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Comprehensive Review of REDUCE-IT

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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, 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.

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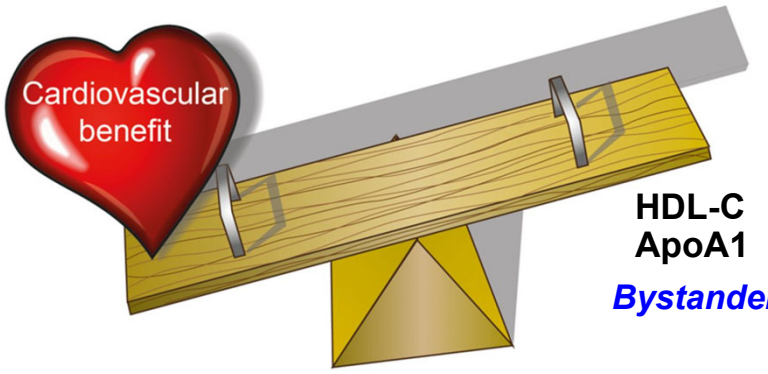
Triglycerides a Causal Risk Factor?



HDL-C
ApoA1

Bystanders?

Triglyceride-rich lipoproteins
ApoC3, ApoA5, AngPTL4

Causal risk factors?

European Heart Journal

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

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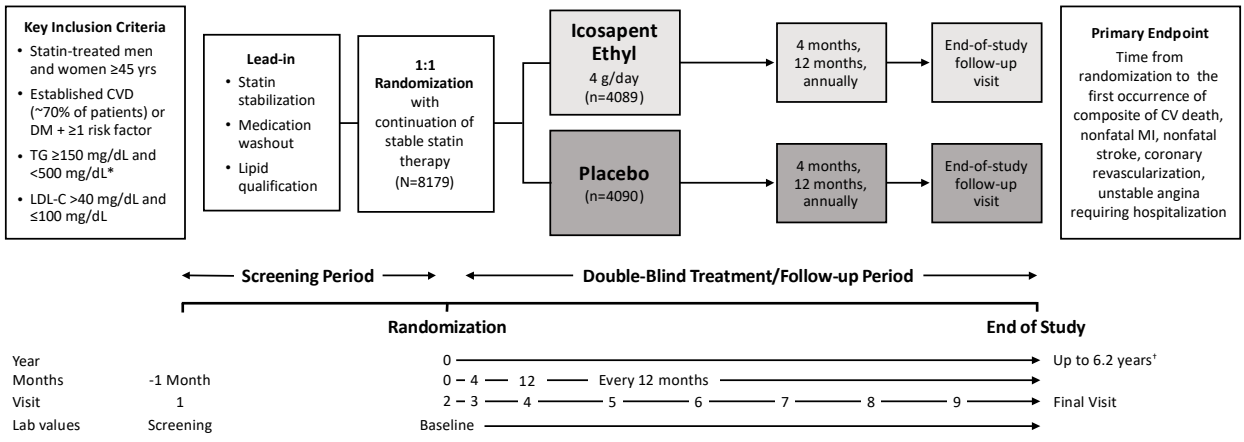
REDUCE-IT Design



* 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.
[‡https://creativecommons.org/licenses/by-nc/4.0/]

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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.

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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

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/]

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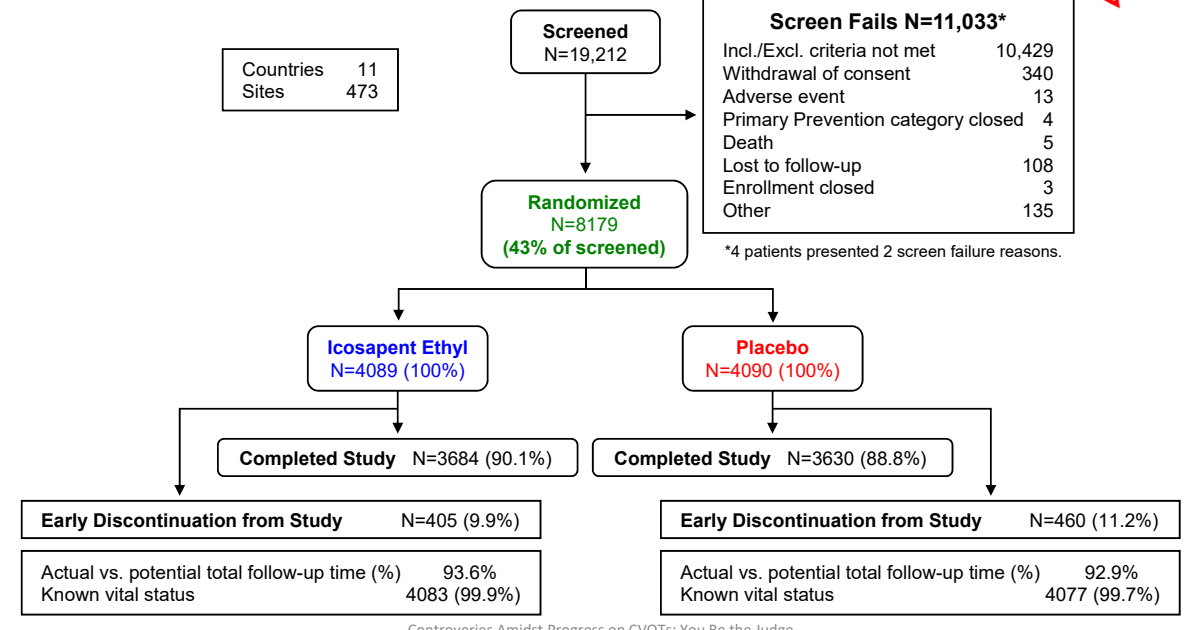
CONSORT Diagram



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

Median trial follow up duration was 4.9 years.

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Key Baseline Characteristics

	Icosapent Ethyl (N=4089)	Placebo (N=4090)
Age (years)	64	64
Female, %	28.4%	29.2%
CV Risk Category, %		
Secondary Prevention Cohort	70.7%	70.7%
Primary Prevention Cohort	29.3%	29.3%
Prior Atherosclerotic Coronary Artery Disease, %	58.4%	58.5%
Prior Atherosclerotic Cerebrovascular Disease, %	15.7%	16.2%
Prior Atherosclerotic Peripheral Artery Disease, %	9.5%	9.5%
LDL-C (mg/dL), Median (Q1-Q3)	74 (62 - 88)	76 (63 - 89)
Triglycerides (mg/dL), Median (Q1-Q3)	217 (177 - 272)	216 (176 - 274)
Triglyceride Category (by Tertiles)*		
≥81 to ≤190 mg/dL	median 163 mg/dL	
>190 to ≤250 mg/dL	median 217 mg/dL	
>250 to ≤1401 mg/dL	median 304 mg/dL	

*Baseline TG calculated as average of final screening TG and subsequent TG value from date of randomization.

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

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Key Medical Therapy

	Icosapent Ethyl (N=4089)	Placebo (N=4090)
Antiplatelet	3257 (79.7%)	3236 (79.1%)
One Antiplatelet	2416 (59.1%)	2408 (58.9%)
Two or More Antiplatelets	841 (20.6%)	828 (20.2%)
Anticoagulant	385 (9.4%)	390 (9.5%)
ACEi or ARB	3164 (77.4%)	3176 (77.7%)
Beta Blocker	2902 (71.0%)	2880 (70.4%)
Statin	4077 (99.7%)	4068 (99.5%)

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

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Effects on Biomarkers from Baseline to Year 1

	Icosapent Ethyl (N=4089) Median		Placebo (N=4090) Median		Median Between Group Difference at Year 1		
Biomarker*	Baseline	Year 1	Baseline	Year 1	Absolute Change from Baseline	% Change from Baseline	% Change P-value
Triglycerides (mg/dL)	216.5	175.0	216.0	221.0	-44.5	-19.7	<0.0001
Non-HDL-C (mg/dL)	118.0	113.0	118.5	130.0	-15.5	-13.1	<0.0001
LDL-C (mg/dL)	74.0	77.0	76.0	84.0	-5.0	-6.6	<0.0001
HDL-C (mg/dL)	40.0	39.0	40.0	42.0	-2.5	-6.3	<0.0001
Apo B (mg/dL)	82.0	80.0	83.0	89.0	-8.0	-9.7	<0.0001
hsCRP (mg/L)	2.2	1.8	2.1	2.8	-0.9	-39.9	<0.0001
Log hsCRP (mg/L)	0.8	0.6	0.8	1.0	-0.4	-22.5	<0.0001
EPA (µg/mL)	26.1	144.0	26.1	23.3	+114.9	+385.8	<0.0001

*Apo B and hsCRP were measured at Year 2.

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

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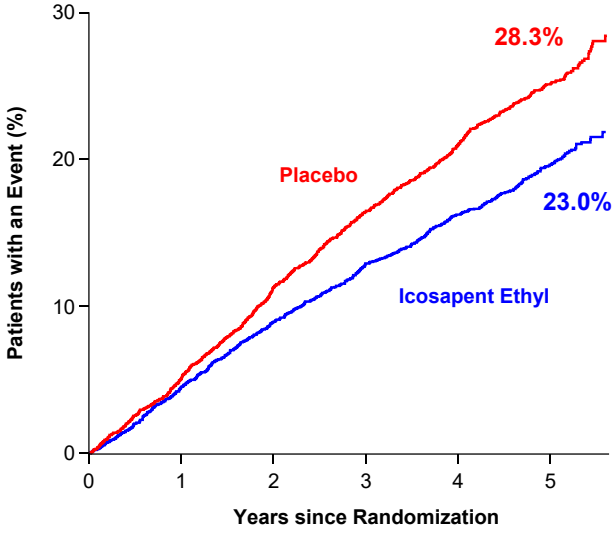
Primary End Point:

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



Hazard Ratio, 0.75
(95% CI, 0.68–0.83)
RRR = 24.8%
ARR = 4.8%
NNT = 21 (95% CI, 15–33)
P=0.00000001

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

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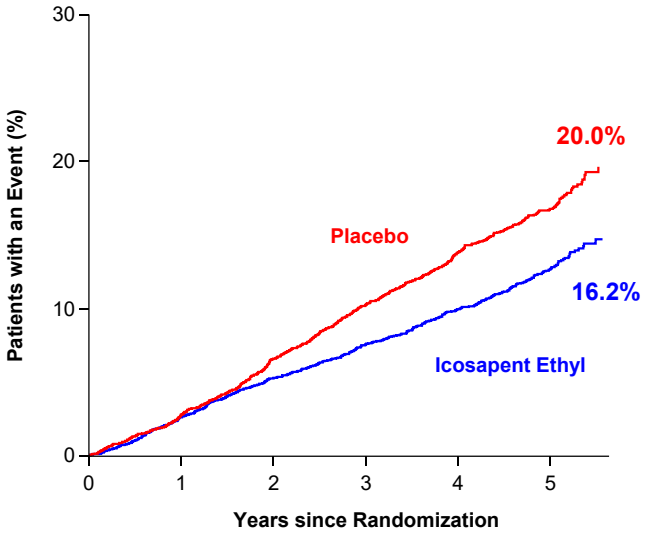
Key Secondary End Point:
CV Death, MI, Stroke



Hazard Ratio, 0.74
(95% CI, 0.65–0.83)
RRR = 26.5%
ARR = 3.6%
NNT = 28 (95% CI, 20–47)
P=0.0000006

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

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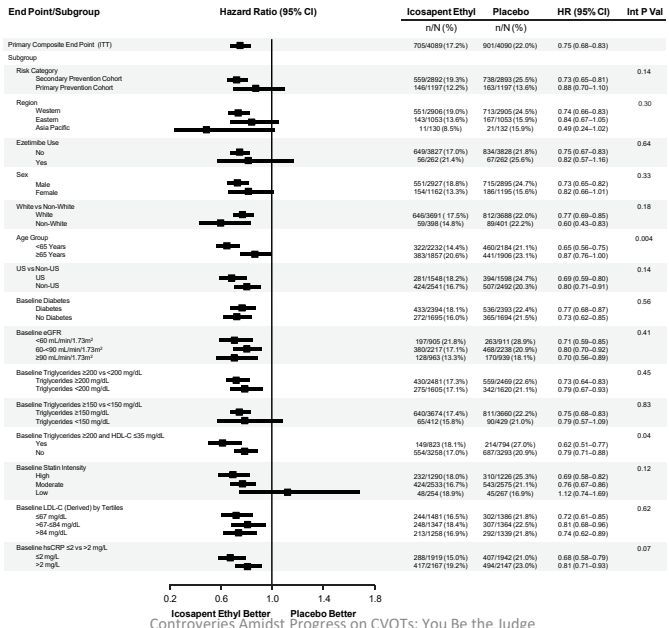
Primary End Point in Subgroups



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

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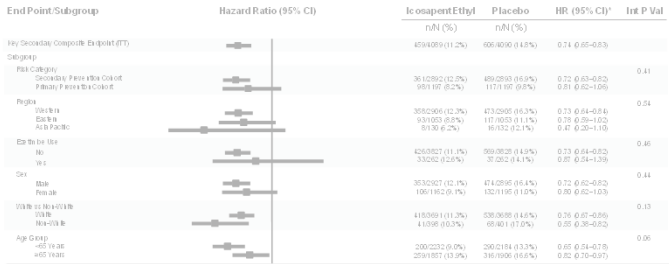
Key Secondary End Point in Subgroups



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.* 2019; 380:11-22.

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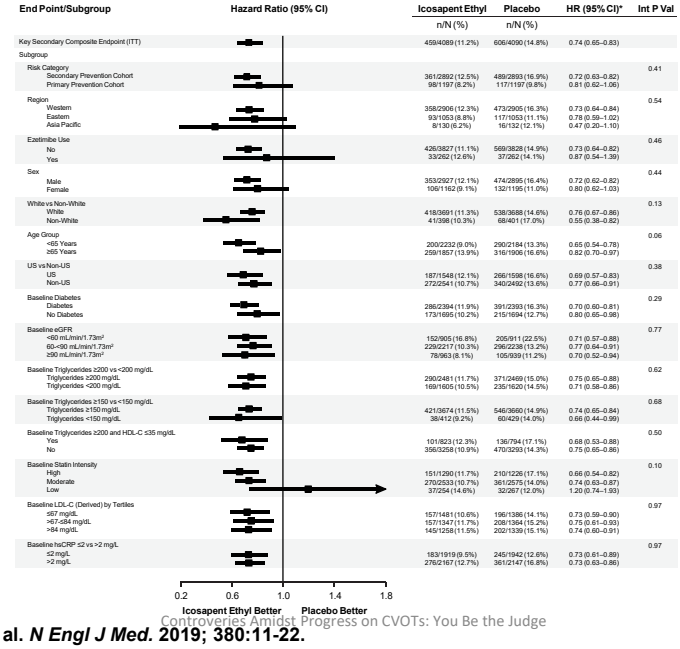
Key Secondary End Point in Subgroups



End Point/Subgroup	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)*	Int P Val
Key Secondary Composite Endpoint (ITT)	459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65–0.83)	
Subgroup				
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)	
Region				0.54
Western	358/2906 (12.3%)	473/2905 (16.3%)	0.73 (0.64–0.84)	
Eastern	93/1053 (8.8%)	117/1053 (11.1%)	0.78 (0.59–1.02)	
Asia Pacific	8/130 (6.2%)	16/132 (12.1%)	0.47 (0.20–1.10)	
Ezetimibe Use				0.46
No	426/3827 (11.1%)	569/3828 (14.9%)	0.73 (0.64–0.82)	
Yes	33/262 (12.6%)	37/262 (14.1%)	0.87 (0.54–1.39)	
Sex				0.44
Male	353/2927 (12.1%)	474/2895 (16.4%)	0.72 (0.62–0.82)	
Female	106/1162 (9.1%)	132/1195 (11.0%)	0.80 (0.62–1.03)	
White vs Non-White				0.13
White	418/3691 (11.3%)	538/3688 (14.6%)	0.76 (0.67–0.86)	
Non-White	41/398 (10.3%)	68/401 (17.0%)	0.55 (0.38–0.82)	
Age Group				0.06
<65 Years	200/2232 (9.0%)	290/2184 (13.3%)	0.65 (0.54–0.78)	
≥65 Years	259/1857 (13.9%)	316/1906 (16.6%)	0.82 (0.70–0.97)	
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)	
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)	
Baseline eGFR				0.77
<60 mL/min/1.73m²	152/905 (16.8%)	205/911 (22.5%)	0.71 (0.57–0.88)	
60–<90 mL/min/1.73m²	229/2217 (10.3%)	296/2238 (13.2%)	0.77 (0.64–0.91)	
≥90 mL/min/1.73m²	78/963 (8.1%)	105/939 (11.2%)	0.70 (0.52–0.94)	
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)	
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)	
Baseline Triglycerides ≥200 and HDL-C ≤35 mg/dL				0.50
Yes	101/823 (12.3%)	136/794 (17.1%)	0.68 (0.53–0.88)	
No	356/3258 (10.9%)	470/3293 (14.3%)	0.75 (0.65–0.86)	
Baseline Statin Intensity				0.10
High	151/1290 (11.7%)	210/1226 (17.1%)	0.66 (0.54–0.82)	
Moderate	270/2533 (10.7%)	361/2575 (14.0%)	0.74 (0.63–0.87)	
Low	37/254 (14.6%)	32/267 (12.0%)	1.20 (0.74–1.93)	
Baseline LDL-C (Derived) by Tertiles				0.97
≤67 mg/dL	157/1481 (10.6%)	196/1386 (14.1%)	0.73 (0.59–0.90)	
>67–≤84 mg/dL	157/1347 (11.7%)	208/1364 (15.2%)	0.75 (0.61–0.93)	
>84 mg/dL	145/1258 (11.5%)	202/1339 (15.1%)	0.74 (0.60–0.91)	
Baseline hsCRP ≤2 vs >2 mg/L				0.97
≤2 mg/L	183/1919 (9.5%)	245/1942 (12.6%)	0.73 (0.61–0.89)	
>2 mg/L	276/2167 (12.7%)	361/2147 (16.8%)	0.73 (0.63–0.86)	

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

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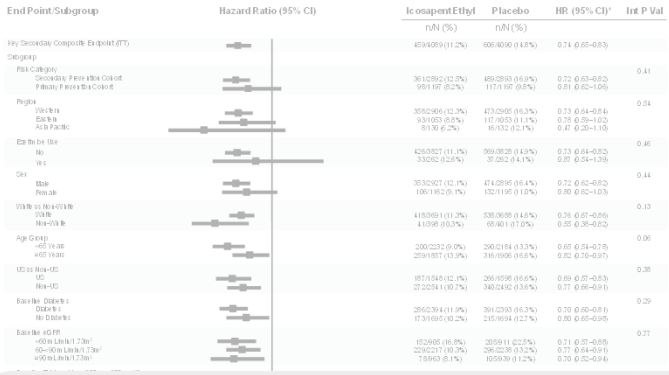
Key Secondary End Point in Subgroups



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)	

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

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Prespecified Hierarchical Testing

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

RRR denotes relative risk reduction

Bhatt DL. AHA 2018, Chicago.

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

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REDUCE-IT Tertiary Endpoints: Cardiac Arrest, Sudden Cardiac Death, Arrhythmias

Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)
Cardiac Arrest	**22/4089 (0.5%)**	**42/4090 (1.0%)**	**0.52 (0.31, 0.86)**
Sudden Cardiac Death	**61/4089 (1.5%)**	**87/4090 (2.1%)**	**0.69 (0.50, 0.96)**
Cardiac Arrhythmias Requiring Hospitalization of ≥ 24 Hours	188/4089 (4.6%)	154/4090 (3.8%)	1.21 (0.97, 1.49)

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

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REDUCE-IT Tertiary Endpoints: Revascularization

Revascularization Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)
Coronary	**376/4089 (9.2%)**	**544/4090 (13.3%)**	**0.66 (0.58, 0.76)**
Emergent	**41/4089 (1.0%)**	**65/4090 (1.6%)**	**0.62 (0.42, 0.92)**
Urgent	**181/4089 (4.4%)**	**268/4090 (6.6%)**	**0.66 (0.54, 0.79)**
Elective	**194/4089 (4.7%)**	**278/4090 (6.8%)**	**0.68 (0.57, 0.82)**
Carotid Revascularization	31/4089 (0.8%)	26/4090 (0.6%)	1.18 (0.70, 1.98)
Salvage Revascularization	0/4089 (0.0%)	2/4090 (0.0%)	0.00 (0.00, -)

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

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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.* 2019; 380:11-22.

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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.* 2019; 380:11-22.

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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.* 2019; 380:11-22.

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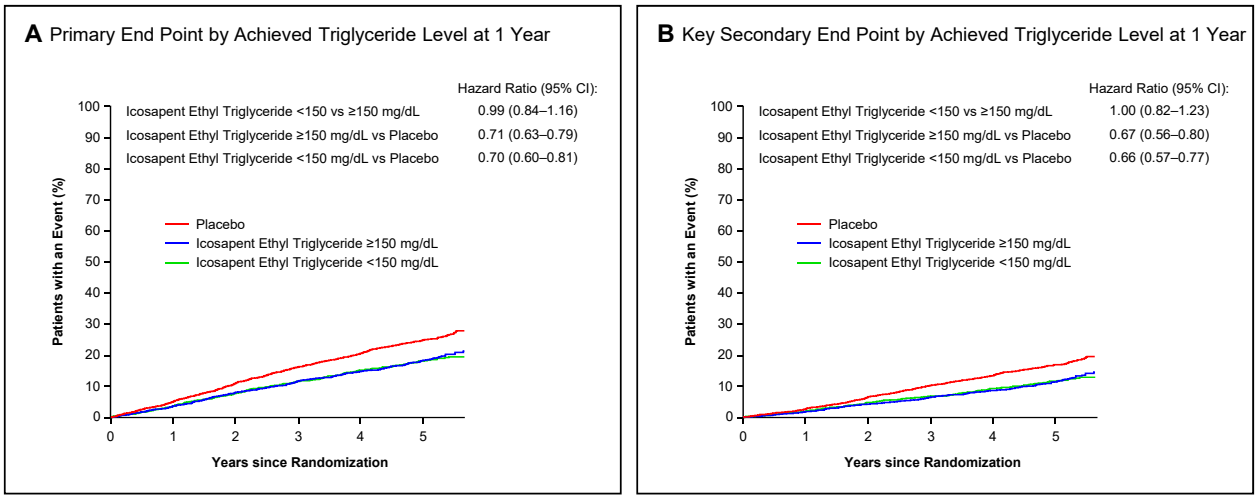
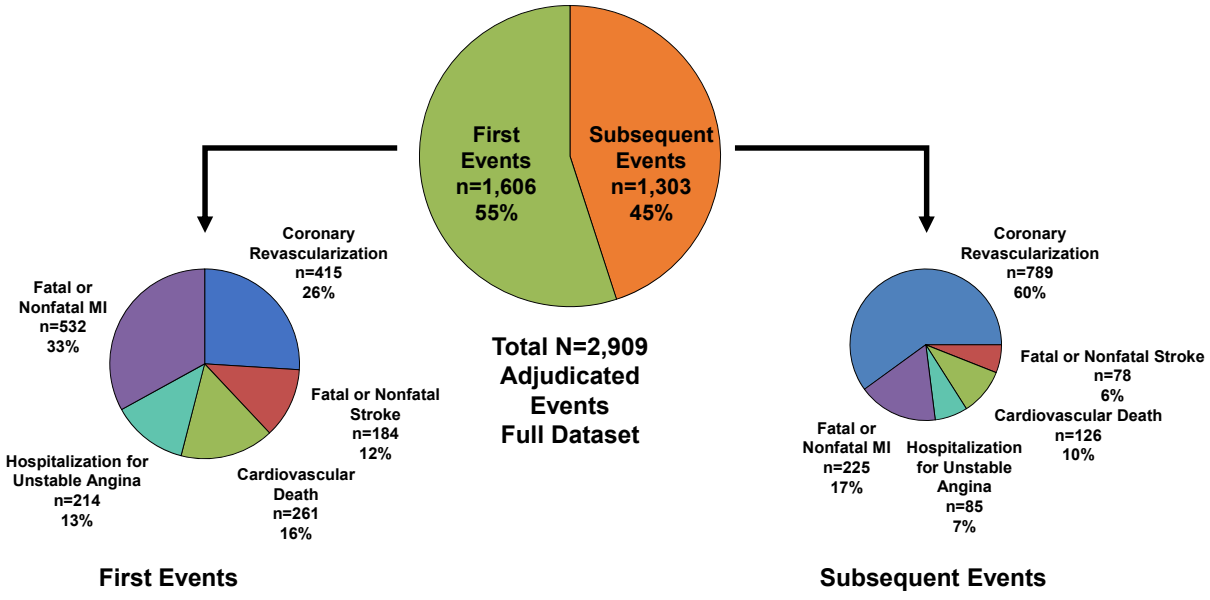
Achieved Triglyceride Levels: <150 mg/dL and ≥150 mg/dL



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

24

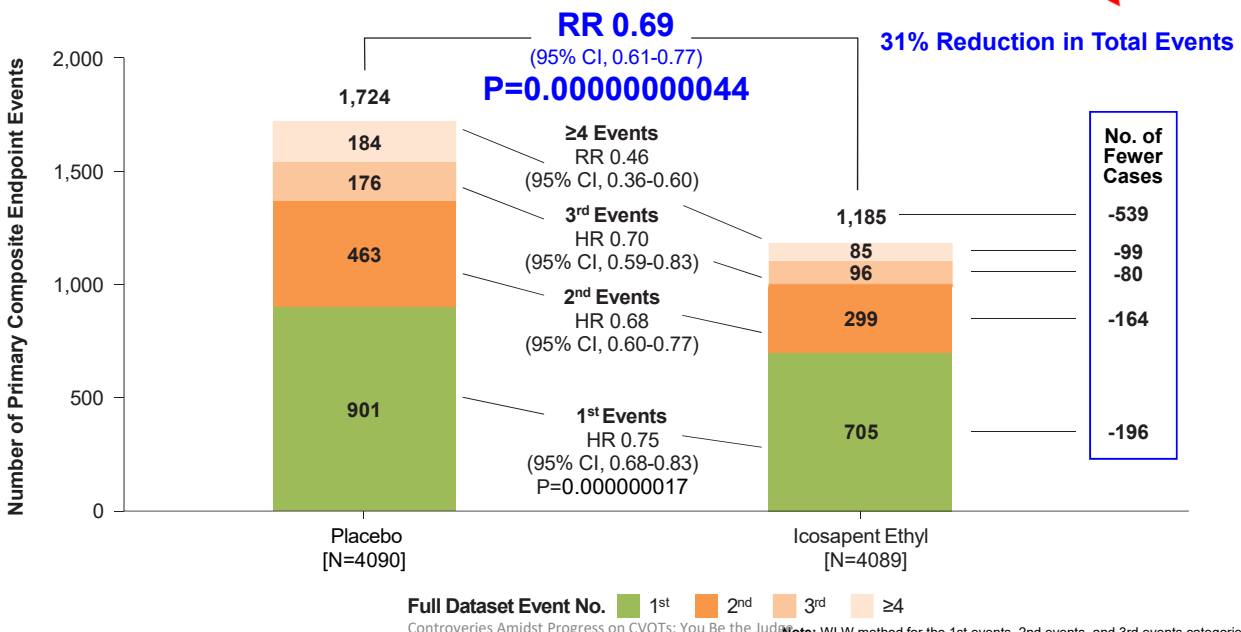
Proportions of First and Subsequent Events



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

25

First and Subsequent Events – Full Data



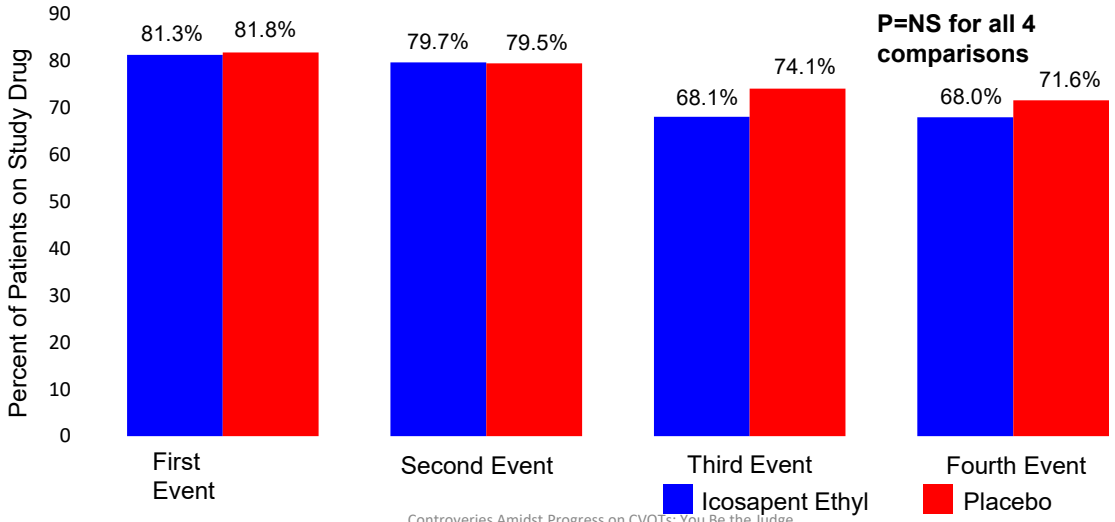
Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019;73:2791-2802.

