reduce-it EPA

EPA Levels and Cardiovascular Outcomes in the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial

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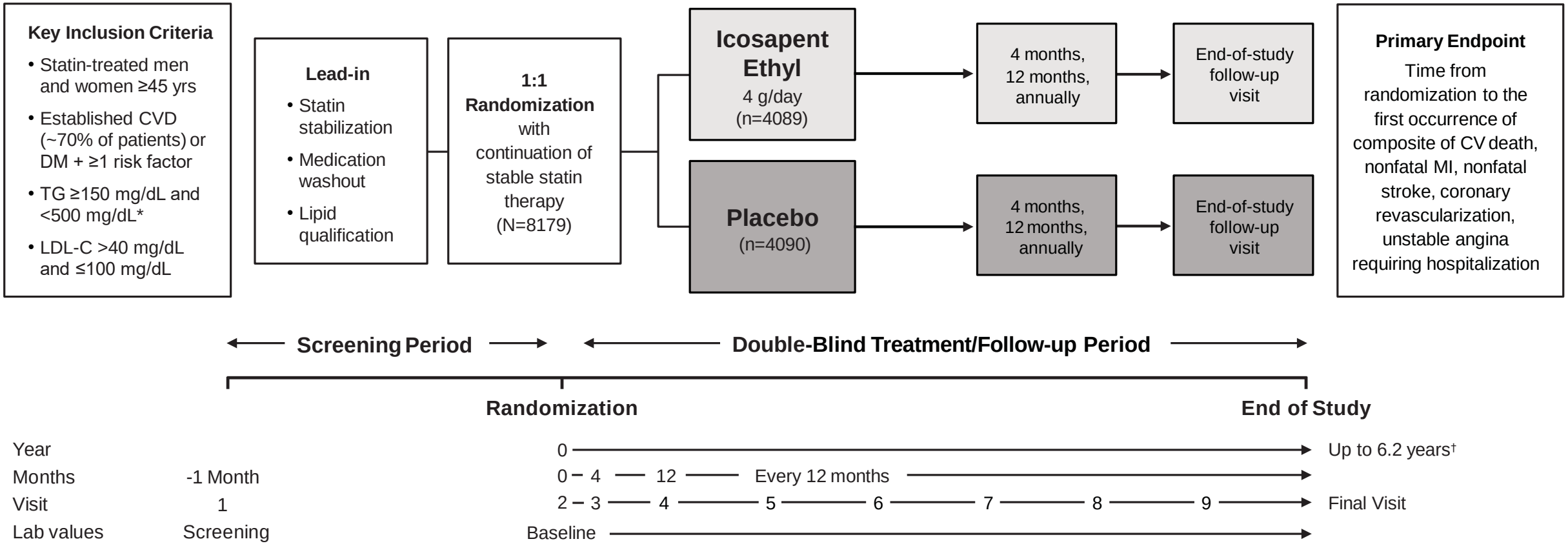
on Behalf of the **REDUCE-IT** Investigators

Disclosures

Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, Cereno Scientific, Elsevier Practice Update Cardiology, 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.**

REDUCE-IT was sponsored by Amarin Pharma, Inc.

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.
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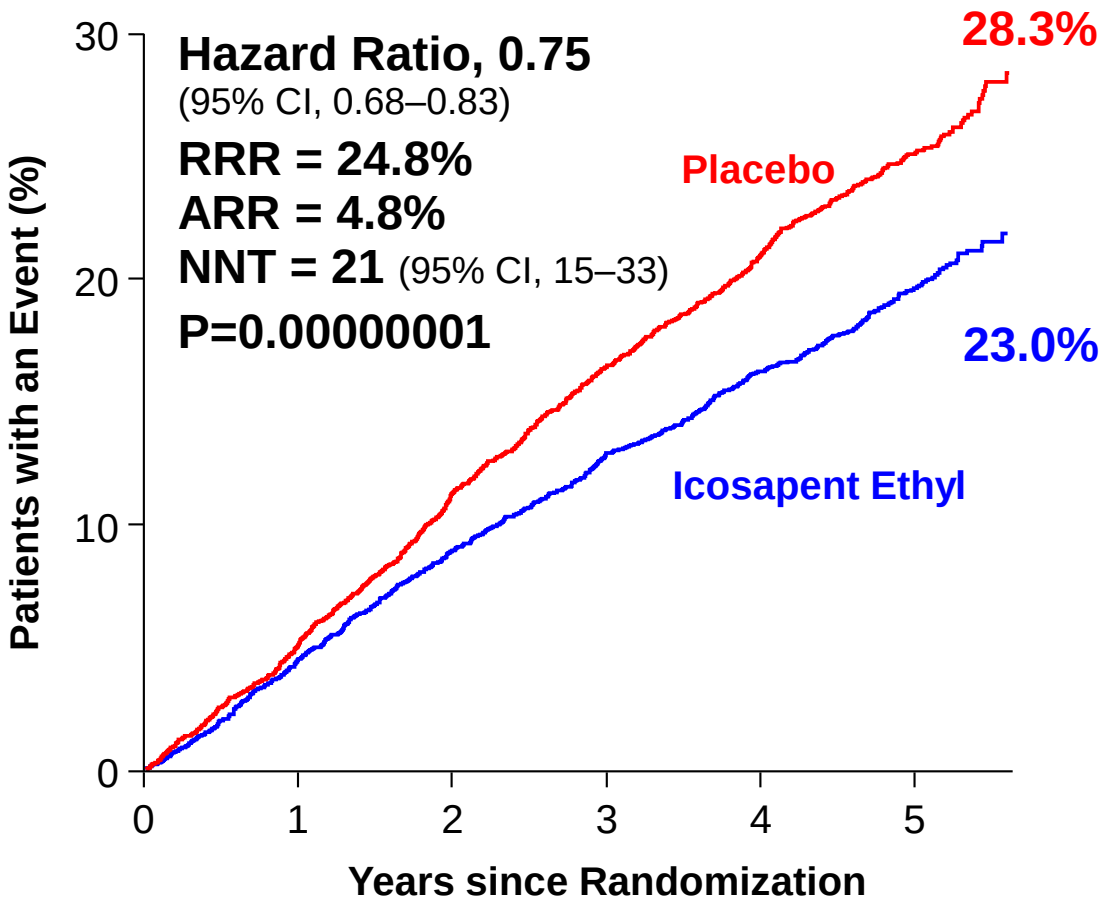
Primary and Key Secondary Composite Endpoints

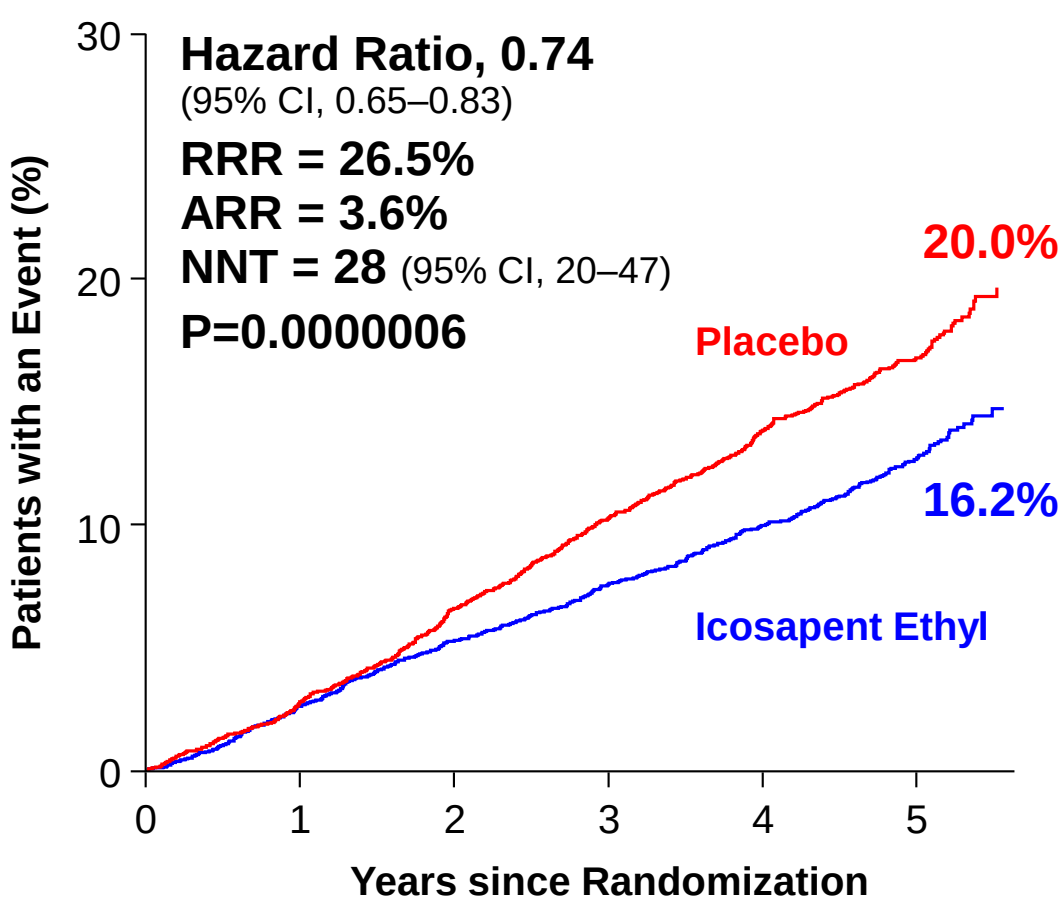
Primary Composite Endpoint:

