State of the Art in Dyslipidemia

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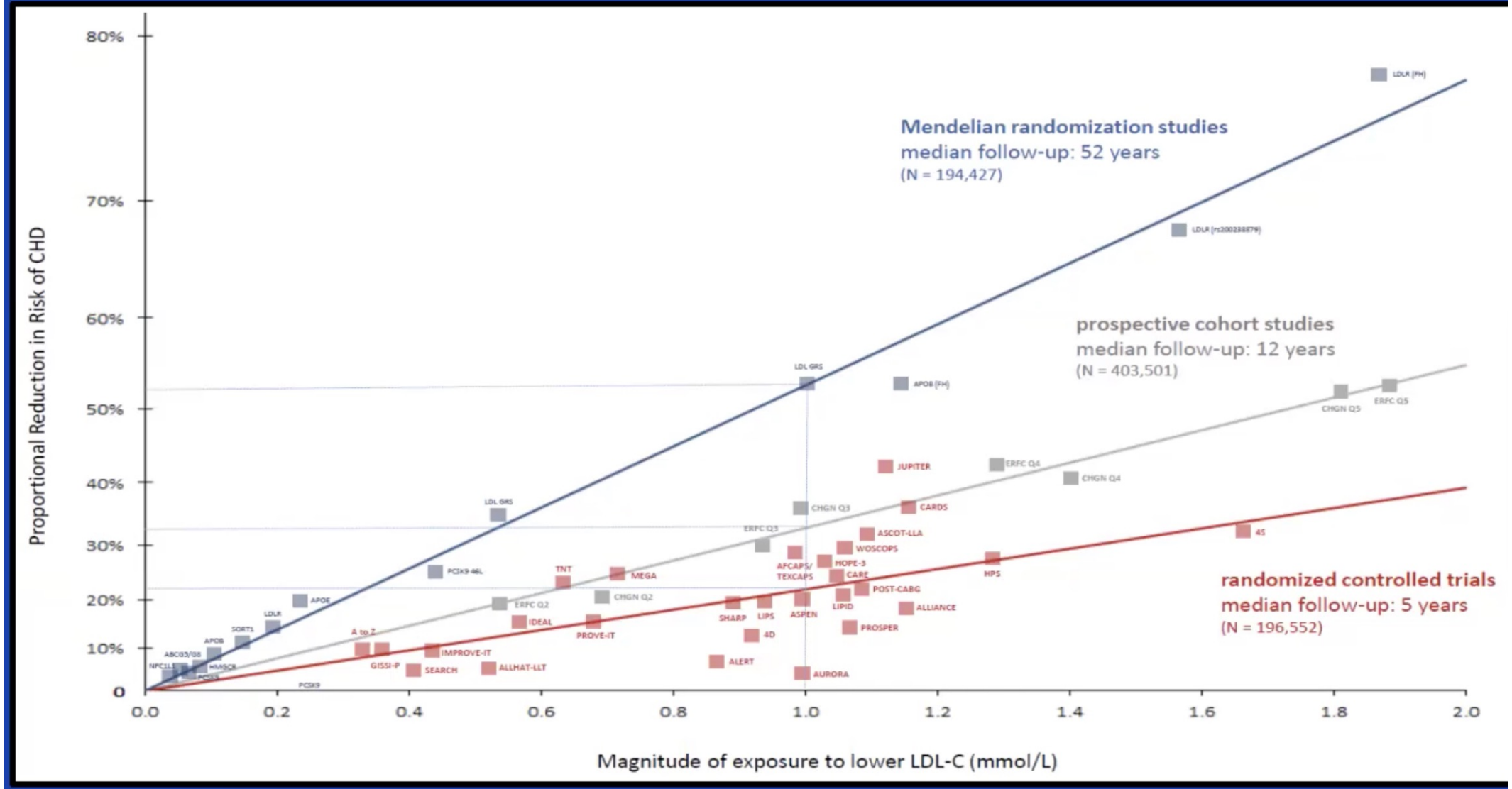
Conflits d’intérêt

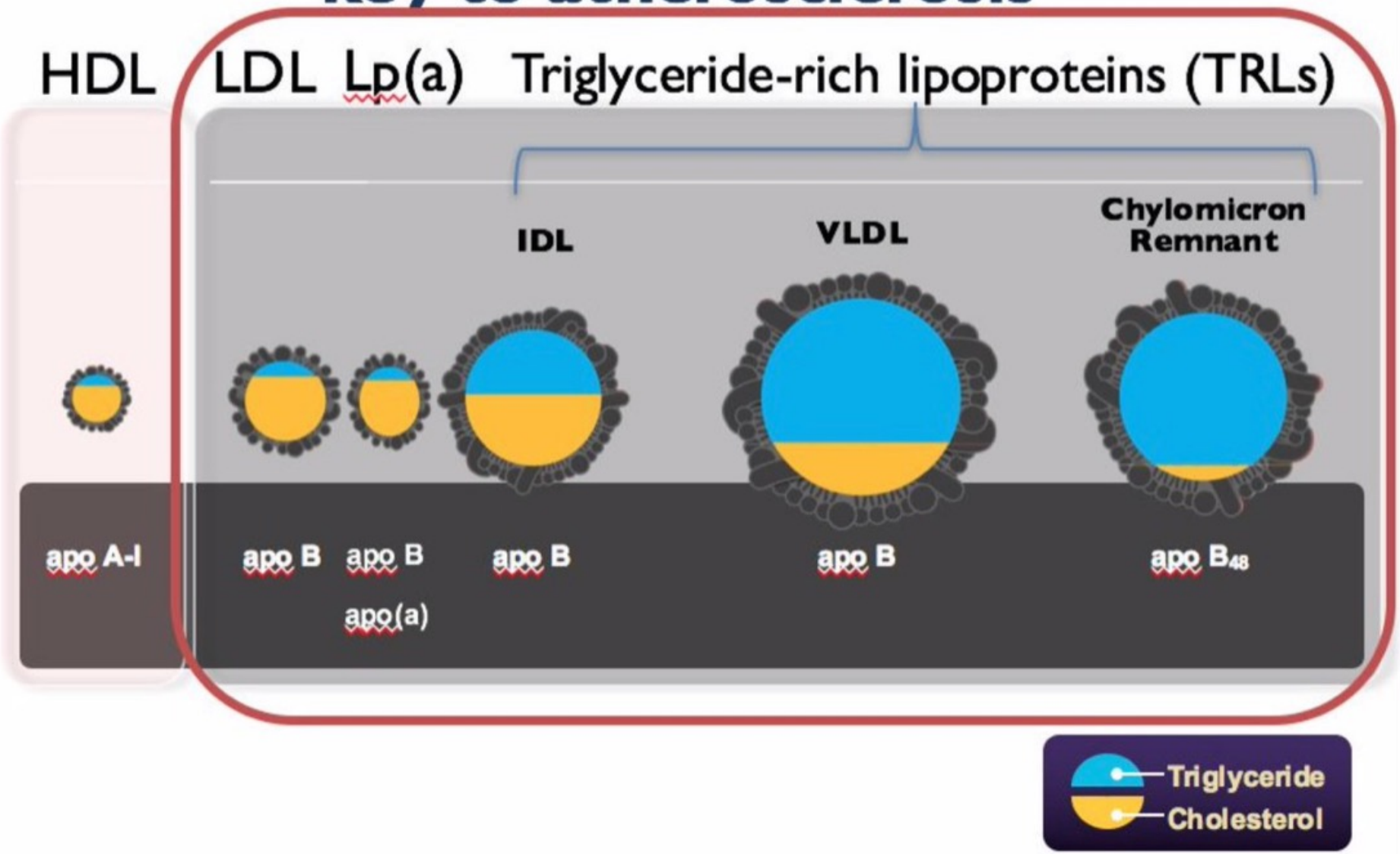
Amgen, Daiichy Sankyo, Sanofi, Novartis, Amarin

Benefits of Lower LDL-C Levels



Ference, Nicholls et al. *Eur Heart J* 2017;38:2459-72.

apoB-containing lipoproteins: key to atherosclerosis



Treatment targets and goals for cardiovascular disease prevention

LDL-C	**Very-high-risk in primary or secondary prevention** A therapeutic regimen that achieves at least a 50% LDL-C reduction from baseline[b] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL). No current statin use: this is likely to require high-intensity LDL-lowering therapy. Current LDL-lowering treatment: an increased treatment intensity is required. **High risk:** A therapeutic regimen that achieves at least a 50% LDL-C reduction from baseline[b] and an LDL-C goal of <1.8 mmol/L (<70 mg/dL).
LDL-C	**Moderate risk:** A goal of <2.6 mmol/L (<100 mg/dL). **Low risk:** A goal of <3.0 mmol/L (<116 mg/dL)
Non-HDL-C	Non-HDL-C secondary goals are <2.2, 2.6 and 3.4 mmol/L (<85, 100 and 130 mg/dL) for very-high-, high- and moderate-risk people, respectively.
Apolipoprotein B	ApoB secondary goals are <65, 80 and 100 mg/dL for very-high-, high- and moderate-risk people, respectively.
Triglycerides	No goal but <1.7 mmol/L (<150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.

Moderate and low risk
A goal <2,6 mmolL (<100 mg/dl)
ESC Prevention Guidelines 2021

www.escardio.org/guidelines

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

Patient categories and associated cardiovascular disease risk (1)

