Place des thérapeutiques ciblant l'ARNm dans la prise en charge des dyslipidémies

Pr Bertrand CARIOU

Service d'Endocrinologie-Diabétologie-Nutrition (EDN)

L'unité de recherche de l'institut du thorax
Inserm UMR 1087 / CNRS UMR 6291
Nantes, France

Séance Thématique, Academie Nationale de Pharmacie, 25 sept 2024

Déclaration de liens d'intérêt

Pr Bertrand CARIOU								
Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties / Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
Abbott	x							
Amgen	x		x					
Astra-Zeneca	x							
Eli Lilly	x	x						
Novartis	x	x						
Novo Nordisk	x	x						
MSD		x						
Sanofi	x		x					
Ultragenyx	x	x						

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PLAN

Trois pathologies pour trois cibles

Hypercholestérolémie Familiale (HF)


PCSK9

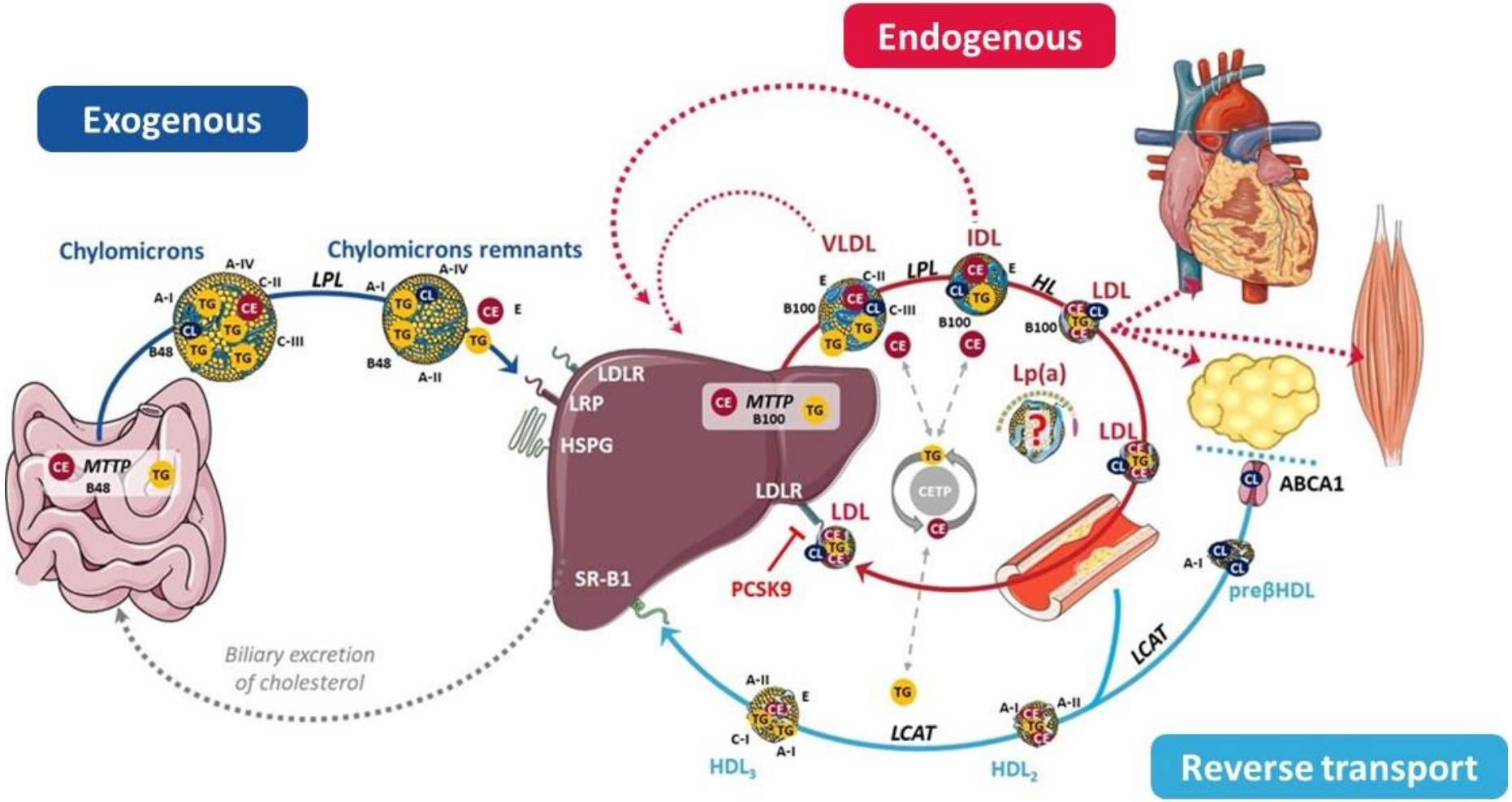
Augmentation de la Lp(a)


Apo(a)

Hyperchylomicronémie (FCS)

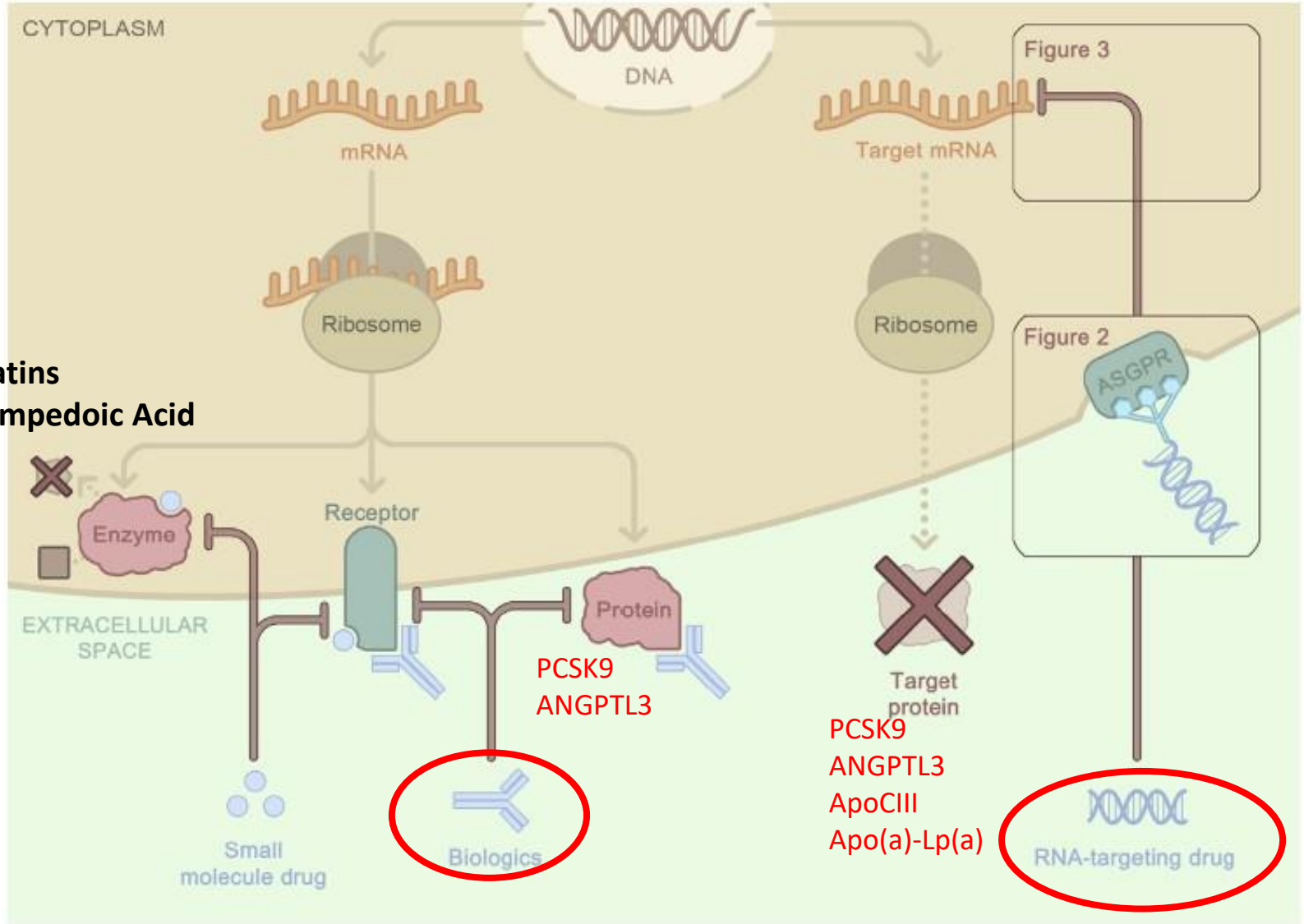

ApoC-III

METABOLISME DES LIPOPROTEINES



LES DIFFERENTES STRATEGIES PHARMACOLOGIQUES

Statins
Bempedoic Acid



Katzmann JL et al. *J Am Coll Cardiol* 2020; 76: 563-79

COMPARAISON DES DIFFERENTES STRATEGIES PHARMACOLOGIQUES

Parameter	Drug technology			
	Small molecules	Antibodies	Gene silencing with antisense oligonucleotides	Gene silencing with small interfering RNA
Chemical structure	Organic compound	Protein	Single-stranded RNA	Double-stranded RNA
Mass (kDa)	<1	~150	~12	~21
Mechanism of action	Blocks enzyme or receptor in cells	Blocks protein in plasma	Blocks gene mRNA transcripts in cell	Blocks gene mRNA transcripts in cell
Potential for off-target adverse effects	High likelihood of off-target, non-tissue-specific effects	Low, given high specificity for target	Low, given high specificity for target with third-generation agents	Low, given high specificity for target
Immunogenicity	Low	High	High	High
Variation of within-person drug response	High	High	Low	Low
Half-life	Days	Weeks	Months	>1 year
Administration route	Oral	Subcutaneous	Subcutaneous	Subcutaneous
Dosing frequency	Daily	Weekly to twice monthly	Monthly	Twice yearly
Targets	Proteins in ng to µg	Proteins in µg to mg	Lipoproteins in g	Lipoproteins in g

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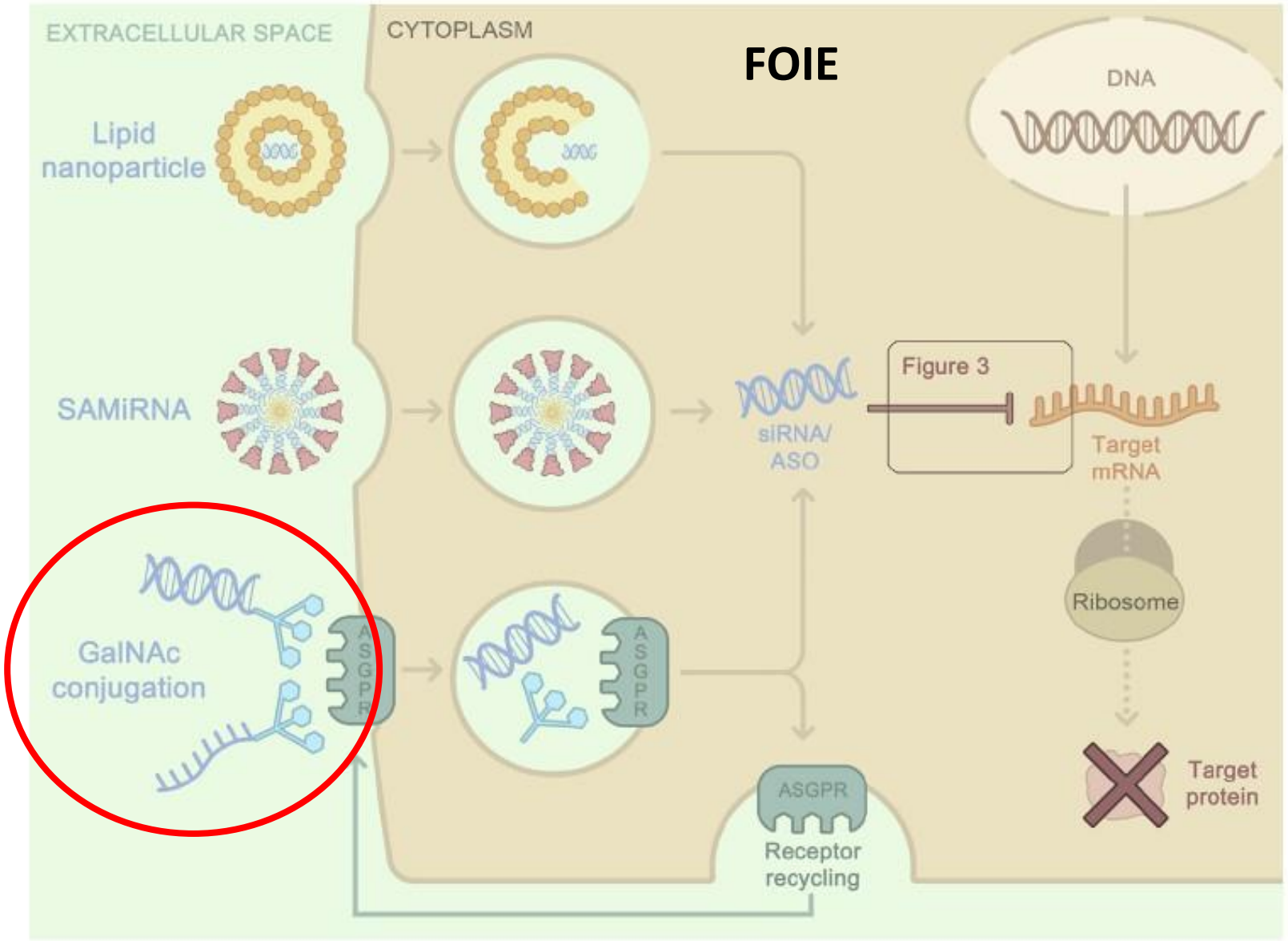
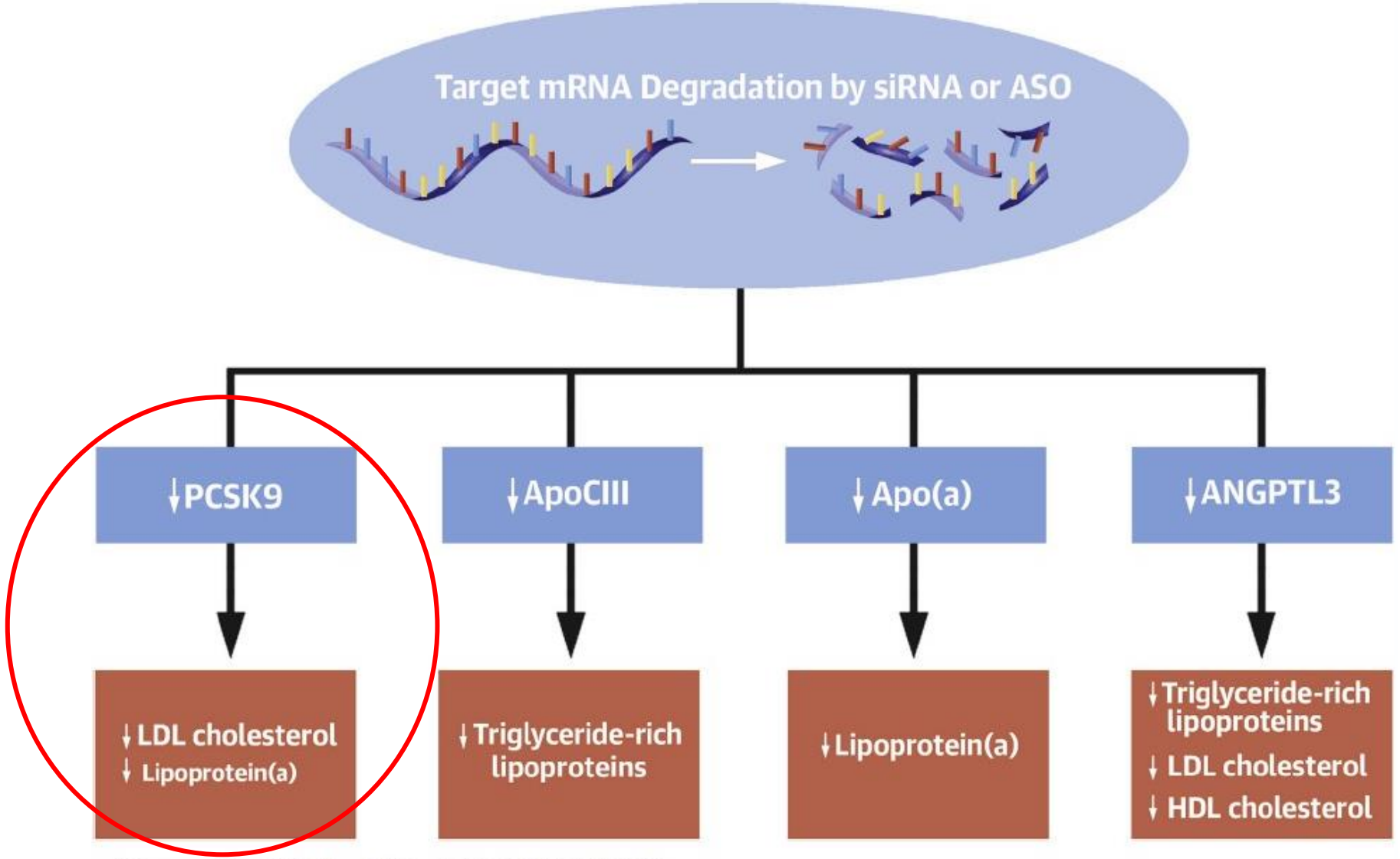
Nordestgaard BGet al. *Nat Rev Cardiol* 2018; 15: 261-72

