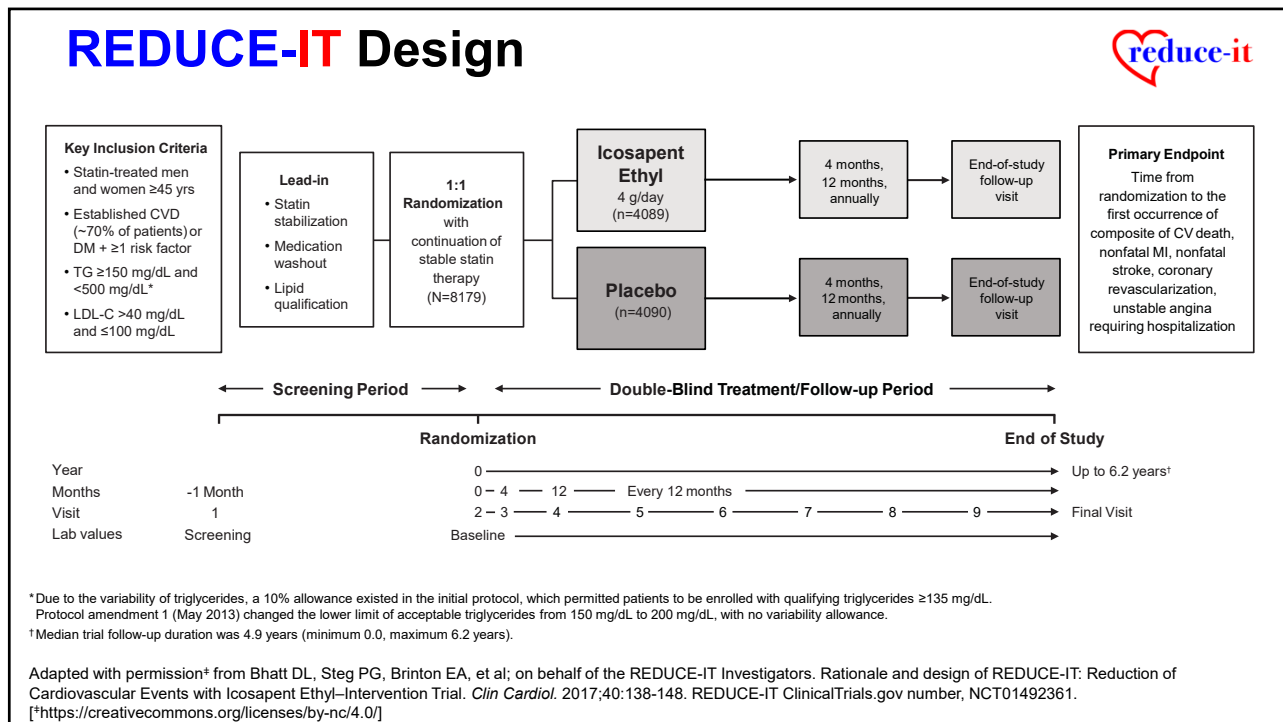
Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, Cereno, Elsevier Practice Update Cardiology, Medscape Cardiology, PhaseBio, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart 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 (including for the ExCEED trial, funded by Edwards), 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), Medtelligence/ReachMD (CME steering committees), 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, Afimmune, **Amarin**, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Fractyl, 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, CSI, 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.

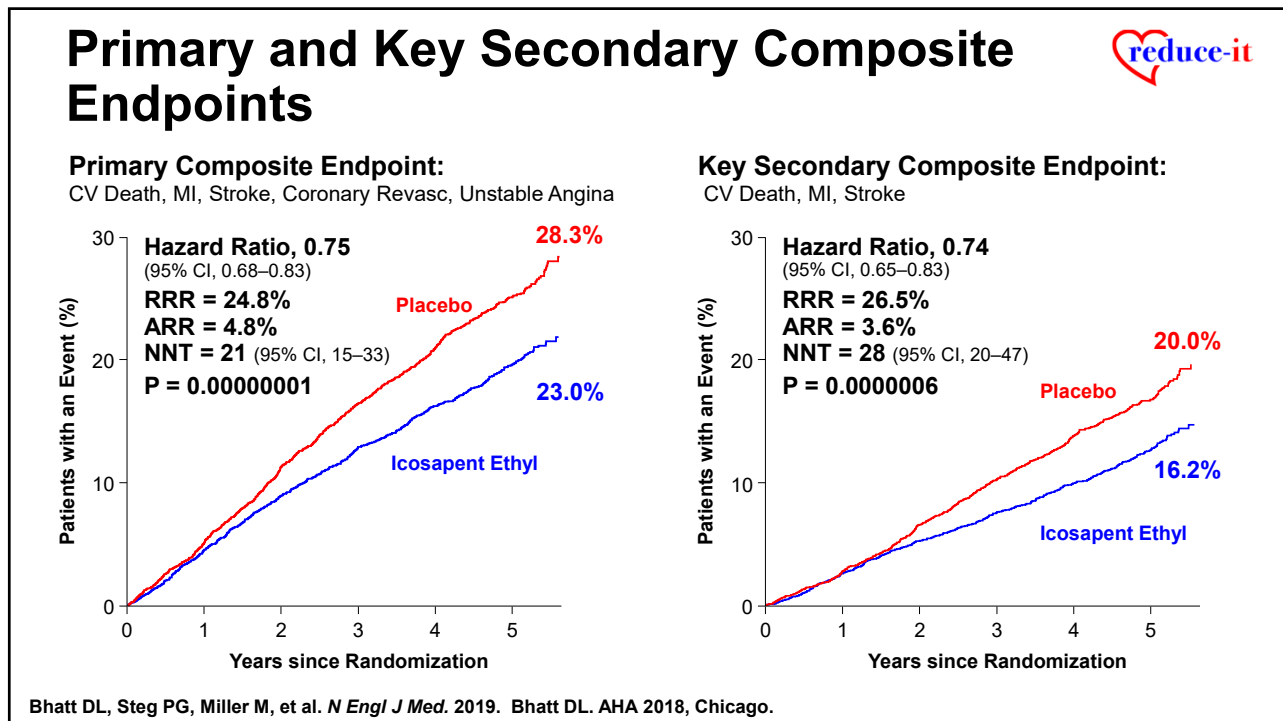
REDUCE-IT was sponsored by Amarin Pharma, Inc.

