2020 Update on Lipid Management: Beyond Statins

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2016 CCS Lipid Guideline Recommendations: Targeting Lower LDL-C to Lower the Risk for CV Events

STATIN INDICATED CONDITIONS

(those who will benefit the most):

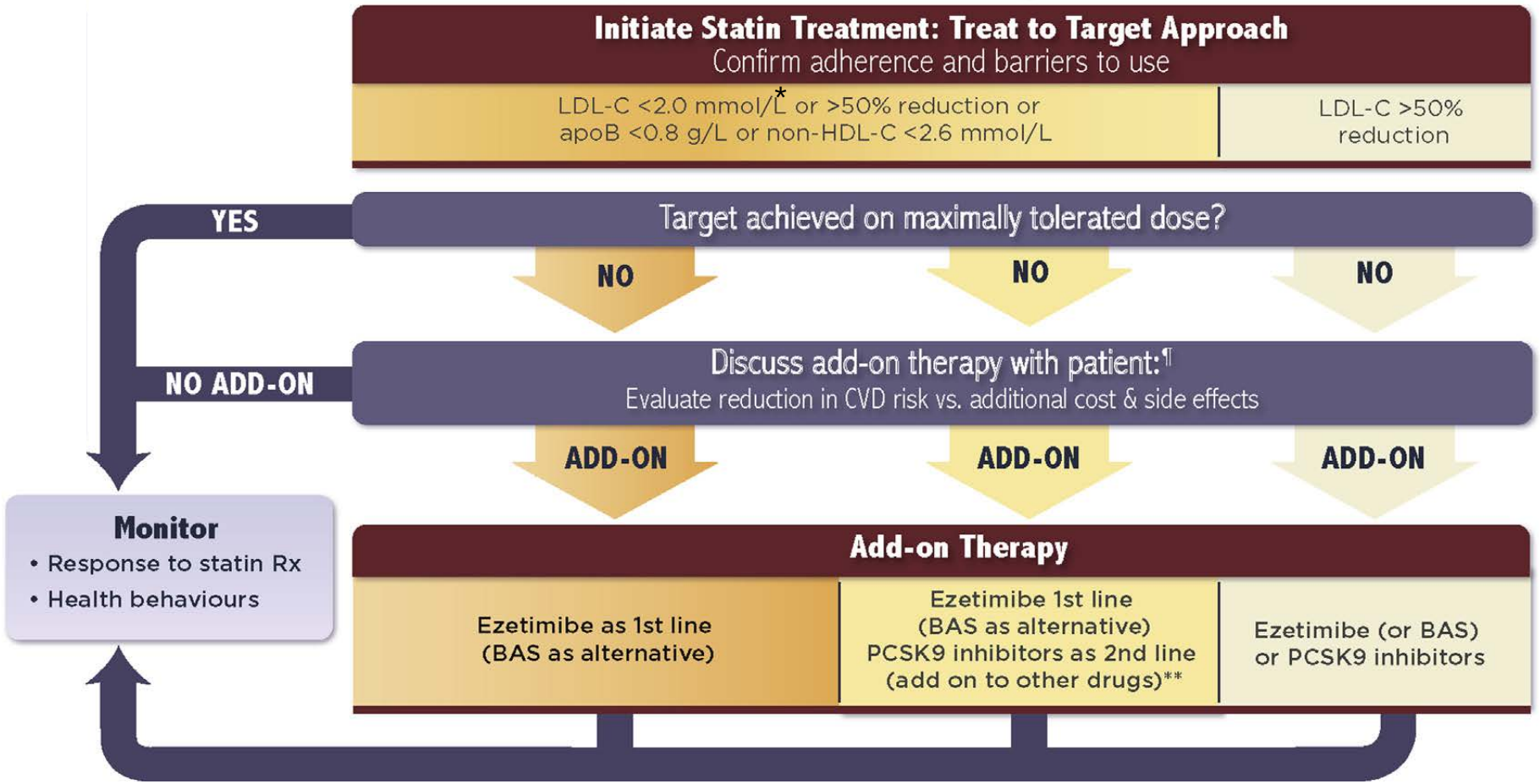
- Clinical atherosclerosis*
- Abdominal aortic aneurysm
- Most diabetes mellitus
- CKD (age >50 years)
- LDL-C ≥5.0 mmol/L

TREATMENT TARGETS:

- LDL-C consistently <2.0 mmol/L or >50% reduction
- Consider <1.8 mmol/L in patients with clinical atherosclerosis
- Apo B ≤0.80 g/L or non-HDL-C ≤2.6 mmol/L can be considered as alternative treatment targets

