EAS

LINEE GUIDA PER LE DISLIPIDEMIE: QUALE FUTURO?

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Università degli Studi di Milano

GUIDELINES EAS/ESC PER LE DISLIPIDEMIE2019: Presente e Futuro

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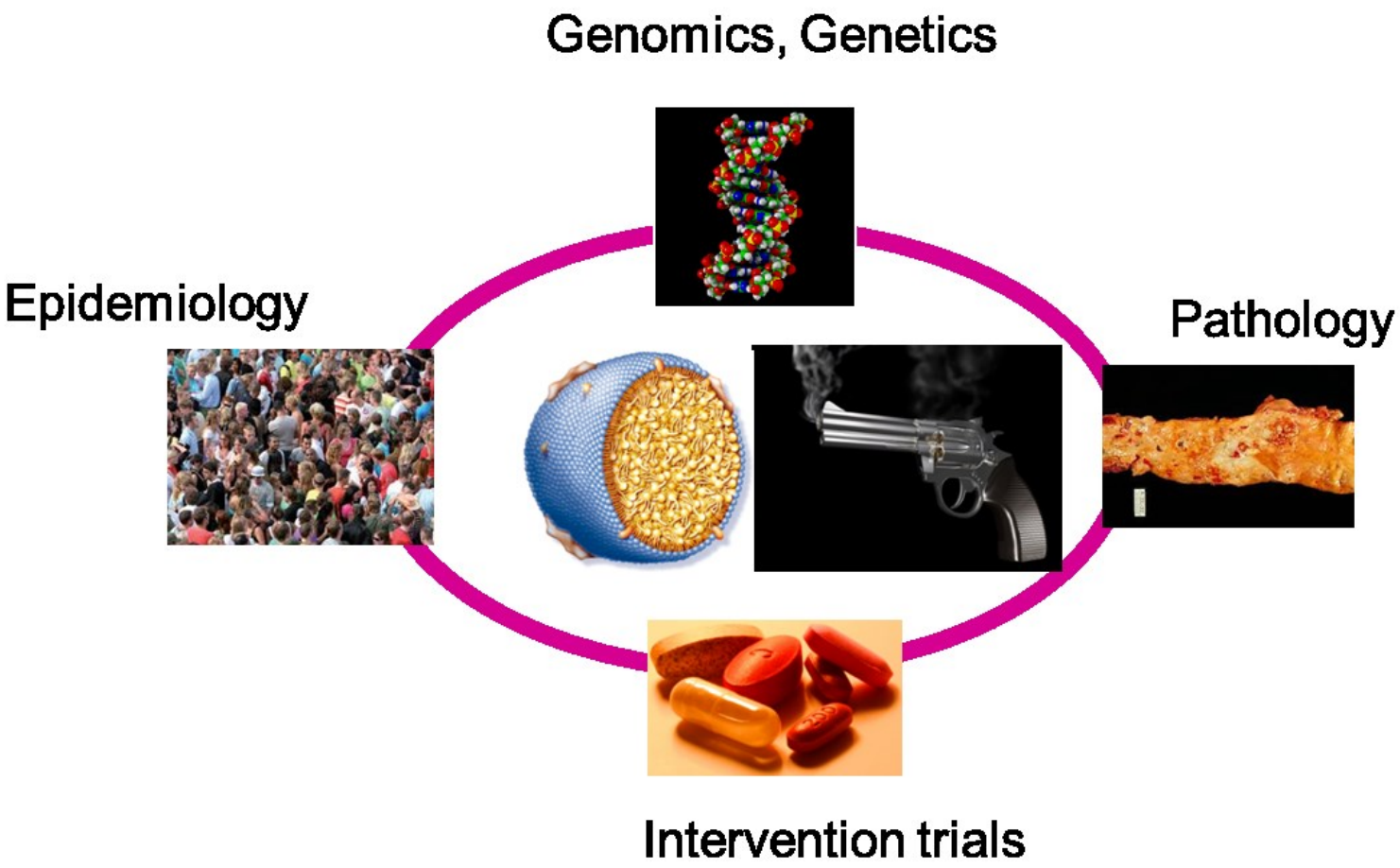
UNIVERSITÀ DEGLI STUDI DI MILANO

CONFLICT OF INTEREST

- Prof. Catapano has received honoraria, lecture fees, or research grants from:

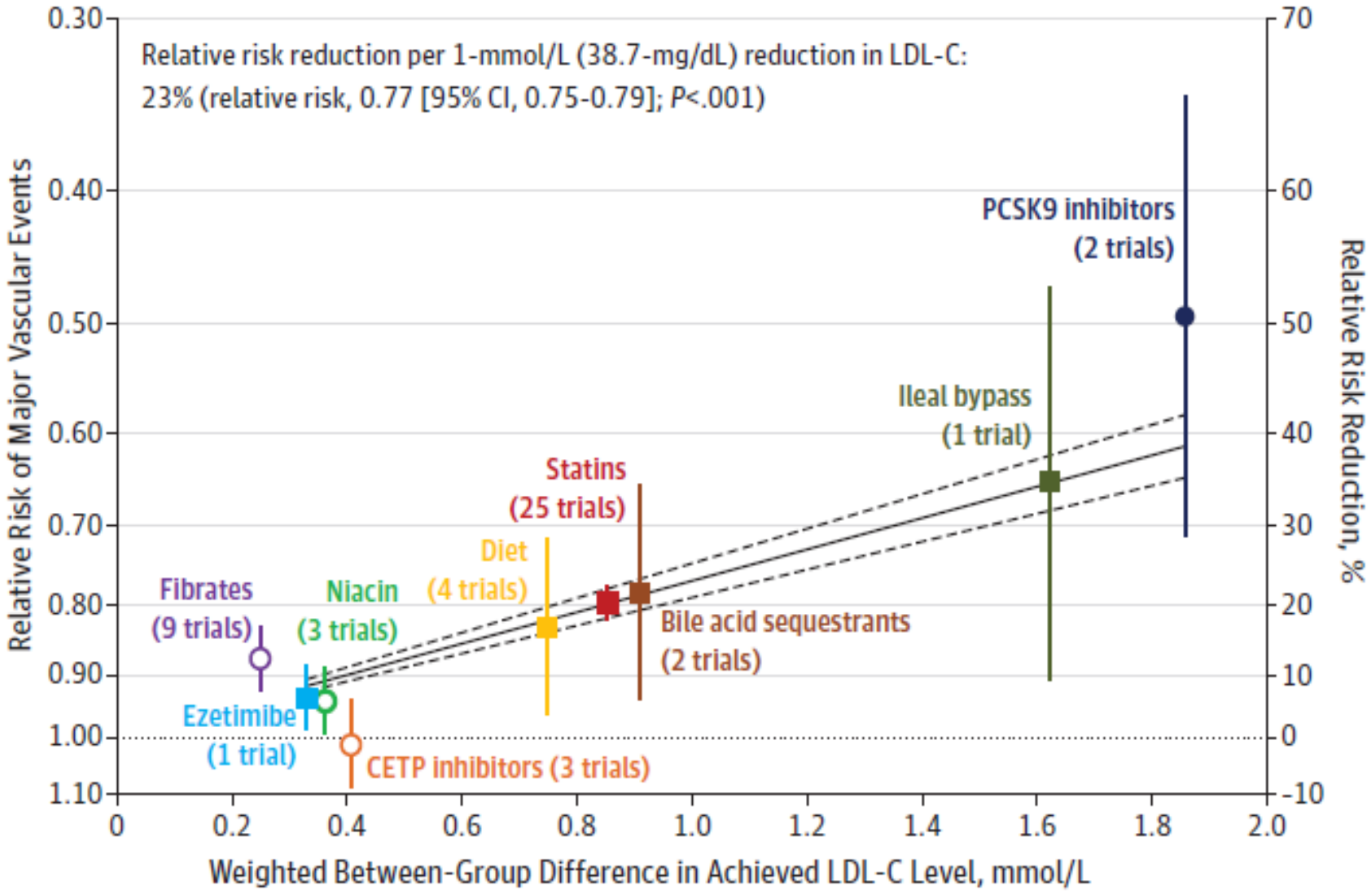
- Sigma-Tau, Manarini, Kowa, Recordati, Eli Lilly, Astrazeneca, Mediolanum, Pfizer, Merck, Sanofi, Aegerion, Amgen, Genzyme, Bayer, Sanofi and Regeneron Daiichi-Sankyo

LDL-C and Atherosclerosis: a Coalescence of Evidence



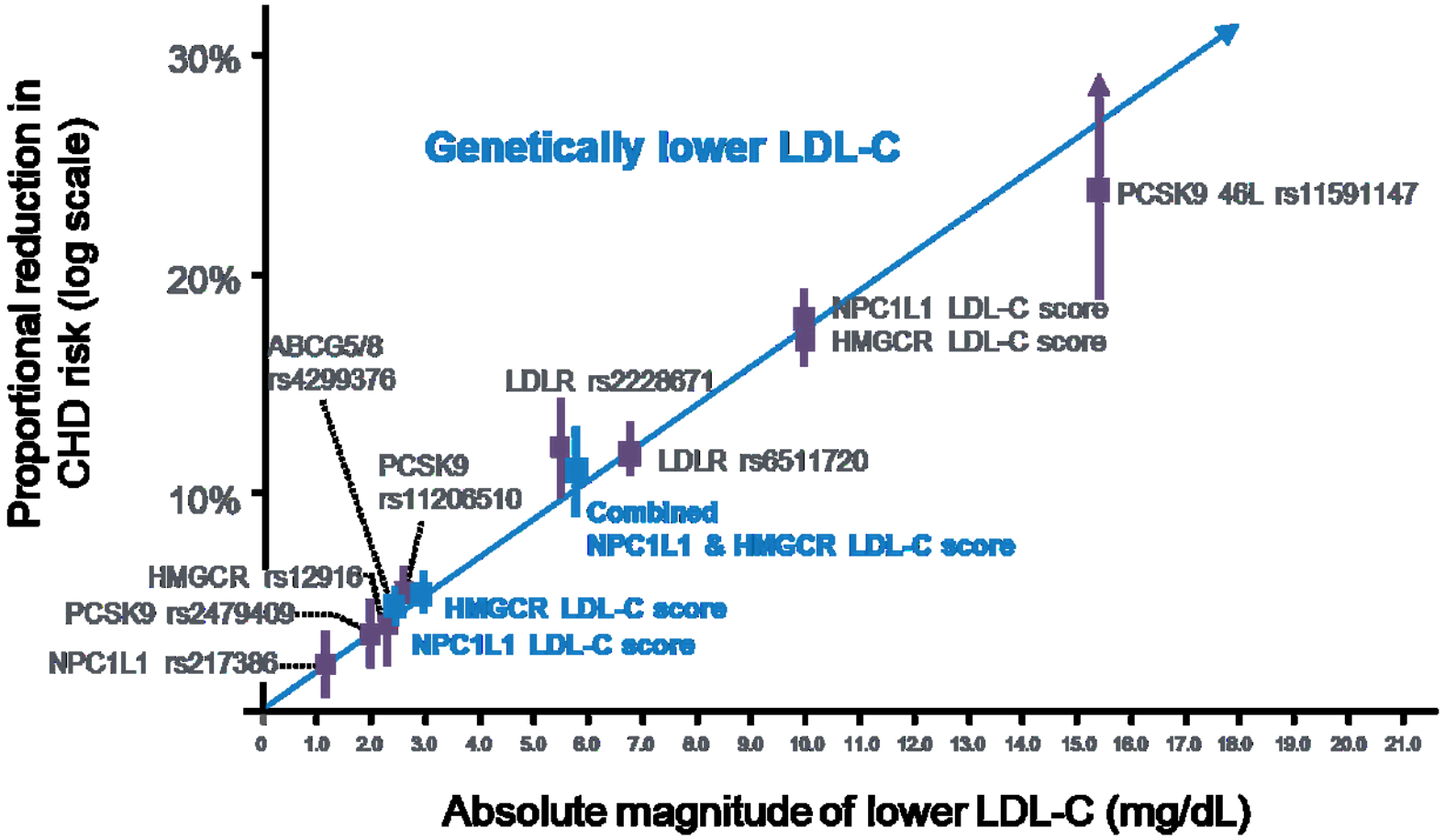
LDL-C, low-density lipoprotein cholesterol

