Stimare il rischio cardiovascolare: un approccio innovativo per controllare il rischio CV della popolazione

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DISCLOSURES

A.L. Catapano, in the last three years, has received honoraria, lecture fees or research grants from:

Aegerion, Akcea Therapeutics, Amarin, Amgen, Amryt Pharma, AstraZeneca, Daiichi Sankyo, Esperion, Ionis Pharmaceutical, Medscape Education, Menarini, Merck, Mylan, Novartis, Novo Nordisk, PeerVoice, Pfizer, Recordati, Regeneron, Sanofi, The Corpus, Viatris

CV RISK ESTIMATION

10-year CV risk vs lifetime CV risk

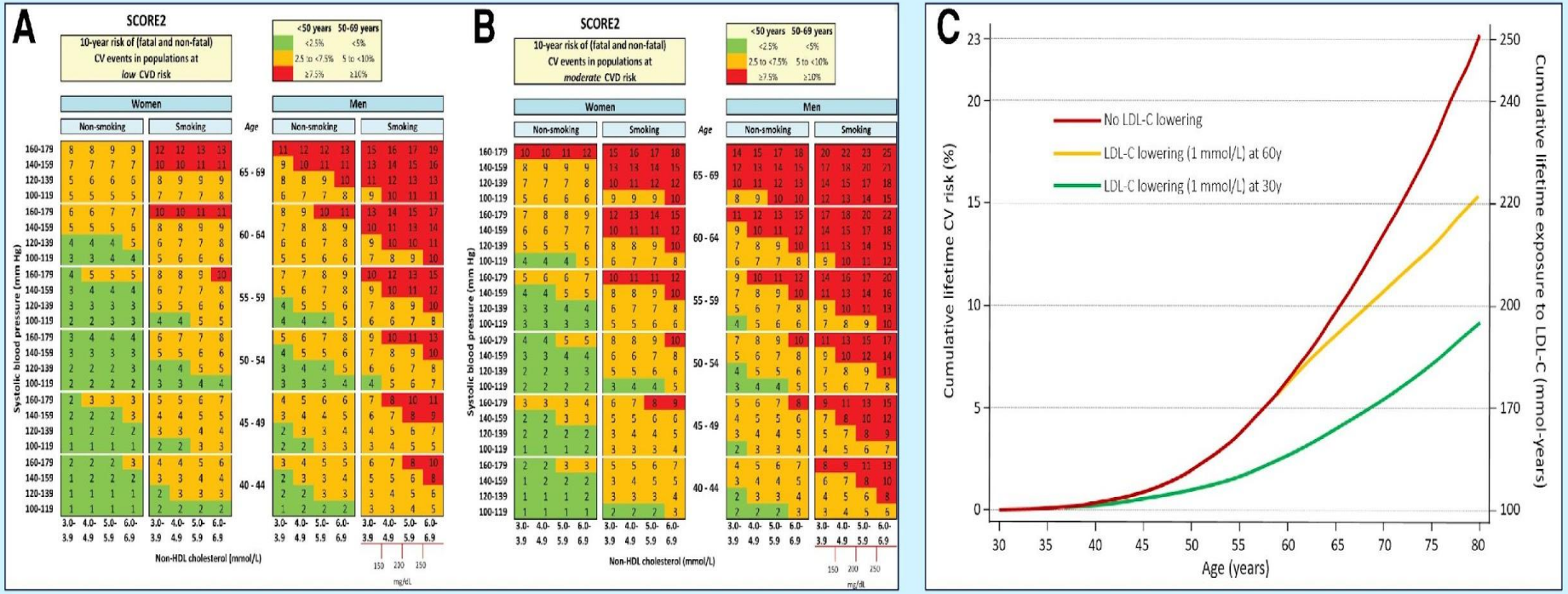
A, B: SCORE2 charts for estimation of CVD risk in low (A) and moderate (B) CV risk people

C: Effect of lowering LDL-C by 1 mmol/L beginning at 30 or 60 years of age

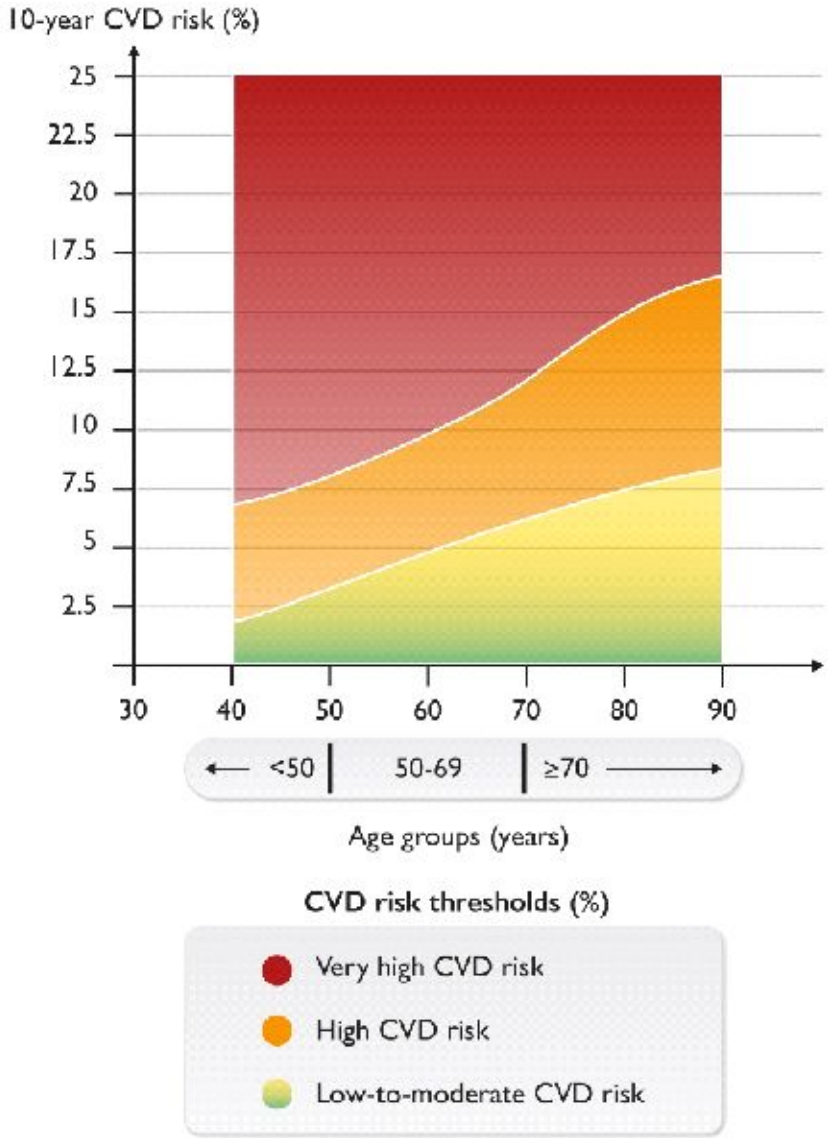
10-YEAR CV RISK

LIFETIME CV RISK

Benefit is proportional to intensity and duration



Eur. J. Prev. Cardiol., zwad247, https://doi.org/10.1093/eurjpc/zwad247

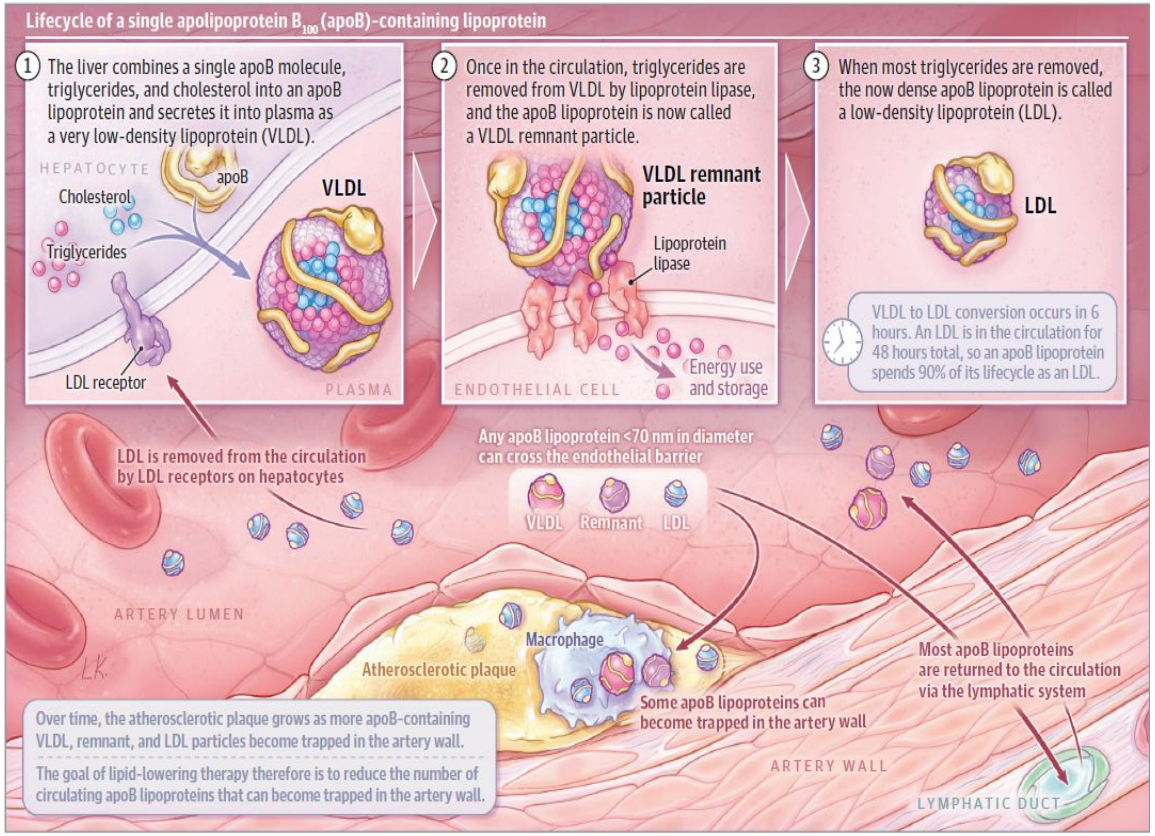

10-year CVD risk (%)
25
22.5
20
17.5
15
12.5
10
7.5
5
2.5
30
40
50
60
70
80
90
<50
50-69
≥70
Age groups (years)
CVD risk thresholds (%)
Very high CVD risk
High CVD risk
Low-to-moderate CVD risk

