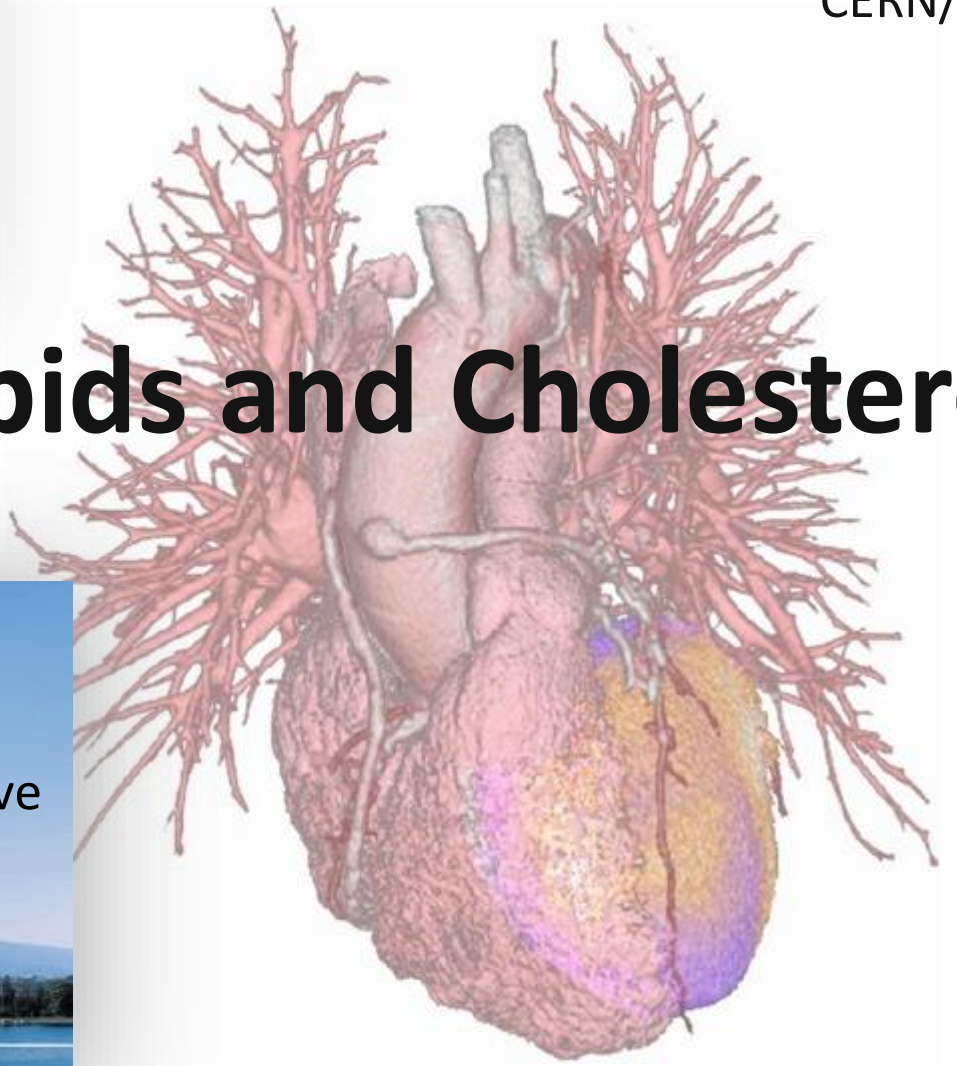
Campagne sur le risque cardiovasculaire
CERN/Genève, le 26 septembre 2023

Lipids and Cholesterol



Prof. François Mach, MD, FESC
Service de cardiologie
Hôpitaux Universitaires de Genève
francois.mach@hcuge.ch

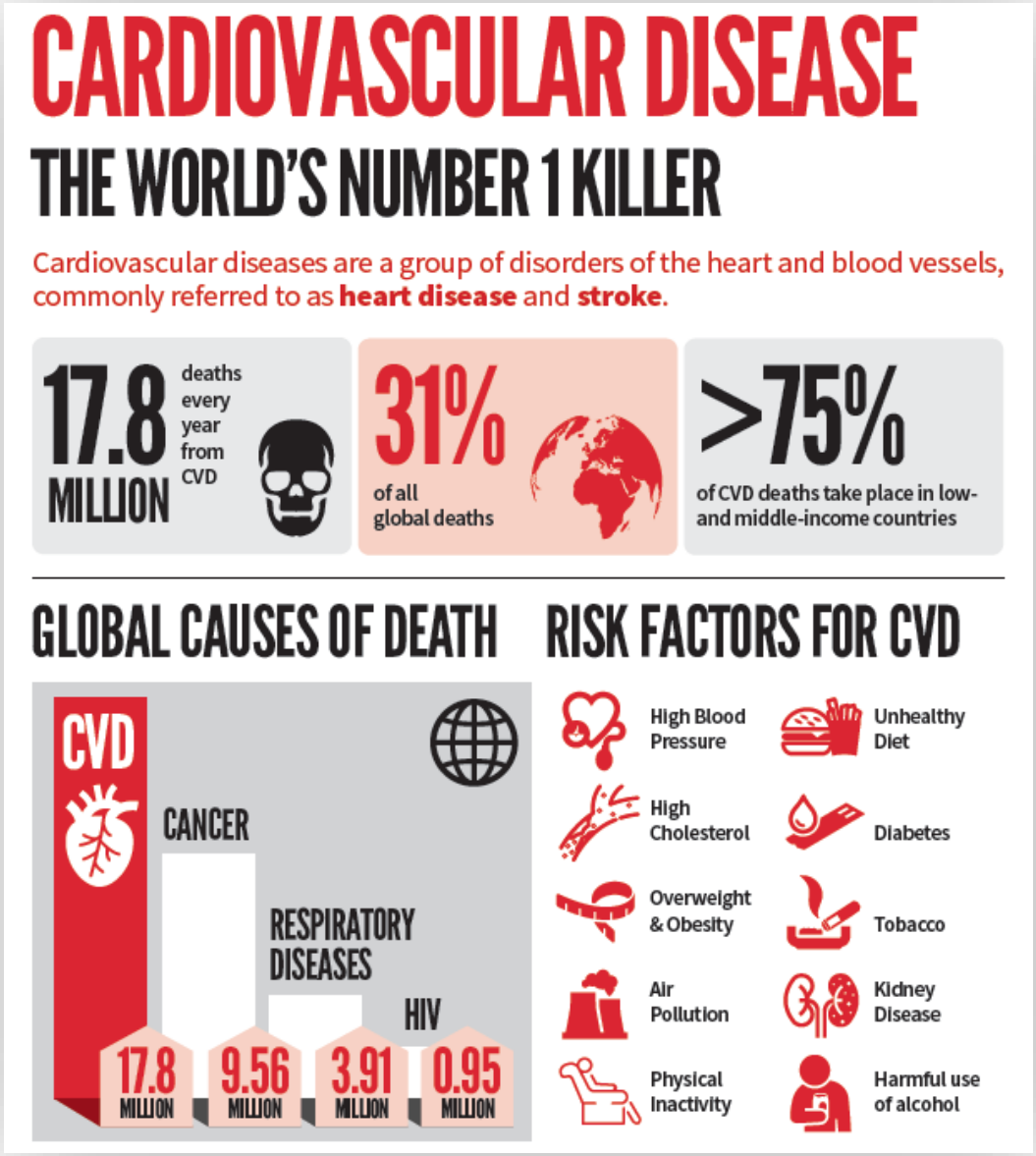
Service de Cardiologie

HUG Hôpitaux Universitaires Genève

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE


SEPTEMBER 29
WORLD
HEART DAY

Cardiovascular Disease



No financial conflicts of interest

All my honoraria for conferences and advisory board are intended for the GEcor Foundation, which supports cardiovascular research within Geneva University Hospital.
Our cardiology department has received financial support for clinical research from pharmaceutical companies, with contracts always signed by our legal authorities within Geneva University Hospital

Cardiovascular Diseases

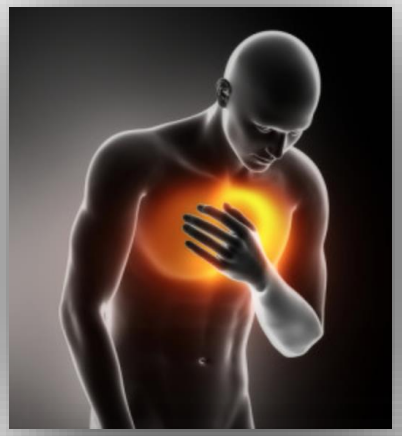
Coronary Artery Disease

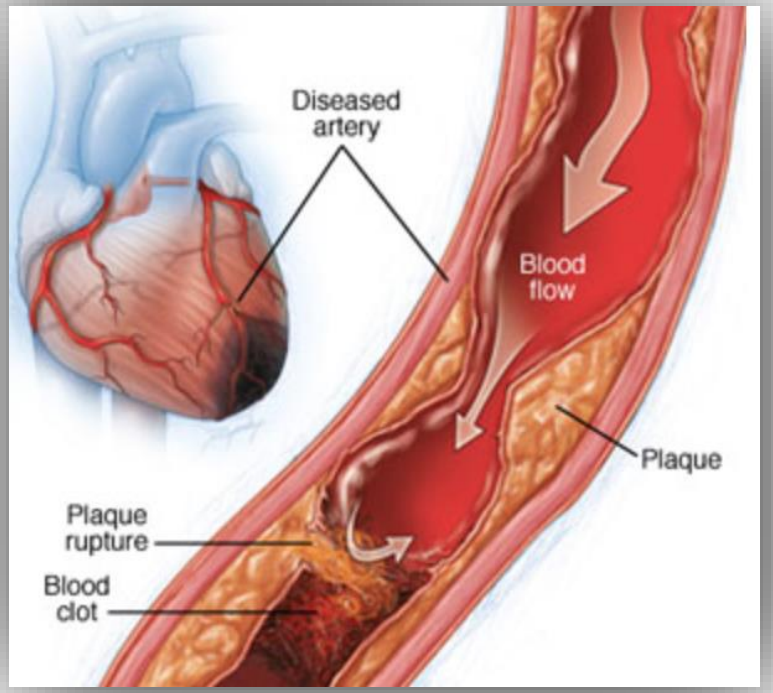
- Leading cause of mortality
- Happened globally
- Increase new cases
- Leading cause of loss of productivity

TRUE PANDEMIC

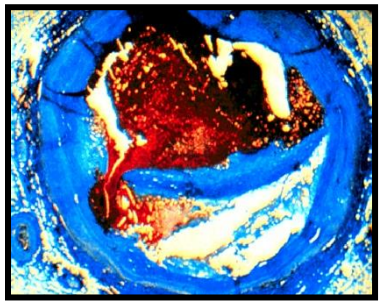
WHO (2009):

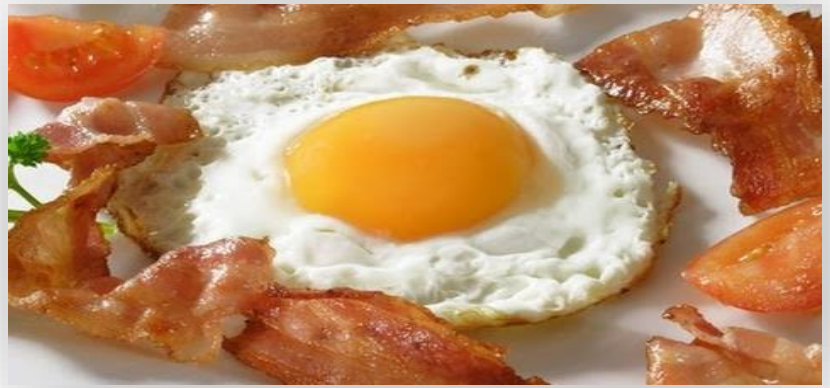
"CHD is now the leading cause of death worldwide; it is on the rise and has become a true pandemic that respects no borders"