Meta-analysis of Various Methods to Lower LDL-C

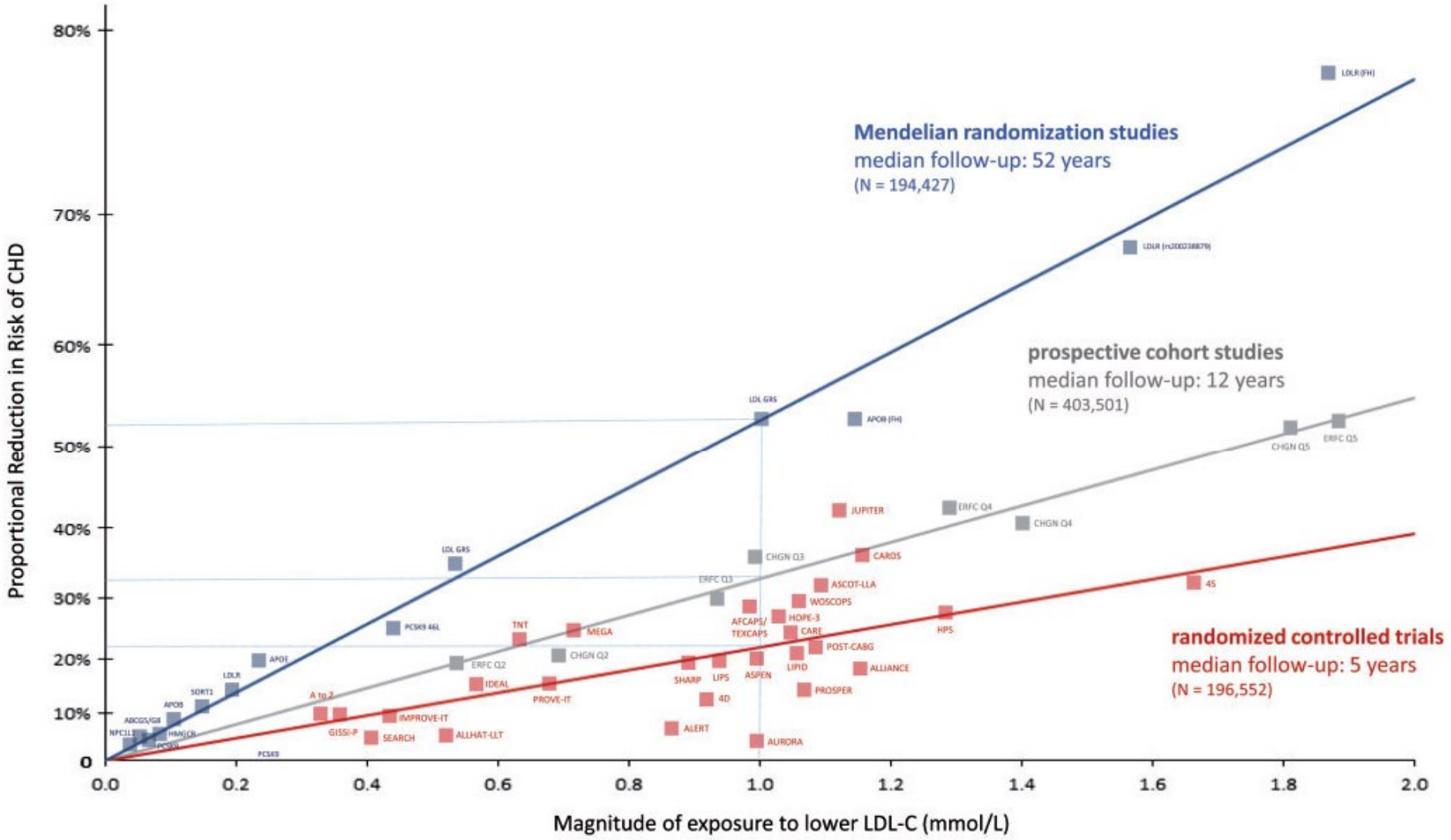


Genetic Evidence Supports LDL-C As A Risk Factor For CV Events

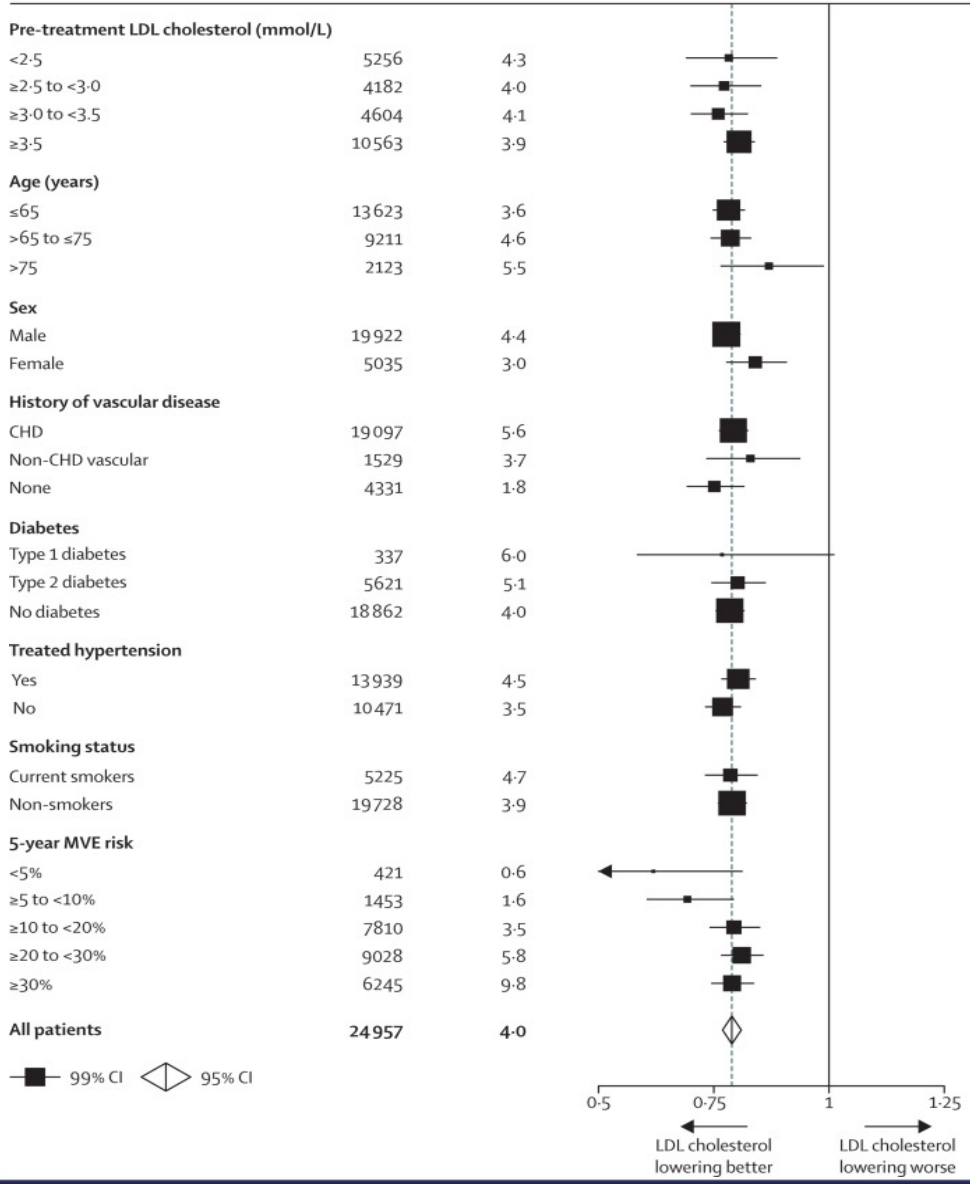
54.5% reduction in CHD risk per 1mmol/L lower LDL-C



Effect Of LDL-C By Magnitude And Duration Of Exposure



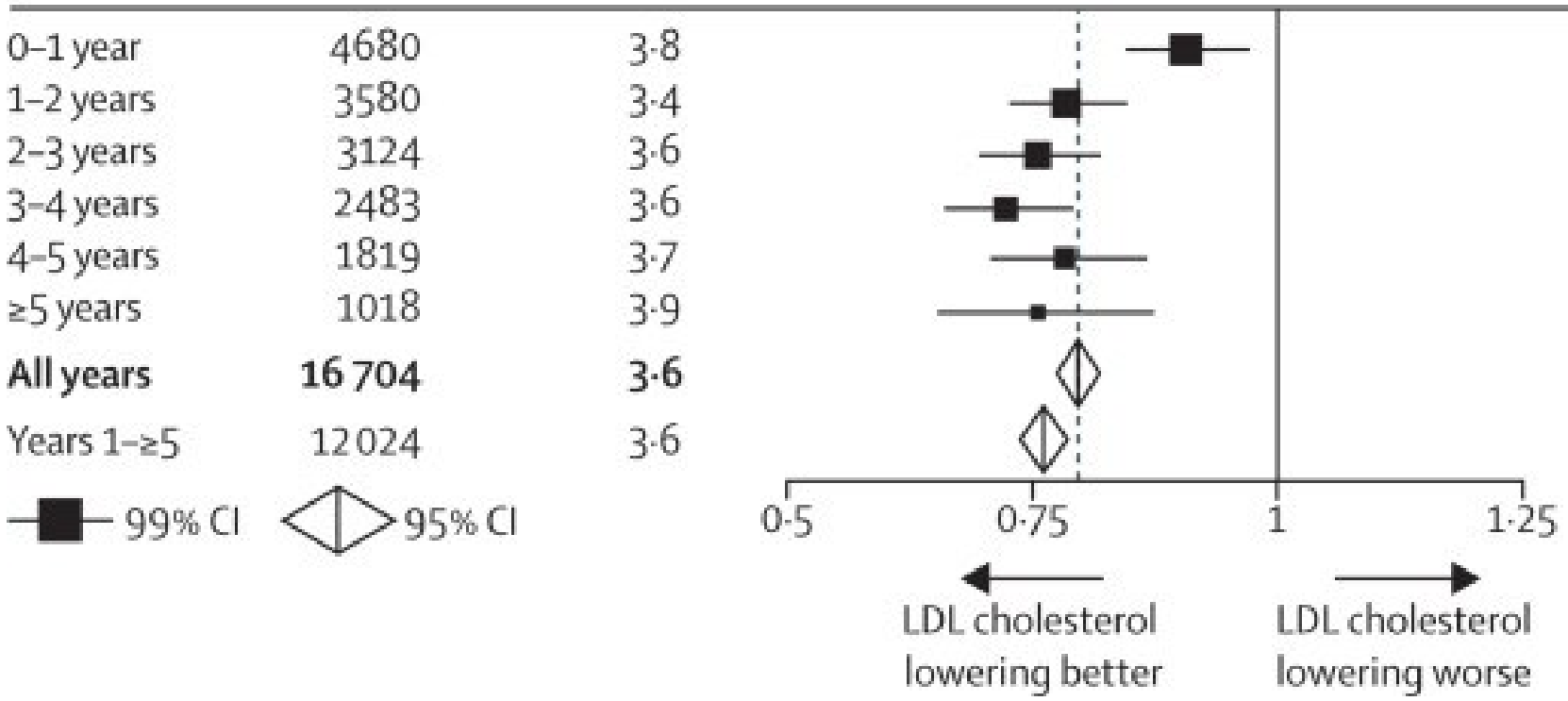
Presenting characteristics	Total number of MVEs	Annual event rate in control arm (% per year)	RR (CI) per 1 mmol/L reduction in LDL cholesterol	p value for heterogeneity or trend
Pre-treatment LDL cholesterol (mmol/L)				p=0·22
<2·5	5256	4·3	0·78 (0·69–0·89)	
≥2·5 to <3·0	4182	4·0	0·77 (0·70–0·85)	
≥3·0 to <3.5	4604	4·1	0·76 (0·70–0·82)	
≥3·5	10563	3·9	0·80 (0·77–0·84)	
Age (years)				p=0·14
≤65	13623	3·6	0·78 (0·75–0·82)	
>65 to ≤75	9211	4·6	0·79 (0·74–0·83)	
>75	2123	5·5	0·87 (0·76–0·99)	
Sex				p=0·02
Male	19922	4·4	0·78 (0·75–0·81)	
Female	5035	3·0	0·84 (0·78–0·91)	
History of vascular disease				p=0·18
CHD	19097	5·6	0·79 (0·76–0·82)	
Non-CHD vascular	1529	3·7	0·83 (0·73–0·94)	
None	4331	1·8	0·75 (0·69–0·82)	
Diabetes				p=0·78
Type 1 diabetes	337	6·0	0·77 (0·58–1·01)	
Type 2 diabetes	5621	5·1	0·80 (0·74–0·86)	
No diabetes	18862	4·0	0·78 (0·76–0·82)	
Treated hypertension				p=0·11
Yes	13939	4·5	0·80 (0·77–0·84)	
No	10471	3·5	0·77 (0·73–0·81)	
Smoking status				p=0·88
Current smokers	5225	4·7	0·79 (0·73–0·85)	
Non-smokers	19728	3·9	0·79 (0·76–0·82)	
5-year MVE risk				p=0·04
<5%	421	0·6	0·62 (0·47–0·81)	
≥5 to <10%	1453	1·6	0·69 (0·60–0·79)	
≥10 to <20%	7810	3·5	0·79 (0·74–0·85)	
≥20 to <30%	9028	5·8	0·81 (0·77–0·86)	
≥30%	6245	9·8	0·79 (0·74–0·84)	
All patients	**24957**	**4·0**	**0·79 (0·77–0·81)**	



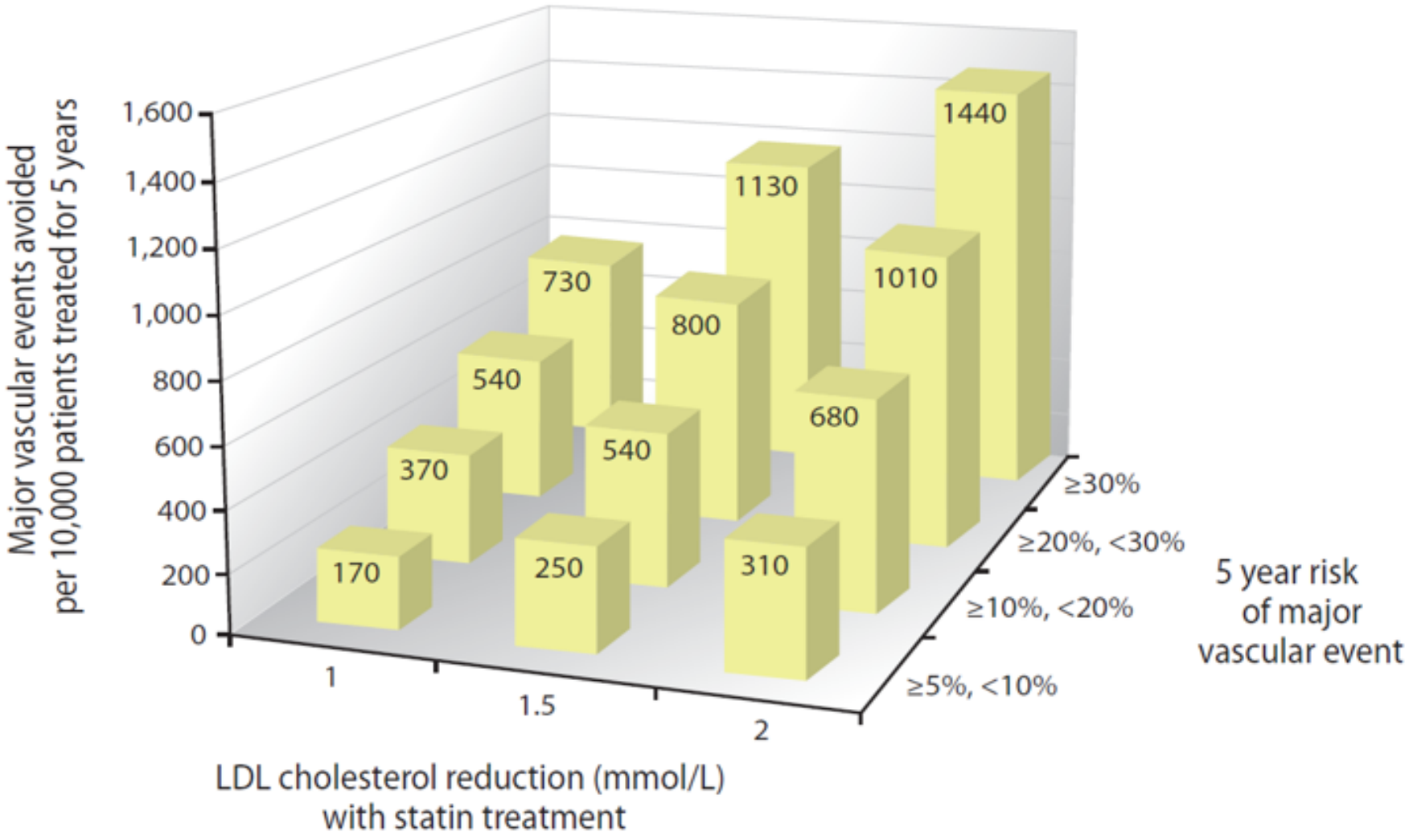
Similar proportional reductions in risks of major vascular events per mmol/L LDL cholesterol reduction in randomised trials of statin therapy among people with different presenting characteristics