VECTORISATION DES OLIGONUCLEOTIDES CIBLANT L'ARNm



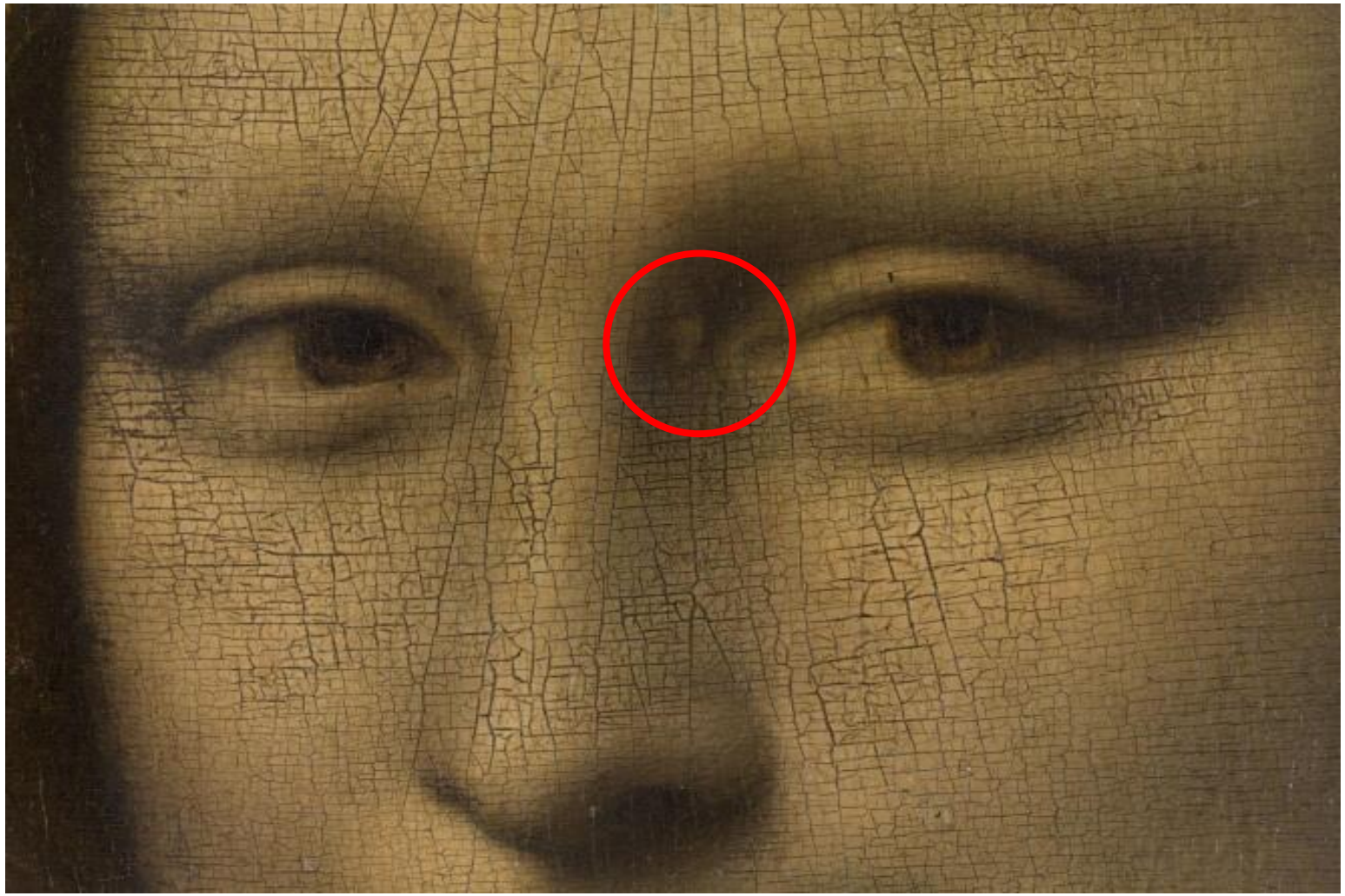
Katzmann JL et al. *J Am Coll Cardiol* 2020; 76: 563-79

LES OLIGONUCLEOTIDES CIBLANT L'ARNm EN LIPIDOLOGIE



Katzmann, J.L. et al. J Am Coll Cardiol. 2020;76(5):563-79.

L'HYPERCHOLESTEROLEMIE FAMILIALE (HF)



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HF: la maladie monogénique la plus fréquente

Circulation

ORIGINAL RESEARCH ARTICLE

Prevalence of Familial Hypercholesterolemia Among the General Population and Patients With Atherosclerotic Cardiovascular Disease

A Systematic Review and Meta-Analysis

Prevalence: 1/311-313

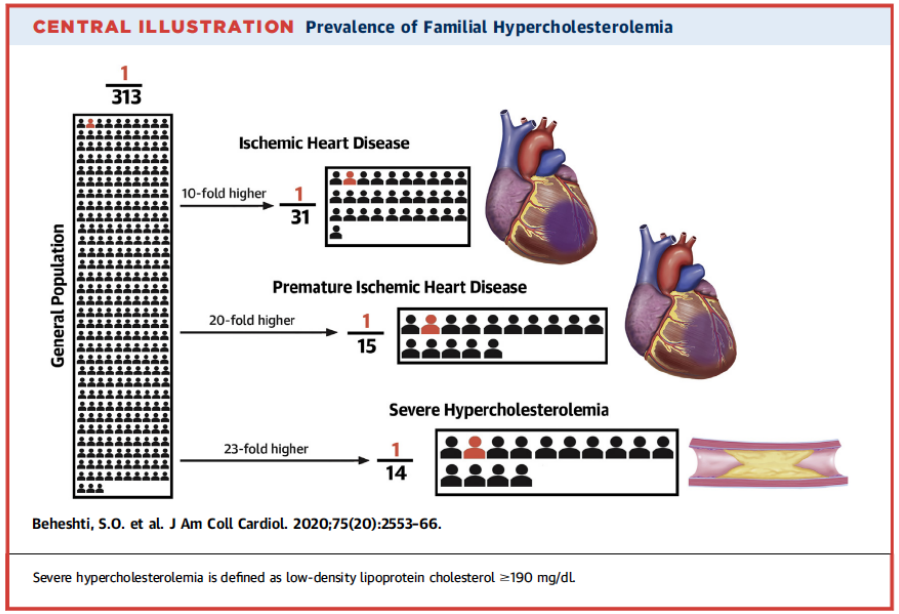
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 75, NO. 20, 2020

PUBLISHED BY ELSEVIER

Worldwide Prevalence of Familial Hypercholesterolemia

Meta-Analyses of 11 Million Subjects

Sabina O. Beheshti, BSc, Christian M. Madsen, MD, Anette Varbo, MD, PhD, Børge G. Nordestgaard, MD, DMSc



213 000 personnes en France

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Diagnostiquer tôt pour traiter tôt et éviter le « cholesterol burden »

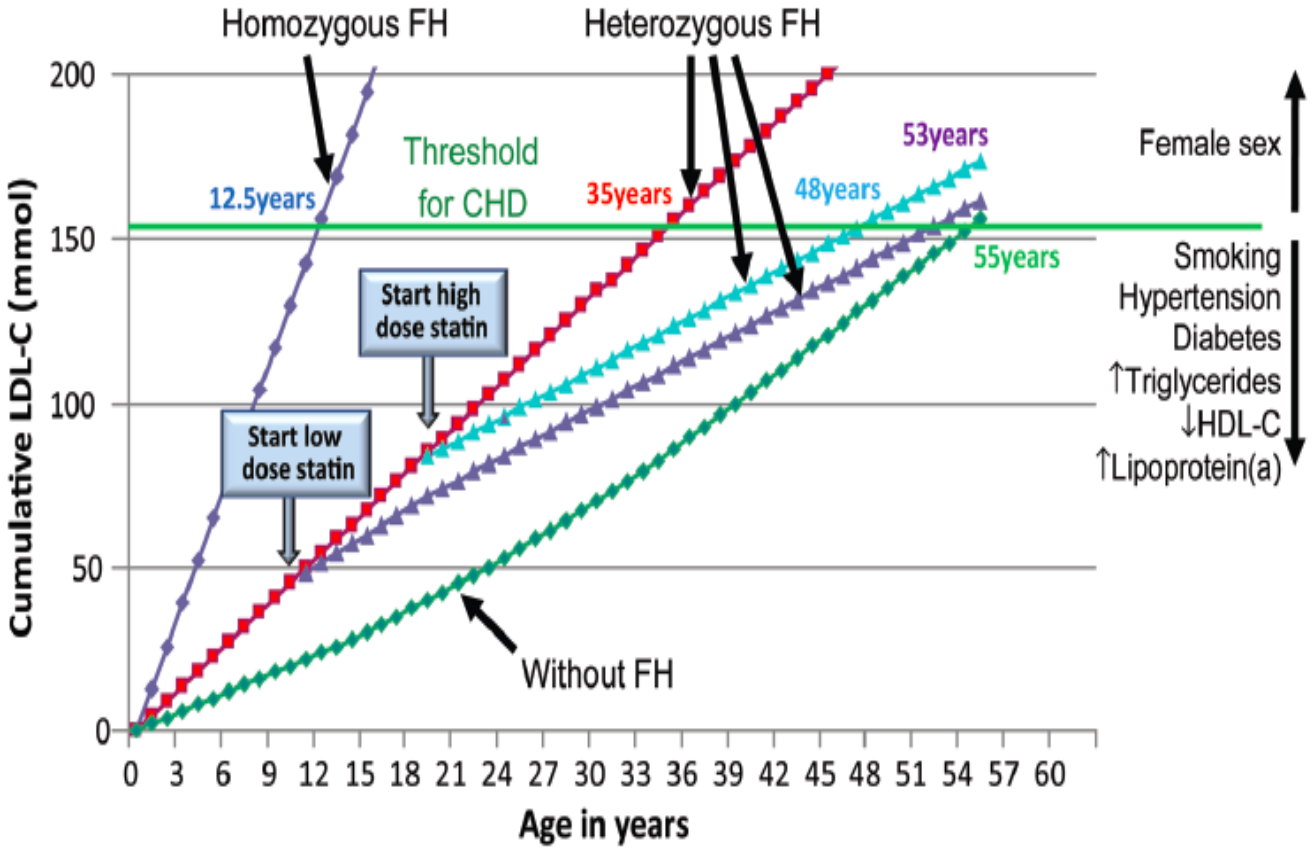
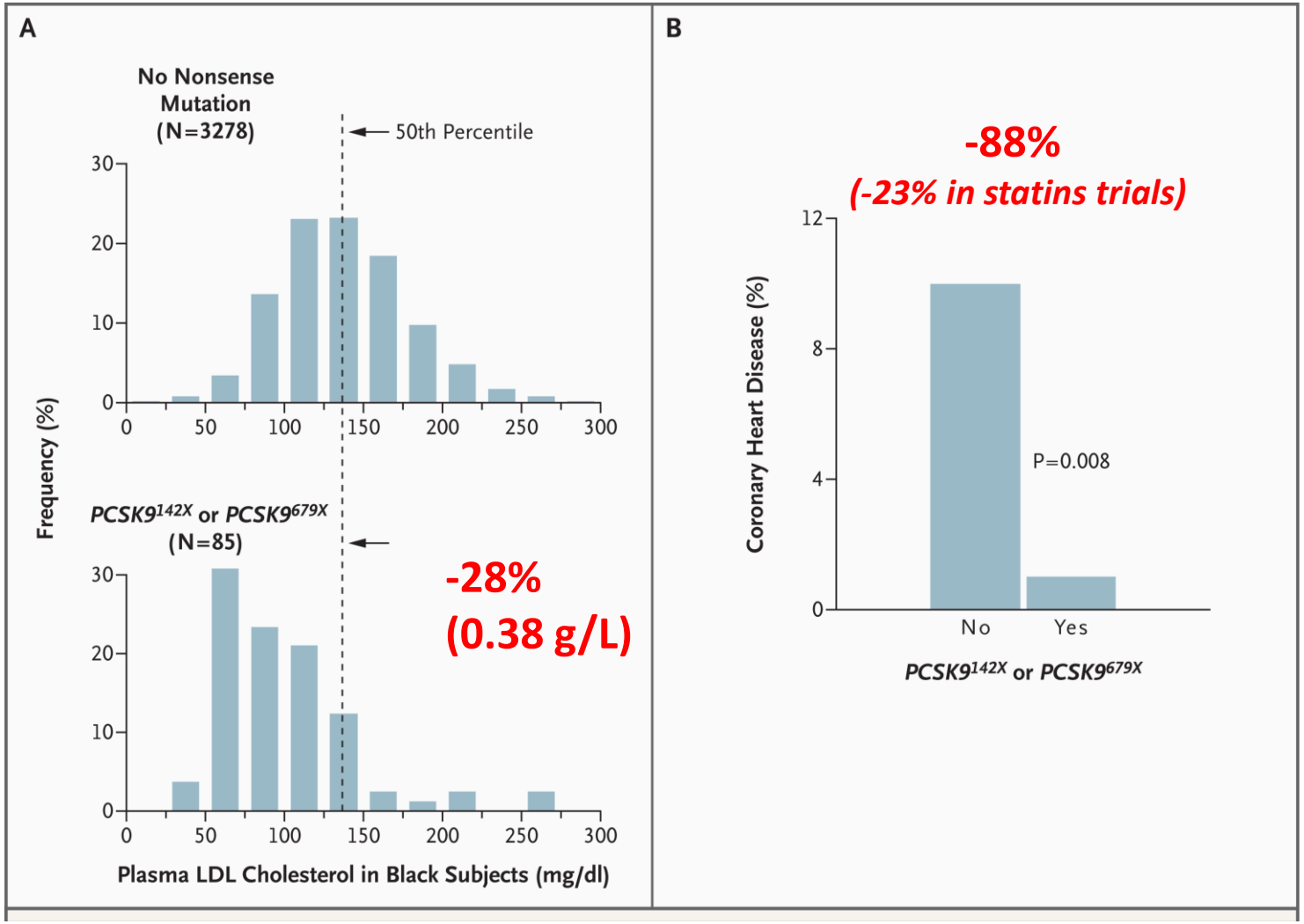


Figure 8 LDL cholesterol burden in individuals with or without familial hypercholesterolaemia as a function of the age of initiation of statin therapy. Data derived from Huijgen *et al.*[20] and Starr *et al.*[21] LDL, low-density lipoprotein; LDL-C, LDL cholesterol; HDL-C, high-density lipoprotein cholesterol; CHD, coronary heart disease; FH, familial hypercholesterolaemia.