Anderson TJ et al. 2016;32:1263-1282

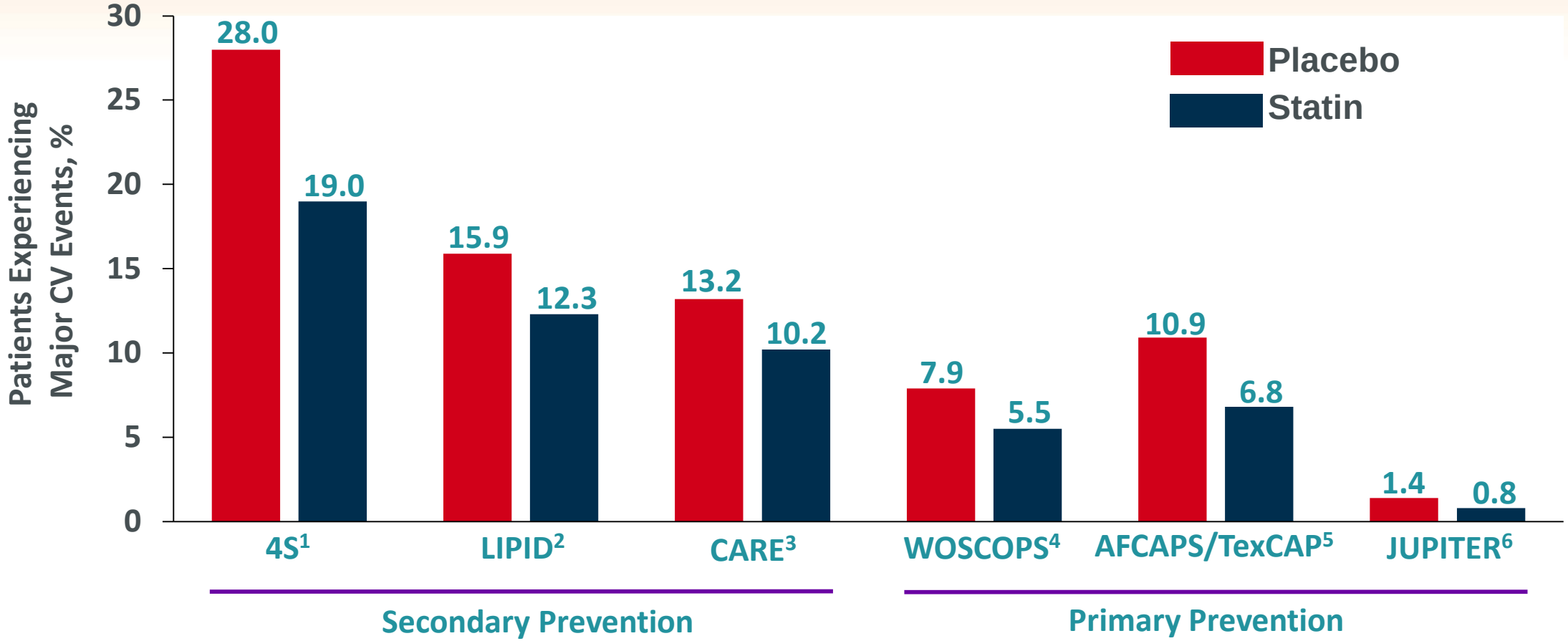
2016 CCS Dyslipidemia Guidelines



* LDL<1.8 mmol/L after ACS

Anderson TJ et al. 2016;32:1263-1282

Cardiovascular Risk Persists Despite the Benefit of LDL-C Lowering With Current Standards of Care

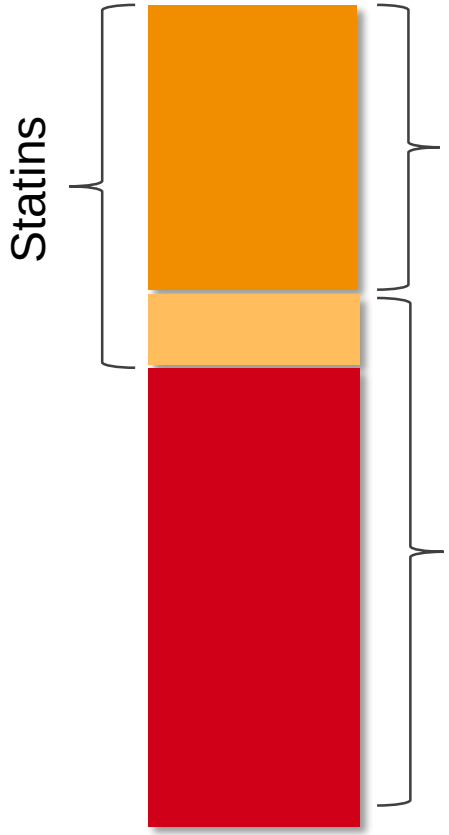


On-Treatment LDL-C (mmol/L)	4S[1]	LIPID[2]	CARE[3]	WOSCOPS[4]	AFCAPS/TexCAP[5]	JUPITER[6]
	3.02	2.93	2.50	3.67	2.96	1.40

CV: cardiovascular; RRR: relative risk reduction.

1. Scandinavian Simvastatin Survival Study Group. Lancet. 1994; 344:1383-89. 2. LIPID Study Group. N Engl J Med. 1998;339(19):1349-1357. 3. Sacks FM et al. N Engl J Med. 1996;335(14):1001-1009. 4. Shepherd J et al. N Engl J Med. 1995;333(20):1301-7. 5. Downs JR et al. JAMA. 1998;279(20):1615-1622. 6. Ridker PM et al. N Engl J Med. 2008;359:2195-207.

Cardiovascular Risk Goes Beyond LDL-C



CV risk persists in patients on stable statin therapy

Many factors beyond LDL-C play a role in the pathogenesis of CV disease, thus contributing to CV risk

- **Triglycerides**
- Oxidation
- Diabetes mellitus
- Hypertension
- Lp(a)
- Thrombosis
- Endothelial dysfunction
- Inflammation
- Membrane instability/cholesterol crystals
- Plaque instability

Lp(a)=lipoprotein(a).

Ference BA et al. *JAMA*. 2019;321(4):364-373; Ganda OP et al. *J Am Coll Cardiol*. 2018;72:330-343; Libby P. *Eur Heart J*. 2015;36:774-776.