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

	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)



Absolute Reductions in Major Vascular Events with Statin Therapy



Main Principles for LDL-lowering Therapy

- Genetic, epidemiological and trial evidence indicates that LDL cholesterol is a CAUSE of atherosclerotic vascular disease

- Trials of LDL-lowering indicate RELATIVE RISK reduction is proportional to the ABSOLUTE REDUCTION in LDL-C

- Lower is better: lowering LDL-C with statins, ezetimibe, or PCSK9-inhibitors safe and effective to <1.4 mmol/L (55 mg/dL)

- Intensity of LDL-lowering should be based on risk, irrespective of cause(s) of the risk (e.g., primary or secondary prevention, diabetes, or chronic kidney disease)

Cardiovascular Risk Categories (1)

VERY-HIGH-RISK	People with any of the following: Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularisation (PCI, CABG and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis) or on carotid ultrasound. DM with target organ damage, ≥3 major risk factors or early onset of T1DM of long duration (>20 years). Severe CKD (eGFR <30 mL/min/1.73 m^2). A calculated SCORE ≥10% for 10-year risk of fatal CVD. FH with ASCVD or with another major risk factor.

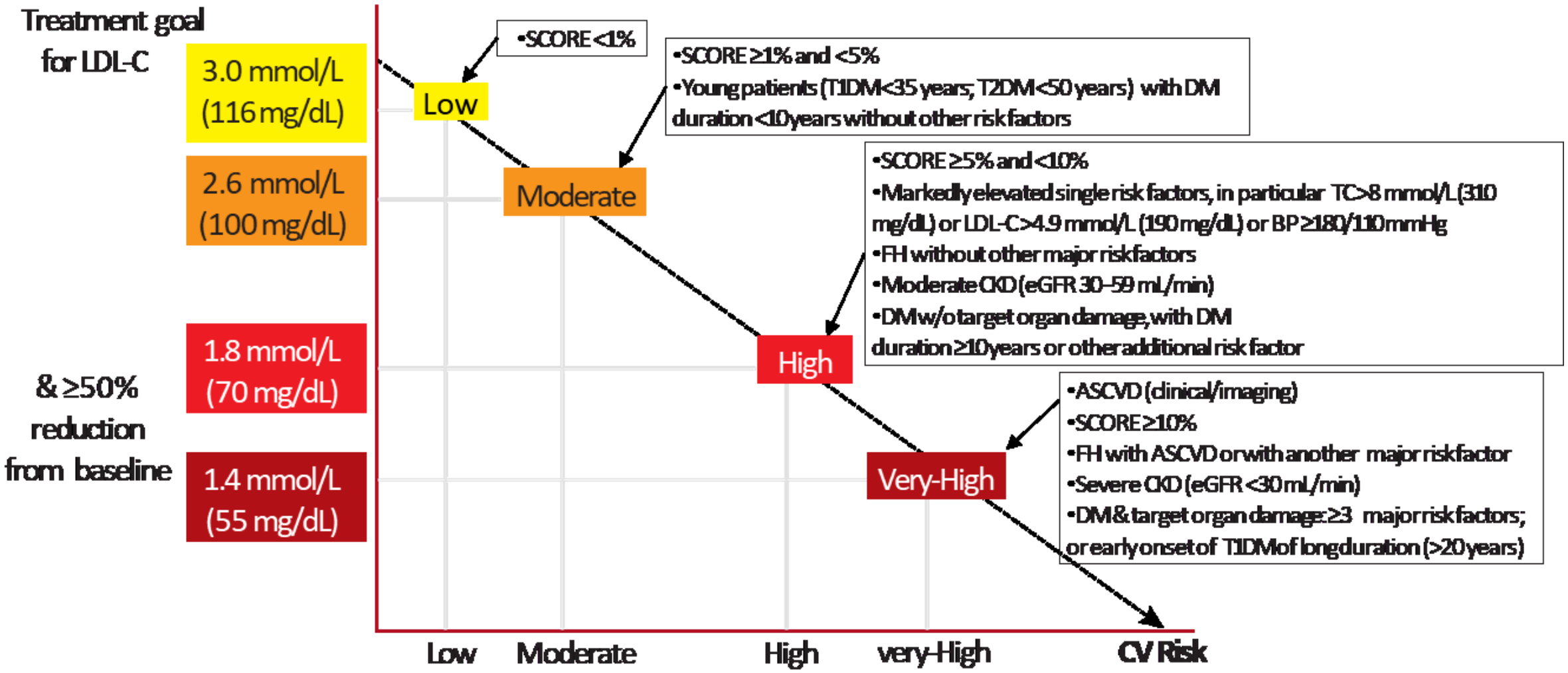
Cardiovascular Risk Categories (2)

HIGH-RISK	People with: Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP ≥180/110 mmHg. Patients with FH without other major risk factors. Patients with DM without target organ damage*, with DM duration ≥10 years or another additional risk factors. Moderate CKD (eGFR 30–59 mL/min/1.73 m^2). A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
MODERATE-RISK	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1% and <5% for 10-year risk of fatal CVD.
LOW-RISK	Calculated SCORE <1% for 10-year risk of fatal CVD.

Intervention Strategies as a Function of Total Cardiovascular Risk and Untreated Low-density Lipoprotein Cholesterol Levels

	Total CV risk (SCORE) %	Untreated LDL-C levels					
		<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)
Primary Prevention	<1 low-risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	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
	Class[a]/Level[b]	IIa/B	IIa/A	I/A	I/A	I/A	I/A
Secondary Prevention	Very-high risk	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	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	IIa/A	I/A	I/A	I/A	I/A	I/A

Treatment Goals for Low-density Lipoprotein Cholesterol (LDL-C) Across Categories of Total Cardiovascular Disease Risk



Future Challenges

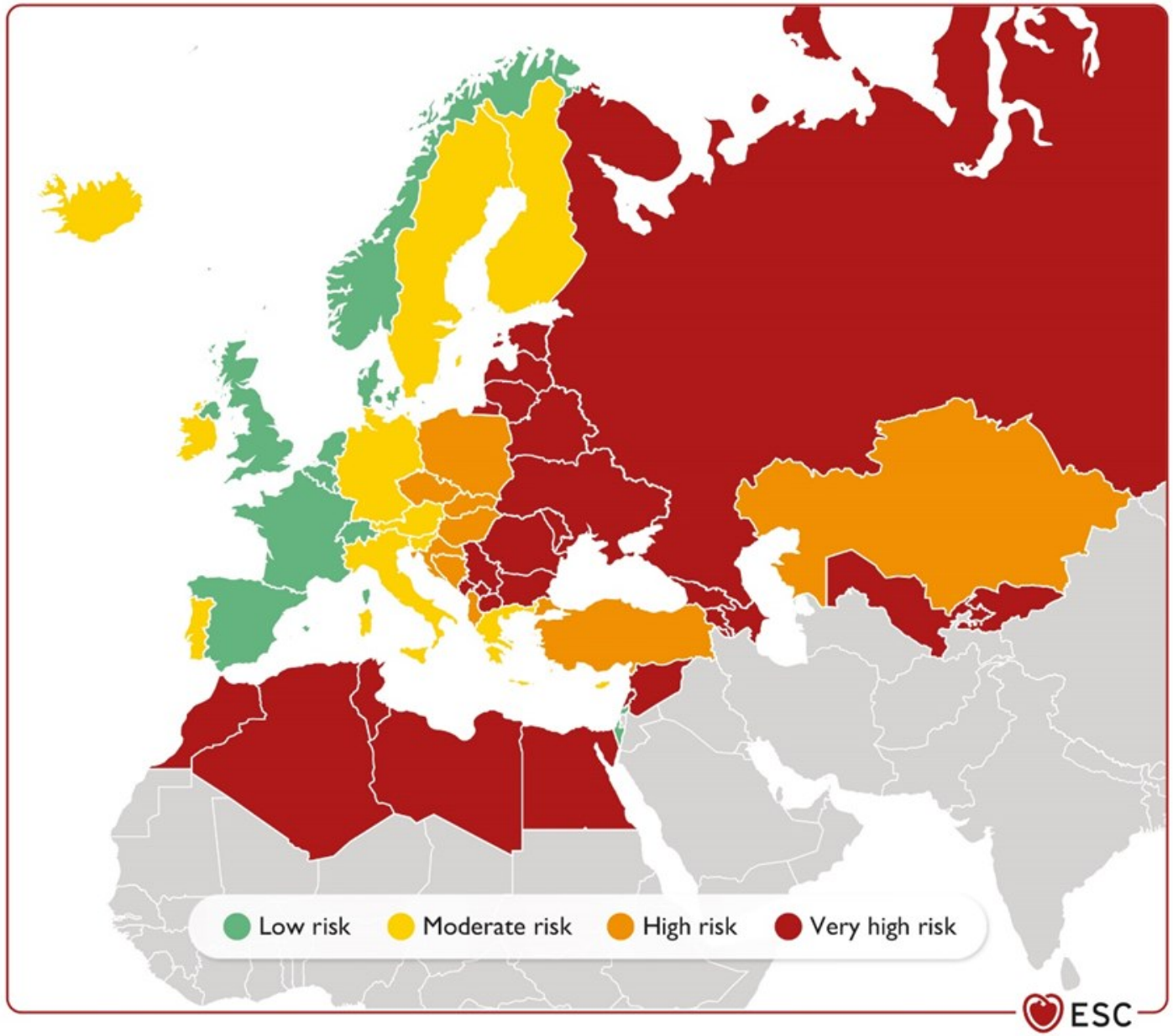
- **LIFETIME RISK**
- HDL
- NON HDL AND/OR APO B IN EVERYBODY?
- Lp(a)
- PERCENT REDUCTION VS GOALS
- TRIAL DESIGN
- STEPWISE APPROACH?
- ADHERENCE TO THERAPY

SCORE Cardiovascular Risk Chart
10-year Risk of Fatal CVD

Systolic blood pressure (mmHg)	WOMEN Non-smoker				WOMEN Smoker				Age	MEN Non-smoker				MEN Smoker			
	4	5	6	7	4	5	6	7		4	5	6	7	4	5	6	7
180	12	13	14	15	17	19	20	21	70	24	26	30	33	33	36	40	45
160	10	11	12	13	14	15	16	18		20	22	25	28	27	31	34	39
140	8	9	10	10	12	13	14	15		16	18	21	24	23	26	29	33
120	7	7	8	9	10	10	11	12		13	15	17	20	19	22	25	28
180	7	8	8	9	11	12	13	15	65	15	17	20	23	23	26	30	34
160	5	6	6	7	9	9	10	11		12	14	16	18	18	21	24	27
140	4	4	5	5	7	7	8	9		9	11	12	14	14	16	19	22
120	3	3	4	4	5	5	6	7		7	8	10	11	11	13	15	17
180	4	4	5	5	7	8	9	10	60	10	11	13	15	16	19	22	25
160	3	3	3	4	5	6	6	7		7	8	10	11	12	14	16	19
140	2	2	2	3	4	4	4	5		5	6	7	8	9	10	12	14
120	1	1	2	2	3	3	3	3		4	4	5	6	6	7	9	10
180	2	2	3	3	5	5	6	7	55	6	7	9	10	11	13	16	18
160	1	2	2	2	3	3	4	4		4	5	6	7	8	9	11	13
140	1	1	1	1	2	2	2	3		3	3	4	5	5	6	7	9
120	1	1	1	1	1	1	2	2		2	2	3	3	4	4	5	6
180	1	1	2	2	3	3	4	4	50	4	5	6	7	8	9	11	13
160	1	1	1	1	2	2	2	3		2	3	3	4	5	6	7	9
140	0	0	1	1	1	1	1	2		2	2	2	3	3	4	5	6
120	0	0	0	0	1	1	1	1		1	1	1	2	2	2	3	4
180	0	0	1	1	1	1	2	2	40	2	2	2	3	4	4	5	7
160	0	0	0	0	1	1	1	1		1	1	1	2	2	2	3	4
140	0	0	0	0	0	0	0	1		0	1	1	1	1	1	2	2
120	0	0	0	0	0	0	0	0		0	0	0	1	1	1	1	1

Total cholesterol (mmol/L)