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

26

Adherence

- As is common in long-term trials, study drug adherence waned over time
- Despite this, there was strong sustained treatment effect on total events

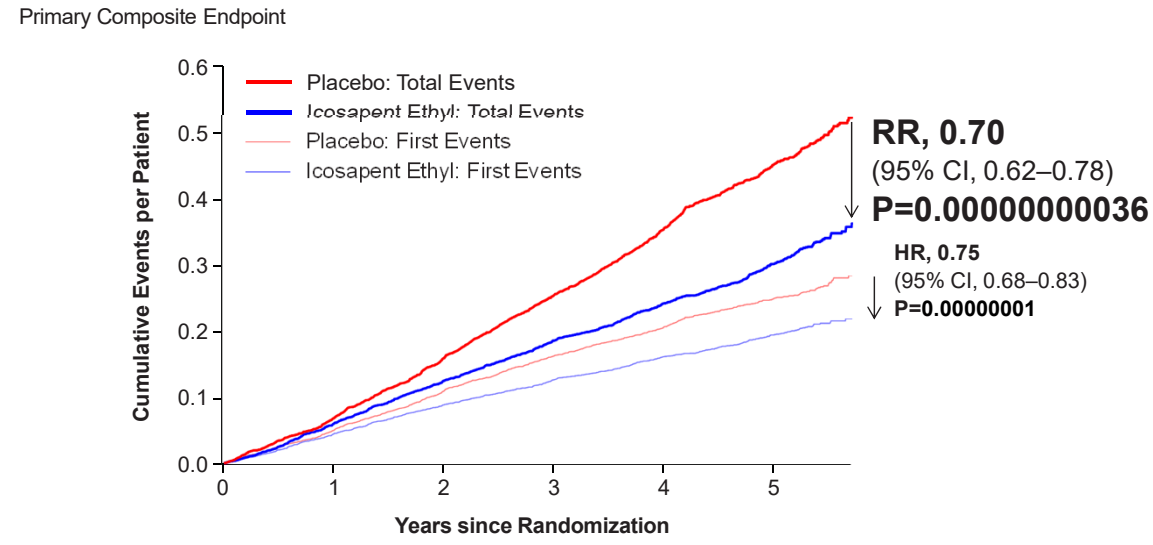


Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol.* 2019;73:2791-2802. Bhatt DL. ACC 2019, New Orleans.

27

Total (First and Subsequent) Events

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

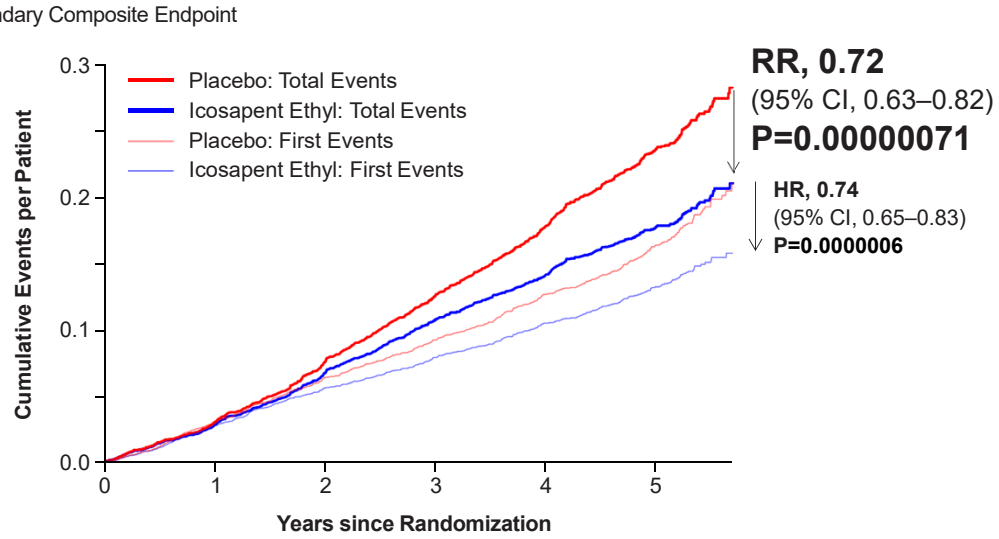


Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol.* 2019;73:2791-2802.

28

Total (First and Subsequent) Events

Key Secondary: CV Death, MI, Stroke

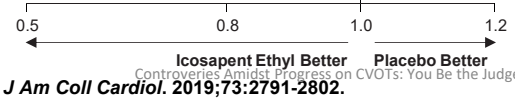


Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019;73:2791-2802.

29

Total Primary and Key Secondary Composite Endpoint Events and First, Second, and Third Occurrences (Full Dataset, Unadjusted)

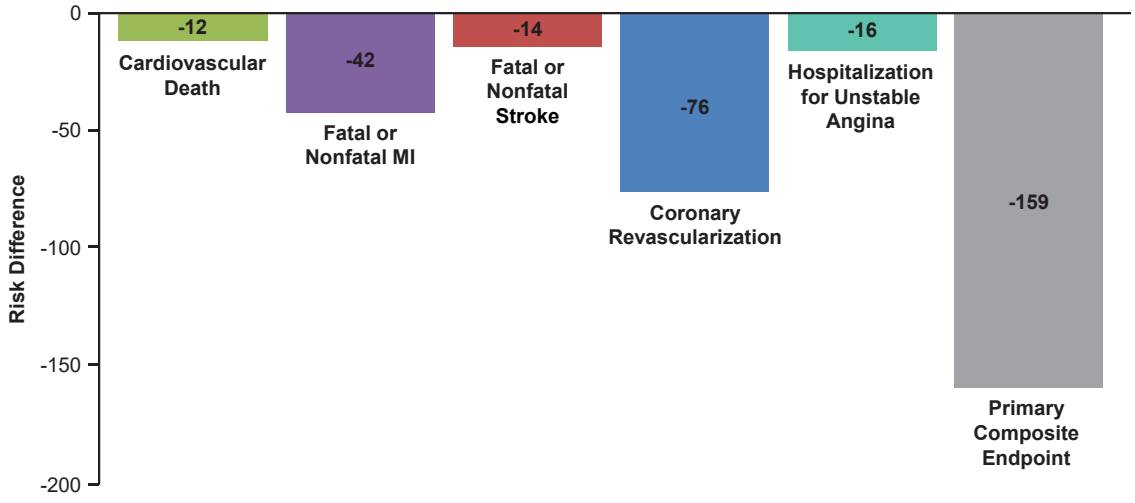
Endpoint/Model	Unadjusted Rate/Hazard Ratio (95% CI)	Unadjusted P-value
Primary Composite Endpoint		
Negative binomial	0.67 (0.60, 0.76)	1.6×10^{-10}
Andersen-Gill (I)	0.68 (0.63, 0.74)	3.4×10^{-22}
Andersen-Gill (II)	0.68 (0.61, 0.77)	4.5×10^{-11}
Modified WLW		
First event	0.76 (0.69, 0.83)	2.7×10^{-8}
Second event	0.69 (0.61, 0.78)	4.6×10^{-9}
Third event	0.70 (0.60, 0.83)	2.2×10^{-5}
Key Secondary Composite Endpoint		
Negative binomial	0.71 (0.62, 0.81)	1.4×10^{-6}
Andersen-Gill (I)	0.71 (0.64, 0.79)	1.8×10^{-10}
Andersen-Gill (II)	0.71 (0.62, 0.81)	4.1×10^{-7}
Modified WLW		
First event	0.74 (0.65, 0.83)	7.4×10^{-7}
Second event	0.75 (0.63, 0.89)	0.0011
Third event	0.79 (0.65, 0.96)	0.0170



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

30

For Every 1000 Patients Treated with Icosapent Ethyl for 5 Years:



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

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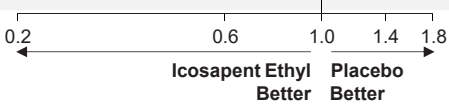
Primary Composite Endpoint: Total Endpoint Events by Baseline TG Tertiles

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*				
≥81 to ≤190 mg/dL	56.4	74.5	0.74 (0.61–0.90)	0.0025
>190 to ≤250 mg/dL	63.2	86.8	0.77 (0.63–0.95)	0.0120
>250 to ≤1401 mg/dL	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-

32

Total Ischemic Events by Baseline TG and Achieved TG at 1 Year

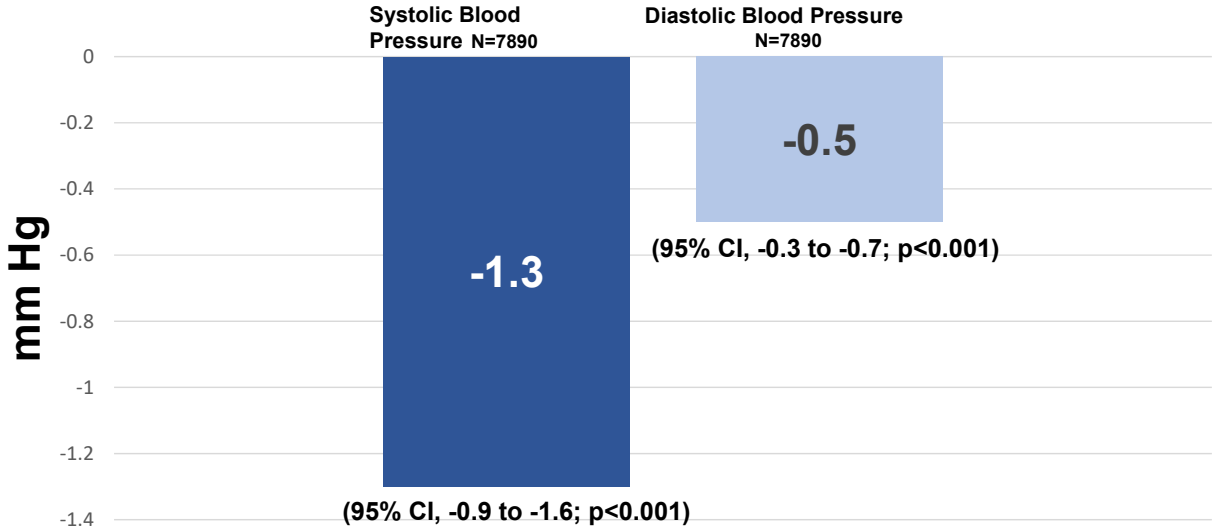
		Total Primary Composite Endpoint		Total Key Secondary Composite Endpoint	
	n (%)† (N=8179)	RR (95% CI)	Interaction p-value	RR (95% CI)	Interaction p-value
Baseline triglycerides			0.26		0.89
≥200 mg/dl	4950 (60.5)	0.66 (0.57-0.77)		0.71 (0.60-0.84)	
<200 mg/dl	3225 (39.4)	0.76 (0.63-0.91)		0.72 (0.58-0.90)	
Baseline triglycerides			0.94		0.88
≥150 mg/dl	7334 (89.7)	0.70 (0.62-0.78)		0.72 (0.62-0.82)	
<150 mg/dl	841 (10.3)	0.71 (0.49-1.03)		0.69 (0.44-1.08)	
Baseline triglycerides tertiles			0.17		0.18
≥81 to ≤190 mg/dl	2759 (33.7)	0.74 (0.61-0.90)		0.68 (0.54-0.87)	
>190 to ≤250 mg/dl	2696 (33.0)	0.77 (0.63-0.95)		0.85 (0.67-1.08)	
>250 to ≤1401 mg/dl	2720 (33.3)	0.60 (0.50-0.73)		0.63 (0.51-0.78)	
Achieved triglycerides at 1 year*	(N=4089)		-		-
Icosapent ethyl TG ≥150 mg/dl vs Placebo	2364 (57.8)	0.66 (0.57-0.75)		0.63 (0.54-0.74)	
Icosapent ethyl TG <150 mg/dl vs Placebo	- 1325 (32.4)	0.62 (0.53-0.74)		0.65 (0.53-0.78)	

* Statistical comparisons of each icosapent ethyl triglyceride group (≥150 mg/dl or <150 mg/dl at 1 year) against the entire placebo group; no interaction p values are generated.
†Number and percentage of patients in each baseline TG subgroup across combined icosapent ethyl and placebo groups; and number and percentage of patients in each 1-year TG group (≥150 mg/dl or <150 mg/dl) for icosapent ethyl.

Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol.* 2019;74:1845-50.

33

Placebo-corrected Reductions in Blood Pressure from Baseline with Icosapent Ethyl 4g/day

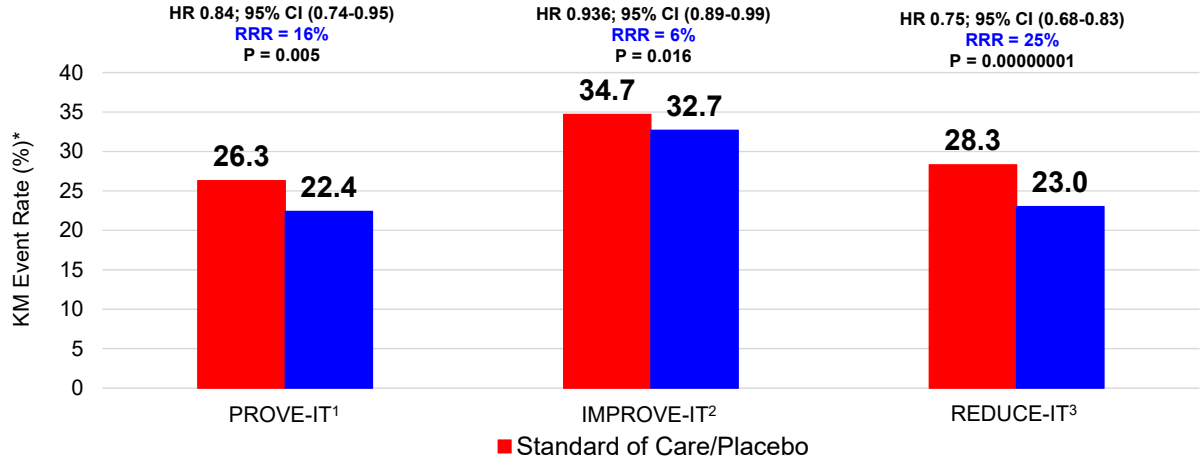


Prespecified exploratory analysis with no adjustment for multiple comparisons. Repeated-measurements analysis of change from baseline blood pressure over time by mixed-effects model. ITT population. Icosapent ethyl n=4089, Placebo n=4091. Maximum number of observations per patient = 6.

Bhatt DL, Steg PG, Miller M. *N Engl J Med.* 2019;380:1678.

34

Time to First Event Residual Risk Reduction: PROVE-IT, IMPROVE-IT, REDUCE-IT



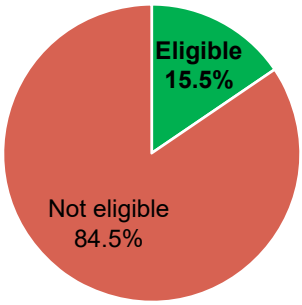
*Kaplan-Meier event rates based on the following time periods: PROVE-IT, 2 years; IMPROVE-IT, 7 years; REDUCE-IT, 5.7 years.
First events PROVE-IT: Death from any cause, myocardial infarction, stroke, coronary revascularization, hospitalization for unstable angina.

1. Cannon CP, Braunwald E, et al. *N Engl J Med* 2004;350:1495-1504. 2. Cannon CP, Blazing MA, Giugliano RP, et al. Braunwald E, Califf RM. *N Engl J Med.* 2015;372:2387–2397. 3. Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019;380:11-22. Bhatt DL. AHA 2018, Chicago. Boden WE, Bhatt DL, et al. *EHJ* 2019 in press

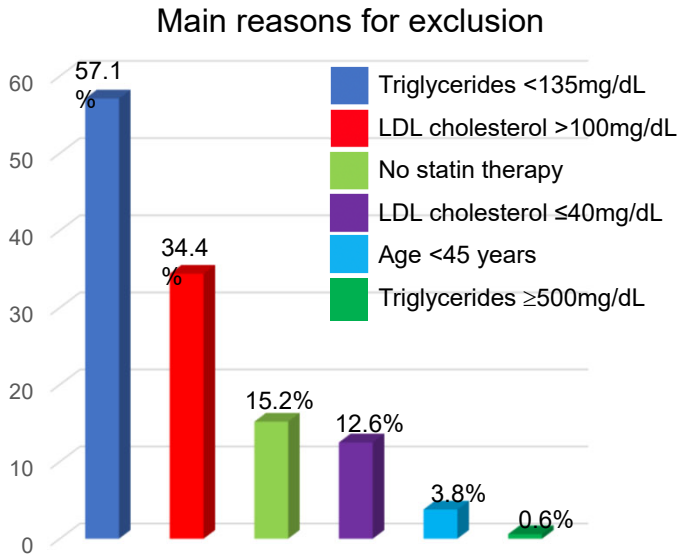
35

Generalizability of REDUCE-IT in Patients with Stable CAD

An analysis of 24,146 patients from the CLARIFY registry



Key Inclusion Criteria for CLARIFY Analysis
- Statin-treated men or women
- Age ≥45 years with either established CV disease OR age ≥50 years with diabetes mellitus and at least one additional CV risk factor
- AND triglycerides ≥135 and <500 mg/dL
- AND LDL-cholesterol >40 and ≤100 mg/dL



Picard F, Bhatt DL, Ducrocq G, et al. Steg PG. *JACC.* 2019.

36

Generalizability of REDUCE-IT in Patients with Stable CAD

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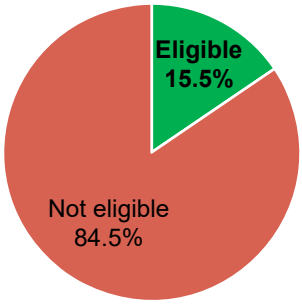

Key Inclusion Criteria for CLARIFY Analysis
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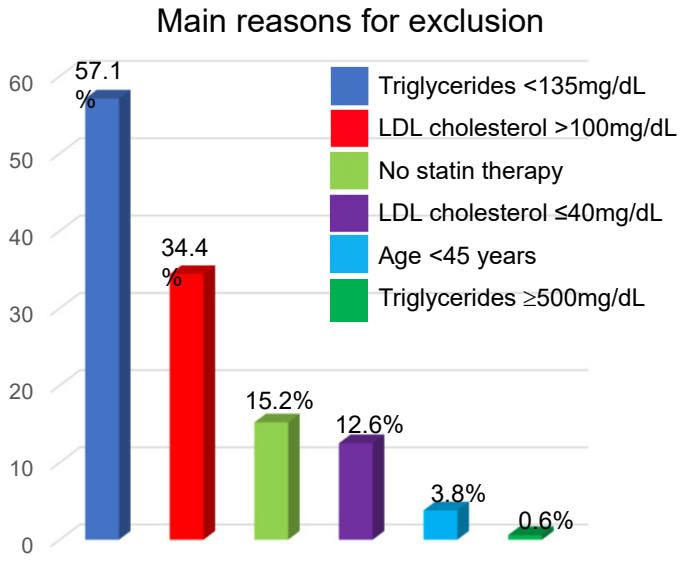
- Age ≥45 years with either established CV disease OR age ≥50 years with diabetes mellitus and at least one additional CV risk factor
- AND triglycerides ≥135 and <500 mg/dL
- AND LDL-cholesterol >40 and ≤100 mg/dL

NOTE: REDUCE-IT also enrolled patients with PAD, CVD, and DM with at least one risk factor



Picard F, Bhatt DL, Ducrocq G, et al. Steg PG. *JACC.* 2019.

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ICER Base Case and Sensitivity Analyses

Base-Case Incremental Results						
Intervention	**Incremental Costs**	**Incremental LYs**	**Incremental QALYs**	**Cost per LY**	**Cost per QALY**	**Cost per MACE Avoided**
Icosapent Ethyl vs. Medical Management	$9,000	0.54	0.50	$17,000 per LY gained	$18,000 per QALY gained	$53,000 per MACE avoided

Probabilistic Sensitivity Analysis Results			
Intervention	**Cost-Effective at $50,000 per QALY**	**Cost-Effective at $100,000 per QALY**	**Cost-Effective at $150,000 per QALY**
Icosapent Ethyl vs. Medical Management	100%	100%	100%

LY= life year; MACE = major cardiovascular event; QALY = quality adjusted life year.

1. Institute for Clinical and Economic Review (ICER). Draft Evidence Report. Additive Therapies for Cardiovascular Disease: Effectiveness and Value. https://icer-review.org/wp-content/uploads/2019/02/ICER_CVD_Draft_Evidence_Report_072419.pdf. Posted July 24, 2019. Accessed July 24, 2019

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BRIGHAM AND WOMEN'S HOSPITAL

| Heart & Vascular Center |

Thank You!

