S.I.Te.C.S.

SOCIETÀ ITALIANA DI TERAPIA CLINICA E SPERIMENTALE

DYSLIPIDAEMIAS: PRESENT AND FUTURE APPROACHES TO PHARMACOLOGICAL INTERVENTION

November 9th-10th, Sorrento (NA) - Italy

Early intervention for future benefit

Prof. Matteo Pirro

Dipartimento di Medicina

Università degli Studi di Perugia, ITALIA

Il sottoscritto **Matteo Pirro**

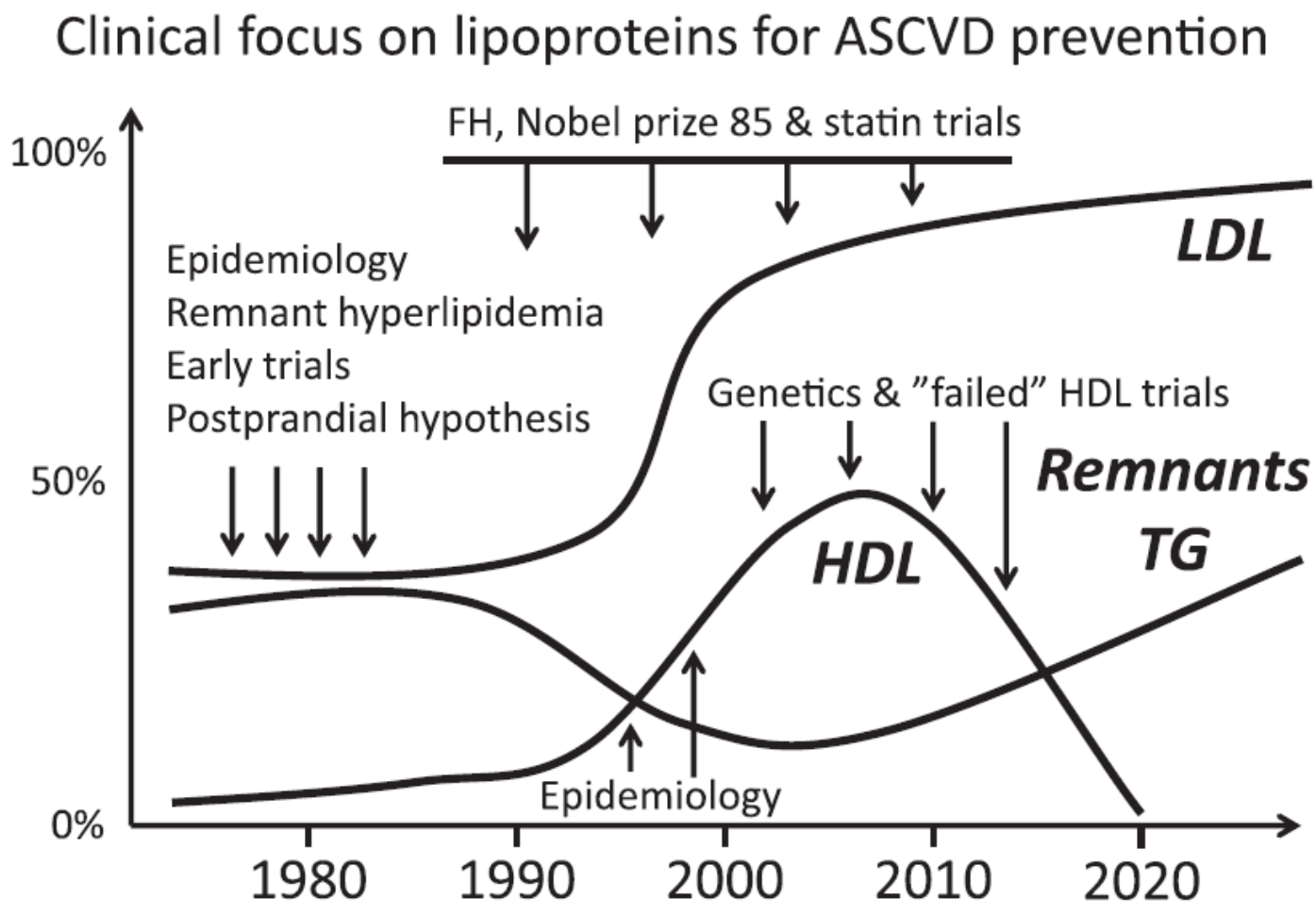
ai sensi dell’art. 76 comma 4 dell’Accordo Stato-Regioni del 2 febbraio 2017

dichiara

l’esistenza negli ultimi due anni di rapporti di natura finanziaria e lavorativa con le seguenti imprese commerciali operanti in ambito sanitario

• Amgen, AlfaSigma, Bayer, Mediolanum, Mylan, Sanofi, Servier

Cholesterol, particularly LDL-C, still attracts the attention of CVD preventive doctors



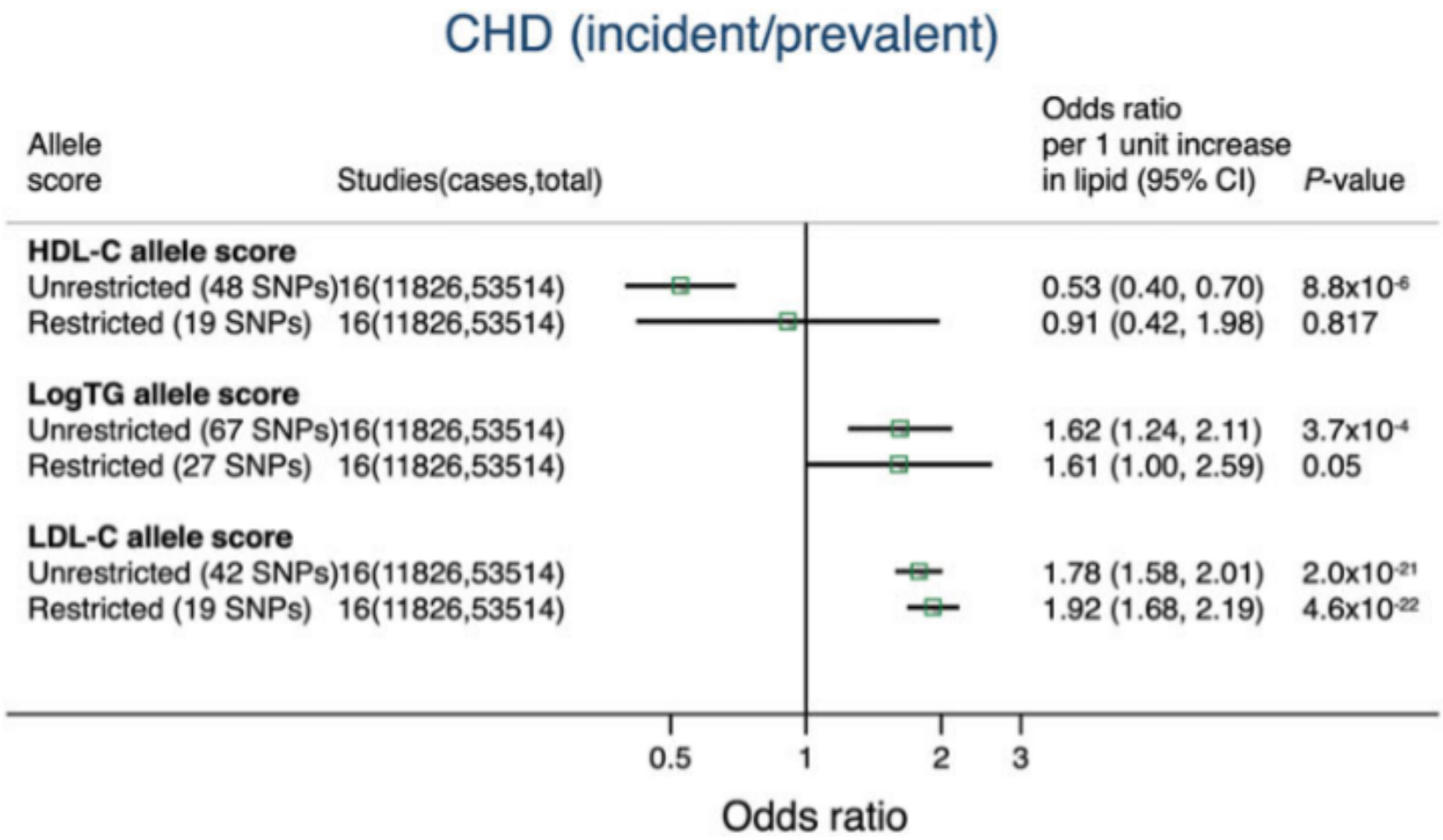
Nordestgaard BG. Circ Res. 2016 Feb 19;118(4):547-63.

