Chi ha diabete (anche tipo 1) va sempre considerato in *prevenzione secondaria*? I target di LDL

University of Rome "Tor Vergata"
Department of Systems Medicine

Center for Atherosclerosis
"Tor Vergata University Hospital"

Massimo Federici, M.D.
Professor in Internal Medicine

PTV
Azienda Ospedaliera Universitaria
POLICLINICO TOR VERGATA

Massimo Federici

- received unrestricted research grant by EFSD/Sanofi initiative;
- has given lectures for Novo Nordisk, Lilly & Co, Boehringer Ingelheim, Daiichi-Sankyo, Amgen, and Merck Sharp & Dohme;
- and has served as an advisor for Novo Nordisk, Lilly & Co, Boehringer Ingelheim, Amarin, Amgen, Merck Sharp & Dohme, and Organon;
- all fees were approved by the University of Rome Tor Vergata (according to Italian law n. 165/2001, art. 53)

Agenda

- Il concetto di rischio: categorie o continuum?
- I target di LDL in rapporto al calcolo del rischio e la loro efficacia: cosa torna e cosa non torna
- T2D: le LDL sono sufficienti a catturare il rischio CV?

Diabetes-specific risk prediction models ESC 2021 Prevention GLs proposed ADVANCE or DIAL

- Risk models help refine CVD risk estimations and identify patients who will benefit most from treatment
- Include duration of diabetes, glycated haemoglobin (HbA1c), and TOD
- Examples are:

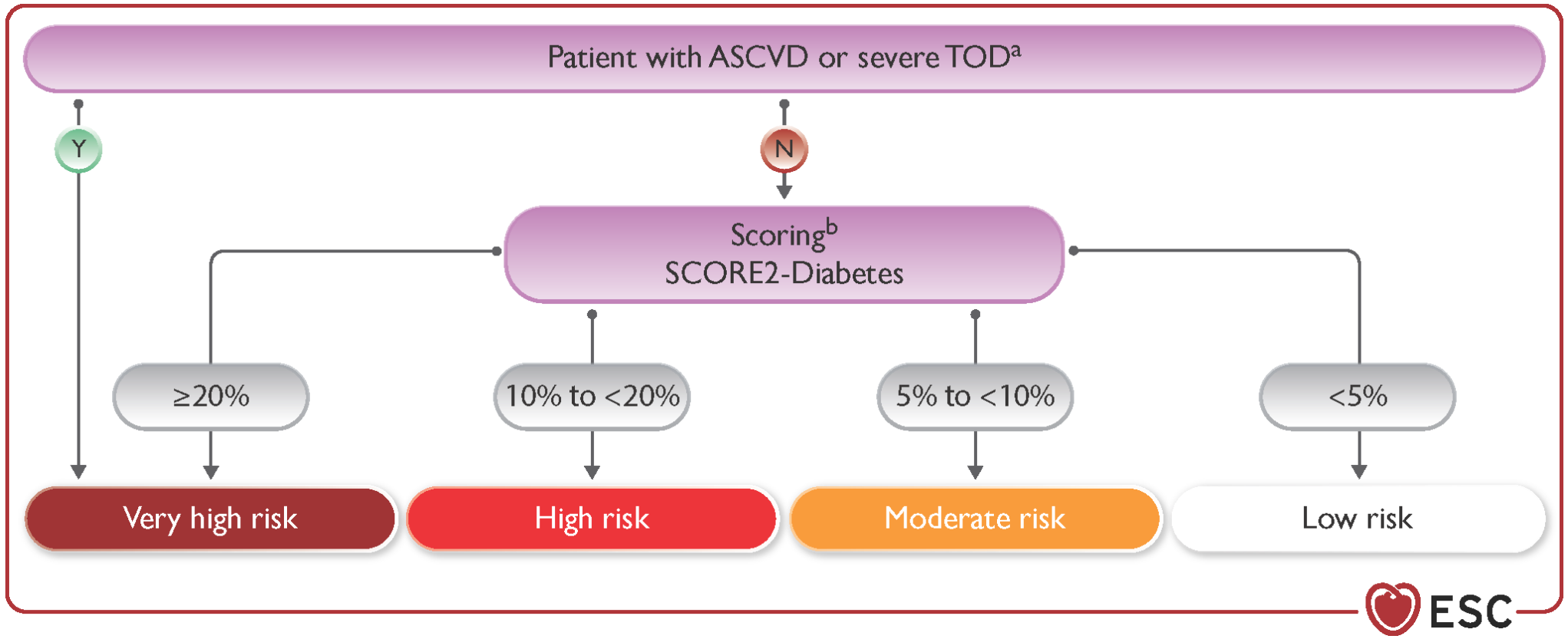
ADVANCE	predicts 4-year CVD risk
UKPDS	predicts CVD risk in the UK
DIAL	prediction of life-time risk

These models have some limitations for use in Europe:

- they do not allow for substantial variations of risk across countries, meaning they may misestimate risk in these circumstances.
- Furthermore, these models have been developed from a narrow set of studies
- have not been systematically 'recalibrated' (i.e. statistically adapted) to contemporary CVD rates, meaning they are not ideal for use in contemporary European populations.

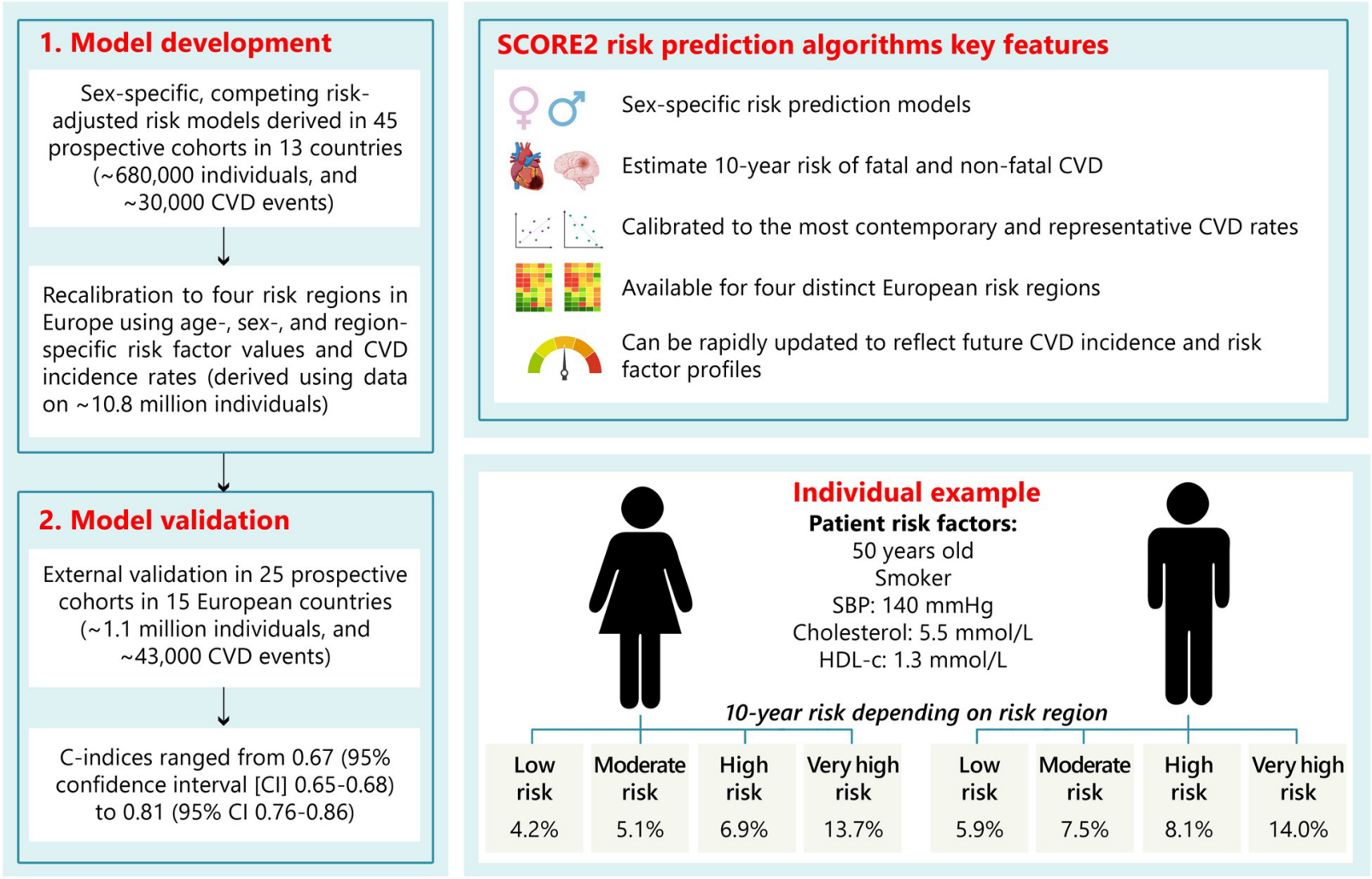
Figure 3

Cardiovascular risk categories in patients with type 2 diabetes



2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

Development process and key features of SCORE2



Hageman et al, *Eur Heart J* 2021

SCORE2-Diabetes: a risk tool for T2D

Development process

Original SCORE2 algorithms:
Predictors: age, sex, smoking, diabetes, SBP, total and HDL cholesterol

Calibrated to predict CVD risk in:
low, moderate, high and very high risk regions of Europe

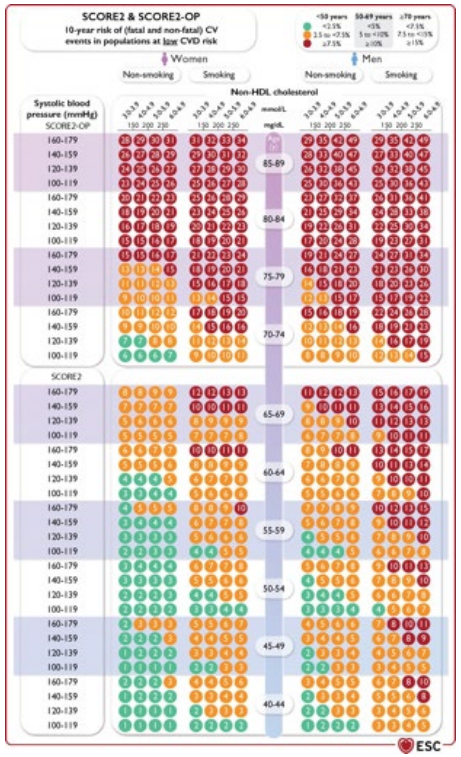
Adaptation of SCORE2 for individuals with type-2 diabetes:
Added predictors: age at diabetes diagnosis, HbA1c and eGFR