Evidence Associating TG Levels with Increased Risk of CV Disease

TG

Higher levels of TGs identify patients at increased CV risk

Biology

- Elevated TGs associated with higher concentrations of sdLDL particles

LDL **Oxidation**

Atherogenicity

LDL **Clearance**

Meta-analyses/ clinical trials

- Large, randomized control trial with fibrates
- Copenhagen City Heart Study and Copenhagen General Population Study
- PROVE IT-TIMI
- Framingham Offspring Study

Genetic studies

- Mutational analyses, genome-wide association studies, Mendelian randomization studies

Associations between

Elevated TG **+** **CV disease/ all-cause mortality**

Ference BA et al. *JAMA*. 2019;321(4):364-373; Ganda OP et al. *J Am Coll Cardiol.* 2018;72:330-343; Miller M et al. *Circulation*. 2011;123:2292-333. Nordestgaard BG, Varbo A. *Lancet*. 2014;384:626-635.

Prior TG Lowering Therapies: Failure of CV Benefit in Cardiovascular Outcome Trials

	Key trials	Achieved primary MACE endpoint?	Possible reasons for lack of benefit
Fibrates	• ACCORD • FIELD	✘	Trials did not prospectively enroll patients with elevated TG levels despite statin therapy (although subgroup analyses suggested possible CV benefits to TG lowering in patients with dyslipidemia)
Niacin	• AIM-HIGH • HPS2-THRIVE	✘	
Rx & supplement, mixtures of omega-3 fatty acids (EPA + DHA)[a] as common fish oil (including carboxylic acids) and krill oil	• ASCEND • OMEGA • ORIGIN • RISK & PREVENTION • VITAL	✘	Trials evaluated people with TG <2.26 mmol/L (non-hypertriglyceridemic) treated with low omega-3 fatty acid doses
	• STRENGTH	✘	Unknown
	• TRILOGY1	✘	Large placebo effect

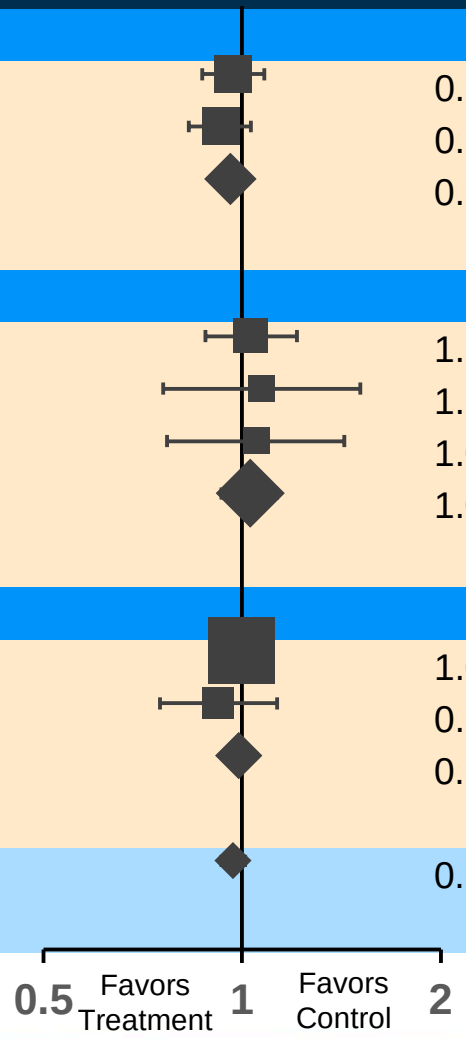
[a] Acasti Pharma Inc Press Release January 13, 2020: https://ca.proactiveinvestors.com/companies/news/910460/acasti-pharma-says-further-analysis-underway-after-trilogy-1-topline-results-show-unexpected-placebo-effect-910460.html. AstraZeneca Press release January 13, 2020: https://www.astrazeneca.com/media-centre/press-releases/2020/update-on-phase-iii-strength-trial-for-epanova-in-mixed-dyslipidaemia-13012020.html. Anderson TJ et al. *Can J Cardiol*. 2016; 32:1263-1282. ASCEND Study Collaborative Group. *N Engl J Med*. 2018;379:1540-1550. Bhatt DL et al. *Clin Cardiol*. 2017;40:138-148. Ganda Om Pet al. *J Am Coll Cardiol*. 2018;72:330-343. Manson JE et al. *N Engl J Med*. 2019;380:23-32.

The CCS in 2016 Recommended the Use of Omega-3 Supplements in Which Population?

1. Primary prevention
2. Secondary prevention
3. Primary and secondary prevention
4. The CCS did not recommend the use of Omega-3 supplements.

Mixtures of Omega-3 Fatty Acids (EPA Plus DHA): No Significant Cardiovascular Benefit

	Number of events (%)		Rate ratio (CI)
	Treatment	Control	
Coronary heart disease			
Nonfatal myocardial infarction	1121 (2.9)	1155 (3.0)	0.97 (0.87–1.08)
Coronary heart disease	1301 (3.3)	1394 (3.6)	0.93 (0.83–1.03)
Any	3085 (7.9)	3188 (8.2)	0.96 (0.90–1.01)
			P = .12
Stroke			
Ischemic	574 (1.9)	554 (1.8)	1.03 (0.88–1.21)
Hemorrhagic	117 (0.4)	109 (0.4)	1.07 (0.76–1.51)
Unclassified/other	142 (0.4)	135 (0.3)	1.05 (0.77–1.43)
Any	870 (2.2)	843 (2.2)	1.03 (0.93–1.13)
			P = .60
Revascularization			
Coronary	3040 (9.3)	3044 (9.3)	1.00 (0.93–1.07)
Non-coronary	305 (2.7)	330 (2.9)	0.92 (0.75–1.13)
Any	3290 (10.0)	3313 (10.2)	0.99 (0.94–1.04)
			P = 0.60
Any major vascular event	5930 (15.2)	6071 (15.6)	0.97 (0.93–1.01)
			P = .60



Aung T et al. *JAMA Cardiol.* 2018;3:225-234.