Agenda

- Cholesterol: why is it still an attracting topic ?
- Which factors increases the deleterious impact of cholesterol on CVD risk
- Early intervention for greater benefit

…because research on this topic is stil HOT ?

Mendelian randomization meta-analyses were conducted in 17 studies including 62,199 participants and 12,099 CHD events



Holmes MV, Eur Heart J. 2015 Mar 1;36(9):539-50.

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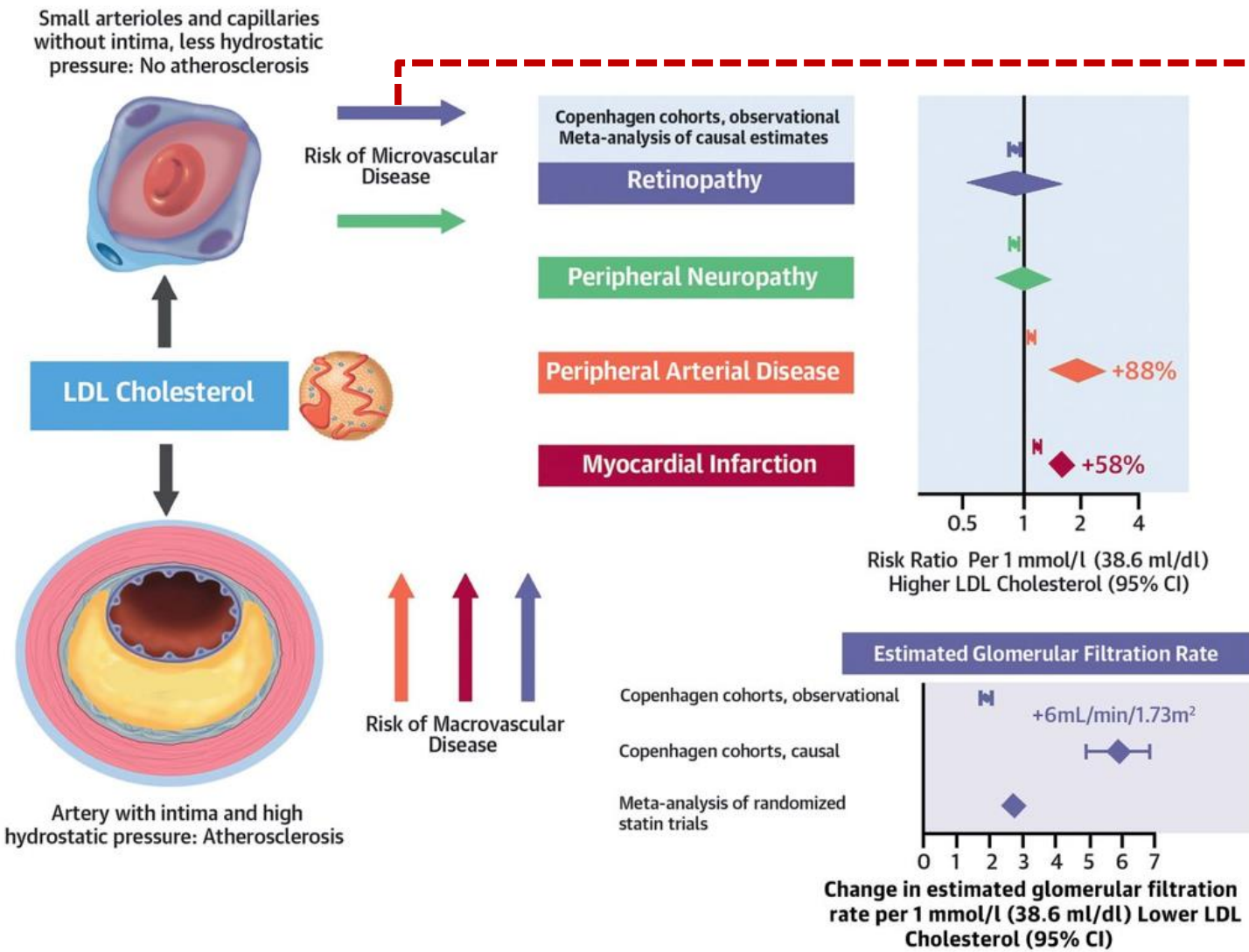


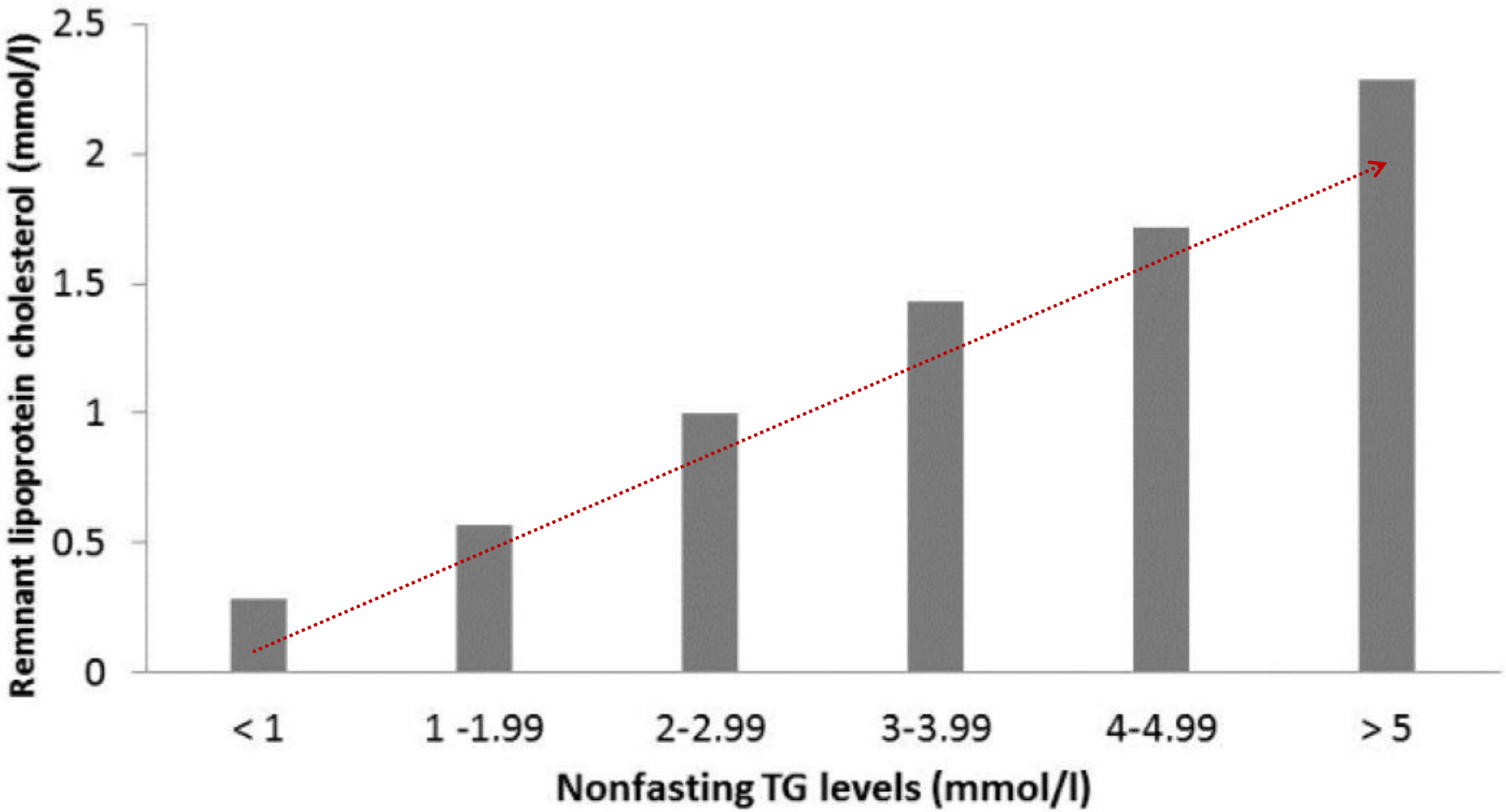
1 mmol/l ↑ LDL-C

HR-CKD 3.83
(95% CI: 2.00 to 7.34)