LDL is NOT a risk factor for ASCVD

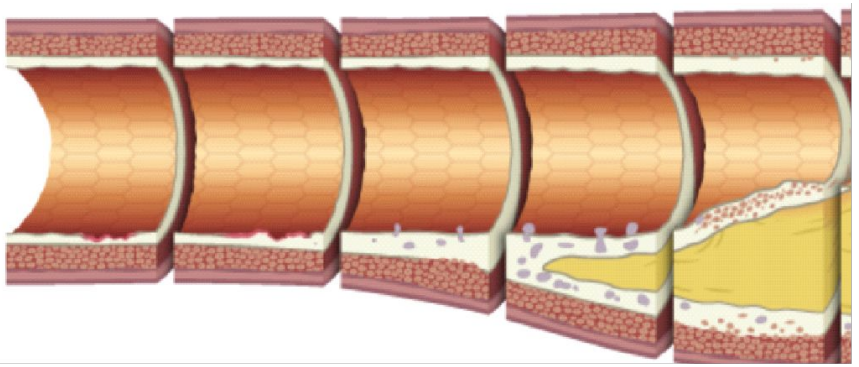
*LDL is the main **CAUSE** of atherosclerosis*

Therefore - lowering LDL MUST be the main FOCUS
for preventing Atherosclerotic Cardiovascular events

Central role of LDL (apoB-containing lipoproteins) in ASCVD



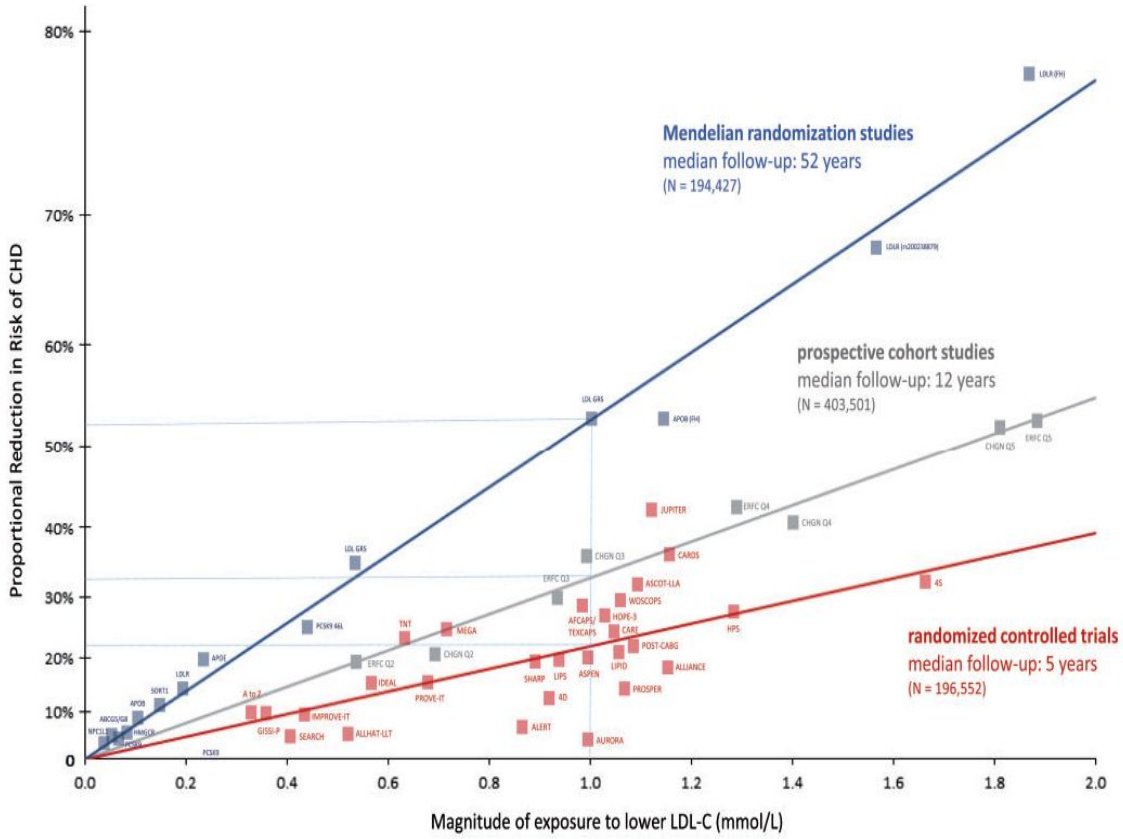
Over time, trapping of LDL particles leads to progressive development of atherosclerotic plaque



Ference BA, Kastelein JPP, Catapano AL. JAMA, 2020: doi:10.1001/jama.2020.5685

Evidence for causal & cumulative effect of LDL on risk of ASCVD

EAS Consensus: LDL **CAUSES** ASCVD



Ference BA, et al. EAS Consensus Statement on LDL Causality. Eur Heart J 2018

GUIDELINES: LDL **main cause of** ASCVD

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

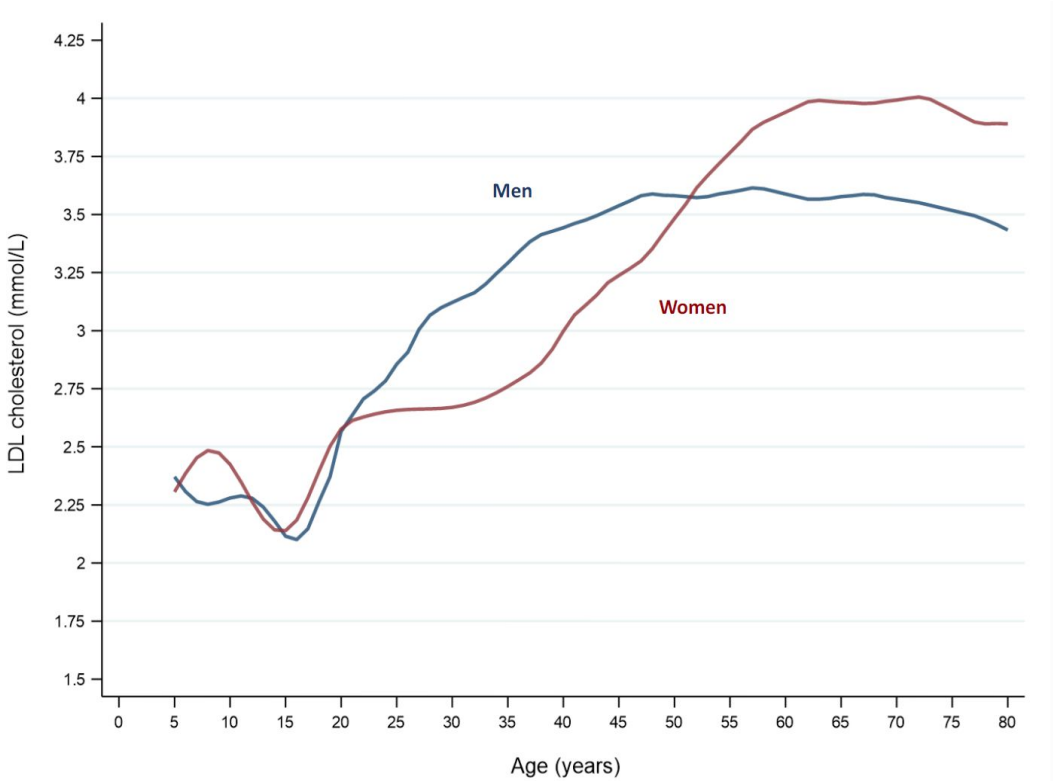
Authors/Task Force Members: François Mach* (Chairperson) (Switzerland), Colin Baigent* (Chairperson) (United Kingdom), Alberico L. Catapano[1]* (Chairperson) (Italy), Konstantinos C. Koskinas (Switzerland), Manuela Casula[1] (Italy), Lina Badimon (Spain), M. John Chapman[1] (France), Guy G. De Backer (Belgium), Victoria Delgado (Netherlands), Brian A. Ference (United Kingdom), Ian M. Graham (Ireland), Alison Halliday (United Kingdom), Ulf Landmesser (Germany), Borislava Mihaylova (United Kingdom), Terje R. Pedersen (Norway), Gabriele Riccardi[1] (Italy), Dimitrios J. Richter (Greece), Marc S. Sabatine (United States of America), Marja-Riitta Taskinen[1] (Finland), Lale Tokgozoglu[1] (Turkey), Olov Wiklund[1] (Sweden)

