Clinical Benefit of Lowering Triglycerides and non-HDL-C

Brian A. Ference, M.D., M.Phil., M.Sc., F.A.C.C.

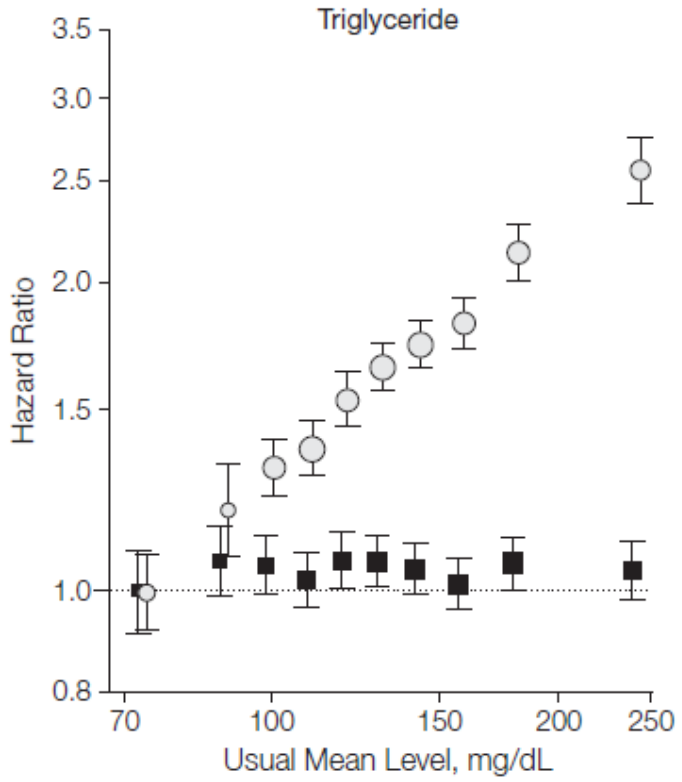
Director of Research / Professor in Translational Therapeutics
Executive Director, Centre for Naturally Randomized Trials
University of Cambridge

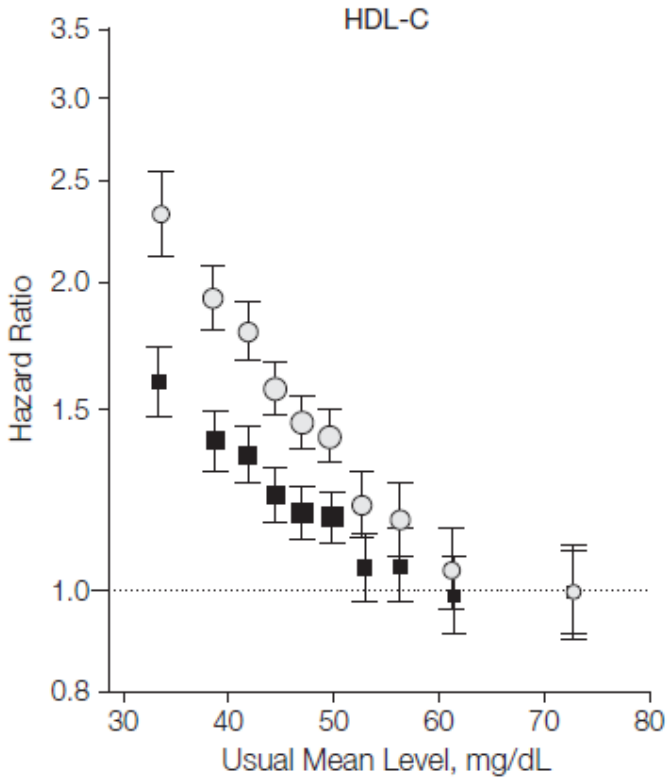
Financial Disclosures

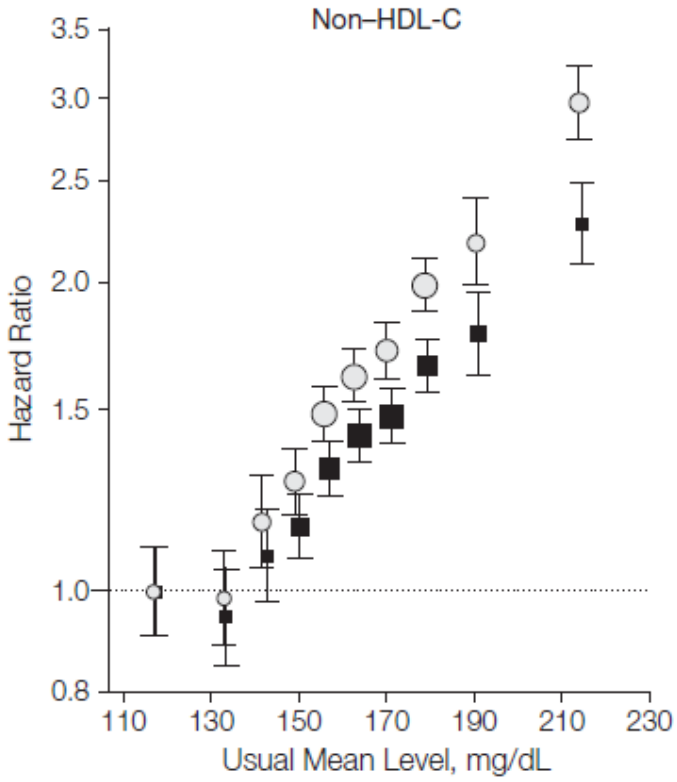
Research Grants: Merck, Novartis, Amgen, Esperion Therapeutics, Ionis Pharmaceuticals

Consulting Fees, Advisory Boards, Honoraria: Merck, Amgen, Pfizer, Regeneron, Sanofi, Ionis Pharmaceuticals, dalCOR, The Medicines Co; CiVi Pharma; KrKa Phamaceuticals, Medtronic, Celera, Quest Diagnostics, American College of Cardiology, European Atherosclerosis Society

Triglycerides, non-HDL and risk of CHD





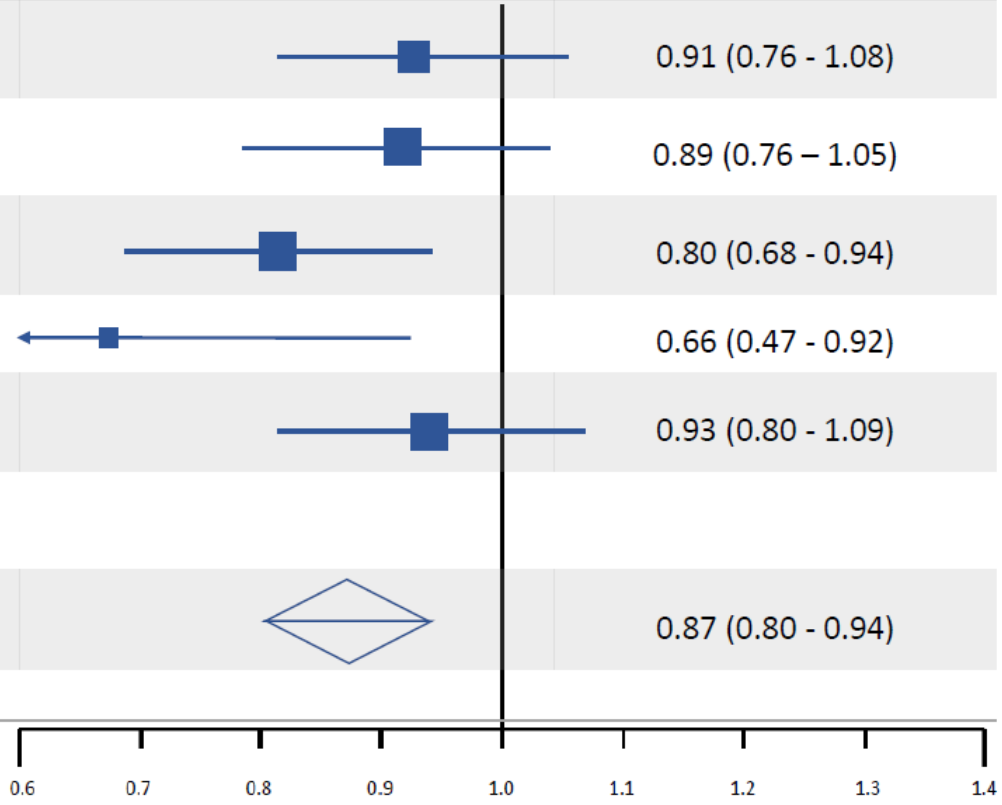


The Emerging Risk Factors Collaboration. JAMA. 2009;302:1993-2000.

Triglycerides and risk of CHD

Fibrate randomized trials

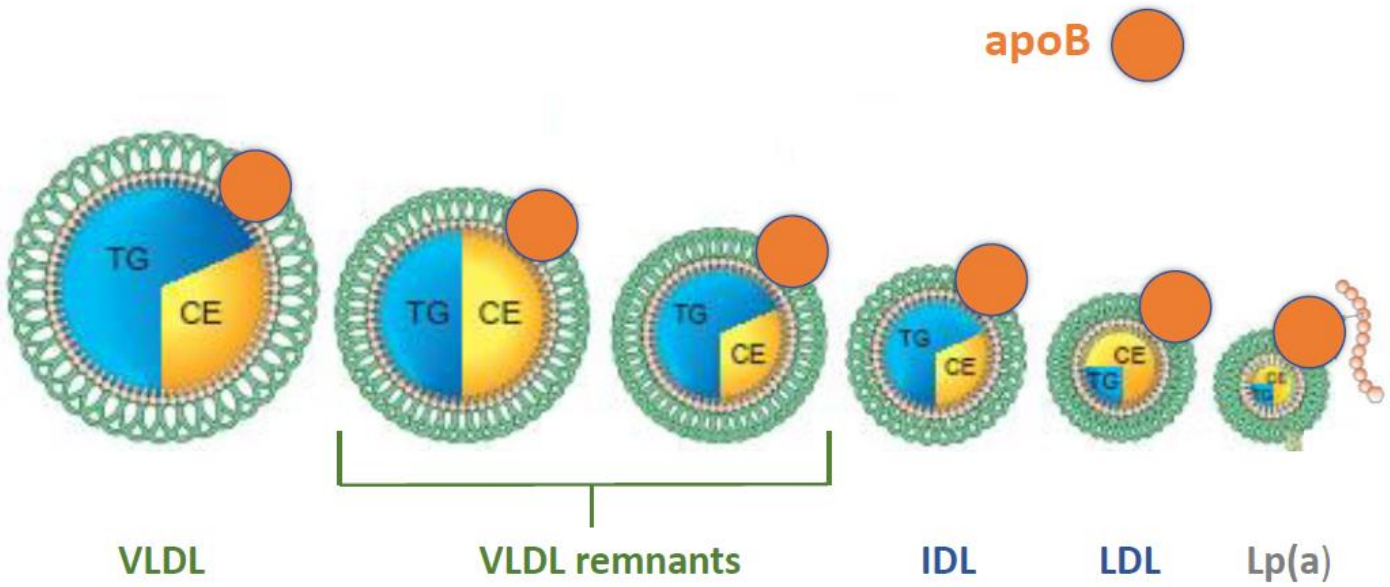
Trial	Δ TG (mmol/L)	Sample Size (No. Events)	HR (95% CI)
BIP	0.28	3090 (443)	0.91 (0.76 - 1.08)
FIELD	0.52	9795 (544)	0.89 (0.76 – 1.05)
VA-HIT	0.58	2531 (434)	0.80 (0.68 - 0.94)
HELSINKI	0.72	4081 (140)	0.66 (0.47 - 0.92)
ACCORD	0.34	5518 (501)	0.93 (0.80 - 1.09)
Overall		25,015 (2,062)	0.87 (0.80 - 0.94)



BIP: Circulation. 2000;102:21-27; Field: Lancet 2005; 366: 1849–61; VA-HIT: N Engl J Med 1999;341:410-8; Helsinki: N Engl J Med 1987;317:1237-45; ACCORD: N Engl J Med 2010;362:1563-74.

Triglyceride-rich lipoproteins and LDL particles

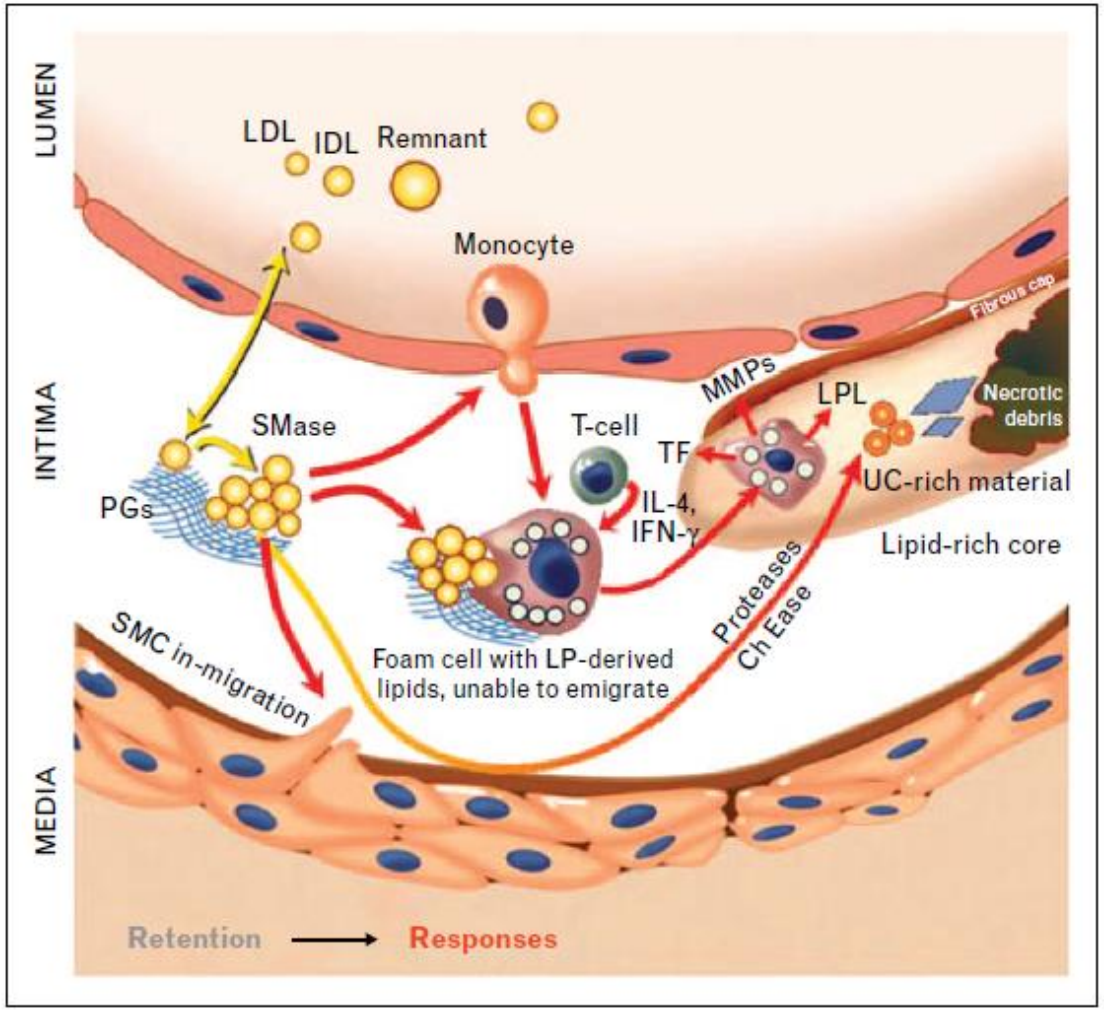
- Triglyceride-rich VLDL and their remnants particles, and LDL particles each have one apoB100