HR-PAD 2.09
(95% CI: 1.30 to 2.38)

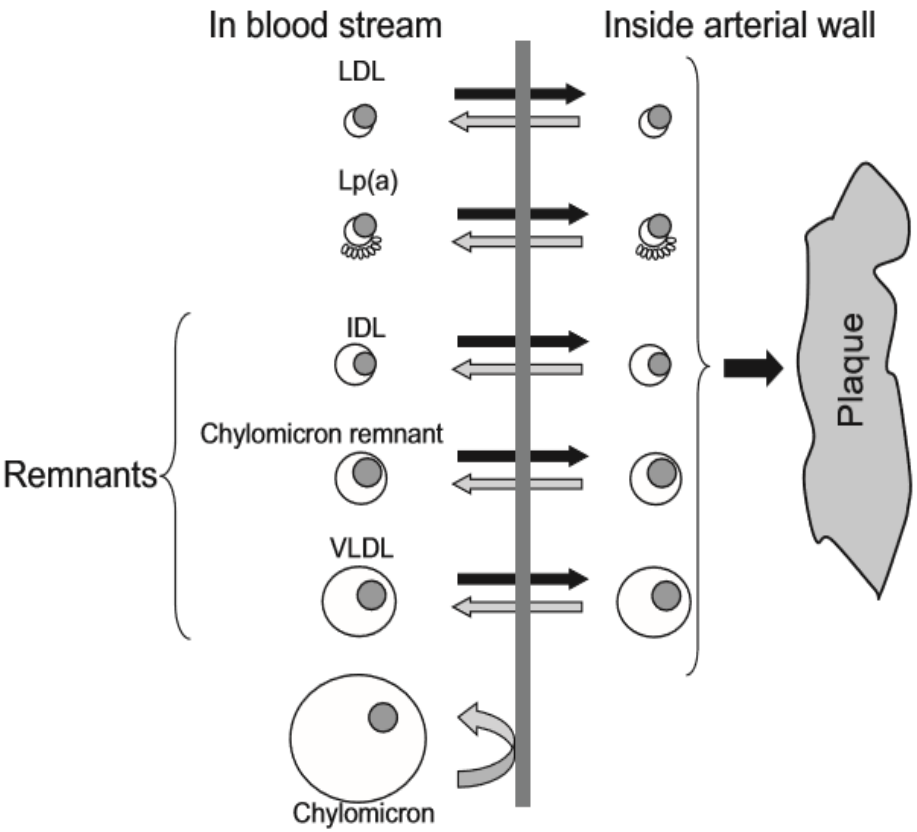
Adapted from: Emanuelsson F, J Am Coll Cardiol. 2019;74(11):1465-76.

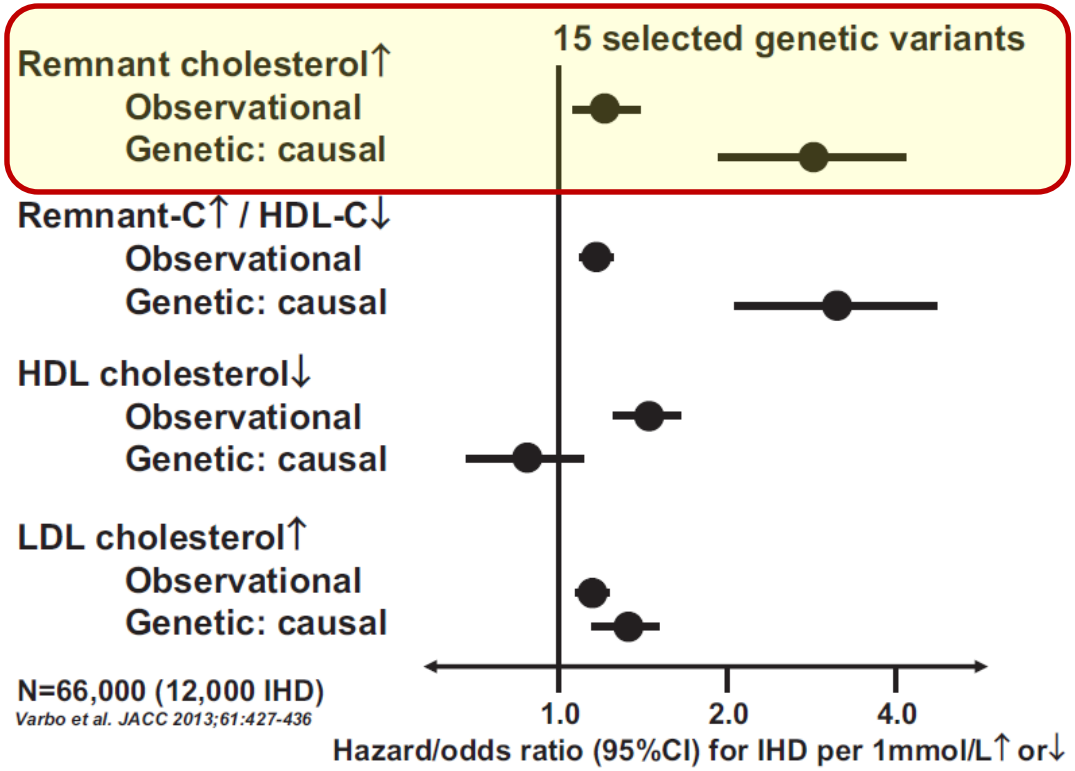
The “bad cholesterol” is not only contained in LDLs



Catapano AL. European Heart Journal (2016) 37, 2999–3058

Remnant cholesterol and CVD risk: results from Mendelian randomization analysis and more…





Varbo A, et al. Arterioscler Thromb Vasc Biol. 2016;36:2133-2135.

Nordestgaard BG. Circ Res. 2016 Feb 19;118(4):547-63.

There is the causal role for cholesterol (contained in different lipoproteins) in the pathophysiology of ATS-mediated CVD

Agenda

- Cholesterol: why is it still an attracting topic ?
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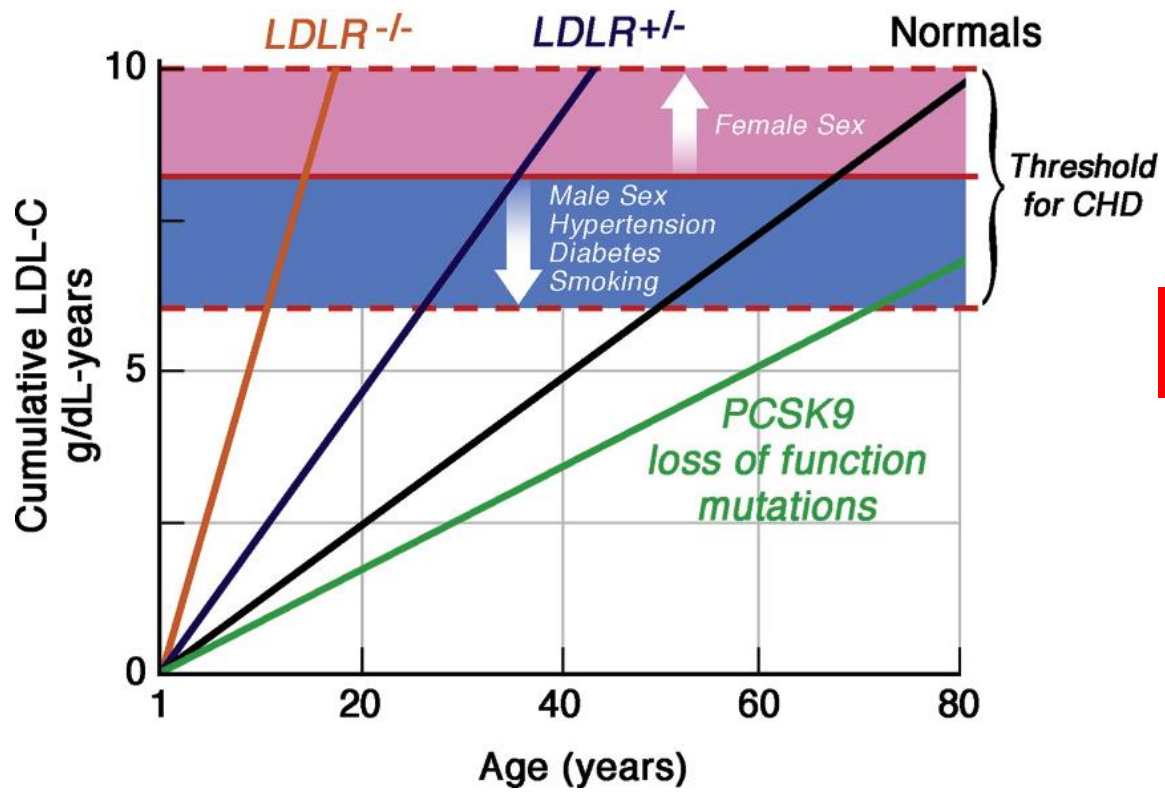
- Early intervention for greater benefit