European Heart Journal (2013) 34, 3478–3490

La preuve par la génétique du bénéfice de l'inhibition de PCSK9



Of the 3363 black subjects examined, 2.6 percent had nonsense mutations in *PCSK9*; these mutations were associated with a 28 percent reduction in mean LDL cholesterol and an 88 percent reduction in the risk of CHD.

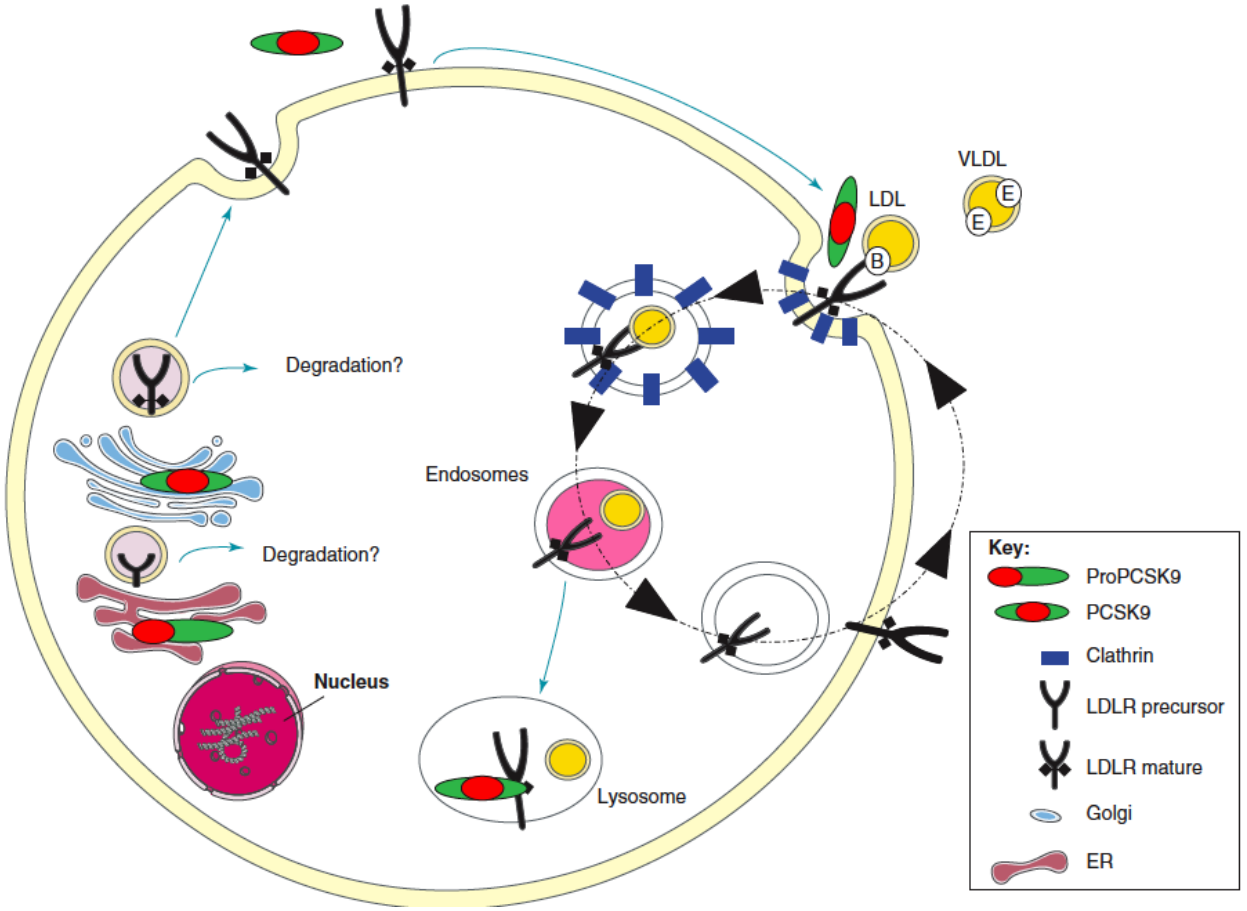
Cohen JC et al. *N Engl J Med* 2006; **354**:1264-1272

Mécanisme d'action de PCSK9

↑ PCSK9

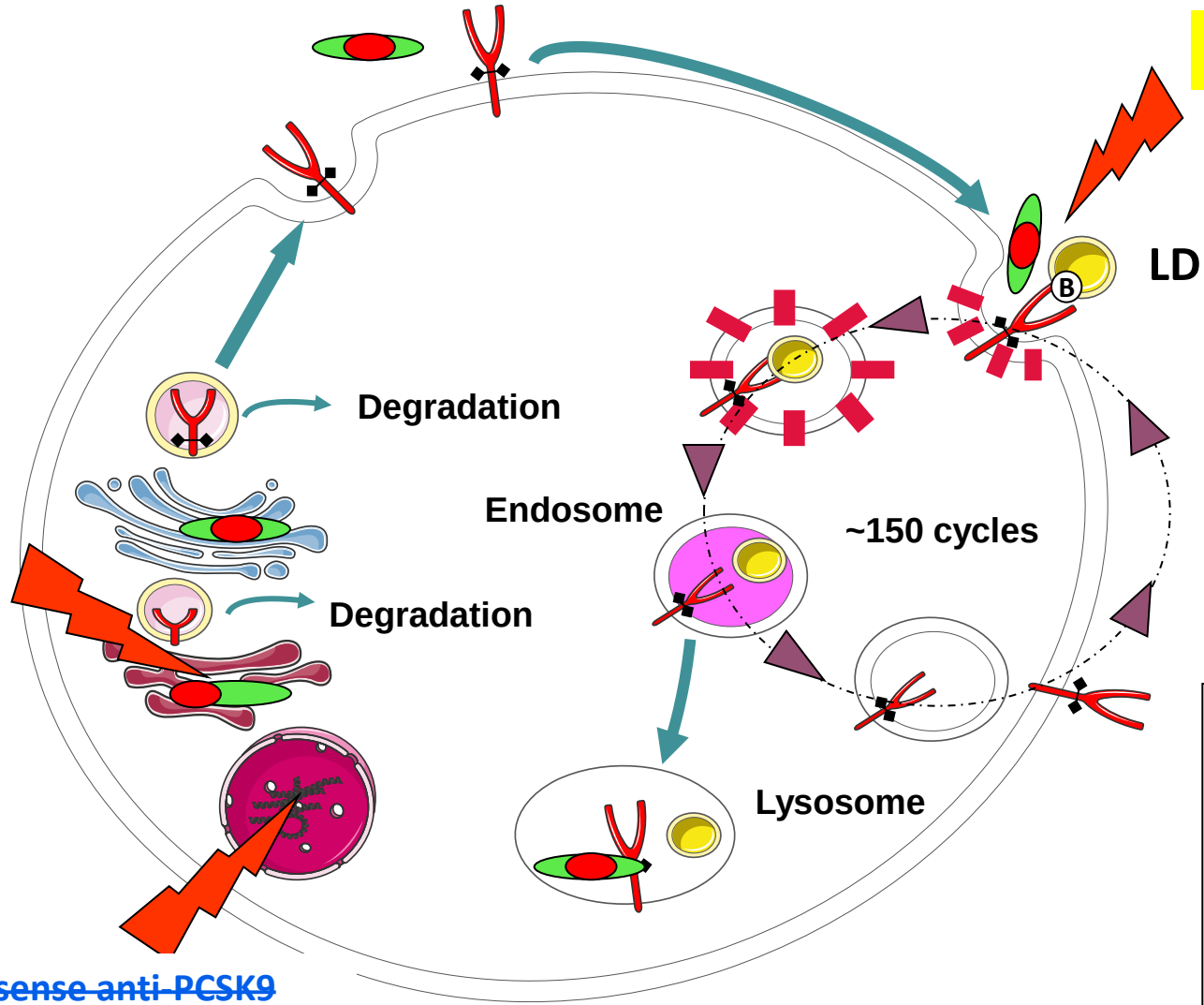
↓ LDL-R

↑ LDL-C



Costet P, Krempf M, Cariou B. *Trends Bioch Sci* 2008**, 33**: 426.

Les stratégies d'inhibition de PCSK9



anticorps anti-PCSK9 (mAbs)

Adnectines (lerodalcibep)

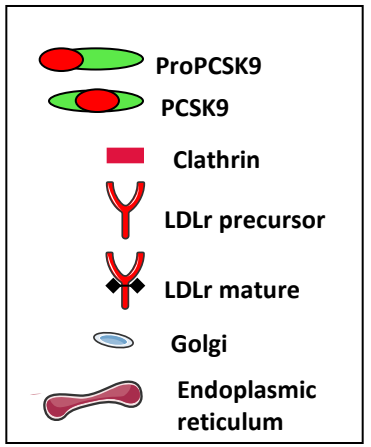
Vaccin

Peptides bloquants (MK-0616)

~~Anti-sense anti-PCSK9~~

siRNA anti-PCSK9

CRISPR-Cas9: édition génomique



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La courte vie des premiers anti-sens (ASOs) anti-PCSK9

ELSEVIER

American Journal of Kidney Diseases

Volume 62, Issue 4, October 2013, Pages 796-800

Case Report

Acute Kidney Injury During Therapy With an Antisense Oligonucleotide Directed Against PCSK9

Eveline P. van Poelgeest MD [1], Reinout M. Swart MD [2], Michiel G.H. Betjes MD [2], Matthijs Moerland PhD [1], Jan J. Weening MD [3], Yann Tessier DVM [4], Michael R. Hodges MD [4], Arthur A. Levin PhD [4], Jacobus Burggraaf MD, PhD [1]

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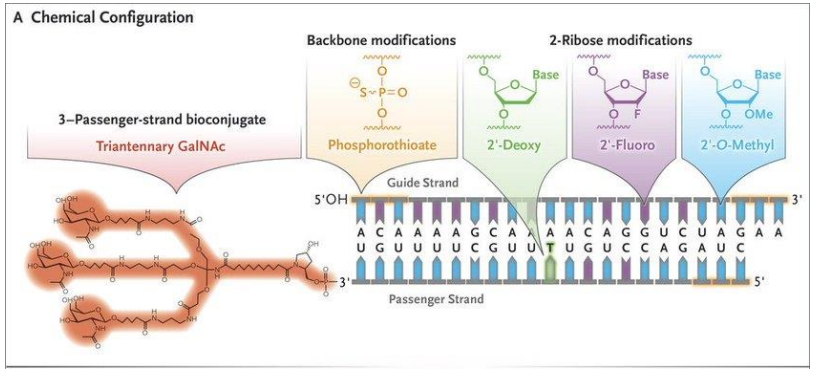
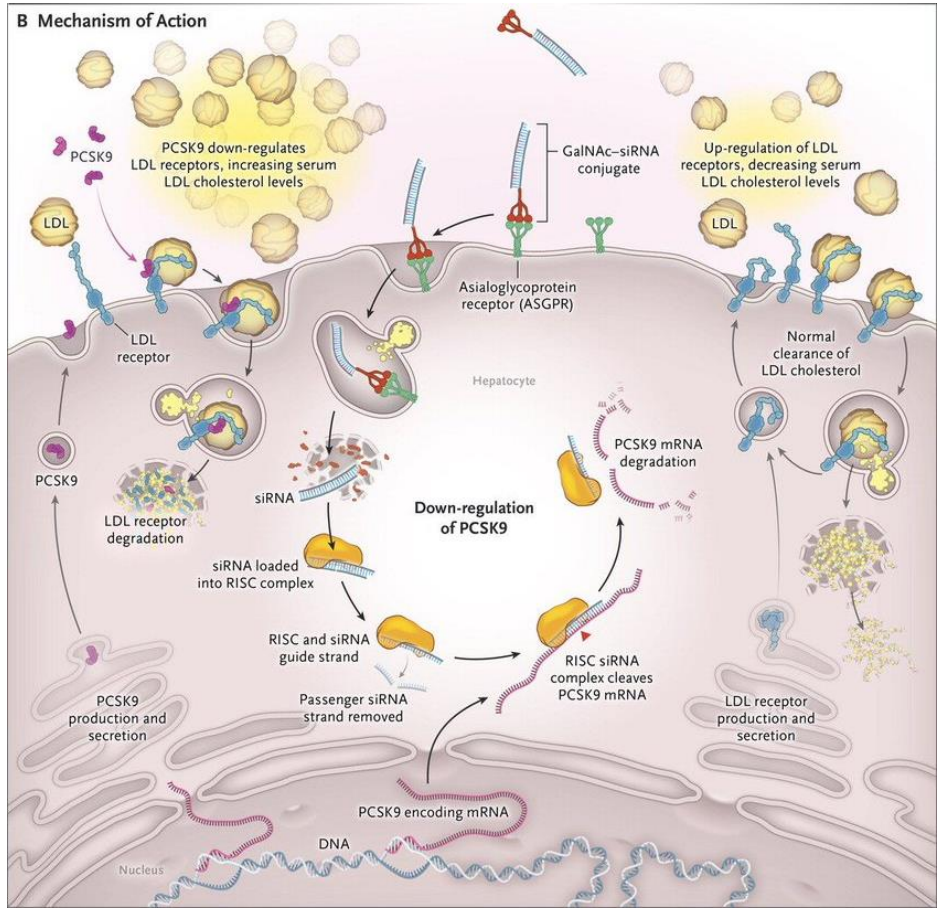
INCLISIRAN: un siRNA anti-PCSK9