2019 ESC/EAS Guidelines for the management of dyslipidaemias. Eur Heart J. 2019 ehz455.

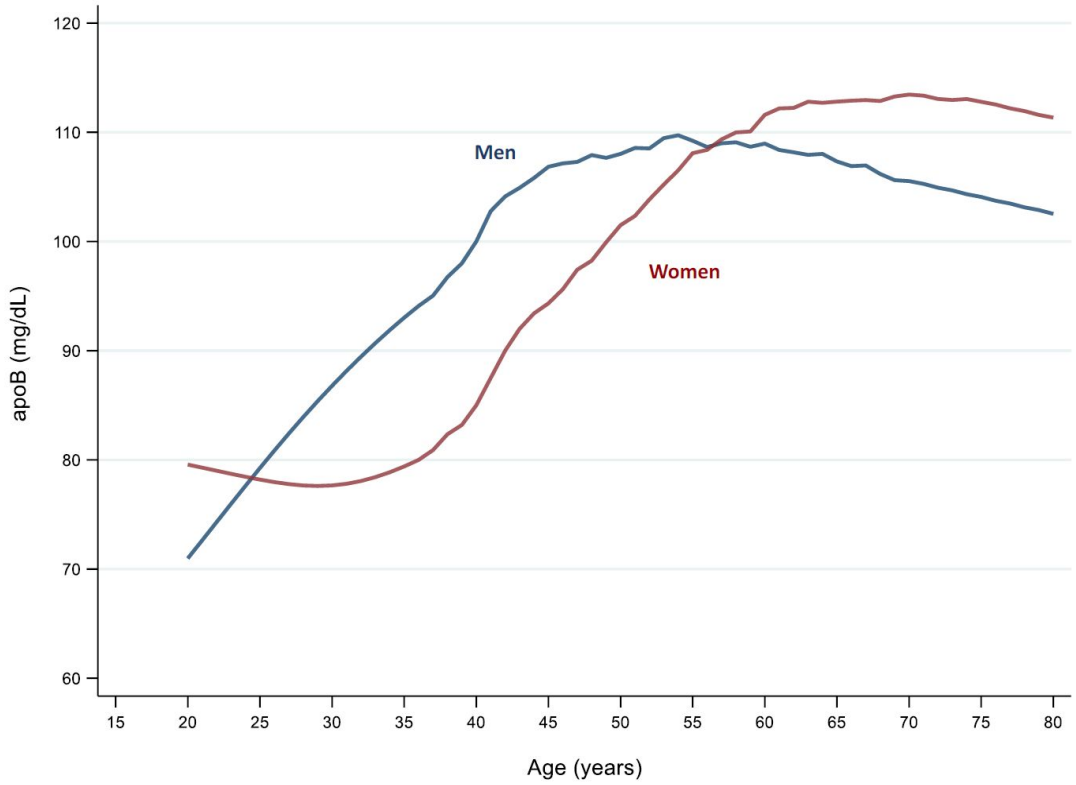
Cumulative exposure to LDL: Tracking plaque progression in Plaque Years of LDL

- Cumulative exposure to LDL is direct measure of number of atherogenic lipoproteins that have become trapped within artery wall
- Therefore, can be used to estimate size plaque burden, track rate of plaque progression, corresponding absolute risk of MACE

Cumulative exposure to LDL



Cumulative exposure to apoB

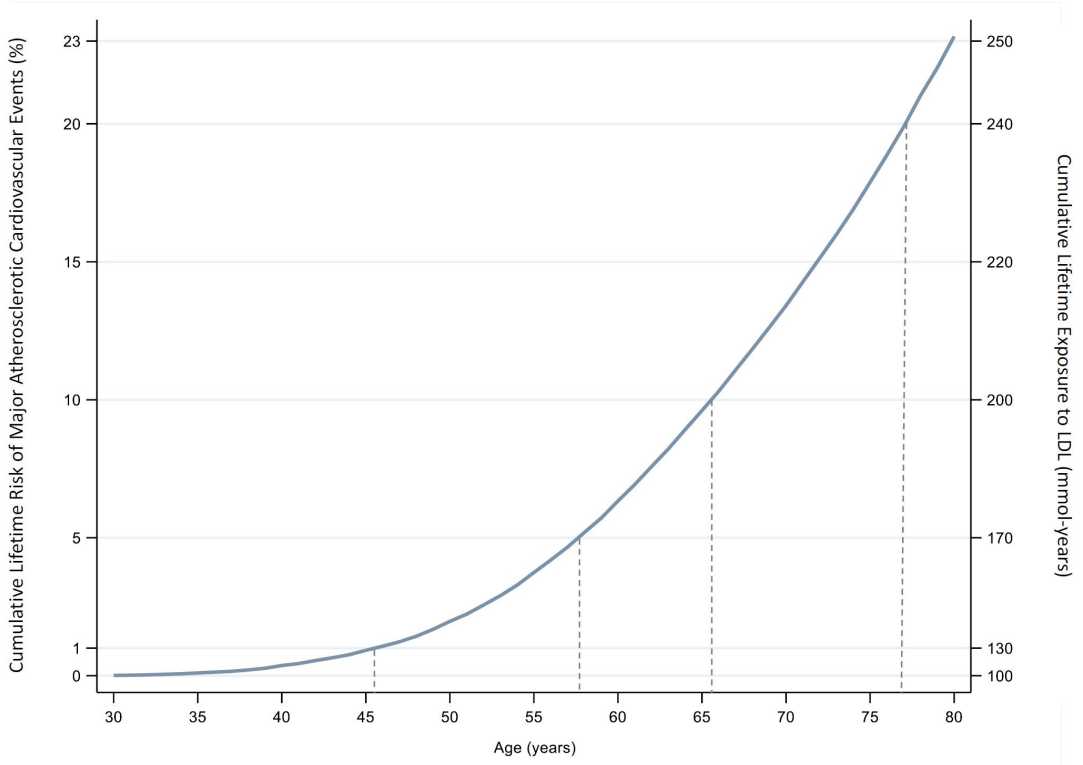


Ference BA, Braunwald E, Catapano AL. Nature Reviews Cardiology, *2024 in press*

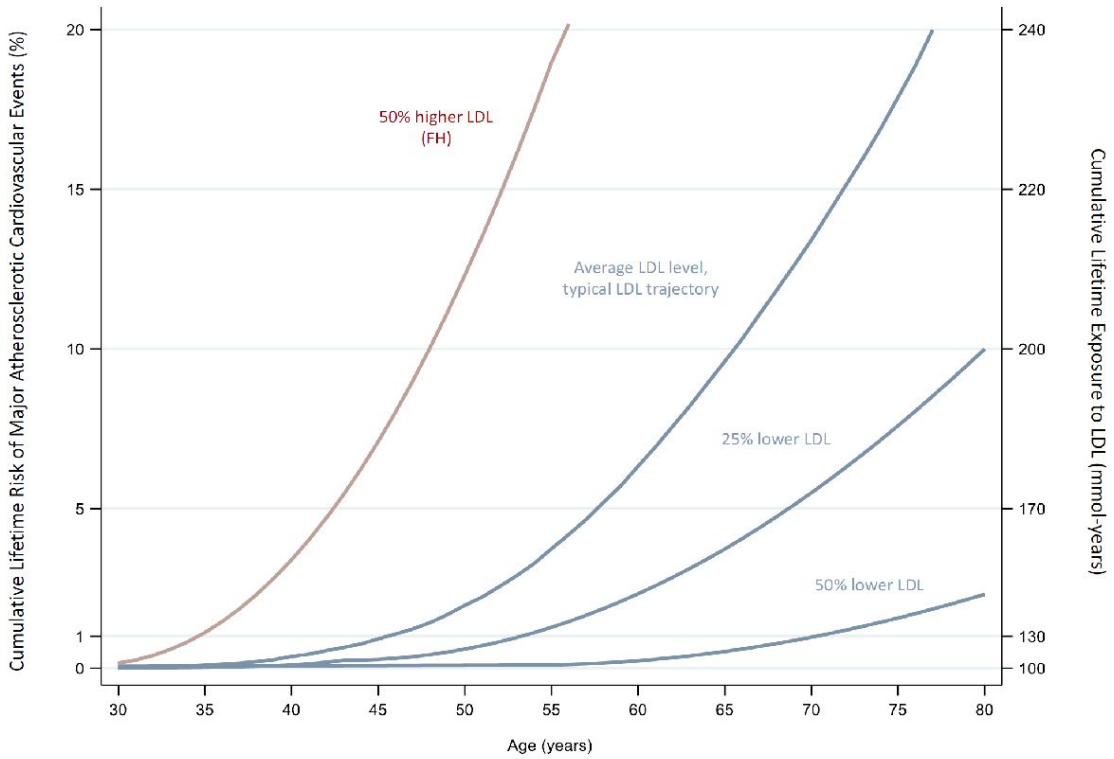
Using cumulative exposure to LDL estimate ASCVD Risk

- Plotting cumulative lifetime risk of major cardiovascular events by cumulative exposure to LDL reveals the cumulative exposure thresholds at which acute cardiovascular events occur
- Changes LDL from static to a dynamic measurement (like SBP or HbA1c) – that can be used as a biomarker to monitor plaque progression, as a therapeutic target, and monitor response to selected intervention

Thresholds for Cumulative exposure to LDL



Reducing Cumulative slows progression of atherosclerosis & delays onset of events