Ference BA, et al. Late Breaking Clinical Trial, ESC 2018. Munich

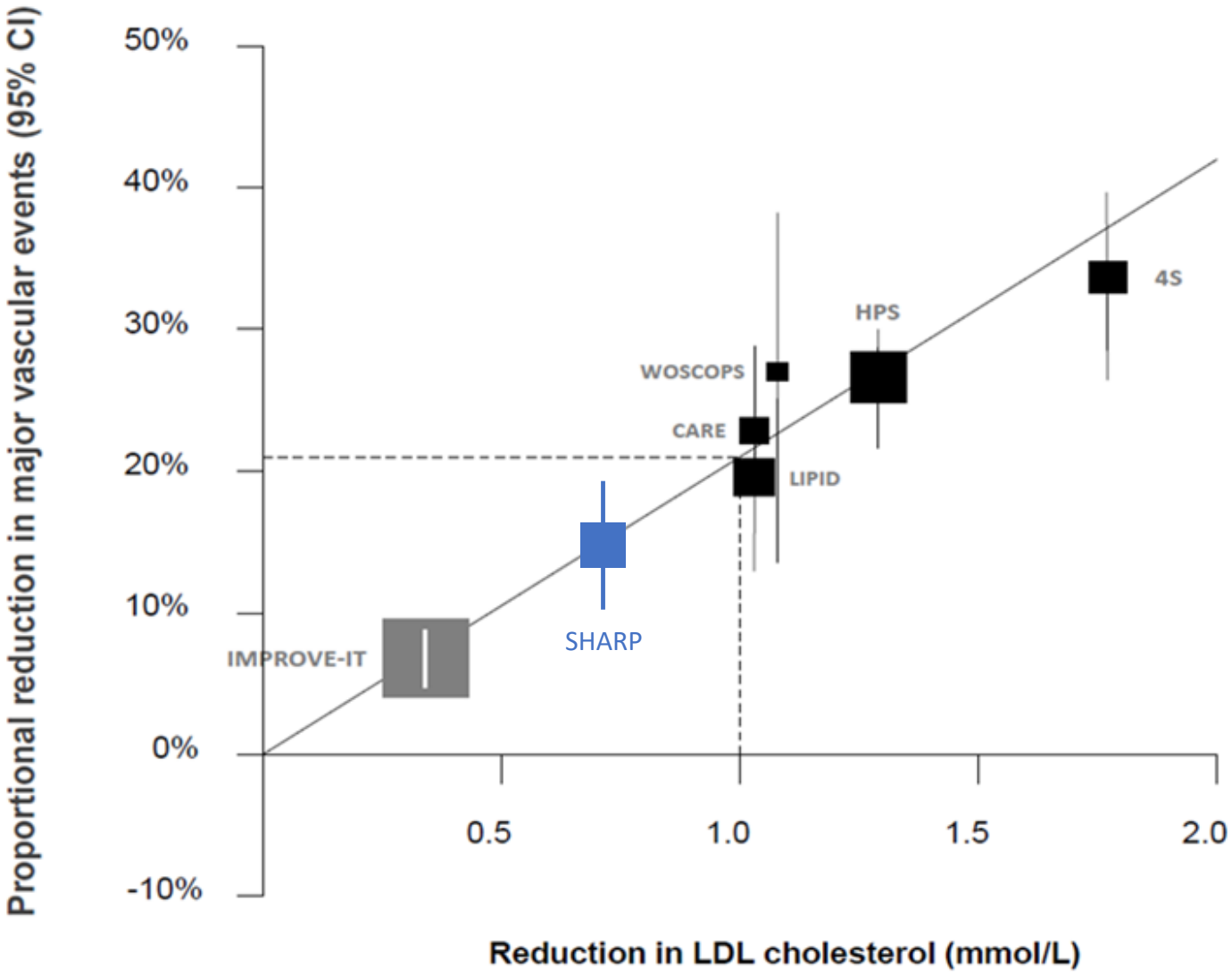
Retention of apoB-containing lipoproteins in atherosclerosis

ASCVD: Response-to-retention



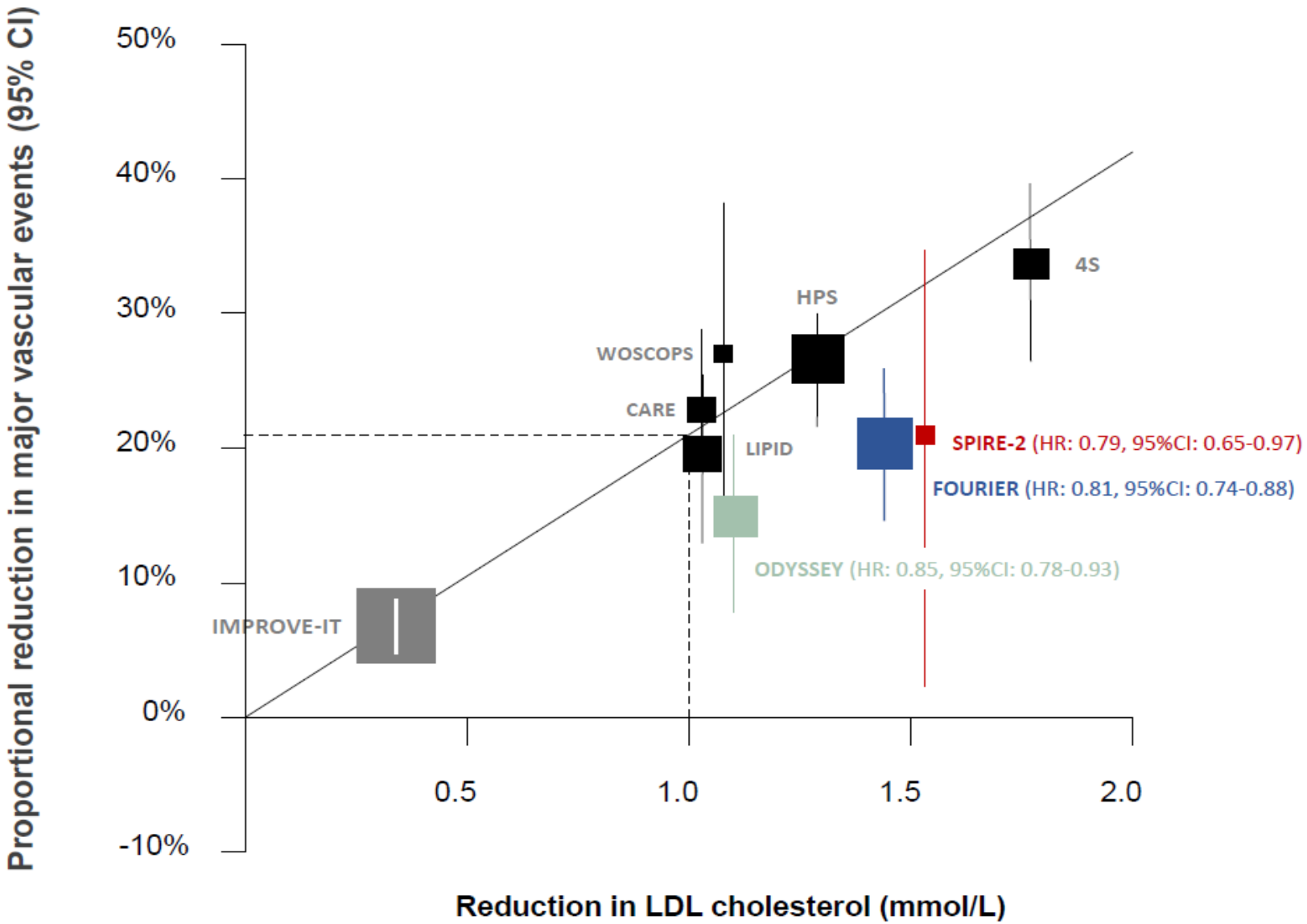
Boren J, Williams KJ. Curr Opin Lipidol 2016, 27:473–483.

Randomized trials of lowering LDL-C



Cholesterol Treatment Trialists Collaboration. Lancet. 2010 376:1670-81

Comparison of statin CTT and PCSK9 inhibitor trials

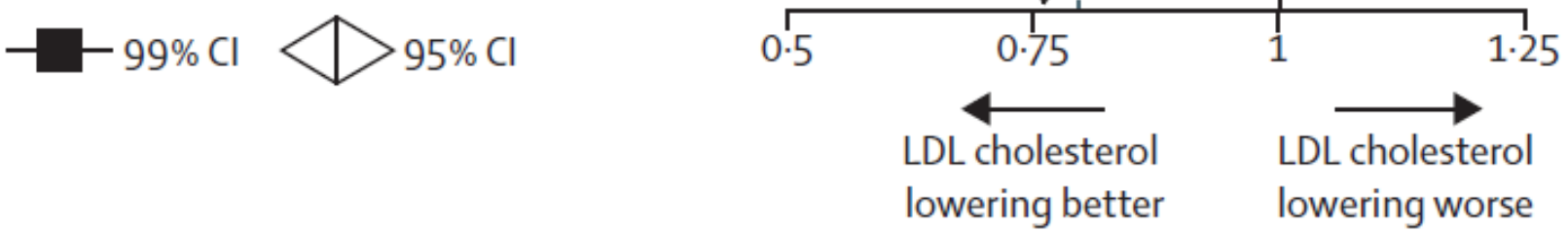


Cholesterol Treatment Trialists Collaboration. Lancet. 2010 376:1670-81

Sabatine MS, et al. N Engl J Med. 2017; 10.1056/NEJMoa1615664.

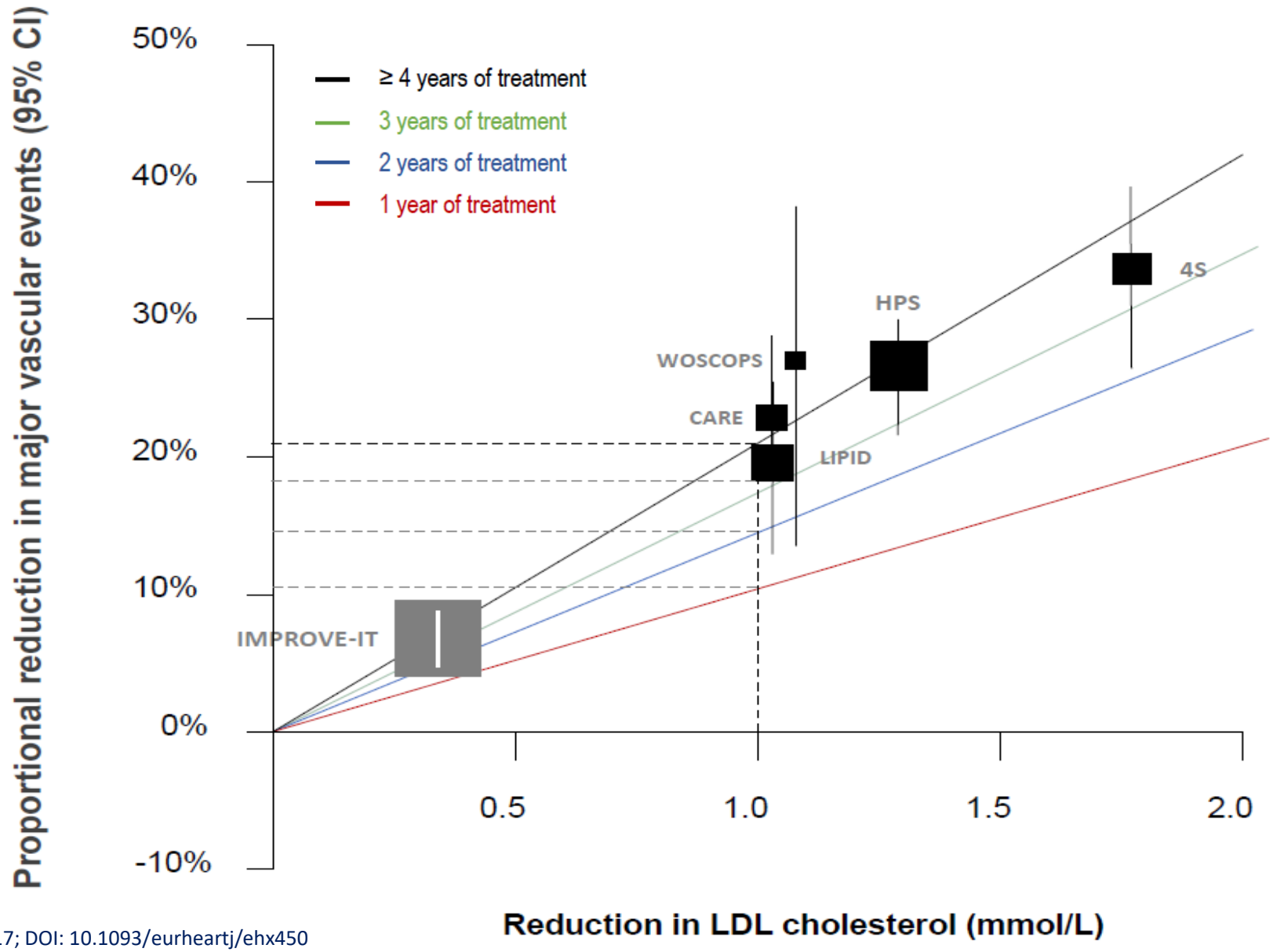
CTT: Effect size by year of treatment

	Total number of MVEs	Annual event rate in control arm (% per year)	RR (CI) per 1 mmol/L reduction in LDL cholesterol
0–1 year	4680	3·8	0·91 (0·85–0·97)
1–2 years	3580	3·4	0·78 (0·73–0·85)
2–3 years	3124	3·6	0·76 (0·70–0·82)
3–4 years	2483	3·6	0·72 (0·66–0·79)
4–5 years	1819	3·7	0·78 (0·71–0·87)
≥5 years	1018	3·9	0·76 (0·65–0·87)
All years	**16 704**	**3·6**	**0·80 (0·78–0·82)**
Years 1–≥5	12 024	3·6	0·76 (0·74–0·79)



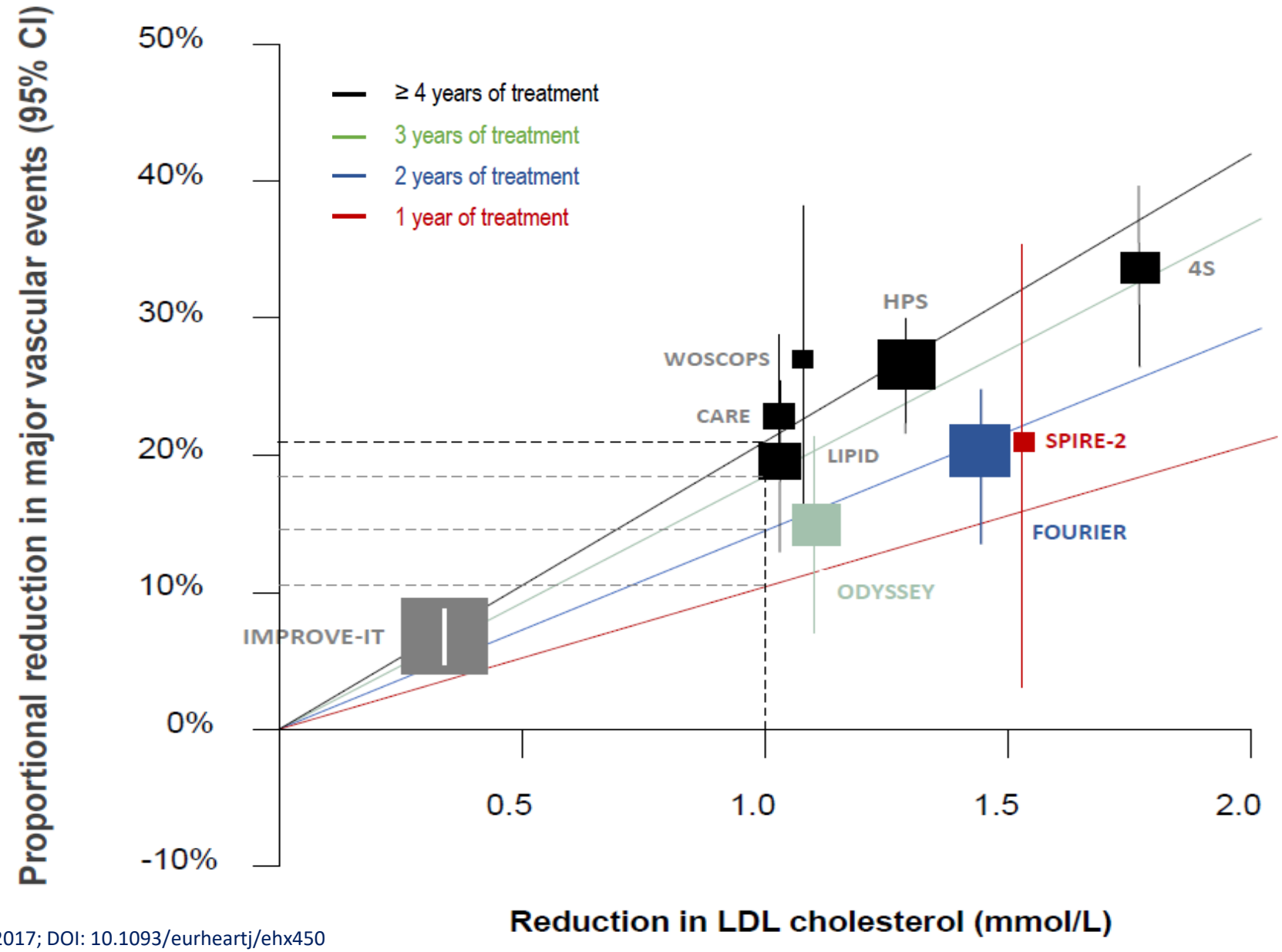
Cholesterol Treatment Trialists Collaboration. Lancet. 2010 376:1670-81

