Actualités thérapeutiques dans les dyslipidémies en 2026

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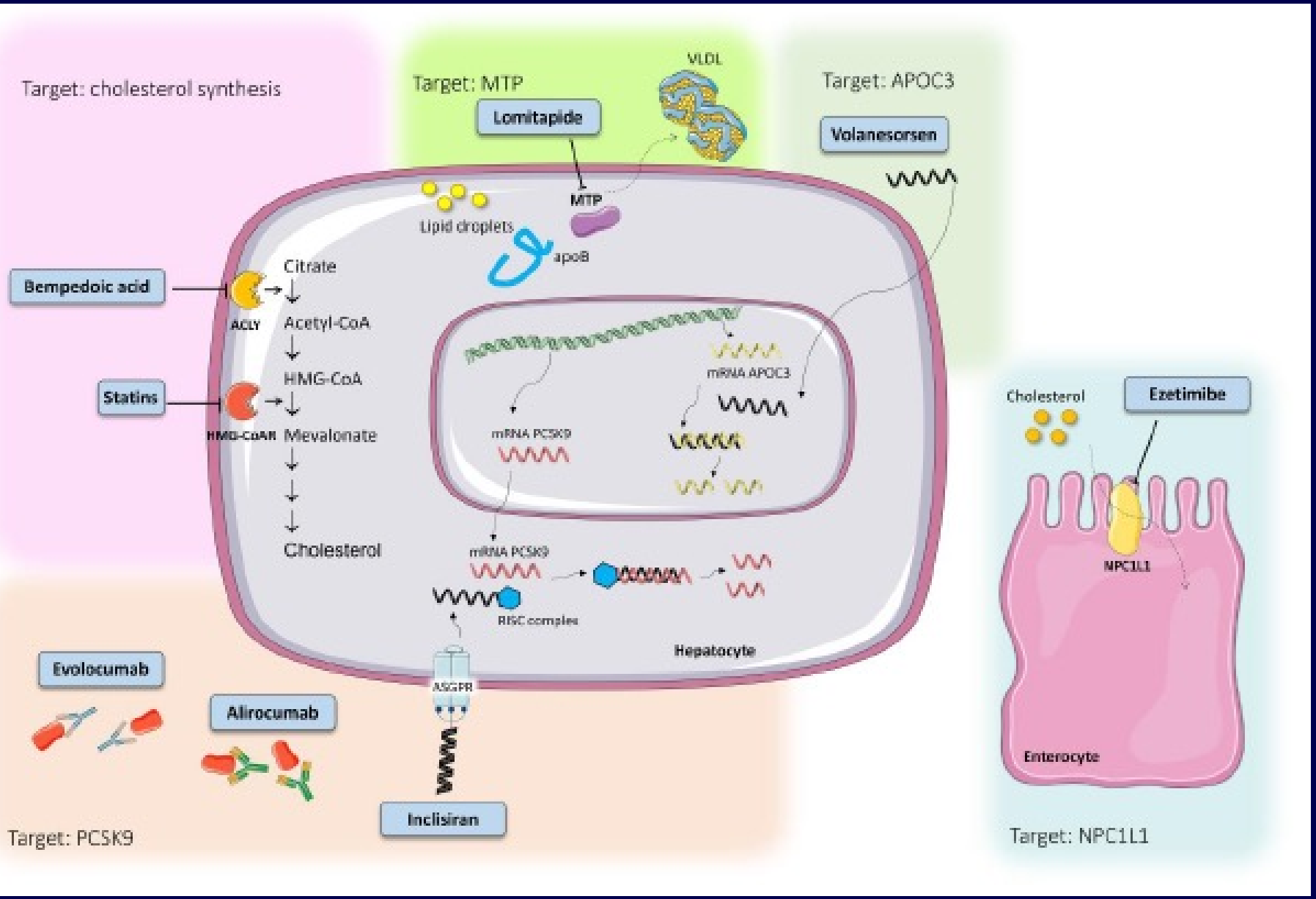
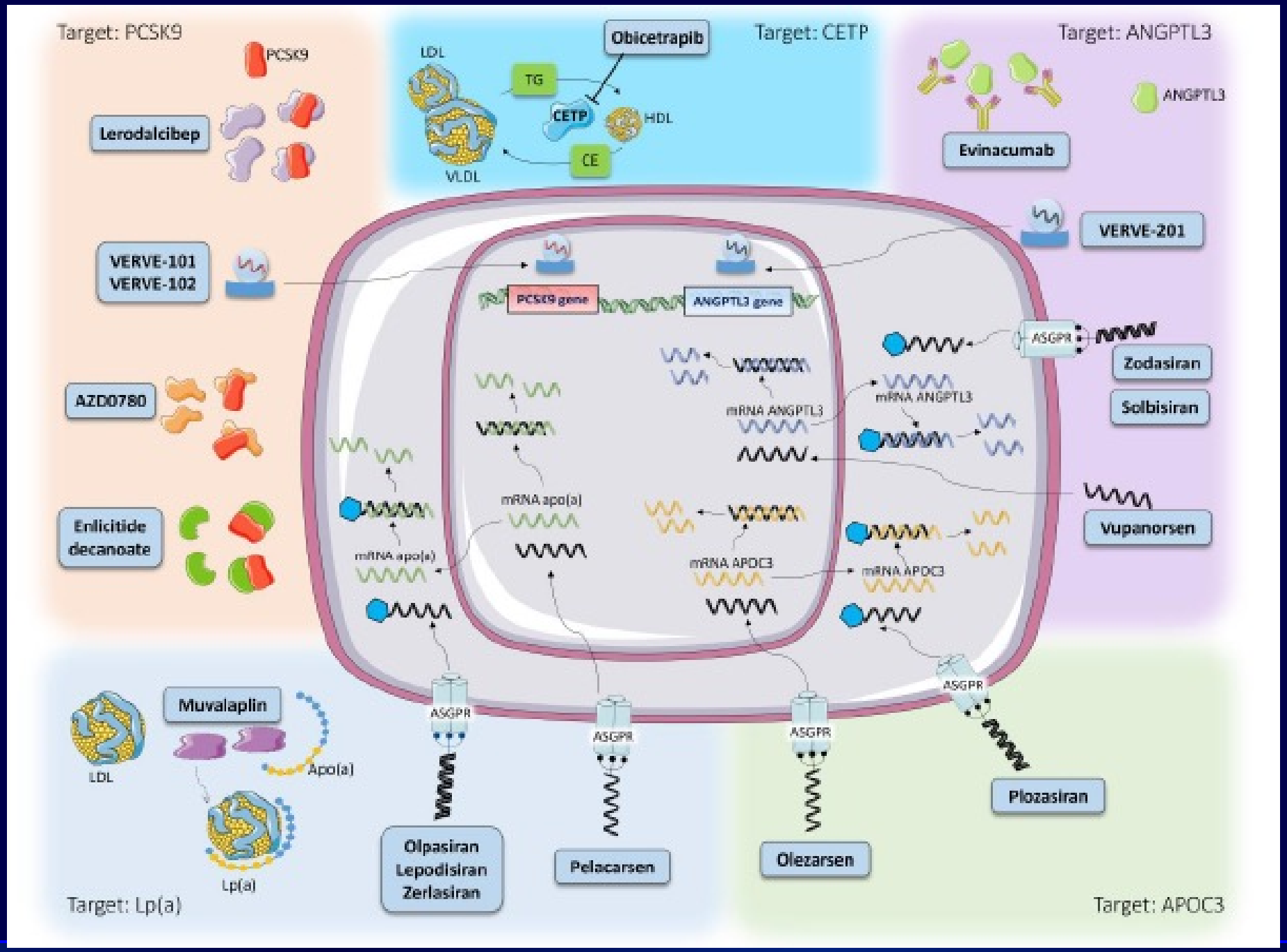
Dr Farnier reports having received consulting fees and/or honoraria and delivering lectures for:

Abbott, Daiichi-Sankyo, Menarini,
Novartis, Organon, Sobi, Servier, and Ultragenyx.



Cellular and molecular targets of current lipid-lowering therapies

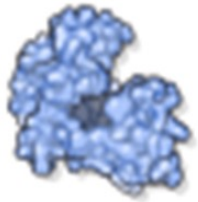
Ballantyne et al.
Eur Heart J 2025



Cellular and molecular targets of novel lipid-lowering therapies

Ballantyne et al.
Eur Heart J 2025

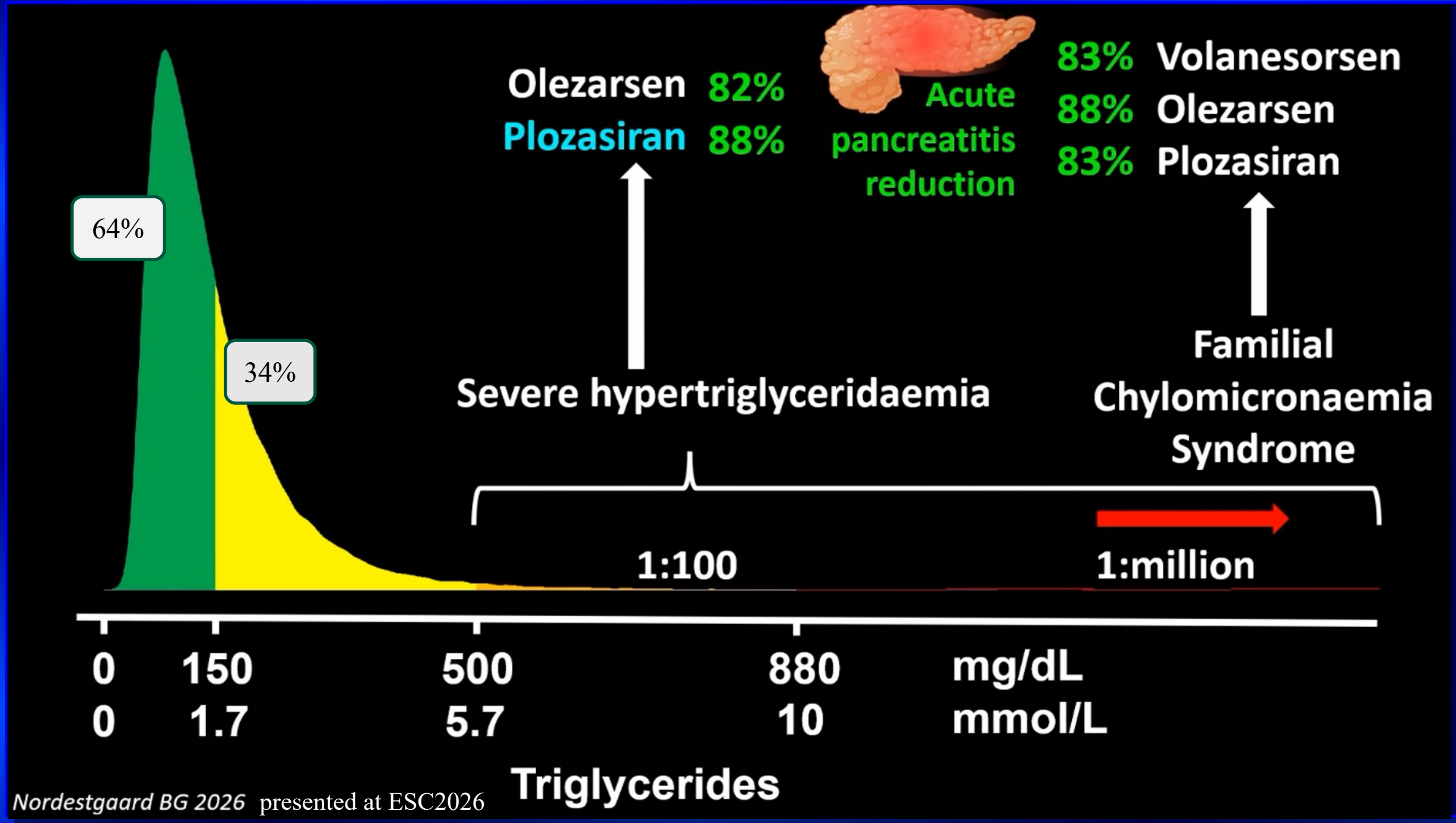
Diverses classes of new lipid-lowering drugs

Small molecules	Antibodies	ASO	siRNA	Proteins and peptides	CRISPR-Cas9 Gene editing
					
Bempedoic Acid Laroprovstat Obicetrapib Muvalaplin (Lomitapide)	Evolocumab Alirocumab … Evinacumab	Volanesorsen Olezarsen (Vupanorsen) Pelacarsen (Mipomersen)	Inclisiran Olpasiran Lepodisiran Zerlasiran Plozasiran Zodasiran Solbisiran	Lerodalcibep Enlicitide Pegozafermin CSL-112	VERVE-102 VERVE-201 (CTX310)

Objectifs Thérapeutiques « globaux »

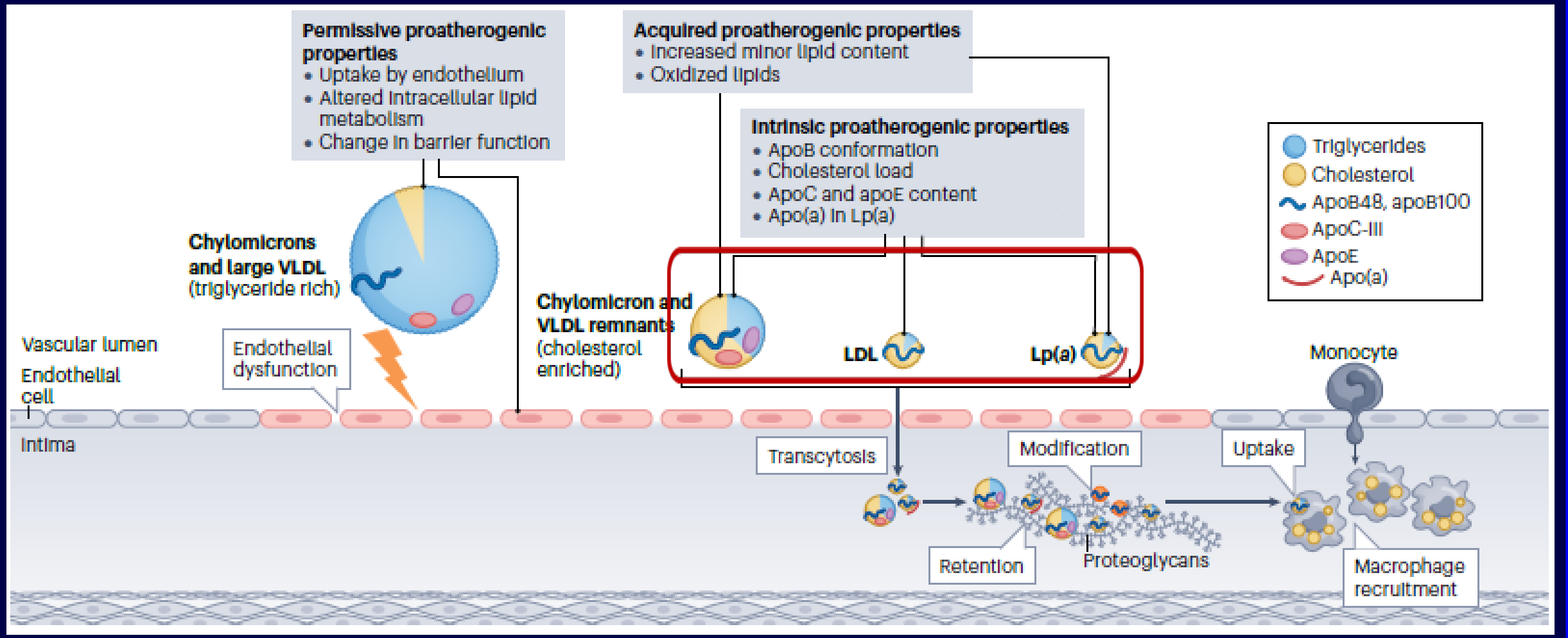
- Prévention des maladies cardiovasculaires liées à l'athérosclérose (ASCVD)
  « hypercholestérolémies » pures ou mixtes