Icosapent Ethyl (IPE) Represents a New Class of Therapy Distinct From Fish Oil

IPE[1,4,67]

- Highly purified and stable form of EPA
- Distinct in structure and composition from EPA and omega-3 fatty acid
- Not a fish oil

Commercial fish oil[1-4]

Mixtures of omega-3 fatty acids in variable concentrations and containing:

- Saturated fats
- Other fatty acids
- Oxidation products
- Cholesterol
- Contaminants

EPA[5]

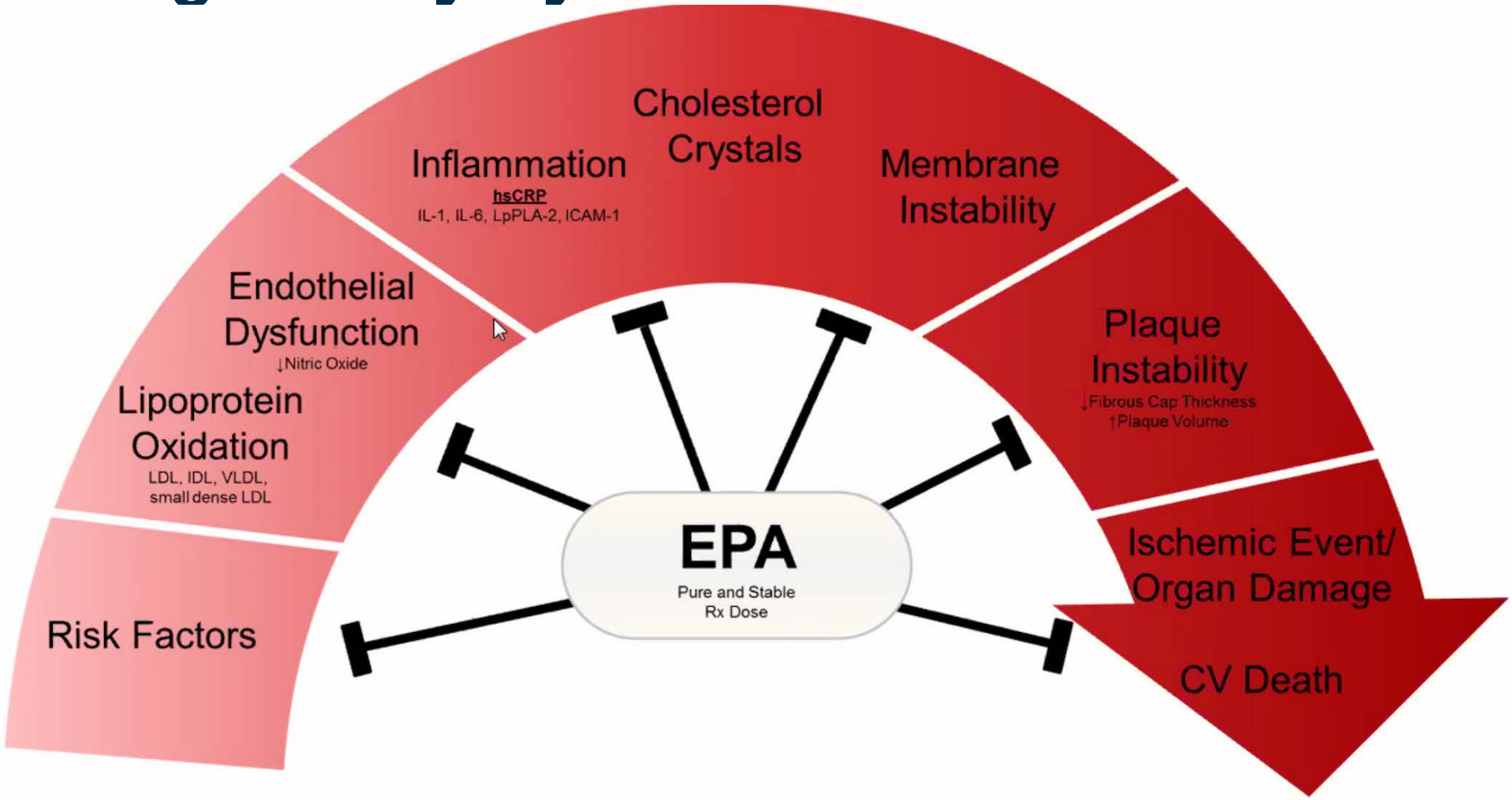
- Constituent of omega-3 fatty acid
- Anti-inflammatory and endothelial benefits

Omega-3 fatty acid[1-4]

