



PRESENT
AND FUTURE
APPROACHES TO
THE CONTROL OF
DYSLIPIDAEMIAS

S.I.Te.C.S.
SOCIETÀ ITALIANA DI TERAPIA CLINICA E Sperimentale

EAS/ESC GUIDELINES FOR PLASMA LIPID CONTROL: CURRENT STATUS AND FUTURE CHALLENGES

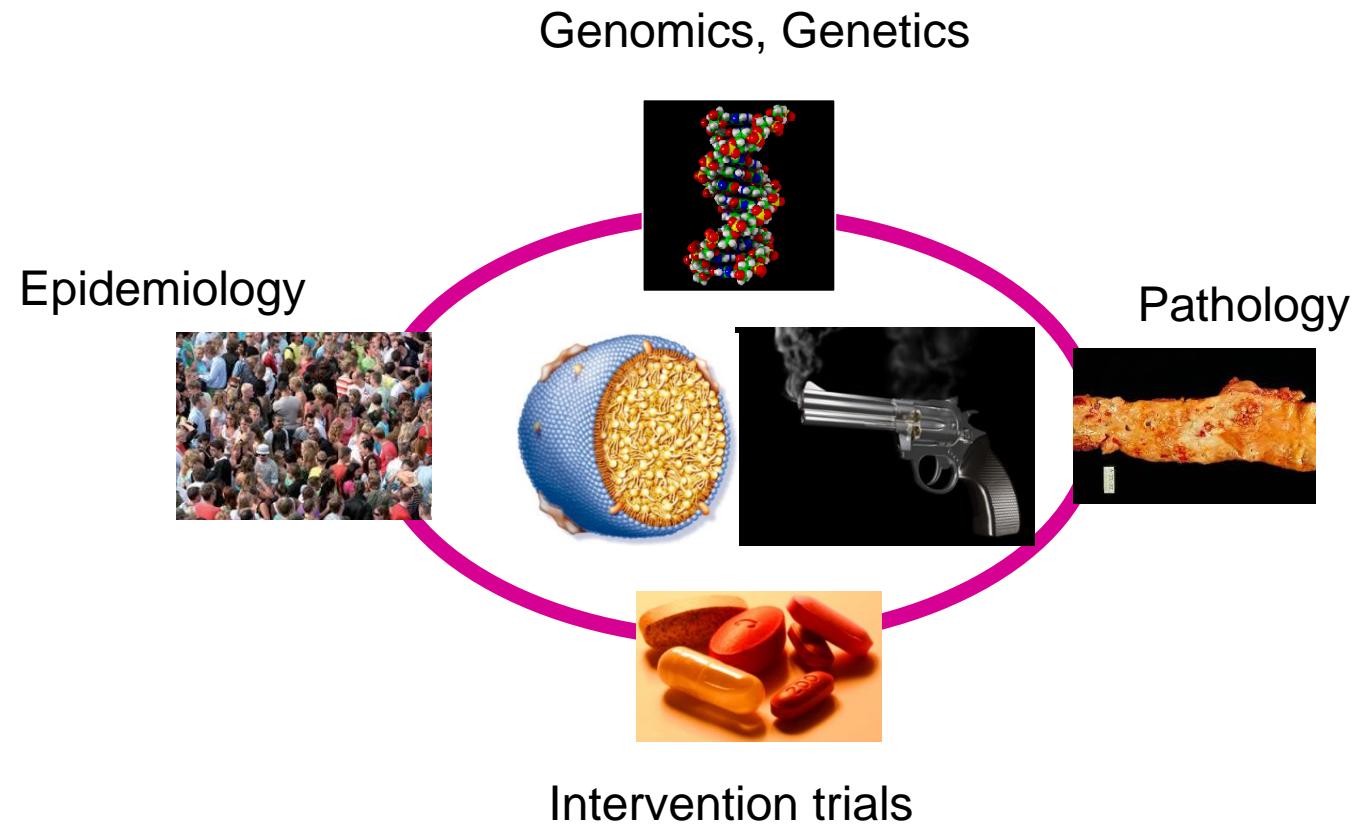
Alberico L. Catapano - University of Milan, Italy

Disclosure of potential conflicts of interest

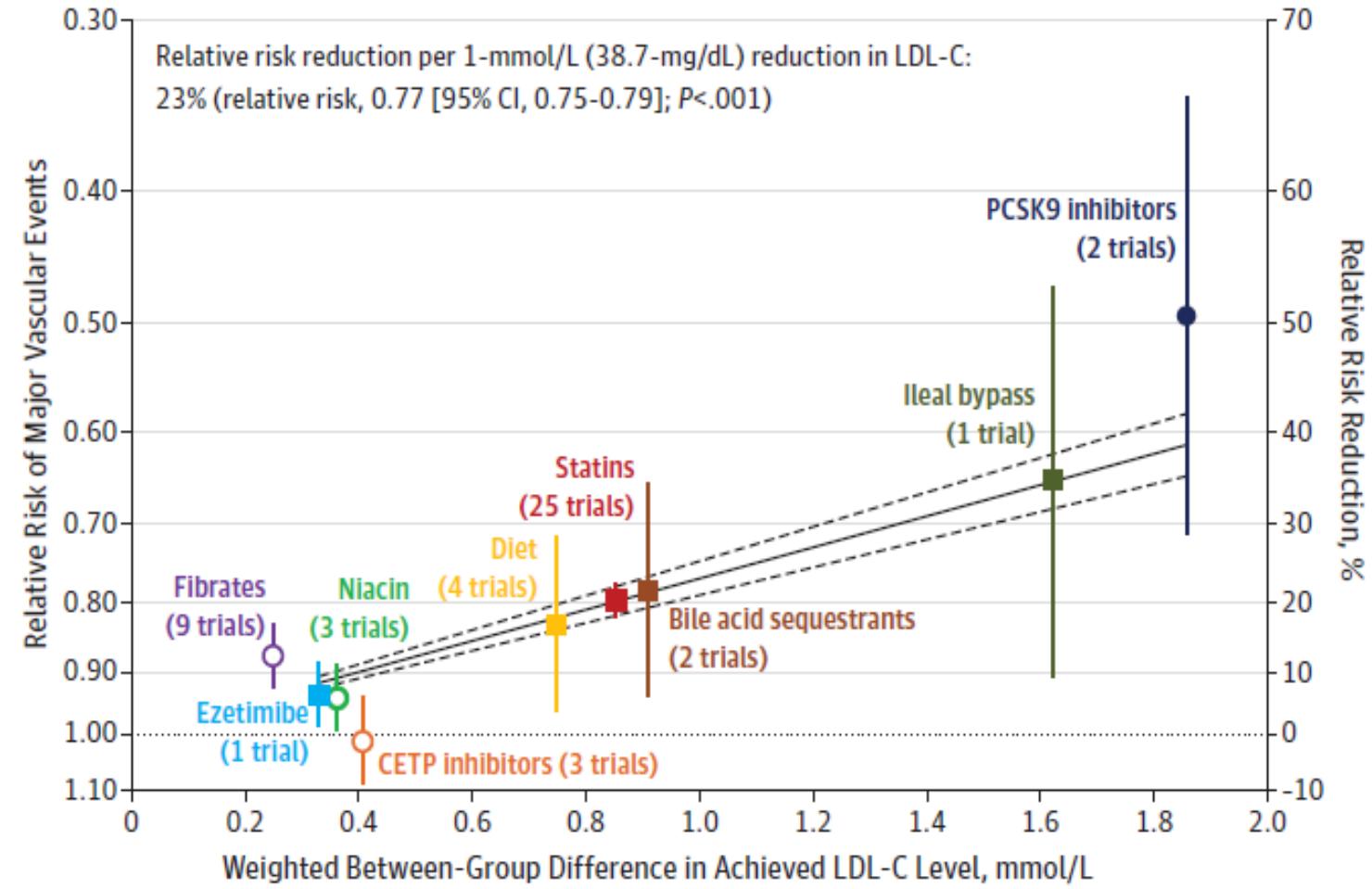
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| RESEARCH GRANT / RESEARCH SUPPORT | Sanofi, Sanofi Regeneron, Amgen, Mylan, Menarini, Eli Lilly |
| SPEAKER BUREAU | Akcea, Amgen, Sanofi, Esperion, Kowa, Novartis, Ionis Pharmaceuticals, Mylan, Menarini, Merck , Recordati, Regeneron, Daiichi Sankyo, AstraZeneca, Aegerion, Amryt, Sandoz |
| HONORARIA | Akcea, Amgen, Sanofi, Esperion, Kowa, Novartis, Ionis Pharmaceuticals, Mylan, Menarini, Merck, Recordati, Regeneron Daiichi Sankyo, AstraZeneca, Aegerion, Amryt, Sandoz |
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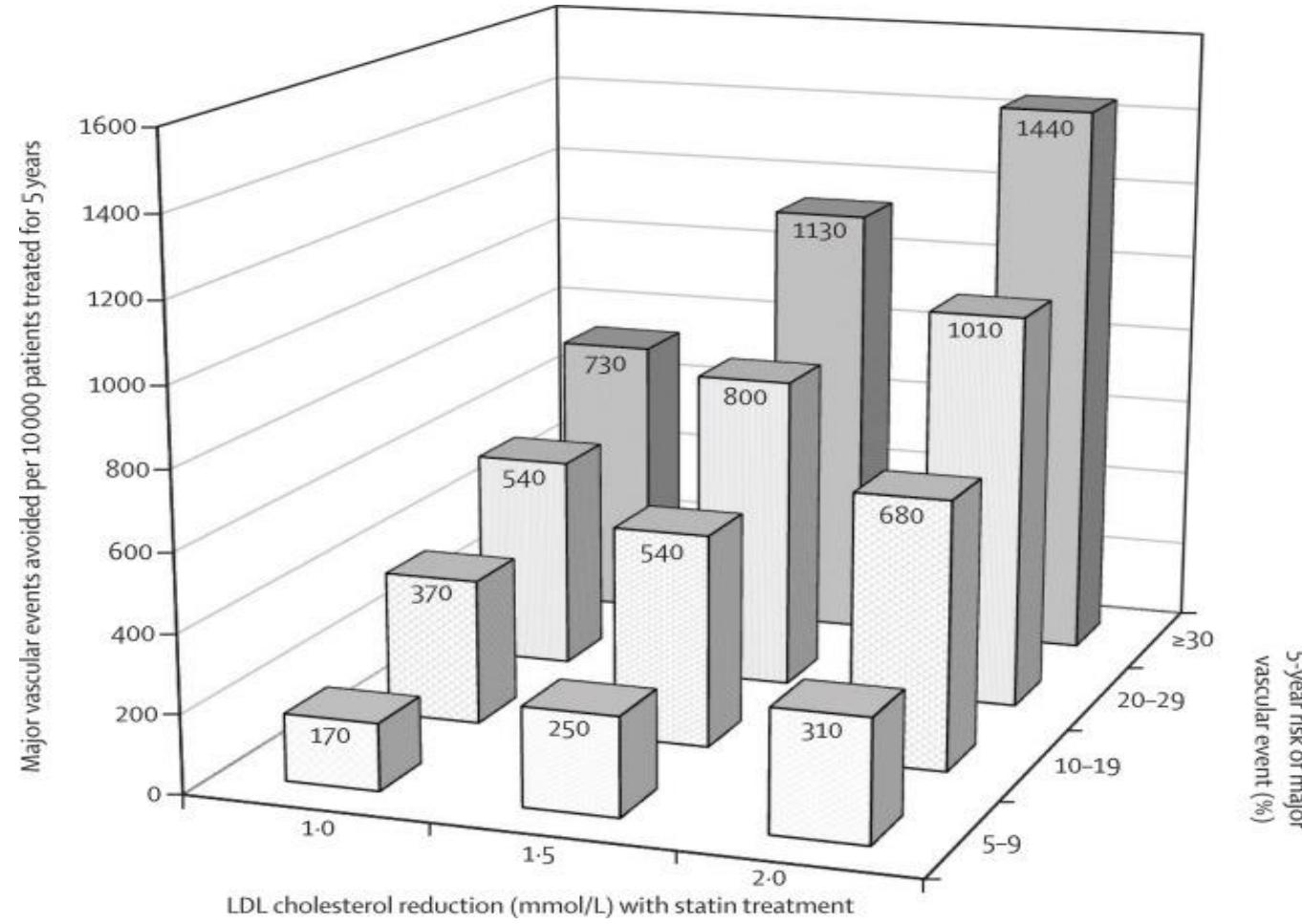
LDL-C and atherosclerosis: a coalescence of evidence



Meta-analysis of various methods to lower LDL-C



Predicted absolute reductions in risks of major vascular events (after the first year) by lowering LDL cholesterol with statin therapy for 5 years in people at different levels of absolute risk



Intervention strategies as a function of total cardiovascular risk and untreated low-density lipoprotein cholesterol levels