All analyses independently validated by Baim Clinical Research Institute.

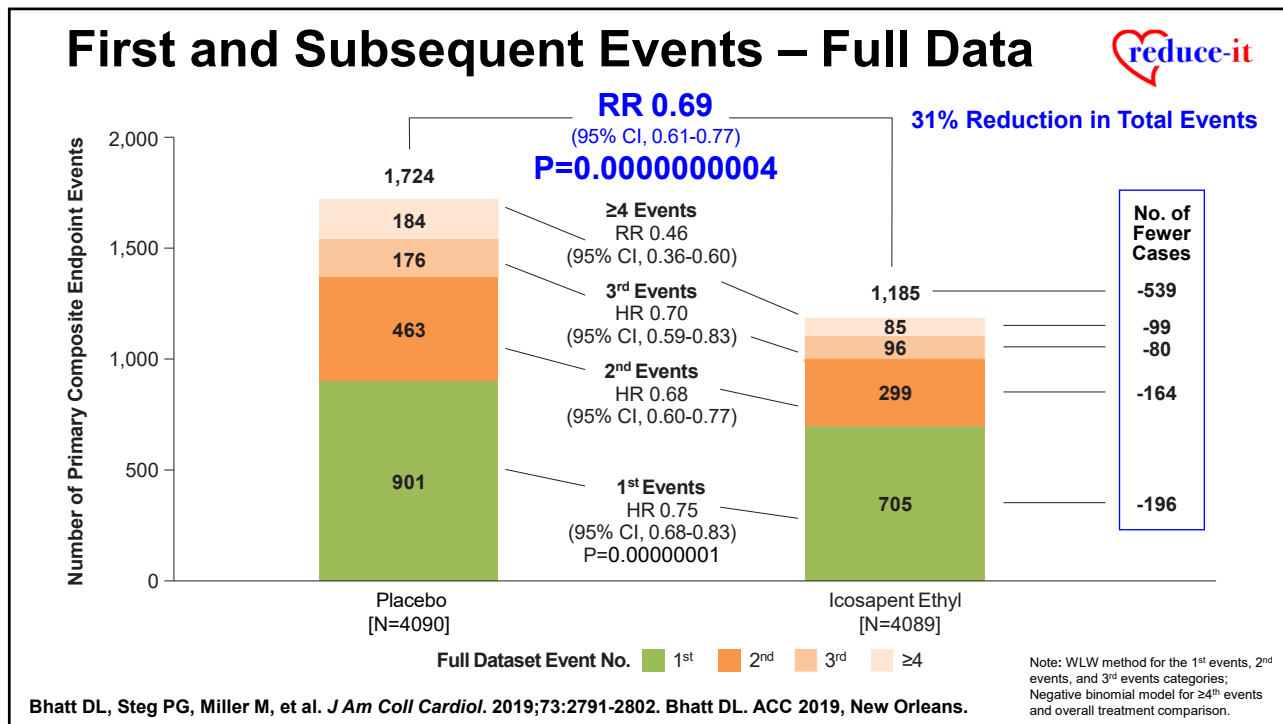
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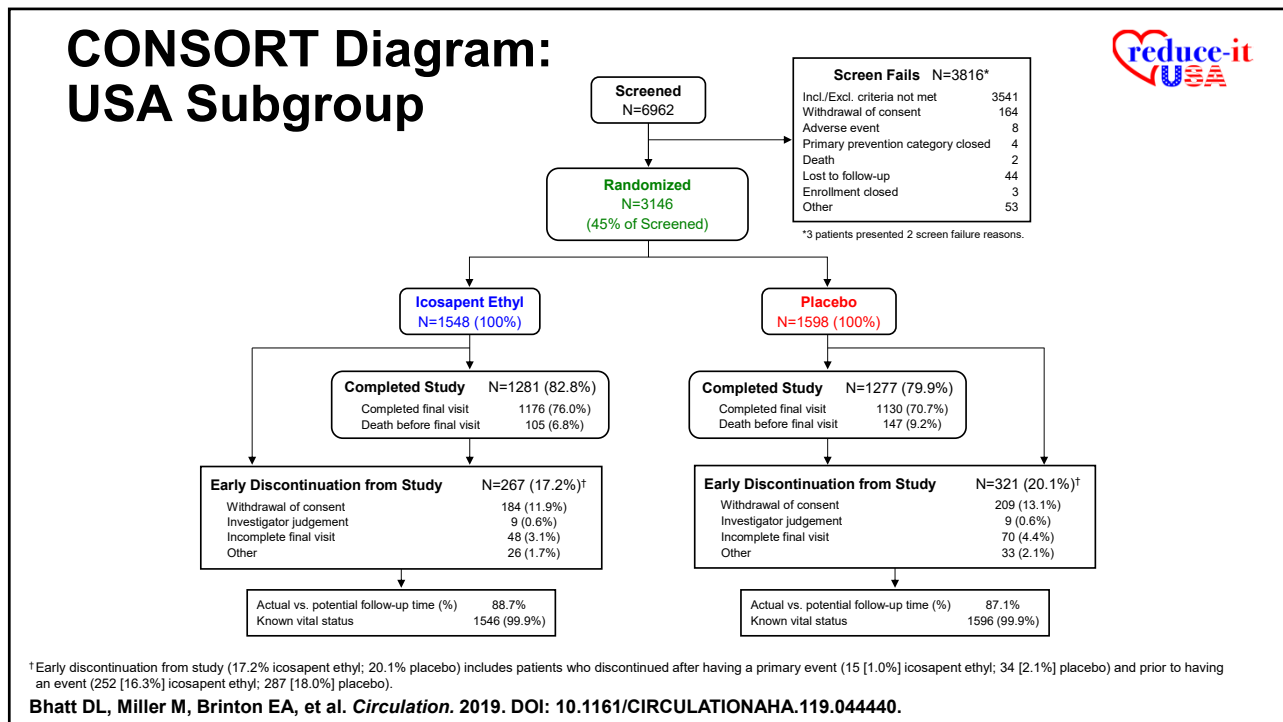
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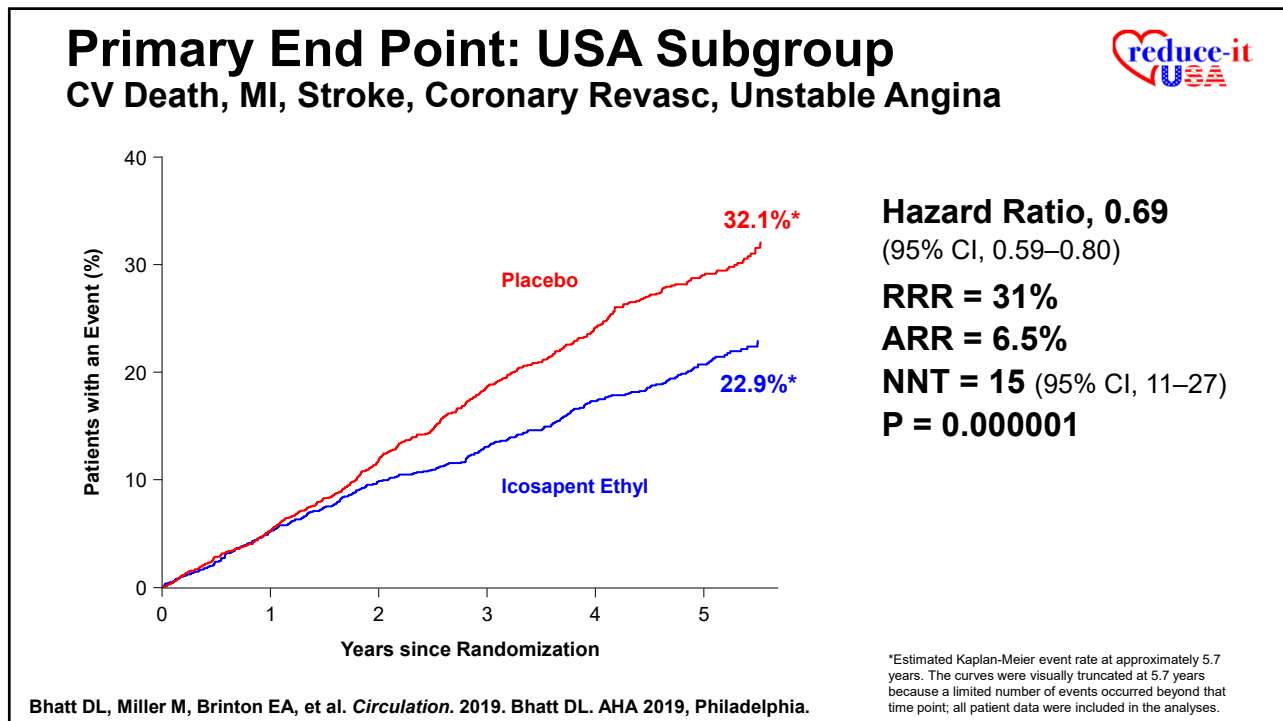
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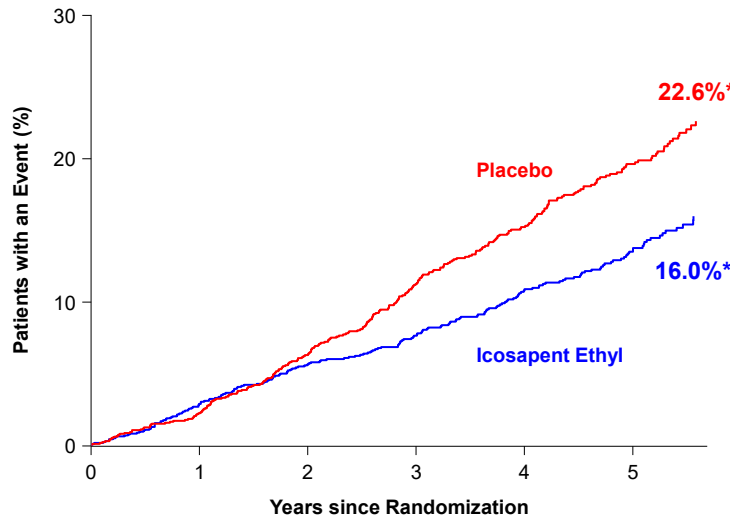
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Key Secondary End Point: USA Subgroup