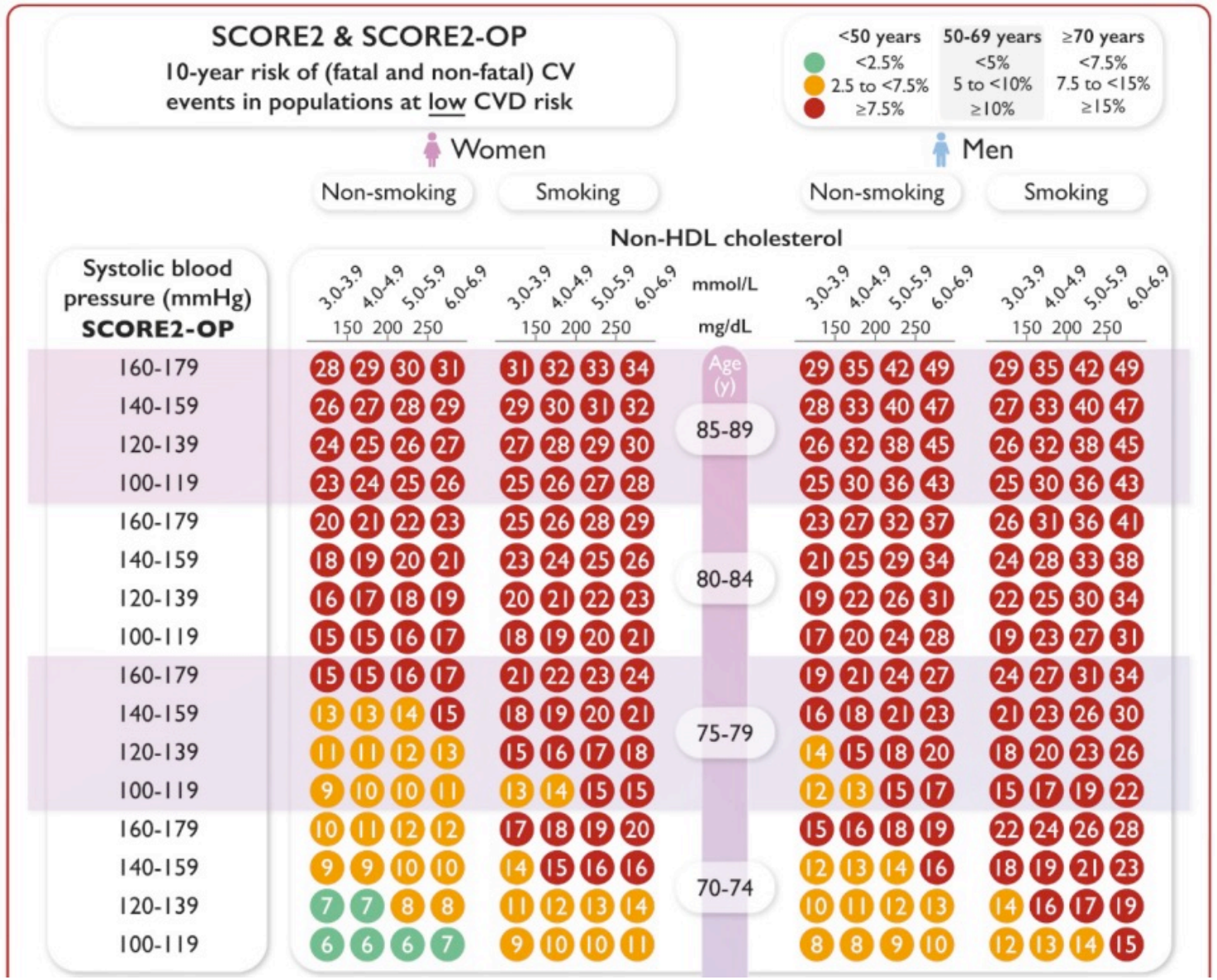
Patient category	Subgroups	Risk categories	CVD risk and therapy benefit estimation
Apparently healthy persons			
Persons without established ASCVD, diabetes mellitus, CKD, Familial Hypercholesterolemia	<50 years	Low- to high-risk	10-year CVD risk estimation (SCORE2). Lifetime risk and benefit estimation of risk factor treatment (e.g. with the LIFE-CVD lifetime model) to facilitate the communication of CVD risk and treatment benefits.
	50-69 years	Low- to very high-risk	10-year CVD risk estimation (SCORE2). Lifetime benefit estimation of risk factor treatment (e.g. with the LIFE-CVD lifetime model) to facilitate the communication of treatment benefits.
	≥70 years	Low- to very high-risk	10-year CVD risk estimation (SCORE2-OP). Lifetime benefit estimation of risk factor treatment (e.g. with the LIFE-CVD lifetime model) to facilitate the communication of treatment benefits.
Patients with CKD			
CKD without diabetes or ASCVD	Moderate CKD (eGFR 30–44 mL/min/1.73 m^2 and ACR <30 mg/g **or** eGFR 45–59 mL/min/1.73 m^2 and ACR 30 mg/g –300 mg/g **or** eGFR ≥60 mL/min/1.73 m^2 and ACR >300 mg/g)	High-risk	N/A
	Severe CKD (eGFR <30 mL/min/1.73 m^2 **or** eGFR 30–44 mL/min/1.73 m^2 and ACR >30 mg/g)	Very high-risk	N/A
Familial Hypercholesterolemia			
Associated with markedly elevated cholesterol levels	N/A	High-risk	N/A
Patients with type 2 diabetes mellitus			
Patients with type 1 DM above 40 years of age may also be classified according to these criteria	Patients with well controlled short-standing DM (e.g. <10 years), no evidence of TOD and no additional ASCVD risk factors	Moderate-risk	N/A
	Patients with DM without ASCVD and/or severe TOD, and not fulfilling the moderate risk criteria.	High-risk	Residual 10-year CVD risk estimation after general prevention goals (e.g. with the ADVANCE risk score or DIAL model). Consider lifetime CVD risk and benefit estimation of risk factor treatment (e.g. DIAL model).

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

Patient categories and associated cardiovascular disease risk (2)

Patient category	Subgroups	Risk categories	CVD risk and therapy benefit estimation
Patients with type 2 diabetes mellitus (continued)			
	Patients with DM with established ASCVD and/or severe TOD: • eGFR <45 mL/min/1.73 m² irrespective of albuminuria • eGFR 45-59 mL/min/1.73 m² and microalbuminuria (ACR 30 mg/g – 300 mg/g) • Proteinuria (ACR >300 mg/g) • Presence of microvascular disease in at least 3 different sites (e.g. microalbuminuria plus retinopathy plus neuropathy)	**Very high-risk**	Residual 10-year CVD risk estimation after general prevention goals (e.g. with the SMART risk score for established CVD or with the ADVANCE risk score or with the DIAL model). Consider lifetime CVD risk and benefit estimation of risk factor treatment (e.g. DIAL model).
Patients with established ASCVD			
Documented ASCVD, clinical or unequivocal on imaging. Documented clinical ASCVD includes previous AMI, ACS, coronary revascularization and other arterial revascularization procedures, stroke and TIA, aortic aneurysm and PAD. Unequivocally documented ASCVD on imaging includes plaque on coronary angiography or carotid ultrasound or on CTA. It does NOT include some increase in continuous imaging parameters such as intima–media thickness of the carotid artery.	N/A	**Very high-risk**	Residual CVD risk estimation after general prevention goals (e.g. 10-year risk with the SMART risk score for patients with established CVD or 1- or 2-year risk with EUROASPIRE risk score for patients with CHD). Consider lifetime CVD risk and benefit estimation of risk factor treatment (e.g. SMART-REACH model; or DIAL model if diabetes).

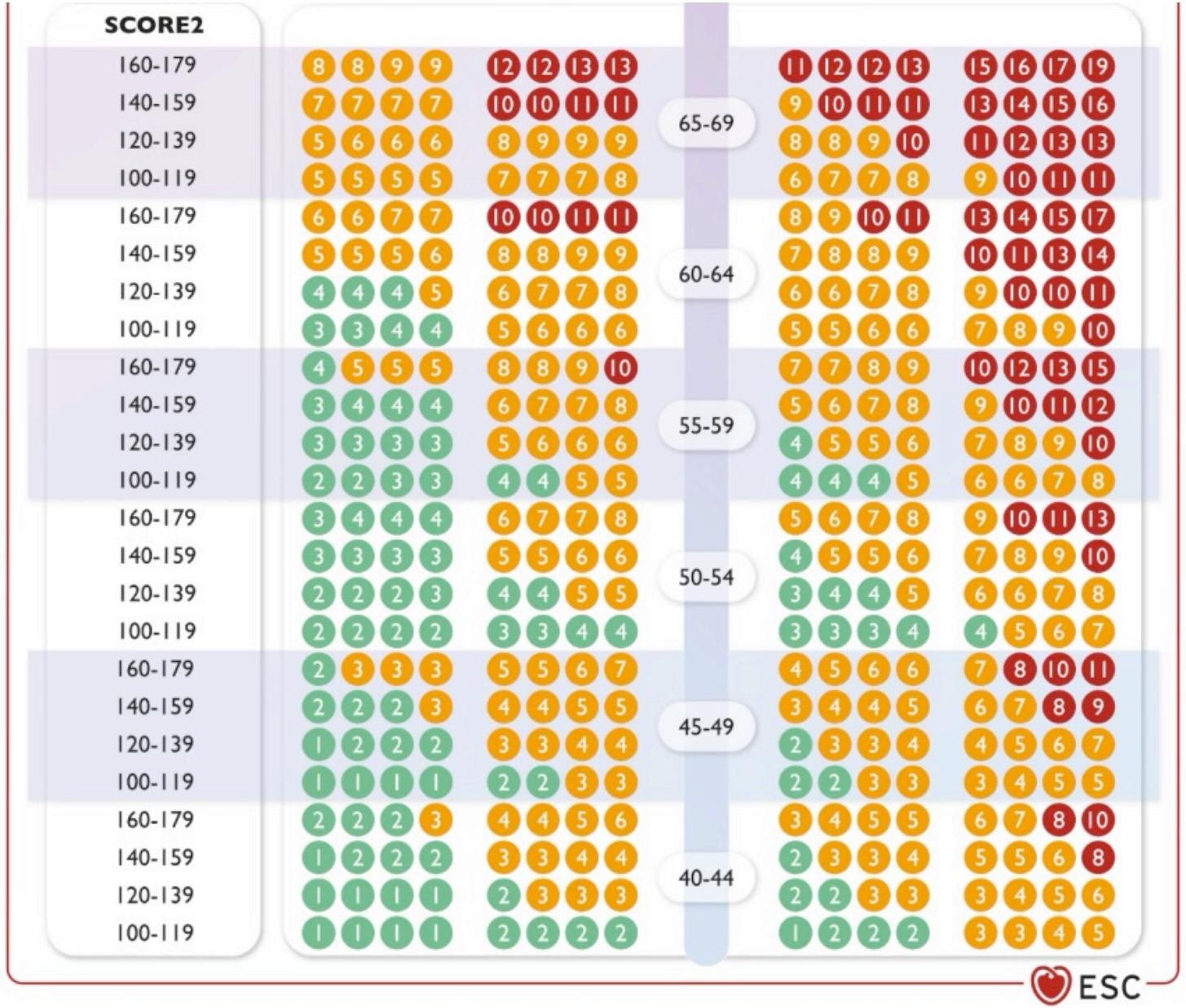
2021 ESC Guidelines on cardiovascular disease prevention in clinical practice
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab484)



SCORE2 and SCORE2-OP risk chart for fatal and non-fatal (MI, stroke) ASCVD

Low CVD Risk (1)

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



SCORE2 and SCORE2-OP risk chart for fatal and non-fatal (MI, stroke) ASCVD

Low CVD Risk (2)