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



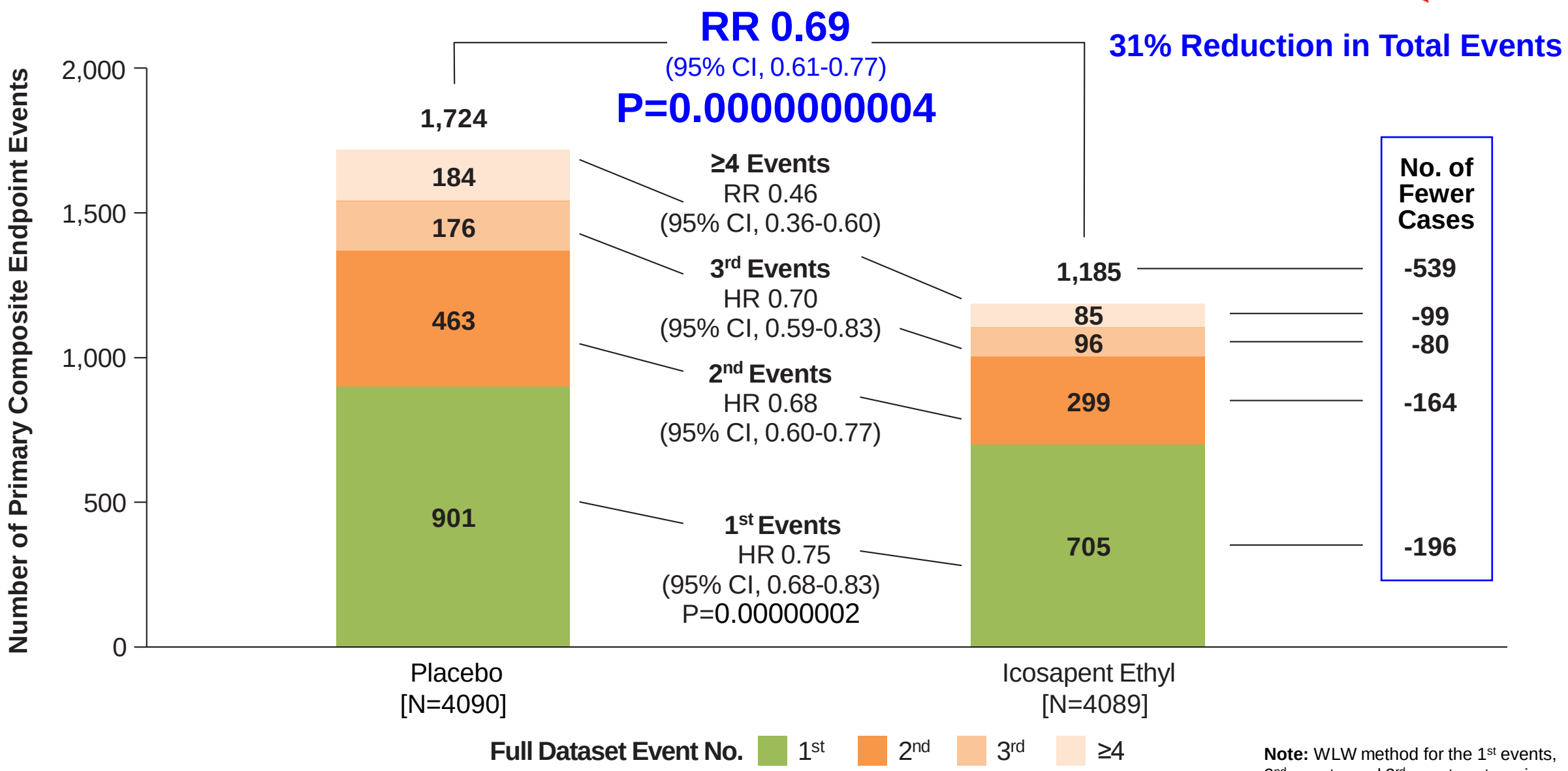
Key Secondary Composite Endpoint:

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.

First and Subsequent Events – Full Data



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

Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019;73:2791-2802. Bhatt DL. ACC 2019, New Orleans.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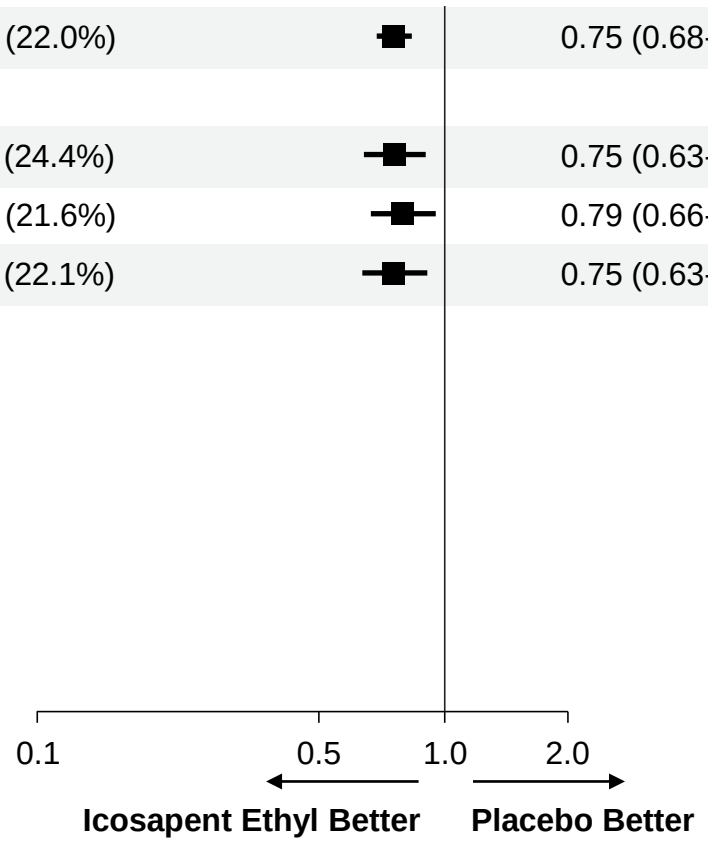
Primary and Key Secondary Composite Endpoints by Baseline Serum EPA Tertiles

Endpoint		Icosapent Ethyl	Placebo	Hazard Ratio (95% CI)	Interaction P-value
		n/N (%)	*n/N (%)*		
Primary Composite Endpoint (ITT)		705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68-0.83)	
Baseline EPA Tertiles (median) µg/mL					0.91
≤20 µg/mL	14	230/1199 (19.2%)	283/1161 (24.4%)	0.75 (0.63-0.90)	
>20–34 µg/mL	26	203/1135 (17.9%)	263/1217 (21.6%)	0.79 (0.66-0.95)	
>34 µg/mL	48	203/1195 (17.0%)	255/1155 (22.1%)	0.75 (0.63-0.91)	