- Prévention des pancréatites
  hypertriglycéridémies sévères

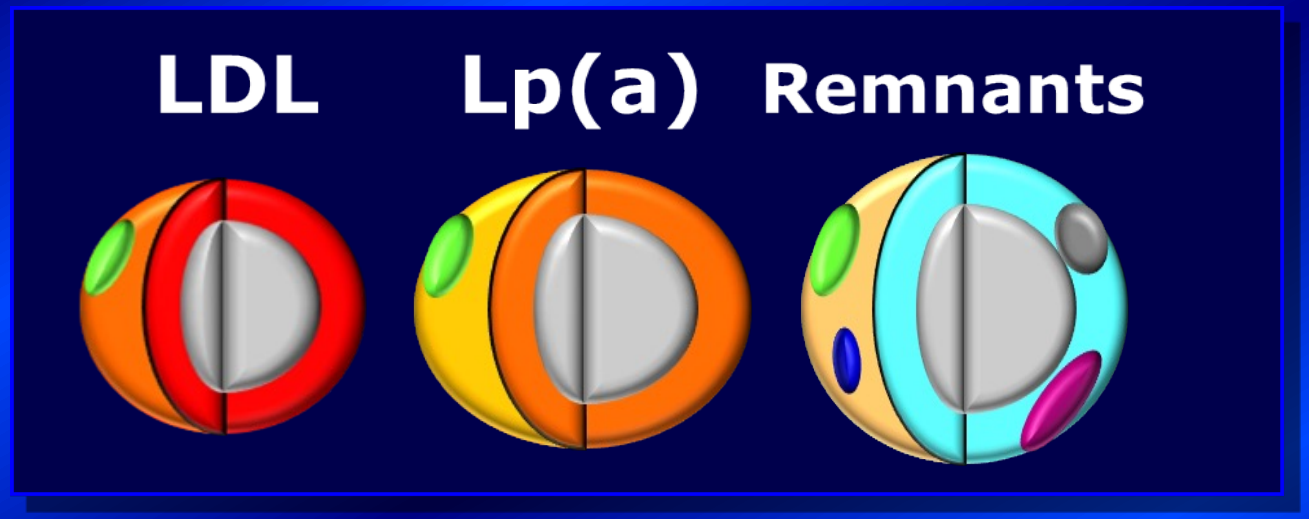


Nordestgaard BG 2026 presented at ESC2026

Concepts in atherogenicity of apoB-containing Lp



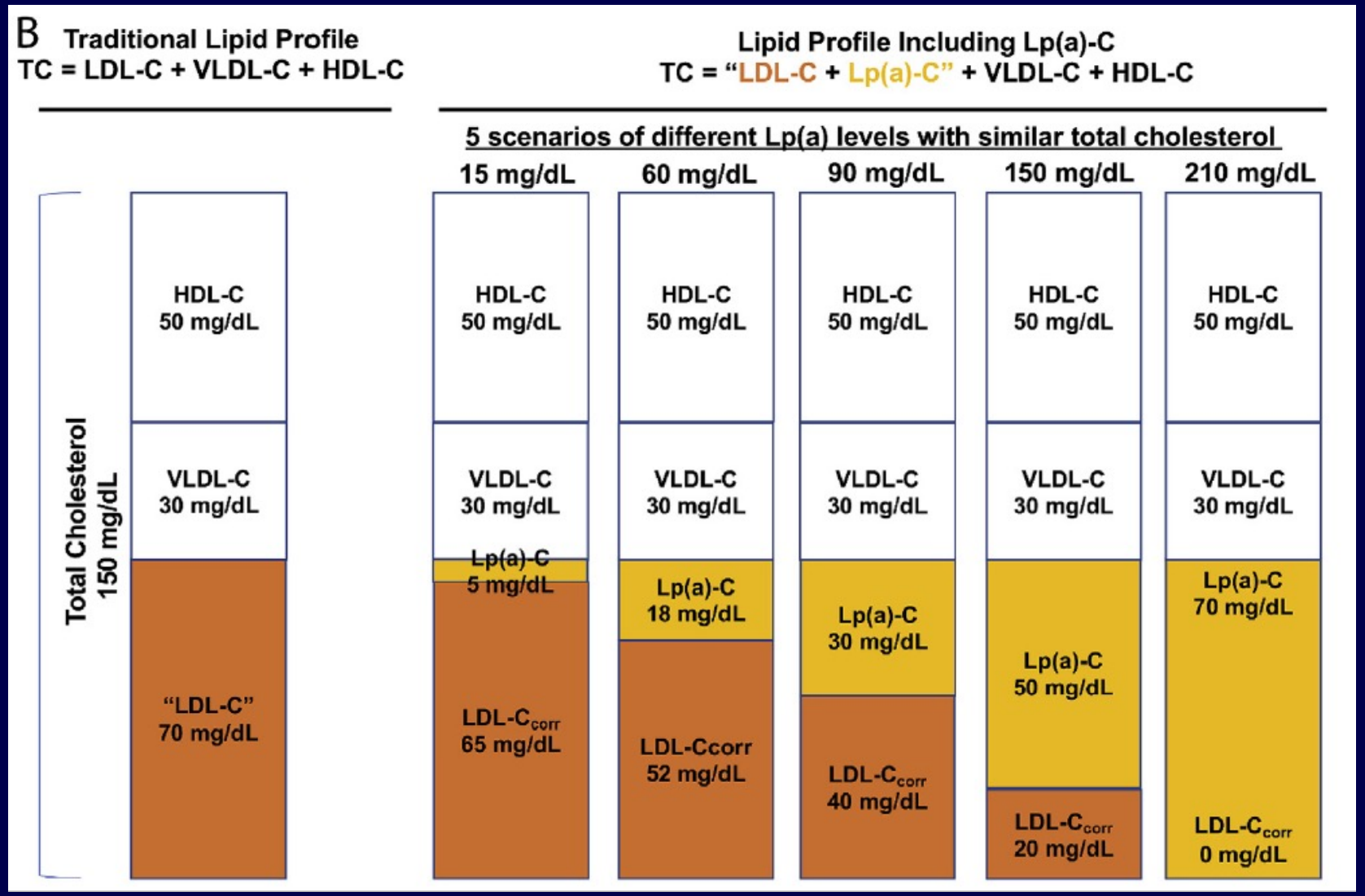
Borén, Packard & Binder. Nat Rev Cardiol 2025 Jan 2



1 particule de remnant ou 1 particule de Lp(a) est 4 à 6 fois plus athérogène qu'1 particule LDL

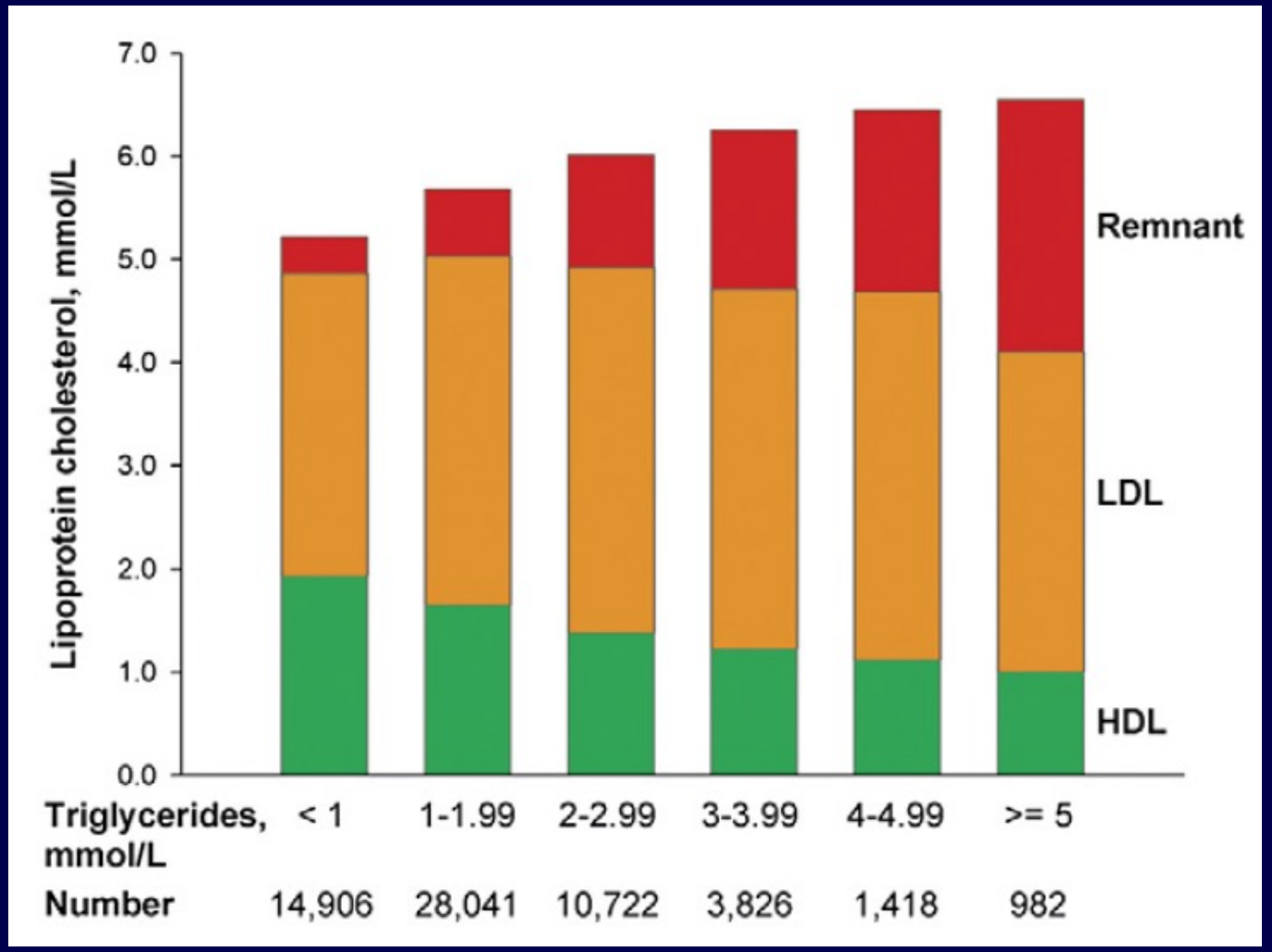
En prévention cardiovasculaire, pourquoi la réduction des LDL reste la priorité ?

Theoretical contribution of Lp(a) to laboratory measured "LDL-C"



Tsimikas et al. Atherosclerosis 2020; 300: 1-9

Association of lipoprotein cholesterol and triglycerides



Non-HDL-cholesterol

Varbo et al. J Am Coll Cardiol 2013; 61: 427–36

Prise en charge des dyslipidémies

- Agir prioritairement sur les LDL: actualités
- Agir spécifiquement sur la Lp(a) ?
- Abaisser les lipoprotéines riches en TG ?
- Une surprise possible ?
- Quel challenge majeur pour le futur ?

ESC European Society of Cardiology
European Heart Journal (2021) 42, 3227–3337
doi:10.1093/eurheartj/ehab484

ESC GUIDELINES

2021 ESC Guidelines on cardiovascular disease prevention in clinical practice

Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies

ESC European Society of Cardiology
European Heart Journal (2025) 00, 1–20
https://doi.org/10.1093/eurheartj/ehaf190

ESC GUIDELINES

2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias

Developed by the task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS)

Patients à haut/très haut risque cardiovasculaire

Objectifs thérapeutiques :

- ⇩ LDL-C > 50%
- très haut risque < 0.55, haut risque < 0.70 g/l

SCORE2 recommandé chez les personnes en bonne santé apparente pour évaluer le risque cardiovasculaire

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intensive LDL Cholesterol Targeting in Atherosclerotic Cardiovascular Disease

Yong-Joon Lee, M.D.,[1] Seung-Jun Lee, M.D.,[1] Jin Won Kim, M.D.,[2] Sang-Hyup Lee, M.D.,[1] Gwang-Sil Kim, M.D.,[3] Jae Hyoung Park, M.D.,[4] Jin-Man Cho, M.D.,[5] Woong Chol Kang, M.D.,[6] Hyuck-Jun Yoon, M.D.,[7] Won Ho Kim, M.D.,[8] Seung-Jin Lee, M.D.,[9] Jin Bae Lee, M.D.,[10] Ji-Yong Jang, M.D.,[11] Sanghoon Shin, M.D.,[12] Ik Hyun Park, M.D.,[13] Sung Uk Kwon, M.D.,[14] Sunwon Kim, M.D.,[15] Sung-Jin Hong, M.D.,[1] Chul-Min Ahn, M.D.,[1] Jung-Sun Kim, M.D.,[1] Young-Guk Ko, M.D.,[1] Donghoon Choi, M.D.,[1] Myeong-Ki Hong, M.D.,[1] Yangsoo Jang, M.D.,[1] and Byeong-Keuk Kim, M.D.,[1] for the Ez-PAVE Investigators*

Open-label superiority trial conducted in South Korea

3048 patients with ASCVD randomly assigned to the intensive-targeting group (LDL-C<55 mg/dL) or the conventional-targeting group (LDL-C<70 mg/dL)

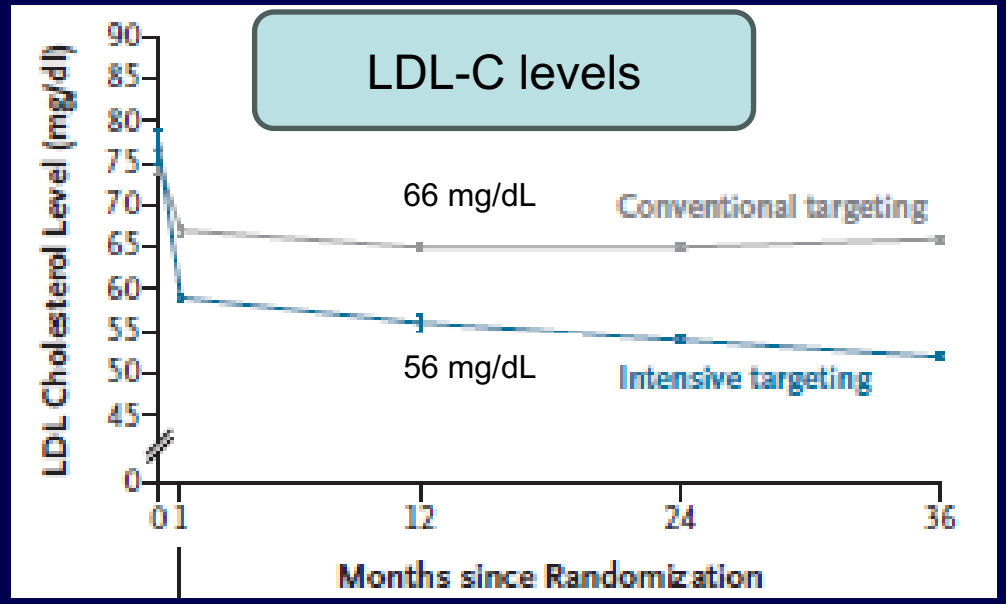
Primary end-point: death from CV causes, nonfatal MI, nonfatal stroke, any revascularization, or hospitalization for unstable angina