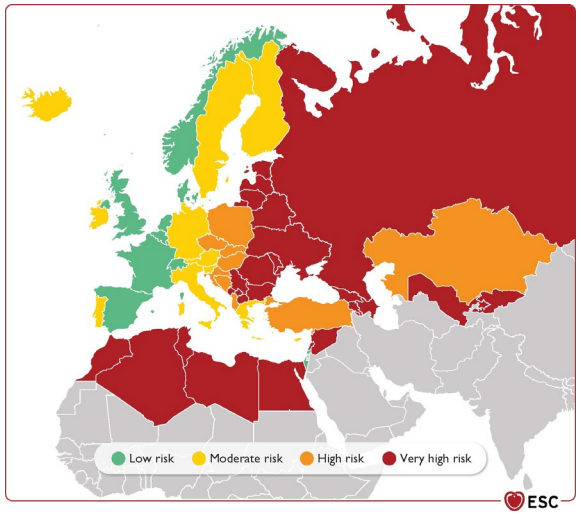
→ SCORE2-Diabetes

Data used: 229,460 individuals with type-2 diabetes from electronic health records, diabetes registry, cohort studies

Validation of SCORE2-Diabetes:
External validation in 217,036 individuals with type-2 diabetes from Sweden, Spain, Malta and Croatia

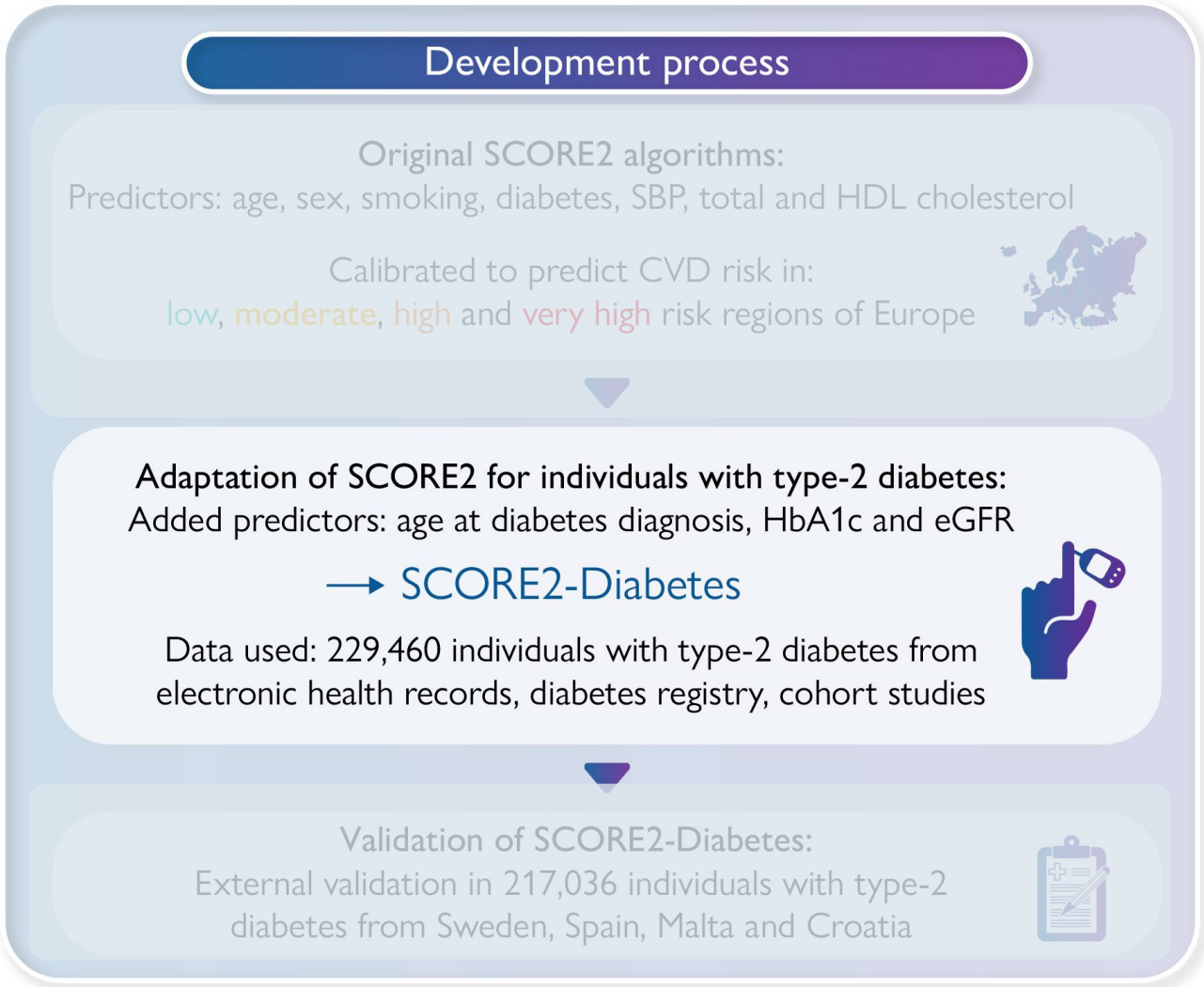
SCORE2
10-year risk of (fatal and non-fatal) CV events





Pennells L et al, *Eur Heart J* 2023

SCORE2-Diabetes: a risk tool for T2D



SCI-DC SCOTTISH CARE INFORMATION DIABETES COLLABORATION | CPRD | ERFC | biobank uk Enabling scientific discoveries that improve human health

~230K individual with type 2 diabetes and information on age at diagnosis, HbA1c and eGFR

⇩

SCORE2-Diabetes

Pennells L et al, *Eur Heart J* 2023

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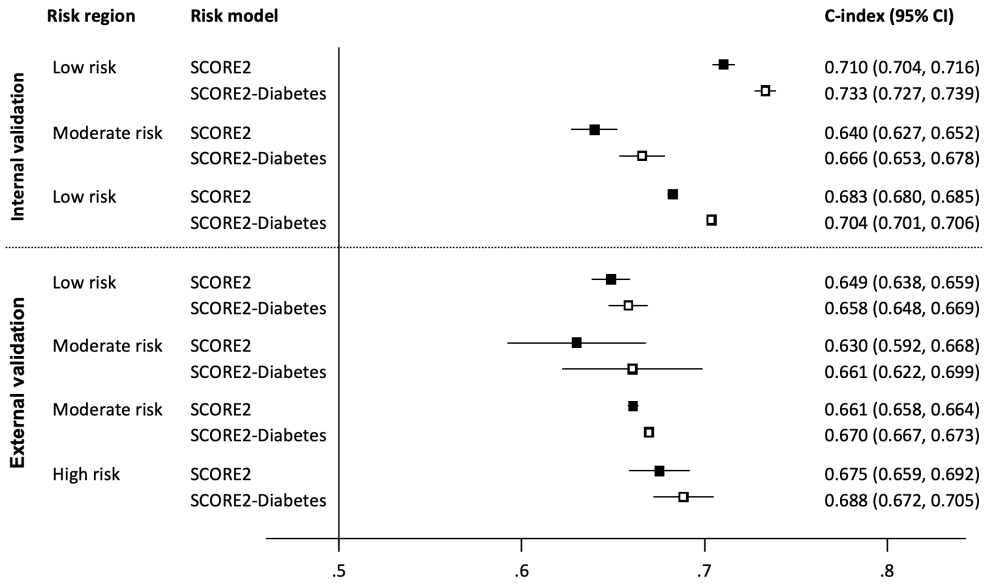
Internal and external validation across Europe



SCORE2-Diabetes: a risk tool for T2D

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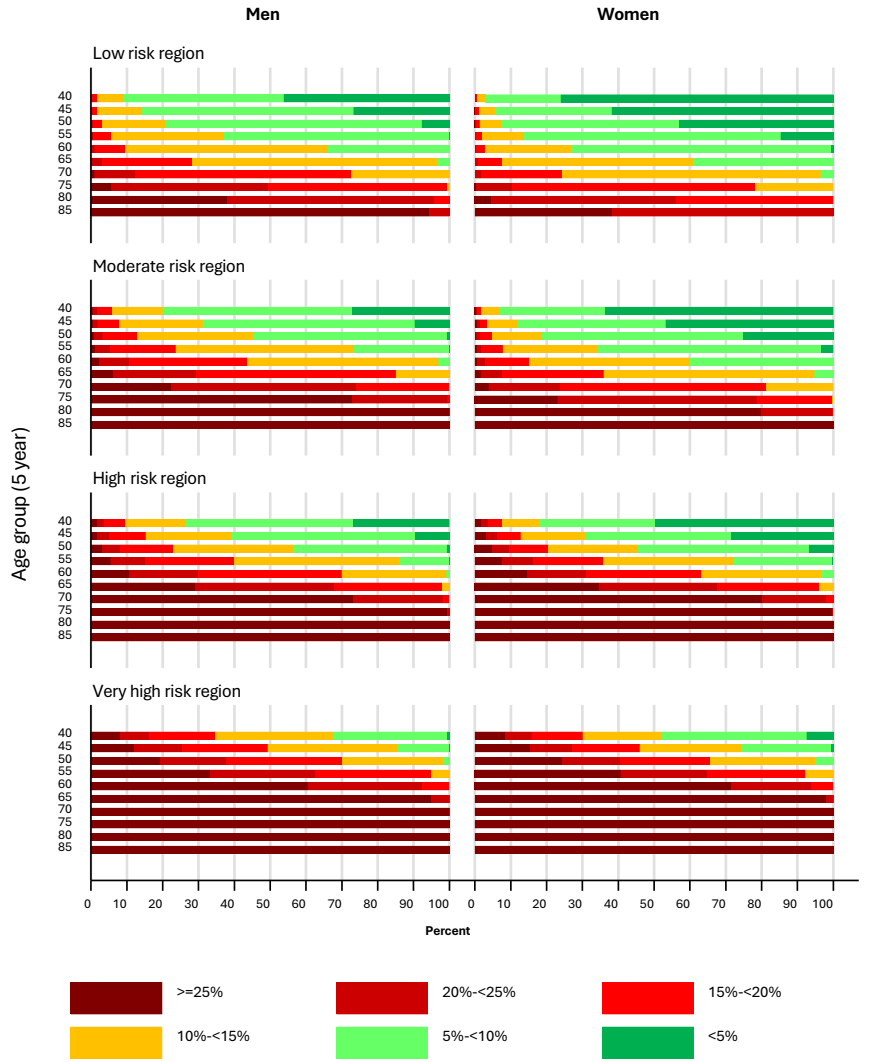
Expected CVD risk distribution across Europe



SCORE2-Diabetes: a new risk prediction tool

Development process

Original SCORE2 algorithms:
Predictors: age, sex, smoking, diabetes, SBP, total and HDL cholesterol

