IMPERIAL

Managing a Patient with Residual Risk: Applying recent evidence with EPA to practice

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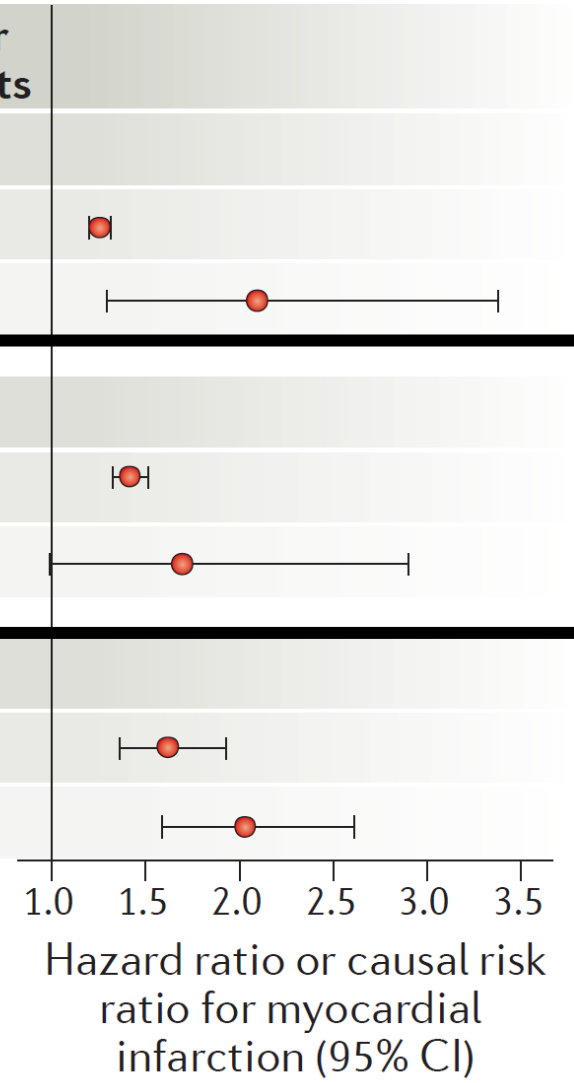
Disclosures: KK Ray

Disclosure of speaker's interests	
Relations that could be relevant for the meeting:	**Company names**
• Sponsorship or research funds • Payment or other (financial) renumeration	• Amgen, Sanofi, Regeneron, MSD, Pfizer, Daiichi Sankyo, Ultragenix • Consultancy: Amgen, Sanofi, Regeneron, Pfizer, Viatris, Abbott, AstraZeneca, Lilly, Kowa Pharmaceutics, Novo Nordisk, Boehringer Ingelheim, Esperion, Cargene Therapeutics, Resverlogix, Novartis, Silence Therapeutics, NewAmsterdam Pharma, Scribe Therapeutics, CRISPR Therapeutics, VAXXINITY, Amarin, CSL Behring, Bayer, Cleerly Health, Emendobio • Stock Options PEMI31, SCRIBE, New Amsterdam Pharma

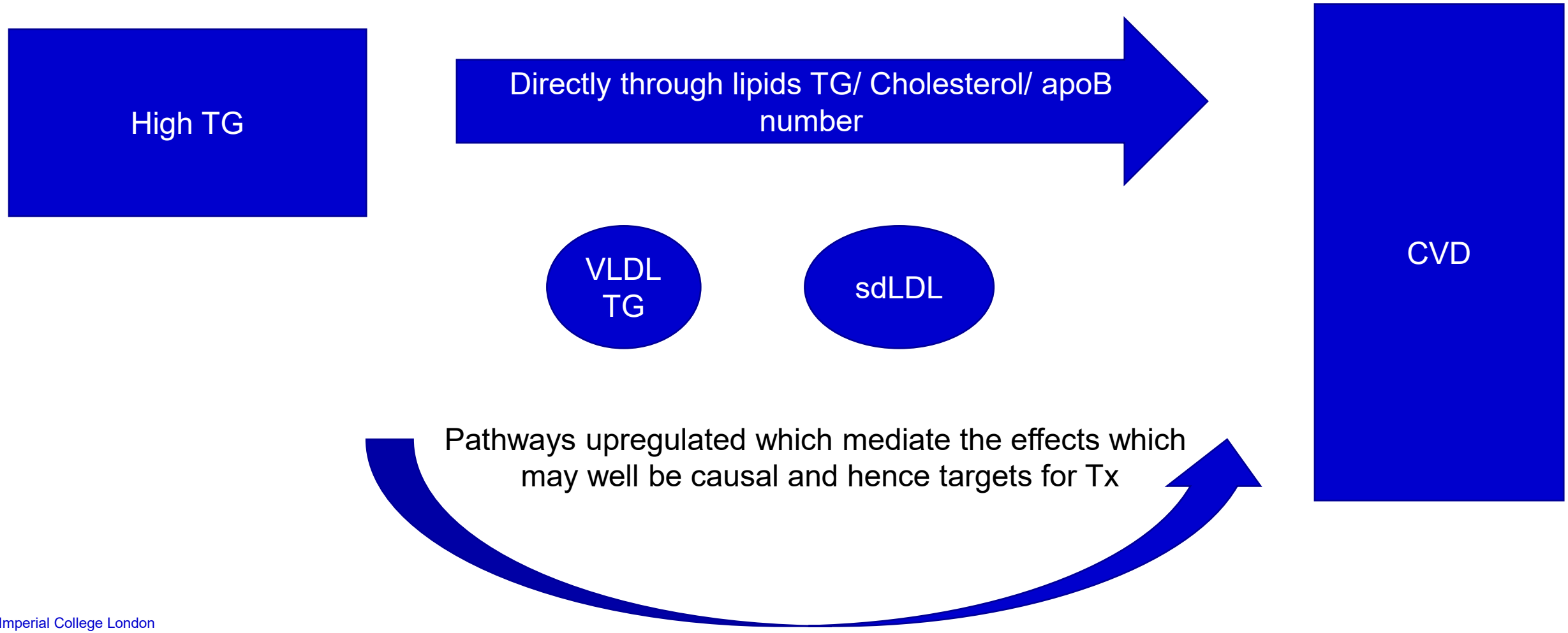
Copenhagen General Population Study - all apoB containing lipoproteins are likely causally linked to ASCVD

