Challenges in Atherosclerotic Cardiovascular Disease reduction and Triglyceride-related risk

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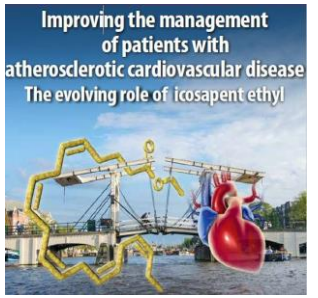
Improving the management of patients with atherosclerotic cardiovascular disease - The evolving role of icosapent ethyl



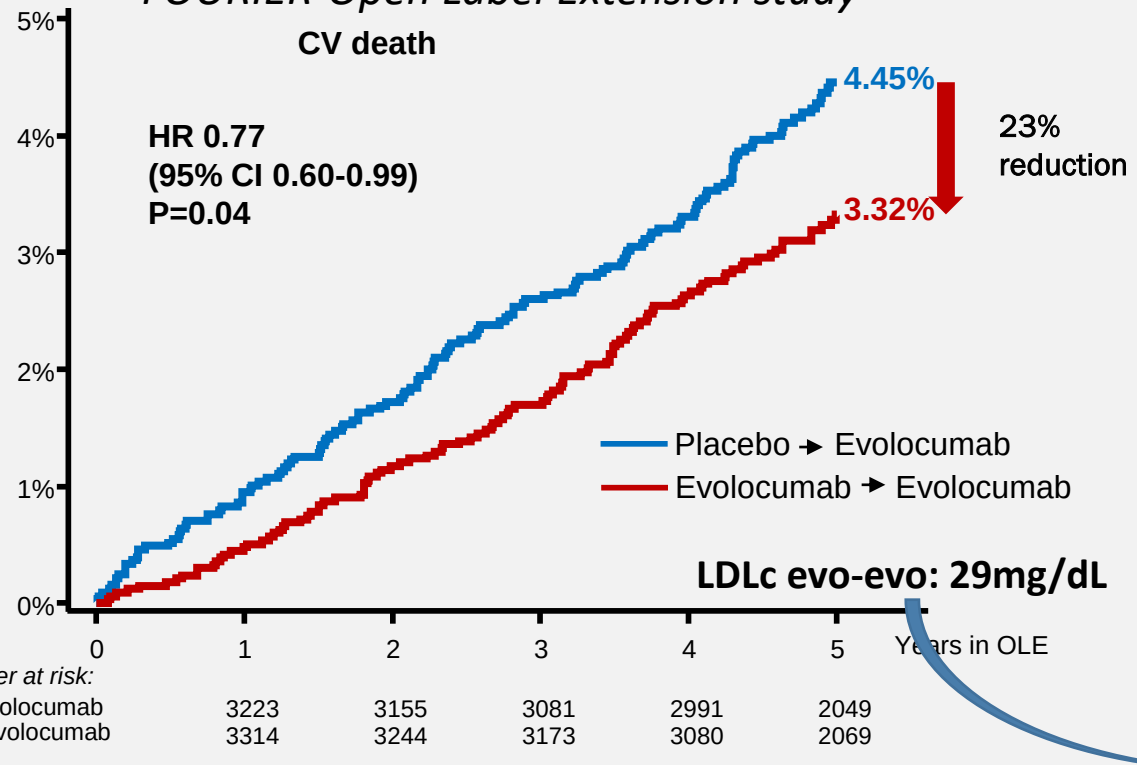
PHYSICIANS' ACADEMY FOR
PACE-CME
CARDIOVASCULAR EDUCATION

Disclosures

Speaker/ad-board paid to institution	Amgen, Sanofi, Ionis NovoNordisk, Merck
Research finances	Dutch heart foundation, European Union
Stocks	none
Other	none

Residual risk in patients with very-low LDLc levels

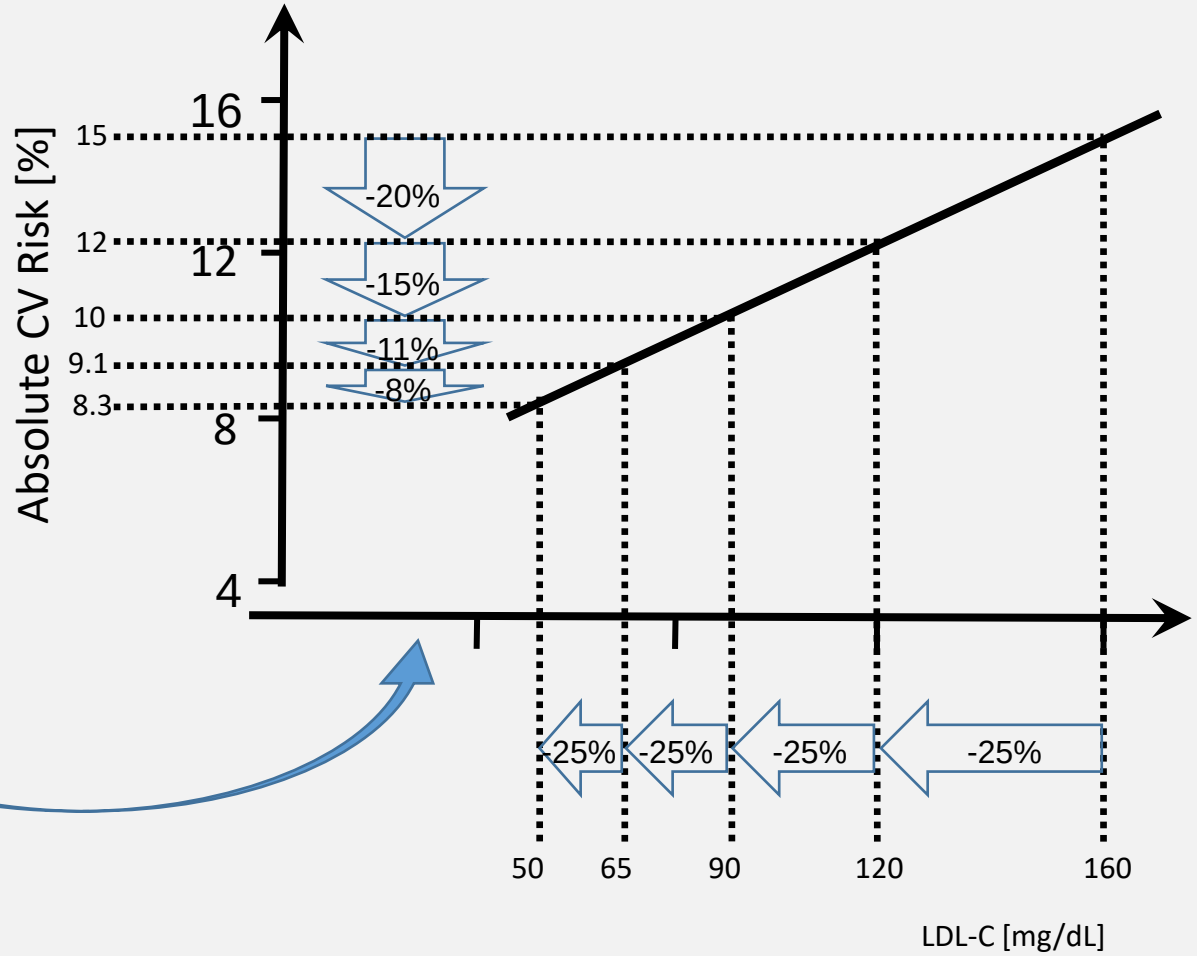
Significant benefit with marked residual risk
FOURIER-Open Label Extension study



Number at risk:

Placebo-Evolocumab	3223	3155	3081	2991	2049
Evolocumab-Evolocumab	3314	3244	3173	3080	2069