- DHA and EPA as active ingredients

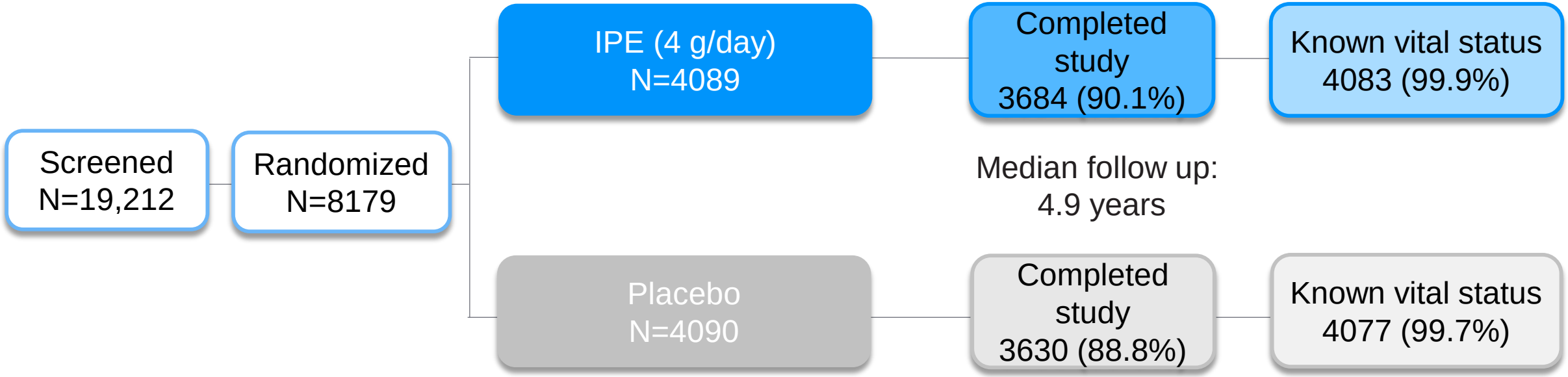
[1] Hilleman DE et al. *Adv Ther*. 2020;37:656-670. [2] Mason RP, Sherratt SCR. *Biochem Biophys Res Commun*. 2017;483:425-429. [3] Anderson TJ et al. Can J Cardiol. 2016; 32:1263-1282. [4] Bhatt DL et al. *Clin Cardiol*. 2017;40:138-148. [5] Mason RP. *Curr Atheroscler Rep*. 2019;21:2. [6] Bhatt DL et al. *N Engl J Med*. 2019;380:11-22. [7] Bhatt DL et al. *J Am Coll Cardiol*. 2019;73:2791-2802.

IPE Potentially Reduces CV Events Beyond TG Lowering: Likely by a Multifactorial Effect



Nelson JR et al. *Vascul Pharmacol.* 2017;91:1-9.

REDUCE-IT: A Multicenter, Randomized, Double-Blinded, Event-Driven, Placebo-Controlled Trial



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

REDUCE-IT Key Inclusion Criteria

Prevention cohorts		
Secondary	≥45 years with: • Established CVD (documented CAD, CVD, or PAD)	• **Fasting TG level** ≥1.52 mmol/L and <5.63 mmol/L[a] • **LDL-C** >1.06 mmol/L and ≤2.59 mmol/L and on stable statin therapy (± ezetimibe) for ≥4 weeks prior to qualifying measurements for randomization
Primary	≥50 years with: • Diabetes • ≥1 additional risk factor for CVD	

[a] Due to the variability of TGs, a 10% allowance existed in the initial protocol, which permitted patients to be enrolled with qualifying TGs ≥1.52 mmol/L. In May 2013, the protocol was amended whereby the acceptable TG range was 1.69 mmol/L to 2.25 mmol/L, with no variability allowance.
PAD=peripheral artery disease.
Bhatt DL et al. *N Engl J Med*. 2019;380:11-22.

REDUCE-IT: Study Endpoints

Primary Endpoint (5-point MACE)

Composite of
- CV death
- Nonfatal MI
- Nonfatal stroke
- Coronary revascularization
- Unstable angina

Key Secondary Endpoint (3-point MACE)

Composite of
- CV death
- Nonfatal MI
- Nonfatal stroke

Additional individual or composite secondary endpoints, tested in the following order:

1. Primary composite
2. Key secondary composite
3. CV death or nonfatal MI
4. Fatal or nonfatal MI
5. Urgent or emergency revascularization
6. CV death
7. Hospitalization for unstable angina
8. Fatal or nonfatal stroke
9. Death from any cause, nonfatal MI, or nonfatal stroke
10. Death from any cause

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

REDUCE-IT: Key Baseline Characteristics

	IPE (n=4089)	Placebo (n=4090)
Age (years), median (Q1-Q3)	64.0 (57.0-69.0)	64.0 (57.0-69.0)
Female, %	28.4	29.2
Non-white, %	9.7	9.8
Westernized region, %	71.1	71.0
CV risk category, %		
Secondary prevention cohort	70.7	70.7
Primary prevention cohort	29.3	29.3
Ezetimibe use, %	6.4	6.4
Statin intensity, %		
Low	6.2	6.5
Moderate	61.9	63.0
High	31.5	30.0
Type 2 diabetes, %	57.9	57.8