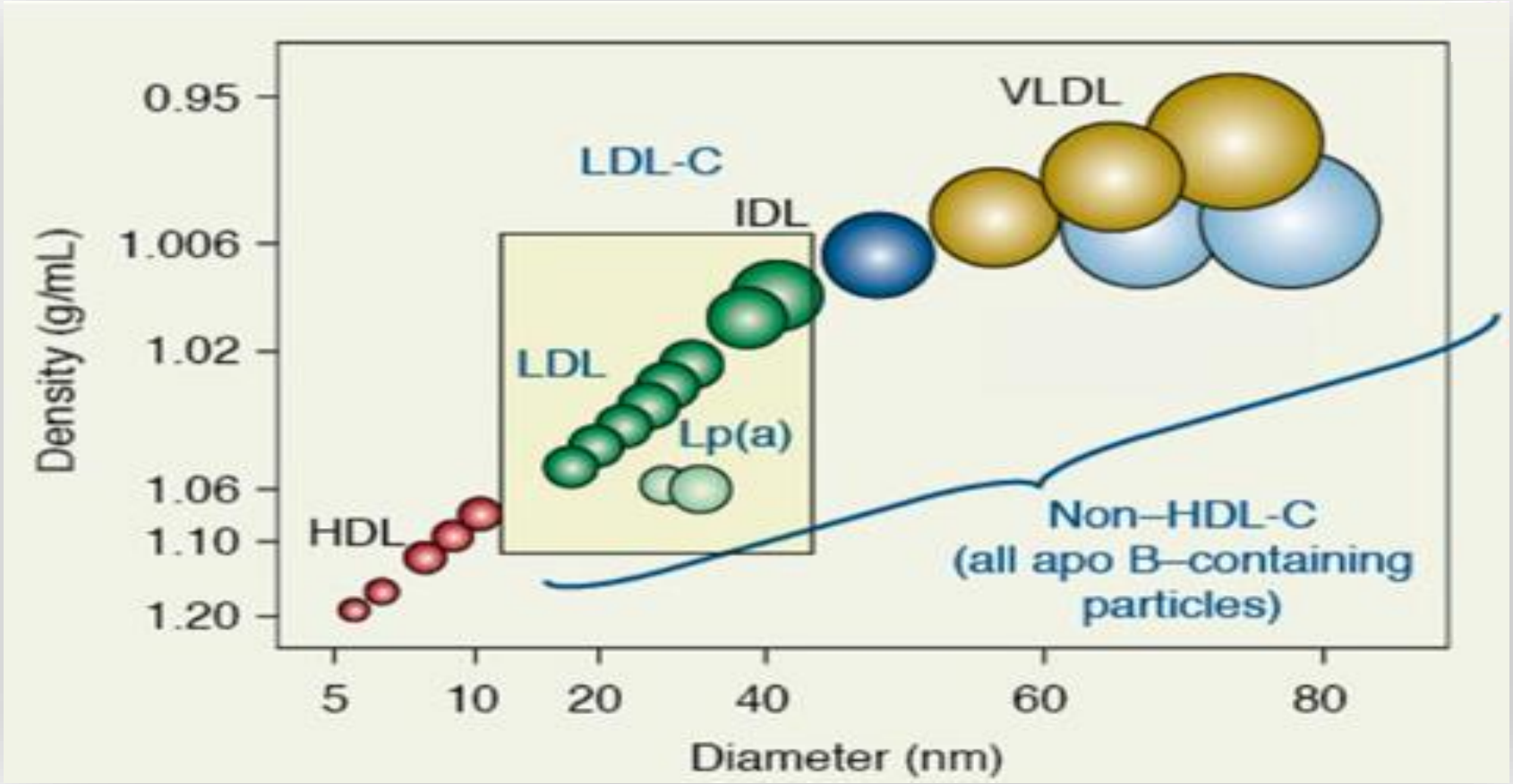


Major cardiovascular risk factors for atherosclerosis

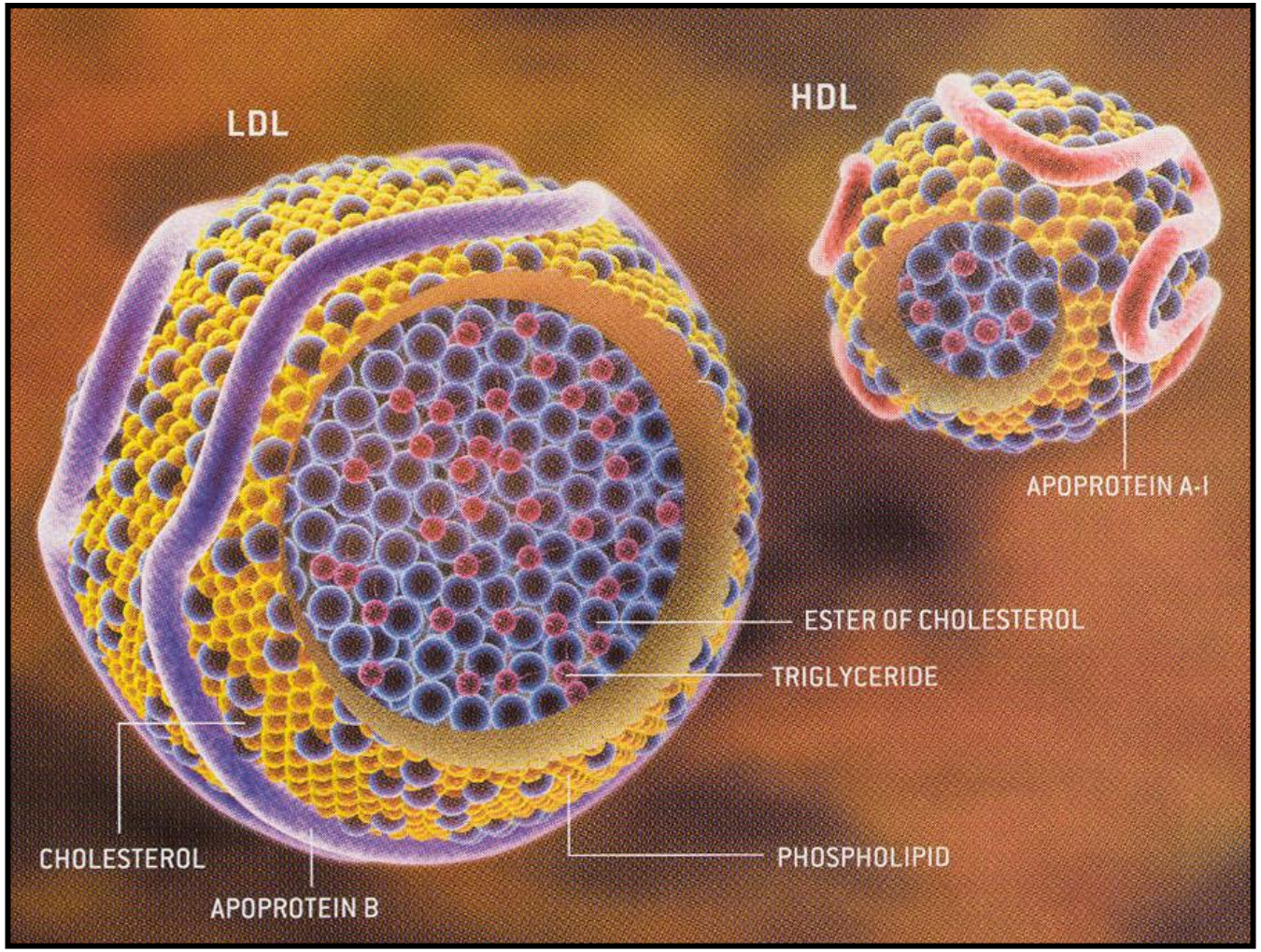




Cholesterol



Structure of cholesterol particules



MAGAZINE D'AOÛT 2016
DE LA CAISSE MALADIE CSS

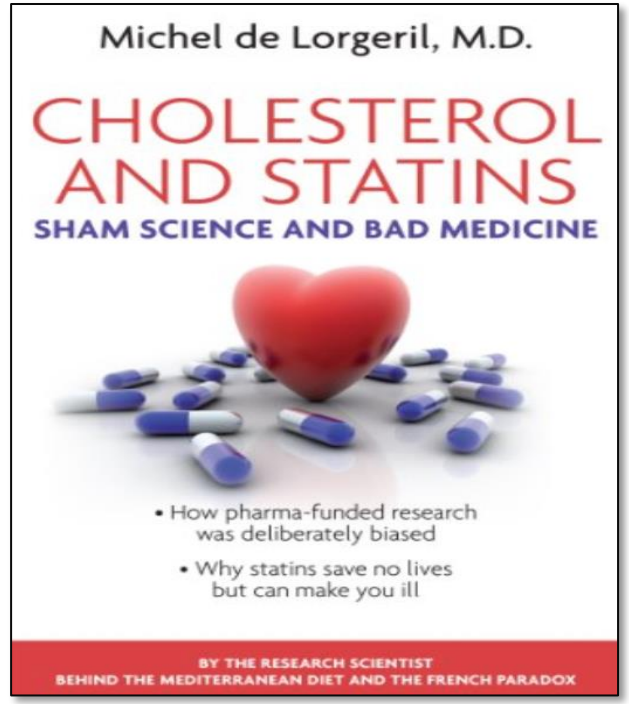
CSS MAGAZINE DOSSIER

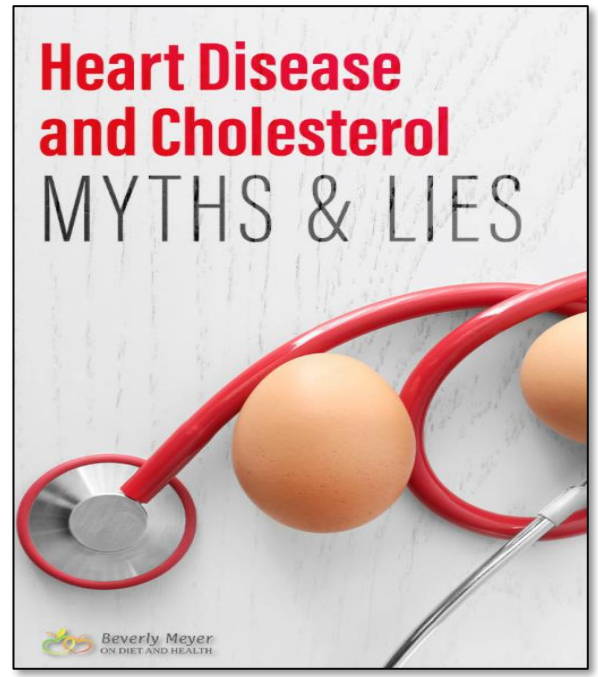
Et si le cholestérol n'était pas dangereux?

Le cholestérol a longtemps été considéré comme nocif. Aujourd'hui, ces craintes se dissipent, car cette substance lipoïdique assume des fonctions essentielles dans l'organisme.