Lee et al. New Engl J Med 2026; 394: 1365-75

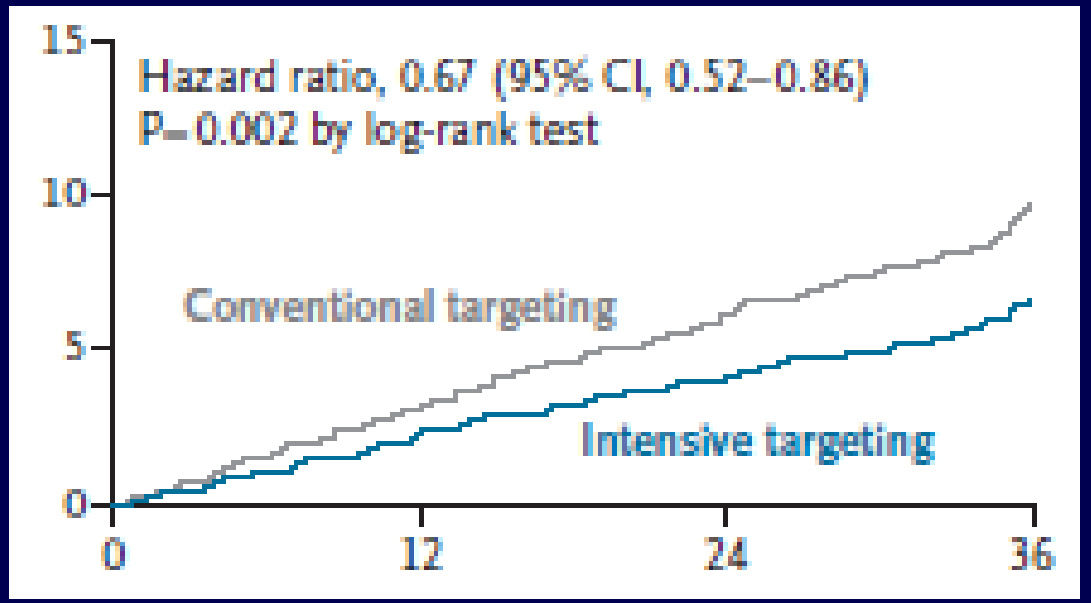
Ez-PAVE trial: Primary End-Point

At baseline : LDL-C 76 mg/dL
Statin 91%, Ezetimibe 29%

LDL-C levels



Primary End-Point Events



Lee et al. New Engl J Med 2026; 394: 1365-1375

SANTORINI observational study

621 French patients at high/very high risk

Characteristic	France (n = 621)	RoE (n = 6,589)
Male, n (%)	453 (73.0)	4,744 (72.0)
Age, years, mean (SD)	65.0 (10.8)	65.0 (10.9)
Hypertension, n (%)	356 (57.3)	4,734 (71.9)
Diabetes, n (%)	157 (25.3)	2,358 (35.8)
BMI, kg/m^2, mean (SD)	27.6 (4.7)	28.3 (4.8)
LDL-C, mmol/L, mean (SD)	2.6 (1.3)	2.4 (1.2)
Familial hypercholesterolemia, n (%)	53 (8.5)	747 (11.3)
ASCVD, n (%)	508 (81.8)	5,013 (76.1)

1.0 g/l

At 1-year LDL-C 0.85 g/l

n, %	France (n = 621)	
	Baseline	1-year follow-up
No LLT documented	146 (23.5)	21 (3.4)
Total monotherapy	318 (51.2)	363 (58.5)
Statin alone[b]	288 (46.4)	330 (53.1)
Low intensity	22 (3.5)	23 (3.7)
Moderate intensity	154 (24.8)	147 (23.7)
High intensity	104 (16.8)	155 (25.0)
Ezetimibe alone	10 (1.6)	14 (2.3)
PCSK9i alone	9 (1.5)	10 (1.6)
Any other oral LLT alone	11 (1.8)	9 (1.5)
Total combination therapy	157 (25.3)	237 (38.2)
Combination statin + ezetimibe[b]	136 (21.9)	196 (31.6)
Low-intensity statin	4 (0.6)	4 (0.6)
Moderate-intensity statin	56 (9.0)	65 (10.5)
High-intensity statin	69 (11.1)	119 (19.2)
PCSK9i combination	10 (1.6)	30 (4.8)
Any other oral combination LLT	11 (1.8)	11 (1.8)

Ferrières et al. Frontiers Cardiovasc Med 2026; 13: 1748457

Stratégie Thérapeutique en Prévention Secondaire

Après un syndrome coronaire aigü

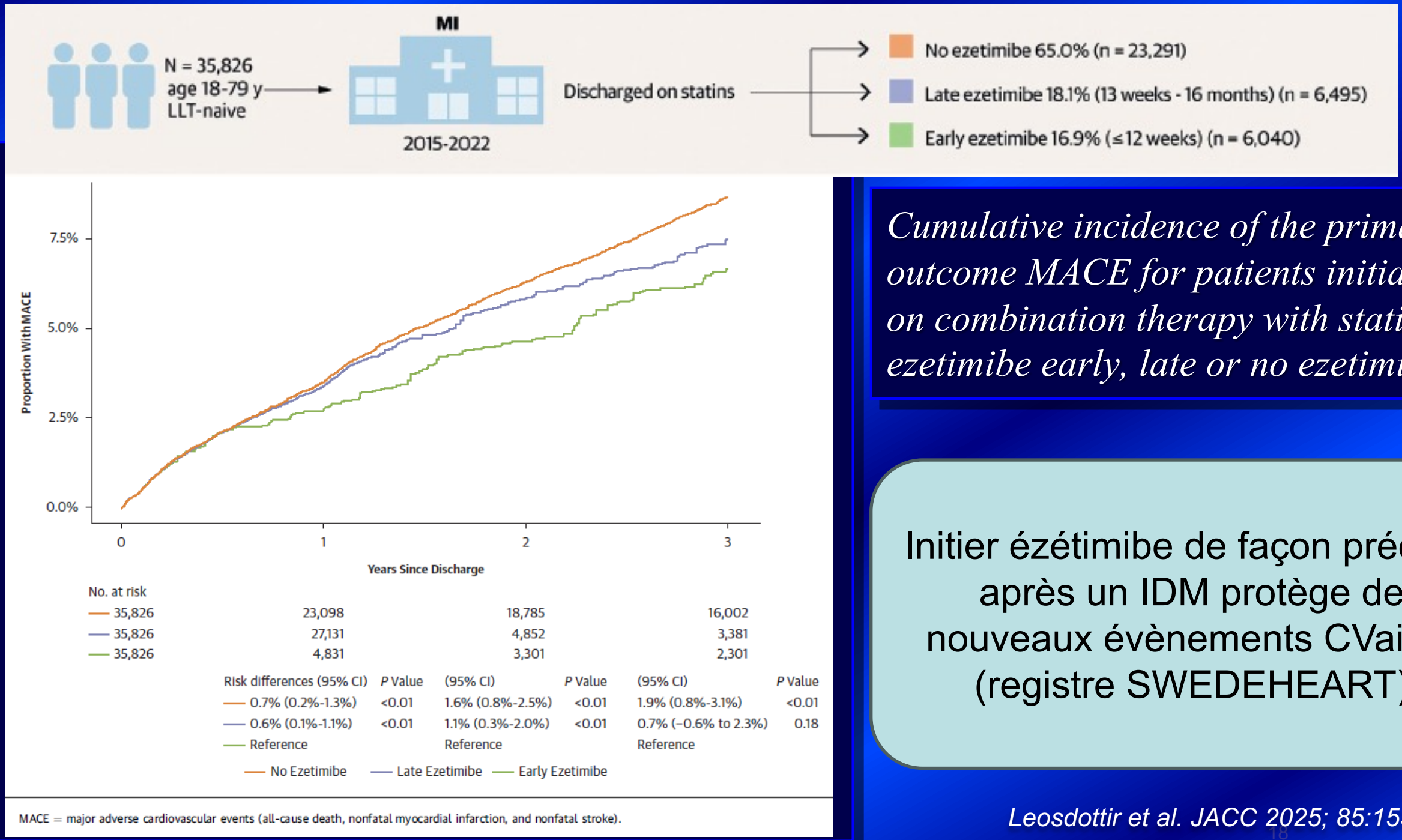
Recommendations	Class[a]	Level[b]
Intensification of lipid-lowering therapy during the index ACS hospitalization is recommended for patients who were on any lipid-lowering therapy before admission in order to further lower LDL-C levels.	I	C
Initiating combination therapy with high-intensity statin plus ezetimibe during index hospitalization for ACS should be considered in patients who were treatment-naïve and are not expected to achieve the LDL-C goal with statin therapy alone.[66]	IIa	B

Sauf si LDL-C spontanément bas (< 1 g/L sans traitement)

Statine (dose max. tolérée)* + Ezétimibe

* > 70(80) ans : statine intensité modérée ?

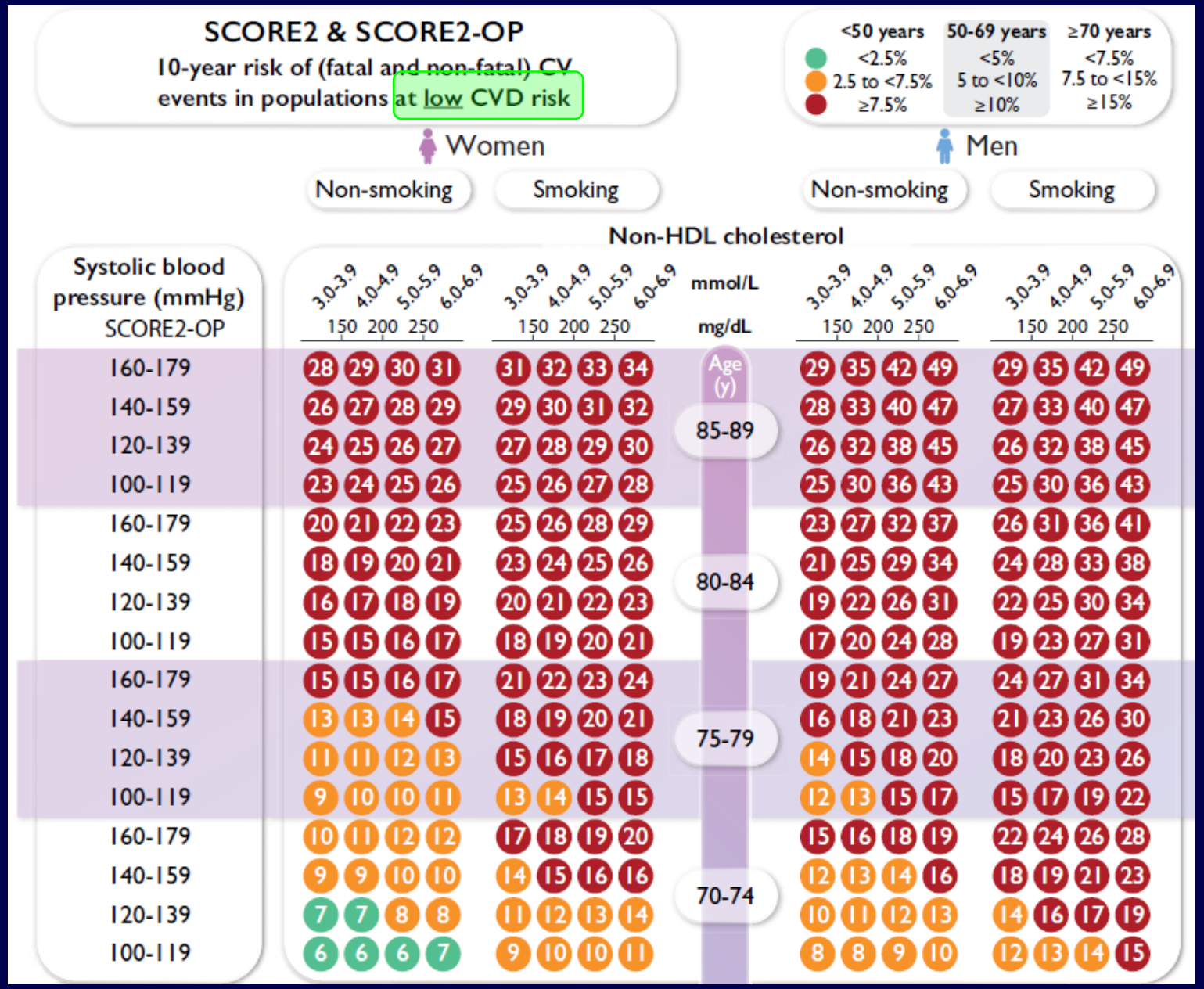
2025 updated ESC/EAS guidelines, Eur Heart J 2025 online



Cumulative incidence of the primary outcome MACE for patients initiated on combination therapy with statin and ezetimibe early, late or no ezetimibe

Initier ézétimibe de façon précoce après un IDM protège de nouveaux évènements CVaires (registre SWEDEHEART)

Leosdottir et al. JACC 2025; 85:1550-64



Grille SCORE2-OP pour les pays à bas risque

Très haut risque chez le sujet âgé de 70 ans ou+

2021 ESC Guidelines. Eur Heart J 2021; 42: 3227-3337

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Atorvastatin, Cardiovascular Events, and Disability-free Survival in Older Adults

S. Zoungas,[1] R. Wolfe,[1,2] C. Moran,[1,3] S.J. Nicholls,[4] G.C. Cloud,[5,6] C.M. Reid,[1,7] A.M. Tonkin,[1] L. Beilin,[8] A.S. Wierzbicki,[9] T.T.-J. Chong,[5,10] J.C. Broder,[1,2] A.J. Curtis,[1] Z. Flanagan,[1,2] I. Hopper,[1,11,12] J. Ryan,[1] S. Spark,[1,2] J.J. McNeil,[1] and M.R. Nelson,[1,13] for the STAREE Investigators

Double-blind, randomized, placebo-controlled trial, conducted in Australia
9971 participants, at least 70 years of age (mean 74.7 y.)
with no history of CVD, diabetes or dementia
randomized to receive atorvastatin 40mg or placebo, median follow-up 5.9 y.