The association between cholesterol and CVD risk is related to…

Genetics

Quantity



Interactions

Duration of exposure

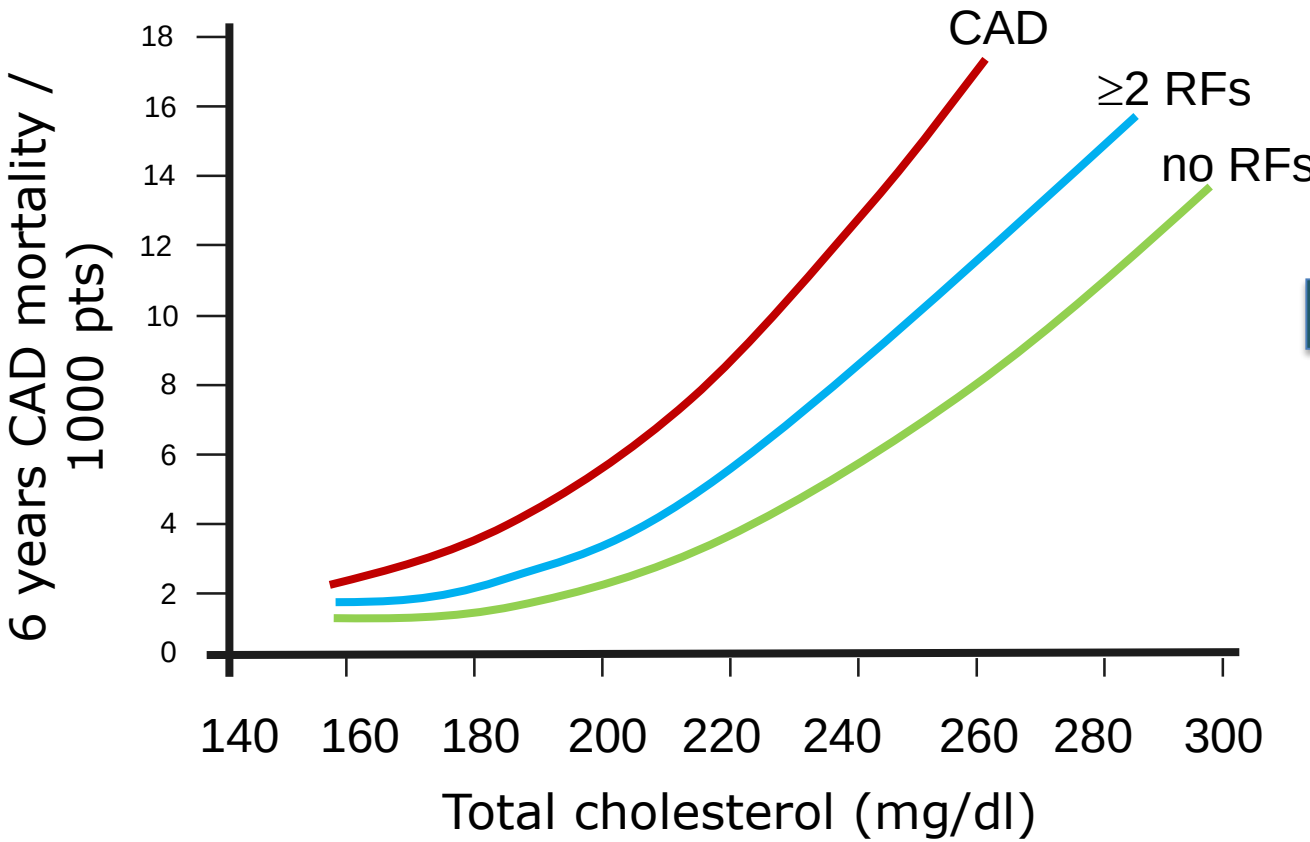
Adapted from: Sniderman AD et al. J Am Coll Cardiol. 2014;63(19):1935-1947.

Factors increasing the deleterious impact of cholesterol on CVD risk

QUANTITY

CAD mortality increases with plasma TC levels in subjects at different CV risk

*For 6-12-25 years, 350,977 men aged 35 to 57 years who had been screened for the **Multiple Risk Factor Intervention Trial** were followed up*

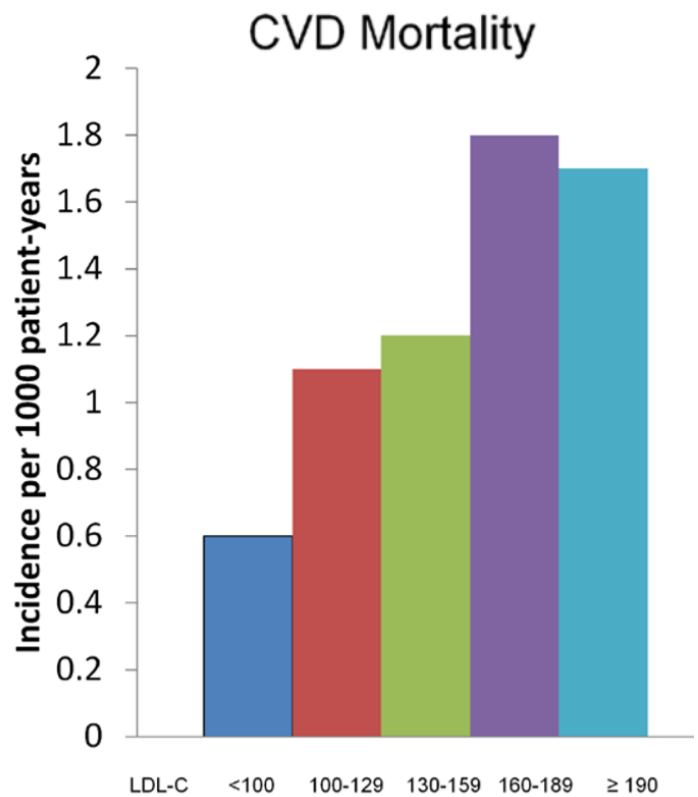


This relationship persisted over the 12/25-year follow-up period

Neaton JD et al. Arch Intern Med. 1992 Jul;152(7):1490-500

Long-term association of LDL-C with CVD mortality in individuals at low 10-y CVD risk

36,375 **Individuals at Low 10-Year Risk** of Atherosclerotic Cardiovascular Disease. Results From the Cooper Center Longitudinal Study



27-y follow-up

Abdullah SM, et al. Circulation. 2018 Nov 20;138(21):2315-2325.

