VASCEPA COVID-19 CardioLink-9: First Human Trial of a Loading Dose of Icosapent Ethyl in Patients with COVID-19

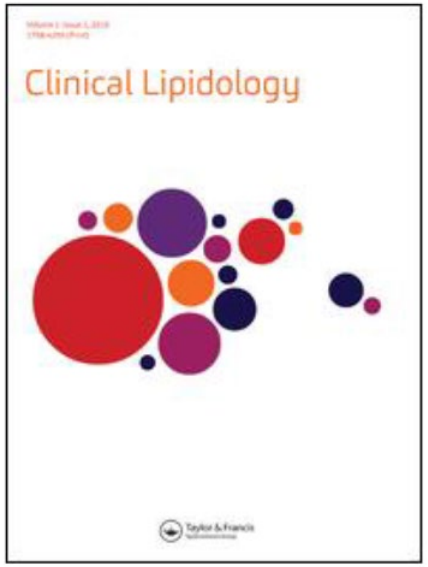
Andrew Kosmopoulos, BHSc, **Subodh Verma, MD, PhD**, Gus Meglis, MD, Raj Verma, Adrian Quan, MPhil, Hwee Teoh, PhD, Maya Verma, Lixia Jiao, PhD, Robert Wang, PhD, Rebecca A. Juliano, PhD, Mahesh Kajil, MD, Mikhail N. Kosiborod, MD, Basel Bari, MD, Abdullahi A. Berih, MD, Mallory Aguilar, RN, Antonnette Escano, Andrew Leung, Idelta Coelho, Rafael Díaz, MD, R. Preston Mason, PhD, Ph. Gabriel Steg, MD, Tabassome Simon, MD, PhD, Alan S. Go, MD, Andrew P. Ambrosy, MD, Richard Choi, MD, Arthur M. Kushner, MD, Lawrence A. Leiter, MD, C. David Mazer, MD, **Deepak L. Bhatt, MD, MPH,** on behalf of the **COVID-19 CardioLink-9** Investigators

Disclosures

Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, Cereno Scientific, Elsevier Practice Update Cardiology, LevelEx, Medscape Cardiology, PhaseBio, PLx Pharma, 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; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), 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), MJH Life Sciences, 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, Cardax, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Idorsia, Ironwood, Ischemix, Lexicon, Lilly, Medtronic, Pfizer, PhaseBio, PLx Pharma, 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, Takeda.

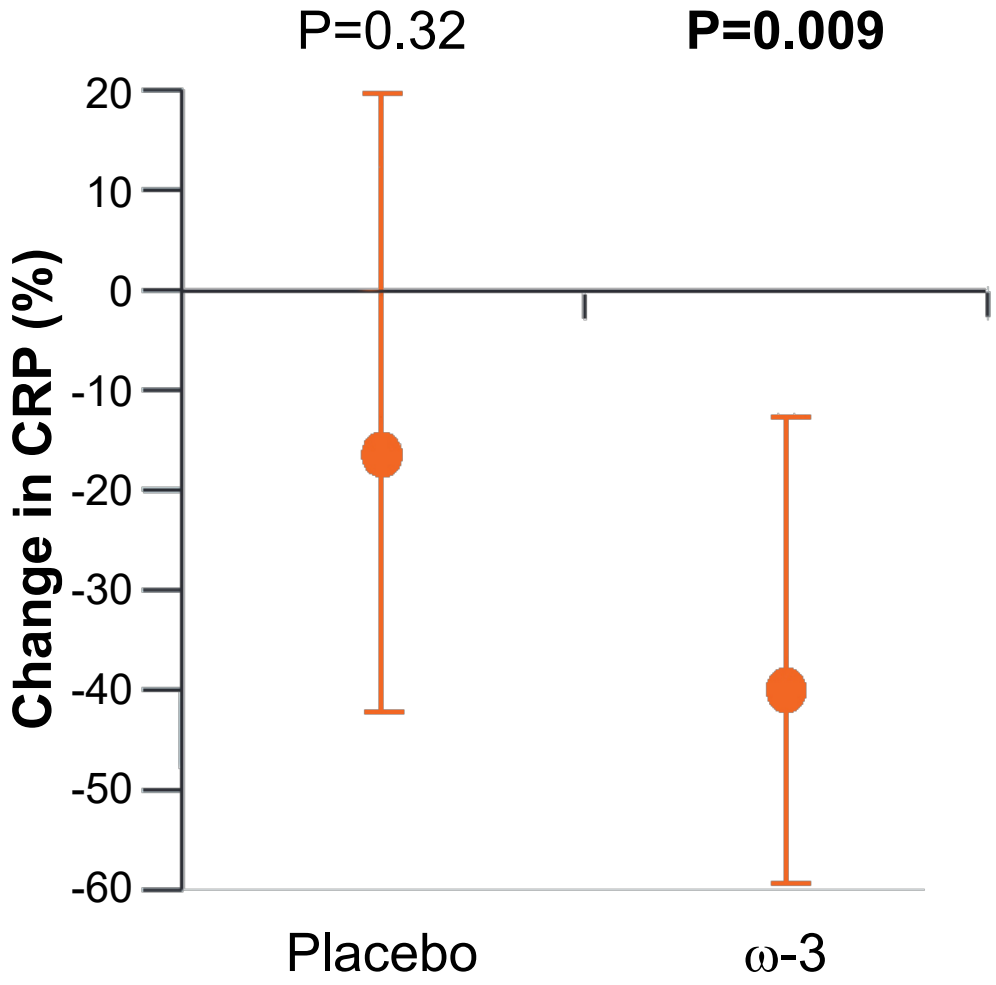
This presentation includes off-label and/or investigational uses of drugs. COVID-19 CardioLink-9 was sponsored by Amarin Pharma, Inc. and HLS Therapeutics, Inc.

Omega-3 Fatty Acids and Inflammation



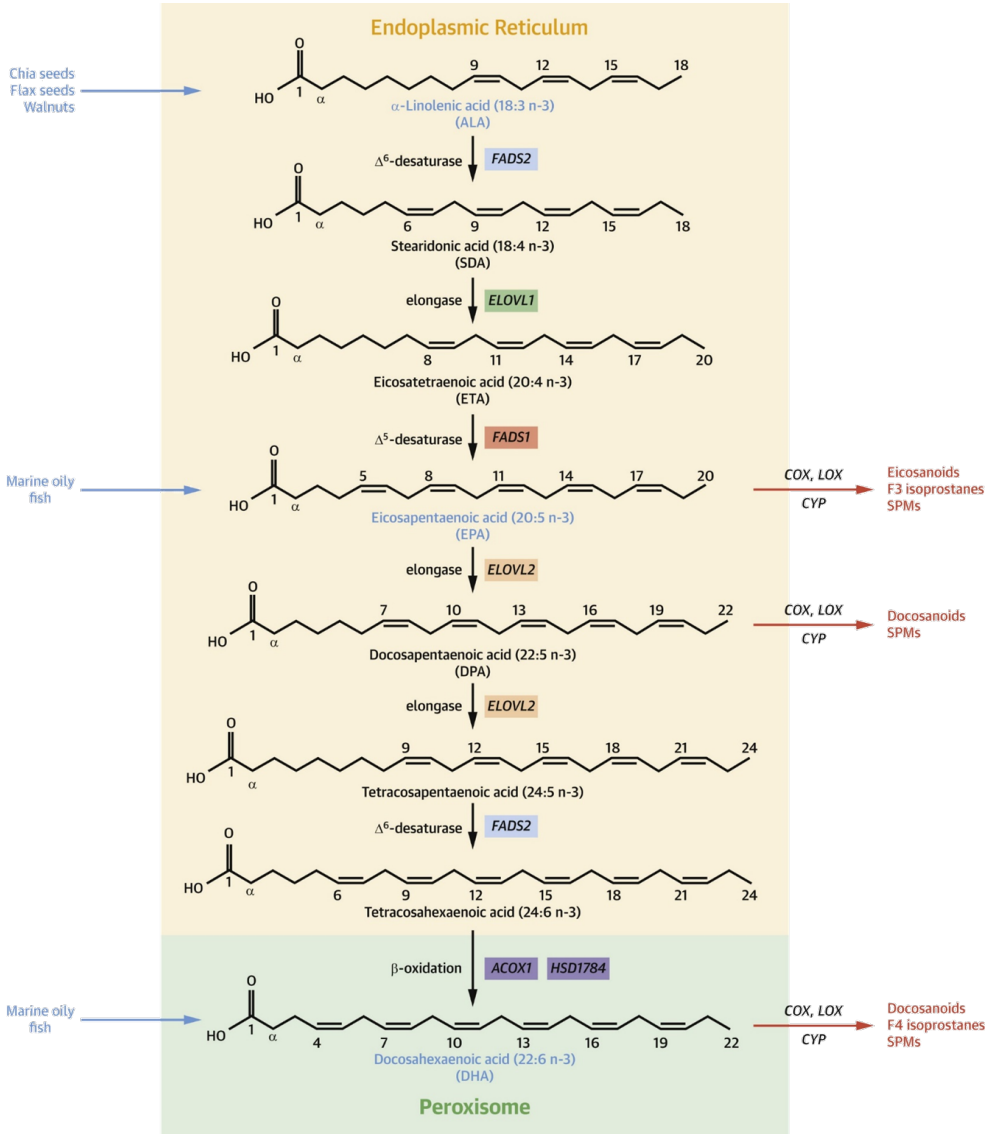
Treatment with w-3 fatty acids reduces serum C-reactive protein concentration

Kamran I. Muhammad, Thomas Morledge, Ravish Sachar, Annette Zeldin, Kathy Wolski & Deepak L. Bhatt



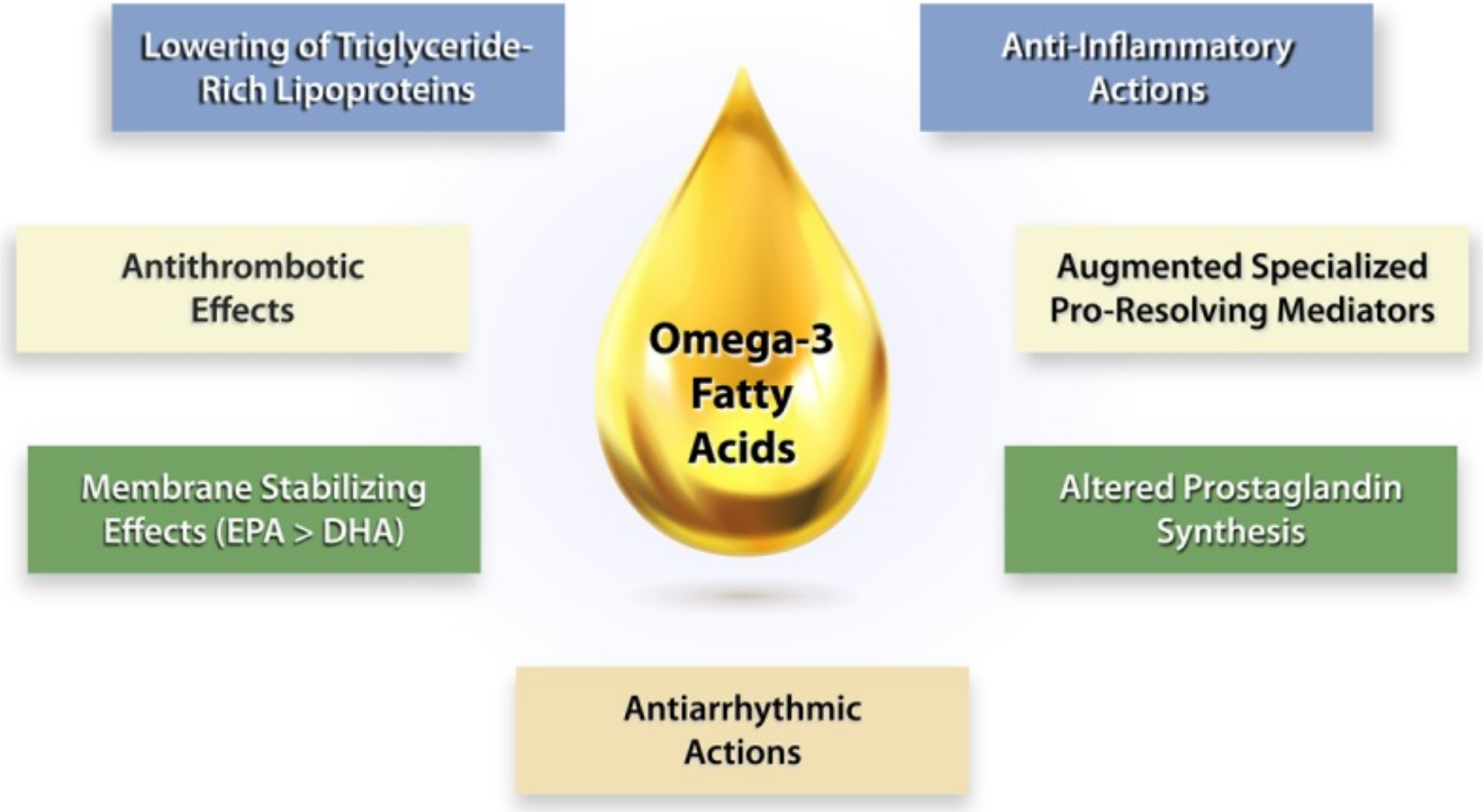
Muhammad KI, Morledge T, Sachar R, Zeldin A, Wolski K, Bhatt DL. *Clin Lipidol.* 2011; 6:723-729.