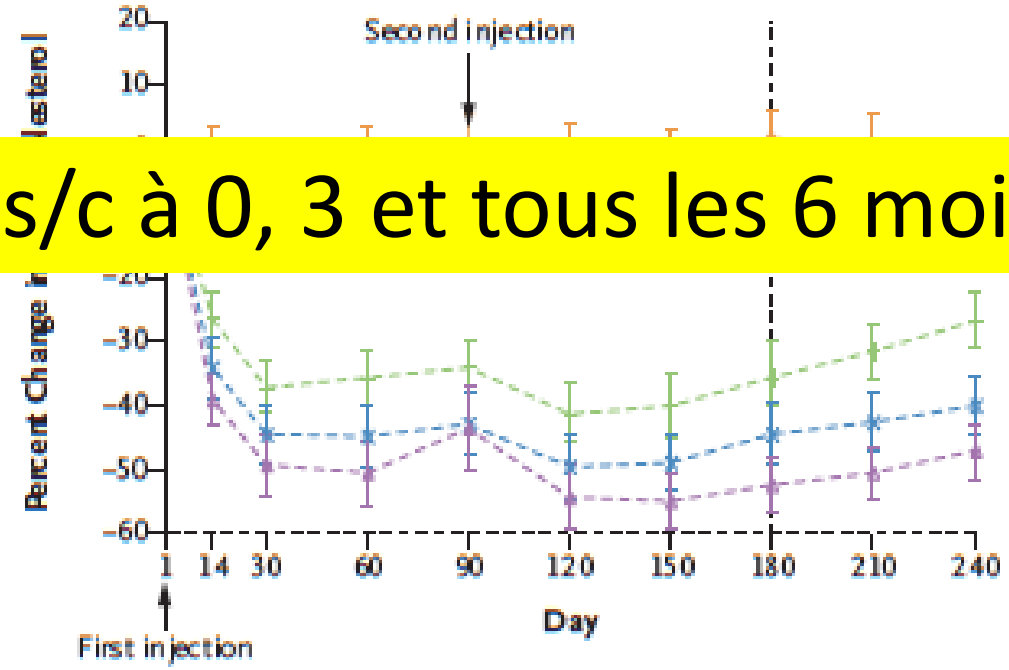
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inclisiran in Patients at High Cardiovascular Risk with Elevated LDL Cholesterol

Kausik K. Ray, M.D., Ulf Landmesser, M.D., Lawrence A. Leiter, M.D., David Kallend, M.D., Robert Dufour, M.D., Mahir Karakas, M.D., Tim Hall, M.D., Roland P.T. Troquay, M.D., Traci Turner, M.D., Frank L.J. Visseren, M.D., Peter Wijngaard, Ph.D., R. Scott Wright, M.D., and John J.P. Kastelein, M.D., Ph.D.

D Changes in LDL Cholesterol Levels with the Two-Dose Regimen



1 injection s/c à 0, 3 et tous les 6 mois

No. at Risk										
Two-dose placebo	62	62	61	62	60	61	61	61	60	29
Two-dose inclisiran, 100 mg	61	58	60	58	60	58	57	59	59	49
Two-dose inclisiran, 200 mg	62	62	62	62	61	59	58	60	60	56
Two-dose inclisiran, 300 mg	61	61	61	61	60	59	59	59	58	57

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Ray KK et al. *N Engl J Med*. 2017; **376**:1430-1440.

Long-term efficacy and safety of inclisiran in patients with high cardiovascular risk and elevated LDL cholesterol (ORION-3): results from the 4-year open-label extension of the ORION-1 trial

Kausik K Ray, Roel P T Troquay, Frank L J Visseren, Lawrence A Leiter, R Scott Wright, Sheikh Vikarunnessa, Zsolt Talloczy, Xiao Zang, Pierre Maheux, Anastasia Lesogor, Ulf Landmesser

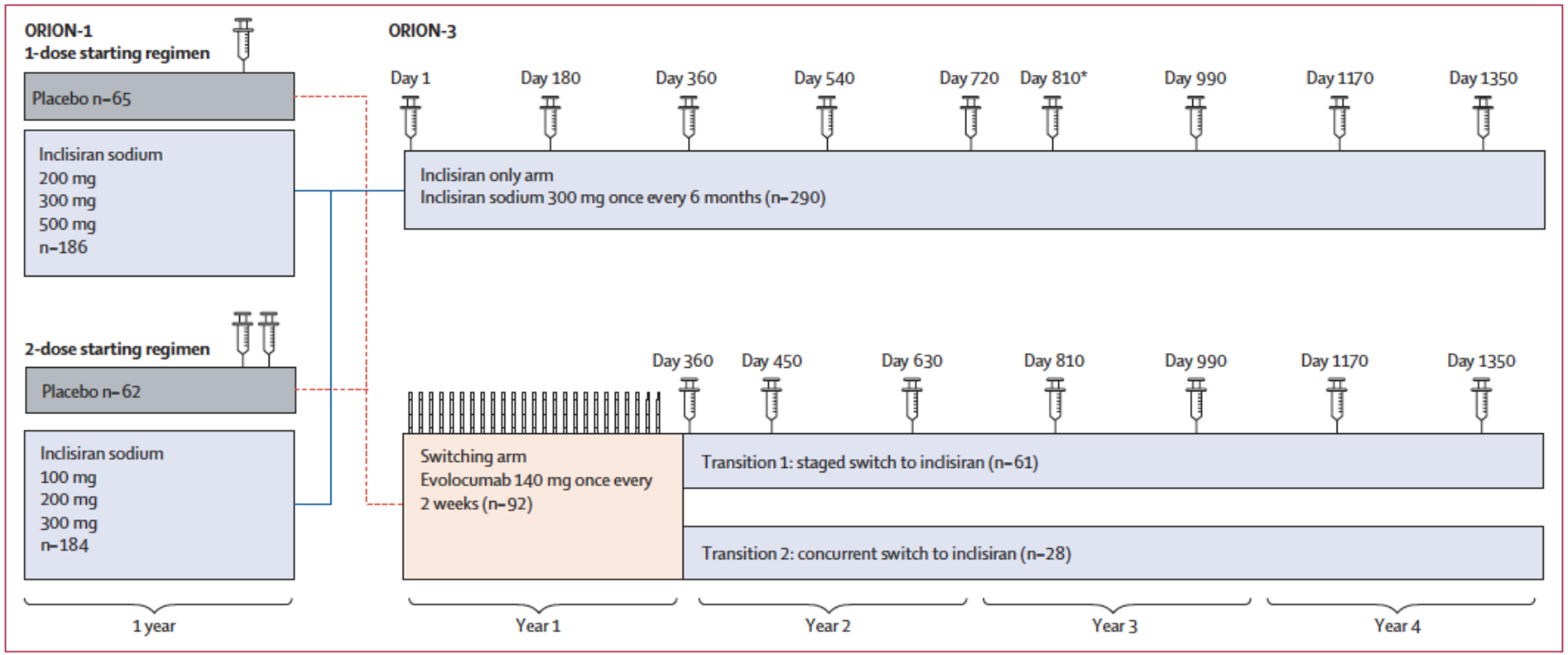

Figure 1: **Study design**

*Day 810 injection in the inclisiran-only arm was administered as a one-time 90-day dosing interval as per the initial study design for exploratory purposes. In the switching arm patients received the second inclisiran dose 90 days apart on day 450.

Lancet Diabetes Endocrinol 2023; 11: 109–19

Efficacité hypocholestérolémiante de l'inclisiran

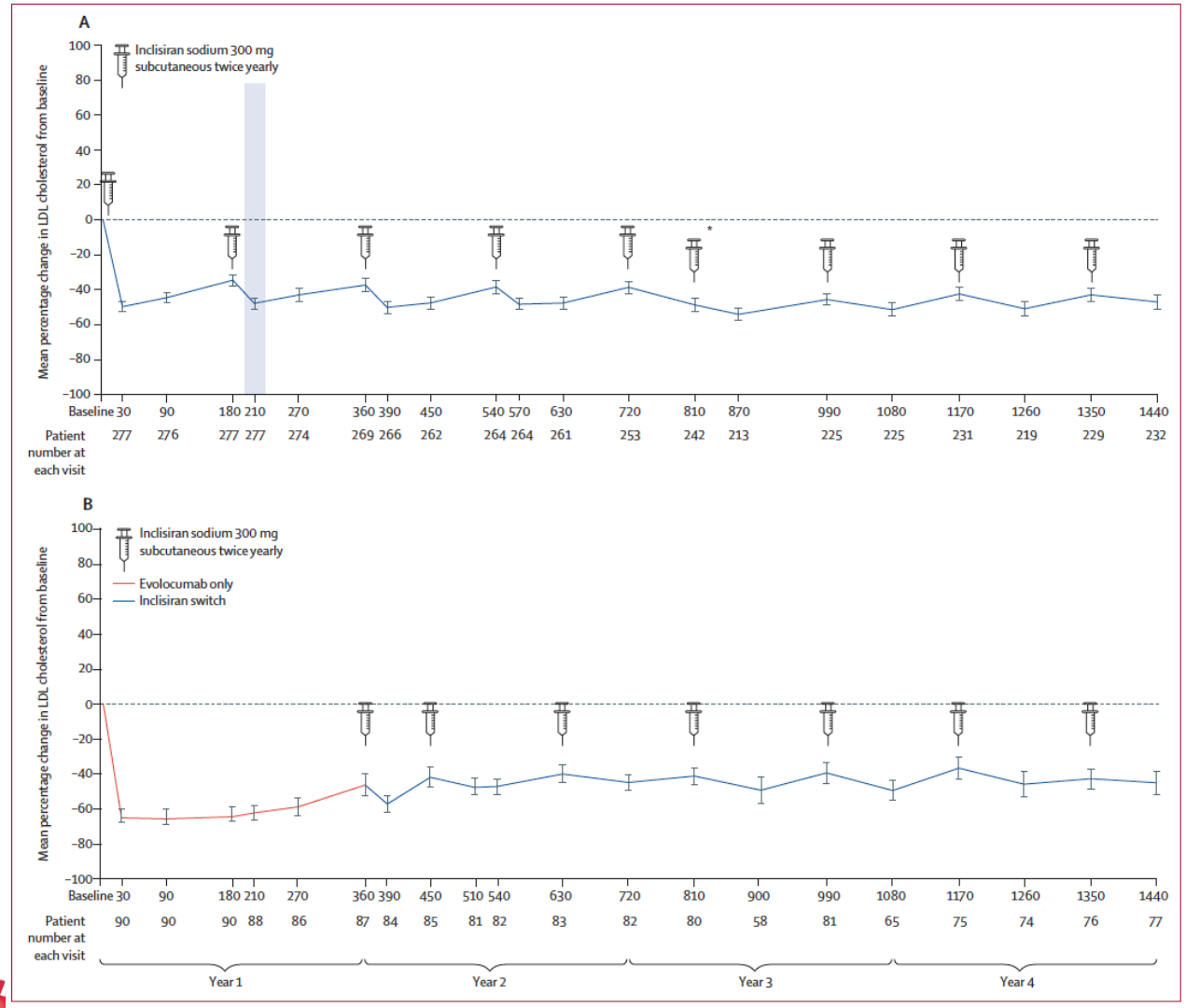

Figure 2: **Mean percentage change in LDL cholesterol (A) from ORION-1 baseline to day 1440 (4 years) of ORION-3 (inclisiran-only arm), and from (B) ORION-3 baseline to day 1440 (4 years) of ORION-3 (switching arm)**

	Inclisiran-only arm (n=277)*		Switching arm (n=92)*	
	N	Least squares mean (95% CI)	N	Least squares mean (95% CI)
Year 1	277	−42·5 (−45·3 to −39·7)	90	−61·0 (−64·5 to −57·4)
Year 2	271	−44·5 (−47·6 to −41·4)	87	−47·9 (−51·8 to −44·0)
Year 3	252	−49·4 (−52·5 to −46·3)	84	−45·4 (−50·8 to −40·1)
Year 4	242	−45·4 (−48·9 to −41·9)	80	−43·9 (−49·5 to −38·3)
Year 1–4	277	−44·2 (−47·1 to −41·4)	87	−45·3 (−49·7 to −40·9)†

Data are n or least squares mean (95% CI). ITT=intention-to-treat. LDL=low-density lipoprotein. mITT=modified intention-to-treat. *For the inclisiran-only arm, data were analysed in the mITT population; for the switching arm, data were analysed in the ITT population. The inclisiran-only arm uses ORION-1 baseline and the switching arm uses ORION-3 baseline. †For the switching arm, the time period was year 2–4.