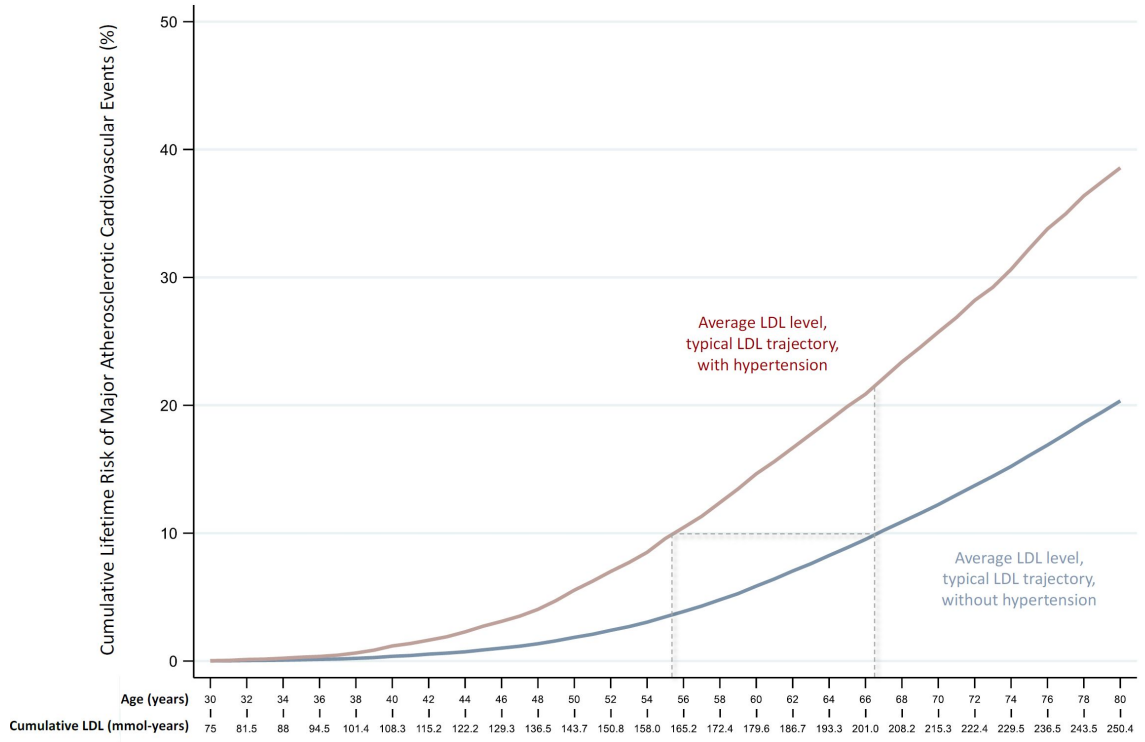


Ference BA, Braunwald E, Catapano AL. Nature Reviews Cardiology, *2024 in press*

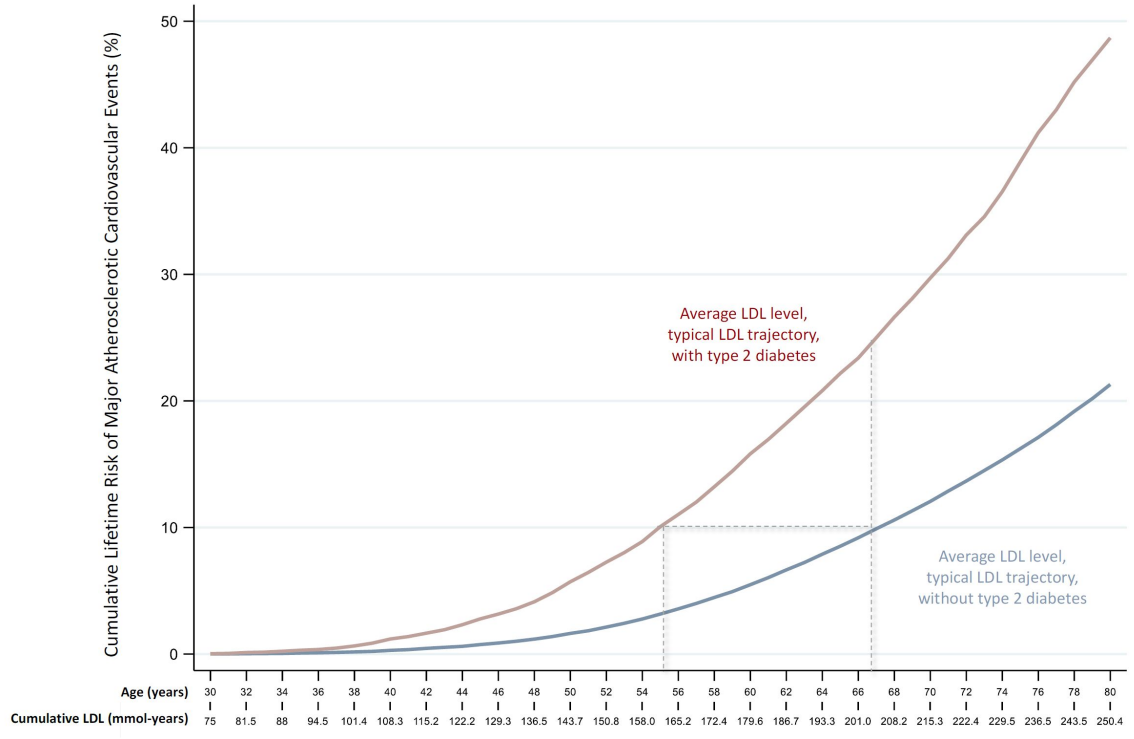
LDL cumulative exposure thresholds depend on presence other exposures

- Cardiovascular events begin to occur at LOWER LDL cumulative exposure threshold, and the risk of acute atherosclerotic cardiovascular events is higher at all cumulative LDL levels (and corresponding accumulated plaque burden) – when other causes of injury to artery wall are present

Effect of Hypertension on thresholds for cumulative exposure to LDL



Effect of diabetes on thresholds for cumulative exposure to LDL

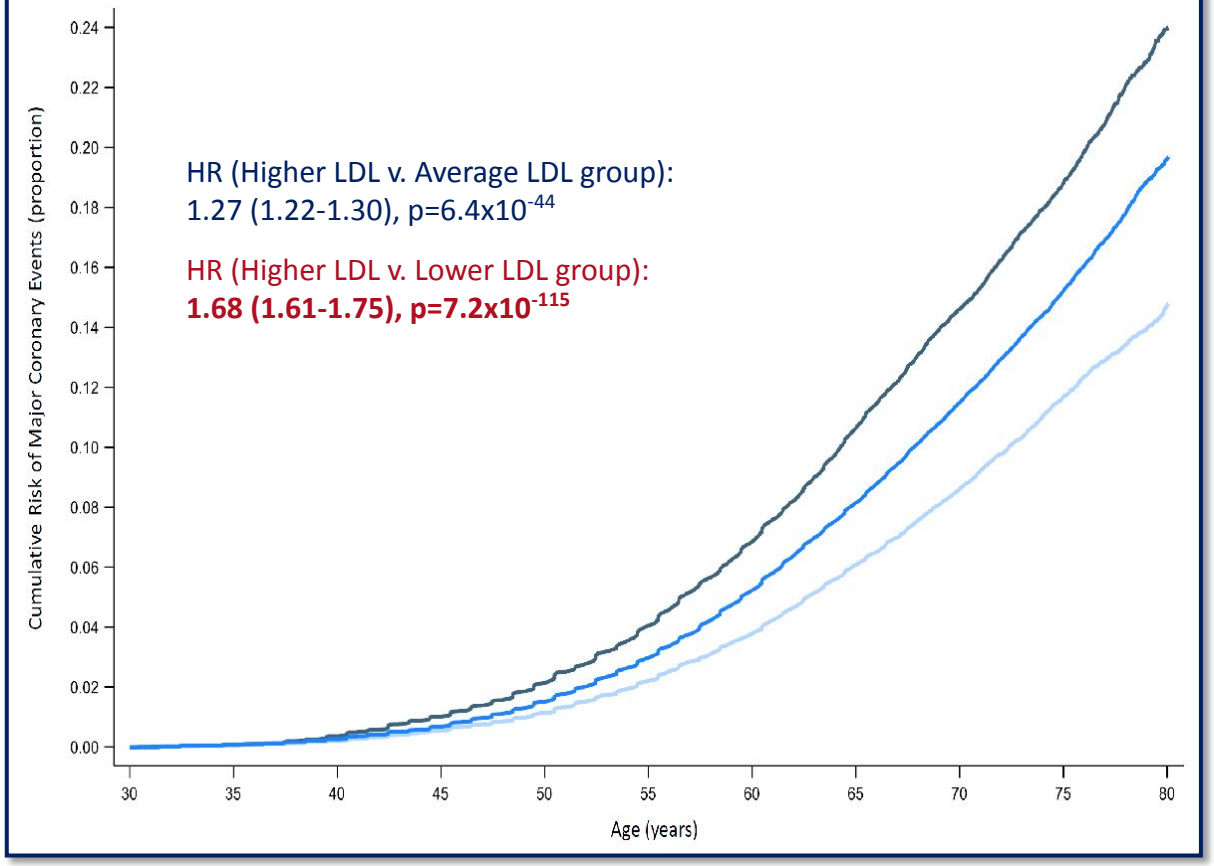


Ference BA, Braunwald E, Catapano AL. Nature Reviews Cardiology, *2024 in press*

Empirical validation of the LDL cumulative exposure hypothesis

- Persons randomized to higher LDL by nature have higher, LDL, greater cumulative exposure to LDL & higher risk of MCE at all ages
- However, all persons have same risk of MCE at same cumulative exposure to LDL regardless of age cumulative exposure occurs