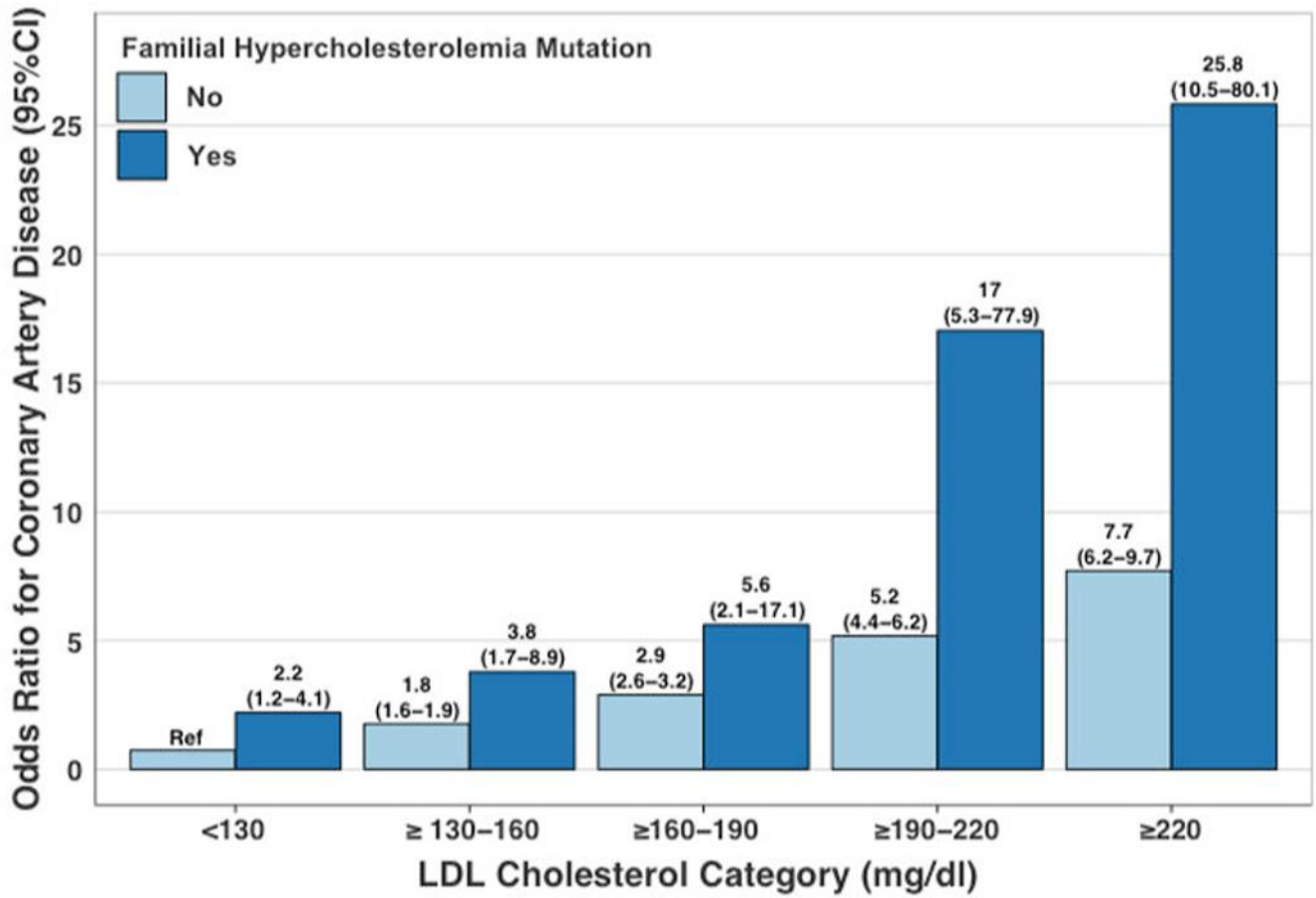
The association between plasma LDL-C levels and CVD risk is strictly correlated with the absolute (single) LDL-C concentration at a definite timepoint

Factors increasing the deleterious impact of cholesterol on CVD risk

GENETICS

For a definite LDL-C range of values, patients carrying FH mutations are at higher CAD risk than those without

26,025 participants from 7 case-control studies and 5 prospective cohort studies



Khera AV, et al. J Am Coll Cardiol. 2016 Jun 7;67(22):2578-89.

Lifelong LDL cholesterol elevations in FH mutation carriers may confer CVD risk beyond that captured by a single LDL cholesterol measurement