***Table 3:* Mean percentage change from baseline in LDL cholesterol averaged over time by treatment group**

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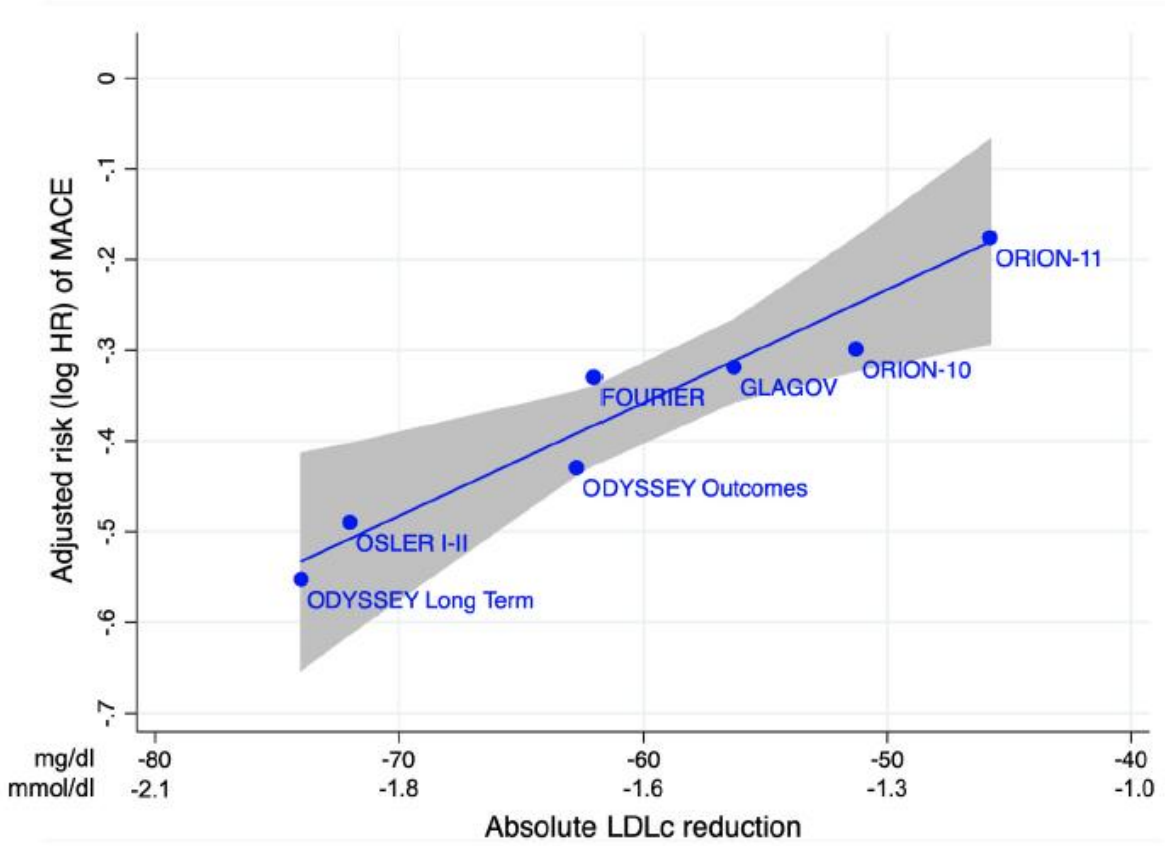
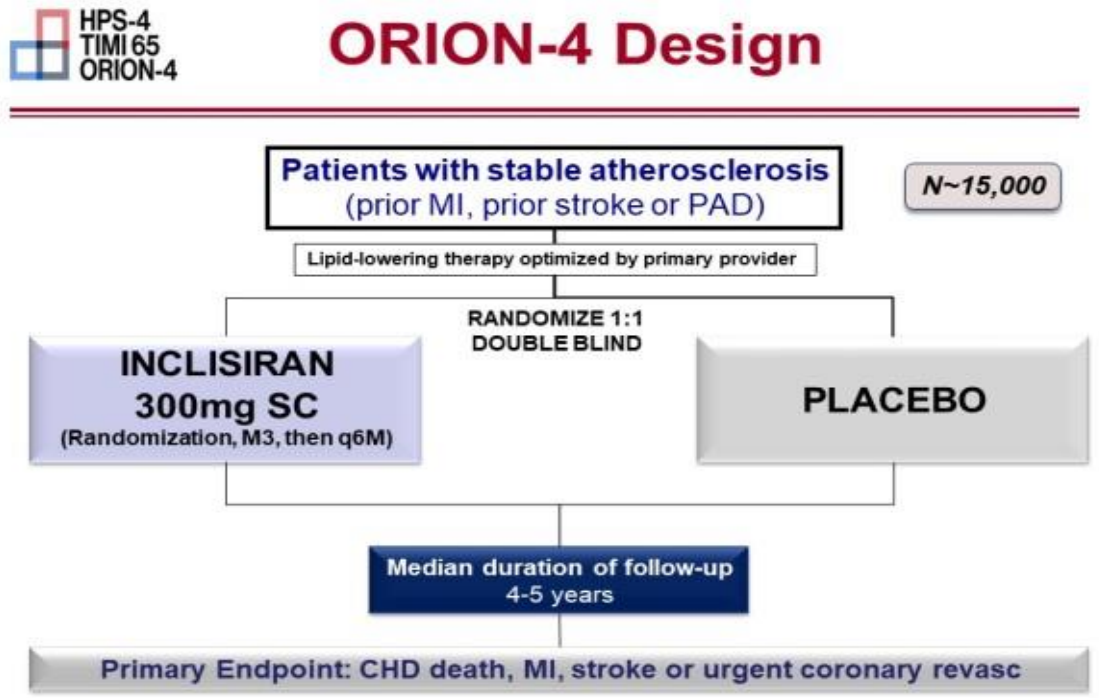
Lancet Diabetes Endocrinol 2023; 11: 109–19

Efficacité cardiovasculaire de l'inclisiran : les études sont en cours





ClinicalTrials.gov Identifier: NCT03705234

Cordero A. et al. *Atherosclerosis* 2020; 313: 76-80

+ Victorion-2 Prevent study

HAS
HAUTE AUTORITÉ DE SANTÉ

ÉVALUER LES TECHNOLOGIES DE SANTÉ

AVIS SUR LES MEDICAMENTS

inclisiran

LEQVIO 284 mg,

solution injectable en seringue préremplie

Primo-inscription

Adopté par la Commission de la transparence le 28 août 2024

Avis favorable au remboursement de LEQVIO (inclisiran) uniquement en prévention primaire dans le traitement des patients adultes présentant une hypercholestérolémie familiale hétérozygote (HFHe), en complément d'un régime alimentaire :

- **avec une statine seule ou une statine avec d'autres thérapies hypolipidémiantes chez les patients ne pouvant atteindre les objectifs de LDL-C sous statine à la dose maximale tolérée ;**
- **seul ou en association avec d'autres thérapies hypolipidémiantes chez les patients avec une intolérance avérée aux statines ou chez qui les statines sont contre-indiquées.**

Avis défavorable au remboursement de LEQVIO (inclisiran) dans les autres situations cliniques couvertes par l'AMM.

Population cible	La population cible est estimée à 215 000 patients adultes présentant une hypercholestérolémie familiale hétérozygote.

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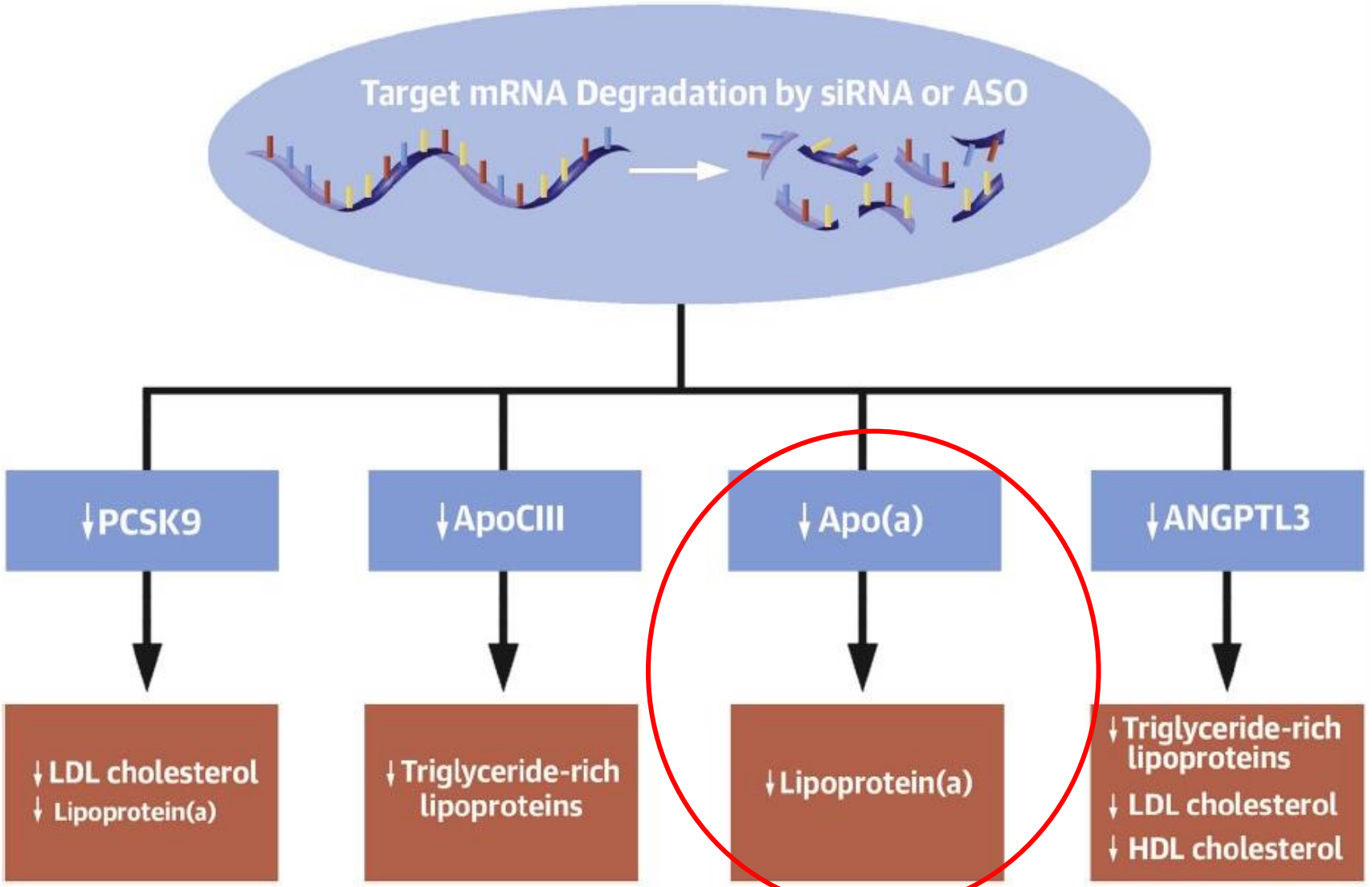
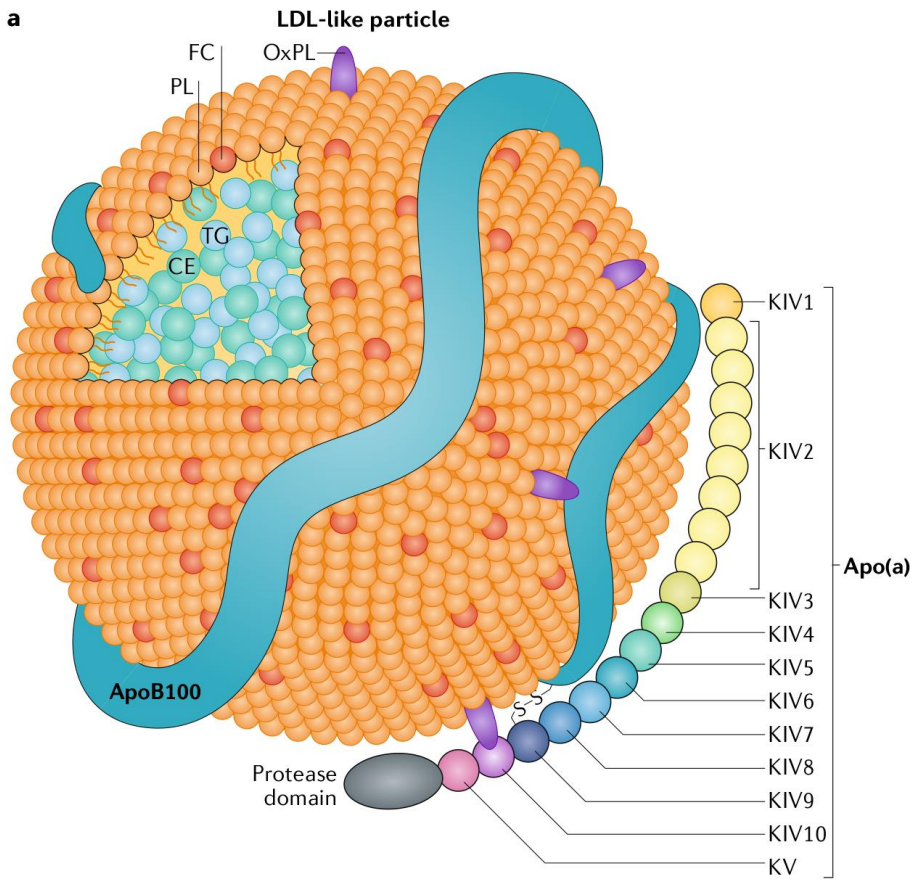
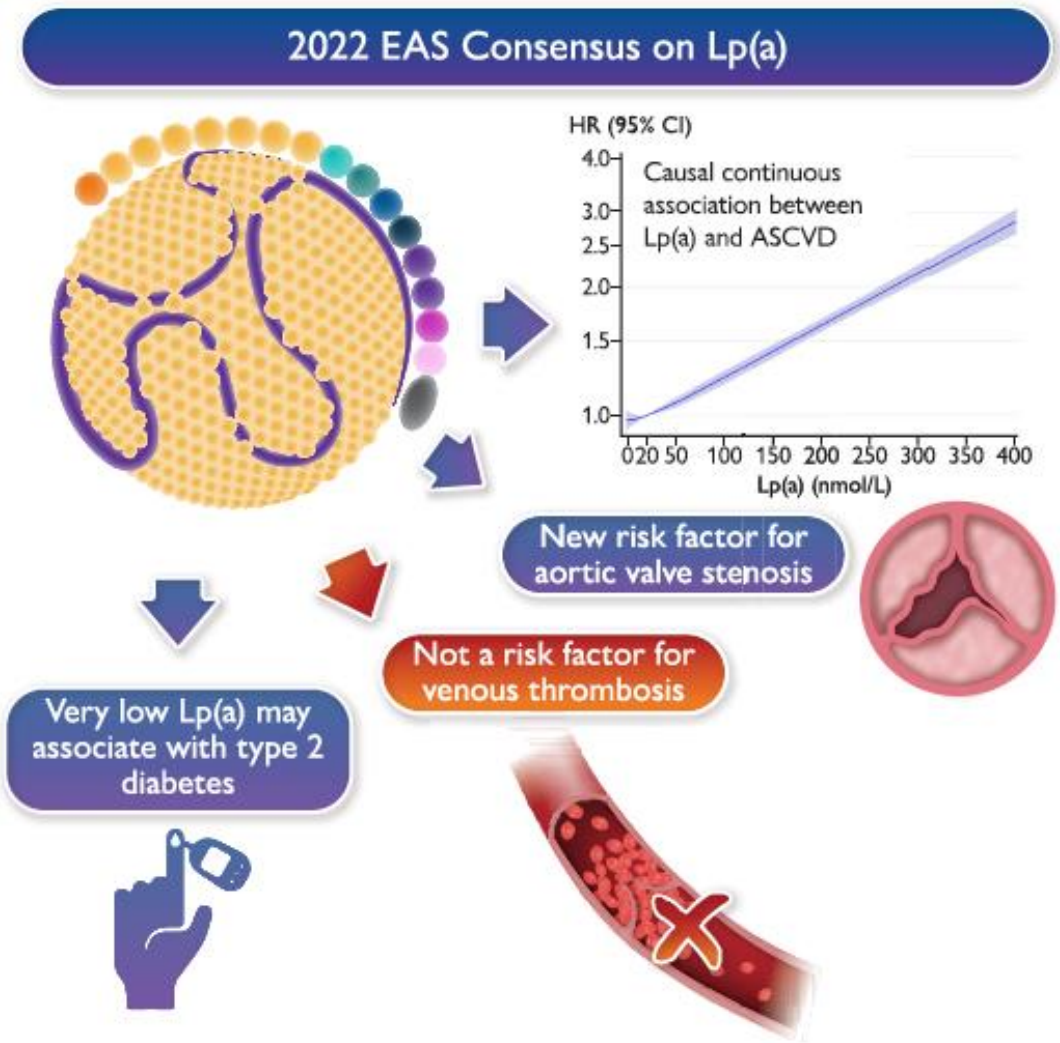
LES OLIGONUCLEOTIDES CIBLANT L'ARNm EN LIPIDOLOGIE



Katzmann, J.L. et al. J Am Coll Cardiol. 2020;76(5):563-79.