Calibrated to predict CVD risk in:
low, moderate, high and very high risk regions of Europe

Adaptation of SCORE2 for individuals with type-2 diabetes:
Added predictors: age at diabetes diagnosis, HbA1c and eGFR

→ SCORE2-Diabetes

Data used: 229,460 individuals with type-2 diabetes from electronic health records, diabetes registry, cohort studies

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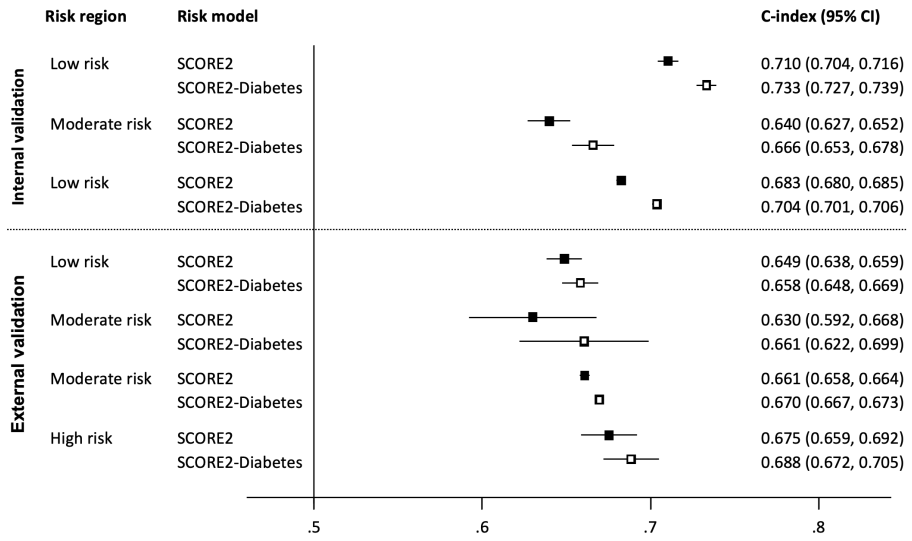
SCORE2-Diabetes

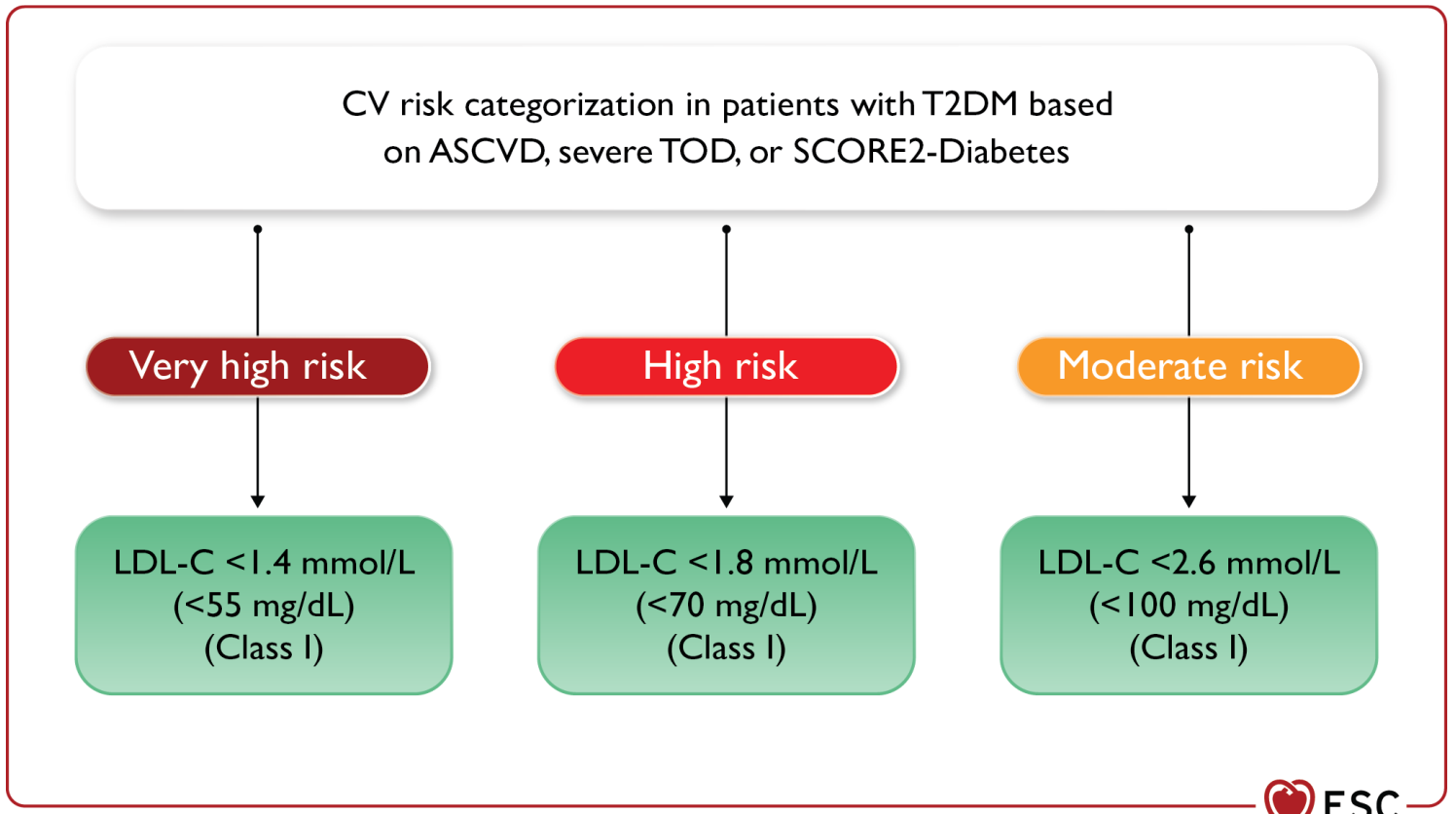
Internal and external validation across Europe



Pennells L et al, Eur Heart J 2023 Eur Heart J. 2023 Jul 21;44(28):2544-2556

Figure 10

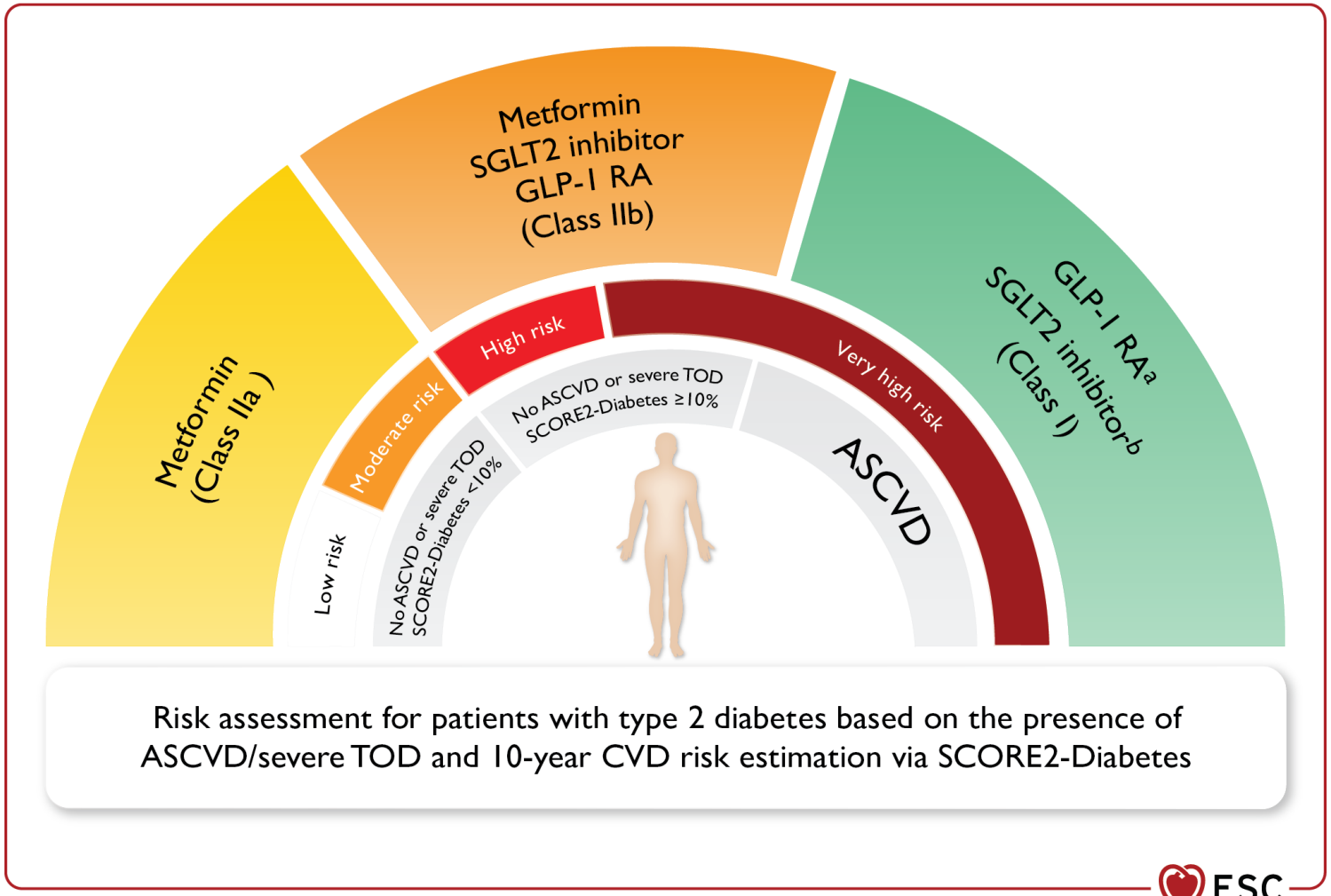
Recommended low-density lipoprotein-cholesterol targets by cardiovascular risk categories in patients with type 2 diabetes



2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

Figure 7

Glucose-lowering treatment for patients with type 2 diabetes to reduce cardiovascular risk based on the presence of ASCVD/severe target-organ damage and 10-year cardiovascular disease risk estimation via SCORE2-Diabetes



2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes

ESC European Society of Cardiology

ESC GUIDELINES

European Heart Journal (2023) 44, 4043–4140
https://doi.org/10.1093/eurheartj/ehad192

Developed by the task force on the management of cardiovascular disease in patients with diabetes of the European Society of Cardiology (ESC)