A Revolution in Omega-3 Fatty Acid Research



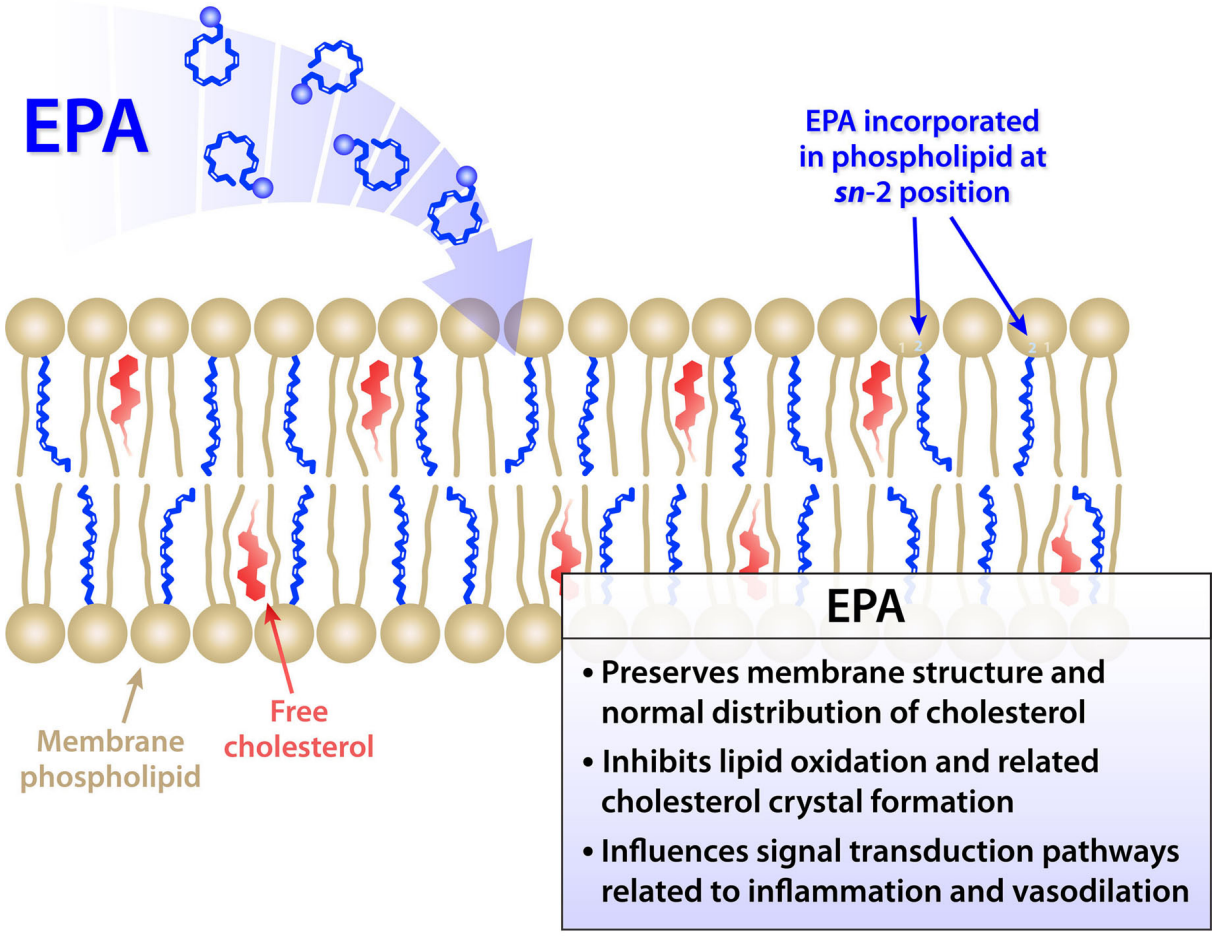
Bhatt DL, Budoff MJ, Mason RP. *J Am Coll Cardiol.* 2020;76:2098-2101.

Potential Mechanisms of Cardioprotection for Omega-3 Fatty Acids



Mason RP, Libby P, Bhatt DL. *Arterioscler Thromb Vasc Biol.* 2020;40:1135-1147.

Contrasting Effects of EPA and DHA



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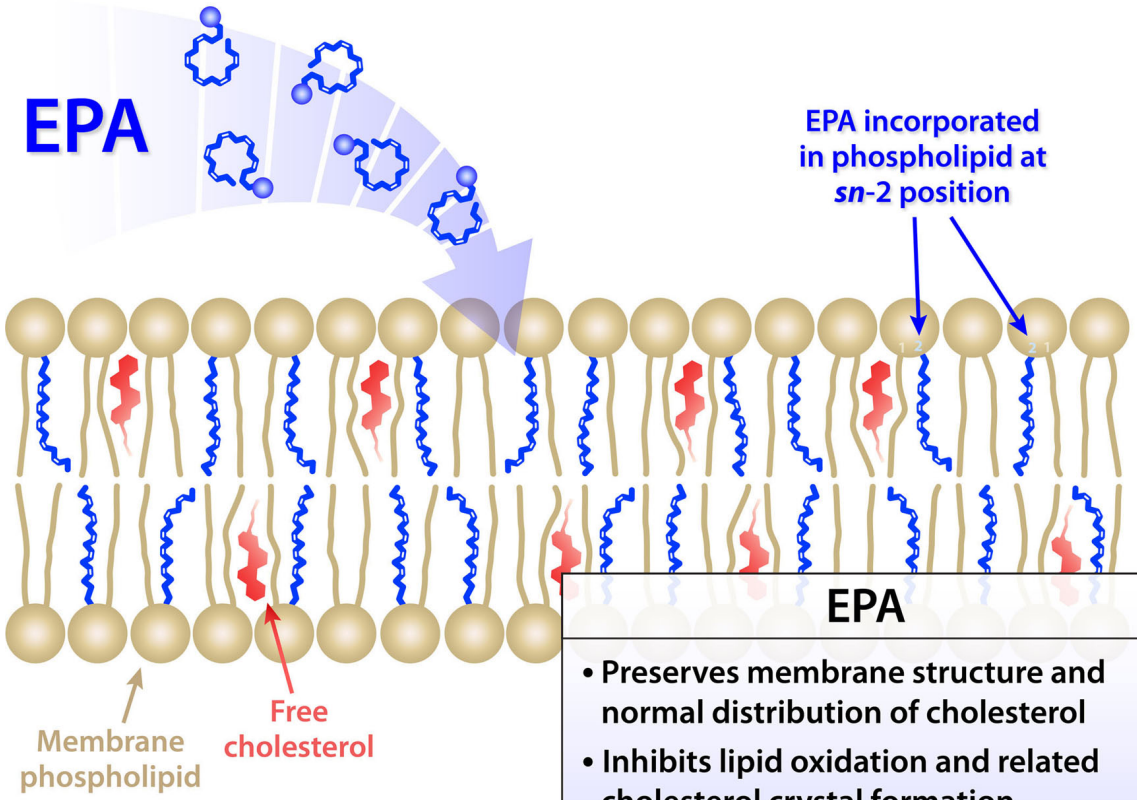
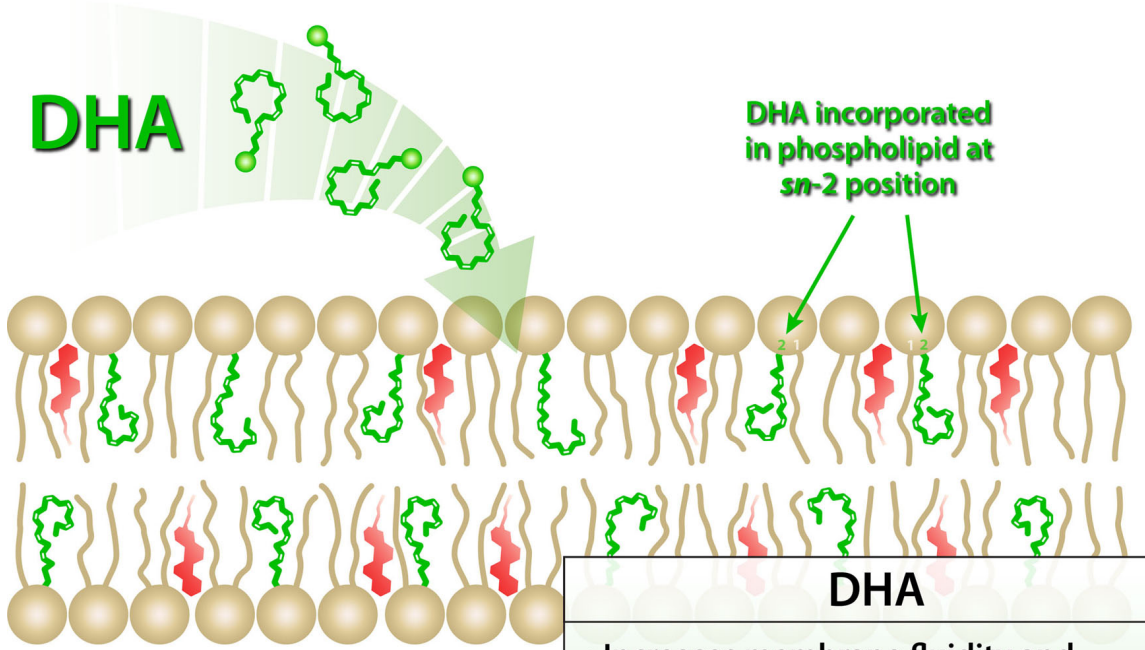
Contrasting Effects of EPA and DHA



EPA

- Preserves membrane structure and normal distribution of cholesterol
- Inhibits lipid oxidation and related cholesterol crystal formation
- Influences signal transduction pathways related to inflammation and vasodilation



DHA

- Increases membrane fluidity and promotes lipid domain changes
- Has reduced antioxidant activity due to lipid disordering effects
- Is concentrated in brain and retinal membranes

Mason RP, Libby P, Bhatt DL. *Arterioscler Thromb Vasc Biol.* 2020;40:1135-1147.