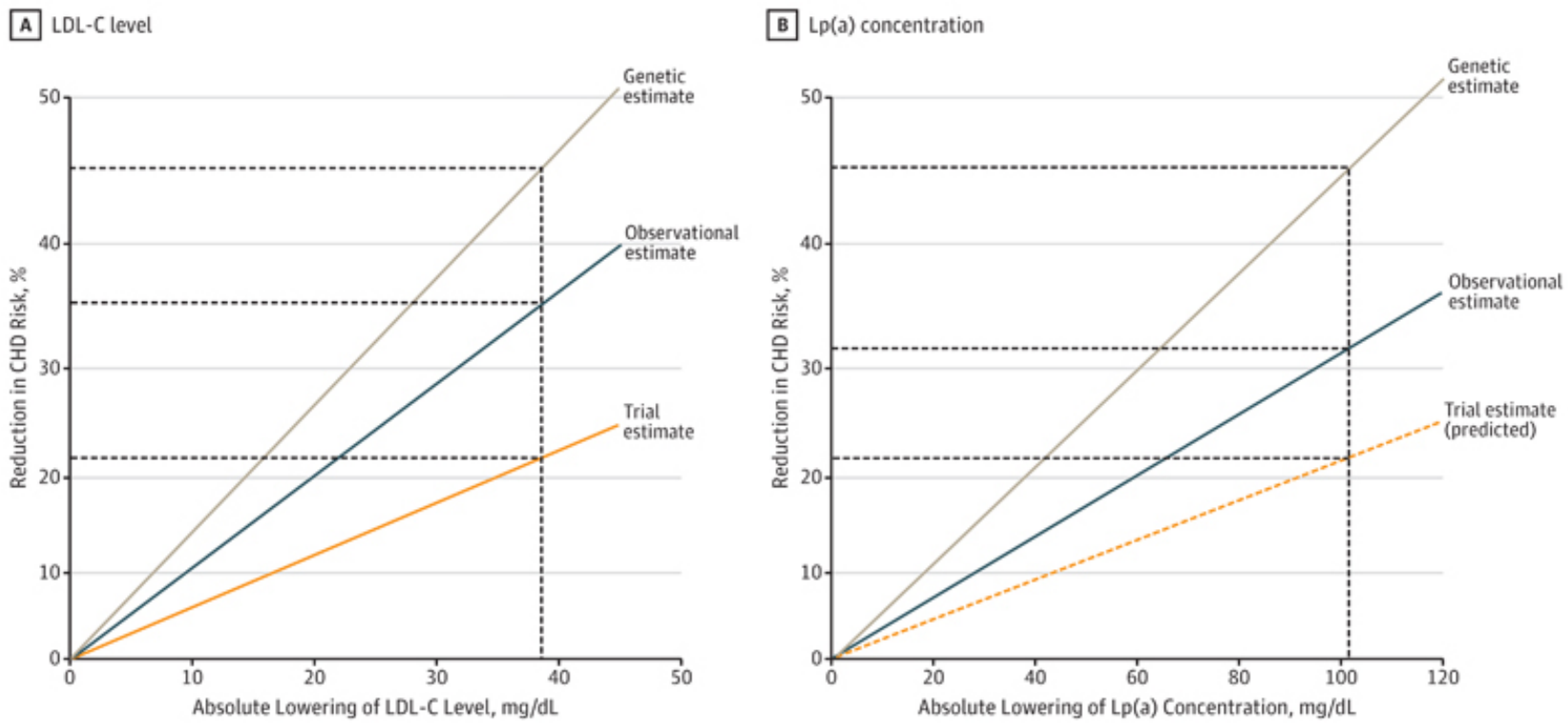
Lp(a): la dernière cible en lipidologie ?





Abaisser la Lp(a): ce que nous suggère la génétique

Estimation du risque de coronaropathie en fonction de la baisse du LDL-C et de la Lp(a)



Il faut une baisse de **101.5 mg/dL de la Lp(a)** pour conférer la même protection CV que celle obtenue avec une baisse de **38.7 mg/dL du LDL-C**

Burgess S. et al. *JAMA Cardiol.* 2018; 3: 619-27.

Quelles options thérapeutiques pour abaisser la Lp(a)?

Table 1 Lipid lowering and Lp(a)-directed therapies

Drug/class name	Drug target	Development stage	Lp(a) reduction	LDL-C reduction	References
Approved lipid lowering therapies					
Statins	HMGCR	Available	No change	20–50%	[28, 47, 48]
Ezetimibe	NPC1L1	Available	0–7% (on top of statins)	18–22% (on top of statins)	[29, 30, 49]
Lipoprotein apheresis	Plasma lipoprotein removal	Available	63%	64%	[32]
Bempedoic acid	ACLY	Available	No change	17–21%	[34, 50–52]
PCSK9i monoclonal antibodies	PCSK9	Available	23–27% (on top of statins + ezetimibe)	50–60% (on top of statins + ezetimibe)	[35, 36]
Inclisiran	PCSK9	Available	22%	50%	[42]
Lp(a)-directed therapies					
Pelacarsen	ASO with GalNAc3 conjunction	Phase 3	80%	10–20%	[43, 44••, 53]
Olpasiran	siRNA	Phase 2	Up to 90%	No change	[45•]
SLN360	siRNA	Phase 1	Up to 98%	Up to 25%	[46•]

Lp(a), lipoprotein(a); *PCSK9i*, proprotein convertase subtilisin kexin type 9 inhibiting; *HMGCR*, 3-hydroxy-3-methylglutaryl coenzyme reductase; *NPC1L1*, Niemann-Pick-like protein 1C1; *ACLY*, ATP citrate lyase; *siRNA*, small interfering RNA; *ASO*, antisense oligonucleotide; *GalNAc3*, N-acetylgalactosamine; *LDL-C*, low-density lipoprotein-cholesterol

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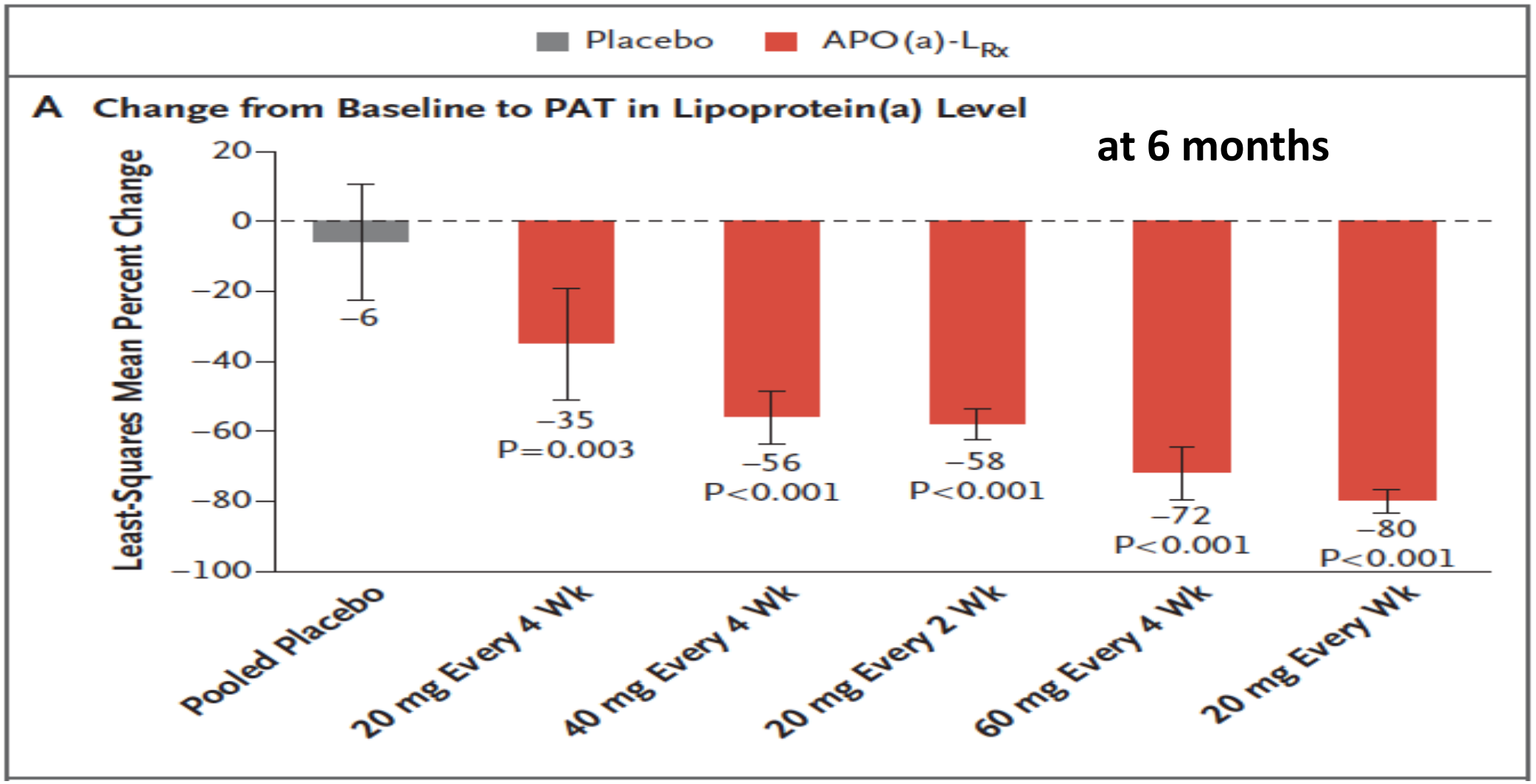
Nurmohamed NS et al. *Curr Atheroscler Rep* 2022; 24: 831-8

ASO anti-Apo(a): pelacersen (HORIZON(a))

Patients with ASCVD and Lp(a) ≥ 150 nmol/L (60 mg/dL)

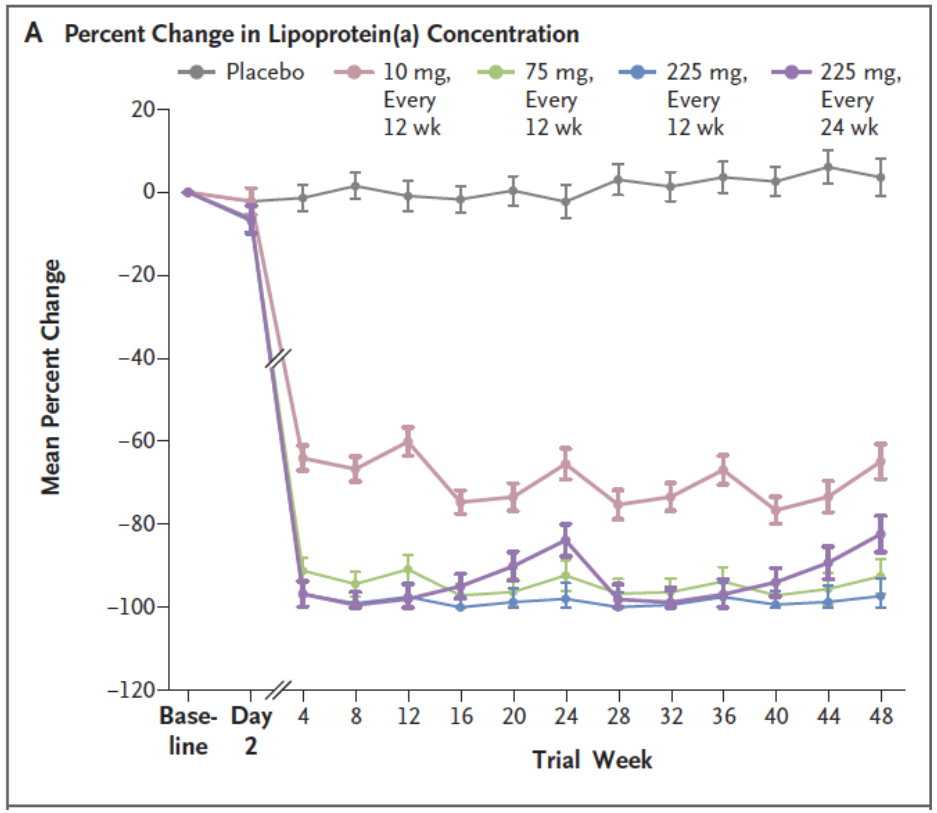


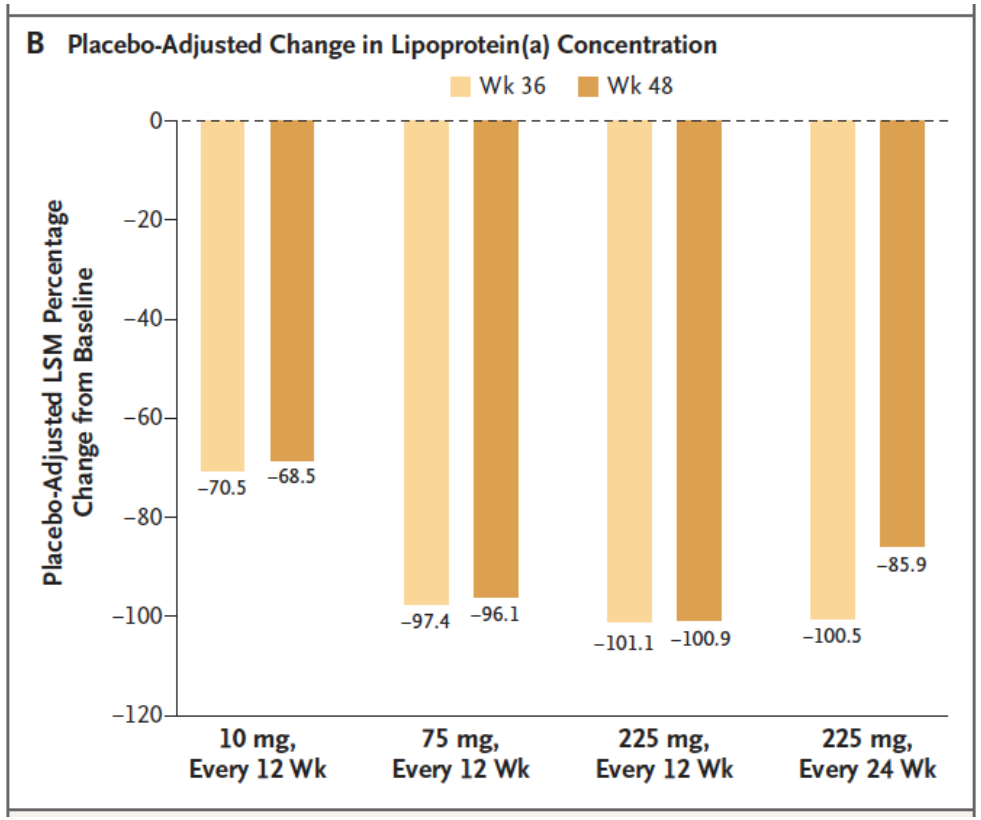
Tsimikas S. et al. *N Eng J Med* 2020; 382: 244-55

siRNA anti-Apo(a): olpasiran (OCEAN(a))