Effect of statins by total duration of treatment



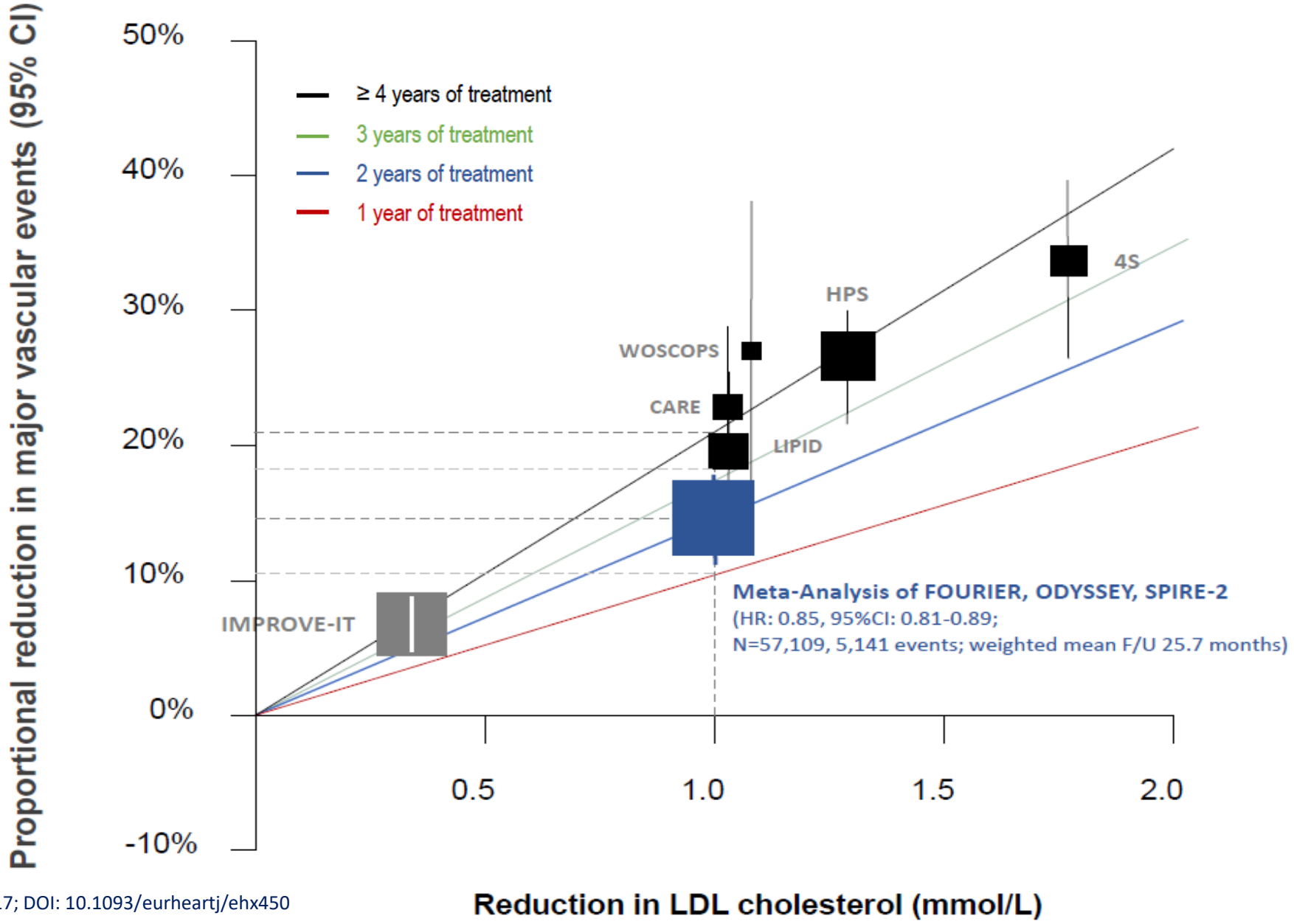
Ference BA, et al. Eur Heart J. 2017; DOI: 10.1093/eurheartj/ehx450

Comparison of PCSK9 inhibitors and statins by duration of treatment



Ference BA, et al. Eur Heart J. 2017; DOI: 10.1093/eurheartj/ehx450

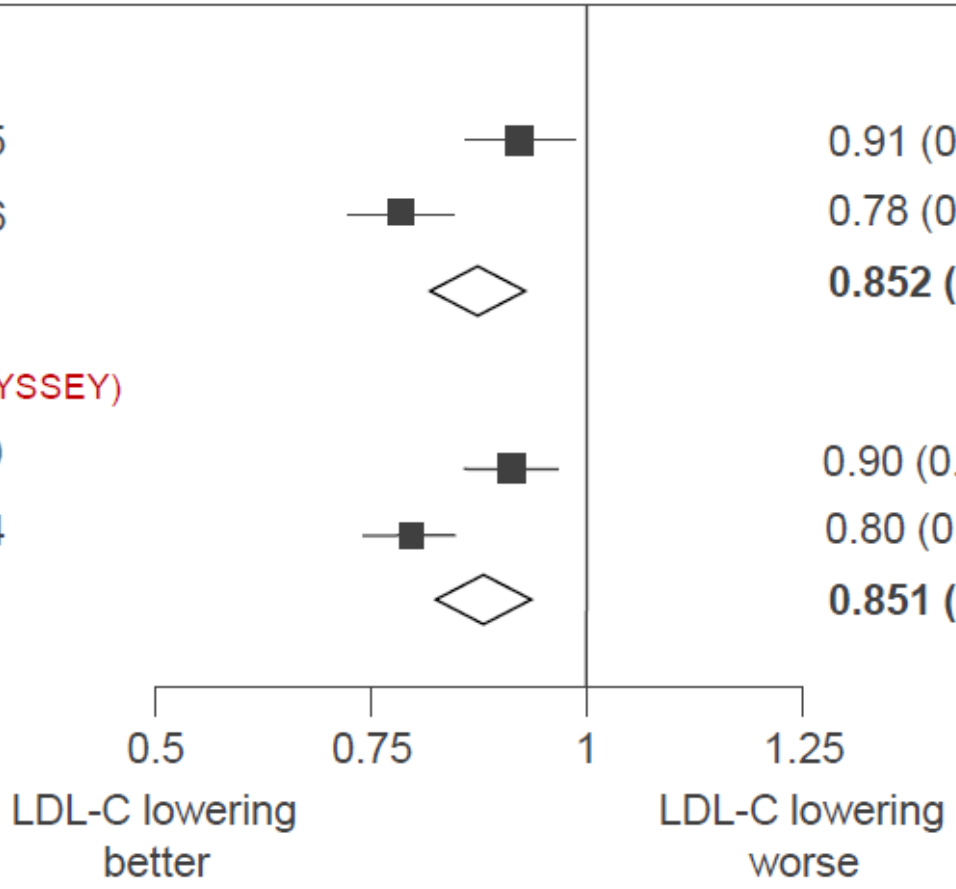
Comparison of PCSK9 inhibitors and statins by duration of treatment



Ference BA, et al. Eur Heart J. 2017; DOI: 10.1093/eurheartj/ehx450

CTT and PCSK9: Effect size by year of treatment

Year	Sample Size Treatment	Sample Size Control	RR (CI) per 1 mmol/L reduction in LDL-C
Statins			
0-1 year	84,573	84,565	0.91 (0.85 - 0.97)
1-2 years	82,352	82,106	0.78 (0.73 - 0.85)
			0.852 (0.81 - 0.90)
PCSK9 mAbs (SPIRE-2, FOURIER, ODYSSEY)			
0-1 year	28,550	28,559	0.90 (0.84 - 0.96)
1-2 years	23,234	23,254	0.80 (0.75 - 0.86)
			0.851 (0.81 - 0.89)



Test for heterogeneity between RR in first year and RR in years 1-2+: $p<0.001$

European Heart Journal (2017) **00**, 1–14
doi:10.1093/eurheartj/ehx144

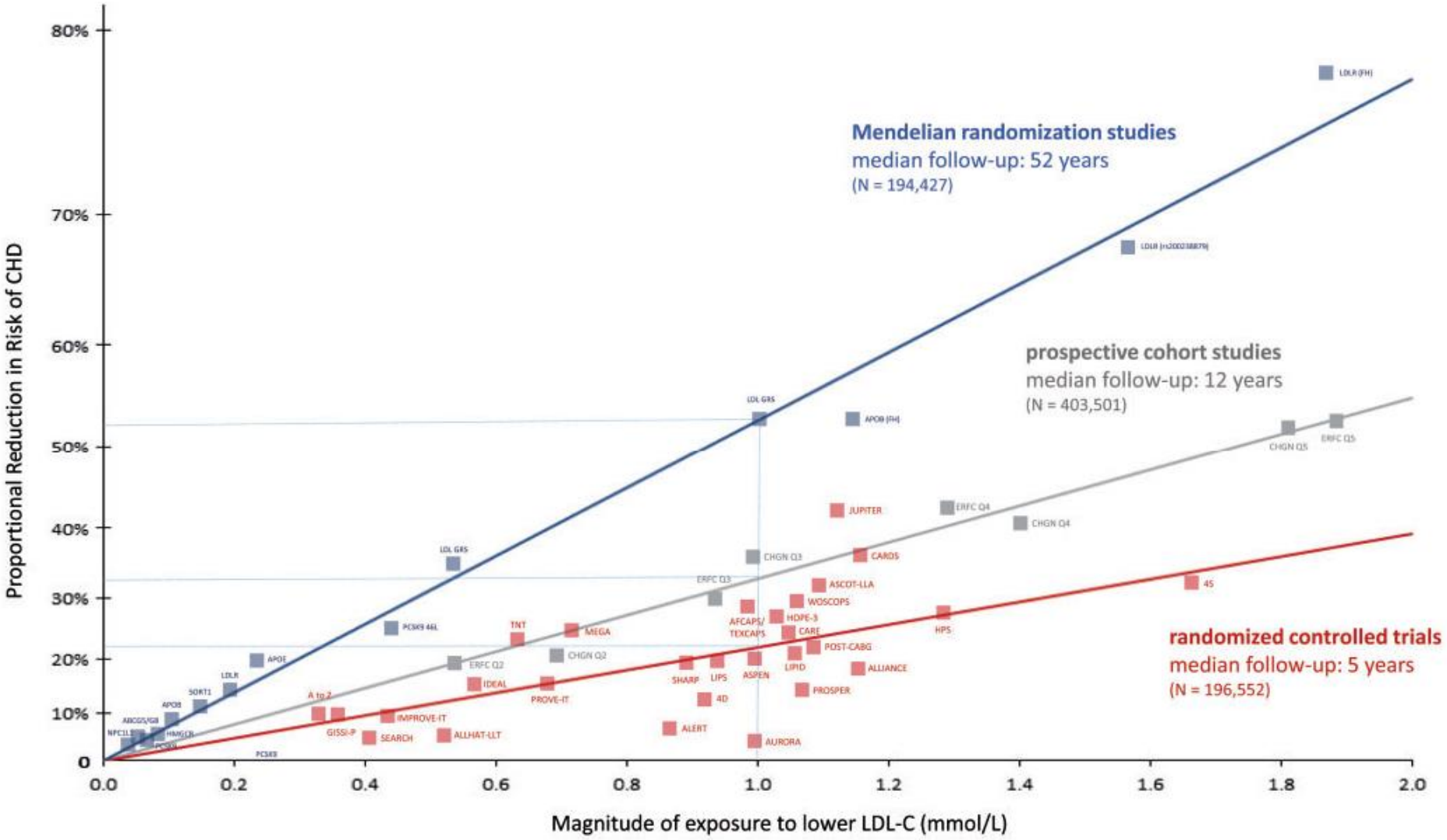
CURRENT OPINION

Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel

Brian A. Ference[1]*, Henry N. Ginsberg[2], Ian Graham[3], Kausik K. Ray[4], Chris J. Packard[5], Eric Bruckert[6], Robert A. Hegele[7], Ronald M. Krauss[8], Frederick J. Raal[9], Heribert Schunkert[10,11], Gerald F. Watts[12], Jan Borén[13], Sergio Fazio[14], Jay D. Horton[15,16], Luis Masana[17], Stephen J. Nicholls[18], Børge G. Nordestgaard[19,20,21], Bart van de Sluis[22], Marja-Riitta Taskinen[23], Lale Tokgözoğlu[24], Ulf Landmesser[25,26], Ulrich Laufs[27], Olov Wiklund[28,29], Jane K. Stock[30], M. John Chapman[31]†, and Alberico L. Catapano[32]†

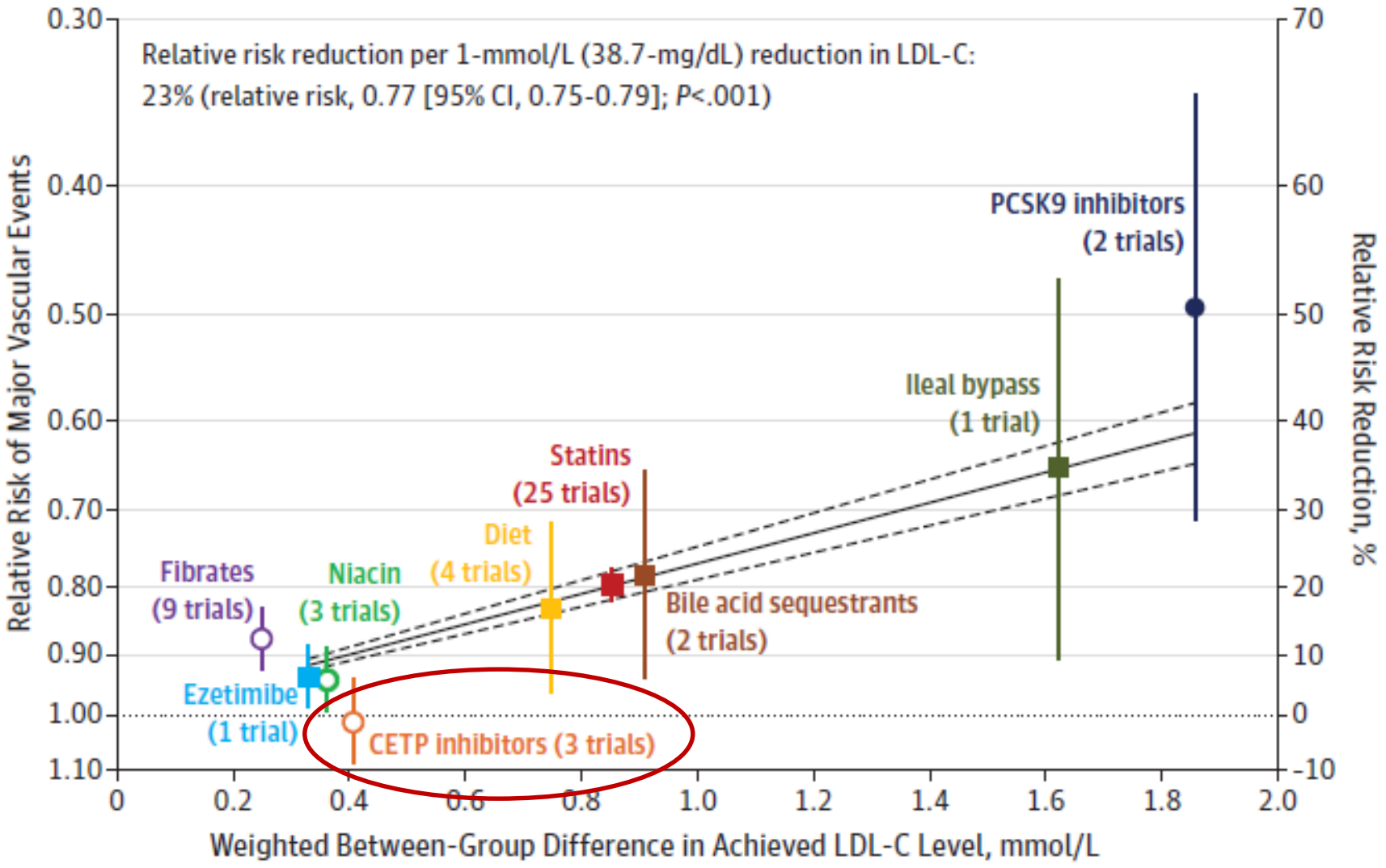
Ference BA, et al. EAS Consensus Statement on LDL Causality. Eur Heart J 2017; doi: 10.1093/eurheartj/ehx144