CV Risk, Target and Pharmacological Approaches to Achieve Target Goals

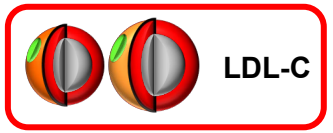


Table 7 Cardiovascular risk categories in type 2 diabetes

Very high CV risk	Patients with T2DM with: • Clinically established ASCVD or • Severe TOD or • 10-year CVD risk ≥20% using SCORE2-Diabetes
High CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: • 10-year CVD risk 10 to <20% using SCORE2-Diabetes
Moderate CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: • 10-year CVD risk 5 to <10% using SCORE2-Diabetes
Low CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: • 10-year CVD risk <5% using SCORE2-Diabetes

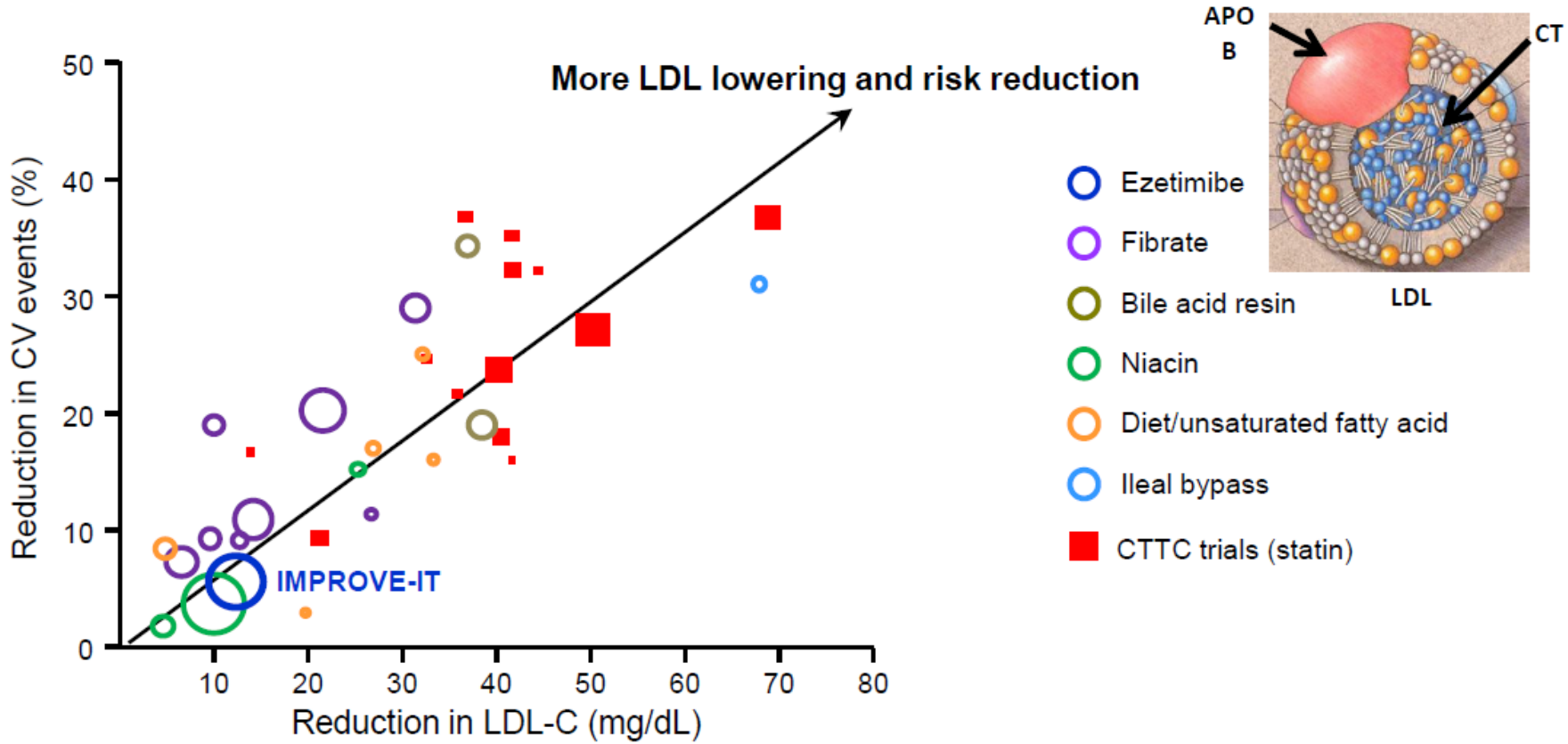
ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; SCORE2-Diabetes, type 2 diabetes-specific 10-year CVD risk score; T2DM, type 2 diabetes mellitus; TOD, target-organ damage; UACR, urinary albumin-to-creatinine ratio.
Severe TOD defined as eGFR <45 mL/min/1.73 m^2 irrespective of albuminuria; or eGFR 45–59 mL/min/1.73 m^2 and microalbuminuria (UACR 30–300 mg/g; stage A2); or proteinuria (UACR >300 mg/g; stage A3); or presence of microvascular disease in at least three different sites [e.g. microalbuminuria (stage A2) plus retinopathy plus neuropathy].[43–45]

Recommendation Table 11 — Recommendations for the management of dyslipidaemia in patients with diabetes

Recommendations	Class[a]	Level[b]
Lipid targets		
In patients with T2DM at moderate CV risk, an LDL-C target of <2.6 mmol/L (<100 mg/dL) is recommended.[248,249]	I	A
In patients with T2DM at high CV risk, an LDL-C target of <1.8 mmol/L (<70 mg/dL) and LDL-C reduction of at least 50% is recommended.[248,249]	I	A
In patients with T2DM at very high CV risk, an LDL-C target of <1.4 mmol/L (<55 mg/dL) and LDL-C reduction of at least 50% is recommended.[248,249]	I	B
In patients with T2DM, a secondary goal of a non-HDL-C target of <2.2 mmol/L (<85 mg/dL) in very high CV risk patients and <2.6 mmol/L (<100 mg/dL) in high CV risk patients is recommended.[283–285]	I	B

Mach F, et al. *Eur Heart J.* 2019;00:1–78 European Heart Journal (2021) 42, 3227-3337 - doi:10.1093/eurheartj/ehab484

Every 39 mg/dl (1 mmol/L) reduction in LDL-C reduces annual CV risk by up to 28%, regardless of mechanism

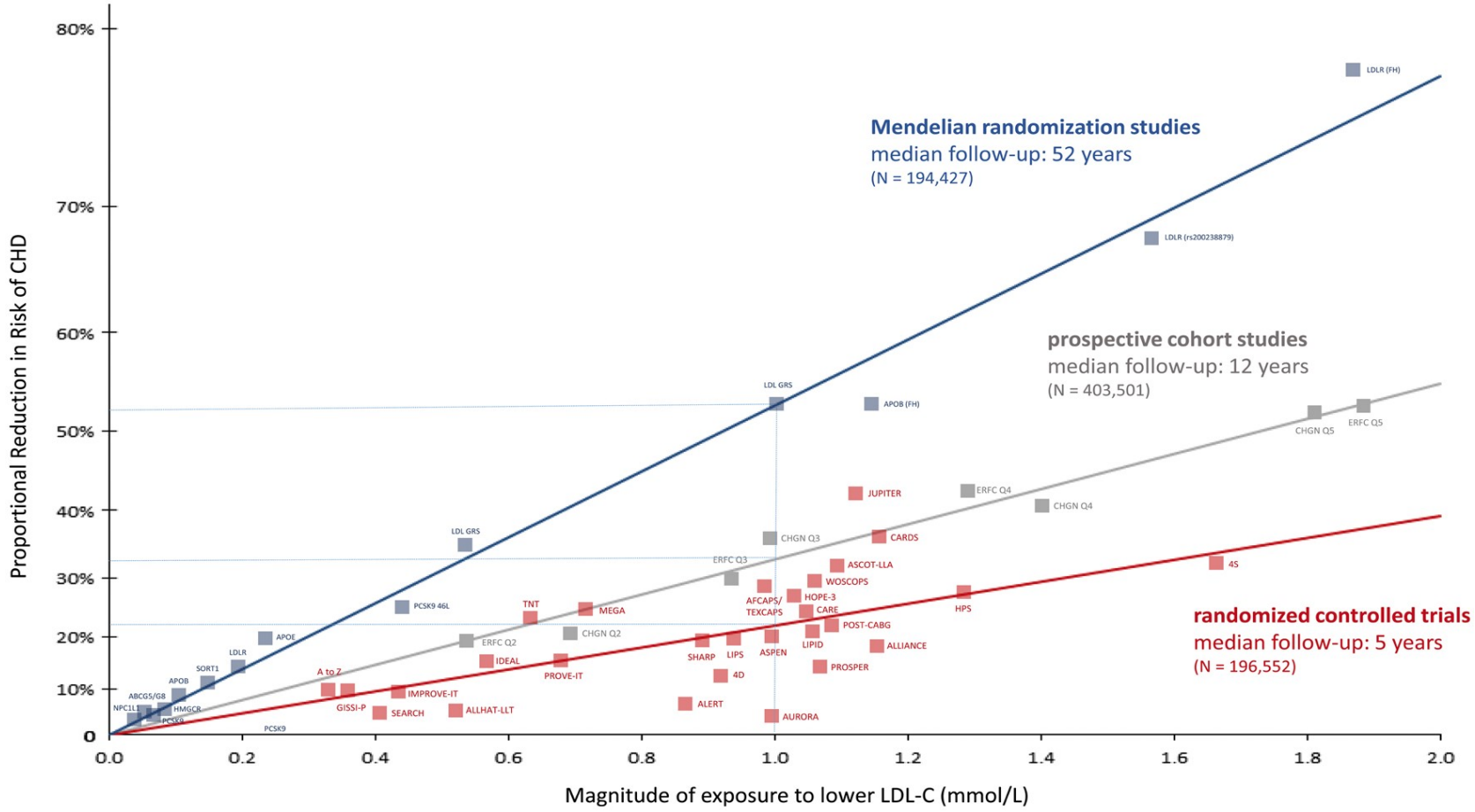


There is no evidence of any lower LDL-C threshold

Data from studies of non-statin lipid-lowering medications superimposed upon data from the Cholesterol Treatment Trialists Collaboration (CTTC) 2005 meta-analysis. The IMPROVE-IT trial was adequately powered to show the efficacy on incremental LDL-C lowering on CV outcomes. [To convert, 100 mg/dL=2.59 mmol/L].
CV, cardiovascular; IMPROVE-IT, IMProved Reduction of Outcomes: Vytorin Efficacy International Trial; LDL-C, low-density lipoprotein cholesterol.
CTT Collaboration. Lancet 2005:366;1267–78; CTT Collaboration. Lancet 2010;376:1670–81;
Cannon CP, et al. N Engl J Med 2015;372:2387–97.