Texte: Vera Sohmer

On parle souvent de «bon» cholestérol pour le premier et de «mauvais» pour le second. Le docteur Imoberdorf ne partage pas cette classification. Il est en effet d'avis que les deux formes de cholestérol accomplissent une mission importante. D'après lui, les personnes en bonne santé n'ont pas à re-





Clear relationship between LDL-C and risk of CV events

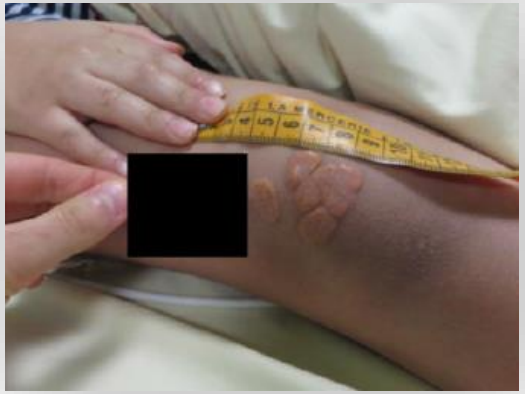
ESC European Society of Cardiology
European Heart Journal - Case Reports
doi:10.1093/ehjcr/ytz233

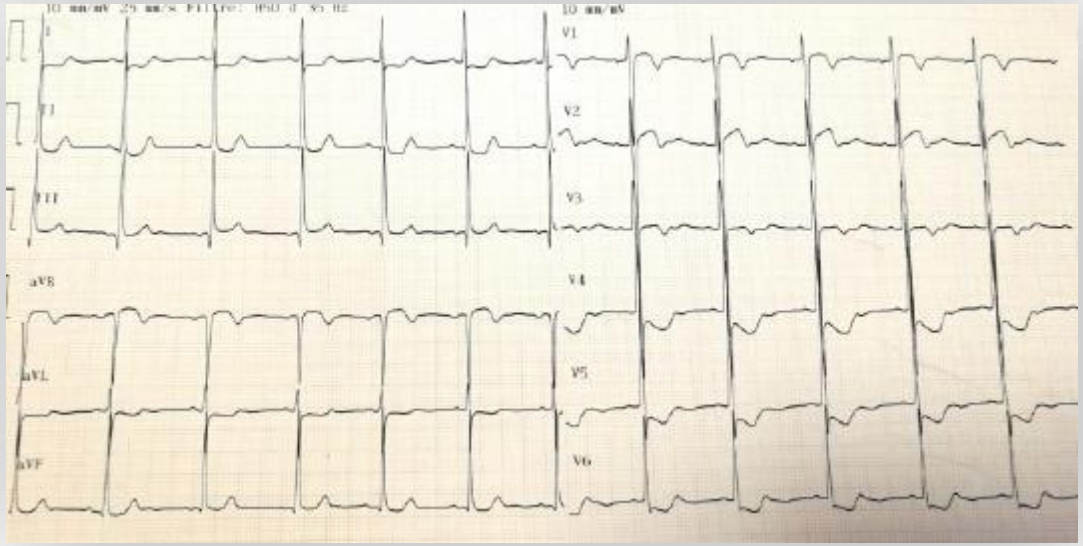
GRAND ROUND
Coronary heart disease

A case report of an acute coronary syndrome in a 10-year-old boy with homozygous familial hypercholesterolaemia

Thibault Leclercq [1]*, Sylvie Falcon-Eicher[1], Michel Farnier[1,2], Emmanuel Le Bret [3], Raphaëlle Maudinas[4], Stéphanie Litzler-Renault[5], Christiane Mousson[6], Luc Lorgis[1], and Yves Cottin[1]

Three years prior to presentation	Appearance of xanthomas (*Figure 1*)
	LDL cholesterol (LDL-C): 802 mg/dL (20.73 mmol/L)
	Lipoprotein A: 124 mg/dL (4.43 µmol/L)
	Genetic diagnosis
One year prior presentation	Patient put on rosuvastatin 10 mg and ezetimibe 10 mg, LDL-C 650 mg/dL (16.8 mmol/L)