ESC

CVD Risk

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

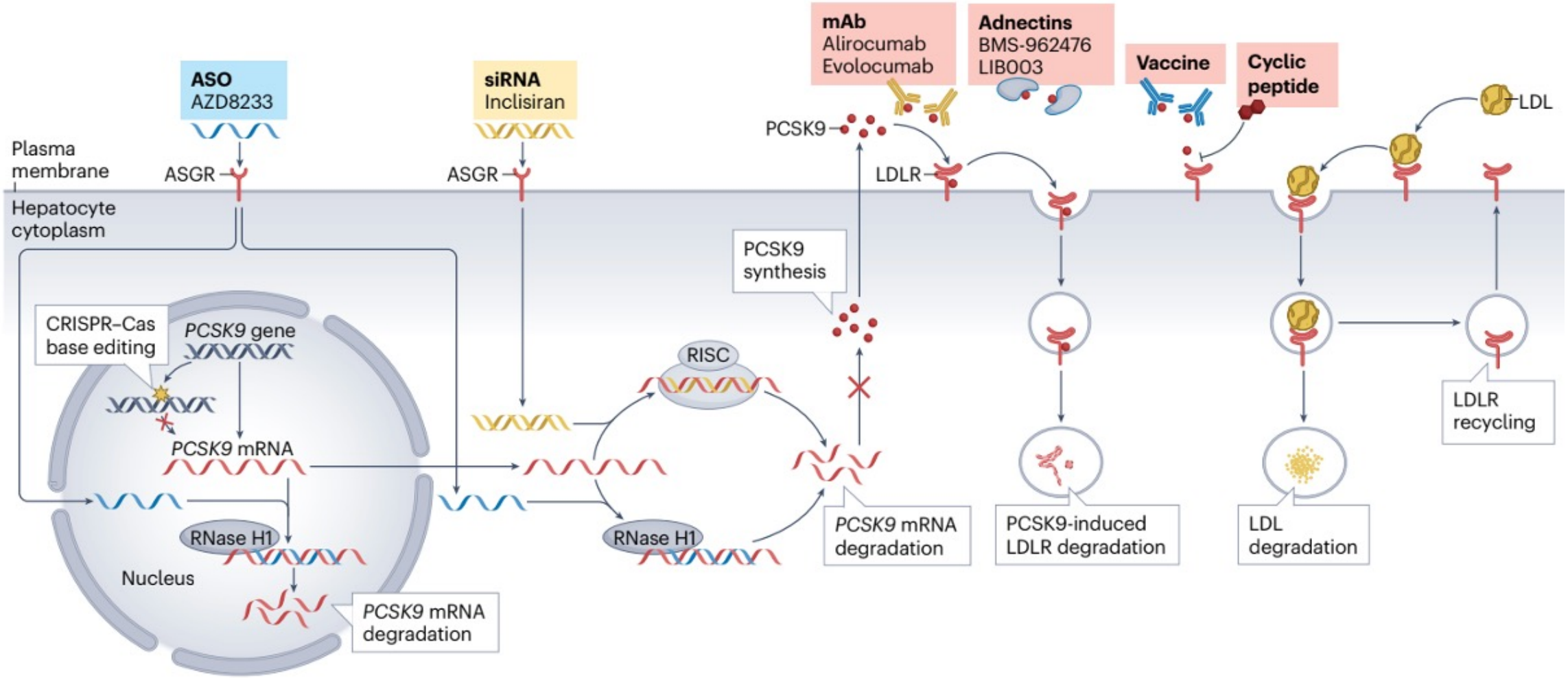
	<50 years	50-69 years	≥70 years[a]
Low-to-moderate CVD risk: risk factor treatment generally not recommended	<2.5%	<5%	<7.5%
High CVD risk: risk factor treatment should be considered	2.5 to <7.5%	5 to <10%	7.5 to <15%
Very high CVD risk: risk factor treatment generally recommended[a]	≥7.5%	≥10%	≥15%

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

Recommendations for pharmacological low-density lipoprotein cholesterol lowering up to 70 years of age (recommendations for persons aged >70 years, see respective recommendations tables) (1)

Recommendations	Class	Level
It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the LDL-C goals set for the specific risk group.	I	A
In patients with established ASCVD, lipid-lowering treatment with an ultimate LDL-C goal of ≥50% reduction vs baseline and an LDL-C of <1.4 mmol/L (<55 mg/dL) is recommended.	I	A
If the goals are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended.	I	B
For secondary prevention patients not achieving their goals on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor is recommended.	I	A

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



Novel and emerging LDL-lowering therapies targeting PCSK9

Brandts, J., Ray, K.K. Novel and future lipid-modulating therapies for the prevention of cardiovascular disease. *Nat Rev Cardiol* **20**, 600–616 (2023). https://doi.org/10.1038/s41569-023-00860-8

Inhibiteurs des PCSK9

Anticorps monoclonaux :

Praluent® (alirocumab) Odyssey Outcomes , remboursé en cat. a chez patients HFHé

Repatha ®(evolocumab) Fourier, remboursé en cat. a chez patients HFHo et HFHé, en cat. b en prévention secondaire après statine et ezetimibe si LDLc >100 mg/dl

siRNA

Leqvio® (inclisiran) ORION 4 en cours, remboursé en cat a HFHé, en cat. b en prévention secondaire après statine et ezetimibe si LDLc >100 mg/dl

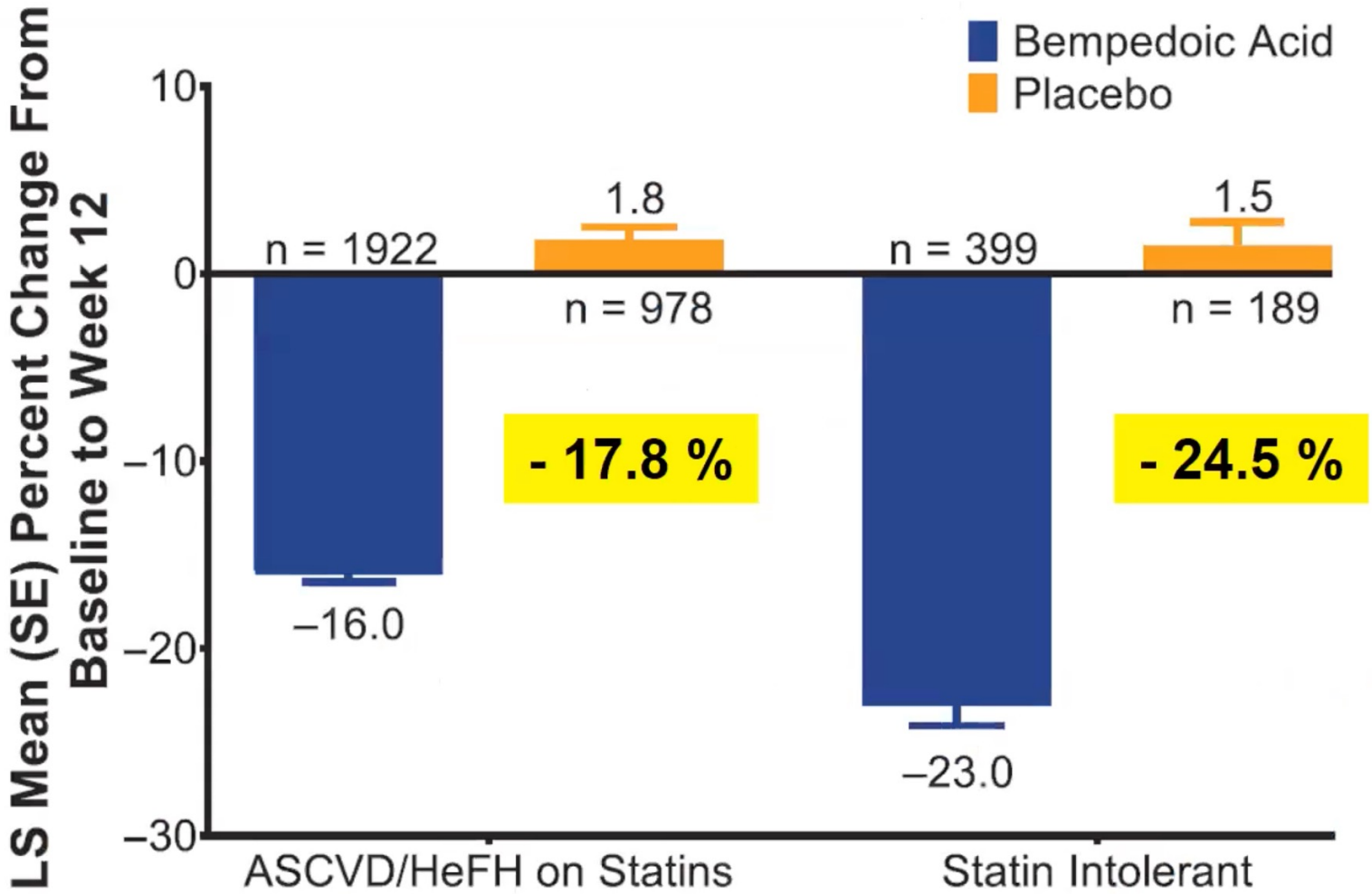
Recommendations for pharmacological low-density lipoprotein cholesterol lowering up to 70 years of age (recommendations for persons aged >70 years, see respective recommendations tables) (1)

Recommendations	Class	Level
It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the LDL-C goals set for the specific risk group.	I	A
An ultimate LDL-C goal of ≥50% reduction vs baseline and an LDL-C of <1.4 mmol/L (<55 mg/dL) should be considered in apparently healthy persons <70 years at very high risk.	IIa	C
An ultimate LDL-C goal of ≥50% reduction vs baseline and an LDL-C of <1.8 mmol/L (<70 mg/dL) should be considered in apparently healthy persons <70 years at high risk.	IIa	C
If the goals are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended.	I	B
For primary prevention patients at very high risk, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor may be considered.	IIb	C

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

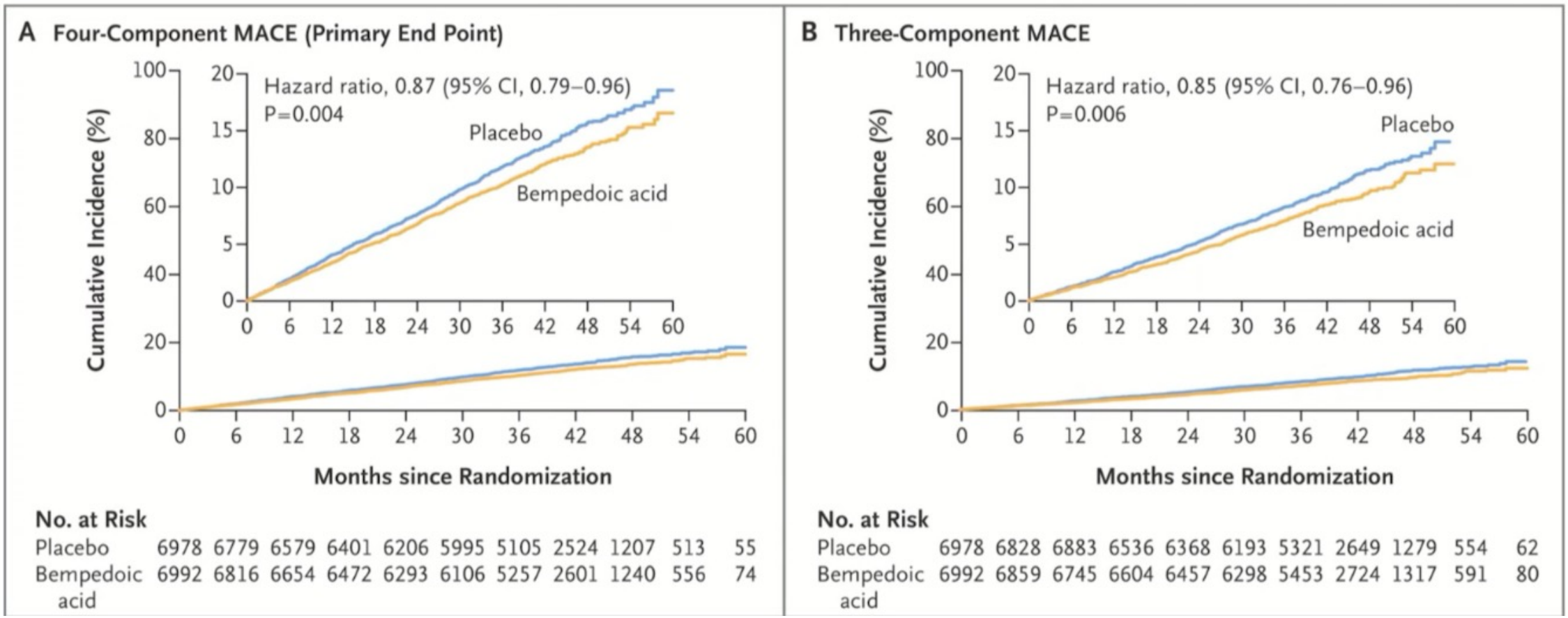
EFFICACY OF BEMPEDOIC ACID
POOLED ANALYSIS OF 4 PHASE 3 TRIALS