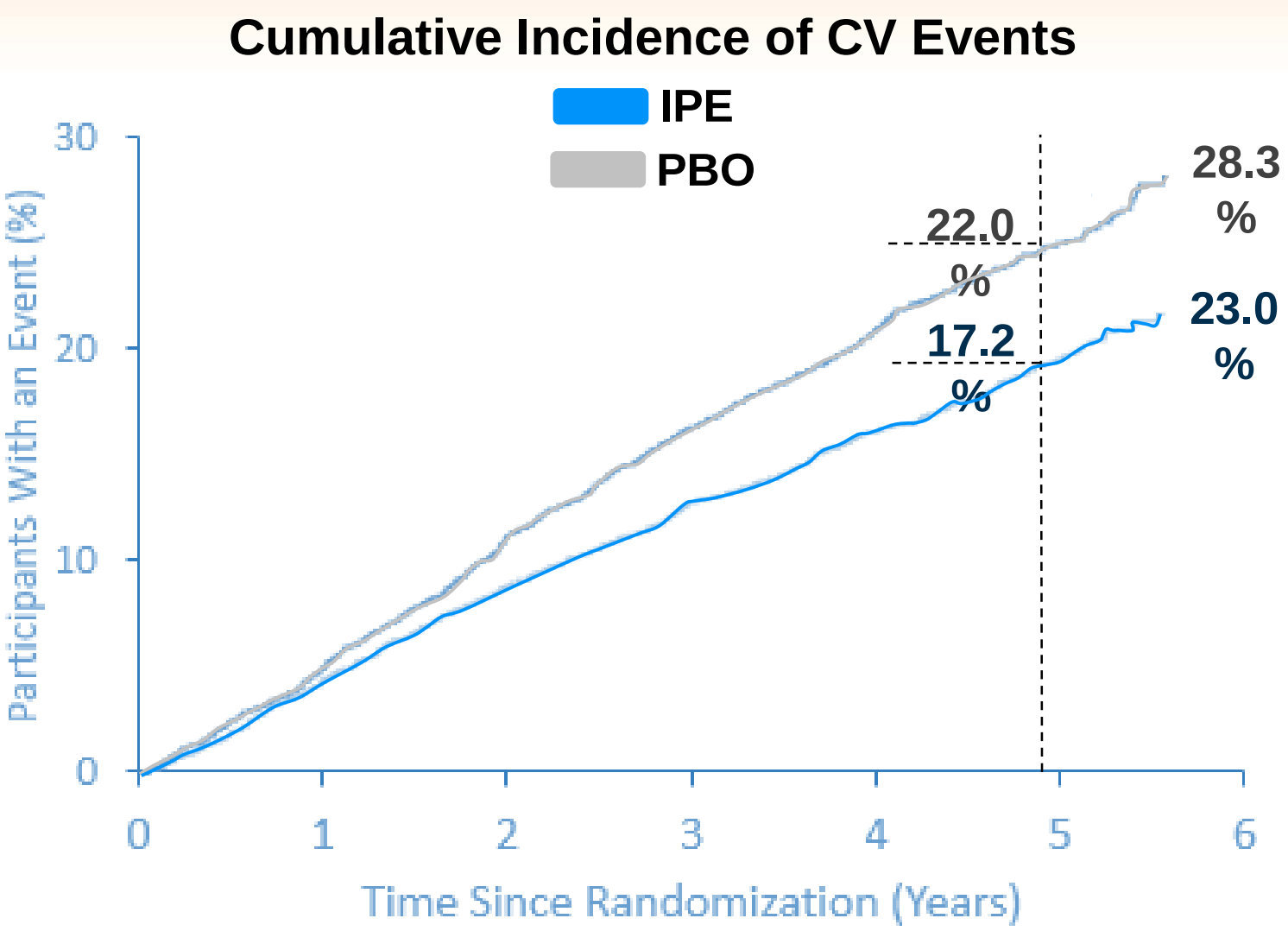
Bhatt DL et al. *N Engl J Med*. 2019;380:11-22.

REDUCE-IT: Key Baseline Characteristics (continued)

	IPE (n=4089)	Placebo (n=4090)
TGs (mmol/L), median (Q1-Q3)	2.44 (1.99-3.07)	2.44 (1.98-3.09)
HDL-C (mmol/L), median (Q1-Q3)	1.03 (0.89-1.19)	1.03 (0.91-1.19)
LDL-C (mmol/L), median (Q1-Q3)	1.91 (1.59-2.28)	1.97 (1.63-2.30)
TG category, %		
<1.69 mmol/L	10.1	10.5
1.69 to <2.26 mmol/L	29.2	29.1
>2.26 mmol/L	60.7	60.4

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

REDUCE-IT: Primary Endpoint



Primary Endpoint
5-Point MACE[a]
(median follow-up: 4.9

25%
RRR

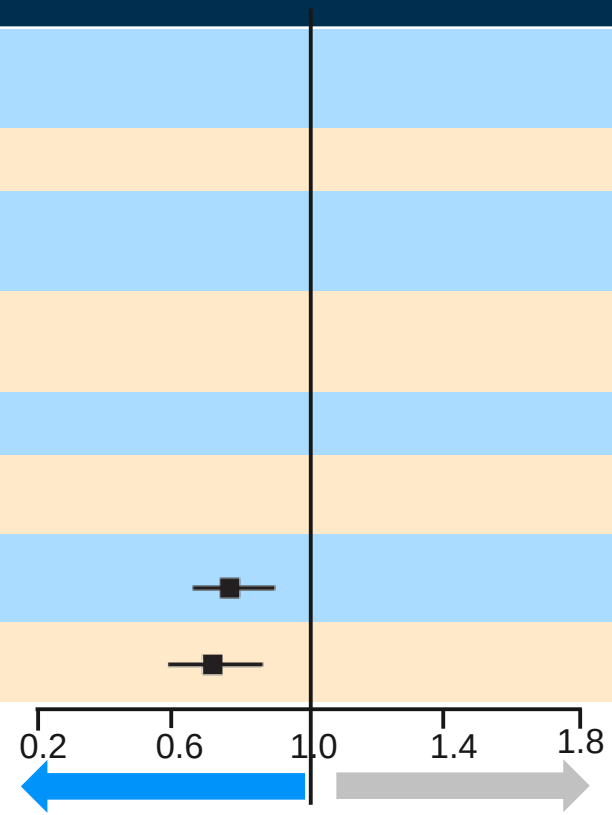
NNT = 21

HR (95% CI): 0.75 (0.68-0.83)
ARR: 4.8%
***P* = .00000001**

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

REDUCE-IT Subgroup Analysis of Primary Endpoint: Outcomes Consistent With Main Result