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

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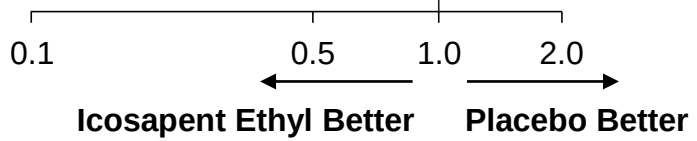
>34 µg/mL	48	203/1195 (17.0%)	255/1155 (22.1%)	0.75 (0.63-0.91)	
Key Secondary Composite Endpoint (ITT)		459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65-0.83)	
Baseline EPA Tertiles (median) µg/mL					0.90
≤20 µg/mL	14	157/1199 (13.1%)	195/1161 (16.8%)	0.76 (0.61-0.93)	
>20–34 µg/mL	26	125/1135 (11.0%)	174/1217 (14.3%)	0.74 (0.59-0.94)	
>34 µg/mL	48	132/1195 (11.0%)	177/1155 (15.3%)	0.71 (0.57-0.89)	



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

Levels of Eicosapentaenoic Acid (EPA) in Serum

Eicosapentaenoic Acid (EPA)

	Icosapent Ethyl (N=4089)				*Placebo (N=4090)*				*Between Group Difference*		
Visit	Median Observed Values (µg/mL)	Median Absolute Change from Baseline	Median % Change from Baseline	Median % Change P-value	Median Observed Values (µg/mL)	Median Absolute Change from Baseline	Median % Change from Baseline	Median % Change P-value	Median Absolute Change from Baseline	Median % Change from Baseline	Median % Change P-value
Baseline	**26.1**				**26.1**						
Year 1	**144**	**112.6**	**393.5**	**<0.0001**	**23.3**	**-2.9**	**-12.8**	**<0.0001**	**114.9**	**385.8**	**<0.0001**
Year 2	169	137.3	478.6	<0.0001	28	0.5	2.8	<0.0001	137.1	457.4	<0.0001
Year 3	168	137.4	464.5	<0.0001	27.3	-0.1	-0.4	<0.0001	136.9	447.5	<0.0001
Year 4	162	132.6	452.1	<0.0001	26.2	-1.1	-5.2	0.15	133	439.8	<0.0001
Year 5	158	130.5	463.6	<0.0001	25.3	-0.5	-2	0.09	130.8	448.1	<0.0001
Last Visit	150	117.9	395.2	<0.0001	26.5	-0.9	-3.8	0.08	119	380.3	<0.0001
On-Treatment EPA Daily Average (derived)	**135.2**	**103.9**	**363.9**	**<0.0001**	**27.7**	**0**	**0.2**	**<0.0001**	**103.8**	**347.7**	**<0.0001**

Year 6 values are not included as the number of patients = 9.

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Stratified Analysis of Time to Primary Endpoint by Adjusting Time-Varying Covariates of Post-Baseline Biomarkers

	Impact on the HR of Between-group Biomarker Differences (Icosapent Ethyl vs Placebo)			
	Primary Composite Endpoint		Key Secondary Composite Endpoint	
	HR (95% CI)	Significance P-value	HR (95% CI)	Significance P-value
Overall Trial	0.75 (0.68–0.83)	0.00000001	0.74 (0.65–0.83)	0.0000006
Lipid/Biomarker Covariate	**HR (95% CI) for Treatment Comparison (Adjusting Covariate)**	**Significance P-value**	**HR (95% CI) for Treatment Comparison (Adjusting Covariate)**	**Significance P-value**
EPA (µg/mL)	1.03 (0.91–1.16)	<0.0001	0.98 (0.84–1.14)	<0.0001
Triglycerides (mg/dL)	**0.77 (0.70–0.85)**	**<0.0001**	**0.75 (0.66–0.85)**	**<0.0001**
LDL-C derived (mg/dL)	0.75 (0.68–0.83)	0.80	0.74 (0.65–0.84)	0.38
HDL Cholesterol-CDC (mg/dL)	0.73 (0.66–0.81)	<0.0001	0.71 (0.63–0.80)	<0.0001
Non-HDL Cholesterol (mg/dL)	0.78 (0.71–0.87)	<0.0001	0.77 (0.68–0.87)	<0.0001
Apolipoprotein B (mg/dL)	0.76 (0.69–0.84)	0.03	0.75 (0.66–0.85)	0.0004
hsCRP (mg/L)	0.76 (0.69–0.84)	0.004	0.74 (0.66–0.84)	<0.0001
RLP-C (mg/dL)	0.78 (0.71–0.87)	<0.0001	0.77 (0.68–0.87)	<0.0001

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

Stratified Analysis of Time to Primary Endpoint by Adjusting Time-Varying Covariates of Post-Baseline Biomarkers

	Impact on the HR of Between-group Biomarker Differences (Icosapent Ethyl vs Placebo)			
	Primary Composite Endpoint		Key Secondary Composite Endpoint	
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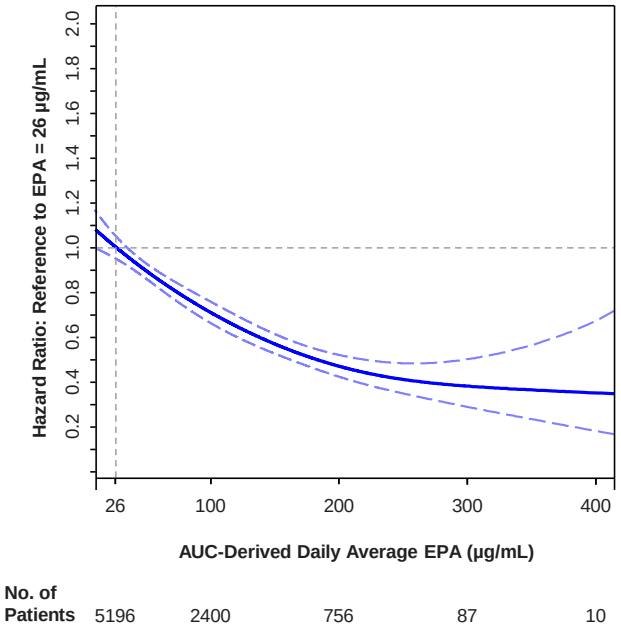
Primary and Key Secondary Composite Endpoints, Cardiovascular Death, and Total Mortality by On-Treatment Serum EPA

Primary Endpoint[1-5]



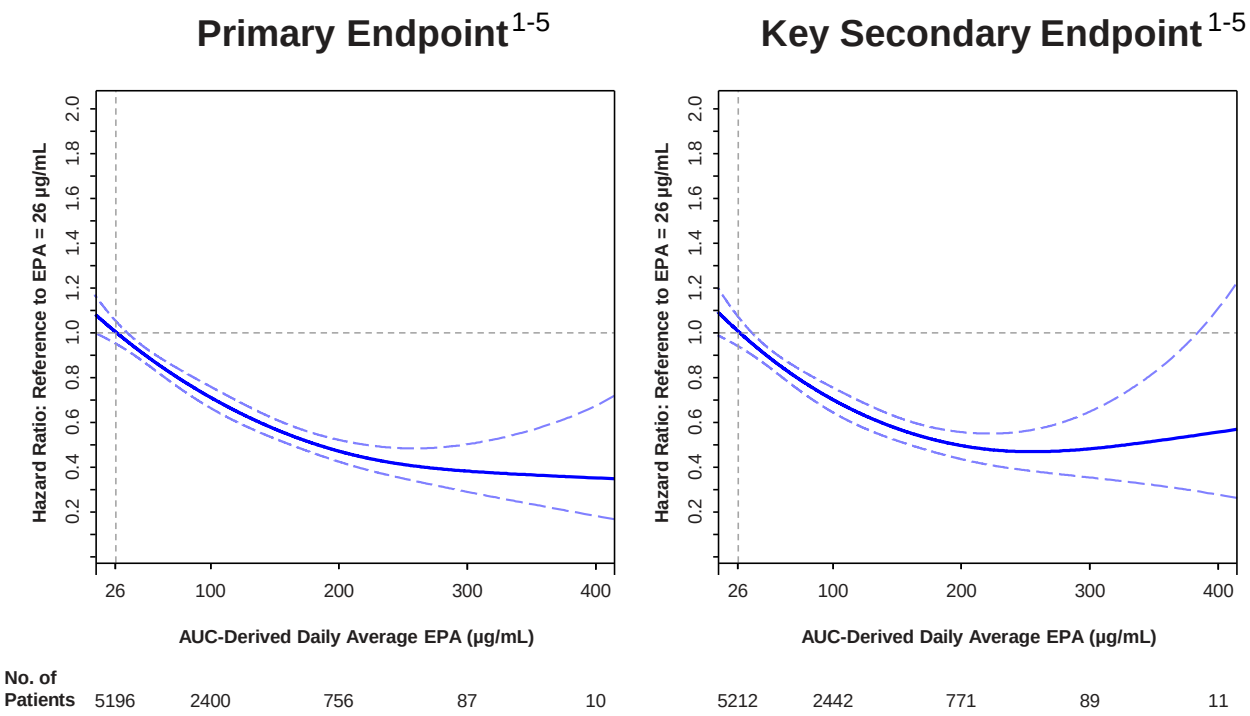
P*<0.001

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).