n= 3623, % change from baseline in LDL-C at week 12



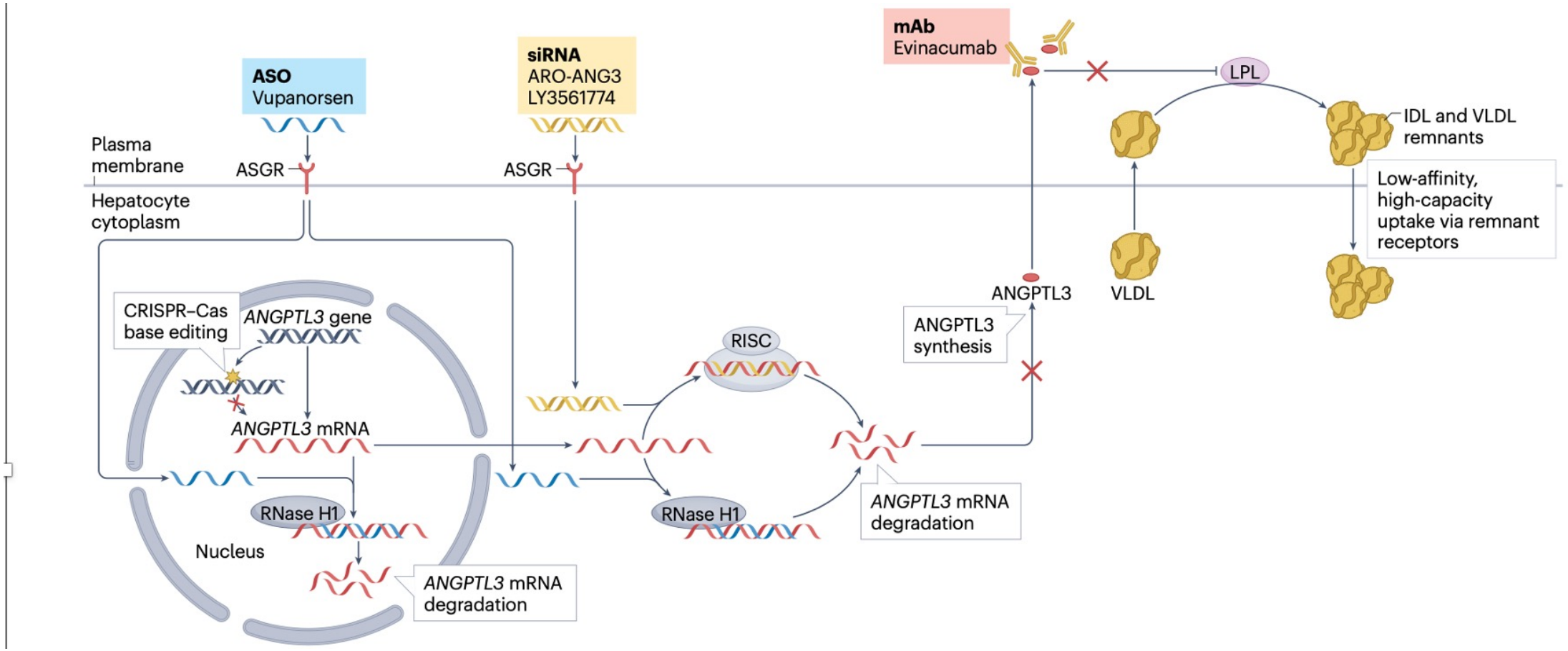
CLEAR Harmony (NCT02666664)
CLEAR Wisdom (NCT02991118)
CLEAR Tranquility (NCT03001076)
CLEAR Serenity (NCT02988115)
JAMA Cardiol 2020 in press

ETUDE CLEAR Outcomes trial



Nissen SE et al. *N Engl J Med* 2023; March 4

Traitements futurs

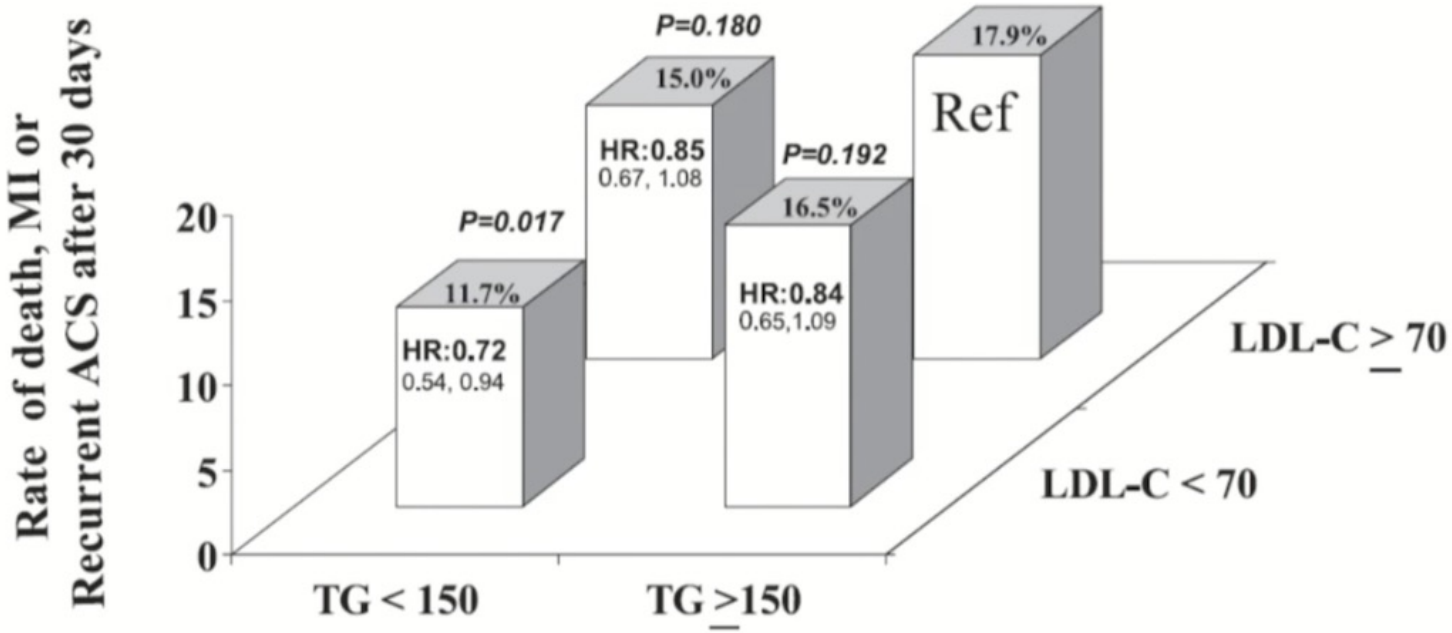


Novel and emerging therapies targeting ANGPTL3

Brandts, J., Ray, K.K. Novel and future lipid-modulating therapies for the prevention of cardiovascular disease. *Nat Rev Cardiol* **20**, 600–616 (2023). https://doi.org/10.1038/s41569-023-00860-8

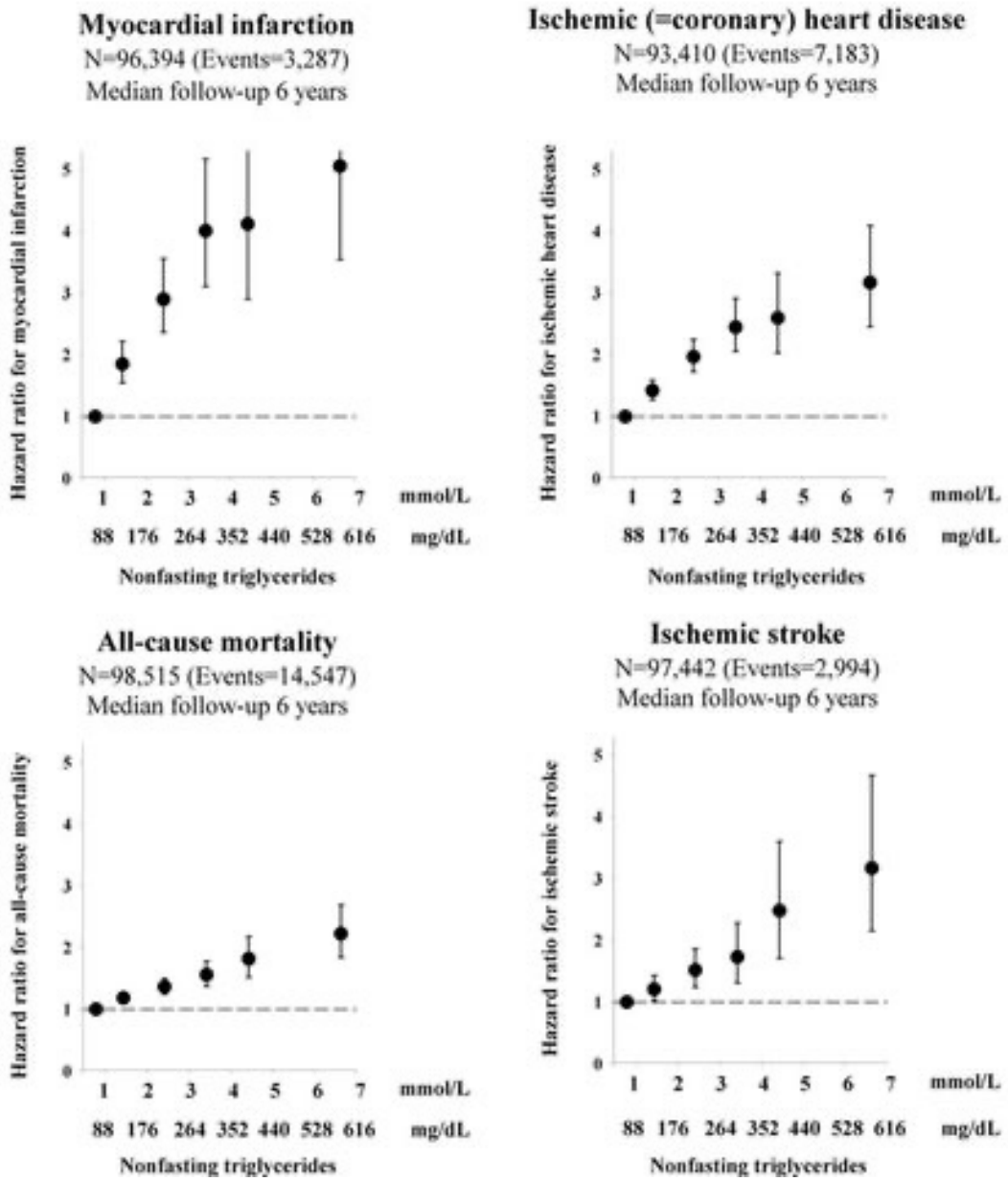
Risque CV Résiduel

PROVE IT-TIMI: Chez patients avec LDL-C bas (<70 mg/dl), risque d'évènements CV récurrents plus faible si TG <150 mg/dl



Miller et al. J Am Coll Cardiol 2008 : 51: 724-30.