MGEN® vascular

Log-linear association per unit change in low-density lipoprotein cholesterol (LDL-C) and the risk of cardiovascular disease



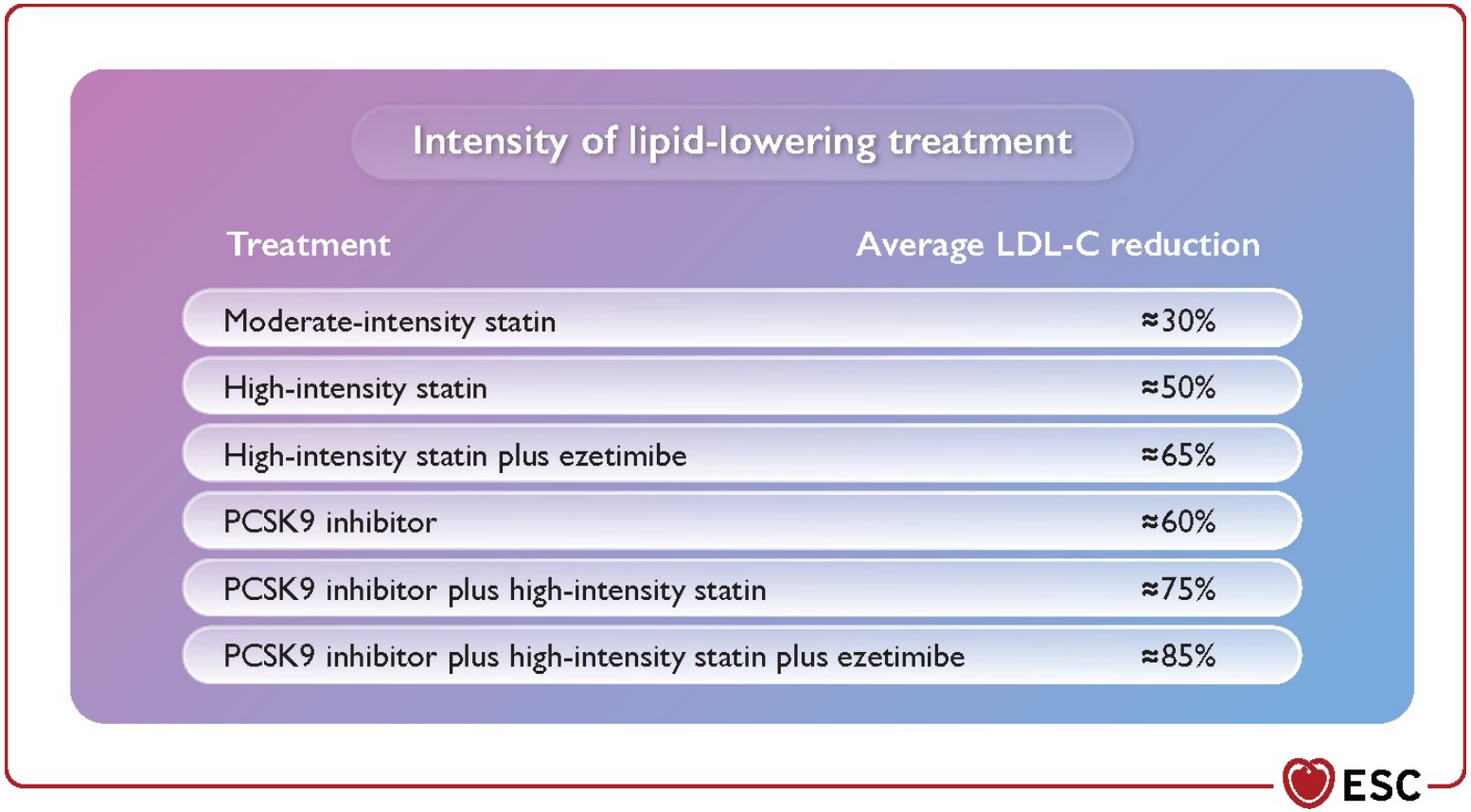
Eur Heart J, Volume 38, Issue 32, 21 August 2017, Pages 2459–2472, https://doi.org/10.1093/eurheartj/ehx144

T1D ESC2023 GLs

Recommendation	Class[a]	Level[b]
In patients with T1DM, it is recommended that adjustment of glucose-lowering medication follows principles of patient self-management under the guidance of the diabetes healthcare multidisciplinary team.	I	C
Avoiding hypoglycaemic episodes is recommended, particularly in those with established CVD.[780–782]	I	C
Statins should be considered for LDL-C lowering in adults older than 40 years with T1DM without a history of CVD to reduce CV risk.[787]	IIa	B
Statins should be considered for use in adults younger than 40 years with T1DM and other risk factors of CVD or microvascular end-organ damage or 10-year CVD risk ≥10% to reduce CVD risk.[787,788]	IIa	B
The use of the Scottish/Swedish risk prediction model may be considered to estimate 10-year CVD risk in patients with T1DM.[793]	IIb	B

CV, cardiovascular; CVD, cardiovascular disease; LDL-C, low-density lipoprotein-cholesterol; T1DM, type 1 diabetes mellitus.
[a]Class of recommendation.
[b]Level of evidence.

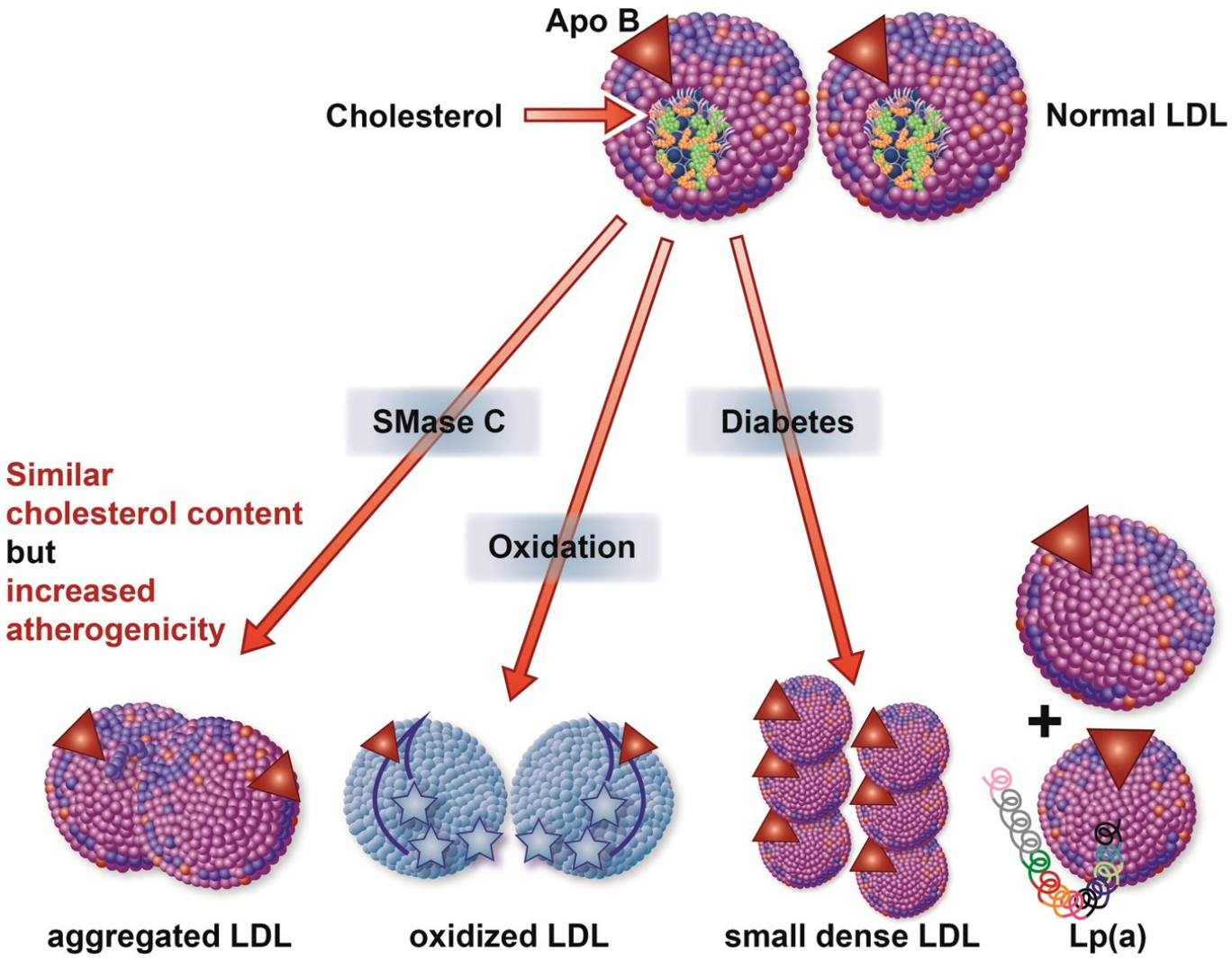
Expected low-density lipoprotein cholesterol reductions for combination therapies



"Treat to Target" = selezionare subito la terapia in grado di raggiungere obiettivo LDL, la titolazione non serve

Eur Heart J, Volume 42, Issue 34, 7 September 2021, Pages 3227–3337, https://doi.org/10.1093/eurheartj/ehab484

Pathological phenotypes of LDL particles



Eur Heart J, Volume 39, Issue 27, 14 July 2018, Pages 2574–2576, https://doi.org/10.1093/eurheartj/ehy387

Calculated Small Dense LDL-C has a Stronger Association to Atherosclerotic Cardiovascular Events than other Components of the Lipid Panel.

Table 1.