Zoungas et al. New Engl J Med 2026; online August29

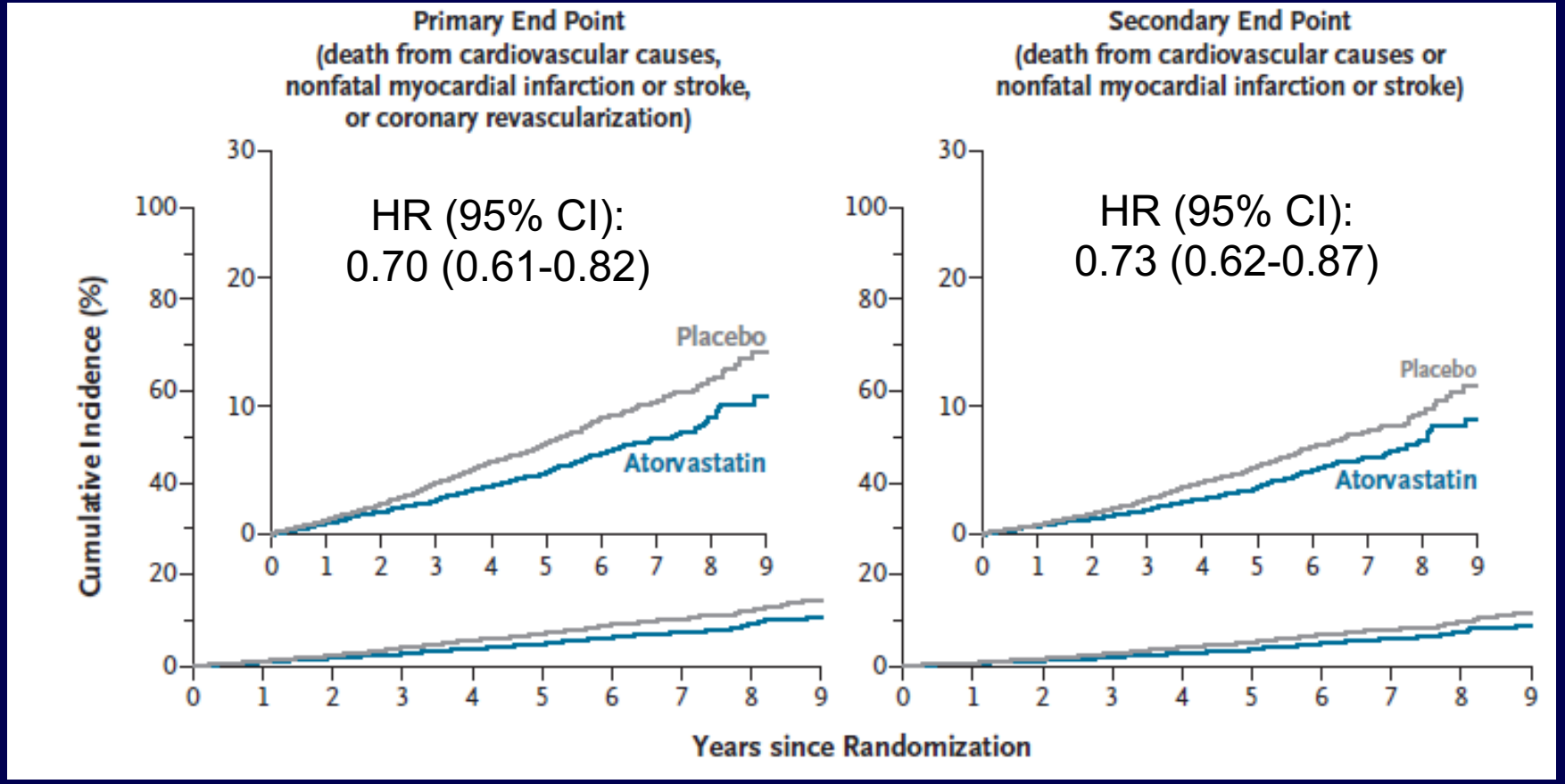
STAREE trial: major cardiovascular events

Population de l'étude:

Fumeurs: 2.5%
LDL-C 1.26 g/l
PAS 135 mmHg
25% > 75 ans

Death from any cause:

HR (95% CI)
0.91 (0.79-1.04)



Zoungas et al. New Engl J Med 2026; online August29

STAREE trial: second primary end-point

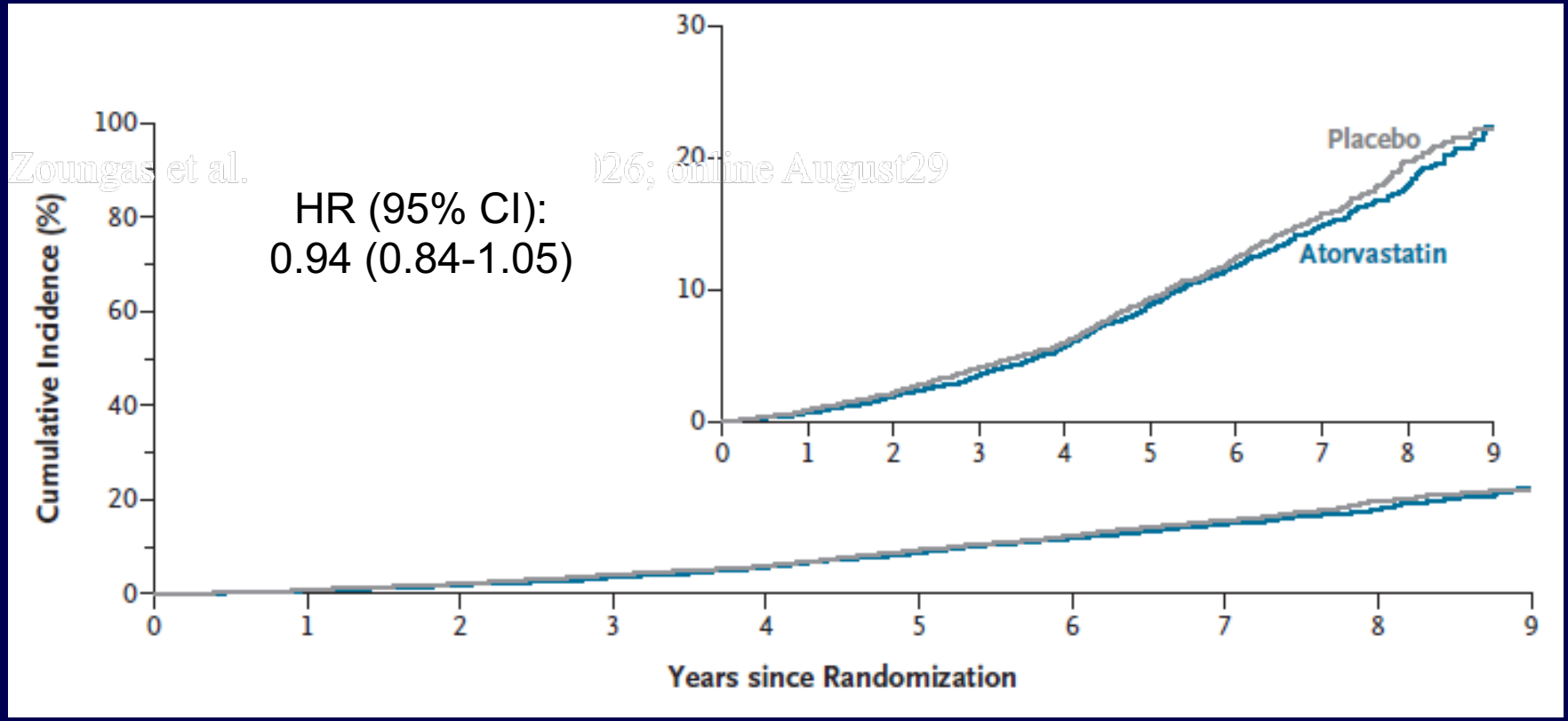
Population de l'étude:

Fumeurs: 2.5%
LDL-C 1.26 g/l
PAS 135 mmHg
25% > 75 ans

Death from any cause:

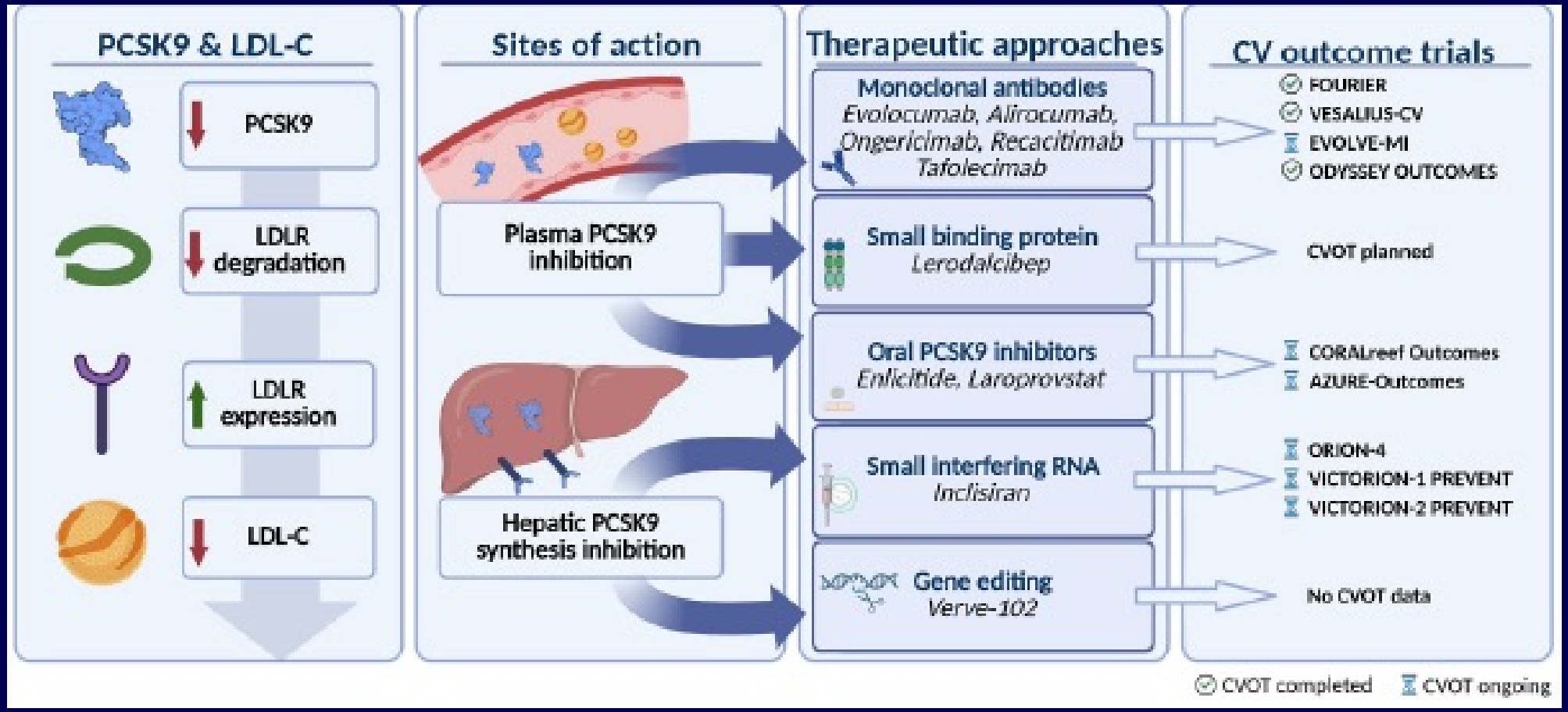
HR (95% CI)
0.91 (0.79-1.04)

Death from any cause, dementia, or persistent physical disability



Zoungas et al. New Engl J Med 2026; online August29

The evolving therapeutic landscape of PCSK9 inhibition

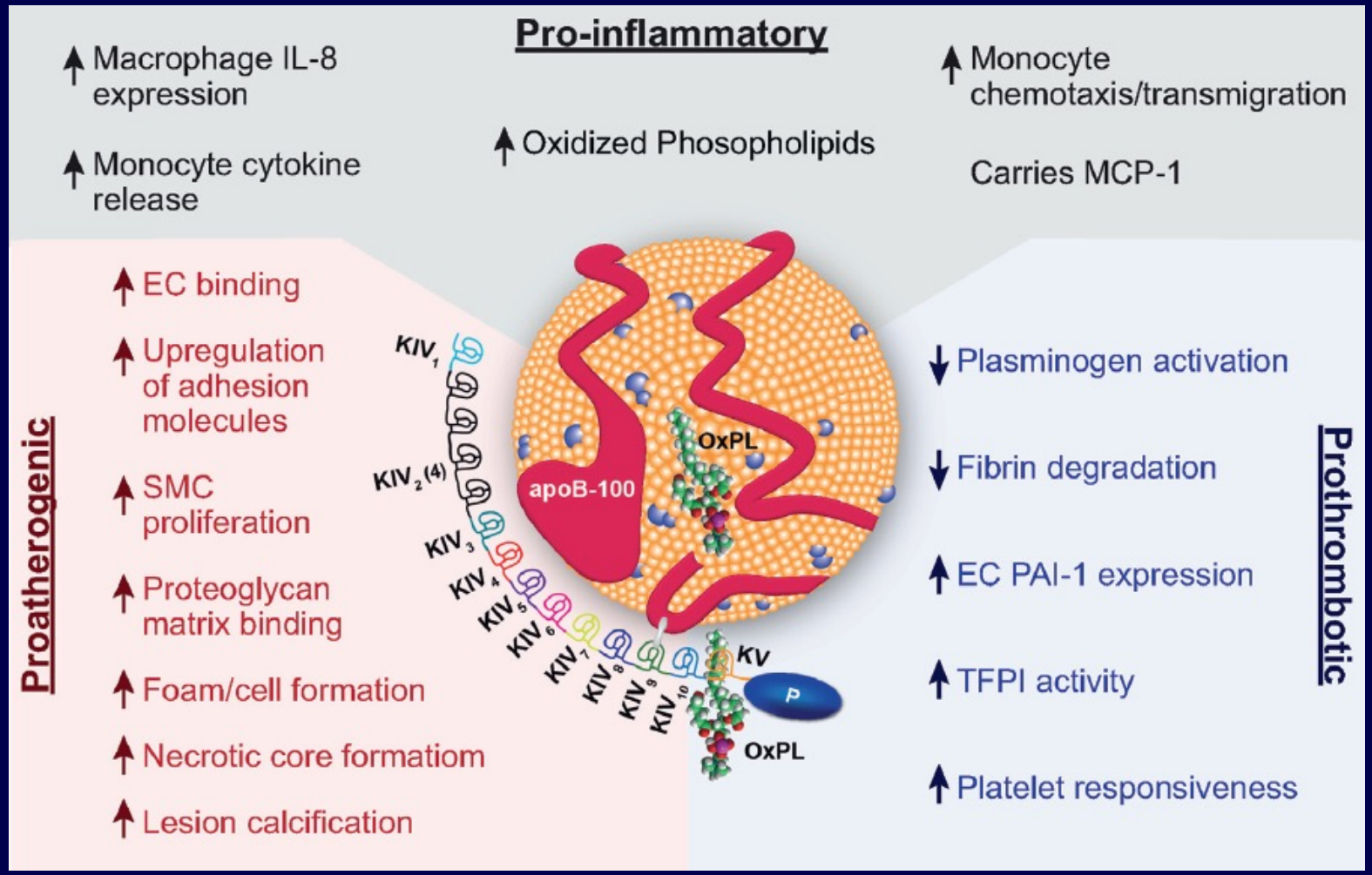


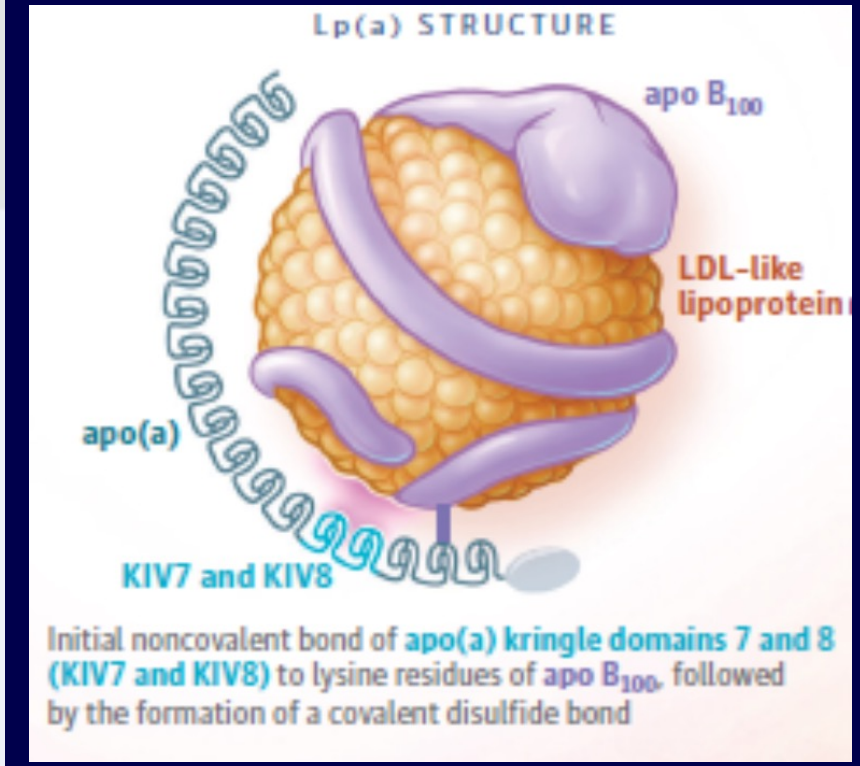
Mansfield et al. Atheroclerosis 2026; 414: 120670

Prise en charge des dyslipidémies

- Agir prioritairement sur les LDL: actualités
- Agir spécifiquement sur la Lp(a) ?
- Abaisser les lipoprotéines riches en TG ?
- Une surprise possible ?
- Quel challenge majeur pour le futur ?