	n	Number of events
LDL cholesterol: increase of 39 mg/dl (1 mmol/l)		
Observational	108,554	2,210
Genetic (*APOB, HMGCR, LDLR, PCSK9*)	95,908	4,155
Remnant cholesterol: increase of 39 mg/dl (1 mmol/l)		
Observational	108,508	2,219
Genetic (*APOA5, GCKR, LPL, TRIB1*)	97,745	4,199
Lipoprotein(a) cholesterol: increase of 39 mg/dl (1 mmol/l)		
Observational	108,550	2,210
Genetic (*LPA*)	103,715	4,425

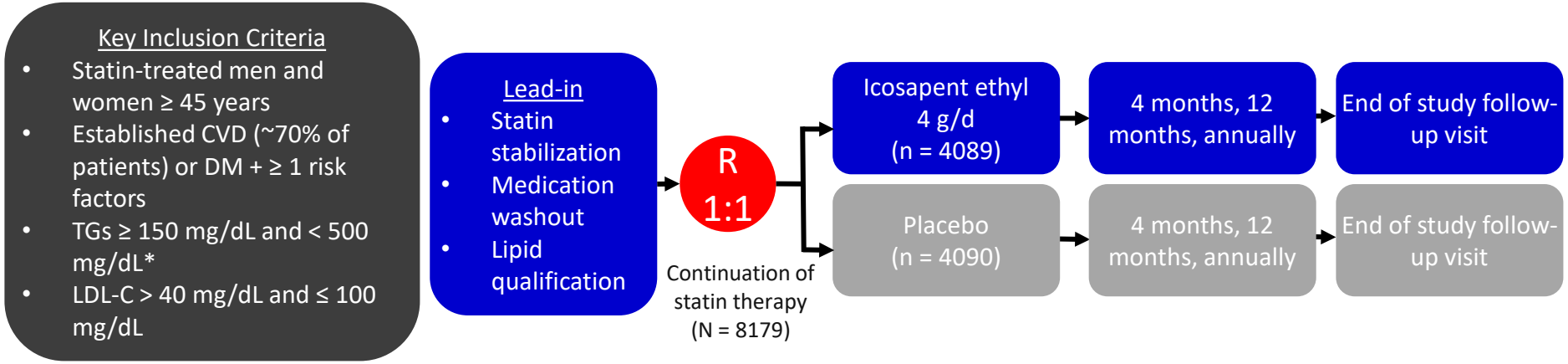


Nordestgaard, Nicholls, Langsted, Ray & Tybjærg-Hansen. Nat Rev Cardiol 2018 2018; 15: 261-272

Mendelian Randomization does not tell you which part of the TG related pathway you need to target ?

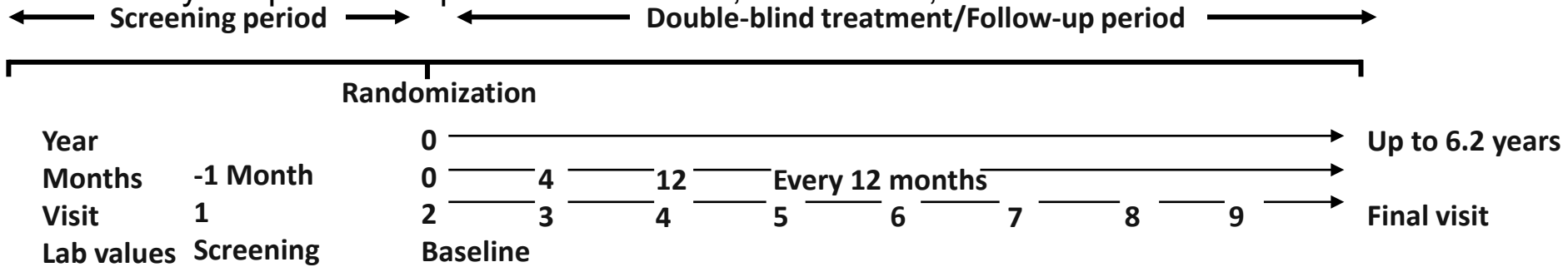


REDUCE-IT
Study Design



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

Secondary endpoint: Composite of CV death, nonfatal MI, or nonfatal stroke



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

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

REDUCE-IT: Baseline characteristics[1]

Characteristics[1]	Icosapent ethyl (n=4,089)	Placebo (n=4,090)
Age (years), Median (Q1–Q3)	64.0 (57.0–69.0)	64.0 (57.0–69.0)
Female, n (%)	1,162 (28.4%)	1,195 (29.2%)
Non-white, n (%)	398 (9.7%)	402 (9.8%)
CV Risk Category, n (%)		
Secondary Prevention Cohort	2,892 (70.7%)	2,893 (70.7%)
Primary Prevention Cohort	1,197 (29.3%)	1,197 (29.3%)
Ezetimibe Use, n (%)	262 (6.4%)	262 (6.4%)
Statin Intensity, n (%)		
Low	254 (6.2%)	267 (6.5%)
Moderate	2,533 (61.9%)	2,575 (63.0%)
High	1,290 (31.5%)	1,226 (30.0%)
T2DM, n (%)	2,367 (57.9%)	2,363 (57.8%)
TG (mmol/L), Median (Q1–Q3)	2.5 (2.0–3.1)	2.4 (2.0–3.1)
HDL-C (mmol/L), Median (Q1–Q3)	1.0 (0.9–1.2)	1.0 (0.9–1.2)
LDL-C (mmol/L), Median (Q1–Q3)	1.9 (1.6–2.3)	2.0 (1.6–2.3)
TG Category, n (%)		
<1.7 mmol/L	412 (10.1%)	429 (10.5%)
1.7–<2.3 mmol/L	1,193 (29.2%)	1,191 (29.1%)
≥2.3 mmol/L	2,481 (60.7%)	2,469 (60.4%)
hsCRP (mg/L)*	2.2	2.1