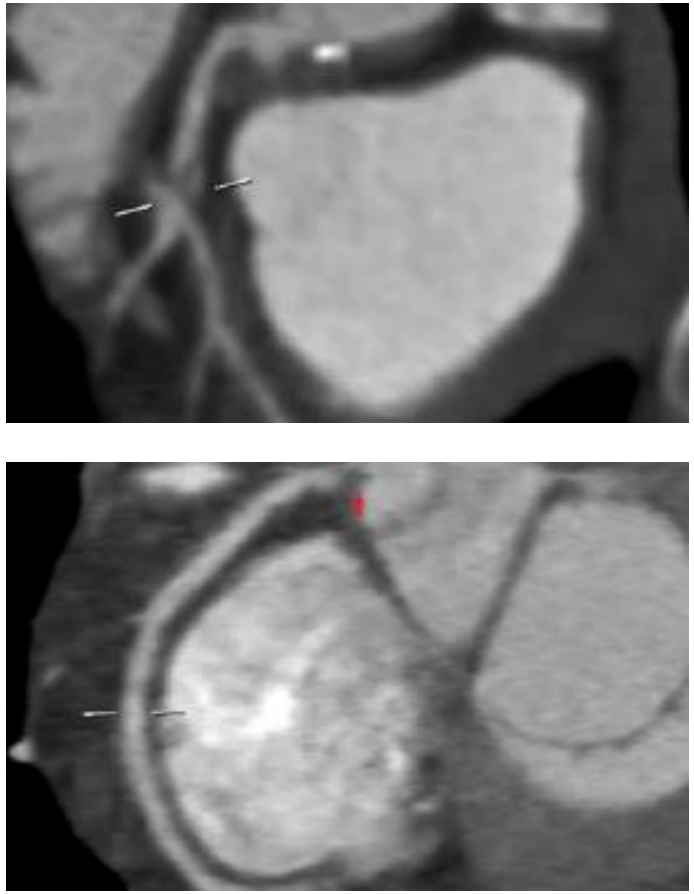




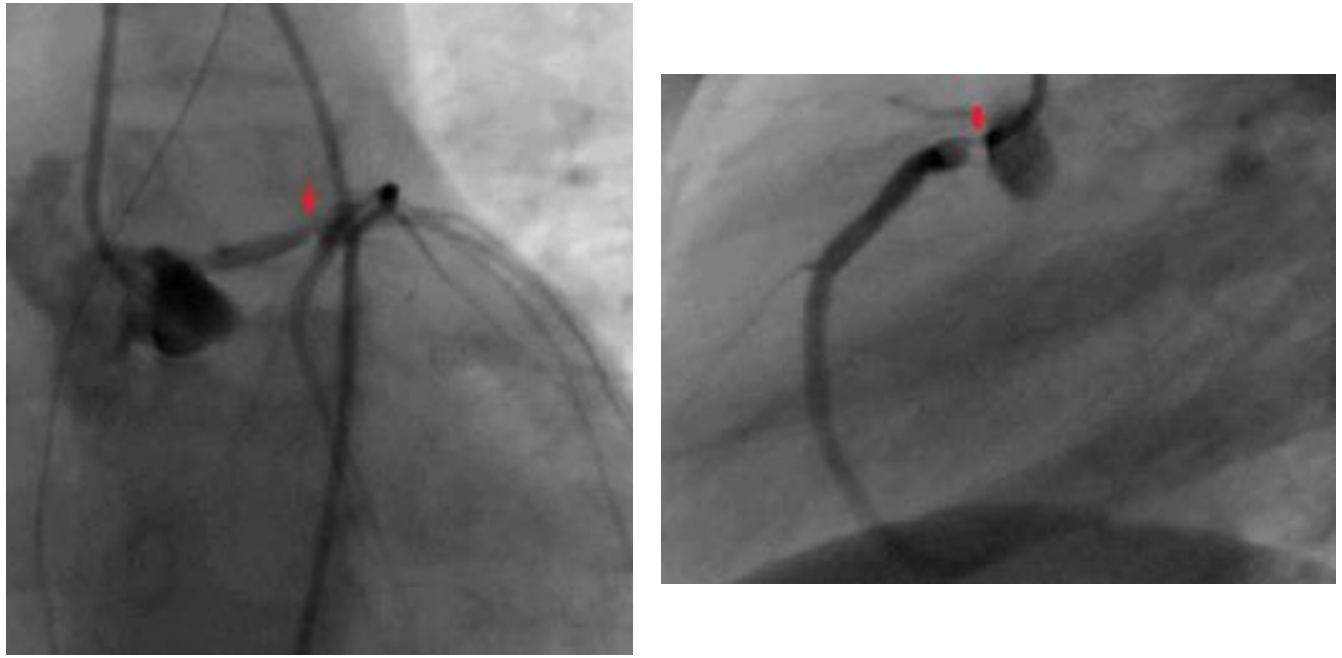
Eur Heart J Case Rep 2020;4:1

Clear relationship between LDL-C and risk of CV events

Cardiac CT-Scan



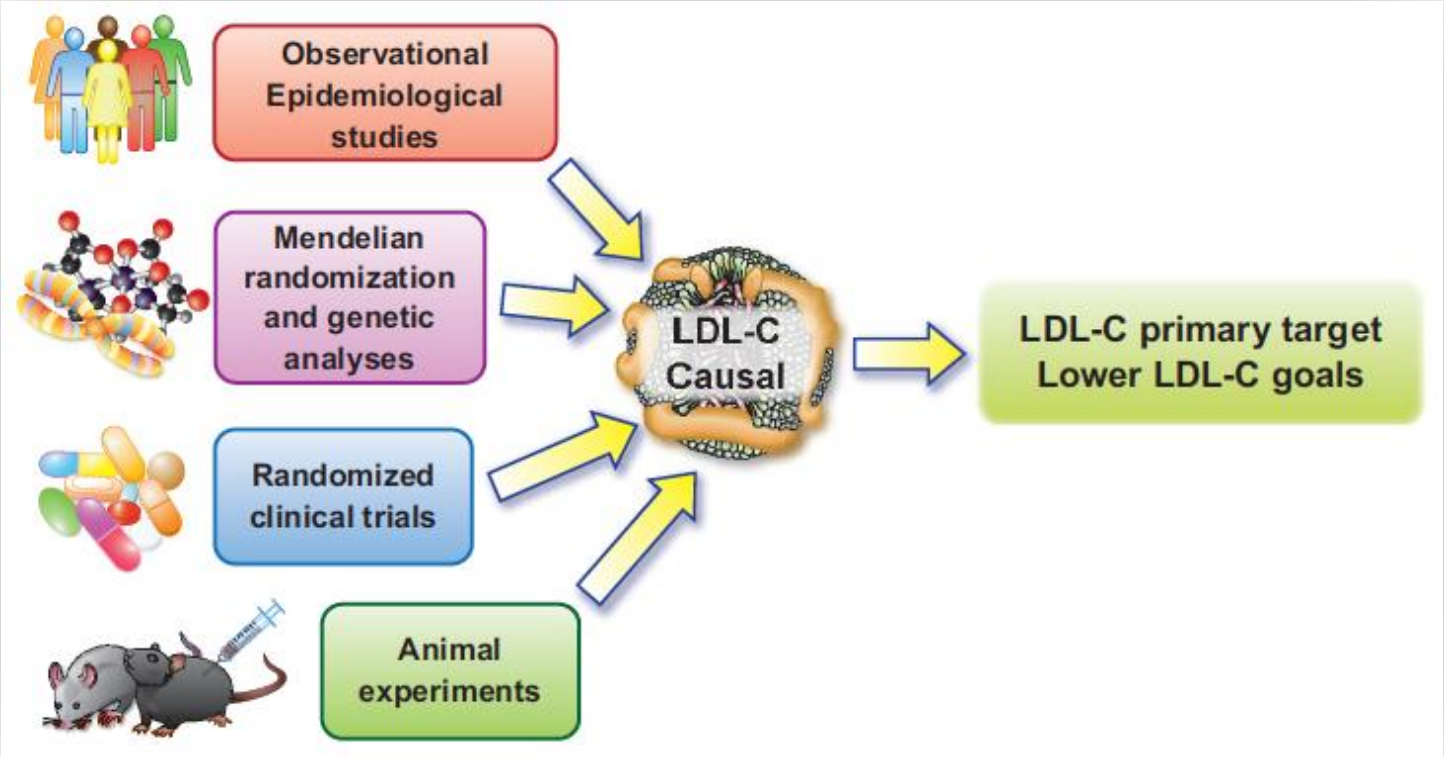
Coronary angiography

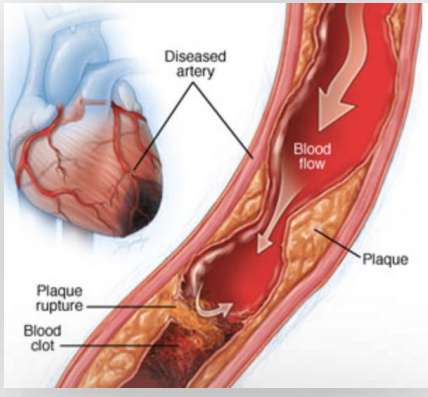


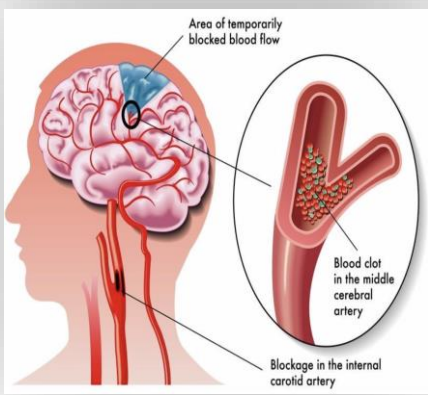
Eur Heart J Case Rep 2020;4:1

LDL-Cholesterol

LDL-C is the main driver for atherosclerosis: 4 compelling lines of evidence







Eur Heart J 2022;43:3198

LDL-Cholesterol and Atherosclerosis

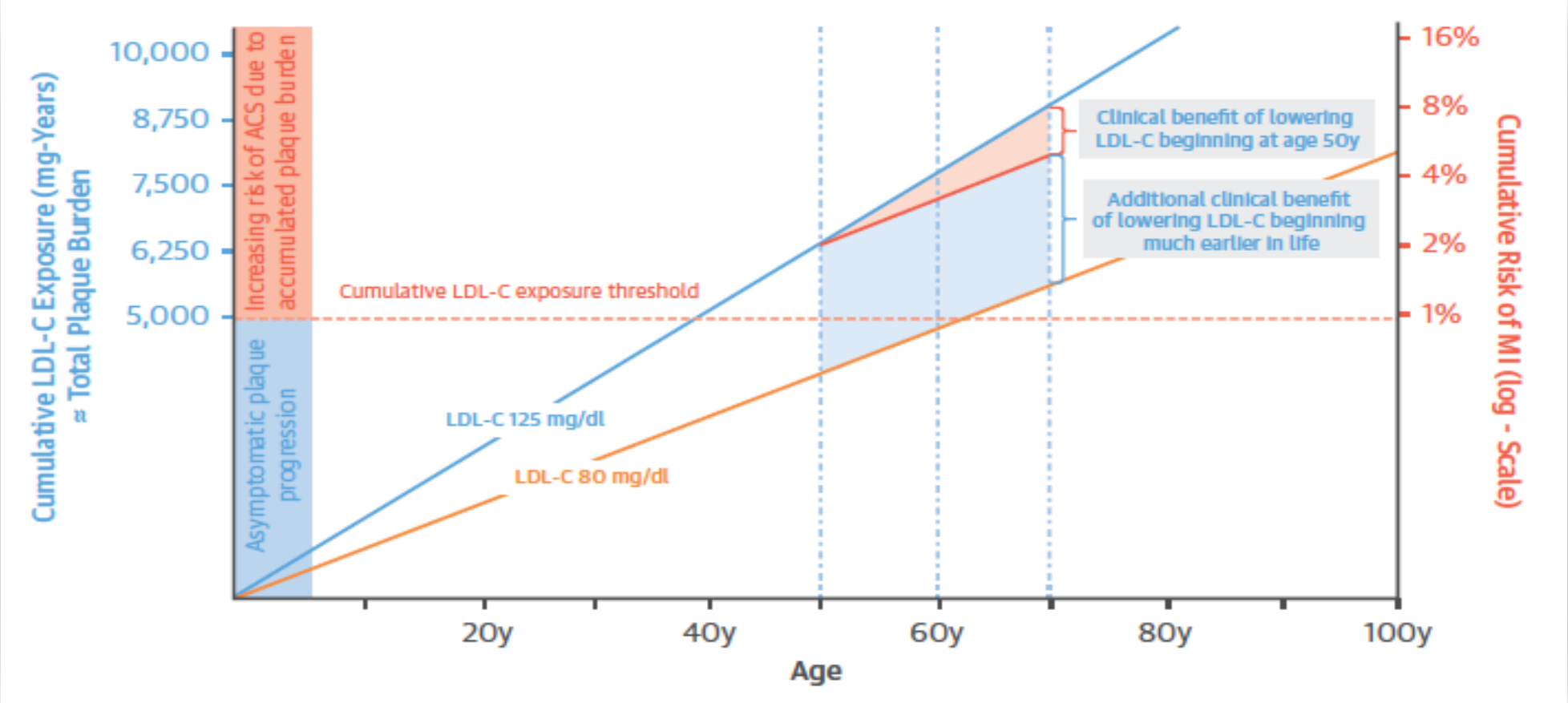
Table I Criteria for causality: low-density lipoprotein (LDL) and atherosclerotic cardiovascular disease (ASCVD)

Criterion (modified from reference[5])	Evidence grade	Summary of the evidence (references)
1. Plausibility	1	LDL and other apolipoprotein (apo) B-containing lipoproteins (very low-density lipopro… their remnants, intermediate-density lipoprotein and lipoprotein(a)) are directly implicated in… and progression of ASCVD; experimentally induced elevations in plasma LDL and oth… proteins lead to atherosclerosis in all mammalian species studied.[2,5–12]
2. Strength	1	Monogenic and polygenic-mediated lifelong elevations in L… time risk.[13–20,27–31,40,43]
3. Biological gradient	1	Monogenic lipid disorders, prospective cohort … ation studies, and randomized intervention trials uniformly demonstrate… association between the absolute magnitude of exposure to LDL an… [12–47]
4. Temporal sequence	1	Monogenic lipid disord… ation studies demonstrate that exposure to elevated LDL precedes th…
5. Specificity	1	Mendel… randomized intervention trials both provide unconfounded randomized …ciated with ASCVD independent of other risk factors[28,31–33,40,43]
6. Consistency	1	…volving more than 2 million participants with over 20 million person-years of follow-up and …an 150 000 cardiovascular events consistently demonstrate a dose-dependent, log-linear association …etween the absolute magnitude of exposure to LDL and risk of ASCVD[13–22,27–36,38–40,42–47]
7. Coherence		Monogenic lipid disorders, prospective cohort studies, Mendelian randomization studies, and randomized intervention trials all show a dose-dependent, log-linear association between the absolute magnitude of exposure to LDL and risk of ASCVD[15–18,21,22,28,30–32,35,36,43,44,47]
8. Reduction in risk with intervention	1	More than 30 randomized trials involving over 200 000 participants and 30 000 ASCVD events evaluating therapies specifically designed to lower LDL (including statins, ezetimibe, and PCSK9 inhibitors) consistently demonstrate that reducing LDL cholesterol (LDL-C) reduces the risk of ASCVD events proportional to the absolute reduction in LDL-C[32–34,38,39,42,45–47]