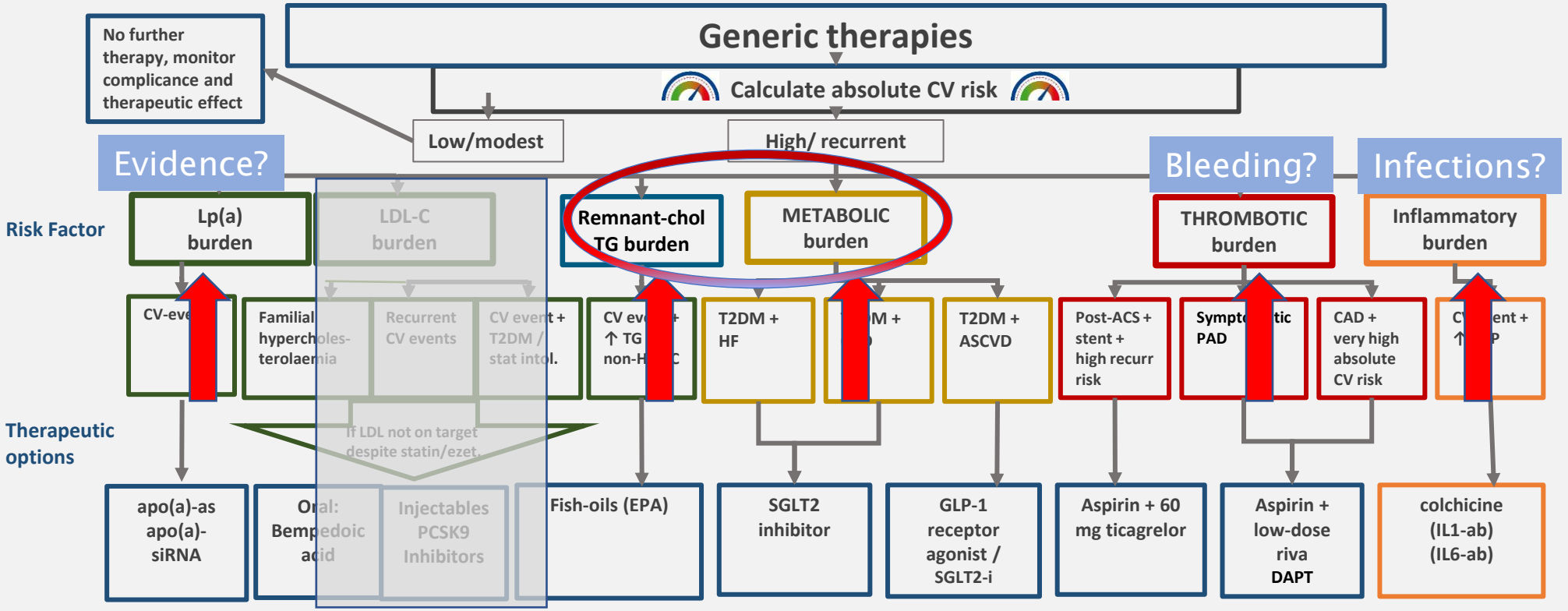
Further LDLc lowering - limited benefit



Recurrent CV-event rate in evo-evolocumab : **14.6% /5yr**
Recurrent CV-event rate in placebo-evolocumab: **16.8% /5yr**

O'Donaghue, *Circulation* 2022; Gaba P, *Circulation* 2023; Laufs, *Eur Heart J* 2014

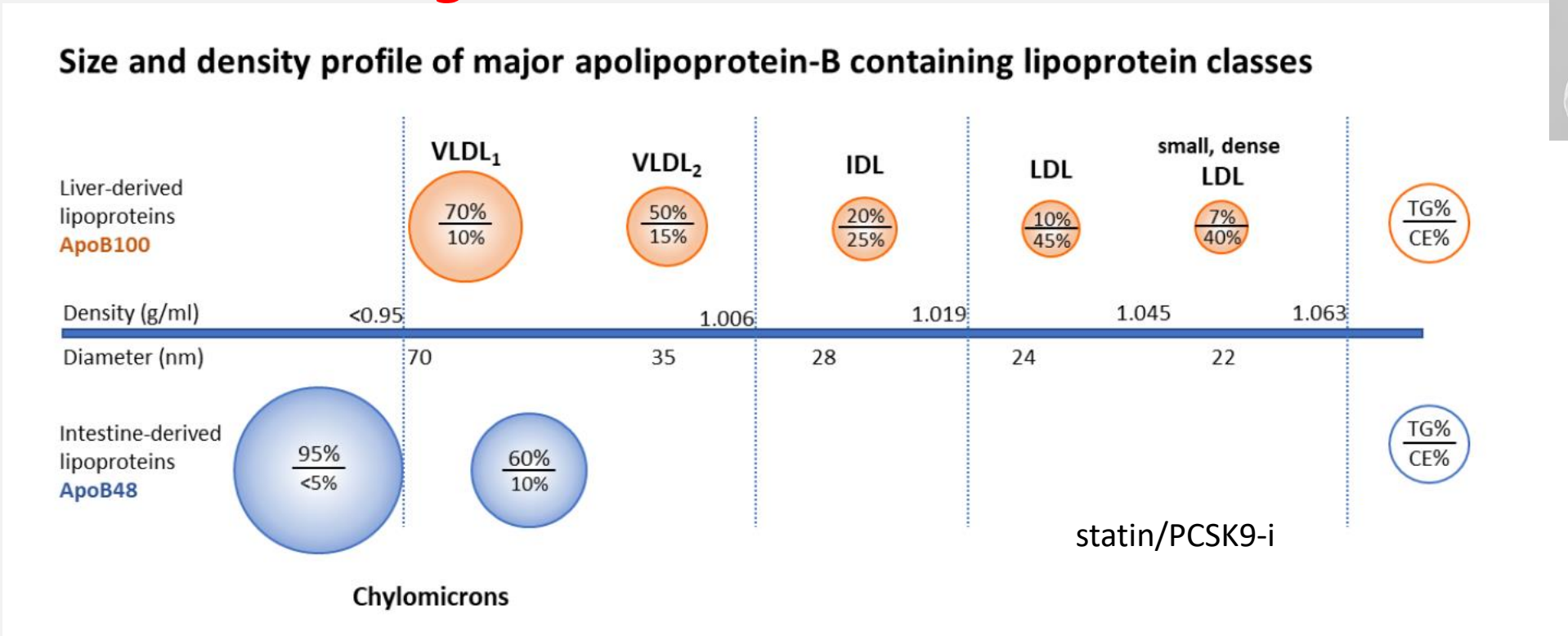
Other pillars 'contributing' to atherogenesis



Hoogeveen, Stroes, Neth Heart J 2021

When cardiologist talk about high TGs .