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



P*<0.001 for all

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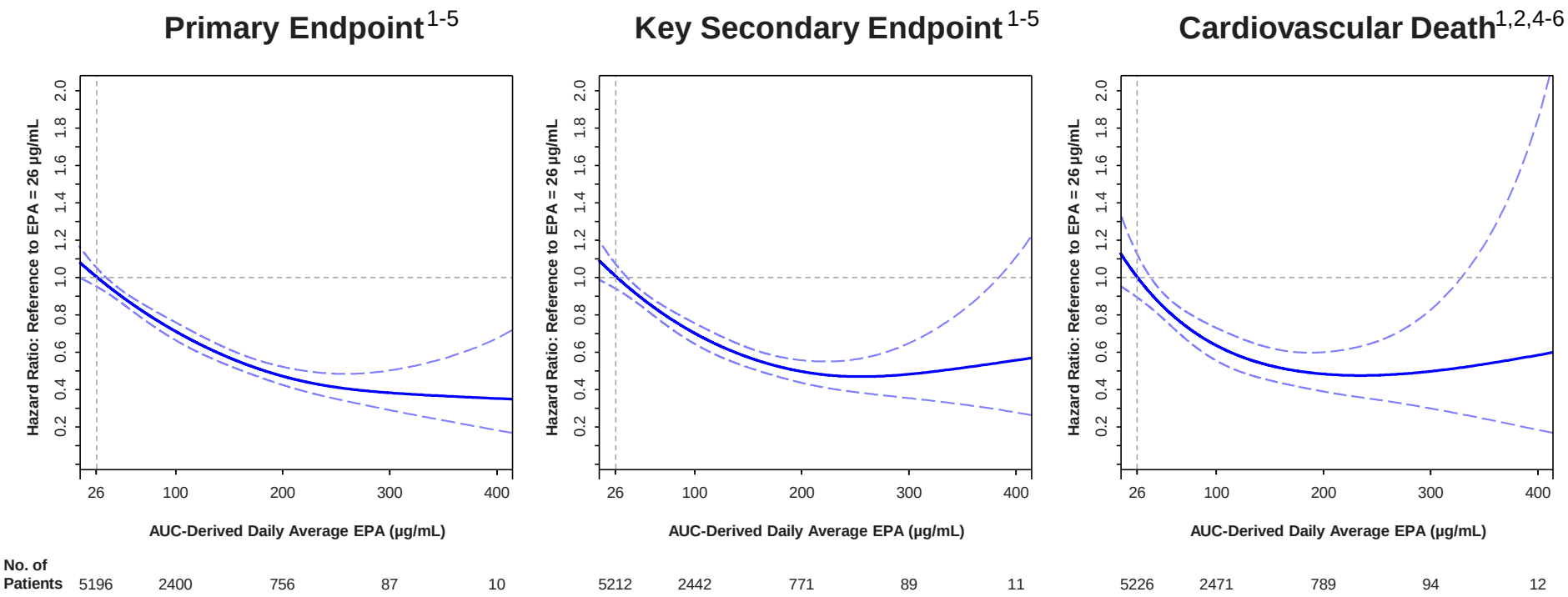
Bhatt DL. ACC/WCC 2020, Chicago (virtual).

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



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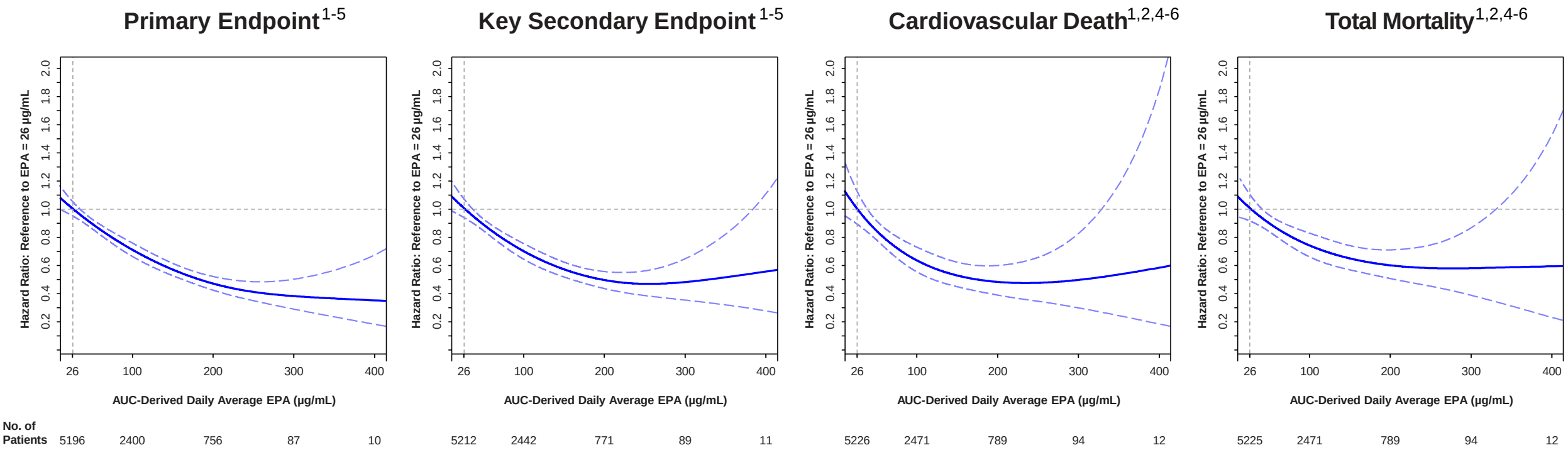
Primary and Key Secondary Composite Endpoints, Cardiovascular Death, and Total Mortality by On-Treatment Serum EPA



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

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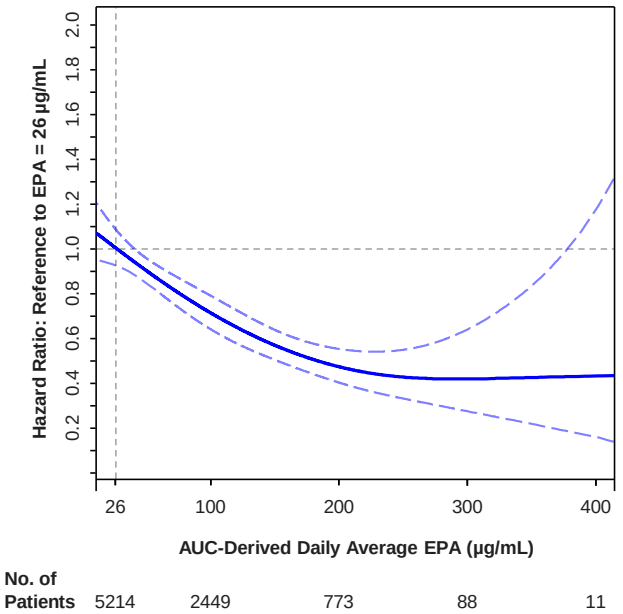
Dose-Response of Hazard Ratio (95% CI) Any Myocardial Infarction, Any Stroke, Coronary Revascularization, Unstable Angina by On-Treatment Serum EPA