Effect of LDL-C by magnitude and duration of exposure



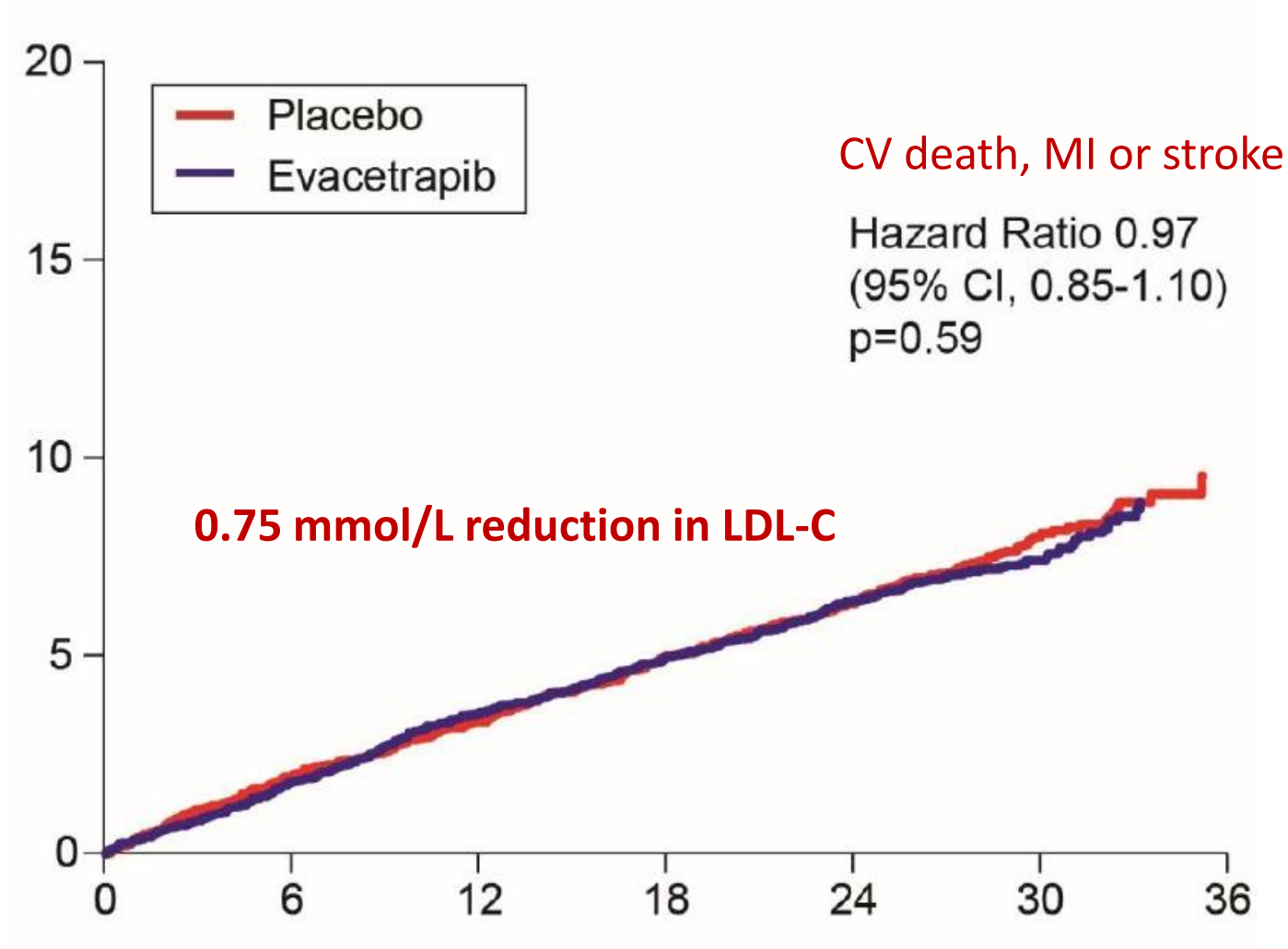
Ference BA, et al. EAS Consensus Statement on LDL Causality. Eur Heart J 2017; doi: 10.1093/eurheartj/ehx144

Meta-Analysis of Various Methods to Lower LDL-C



Silverman MG, et al. JAMA 2016;316:1289-1297.

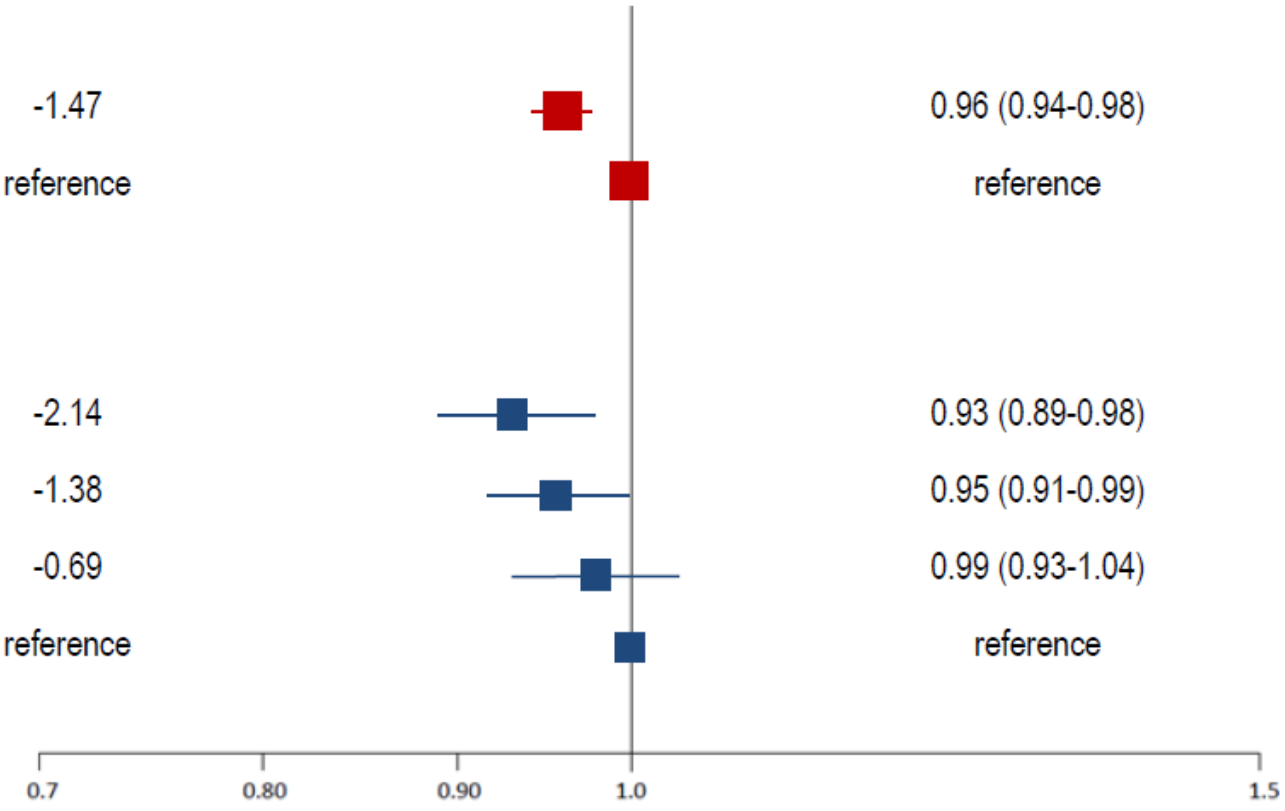
Accelerate Trial



Lincoff AM, et al. N Engl J Med. 2017; 376:1933-1942.

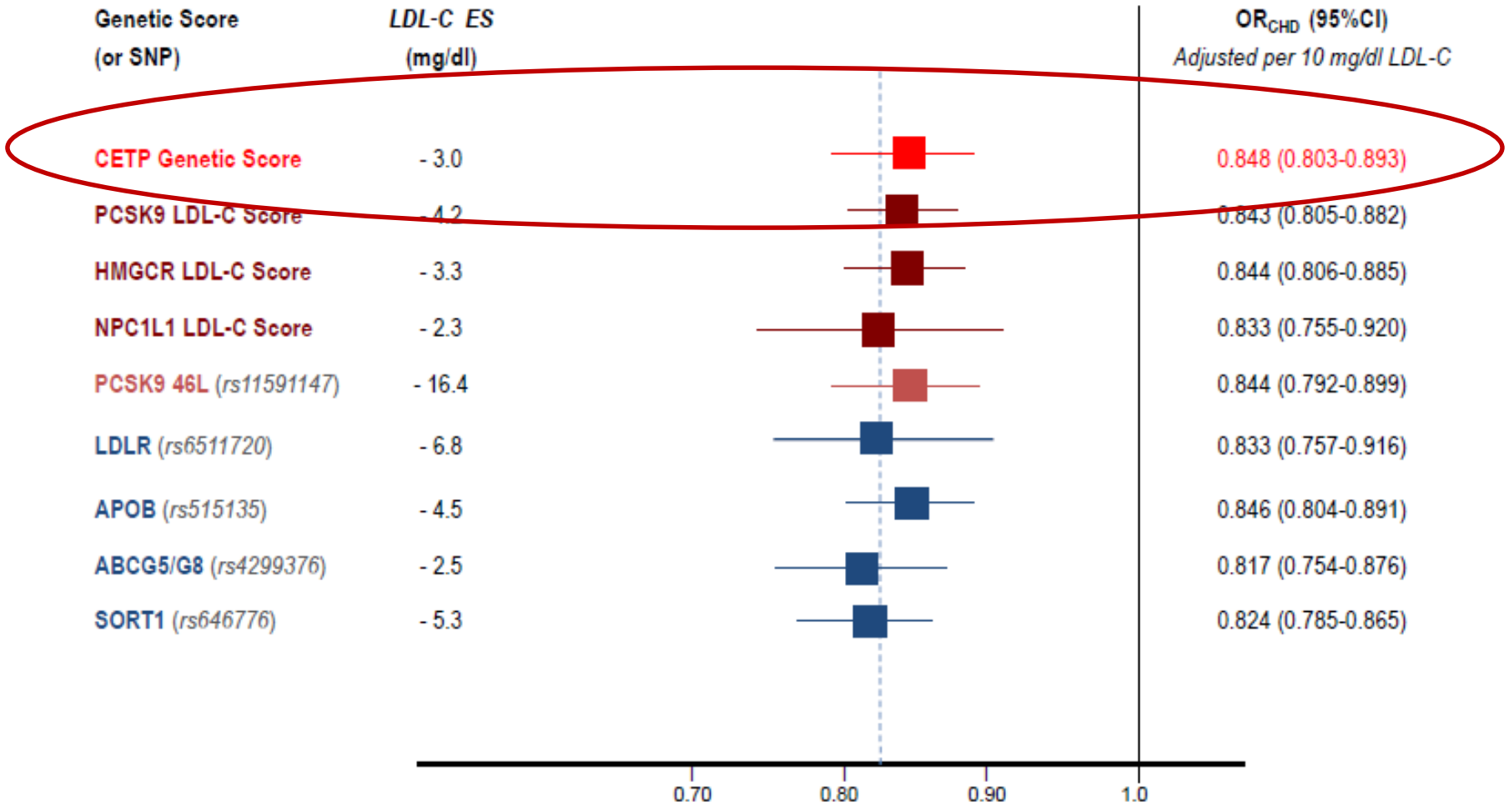
Dose response of genetic CETP inhibition and CHD risk

Analysis	Δ HDL-C (95% CI)	Δ LDL-C (95% CI)	Δ apoB (95% CI)	OR_{MVE} (95%CI)
Primary Analysis				
CETP score ≥ median	4.62	-2.15	-1.47	0.96 (0.94-0.98)
CETP score < median	Reference	reference	reference	reference
Dose Response				
CETP score quartile 4	7.12	-3.29	-2.14	0.93 (0.89-0.98)
CETP score quartile 3	4.98	-2.32	-1.38	0.95 (0.91-0.99)
CETP score quartile 2	2.37	-0.95	-0.69	0.99 (0.93-1.04)
CETP score quartile 1	reference	reference	reference	reference



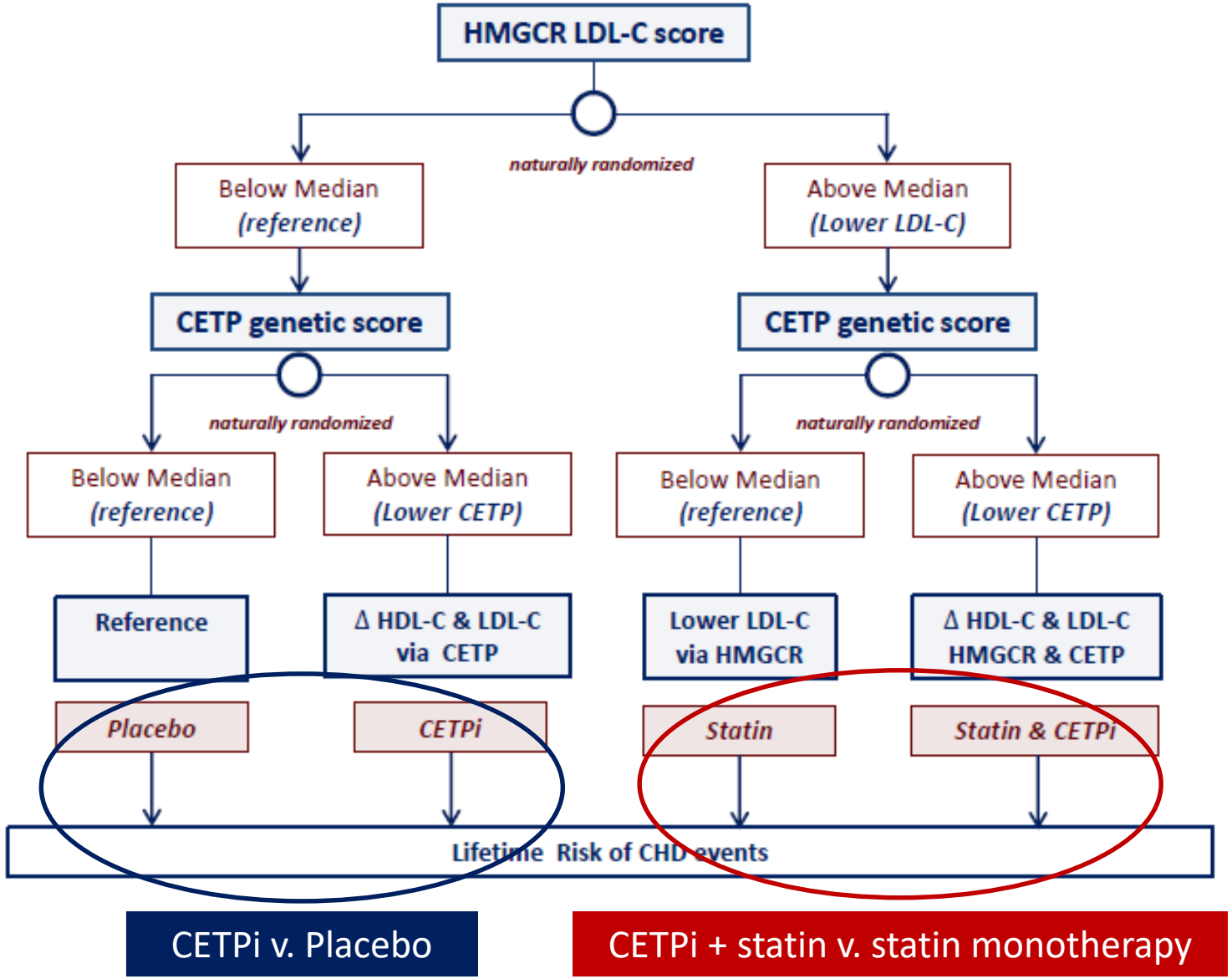
Ference BA, et al. JAMA. 2017; 318(10):947-956