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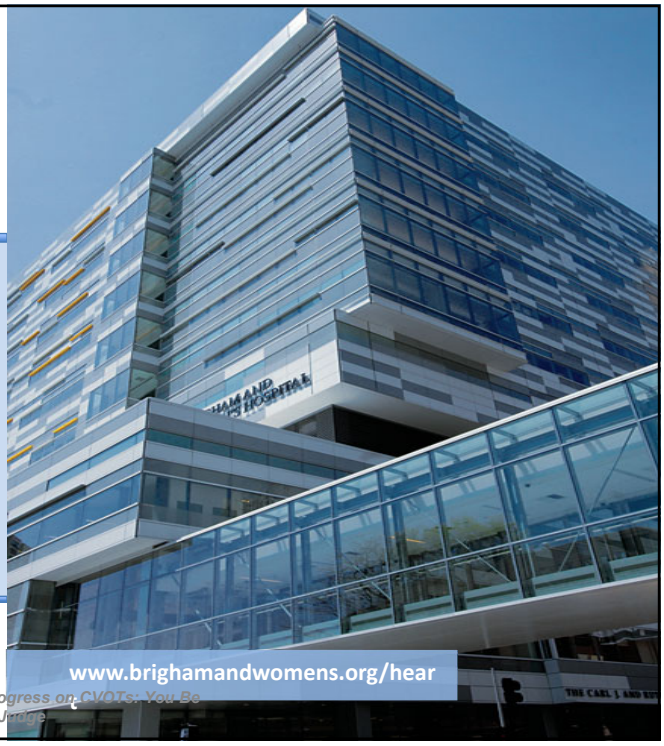
HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL



Clinical Implications of 2019 Level A CVOTs on CVD Risk Reduction

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Charles A. Boettcher Chair in Atherosclerosis
Professor of Medicine, Emeritus
Division of Endocrinology, Metabolism & Diabetes
Division of Cardiology
CU Anschutz Medical Campus
American Heart Association, Past President
American Diabetes Association, President Elect

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Robert H. Eckel, MD

Disclosures: Consulting Fees: Novo Nordisk, Sanofi; Contracted Research: ENDEC

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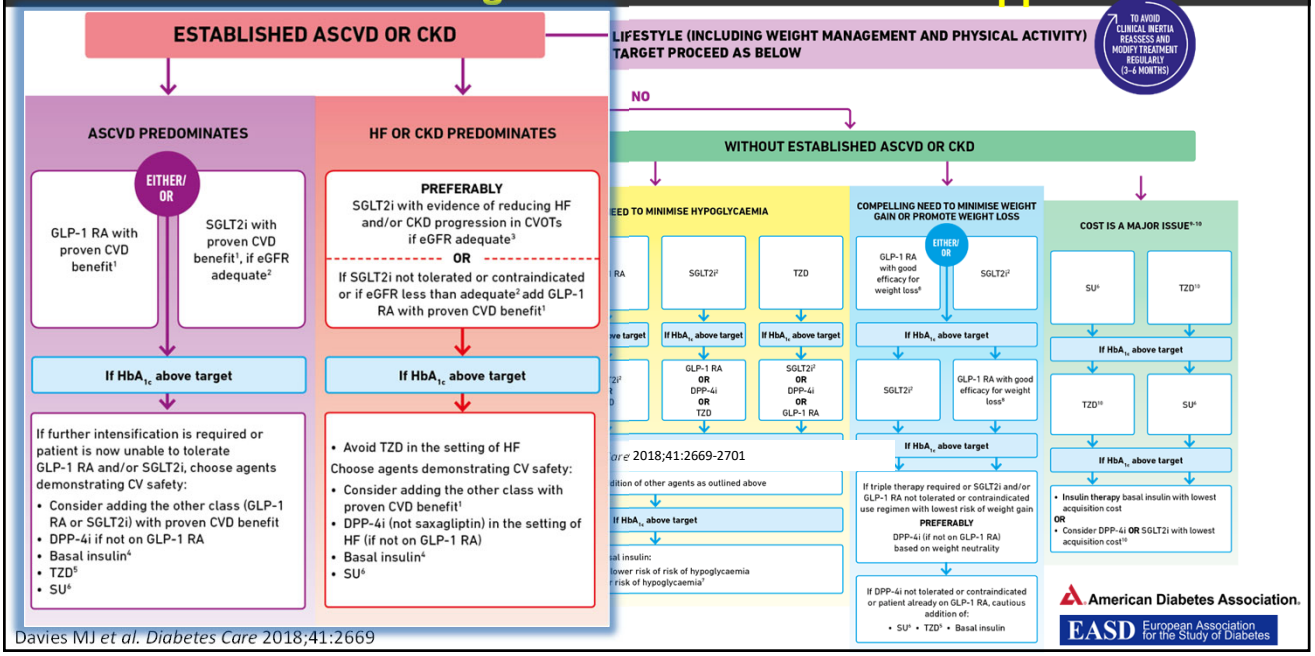
Let's first look at the updated 2019 ADA/EASD Standards of Care for management of glycemia in patients with diabetes based on CVOTs

42

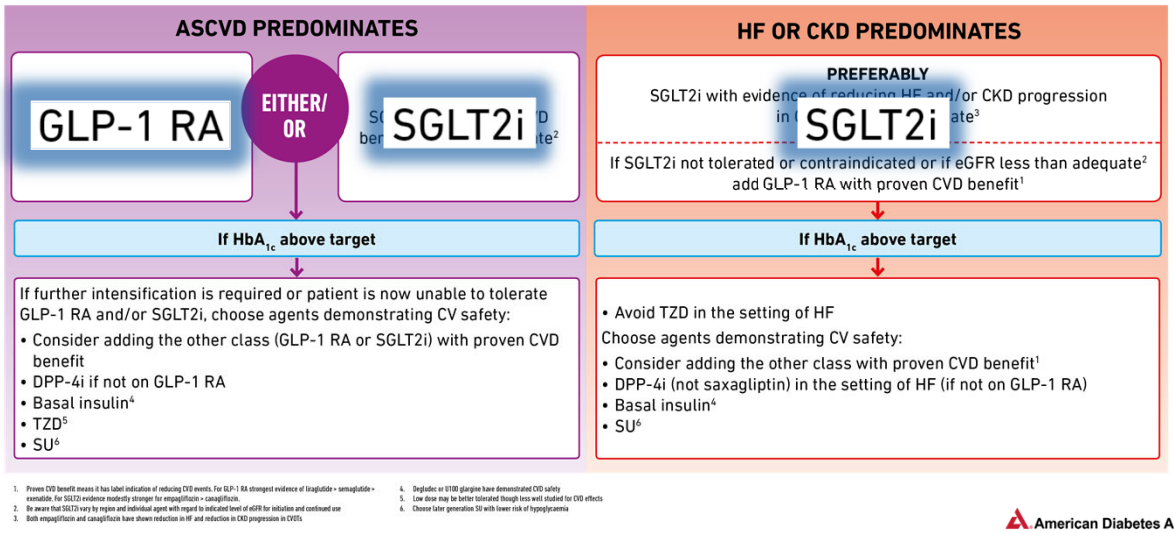
2018 ADA-EASD Consensus & 2019 ADA Standards of Care: Glucose-Lowering Meds in T2DM - Overall Approach



Davies MJ *et al. Diabetes Care* 2018;41:2669

43

2018 ADA-EASD Consensus & 2019 ADA Standards of Care: Glucose-Lowering Meds in T2DM – Established ASCVD / CKD

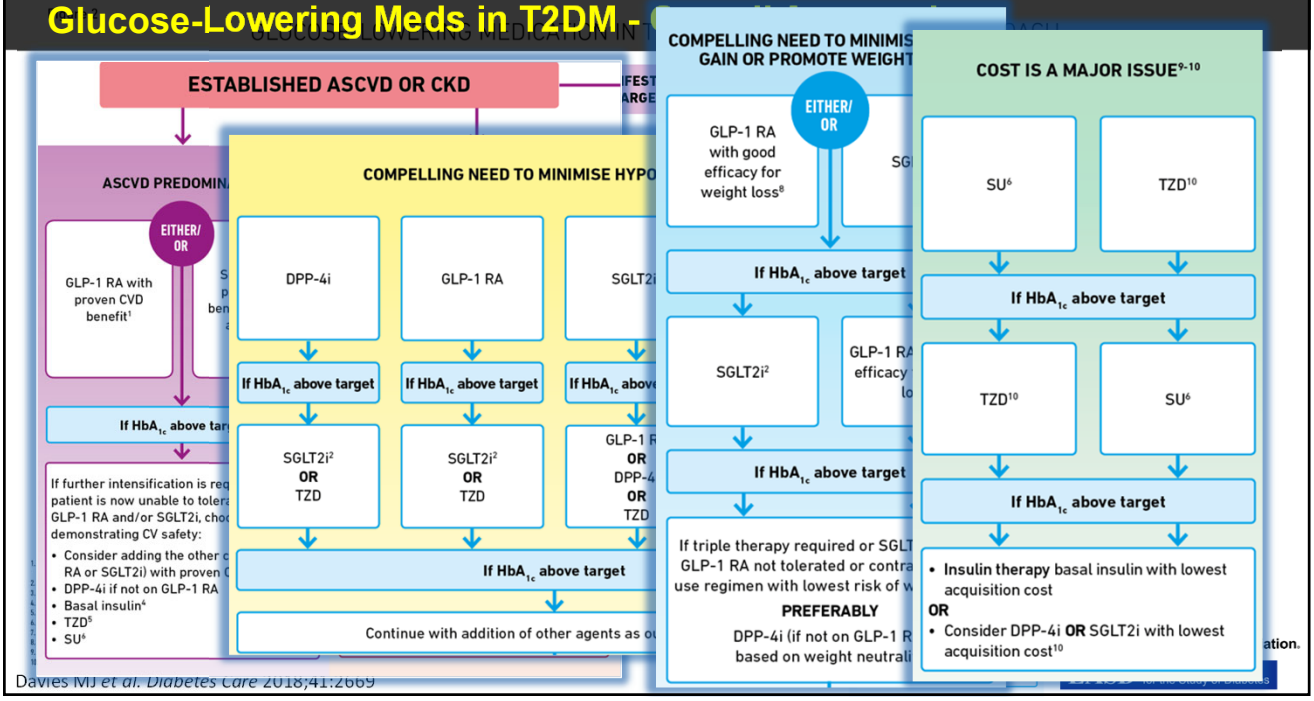


Davies MJ *et al. Diabetes Care* 2018;41:2669

American Diabetes Association.
EASD European Association for the Study of Diabetes

44

2018 ADA-EASD Consensus & 2019 ADA Standards of Care: Glucose-Lowering Meds in T2DM -



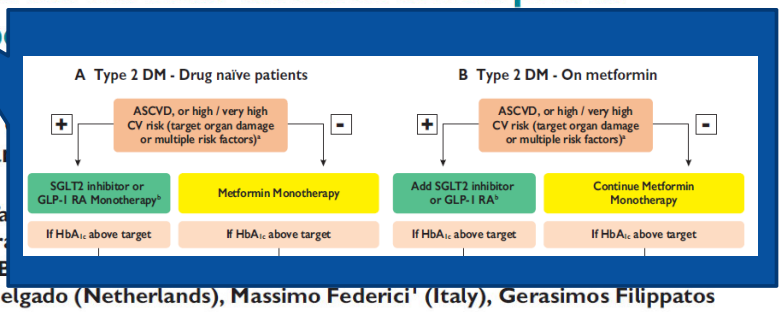
Davies MJ *et al. Diabetes Care* 2018;41:2669

45

ESC European Society of Cardiology
European Heart Journal (2019) 00, 1–69
doi:10.1093/eurheartj/ehz486

ESC GUIDELINES

2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in col



The Ta
diseases
Europea

Authors/Ta
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46

Deciding Between SGLT2 Inhibitors and GLP-1 RAs

First, do we really understand how these two classes of agents work?

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ACC 2018: Deciding Between SGLT2 Inhibitors and GLP-1 RAs

Consider SGLT2 Inhibitor	Consider GLP-1 RA
Reducing MACE and CV death	Reducing MACE and CV death
Preventing heart failure hospitalization	Substantial weight loss
Reducing blood pressure	Once weekly (subcutaneous) dosing - *Semaglutide orally available*
Orally administered therapies	Therapy when eGFR consistently <45 mL/min/1.73 m^2
Consider alternative agents if: • Significant CKD • History of prior amputation, severe peripheral arterial disease, neuropathy, or diabetic foot ulcers (avoid canagliflozin) • History of recurrent genital candidiasis • History of diabetic ketoacidosis • History of osteoporosis (avoid canagliflozin)	Consider alternative agents if: • Persistent nausea, even at low doses • History of pancreatitis • History of gastroparesis • History of MEN2 or medullary thyroid cancer • History of proliferative retinopathy (semaglutide)

Das SR, et al. *J Am Coll Cardiol.* 2018 Dec 18;72(24):3200-3223.

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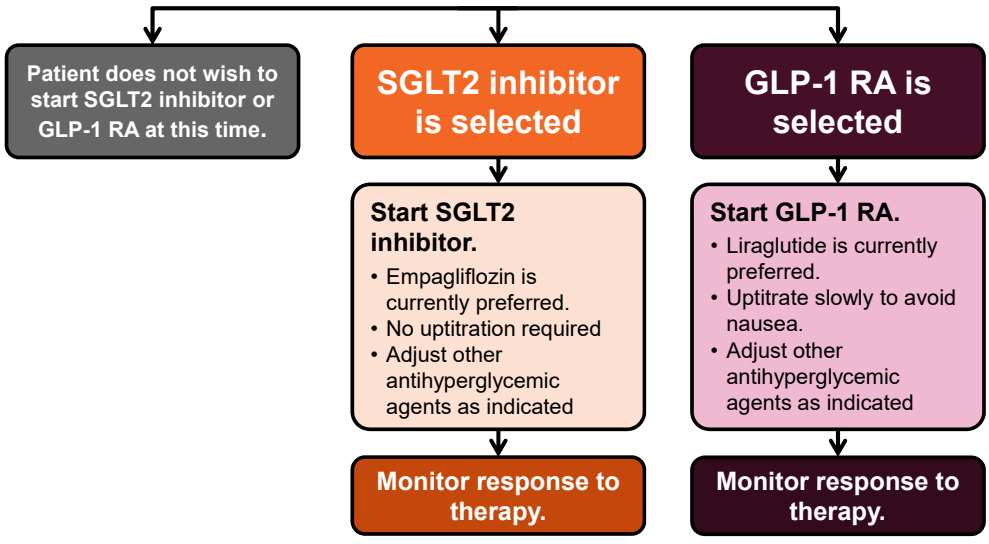
2018 ACC Decision Pathway



Das SR, et al. *J Am Coll Cardiol.* 2018 Dec 18;72(24):3200-3223.

49

Let's now look at the updated 2019 ADA/EASD Standard of Care for lipid management based on CVOTs

50

Lifestyle

- Lifestyle modification focusing on weight loss (if indicated); application of a **Mediterranean eating plan or DASH dietary pattern**; the reduction of saturated fat and *trans* fat; increase of dietary n-3 fatty acids, viscous fiber, and plant stanols/sterols intake; and increased physical activity should be recommended to improve the lipid profile and reduce the risk of developing ASCVD in patients with diabetes. **A**
- **Intensify lifestyle therapy and optimize glycemic control** for patients with **elevated triglyceride levels** (≥150 mg/dL [1.7 mmol/L]) and/or low HDL cholesterol (<40 mg/dL [1.0 mmol/L] for men, <50 mg/dL [1.3 mmol/L] for women). **C**

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Maintain an Overall Healthy Diet!






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Get or Stay Active

53

Ongoing Therapy and Monitoring With Lipid Panel

- In adults not taking statins or other lipid-lowering therapy, it is reasonable to obtain a lipid profile at the time of diabetes diagnosis, at an initial medical evaluation, and **every 5 years** thereafter if under the age of 40 years, or more frequently if indicated. **E**
- Obtain a lipid profile at initiation of statins or other lipid-lowering therapy, **4–12 weeks after initiation or a change in dose**, and annually thereafter as it may help to monitor the response to therapy and inform medication adherence. **E**

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Statin Treatment

- For patients of all ages with diabetes and ASCVD or **10-year ASCVD risk >20%, high-intensity statin therapy** should be added to lifestyle therapy. **A**
- For patients with **diabetes aged <40 years with additional ASCVD risk factors**, the patient and provider should consider using **moderate-intensity statin** in addition to lifestyle therapy. **C**
- For patients with **diabetes aged 40–75 years A and >75 years without ASCVD**, use **moderate-intensity statin** in addition to lifestyle therapy. **B**

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Statin Treatment

- In patients with **diabetes who have multiple ASCVD risk factors**, it is reasonable to consider **high-intensity statin** therapy. **C**
- For patients who do not tolerate the intended intensity, the **maximum tolerated statin dose** should be used. **E**
- For patients with **diabetes and ASCVD, if LDL cholesterol is ≥70 mg/dL** on maximally tolerated statin dose, consider adding additional LDL-lowering therapy (**such as ezetimibe or PCSK9 inhibitor**). **A**
  - *Ezetimibe may be preferred due to lower cost.*

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Other Combination Therapy

- Combination therapy (**statin/fibrate**) has not been shown to improve ASCVD outcomes and is generally **not recommended**. **A**
- Combination therapy (**statin/niacin**) has not been shown to provide additional cardiovascular benefit above statin therapy alone, may increase the risk of stroke with additional side effects, and is generally **not recommended**. **A**

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REDUCE-IT

- **Icosapent ethyl (Vascepa, Amarin) be considered** to reduce CV risk for patients with diabetes who have atherosclerotic CVD or other CV risk factors and who are prescribed a statin and have controlled LDL cholesterol but persistently elevated triglycerides.
- The recommendation is based on findings from the REDUCE-IT trial, which found that icosapent ethyl was superior to placebo for reducing risk for ischemic events in **patients with elevated triglycerides at high CV risk despite statin therapy.**

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ACC/AHA Multiple Society 2018 Cholesterol Guidelines – Top 10 Take Home Messages

1. **In all individuals, emphasize a heart-healthy lifestyle across the life course**.

A healthy lifestyle reduces atherosclerotic cardiovascular disease (ASCVD) risk at all ages. In younger individuals, healthy lifestyle can reduce development of risk factors and is the foundation of ASCVD risk reduction.

In young adults 20 to 39 years of age, an assessment of lifetime risk facilitates the clinician–patient risk discussion (see No. 6) and emphasizes intensive lifestyle efforts. In all age groups, lifestyle therapy is the primary intervention for metabolic syndrome.

Grundy SM et al. *Circulation*. 2019;139:e1082-e1143.

59

Top 10 Take Home Messages

2. In patients with clinical ASCVD, reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy.

The more LDL-C is reduced on statin therapy, the greater will be subsequent risk reduction.

Use a maximally tolerated statin to lower LDL-C levels by ≥50%.

Grundy SM et al. *Circulation*. 2019;139:e1082-e1143.

60

Top 10 Take Home Messages

3. In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL to consider addition of nonstatins to statin therapy.

- Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.
- In very high-risk ASCVD patients, it is reasonable to add ezetimibe to maximally tolerated statin therapy when the LDL-C level remains ≥70 mg/dL.
- In patients at very high risk whose LDL-C level remains ≥70 mg/dL on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable, although the long-term safety (>3 years) is uncertain and cost-effectiveness is low at mid-2018 list prices.

Grundy SM et al. *Circulation*. 2019;139:e1082-e1143.

61

Top 10 Take Home Messages

4. In patients with severe primary hypercholesterolemia (LDL-C level ≥190 mg/dL) without calculating 10-year ASCVD risk, begin high-intensity statin therapy without calculating 10-year ASCVD risk.

- If the LDL-C level remains ≥100 mg/dL, adding ezetimibe is reasonable
- If the LDL-C level on statin plus ezetimibe remains ≥100 mg/dL & the patient has multiple factors that increase subsequent risk of ASCVD events, PCSK9 inhibitor may be considered.

Grundy SM et al. *Circulation*. 2019;139:e1082-e1143.

62

Top 10 Take Home Messages

5. In patients 40 to 75 years of age with diabetes mellitus and LDL-C ≥70 mg/dL, start moderate-intensity statin therapy without calculating 10-year ASCVD risk.

In patients with diabetes mellitus at higher risk, especially those with multiple risk factors or those 50 to 75 years of age, it is reasonable to use a high-intensity statin to reduce the LDL-C level by ≥50%.

Grundy SM et al. *Circulation*. 2019;139:e1082-e1143.

63

Top 10 Take Home Messages

6. In adults 40 to 75 years of age evaluated for primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy.

Risk discussion should include a review of

- major risk factors (eg, cigarette smoking, elevated blood pressure, LDL-C, hemoglobin A1C [if indicated], and calculated 10-year risk of ASCVD);
- the presence of risk-enhancing factors (see No. 8);
- the potential benefits of lifestyle and statin therapies;
- the potential for adverse effects and drug–drug interactions;
- the consideration of costs of statin therapy; and
- the patient preferences & values in shared decision-making.

Grundy SM et al. *Circulation*. 2019;139:e1082-e1143.

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Top 10 Take Home Messages

7. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL, at a 10-year ASCVD risk of ≥7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy.

Risk-enhancing factors favor statin therapy (see No. 8).

If risk status is uncertain, consider using coronary artery calcium (CAC) to improve specificity (see No. 9). If statins are indicated, reduce LDL-C levels by ≥30%, and if 10-year risk is ≥20%, reduce LDL-C levels by ≥50%.

Grundy SM et al. *Circulation*. 2019;139:e1082-e1143.

65

Top 10 Take Home Messages

8. In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy (see No. 7).

Risk-enhancing factors include
- family history of premature ASCVD;
- persistently elevated LDL-C levels ≥160 mg/dL;
- metabolic syndrome;
- chronic kidney disease;
- history of preeclampsia or premature menopause (age <40 yrs);
- chronic inflammatory disorders (eg, rheumatoid arthritis, psoriasis, or chronic HIV);
- high-risk ethnic groups (eg, South Asian);
- persistent elevations of triglycerides ≥175 mg/dL

Grundy SM et al. *Circulation*. 2019;139:e1082-e1143.

66

Top 10 Take Home Messages

8. In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy (see No. 7).

Risk-enhancing factors include family history of premature ASCVD; persistently elevated LDL-C levels ≥160 mg/dL; metabolic syndrome; chronic kidney disease; history of preeclampsia or premature menopause (age <40 years); chronic inflammatory disorders (eg, rheumatoid arthritis, psoriasis, or chronic HIV); high-risk ethnic groups (eg, South Asian); persistent elevations of triglycerides ≥175 mg/dL; and, if measured in selected individuals
- apolipoprotein B ≥130 mg/dL;
- high-sensitivity C-reactive protein ≥2.0 mg/L;
- ankle-brachial index <0.9 and Lp(a) ≥50 mg/dL, especially at higher values of Lp(a).

Risk-enhancing factors may favor statin therapy in patients at 10-year risk of 5–7.5% (borderline risk)

Grundy SM et al. *Circulation*. 2019;139:e1082-e1143.

67

Top 10 Take Home Messages

9. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL – 189 mg/dL, at a 10-year ASCVD risk of ≥7.5% to 19.9%, if a decision about statin therapy is uncertain, consider measuring CAC.

- If CAC is zero, treatment with statin therapy may be withheld or delayed, except in cigarette smokers, those with diabetes mellitus, and those with a strong family history of premature ASCVD.
- A CAC score of 1 to 99 favors statin therapy, especially in those ≥55 years of age.
- For any patient, if the CAC score is ≥100 Agatston units or ≥75th percentile, statin therapy is indicated unless otherwise deferred by the outcome of clinician-patient risk discussion.

Grundy SM et al. *Circulation*. 2019;139:e1082-e1143.

68

Top 10 Take Home Messages

10. Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes with repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment, repeated every 3 to 12 months as needed.

- Define responses to lifestyle and statin therapy by percentage reductions in LDL-C levels compared with baseline.
- In ASCVD patients at very high-risk, triggers for adding nonstatin drug therapy are defined by threshold LDL-C levels ≥70 mg/dL (≥1.8 mmol/L) on maximal statin therapy (see No. 3).

Grundy SM et al. *Circulation*. 2019;139:e1082-e1143.

69

2019 ACC/AHA Guideline on the Primary & Secondary Prevention of Cardiovascular Disease: Hypertension

- In adults with **elevated or borderline hypertension (BP 120-129/<80 mm Hg) or hypertension**, the initial recommendations include
  - Weight loss, heart-healthy diet (DASH or DASH Mediterranean), sodium restriction of 1000 mg reduction and optimal <1500 mg/d), diet rich in potassium with supplements as necessary, exercise as described including aerobic, isometric resistance (hand-grip), dynamic resistance (weights), and limited alcohol (men <3 and women <2 per day).
- In adults with **stage I hypertension (BP 130-139/80-89 mm Hg) and estimated 10-year ASCVD risk of <10%**, nonpharmacologic therapy is recommended.
- In those with a **10% or higher 10-year ASCVD risk, use of BP-lowering medication is recommended with a BP target of <130/80 mm Hg** including persons with chronic kidney disease and diabetes. A target of <130/80 mm Hg is also recommended for Stage 2 hypertension, defined as BP ≥140/90 mm Hg with nonpharmacological and BP-lowering medication.

Jones R et al, *JACC* April, 2018; Arnett DK et al, *JACC* March, 2019

70

2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Aspirin

- **Low-dose aspirin might be considered** for primary prevention of ASCVD in select higher ASCVD adults aged 40-70 years who are **not at increased bleeding risk.**
- **Low-dose aspirin should not** be administered on a routine basis for **primary prevention of ASCVD among adults >70 years**.
- **Low-dose aspirin** should not be administered for primary prevention among adults **at any age who are at increased bleeding risk.**

Arnett DK et al, *JACC*, March, 2019

71

2019 ACC/AHA Guideline on the Secondary Prevention of Cardiovascular Disease: Aspirin

- **Aspirin 81-162 mg/day indefinitely.**
- **Clopidogrel, prasugrel, or ticagrelor (i.e., P2Y12 inhibitor) in addition to aspirin after PCI.**
- If bare-metal stent, P2Y12 inhibitors should be taken for ≥1 month.
- If drug-eluting stent, P2Y12 inhibitors for ≥1 year.
- If on dual antiplatelet therapy (DAPT), use aspirin 81 mg/day.
- If no PCI was performed after an ACS event, either clopidogrel or ticagrelor should be used.
- **Do not use prasugrel if history of stroke or TIA [Class III]. Caution in those over 70 years of age**.
- Aspirin 81 to 325 mg/day or clopidogrel for all patients following a non-cardioembolic ischemic stroke.

Arnett DK et al, *JACC*, March, 2019

72

Thank you for your attention!

Robert H. Eckel, MD
Charles A. Boettcher Chair in Atherosclerosis
Professor of Medicine, Emeritus
Division of Endocrinology, Metabolism & Diabetes
Division of Cardiology
CU Anschutz Medical Campus
American Heart Association, Past President
American Diabetes Association, President Elect

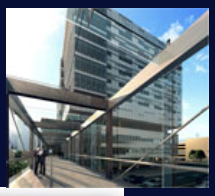
73

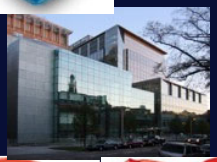
Controversies 1: What is the MOA for EPAs Effect on ASCVD?

PETER LIBBY
PRESTON MASON

74

What is the MOA for EPAs Effect on ASCVD?