TGs are 'heterogeneous'



apoB containing lipoproteins

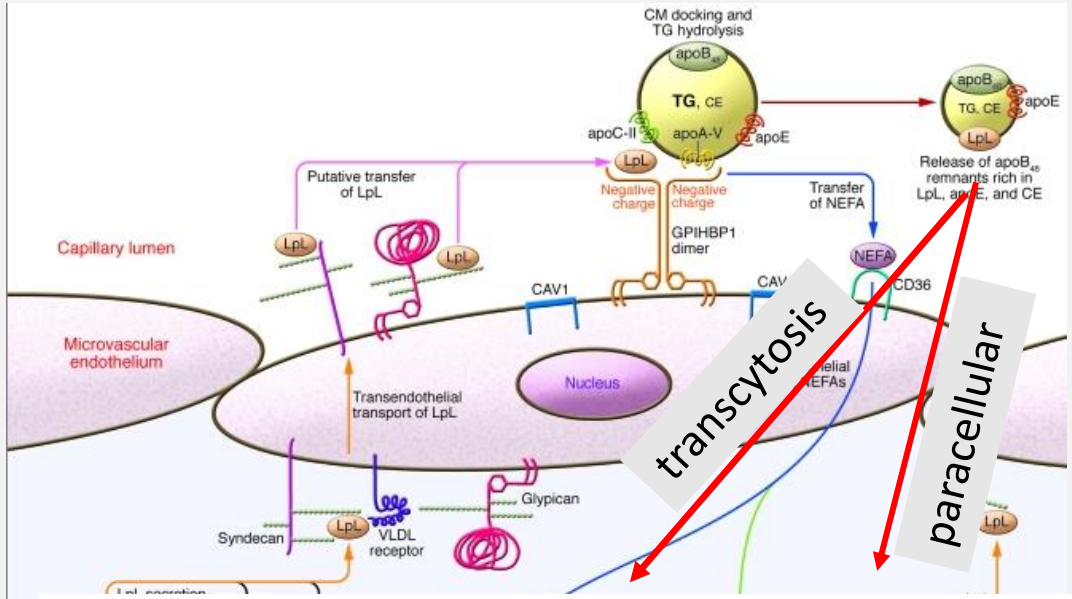
Triglycerides / Triglyceride-rich lipoproteins

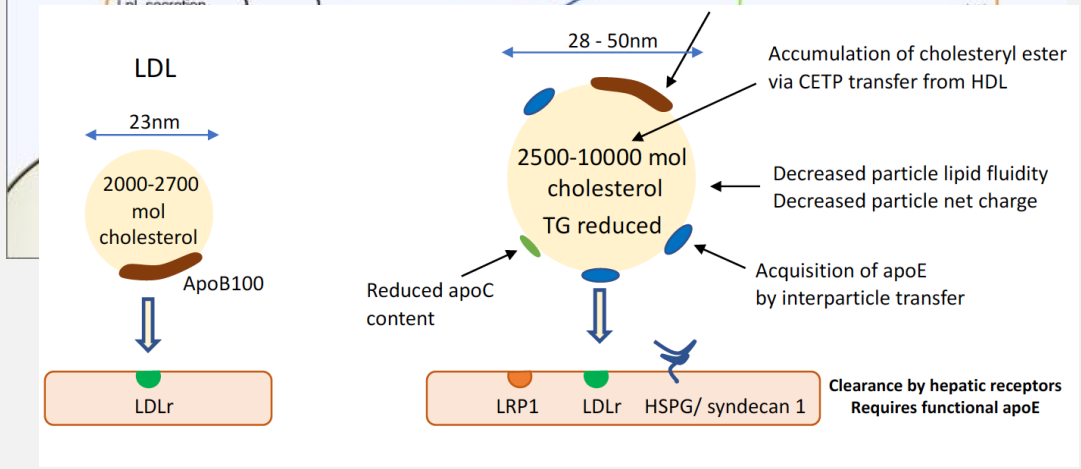
Triglyceride-remants /
Remnant cholesterol

Ginsberg H, et al. Consensus on HTG. *Eur Heart J 2021*

Why are Triglyceride-rich particles atherogenic?

Experimental evidence: direct uptake in the arterial wall





Yang, Int J Mol Sciences 2018; Hassing, BBA 2012;
Ginsberg, Eur H J 2022; Steender & Zilversmit, Atherosclerosis 1981

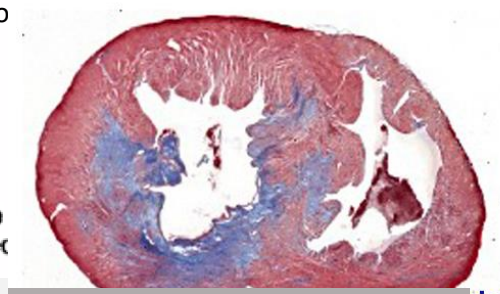
Table 1. Labeled Esterified Cholesterol in Plasma and Tissues after Injection of ^{14}C-Cholesterol-Labeled Chylomicrons and ^{3}H-Cholesterol-Labeled d < 1.019 Lipoproteins

Animal*	Duration (hr)	Mean plasma ^{14}C (% of d	^{3}H	Intima-media†		Liver†	
1	1.4	0.78					
2	1.8	0.61					
3	3.2	0.74					
4	3.3	0.64					
5	3.8	0.53					
6	4.3	0.42					
7	4.4	0.47					

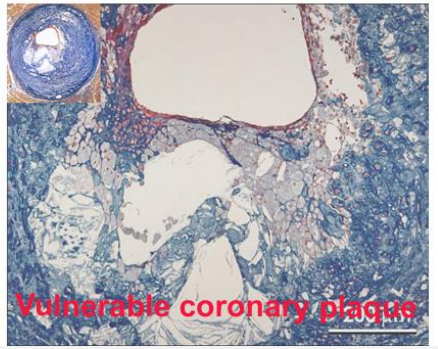
Anitschkow

Chylomicro

Figure 4. The
take of labelec



Atherosclerosis in rabbits



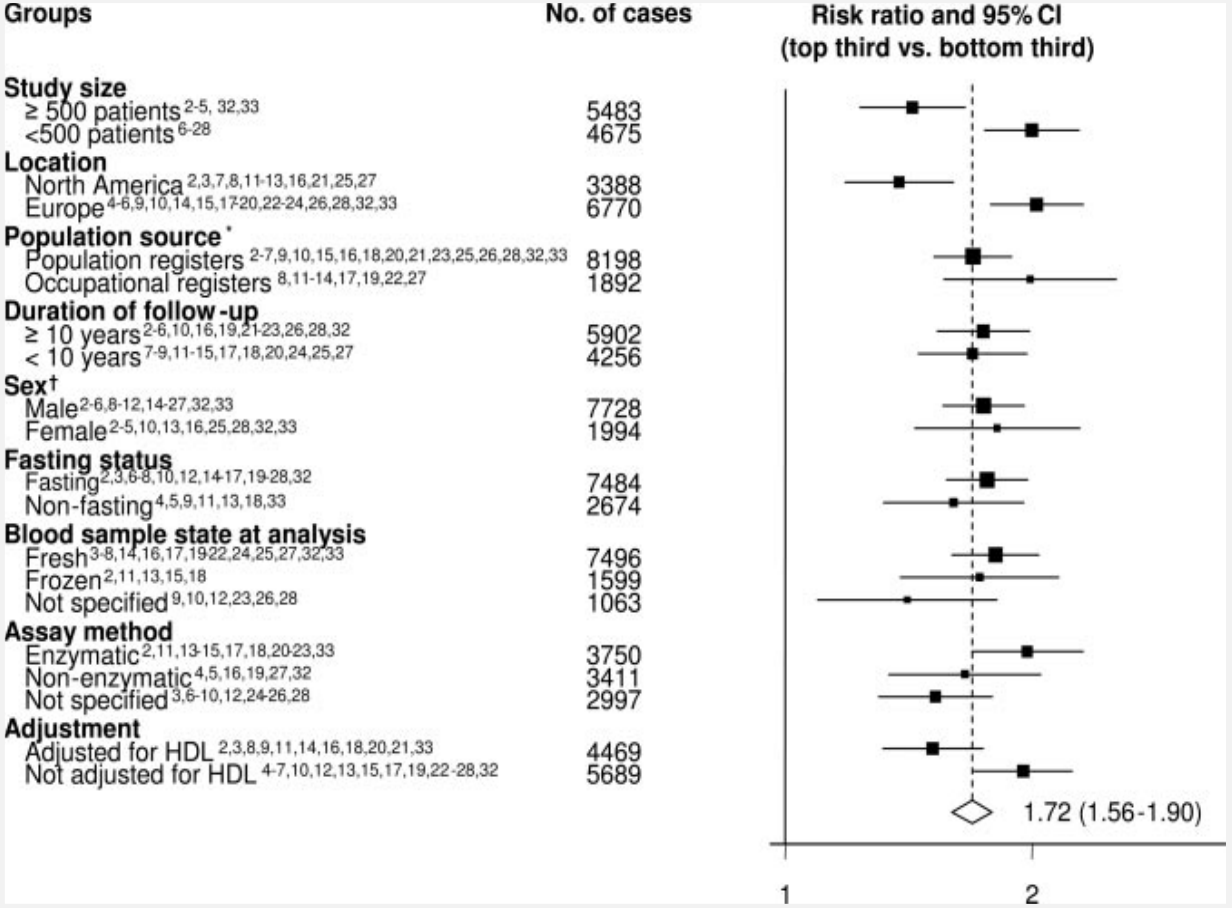
sion Vulnerable coronary plaque

Are Triglycerides associated with Atherogenesis?