CV Death, MI, Stroke



Hazard Ratio, 0.69

(95% CI, 0.57–0.83)

RRR = 31%

ARR = 4.6%

NNT = 22 (95% CI, 14–47)

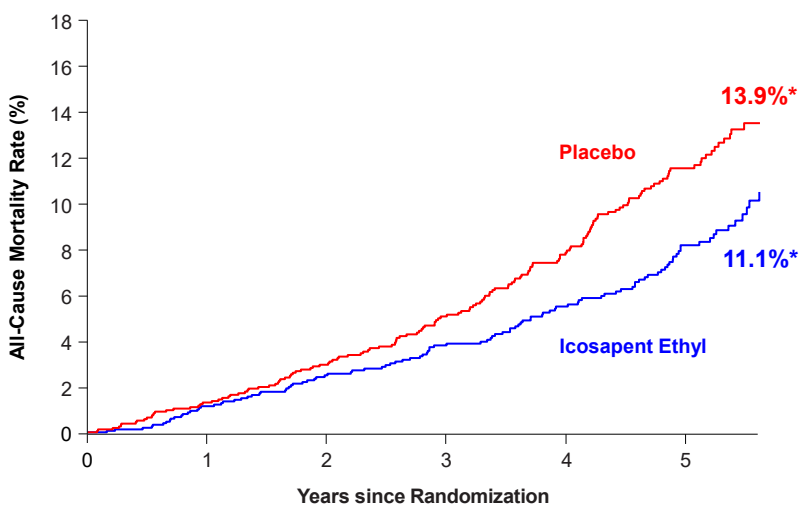
P = 0.00008

*Estimated Kaplan-Meier event rate at approximately 5.7 years. The curves were visually truncated at 5.7 years because a limited number of events occurred beyond that time point; all patient data were included in the analyses.