Mécanismes Pathogéniques de la Lp(a)





Tsimikas, JACC 2017; 69: 692-711

Lipoprotein(a)-targeting therapies

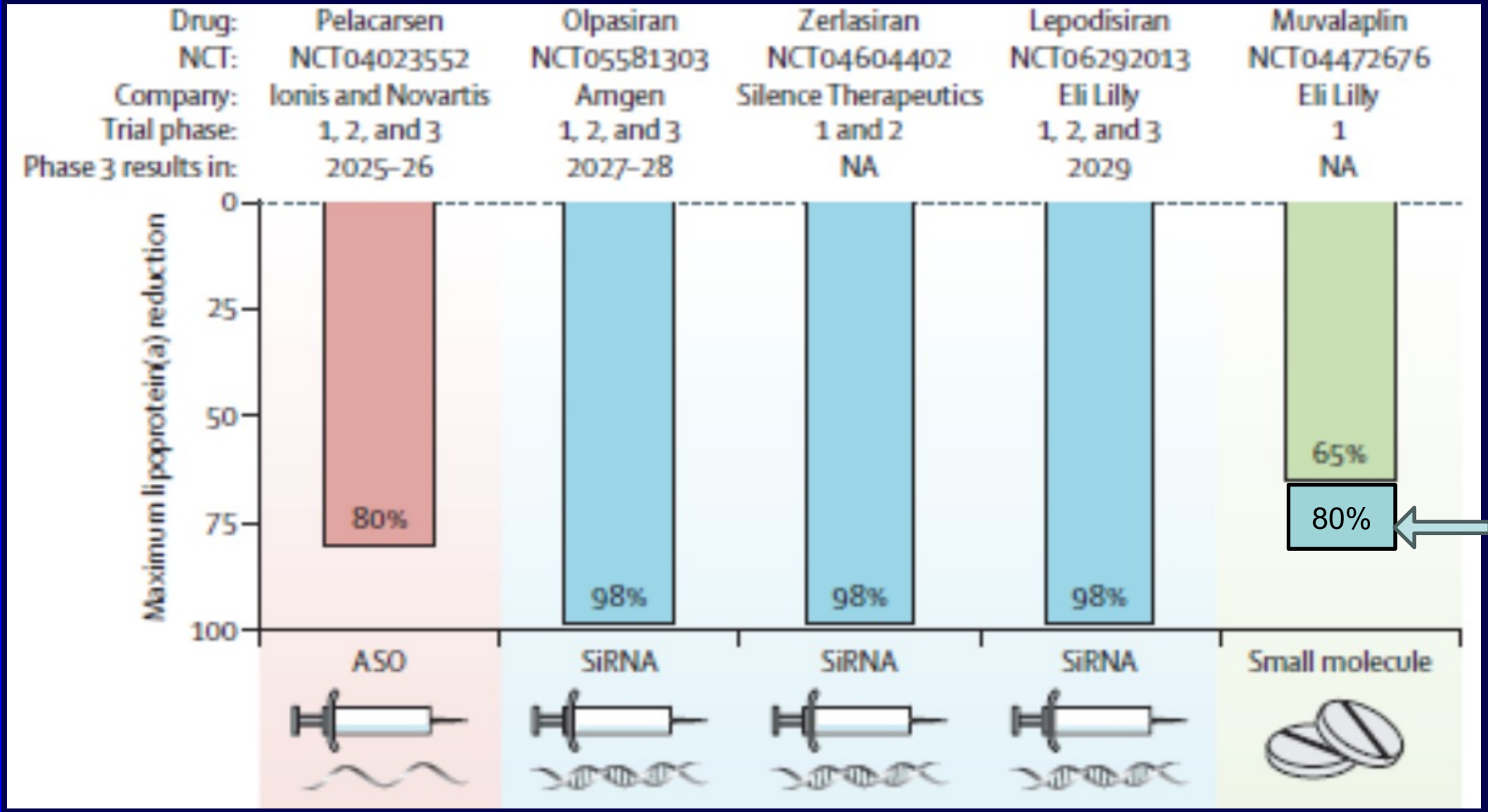
Injectable RNA-based therapies

Agent	Description	Status
Pelacarsen	ASO to apo(a)	3: Lp(a)HORIZON outcomes trial enrolled (~5/2025)
Olpasiran	siRNA to apo(a)	3: OCEAN(a)-Outcomes trial enrolled (~12/2026)
Lepodisiran	siRNA to apo(a)	3: ACCLAIM-Lp(a) outcomes trial recruiting (~3/2029)
Zerlasiran	siRNA to apo(a)	2: ALPACAR-360 published
Muvalaplin	Oral small molecule binding to apo(a)	2: KRAKEN published
VERVE-301	Gene editing to inactivate *LPA* in the liver	Early development

Kylo-11 very long acting siRNA phase 1 (ESC2026, Lancet)

Ballantyne & Norata Eur Heart J 2025 online

Maximum achieved Lp(a) reduction for 5 drugs in development

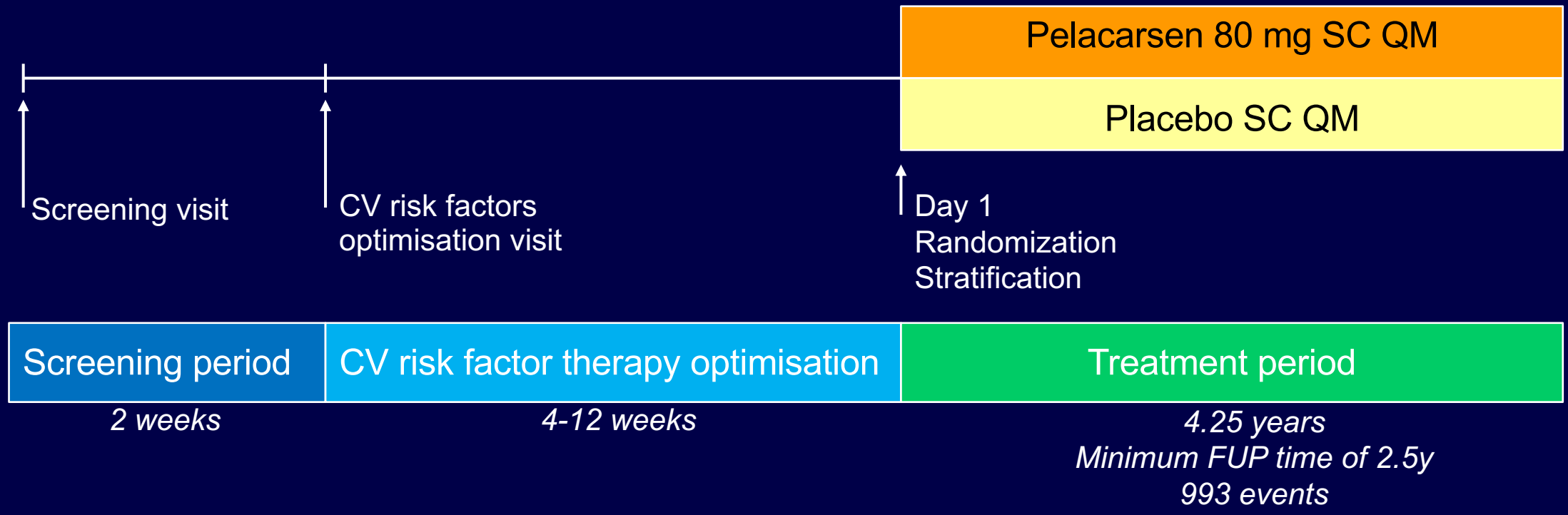


Nicholls et al. JAMA 2025; 333: 222-31

Nordestgaard et al. Lancet 2024; 404: 1255-64

CVOT Targeting Lp(a) – HORIZON Study

Study population: Patients with established CVD (prior MI, stroke, PAD) and Lp(a) ≥ 70 mg/dL with optimal therapy for cholesterol lowering and other CV risk factors



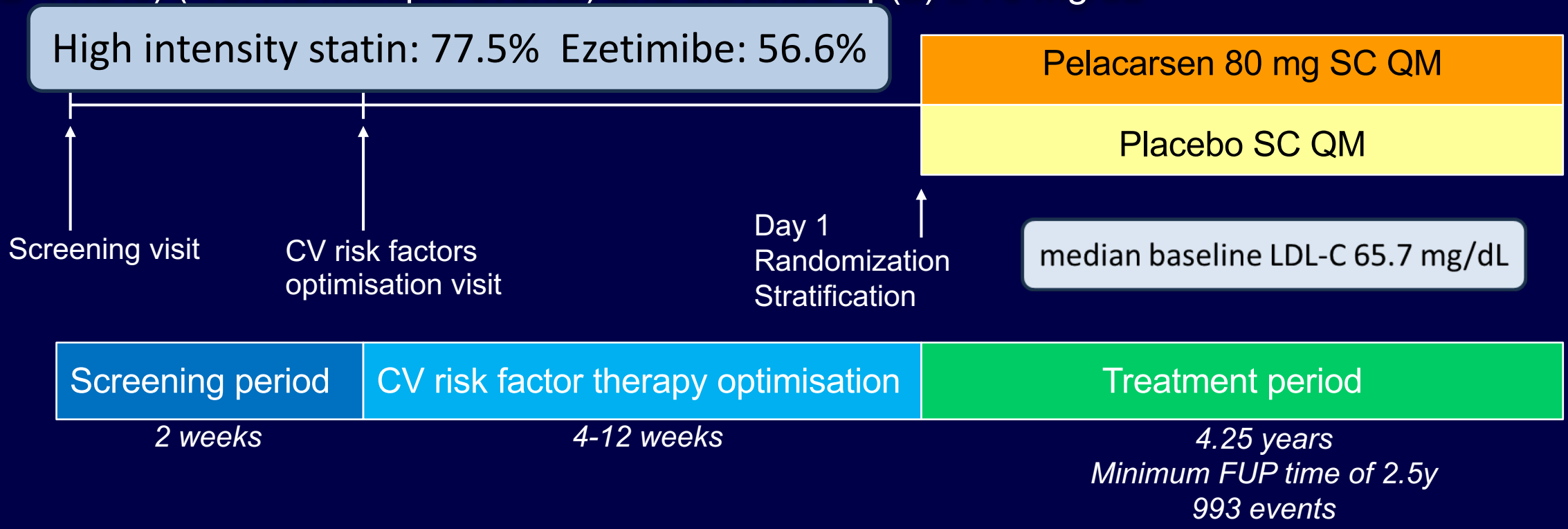
Study is positive if primary EP is met in either overall (patients with Lp(a) ≥ 70 mg/dL) or sub-population (stratum with Lp(a) ≥ 90 mg/dL)

Primary Endpoint: MI, stroke, CV death or urgent coronary revascularization

Cho et al. Am Heart J 2025; 287: 1-9

Lp(a) – HORIZON Study

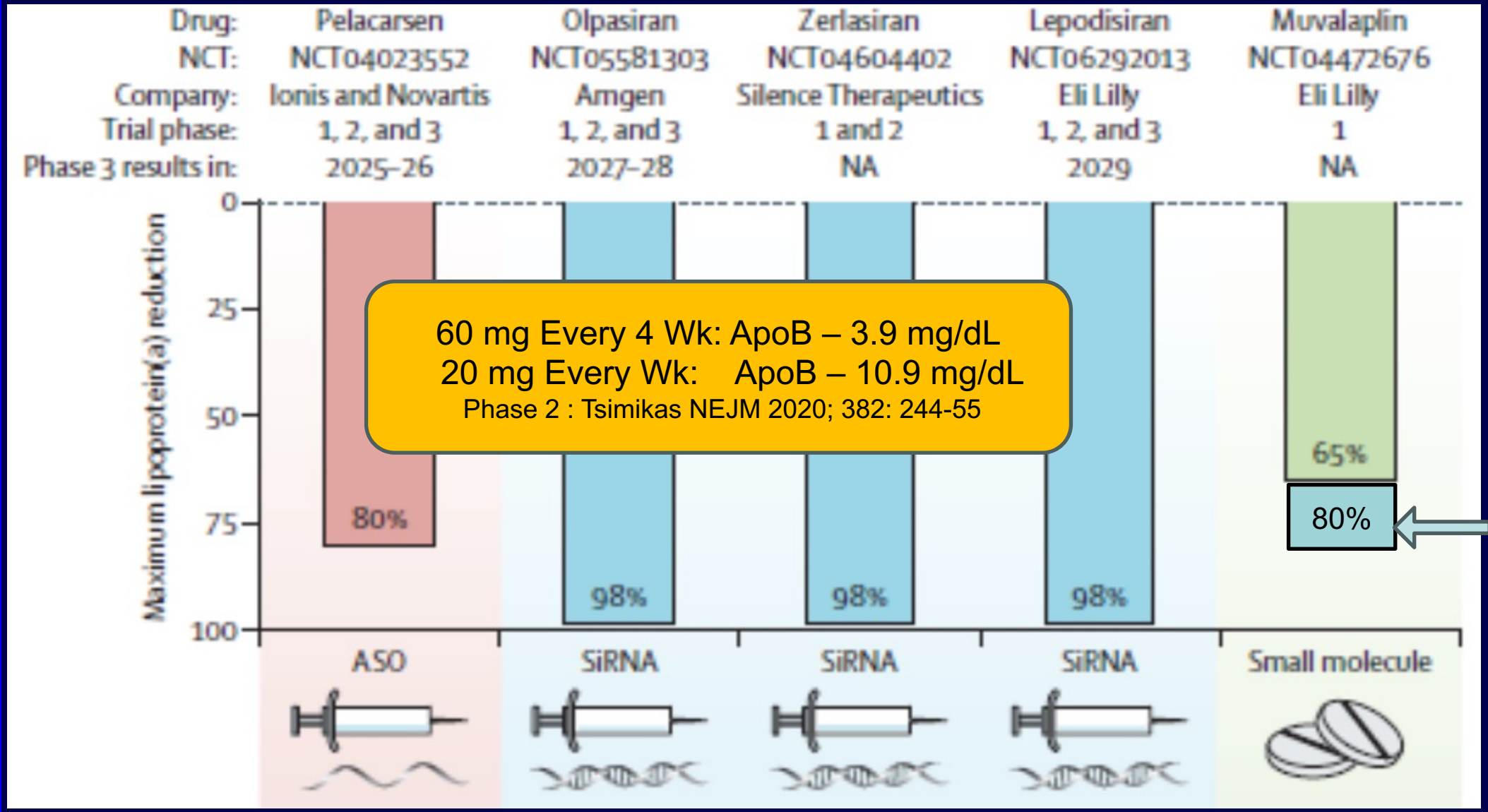
Study population: 8,323 patients with established CVD (prior MI 81.5%, stroke 9.8%, symptomatic PAD 14.8%) (18.1% multiple events) and elevated Lp(a) ≥ 70 mg/dL