Epidemiological evidence: TG associated with CV-risk

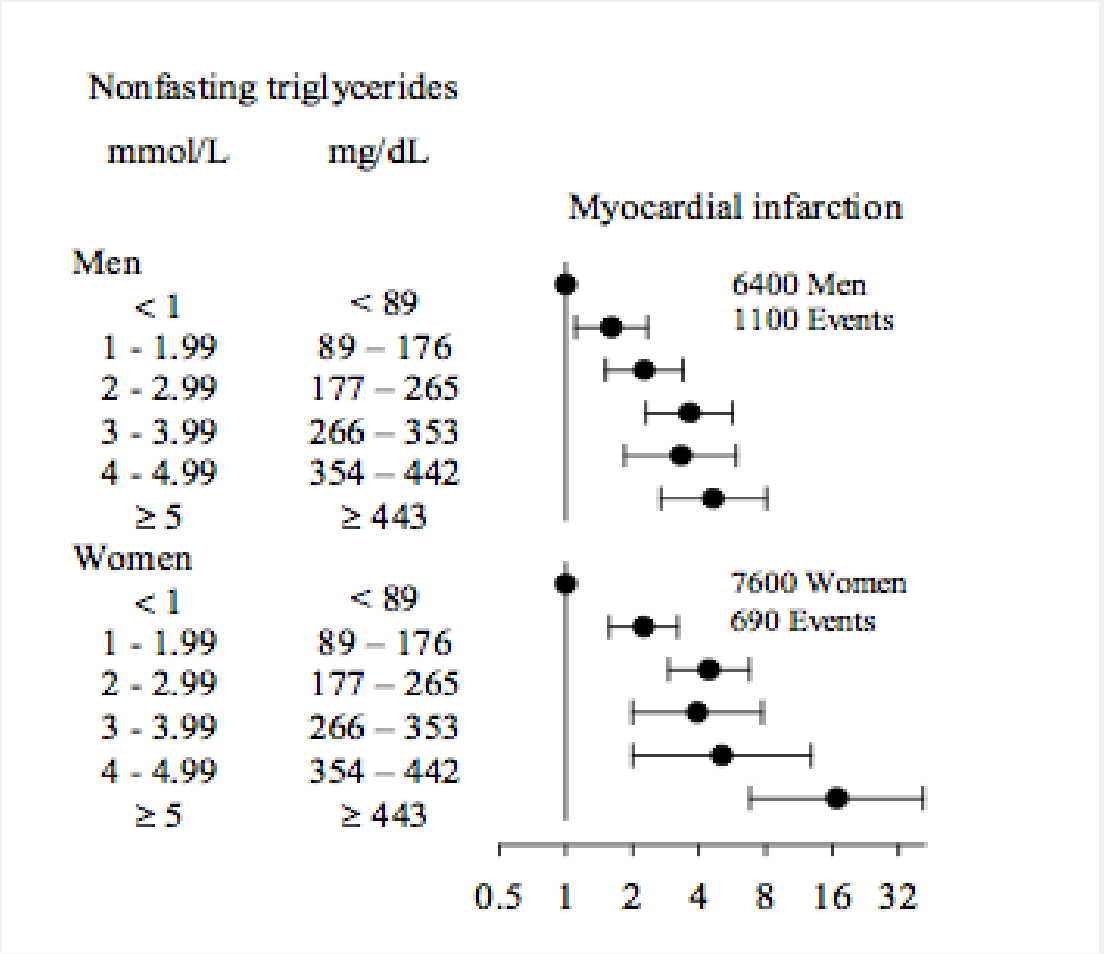
TGs association with CV-risk

10.158 Cases in 262.525 subjects



non-fasting TGs associate with CV-risk

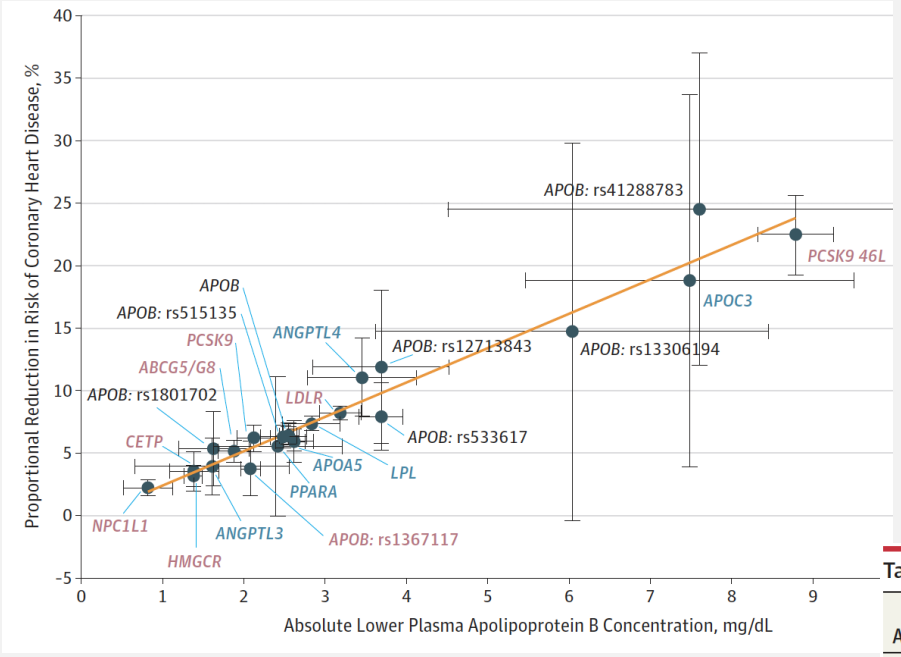
in both men and women



Sarwar. Circulation 2007; Nordestgaard B, Circ Res 2016 Kolovou etal Curr Vasc Rep 2011, 9:258-270

Are Triglycerides a 'causal' factor in Atherogenesis?