RRM Charitable Fund

Peter Libby
Brigham & Women's Hospital
Harvard Medical School

Controversies Amidst Progress on CVOTs: You Be The Judge
Philadelphia, PA
November 17, 2019

75

Lipids Beyond LDL

♡Blood triglycerides are a biomarker for triglyceride-rich lipoproteins (TGRL) aka "remnant particles"

76

European Heart Journal Advance Access published December 29, 2014

European Heart Journal
doi:10.1093/eurheartj/ehu500

CURRENT OPINION

Triglycerides on the rise: should we swap seats on the seesaw?

Peter Libby*

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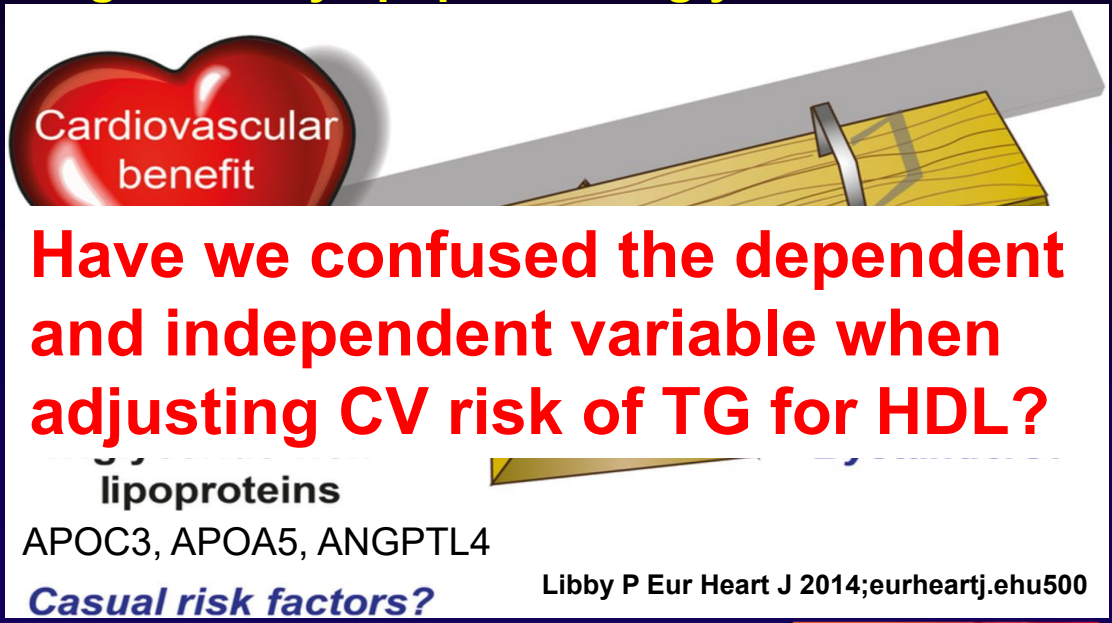
Received 2 July 2014; revised 15 December 2014; accepted 15 December 2014

77

The high-density lipoprotein/triglyceride teeter-totter



European Heart Journal

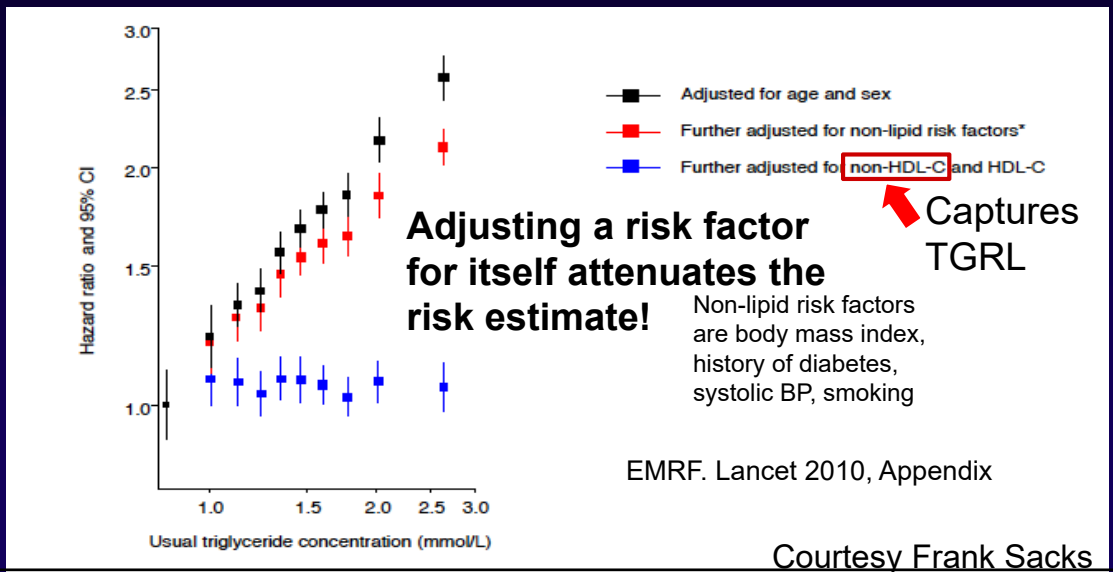
78

Tradition has generally disregarded triglycerides as a causal cardiovascular risk factor

♡ Does adjustment for HDL attenuate the association of triglycerides with cardiovascular events?

79

TG Independently Predicts CVD: Confusion About Adjusting for non-HDL-C: 302,430 Participants in 68 Studies: 12,735 First Incident CHD

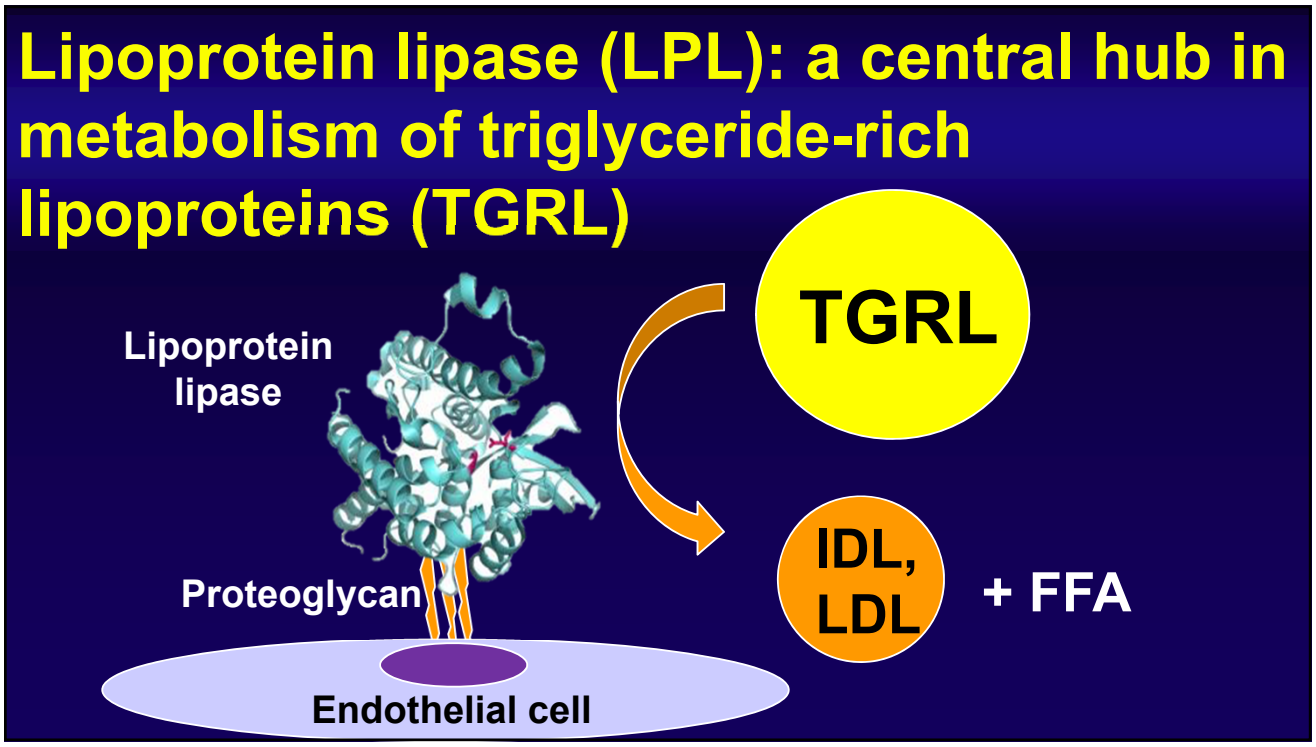


80

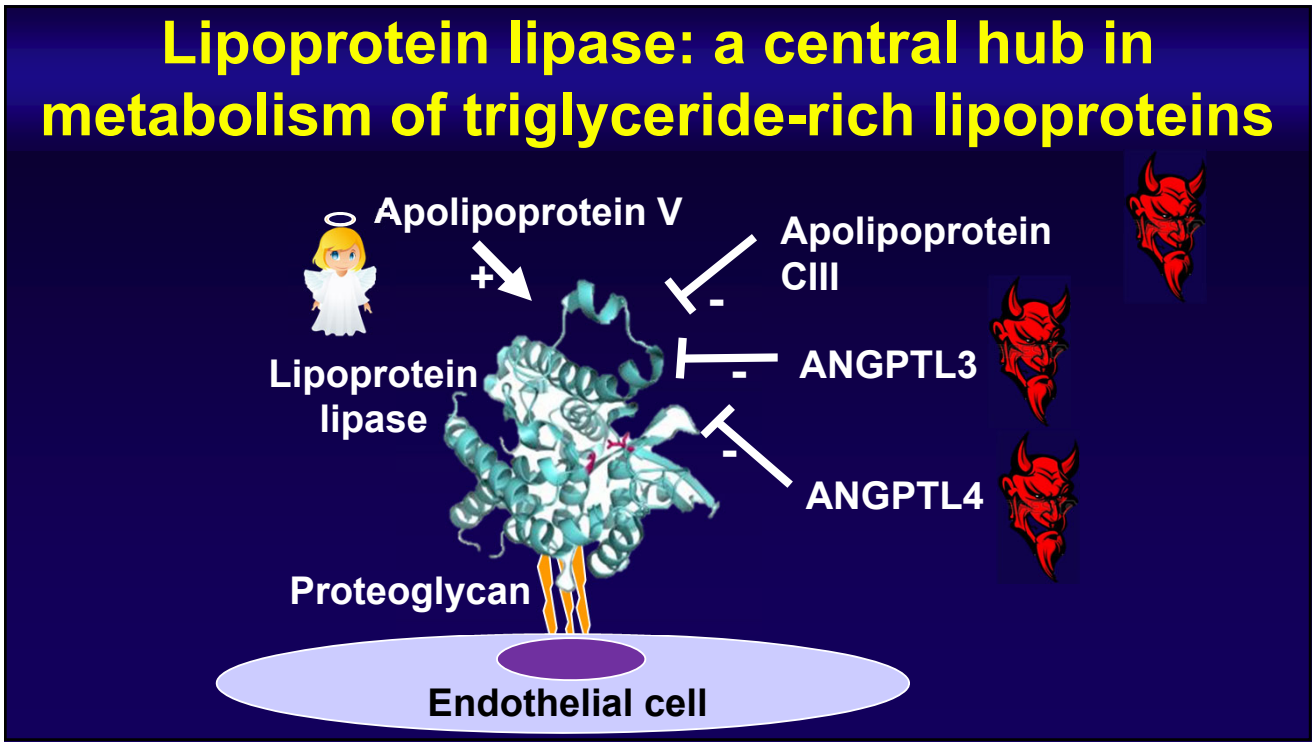
Recent genetic studies *do* support causality of triglyceride-rich lipoproteins (TGRLP) in CV risk

- Apolipoprotein A5
- Apolipoprotein C3
- ANGPTL4
- ANGPTL3
- Lipoprotein lipase

81


Lipoprotein lipase (LPL): a central hub in metabolism of triglyceride-rich lipoproteins (TGRL)
Lipoprotein lipase
TGRL
IDL, LDL
+ FFA
Proteoglycan
Endothelial cell

82


Lipoprotein lipase: a central hub in metabolism of triglyceride-rich lipoproteins
Apolipoprotein V
+
Apolipoprotein CIII
-
ANGPTL3
-
ANGPTL4
-
Lipoprotein lipase
Proteoglycan
Endothelial cell

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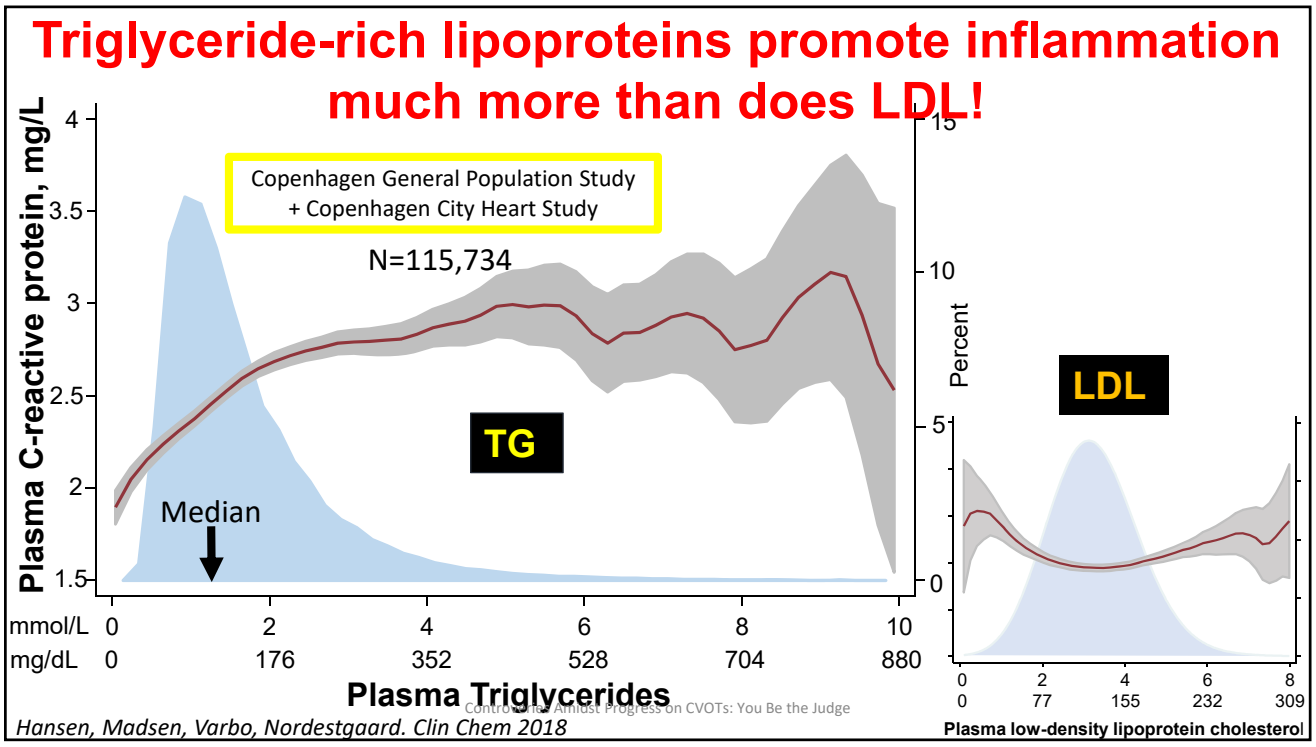
84

Challenging the Traditional Lipid-Inflammation Axioms

♡Triglyceride-rich lipoproteins promote inflammation much more than does LDL

85


Triglyceride-rich lipoproteins promote inflammation much more than does LDL!
Copenhagen General Population Study
+ Copenhagen City Heart Study
N=115,734
TG
LDL
Median
Plasma C-reactive protein, mg/L
Percent
mmol/L 0 2 4 6 8 10
mg/dL 0 176 352 528 704 880
Plasma Triglycerides
0 2 4 6 8
0 77 155 232 309
Plasma low-density lipoprotein cholesterol
Hansen, Madsen, Varbo, Nordestgaard. Clin Chem 2018
Controversies Amidst Progress on CVOTs: You Be the Judge

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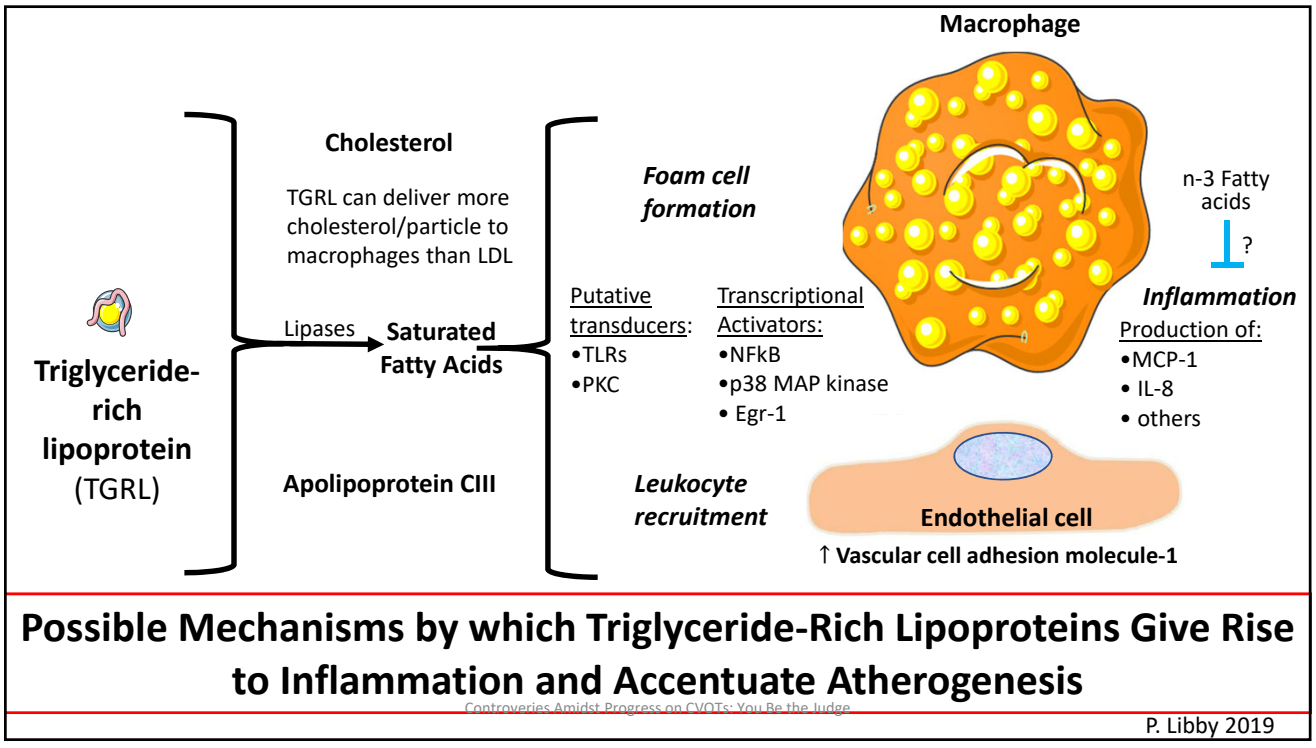
Macrophage
Triglyceride-rich lipoprotein (TGRL)
Cholesterol
TGRL can deliver more cholesterol/particle to macrophages than LDL
Lipases
Saturated Fatty Acids
Apolipoprotein CIII
Foam cell formation
Leukocyte recruitment
Putative transducers:
•TLRs
•PKC
Transcriptional Activators:
•NFkB
•p38 MAP kinase
• Egr-1
n-3 Fatty acids
?
Inflammation
Production of:
•MCP-1
• IL-8
• others
Endothelial cell
↑ Vascular cell adhesion molecule-1
Possible Mechanisms by which Triglyceride-Rich Lipoproteins Give Rise to Inflammation and Accentuate Atherogenesis
Controversies Amidst Progress on CVOTs: You Be the Judge
P. Libby 2019

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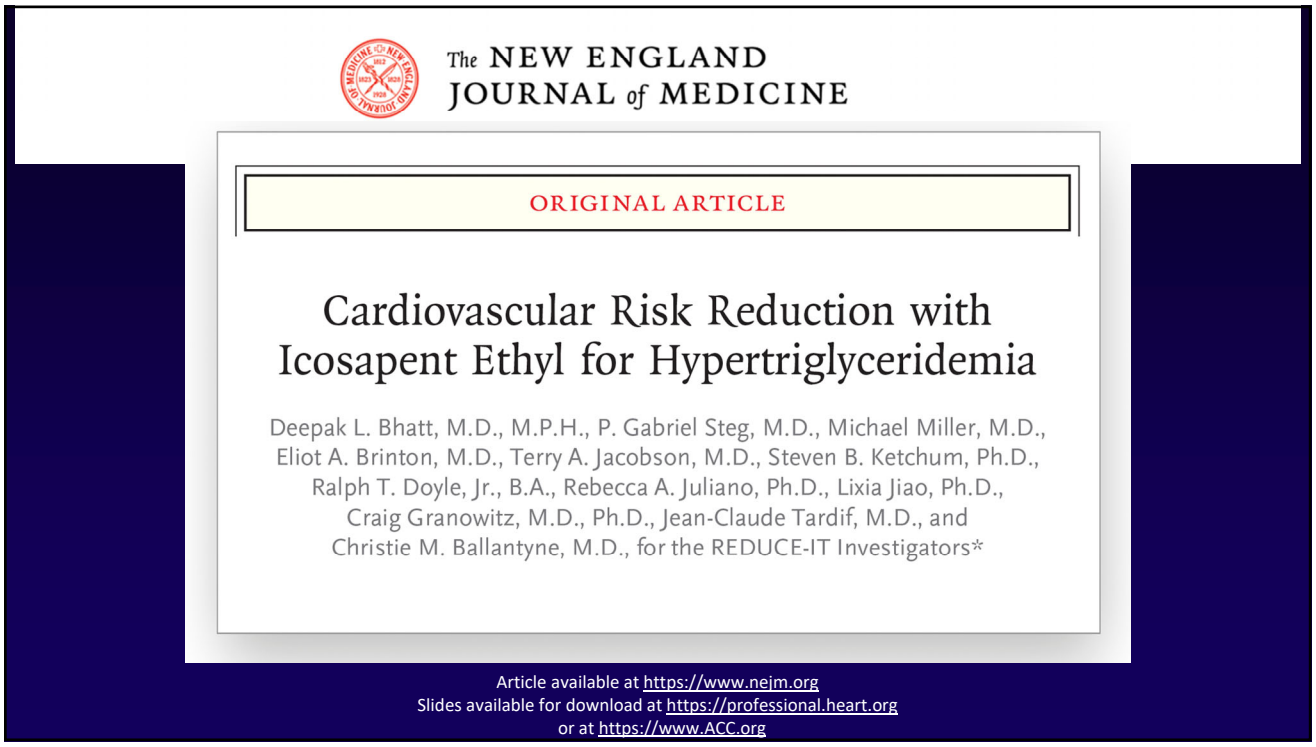

89

Was the benefit of EPA treatment in REDUCE-IT primarily due to triglyceride lowering?

90

REDUCE-IT: Effects on Biomarkers from Baseline to Year 1

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

*Apo B and hsCRP were measured at Year 2.

Bhatt DL et al. *N Engl J Med*. 2019;380:11-22.

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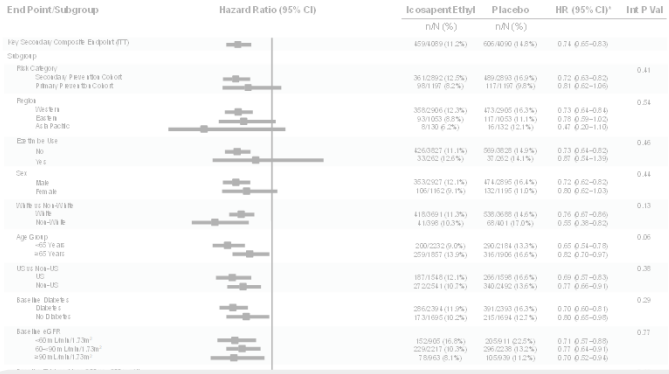
But Triglycerides are not the whole story



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)	

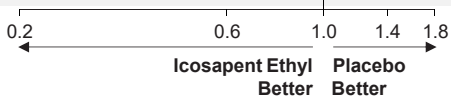
Icosapent Ethyl Better Placebo Better

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

92

Triglyceride lowering is not the whole story: Primary Composite Endpoint: Total Endpoint Events by Baseline TG Tertiles

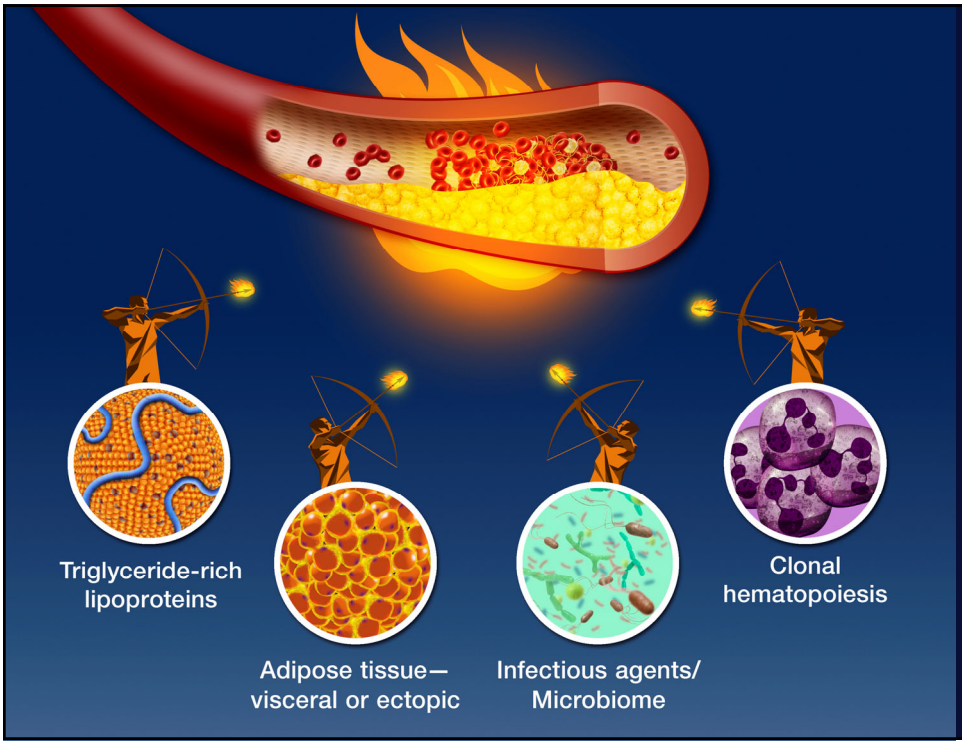
TOTAL EVENTS – Primary Composite Endpoint/Subgroup	Icosapent Ethyl	Placebo	RR (95% CI)	P-value
	Rate per 1000 Patient Years	Rate per 1000 Patient Years		
Primary Composite Endpoint (ITT)	61.1	88.8	0.70 (0.62–0.78)	<0.0001
Baseline Triglycerides by Tertiles*				
≥81 to ≤190 mg/dL	56.4	74.5	0.74 (0.61–0.90)	0.0025
>190 to ≤250 mg/dL	63.2	86.8	0.77 (0.63–0.95)	0.0120
>250 to ≤1401 mg/dL	64.4	107.4	0.60 (0.50–0.73)	<0.0001



***P (interaction) = 0.17**

Bhatt DL. ACC 2019, New Orleans.