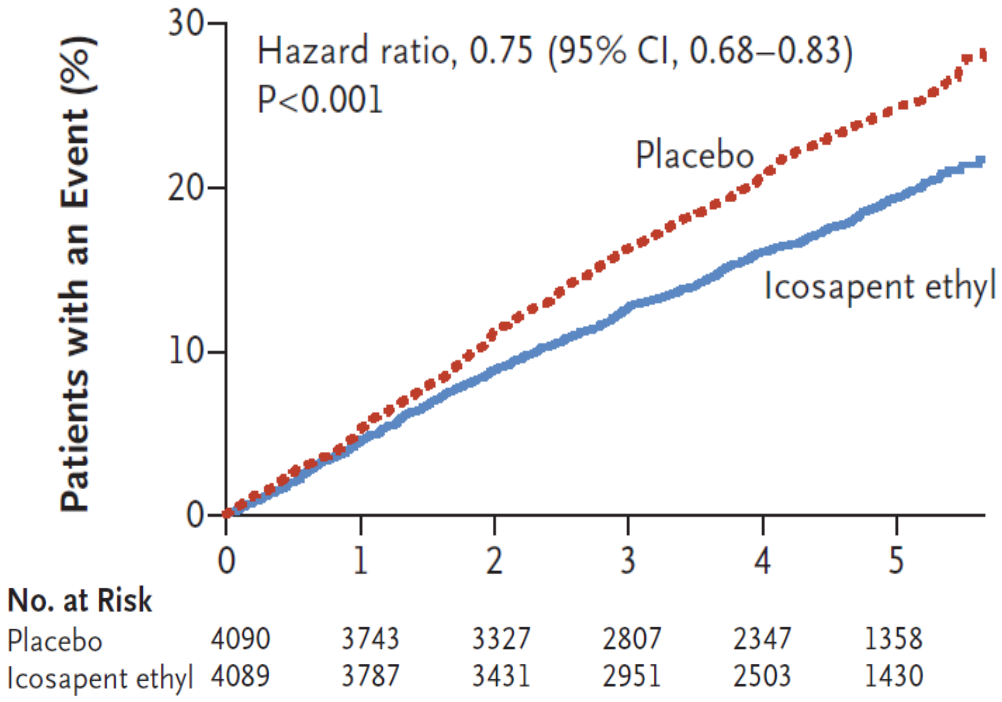
71% of enrolled patients were secondary prevention[1]

Adapted from Bhatt DL, *et al. N Engl J Med.* 2019.[1]

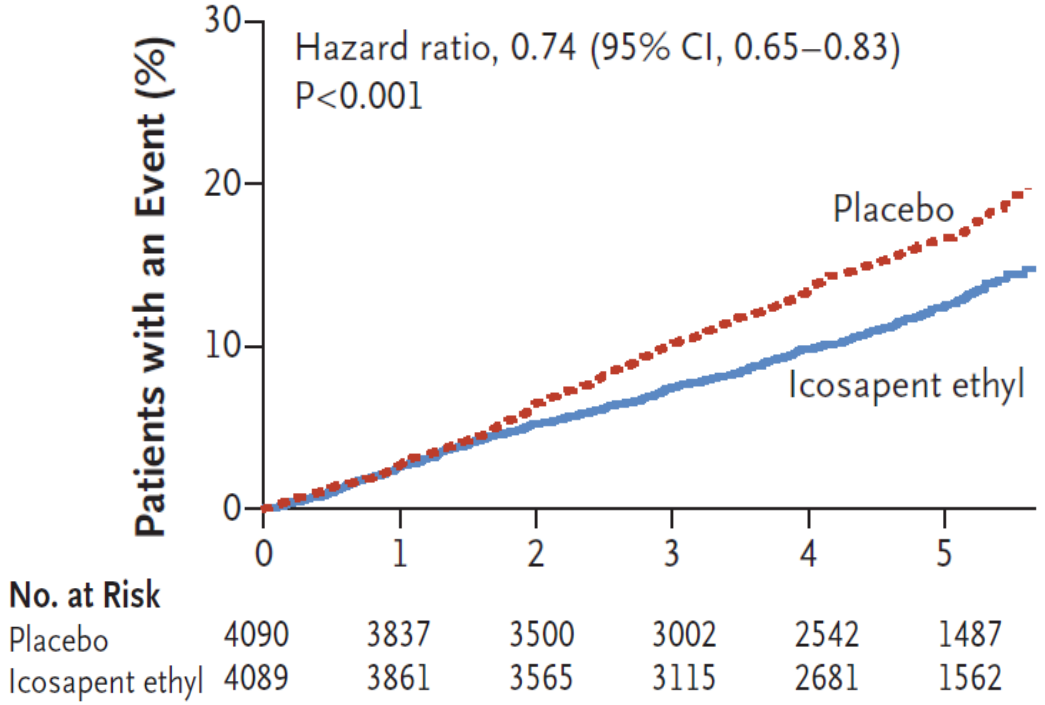
*Median observed value.
CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; T2DM, type 2 diabetes mellitus.
1. Bhatt DL, *et al. N Engl J Med.* 2019;380(1):11–22 and supplementary appendix.