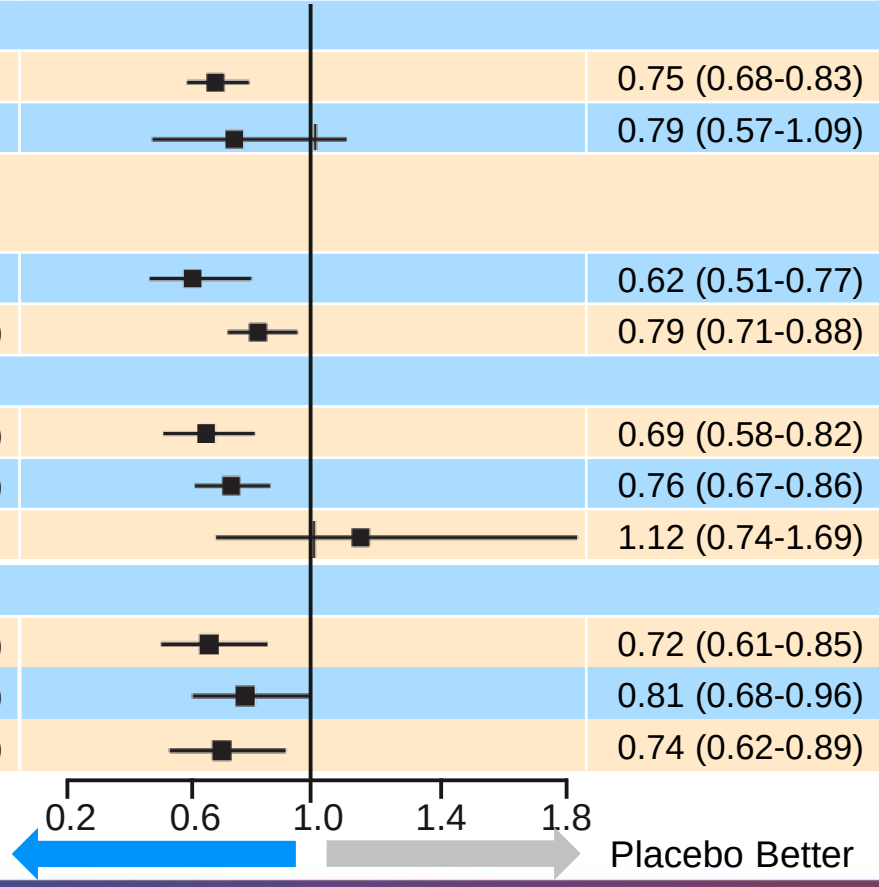
Subgroup	No. of patients with event/ total no. of patients (%)		Hazard ratio (95% CI)	*P* value for interaction
	IPE	Placebo		
All patients	705/4089 (17.2)	901/4090 (22.0)	0.75 (0.68-0.83)	
Risk stratum				.14
Secondary prevention cohort	559/2892 (19.3)	738/2893 (25.5)	0.73 (0.65-0.81)	
Primary prevention cohort	146/1197 (12.2)	163/1197 (13.6)	0.88 (0.70-1.10)	
Region				.30
Diabetes at baseline				.56
Yes	433/2394 (18.1))	536/2393 (22.4)	0.77 (0.68-0.87)	
No	272/1695 (16.0)	365/1694 (21.5)	0.73 (0.62-0.85)	



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

REDUCE-IT Subgroup Analysis of Primary Endpoint: Outcomes Consistent With Main Result