Potential Benefits of EPA

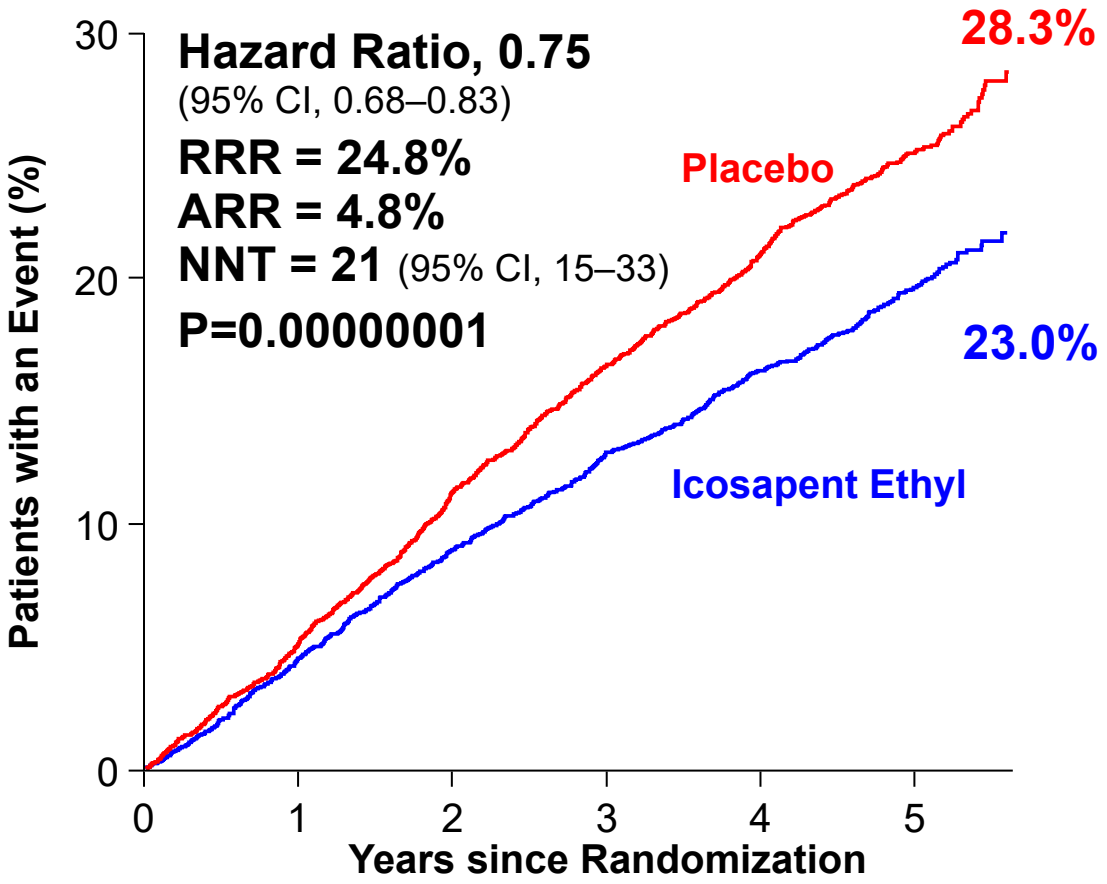
	Endothelial Dysfunction/ Oxidative Stress	Inflammation/ Plaque Growth	Unstable Plaque
Increase	Endothelial function Nitric oxide bioavailablity	EPA/AA ratio IL-10	Fibrous cap thickness Lumen diameter Plaque stability
Decrease	Cholesterol crystalline domains Ox-LDL RLP-C Adhesion of monocytes Macrophages Foam cells	IL-6 ICAM-1 hsCRP Lp-PLA_2 MMPs	Plaque volume Arterial stiffness Plaque vulnerability Thrombosis Platelet activation

Ganda OP, Bhatt DL, Mason RP, Miller M, Boden WE. *J Am Coll Cardiol.* 2018;72:330-343.

Primary and Key Secondary Composite Endpoints

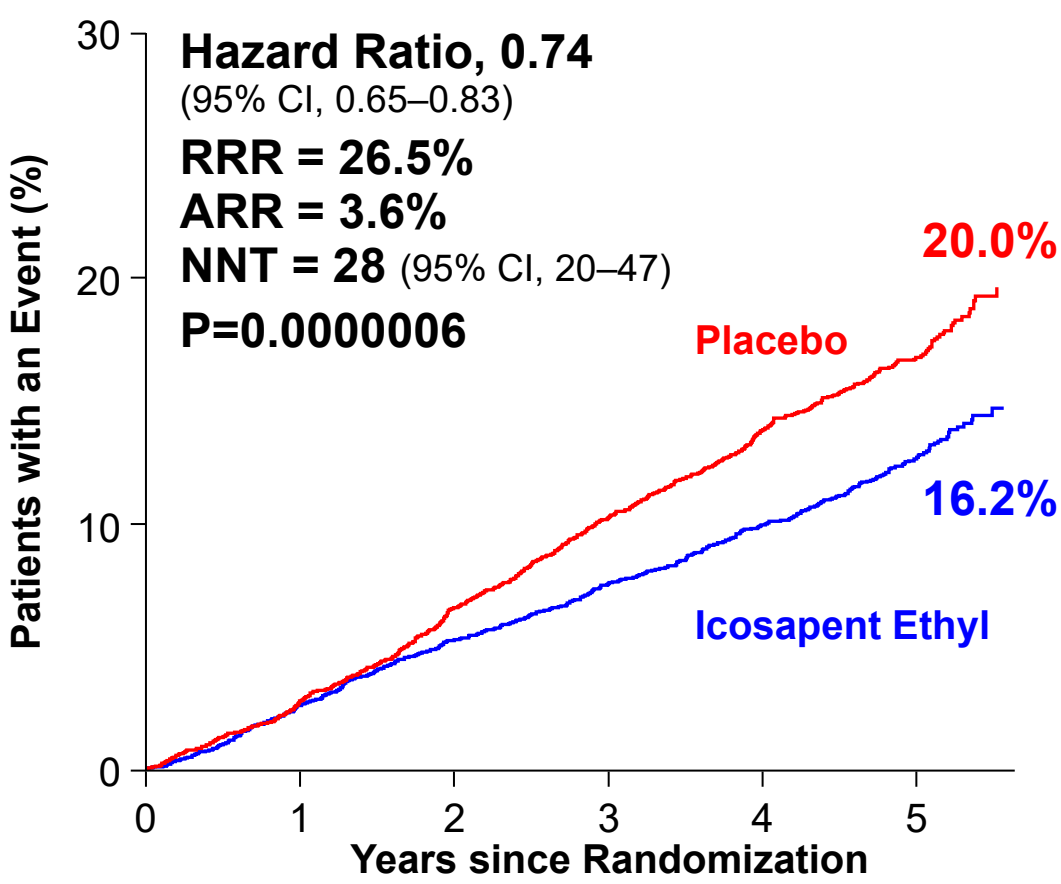
Primary Composite Endpoint:

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



Key Secondary Composite Endpoint:

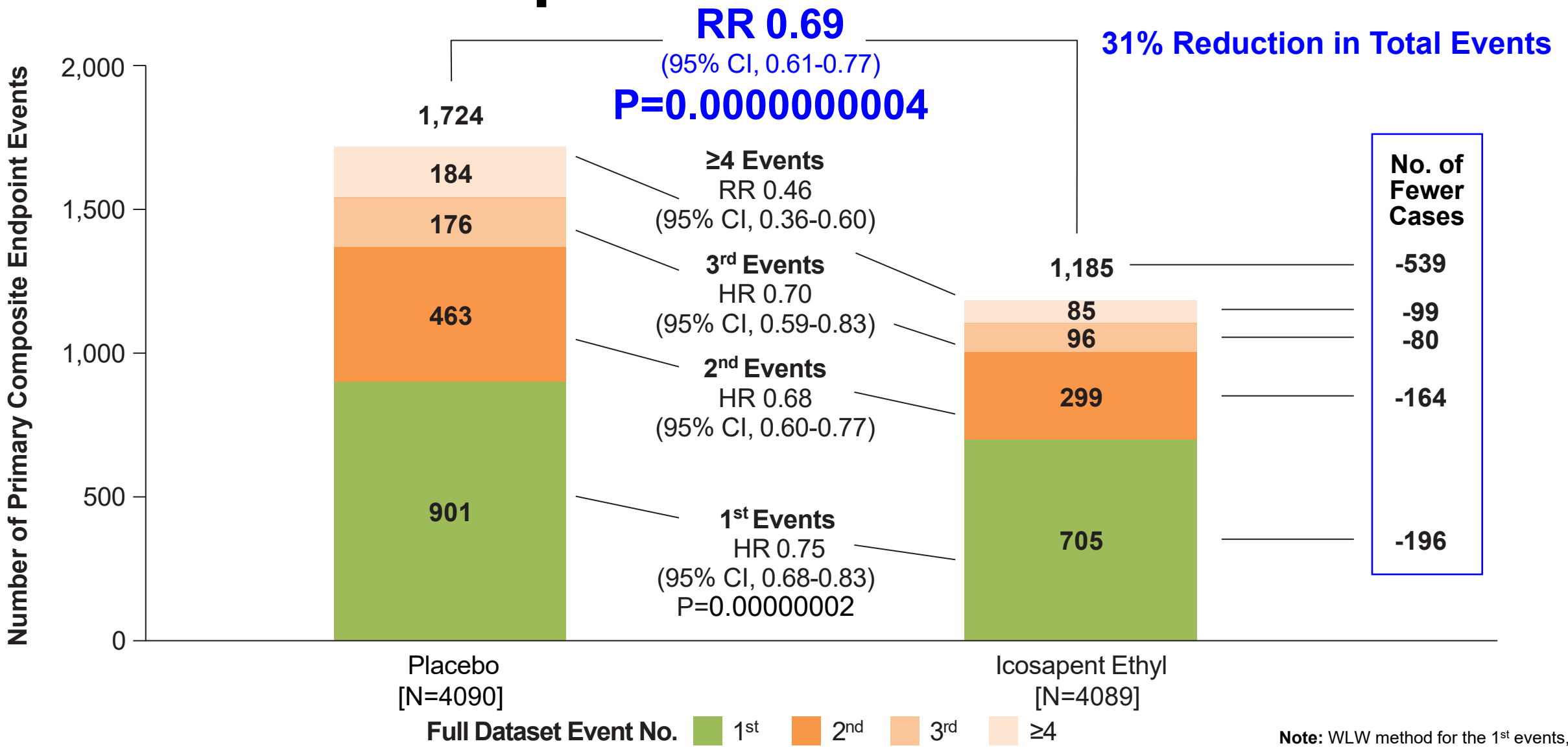
CV Death, MI, Stroke



Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019; 380:11-22. Bhatt DL. AHA 2018, Chicago, IL.

First and Subsequent Events – Full Data

reduce-it TOTAL EVENTS

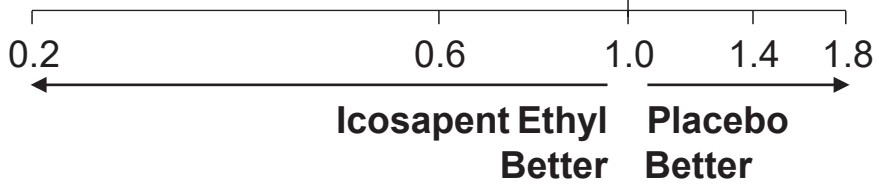


Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol.* 2019;73:2791-2802. Bhatt DL. ACC 2019, New Orleans, LA.