Any Myocardial Infarction[1-3]



P*<0.001

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

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 sex[1], baseline diabetes[2], hsCRP[3], statin compliance[4], age[5].
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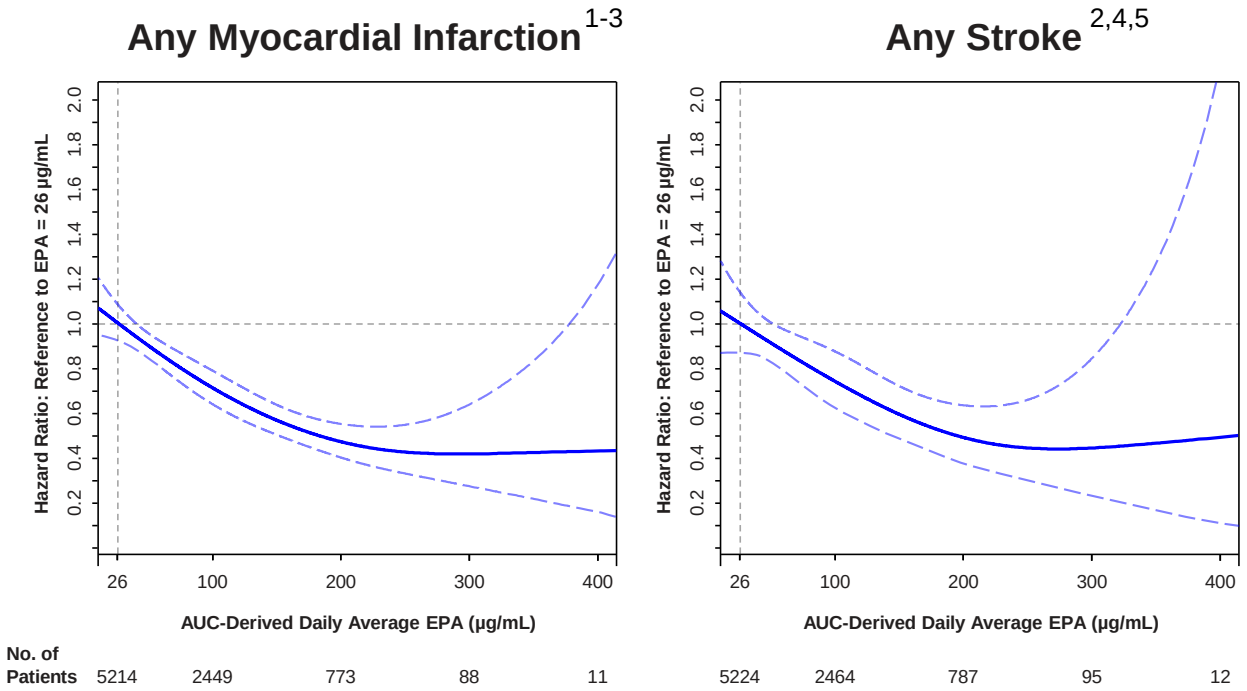
Dose-Response of Hazard Ratio (95% CI) Any Myocardial Infarction, Any Stroke, Coronary Revascularization, Unstable Angina by On-Treatment Serum EPA



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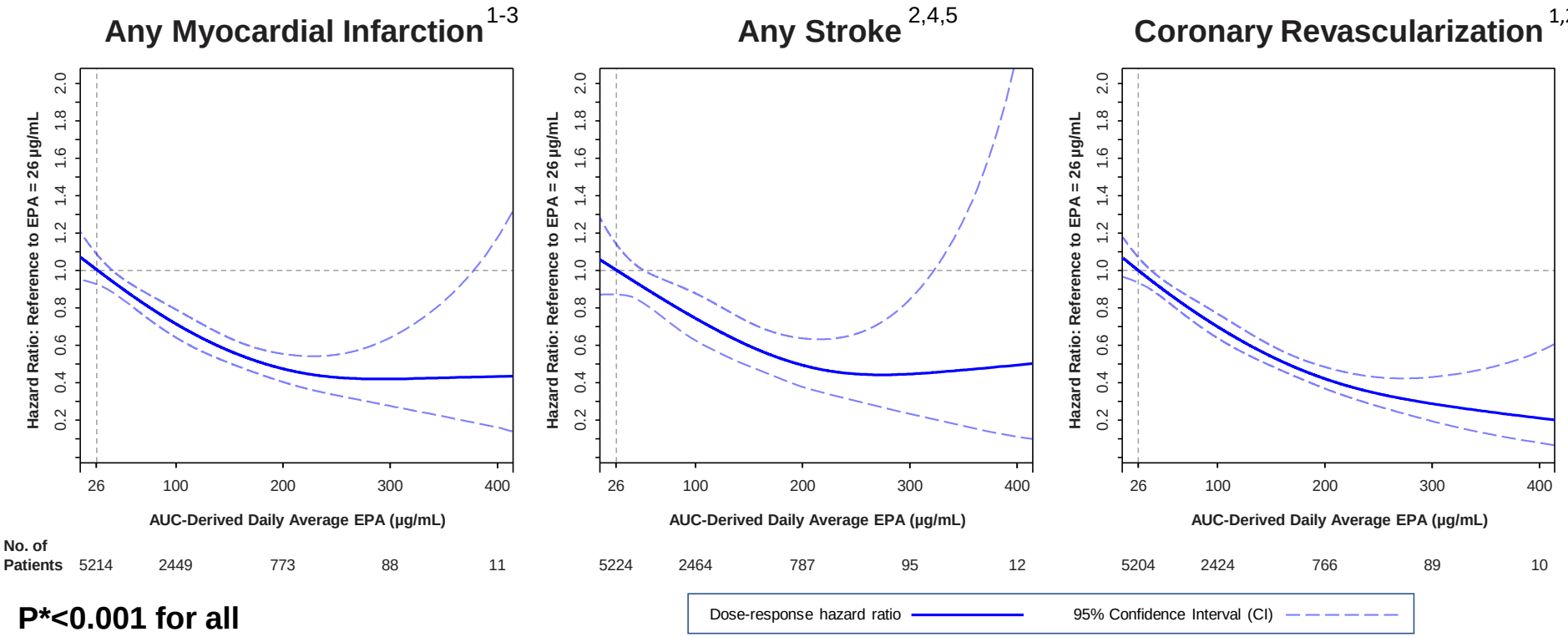
Bhatt DL. ACC/WCC 2020, Chicago (virtual).

Dose-Response of Hazard Ratio (95% CI) Any Myocardial Infarction, Any Stroke, Coronary Revascularization, Unstable Angina by On-Treatment Serum EPA



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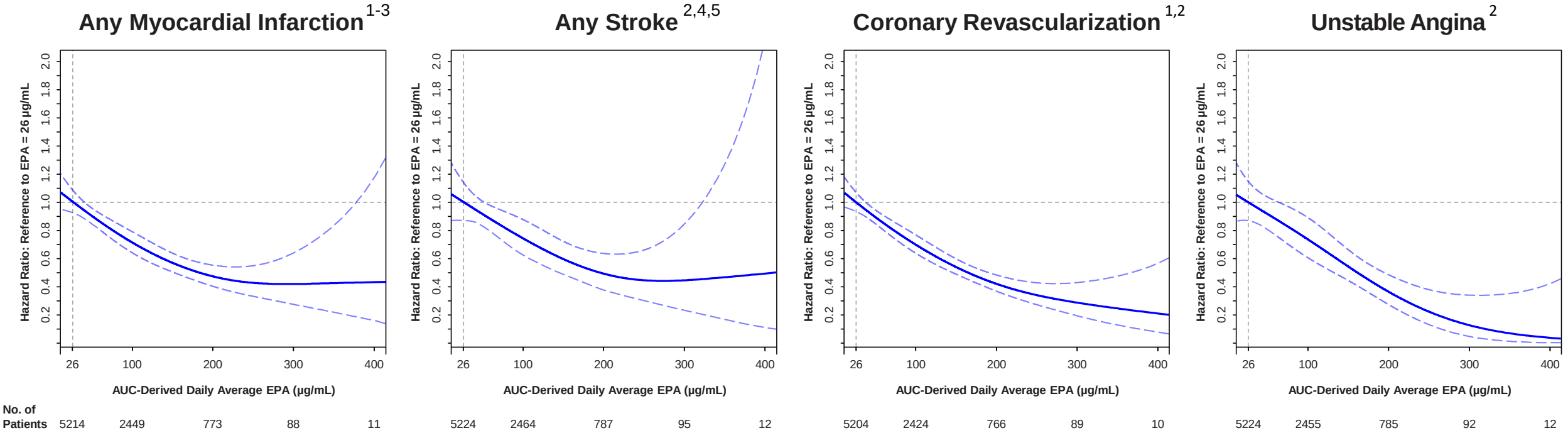