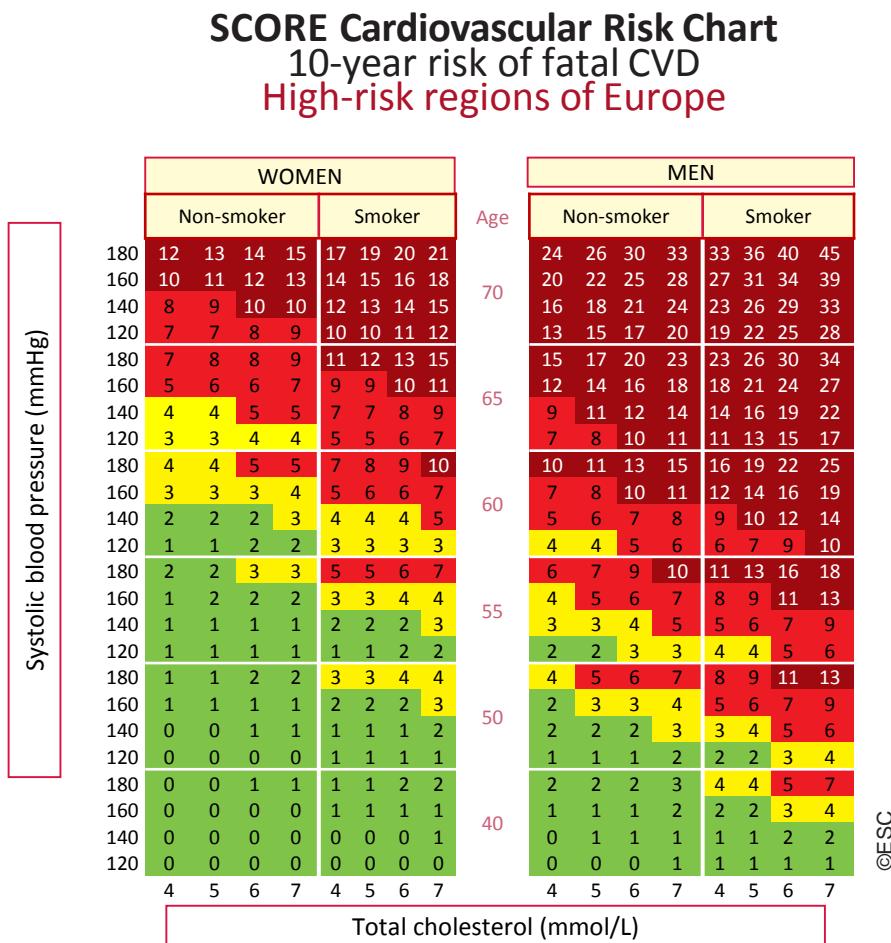
| Total CV risk (SCORE) % | | Untreated LDL-C levels | | | | | | |
|--|---|--|--|--|--|--|--|-------|
| Primary Prevention | <1 low-risk | <1.4 mmol/L (55 mg/dL) | 1.4 to <1.8 mmol/L (55 to <70 mg/dL) | 1.8 to <2.6 mmol/L (70 to <100 mg/dL) | 2.6 to <3.0 mmol/L (100 to <116 mg/dL) | 3.0 to <4.9 mmol/L (116 to <190 mg/dL) | ≥4.9 mmol/L (≥ 190 mg/dL) | |
| | Class ^a /Level ^b | I/C | I/C | I/C | I/C | I/C | IIa/A | IIa/A |
| | ≥1 to <5, or moderate risk | Lifestyle advice | Lifestyle advice | Lifestyle advice | Lifestyle intervention, consider adding drug if uncontrolled | Lifestyle intervention, consider adding drug if uncontrolled | Lifestyle intervention and concomitant drug intervention | |
| | Class ^a /Level ^b | I/C | I/C | IIa/A | IIa/A | IIa/A | IIa/A | |
| | ≥5 to <10, or high- risk | Lifestyle advice | Lifestyle advice | Lifestyle intervention, consider adding drug if uncontrolled | Lifestyle intervention and concomitant drug intervention | Lifestyle intervention and concomitant drug intervention | Lifestyle intervention and concomitant drug intervention | |
| | Class ^a /Level ^b | IIa/A | IIa/A | IIa/A | I/A | I/A | I/A | |
| | ≥10, or at very-high risk due to a risk condition | Lifestyle advice | Lifestyle intervention, consider adding drug if uncontrolled | Lifestyle intervention and concomitant drug intervention | Lifestyle intervention and concomitant drug intervention | Lifestyle intervention and concomitant drug intervention | Lifestyle intervention and concomitant drug intervention | |
| Secondary Prevention | Class ^a /Level ^b | IIa/B | IIa/A | I/A | I/A | I/A | I/A | |
| | Very-high risk | Lifestyle intervention, consider adding drug if uncontrolled | Lifestyle intervention and concomitant drug intervention | Lifestyle intervention and concomitant drug intervention | |
| Class ^a /Level ^b | | IIa/A | I/A | I/A | I/A | I/A | I/A | |

©ESC

FUTURE CHALLENGES

- LIFETIME RISK
- HDL
- NON HDL AND/OR APO B IN EVERYBODY?
- Lp(a)
- PERCENT REDUCTION VS GOALS
- TRIAL DESIGN
- STEPWISE APPROACH?
- ADHERENCE TO THERAPY

SCORE chart for European populations at high cardiovascular disease risk

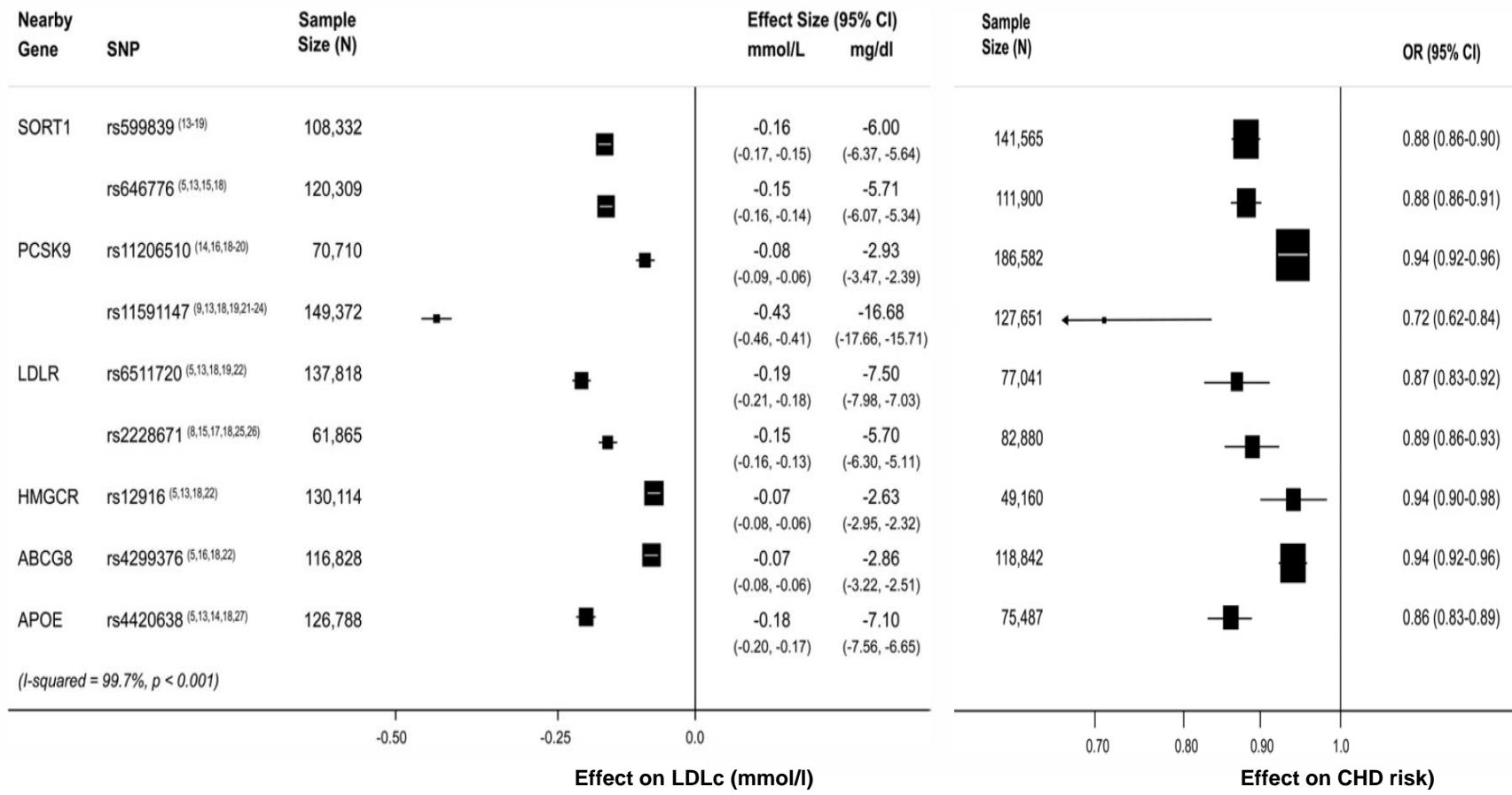


SCORE chart for European populations at high cardiovascular disease risk

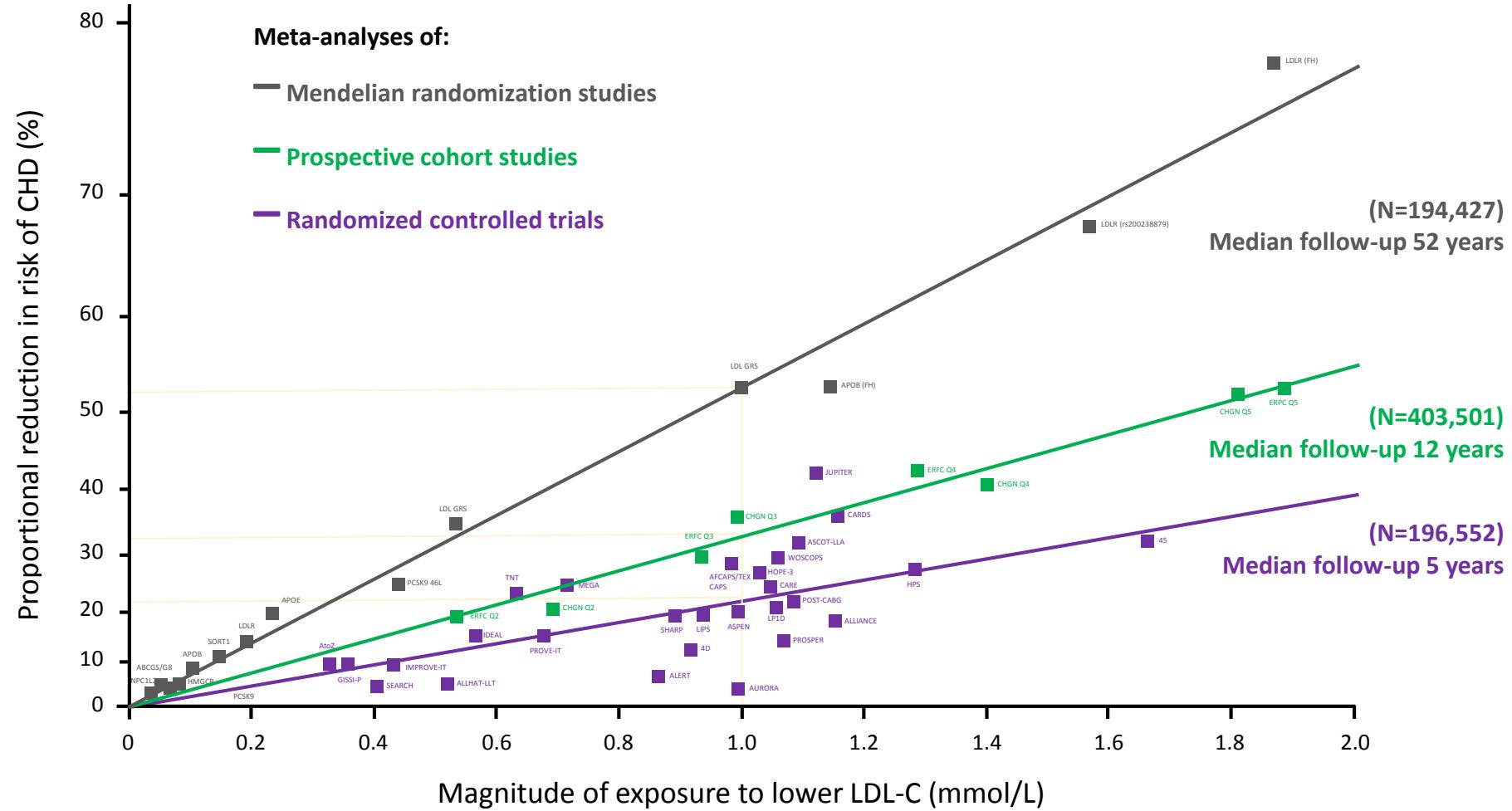
A horizontal color scale consisting of four segments. The first segment is yellow and labeled <3%. The second segment is orange-red and labeled 3-4%. The third segment is dark red and labeled 5-9%. The fourth segment is black and labeled ≥10%.