SCORE chart for European populations at high cardiovascular disease risk



Risk regions based on World Health Organization cardiovascular mortality rates

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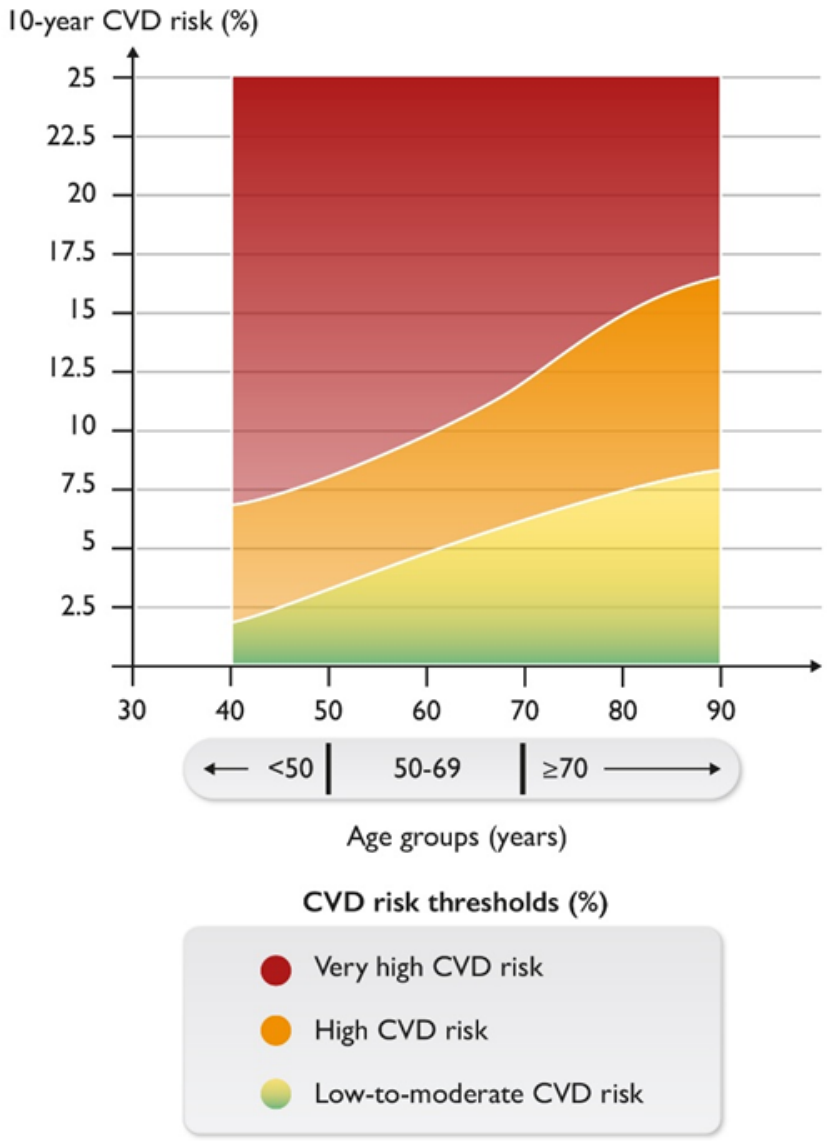
2021 ESC Guidelines on cardiovascular disease prevention in clinical practice
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab484)

Cardiovascular disease risk categories based on SCORE2 and SCORE2-OP in apparently healthy people according to age

	<50 years	50-69 years	≥70 years[a]
Low-to-moderate CVD risk: risk factor treatment generally not recommended	<2.5%	<5%	<7.5%
High CVD risk: risk factor treatment should be considered	2.5 to <7.5%	5 to <10%	7.5 to <15%
Very high CVD risk: risk factor treatment generally recommended[a]	≥7.5%	≥10%	≥15%

© ESC

2021 ESC Guidelines on cardiovascular disease prevention in clinical practice
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab484)



Schematic representation of increasing 10-year CVD risk thresholds across age groups

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(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab484)

Future Challenges

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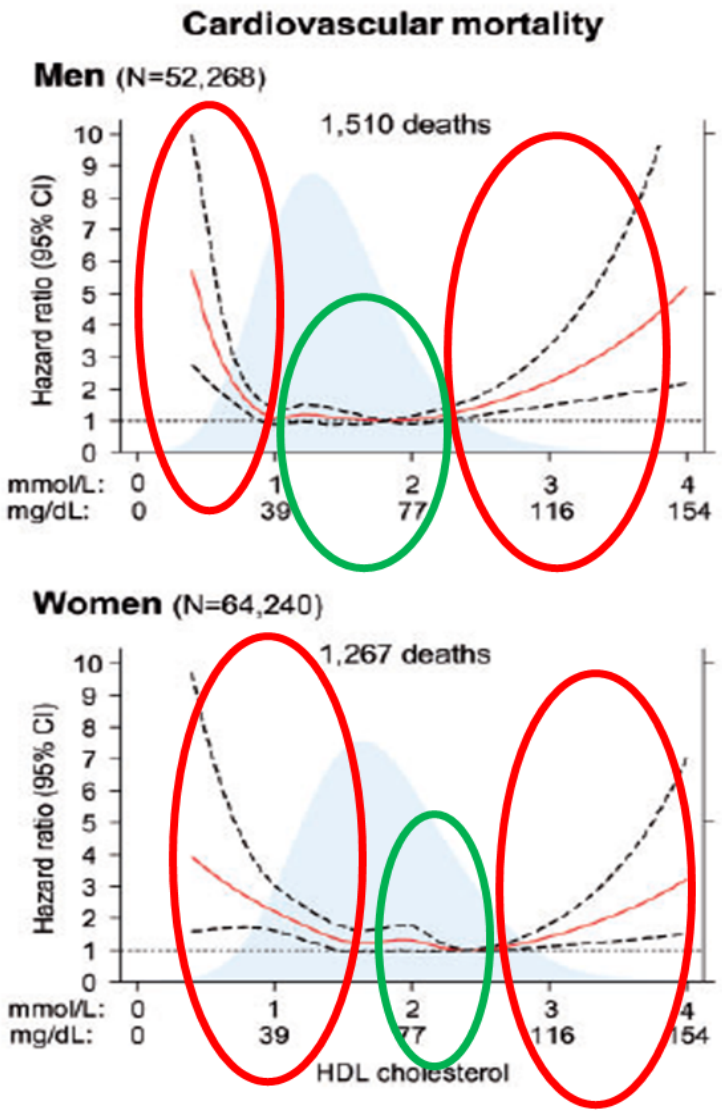
CV Mortality and Elevated Values of HDL-C



HDL-C associated with lowest CV mortality

Males : 50–80 mg/dL

Females : 70–90 mg/dL

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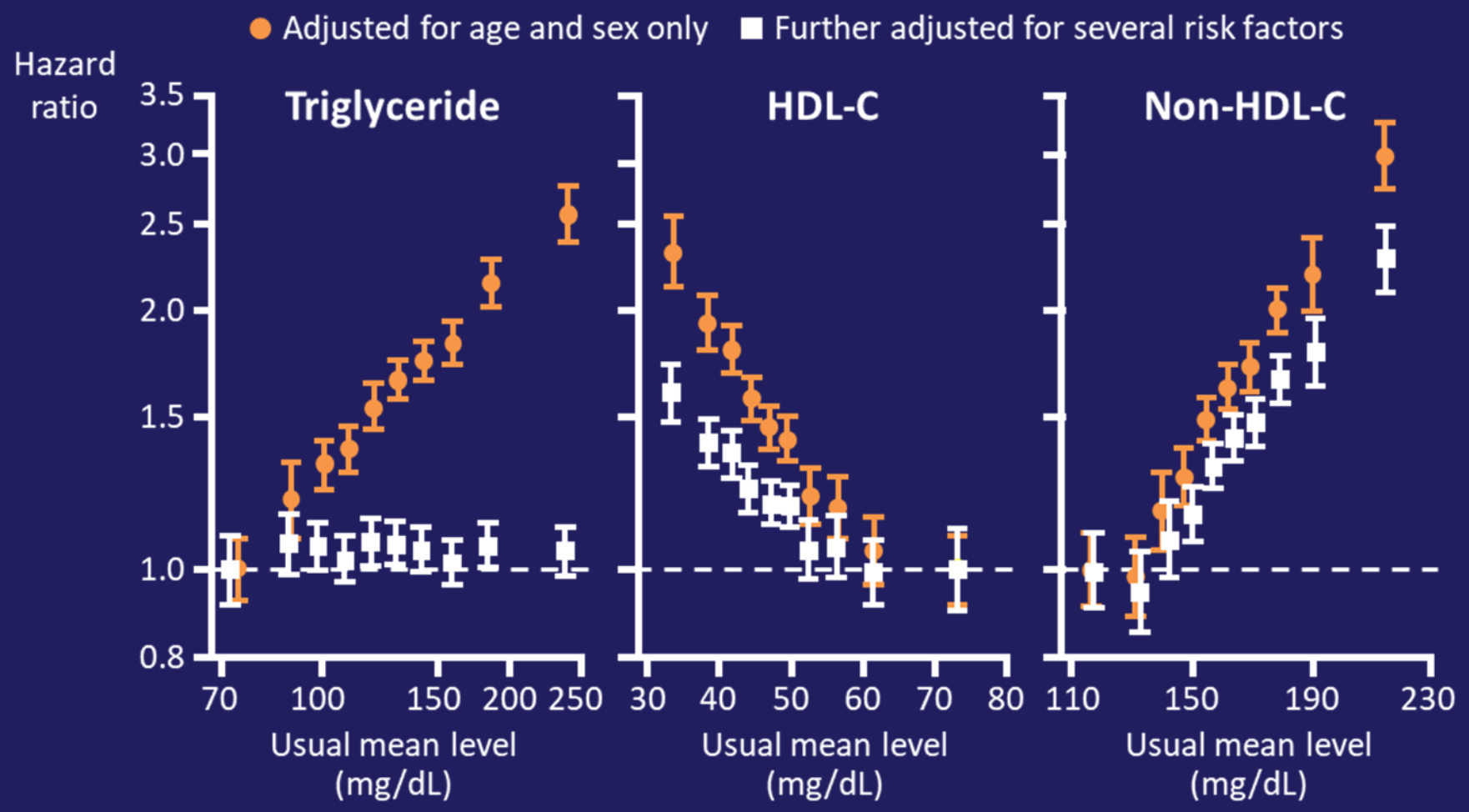
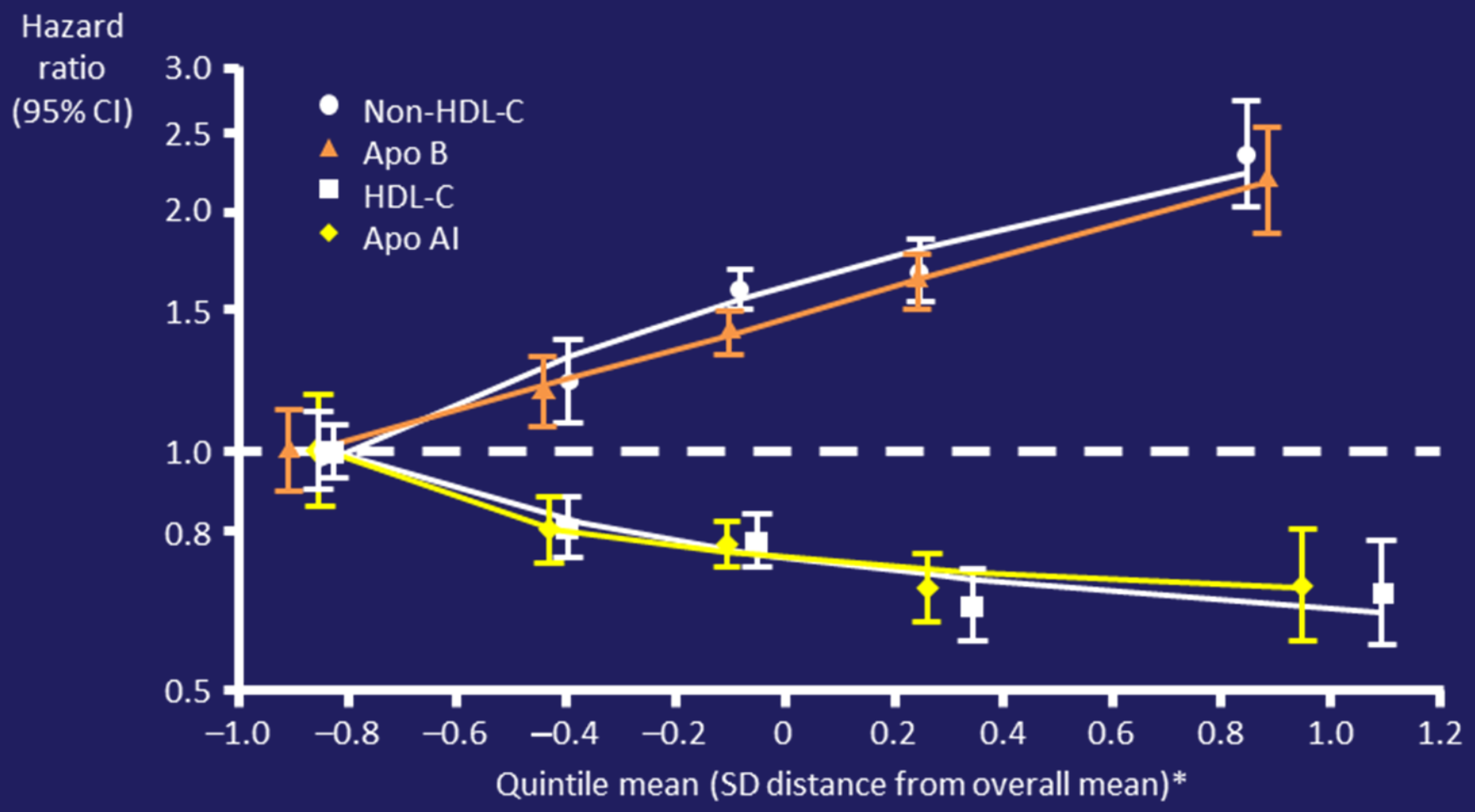
Hazard Ratios for Coronary Heart Disease Across Quintiles