Factors increasing the deleterious impact of cholesterol on CVD risk

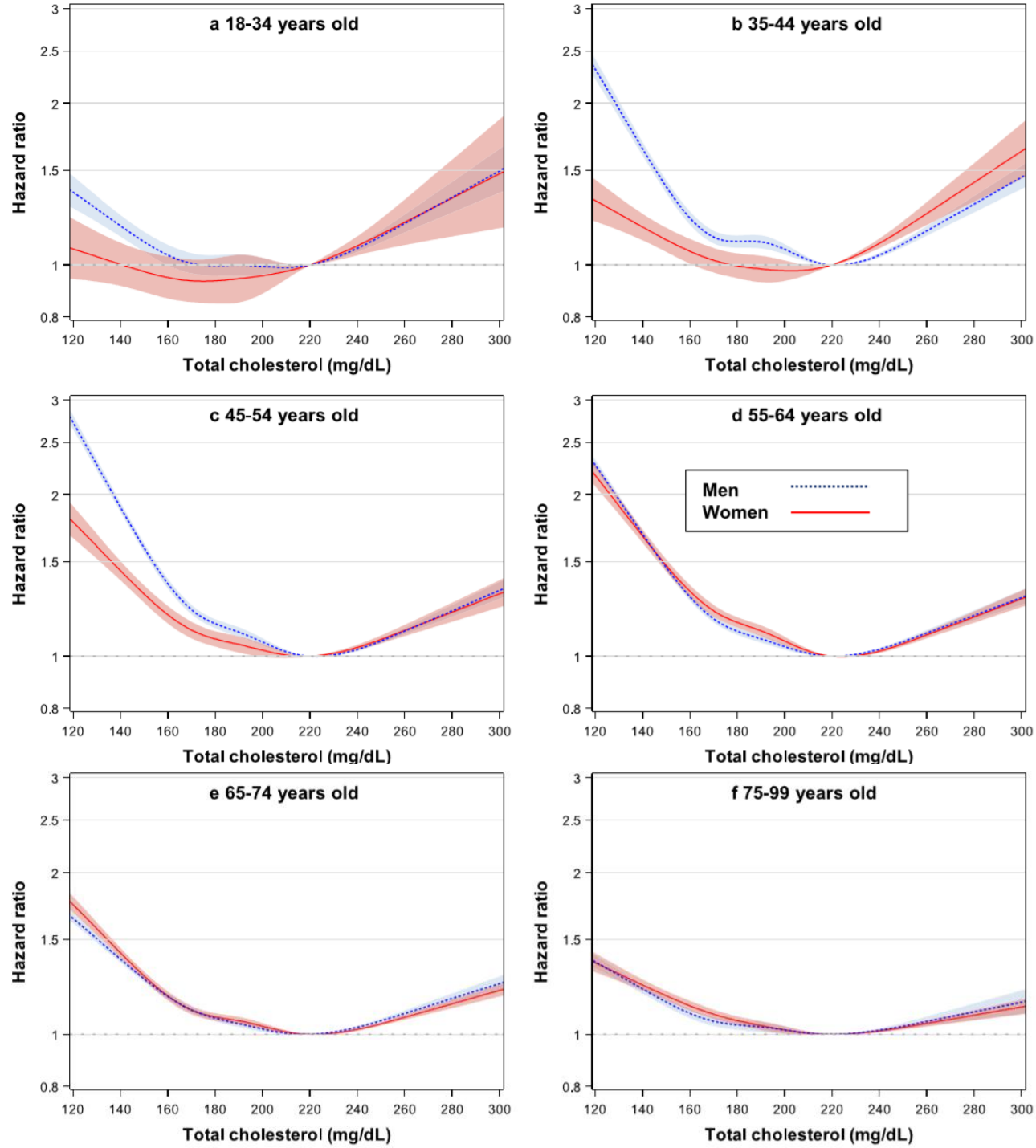
TIME OF APPEARANCE
DURATION OF EXPOSURE

Total cholesterol and risk of all cause mortality in relation to age

12,815,006 Korean adults. During 10 y follow-up 694,423 individuals died

1 mmol/L TC increase

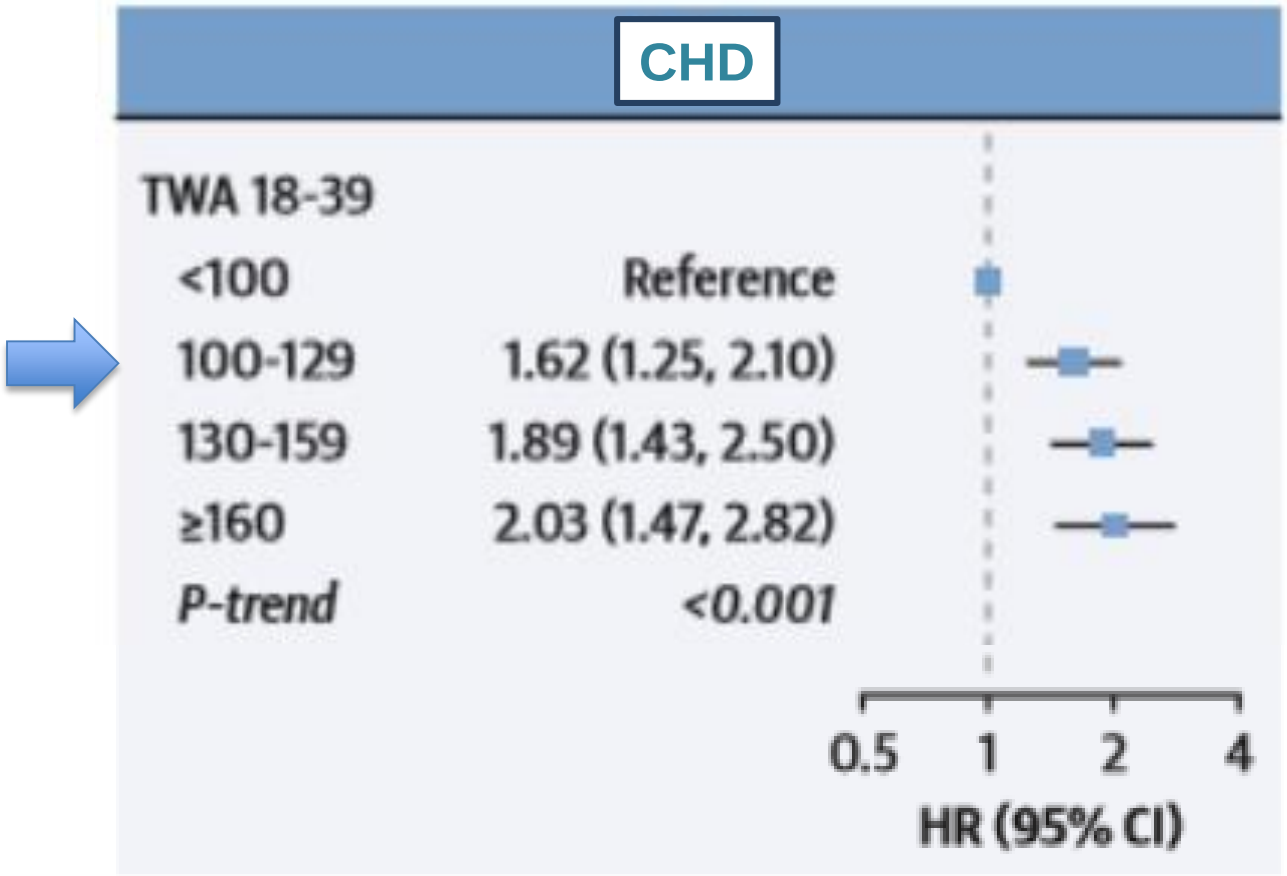
	p-value	HR	(95% CI)	
18-34	<0.001	**1.14**	**(1.10-1.19)**	$P_{interaction}$
35-44	<0.001	**1.13**	**(1.11-1.15)**	<0.001
45-54	<0.001	**1.08**	**(1.06-1.09)**	
55-64	<0.001	**1.07**	**(1.06-1.08)**	
65-74	<0.001	**1.06**	**(1.05-1.07)**	
75-99	<0.001	**1.03**	**(1.02-1.04)**	
All ages	<0.001	**1.07**	**(1.06-1.07)**	



Yi SW, et al. Sci Rep. 2019 Feb 7;9(1):1596.

The association between LDL-C and CHD risk in individuals aged less than 40-y

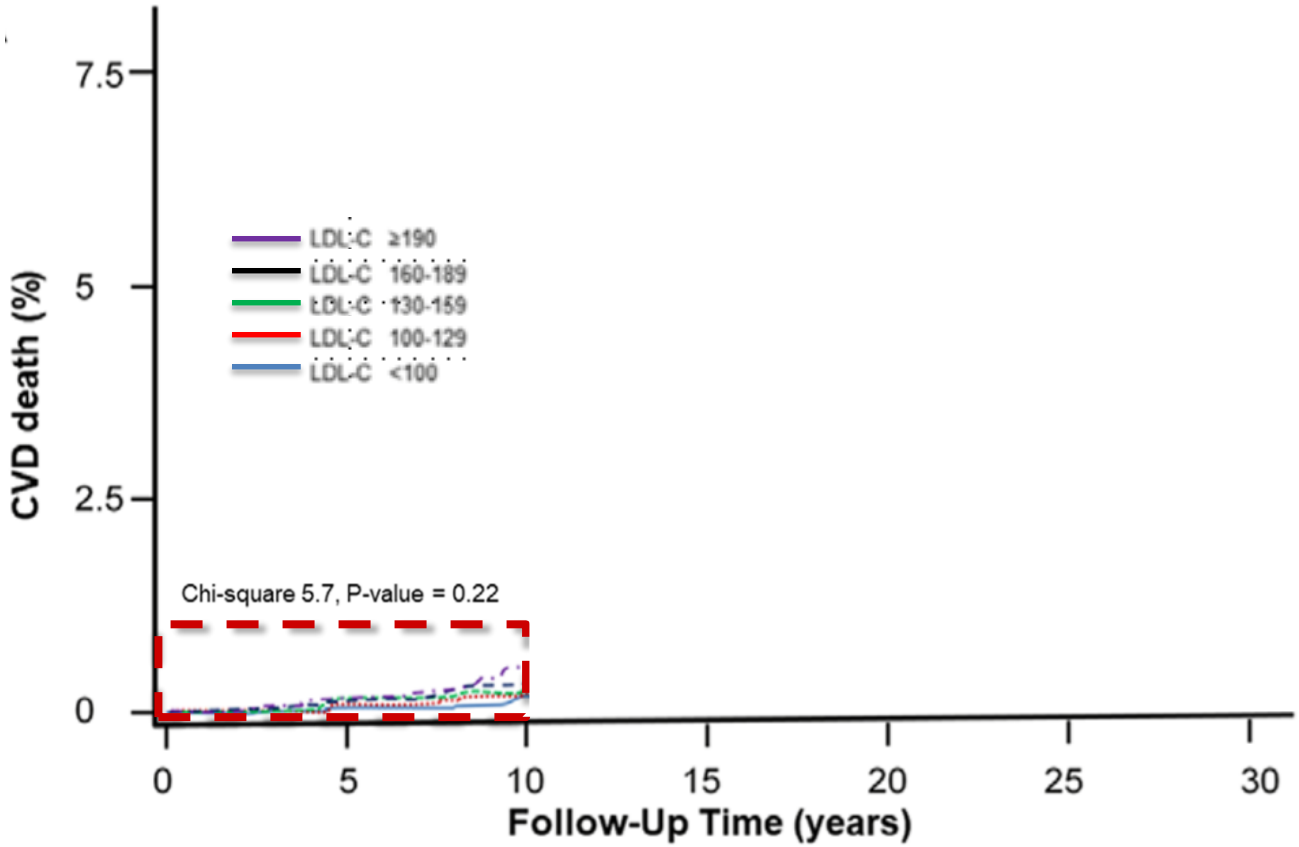
6 U.S. cohorts: a total of 36,030 participants were included. During a median follow-up of 17 years, there were 4,570 CHD, and 2,862 stroke events



Zhang Y, et al. J Am Coll Cardiol. 2019 Jul 23;74(3):330-341.