P*<0.001 for all

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

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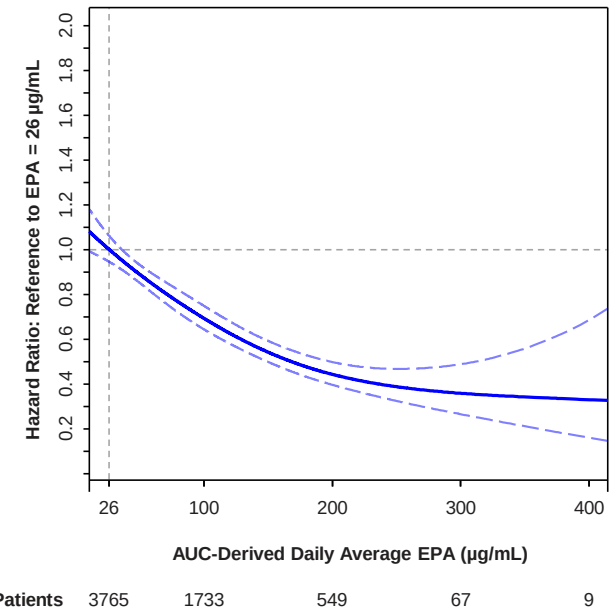
Dose-Response of Hazard Ratio (95% CI) Primary Composite Endpoint by On-Treatment Serum EPA

Established Cardiovascular Disease or Diabetes with Risk Factors

Primary Endpoint: Established Cardiovascular Disease[1-5]



P*<0.001

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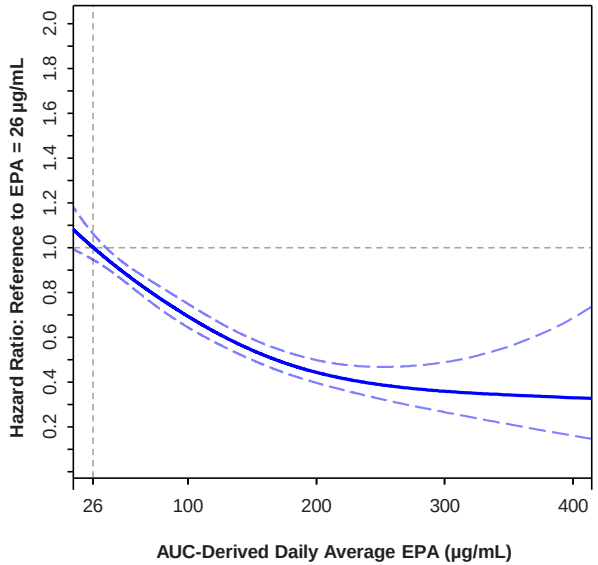
Dose-Response of Hazard Ratio (95% CI) Primary Composite Endpoint by On-Treatment Serum EPA

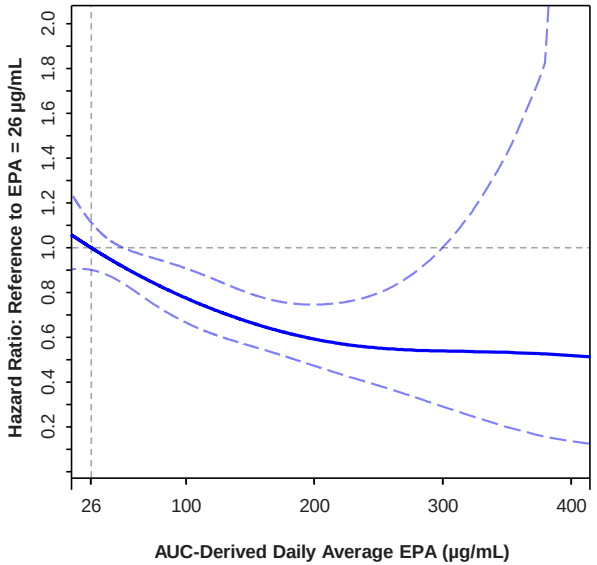
Established Cardiovascular Disease or Diabetes with Risk Factors

Primary Endpoint: Established Cardiovascular Disease[1-5]



No. of Patients	3765	1733	549	67	9

Primary Endpoint: Diabetes with Risk Factors[1-5]



No. of Patients	1431	667	207	20	1

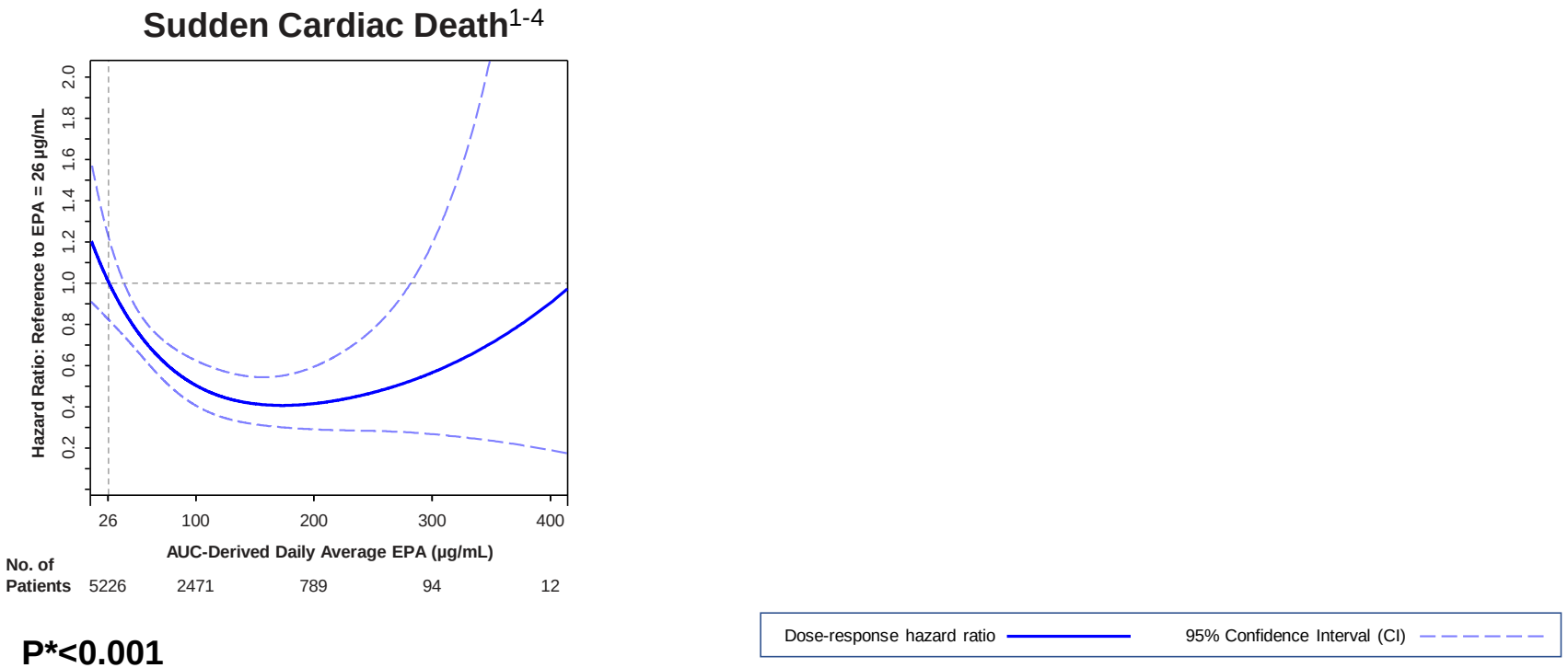
Dose-response hazard ratio — 95% Confidence Interval (CI) - - -