Bhatt DL, Miller M, Brinton EA, et al. *Circulation*. 2019. Bhatt DL. AHA 2019, Philadelphia.

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All-Cause Mortality: USA Subgroup



Hazard Ratio, 0.70

(95% CI, 0.55–0.90)

RRR = 30%

ARR = 2.6%

NNT = 39 (95% CI, 22–154)

P = 0.004

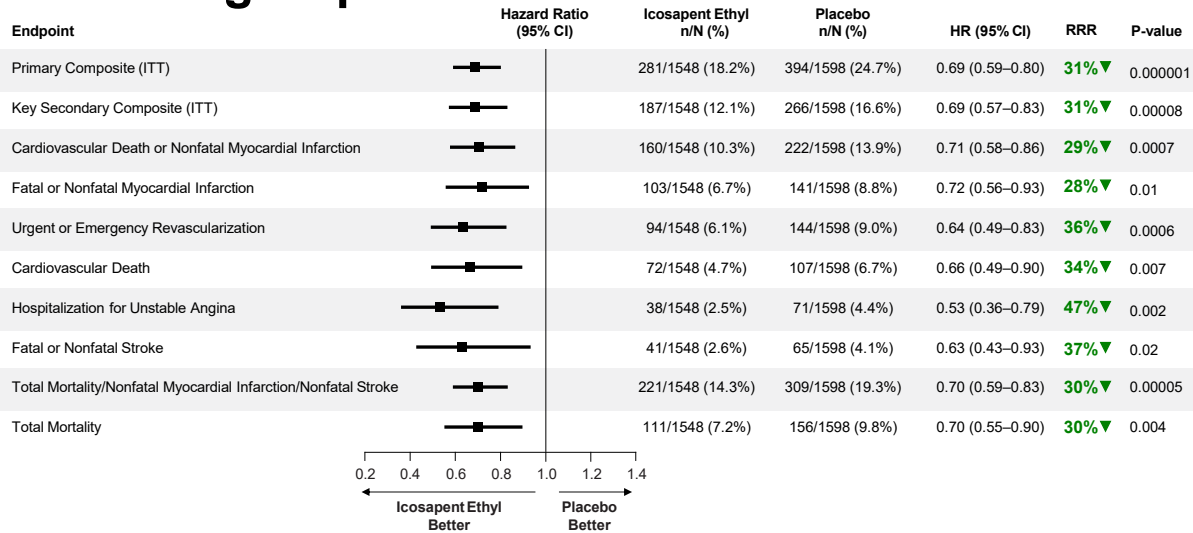
P_{interaction} = 0.02

*Estimated Kaplan-Meier event rate at approximately 5.7 years. The curves were visually truncated at 5.7 years because a limited number of events occurred beyond that time point; all patient data were included in the analyses.

Bhatt DL, Miller M, Brinton EA, et al. *Circulation*. 2019. Bhatt DL. AHA 2019, Philadelphia.

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Prespecified Hierarchical Testing: USA Subgroup

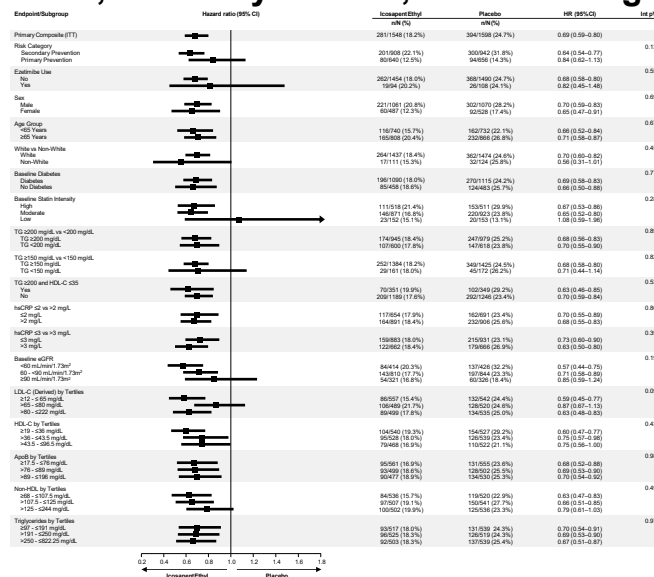


Bhatt DL, Miller M, Brinton EA, et al. *Circulation*. 2019. Bhatt DL. AHA 2019, Philadelphia.

RRR denotes relative risk reduction

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Primary Endpoint: USA Subgroup CV Death, MI, Stroke, Coronary Revasc, Unstable Angina

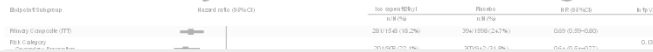


Bhatt DL, Miller M, Brinton EA, et al. *Circulation*. 2019. Bhatt DL. AHA 2019, Philadelphia.

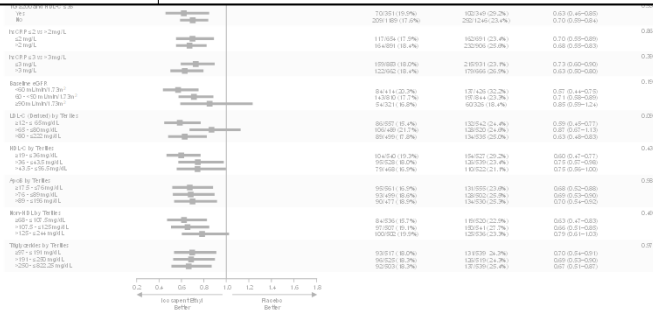
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Primary Endpoint: Subgroups – USA

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



Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Risk Category					0.13
Secondary Prevention		201/908 (22.1%)	300/942 (31.8%)	0.64 (0.54–0.77)	
Primary Prevention		80/640 (12.5%)	94/656 (14.3%)	0.84 (0.62–1.13)	

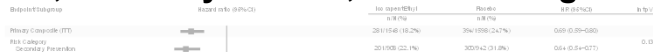


Bhatt DL, Miller M, Brinton EA, et al. *Circulation*. 2019. Bhatt DL. AHA 2019, Philadelphia.