LDL-C is causal of atherosclerosis

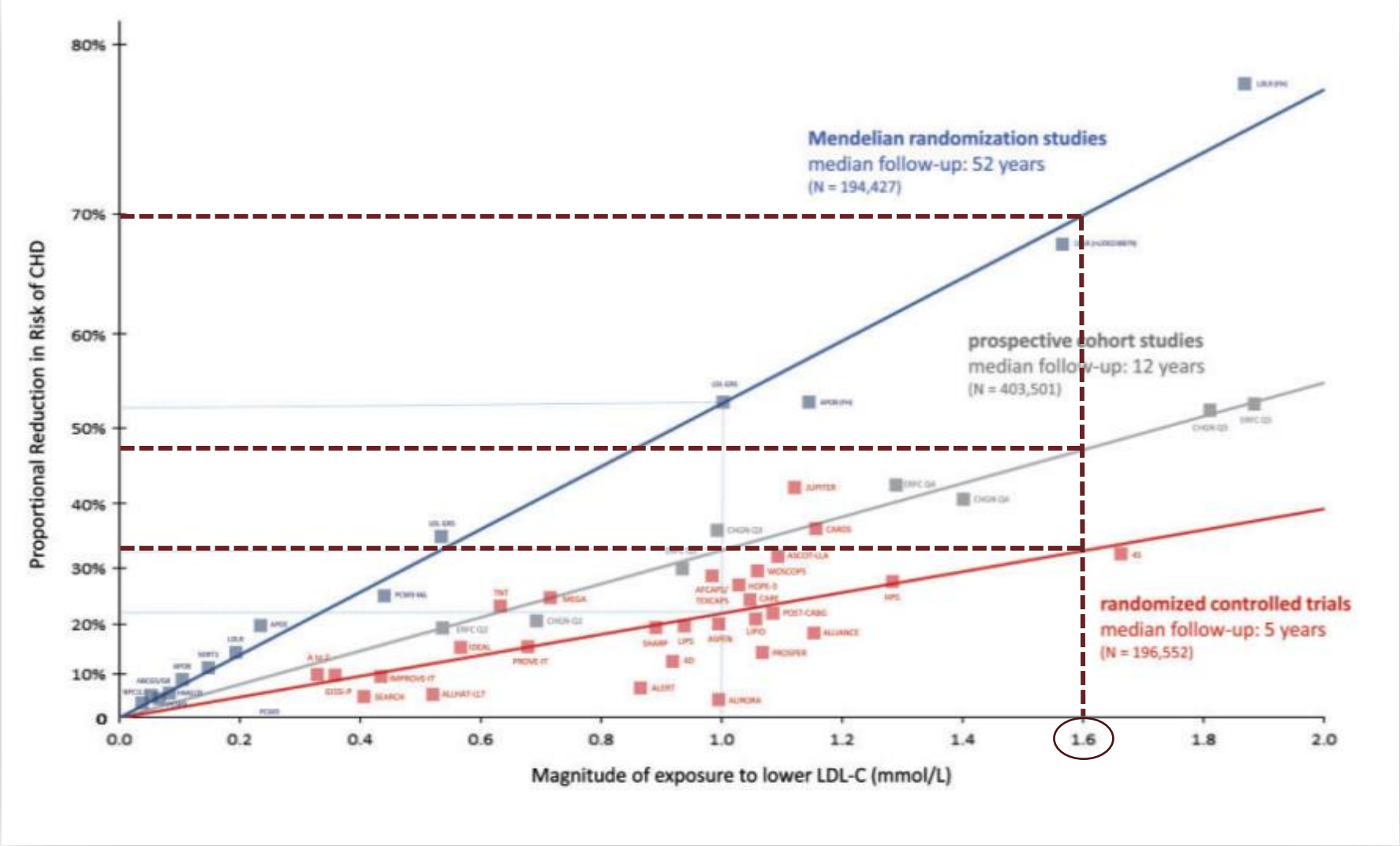
Eur Heart J 2017;38:2459

Time-Exposure to LDL-C



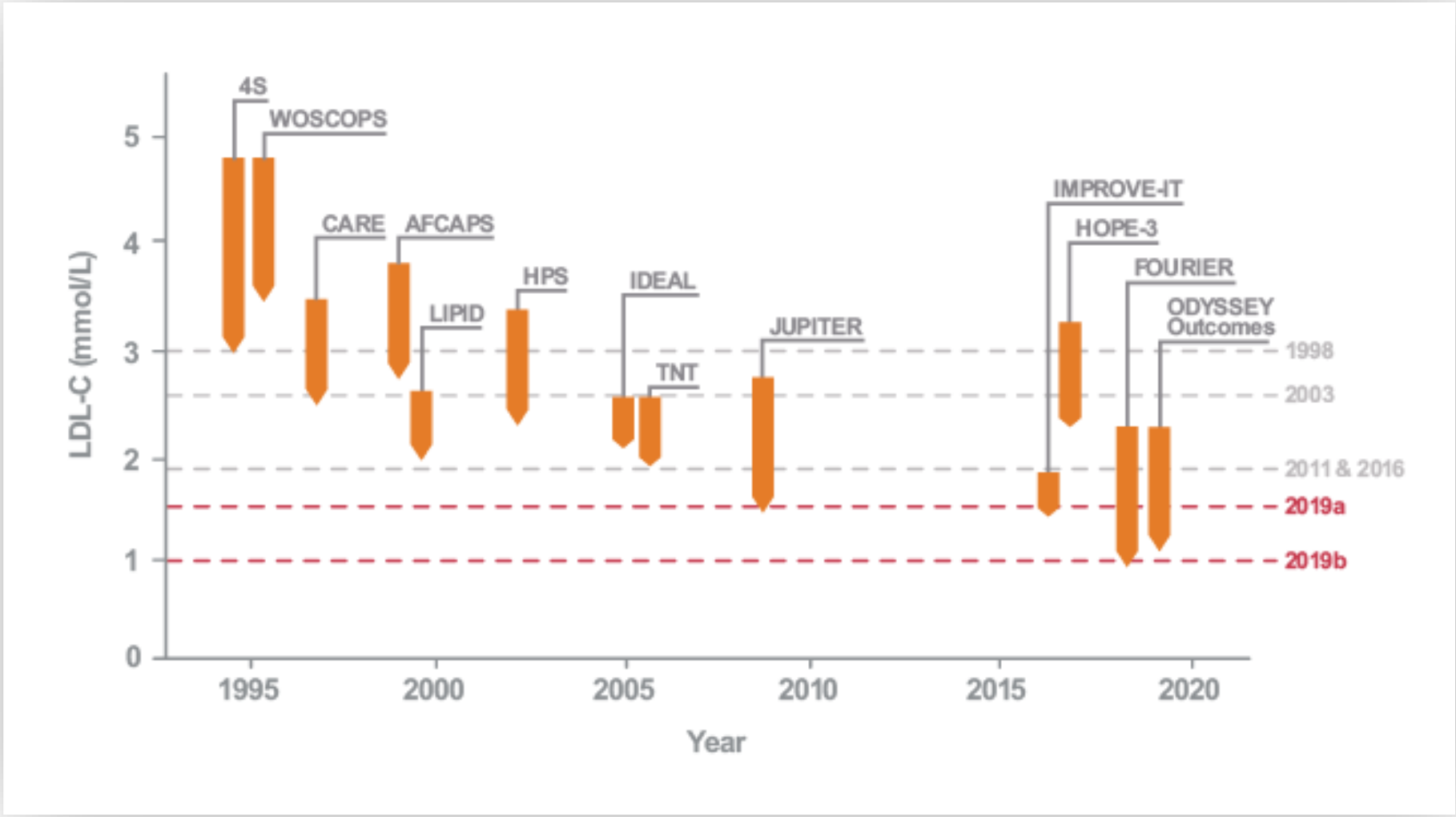
JACC 2018;72:2890

Time-Exposure to low LDL-C



Eur Heart J 2017;38:2459

History of LDL-C lowering trials



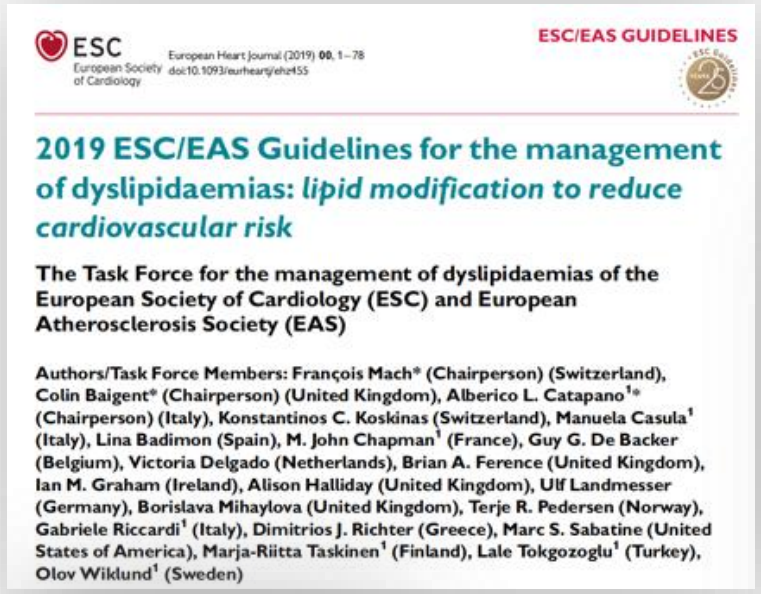
Heart 2021;0:1-7

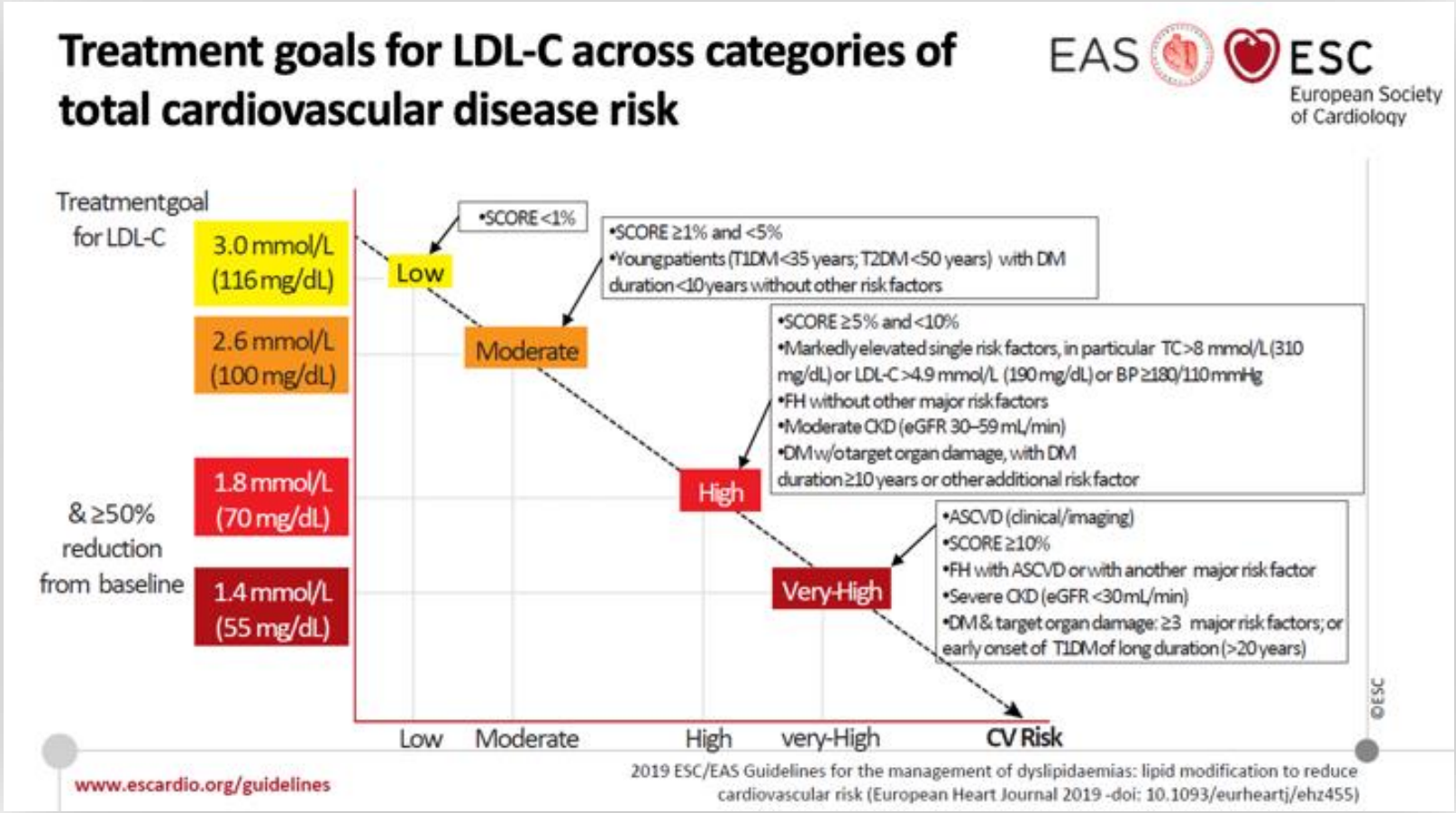
Intensity of pharmacological LDL-C lowering

Intensity of lipid lowering treatment

Treatment	Average LDL-C reduction
Moderate intensity statin	≈ 30%
High intensity statin	≈ 50%
High intensity statin plus ezetimibe	≈ 65%
PCSK9 inhibitor	≈ 60%
PCSK9 inhibitor plus high intensity statin	≈ 75%
PCSK9 inhibitor plus high intensity statin plus ezetimibe	≈ 85%

Eur Heart J 2020;41:111





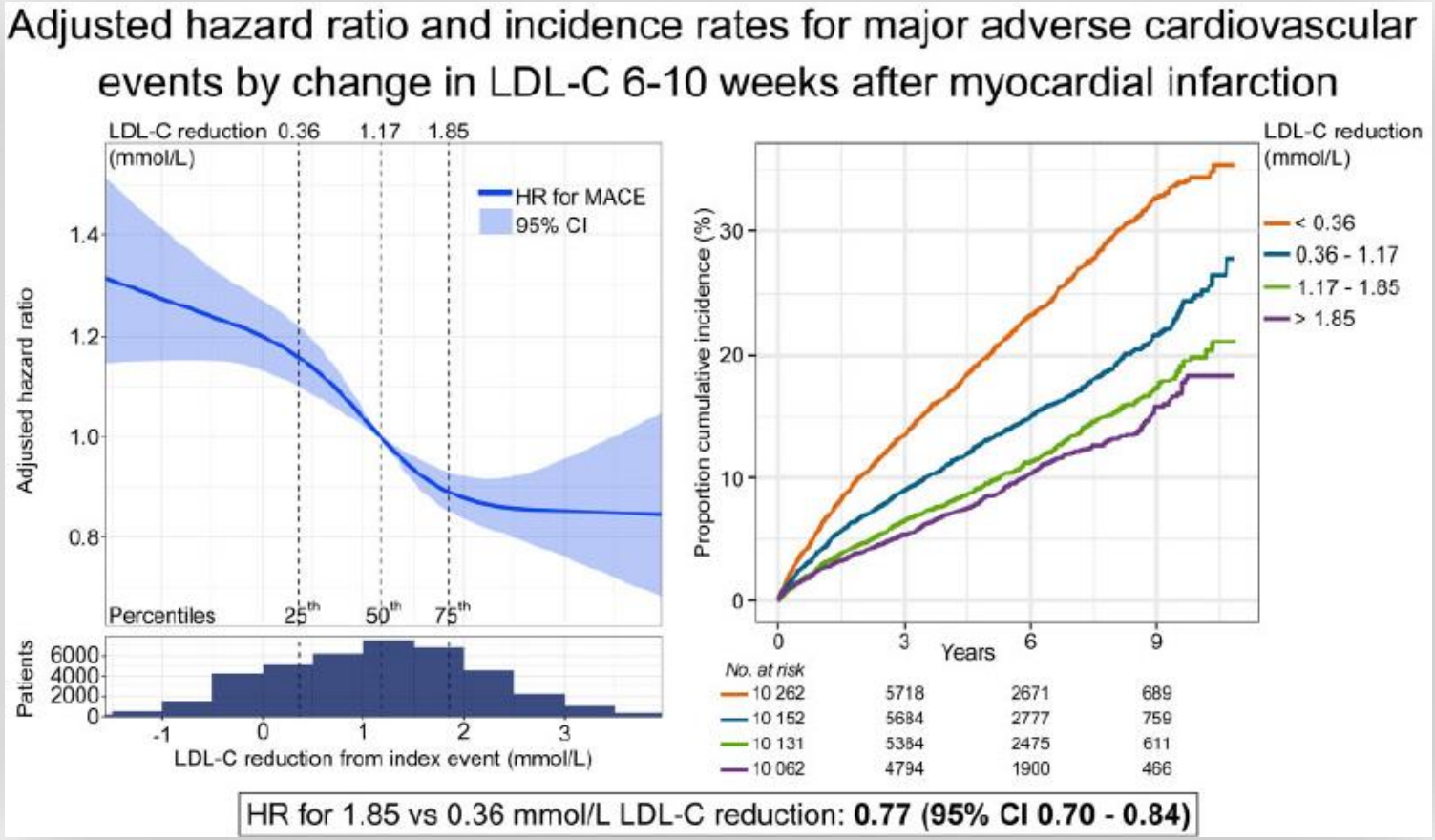
Eur Heart J 2020;41:111

LDL-C : should we go lower after ACS ?