Lessons from nature: Lifetime LDL variation and CHD risk

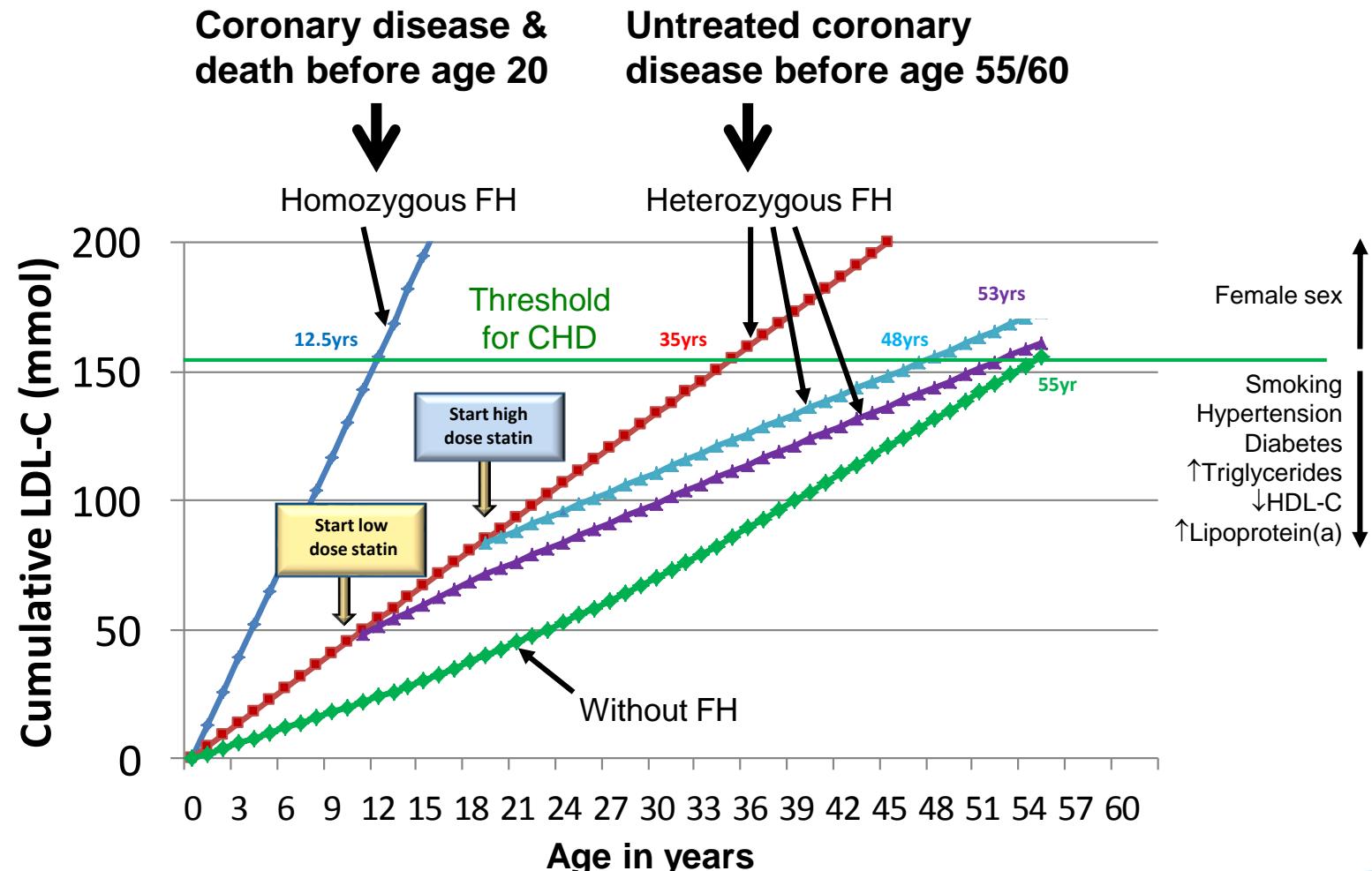
Analysis of genes regulating LDL cholesterol and association with CHD risk



Log-linear association per unit change in LDL-C and the risk of CV disease



LDL cholesterol burden in individuals with or without familial hypercholesterolaemia as a function of the age of initiation of statin therapy

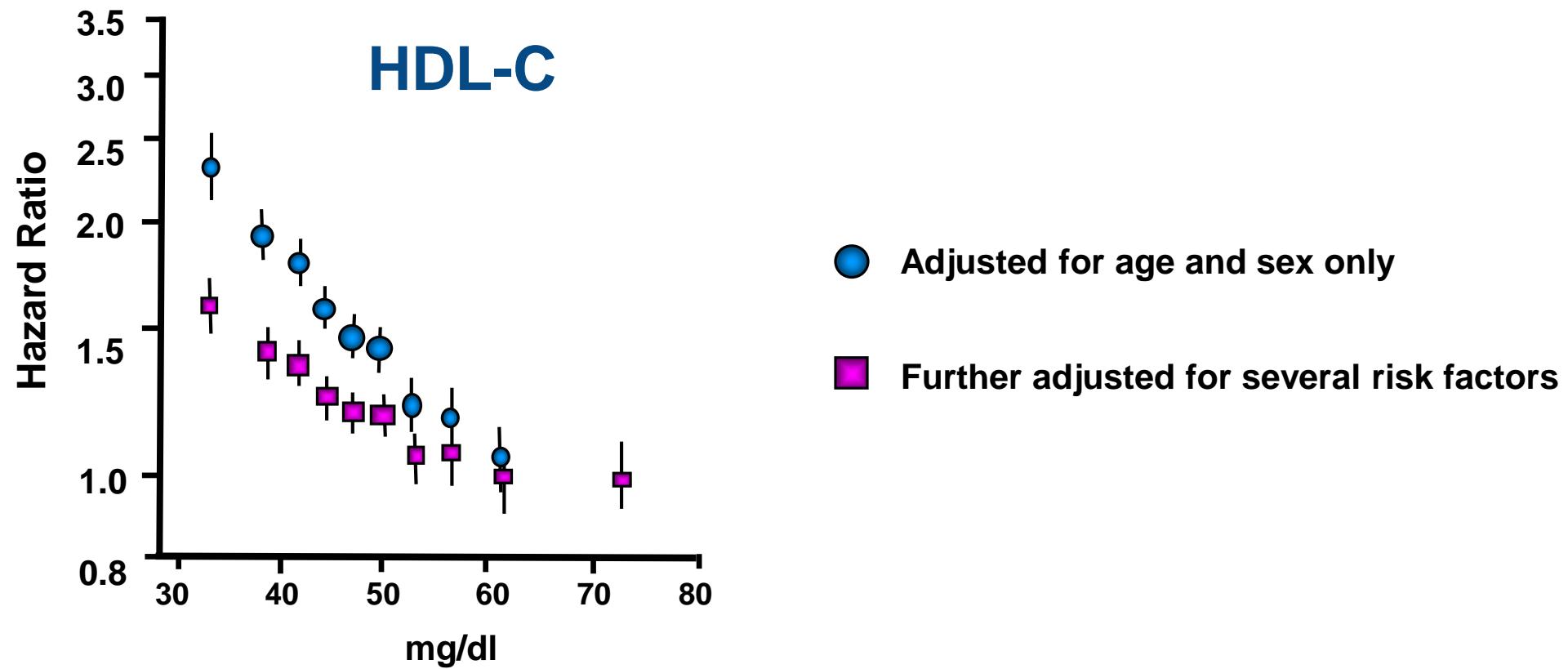


FUTURE CHALLENGES

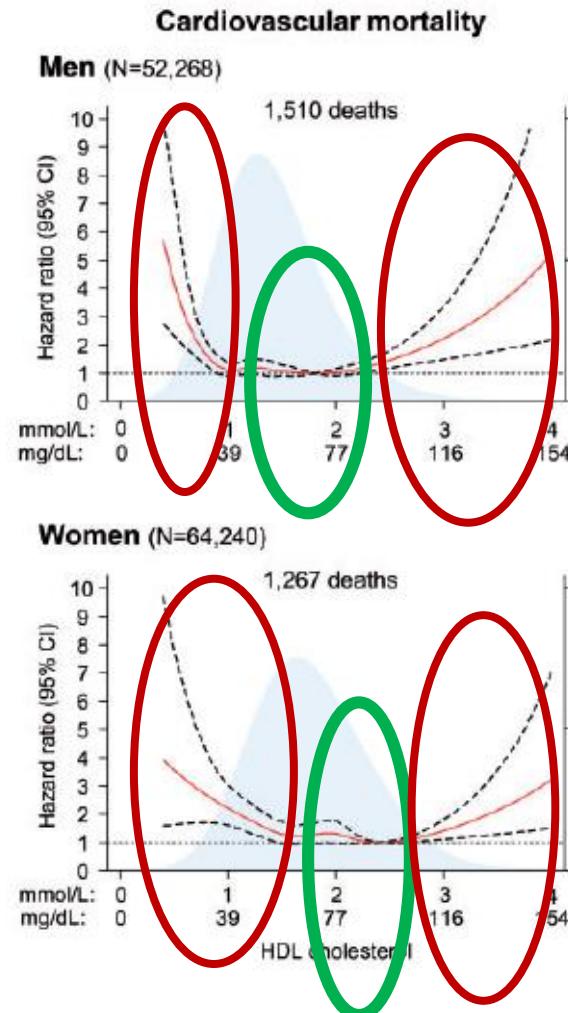
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Hazard Ratios for CHD Across Quantiles of HDL-Cholesterol

From the Emerging Risk Factors Collaboration (68 studies in 302 430 participants)