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

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

Dose-Response of Hazard Ratio (95% CI) Sudden Cardiac Death, Cardiac Arrest, New Heart Failure Requiring Hospitalization, New Heart Failure by On-Treatment Serum EPA



P*<0.001

Note: On-treatment post baseline 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], baseline diabetes[2], and hsCRP[3], treatment compliance[4] age[5].
***P value is <0.001 for both non-linear trend and for regression slope.**

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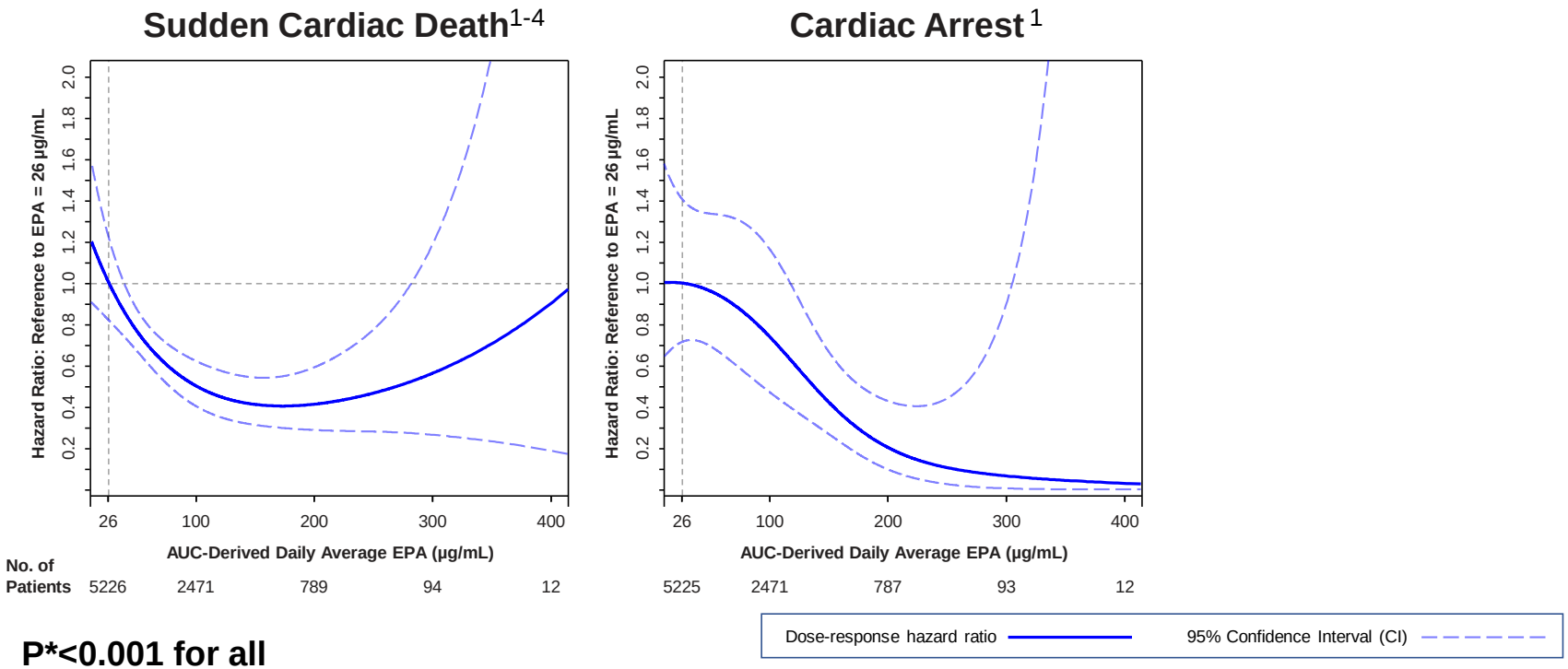

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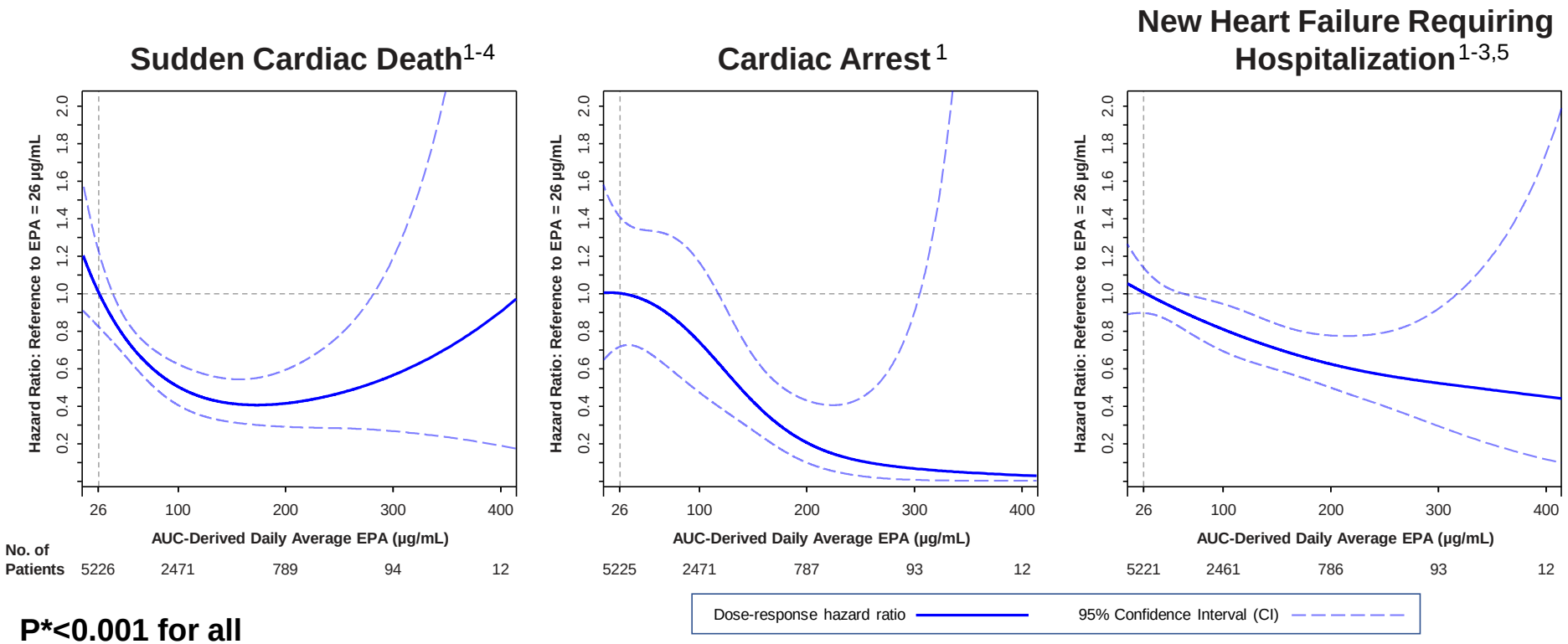