Study is positive if primary EP is met in either overall (patients with Lp(a) ≥ 70 mg/dL) or sub-population (stratum with Lp(a) ≥ 90 mg/dL 78.6%)
Primary Endpoint: MI, stroke, CV death or urgent coronary revascularization

Cho et al. Am Heart J 2025; 287: 1-9

Maximum achieved Lp(a) reduction for 5 drugs in development



60 mg Every 4 Wk: ApoB – 3.9 mg/dL
20 mg Every Wk: ApoB – 10.9 mg/dL
Phase 2 : Tsimikas NEJM 2020; 382: 244-55

Nicholls et al. JAMA 2025; 333: 222-31

Nordestgaard et al. Lancet 2024; 404: 1255-64

Prise en charge des dyslipidémies

- Agir prioritairement sur les LDL: actualités
- Agir spécifiquement sur la Lp(a) ?
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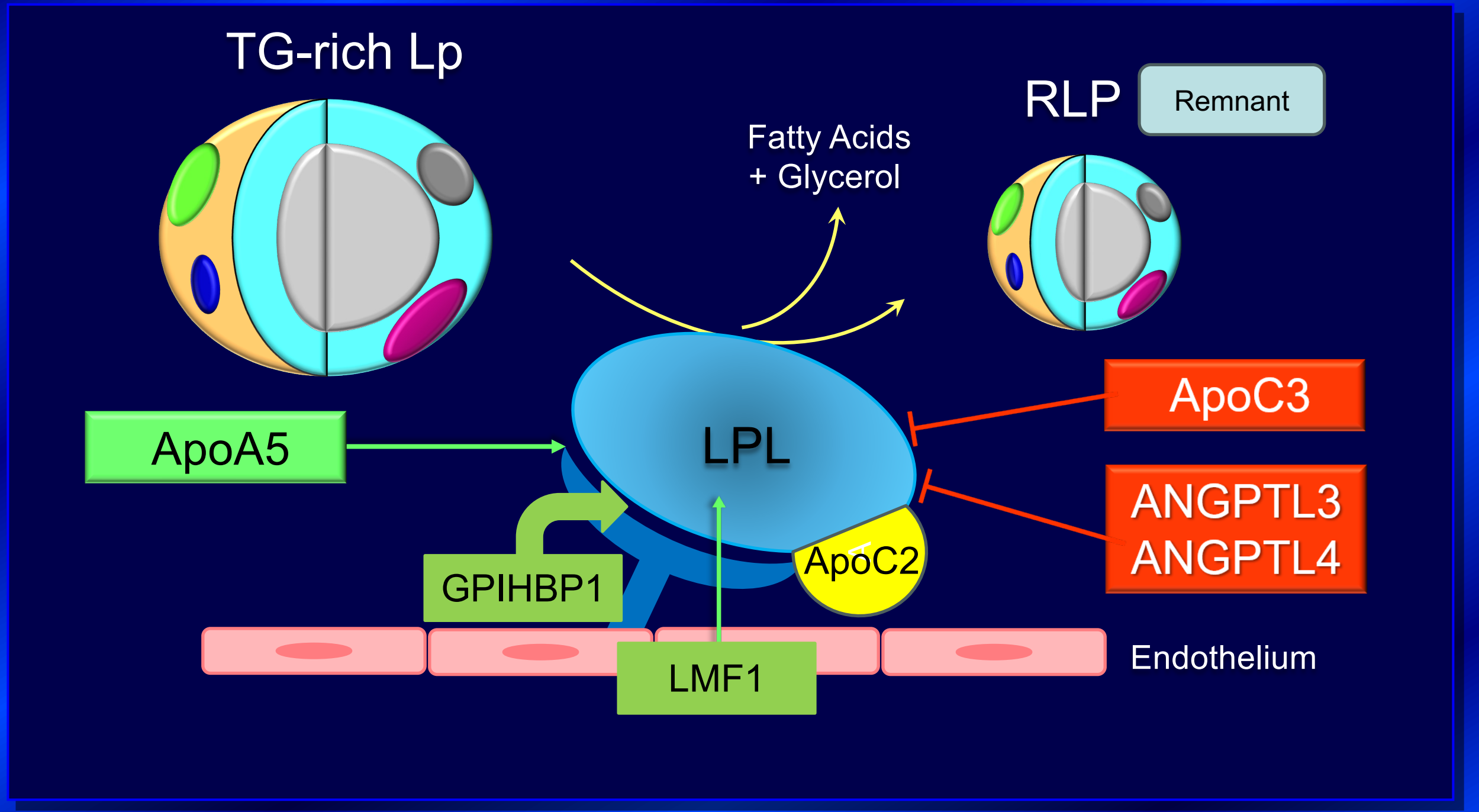
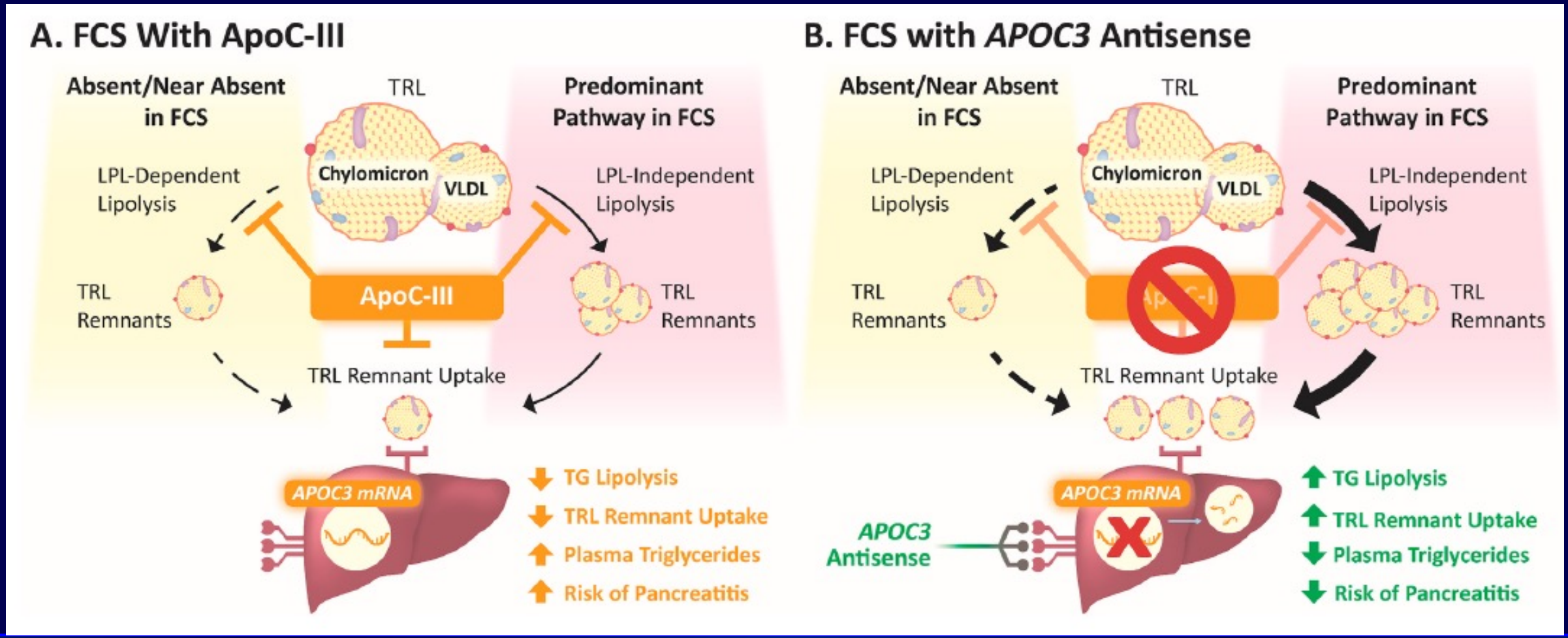

TG-rich Lp
RLP
Remnant
Fatty Acids
+ Glycerol
ApoA5
LPL
ApoC3
ANGPTL3
ANGPTL4
ApoC2
GPIHBP1
LMF1
Endothelium

Reduction in apoC3 decreases TG levels even in patients with FCS by promoting the LPL-independent pathway of TRL hydrolysis and clearance mediated by hepatic receptors



Brinton et al. Atherosclerosis 2025; 403: 119114

TG-rich Lp

RLP

Fatty Acids
+ Glycerol

ApoC3 Null mutations

TRLs ↓ 39%

MI risk ↓ 40%

Crosby et al. NEJM 2014

ANGPTL3 LOF mutations

TG ↓ 17 %, LDL-C ↓ 12 %

MI risk ↓ 34 %

Stitziel et al. JACC 2017, Dewey et al. NEJM 2016

ApoC3

ANGPTL3
ANGPTL4

Endothelium

ApoC3: Direct Atherogenic Effects Beyond Lipid Metabolism

- Lipoprotein retention in the artery wall

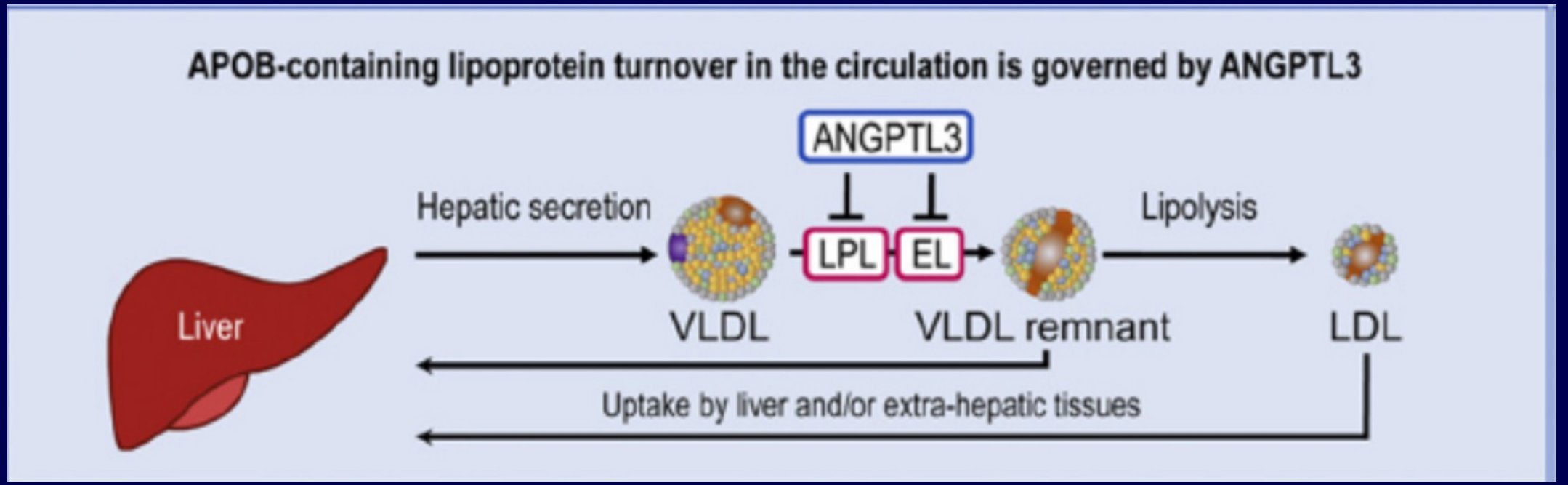
  ApoC3 increases the affinity of atherogenic lipoproteins for proteoglycans, facilitating their retention in the subendothelial space

- Proinflammatory and prothrombotic effects

- …

Björnson et al. Curr Athero Rep 2026, Feb16

ANGPTL3 inhibe les activités de la LPL et de l'EL, régulant ainsi le turnover des ApoB-lipoprotéines