93



Some non-traditional risk factors drivers of arterial inflammation

Arson in the Artery: Who Set the Atheroma Aflame?

Peter Libby

Trends in Cardiovascular Medicine (in press)

94

What is the MOA for EPA's Effect on ASCVD?

R. PRESTON MASON, PHD

95

R. Preston Mason, PhD

Cardiovascular Division, Brigham and Women's Hospital
Harvard Medical School
Boston, MA

Scientific Director and Founder, Elucida Research
Beverly, MA

Disclosures: Contracted Research: Amarin, Amgen, ARCA Biopharma, Daiichi Sankyo, Pfizer

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Questions

1. Does EPA have effects on atherosclerosis beyond TG reduction?
2. Are these effects of Omega-3 FAs different from other TG-lowering agents?

97

Primary Composite Endpoint: Total Endpoint 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		
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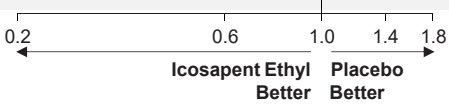


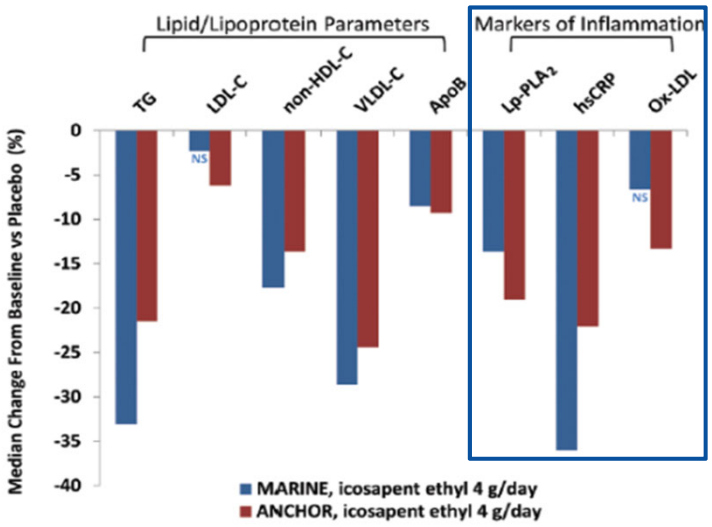
***P (interaction) = 0.17**

98

Bhatt DL. ACC 2019, New Orleans.

98

Effects of EPA on Non-HDL-C and Inflammatory Markers in Patients With Elevated TGs at 4 g/d



Bays HE et al. *Am J Cardiovasc Drugs*. 2013;13:37-46.

99

Lipid Therapies Have Different Effects on hsCRP

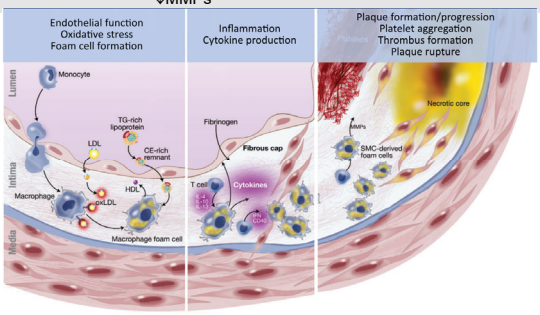
Lipid Therapy	hsCRP Levels
Statins	↓
EPA (4 g)	↓
EPA (4 g) + Statin	↓↓
EPA/DHA (4 g)	⇔
Ezetimibe	⇔
Ezetimibe + Statin	↓
PCSK9i + Statin	⇔

Bays HE et al. *Am J Cardiovasc Drugs*. 2013;13:37-46. Dunbar RL et al. *Lipids Health Dis.* 2015:14:98. Ridker PM et al. *N Engl J Med.* 2008;359:2195-207. Bohula EA et al. *Circulation*. 2015;132:1224-33. Pradhan AD et al. *Circulation*. 2018;138:141-9.

100

EPA Interferes with Plaque Development at Multiple Stages Beyond TG-Lowering

Pathological Parameters and Processes in Atherosclerosis				
Circulating parameters	Endothelial cell dysfunction & activation	Inflammation, monocyte recruitment, & proteolysis	Lipid core and fibrous cap formation with ongoing inflammation	Plaque formation, progression, & thrombosis
Beneficial Effects of EPA				
↓TGRLs ↓Non-HDL-C ↓ApoB ↓VLDL-C	↓LDL, sdLDL, VLDL Oxidation ↑Endothelial function ↓Cholesterol crystalline domains ↓RLP-C	↑EPA/AA ratio ↑Resolvins, protectins & IL-10 ↓Inflammation: ox-LDL, IL-6, hsCRP, LpPLA$_2$, & ICAM-1 ↓Monocyte adhesion ↓MMPs	↑Fibrous cap thickness ↑Lumen diameter ↓Macrophages ↓Foam cell formation ↓Ongoing inflammation	↑Plaque stability ↓Plaque formation & progression ↓Plaque volume & vulnerability ↓Arterial stiffness ↓Platelet response ↓Thrombosis

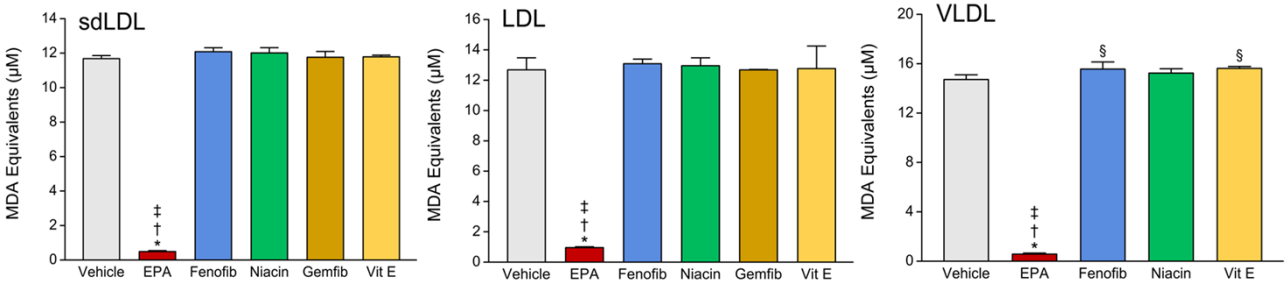


Borow K, Nelson JR, Mason RP. *Atherosclerosis* 2015;242:357-366. Budoff M, et al. *Clinical Cardiology*. 2018;41:13–19.

101

Comparative Effects of EPA (4 g/d) and TG-lowering Agents on Lipoprotein Oxidation

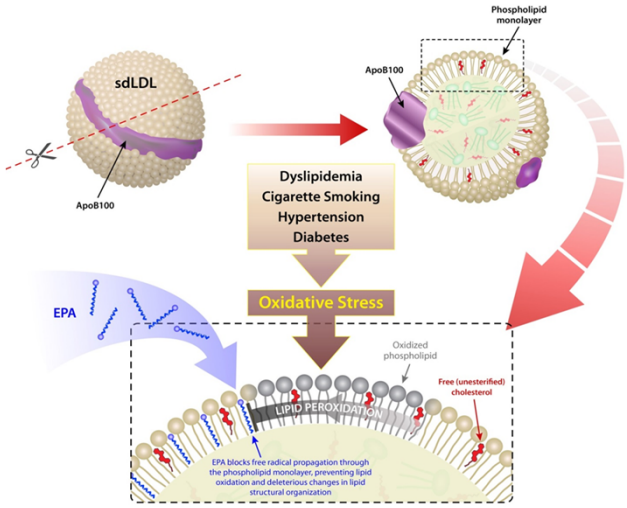
Each agent was tested at 10 μM



Mason RP, et al. *J Cardiovasc Pharmacol* 2016;68:33-40.

102

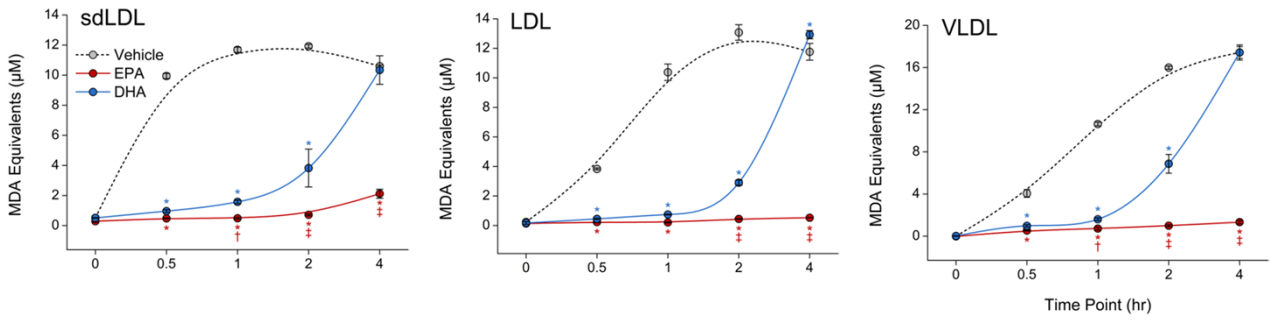
Schematic Illustration of the Protective Effects of EPA on sdLDL Lipid Oxidation



Adapted from: Mason RP, Jacob RF. *Diabetes.* 2015;64(Suppl 1):A178-A179.

103

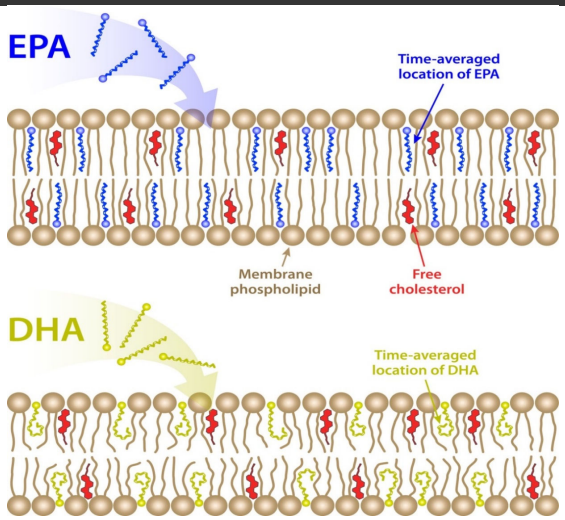
Comparative Effects of EPA and DHA on Oxidation in Different ApoB Particles



Mason RP et al. *J Cardiovasc Pharmacol* 2016;68:33-40.

104

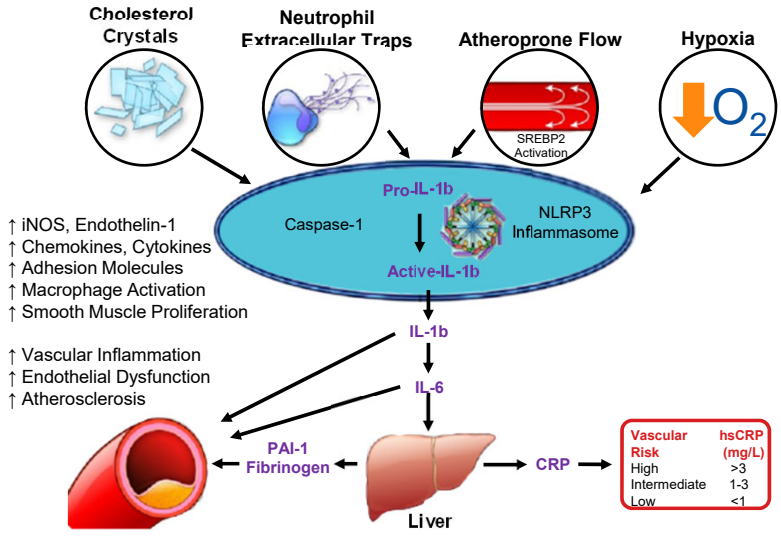
Biophysical Analysis: EPA Has Stable Extended Conformation in the Membrane While DHA Has Disordering Effect



Sherratt SCR, Mason RP. *Chem Phys Lipids* 2018;212:73-79.

105

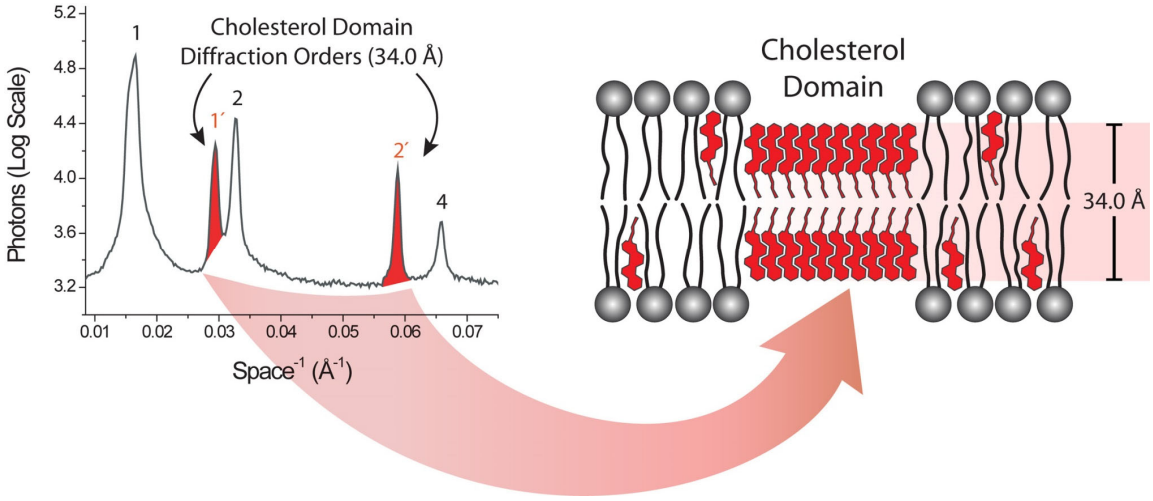
Cholesterol Crystals Trigger IL-1β Formation



Ridker PM. *Circ Res* 2016;118:145-156.

106

Characterizing Membrane Cholesterol Crystalline Domains by X-ray Diffraction

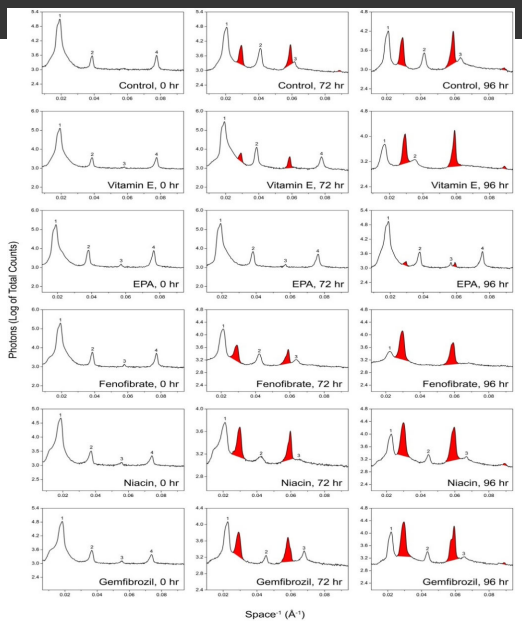


Mason RP et al. *J Biol Chem*. 2006;281:9337-9345.

107

Effects of TG-Lowering Agent on Cholesterol Crystalline Domains

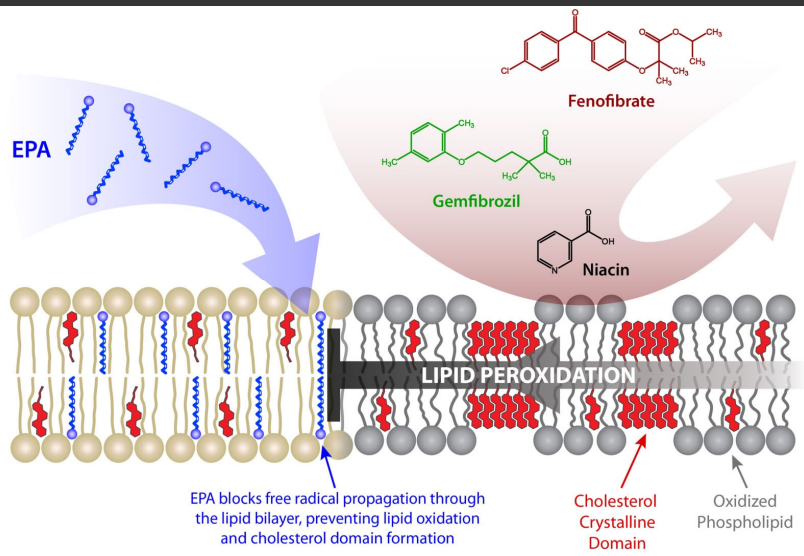
Comparison of Vitamin E, EPA, Fenofibrate, Niacin, and Gemfibrozil



Mason RP, et al. *Biochim Biophys Acta* 2015;1848:502-509.

108

EPA, But Not Other TG-lowering Agents, Inhibits Lipid Oxidation & Cholesterol Domain Formation



Adapted from Mason RP, Jacob RF. *Biochim Biophys Acta*. 2015;1848:502-509.

109

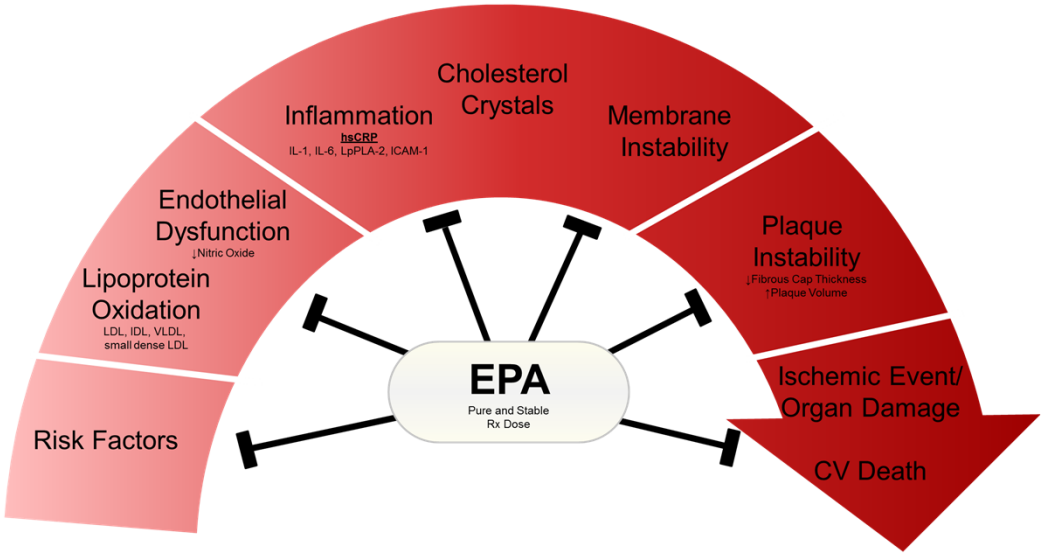
Distinct Effects of EPA on Plaque Development

- Reverses human endothelial dysfunction: enhanced with a statin;
- Inhibits cholesterol crystal formation linked to inflammation and plaque destabilization;
- Membrane stabilizing in contrast to DHA;
- Prevents membrane damage with hyperglycemia;
- Preserves HDL function

Mason RP and Jacob RF. *Biochim Biophys Acta* 2015;1848:502-509; Mason RP et al. *Biomed Pharmacother*. 2018;103:1231-1237; Sherratt SCR and Mason RP. *Biochem Biophys Res Comm*. 2018; 496:335-338; Mason RP et al. *J Cardiovasc Pharmacol* 2016;68:33-40; Mason RP et al. *Biochim Biophys Acta*. 2016;1858:3131-3140; Mason RP. *Curr Atheroscler Rep*. 2019;21:2.

110

EPA Interferes with the Cardiovascular Disease Continuum at Multiple Points to Reduce CV Events



Bays HE et al. *Am J Cardiovasc Drugs*. 2013;13:37-46; Borow KM, Nelson JR, Mason RP. *Atherosclerosis*. 2015;242:357-66; Bhatt DL et al. *N Engl J Med*. 2019;380:11-22; Ganda OP et al. *J Am Coll Cardiol*. 2018;72:330-43; Jia X et al. *Curr Atheroscler Rep*. 2019;21:1; Mason RP et al. *Biomed Pharmacother*. 2018;103:1231-7; Ference BA et al. *JAMA*. 2019;321:364-73. Sherratt SCR and Mason RP. *Biochem Biophys Res Comm*. 2018; 496:335-338.

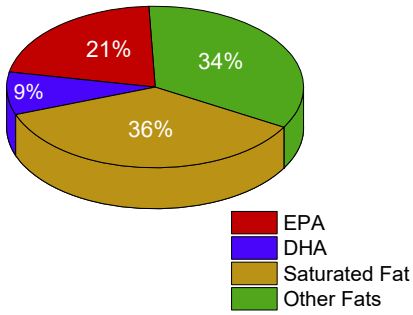
111

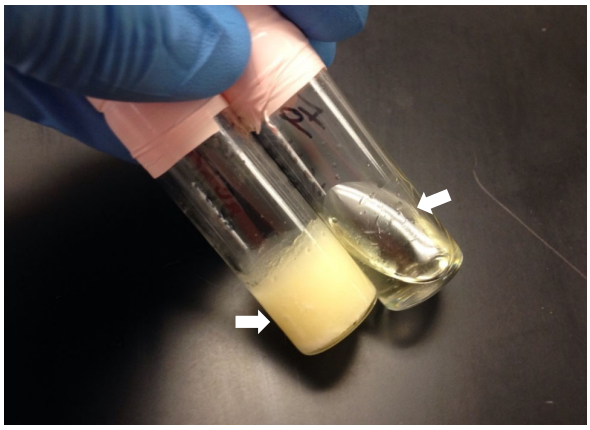
What's the Basis for Benefit with EPA in REDUCE-IT?

- Right dose (4 g/d)
- Right formulation (EPA)
- Right patients (↑ TGs, ↑ CV risk)

112

Fatty Acid Content of Leading US Fish Oil Supplement





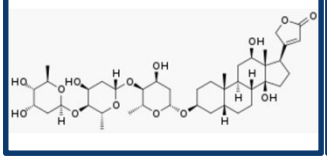
Mason RP, Sherratt SCR. *Biochem Biophys Res Commun*. 2017;483:425-429.

113

Transformational Medicines Isolated from Nature: Unique Molecules with Proven Clinical Efficacy

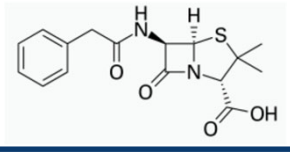
Digoxin

Purple Foxglove



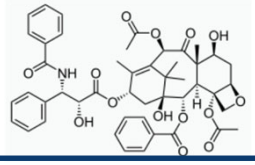
Penicillin

Penicillium Mold



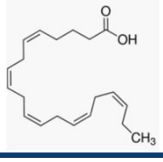
Paclitaxel

Pacific Yew



Icosapent ethyl

Marine Fish



Lero M, Sherratt SCR, Mason RP (2019)

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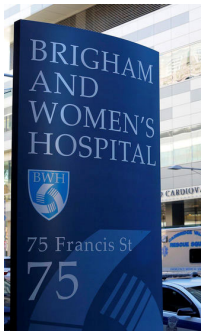
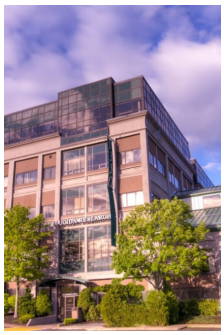
BRIGHAM AND WOMEN'S HOSPITAL

ELUCIDA RESEARCH





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Controversies 2: What's the Optimal Pharmacotherapy Algorithm for Patients with Diabetes to Reduce CVD Risk?

GABRIEL STEG
ROBERT H. ECKEL

116

Today, **Pr. Steg** received the AHA's Joseph A. Vita award, established by the AHA's Publishing Committee to honor Joseph A. Vita, an accomplished clinical researcher in vascular biology and founding editor-in-chief of *the Journal of the American Heart Association* (JAHA).

CONGRATULATIONS TO PR. STEG!