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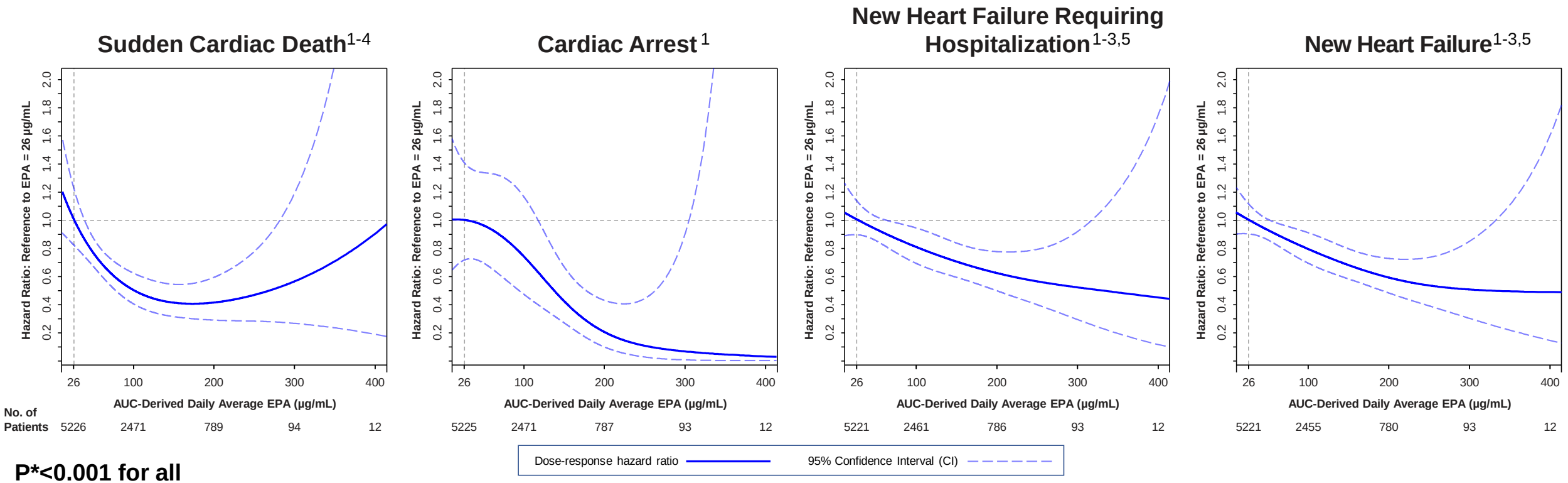

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- EPA and DHA appear to have many differing biological effects in clinical studies and experimental models
- Might explain lack of benefit of other omega-3 trials

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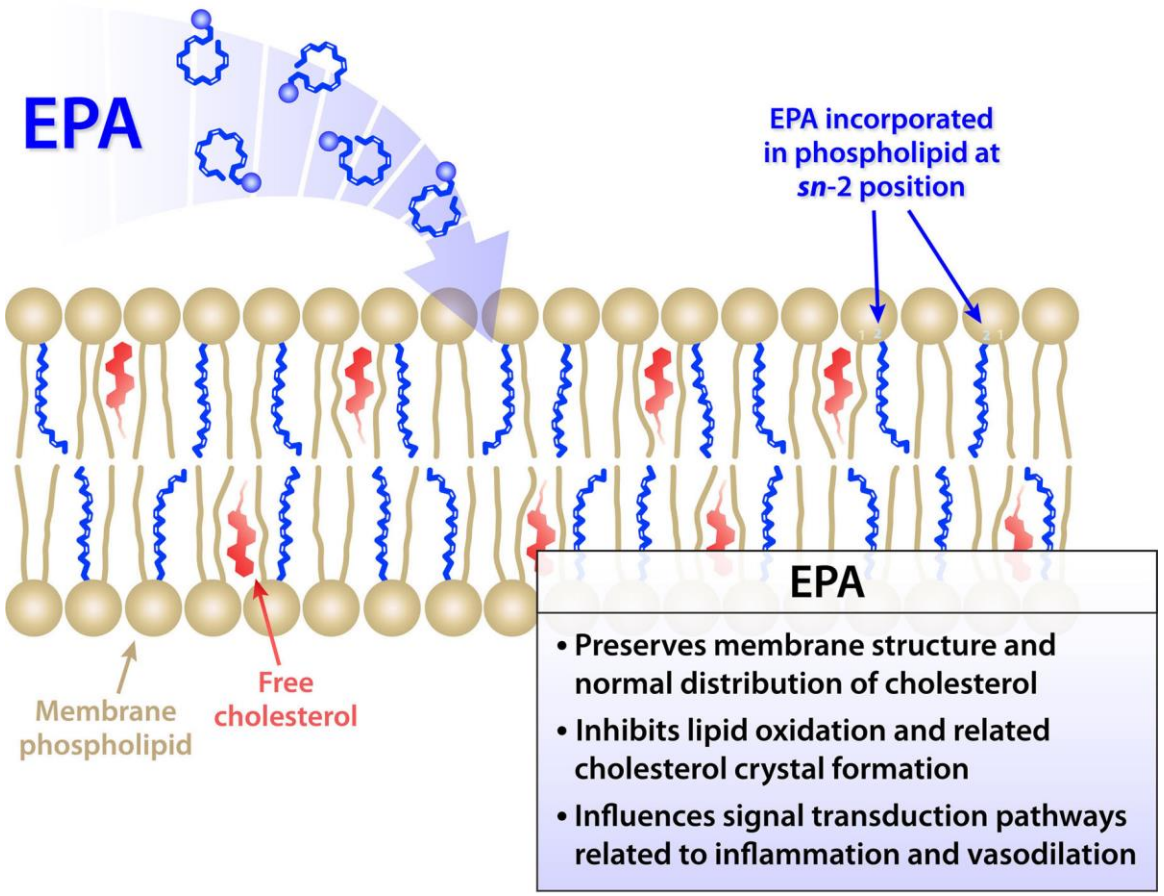
Contrasting Effects of EPA and DHA



Mason RP, Libby P, Bhatt DL. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2020.

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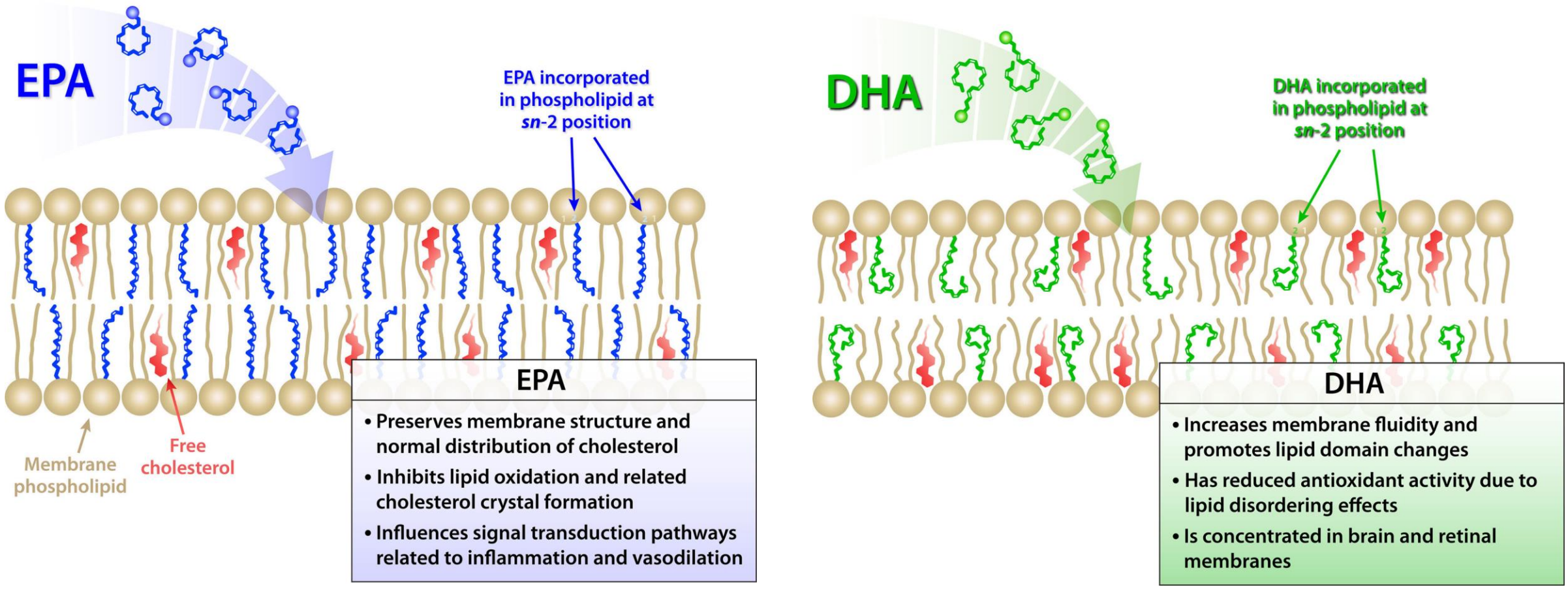

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Conclusions

Compared with placebo, icosapent ethyl 4g/day significantly reduced first and total cardiovascular events by **25%** and **30%**, respectively.

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These data provide a mechanistic underpinning for the large risk reductions seen in multiple endpoints with icosapent ethyl in REDUCE-IT.

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

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

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