Low-density lipoprotein cholesterol reduction and statin intensity in myocardial infarction patients and major adverse outcomes: a Swedish nationwide cohort study

Jessica Schubert [1]*, Bertil Lindahl [1,2], Håkan Melhus [1], Henrik Renlund [2], Margrét Leosdottir [3,4], Ali Yari [5], Peter Ueda [6], Stefan James [1,2], Stephanie R. Reading [7], Paul J. Dluzniewski[7], Andrew W. Hamer[7], Tomas Jernberg [5], and Emil Hagström[1,2]

40’607 patients after acute myocardial infarction



Eur Heart J 2021;42:243

LDL-C : should we go lower after ACS ?

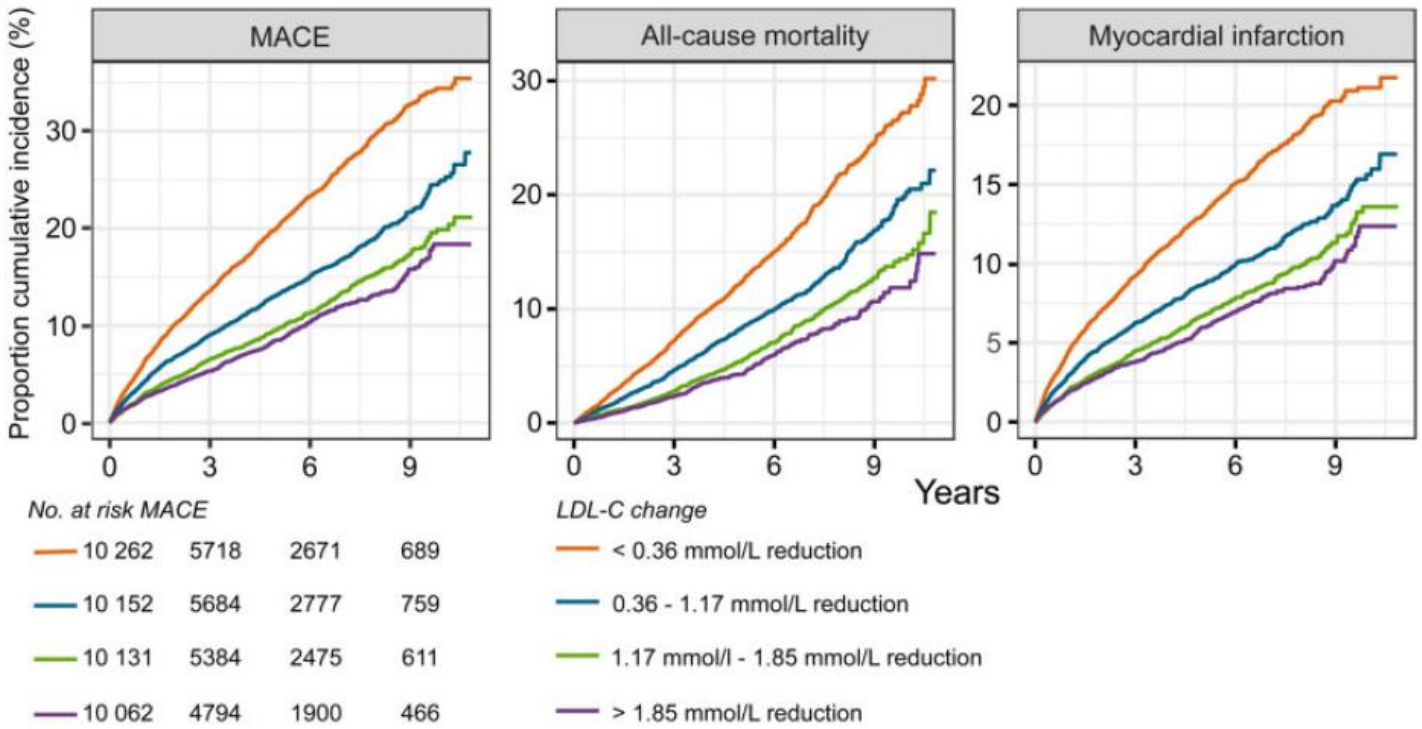
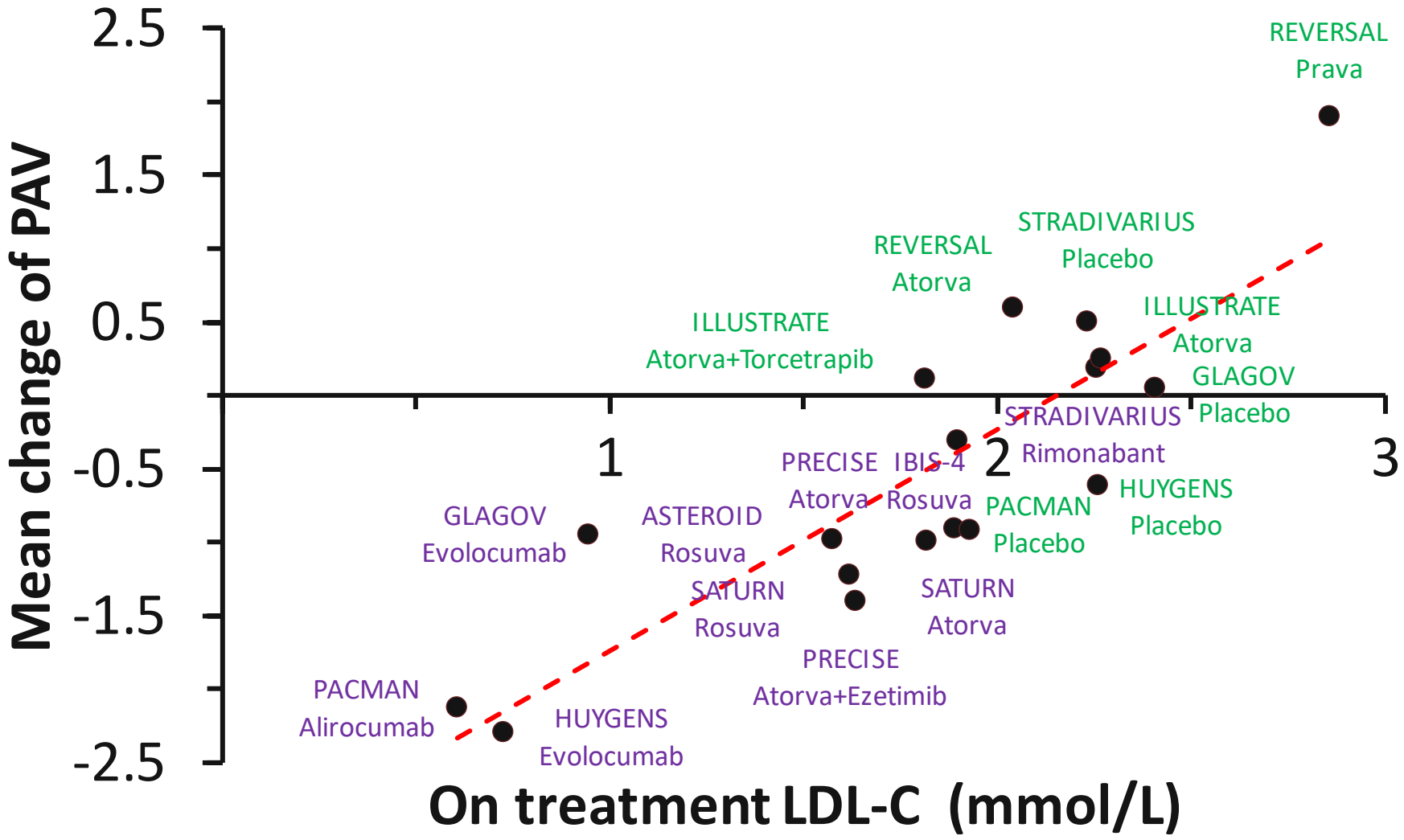


Figure 1 Kaplan–Meier curves of the cumulative incidence rates by quartile low-density lipoprotein cholesterol (LDL-C) change from index event to the cardiac rehabilitation visit. Outcomes are assessed after the cardiac rehabilitation visit. Numbers at risk shown for MACE. MACE, major adverse cardiovascular event is the composite outcome of cardiovascular mortality, myocardial infarction, and ischaemic stroke.

Eur Heart J 2021;42:243

Atherosclerosis plaque regression with lipid lowering therapies

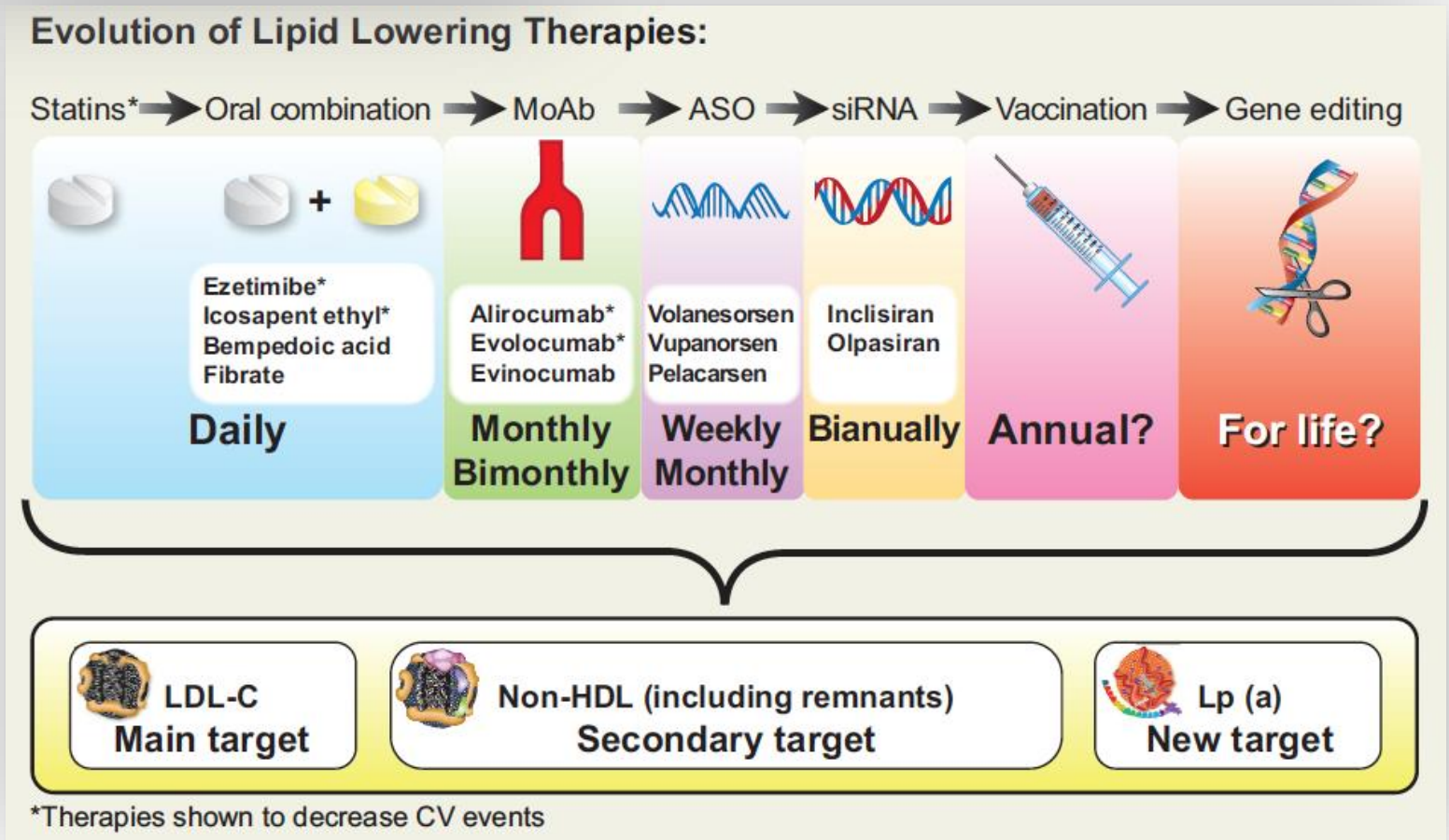


ESC European Society of Cardiology
European Heart Journal (2022) 43, 3198–3208
https://doi.org/10.1093/eurheartj/ehab841