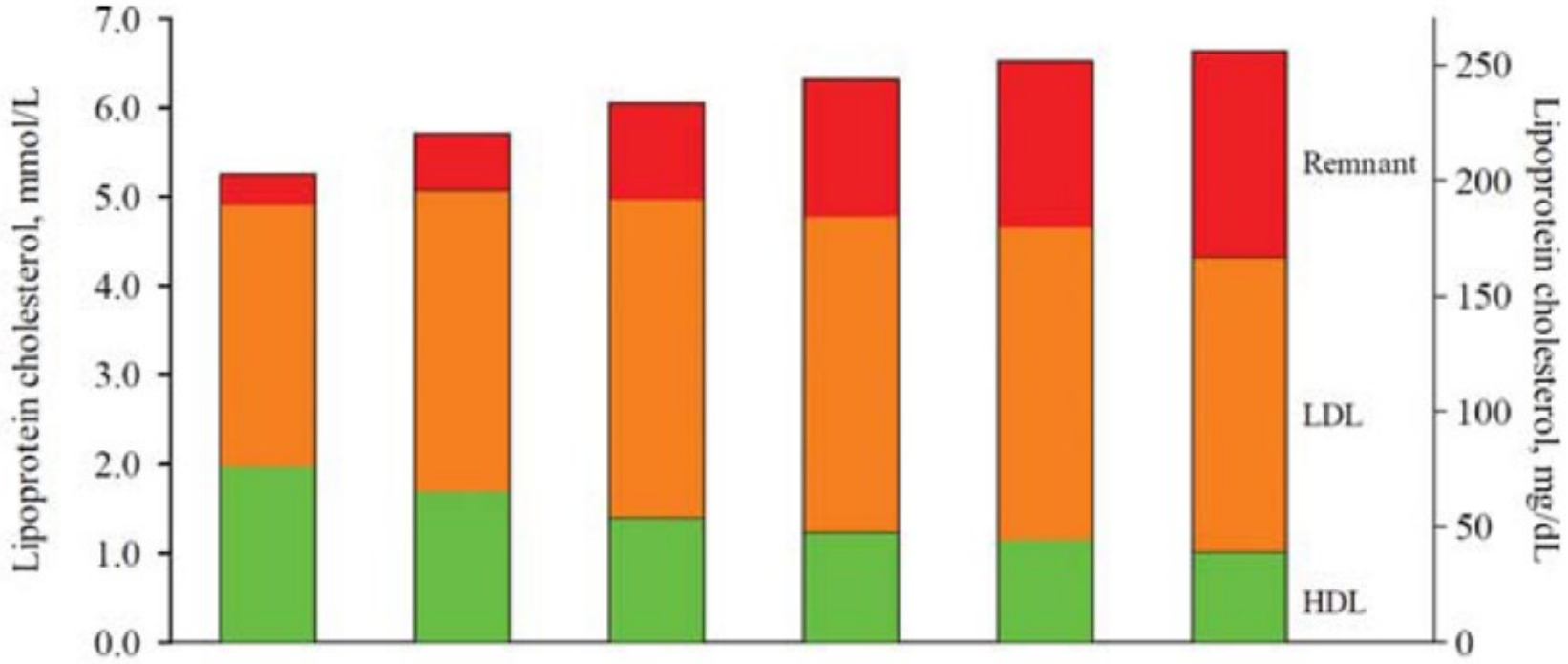
The Emerging Risk Factors Collaboration. JAMA 2009;302:1993–2000

Risk Ratios for Coronary Heart Disease Across Fifths of Usual Lipids or Apolipoproteins



*shown on a Z-transformed scale

Cholesterol in Atherogenic Lipoproteins: non-HDL



Triglycerides, mmol/L	< 1	1–1.99	2–2.99	3–3.99	4–4.99	≥ 5
mg/dL	< 89	89–176	177–265	266–353	354–442	≥ 443
Observations, No.	9347	16621	6348	2268	867	709

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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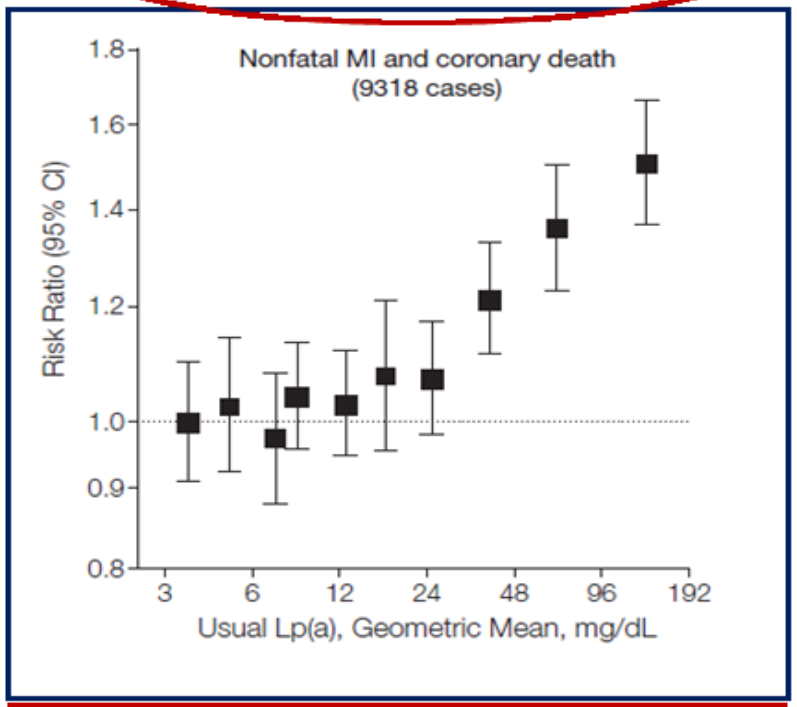
Effect of Lp(a) Compared to Effect of LDL-C on Risk of CVDA

Lp(a) OR per 1-ln(SD): 1.16

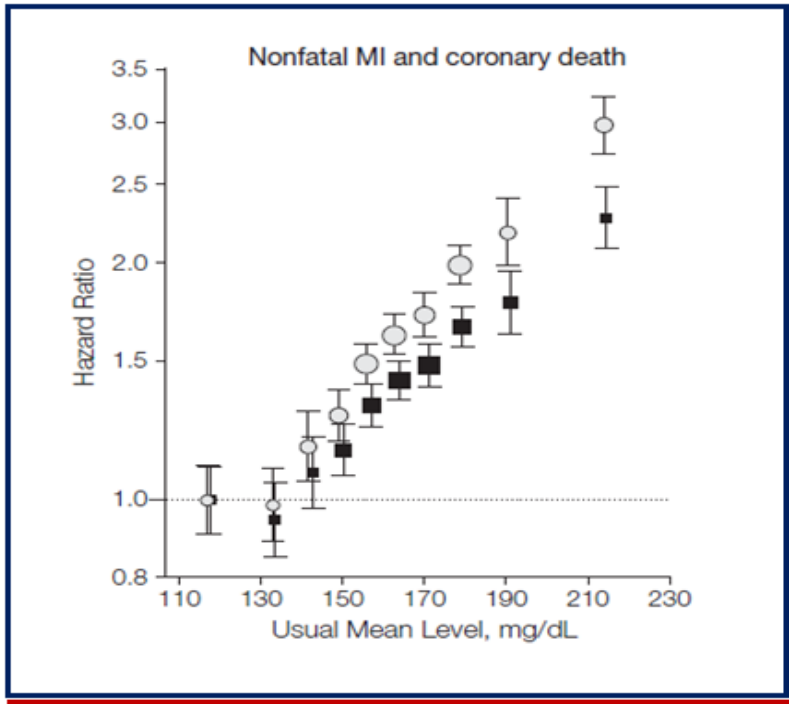


Ln-SD = 1.1 $e^{1.1}$ = 3-fold increase

Tripling in Lp(a)

16% increased risk

LDL-C OR per 1-SD (33 mg/dl): 1.39



Mean population LDL-c 3.5 mmol/L

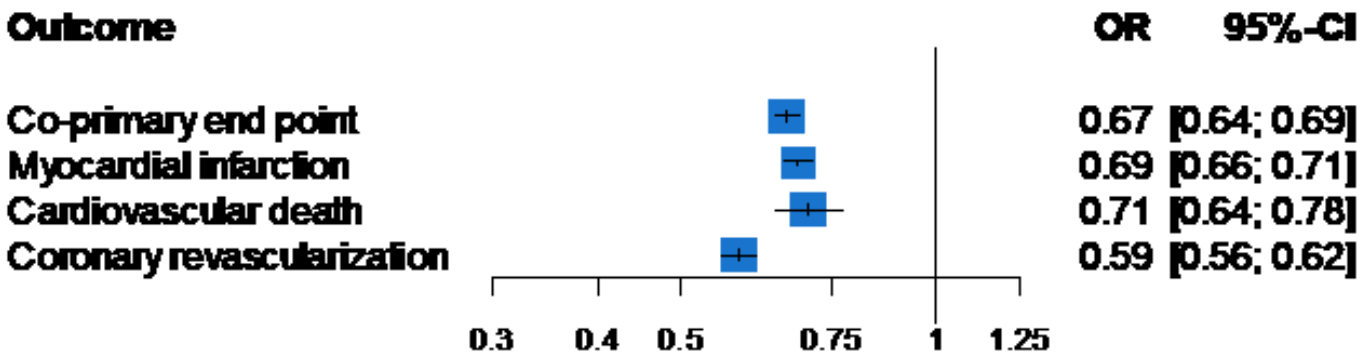
Tripling in LDL-c

386% increased risk

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

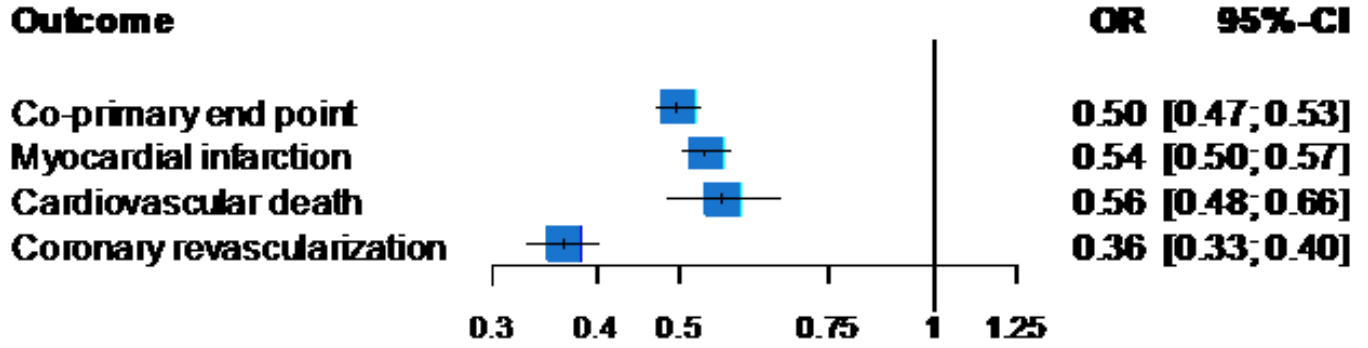
100 nmol/L lower Lp(a)

33% RRR per 100 nmol/L



1 mmol/L lower LDL-C
(98 variant LDL-exome score)

50% RRR per mmol/L



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

Katzman J, ... Ference BA. EAS 2019, Maasstricht

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

1.0 mmol/L lifetime lower LDL-C

↓

50% reduction in ***lifetime*** risk of CHD

↑

80.4 - 101.5 mg/dl lifetime lower Lp(a)

- 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***

Burgess SB, Ference BA, et al. 2018; JAMA Cardiology doi: 10.1001/jamacardio.2018.1470

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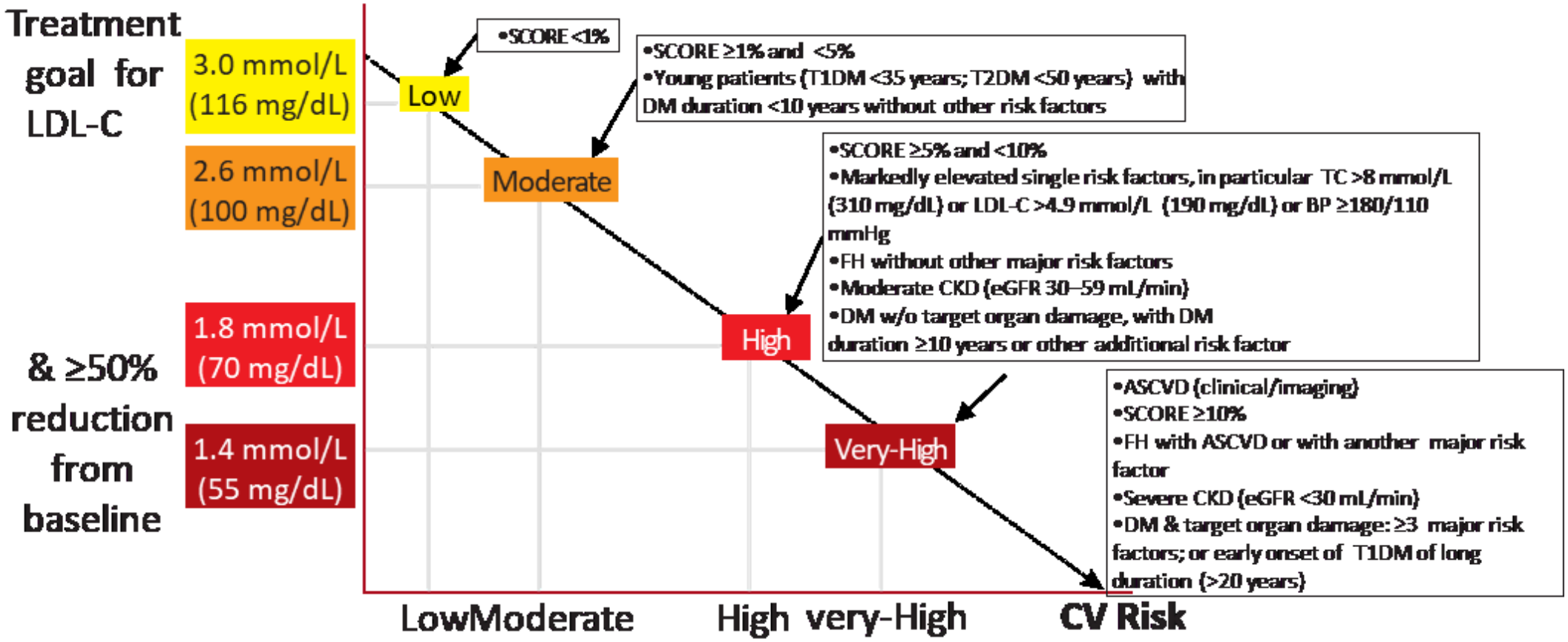
Treatment Goals for Low-density Lipoprotein Cholesterol (LDL-C) Across Categories of Total Cardiovascular Disease Risk