Copenhagen City Heart Study and Copenhagen General Population Study



Circulation Research
Volume 118, Issue 4, 19 February 2016; Pages 547-563

Résultats des CVOT avec les fibrates

Table I. Effects of fibrates on cardiovascular events in large randomized controlled trials

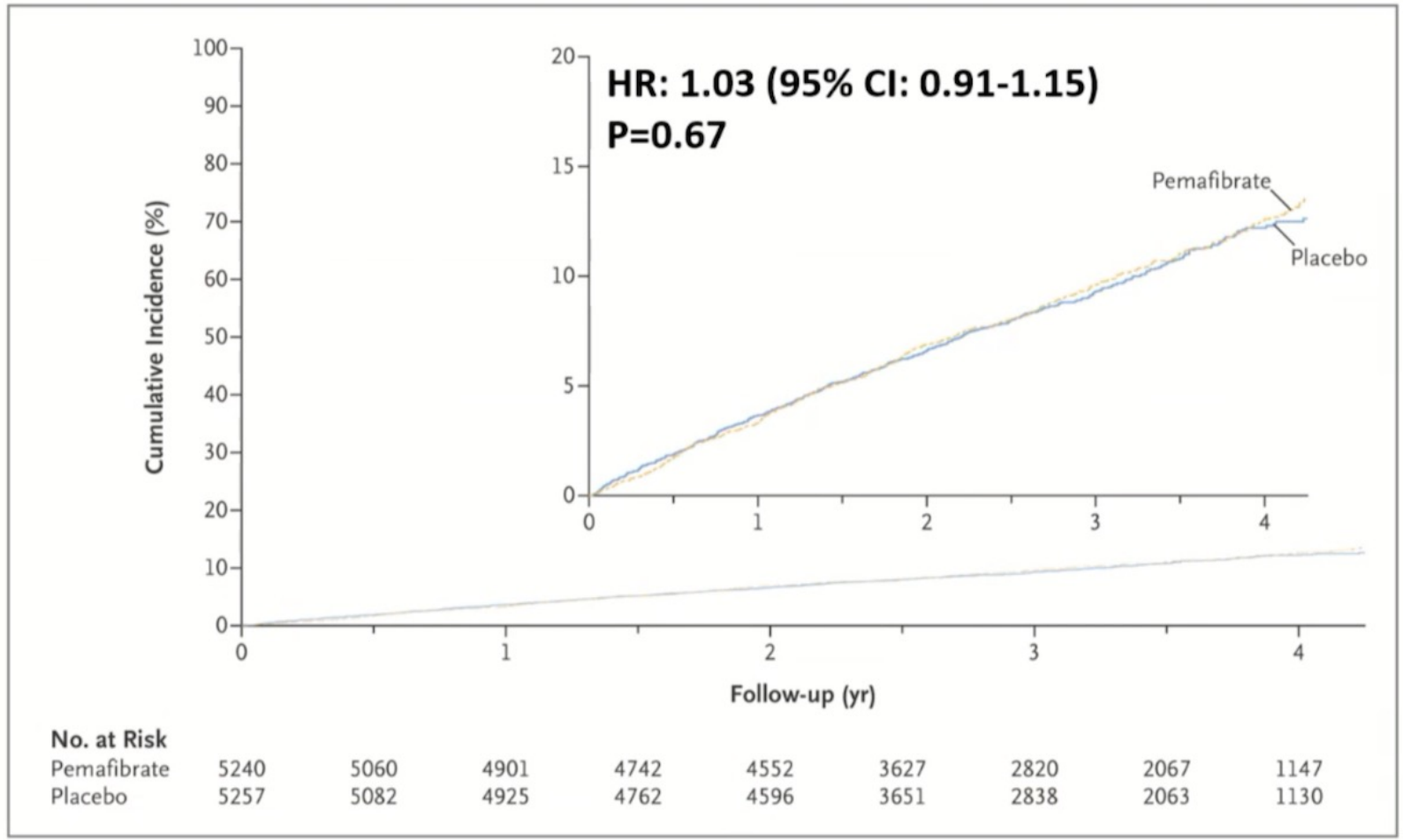
Trial	Drug	Patient Characteristics	CV Outcome*	Trial Duration (years)	RR Reduction Entire Cohort	Atherogenic Dyslipidemia Subgroup	RR Reduction Subgroup‡
HHS[82,83]	Gemfibrozil	Non-HDL-C >5.2 mmol/l No CHD Men	Non-fatal MI and CHD Death	5.0	−34% ($P < .02$)	TG >204 mg/dL LDL-C/HDL-C ratio> 5.0	−71% ($P = .005$)
V A - HIT[56,84,85]	Gemfibrozil	HDL-C <1.0 mmol/l CHD Men	Nonfatal MI and CHD Death	5.1	−22% ($P = .006$)	TG >180 mg/dL <40 mg/dl	−30% ($P < .05$)
BIP[86]	Bezafibrate	Previous MI or angina Men and women	Fatal/Nonfatal MI and Sudden Death	6.2	−7% ($P = .26$)	TG ≥200 mg/dL	−40% ($P = .02$)
FIELD[54,87]	Fenofibrate	Type 2 diabetes Some patients receiving statins Men and women	MI, stroke, CVD death, coronary or carotid revascularization	5.0	−11 ($P = .035$)	TG ≥204 mg/dL HDL-C < 40 mg/dL (men) or <50 mg/dL (women)	−27% (P = .005)
ACCORD[55,56]	Fenofibrate	Type 2 diabetes CVD or >2 CVD risk factors Patients receiving simvastatin Men and women	Nonfatal MI, Nonfatal stroke, and CVD death	4.7	−8% ($P = .32$)	TG ≥204 mg/dL HDL-C ≤34 mg/dL	−29% (P < .05)

Pradhan A. et al. *Am Heart J* 2018; 206: 80-93

PROMINENT

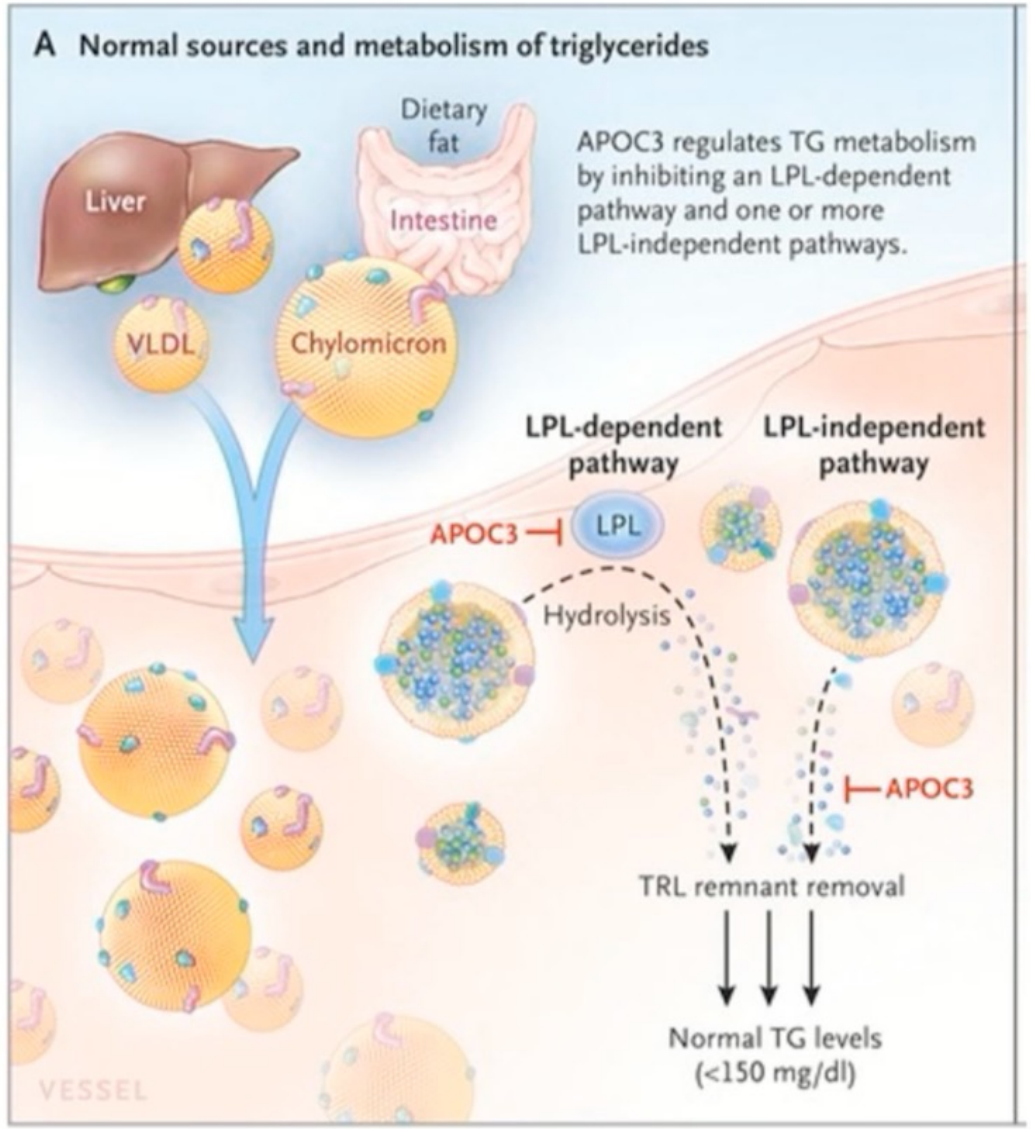
Pemafibrate (agoniste PPAR α supersélectif) vs placebo
Diabète type 2 , TGL 200 à 499 mg/dl, HDL-c <40 mg:dl, LDL-c <100 mg/dl
10497
Suivi médian de 3,4 ans
Critère d'évaluation principal : décès CV + IDM non fatal+ AVC ischémique non fatal+ revasc coronaire