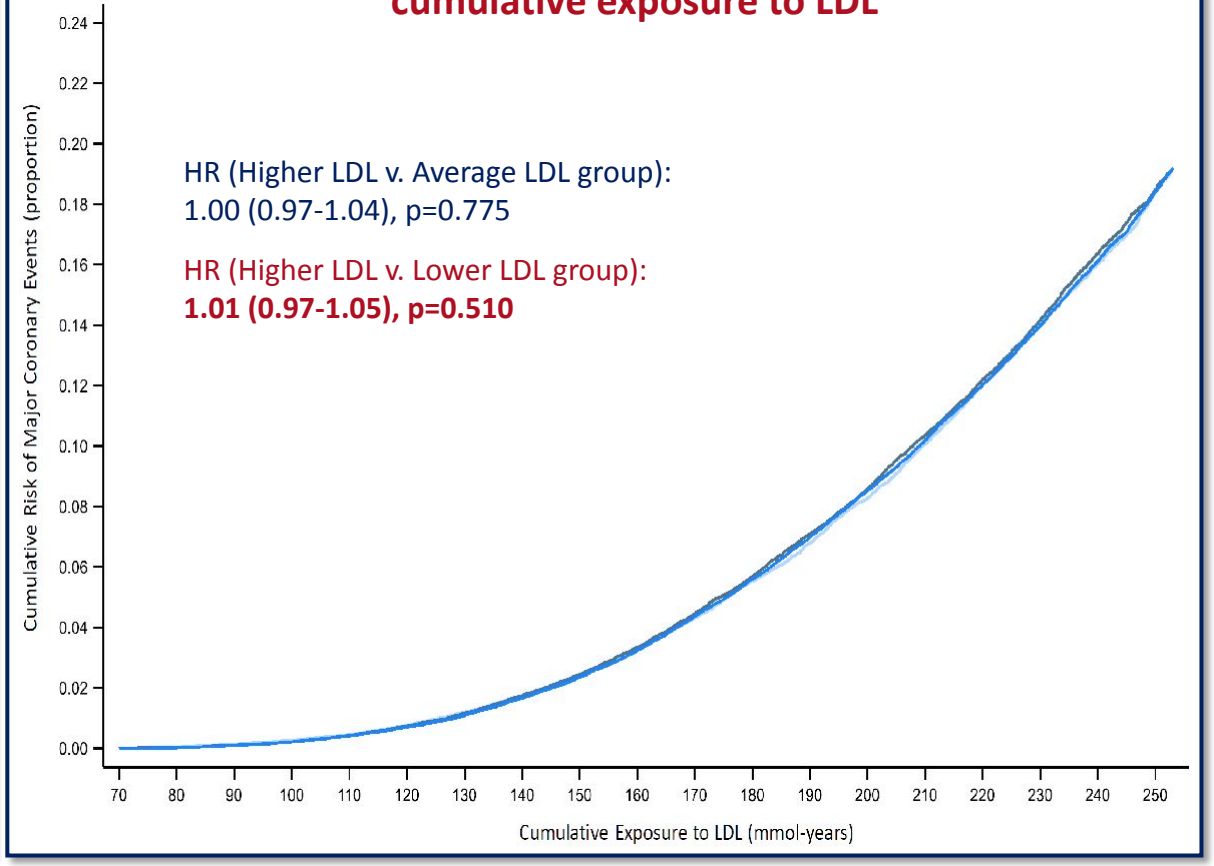
Comparing risk of MCE at same age



HR (Higher LDL v. Average LDL group):
1.27 (1.22-1.30), $p=6.4 \times 10^{-44}$

HR (Higher LDL v. Lower LDL group):
1.68 (1.61-1.75), $p=7.2 \times 10^{-115}$

Comparing risk of MCE at same cumulative exposure to LDL



HR (Higher LDL v. Average LDL group):
1.00 (0.97-1.04), p=0.775

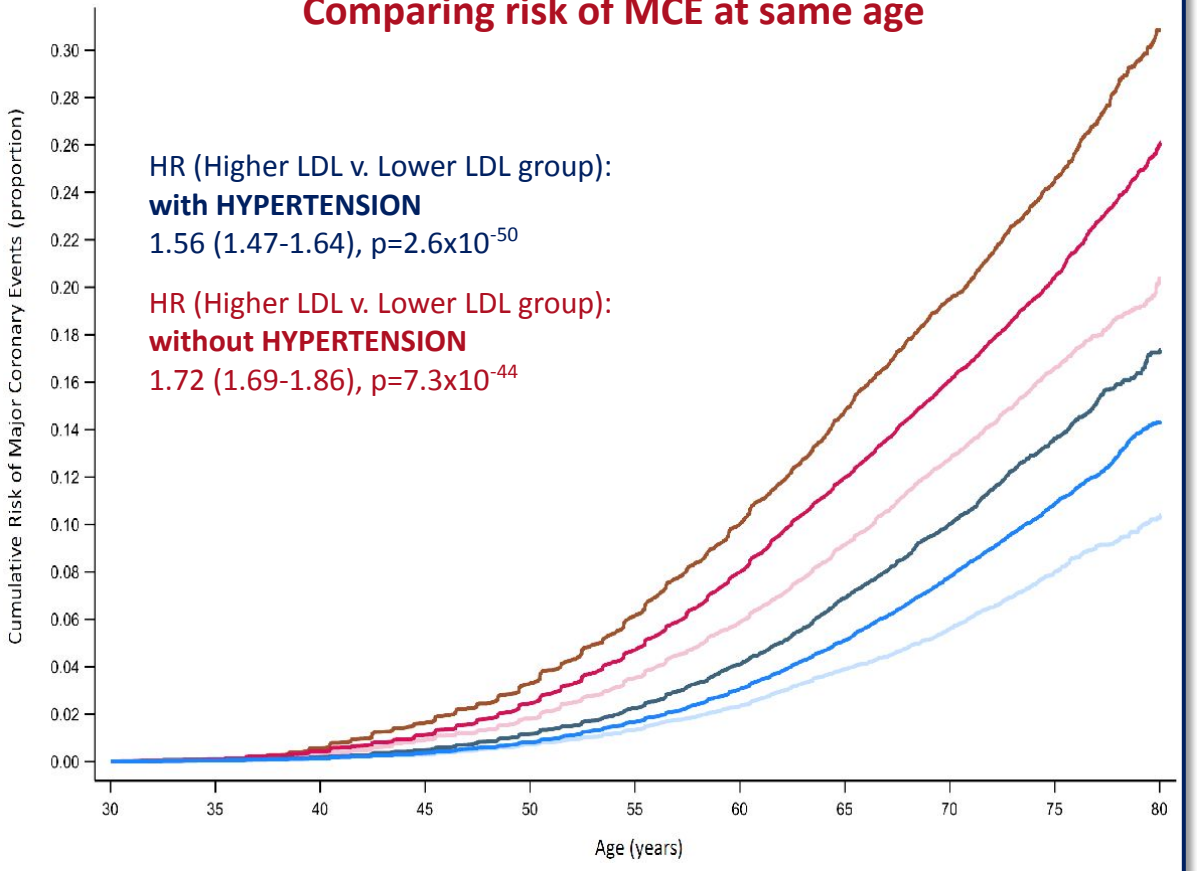
HR (Higher LDL v. Lower LDL group):
1.01 (0.97-1.05), p=0.510

Ference BA, et al. *Late Breaking Clinical Trial, ESC 2023, Amsterdam*

Benefit of lowering LDL & SBP (preventing HTN)

- LDL and SBP have independent effects on risk of Major Cardiovascular Events (MCE)
- Preventing HTN (lowering SBP) reduces the amount of LDL lowering needed to effectively prevent MCE