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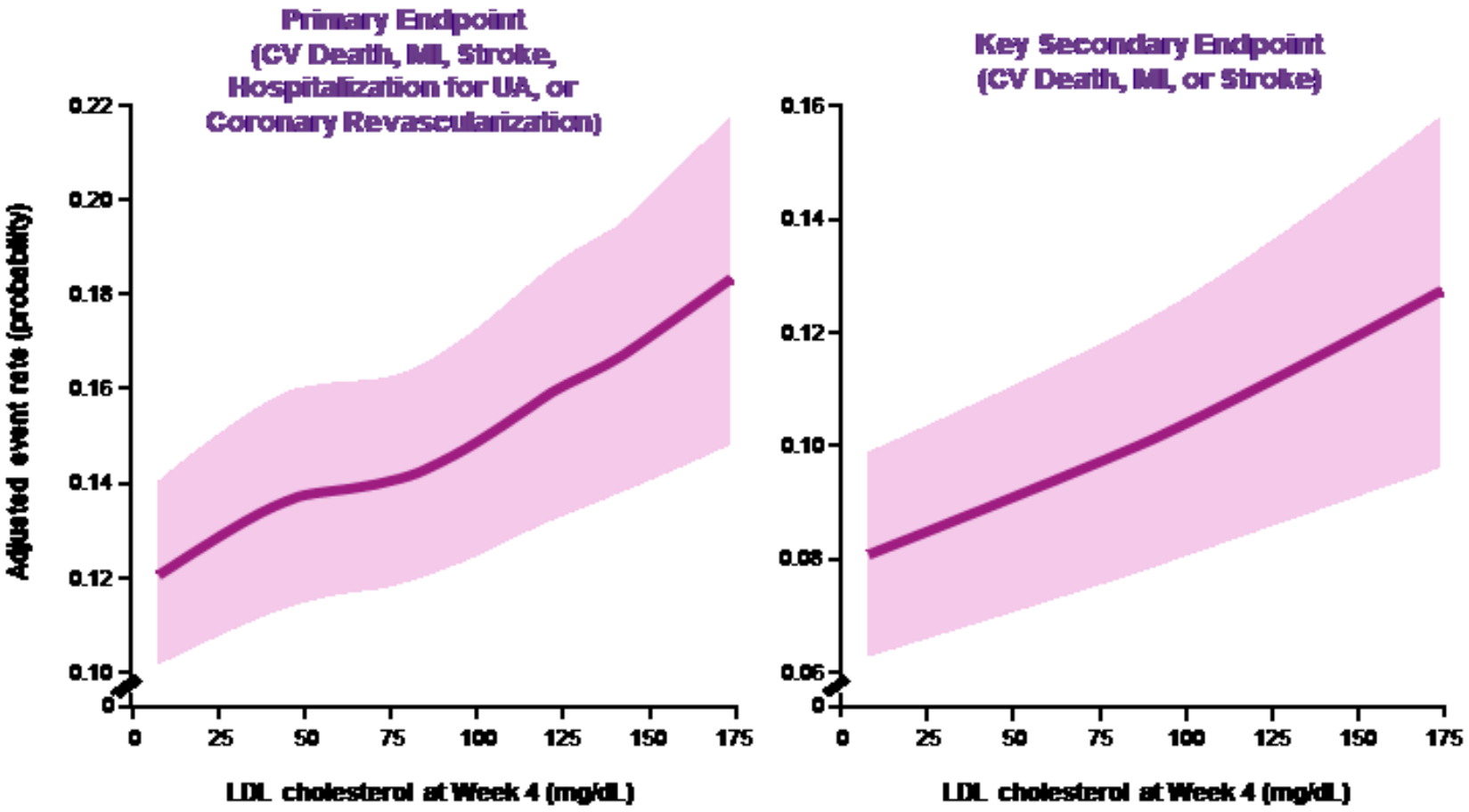
Relationship Between Achieved LDL-C Level At Week 4 and Risk for the Primary and Key Secondary Efficacy Composite Endpoints



Giugliano RP, et al. *Lancet* 2017; 390:1962-71. doi: 10.1016/ S0140-6736(17)32290-0

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	– 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	– 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	– ≥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.

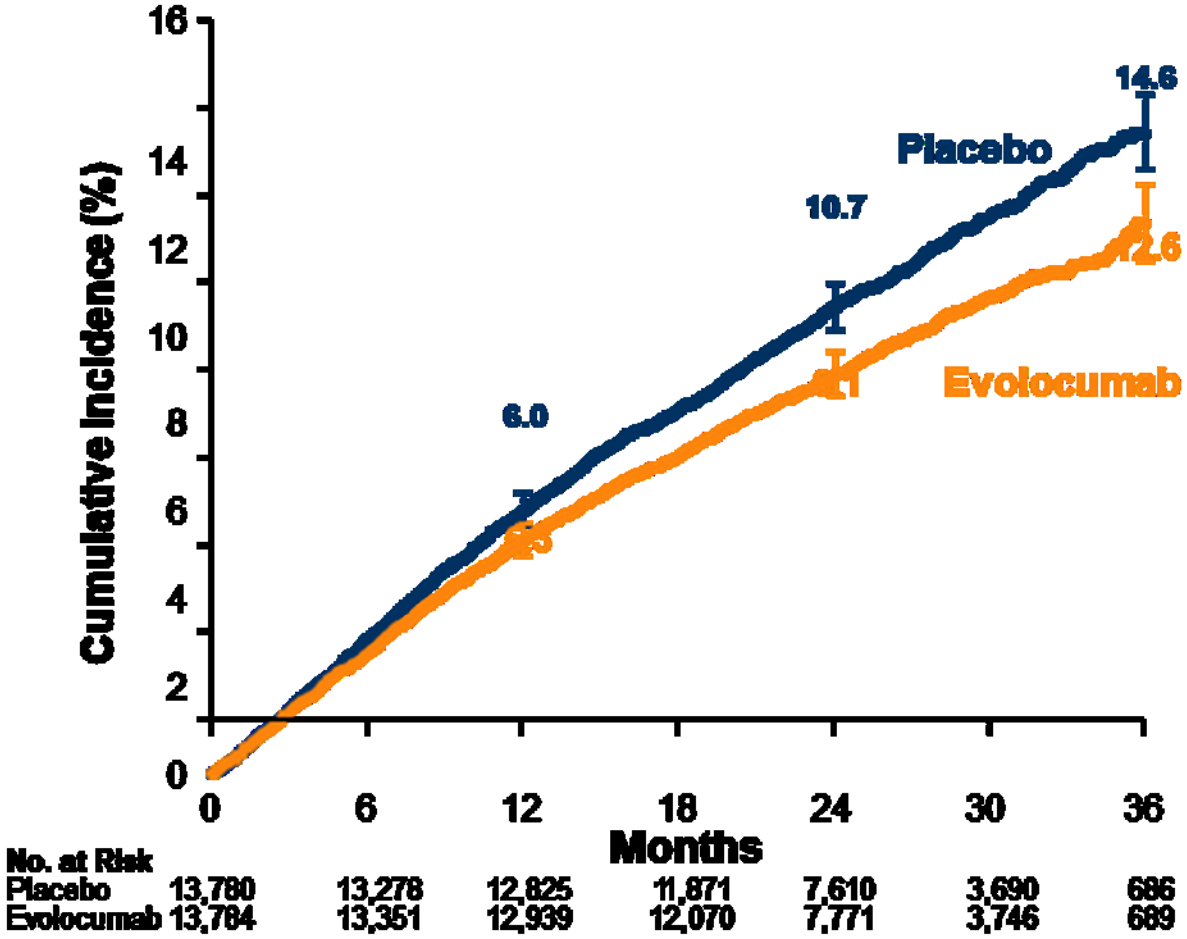
[b] Framingham risk scoring is applied to determine 10-year risk.

Target	UK 2016 NICE	Canada 2021	Europe 2019 ESC/EAS	US 2018 ACC/AHA
Secondary prevention: ASCVD				
LDL cholesterol	≥50%	>50% or <70 mg/dL <1.8 mmol/L	≥50% & <55 mg/dL <1.4 mmol/L	≥50% & <70 mg/dL <1.8 mmol/L
Non HDL cholesterol		<100 mg/dL <2.5 mmol/L	<85 mg/dL <2.2 mmol/L	<100 mg/dL <2.5 mmol/L
Apolipoprotein B		<70 mg/dL	<65 mg/dL	
Primary prevention: Familial hypercholesterolemia				
LDL cholesterol	≥50%	>50% or > 2.5mmol/L	≥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 <2.0 mmol/L	≥50% & <55, <70 or (<100 mg/dL) <1.4, <1.8 or (<2.6 mmol/L)	≥30% or ≥50%
Non HDL cholesterol		<100 mg/dL <2..5 mmol/L	<85 mg/dL <2.2 mmol/L	
Apolipoprotein B		<80 mg/dL	<65 mg/dL	

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

Primary Endpoint: Composite of CV Death, MI, Stroke, Hospitalization for UA, or Coronary Revascularization

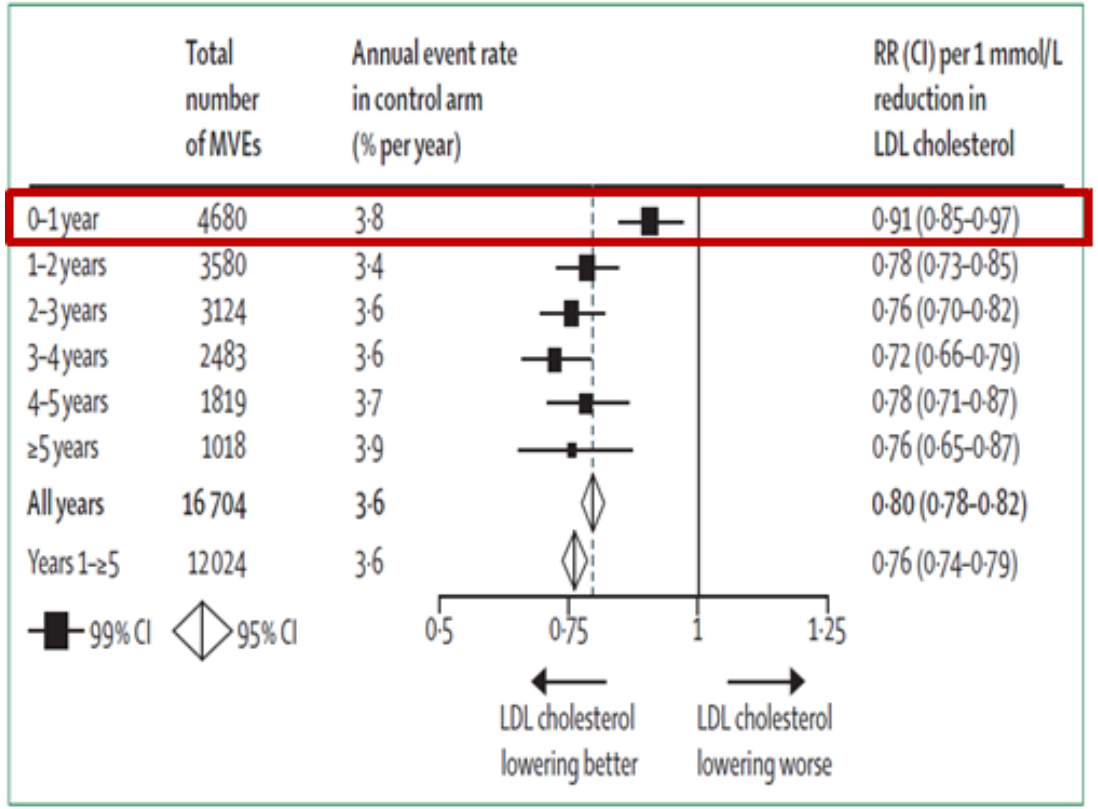


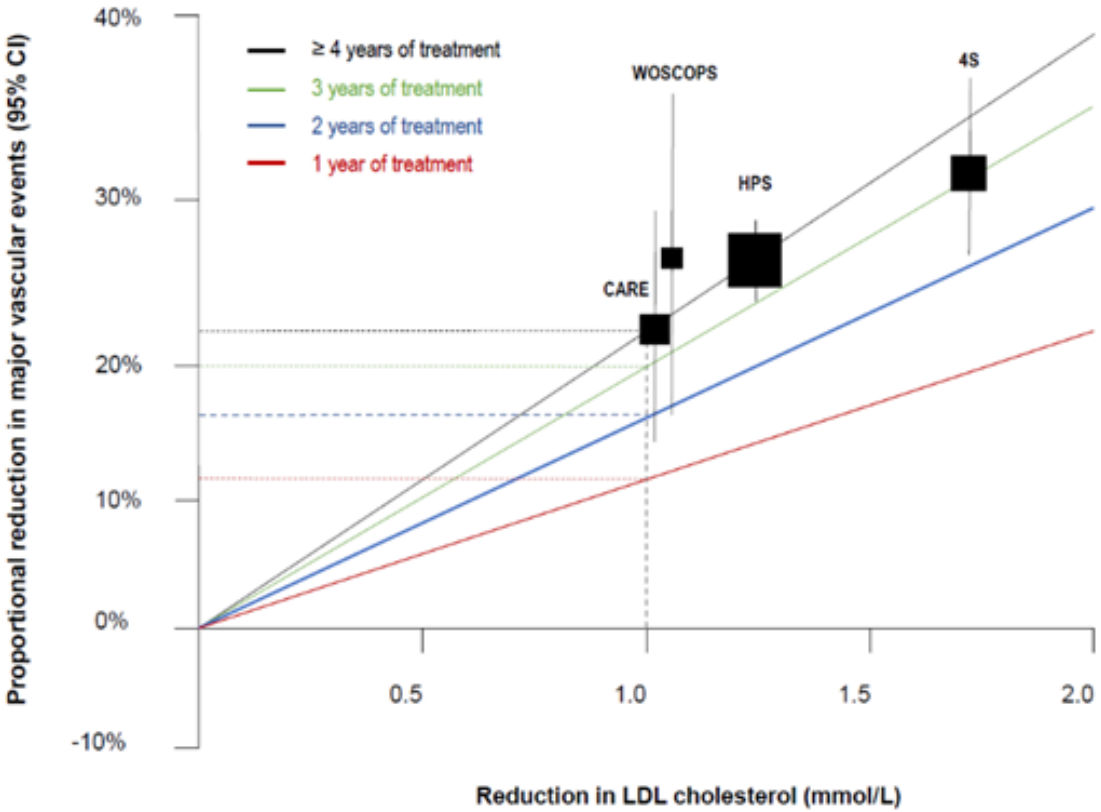
CV = Cardiovascular; MI = Myocardial infarction;
UA = Unstable angina; HR = Hazard ratio