PEMAFIBRATE: résultats de l'étude PROMINENT



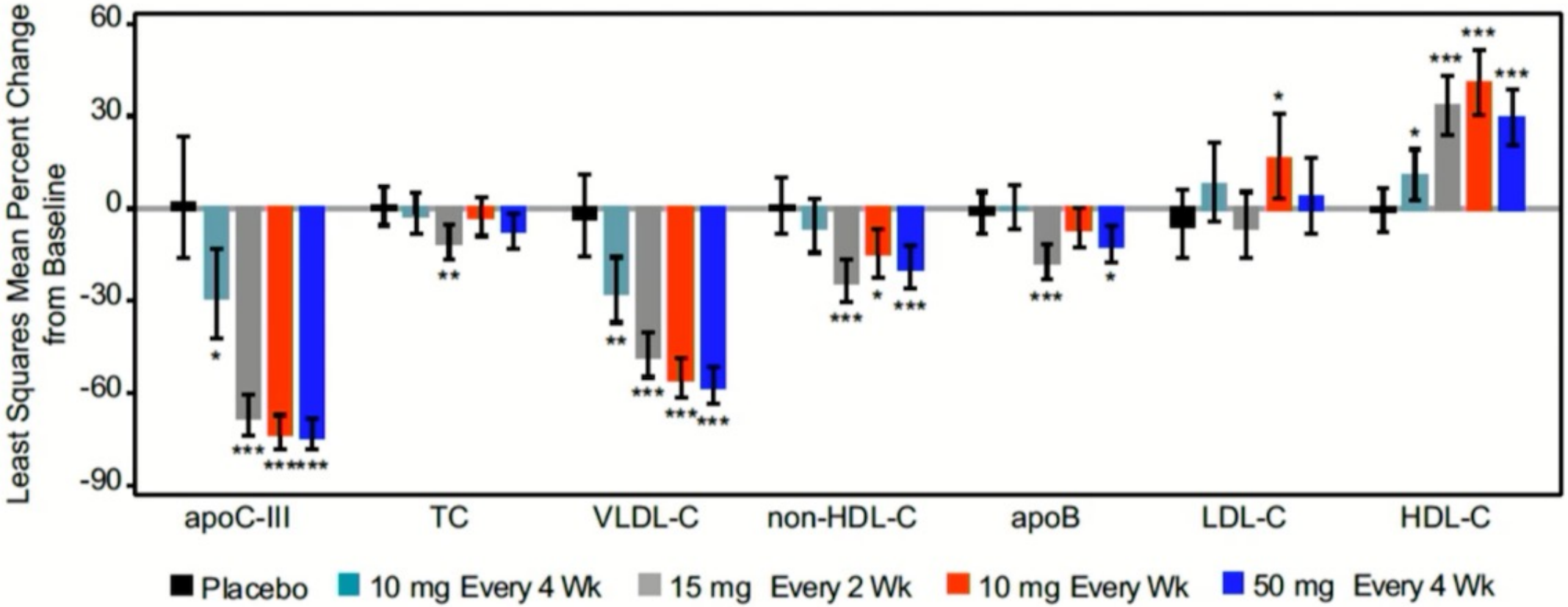
Das Pradhan A et al. *N Engl J Med* 2022; 387: 1923-1934

APOC3: un acteur majeur du métabolisme des TG



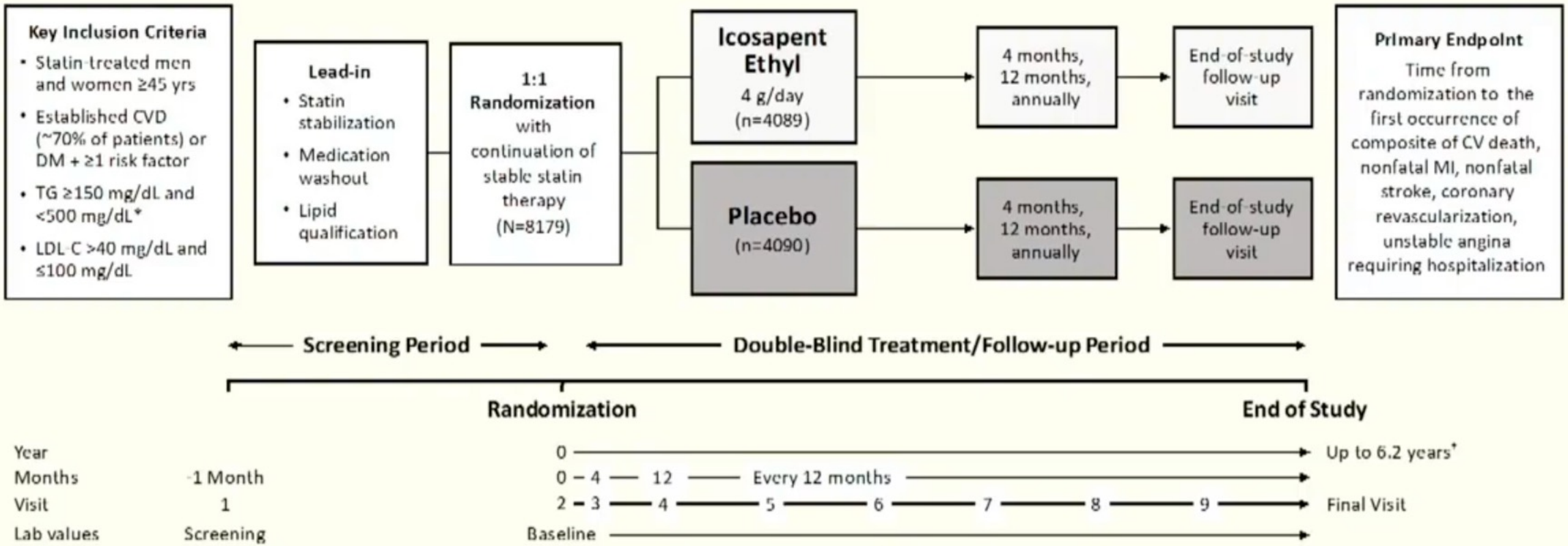
Gaudet D et al. *N Engl J Med* 2014; 371: 2200-2206

Apolipoprotein C-III reduction in subjects with moderate hypertriglyceridaemia and at high cardiovascular risk



Tardif JC et al. *Eur Heart J* 2022; 43: 1401-1412

REDUCE-IT Design



* Due to the variability of triglycerides, a 10% allowance existed in the initial protocol, which permitted patients to be enrolled with qualifying triglycerides ≥135 mg/dL. Protocol amendment 1 (May 2013) changed the lower limit of acceptable triglycerides from 150 mg/dL to 200 mg/dL, with no variability allowance.

† Median trial follow-up duration was 4.9 years (minimum 0.0, maximum 6.2 years).

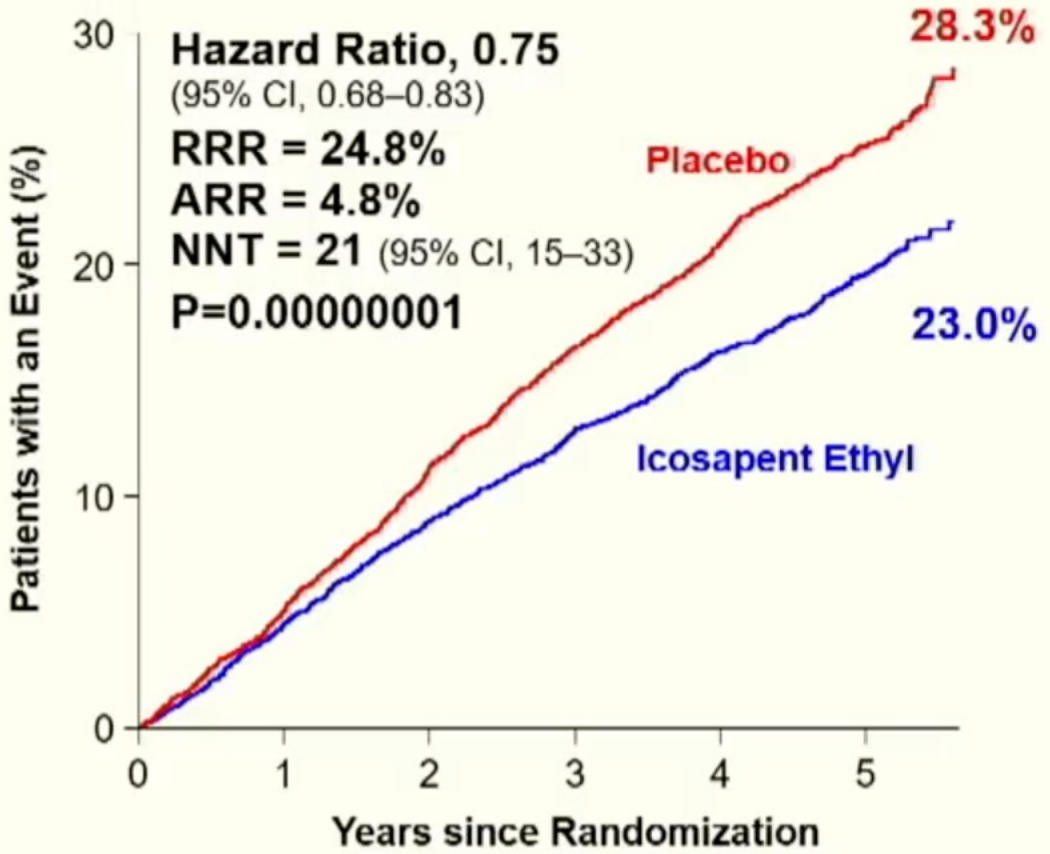
Adapted with permission[‡] from Bhatt DL, Steg PG, Brinton EA, et al; on behalf of the REDUCE-IT Investigators. *Clin Cardiol*. 2017;40:138-148.
REDUCE-IT ClinicalTrials.gov number, NCT01492361. [‡https://creativecommons.org/licenses/by-nc/4.0/]