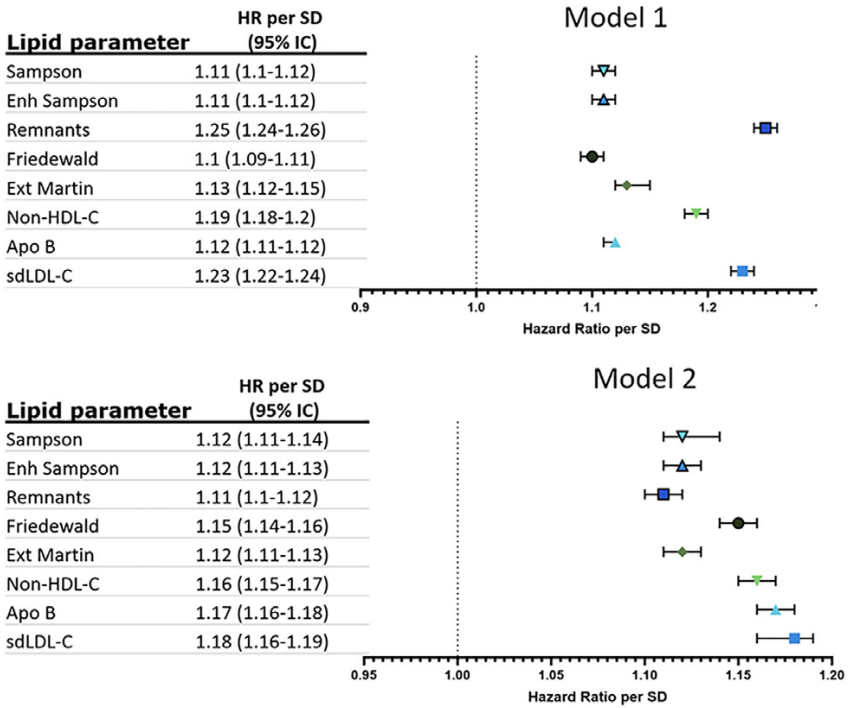
Variable	Test hazard ratio per SD (95% CI) Model 1	p	Test hazard ratio per SD (95% CI) Model 2	p
sdLDL-C	1.23 (1.22-1.24)	<0.001	1.18 (1.16-1.19)	<0.001
Apo B	1.12 (1.11-1.12)	<0.001	1.17 (1.16-1.18)	<0.001
Non-HDL-C	1.19 (1.18-1.2)	<0.001	1.16 (1.15-1.17)	<0.001
Ext Martin	1.13 (1.12-1.15)	<0.001	1.12 (1.11-1.13)	<0.001
Friedewald	1.1 (1.09-1.11)	<0.001	1.15 (1.14-1.16)	<0.001
Remnants	1.25 (1.24-1.26)	<0.001	1.11 (1.1-1.12)	<0.001
Enh Sampson	1.11 (1.1-1.12)	<0.001	1.12 (1.11-1.13)	<0.001
Sampson	1.11 (1.1-1.12)	<0.001	1.12 (1.11-1.14)	<0.001
Lp(a)	1.06 (1.05-1.08)	<0.001	1.08 (1.07-1.51)	<0.001

Cox Proportional Hazard ratio for any ASCVD event, Model 1 unadjusted and Model 2 adjusted for age, sex, race, diabetes, systolic blood pressure, smoking and hypertension. sd-LDL-C: small dense LDL cholesterol, Apo B: Apolipoprotein B, Non-HDL-C: non-HDL cholesterol, Lp(a): Lipoprotein (a)

Table 2.

Term	Model 1 Test hazard ratio (95% CI)	p	Model 2 Test hazard ratio (95% CI)	P
Sd-LDL-C/S-LDL-C discordance Quadrants				
Q3 (Reference)				
Q1	1.02(0.94-1.07)	0.1761	1.17(1.07-1.28)	0.0003
Q2	1.51(1.47-1.66)	<0.0001	1.46(1.38-1.56)	<0.0001
Q4	1.56(1.5-1.61)	<0.0001	1.31(1.21-1.42)	<0.0001

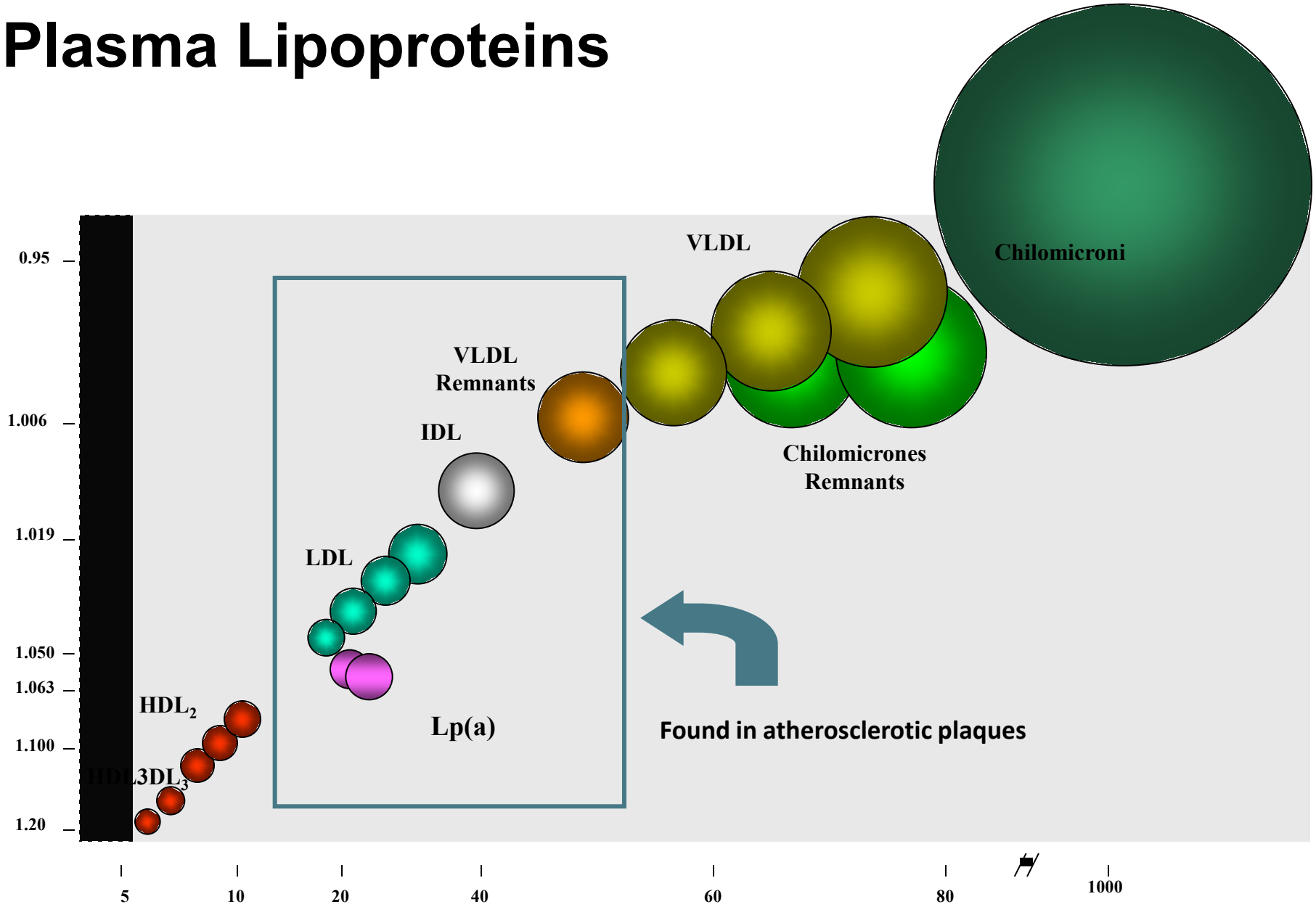
Cox Proportional Hazard ratio for any ASCVD event when discordance between S-LDL-C and sd-LDL-C, Model 1 unadjusted and Model 2 adjusted for age, sex, race, diabetes, systolic blood pressure, smoking and hypertension Q1 = S-LDL percentile >50 and sd-LDL-C <50, Q2 = S-LDL percentile >50 and sd-LDL-C >50, Q3 = S-LDL percentile <50 and sd-LDL-C <50, Q4 = S-LDL percentile <50 and sd-LDL-C >50. sd-LDL-C: small dense LDL cholesterol, S-LDL-C: Sampson's LDL cholesterol formula.



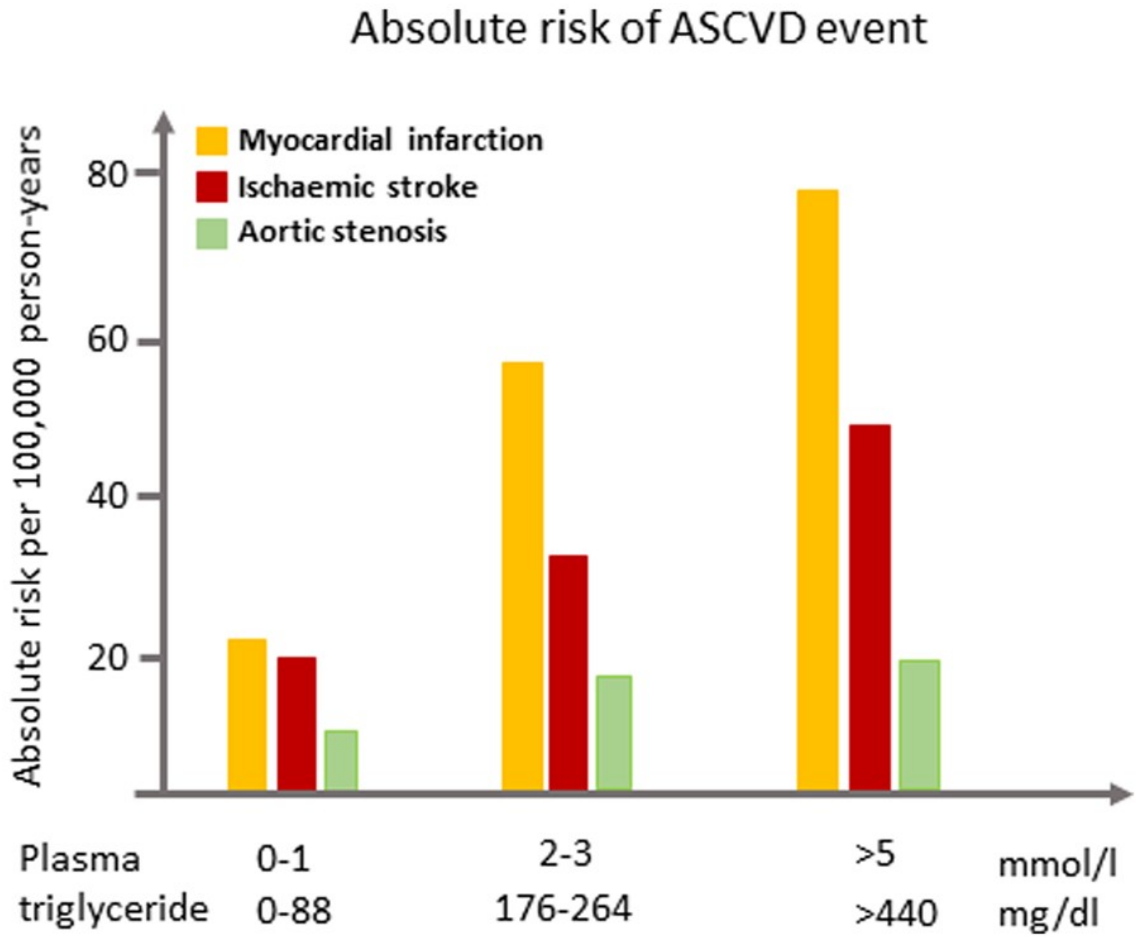
Cox Proportional Hazard ratio for any ASCVD event, Model 1 unadjusted and Model 2 adjusted for age, sex, race, diabetes, systolic blood pressure, smoking and hypertension.