HR 0.85 (95% CI 0.79 to 0.92); *P* < 0.001

Sabatine MS, et al. *N Engl J Med.* 2017;376:1713-1722

CTT Regression Lines by Duration of Follow-up

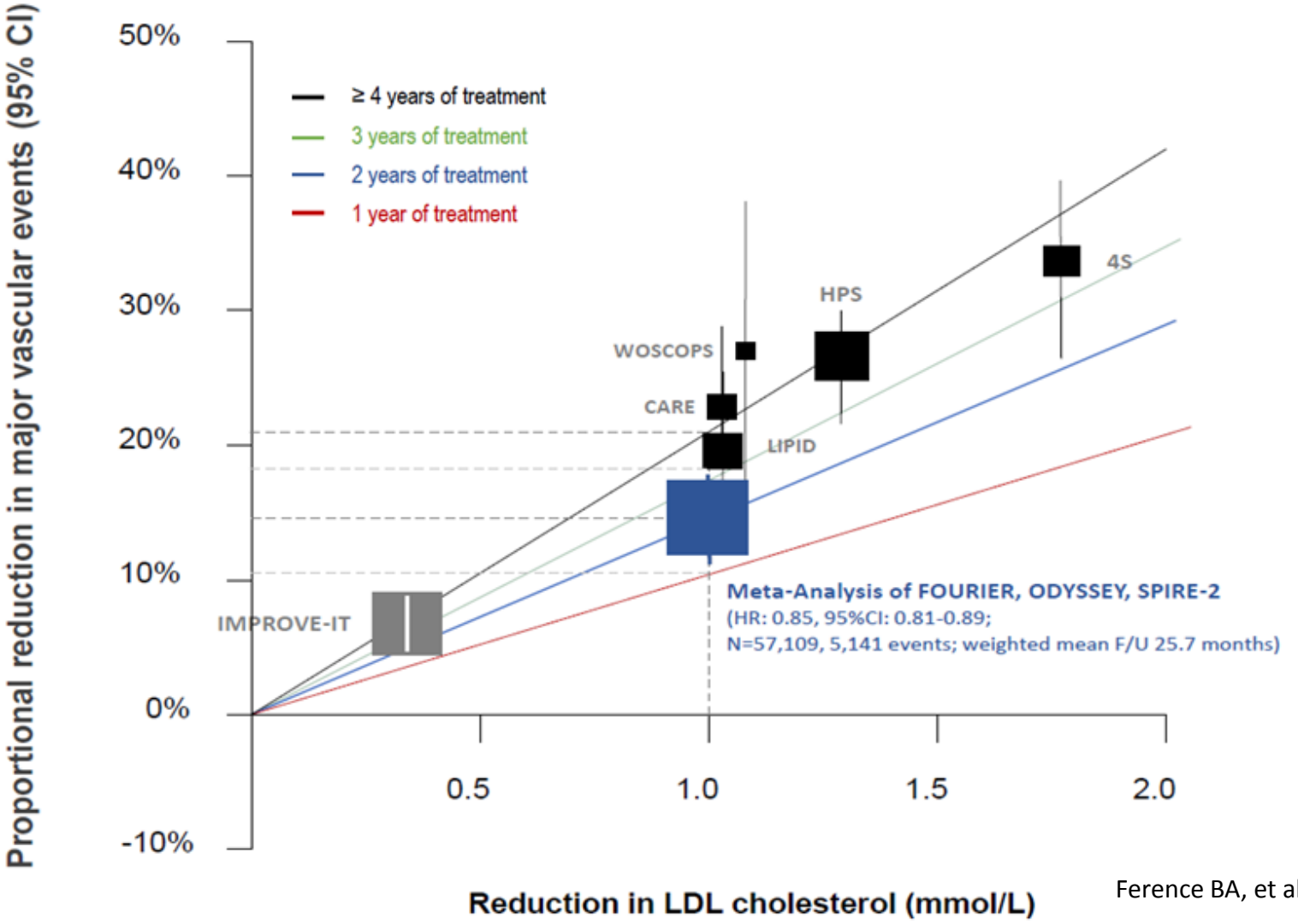




Cholesterol Treatment Trialists Collaboration.
Lancet. 2010 376:1670-81

Ference BA, et al. Eur Heart J. 2018; 39(27):2540-2545;
DOI: 10.1093/eurheartj/ehx450

Comparison of PCSK9 Inhibitors and Statins by Duration of Treatment



Ference BA, et al. Eur Heart J. 2018; 39(27):2540-2545;
DOI: 10.1093/eurheartj/ehx450

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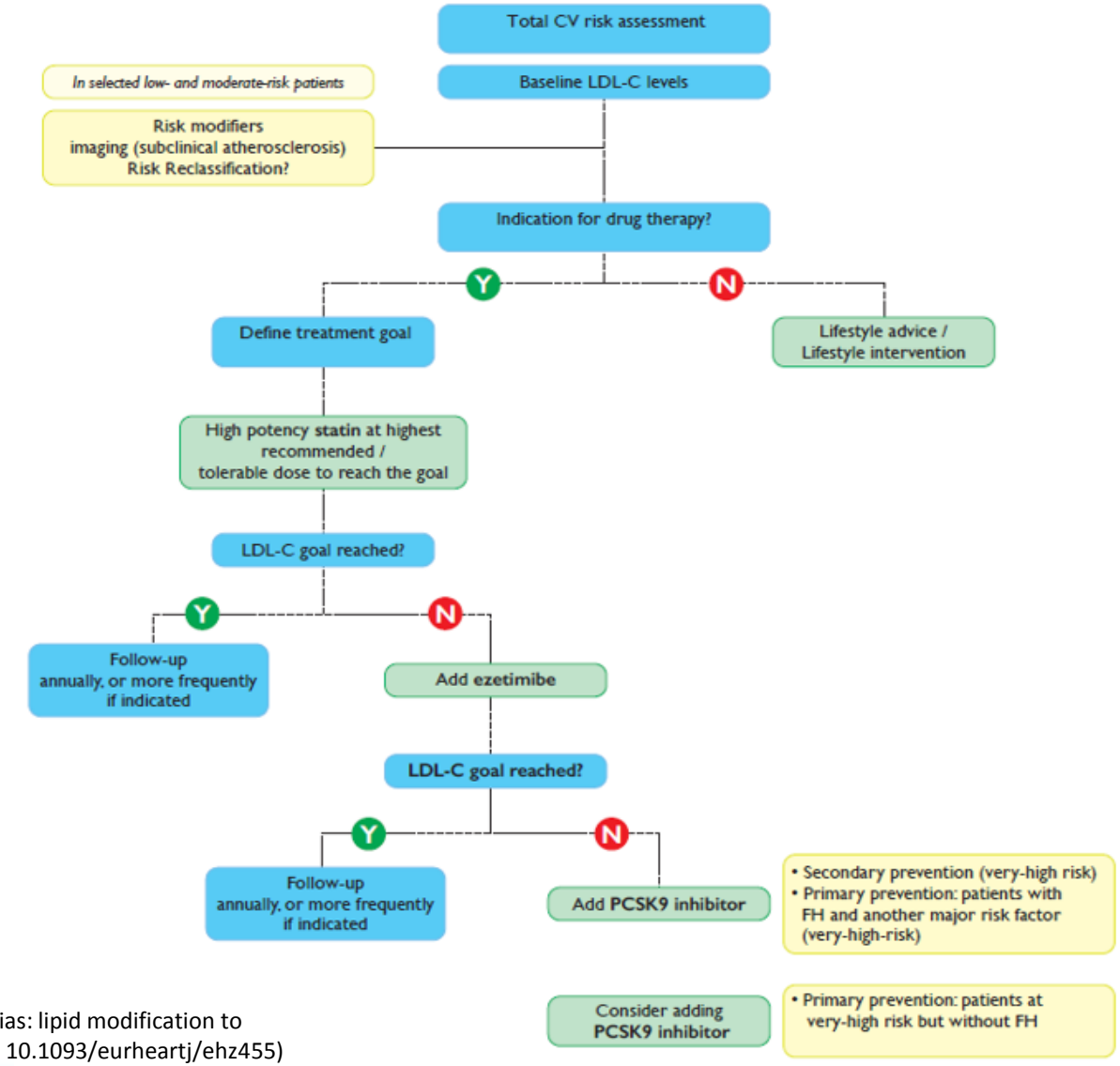
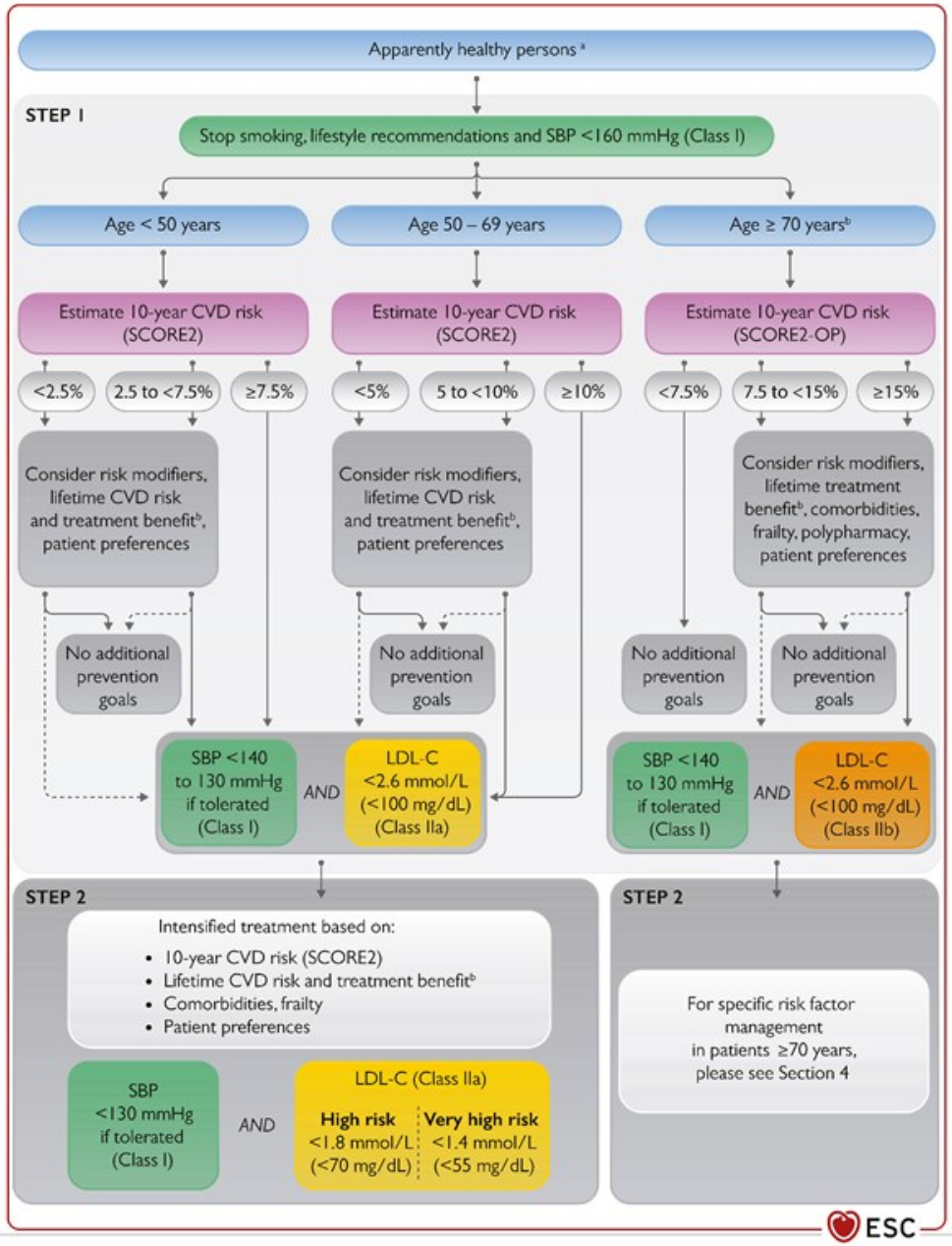
- ADHERENCE TO THERAPY

Treatment Algorithm for Pharmacological LDL-C Lowering



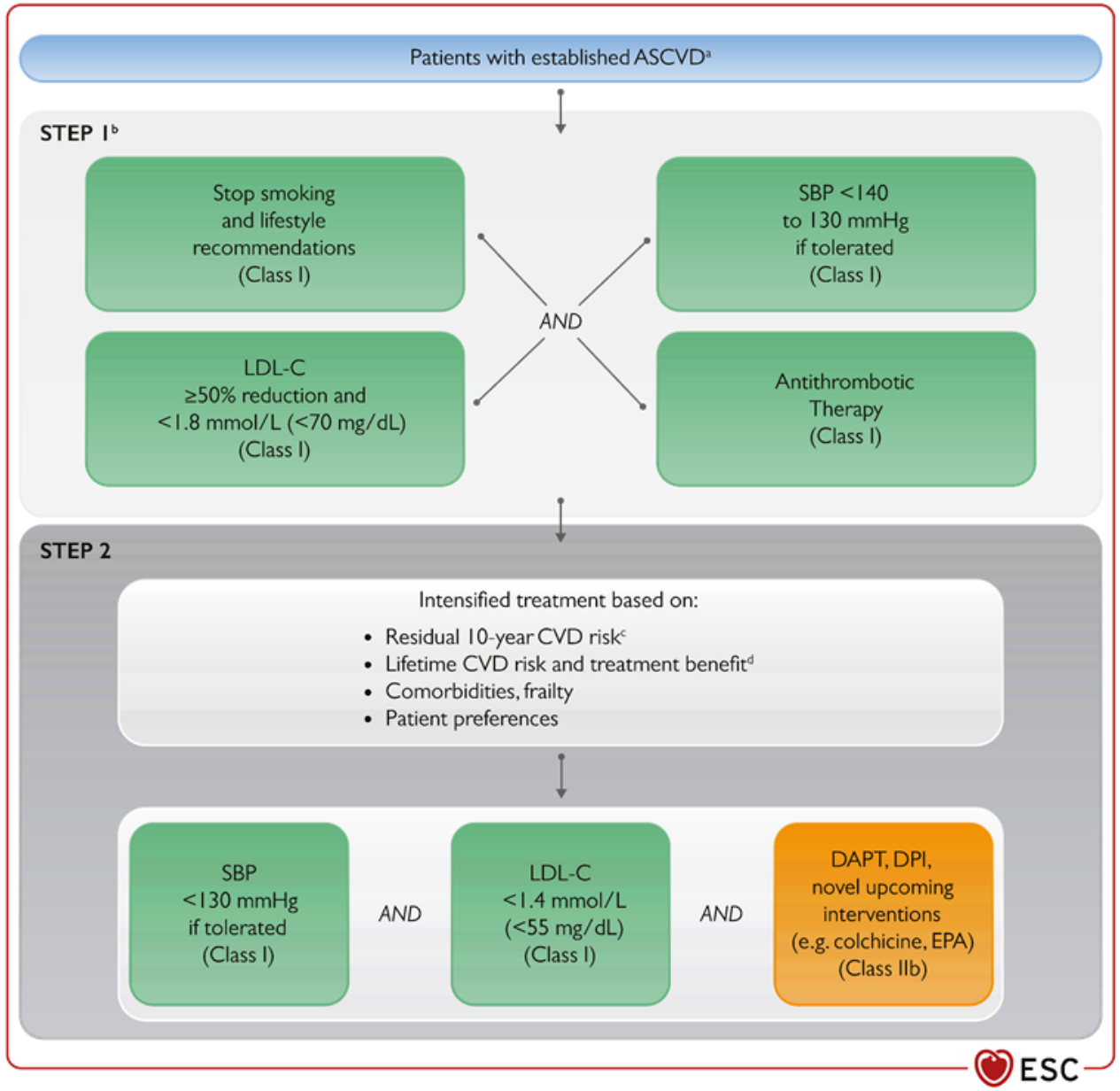
2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019-doi: 10.1093/eurheartj/ehz455)