CV mortality and elevated values of HDL-C



***HDL-C associated
with lowest CV mortality***

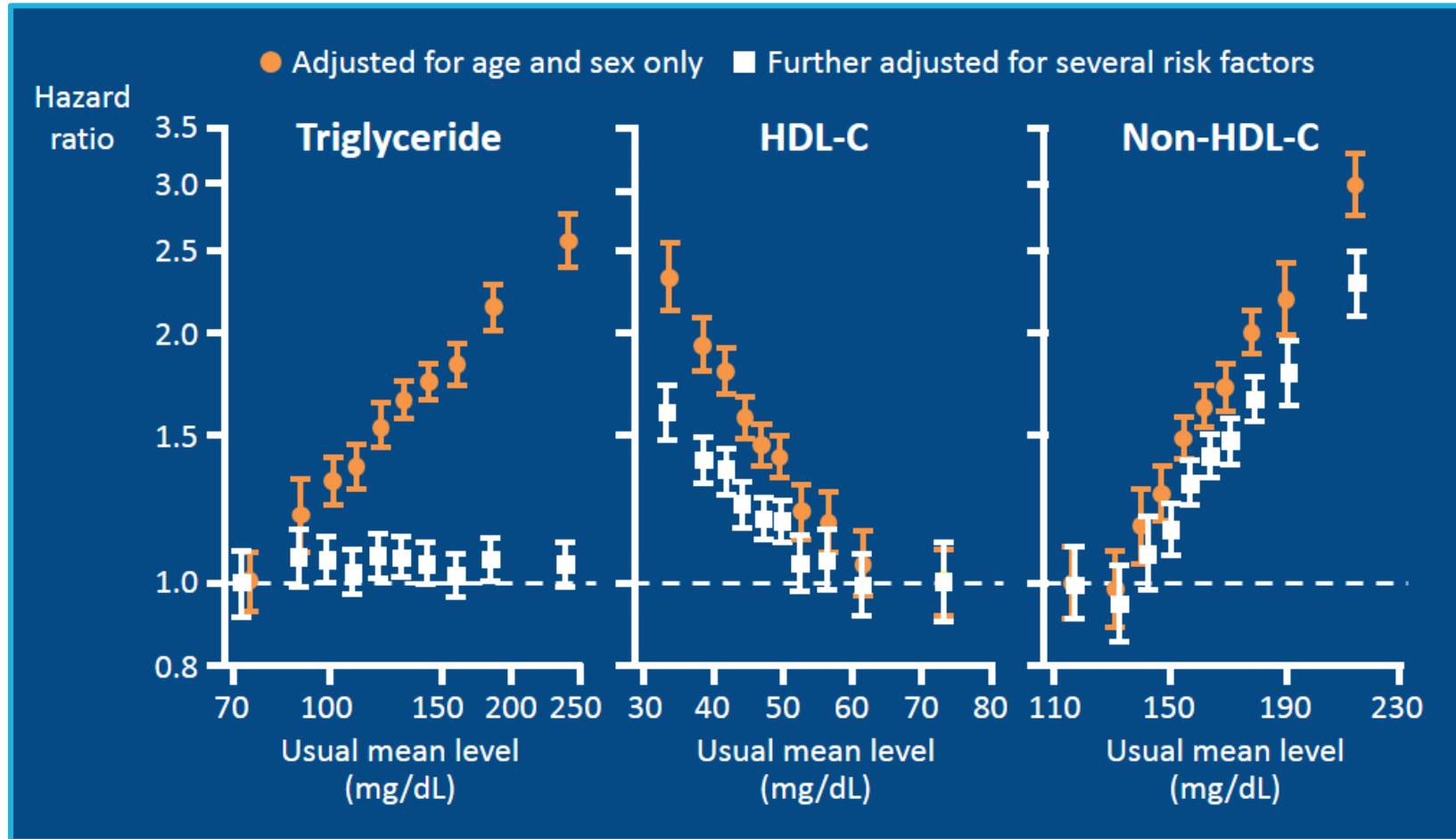
Males : 50–80 mg/dL

Females : 70–90 mg/dL

FUTURE CHALLENGES

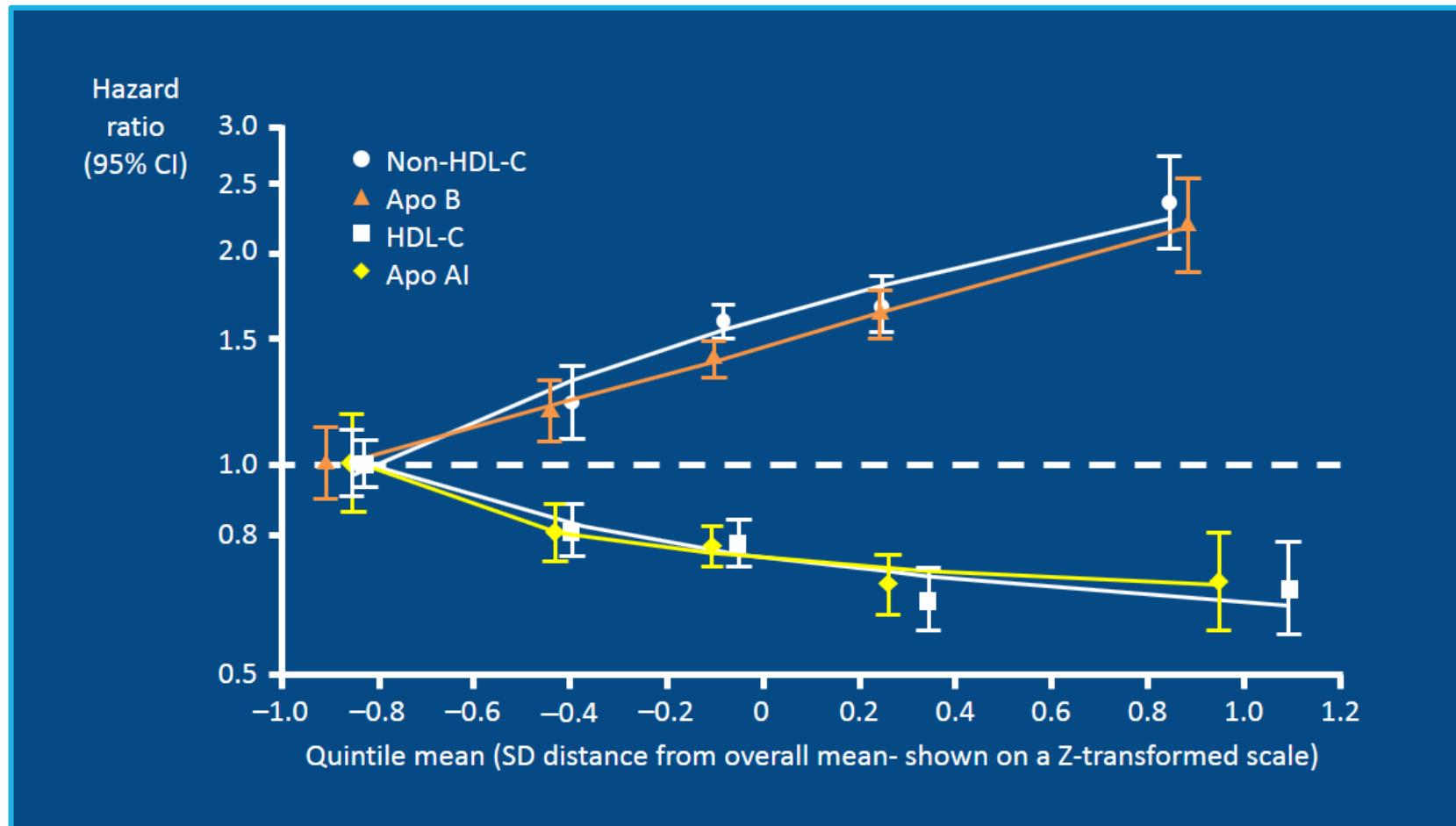
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Hazard ratios for coronary heart disease across quintiles

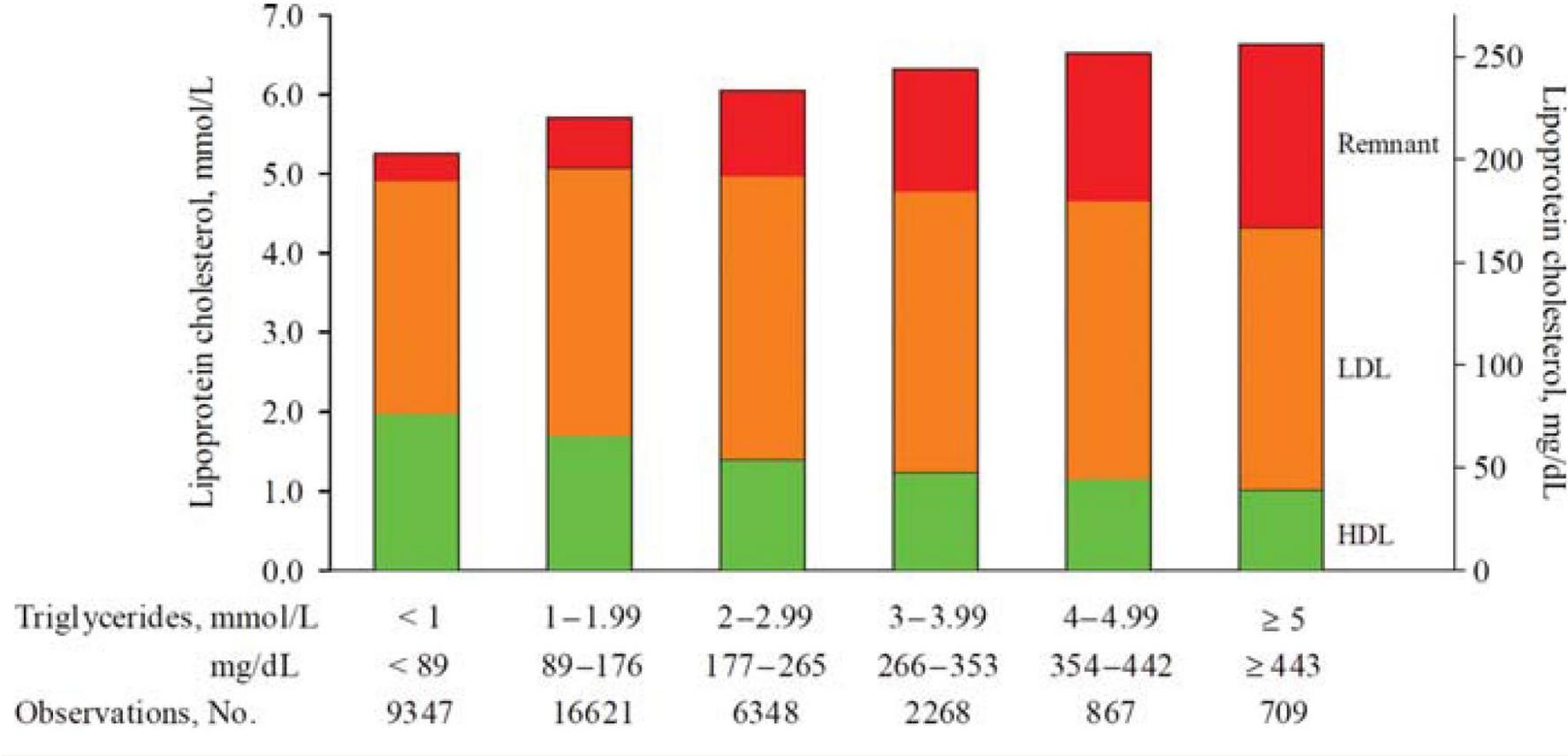


The Emerging Risk Factors Collaboration. JAMA 2009;302:1993–2000

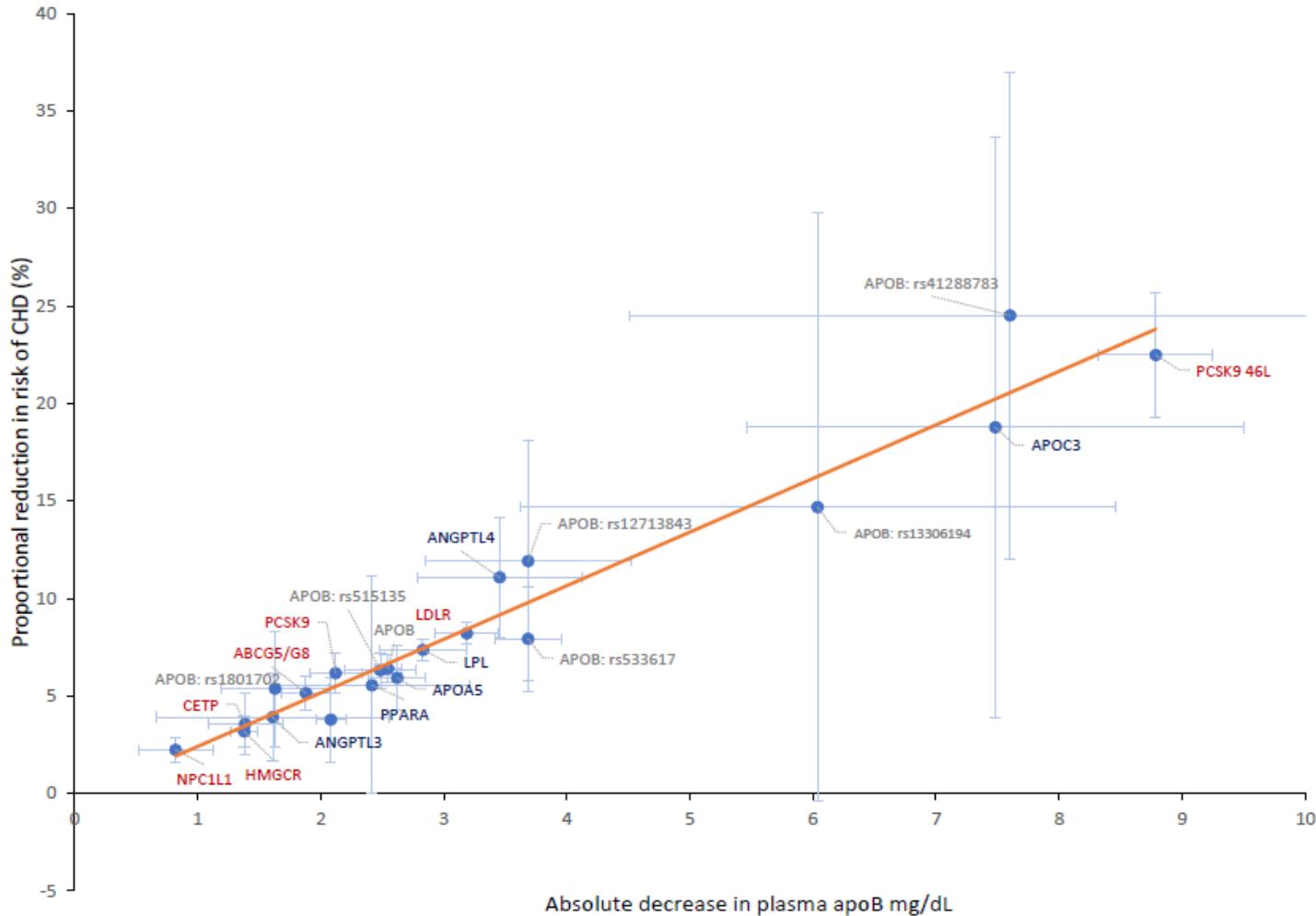
Risk ratios for coronary heart disease across fifths of usual lipids or apolipoproteins