In low-risk individuals with a median age of 42-y, 10-y follow-up is not sufficient to discriminate the negative prognostic value of high LDL-C levels

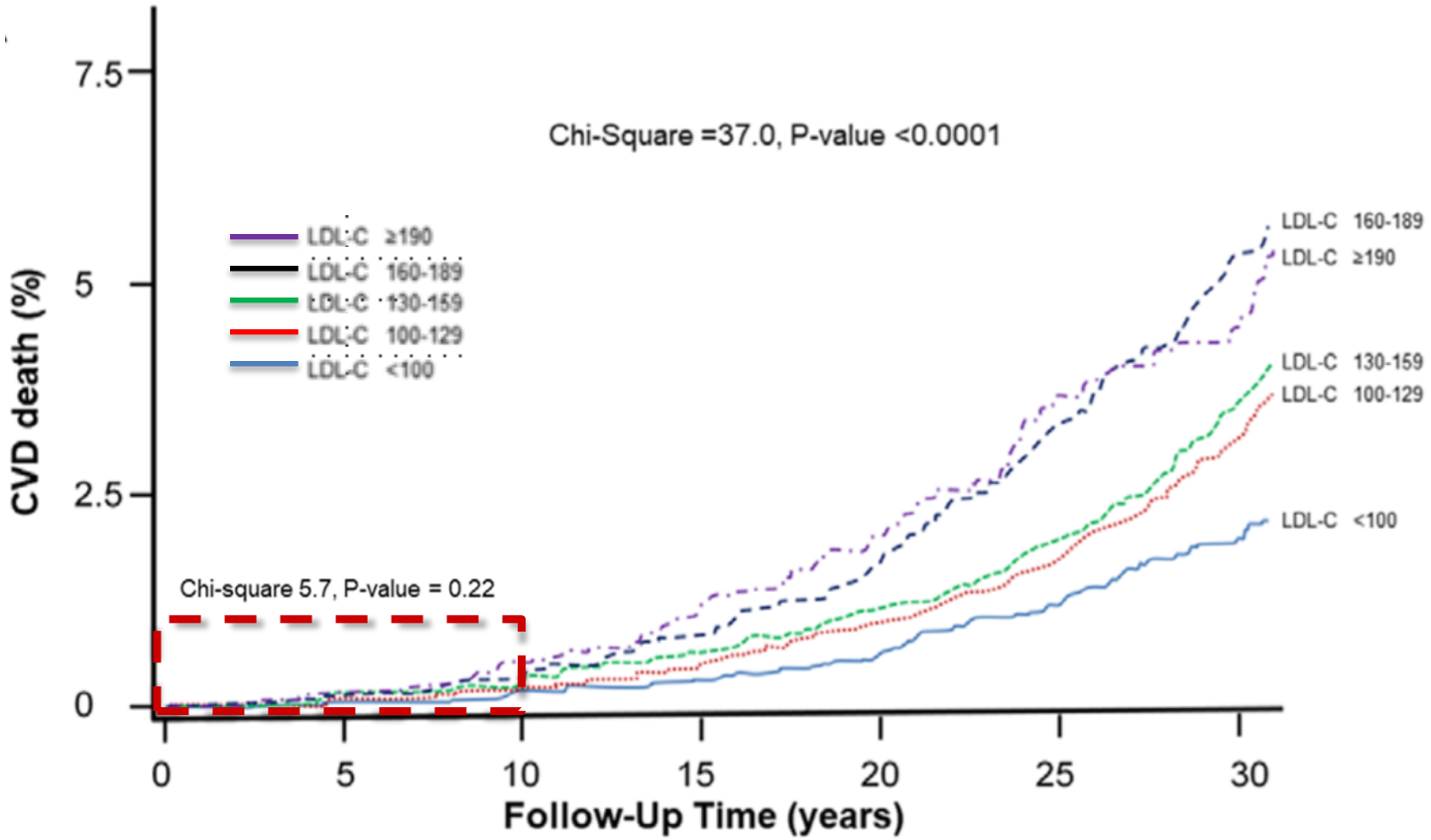
Long-Term Association of LDL-C With Cardiovascular Mortality in 36,375 Individuals (median age 42-y) at Low 10-Year Risk of Atherosclerotic Cardiovascular Disease. Results From the Cooper Center Longitudinal Study



Abdullah SM, et al. Circulation. 2018 Nov 20;138(21):2315-2325.

A longer follow-up is necessary to discriminate the negative prognostic value of elevated LDL-C levels in low-risk individuals

Long-Term Association of LDL-C With Cardiovascular Mortality in 36,375 Individuals (median age 42-y) at Low 10-Year Risk of Atherosclerotic Cardiovascular Disease. Results From the Cooper Center Longitudinal Study



Abdullah SM, et al. Circulation. 2018 Nov 20;138(21):2315-2325.

Even mild LDL cholesterol elevations at a young age may have a greater unfavorable prognostic impact than in older individuals

10-y CVD risk scores have not sufficient sensibility to detect long-term CV risk in younger individuals

The use of systems highlighting the long-term CV risk in younger individuals is desirable

Additional tools for CVD risk estimation in younger individuals

Relative risk →

CV risk age →

ESC/EAS

Lifetime CV risk → **ACC/AHA**

Factors increasing the deleterious impact of cholesterol on CVD risk

TIME-RELATED VARIATION OF EXPOSURE

Cholesterol levels changes have a strong impact on CVD incidence at a young age

A total of 2,682,045 young adults (aged 20–39 years) who had undergone 2 consecutive national health check-ups provided by Korean National Health Insurance Service between 2002 and 2005
Hazard Ratios for Cardiovascular Diseases Incidence by Change of Total Cholesterol

Baseline TC	Low (TC <180 mg/dL)			Middle (180≤ TC <240 mg/dL)			High (TC ≥240 mg/dL)		
Follow-Up TC	Low	Middle	High	Low	Middle	High	Low	Middle	High
Change, mg/dL, mean (SD)	1.0 (18.1)	32.8 (19.3)	112.2 (147.8)	−32.0 (18.1)	0.3 (19.0)	44.1 (69.7)	−130.8 (198.4)	−46.6 (90.2)	−0.9 (59.1)
Number of people (%)	866 178 (70.2)	353 605 (28.7)	12 885 (1.0)	325 271 (25.8)	835 005 (66.3)	99 227 (7.9)	12 504 (6.6)	99 103 (52.2)	78 267 (41.2)
Ischemic heart disease									
Cases, n	6370	3231	155	3227	10 738	1824	200	2000	2557
Incidence rates*	0.74	0.92	1.21	1.00	1.30	1.86	1.62	2.05	3.33
Model 1									
aHR	1.00	1.11	1.52	0.88	1.00	1.35	0.64	0.64	1.00
95% CI		1.06 to 1.16	1.30 to 1.78	0.84 to 0.91		1.29 to 1.42	0.55 to 1.74	0.61 to 0.68	
P-value		<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	
Model 2									
aHR	1.00	1.05	1.21	0.91	1.00	1.21	0.65	0.68	1.00
95% CI		1.00 to 1.09	1.03 to 1.42	0.88 to 0.95		1.15 to 1.27	0.56 to 0.75	0.65 to 0.73	
P-value		0.059	0.022	<0.001		<0.001	<0.001	<0.001	

Jeong SM, et al. J Am Heart Assoc. 2018 Jun 13;7(12).