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

Primary Composite Endpoint: Total Events by Baseline TG Tertiles

TOTAL EVENTS – Primary Composite Endpoint/Subgroup	Icosapent Ethyl	Placebo	RR (95% CI)	P-value
	Rate per 1000 Patient Years	Rate per 1000 Patient Years		
Primary Composite Endpoint (ITT)	61.1	88.8	0.70 (0.62–0.78)	<0.0001
Baseline Triglycerides by Tertiles*				
≥0.9 to ≤2.1 mmol/L	56.4	74.5	0.74 (0.61–0.90)	0.0025
>2.1 to ≤2.8 mmol/L	63.2	86.8	0.77 (0.63–0.95)	0.0120
>2.8 to ≤15.8 mmol/L	64.4	107.4	0.60 (0.50–0.73)	<0.0001



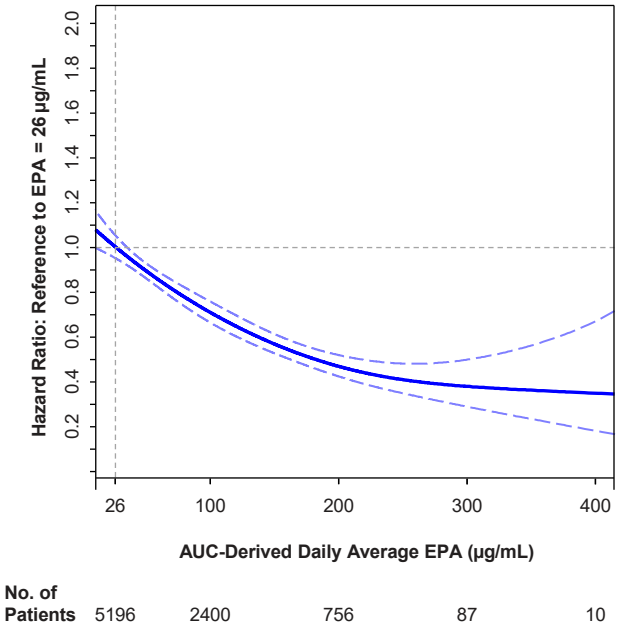
***P (interaction) = 0.17**

Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol.* 2019;74:1159-61.

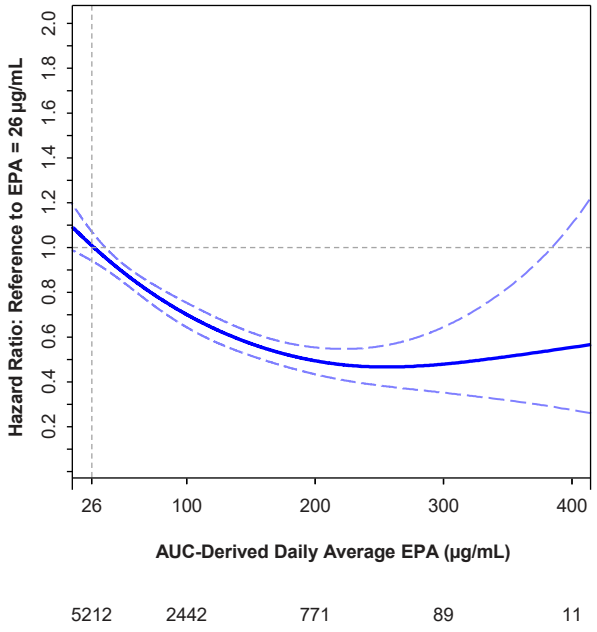
Primary and Key Secondary Composite Endpoints, Cardiovascular Death, and Total Mortality by On-Treatment Serum EPA

reduce-it EPA

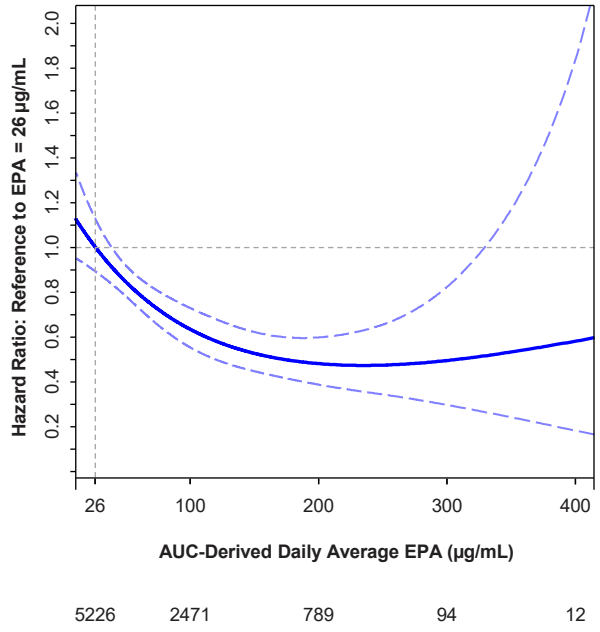
Primary Endpoint[1-5]



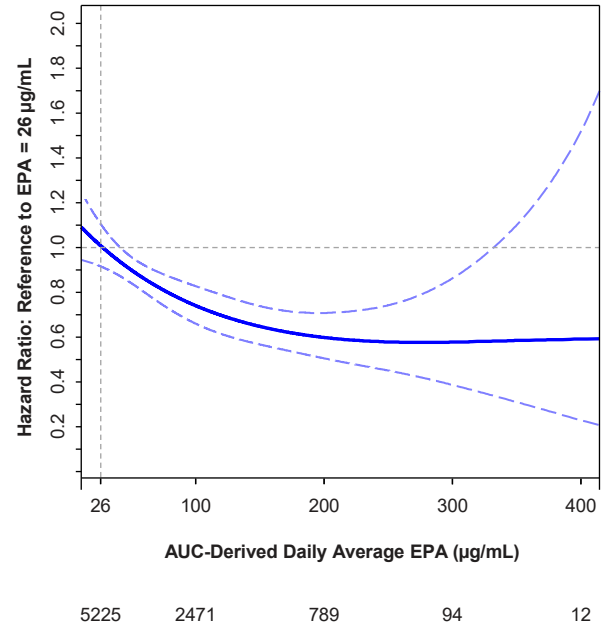
Key Secondary Endpoint[1-5]



Cardiovascular Death[1,2,4-6]



Total Mortality[1,2,4-6]



No. of Patients															
	5196	2400	756	87	10	5212	2442	771	89	11	5226	2471	789	94	12	5225	2471	789	94	12

Dose-response hazard ratio — 95% Confidence Interval (CI) - - -

P*<0.001 for all

Note: Area under the curve (AUC)-derived daily average serum EPA (µg/mL) is the daily average of all available post baseline EPA measurements prior to the event. Dose-response hazard ratio (solid line) and 95% CI (dotted lines) are estimated from the Cox proportional hazard model with a spline term for EPA and adjustment for randomization factors and statin compliance[1], age[2], sex[3], baseline diabetes[4], hsCRP[5], treatment compliance[6].

***P value is <0.001 for both non-linear trend and for regression slope.**

Bhatt DL. ACC/WCC 2020, Chicago (virtual).

Treatment-Emergent Adverse Events

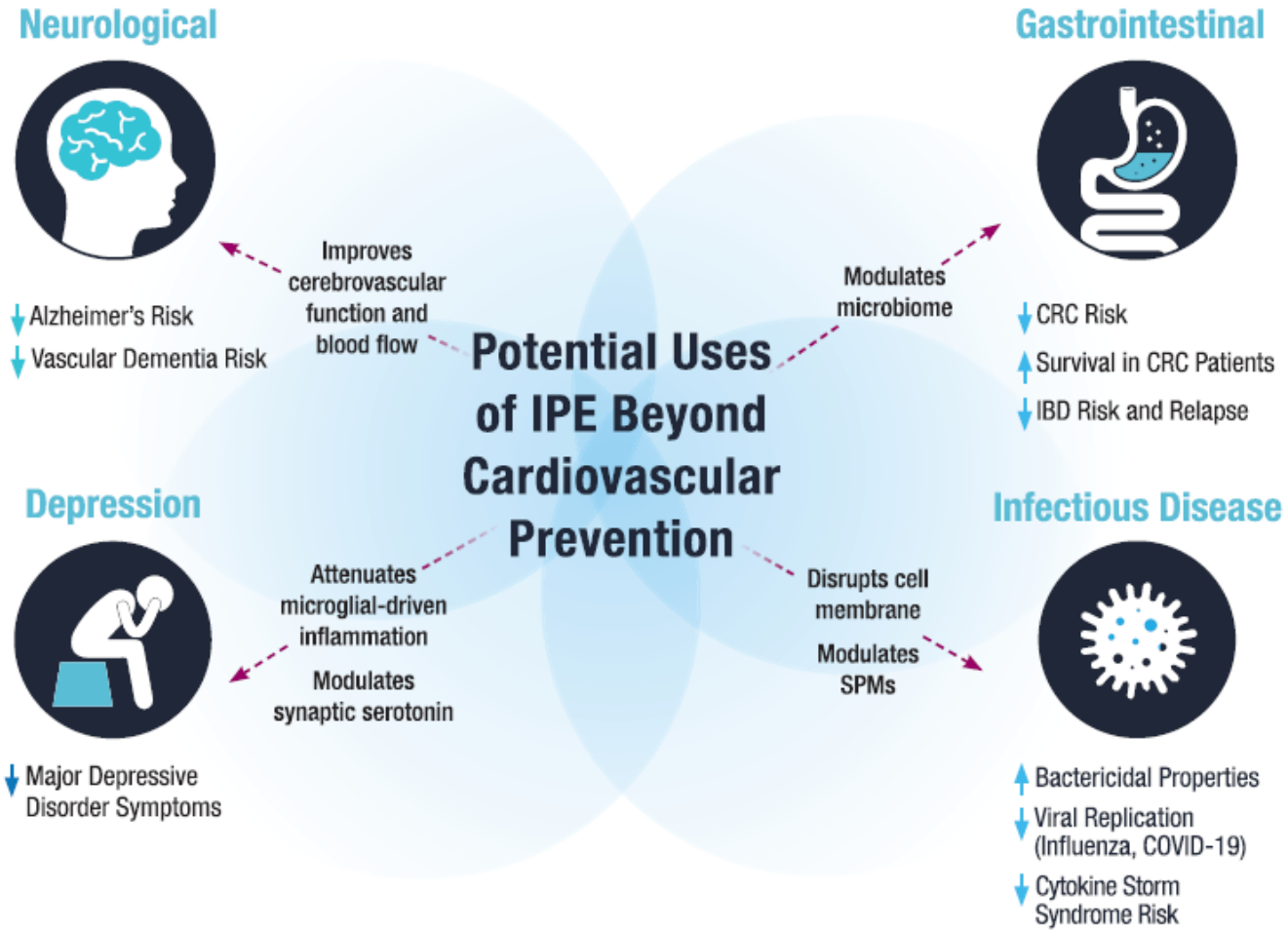
No Overall Treatment Difference in Adverse Event Profiles

	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%)	>0.99
Serious TEAE Leading to Death	94 (2.3%)	102 (2.5%)	0.61

TEAE event rates represent the enrolled high CV risk patients and the 4.9-year median study follow-up.
* From Fisher's exact test.

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

Potential Future Uses of Icosapent Ethyl Beyond CV Prevention

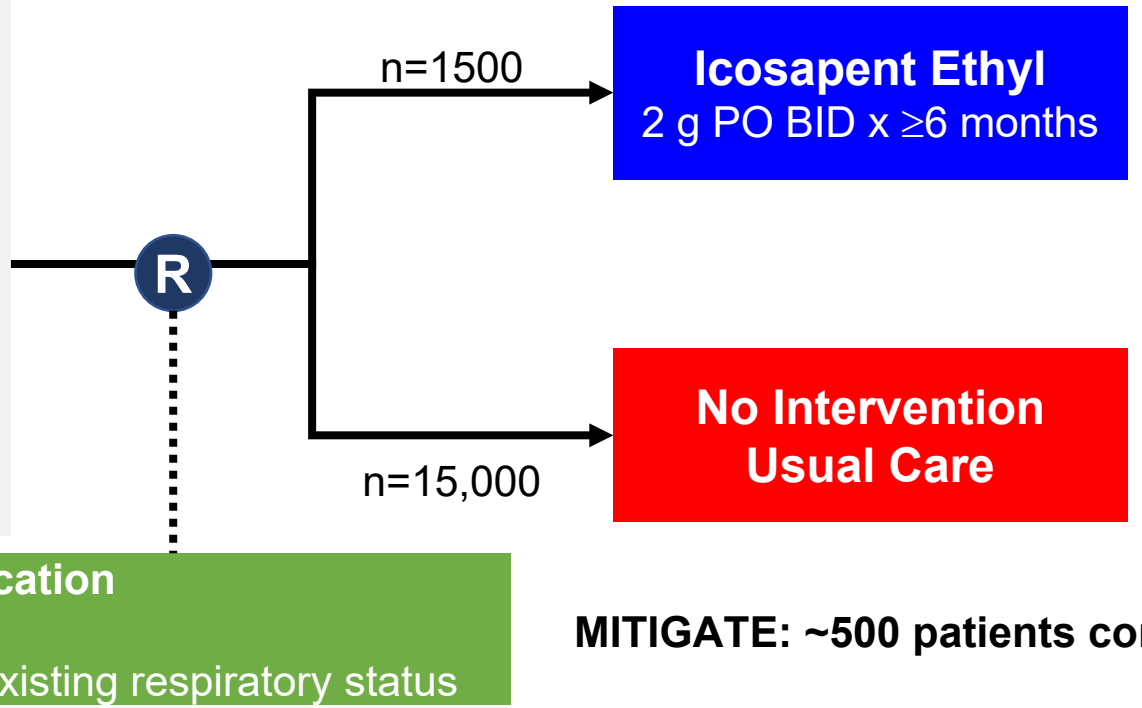


Bhatt DL, Hull MA, Song M, Van Hulle C, Carlsson C, Chapman MJ, Toth PP. *Eur Heart J.* 2020:22 (Supplement J);J54–J64.