CETP, PCSK9, HMGCR & NPC1L1 genetic scores



Ference BA, et al. JAMA. 2017; 318(10):947-956

Reconciling discordance between CETP MR studies and RCTs



CETPi v. Placebo

CETPi + statin v. statin monotherapy

Naturally randomized trial of CETP & HMGCR

- 2x2 factorial Mendelian randomization study

Biomarker	CETP score	HMGCR Score	Combined CETP and HMGCR Scores
CETP mass, μ/L (SE)	-0.375 (0.035)	0.012 (0.016)	-0.367 (0.034)
CETP activity, μ/L/h (SE)	-0.319 (0.073)	-0.008 (0.009)	-0.323 (0.065)
HDL-C, mg/dl (SE)	4.83 (0.571)	0.82 (0.373)	5.43 (0.601)
LDL-C, mg/dl (SE)	-2.11 (0.677)	-3.24 (0.871)	-5.13 (0.916)
ApoB, mg/dl (SE)	-1.62 (0.191)	-2.71 (0.799)	-3.18 (0.901)
LDL-P, nmol/L (SE)	-12.96 (5.081)	-21.77 (6.394)	-26.12 (7.337)
SBP, mmHg (SE)	-0.16 (0.067)	0.01 (0.029)	0.21 (0.081)

Ference BA, et al. JAMA. 2017; 318(10):947-956

Naturally randomized trial of CETP & HMGCR

- 2x2 factorial Mendelian randomization study

Biomarker	CETP score	HMGCR Score	Combined CETP and HMGCR Scores
CETP mass, μ/L (SE)	-0.375 (0.035)	0.012 (0.016)	-0.367 (0.034)
CETP activity, μ/L/h (SE)	-0.319 (0.073)	-0.008 (0.009)	-0.323 (0.065)
HDL-C, mg/dl (SE)	4.83 (0.571)	0.82 (0.373)	5.43 (0.601)
LDL-C, mg/dl (SE)	-2.11 (0.677)	-3.24 (0.871)	-5.13 (0.916)
ApoB, mg/dl (SE)	-1.62 (0.191)	-2.71 (0.799)	-3.18 (0.901)
LDL-P, nmol/L (SE)	-12.96 (5.081)	-21.77 (6.394)	-26.12 (7.337)
SBP, mmHg (SE)	-0.16 (0.067)	0.01 (0.029)	0.21 (0.081)

Ference BA, et al. JAMA. 2017; 318(10):947-956

CETP Randomized Trial Biomarker Data

CETP inhibitor	Δ LDL-C	Δ APOB
JAMA 2011 RCT		
Evacetrapib monotherapy	23%	17%
Evacetrapib + statin	22%	11%
TULIP Trial		
TA-8995 monotherapy	46%	35%
TA-8995 plus statin	45%	17%
ACCELERATE		
Evacetrapib + statin	37%	15%

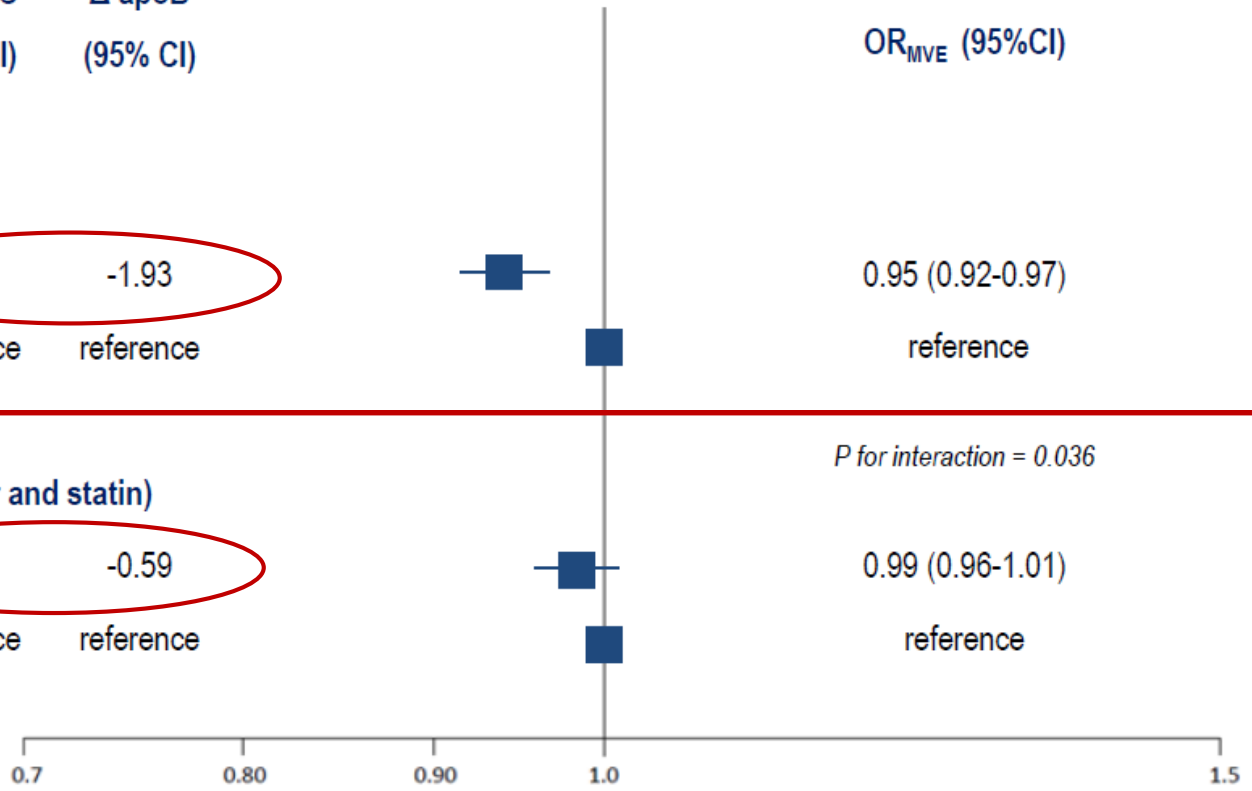
Nicholls SJ et al. JAMA. 2011;306:2099 Hovingh GK, et al. Lancet 2015; 386: 452 Nicholls SJ, et al. Late Breaking Clinical Trial. ACC 2017, Chicago

Causal effect of LDL determined by LDL-C or LDL-P (apoB)?

Combined effect of CETP and HMGCR inhibition

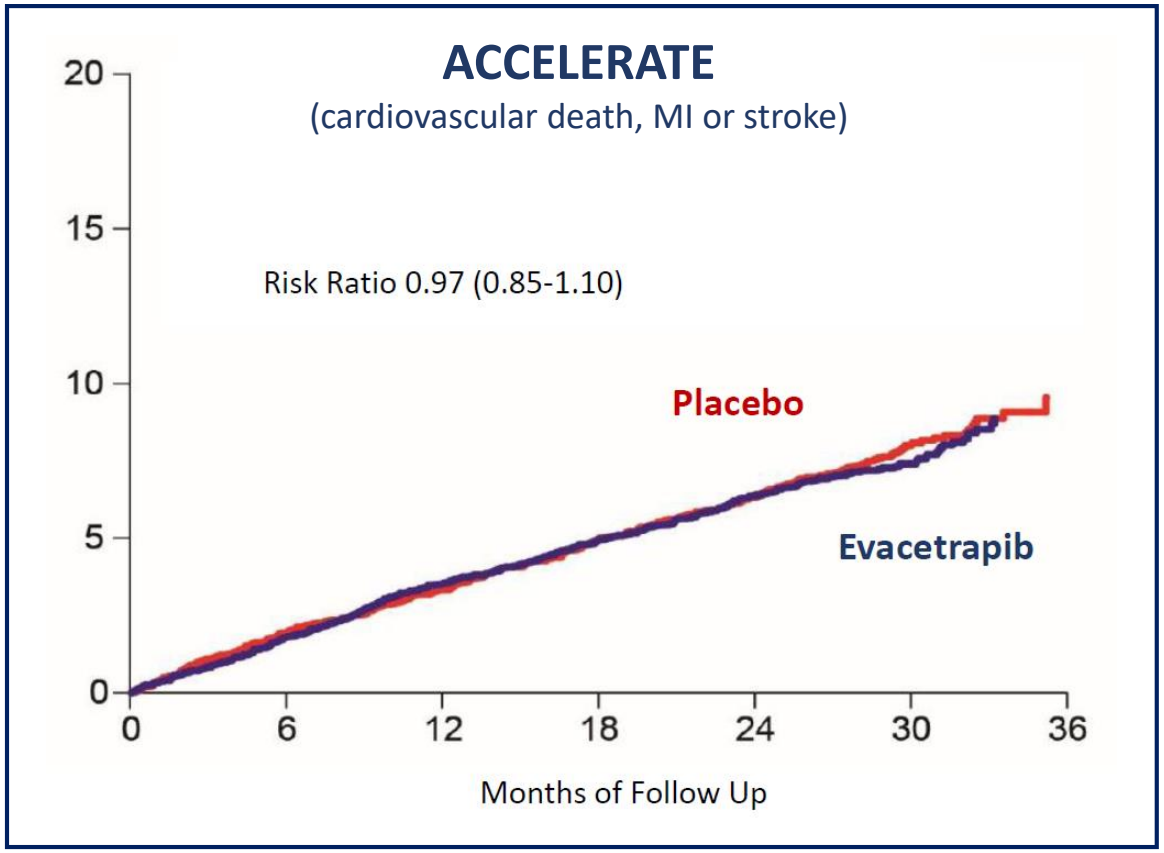
Group	Δ HDL-C (95% CI)	Δ LDL-C (95% CI)	Δ apoB (95% CI)	OR_{MVE} (95%CI)
***HMGCR* score < median (CETP inhibitor alone)**				
CETP score ≥ median	4.64	-2.16	-1.93	0.95 (0.92-0.97)
CETP score < median	reference	reference	reference	reference
***HMGCR* score ≥ median (combined CETP inhibitor and statin)**				
CETP score ≥ median	4.57	-2.02	-0.59	0.99 (0.96-1.01)
CETP score < median	reference	reference	reference	reference

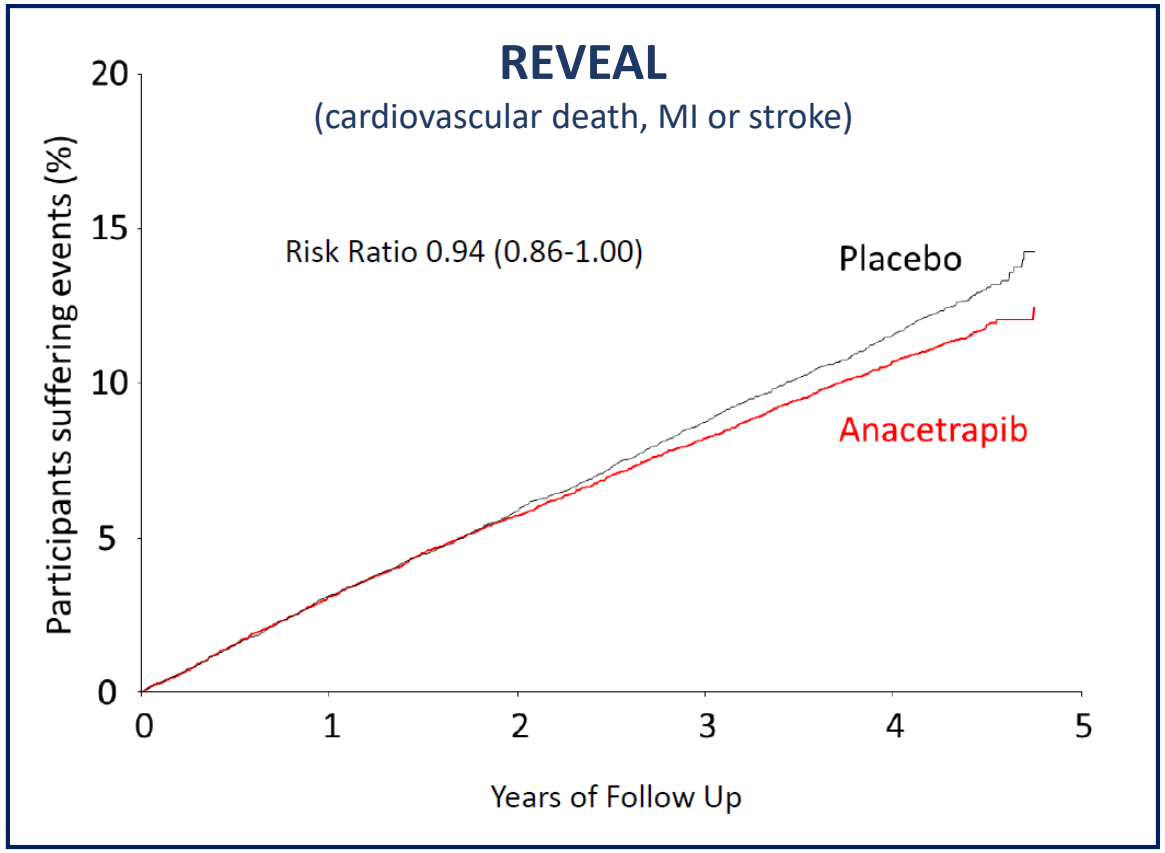
P for interaction = 0.036



Ference BA, et al. JAMA. 2017; 318(10):947-956

Benefit of CETP inhibition proportional absolute apoB reduction





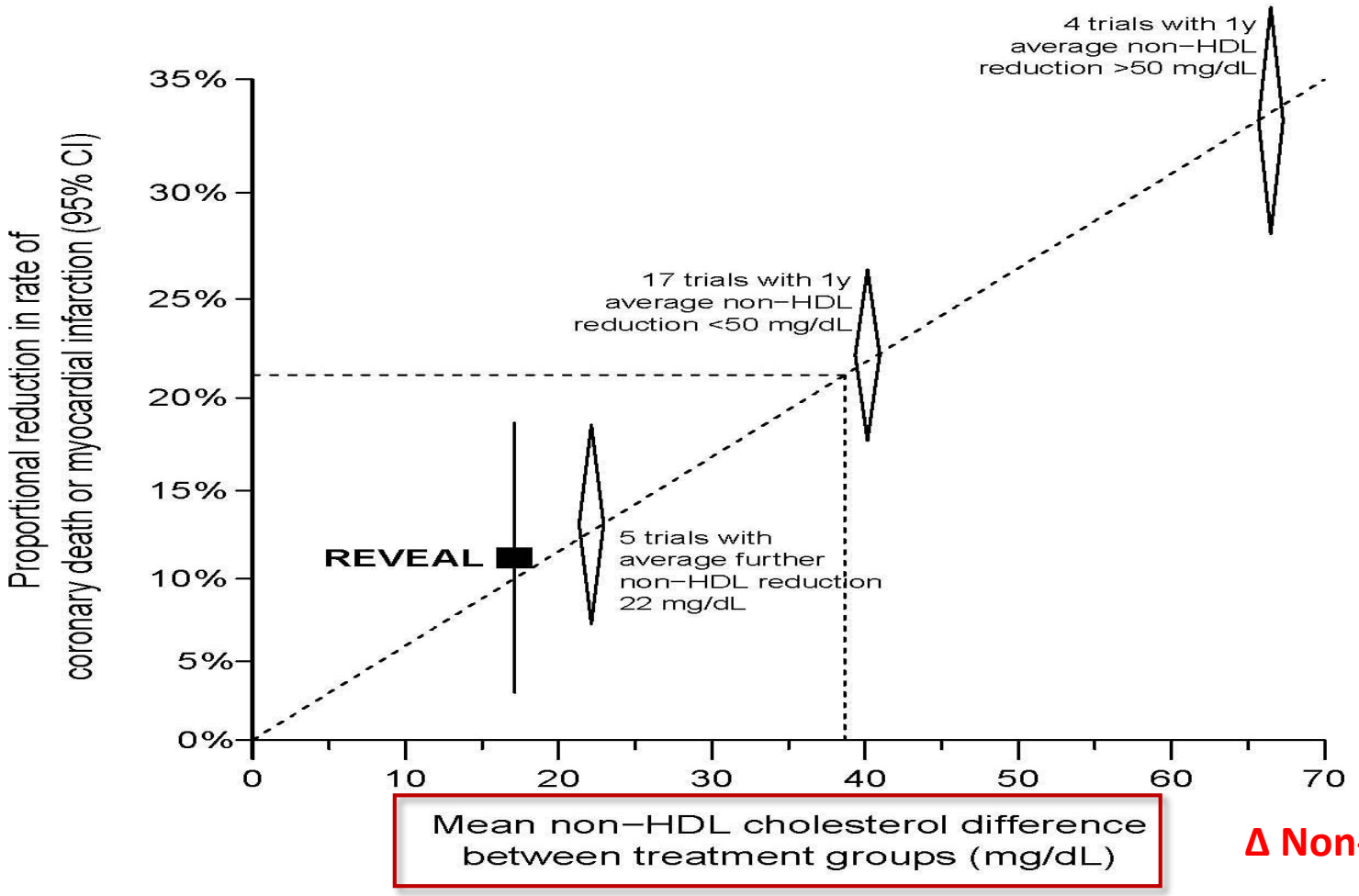
Biomarker	Change mg/dL (%)	Expected RRR	Observed RRR
Beta-Quant	-29 (-37%)	10.5%	3.0%
apoB	-13 (-15%)	3.1%	3.0%

Biomarker	Change mg/dL (%)	Expected RRR	Observed RRR
LDL-C (direct)	-24 (-41%)	15.5%	6.3%
apoB	-12 (-18%)	6.5%	6.3%

Lincoff AM, et al. N Engl J Med 2017;376:1933-42.