REDUCE IT: CV risk reduction with 4 g purified EPA/d in statin-treated pts at high risk with elevated TGs

reduce-it

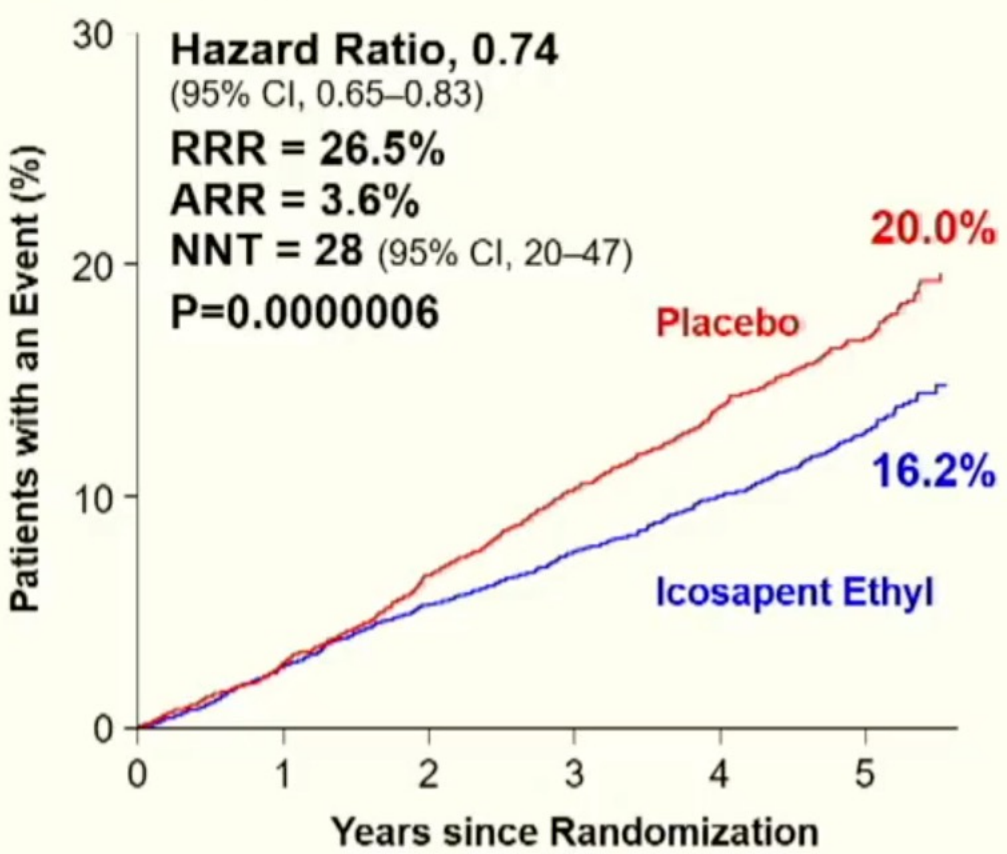
Primary Composite Endpoint:

CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



Key Secondary Composite Endpoint:

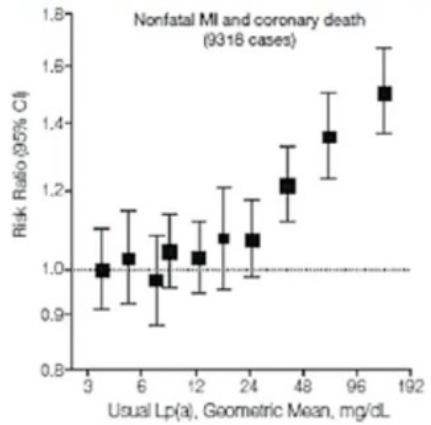
CV Death, MI, Stroke



Bhatt DL, Steg PG, Miller M, et al. ***N Engl J Med.*** 2019

Lp(a) and atherosclerotic cardiovascular disease risk

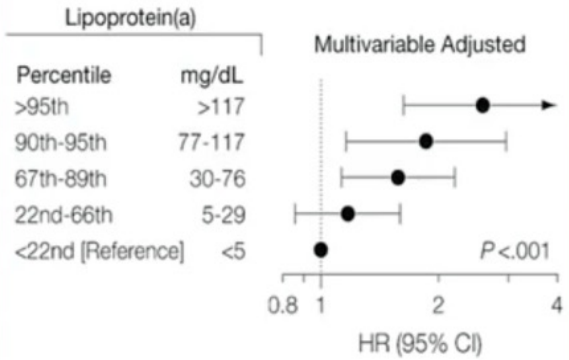
Epidemiological studies



Emerging Risk Factor Collaboration
Individual records of 126,634 participants in 36 long-term, prospective, epidemiological studies

Emerging Risk Factor Collaboration. JAMA 2009; 302:412–423

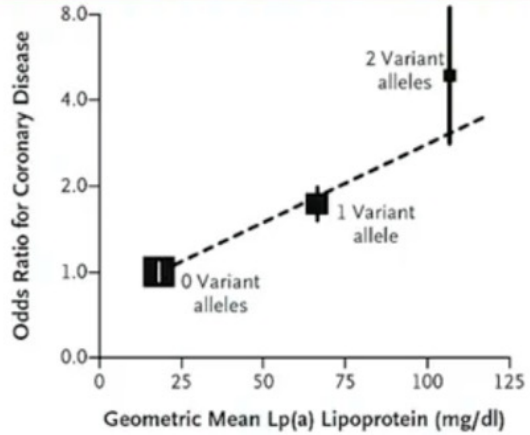
Mendelian Randomization



Copenhagen City Heart Study
Data from the 1991-1994 examination study (n=7,524) with up to 16 years of follow-up

Kamstrup PR et al. JAMA 2009; 301:2331-2339

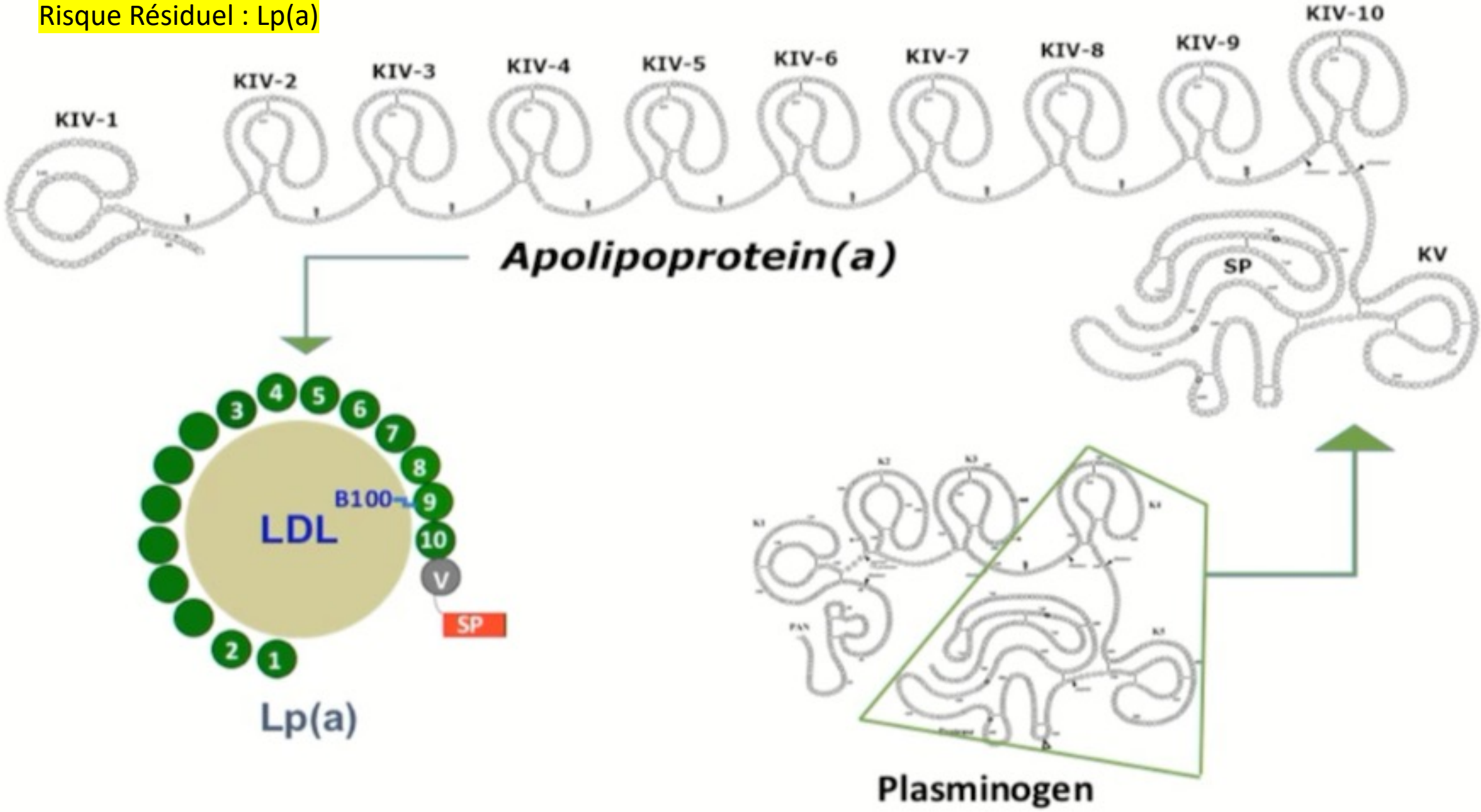
Genome-wide association

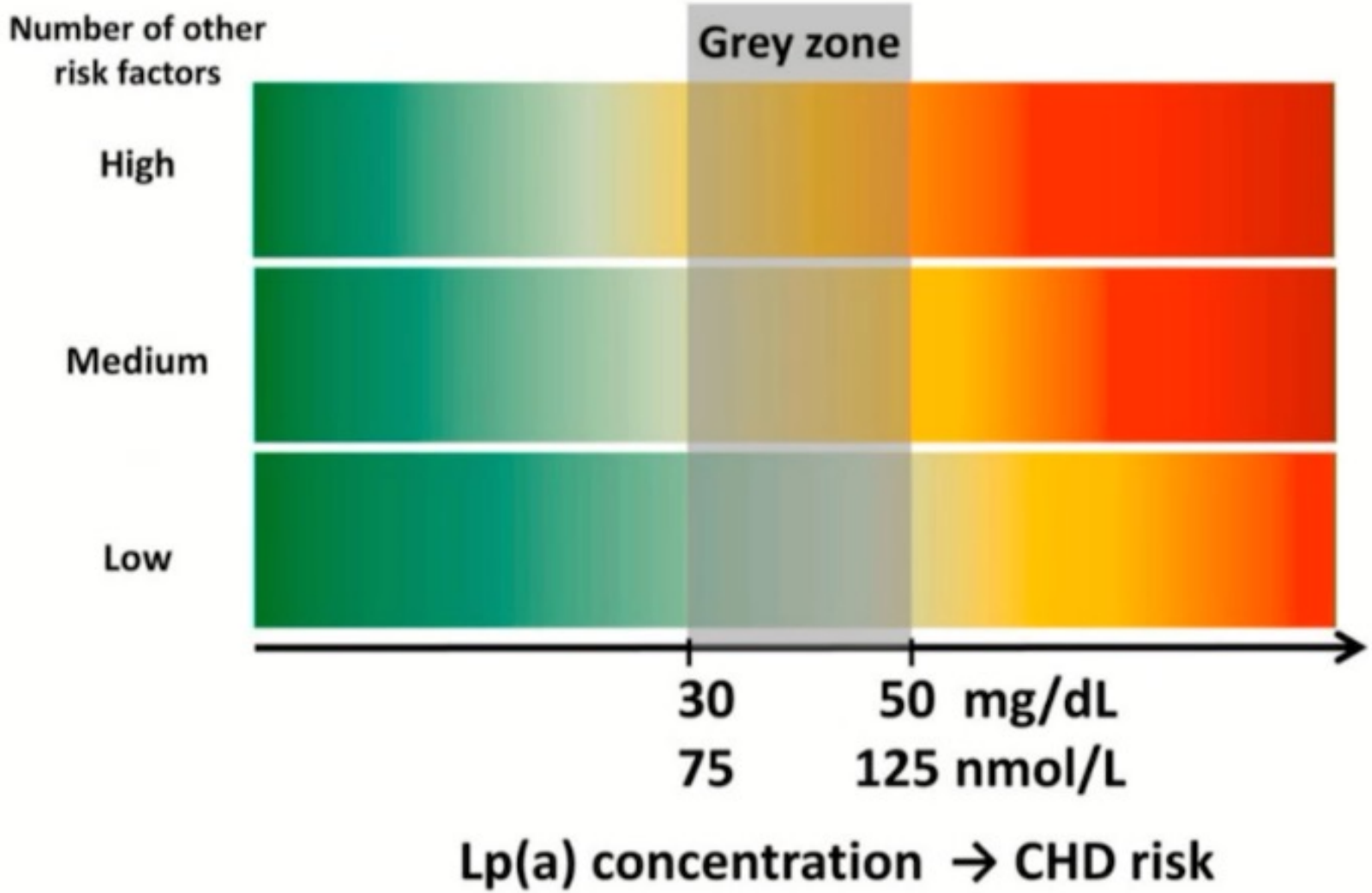


PROCARDIS Cohort
Data from 1,259 "trio families" (families either with 1 proband and 2 parents or with 1 proband, 1 parent, and at least 1 sibling)