Cholesterol in atherogenic lipoproteins: non-HDL



Log-linear association between changes in apoB & CHD



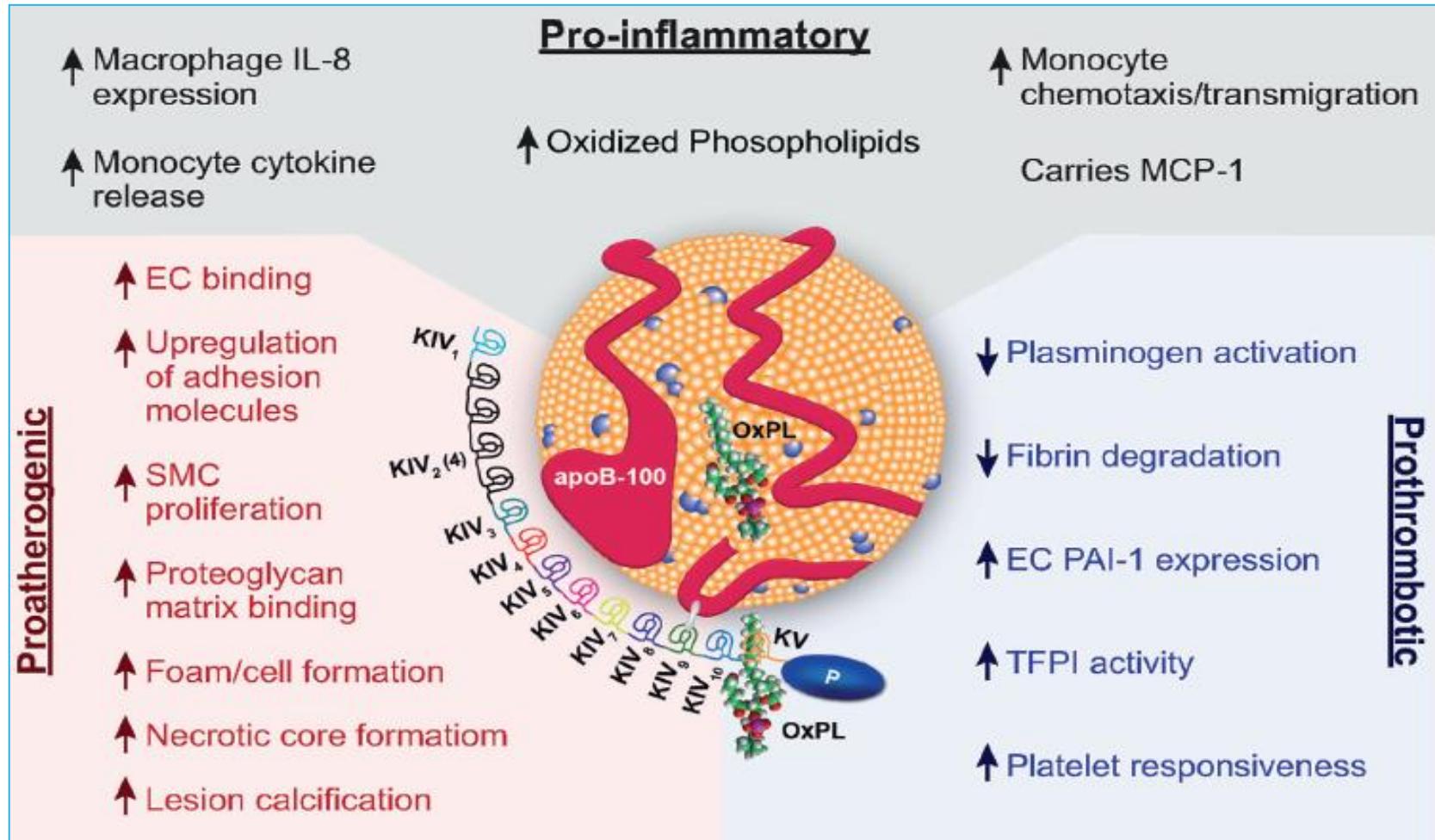
Multivariable Mendelian randomization

| 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 |

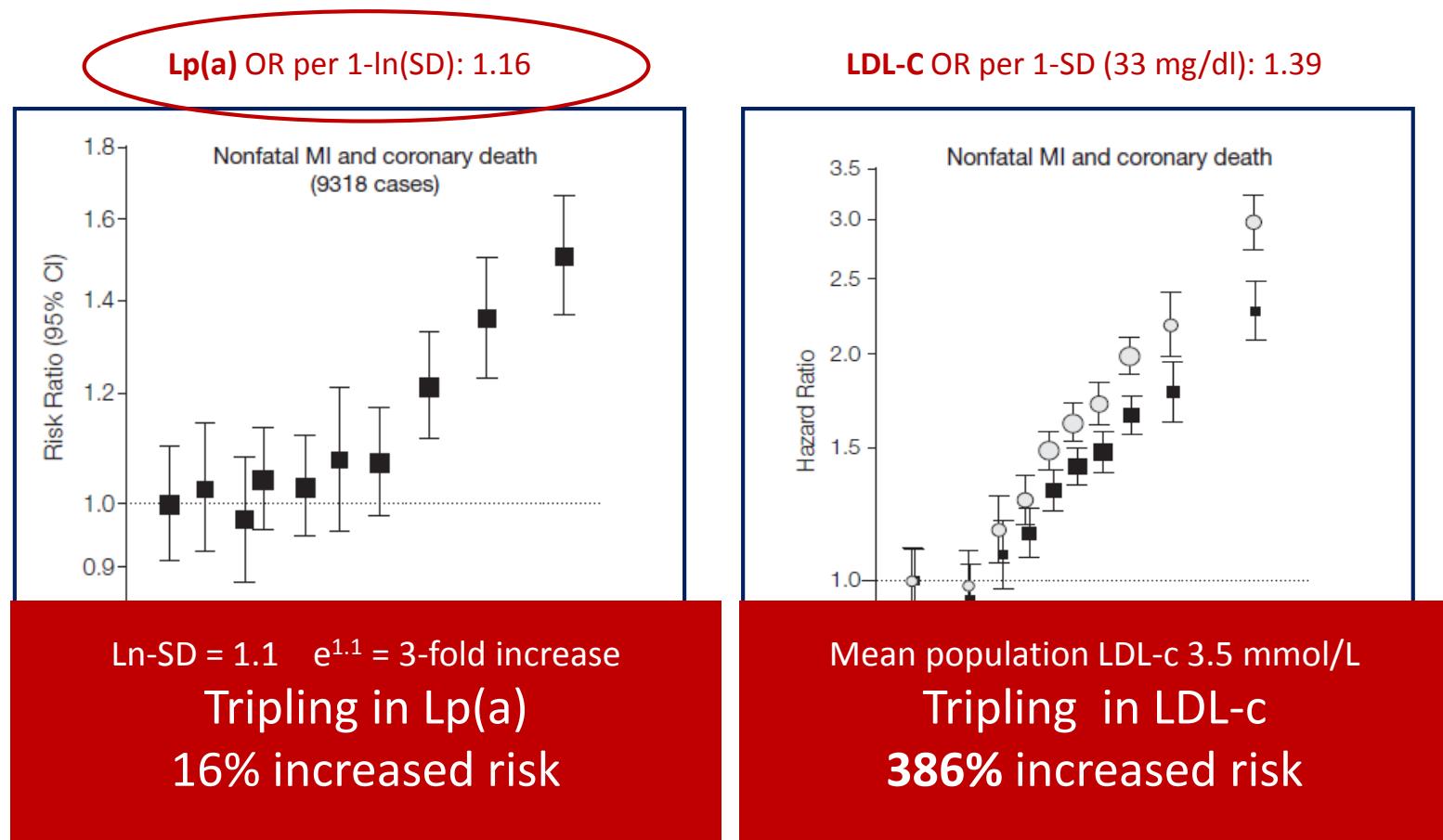
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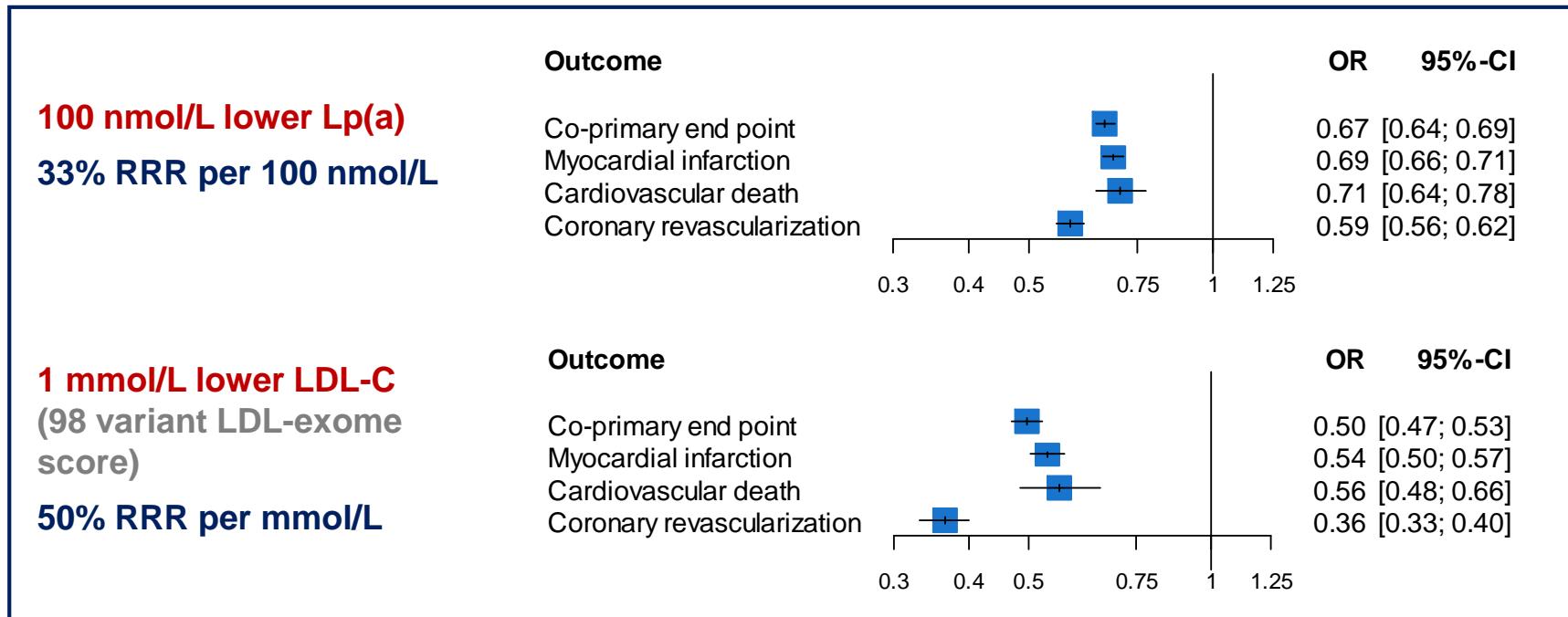
Lp(a)



Effect of Lp(a) compared to effect of LDL-C on risk of CVD

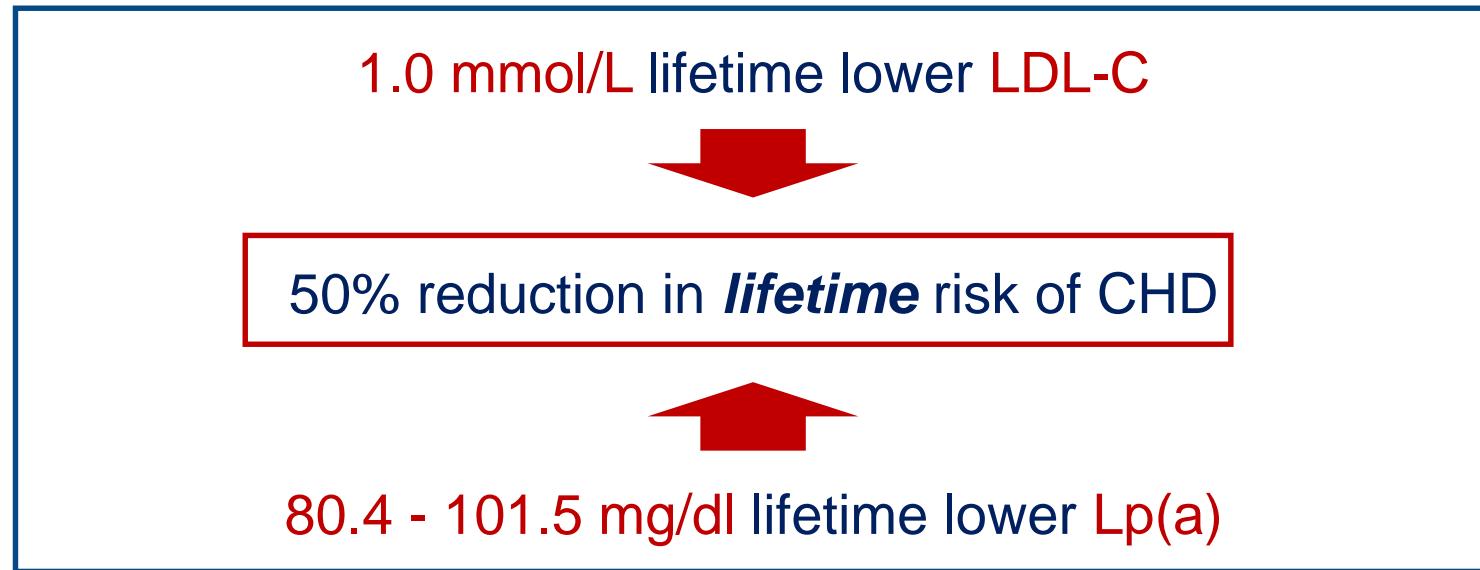


486,000 UK Biobank: How much do need to lower Lp(a) in nmol/L?



164.5 nmol/L (95% CI: 156.8 – 174.7) ~ 1 mmol/L LDL-C

Changes in Lp(a) and LDL-C with equivalent effects on CVD



Reconciles epidemiologic and Mendelian randomization studies

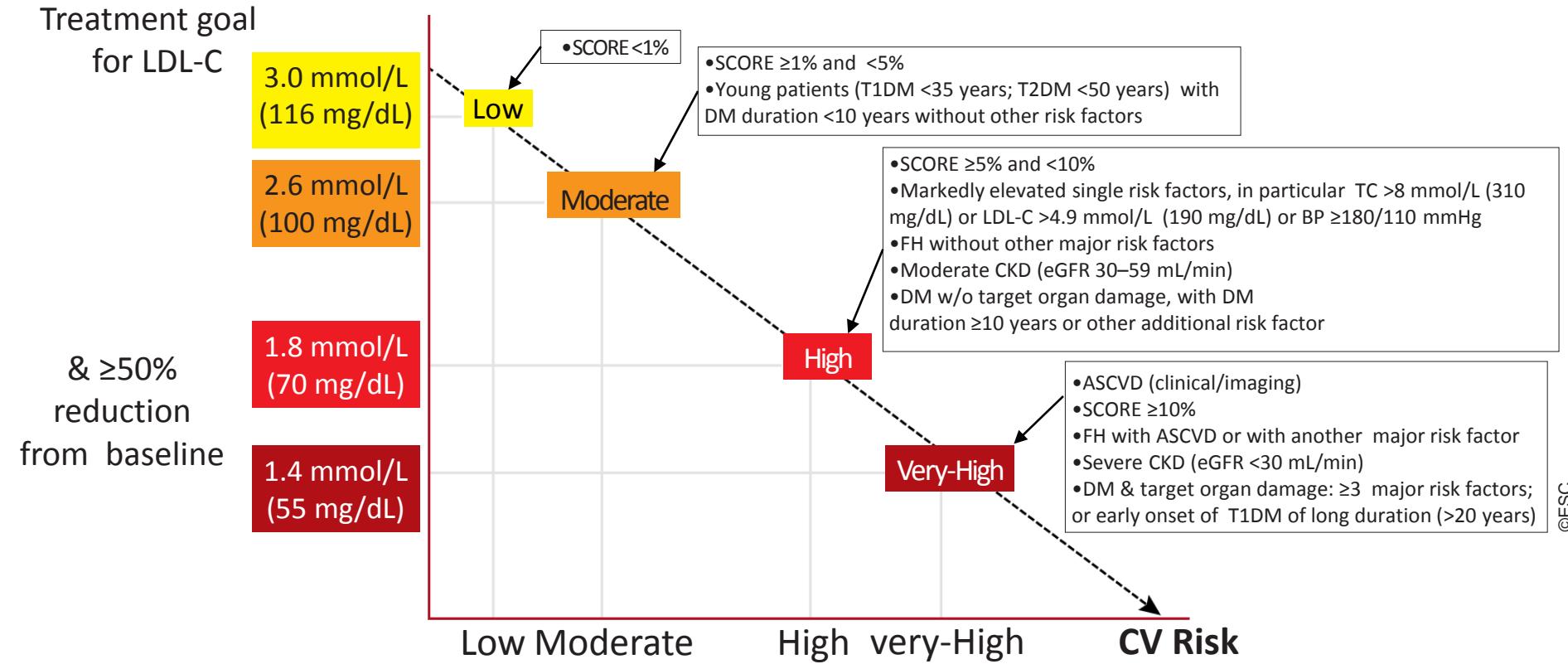
Explains failure of lowering Lp(a) in niacin, CETP and PCSK9 randomized trials