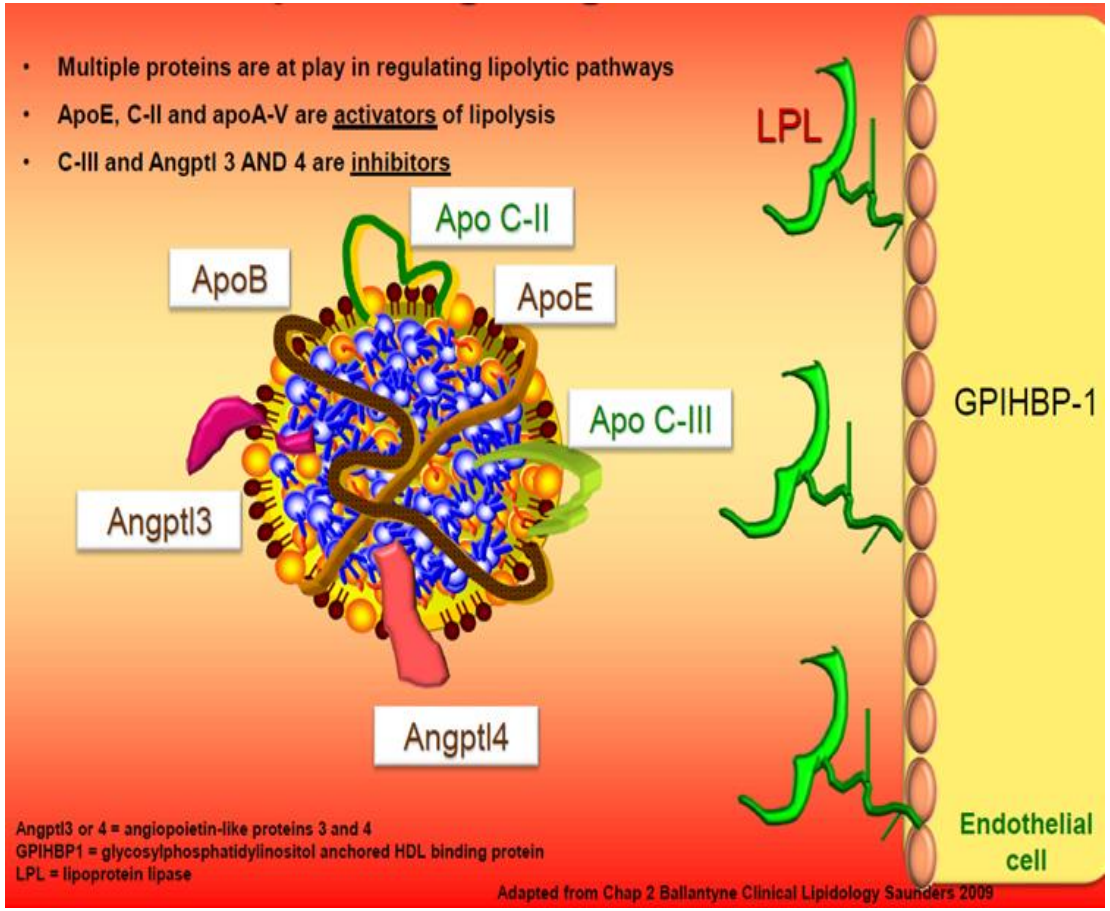
HPS3/TIMI55–REVEAL Collaborative Group. N Engl J Med. 2017;377(13):1217-1227.

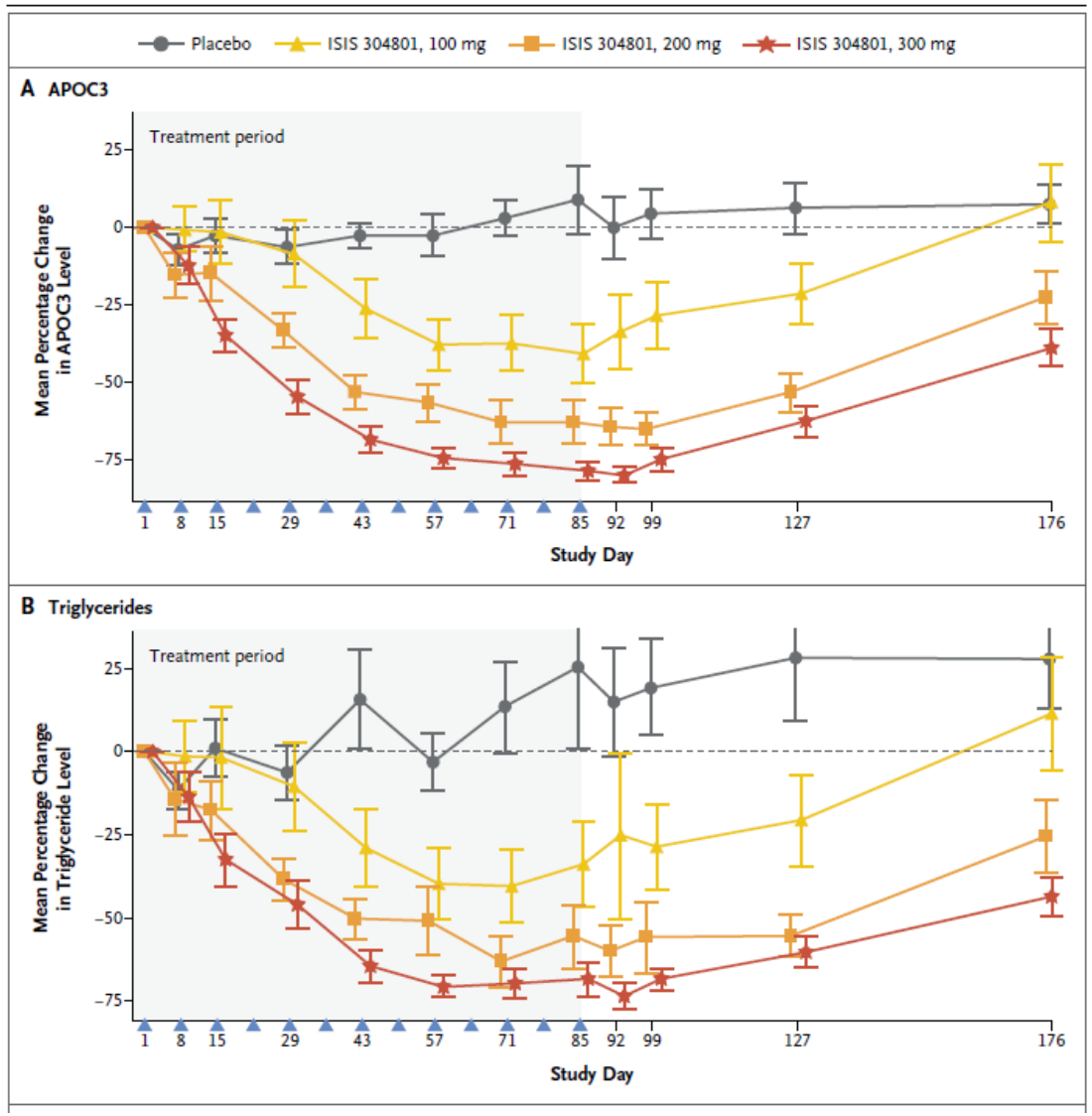
REVEAL trial and statin trials on non-HDL scale



Δ Non-HDL *NOT LDL-C*

APOC3, triglycerides and antisense inhibition trials





Gaudet D, et al. N Engl J Med. 2015;373:438-447.

Designing APOC3 ASO trials: Δ TG, LDL-C, non-HDL-C, or apoB?

Parameter	ISIS 304801 Monotherapy			
	Placebo (N=16)	100 mg (N=11)	200 mg (N=13)	300 mg (N=11)
Triglycerides, mg/dL				
Baseline	522.7 ±369.7	590.6 ±260.3	641.5 ±291.7	559.1 ±224.6
Median (IQR)	459 (356, 582)	558 (351, 825)	588 (464, 717)	566 (355, 702)
Endpoint	547.1 ±355.4	311.6 ±142.6	234.7 ±163.0	139.5 ±36.4 ‡
Median (IQR)	456 (343, 640)	277 (226, 394)	180 (157, 262)	120 (115, 185) ‡
% Change	20.1 ±72.0	-31.3 ±56.8*	-57.7 ±28.3†	-70.9 ±14.1‡
Non-HDL-C, mg/dL				
Baseline	208.1 ±81.7	203.9 ±53.0	208.2±60.8	175.3 ±60.6
Endpoint	198.6 ±32.2	185.8 ±49.3	180.3 ±33.6	144.1 ±56.3
% Change	6.2 ±40.0	-7.2 ±18.8	-6.8 ±17.0	-11.3 ±38.3
LS Mean ±SE	6.2 ±7.8	-6.3 ±9.3	-11.8 ±8.6	-11.7 ±9.3

Parameter	ISIS 304801 Monotherapy			
	Placebo (N=16)	100 mg (N=11)	200 mg (N=13)	300 mg (N=11)
LDL-C, mg/dL				
Baseline	105.1 ±56.3	93.0 ±32.6	80.8 ±25.1	64.6 ±27.7
Endpoint	102.1 ±43.4	132.1 ±46.5	134.3 ±35.6	116.5 ±53.6
% Change	10.8 ±41.1	48.3 ±39.0*	79.4 ±53.3†	118.3 ±177.3*
LS Mean ±SE	10.8 ±23.0	46.9 ±25.8	72.1 ±23.7	110.6 ±25.6†
Total ApoB, mg/dL				
Baseline	117.8 ±38.8	116.3 ±26.1	114.1 ±27.5	100.0 ±20.3
Endpoint	115.2 ±23.1	116.7 ±32.4	120.5 ±21.0	101.7 ±41.9
% Change	3.9 ±26.0	0.5 ±14.9	10.2 ±18.1	1.3 ±36.2
LS Mean ±SE	3.9 ±6.3	3.6 ±7.4	7.1 ±6.9	1.5 ±7.4

Gaudet D, et al. N Engl J Med. 2015;373:438-447.

Designing APOC3 ASO trials: Δ TG, LDL-C, non-HDL-C, or apoB?

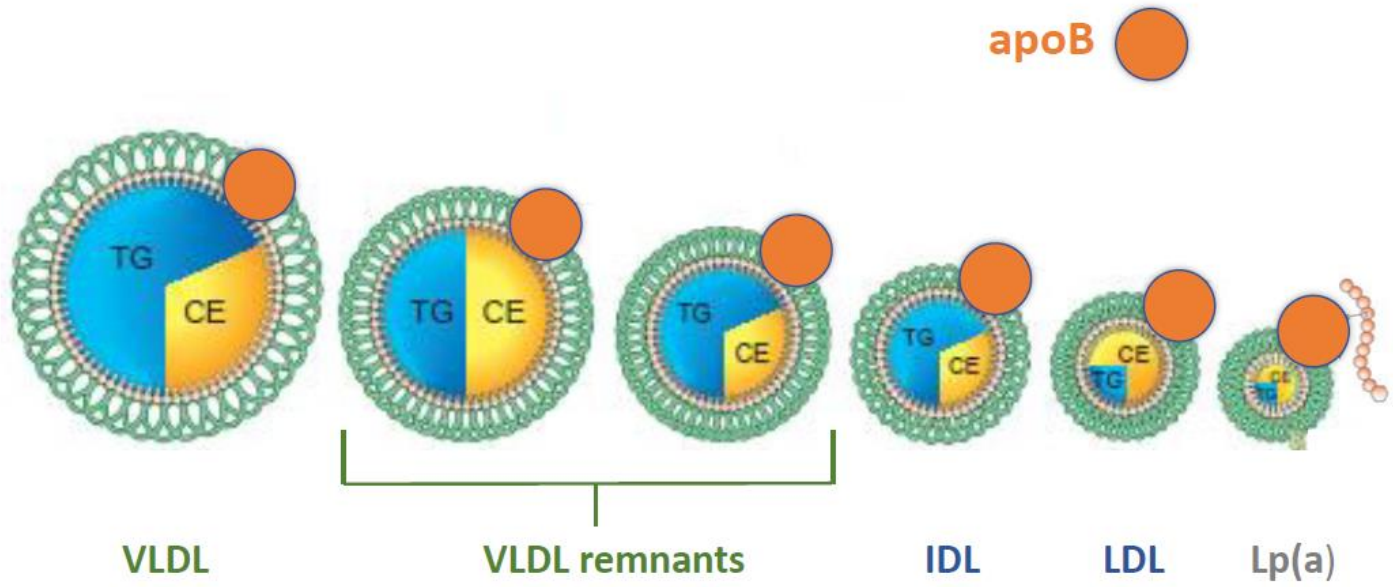
Parameter	ISIS 304801 Monotherapy			
	Placebo (N=16)	100 mg (N=11)	200 mg (N=13)	300 mg (N=11)
Triglycerides, mg/dL				
Baseline	522.7 ±369.7	590.6 ±260.3	641.5 ±291.7	559.1 ±224.6
Median (IQR)	459 (356, 582)	558 (351, 825)	588 (464, 717)	566 (355, 702)
Endpoint	547.1 ±355.4	311.6 ±142.6	234.7 ±163.0	139.5 ±36.4 ‡
Median (IQR)	456 (343, 640)	277 (226, 394)	180 (157, 262)	120 (115, 185) ‡
% Change	20.1 ±72.0	-31.3 ±56.8*	-57.7 ±28.3†	-70.9 ±14.1‡
Non-HDL-C, mg/dL				
Baseline	208.1 ±81.7	203.9 ±53.0	208.2±60.8	175.3 ±60.6
Endpoint	198.6 ±32.2	185.8 ±49.3	180.3 ±33.6	144.1 ±56.3
% Change	6.2 ±40.0	-7.2 ±18.8	-6.8 ±17.0	-11.3 ±38.3
LS Mean ±SE	6.2 ±7.8	-6.3 ±9.3	-11.8 ±8.6	-11.7 ±9.3

Parameter	ISIS 304801 Monotherapy			
	Placebo (N=16)	100 mg (N=11)	200 mg (N=13)	300 mg (N=11)
LDL-C, mg/dL				
Baseline	105.1 ±56.3	93.0 ±32.6	80.8 ±25.1	64.6 ±27.7
Endpoint	102.1 ±43.4	132.1 ±46.5	134.3 ±35.6	116.5 ±53.6
% Change	10.8 ±41.1	48.3 ±39.0*	79.4 ±53.3†	118.3 ±177.3*
LS Mean ±SE	10.8 ±23.0	46.9 ±25.8	72.1 ±23.7	110.6 ±25.6†
Total ApoB, mg/dL				
Baseline	117.8 ±38.8	116.3 ±26.1	114.1 ±27.5	100.0 ±20.3
Endpoint	115.2 ±23.1	116.7 ±32.4	120.5 ±21.0	101.7 ±41.9
% Change	3.9 ±26.0	0.5 ±14.9	10.2 ±18.1	1.3 ±36.2
LS Mean ±SE	3.9 ±6.3	3.6 ±7.4	7.1 ±6.9	1.5 ±7.4

Gaudet D, et al. N Engl J Med. 2015;373:438-447.