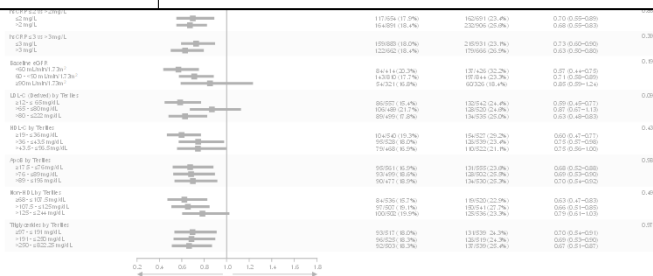
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Primary Endpoint: Subgroups – USA

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



Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Ezetimibe Use					0.55
No		262/1454 (18.0%)	368/1490 (24.7%)	0.68 (0.58–0.80)	
Yes		19/94 (20.2%)	26/108 (24.1%)	0.82 (0.45–1.48)	

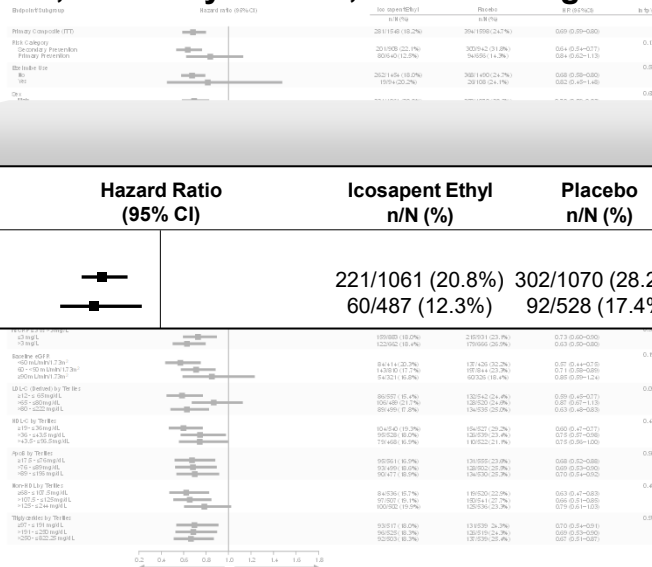


Bhatt DL, Miller M, Brinton EA, et al. *Circulation*. 2019. Bhatt DL. AHA 2019, Philadelphia.

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Primary Endpoint: Subgroups – USA

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



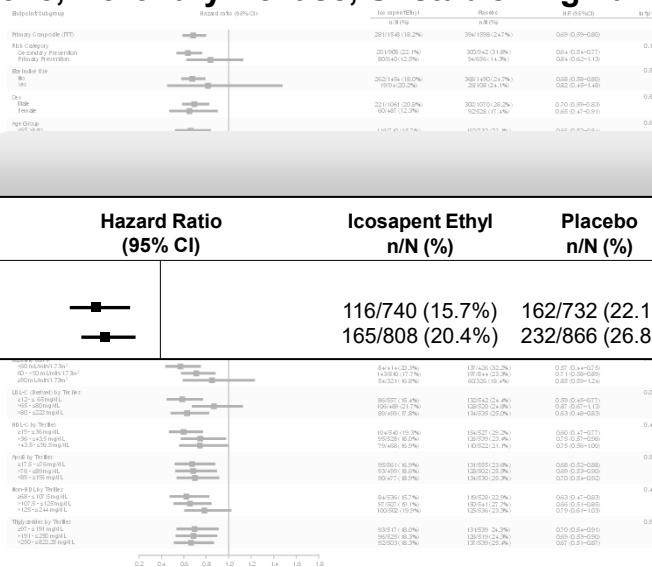
Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Sex					0.69
Male		221/1061 (20.8%)	302/1070 (28.2%)	0.70 (0.59–0.83)	
Female		60/487 (12.3%)	92/528 (17.4%)	0.65 (0.47–0.91)	

Bhatt DL, Miller M, Brinton EA, et al. *Circulation*. 2019. Bhatt DL. AHA 2019, Philadelphia.

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Primary Endpoint: Subgroups – USA

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



Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Age Group					0.67
<65 Years		116/740 (15.7%)	162/732 (22.1%)	0.66 (0.52–0.84)	
≥65 Years		165/808 (20.4%)	232/866 (26.8%)	0.71 (0.58–0.87)	

Bhatt DL, Miller M, Brinton EA, et al. *Circulation*. 2019. Bhatt DL. AHA 2019, Philadelphia.

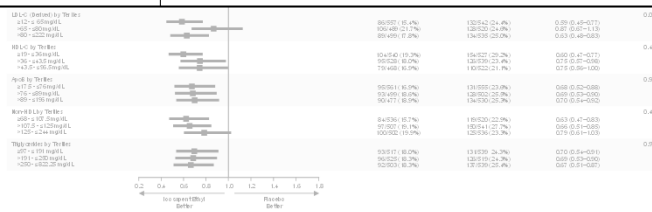
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Primary Endpoint: Subgroups – USA

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



Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
White vs Non-White					0.45
White		264/1437 (18.4%)	362/1474 (24.6%)	0.70 (0.60–0.82)	
Non-White		17/111 (15.3%)	32/124 (25.8%)	0.56 (0.31–1.01)	



Bhatt DL, Miller M, Brinton EA, et al. *Circulation*. 2019. Bhatt DL. AHA 2019, Philadelphia.

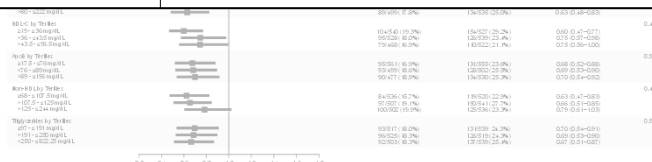
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Primary Endpoint: Subgroups – USA

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



Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Baseline Diabetes					0.77
Diabetes		196/1090 (18.0%)	270/1115 (24.2%)	0.69 (0.58–0.83)	
No Diabetes		85/458 (18.6%)	124/483 (25.7%)	0.66 (0.50–0.88)	

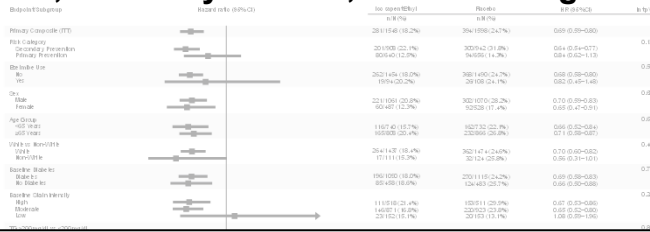


Bhatt DL, Miller M, Brinton EA, et al. *Circulation*. 2019. Bhatt DL. AHA 2019, Philadelphia.