Patients with ASCVD and Lp(a) ≥ 150 nmol/L (60 mg/dL)

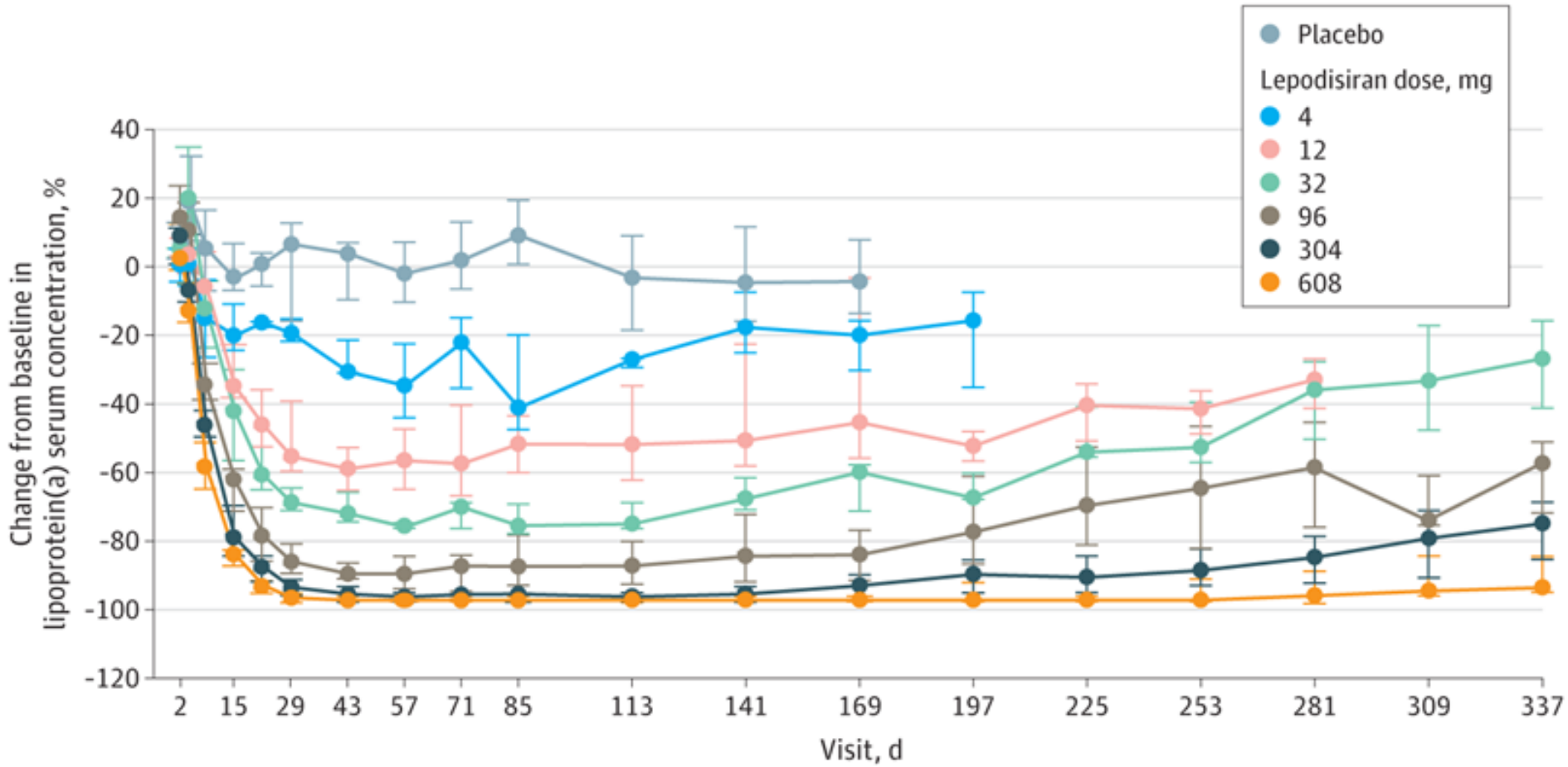
Median laboratory values (IQR)					
Lipoprotein(a) — nmol/liter	246.1 (199.9–343.3)	304.0 (194.2–397.6)	227.5 (188.4–304.2)	265.4 (200.6–342.2)	283.4 (204.6–389.2)
LDL cholesterol — mg/dl	64.8 (47.5–81.0)	69.0 (52.0–83.5)	75.0 (53.5–90.0)	62.3 (48.5–80.5)	66.0 (50.5–79.5)





O'Donoghue ML et al. *N Eng J Med* 2022; 387: 1855-1864

siRNA anti-Apo(a): LEPODISIRAN



=> Phases 3 & CVOT: 3 injections / an la première année puis 1 injection / an

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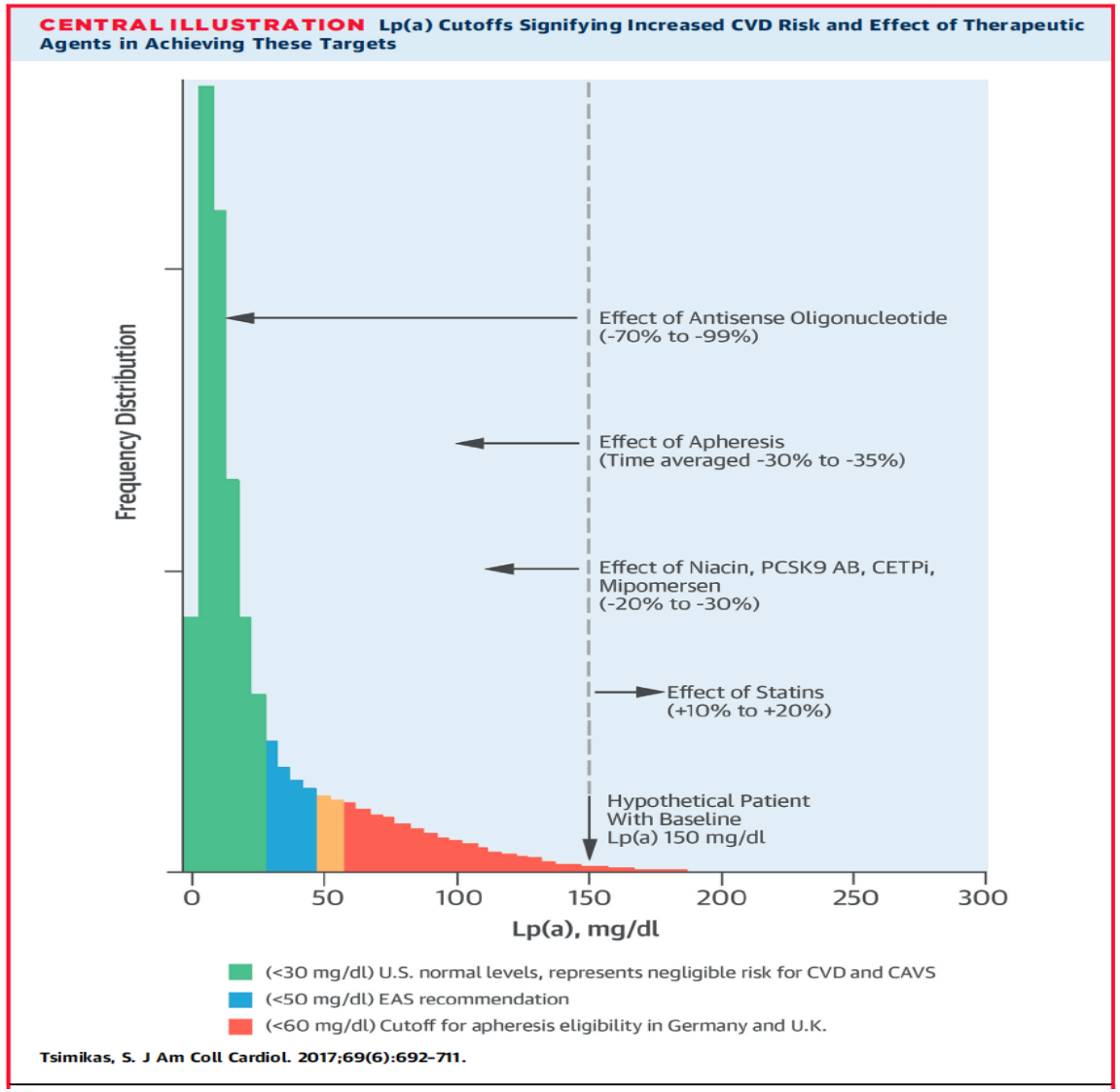
Nissen SE et al. *JAMA*. Online 12 Nov 2023

Dans l'attente des résultats des CVOTs…



- Etude HORIZON (pelacersen, Novartis®)
- Etude OCEAN (olpasiran, Amgen®)
- Etude ACCLAIM-EZEF (lepodisiran, Lilly®)

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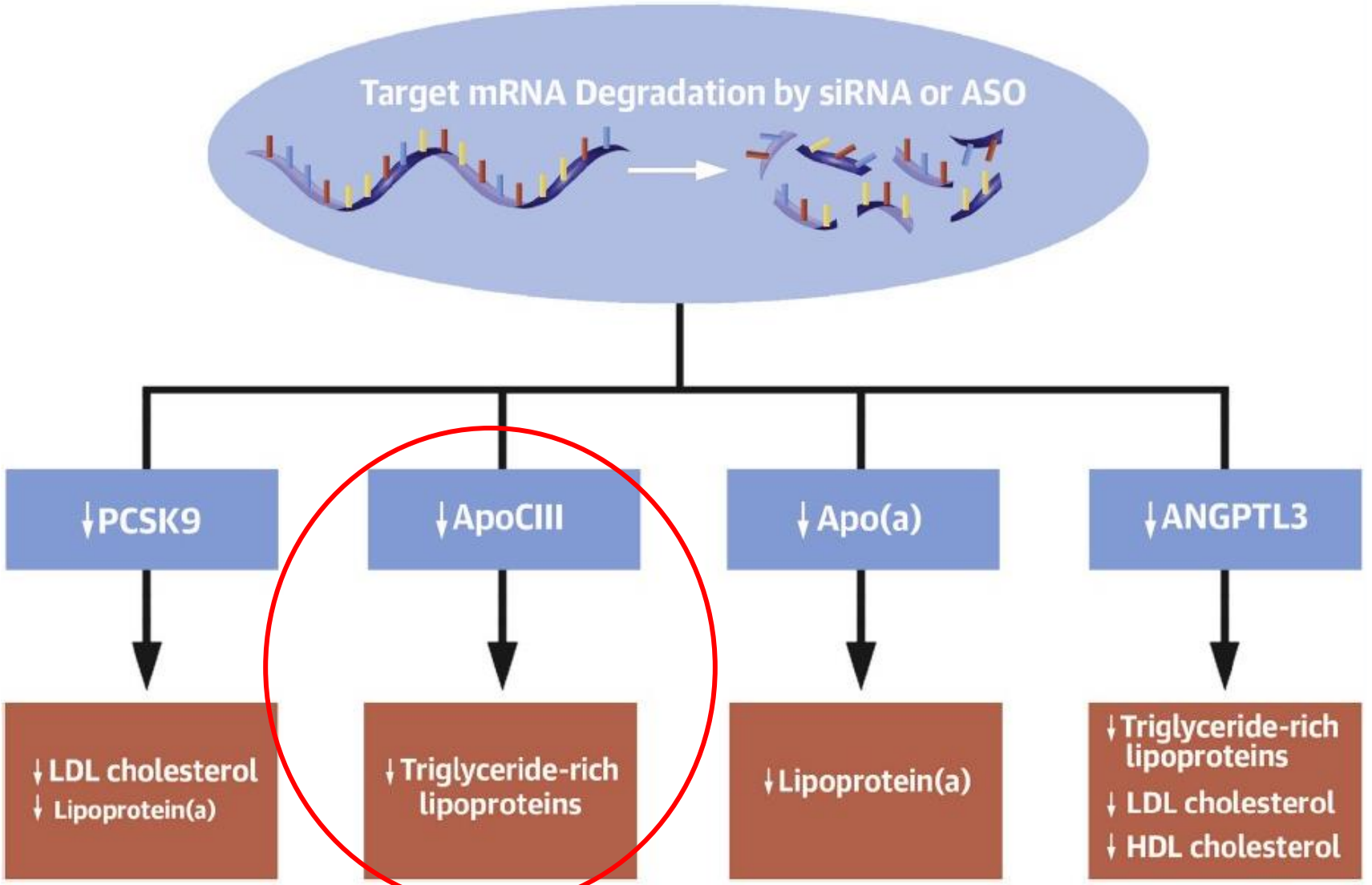
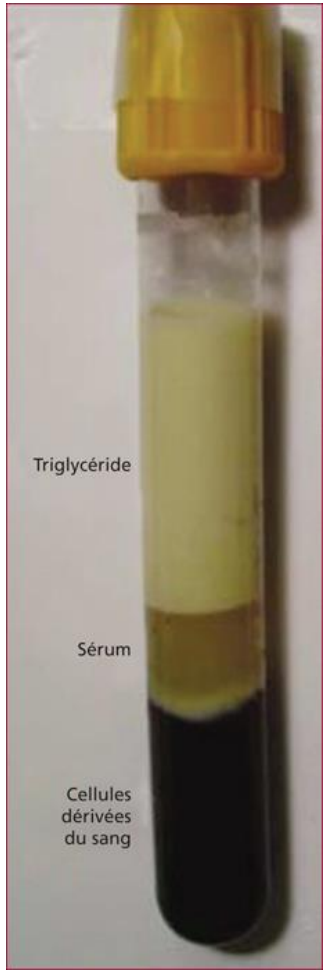
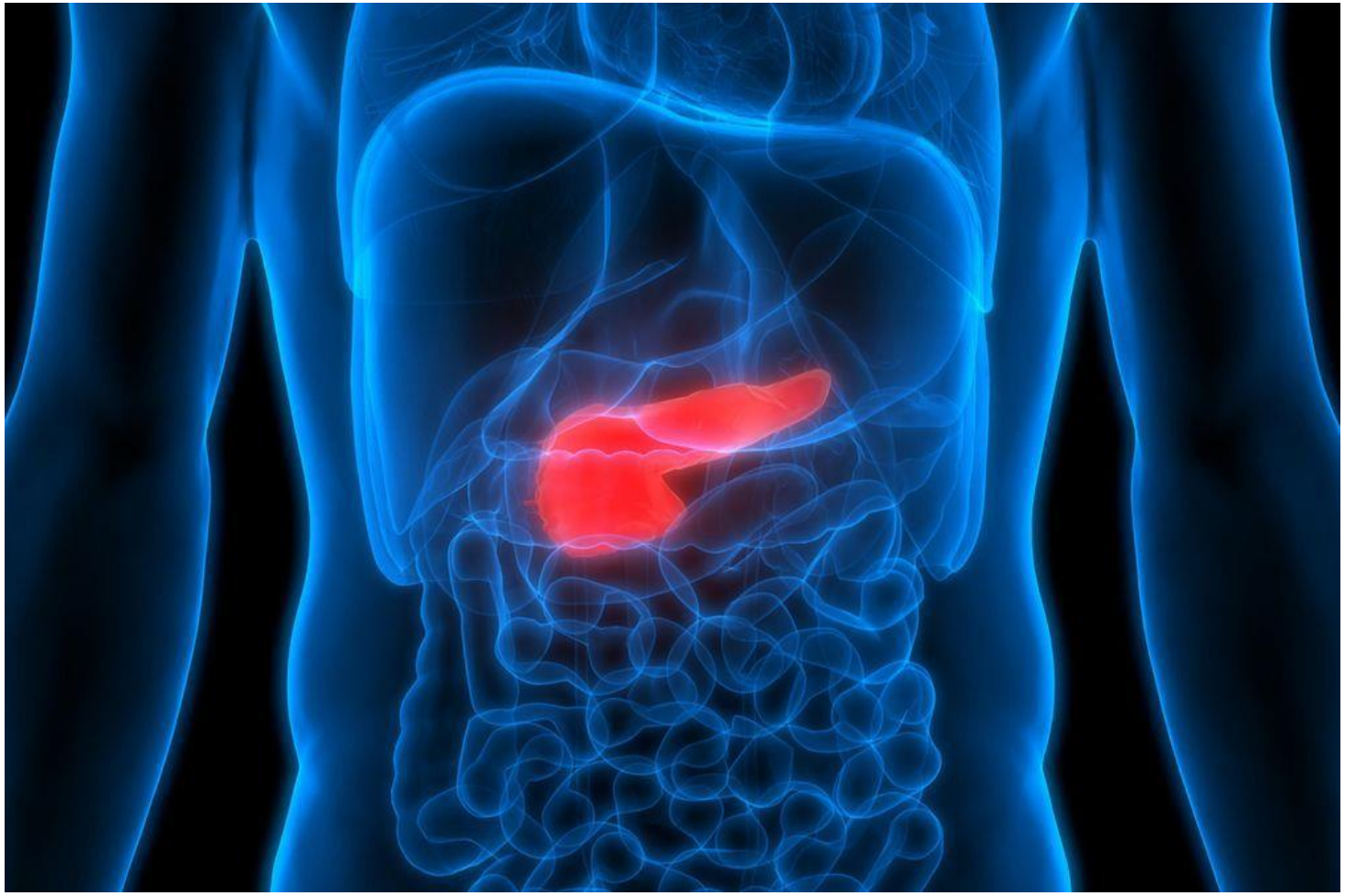