Mendelian Randomisation evidence: TRL-C (particle number) reduction 'beneficial'



Clinical benefit of LDL-C or TG/TRL-C lowering is proportional to the reduction in the number of atherogenic particles, i.e. apoB reduction

Table 3. Multivariable Mendelian Randomization Analysis of the Association Between Plasma Triglycerides, LDL-C, and ApoB With the Risk of CHD[a]

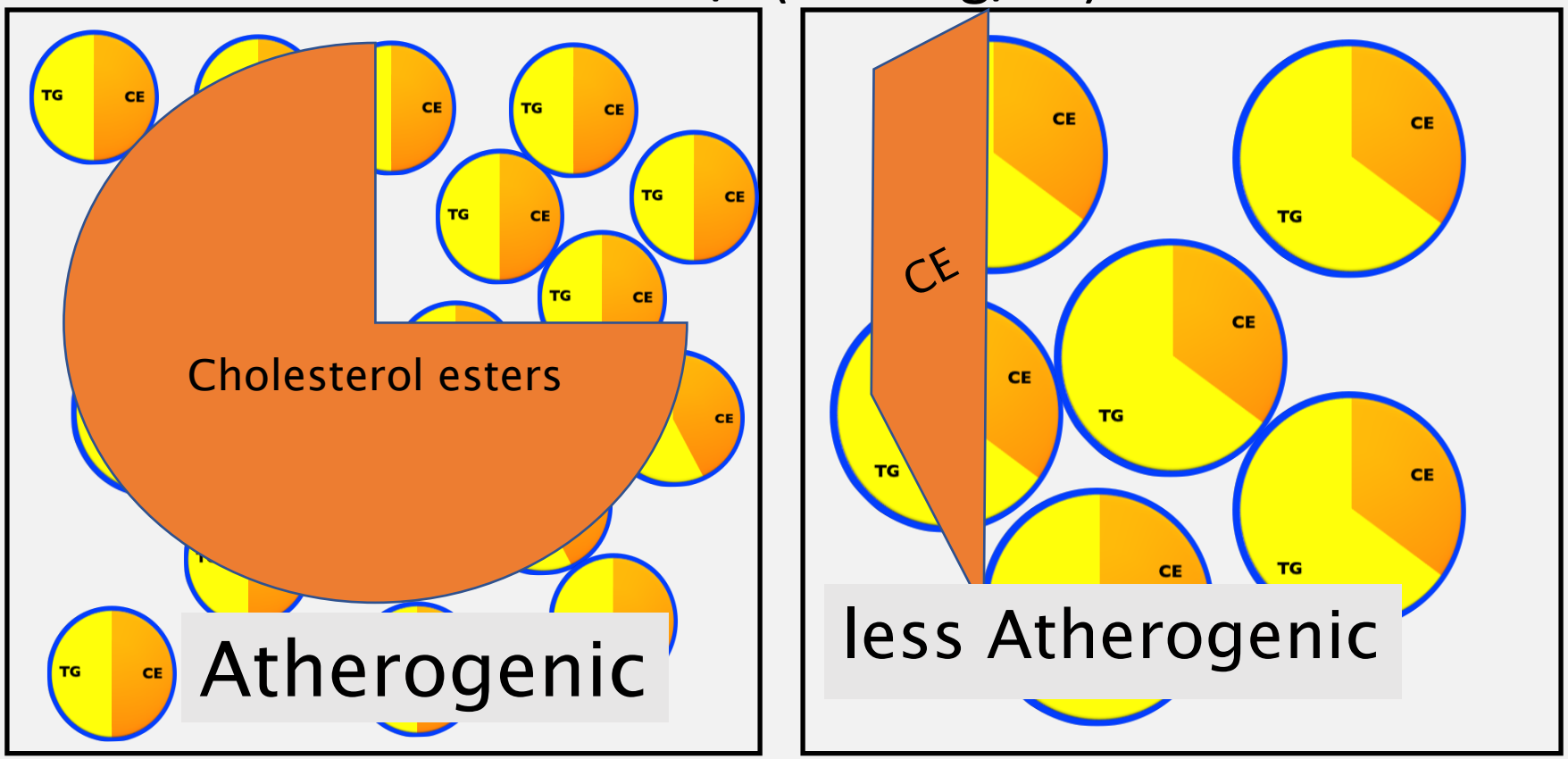
Analysis	Variables	Odds Ratio for CHD (95% CI)	*P* Value
Association of 10-mg/dL lower ApoB with risk of CHD	ApoB	0.770 (0.760-0.781)	1.42E-170
Association of 10-mg/dL lower LDL-C with risk of CHD	LDL-C	0.846 (0.833-0.858)	8.16E-77
Association of 50-mg/dL lower triglycerides with risk of CHD	Triglycerides	0.815 (0.785-0.846)	1.37E-18
Association of 10-mg/dL lower LDL-C and 50-mg/dL lower 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 10-mg/dL lower LDL-C, 50-mg/dL lower triglycerides, and 10-mg/dL lower 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)	.19
	Triglycerides	1.014 (0.965-1.065)	.19

Varbo, Circ 2013; Jorgenson, NEJM 2014; TG working group, NEJM 2014
Cardiogram consortium, NEJM 2016; Helgadottir, Nature genetics 2016
Dewey, NEJM 2016; Dewey, NEJM 2017; …..

Ference, JAMA 2019

But, what is high Triglycerides?
a mixed bag

TG 4.5 mmol/l (405 mg/dL)



High apo B 1350mg/l

Low apo B 870 mg/l

Triglyceride-rich particles ‘drive’ atherogenic risk

	Mg/dl	Mmol/l
TC	231	6.0
TG		3.84
HDL-C	37	0,97
Non-HDL-c	194	5.03
LDL-C	126	3.27
apoB	100	1,0 g/l

VLDL

	Mg/dl	Mmol/l
TC	308	8.0
TG	835	5.95
HDL-C		1,05
Non-HDL-c	268	6,95
LDL-C	nm	nm
apoB	140	1.4 g/l