Informs the optimal design of RCTs for potent Lp(a) lowering agents

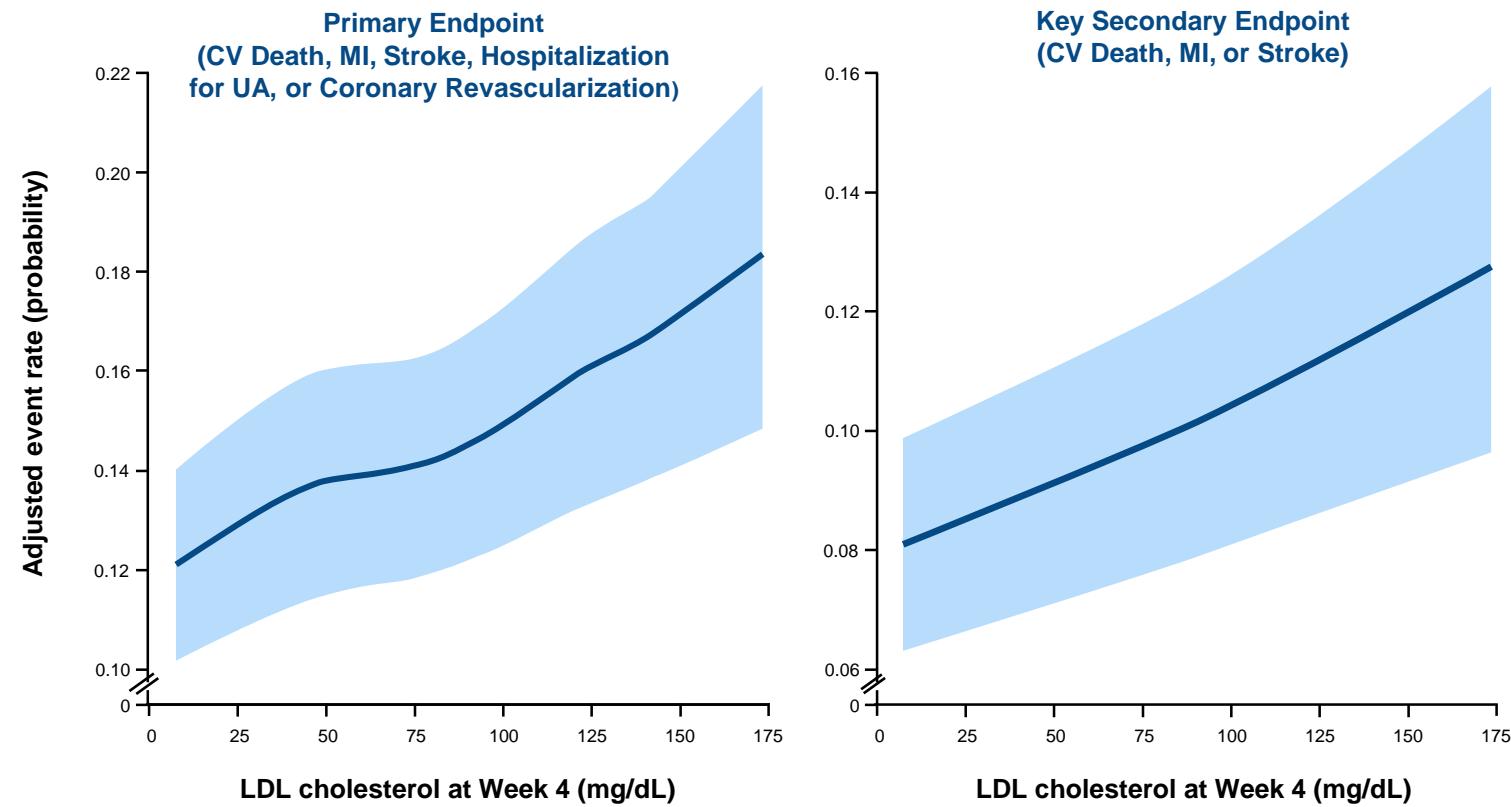
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Treatment goals for low-density lipoprotein cholesterol (LDL-C) across categories of total cardiovascular disease risk



Relationship between achieved LDL-C level at week 4 and risk for the primary and key secondary efficacy composite endpoints



For the primary endpoint $p = 0.0012$ for the β coefficient. For the secondary endpoint $p = 0.0001$ for the β coefficient.

CV = cardiovascular, MI = myocardial infarction, UA = unstable angina. The blue line represents the hazard ratio and shaded areas are the 95% CIs of the regression model estimate

The AACE/ACE have introduced a new “extreme risk” category for cardiovascular disease

AACE 2017 Guidelines

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF CARDIOVASCULAR DISEASE

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American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice are systematically developed statements to assist health care professionals in medical decision-making for specific clinical conditions but are in no way a substitute for a medical professional's independent judgment and should not be considered medical advice.

Most of the content herein is based on literature reviews. In areas of uncertainty, professional judgment was applied. These guidelines are a working document that reflects the state of the field at the time of publication. Because rapid changes in this area are expected, periodic revisions are inevitable. Medical professionals are encouraged to use this information in conjunction with, and not as a replacement for, their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made in light of local resources and individual circumstances.

Table 6
Atherosclerotic Cardiovascular Disease Risk Categories and
Low-Density Lipoprotein Treatment Goals

| Risk category | Risk factors ^a /10-year risk ^b | Treatment goals | | |
|----------------|---|-----------------|-------------------|---------------|
| | | LDL-C (mg/dL) | Non-HDL-C (mg/dL) | Apo B (mg/dL) |
| Extreme Risk | <ul style="list-style-type: none">- Progressive ASCVD including unstable angina in patients after achieving an LDL-C <70 mg/dL- Established clinical cardiovascular disease in patients with DM, CKD 3/4, or HeFH- History of premature ASCVD (<55 male, <65 female) | <55 | <80 | <70 |
| Very High Risk | <ul style="list-style-type: none">- Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20%- Diabetes or CKD 3/4 with 1 or more risk factor(s)- HeFH | <70 | <100 | <80 |
| High Risk | <ul style="list-style-type: none">- ≥2 risk factors and 10-year risk 10%-20%- Diabetes or CKD 3/4 with no other risk factors | <100 | <130 | <90 |
| Moderate Risk | ≤2 risk factors and 10-year risk <10% | <100 | <130 | <90 |
| Low Risk | 0 risk factors | <130 | <160 | NR |

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DM, diabetes mellitus; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; MESA, Multi-Ethnic Study of Atherosclerosis; NR, not recommended; UKPDS, United Kingdom Prospective Diabetes Study.

^a Major independent risk factors are high LDL-C, polycystic ovary syndrome, cigarette smoking, hypertension (blood pressure ≥140/90 mm Hg or on hypertensive medication), low HDL-C (<40 mg/dL), family history of coronary artery disease (in male, first-degree relative younger than 55 years; in female, first-degree relative younger than 65 years), chronic renal disease (CKD) stage 3/4, evidence of coronary artery calcification and age (men ≥45; women ≥55 years). Subtract 1 risk factor if the person has high HDL-C.

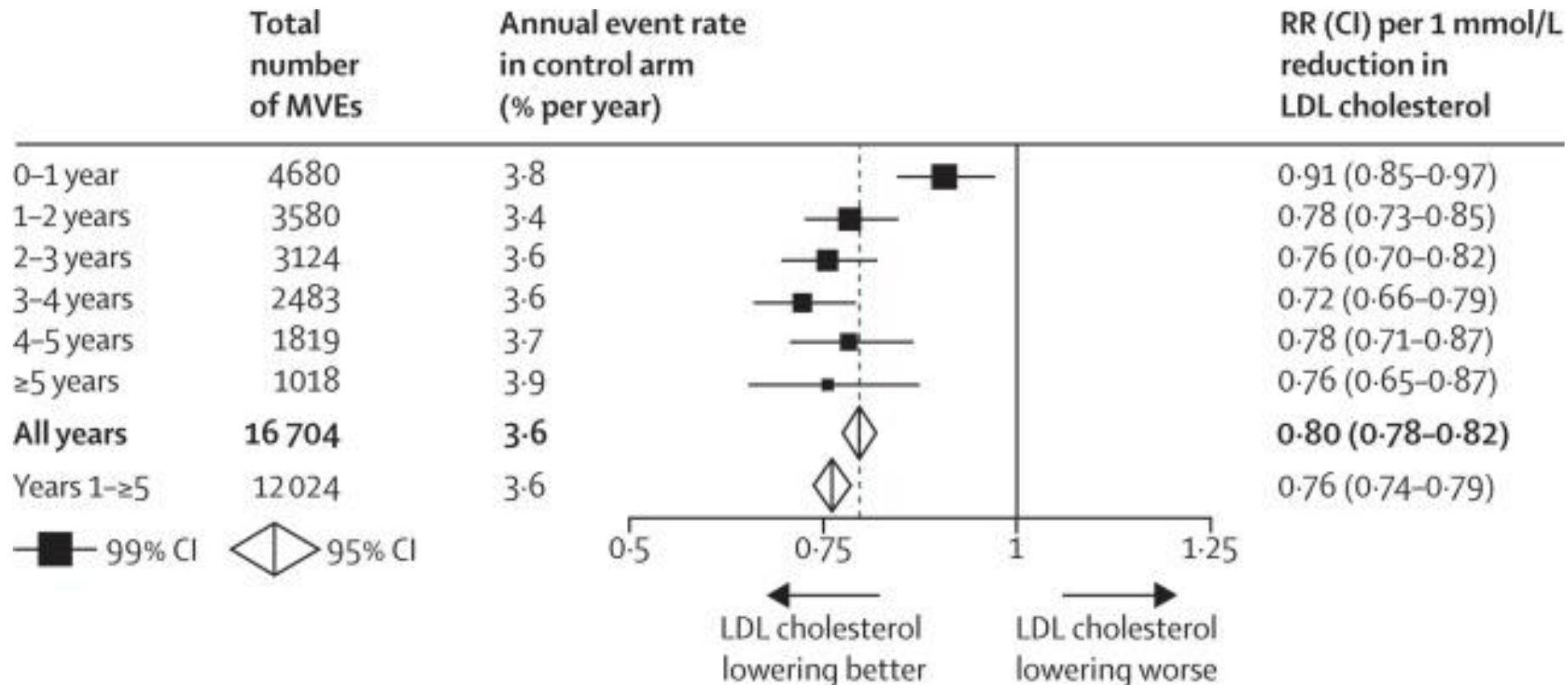
^b Framingham risk scoring is applied to determine 10-year risk.

| Target | UK 2016 NICE | Canada 2016 CCS | Europe 2019 ESC/EAS | US 2018 ACC/AHA |
|--|--------------------------------------|---|---|-------------------------------------|
| Secondary prevention: ASCVD | | | | |
| LDL cholesterol | ≥50% | >50% or <77 mg/dL <2.0 mmol/L | ≥50% & <55 mg/dL <1.4 mmol/L | ≥50% & <70 mg/dL <1.8 mmol/L |
| nonHDL cholesterol | | <100 mg/dL <2.6 mmol/L | <85 mg/dL <2.2 mmol/L | <100 mg/dL <2.6 mmol/L |
| Apolipoprotein B | | <80 mg/dL | <65 mg/dL | |
| Primary prevention: Familial hypercholesterolemia | | | | |
| LDL cholesterol | ≥50% | >50% | ≥50% & <55 or <70 mg/dL <1.4 or <1.8 mmol/L | ≥50% |
| Primary prevention: Absolute 10-year risk based, (diabetes or chronic kidney disease) | | | | |
| LDL cholesterol | ≥40% ≥50% if ↑nonHDL-C | >50% or <77 mg/dL <2.0 mmol/L | ≥50% & <55, <70 or (<100 mg/dL) <1.4, <1.8 or (<2.6 mmol/L) | ≥30% or ≥50% |
| nonHDL cholesterol | | <100 mg/dL <2.6 mmol/L | <85 mg/dL <2.2 mmol/L | |
| Apolipoprotein B | | <80 mg/dL | <65 mg/dL | |