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Optimal Pharmacotherapy algorithm to reduce CV risk in patients with diabetes

Ph.Gabriel Steg
RHU iVASC
DHU-FIRE, Hôpital Bichat, Assistance Publique – Hôpitaux de Paris,
Université Paris – Diderot, INSERM U-1148, Paris, France,
FACT: French Alliance for Cardiovascular clinical Trials
& Imperial College, Royal Brompton Hospital, London, UK
@gabrielsteg

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Disclosures

- **Research grants** : Amarin, Bayer, Sanofi, and Servier
- **Clinical Trial Contract (Steering committee or CEC)** : Amarin, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Novartis, Pfizer, Sanofi, Servier
- **Consulting or speaking**: Amgen, Novo-Nordisk, Regeneron

119

Primary prevention setting

Glucose

- Glucose control probably does not affect CV risk
- except for younger patients

120

Primary prevention setting

Glucose

- Glucose control probably does not affect CV risk,
- except for younger patients

BP control

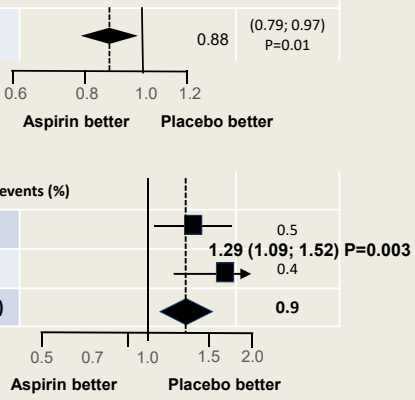
- For most patients
  - Target SBP 130 mm Hg
  - Target DBP 80 mm Hg
- preferably starting with RAAS inhibitor

121

ASCEND – Aspirin 100 mg Daily in 15,480 Patients with Diabetes and No Baseline CV Disease

Primary efficacy and safety endpoints

Type of Event	Aspirin (N=7740)	Placebo (N=7740)	Rate ratio (95% CI)
Vascular outcomes	**No. of participants with events (%)**		
Any serious vascular event (primary outcome)	**658 (8.5)**	**743 (9.6)**	0.88 (0.79; 0.97) P=0.01
Major bleed	**No. of participants with events (%)**		
Serious gastrointestinal hemorrhage	137 (1.8)	101 (1.3)	0.5
Other major bleeding	74 (1.0)	43 (0.6)	0.4
Any major bleeding	**314 (4.1)**	**245 (3.2)**	**1.29 (1.09; 1.52) P=0.003** 0.9



Controversies Amidst Progress on CVOTs: You Be the Judge

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THEMIS: ticagrelor added to aspirin in patients with CAD and diabetes

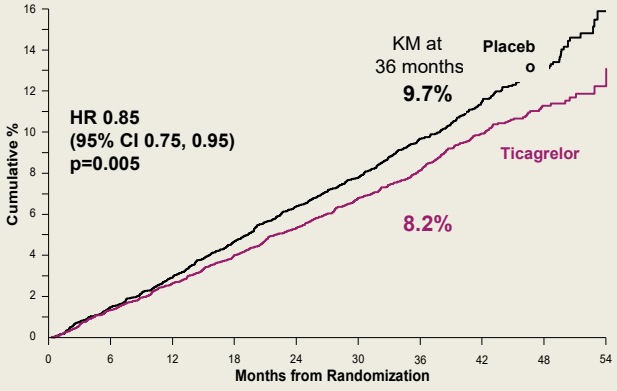
Net Clinical Benefit

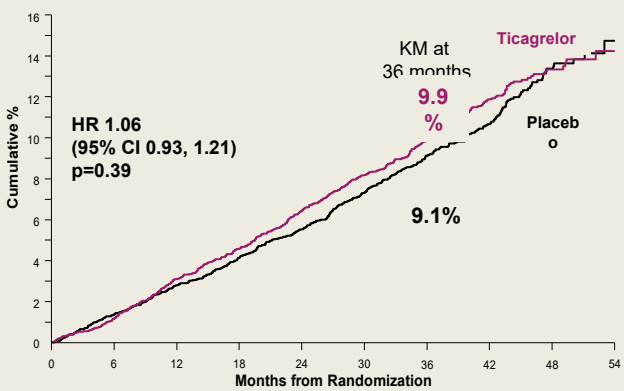
All cause death, MI, stroke, fatal bleed or ICH (ITT)*

History of PCI

Interaction p=0.012

No history of PCI





*Prespecified definition of net clinical benefit.

Controversies Amidst Progress on CVOTs: You Be the Judge

Bhatt DL, Steg PG et al. ***Lancet*** 2019; 394: 1169–80

123

Primary prevention setting

Glucose

- Glucose control probably does not affect CV risk,
- except for younger patients

BP control

- For most patients
  - Target SBP 130 mm Hg
  - Target DBP 80 mm Hg
- preferably starting with RAAS inhibitor

Thrombosis

ASCEND, THEMIS

- Aspirin only for pts at highest CV risk
- Consider adding ticagrelor for very high risk pts post PCI

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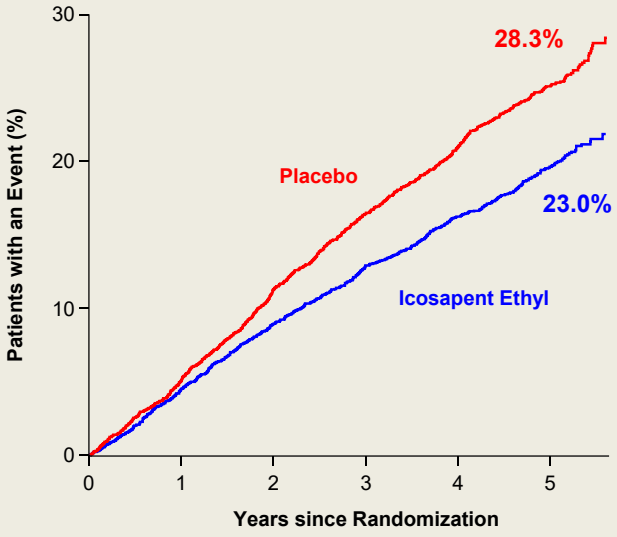
Primary End Point:
CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



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.

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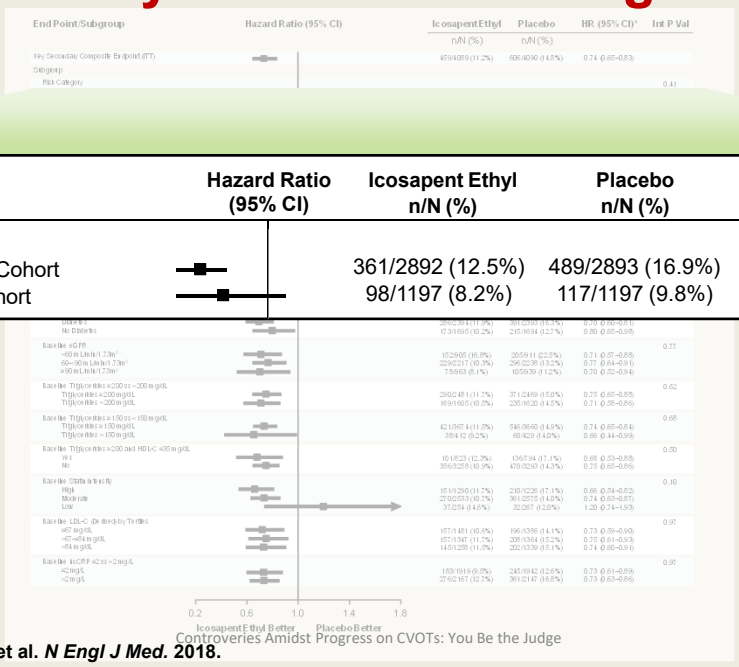
Key Secondary End Point in Subgroups



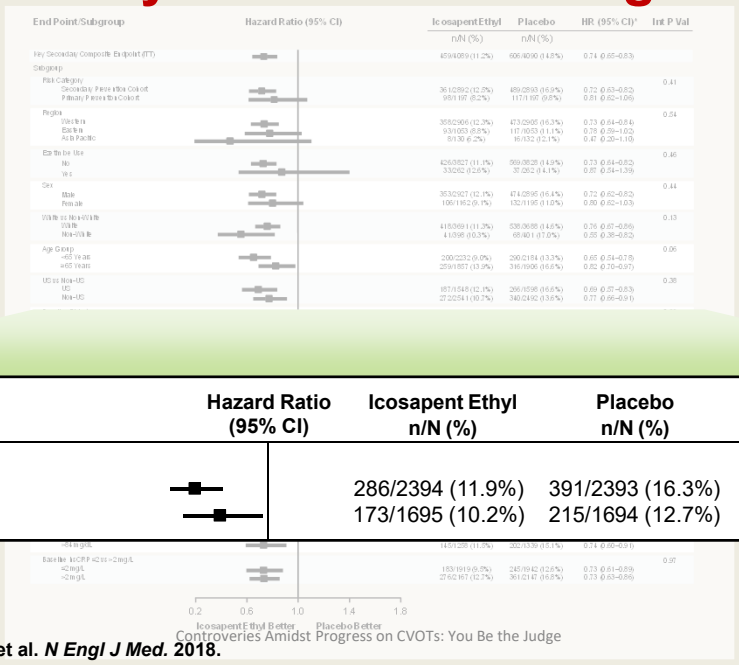
Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Risk Category					0.41
Secondary Prevention Cohort		361/2892 (12.5%)	489/2893 (16.9%)	0.72 (0.63–0.82)	
Primary Prevention Cohort		98/1197 (8.2%)	117/1197 (9.8%)	0.81 (0.62–1.06)	

Controversies Amidst Progress on CVOTs: You Be the Judge

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

126

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)	

Controversies Amidst Progress on CVOTs: You Be the Judge

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

127

Primary prevention setting

Glucose

- Glucose control probably does not affect CV risk,
- except for younger patients

BP control

- For most patients
  - Target SBP 130 mm Hg
  - Target DBP 80 mm Hg
- preferably starting with RAAS inhibitor

Thrombosis

ASCEND, THEMIS

- Aspirin only for pts at highest CV risk
- Consider adding ticagrelor for very high risk pts post PCI

Lipids

Statin trials, REDUCE-IT

- LDL control, starting with statins,
- Consider EPA if TGs are between 135 and 500 mg/dL

128

Secondary prevention setting

Glucose

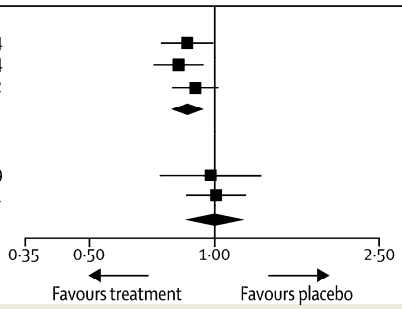
SGLT2 and GLP1RA trials

It is not the glucose level, it is the drugs used to reach it

129

Meta-analysis of SGLT2i trials on the composite of MI, stroke, and CV death stratified by the presence of established atherosclerotic CVD

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4687/7020	2333/7020	772	37·4	43·9	29·4		0·86 (0·74–0·99)
CANVAS Program	3756/6656	2900/6656	796	34·1	41·3	32·4		0·82 (0·72–0·95)
DECLARE-TIMI 58	3474/6974	3500/6974	1020	36·8	41·0	38·2		0·90 (0·79–1·02)
Fixed effects model for atherosclerotic cardiovascular disease (p=0·0002)								**0·86 (0·80–0·93)**
Patients with multiple risk factors								
CANVAS Program	2039/3486	1447/3486	215	15·8	15·5	25·9		0·98 (0·74–1·30)
DECLARE-TIMI 58	5108/10 186	5078/10 186	539	13·4	13·3	74·1		1·01 (0·86–1·20)
Fixed effects model for multiple risk factors (p=0·98)								**1·00 (0·87–1·16)**



No heterogeneity was found in terms of between-study variance in the subgroups (atherosclerotic cardiovascular disease: Q statistic=0·94, p=0·63, I^2=0%; multiple risk factors: Q statistic=0·03, p=0·86, I^2=0%). Tests for subgroup differences were based on F tests in a random effect meta-regression estimated using restricted maximum likelihood and Hartung Knapp adjustment. The p value for subgroup differences was 0·0501. HR=hazard ratio. SGLT2i=sodium-glucose cotransporter-2 inhibitors.

Zelniker et al. *The **Lancet*** 2018

Secondary prevention setting

Glucose

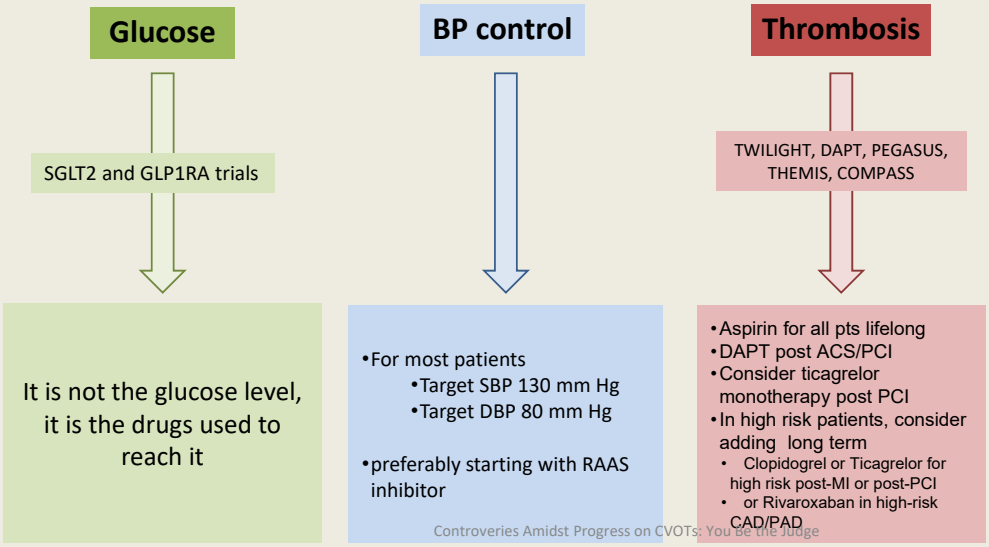
SGLT2 and GLP1RA trials

It is not the glucose level, it is the drugs used to reach it

BP control

- For most patients
  - Target SBP 130 mm Hg
  - Target DBP 80 mm Hg
- preferably starting with RAAS inhibitor

Secondary prevention setting



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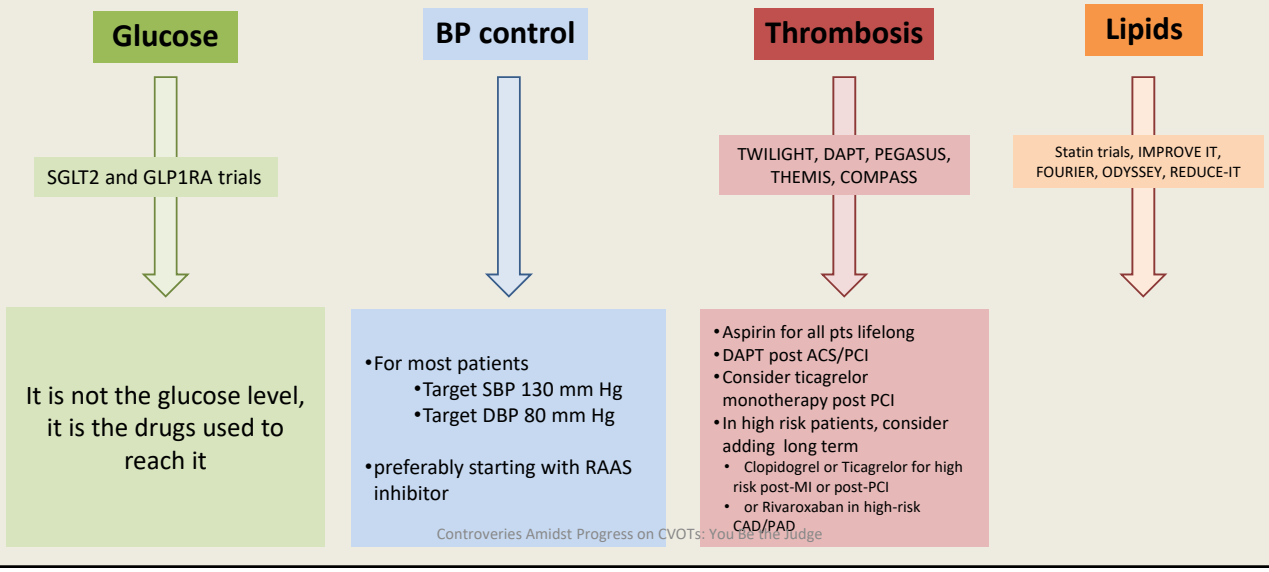
Secondary prevention setting



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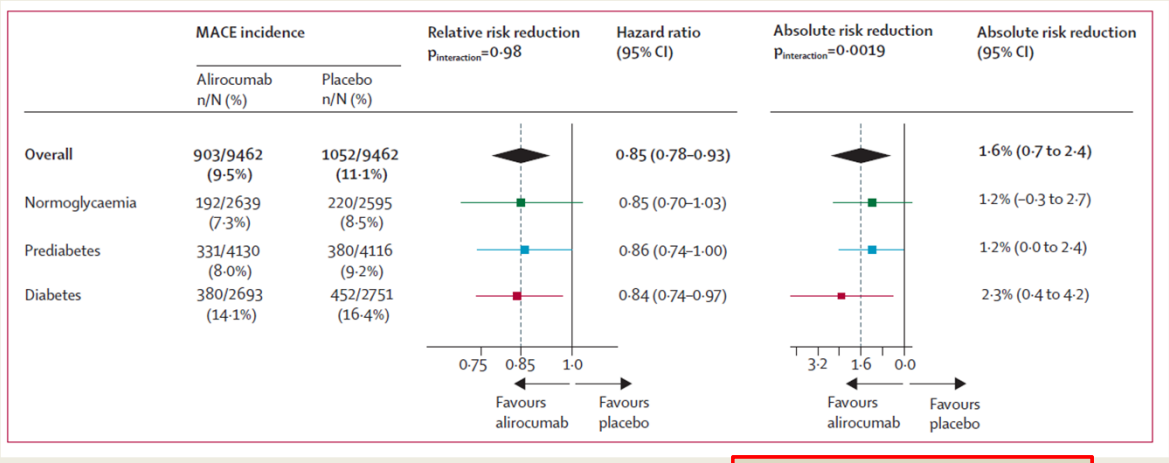
Large absolute benefit of alirocumab in post ACS patients with diabetes



Absolute risk reduction Interaction P=0.002

Ray KK, et al. ***Lancet Diabetes Endocrinol***. 2019;7(8):618–28.

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Secondary prevention setting

Glucose	BP control	Thrombosis	Lipids
SGLT2 and GLP1RA trials		TWILIGHT, DAPT, PEGASUS, THEMIS, COMPASS	Statin trials, IMPROVE IT, FOURIER, ODYSSEY, REDUCE-IT
It is not the glucose level, it is the drugs used to reach it	•For most patients •Target SBP 130 mm Hg •Target DBP 80 mm Hg •preferably starting with RAAS inhibitor	•Aspirin for all pts lifelong •DAPT post ACS/PCI •Consider ticagrelor monotherapy post PCI •In high risk patients, consider adding long term • Clopidogrel or Ticagrelor for high risk post-MI or post-PCI • or Rivaroxaban in high-risk CAD/PAD	•LDL control, starting with statins, •Add Ezetimibe and PCSK9 i to reach 55 mg/dL LDL •Consider EPA if TGs are between 135 and 500 mg/dL

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HPI: GK is a 54-year-old woman with strong FHx of T2DM and CVD. She has new onset T2DM, treated hypertension, dyslipidemia on statin, and is referred for evaluation of cardiometabolic risk for CVD.

PMHx: Hypothyroidism, OSA on CPAP irregularly

Meds: Lisinopril 20 mg daily; levothyroxine 100 μg daily; atorvastatin 40 mg daily.

SHx: no tobacco; rare alcohol, on South Beach diet, almost no physical activity; works at a desk job.

PE: BP 142/82, WC 96 cm, BMI 29.5 kg/m^2

Lab data:
Fasting glucose – 154 mg/dL
HbA1c – 8.3%
Total cholesterol – 222 mg/dL, TG – 347 mg/dL, HDL-C – 32 mg/dL, LDL-C – 137 mg/dL (Martin/Hopkins LDL-C calculator)
Lp(a) – 12 mg/dL
Creatinine – 0.9 mg/dL
Urine microalbumin – 45 μg/mg creatinine
AST, ALT – WNL
Coronary calcium score – 81 Agatston units

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Questions:

- Should TG of 340 mg/dL be treated?

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Range of Triglyceride Lowering with Drugs

- Fibrates 20-45%
- Omega-3 fatty acids 15-35%
- Nicotinic acid 10-30%
- Statins 0-35%
  - Low end – minimal or no effect
  - High end – mod to high dose

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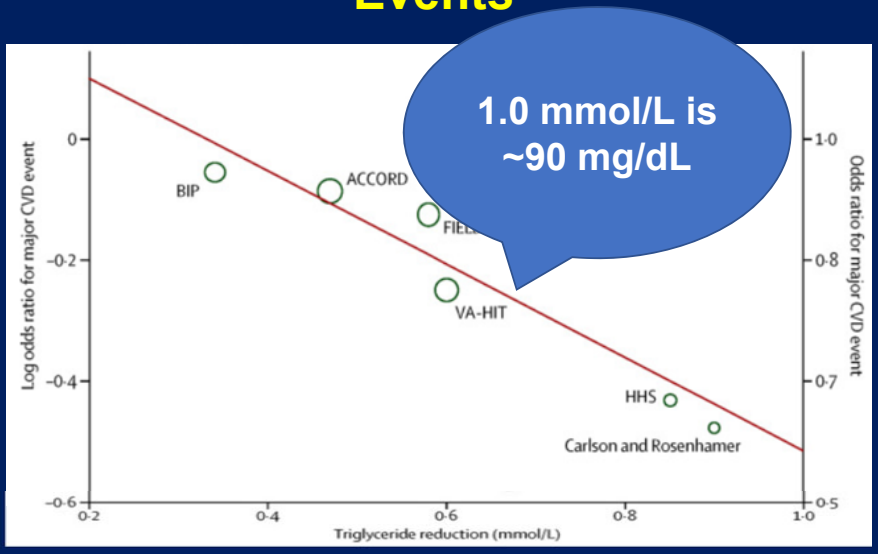
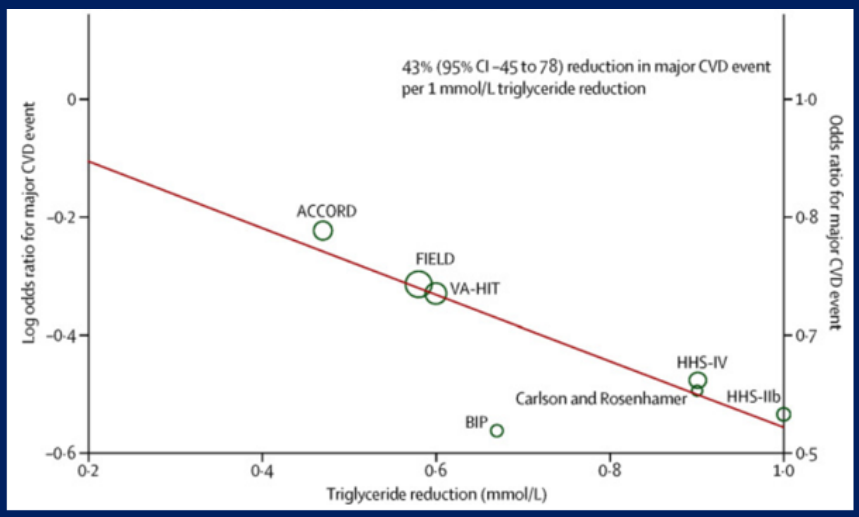
Fibrate Trials: Benefit of Reduction in TG on CVD Events



Nordestgaard BG and Varbo A. *Lancet* 384:626, 2014

139

Fibrate Trials: Benefit of Reduction in TG on CVD Events in Subjects with TG>2 mmol/L (>77.3 mg/dL)

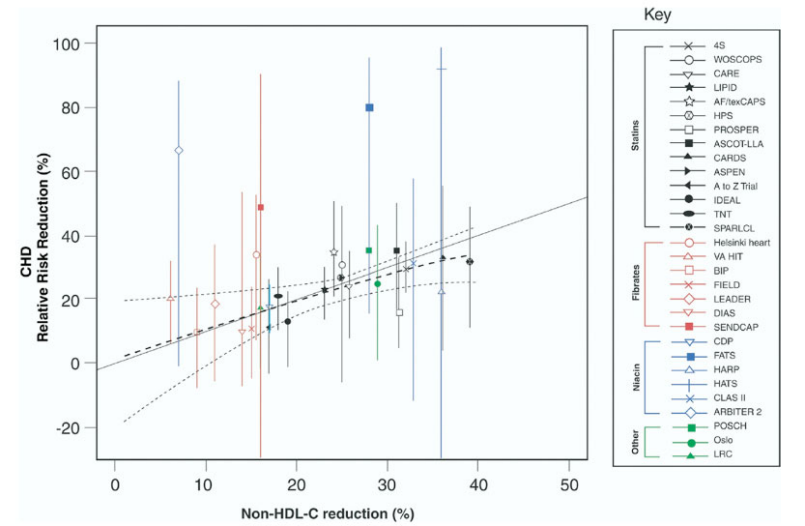


Nordestgaard BG and Varbo A. *Lancet* 384:626, 2014

Questions:

- Should TG of 340 mg/dL be treated?
- What about non-HDL-C vs. LDL-C as a better goal for treatment?