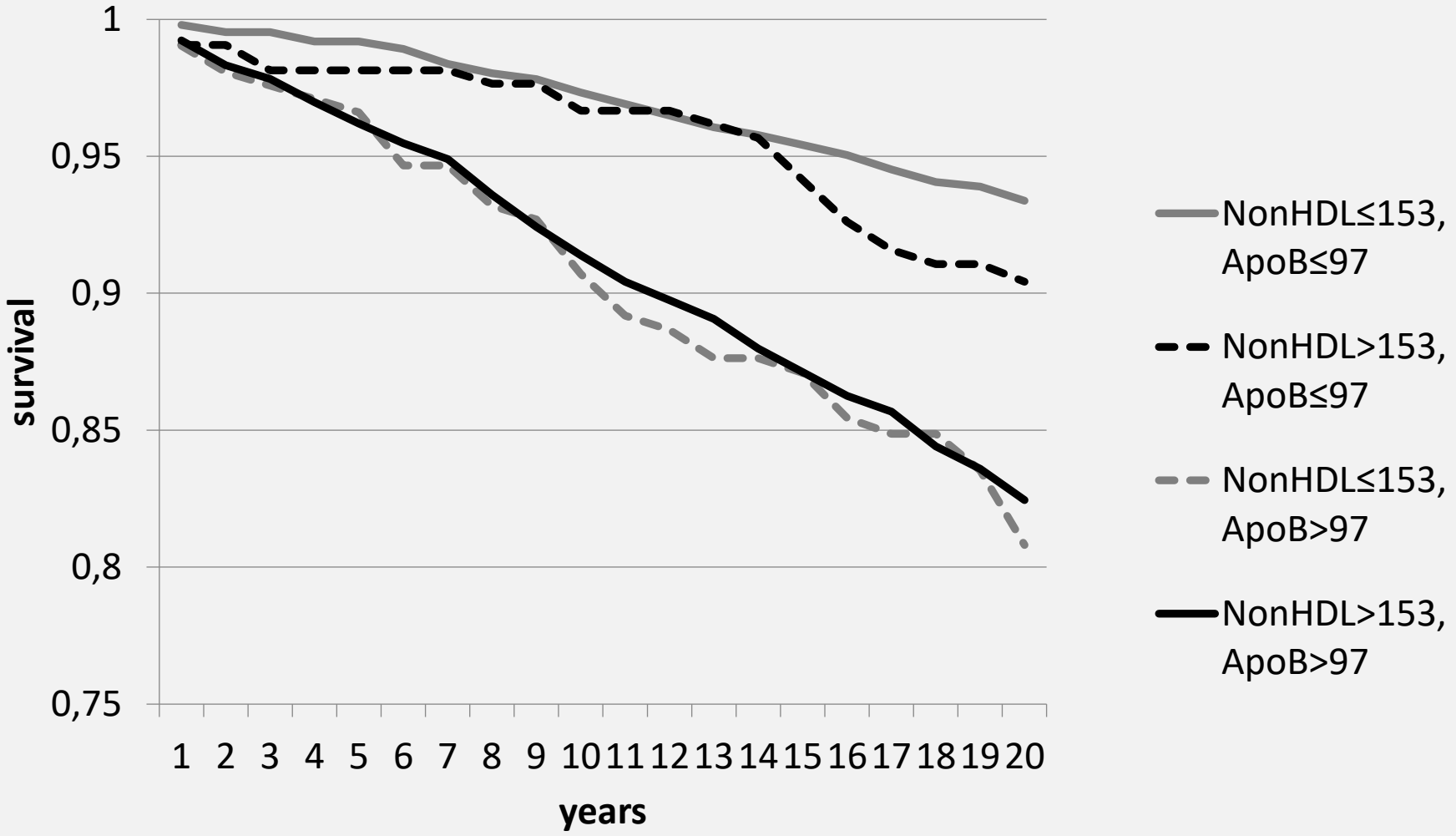
VLDL and LDL

	Mg/dl	Mmol/l
TC	316	8,2
TG	974	11,0
HDL-C		0.60
Non-HDL-c	29	6
LDL-C	nm	nm
apoB	100	1,0 g/l

VLDL + chylomicrons

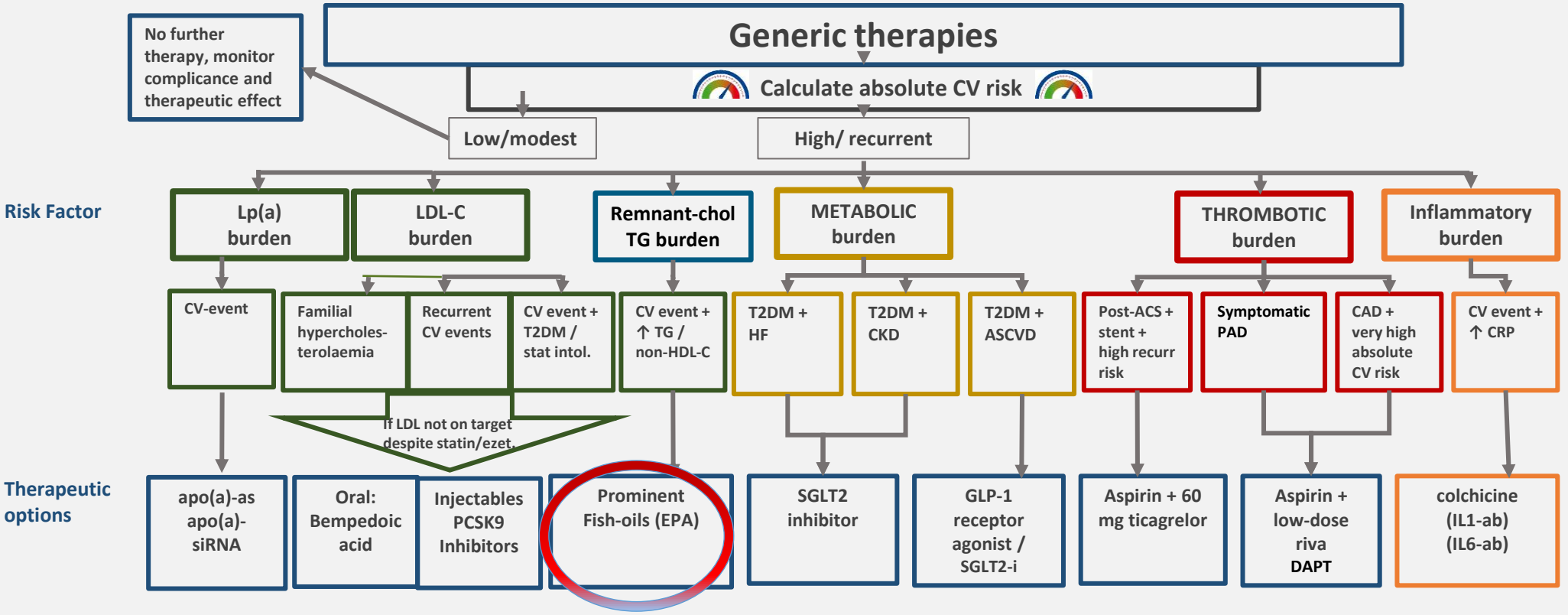
And we have known this for decades:
Only an increased 'number' of TRLs associate with risk

Framingham Heart Study



Schaeffer E, et al, J Lip Res 1994

Does ‘TG’-lowering reduce residual CV-risk?



Hoogeveen R, Neth J Med 2021

PROMINENT:

Pemafibrate in high-risk hypertriglyceridemic DM-II patients

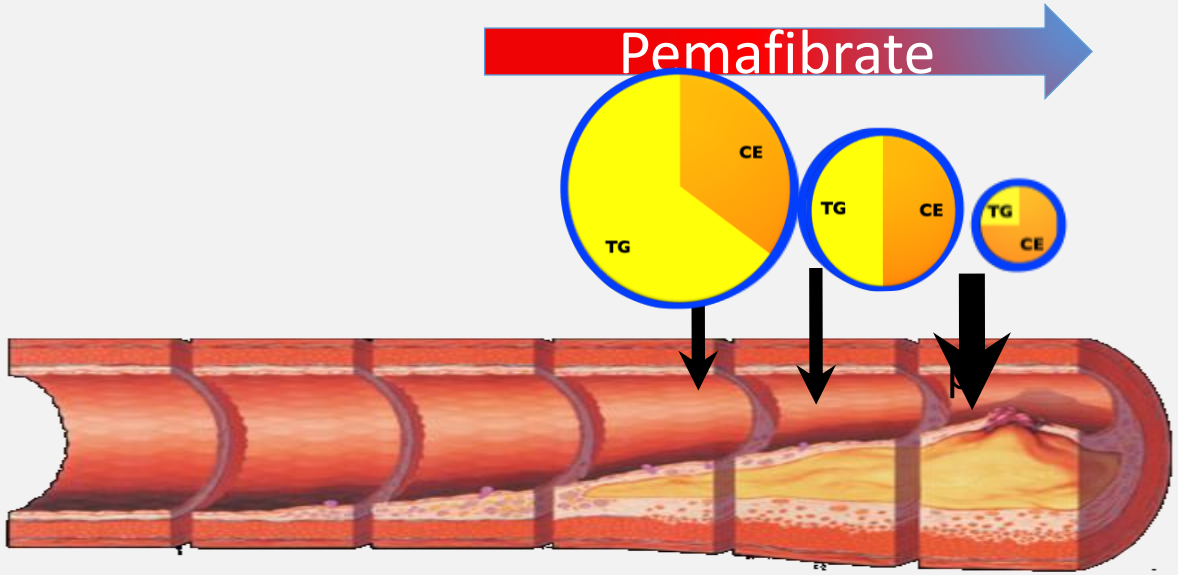
Variable	Pemafibrate (N=5240)	Placebo (N=5257)	Treatment Effect†
	Median Value (IQR)		Mean % Change (95% CI)
Triglyceride-related biomarkers			
Triglyceride level, measured			
Baseline — mg/dl	273 (227 to 342)		
4 Mo — mg/dl	189 (149 to 253)		
Median change from baseline — %	−31.1 (−48.9 to −9.6)	−6.9 (−28.4 to 20.2)	−26.2 (−28.4 to −24.10)
VLDL cholesterol level, calculated — mg/dl‡			
Baseline — mg/dl	49 (39 to 63)	49 (39 to 62)	
4 Mo — mg/dl	31 (23 to 42)	43 (32 to 59)	
Median change from baseline — %	−35.0 (−54.1 to −11.5)	−10.5 (−33.3 to 17.4)	−25.8 (−27.8 to −23.9)
Remnant cholesterol level, calculated§			
Baseline — mg/dl	47 (38 to 60)	47 (37 to 59)	
4 Mo — mg/dl	32 (24 to 42)	39 (29 to 52)	
Median change from baseline — %	−31.3 (−49.1 to −8.2)	−15.6 (−36.8 to 10.8)	−18.2 (−20.3 to −16.1)
Remnant cholesterol level, measured			
Baseline — mg/dl	56 (43 to 73)		
4 Mo — mg/dl	30 (23 to 41)		
Median change from baseline — %	−43.6 (−57.8 to −24.1)		
Apolipoprotein C-III level, measured			
Baseline — mg/dl	15 (13 to 19)	15 (13 to 18)	
4 Mo — mg/dl	11 (9 to 14)	15 (12 to 19)	
Median change from baseline — %	−27.8 (−43.8 to −9.1)	0.0 (−18.8 to 18.8)	−27.6 (−29.1 to −26.1)
Other lipid biomarkers			
Total cholesterol level, measured			
Baseline — mg/dl	161 (139 to 193)	161 (137 to 191)	
4 mo — mg/dl	162 (138 to 190)	158 (134 to 190)	
Median change from baseline — %	−0.5 (−12.2 to 13.2)	−1.2 (−12.1 to 11.0)	0.8 (−0.1 to 1.6)
HDL cholesterol level, measured			
Baseline — mg/dl	33 (29 to 37)	33 (29 to 37)	
4 Mo — mg/dl	36 (30 to 42)	34 (30 to 39)	
Median change from baseline — %	8.3 (−5.3 to 25.0)	3.1 (−7.4 to 15.6)	5.1 (4.2 to 6.1)
LDL cholesterol level, measured			
Baseline — mg/dl	79 (60 to 104)		
4 Mo — mg/dl	91 (71 to 115)		
Median change from baseline — %	14.0 (−6.3 to 41.4)	2.9 (−13.5 to 24.6)	12.5 (10.7 to 14.0)
Apolipoprotein B level, measured			
Baseline — mg/dl	90 (75 to 108)		
4 Mo — mg/dl	93 (77 to 111)		
Median change from baseline — %	3.2 (−12.0 to 19.7)	−1.6 (−15.4 to 11.8)	4.8 (3.8 to 5.8)

84 mg/dl TG decrease

26 mg/dl RC decrease

12 mg/dl LDL-C increase

3 mg/dl apoB increase



Das-Pradhan N Engl J Med 2022;

Fibrates: Enhancing TG-metabolism?

TG lowering in absence of TRL-reduction not beneficial

Effect Pemafibrate	%change compared to placebo	Abs. difference Vs placebo
TG change	-26.2 %	- 69 mg/dl
Remnant chol	-25.6 %	- 12 mg/dl
LDLc	+12.3 %	+ 10 mg/dl
apoB	+ 4.8 %	+ 5 mg/dl

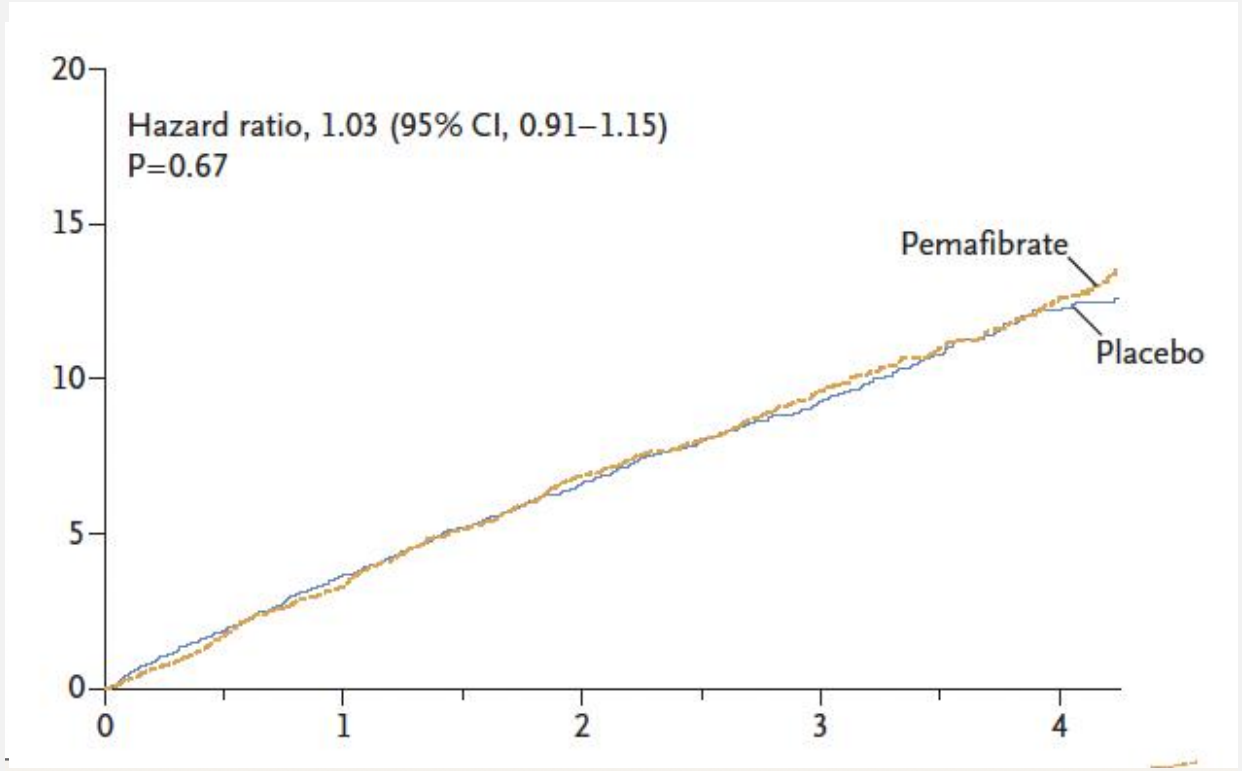


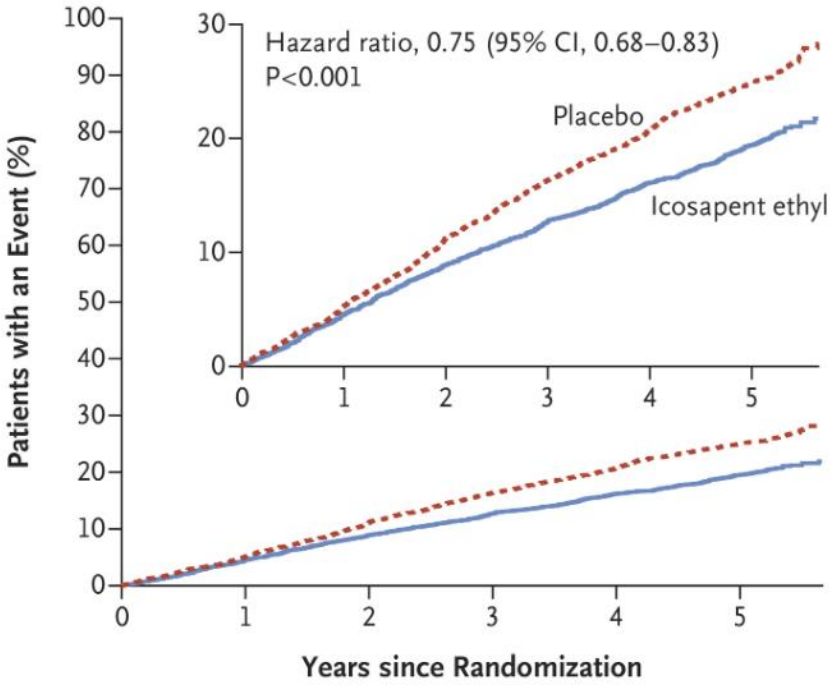
Figure 1. Cumulative Incidence of Cardiovascular Events.
Shown are Kaplan–Meier event curves for the primary trial end point of myocardial infarction, ischemic stroke, coronary revascularization, or death from cardiovascular causes. The inset shows the same data on an expanded y axis.