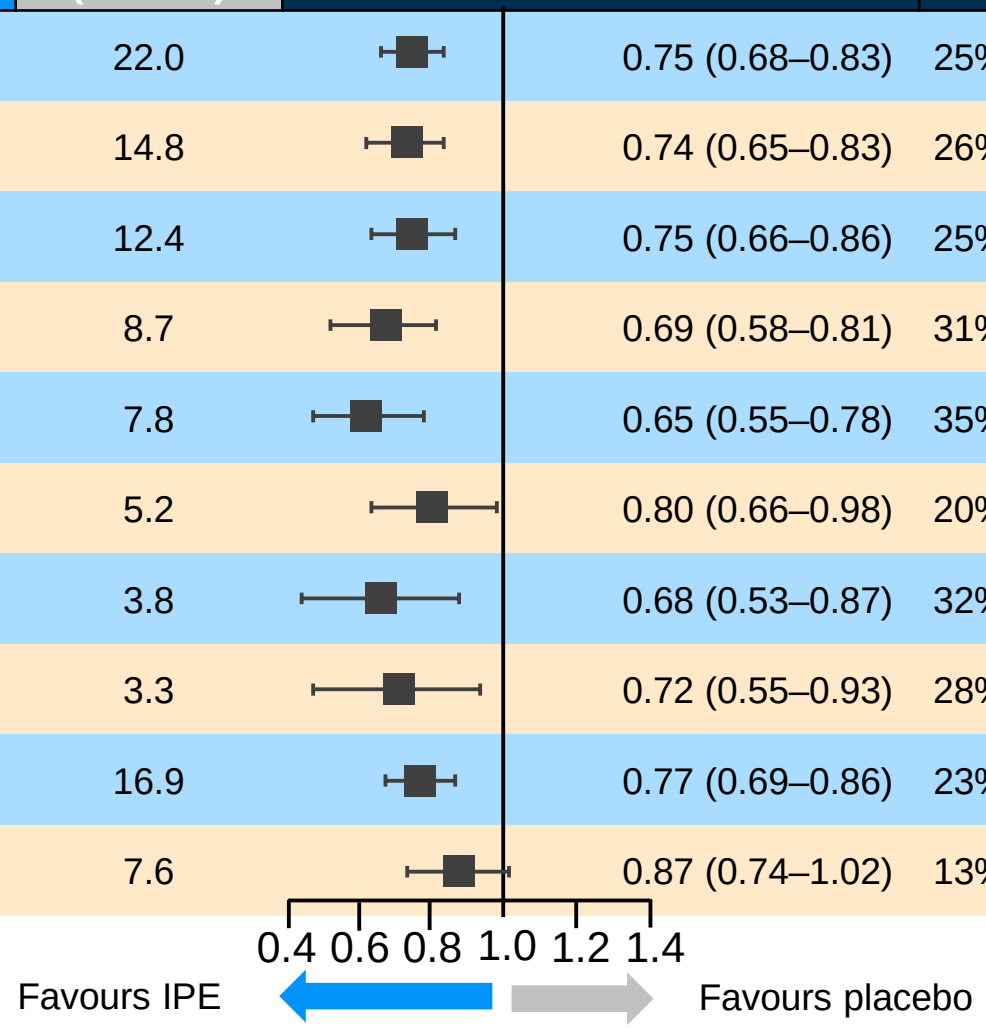
Subgroup	No. of patients with event/total no. of patients (%)		Hazard ratio (95% CI)	*P* value for interaction
	IPE	Placebo		
Baseline TGs				.83
≥1.70 mmol/L	640/3674 (17.4)	811/3660 (22.2)	0.75 (0.68-0.83)	
<1.70 mmol/L	65/412 (15.8)	90/429 (21.0)	0.79 (0.57-1.09)	
Baseline TGs ≥2.26 mmol/L and HDL-C ≤0.90 mmol/L				.04
Yes	149/823 (18.1)	214/794 (27.0)	0.62 (0.51-0.77)	
No	554/3258 (17.0)	687/3293 (20.9)	0.79 (0.71-0.88)	
Baseline statin intensity				.12
High	232/1290 (18.0)	310/1226 (25.3)	0.69 (0.58-0.82)	
Moderate	424/2533 (16.7)	543/2575 (21.1)	0.76 (0.67-0.86)	
Low	48/254 (18.9)	45/267 (16.9)	1.12 (0.74-1.69)	
Baseline LDL cholesterol (derived) in thirds				.62
≤1.73 mmol/L	244/1481 (16.5)	302/1386 (21.8)	0.72 (0.61-0.85)	
>1.73 to ≤2.17 mmol/L	248/1347 (18.4)	307/1364 (22.5)	0.81 (0.68-0.96)	
>2.17 mmol/L	213/1258 (16.9)	292/1339 (21.8)	0.74 (0.62-0.89)	



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

REDUCE-IT: Prespecified Hierarchical Testing

	IPE, % (N=4089)	Placebo, % (N=4090)	HR (95% CI)	RRR	*P*
Primary composite	17.2	22.0	0.75 (0.68–0.83)	25%	< .001
Key secondary composite	11.2	14.8	0.74 (0.65–0.83)	26%	< .001
CV death or nonfatal MI	9.6	12.4	0.75 (0.66–0.86)	25%	< .001
Fatal or nonfatal MI	6.1	8.7	0.69 (0.58–0.81)	31%	< .001
Urgent or emergency revascularization	5.3	7.8	0.65 (0.55–0.78)	35%	< .001
CV death	4.3	5.2	0.80 (0.66–0.98)	20%	.03
Hospitalization for unstable angina	2.6	3.8	0.68 (0.53–0.87)	32%	.002
Fatal or nonfatal stroke	2.4	3.3	0.72 (0.55–0.93)	28%	.01
Death from any cause, nonfatal MI or nonfatal stroke	13.4	16.9	0.77 (0.69–0.86)	23%	< .001
Death from any cause	6.7	7.6	0.87 (0.74–1.02)	13%	.09



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

REDUCE-IT: Adverse Events

TEAEs	IPE, % (N=4089)	Placebo, % (N=4090)	*P*
Subjects with at least one TEAE	81.8	81.3	.63
Serious TEAE	30.6	30.7	.98
TEAE leading to withdrawal of study drug	7.9	8.2	.60
Serious TEAE leading to withdrawal of study drug	2.2	2.2	1.00
Serious TEAE leading to death	2.3	2.5	.61

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

REDUCE-It Summary

Icosapent Ethyl met the 3-Point MACE Key Secondary Endpoint

Primary Endpoint
5-Point MACE[a]

25%
RRR
NNT = 21

HR = 0.75 (95% CI, 0.68-0.83)
***P* = .00000001**

Key Secondary Endpoint
3-Point MACE[b]

26%
RRR
NNT = 28

HR = 0.74 (95% CI, 0.65-0.83)
***P* = .0000006**

Other secondary endpoints

MI Fatal/Nonfatal

31%
RRR

HR = 0.69 (95% CI, 0.58-0.81)
***P* < .001**

Stroke Fatal/Nonfatal

28%
RRR

HR = 0.72 (95% CI, 0.55-0.93)
***P* = .01**

CV Death

20%
RRR

HR = 0.80 (95% CI, 0.66-0.98)
***P* = .03**

Conclusion:

- CV risk persists despite controlling LDL-C with statin alone with/without add-on non-statin therapy (ezetimibe, PCSK9i)
- Elevated TGs are associated with increased CV risk:
  - Can serve to identify persistent CV risk in statin-treated individuals
  - Fish oil (mixtures of omega-3 fatty acids) and Krill oil have not demonstrated CV benefit in clinical trials and are not indicated for management of CV risk
  - IPE, based on the trial REDUCE-IT, is the only pharmaceutical grade product that demonstrates consistent CV risk reduction in statin-treated patients with elevated TGs, who are at high risk of CV events due to:
    - Established CV disease, or
    - Diabetes, and at least one other CV risk factor

Questions