Cardiovascular risk and risk factor treatment in apparently healthy persons

© ESC

2021 ESC Guidelines on cardiovascular disease prevention in clinical practice
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab484)



Cardiovascular risk and risk factor treatment in patients with established cardiovascular disease

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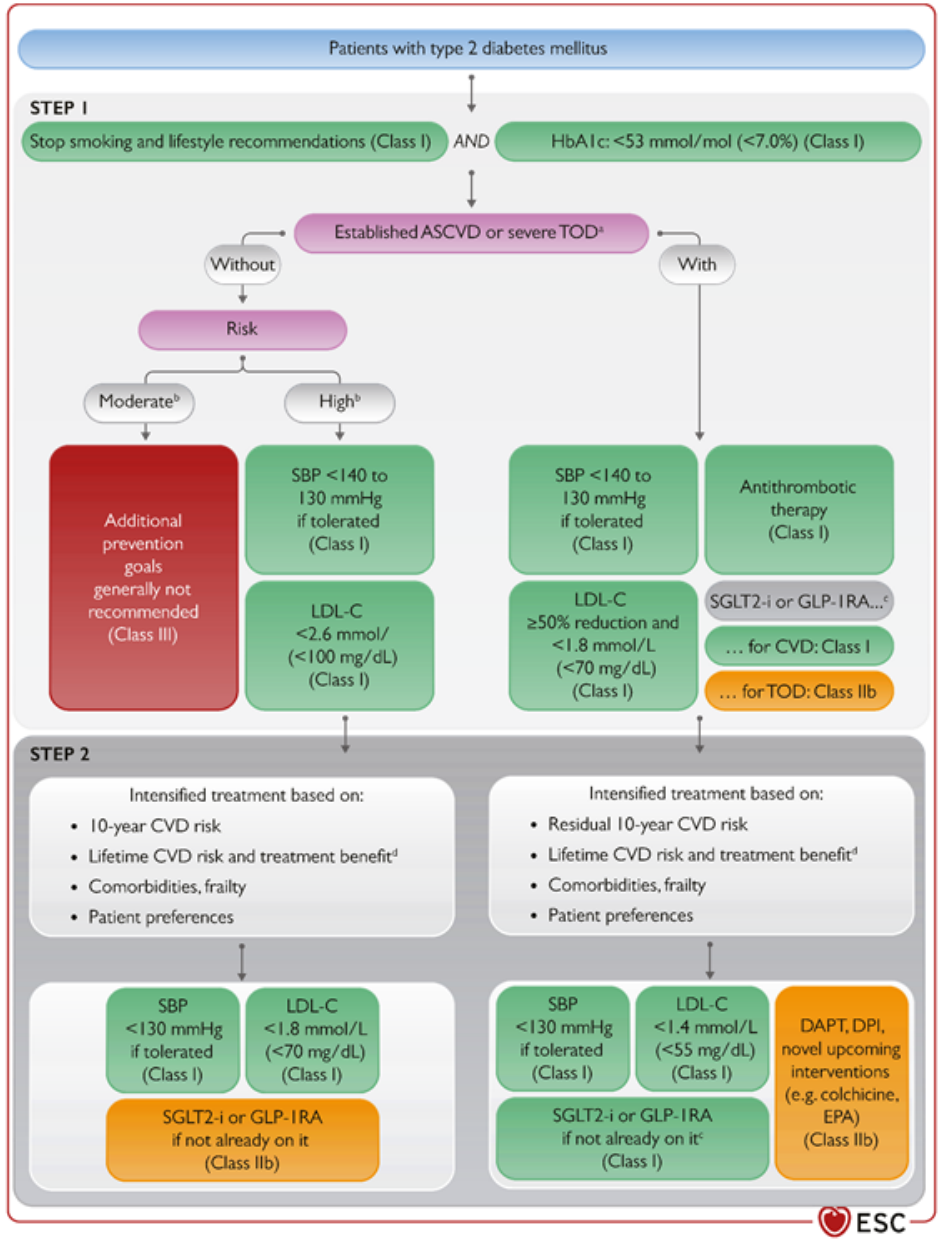


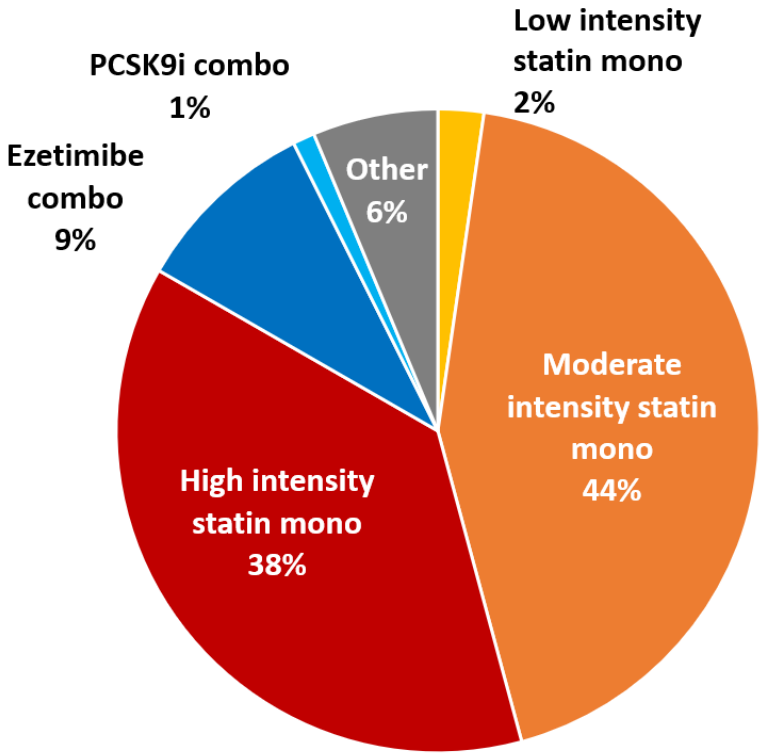
Cardiovascular risk and risk factor treatment in patients with type 2 diabetes mellitus

©ESC

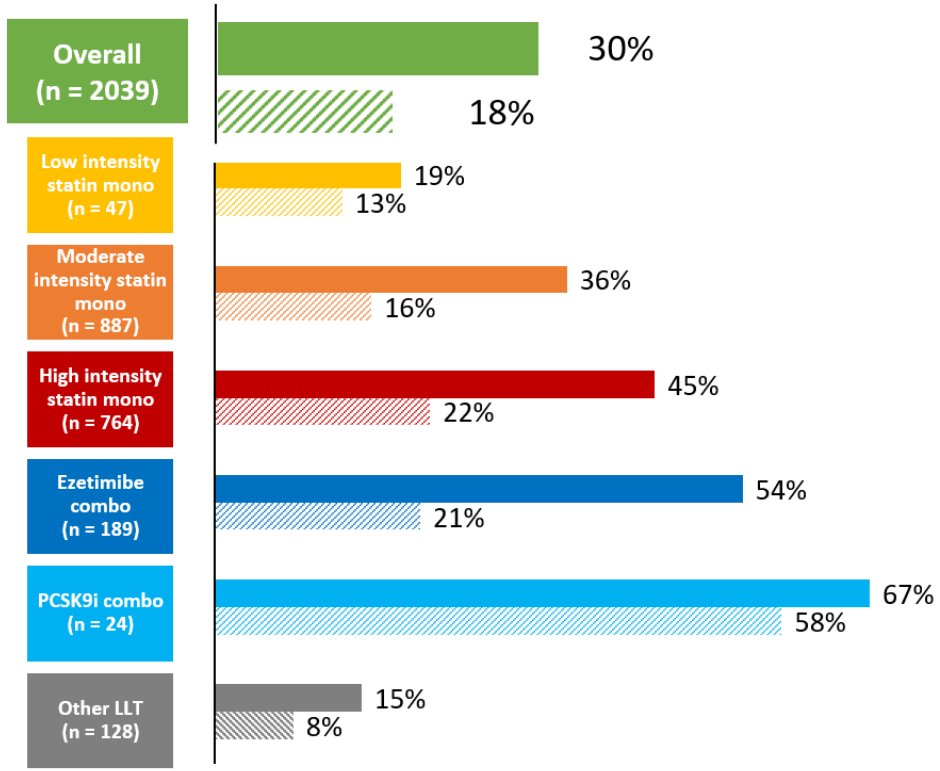
2021 ESC Guidelines on cardiovascular disease prevention in clinical practice
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab484)

DA VINCI STUDY: LDL-C goal Attainment by LLT in Patients with Established ASCVD

LLT use among patients with established ASCVD



2016/2019 goal attainment in patients with established ASCVD



Pie chart shows % of patients receiving each LLT at LDL-C measurement. Bar chart shows % of patients achieving 2016 (solid bars) and 2019 (hashed bars) LDL-C goals. ASCVD, atherosclerotic cardiovascular disease; combo, combination therapy; LDL-C, low-density lipoprotein cholesterol; LLT, lipid lowering therapy; mono, monotherapy; PCSK9i; proprotein convertase subtilisin/kexin type 9 inhibitor

Future Challenges

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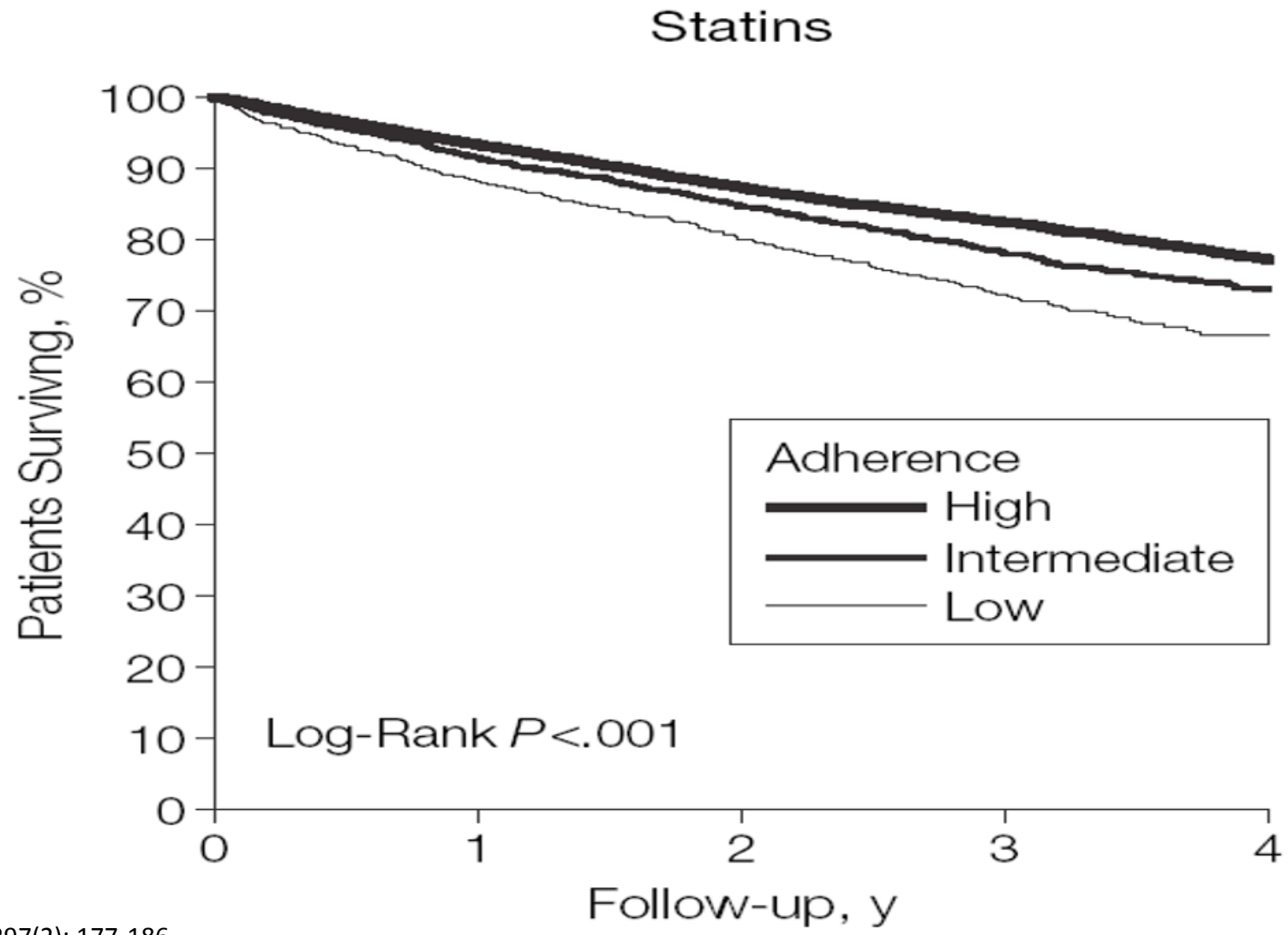
Statin Under-dosing is Associated with an Adverse Outcome



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

GRAZIE PER L'ATTENZIONE