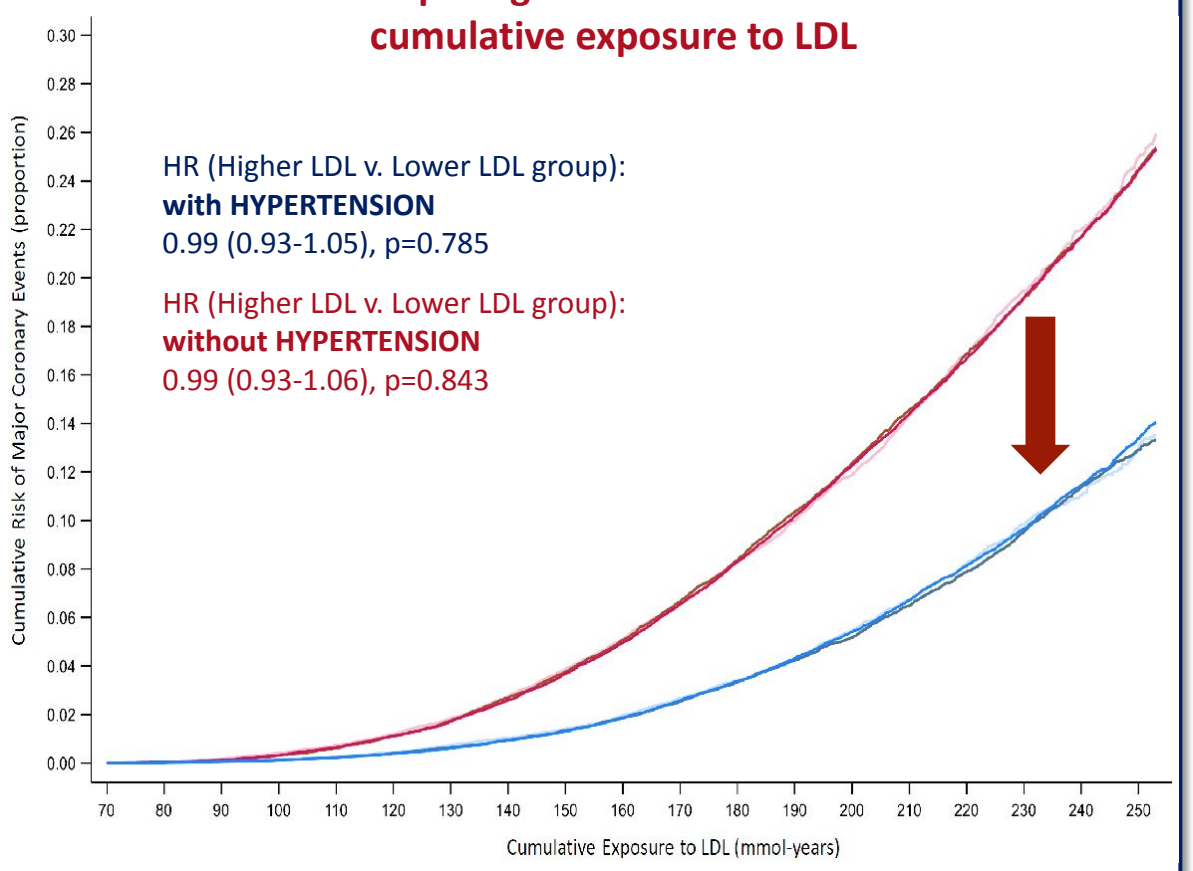
Comparing risk of MCE at same age



HR (Higher LDL v. Lower LDL group):
with HYPERTENSION
1.56 (1.47-1.64), $p=2.6x10^{-50}$

HR (Higher LDL v. Lower LDL group):
without HYPERTENSION
1.72 (1.69-1.86), $p=7.3x10^{-44}$

Comparing risk of MCE at same cumulative exposure to LDL



HR (Higher LDL v. Lower LDL group):
with HYPERTENSION
0.99 (0.93-1.05), p=0.785

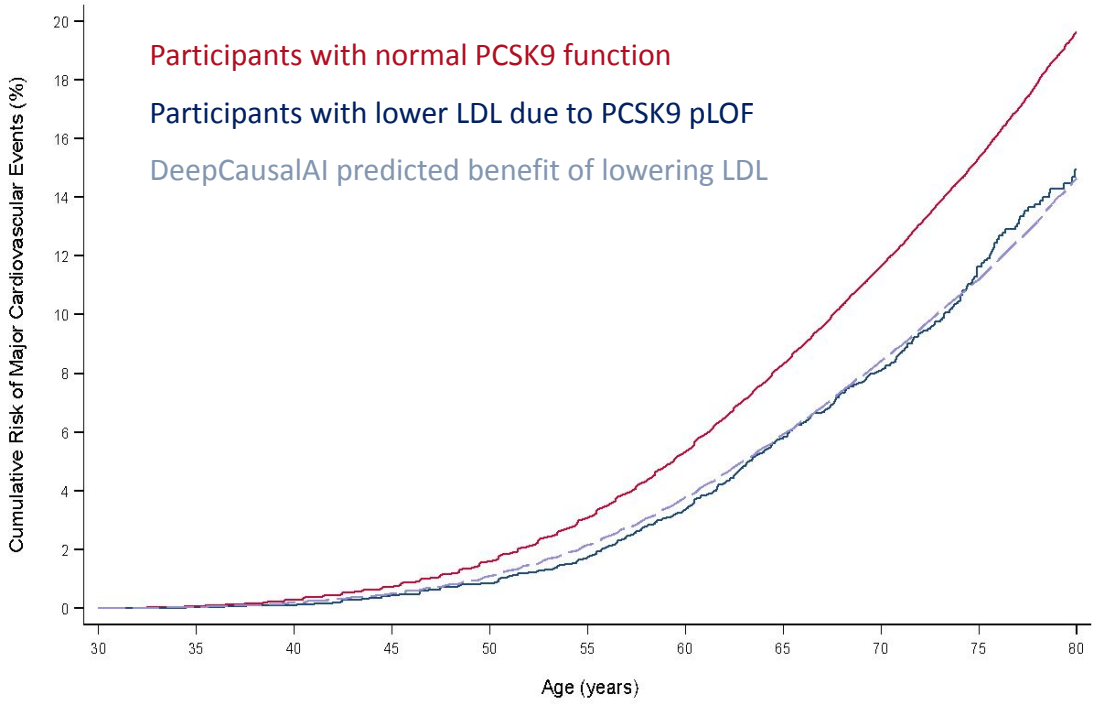
HR (Higher LDL v. Lower LDL group):
without HYPERTENSION
0.99 (0.93-1.06), p=0.843

Ference BA, et al. *Late Breaking Clinical Trial, ESC 2023, Amsterdam*

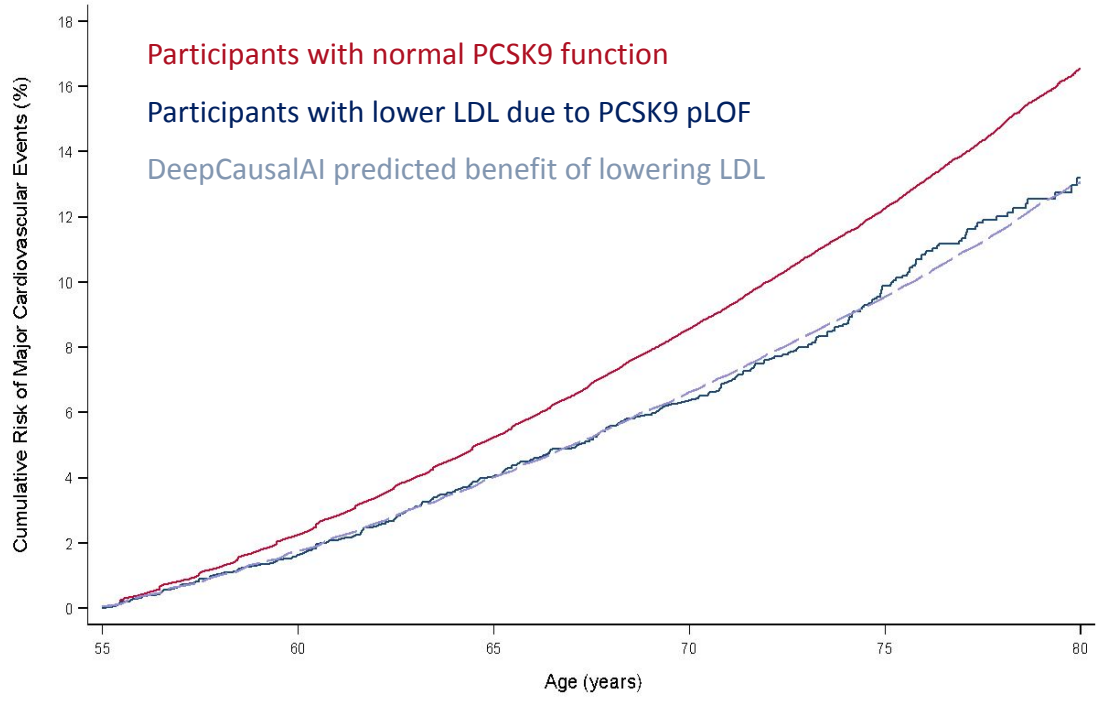
Using DeepCausalAI to estimate the benefit of lifelong lower LDL

- A deep learning AI algorithm that encodes the biological effect of LDL in discrete time-units of exposure accurately predicted the benefit of lifelong exposure to lower LDL at every age throughout life among participants randomized by nature to partial LOF variant in PCSK9