Journal of Clinical Lipidology, Vol 18, No 4S, July/August 2024

Plasma Lipoproteins

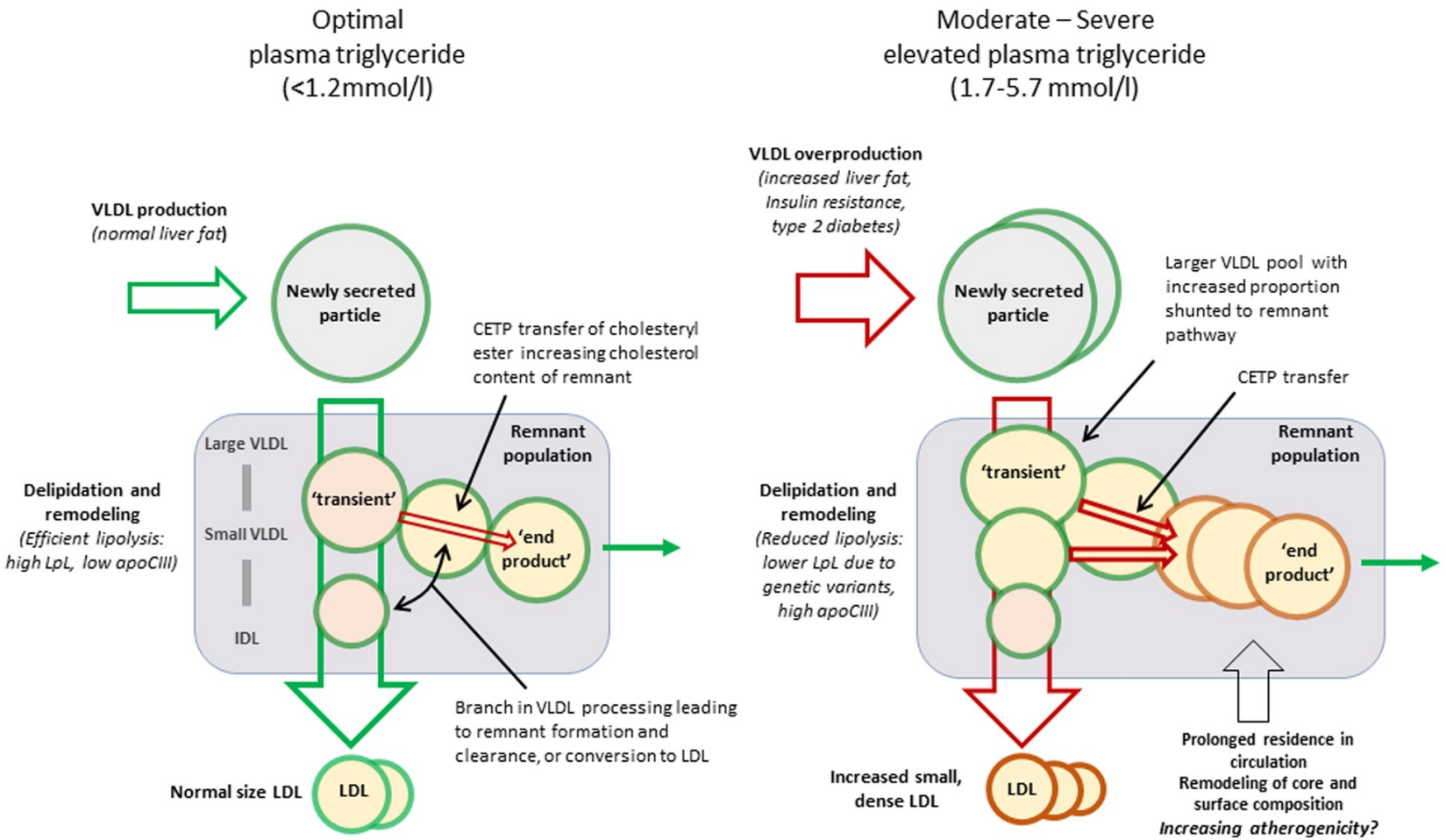


Absolute risk of cardiovascular morbidity as a function of increasing non-fasting plasma triglycerides in the general population.
Based on data from more than 100 000 individuals in the Copenhagen General Population Study



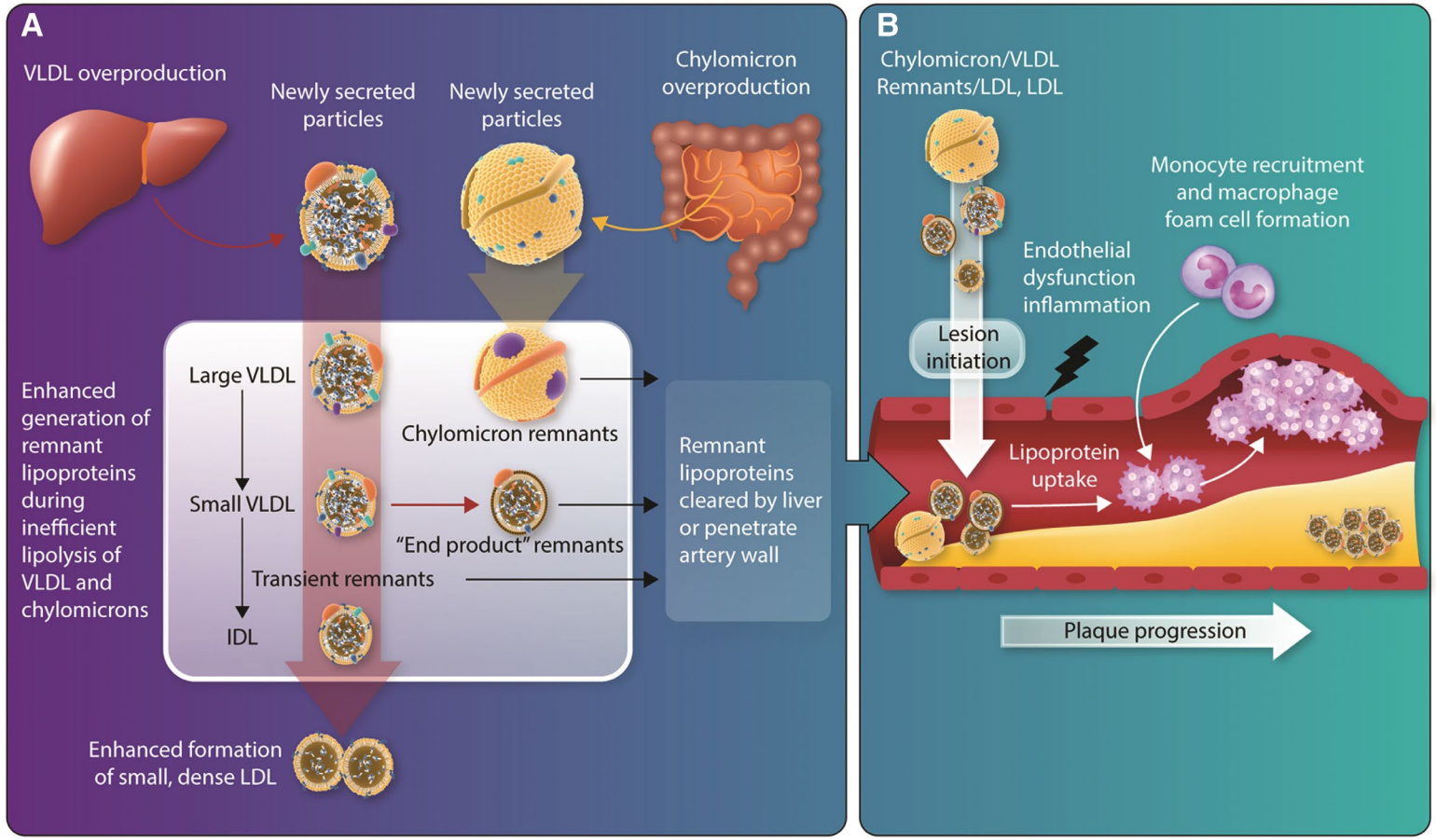
Eur Heart J, Volume 42, Issue 47, 14 December 2021, Pages 4791–4806, https://doi.org/10.1093/eurheartj/ehab551

Metabolism of remnant lipoproteins.
Remnants are a population of particles in the circulation that have been partially lipolysed by lipoprotein lipase



Eur Heart J, Volume 42, Issue 47, 14 December 2021, Pages 4791–4806, https://doi.org/10.1093/eurheartj/ehab551

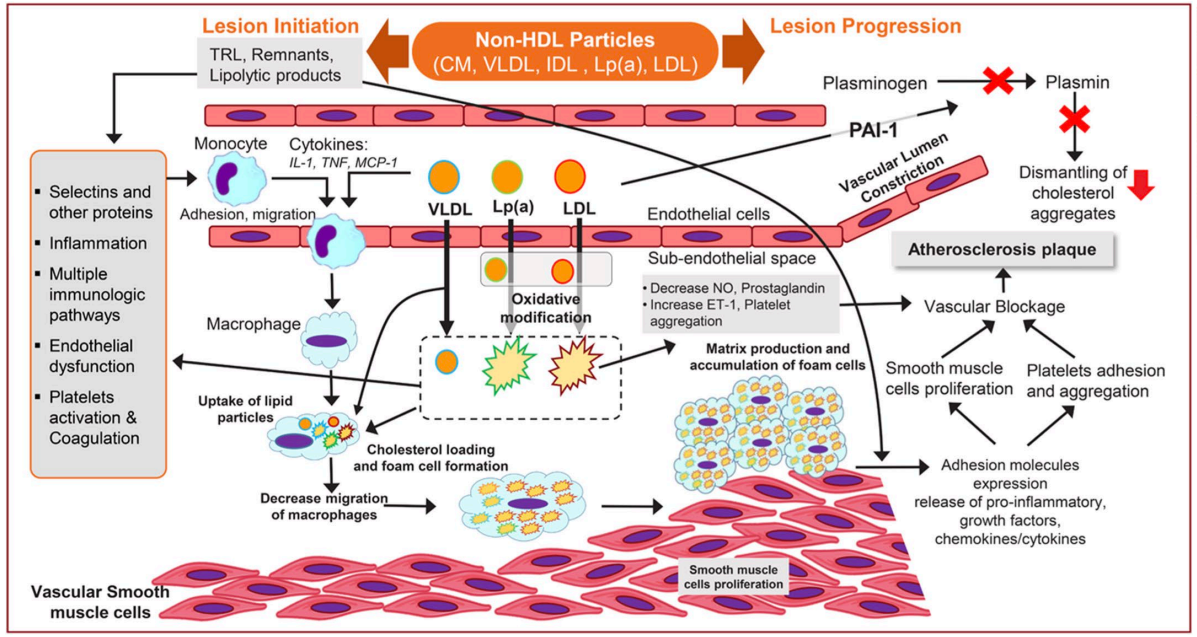
Recent evidence supports a causal association between triglycerides, triglyceride-rich lipoproteins, and triglyceride-rich lipoprotein remnants with cardiovascular events