REDUCE-IT
Key Efficacy Findings

Primary Endpoint: 5-Point MACE



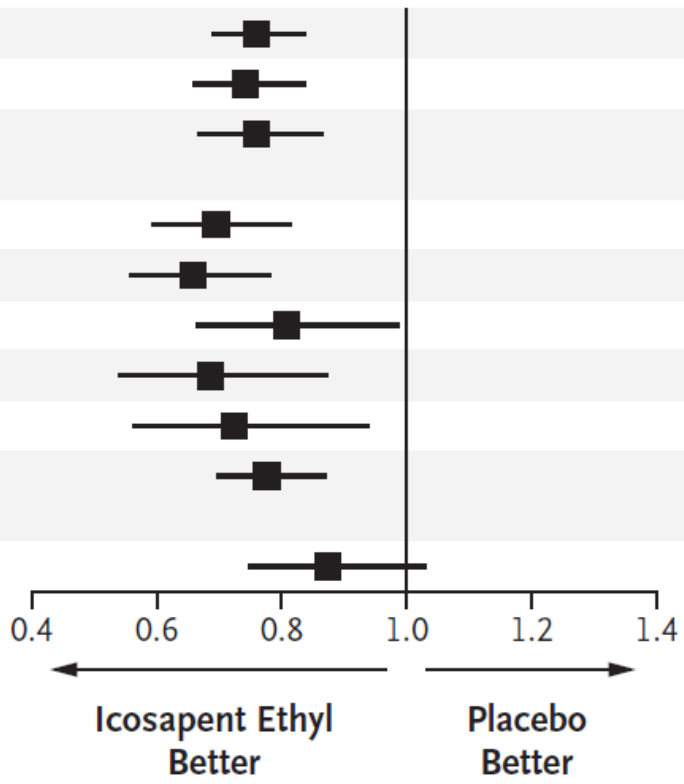
Secondary Endpoint*



*Composite of CV death, nonfatal MI, or nonfatal stroke.
Bhatt DL, et al. *N Engl J Med*. 2019;380:11-22.

REDUCE-IT
Key Efficacy Findings (cont)

End Point	Icosapent Ethyl (N=4089)	Placebo (N=4090)	Hazard Ratio (95% CI)	P Value
	no. of patients with event (%)			
Primary composite	705 (17.2)	901 (22.0)	0.75 (0.68–0.83)	<0.001
Key secondary composite	459 (11.2)	606 (14.8)	0.74 (0.65–0.83)	<0.001
Cardiovascular death or nonfatal myocardial infarction	392 (9.6)	507 (12.4)	0.75 (0.66–0.86)	<0.001
Fatal or nonfatal myocardial infarction	250 (6.1)	355 (8.7)	0.69 (0.58–0.81)	<0.001
Urgent or emergency revascularization	216 (5.3)	321 (7.8)	0.65 (0.55–0.78)	<0.001
Cardiovascular death	174 (4.3)	213 (5.2)	0.80 (0.66–0.98)	0.03
Hospitalization for unstable angina	108 (2.6)	157 (3.8)	0.68 (0.53–0.87)	0.002
Fatal or nonfatal stroke	98 (2.4)	134 (3.3)	0.72 (0.55–0.93)	0.01
Death from any cause, nonfatal myocardial infarction, or nonfatal stroke	549 (13.4)	690 (16.9)	0.77 (0.69–0.86)	<0.001
Death from any cause	274 (6.7)	310 (7.6)	0.87 (0.74–1.02)	—

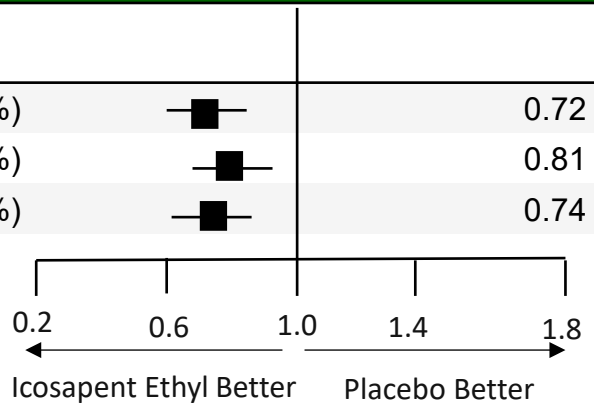


Bhatt DL, et al. *N Engl J Med*. 2019;380:11-22.

REDUCE-IT
CV Benefit of EPA Independent of LDL-C Levels

Baseline Characteristics	Icosapent Ethyl (n = 4086)	Placebo (n = 4089)
TGs (mg/dL), median (Q1-Q3)	216.5 (176.5-272.0)	216.0 (175.5-274.0)
HDL-C (mg/dL), median (Q1-Q3)	40.0 (34.5-46.0)	40.0 (35.0-46.0)
LDL-C (mg/dL), median (Q1-Q3)	74.0 (61.5-88.0)	76.0 (63.0-89.0)
TG Category, n (%)		
< 150 mg/dL	412 (10.1)	429 (10.5)
≥ 150 to < 200 mg/dL	1193 (29.2)	1191 (29.1)
≥ 200 mg/dL	2481 (60.7)	2469 (60.4)