Lifetime risk of MACE



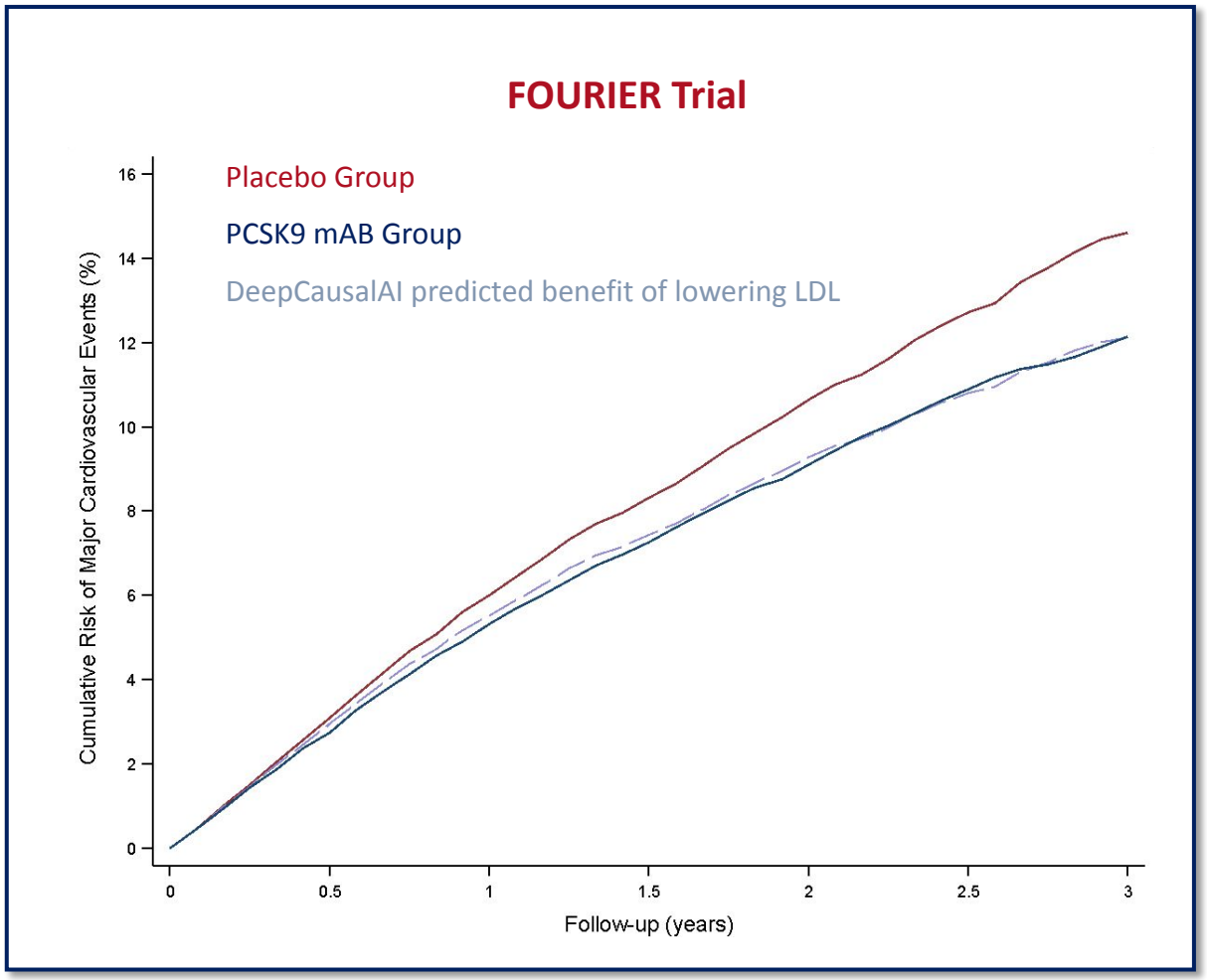
Remaining lifetime risk of MACE among participants who survived to age 55 without an event

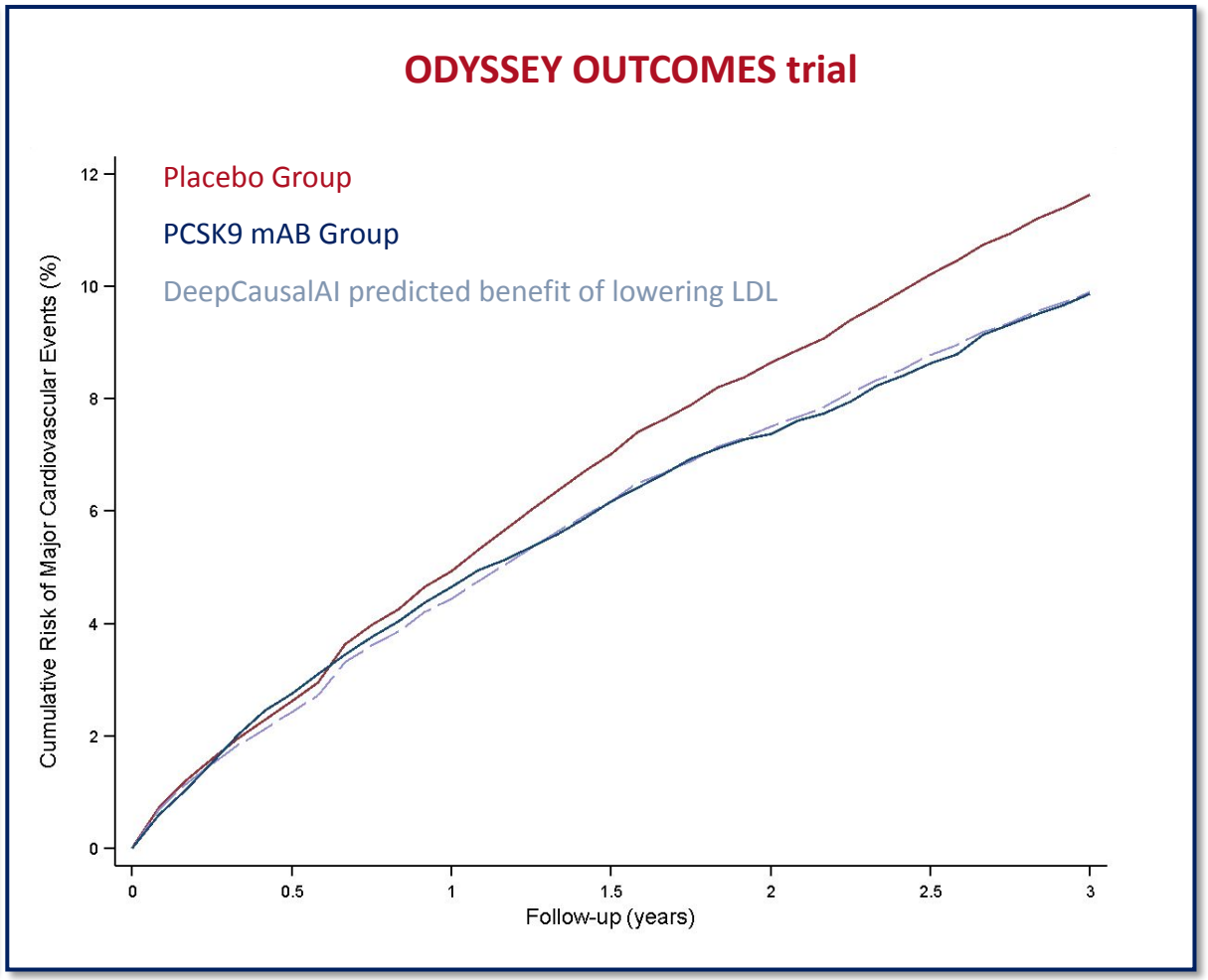


Ference BA, et al. *In press*

Using DeepCausalAI to estimate the benefit of lowering LDL in RCTs

- The deep learning AI algorithm that encodes the biological effect of LDL in discrete time-units of exposure also accurately predicted the benefit of lowering LDL with a PCSK9 mAb at every month of follow-up in two large RCTs





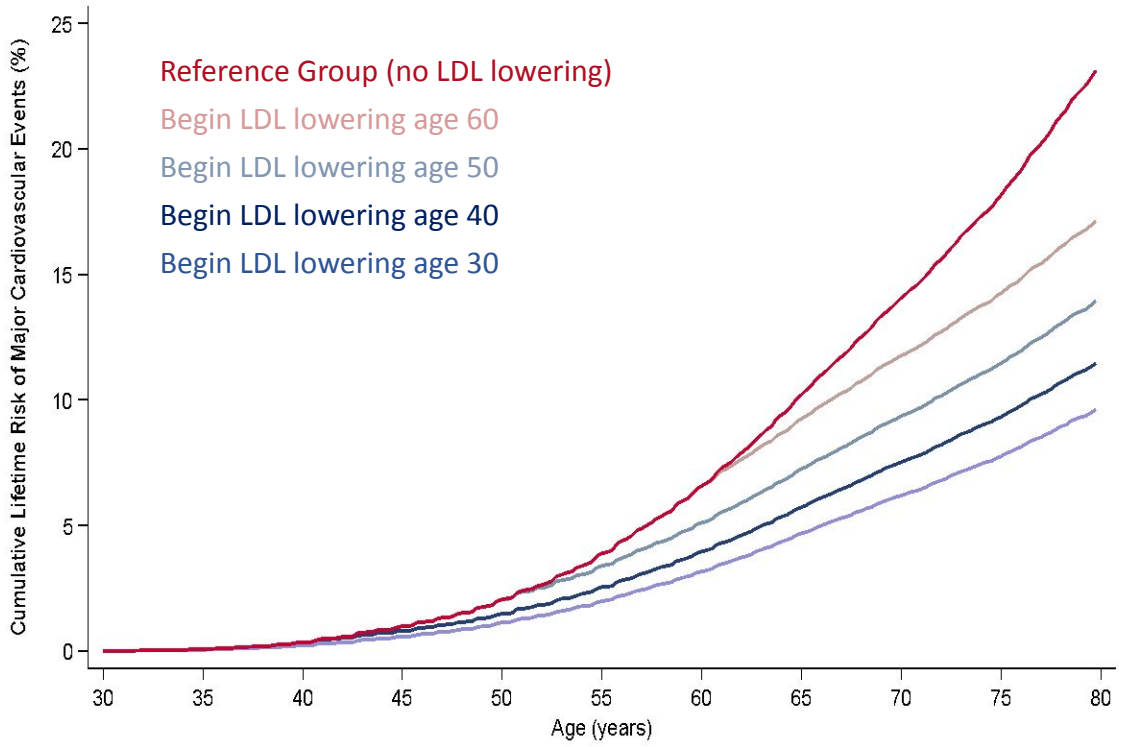
Ference BA, et al. *In press*

Increasing benefit of longer duration of lowering LDL

- There is a step wise increase in the reduction in MACE for the same magnitude of LDL lowering with each decade earlier that LDL lowering is started – confirming that the benefit of lowering LDL depends on magnitude & duration of LDL lowering