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Primary Endpoint: Subgroups – USA

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



Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
ApoB by Tertiles					0.98
≥17.5 - ≤76 mg/dL		95/561 (16.9%)	131/555 (23.6%)	0.68 (0.52–0.88)	
>76 - ≤89 mg/dL		93/499 (18.6%)	128/502 (25.5%)	0.69 (0.53–0.90)	
>89 - ≤196 mg/dL		90/477 (18.9%)	134/530 (25.3%)	0.70 (0.54–0.92)	

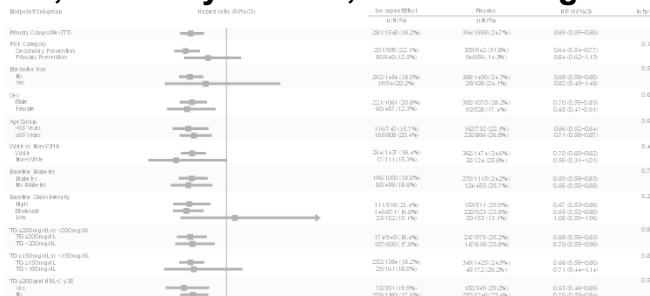


Bhatt DL, Miller M, Brinton EA, et al. *Circulation*. 2019. Bhatt DL. AHA 2019, Philadelphia.

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Primary Endpoint: Subgroups – USA

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



Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Triglycerides by Tertiles					0.97
≥97 - ≤191 mg/dL		93/517 (18.0%)	131/539 (24.3%)	0.70 (0.54–0.91)	
>191 - ≤250 mg/dL		96/525 (18.3%)	126/519 (24.3%)	0.69 (0.53–0.90)	
>250 - ≤822.25 mg/dL		92/503 (18.3%)	137/539 (25.4%)	0.67 (0.51–0.87)	

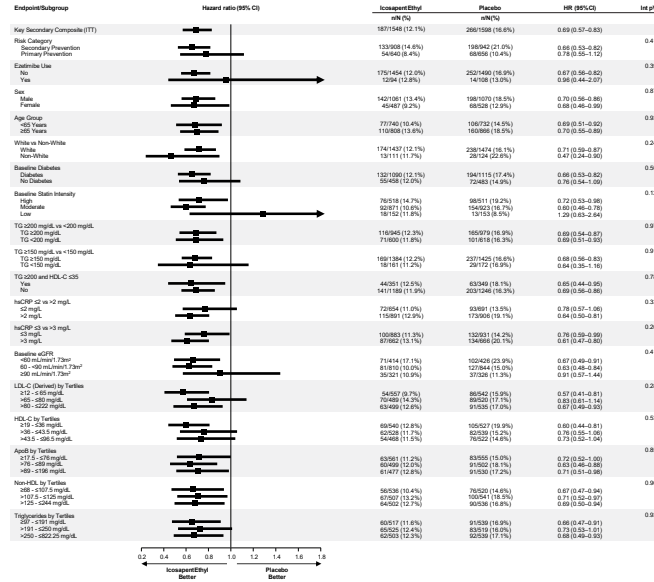


Bhatt DL, Miller M, Brinton EA, et al. *Circulation*. 2019. Bhatt DL. AHA 2019, Philadelphia.

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Key Secondary Endpoint: Subgroups – USA

CV Death, MI, Stroke

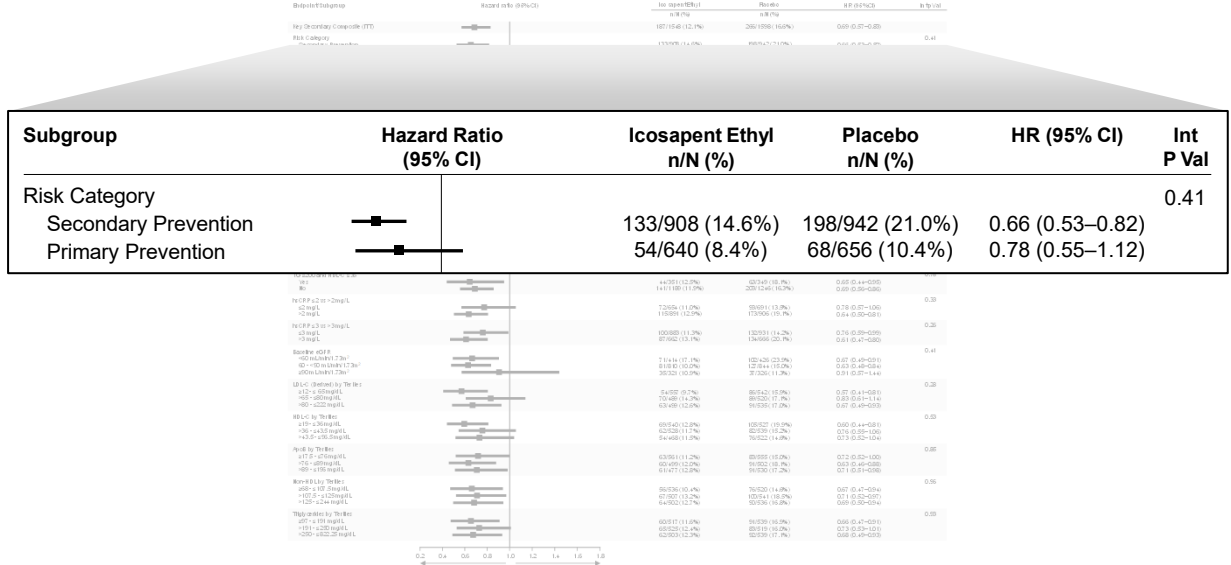


Bhatt DL, Miller M, Brinton EA, et al. *Circulation*. 2019. Bhatt DL. AHA 2019, Philadelphia.