Change in CHD Risk Based on Non-HDL-C in Statin Trails

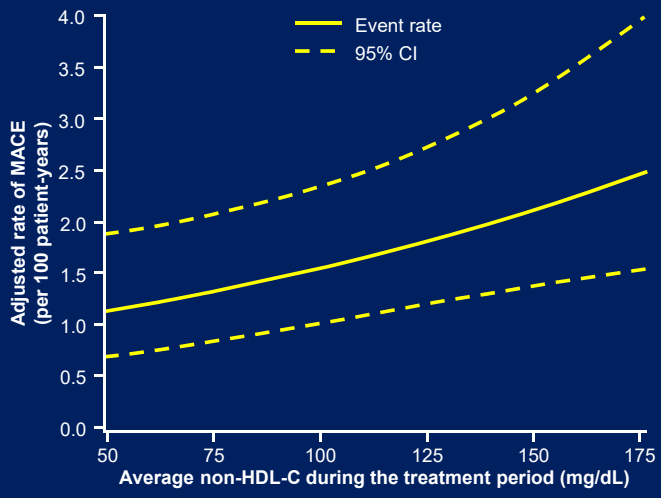


Robinson JS et al, *JACC* 53:316, 2009

142

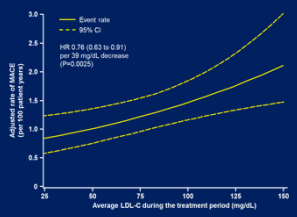
Adjusted MACE Rate by Average Achieved non-HDL-C During Lipid-Altering Treatment

Multivariate analysis adjusted on baseline characteristics; pool of Phase 3 trials



HR [95% CI]: 0.77 [0.65 to 0.93] per 42 mg/dL difference; p=0.0056

LDL-C



4974 patients (84.7% on background maximally tolerated statin) were treated with ALI, PBO or EZE for total follow-up of 6699 patient-yrs

104 patients reported MACE (median time to event: 36 wks)

Courtesy of Michael

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LDL-C vs. Non-HDL-C and NNT to Prevent One CVD Event in Patients on Atorvastatin 20 mg Daily

10-year cardiovascular disease risk, %	Pretreatment LDL cholesterol (change on treatment), mmol/L					
	2 (−0.86)	3 (−1.29)	4 (−1.72)			7 (−3.01)
	NNT* with atorvastatin 20 mg daily					
5	103	73	57			
7.5	69	49	38			
10	52	36	29			
20	26	18	14			
30	17	12	10	8		6

Based on an estimated VLDL-C of 39 mg/dL

10-year cardiovascular disease risk, %	Pretreatment non-HDL cholesterol (LDL cholesterol change on treatment), mmol/L					
	2 (−0.76)	3 (−1.19)	4 (−1.60)	5 (−2.03)	6 (−2.46)	7 (−2.89)
	NNT* with atorvastatin 20 mg daily					
5	116	78	61	50	44	39
7.5	77	52	41	32	29	26
10	58	39	30	25	22	20
20	29	20	15	13	11	10
30	19	13	10	8	7	7

Soran H et al, *Eur Heart J* 36:2975, 2015

144

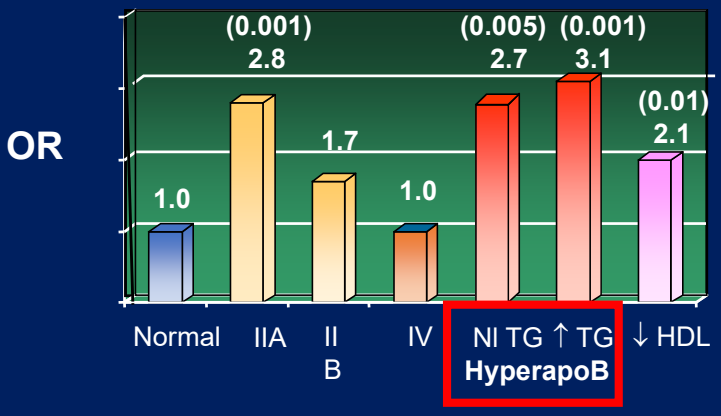
Questions:

- Should TG of 340 mg/dL be treated?
- What about non-HDL-C vs. LDL-C as a better goal for treatment?
- When is apo B useful and isn't it the same as non-HDL-C?

145

Odds Ratios for the Development of CHD: Lipid and Lipoprotein Phenotypes

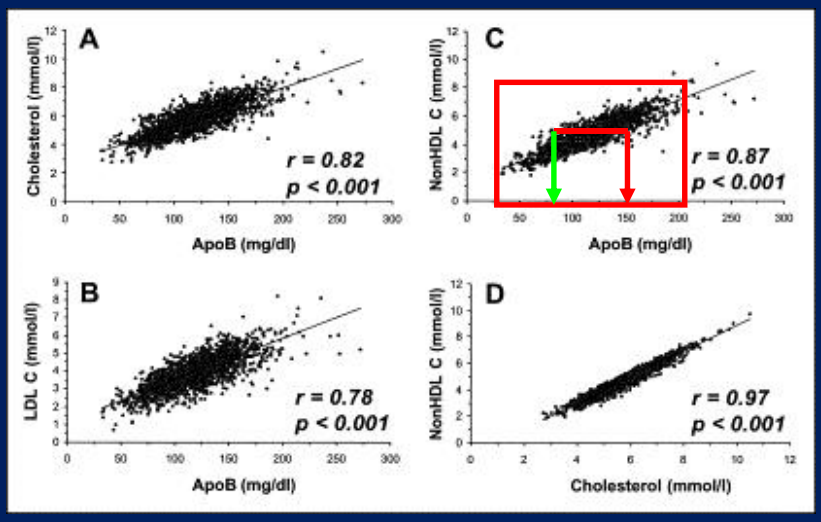
Odds are adjusted for age, smoking, alcohol, blood pressure, gender, and medications



Lamarche B et al, *Am J Card* 75:1189, 1995.

146

Correlations Between ApoB, Cholesterol, LDL Cholesterol and Non-HDL Cholesterol



Sniderman AS et al, *Am J. Card* 91:1173, 2003

147

Questions:

- Should TG of 340 mg/dL be treated?
- What about non-HDL-C vs. LDL-C as a better goal for treatment?
- When Is apo B useful and isn't it the same as non-HDL-C?
- What have the fibrate trials told us?

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Fibrates and ASCVD Outcomes

- In RCTs, fibrates do not consistently reduce CHD events in high risk patient groups.
- Do you treat patients with fibrates who are not hypertriglyceridemic?
- The impact of hypertriglyceridemia on CHD outcomes remains unclear.
- Post-hoc analysis indicates that high risk patients with TGs >200 mg/dL (and ↓ HDL-C) may be more likely to benefit.
- The amount of TG lowering may not predict benefit.
- The optimal trial awaits us!
  - VAFIT?
  - PROMINENT

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Fibrate Outcome Studies Evaluating High TG Subgroups

	Trial (Drug)	Primary Endpoint: Entire Cohort (p-value)	Lipid Subgroup Criterion	Primary Endpoint: HTG Subgroup (p-value)
Pre-Statin Era	HHS (Gemfibrozil)	-34% (0.02)	TG > 204 mg/dL LDL-C/HDL-C > 5.0	-71% (0.005)
Some Statin Use	FIELD (Fenofibrate) (no statins at entry)	-11% (0.16)	TG ≥ 204 mg/dL HDL-C < 42 mg/dL	-27% (0.07)
Statin Add-On	ACCORD (Fenofibrate/simva)	-8% (0.32)	TG ≥ 204 mg/dL HDL-C ≤ 34 mg/dL	-31% (0.057)
	AIM-HIGH Niacin ER/ Simvastatin ± EZE	+2% (0.80)	TG ≥ 198 mg/dL HDL-C ≤ 33 mg/dL	-26% (0.073)

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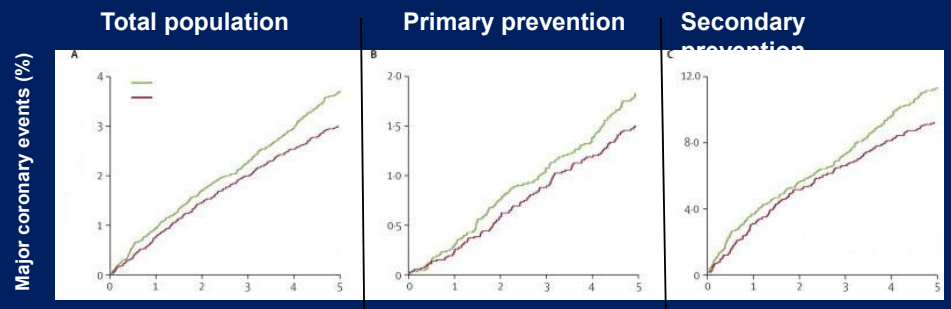
Questions:

- Should TG of 340 mg/dL be treated?
- What about non-HDL-C vs. LDL-C as a better goal for treatment?
- When Is apo B useful and isn't it the same as non-HDL-C?
- What have the fibrate trials told us?
- Fibrates vs. omega-3 fatty acids?

151

JELIS Study: Major Coronary Events



Numbers at risk

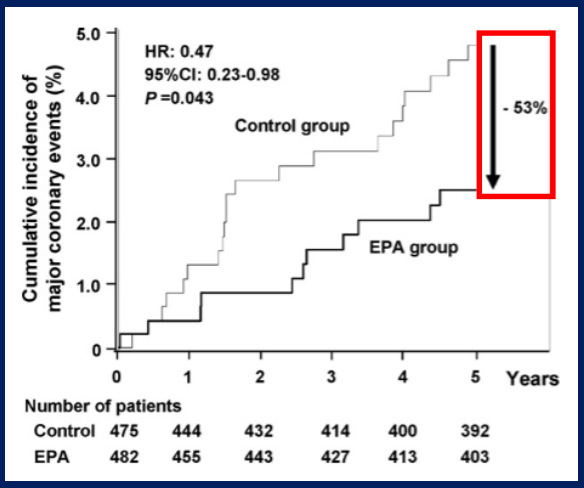
Control	9319	8931	8671	8433	8192	7958	7478	7204	7103	6841	6678	6508	1841	1727	1658	1592	1514	1450
Treatment	9326	8929	8658	8389	8153	7924	7503	7210	7020	6823	6649	6482	1823	1719	1638	1566	1504	1442

N= 18,645; baseline total cholesterol >250 mg/dl; statin ±1.8 g of EPA

Yokoyama M, et al. *Lancet*. 369:1090, 2007

152

JELIS Study: CVD Risk Reduction of EPA in Patients with ↑TG and ↓HDL-C



Saito Y, et al. *Atherosclerosis* 200:135, 2008

153

Primary Prevention of CVD with High Dose Omega-3 Fatty Acids

(Patients with TG 200-500 mg/dL)

Trial	Drug	Size (n)	Primary Outcome	EDC
REDUCE-IT	Icosapent ethyl	8000	5-point MACE	Spring 2018
STRENGTH	Omega-3 carboxylic acids	13,000	5-Point MACE	Sept. 2019

All patients on statins

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Spotlight Presentation: REDUCE-IT USA: Results From the 3,146 Patients Randomized in the United States

DEEPAK L. BHATT, PRESENTER
ROGER BLUMENTHAL, DISCUSSANT

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reduce-it USA

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

BWH

VB RI DS

Controversies Amidst Progress on CVOTs: You Be the Judge

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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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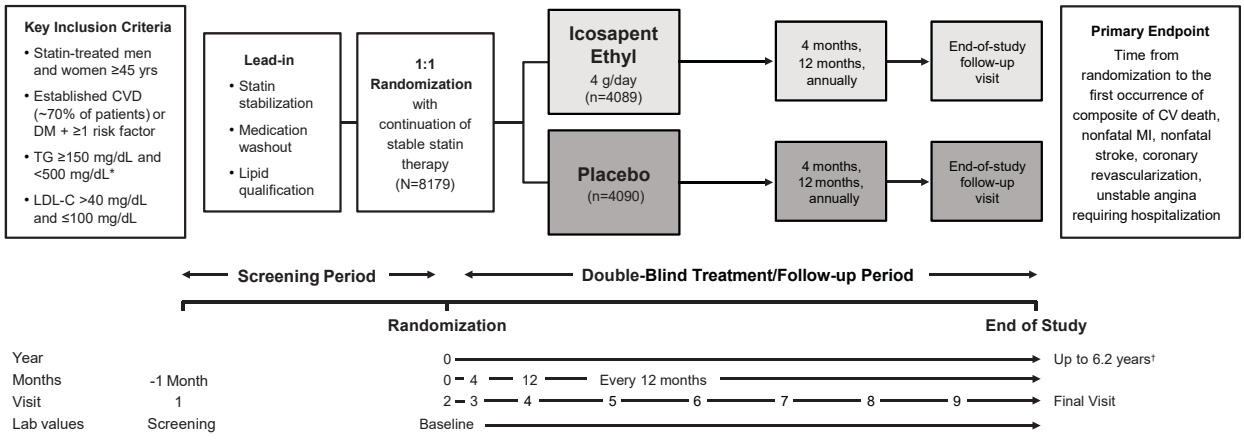
REDUCE-IT Design



*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.
[‡https://creativecommons.org/licenses/by-nc/4.0/]

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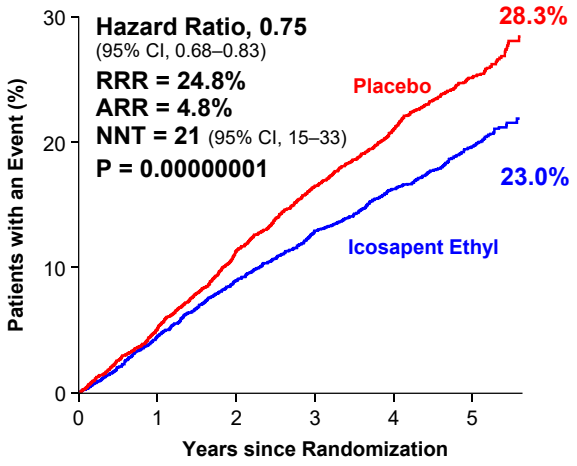
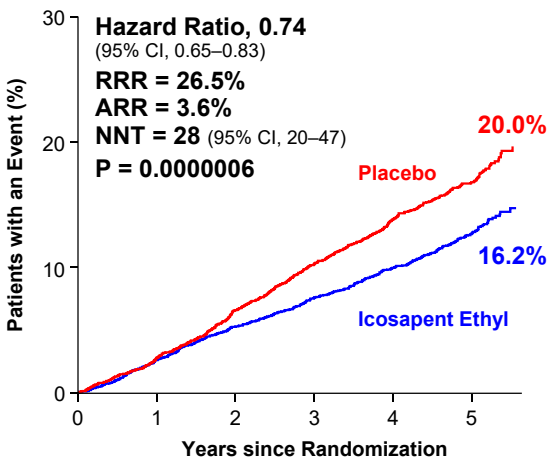
Primary and Key Secondary Composite Endpoints





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

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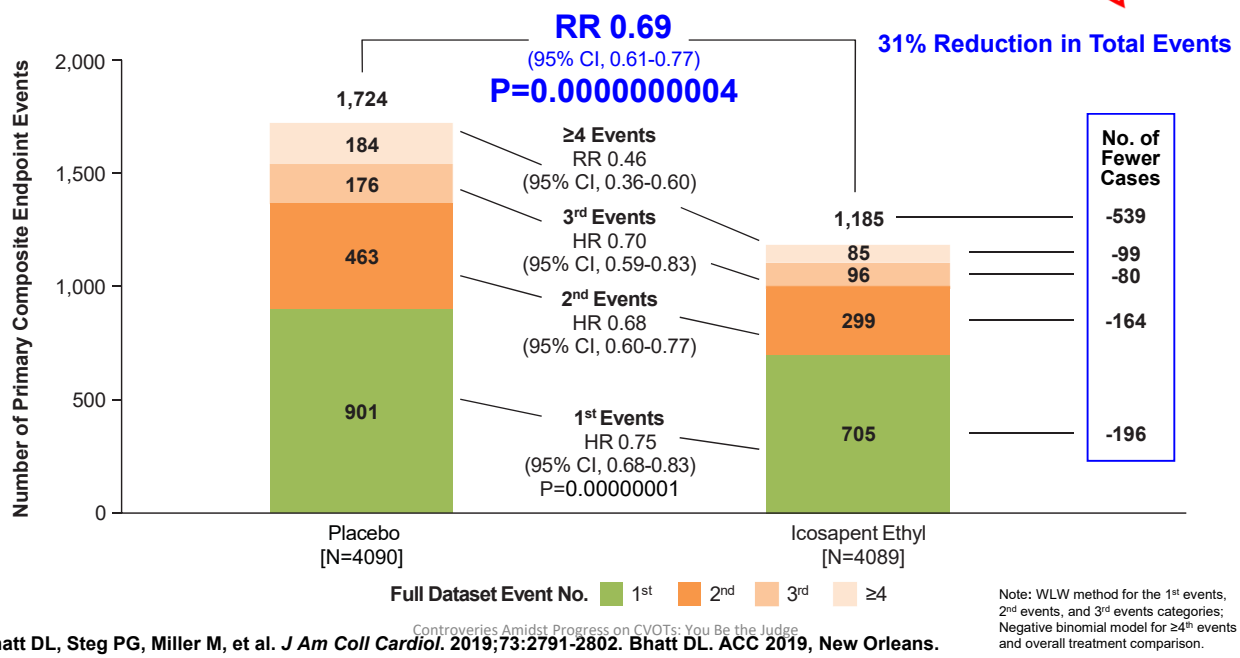
First and Subsequent Events – Full Data



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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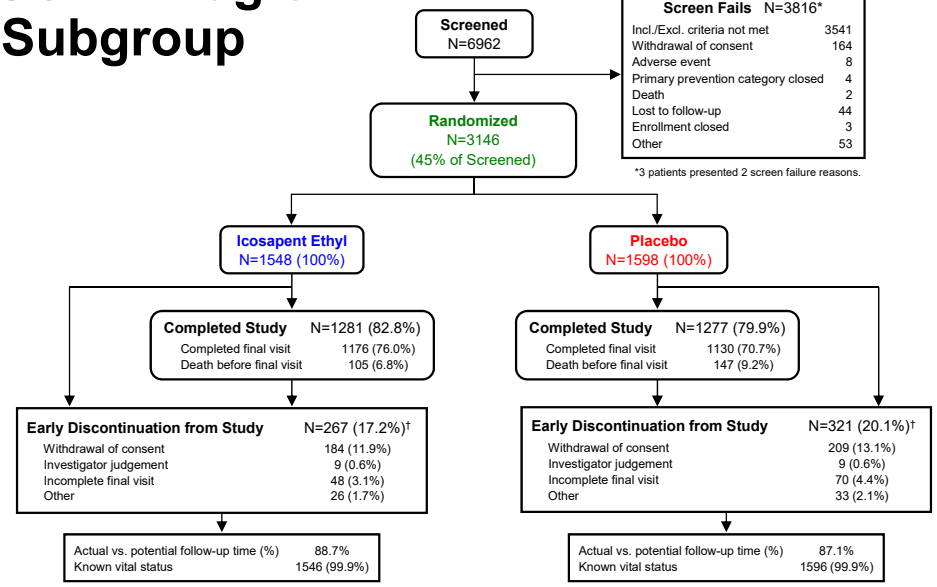
CONSORT Diagram: USA Subgroup



†Early discontinuation from study (17.2% icosapent ethyl; 20.1% placebo) includes patients who discontinued after having a primary event (15 [1.0%] icosapent ethyl; 34 [2.1%] placebo) and prior to having an event (252 [16.3%] icosapent ethyl; 287 [18.0%] placebo).

Controveries Amidst Progress on CVOTs: You Be the Judge

Bhatt DL, Miller M, Brinton EA, et al. *Circulation.* 2019. DOI: 10.1161/CIRCULATIONAHA.119.044440.

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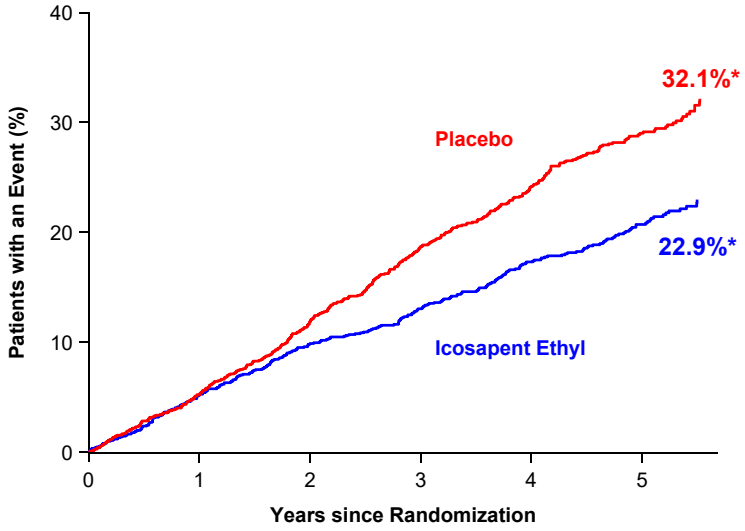
Primary End Point: USA Subgroup

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



Hazard Ratio, 0.69
(95% CI, 0.59–0.80)
RRR = 31%
ARR = 6.5%
NNT = 15 (95% CI, 11–27)
P = 0.000001

*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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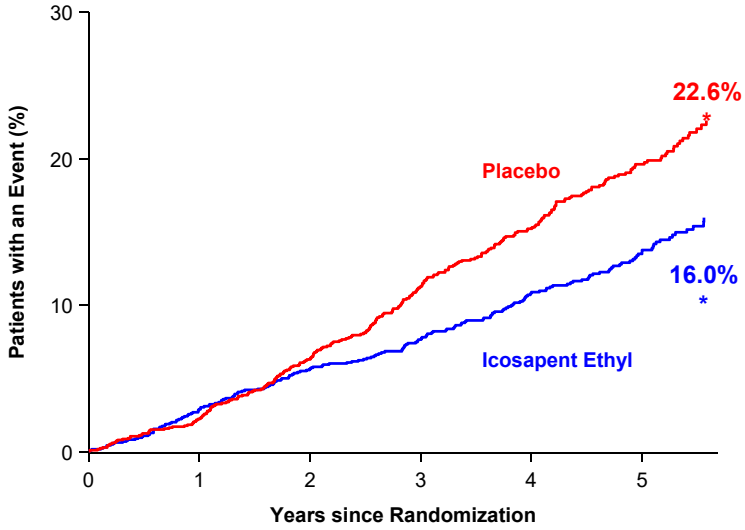
Key Secondary End Point: USA Subgroup

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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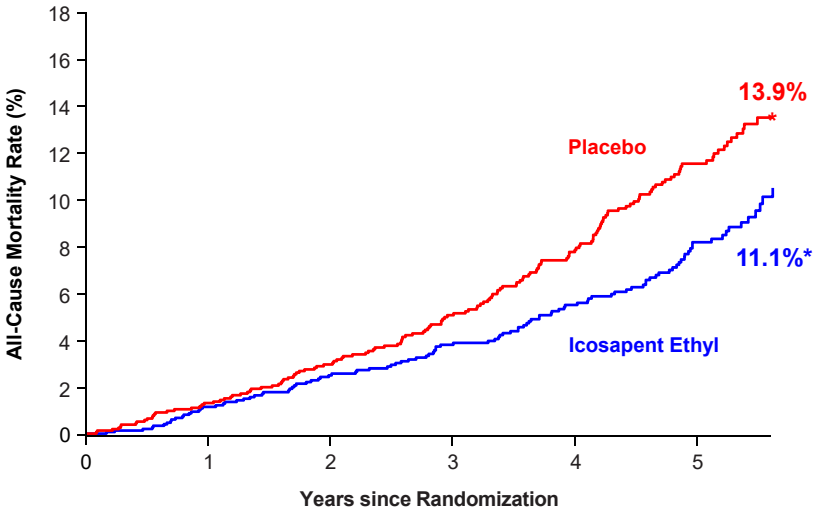
All-Cause Mortality: USA Subgroup



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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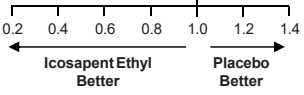
Prespecified Hierarchical Testing: USA Subgroup

reduce-it

Endpoint	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	RRR	P-value
Primary Composite (ITT)		281/1548 (18.2%)	394/1598 (24.7%)	0.69 (0.59–0.80)	31%▼	0.000001
Key Secondary Composite (ITT)		187/1548 (12.1%)	266/1598 (16.6%)	0.69 (0.57–0.83)	31%▼	0.00008
Cardiovascular Death or Nonfatal Myocardial Infarction		160/1548 (10.3%)	222/1598 (13.9%)	0.71 (0.58–0.86)	29%▼	0.0007
Fatal or Nonfatal Myocardial Infarction		103/1548 (6.7%)	141/1598 (8.8%)	0.72 (0.56–0.93)	28%▼	0.01
Urgent or Emergency Revascularization		94/1548 (6.1%)	144/1598 (9.0%)	0.64 (0.49–0.83)	36%▼	0.0006
Cardiovascular Death		72/1548 (4.7%)	107/1598 (6.7%)	0.66 (0.49–0.90)	34%▼	0.007
Hospitalization for Unstable Angina		38/1548 (2.5%)	71/1598 (4.4%)	0.53 (0.36–0.79)	47%▼	0.002
Fatal or Nonfatal Stroke		41/1548 (2.6%)	65/1598 (4.1%)	0.63 (0.43–0.93)	37%▼	0.02
Total Mortality/Nonfatal Myocardial Infarction/Nonfatal Stroke		221/1548 (14.3%)	309/1598 (19.3%)	0.70 (0.59–0.83)	30%▼	0.00005
Total Mortality		111/1548 (7.2%)	156/1598 (9.8%)	0.70 (0.55–0.90)	30%▼	0.004