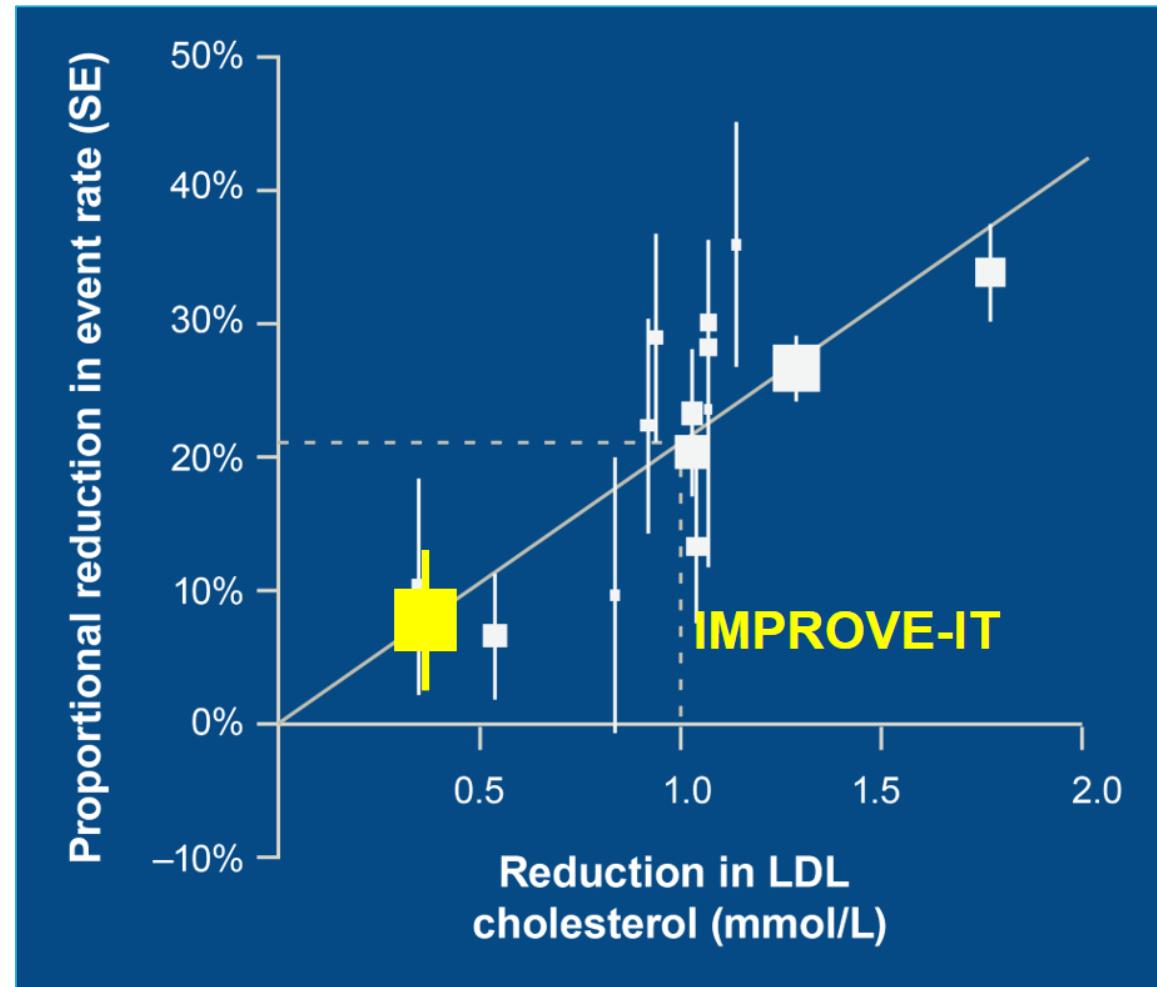
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Proportional reductions in risks of major vascular events per mmol/L reduction in LDL cholesterol during each year of scheduled statin treatment, in randomised trials of routine statin therapy versus no routine statin use

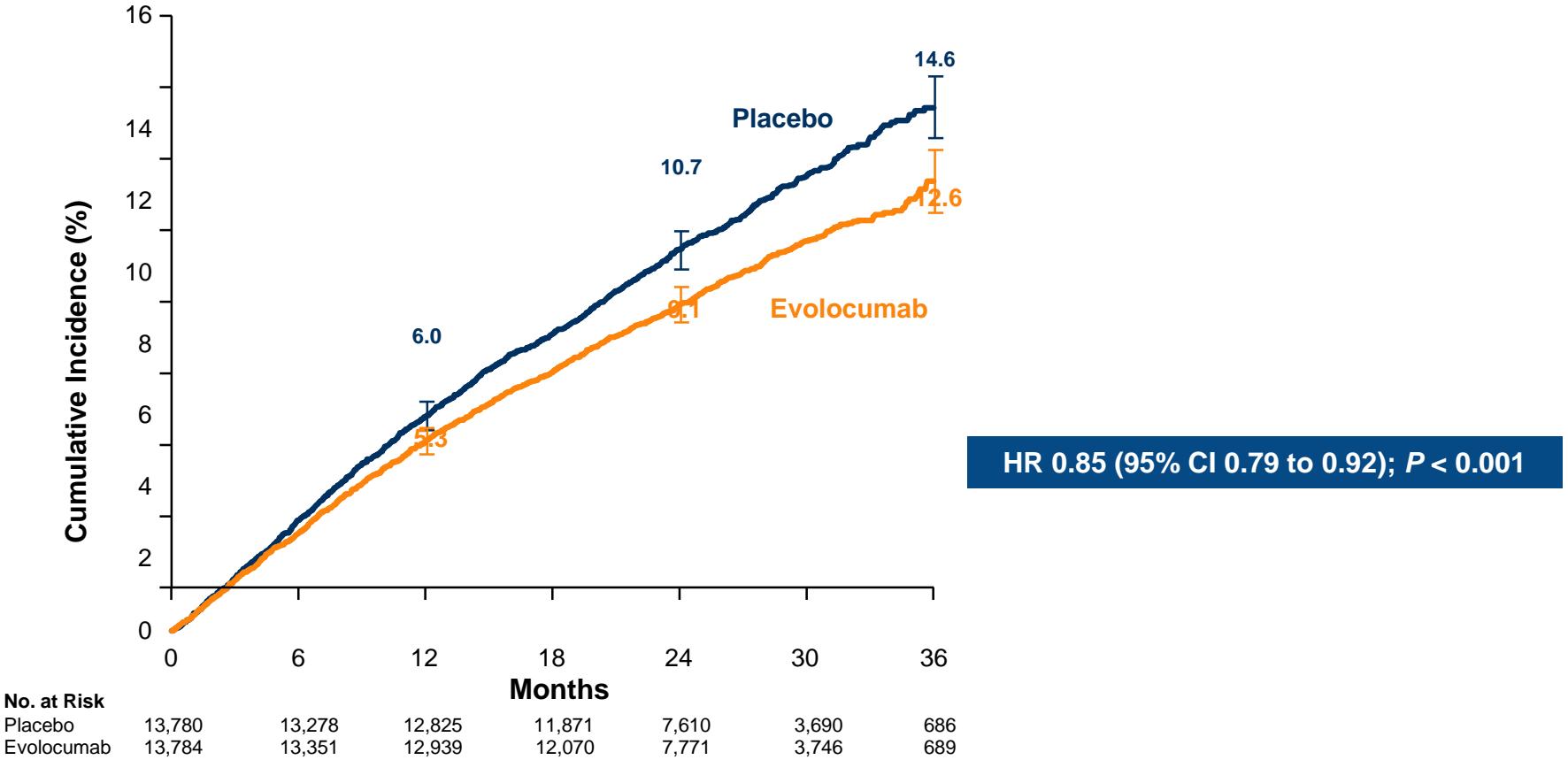


IMPROVE-IT vs. CTT: Ezetimibe vs. statin benefit



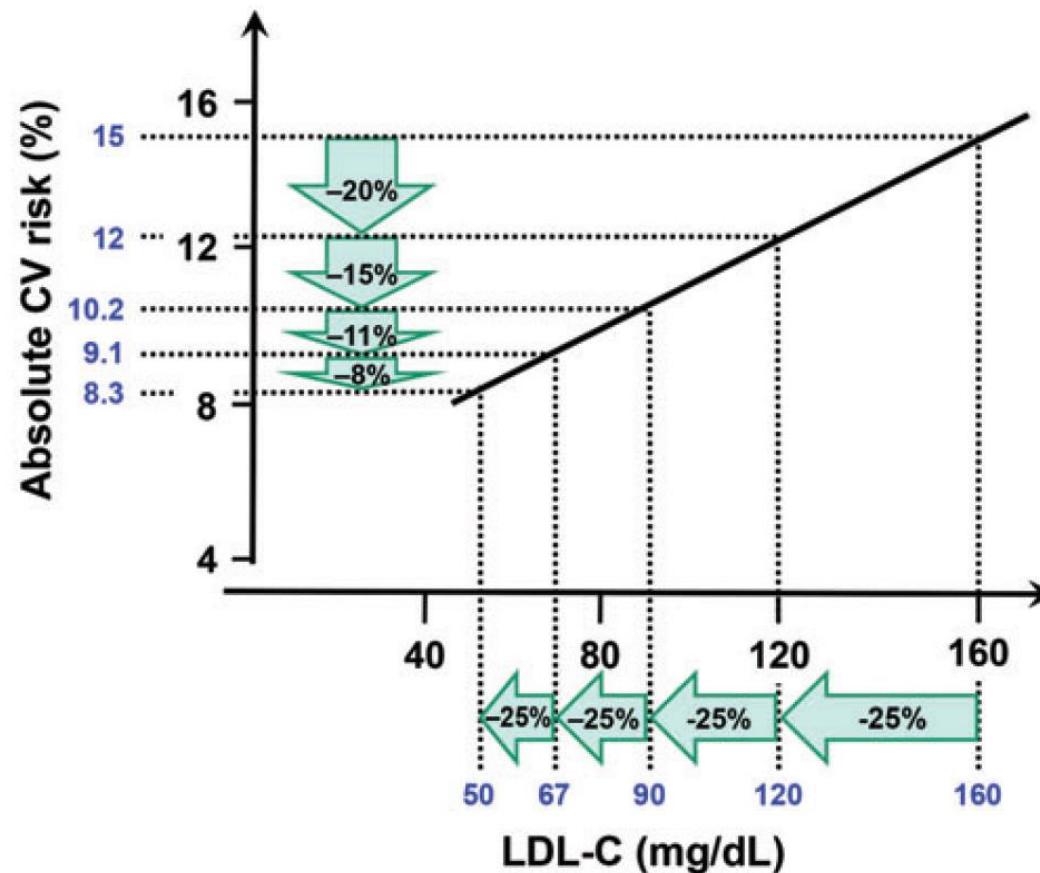
CTT Collaboration. Lancet 2005; 366:1267-78; Lancet 2010;376:1670-81.

Primary endpoint: composite of CV death, MI, stroke, hospitalization for UA, or coronary revascularization

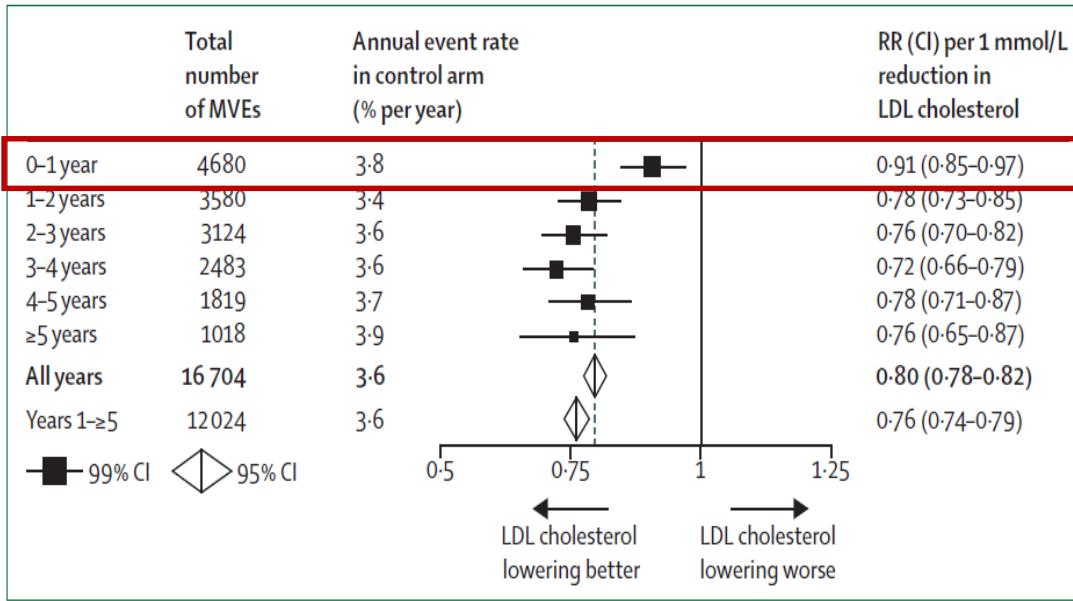


CV = Cardiovascular; MI = Myocardial infarction; UA = Unstable angina; HR = Hazard ratio