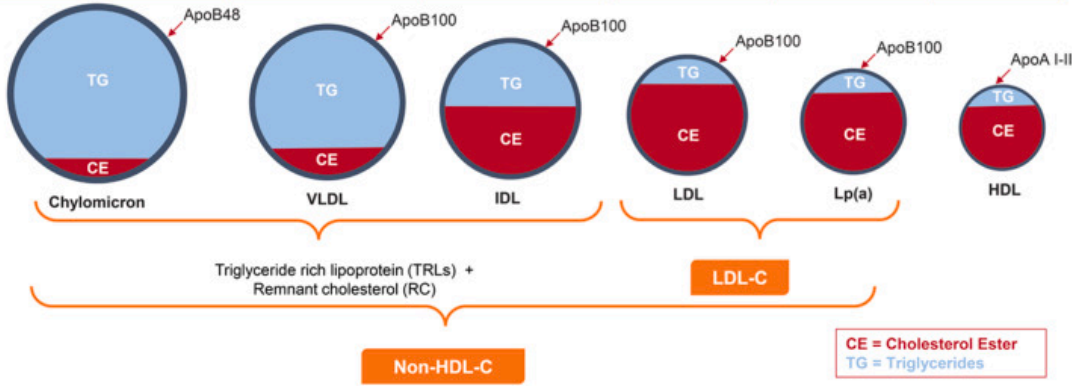
1 TG-RICH LIPOPROTEIN IS AS ATHEROGENIC AS 1 LDL PARTICLE

Eur Heart J, Volume 43, Issue 8, 21 February 2022, Pages 807–817, https://doi.org/10.1093/eurheartj/ehab875

Overview of non-HDL-C pathogenesis



Parameters	Chylomicrons	VLDL	IDL	LDL	Lp(a)	HDL
Size (nm)	~75-1000	30-80	25-35	18- 25	~30	5-12
Density (g/ml)	<0.95	0.950- 1.006	1.006- 1.019	1.019- 1.063	1.055- 1.085	1.063- 1.210
TG Content (%)	~85-90	~50-65	~20-30	~5-10	~5	~5-10
Cholesterol Ester Content (%)	~3-5	~10-15	~30-35	~35-48	~35-40	~12-30
Major Apo-proteins	Apo B-48	Apo B-100	Apo B-100	Apo B-100	Apo (a); Apo B-100	Apo A I-II



V. Raja et al. Atherosclerosis 383 (2023) 117312

Journal of Clinical Lipidology (2025) 000, 1–9

Journal of Clinical Lipidology

Original Research

Non-high-density lipoprotein cholesterol outperforms low-density lipoprotein cholesterol in predicting cardiovascular events among high-risk Asians

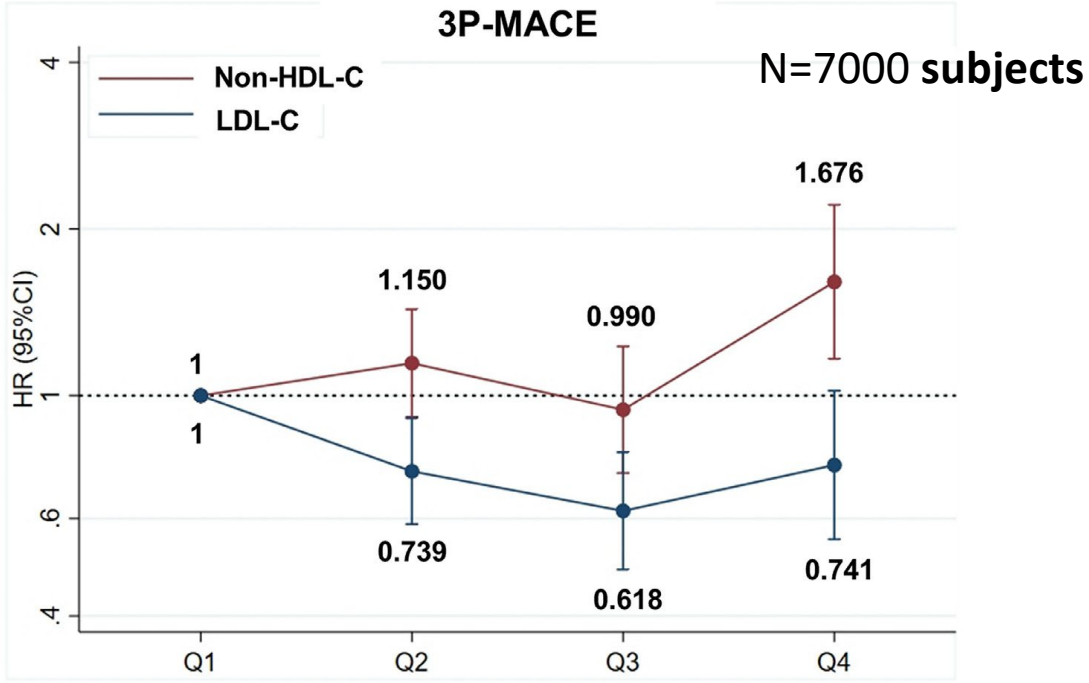


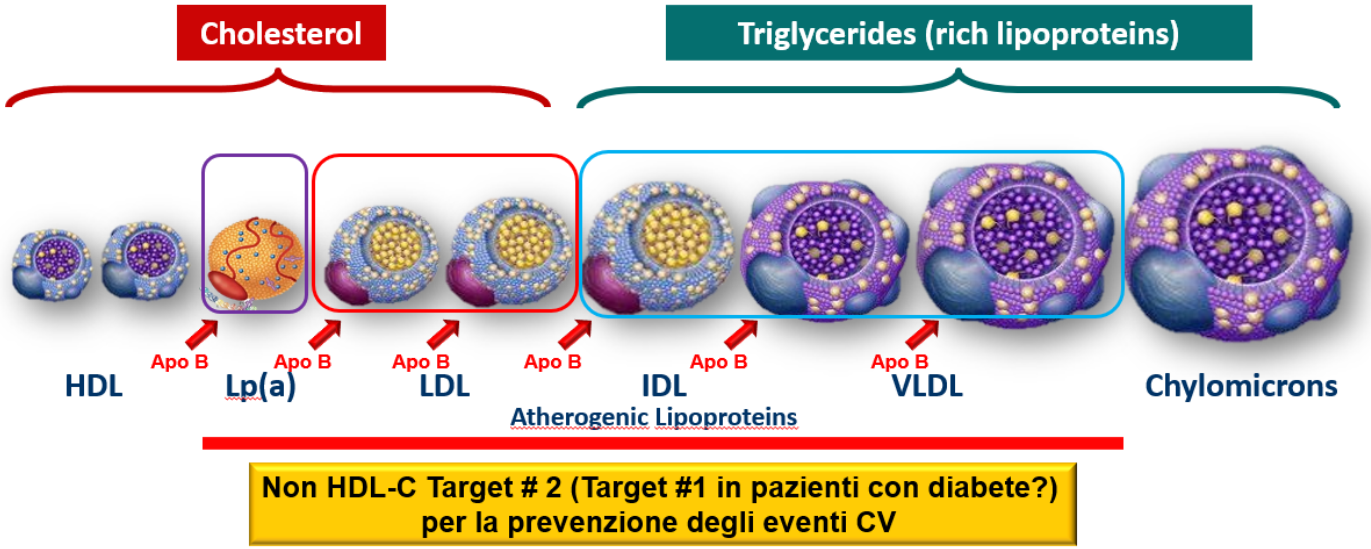
Figure 2. The risk of 3P-MACE by the quartiles of non-HDL-C and LDL-C after adjusting for age, sex, diabetes status, hypertension, history of atrial fibrillation, body mass index, eGFR, the use of ASA or P2Y12i, beta-blocker, ACEIs/ARBs, fibrate, history of multiple risk factors or ASCVD, smoking status and either LDL cholesterol or non-HDL cholesterol depending on independent variable.

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes

ESC European Society of Cardiology

Developed by the task force on the management of cardiovascular disease in patients with diabetes of the European Society of Cardiology (ESC)

Current and New Lipid Targets in Diabetes



Non HDL-C Target # 2 (Target #1 in pazienti con diabete?) per la prevenzione degli eventi CV

LDL, TGRL, Lp(a) each independently associated with CVD

Recommendation Table 11 — Recommendations for the management of dyslipidaemia in patients with diabetes

Recommendations	Class[a]	Level[b]
Lipid targets		
In patients with T2DM at moderate CV risk, an LDL-C target of <2.6 mmol/L (<100 mg/dL) is recommended.[248,249]	I	A
In patients with T2DM at high CV risk, an LDL-C target of <1.8 mmol/L (<70 mg/dL) and LDL-C reduction of at least 50% is recommended.[248,249]	I	A
In patients with T2DM at very high CV risk, an LDL-C target of <1.4 mmol/L (<55 mg/dL) and LDL-C reduction of at least 50% is recommended.[248,249]	I	B
In patients with T2DM, a secondary goal of a non-HDL-C target of <2.2 mmol/L (<85 mg/dL) in very high CV risk patients and <2.6 mmol/L (<100 mg/dL) in high CV risk patients is recommended.[283–285]	I	B

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SUGGESTIONI

- RISCHIO CARDIOVASCOLARE E OBIETTIVI TERAPEUTICI SONO ELEMENTI CLINICI POTENZIALMENTE MUTABILI CHE DIPENDONO DALLA QUALITA' DI EVIDENZE E DI FATTORI DI INTERVENTO DISPONIBILI

- NEL T2D SI COMINCIA A CONSIDERARE CHE LE LDL NON STIMINO ADEGUATAMENTE IL RISCHIO CVD COME NEI NON DIABETICI, AD ESEMPIO LE sdLDL SEMBRANO POTENZIALMENTE PIU' SENSIBILI

- SCORE2, SCORE2D E SCORE-OP SONO BASATI SUL COLESTEROLO NON HDL E QUINDI EVIDENZE CLINICHE PIU' FORTI POTRANNO ALLINEARE IL CALCOLO DEL LIVELLO DI RISCHIO AI TARGET CHE SONO UTILIZZATI PER RAGGIUNGERE L'OBIETTIVO