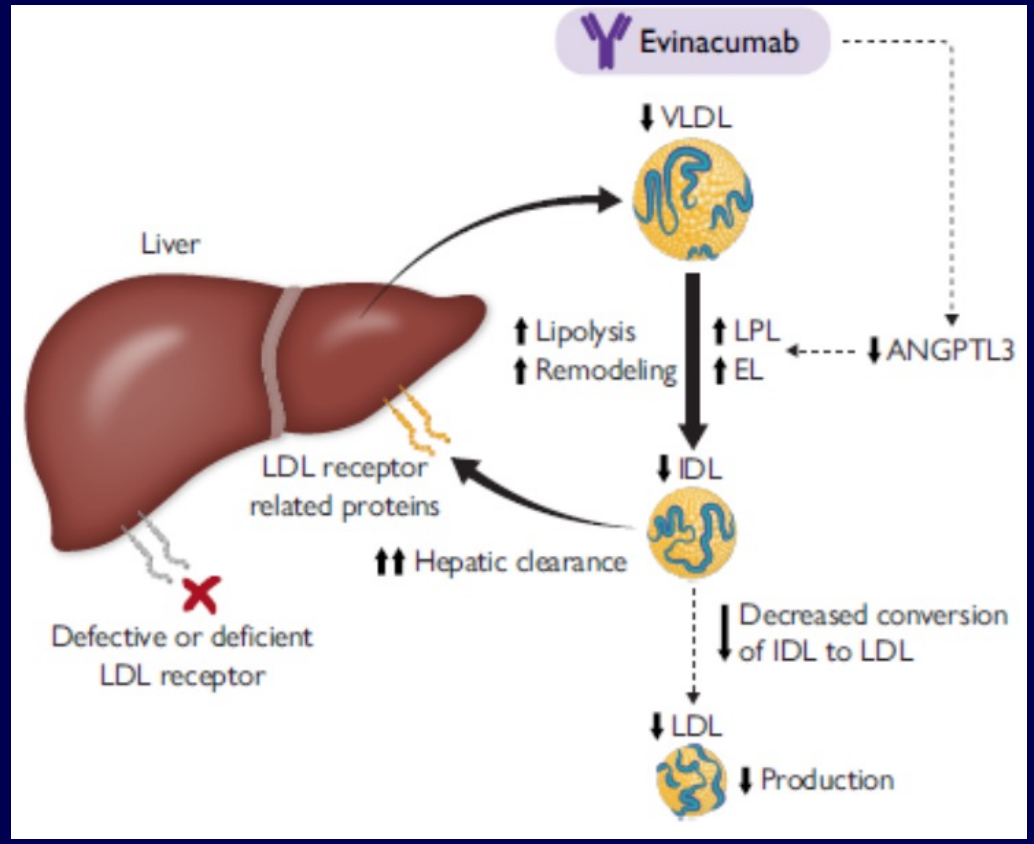


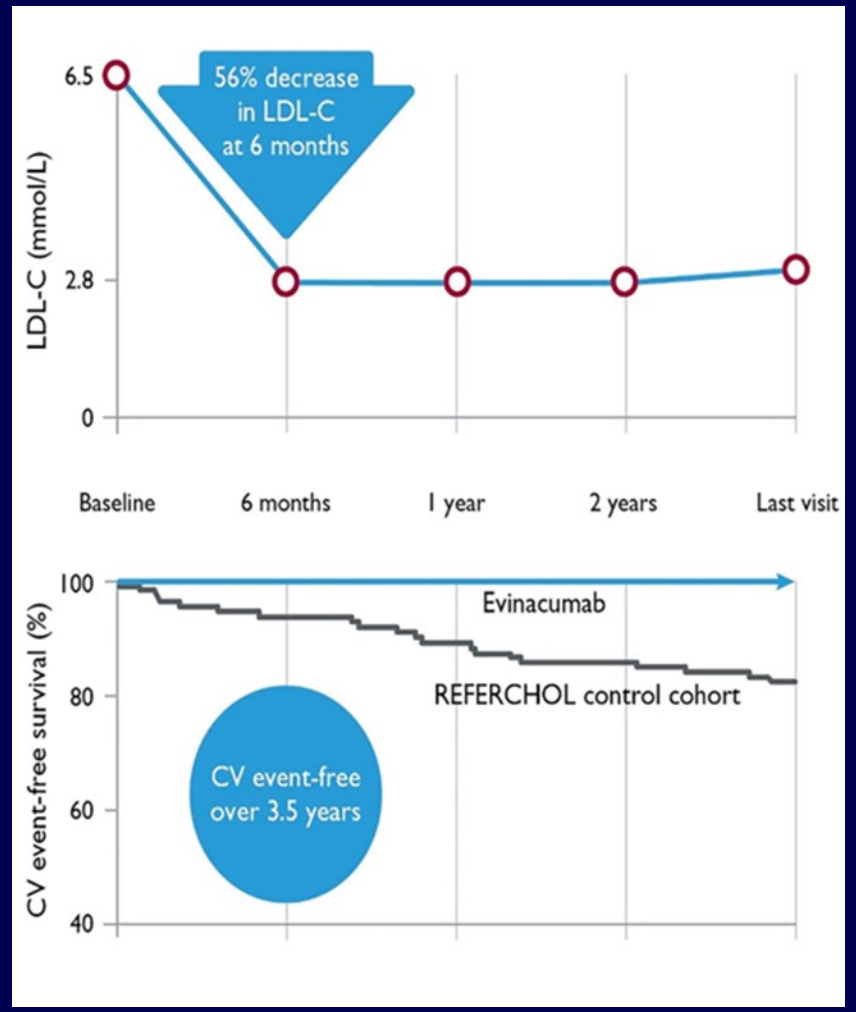
L'inhibition de ANGPTL3 induit une dérépression des 2 lipases, avec un remodelage des VLDL générant des remnants éliminés de la circulation par des récepteurs autres que les LDL-récepteurs

Ainsi l'inhibition de ANGPTL3 limite la formation des particules LDL

Adam et al. J Lipid Res 2020; 61: 1271-86

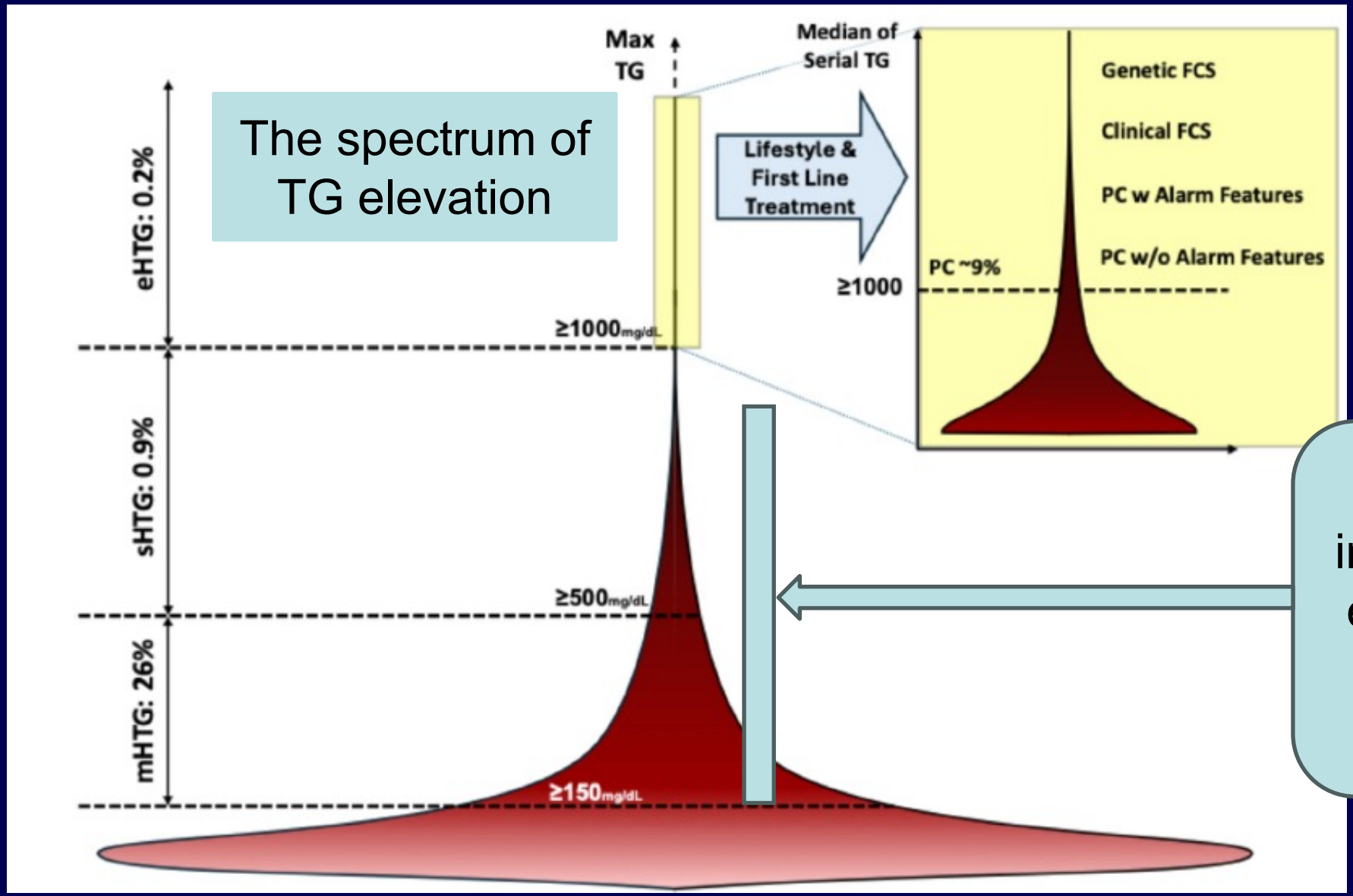
ANGPTL3 as a therapeutic target for HoFH





No patient on evinacumab experienced CV events vs 13 events for 5/21 (24%) in the control cohort (p=0.0267)

Béliard et al. ATVB 2024; 44: 1447-54



Le bénéfice des inhibiteurs d' ApoC3 et de ANGPTL3 en prévention CVaire reste à démontrer

Saadatagah et al. J Clin Lipidol 2025; 19: 723-736

Prise en charge des dyslipidémies

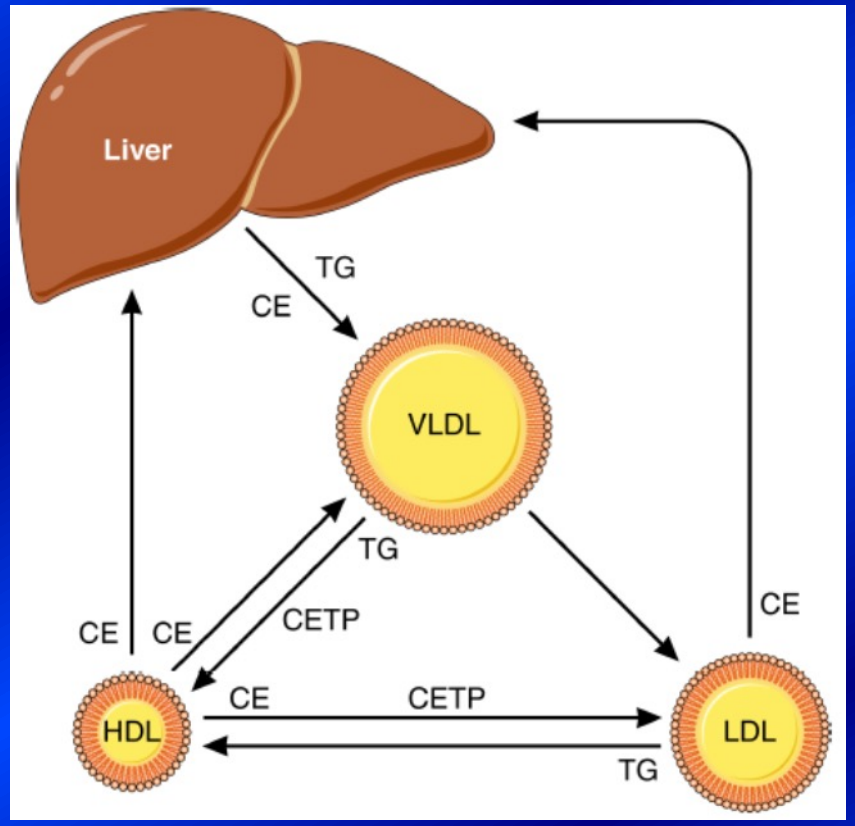
- Agir prioritairement sur les LDL: actualités
- Agir spécifiquement sur la Lp(a) ?
- Abaisser les lipoprotéines riches en TG ?
- Une surprise possible ?
- Quel challenge majeur pour le futur ?

Inhibiteurs de la CETP

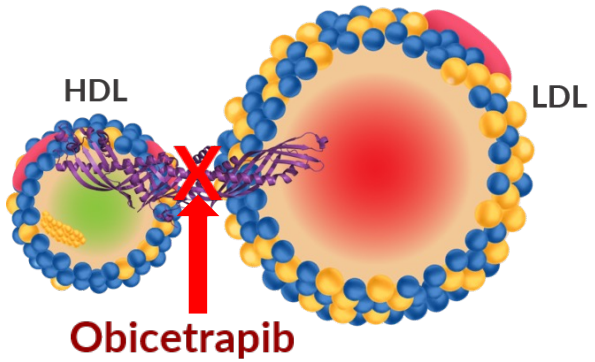
Clinical endpoint trials

- ILLUMINATE → Torcetrapib
- DaI-OUTCOMES → Dalcetrapib
- ACCELERATE → Evacetrapib
- REVEAL → Anacetrapib

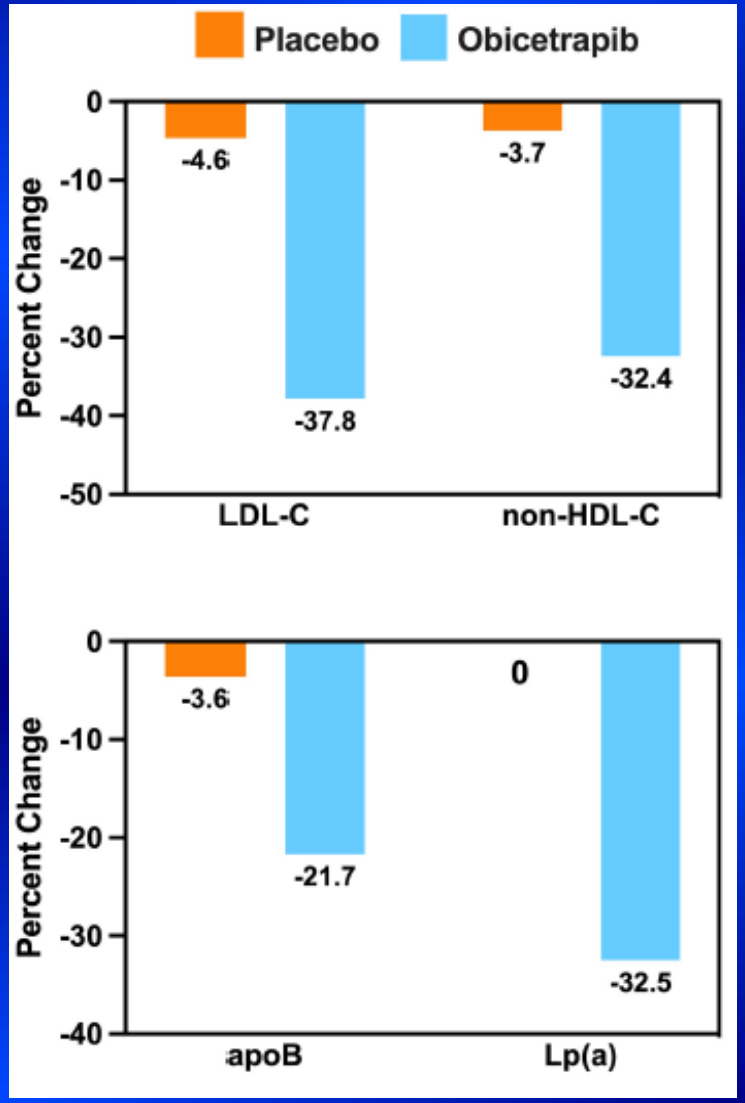
Activité de la CETP



Obicetrapib : CETP inhibitor



- 10 mg obicetrapib **inhibits CETP activity by** up to **99%**
- This leads to **lower** LDL-C and **higher HDL-C concentrations**
- **LDL-C lowering through upregulation of LDL receptors** as a result of increased fractional catabolic rates of LDL and ApoB