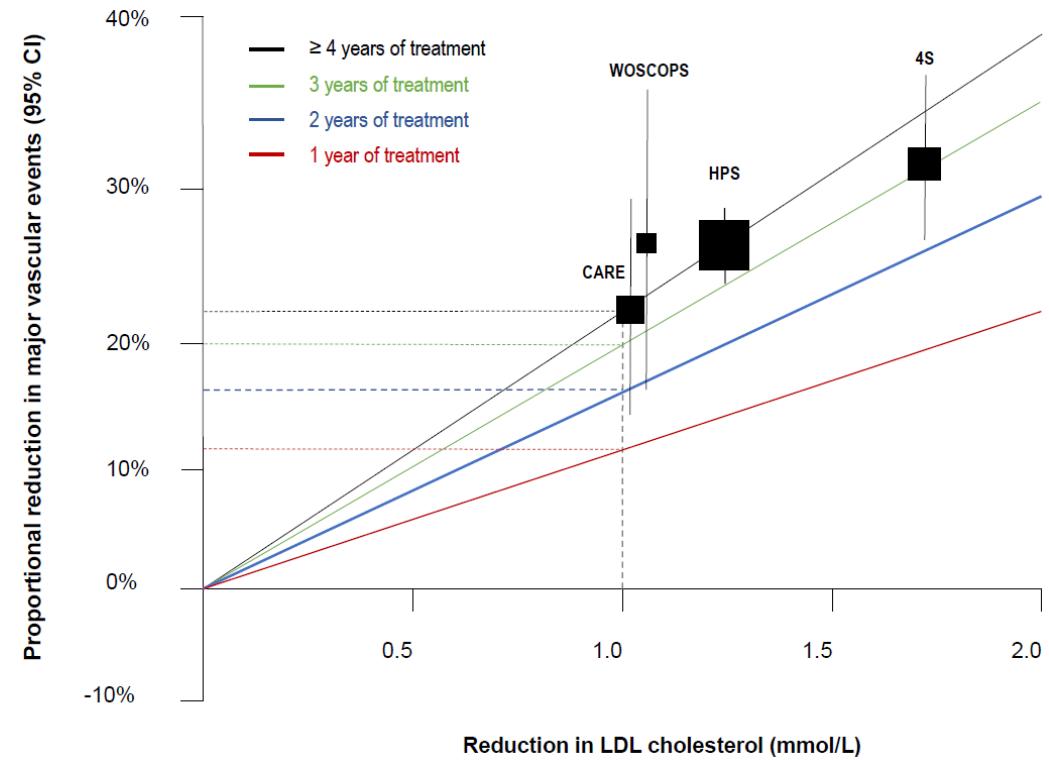
Diminishing risk reduction for the same relative LDL-C lowering with lower baseline LDL-C



CTT regression lines by duration of follow-up

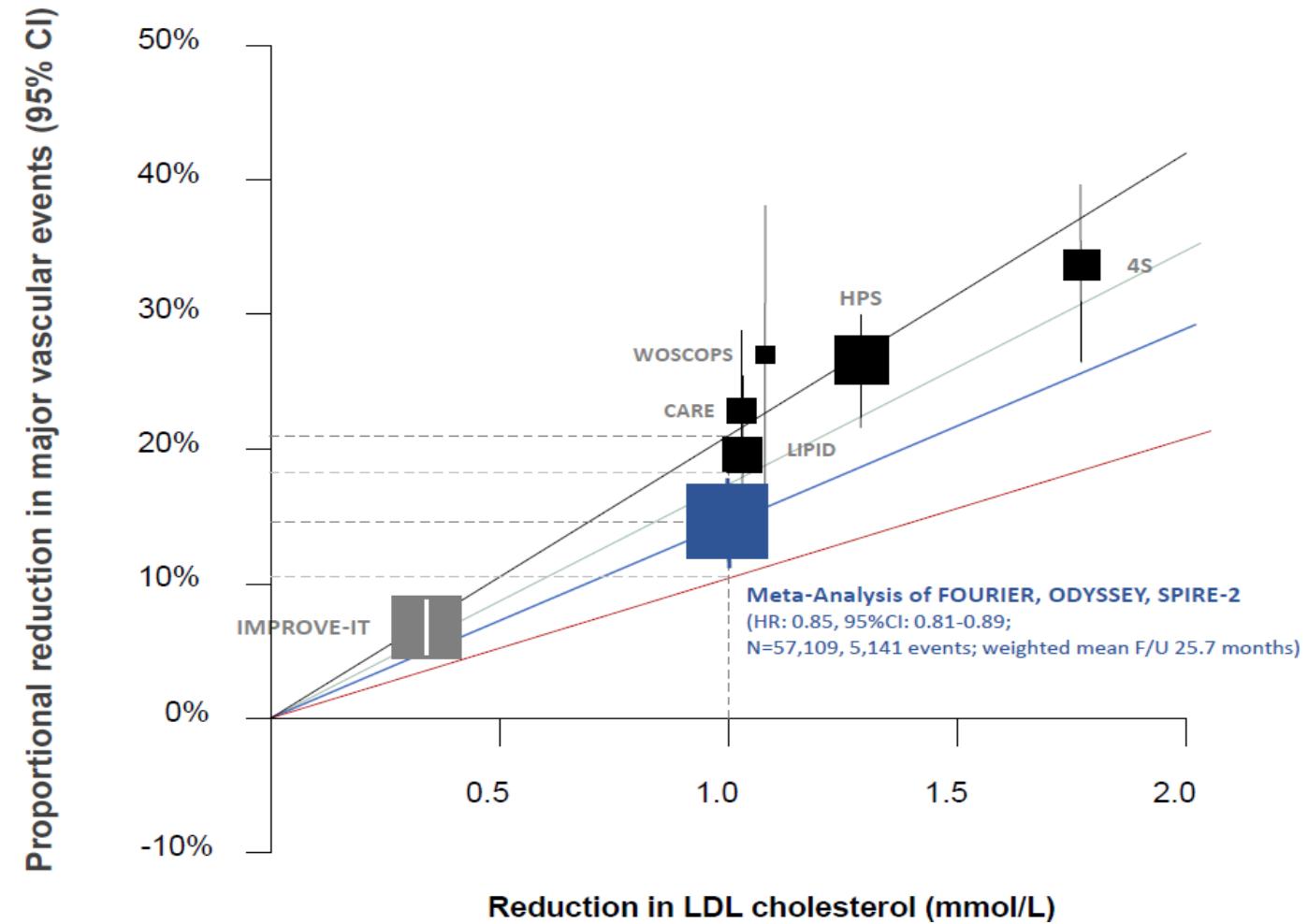


Cholesterol Treatment Trialists Collaboration. Lancet. 2010;376:1670-81



Ference BA, et al. Eur Heart J. 2018; 39(27):2540-2545

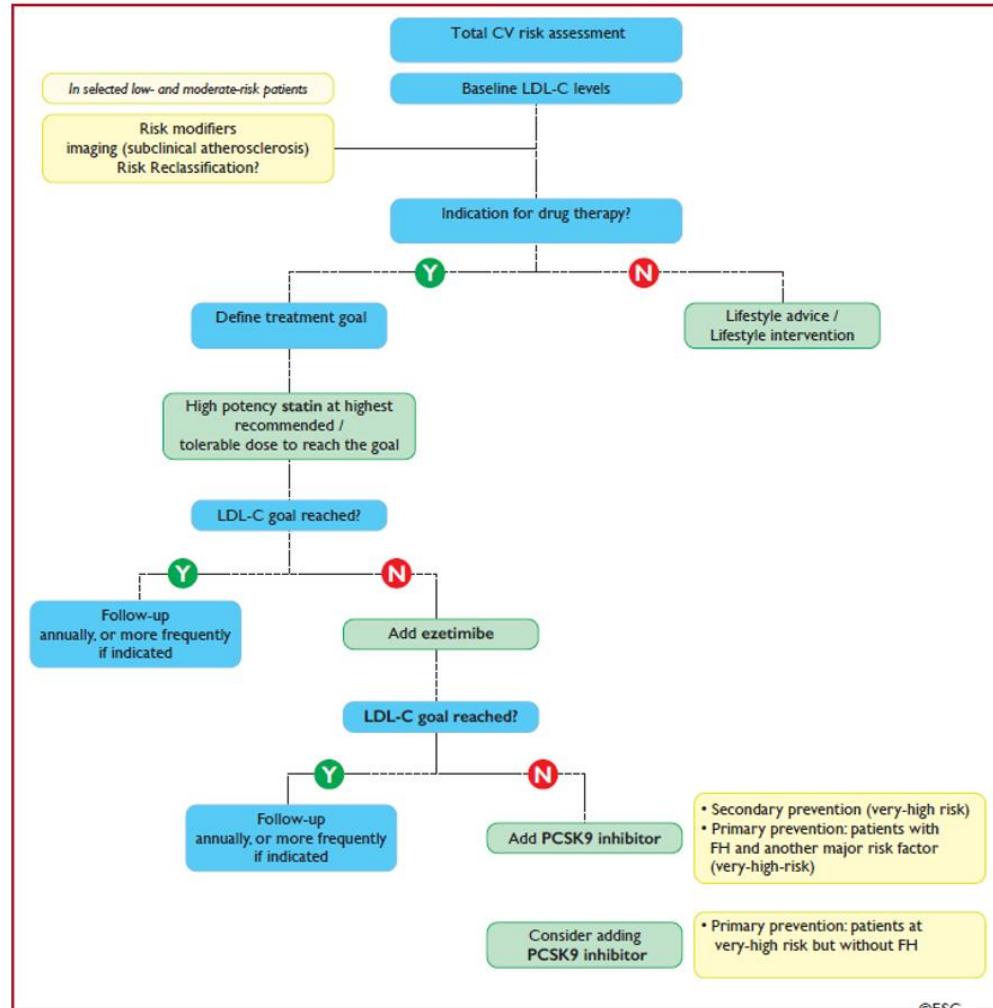
Comparison of PCSK9 inhibitors and statins by duration of treatment



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Treatment algorithm for pharmacological LDL-C lowering

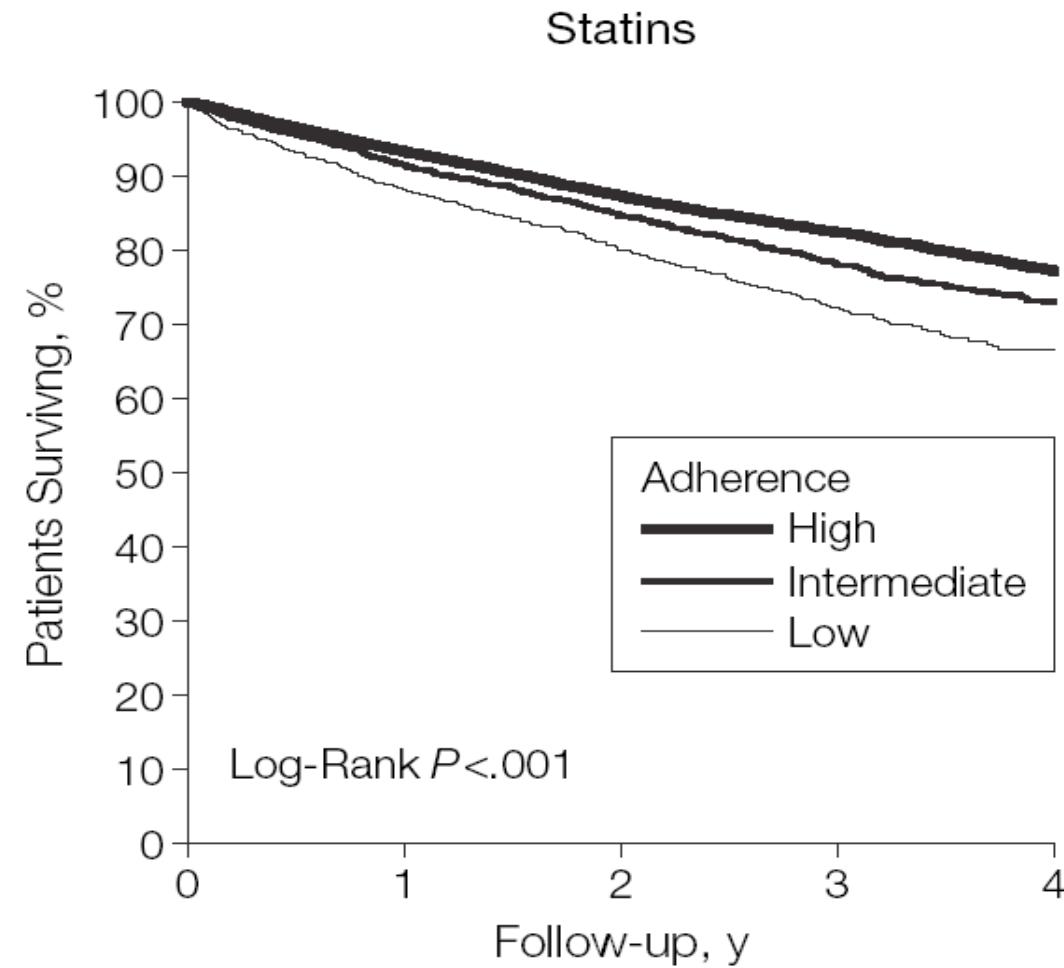


Treatment algorithm for pharmacological LDL-C lowering

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Statin under-dosing is associated with an adverse outcome



Rasmussen et al., JAMA. 2007 Jan; 297(2):177-186