Agenda

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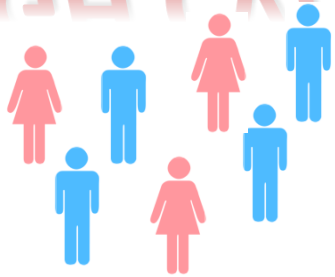
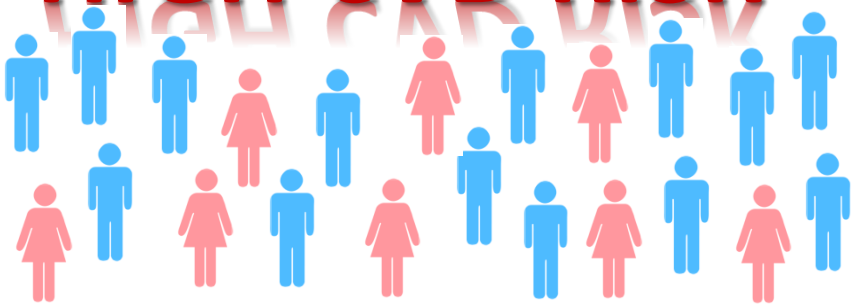
- Early intervention for greater prognostic benefit

Our first intervention should be early IDENTIFICATION of…

PEOPLE AT SHORT-TERM HIGH CVD RISK



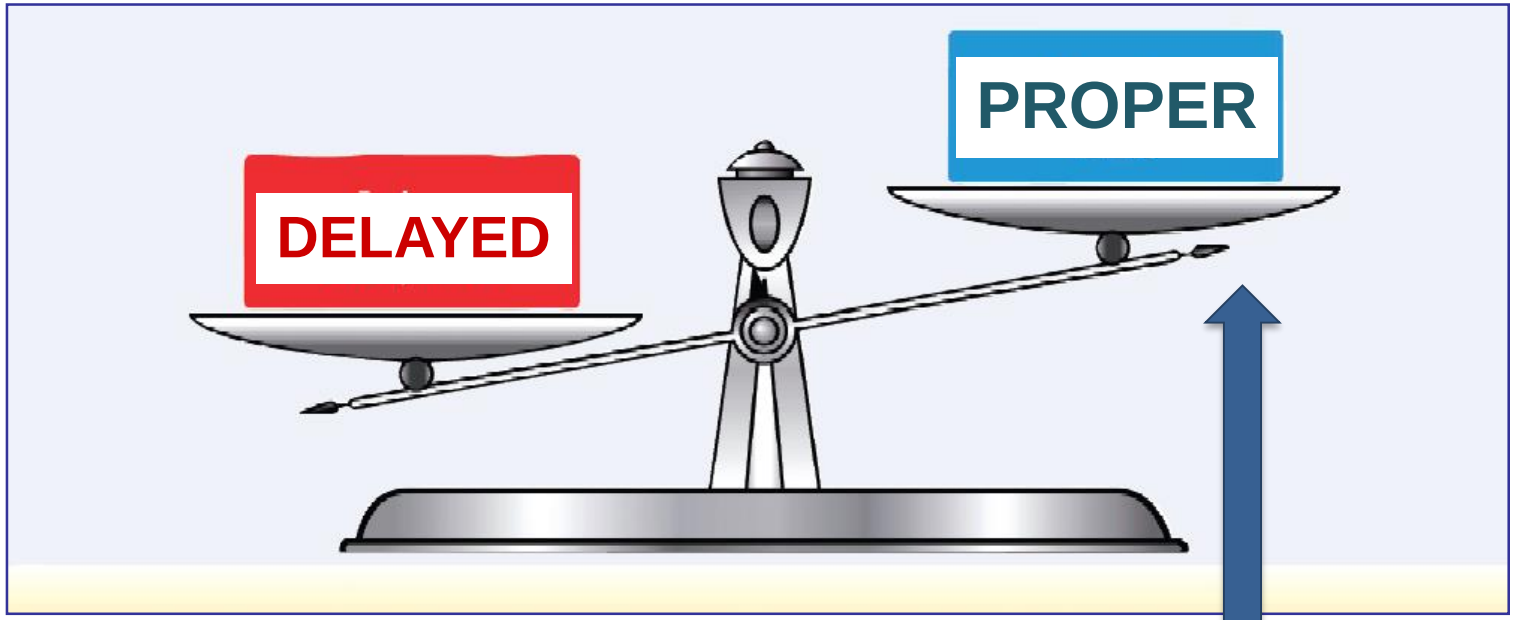
PEOPLE AT LONG-TERM HIGH CVD RISK



Consequences of delayed *vs* proper cholesterol lowering in patients at very high CVD risk

4D, AURORA,
…GISSI-HF,
CORONA…
HPS-PAD…

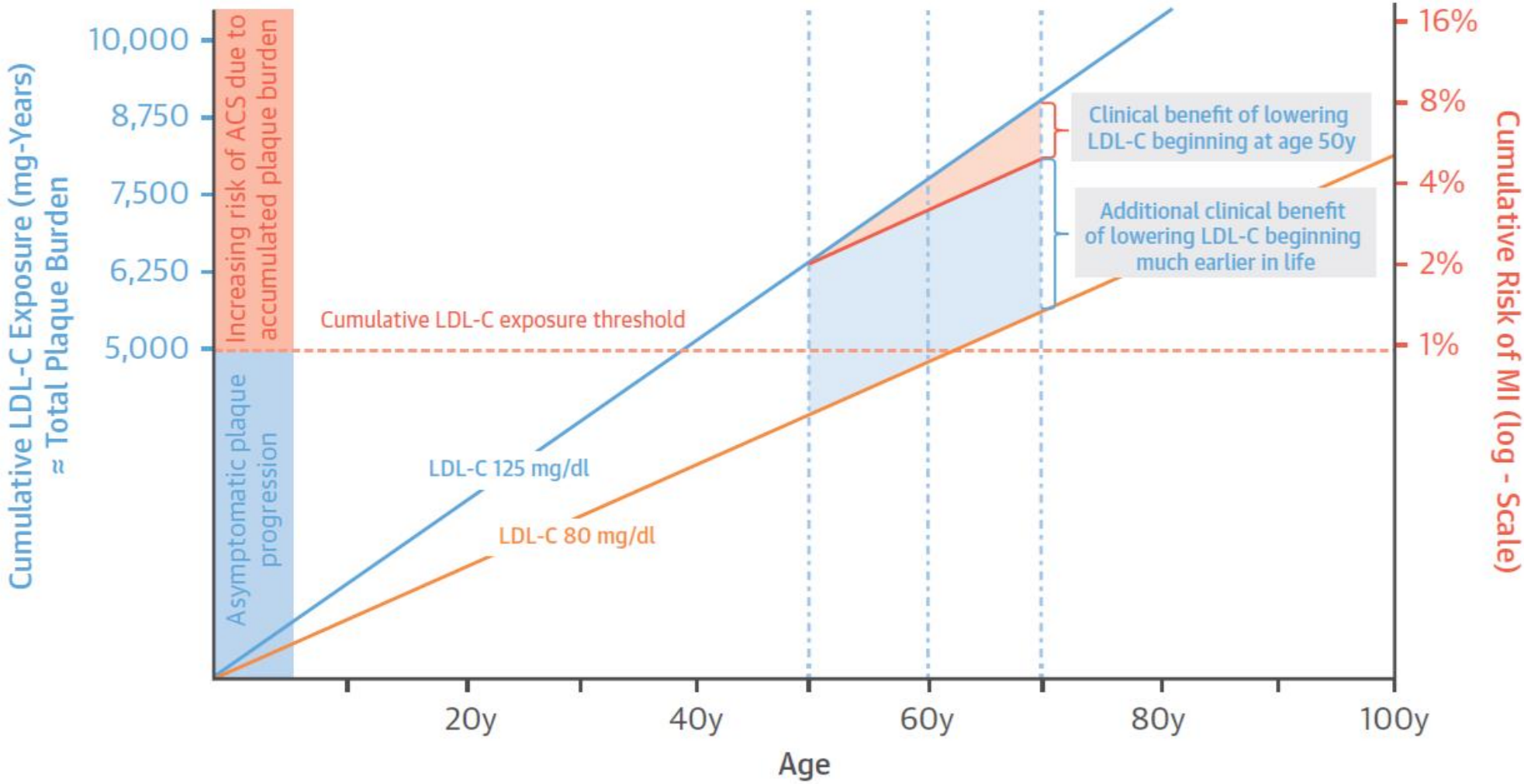
↓ CVD risk



↑ CVD risk

SHARP…, HPS, 4S,
…IMPROVE-IT, FOURIER,
ODYSSEY…

Clinical benefit of lowering LDL-C earlier in life



Ference BA, et al. J Am Coll Cardiol. 2018 Sep 4;72(10):1141-1156.