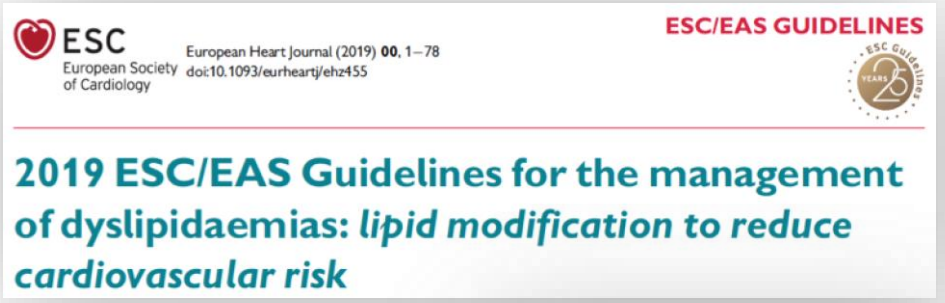
STATE OF THE ART REVIEW
Dyslipidaemias

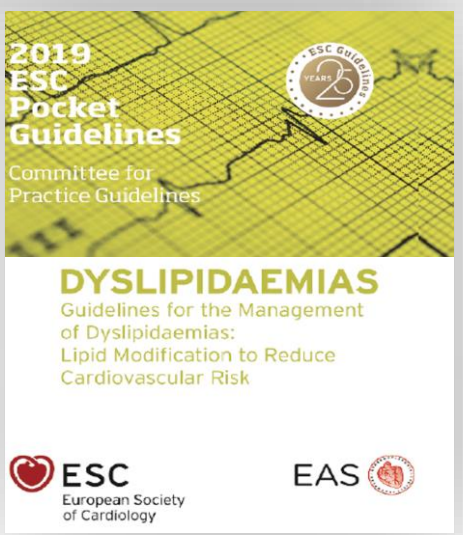
The dawn of a new era of targeted lipid-lowering therapies

Lale Tokgözoğlu[1] and Peter Libby [2]*



The modern concept of lipid-lowering strategies to reduce cardiovascular diseases





I: Start as early as possible
Screening for familial hypercholesterolemia

II: Treat (much more) aggressively
From desirable target to "LDL elimination in the blood"

III: New LDL-C targets for very-high risk
50% reduction from baseline AND < 1.4 mmol/L (55 mg/dL)

IV: Use more lipid-lowering combination therapies
Statins +/- Ezetimibe +/- Bempedoic Acid +/- PCSK9 inhibitors (mAbs)

V: The lower, the better and the lower for life-long
LDL-C lowering with great efficacy, safety and full adherence will reduce the risk of CV events

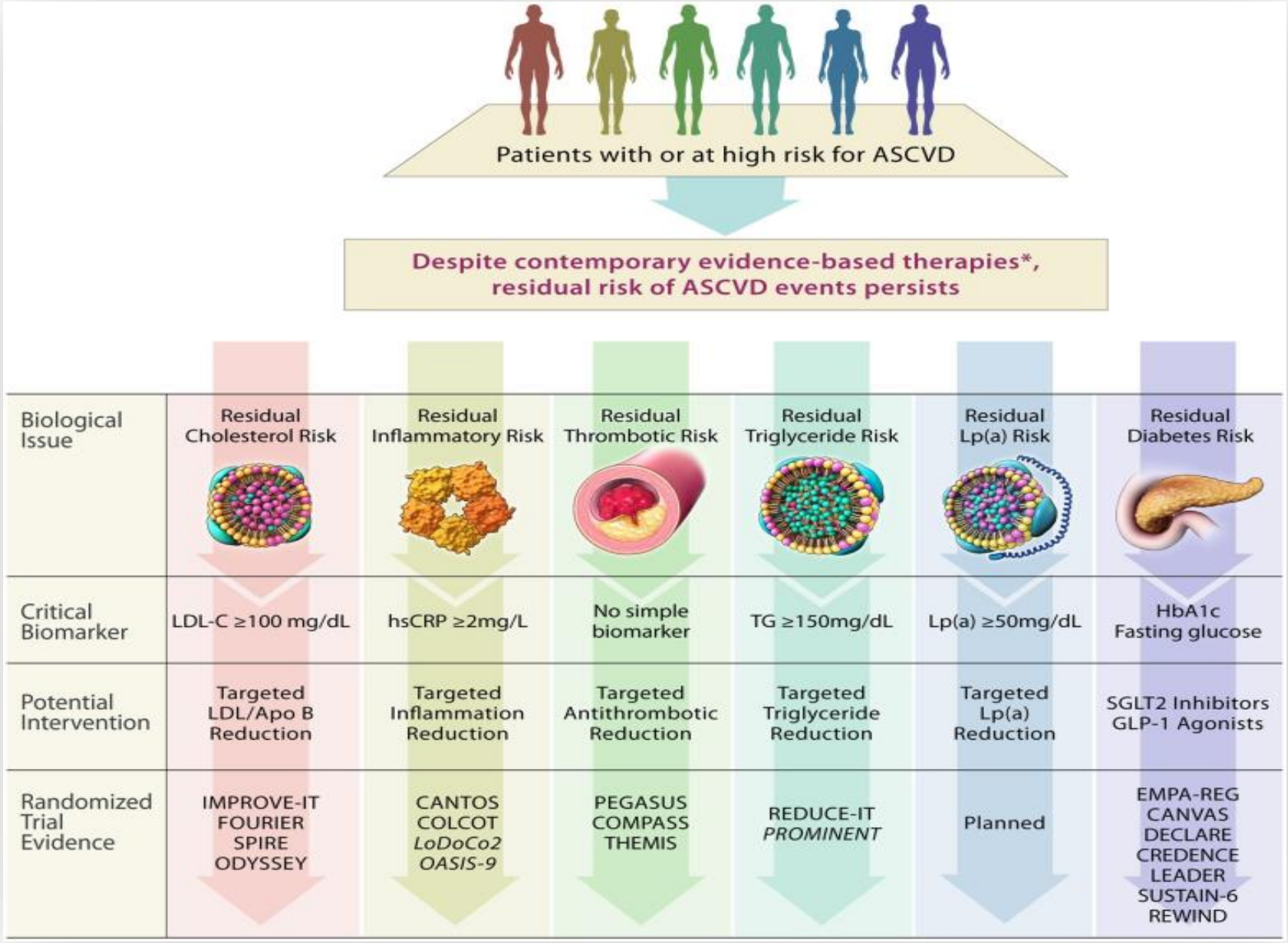
Cardiologie Préventive
Service de cardiologie / HUG

- **Consultation Lipides**: cas difficiles en prévention primaire et secondaire (consultation conjointe avec le Service d'endocrinologie, Pr François Jornayvaz).




- **Infirmière coordinatrice**: Mme Elise Guillermet (cardiopreventive@hcuge.ch, 079-55 35 508).
- **Médecins**: Prof Georg Ehret (responsable - 079-55 33 658), Dre Elena Tessitore, Dr Baris Gencer, Prof François Mach.

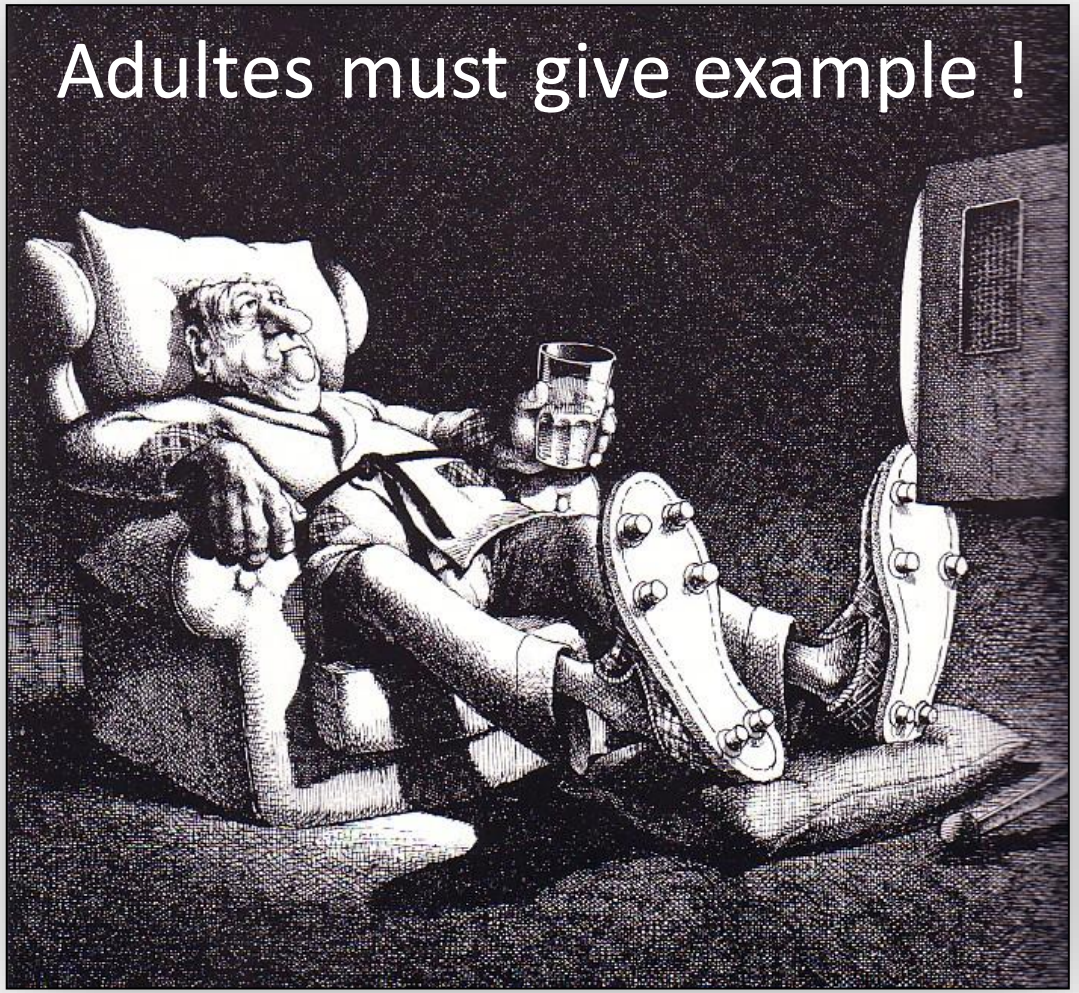
Residual Risk



Biological Issue	Residual Cholesterol Risk	Residual Inflammatory Risk	Residual Thrombotic Risk	Residual Triglyceride Risk	Residual Lp(a) Risk	Residual Diabetes Risk
Critical Biomarker	LDL-C ≥100 mg/dL	hsCRP ≥2mg/L	No simple biomarker	TG ≥150mg/dL	Lp(a) ≥50mg/dL	HbA1c Fasting glucose
Potential Intervention	Targeted LDL/Apo B Reduction	Targeted Inflammation Reduction	Targeted Antithrombotic Reduction	Targeted Triglyceride Reduction	Targeted Lp(a) Reduction	SGLT2 Inhibitors GLP-1 Agonists
Randomized Trial Evidence	IMPROVE-IT FOURIER SPIRE ODYSSEY	CANTOS COLCOT *LoDoCo2* *OASIS-9*	PEGASUS COMPASS THEMIS	REDUCE-IT *PROMINENT*	Planned	EMPA-REG CANVAS DECLARE CREDENCE LEADER SUSTAIN-6 REWIND