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Key Secondary Endpoint: Subgroups – USA

CV Death, MI, Stroke



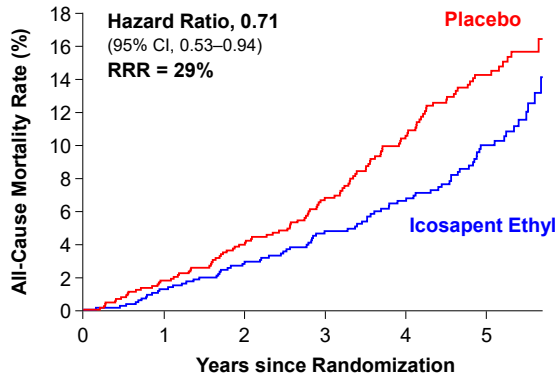
Bhatt DL, Miller M, Brinton EA, et al. *Circulation*. 2019. Bhatt DL. AHA 2019, Philadelphia.

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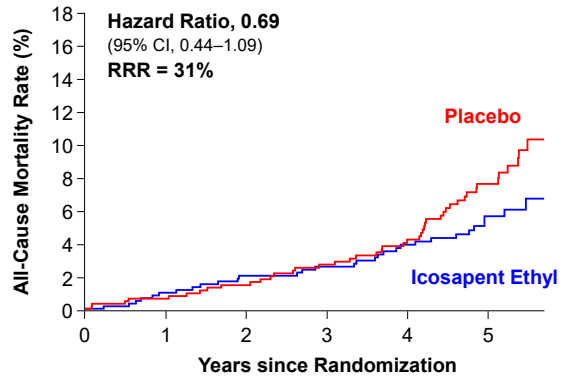
All-Cause Mortality: USA Subgroup by CV Risk Category



Secondary Prevention



Primary Prevention

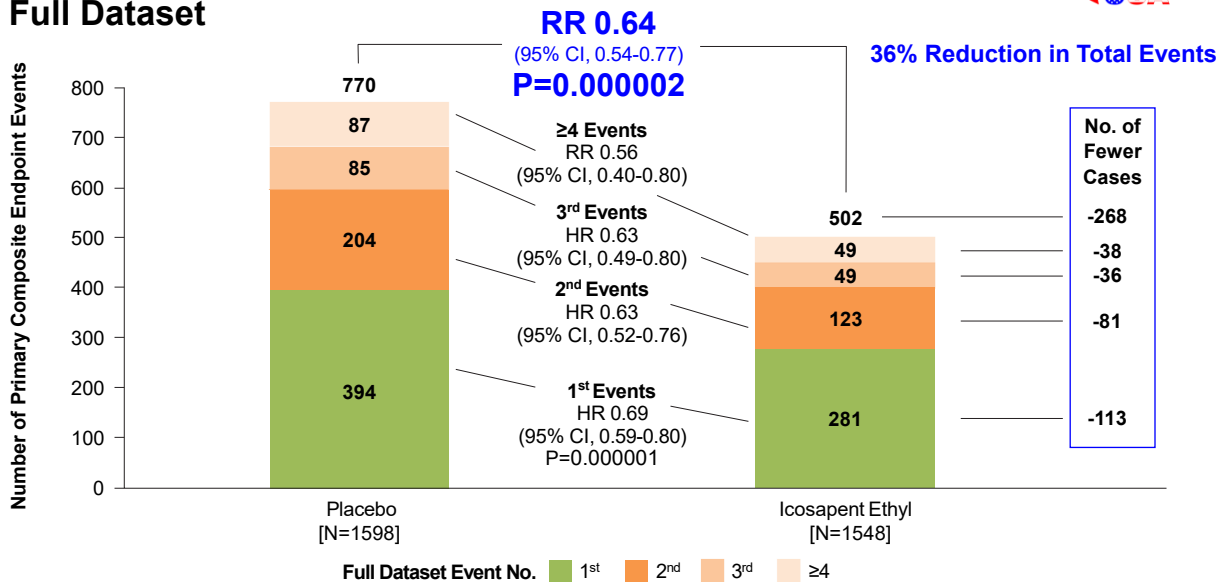


Note: The curves were visually truncated at 5.7 years because a limited number of events occurred beyond that time point; all patient data were included in the analyses.

Bhatt DL. AHA 2019, Philadelphia.

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First and Subsequent Events: USA Full Dataset



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

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Safety Summary: USA Subgroup Treatment Emergent Adverse Events in the Safety Population



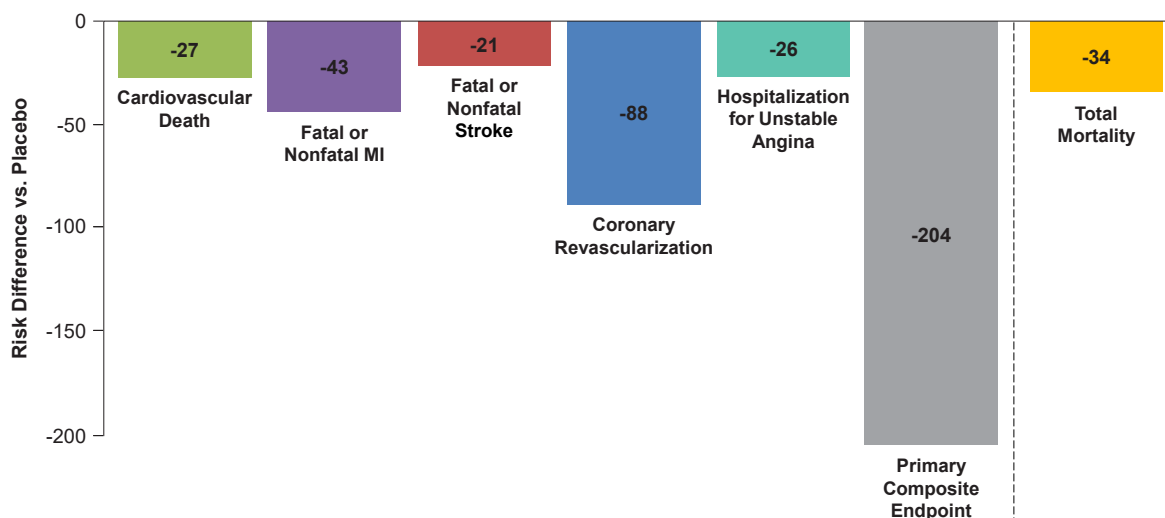
	Icosapent Ethyl (N=1548)	Placebo (N=1598)	P-value
Subjects with at Least One TEAE, n (%)	1354 (87.5)	1387 (86.8)	0.59
Severe TEAE	436 (28.2)	458 (28.7)	0.78
Drug-Related TEAE	188 (12.1)	183 (11.5)	0.58
Serious TEAE	533 (34.4)	571 (35.7)	0.46
Drug-Related Serious TEAE	5 (0.3)	2 (0.1)	0.28
TEAE Leading to Withdrawal of Study Drug	145 (9.4)	170 (10.6)	0.26
Drug-Related TEAE Leading to Withdrawal of Study Drug	56 (3.6)	75 (4.7)	0.15
Serious TEAE Leading to Withdrawal of Study Drug	31 (2.0)	48 (3.0)	0.09
Serious TEAE Leading to Death	36 (2.3)	53 (3.3)	0.11
Drug-Related Serious TEAE Leading to Withdrawal of Study Drug	1 (0.1)	2 (0.1)	>0.99