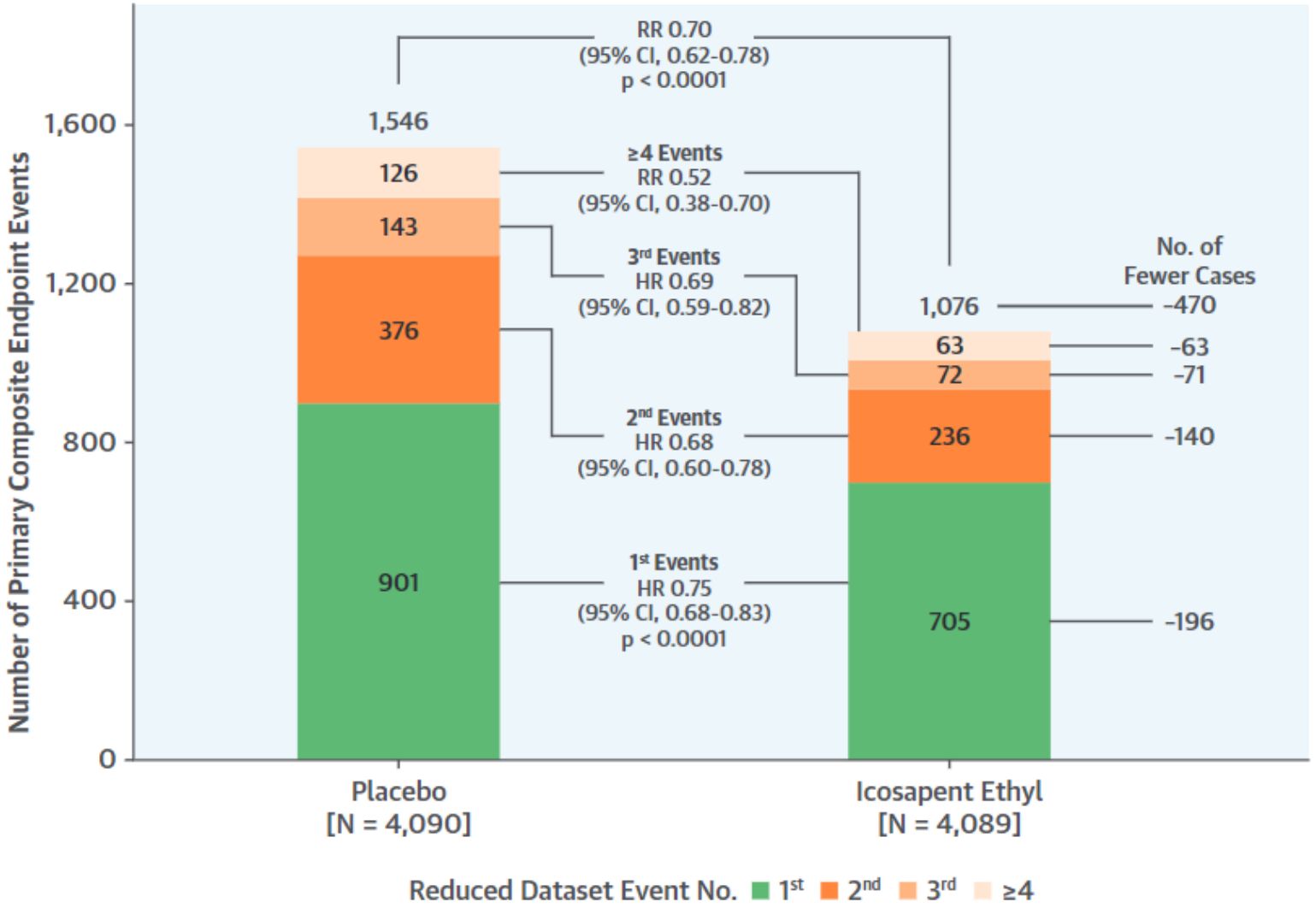
	Icosapent Ethyl	Placebo	HR (95% CI)	*P* Value
Primary Composite Endpoint: Baseline LDL-C*				.62
≤ 67 mg/dL	244/1481 (16.5%)	302/1386 (21.8%)	0.72 (0.61, 0.85)	
> 67 to ≤ 84 mg/dL	248/1347 (18.4%)	307/1364 (22.5%)	0.81 (0.68, 0.96)	
> 84 mg/dL	213/1258 (16.9%)	292/1339 (21.8%)	0.74 (0.62, 0.89)	



CV benefit for EPA reported even among patients in the lowest baseline LDL-C quartile

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

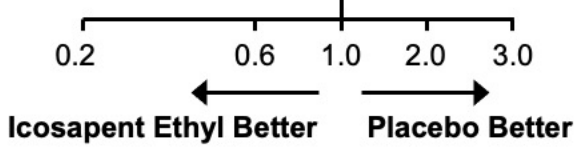
REDUCE-IT
Reduction in Recurrent and Total Ischemic Events



Bhatt DL, et al. *J Am Coll Cardiol.* 2019;74:1159-1161.

There were similar risk reductions across several endpoints in prior MI patients[1]

Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Icosapent Ethyl vs Placebo HR (95% CI)	ARR	Log-Rank P value
Primary Composite Endpoint	378/1,870 (20.2)	475/1,823 (26.1)	0.74 (0.65–0.85)	5.9%	0.00001
Key Secondary Composite Endpoint	248/1,870 (13.3)	328/1,823 (18.0)	0.71 (0.61–0.84)	4.7%	0.00006
Cardiovascular Death or Nonfatal Myocardial Infarction	215/1,870 (11.5)	285/1,823 (15.6)	0.71 (0.60–0.85)	4.1%	0.0002
Fatal or Nonfatal Myocardial Infarction	147/1,870 (7.9)	211/1,823 (11.6)	0.66 (0.53–0.81)	3.7%	0.00009
Urgent or Emergent Revascularisation	124/1,870 (6.6)	188/1,823 (10.3)	0.62 (0.49–0.78)	3.7%	0.00003
Cardiovascular Death	84/1,870 (4.5)	116/1,823 (6.4)	0.70 (0.53–0.92)	1.9%	0.01
Hospitalisation for Unstable Angina	65/1,870 (3.5)	99/1,823 (5.4)	0.63 (0.46–0.86)	1.9%	0.003
Fatal or Nonfatal Stroke	51/1,870 (2.7)	62/1,823 (3.4)	0.79 (0.55–1.14)	0.7%	0.21
Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke	292/1,870 (15.6)	367/1,823 (20.1)	0.75 (0.64–0.87)	4.5%	0.0002
Total Mortality	136/1,870 (7.3)	163/1,823 (8.9)	0.80 (0.64–1.00)	1.6%	0.054