Ongoing SARS-CoV-2/COVID-19 Trials With IPE

MITIGATE:
A Pragmatic Randomized Trial of Icosapent Ethyl for High-Cardiovascular Risk Adults (Open-Label)

Inclusion Criteria
- ≥50 years of age
- No prior history of COVID-19
- Established ASCVD (prior MI, PCI, CABG, ischemic stroke, and/or PAD)



Primary Endpoints
- Rate of patients with moderate or severe confirmed viral URI at minimum follow-up of 6 months
- Worst clinical status due to a confirmed viral URI over a minimum follow-up of 6 months

MITIGATE: ~500 patients consented to IPE arm as of 12/12/2020

ASCVD, atherosclerotic cardiovascular disease; BID, twice daily; CABG, coronary artery bypass graft; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PO, per os; URI, upper respiratory tract infection.
https://clinicaltrials.gov/ct2/show/NCT04505098.

SARS-CoV-2/COVID-19 Trials With IPE

PREPARE-IT 1

Prevention of COVID-19 With EPA in Healthcare Providers at Risk - Intervention Trial (Double-Blind)

Inclusion Criteria

- Doctors, nurses, ancillary/ cleaning staff working in ICU or EDs that care for COVID-19 patients
- Personnel performing aerosol-generating procedures on COVID-19 patients
- Relatives of confirmed COVID-19 patients who have been in contact
- Laboratory staff currently running COVID-19 tests
- General population at risk

Primary Endpoints

- Percentage of patients positive for SARS-CoV-2 up to day 60
- Highest mean WHO descriptive score of COVID-19 in the icosapent ethyl group vs placebo group up to day 60

PREPARE-IT 1 - 1430 Patients Randomized as of 12/12/2020
PREPARE-IT 2 - 9 Patients Randomized as of 12/12/2020

BID, twice daily; ED, emergency department; ICU, intensive care unit; IPE, icosapent ethyl; WHO, World Health Organization.
https://clinicaltrials.gov/ct2/show/NCT04460651.

Novel Anti-inflammatory Effects of EPA in Human Pulmonary and Vascular Endothelium in Vitro

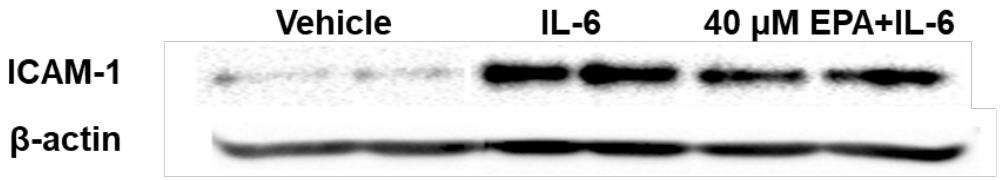
1. EPA Reduces Expression of Pulmonary ACE and ICAM-1 During Inflammation with IL-6[1]

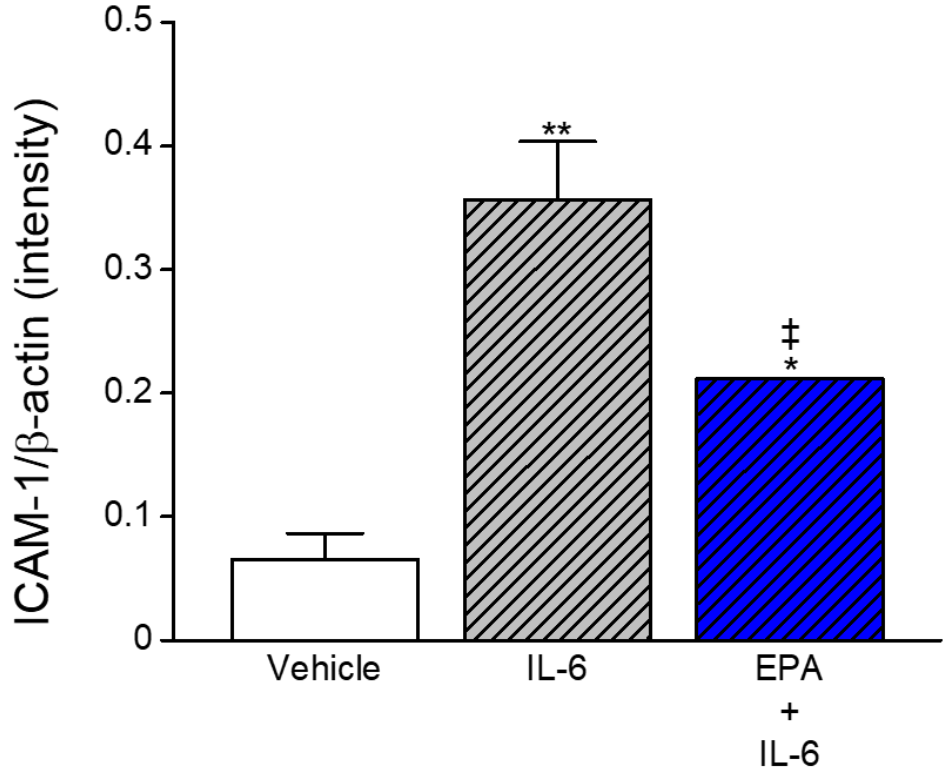
2. EPA Preserves Vascular Endothelial Function Following IL-6 Exposure as Compared to DHA and AA[2]

[1]Presented at NLA 2020 (*Abstract #: 245*). Sherratt SCR, Dawoud H, Malinski T, Libby P, Bhatt DL, Mason RP.
[2]Presented at NLA 2020 (*Abstract #: 244*). Mason RP, Dawoud H, Sherratt SCR, Libby P, Bhatt DL, Malinski T.

EPA Reduces Expression of Pulmonary ACE and ICAM-1 During Inflammation Induced by IL-6

Protein	Up/Down Regulated	Fold Change	*p* value
ACE	DOWN	2.96	0.010

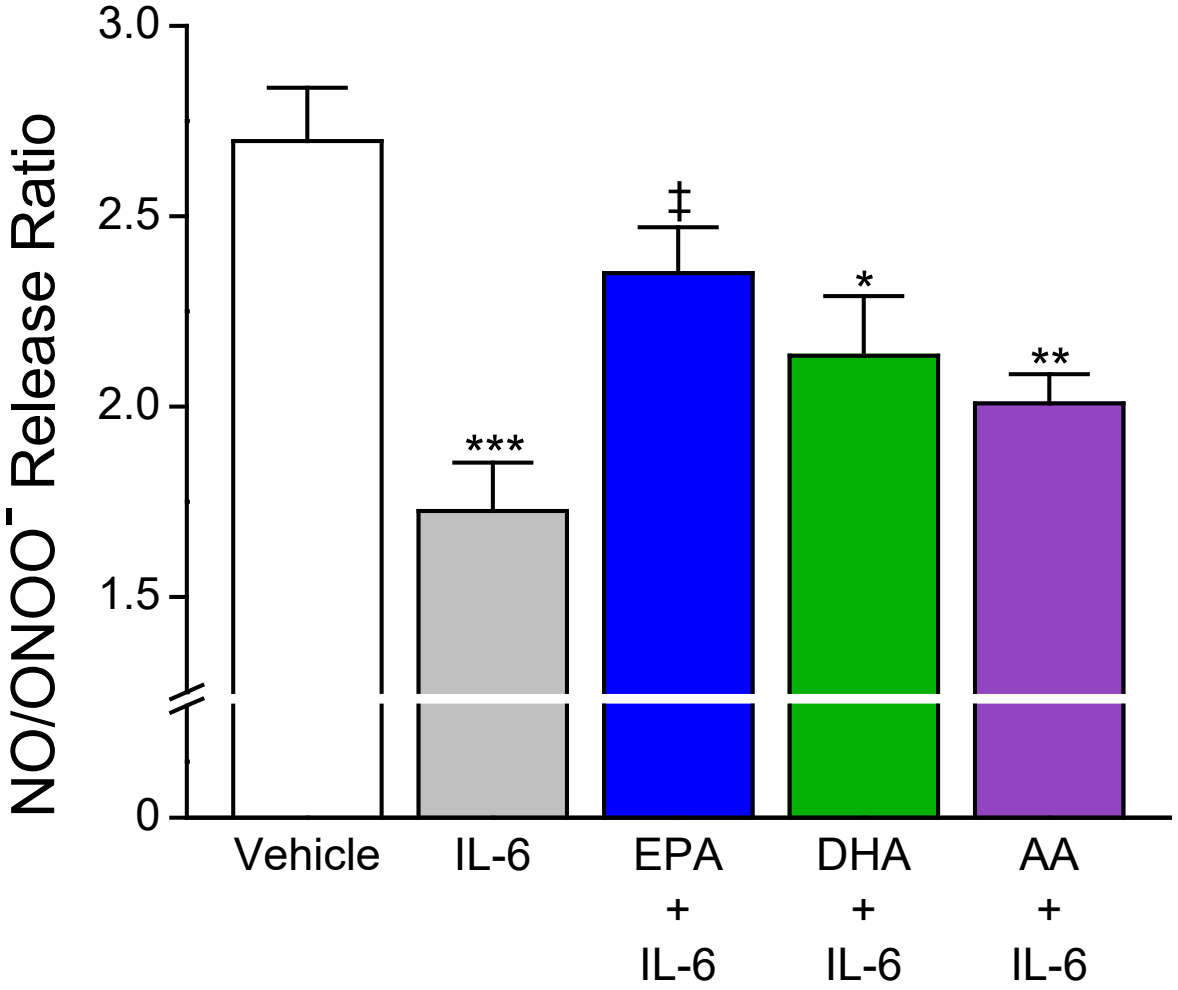




Statistical indicators: **p<0.01 versus vehicle; *p<0.05 versus vehicle; ‡p<0.05 versus IL-6 alone
(Student-Newman-Keuls Multiple Comparisons Test; overall ANOVA: p = 0.0052, F = 48.203). Values are mean ± SD (N = 2).

Presented at NLA 2020 (*Abstract #: 245*). Sherratt SCR, Dawoud H, Malinski T, Libby P, Bhatt DL, Mason RP.

EPA Preserves Vascular Endothelial Function Following IL-6 Exposure Compared with DHA and AA



Statistical indicators: ***p<0.001 versus vehicle; **p<0.01 versus vehicle; *p<0.05 versus vehicle; ‡p<0.05 versus IL-6 alone (Student-Newman-Keuls Multiple Comparisons Test; overall ANOVA: p = 0.0007, F = 8.488). Values are mean ± SEM (N = 4-5).

Presented at NLA 2020 (*Abstract #: 244*). Mason RP, Dawoud H, Sherratt SCR, Libby P, Bhatt DL, Malinski T.