Directly comparing effect of lowering triglycerides and LDL-C on CHD

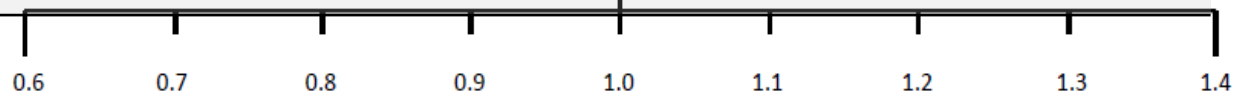
- Triglyceride-rich VLDL and their remnants particles, and LDL particles each have one apoB100
- Therefore, the effect of lowering triglycerides on the risk of cardiovascular events can be directly compared with the effect of lowering LDL-C by comparing their effects per unit change in apoB



Ference BA, et al. Late Breaking Clinical Trial, ESC 2018. Munich

Effect of *LPL* and *LDLR* scores on lipids & CHD per unit change apoB

Genetic Score	Δ triglycerides, mg/dL (95%CI)	Δ LDL-C, mg/dL (95%CI)	OR $_{CHD}$ (95% CI) per 10 mg/dl lower apoB
LPL score	**-69.9** (-68.3, -71.6) **p = 7.1x10 $^{-1363}$**	**0.7** (0.0, 1.4) p = 0.039	0.771 (0.741 - 0.802) p = 3.9x10 $^{-38}$
LDLR Score	**-1.9** (-0.1, -3.9) p = 0.036	**-14.2** (-13.6, -14.8) **p = 1.4x10 $^{-465}$**	0.773 (0.747 - 0.801) p = 1.1x10 $^{-46}$



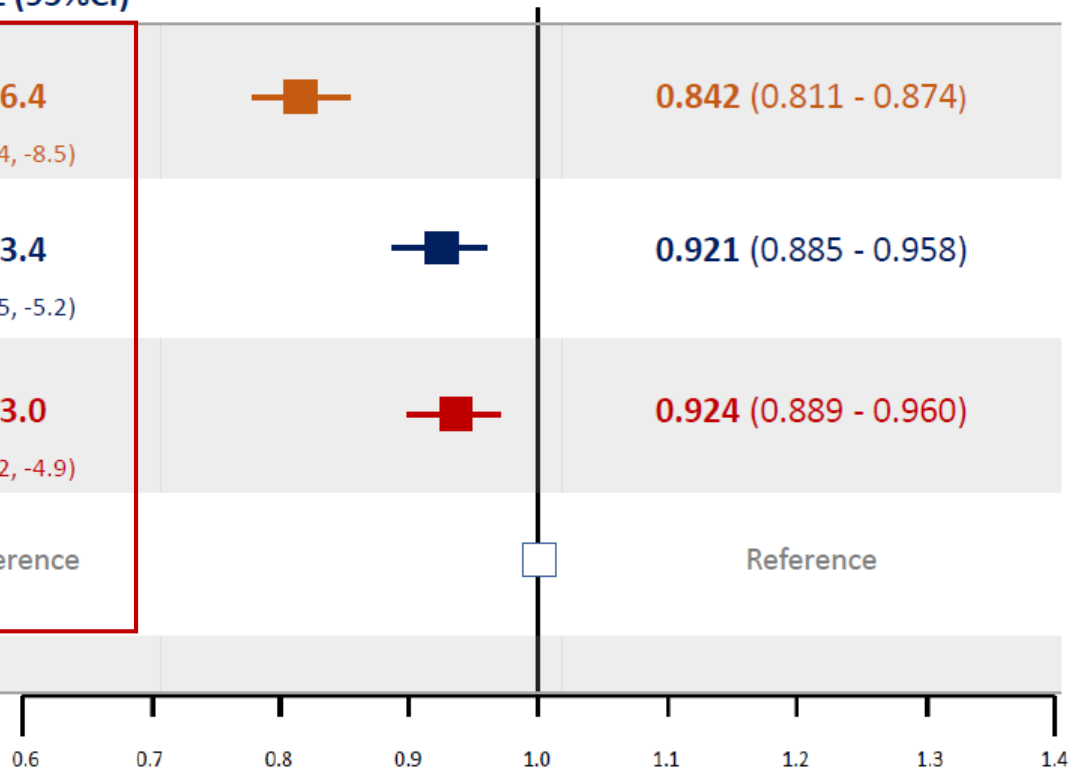
Effects on lipids and CHD for a common 10 mg/dL decrease in apoB-containing lipoproteins

Ference BA, et al. Late Breaking Clinical Trial, ESC 2018. Munich

Combined effect of *LPL* and *LDLR* scores on lipids & CHD

2 x 2 factorial analysis

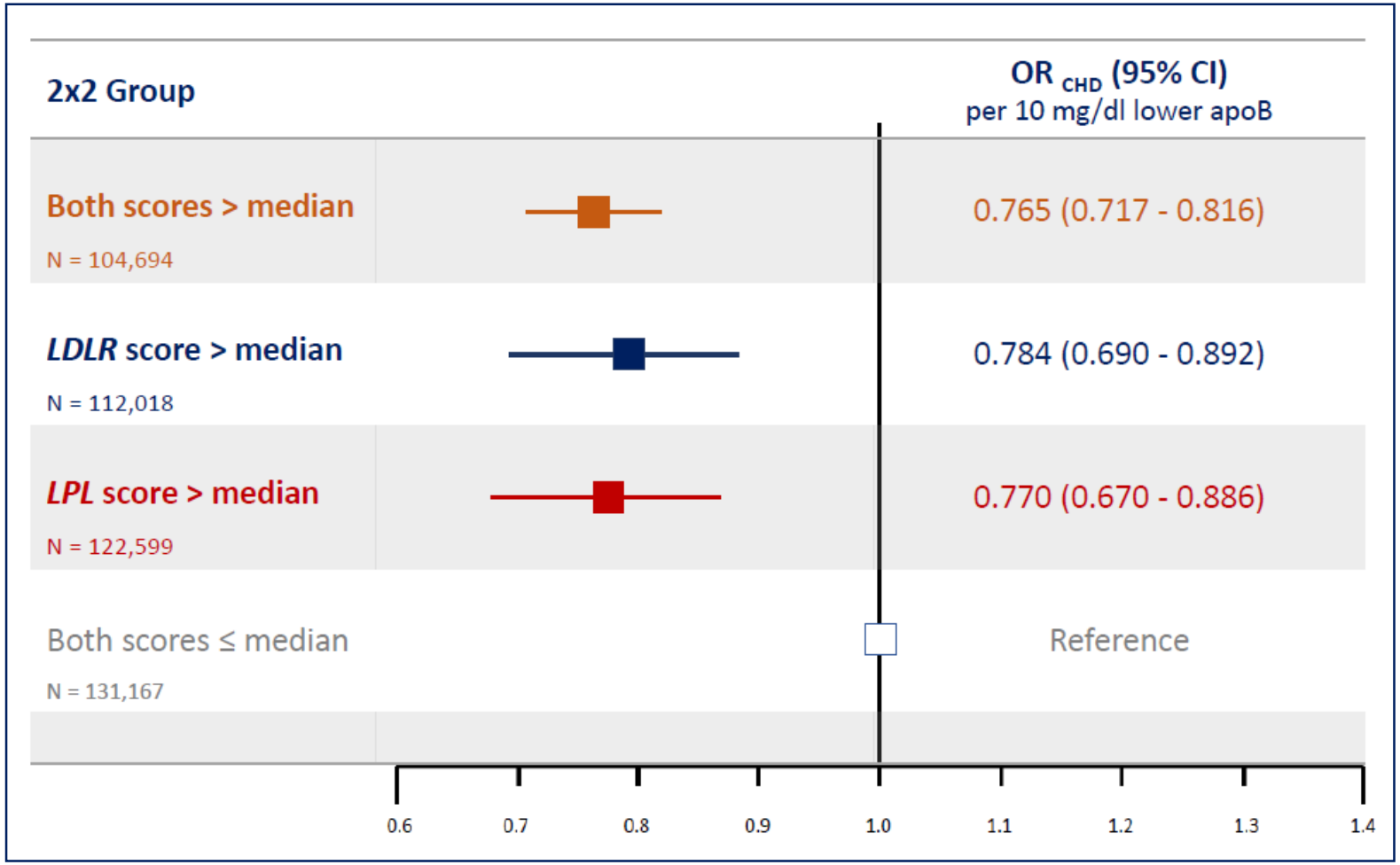
2x2 Group	Δ triglycerides, mg/dL (95%CI)	Δ LDL-C, mg/dL (95%CI)	Δ apoB, mg/dL (95%CI)	OR $_{CHD}$ (95% CI)
Both scores > median N = 104,694	-24.3 (-16.2, -32.4)	-4.9 (-2.1, -7.7)	-6.4 (-4.4, -8.5)	0.842 (0.811 - 0.874)
LDLR score > median N = 112,018	-3.8 (-15.1, 7.5)	-4.8 (-2.0, -7.6)	-3.4 (-1.5, -5.2)	0.921 (0.885 - 0.958)
LPL score > median N = 122,599	-20.1 (-13.3, -28.8)	-0.1 (-0.5, 0.3)	-3.0 (-1.2, -4.9)	0.924 (0.889 - 0.960)
Both scores ≤ median N = 131,167	reference	reference	reference	Reference



Ference BA, et al. Late Breaking Clinical Trial, ESC 2018. Munich

Combined effect of *LPL* and *LDLR* scores on lipids & CHD

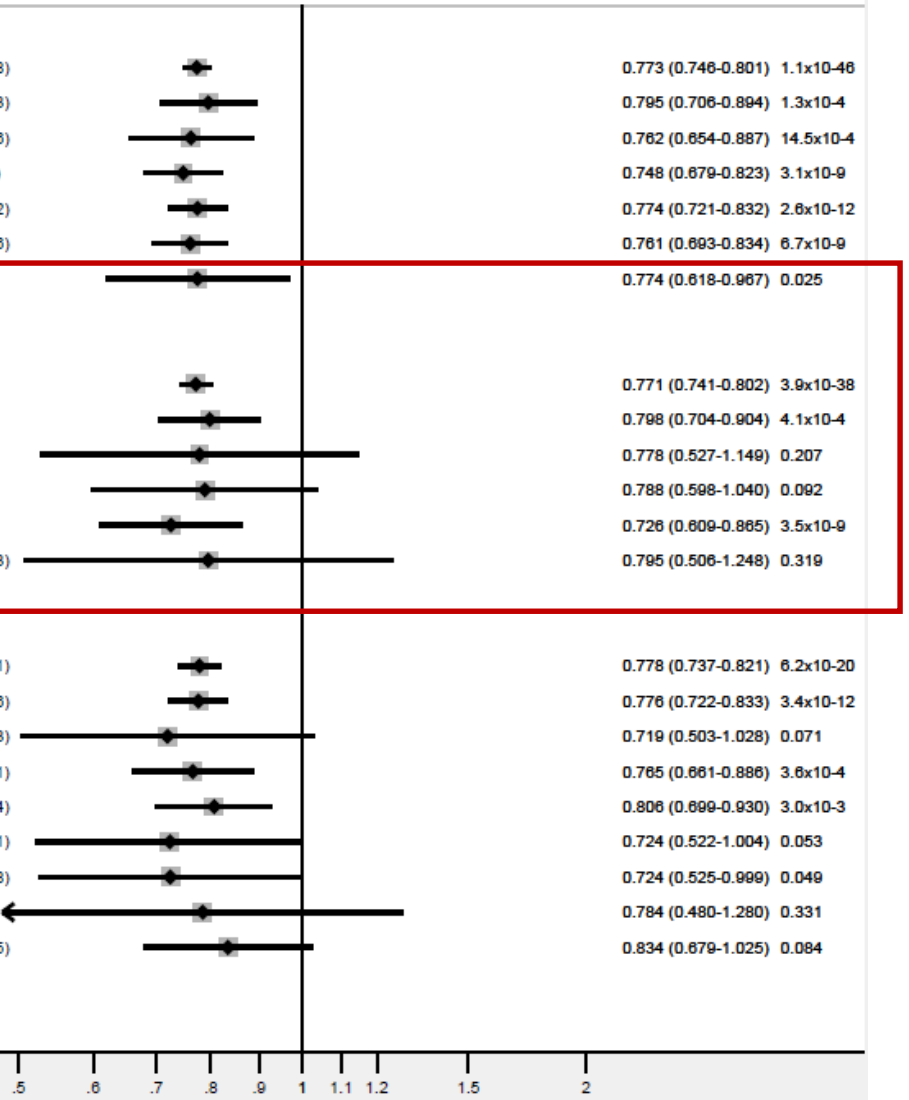
Per 10 mg/dl lower apoB



Ference BA, et al. Late Breaking Clinical Trial, ESC 2018. Munich

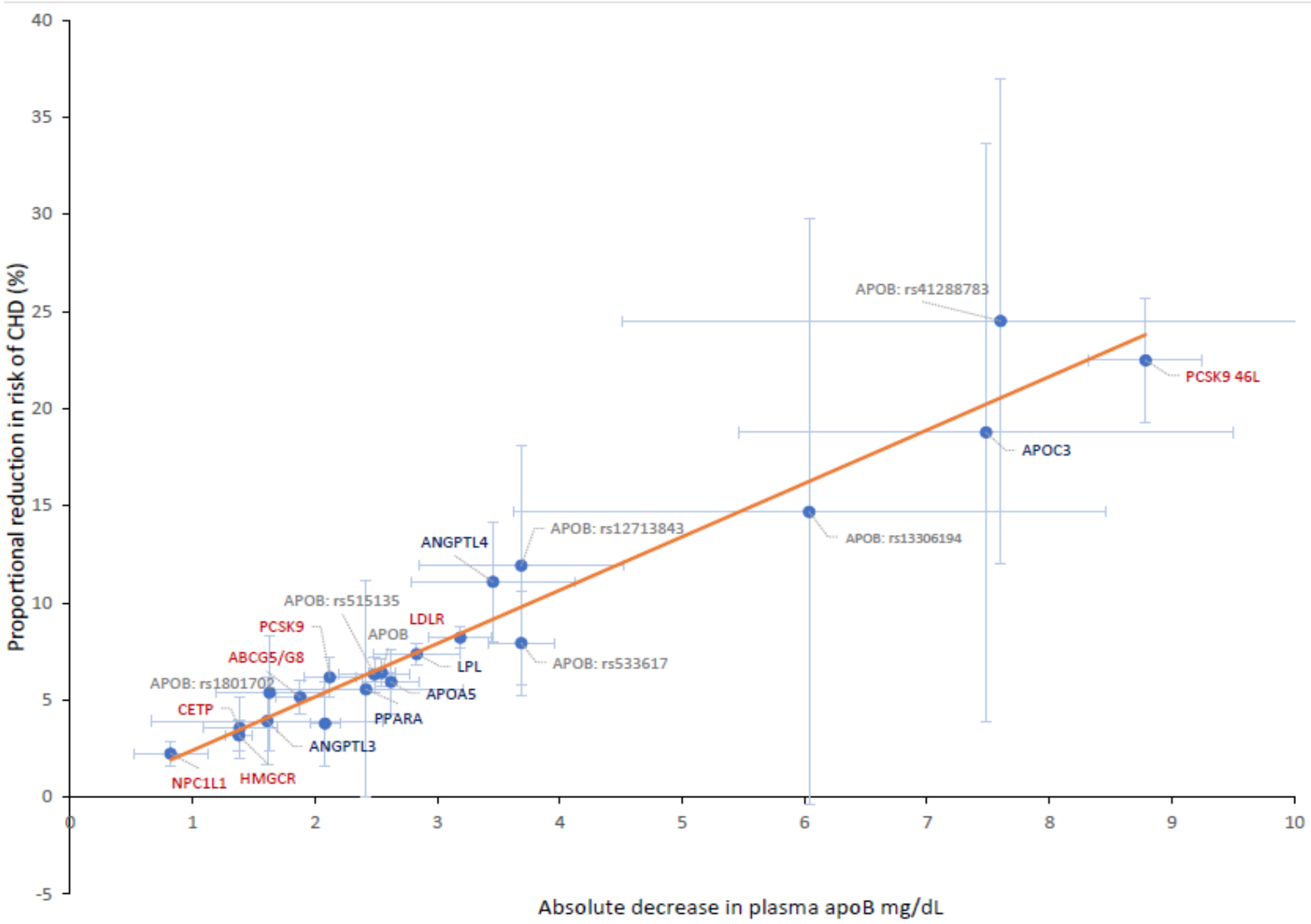
Effect of variants in targets of lipid lowering therapies on CHD