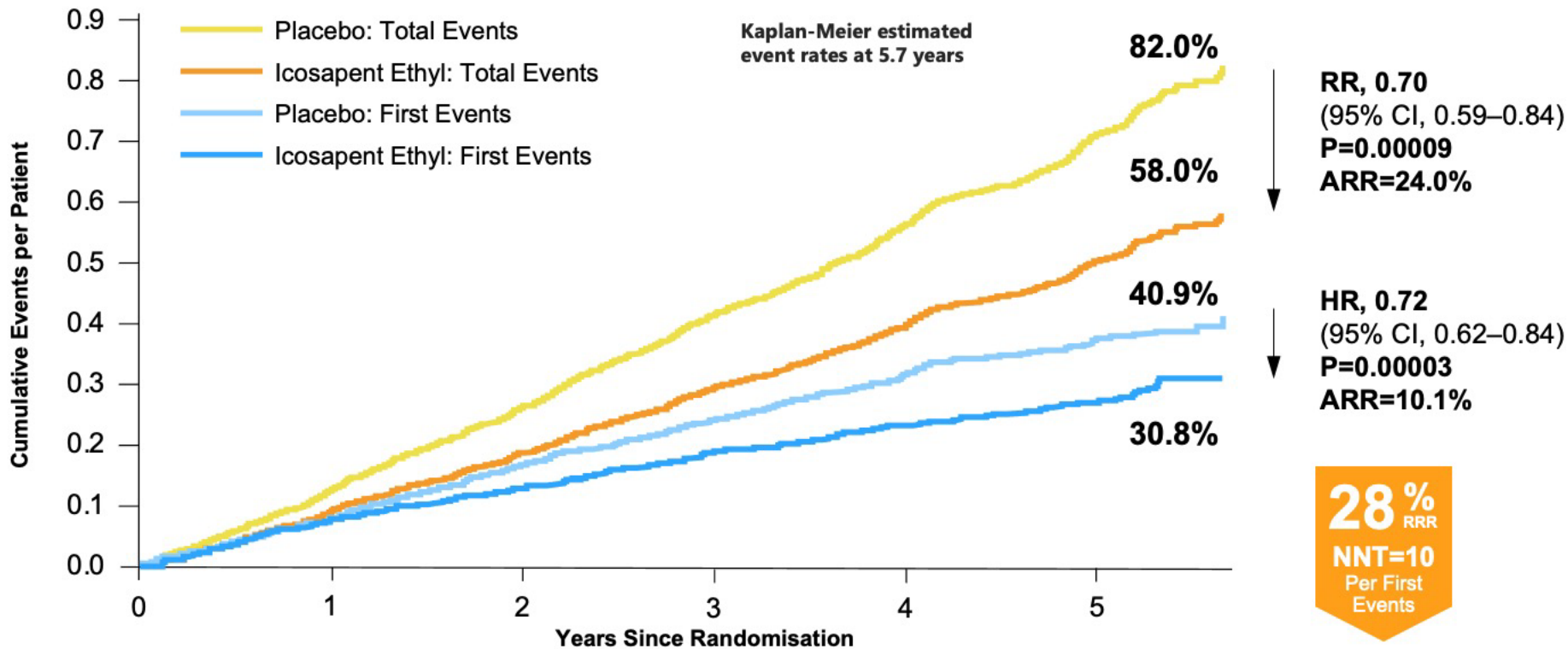
Adapted from Gaba P, *et al. J Am Coll Cardiol.* 2022.[1]

Prior MI subgroup data are available from pre-specified and post hoc analyses of the REDUCE-IT data.[1] Median follow-up 4.8 years.[1]
ARR, absolute risk reduction; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.

1. Gaba P, *et al. J Am Coll Cardiol.* 2022;79(17):1660–1671.

Icosapent ethyl demonstated an NNT of 10 in patients with diabetes and established CVD vs placebo[1]

Time to first and total primary composite* endpoint events



RR, 0.70
(95% CI, 0.59–0.84)
P=0.00009
ARR=24.0%

HR, 0.72
(95% CI, 0.62–0.84)
P=0.00003
ARR=10.1%

28 % RRR
NNT=10
Per First Events

Adapted from Bhatt DL, *et al.* ADA. 2020.[1]

Diabetes subgroup data are available from pre-specified and post hoc analyses of the REDUCE-IT data.[1]
*The composite of CV death, non-fatal MI, non-fatal stroke, coronary revascularisation, hospitalisation for unstable angina.
ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; HR, hazard ratio; NNT, number needed to treat; RR, rate ratio.
1. Bhatt DL, *et al.* ADA. 2020. Chicago (Presentation).