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

RRR denotes relative risk reduction

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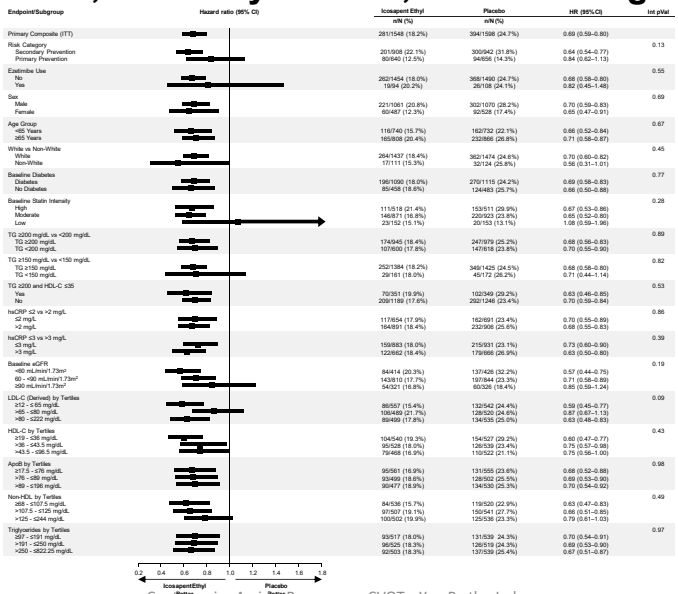
Primary Endpoint: USA Subgroup

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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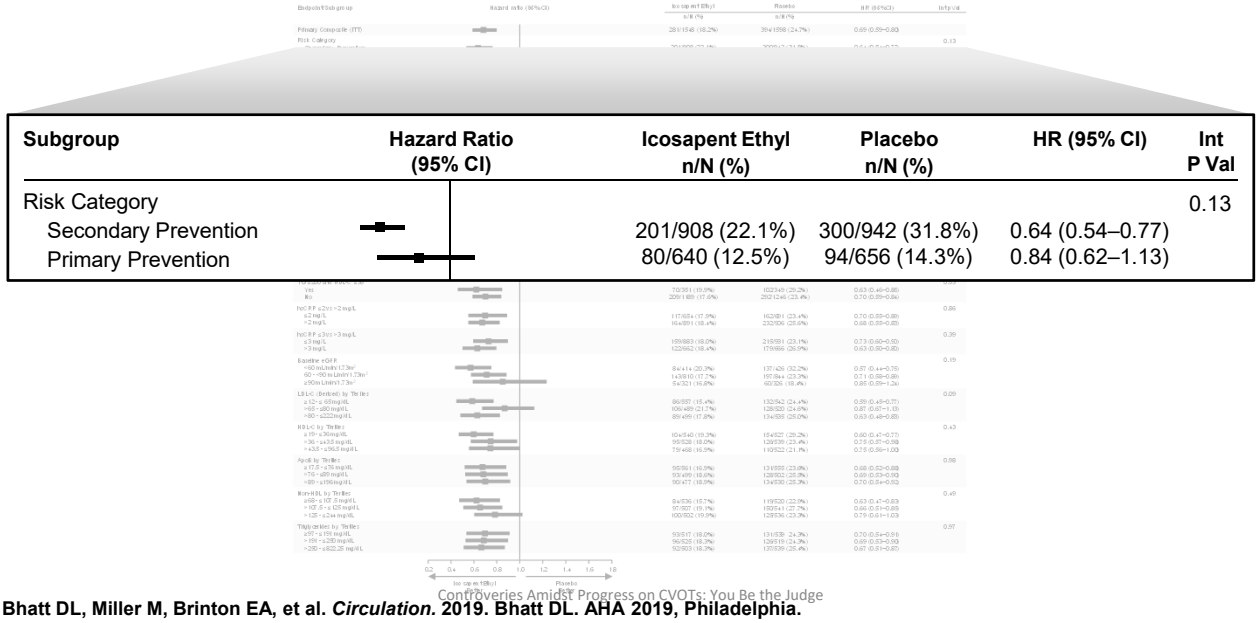
Primary Endpoint: Subgroups – USA

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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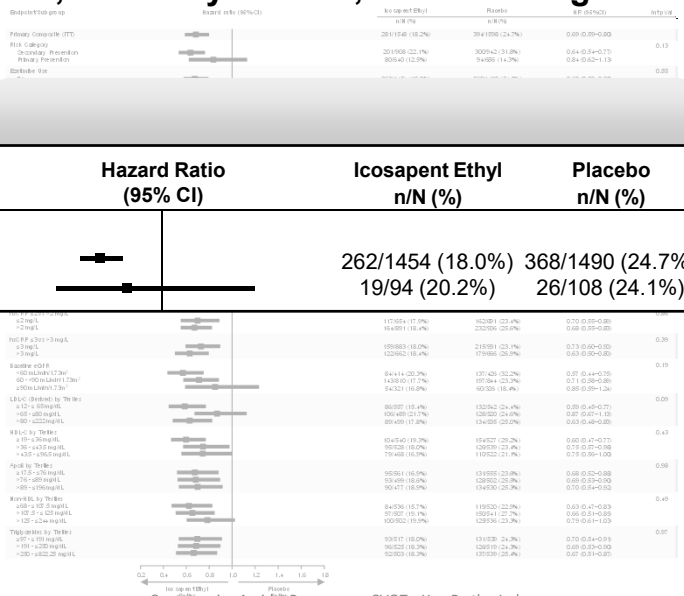
Primary Endpoint: Subgroups – USA

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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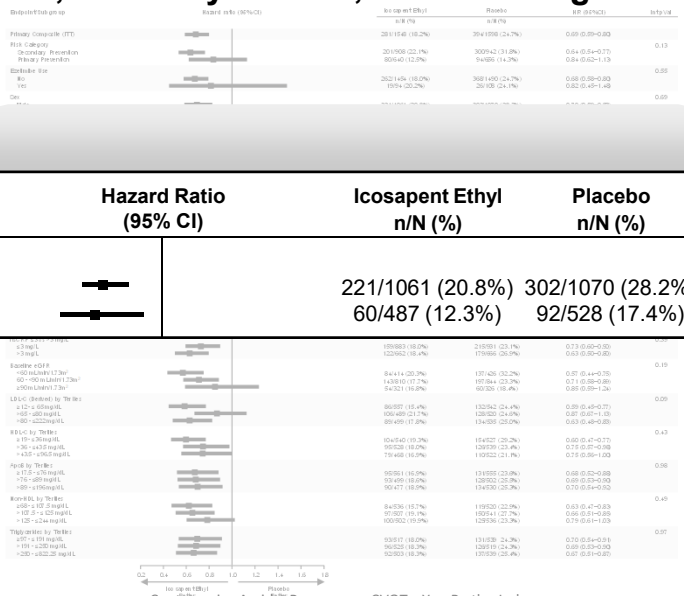
Primary Endpoint: Subgroups – USA

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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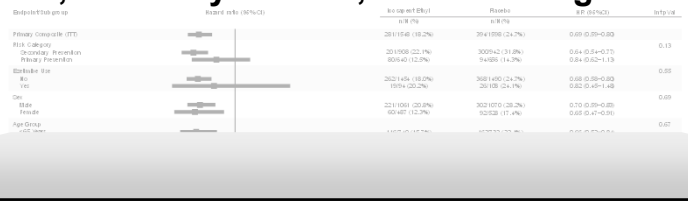
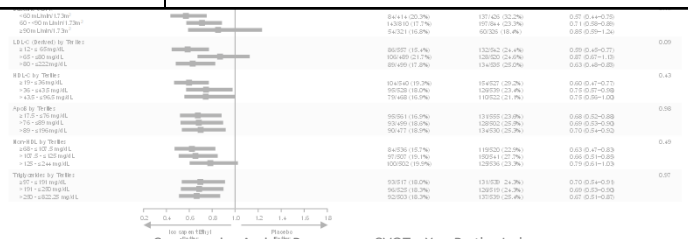
Primary Endpoint: Subgroups – USA

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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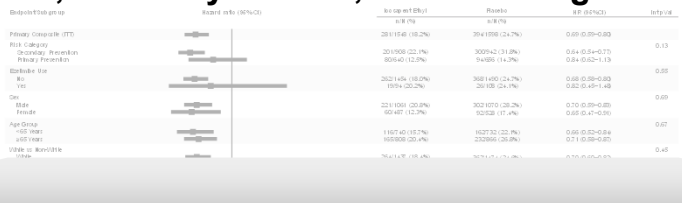
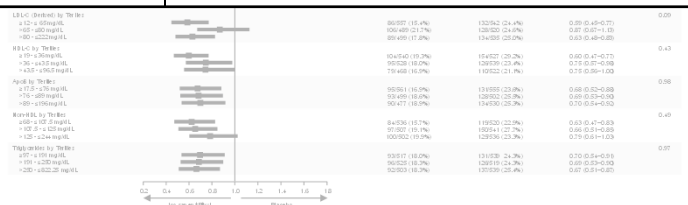
Primary Endpoint: Subgroups – USA

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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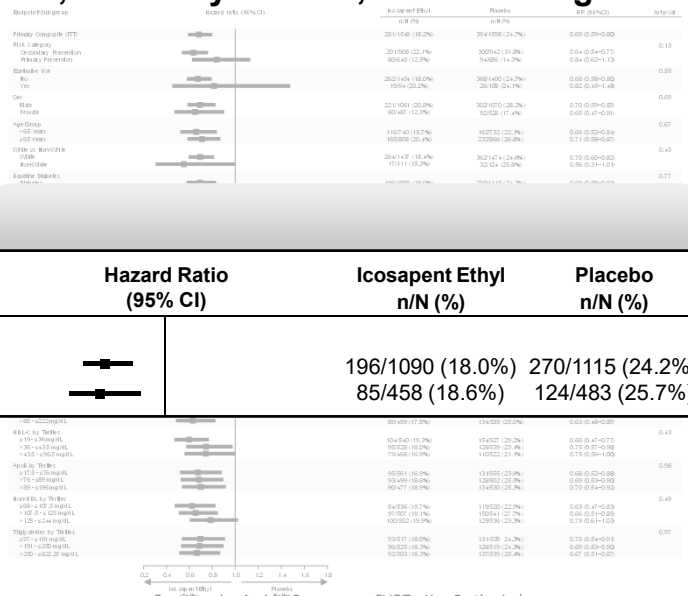
Primary Endpoint: Subgroups – USA

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

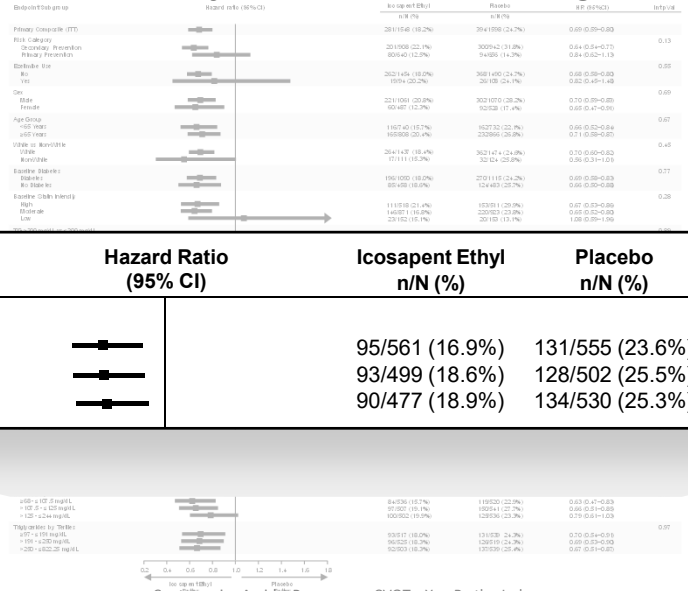


Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Baseline Diabetes					0.77
Diabetes		196/1090 (18.0%)	270/1115 (24.2%)	0.69 (0.58–0.83)	
No Diabetes		85/458 (18.6%)	124/483 (25.7%)	0.66 (0.50–0.88)	

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

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)	

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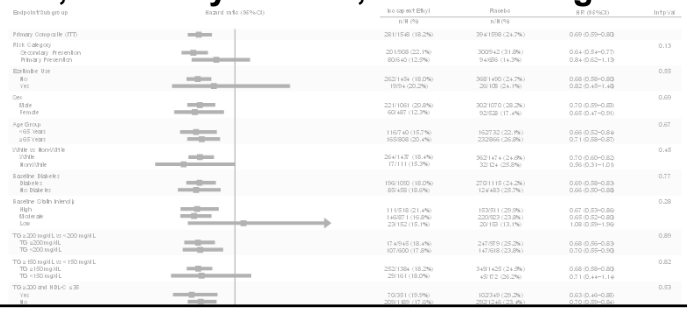
Primary Endpoint: Subgroups – USA

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)	

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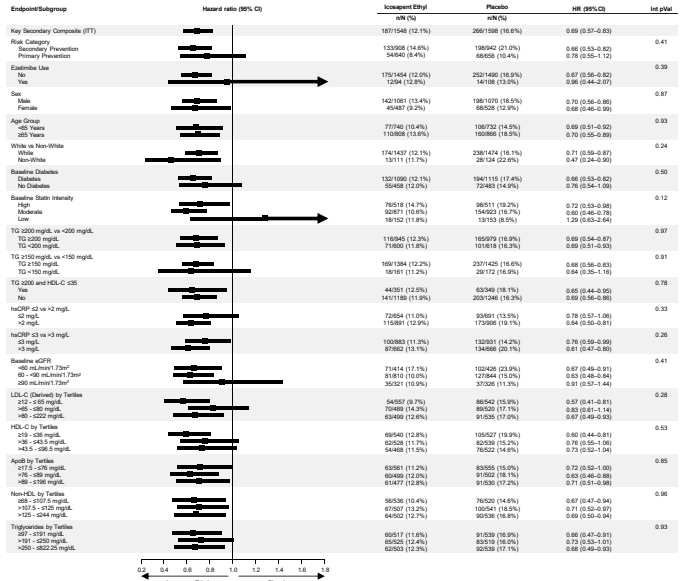
Key Secondary Endpoint: Subgroups – USA

CV Death, MI, Stroke



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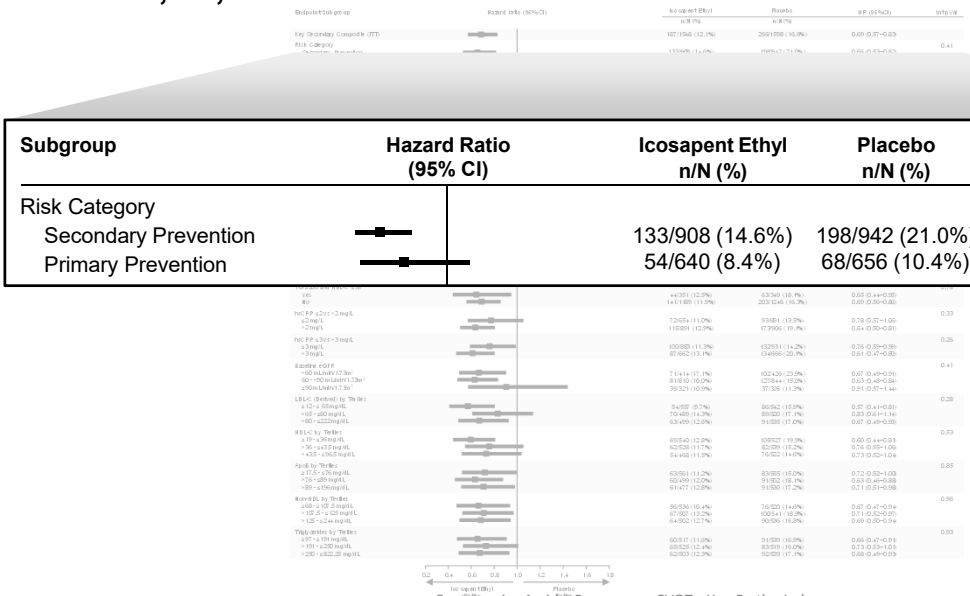
Key Secondary Endpoint: Subgroups – USA

CV Death, MI, Stroke



Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Risk Category					0.41
Secondary Prevention		133/908 (14.6%)	198/942 (21.0%)	0.66 (0.53–0.82)	
Primary Prevention		54/640 (8.4%)	68/656 (10.4%)	0.78 (0.55–1.12)	

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

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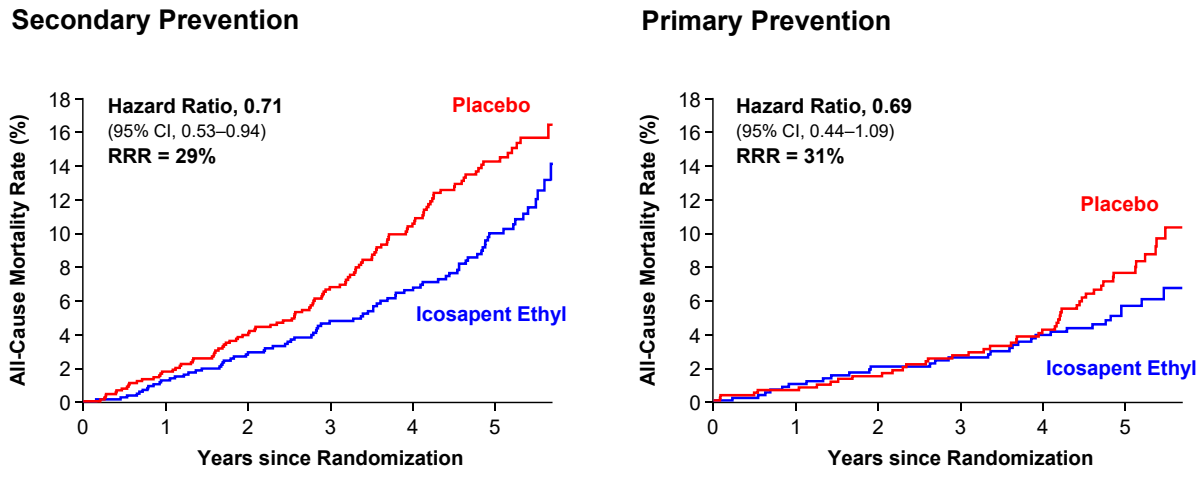
All-Cause Mortality: USA Subgroup by CV Risk Category



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.

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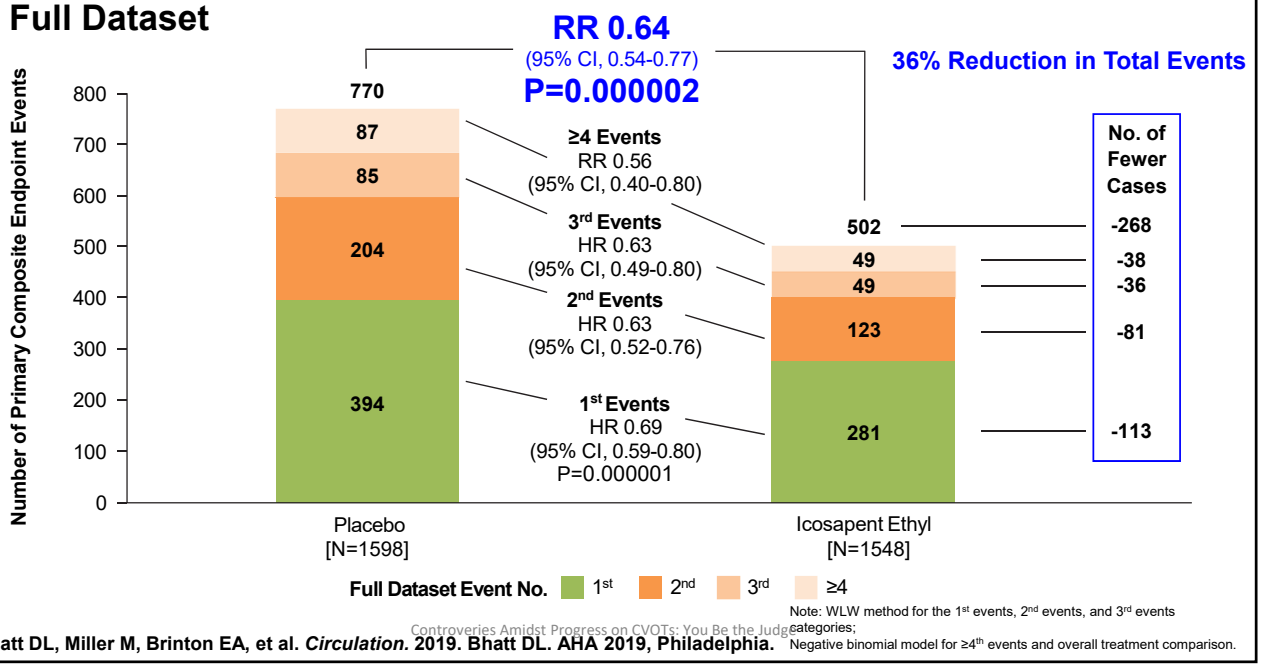
First and Subsequent Events: USA

Full Dataset



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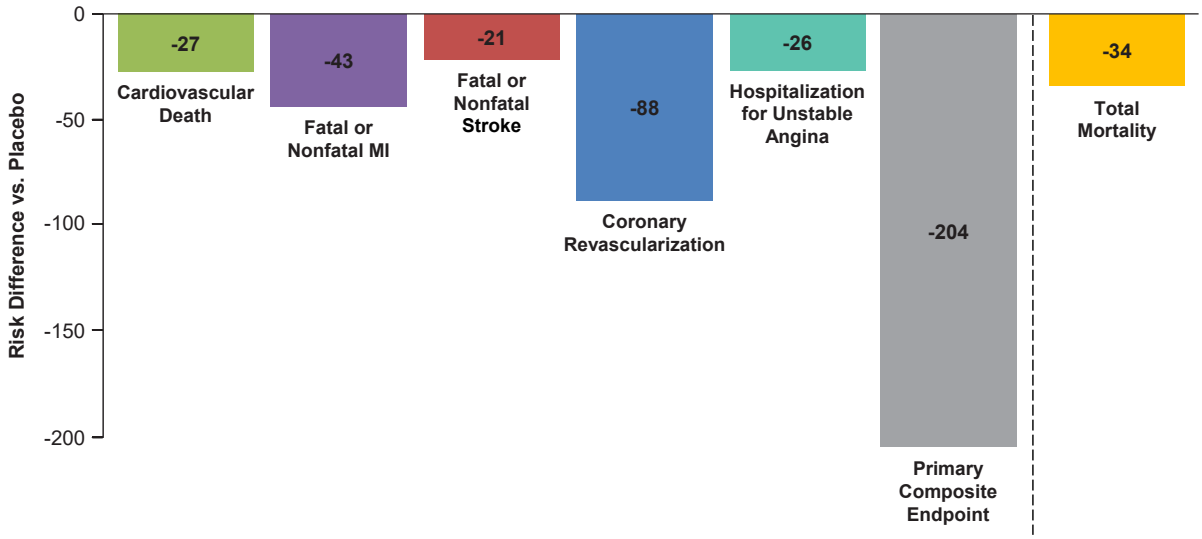
For Every 1000 Patients in the USA Treated with Icosapent Ethyl 4g/day for 5 Years



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!

reduce-it

Controversies Amidst Progress on CVOTs: You Be the Judge

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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

HTTPS://WWW.AHAJOURNALS.ORG/DOI/10.1161/CIRCULATIONAHA.119.044440

American Heart Association.

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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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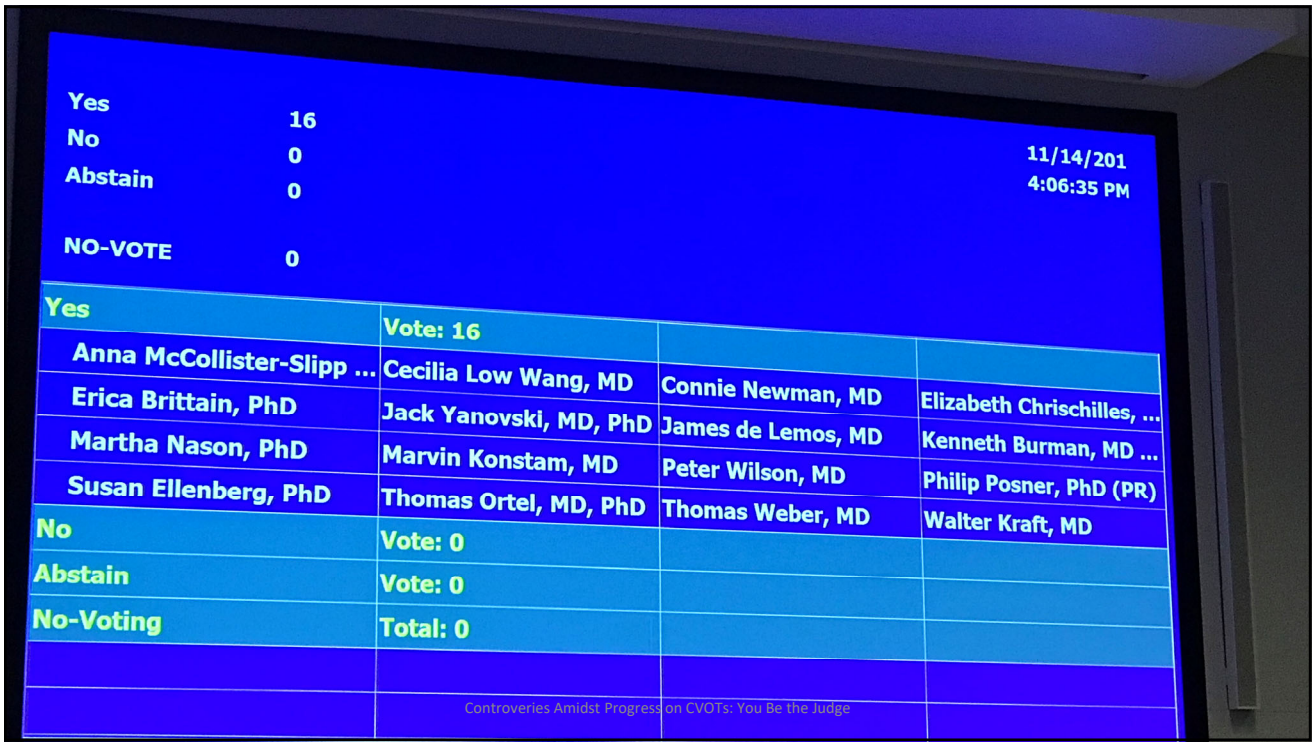

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reduce-it USA

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