Gene	Genetic Variant	Functional Consequence	Therapy	Δ triglycerides (95% CI)	Δ LDL-C (95% CI)	OR (95% CI)	P value
Therapies targeting LDL Receptor Pathway							
LDLR	3 variants	genetic score	therapeutic target	-1.9 (-0.1, -3.9)	-14.2 (-13.6, -14.8)	0.773 (0.746-0.801)	1.1x10-46
HMGCR	rs3846662	Intron	statin	-2.4 (-5.9, 1.0)	-15.6 (-16.8, -14.3)	0.795 (0.706-0.894)	1.3x10-4
NPC1L1	rs217386	intron	ezetimibe	-7.6 (-14.8, -0.5)	-14.6 (-17.6, -11.6)	0.762 (0.654-0.887)	14.5x10-4
PCSK9	rs11206510	Intergenic	PCSK9 inhibitor	-4.2 (-7.1, -1.3)	-10.9 (-12.0, -9.8)	0.748 (0.679-0.823)	3.1x10-9
PCSK9 46L	rs11591147	Arg46Leu	PCSK9 inhibitor	-0.5 (-2.7, 1.7)	-18.0 (-18.8, -17.2)	0.774 (0.721-0.832)	2.6x10-12
ABCG5/G8	rs4245791	Intron	Bile resin	-9.0 (-11.8, -6.2)	-12.6 (-13.7, -11.6)	0.761 (0.693-0.834)	6.7x10-9
CETP	rs5880	Ala390Pro	CETP inhibitor	-24.4 (-32.6, -16.2)	-4.1 (-7.3, -0.8)	0.774 (0.618-0.967)	0.025
Therapies targeting LPL Pathway							
LPL	5 variants	genetic score	therapeutic target	-69.9 (-68.3, -71.6)	0.7 (0.0, 1.4)	0.771 (0.741-0.802)	3.9x10-38
APOA5	rs3135506	Ser19Trp	LPL enhancer	-70.7 (-73.9, -67.5)	-6.0 (-7.4, -4.6)	0.798 (0.704-0.904)	4.1x10-4
APOC3	rs138326449	Essential_Splice_Site	APOC3 inhibitor	-92.3 (-103.8, -80.3)	-5.7 (-9.7, -1.8)	0.778 (0.527-1.149)	0.207
ANGPTL3	rs72649576	intron	ANGPTL3 inhibitor	-30.9 (-69.7, 7.8)	-8.9 (-20.3, 2.4)	0.788 (0.598-1.040)	0.092
ANGPTL4	rs116843064	Glu40Lys	ANGPTL4 inhibitor	-69.4 (-74.3, -64.5)	-0.4 (-2.2, 1.5)	0.726 (0.609-0.865)	3.5x10-9
PPARA	rs1042311	PPARA:Ala268Val	fibrate	-25.0 (-38.7, -11.3)	-16.4 (-21.5, -11.3)	0.795 (0.506-1.248)	0.319
Therapies that lower apoB							
APOB	8 variants	genetic score	therapeutic target	-9.7 (-11.0, -8.3)	-15.6 (-16.1, -15.1)	0.778 (0.737-0.821)	6.2x10-20
APOB	rs515135	intergenic	therapeutic target	-6.1 (-8.4, -3.8)	-15.5 (-16.4, -14.6)	0.776 (0.722-0.833)	3.4x10-12
APOB	rs1801702	Arg4270Thr	therapeutic target	-3.5 (-11.9, 4.9)	-18.4 (-21.6, -15.3)	0.719 (0.503-1.028)	0.071
APOB	rs5742904	Arg3527Gln	therapeutic target	8.8 (3.6, 14.1)	-22.1 (-24.1, -20.1)	0.765 (0.661-0.886)	3.6x10-4
APOB	rs533617	His1923Arg	therapeutic target	-23.6 (-26.8, -20.4)	-11.6 (-12.8, -10.4)	0.806 (0.699-0.930)	3.0x10-3
APOB	rs12713843	Arg1128His	therapeutic target	-18.8 (-28.2, -9.3)	-20.6 (-24.1, -17.1)	0.724 (0.522-1.004)	0.053
APOB	rs41288783	Pro994Leu	therapeutic target	21.0 (9.1, 32.9)	-24.3 (-28.8, -19.8)	0.724 (0.525-0.999)	0.049
APOB	rs13306194	Arg532Trp	therapeutic target	-14.1 (-19.9, -8.4)	-6.6 (-8.7, -4.4)	0.784 (0.480-1.280)	0.331
APOB	rs1367117	Thr98Ile	therapeutic target	-9.8 (-12.2, -7.4)	-17.4 (-18.4, -16.5)	0.834 (0.679-1.025)	0.084



Ference BA, et al. Late Breaking Clinical Trial, ESC 2018. Munich

Log-linear association between changes in apoB & CHD



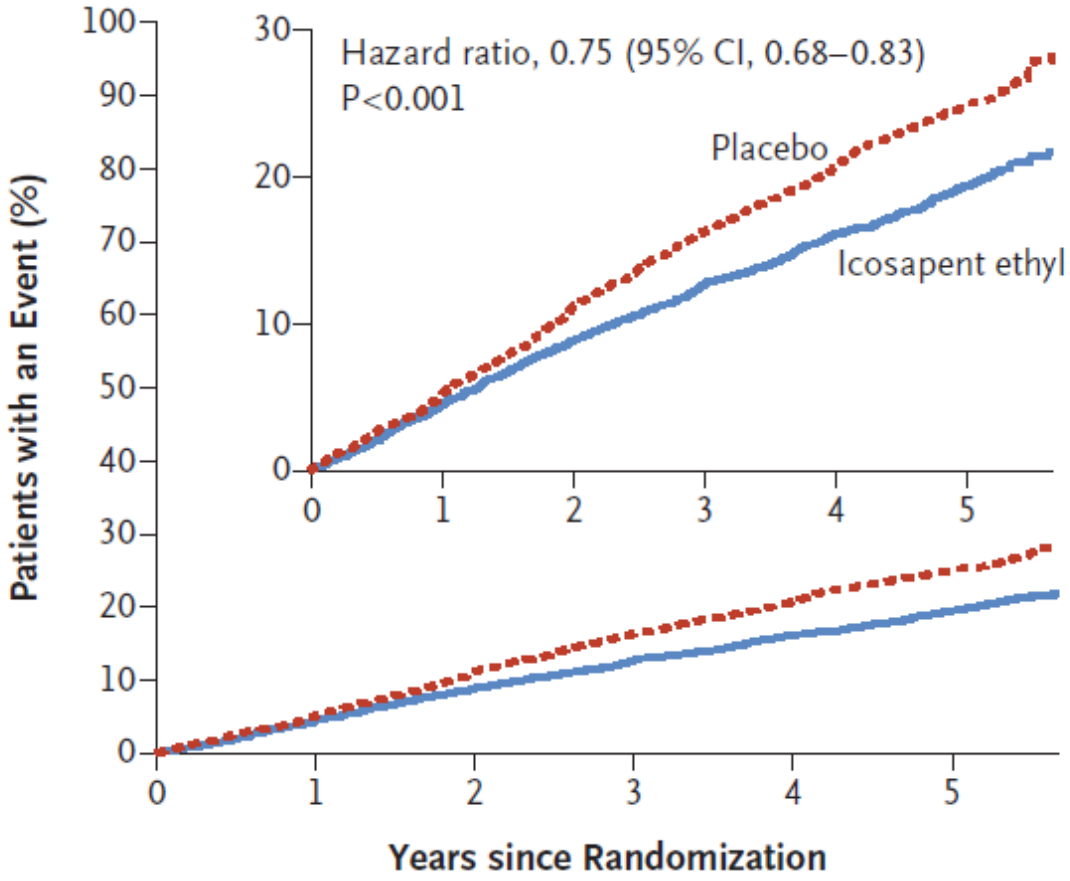
Ference BA, et al. Late Breaking Clinical Trial, ESC 2018. Munich

Multivariable Mendelian randomization

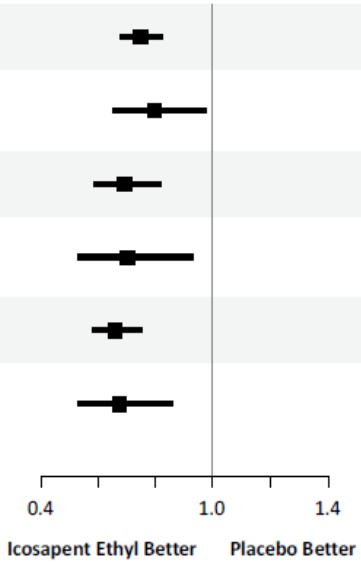
Analysis	variables	OR_{CHD} (95% CI)	p value
Association of apoB with risk of CHD	apoB	0.770 (0.760 - 0.781)	1.42E-170
Association of LDL-C with risk of CHD	LDL-C	0.846 (0.833 - 0.858)	8.16E-77
Association of triglycerides with risk of CHD	Triglycerides	0.815 (0.785 - 0.846)	1.37E-18
Association of LDL-C and triglycerides with risk of CHD included in same model	LDL-C	0.862 (0.849 - 0.875)	6.92E-65
	Triglycerides	0.876 (0.850 - 0.902)	1.36E-14
Association of LDL-C, triglycerides and apoB with risk of CHD included in same model	apoB	0.761 (0.723 - 0.798)	7.51E-20
	LDL-C	1.010 (0.967 - 1.055)	0.186
	Triglycerides	1.014 (0.965 - 1.065)	0.189
Association of LDL-C and apoB with risk of CHD included in same model	apoB	0.762 (0.738 - 0.787)	1.27E-36
	LDL-C	1.009 (0.977 - 1.042)	0.140
Association of triglycerides and apoB with risk of CHD included in same model	apoB	0.765 (0.751 - 0.779)	1.20E-105
	triglycerides	1.011 (0.975 - 1.048)	0.161

Ference BA, et al. Late Breaking Clinical Trial, ESC 2018. Munich

REDUCE-IT trial, triglyceride changes and purified EPA



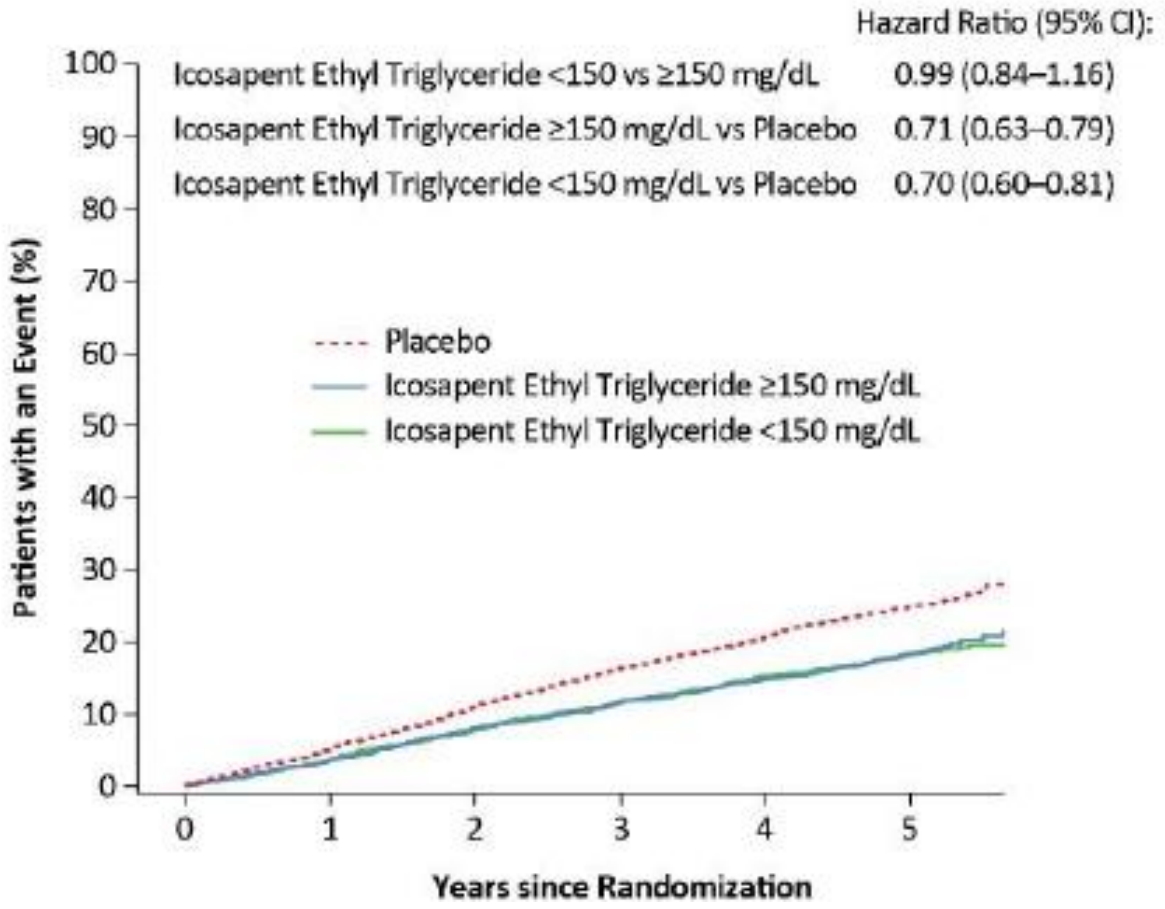
End Point	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)*
Primary Composite (ITT)	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)
Cardiovascular Death	174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66–0.98)
Nonfatal Myocardial Infarction	237/4089 (5.8%)	332/4090 (8.1%)	0.70 (0.59–0.82)
Nonfatal Stroke	85/4089 (2.1%)	118/4090 (2.9%)	0.71 (0.54–0.94)
Coronary Revascularization	376/4089 (9.2%)	544/4090 (13.3%)	0.66 (0.58–0.76)
Hospitalization for Unstable Angina	108/4089 (2.6%)	157/4090 (3.8%)	0.68 (0.53–0.87)



Bhatt Dl, et al. NEJM, 10 November 2018. DOI: 10.1056/NEJMoa1812792

REDUCE-IT trial, triglyceride changes and purified EPA

Exposure	EPA	Placebo	Difference	Expected RRR
triglycerides	-39 mg/dl	+4.5 mg/dL	-43.5 mg/dl	6-8%
LDL-C	+2 mg/dl	+7 mg/dL	-5 mg/dl	3-5%
Non-HDL	-4 mg/dl	+12 mg/dL	-15.5 mg/dl	6-8%
apoB	-2 mg/dl	+6 mg/dL	-8 mg/dl	6-8%
CRP	-0.2 mg/dl	+0.5 mg/dL	-0.9 mg/dl	5-7%



Bhatt Dl, et al. NEJM, 10 November 2018. DOI: 10.1056/NEJMoa1812792

Conclusions

- The causal effect of LDL and TG-rich VLDL remnant particles is determined by the concentration of circulating particles rather than by the cholesterol or triglyceride content carried by those particles
- The clinical benefit of lowering triglycerides is ery similar to the clinical benefit of lowering LDL-C, for the same change in apoB-containing lipoproteins
- The potential clinical benefit of any lipid lowering therapy should be proportional to the achieved absolute reduction in apoB (regardless of the change in LDL-C, TG or both)