REDUCE-IT
Safety

	Icosapent Ethyl (n = 4089)	Placebo (n = 4090)	*P* Value
Patients with at least one TEAE, n (%)	3343 (81.8)	3326 (81.3)	.63
Serious TEAE	1252 (30.6)	1254 (30.7)	.98
TEAE leading to withdrawal of drug	321 (7.9)	335 (8.2)	.60
Serious TEAE leading to withdrawal of drug	88 (2.2)	88 (2.2)	1.00
Serious TEAE leading to death	94 (2.3)	102 (2.5)	.61
Patients with bleeding-related disorders	111 (2.7)	85 (2.1)	.06
GI bleeding	62 (1.5)	47 (1.1)	.15
CNS bleeding	14 (0.3)	10 (0.2)	.42
Other bleeding	41 (1.0)	30 (0.7)	.19

- **AF occurred in more patients treated with EPA than placebo (5.3% vs 3.9%, *P* = .003), mostly in the form of recurrent AF in patients with a history of AF**
  - 28% reduction in fatal and nonfatal stroke with EPA was also seen in this subset of patients with AF

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

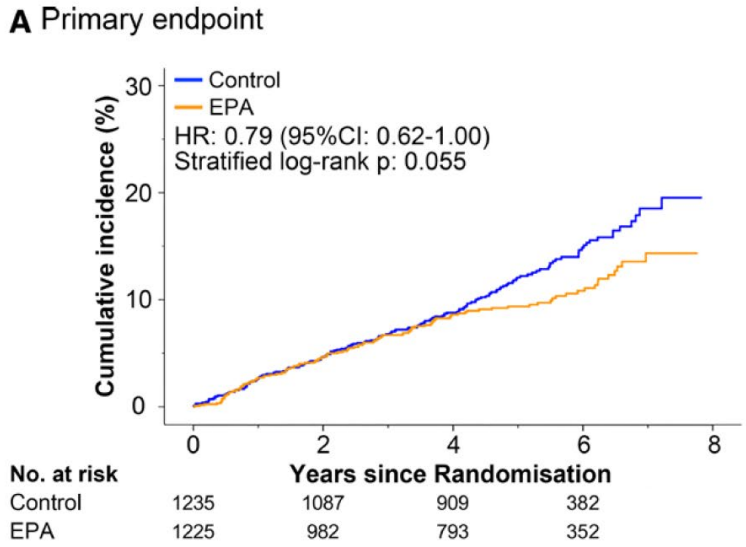
Validation in RESPECT EPA with 2g IPE

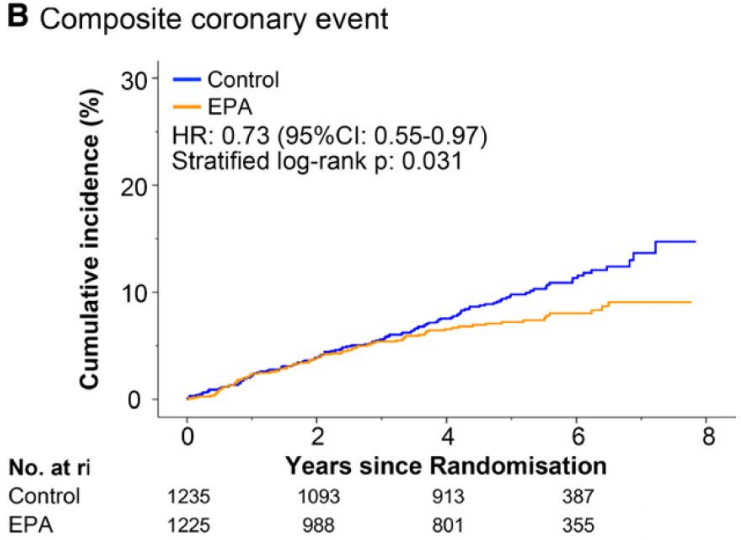
Circulation

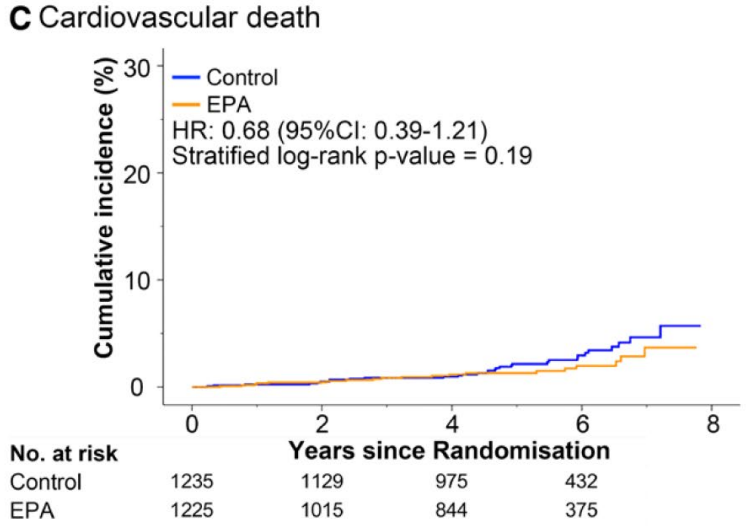
ORIGINAL RESEARCH ARTICLE

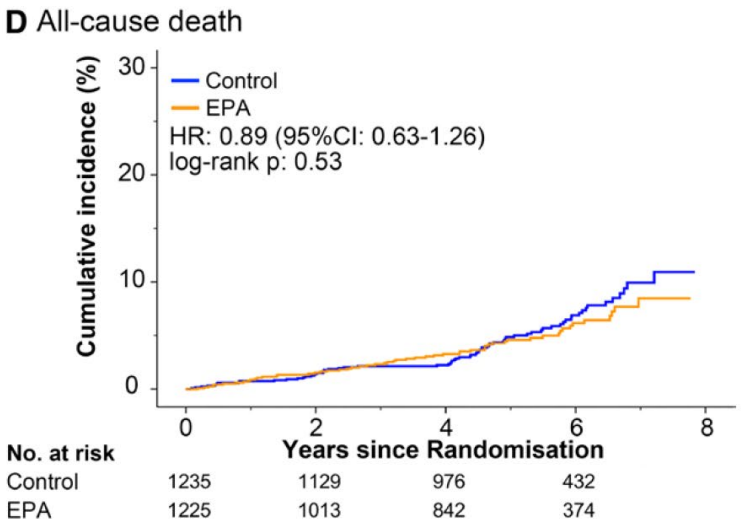
Randomized Trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy–Statin and Eicosapentaenoic Acid (RESPECT-EPA)