Fibrate does not 'remove' Triglyceride-rich particles
It shifts atherogenic particles towards other atherogenic particles

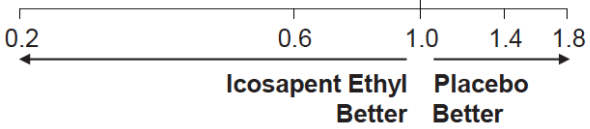
Das-Pradhan N Engl J Med 2022; Ginsberg H, Eur Heart J 2021

REDUCE-IT: Icosapent-ethyl in hyperTG-patients

Benefit 'independent' of TG-effect?



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

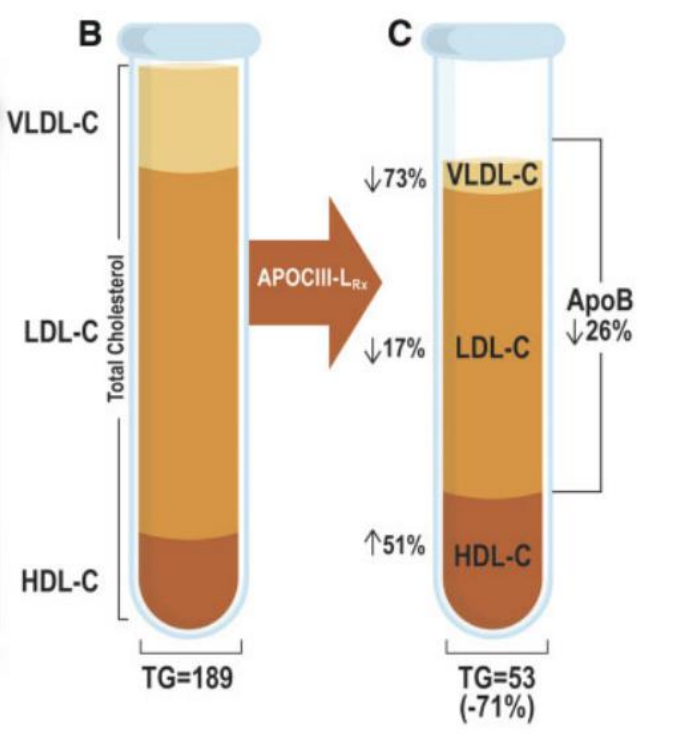
TG-reduction: 39 mg/dl *(pemafibrate: -84mg/dl)*

Icosapent ethyl is not a TG-lowering drug,
Mechanism of benefit? Prof G Steg

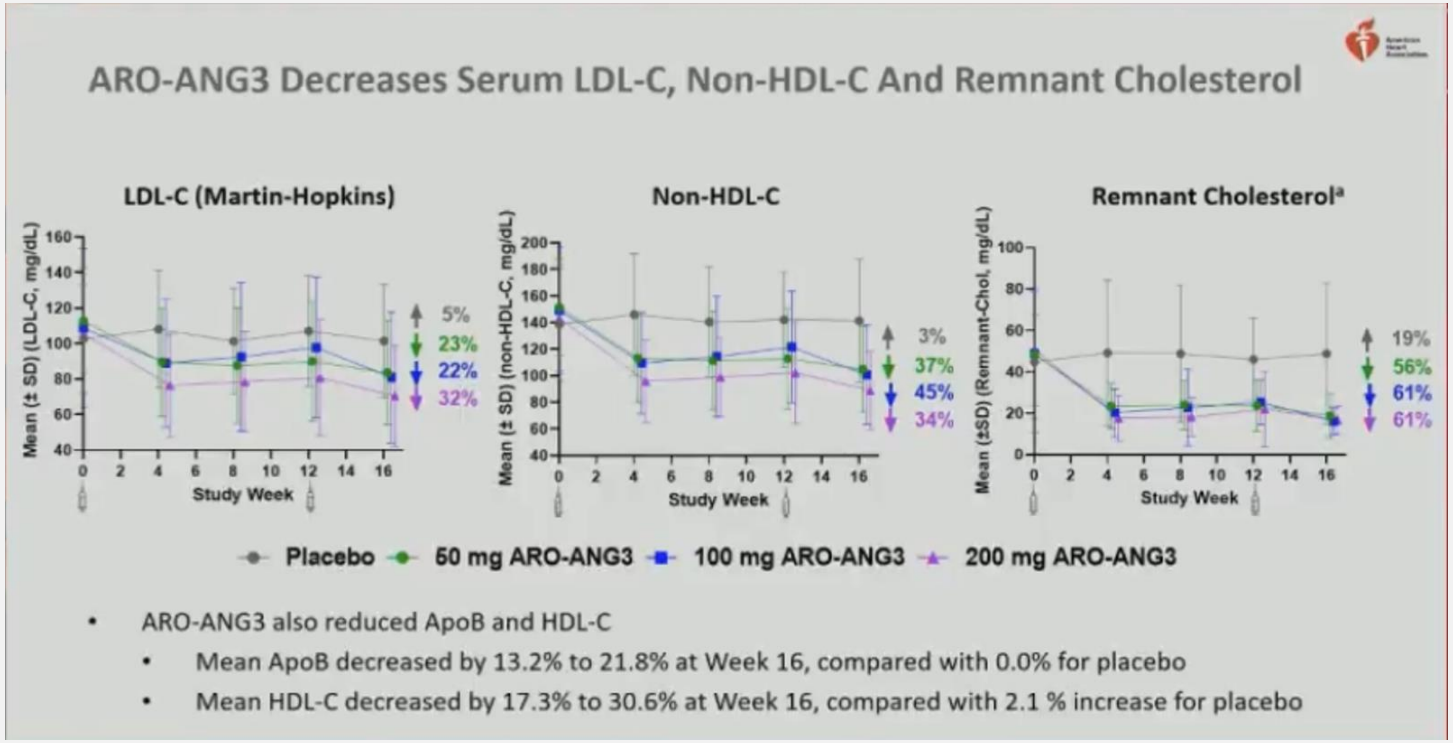
Bhatt, N Engl J Med 2019

Benefit of TLR-lowering on CVD needs to be tested
using TRL-lowering therapies

apoCIII antisense therapy



ANGPTL3 siRNA therapy



Alexander V, Eur Heart J 2019 Rosenson, AHA 2022

Summary: Challenges in Atherosclerotic Cardiovascular Disease reduction and Triglyceride-related risk

- **TG reduction should not be used as target** for CVD-reduction
- **Triglyceride-rich lipoprotein** (**TRL**) **reduction**, i.e. reduction apoB + TG, **best surrogate** for CVD-reduction
- **Beta-lipoprotein reduction, comprising LDLc + TRL-C, is best target**