- Tolerability and safety findings were consistent with the full study population
- The tolerability and safety virtually identical to placebo; no significant differences in the overall rates of TEAEs or serious TEAEs
- A significant increase in minor bleeding (16.7% vs 13.6%, $p=0.02$), but no significant excess in serious adverse events related to bleeding
- There was a significant increase in the overall TEAE rate of atrial fibrillation or flutter (6.6% vs 4.5%, $p=0.012$), but not in either the category of serious adverse events of atrial fibrillation or flutter, or the adjudicated endpoint of hospitalization ≥ 24 hours for atrial fibrillation or flutter

Bhatt DL, Miller M, Brinton EA, et al. *Circulation*. 2019. Bhatt DL. AHA 2019, Philadelphia.

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For Every 1000 Patients in the USA Treated with Icosapent Ethyl 4g/day for 5 Years



Bhatt DL, Miller M, Brinton EA, et al. *Circulation*. 2019. Bhatt DL. AHA 2019, Philadelphia.

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Conclusions: USA Subgroup



- Compared with placebo, in the USA patients, icosapent ethyl 4 grams per day resulted in statistically significant:
 - **31%** reductions in the primary and key secondary endpoints
 - **28% to 47%** reductions in all prespecified hierarchical testing endpoints
 - **36%** reduction in total events, including a **37%** reduction in second events, a **37%** reduction in third events, and a **44%** reduction in 4th or more events
 - **30%** relative risk reduction and **2.6%** absolute risk reduction in all-cause mortality

Bhatt DL, Miller M, Brinton EA, et al. *Circulation*. 2019. Bhatt DL. AHA 2019, Philadelphia.

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We thank the investigators, the study coordinators, and the 3,146 USA patients who participated in **REDUCE-IT!**



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Circulation

CIRCULATION. 2019; [PUBLISHED ONLINE AHEAD OF PRINT]. DOI: 10.1161/CIRCULATIONAHA.119.044440.

REDUCE-IT USA: RESULTS FROM THE 3,146 PATIENTS RANDOMIZED IN THE UNITED STATES

DEEPAK L. BHATT, MD, MPH, FAHA; MICHAEL MILLER, MD; ELIOT A. BRINTON, MD; TERRY A. JACOBSON, MD; PH. GABRIEL STEG, 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; BRIAN OLSHANSKY, MD; MINA K. CHUNG, MD; C. MICHAEL GIBSON, MS, MD; ROBERT P. GIUGLIANO, MD, SM; MATTHEW J. BUDOFF, MD; CHRISTIE M. BALLANTYNE, MD; ON BEHALF OF THE REDUCE-IT INVESTIGATORS*

CIRCULATION

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Results: Costs, QALYs, and ICERs



Analysis	Average Total Cost, 2018 USD			Average QALY Gained			ICER, 2018 USD*
	Icosapent Ethyl	Standard Care	Difference	Icosapent Ethyl	Standard Care	Difference	
In-Trial							
Base Case	\$23,926	\$24,563	-\$637	3.34	3.27	0.07	Dominant
Sensitivity							
0% discount	\$27,576	\$28,205	-\$629	3.90	3.82	0.08	Dominant
5% discount	\$21,837	\$22,474	-\$637	3.02	2.96	0.06	Dominant
WAC costing	\$29,684	\$24,563	+\$5121	3.34	3.27	0.07	\$75,512
Optum costs all patients	\$23,926	\$35,690	-\$11,764	3.34	3.27	0.07	Dominant
Lifetime							
Base Case	\$87,077	\$88,912	-\$1835	11.61	11.35	0.26	Dominant
Scenarios							
Best Case	\$85,493	\$88,912	-\$3419	11.73	11.35	0.38	Dominant
Worst Case	\$87,672	\$88,912	-\$1240	11.57	11.35	0.22	Dominant
Probabilistic Sensitivity	\$102,789	\$104,804	-\$2015	12.22	11.97	0.25	Dominant

Weintraub WS. AHA 2019, Philadelphia.

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FDA – November 14, 2019

- Endocrinologic and Metabolic Drugs Advisory Committee
- 16-0 Vote to Approve Label Expansion

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Yes	16			11/14/201
No	0			4:06:35 PM
Abstain	0			
NO-VOTE	0			
Yes	Vote: 16			
Anna McCollister-Slipp ...	Cecilia Low Wang, MD	Connie Newman, MD	Elizabeth Chrischilles, ...	
Erica Brittain, PhD	Jack Yanovski, MD, PhD	James de Lemos, MD	Kenneth Burman, MD ...	
Martha Nason, PhD	Marvin Konstam, MD	Peter Wilson, MD	Philip Posner, PhD (PR)	
Susan Ellenberg, PhD	Thomas Ortel, MD, PhD	Thomas Weber, MD	Walter Kraft, MD	
No	Vote: 0			
Abstain	Vote: 0			
No-Voting	Total: 0			

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