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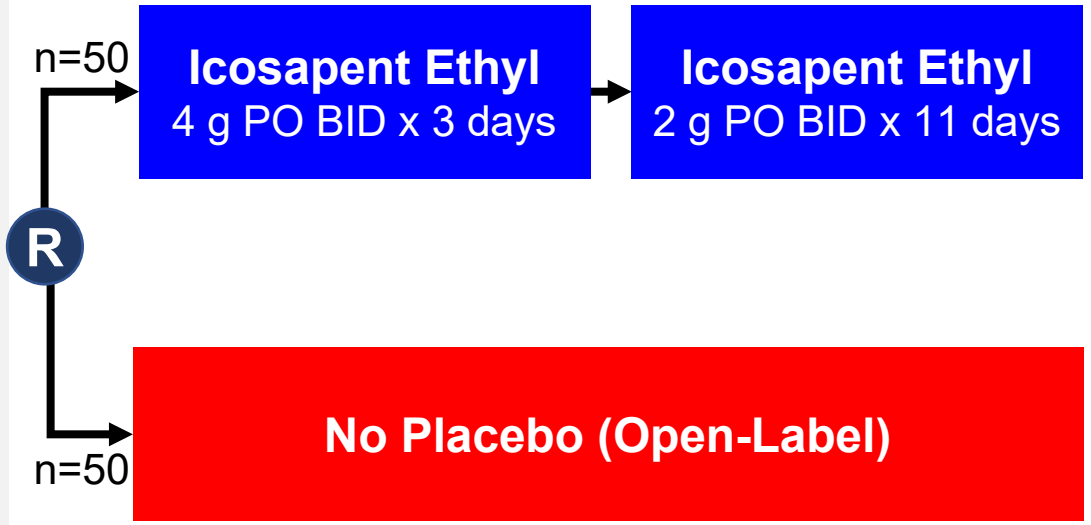
An Investigation on the Effects of Icosapent Ethyl on Inflammatory Biomarkers in Individuals With COVID-19

Jun 04, 2020

Nov 06, 2020

Inclusion Criteria

- Positive local SARS-CoV-2 test result within the preceding 72 hours
- ≥1 of the following:
  - Fever
  - Cough
  - Sore throat
  - Shortness of breath
  - Myalgia



Biomarker Endpoint

Change in hs-CRP levels from randomization to day 14 in the icosapent ethyl arm

Clinical Endpoint

Change in FLU-PRO score from randomization to day 14 in the icosapent ethyl arm

FLU-PRO, InFLUenza Patient-Reported Outcome; hs-CRP, high-sensitivity C-reactive protein.

https://clinicaltrials.gov/ct2/show/NCT04412018; https://www.vascepacovid19.com/#about.

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CONSORT Figure

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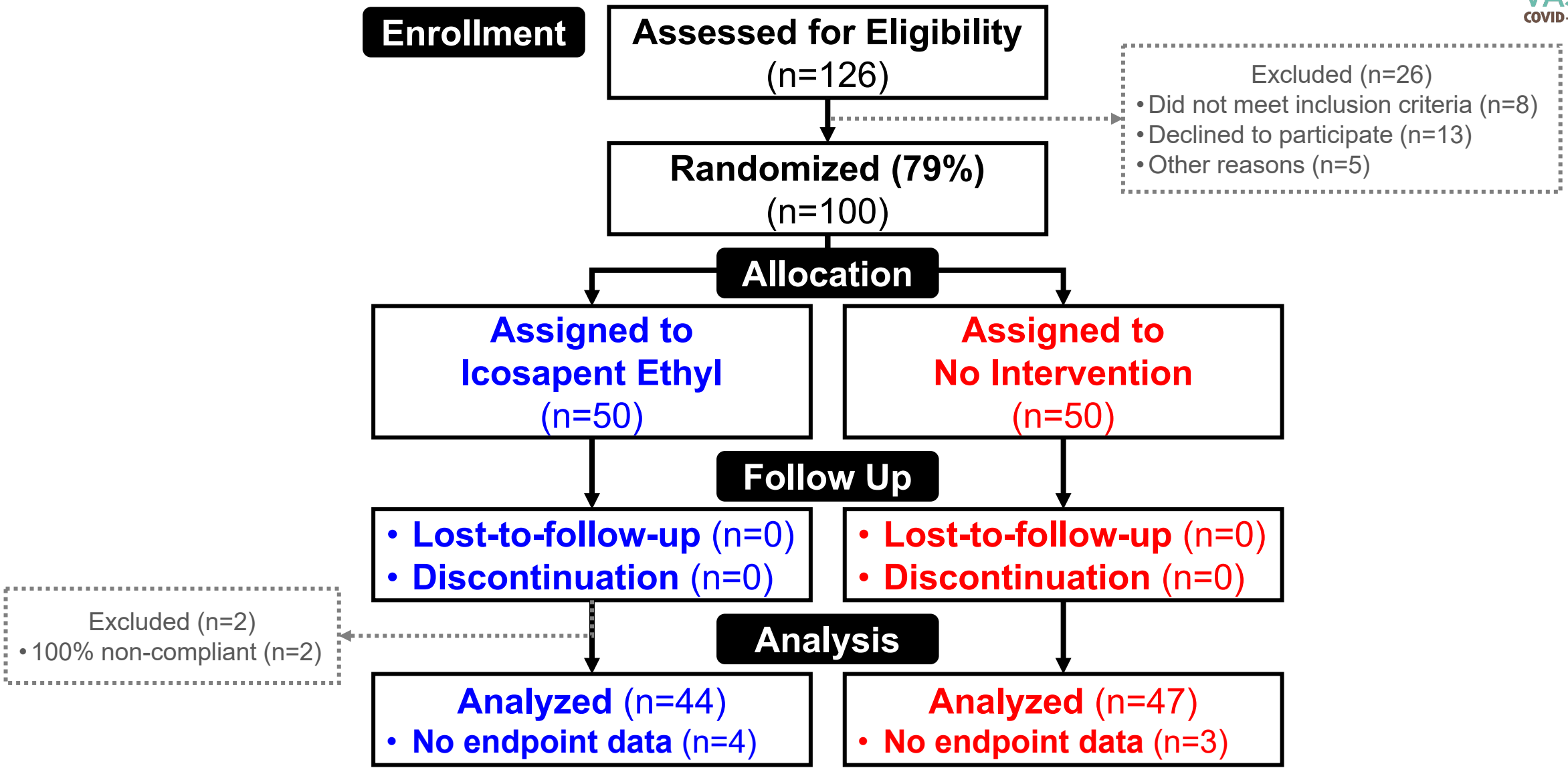

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Baseline Characteristics

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	Icosapent Ethyl (n=50)	Usual Care (n=50)
Age, years	46	40
Women	52%	58%
Median Body Mass Index, kg/m^2	25	24
Blood Pressure, mmHg	121/80	118/79
Total cholesterol, mg/dL	162	166
LDL-cholesterol, mg/dL	85	89
HDL-cholesterol, mg/dL	43	46
Triglycerides, mg/dL	133	124
Any Comorbidity	36%	42%

Data shown are for the intention-to-treat population. Continuous data are presented as median values.

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COVID-19 Symptoms Within 72 h Preceding the Baseline Visit

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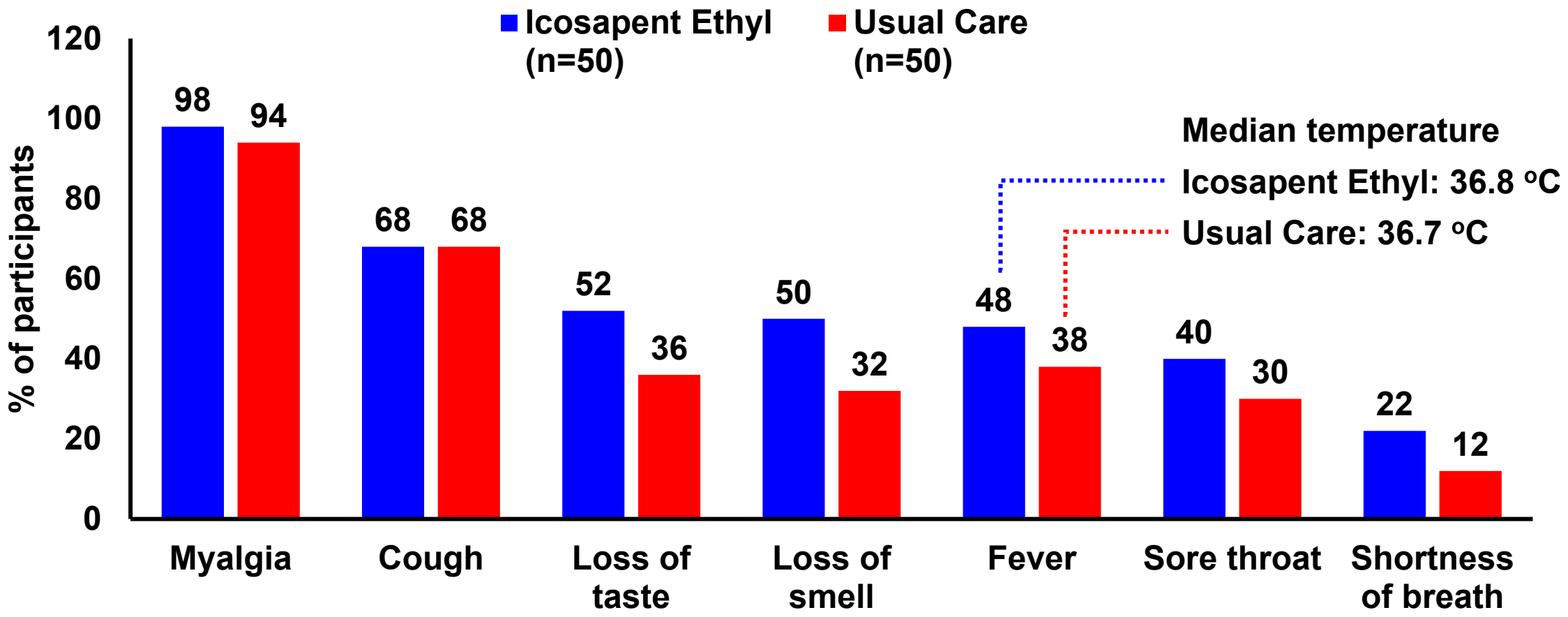

Data shown are for the intention-to-treat population.