Katsumi Miyauchi, MD; Hiroshi Iwata, MD; Yuji Nishizaki, MD; Teruo Inoue, MD; Atsushi Hirayama, MD; Kazuo Kimura, MD; Yukio Ozaki, MD; Toyoaki Murohara, MD; Kenji Ueshima, MD; Yoshihiro Kuwabara, MD; Sachiko Tanaka-Mizuno, PhD; Naotake Yanagisawa, PhD; Tosiya Sato, PhD; Hiroyuki Daida, MD; and RESPECT-EPA Investigators









Meta-analysis of Omega 3 trials show distinct differences by type of Omega 3

EClinicalMedicine 38 (2021) 100997

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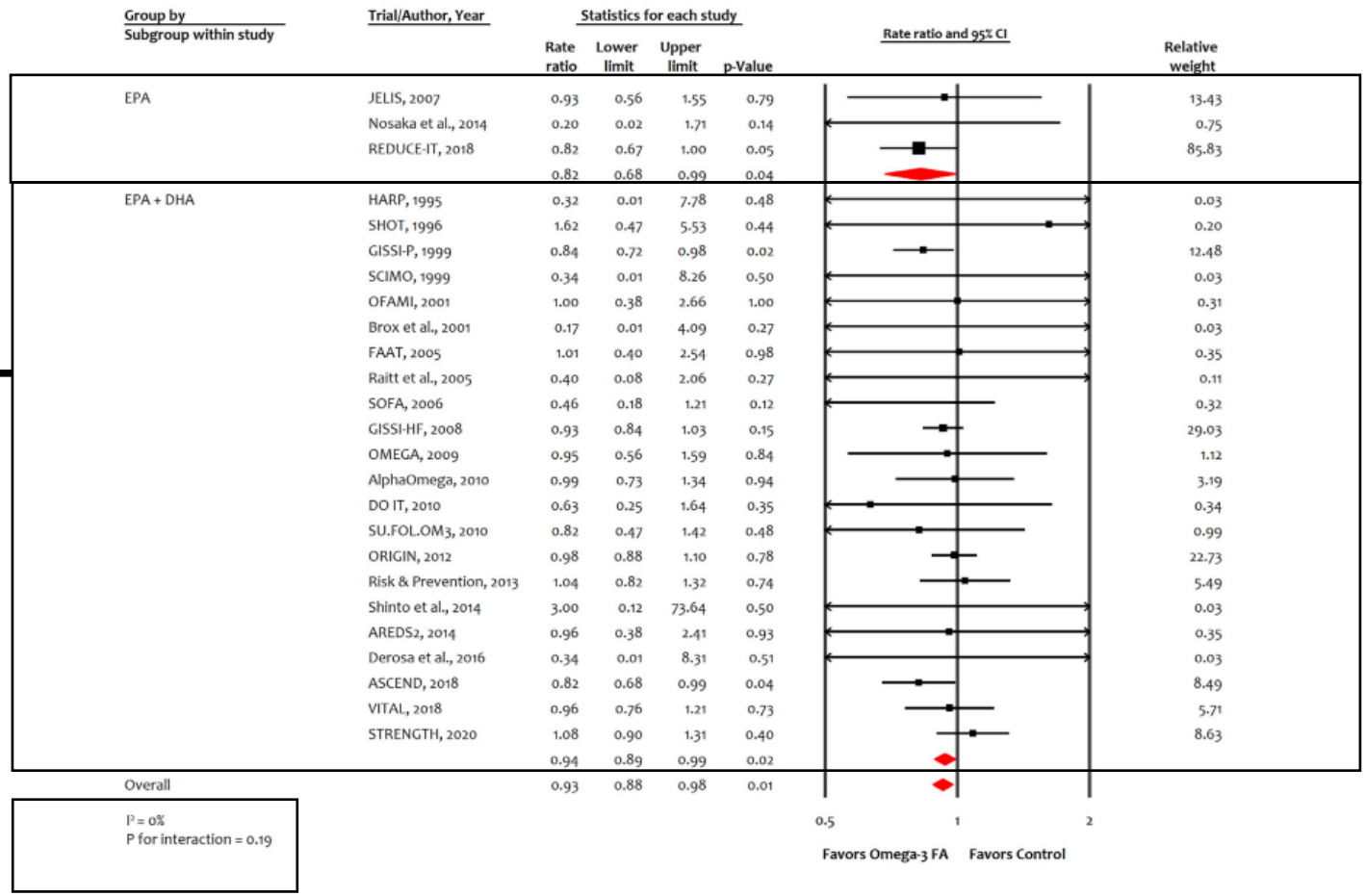
Research paper

Effect of omega-3 fatty acids on cardiovascular outcomes: A systematic review and meta-analysis

Safi U. Khan[a], Ahmad N. Lone[a], Muhammad Shahzeb Khan[b], Salim S. Virani[c], Roger S. Blumenthal[d,e], Khurram Nasir[f,g], Michael Miller[h], Erin D. Michos[d,e], Christie M. Ballantyne[c], William E. Boden[i], Deepak L. Bhatt[j,*]



Conclusion

- Use high TG despite statins and controlled risk factors to identify higher risk patients
- IPE and especially 4g daily reduces CV events, total events with greater absolute benefits in higher risk groups like prior MI and those with DM
- Excess risk of AF but not strokes

- Totality of data suggests there are differences between Omega 3 preparations with CV benefits with IPE especially at 4g