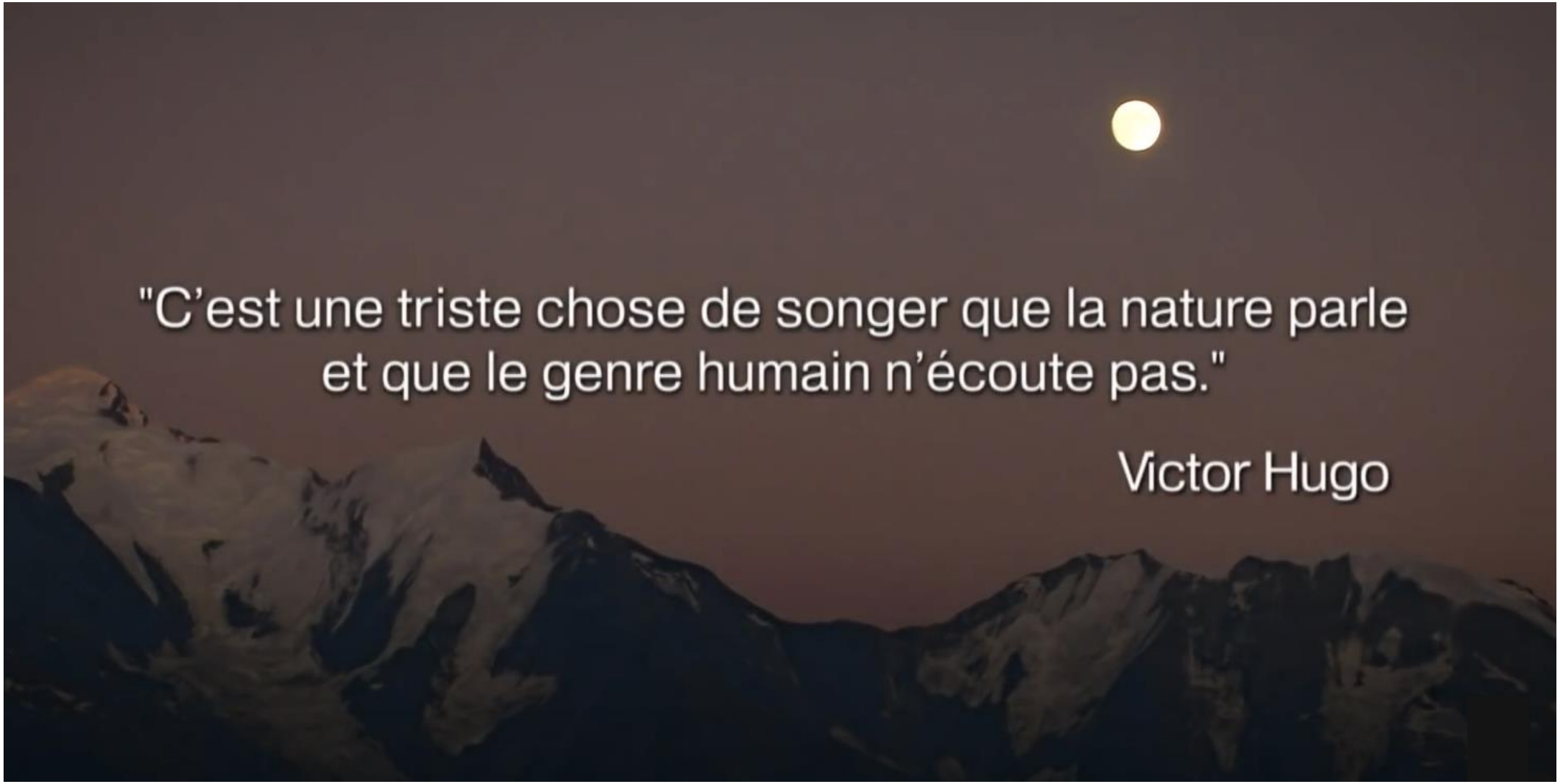
Eur Heart J 2021;42:113


Prevention should starts as
early as possible…

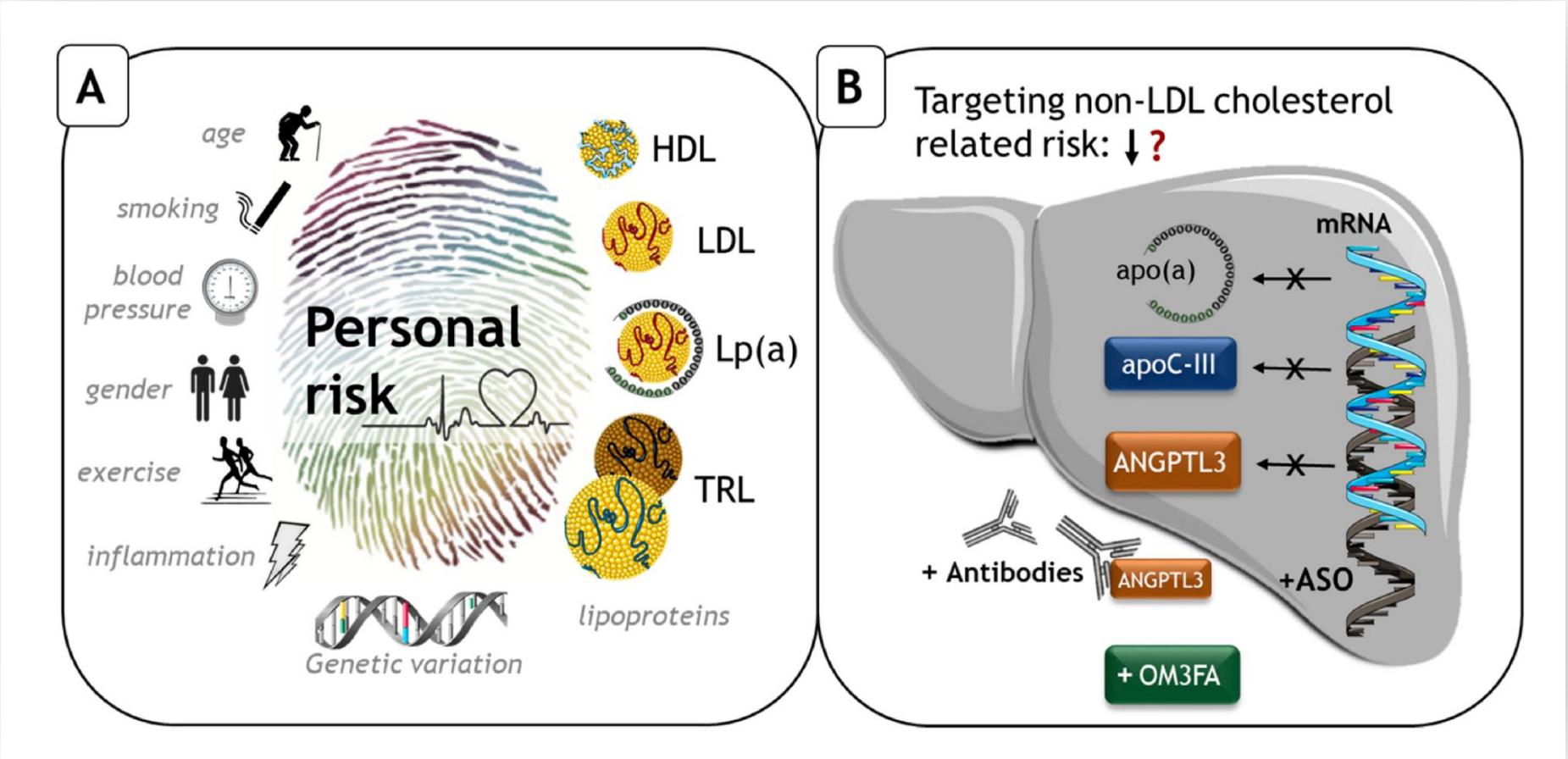

Adultes must give example !

Campagne sur le risque cardiovasculaire
CERN/Genève, le 26 septembre 2023

Thank you for your attention


"C’est une triste chose de songer que la nature parle
et que le genre humain n’écoute pas."
Victor Hugo

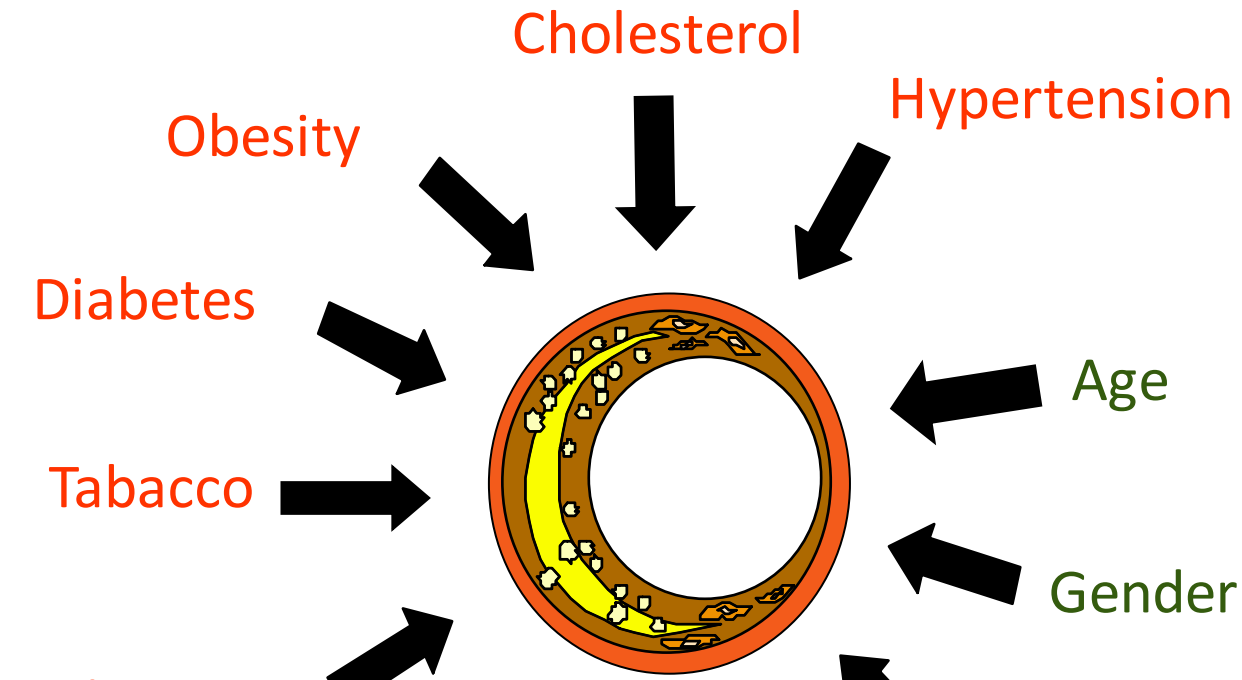
Novel lipid lowering drugs: PCSK9 and beyond



Clin Med. 2019;8:1085

Cardiovascular risk factors

Modifiables



Non-modifiables

Atherosclerosis