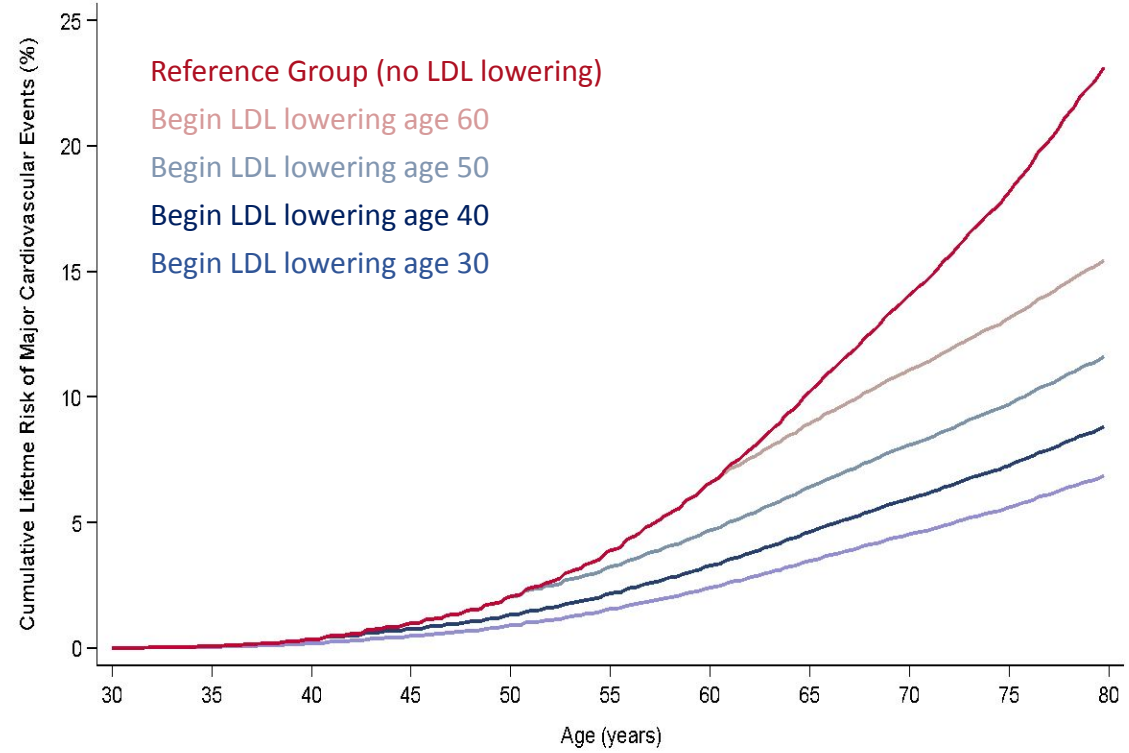
Remaining lifetime risk of MACE 36% reduction in LDL

(approximately equivalent ONCE yearly PCSK9 siRNA)



Remaining lifetime risk of MACE 50% reduction in LDL

(approximately equivalent TWICE yearly PCSK9 siRNA)



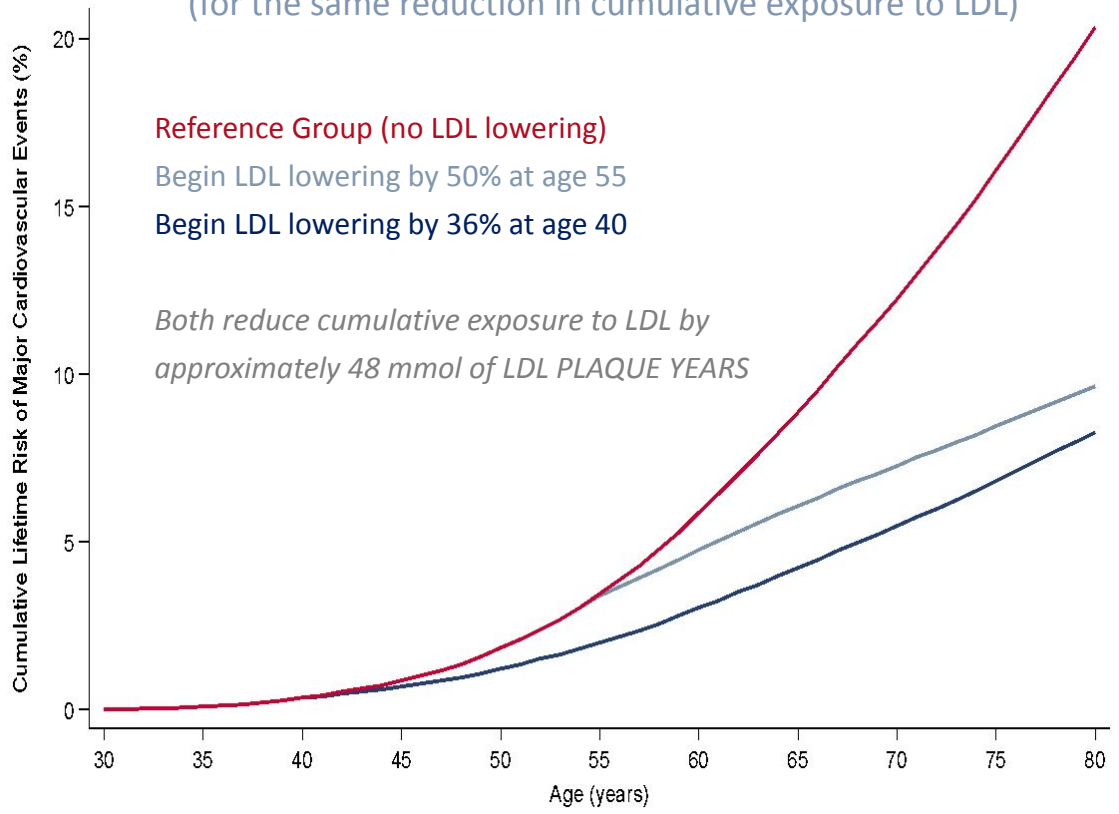
Ference BA, et al. *In press*

Early modest compared to aggressive later LDL lowering

- Modest early LDL lowering is associated with LOWER remaining lifetime risk of MACE at all ages compared to more aggressive later LDL lowering despite same cumulative reduction in LDL – suggesting residual risk is due to plaque burden that accumulated before start to lower LDL
- **RISK** is determined by magnitude & duration of exposure to LDL – but **BENEFIT** is determined by magnitude, duration, & timing of LDL lowering

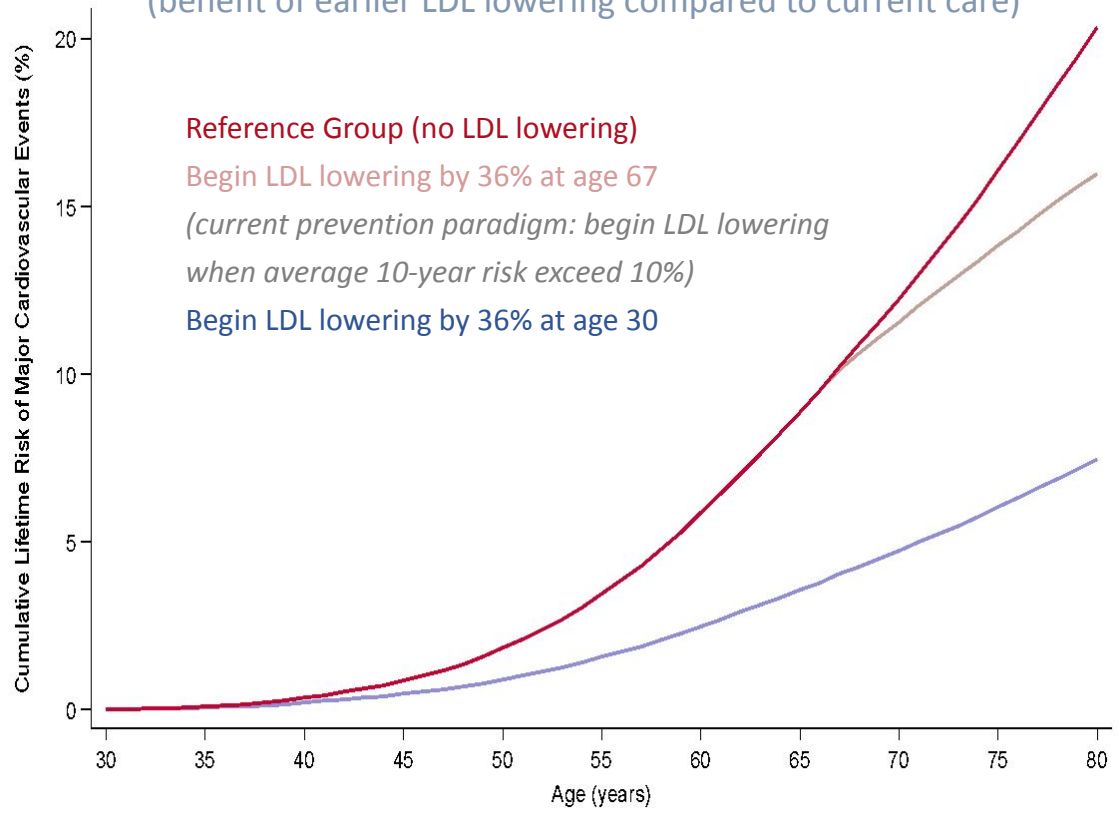
Remaining lifetime risk of MACE

(for the same reduction in cumulative exposure to LDL)



Remaining lifetime risk of MACE

(benefit of earlier LDL lowering compared to current care)



Ference BA, et al. *In press*

TAKE HOME MESSAGE

Cumulative exposure accurately predicts the risk of ASCVD events and the benefit from its reduction can be estimated