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Inflammatory Biomarker Endpoint

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Inflammatory Biomarker Endpoint
Unadjusted hs-CRP Changes from Baseline to Day 14

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	Baseline (mg/L)	Day 14 (mg/L)	Median Percent Change from Baseline	Median Change from Baseline (mg/L)	P-value (within group)
Icosapent Ethyl (n=44)	3.2 (0.9, 11.6)	1.6 (0.6, 4.4)	-25.0 (-80.1, 26.7)	-0.5 (-6.9, 0.4)	0.011
Usual Care (n=47)	2.3 (0.7, 6.5)	2.1 (0.5, 5.8)	-5.6 (57.1, 84.2)	-0.1 (-3.2, 1.7)	0.51

P-value (between groups) 0.082

Data are presented as median (interquartile range).
hs-CRP, high-sensitivity C-reactive protein.
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Inflammatory Biomarker Endpoint
Unadjusted hs-CRP Changes from Baseline to Day 14

VASCEPA
COVID-19 CardioLink-9

	Baseline (mg/L)	Day 14 (mg/L)	Median Percent Change from Baseline	Median Change from Baseline (mg/L)	P-value (within group)
Icosapent Ethyl (n=44)	3.2 (0.9, 11.6)	1.6 (0.6, 4.4)	-25.0 (-80.1, 26.7)	-0.5 (-6.9, 0.4)	**0.011**
Usual Care (n=47)	2.3 (0.7, 6.5)	2.1 (0.5, 5.8)	-5.6 (57.1, 84.2)	-0.1 (-3.2, 1.7)	0.51

P-value (between groups) 0.082

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hs-CRP, high-sensitivity C-reactive protein.
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Inflammatory Biomarker Endpoint

Changes in hs-CRP from Baseline to Day 14

Adjusted by Sex, Age[a] and Baseline CV Risk[b]

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	Baseline (mg/L)	Day 14 (mg/L)	Median Percent Change from Baseline	Median Change from Baseline (mg/L)	P-value (within group)
Icosapent Ethyl (n=44)	3.2 (0.9, 11.6)	1.6 (0.6, 4.4)	-25.0 (-80.1, 26.7)	-0.5 (-6.9, 0.4)	0.011
Usual Care (n=47)	2.3 (0.7, 6.5)	2.1 (0.5, 5.8)	-5.6 (-57.1, 84.2)	-0.1 (-3.2, 1.7)	0.51

P-value (between groups) 0.043

[a], men <45 vs ≥45 years and women <55 vs ≥55 years. [b], absence or presence of cardiovascular comorbidities.
Data are presented as median (interquartile range).
CV, cardiovascular; hs-CRP, high-sensitivity C-reactive protein.
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Inflammatory Biomarker Endpoint

Changes in hs-CRP from Baseline to Day 14

Adjusted by Sex, Age[a] and Baseline CV Risk[b]

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COVID-19 CardioLink-9

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Data are presented as median (interquartile range).
CV, cardiovascular; hs-CRP, high-sensitivity C-reactive protein.
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Other Biomarker Endpoints

Changes in D-Dimer and Erythrocyte Sedimentation Rate from Baseline to Day 14

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D-Dimer	Baseline (µg/L)	Day 14 (µg/L)	P-value (within group)
Icosapent Ethyl (n=44)	324.0	286.5	0.048
Usual Care (n=47)	292.5	270.0	0.53

P-value (between groups) 0.30

Erythrocyte Sedimentation Rate	Baseline (mm/hour)	Day 14 (mm/hour)	P-value (within group)
Icosapent Ethyl (n=44)	18.0	15.5	0.20
Usual Care (n=47)	14.0	15.0	0.96

P-value (between groups) 0.28

Data are presented as medians.

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Other Biomarker Endpoints

Changes in D-Dimer and Erythrocyte Sedimentation Rate from Baseline to Day 14

VASCEPA
COVID-19 CardioLink-9

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Erythrocyte Sedimentation Rate	Baseline (mm/hour)	Day 14 (mm/hour)	P-value (within group)
Icosapent Ethyl (n=44)	18.0	15.5	0.20
Usual Care (n=47)	14.0	15.0	0.96

P-value (between groups) 0.2775

Data are presented as medians.

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Clinical Endpoint

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FLU-PRO SCORE

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- The FLU-PRO score is a validated patient-reported outcome measure to evaluate the presence, severity and duration of flu symptoms in clinical trials

- The 32-item score provides a comprehensive evaluation of the full range of symptoms

- The 6 domains are Nose, Throat, Eyes, Chest/Respiratory, Gastrointestinal, and Body/Systemic

Powers JH, Guerrero ML, Leidy NK, et al. BMC Infect Dis. 2016;16:1.

Clinical Endpoint
Prevalence of FLU-PRO Symptoms

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Values shown are based on number of patients with non-missing assessments at respective visits.
FLU-PRO, InFLUenza Patient-Reported Outcome.

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Clinical Endpoint

Prevalence of FLU-PRO Symptoms

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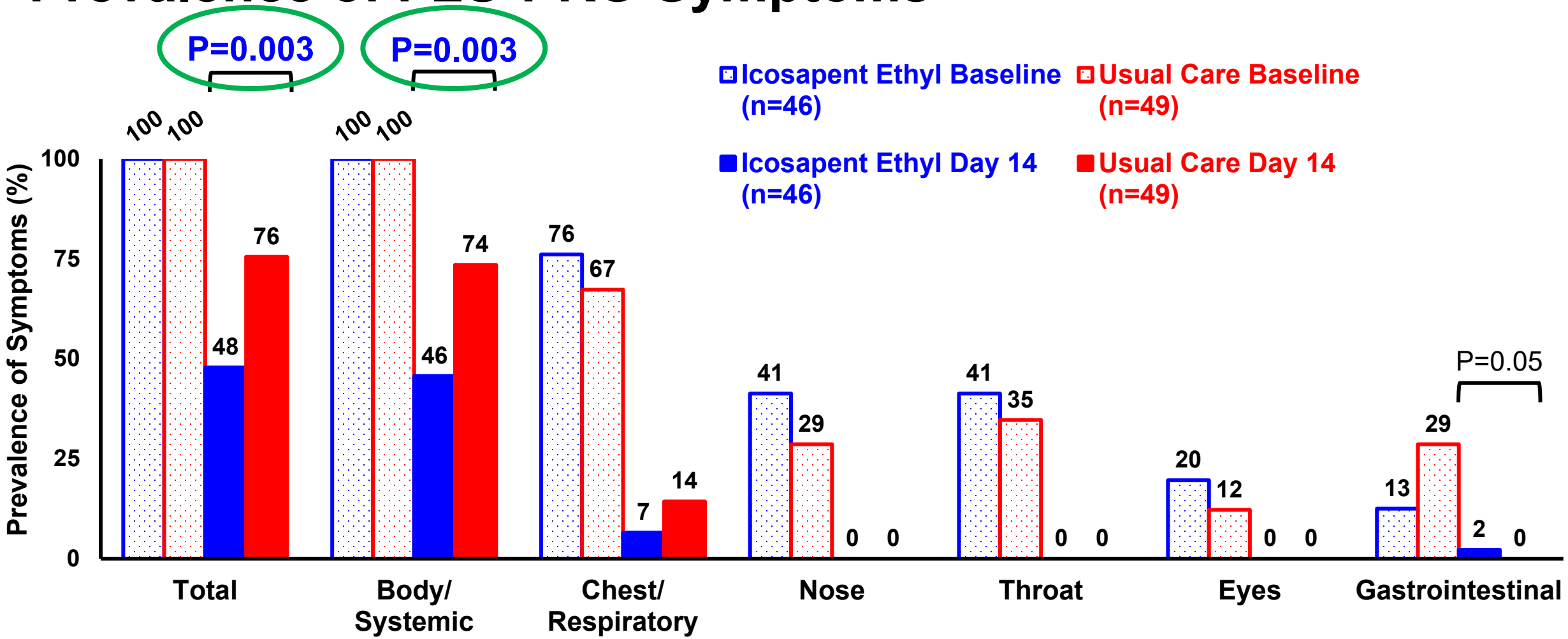

Values shown are based on number of patients with non-missing assessments at respective visits.
FLU-PRO, InFLUenza Patient-Reported Outcome.

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FLU-PRO Scores

Changes in Total and Individual Domain Scores from Baseline to Day 14

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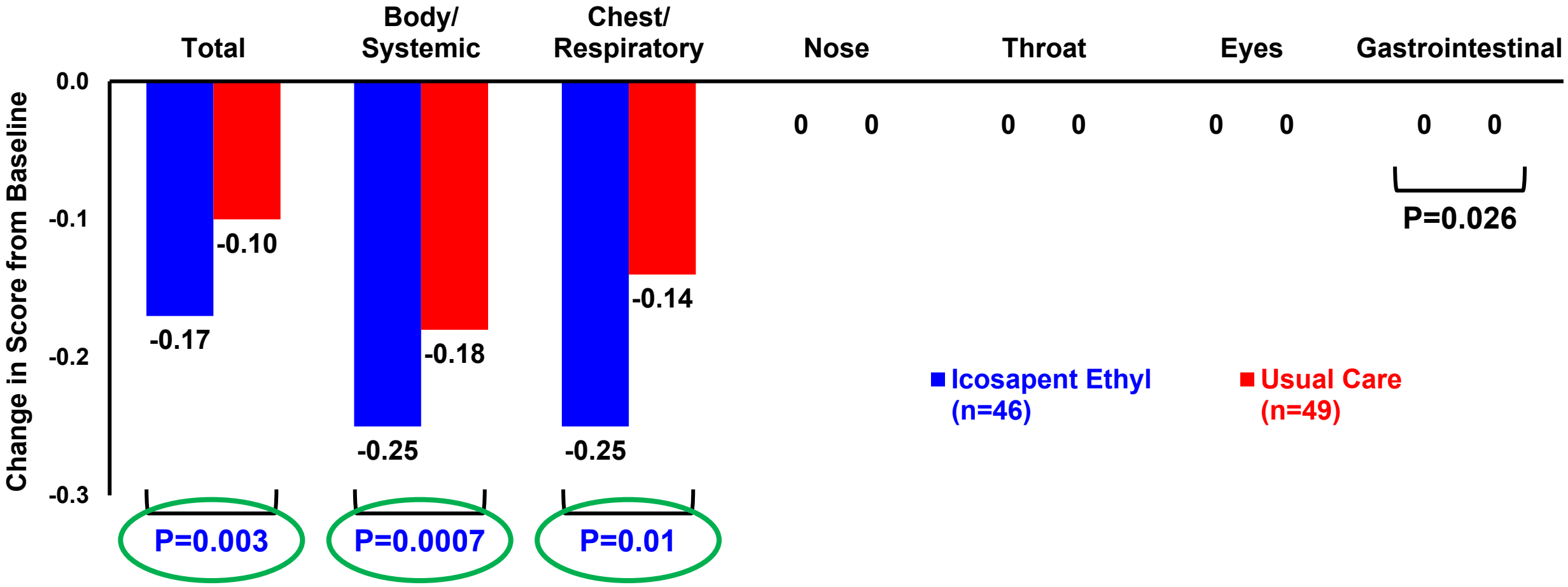

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Adverse Events

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n (%)	Icosapent Ethyl (n=50)	Usual Care (n=50)
Total adverse events	6 (12)	3 (6)
Mild adverse events		
Gastrointestinal disorders	4 (8)	0 (0)
Moderate adverse events		
Gastrointestinal disorders	1 (2)	0 (0)
Respiratory disorders	1 (2)	3 (6)

Data shown are for the intention-to-treat population.
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Limitations

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Limitations include the modest sample size and unblinded nature of this randomized trial.

Also, while the reduction in high sensitivity C-reactive protein within the icosapent ethyl arm was statistically significant, the between group comparison was not statistically significant in the unadjusted model.

Finally, the trial was not powered for clinical events.

- Nevertheless, with the caveats of an unblinded trial, the highly significant improvement in patient-reported outcomes in the context of a pandemic may be important.

Significant Correlation Between Improvement in FLU-PRO and Decrease in hs-CRP with IPE

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FLU-PRO Scores	Icosapent Ethyl (n=44)		Usual Care (n=47)	
	Spearman Correlation Coefficient	P-value	Spearman Correlation Coefficient	P-value
Total	41%	0.004	22%	0.14
Body/Systemic	41%	0.005	18%	0.24
Chest/Respiratory	57%	0.00004	3%	0.86

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Significant Correlation Between Improvement in FLU-PRO and Decrease in hs-CRP with IPE

VASCEPA
COVID-19 CardioLink-9

FLU-PRO Scores	Icosapent Ethyl (n=44) Spearman Correlation Coefficient	Icosapent Ethyl (n=44) P-value	Usual Care (n=47) Spearman Correlation Coefficient	Usual Care (n=47) P-value
Total	41%	**0.004**	22%	0.14
Body/Systemic	41%	**0.005**	18%	0.24
Chest/Respiratory	57%	**0.00004**	3%	0.86

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Conclusions – Loading Dose of IPE

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In conclusion, this randomized trial represents the **first human experience with a loading dose of icosapent ethyl**.

It has demonstrated the **safety and tolerability of this loading dose** in a modest sample size, which is being confirmed in **PREPARE-IT**.

This safety experience opens the door on **future studies using a loading dose in other conditions**, including at the time of:

- Acute coronary syndromes
- Stroke
- PCI
- CABG

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Conclusions – IPE in COVID-19 Outpatients

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Regarding COVID-19, this study provides the **first evidence of an early anti-inflammatory effect of icosapent ethyl** in symptomatic COVID-19 positive outpatients.

The **25% reduction in hsCRP** is consistent with anti-inflammatory effects of **icosapent ethyl** demonstrated in hypertriglyceridemic patients.