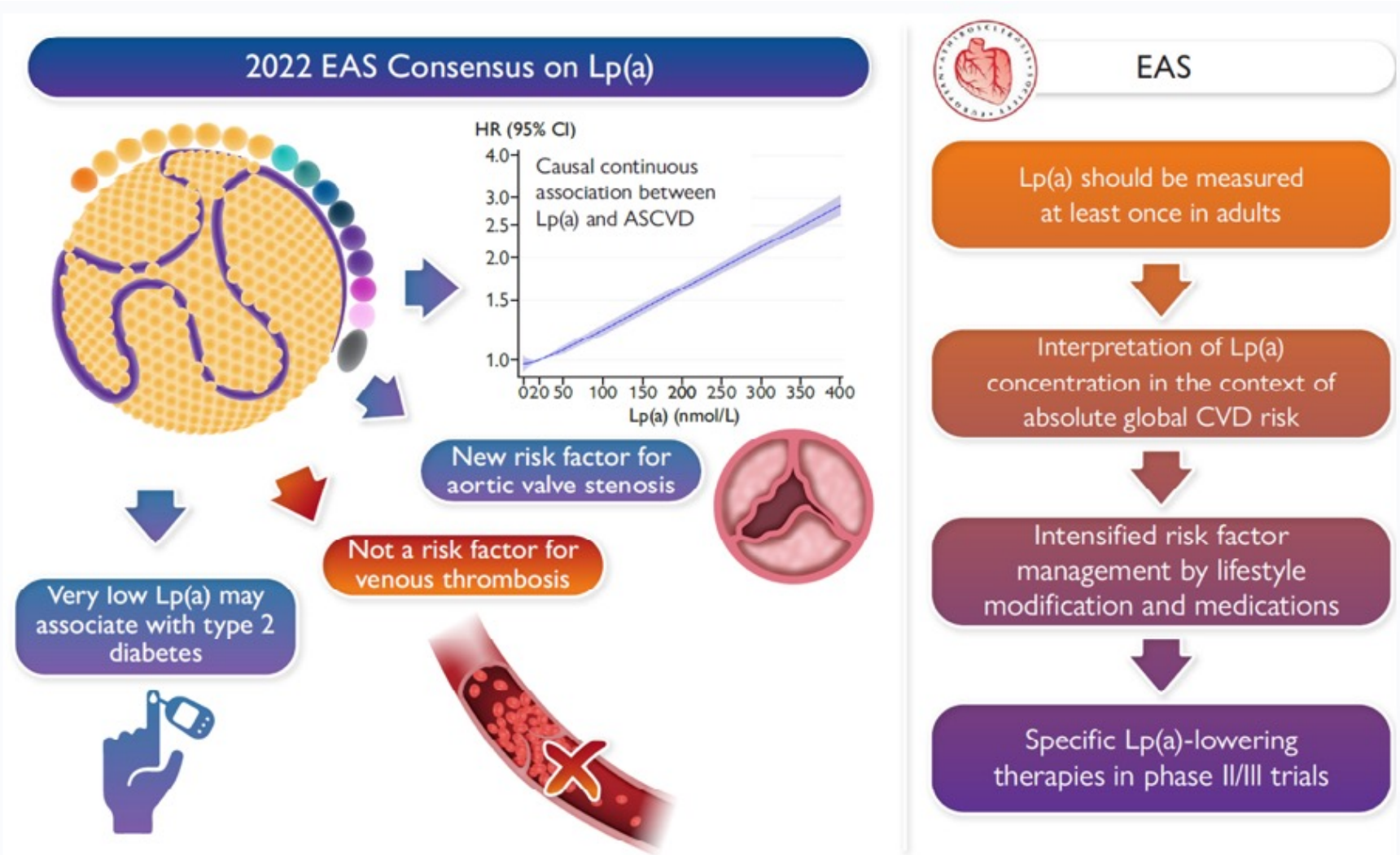
Clarke R et al. N Engl J Med 2009; 361:2518-28

Risque Résiduel : Lp(a)





Kronenberg F. Atherosclerosis 2022; 349: 123–135

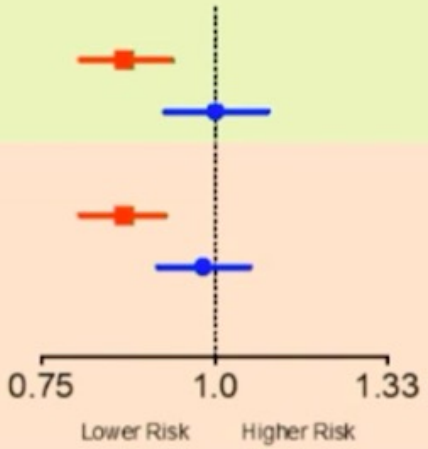


European Heart Journal, 2022. https://doi.org/10.1093/eurheartj/ehac361

Change in Lp(a) predicts lower risk of MACE independently of LDL change: for every 15 mg/dL decrease in Lp(a), there is a 14% RRR in MACE

Time-Weighted Moving Average Lp(a) Absolute Change From Baseline vs MACE

	15 mg/dL Decrease HR (95% CI)	p-value
Unadjusted Model		
Alirocumab	0.86 (0.80, 0.93)	0.0002
Placebo	1.00 (0.92, 1.09)	0.96
Adjusted Model 3		
Alirocumab	0.86 (0.80, 0.92)	<0.0001
Placebo	0.98 (0.91, 1.06)	0.68



Adjusted for Demographic variables, baseline Lp(a) and LDL-C, change in LDL-C and clinical variables

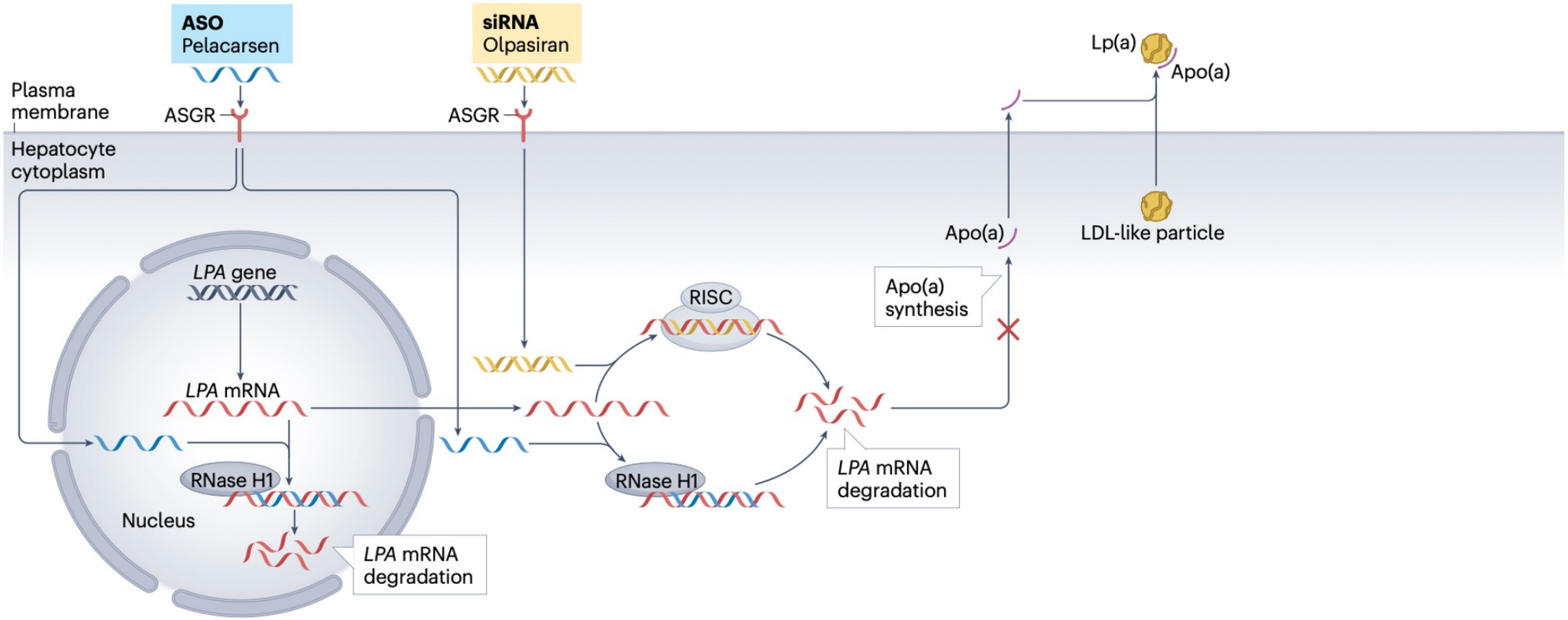
Models fit separately for each treatment group

*Demographic variables: age, sex, race, region

†Clinical variables: time from ACS, BMI, diabetes, smoking history

Alirocumab Placebo

Bittner VA.J Am Coll Cardiol 2020;75:133–44



Emerging therapies targeting Lpa

Brandts, J., Ray, K.K. Novel and future lipid-modulating therapies for the prevention of cardiovascular disease. *Nat Rev Cardiol* **20**, 600–616 (2023). https://doi.org/10.1038/s41569-023-00860-8

Conclusions

- En première intention, réduction des concentrations de LDL-c en dessous de 55 et de 70 mg/dl respectivement chez les sujets à très haut risque et à haut risque cardio-vasculaire

- Utilisation de statines/ezetimibe/ PSCK9, acide bempédoïque

- Risque résiduel :

  - ✓ Les fibrates n'ont pas démontré de bénéfice CV
  - ✓ Parmi les acides gras $\omega 3$, l'EPA à forte dose semble cardio-protecteur (patients en prévention 2aire ou diabétiques sous statine avec élévation des TGL ou HDL-c bas)
  - ✓ Les anti-ApoC3 diminuent les TGL et les remnants et sont en cours d'évaluation CV
  - ✓ Les anti-Lpa sont en cours d'évaluation chez les patients en prévention 2aire