Ongoing CVOT:
PREVAIL
~9000 patients
With ASCVD

Nicholls et al. Circ Res 2026; 138: e327271

Prise en charge des dyslipidémies

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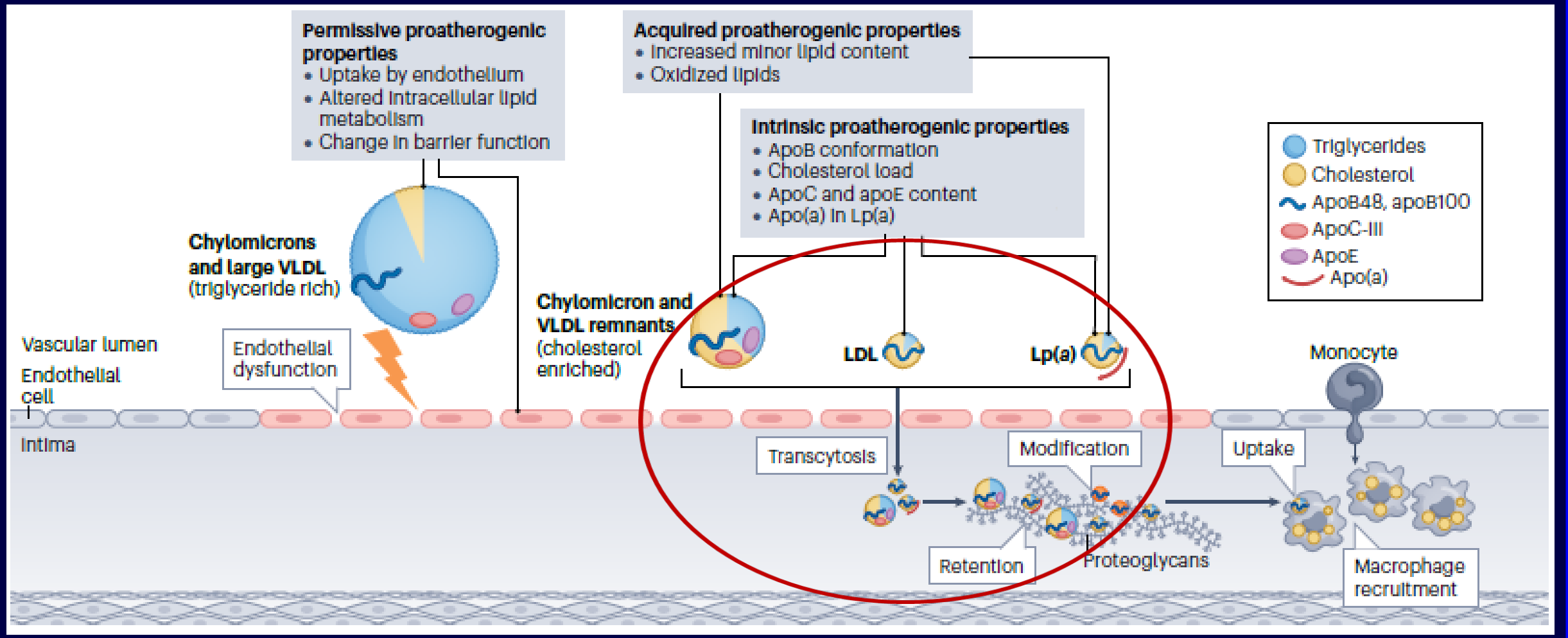
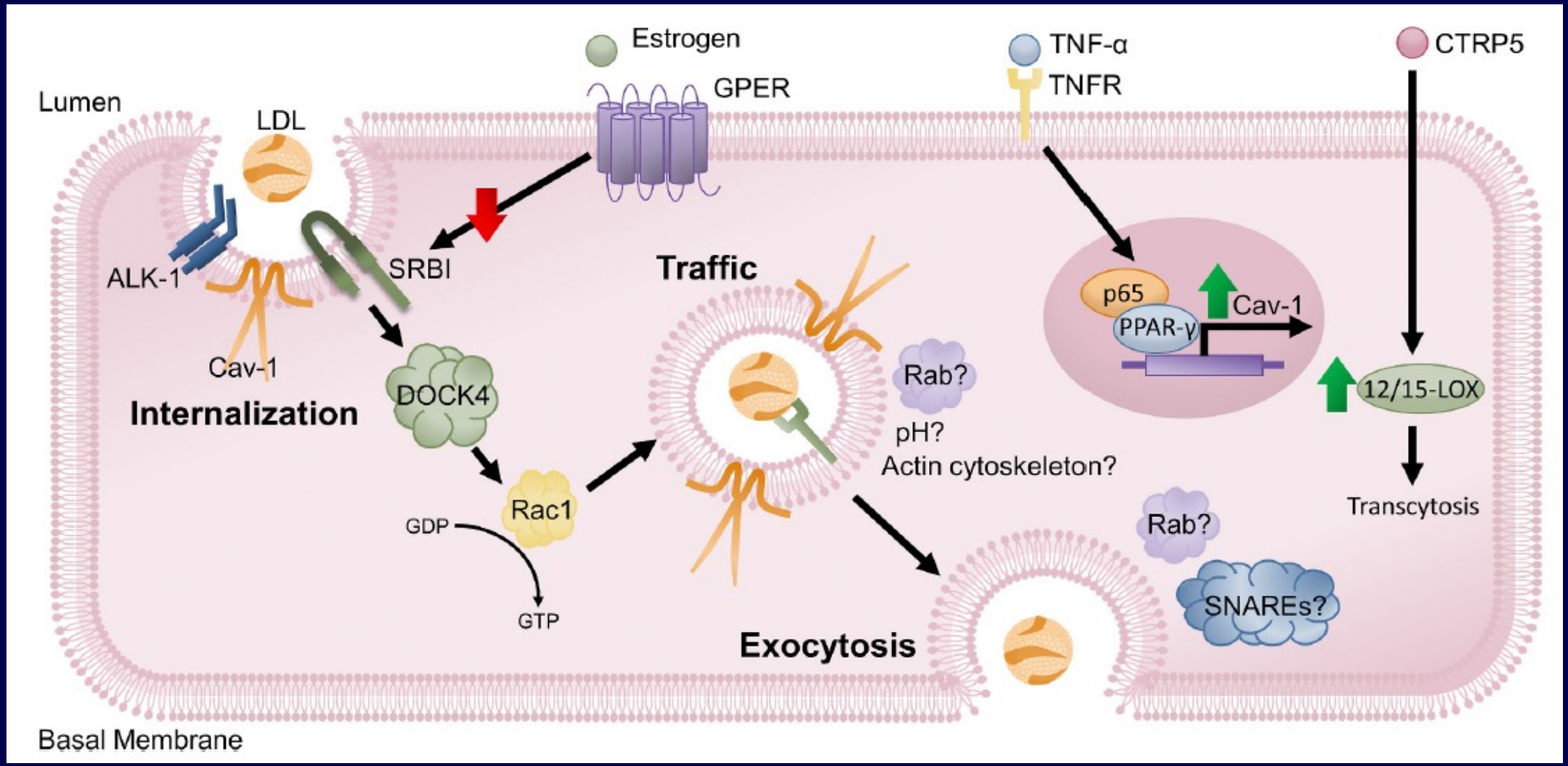
Concepts in atherogenicity of apoB-containing Lp



Borén, Packard & Binder. Nat Rev Cardiol 2025 Jan 2

Model showing the regulation of transendothelial LDL transport



Jang et al. Atherosclerosis 2020; 315 :111–125

nature medicine

Marston et al. Nat Med 2025; 31: 963-9

Article

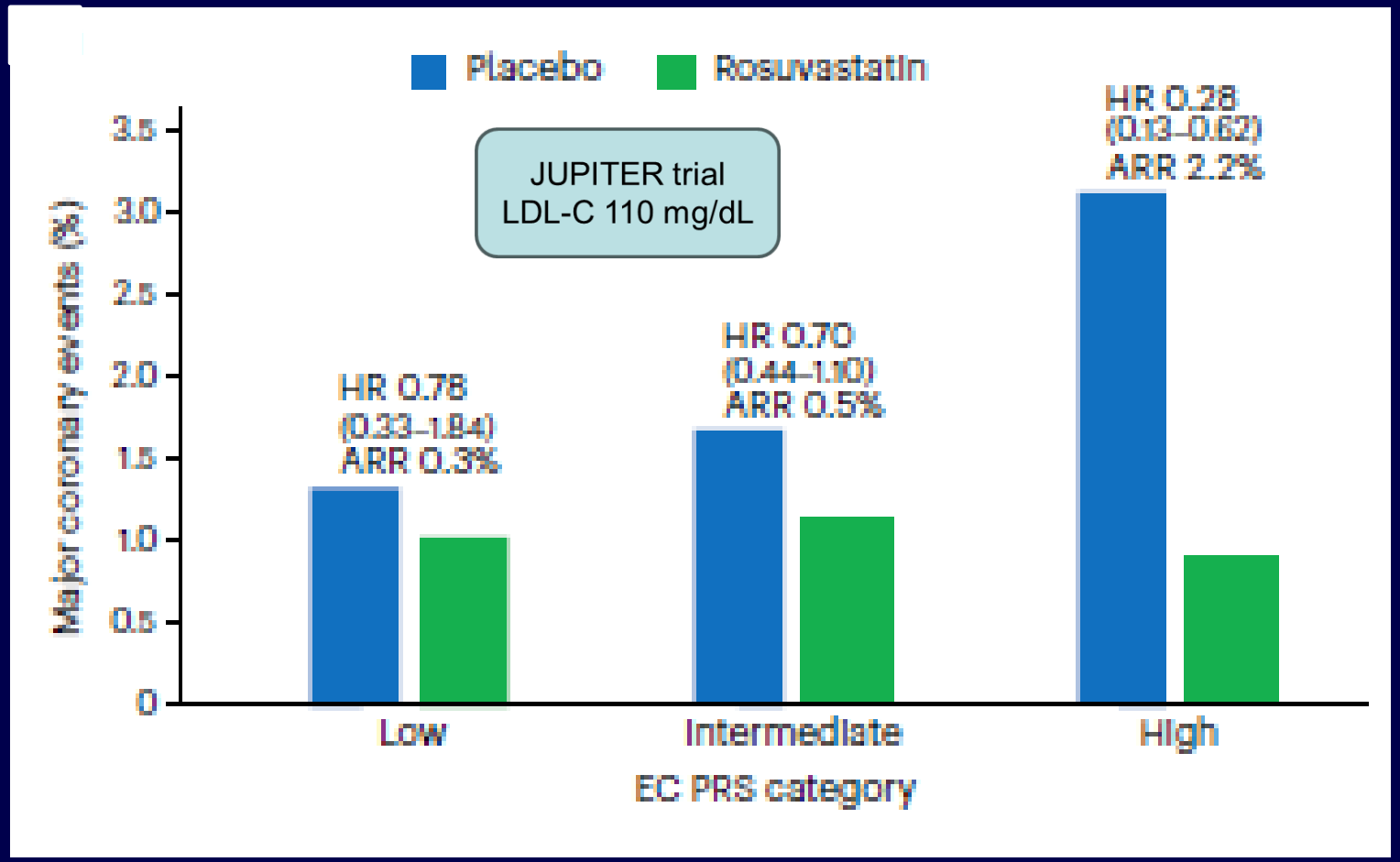
https://doi.org/10.1038/s41591-025-03533-w

Endothelial cell-related genetic variants identify LDL cholesterol-sensitive individuals who derive greater benefit from aggressive lipid lowering

- From GWAS, identification of variants with effects on EC function
  Construction of a 35 SNPs polygenic risk score (EC PRS)

- Association of the EC PRS with the ASCVD risk tested in 3 cohorts:
  UK Biobank(UKBB), JUPITER and FOURIER

The association between genetically mediated EC dysfunction and major cardiovascular events



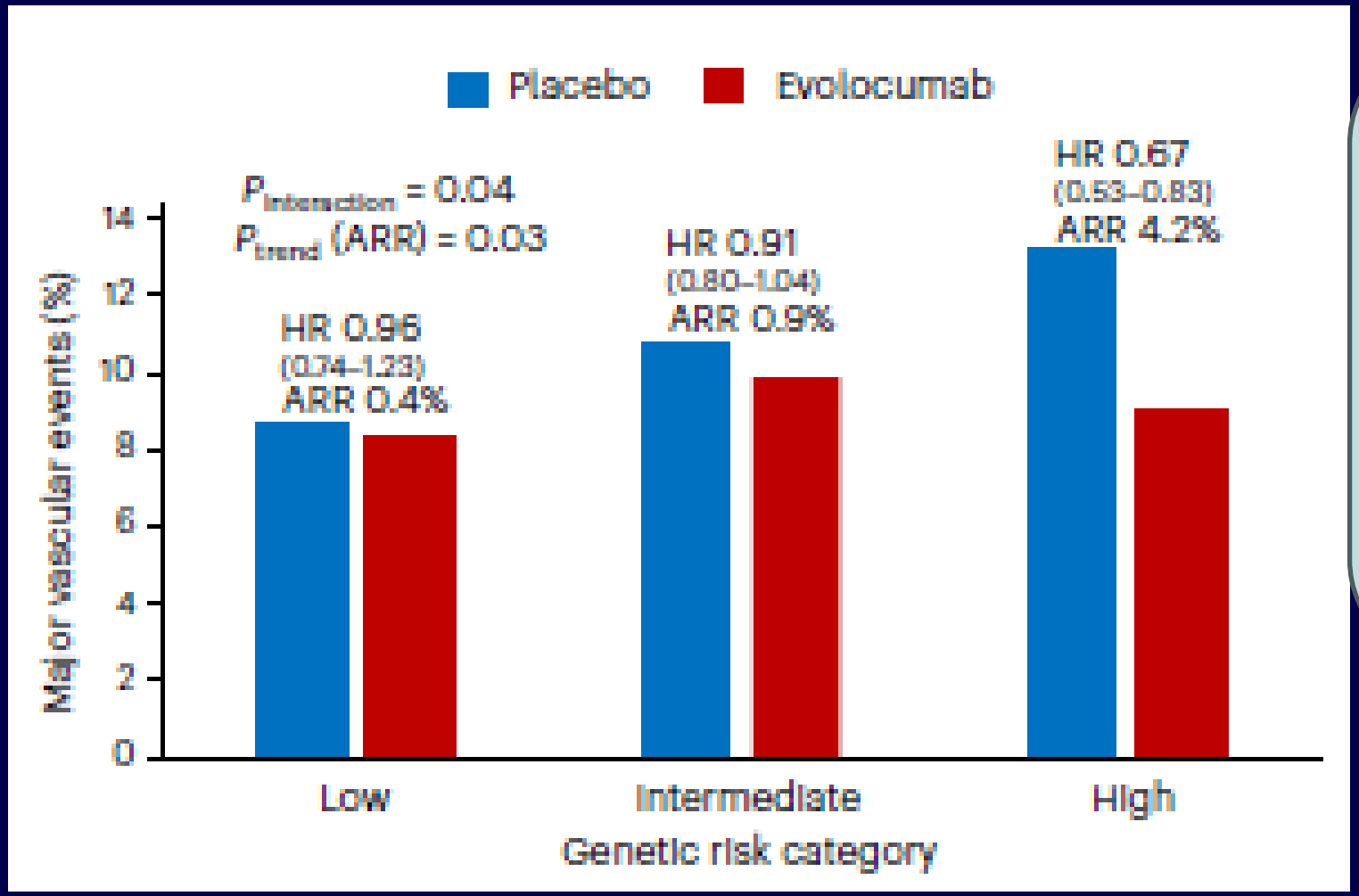
In subjects treated with a high-intensity statin (median LDL-C 54 mg/dL), the EC PRS no longer predicted the development of incident coronary events (HR per 1sd 1.06 (0.85-1.31)

Individuals with the highest degree of genetically predicted EC dysfunction benefited the most from aggressive lipid-lowering therapy

Marston et al. Nat Med 2025; 31: 963-9

The association between genetically mediated EC dysfunction and major cardiovascular events

FOURIER trial



When patients were treated with a PCSK9 inhibitor, the EC PRS no longer predicted major vascular events (HR per 1sd 1.01 (0..94-1.09)

Individuals with high EC PRS had the greatest benefit with a 33% relative risk reduction (ARR 4.2%)

Marston et al. Nat Med 2025; 31: 963-9

KEY MESSAGES

The development of atherosclerosis requires 2 key components :
1- a high level of circulating apoB-containing lipoproteins
2- EC-mediated transcytosis of these lipid particles

EC function seems to play a key role in the individual's susceptibility to a given LDL-C exposure
(some individuals may be protected from EC barrier disruption, which reduces the risk conferred by high levels of apoB-containing lipoproteins)

In the absence of sufficient circulating apoB lipoproteins, EC dysfunction alone seems unable to initiate atherosclerosis

En conclusion: prise en charge des dyslipidémies

- En prévention cardiovasculaire, la réduction des LDL reste et restera la priorité

  3 classes complémentaires : statines, ézétimibe, inhibiteurs de PCSK9

- Les inhibiteurs de ApoC3 et ANGPTL3 sont un apport majeur pour traiter respectivement les HTG sévères et les patients HFHo
- Les bénéfices cardiovasculaires liés à l'inhibition de la Lp(a) et de la CETP restent à démontrer
- L'enjeu: "sélection" des patients à traiter/intensifier le traitement


Merci pour votre attention