The **large and significant improvement in patient-reported symptoms** may provide a safe, well-tolerated, and relatively inexpensive option to impact upon COVID-19 related morbidity.

- Though this finding should be confirmed in a double-blind, placebo-controlled trial.

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BRIGHAM AND WOMEN'S HOSPITAL

Heart & Vascular Center

Thank You!

Deepak L. Bhatt, MD, MPH
Executive Director,
Interventional Cardiovascular Programs,
BWH Heart & Vascular Center;
Professor of Medicine,
Harvard Medical School
Email: DLBhattMD@post.Harvard.edu
Twitter: @DLBhattMD

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

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THANK YOU TO ALL OUR INVESTIGATORS, STUDY COORDINATORS, AND PATIENTS!

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COVID-19 CardioLink-9

BACKUP

REDUCE-IT Design

Key Inclusion Criteria

- Statin-treated men and women ≥45 yrs
- Established CVD (~70% of patients) or DM + ≥1 risk factor
- TGs ≥150 mg/dL and <500 mg/dL*
- LDL-C >40 mg/dL and ≤100 mg/dL

Lead-in

- Statin stabilization
- Medication washout
- Lipid qualification

1:1 Randomization with continuation of stable statin therapy (N=8179)

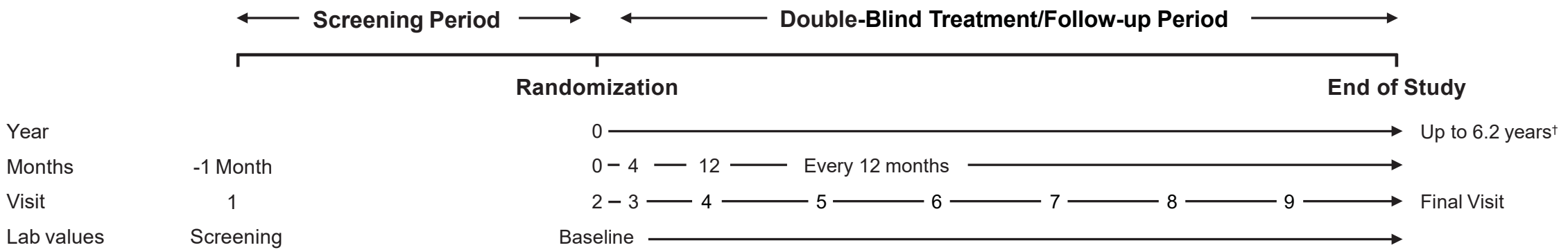
Icosapent Ethyl 4 g/day (n=4089)

Placebo (n=4090)

4 months, 12 months, annually → End-of-study follow-up visit

Primary Endpoint

Time from randomization to the first occurrence of composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, unstable angina requiring hospitalization



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

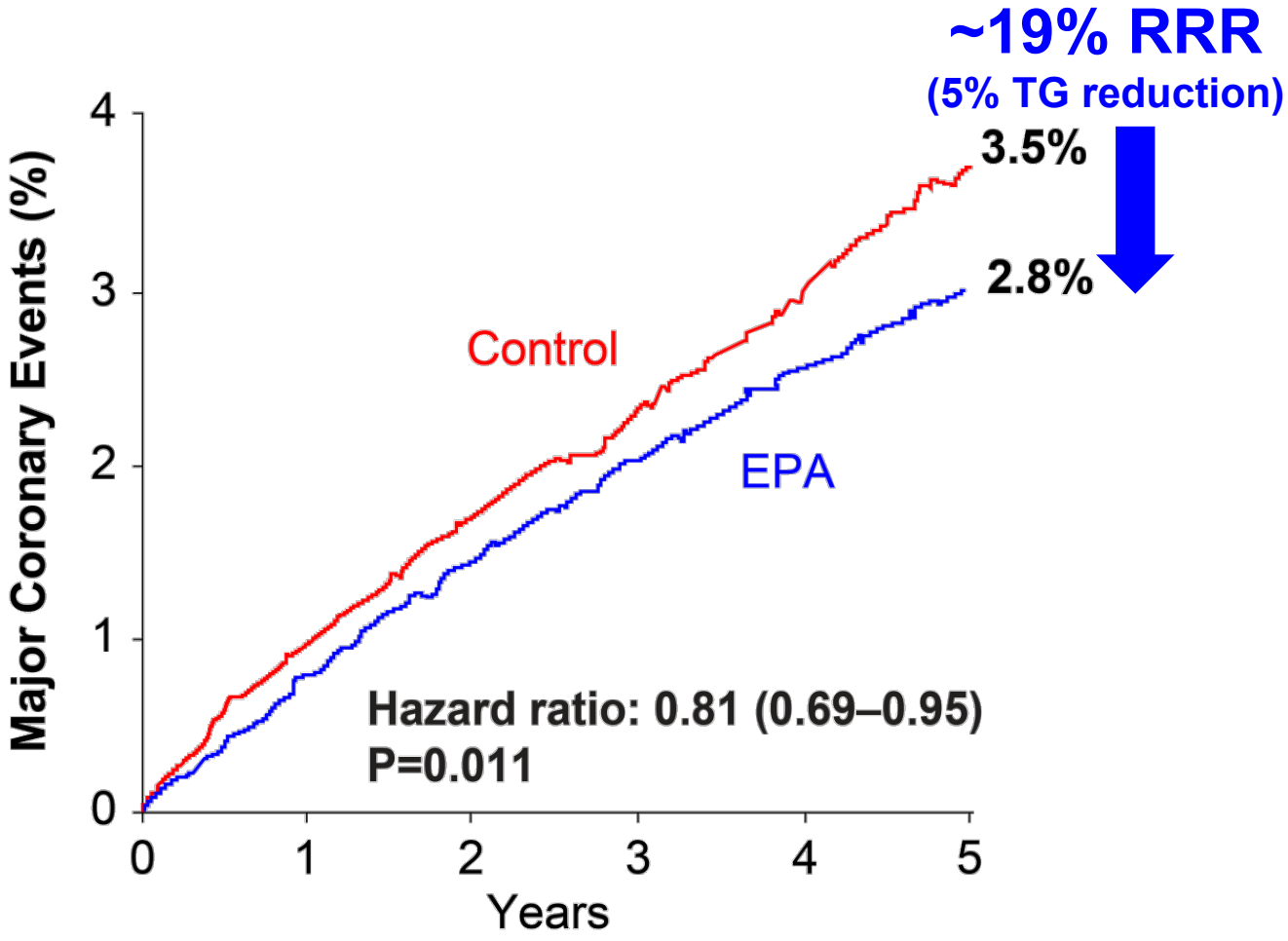
†Median trial follow-up duration was 4.9 years (minimum 0.0, maximum 6.2 years).

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.

JELIS Found Significant CV Risk Reduction with Icosapent Ethyl (EPA)

- N=18,645 Japanese patients
- Elevated total cholesterol
- No pre-specified minimum triglyceride (TG) level
- Randomized, open-label (no placebo)
- Blinded endpoint adjudication (PROBE design)
- 80% primary prevention
- 69% women
- ~Half of patients with baseline normal TGs



Yokoyama M, Origasa H, Matsuzaki M, et al. *Lancet.* 2007;369:1090-8.

JELIS Found Significant Reduction in Joint, Back, and Muscle Pain with Icosapent Ethyl

Common adverse experiences			
Pain (joint pain, lumbar pain, muscle pain)	180 (2.0%)	144 (1.6%)	0.04
Gastrointestinal disturbance (nausea, diarrhea, epigastric discomfort)	155 (1.7%)	352 (3.8%)	<0.0001
Skin abnormality (eruption, itching, exanthema, eczema)	65 (0.7%)	160 (1.7%)	<0.0001
Hemorrhage (cerebral, fundal, epistaxis, subcutaneous)	60 (0.6%)	105 (1.1%)	0.0006

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FLU-PRO Scores
Changes in Total Score from Baseline to Day 14

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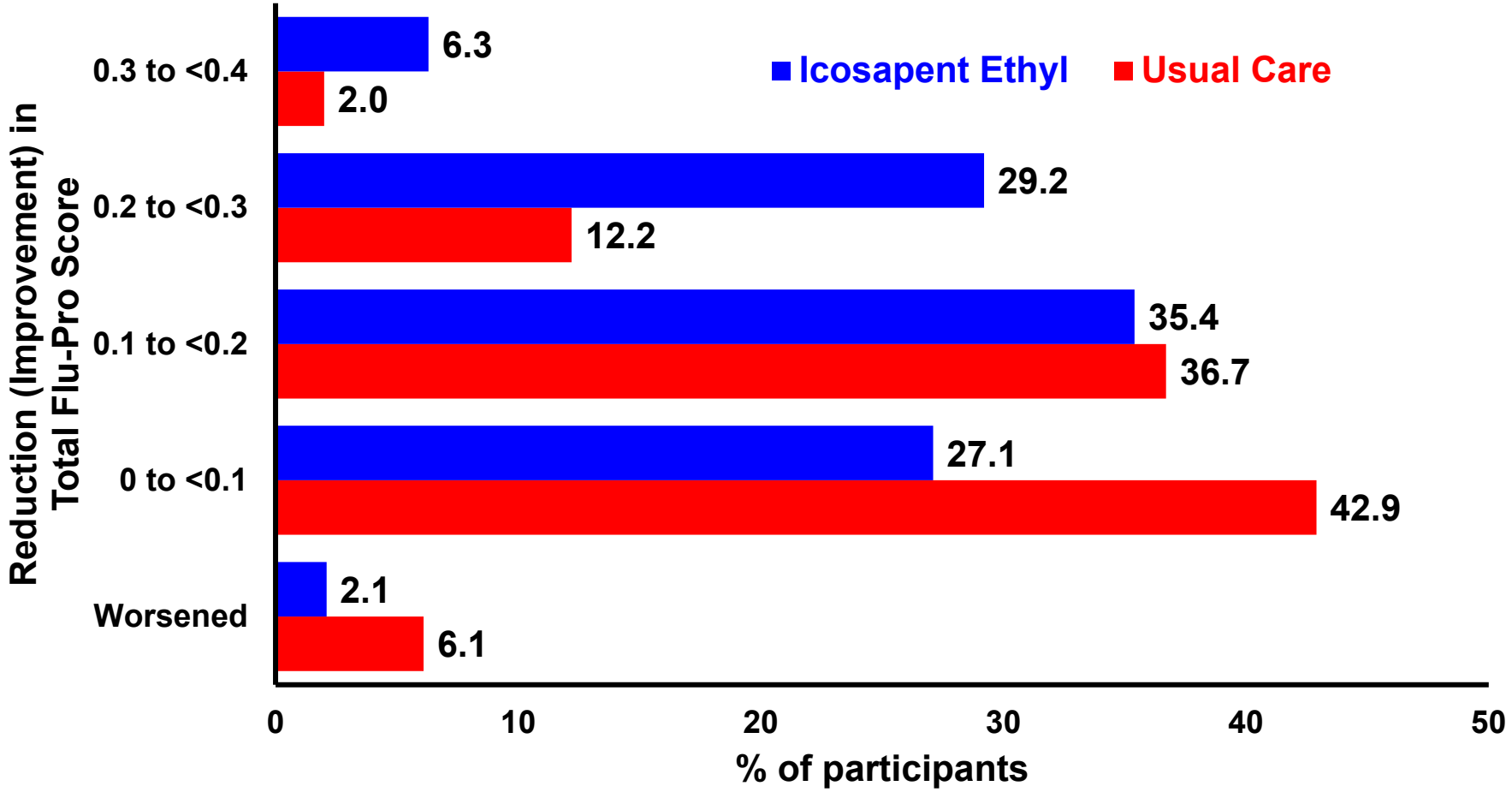
COVID-19 CardioLink-9



Percent values are based on number of patients in each treatment group.
FLU-PRO, InFLUenza Patient-Reported Outcome.
Bhatt DL et al. NLA 2020 Late Breaking Presentation