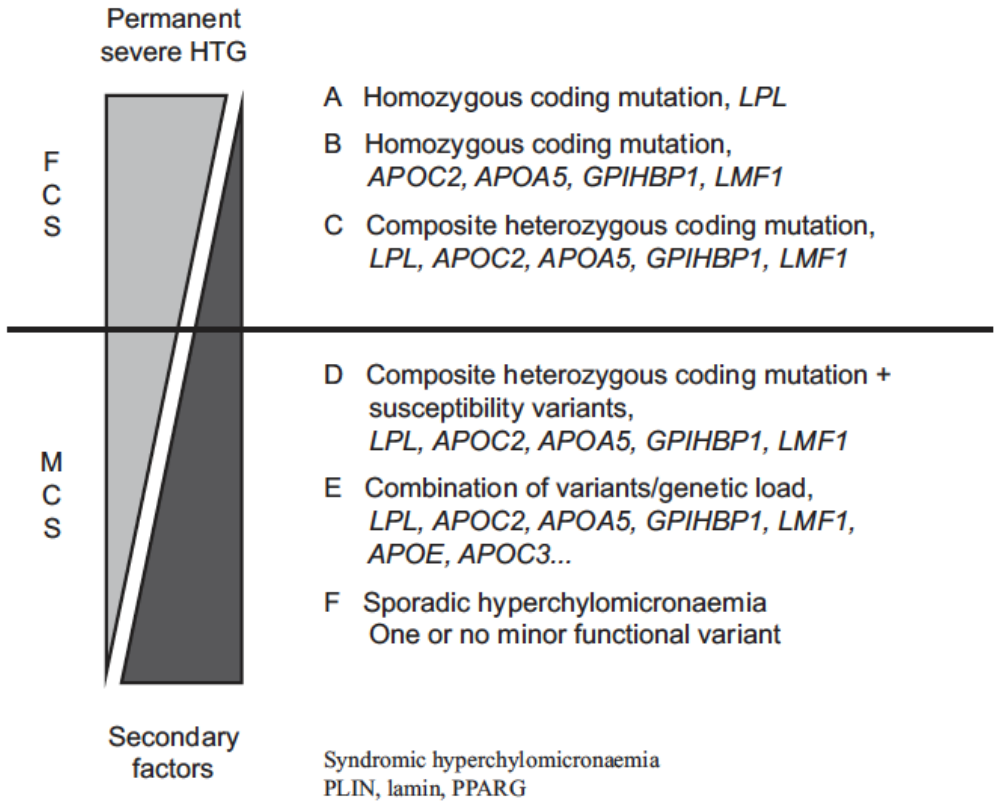
Katzmann, J.L. et al. J Am Coll Cardiol. 2020;76(5):563-79.

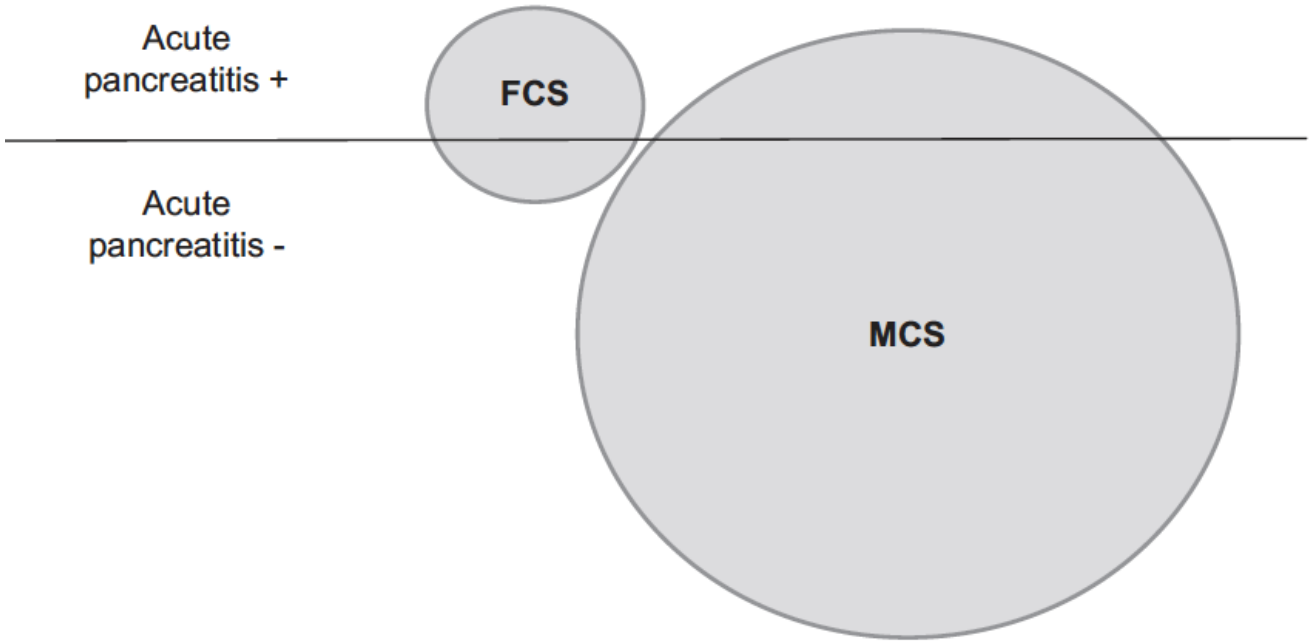
L'HYPERCHYLOMICRONEMIE FAMILIALE





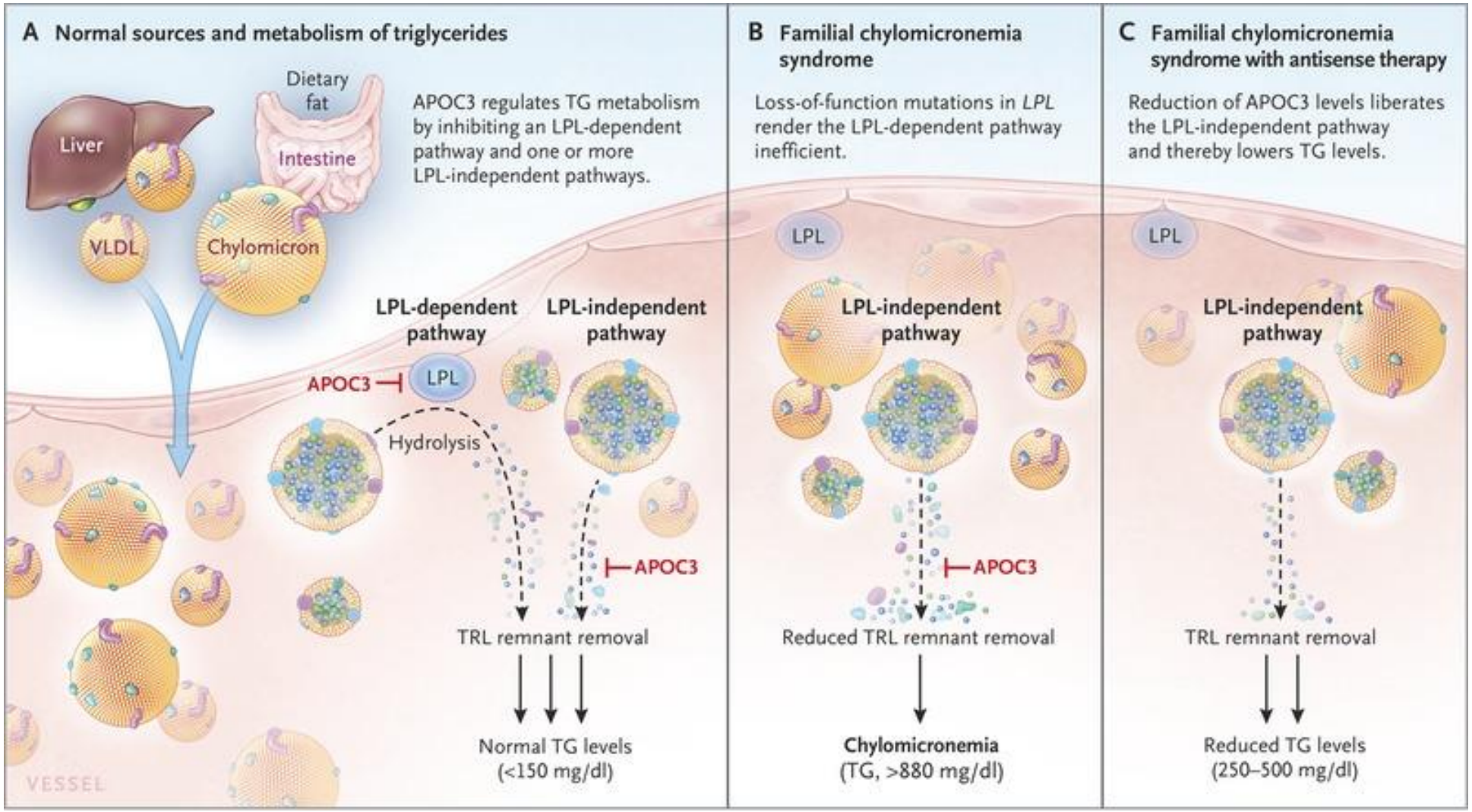
LES HYPERCHYLOMICRONEMIES





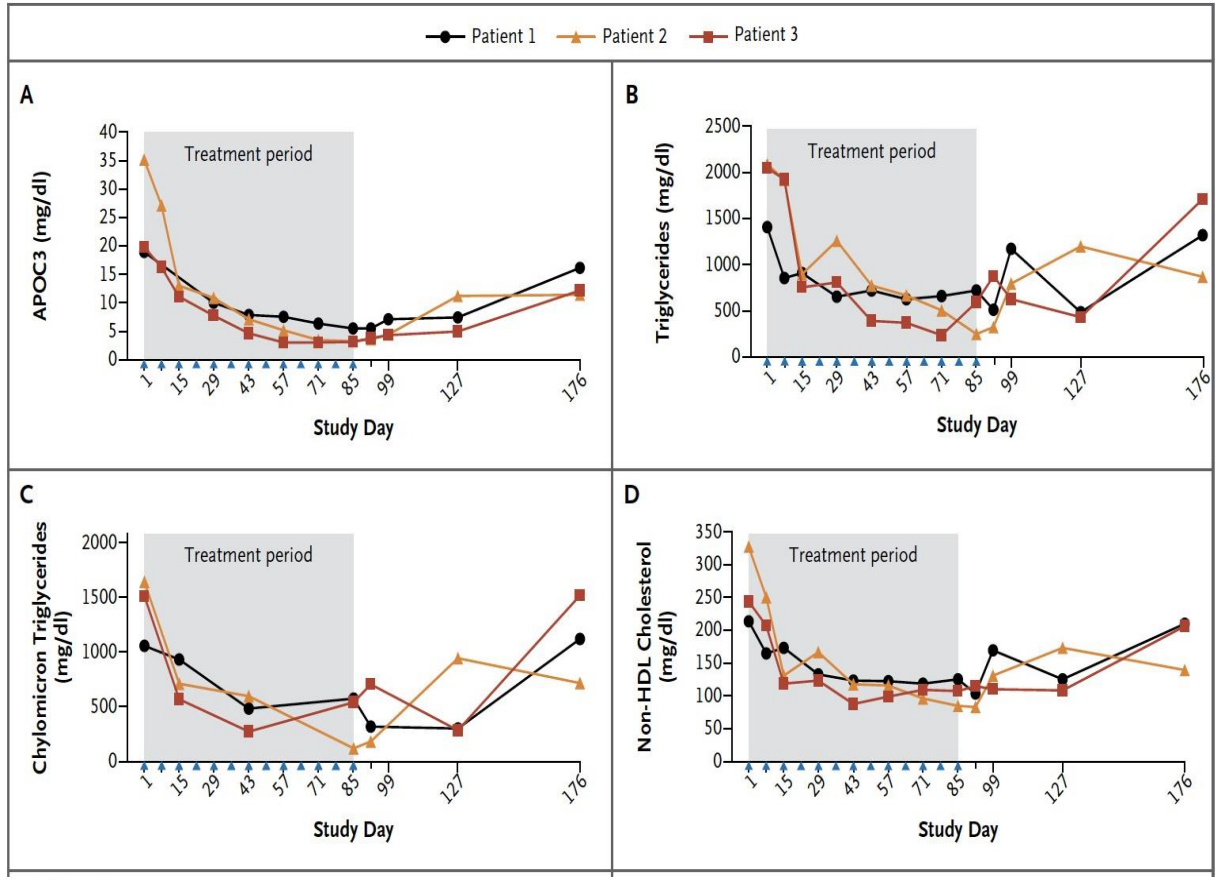
Moulin P et al. *Atherosclerosis.* 2018; 275: 265-72

Mécanisme d'action de l'apoC3

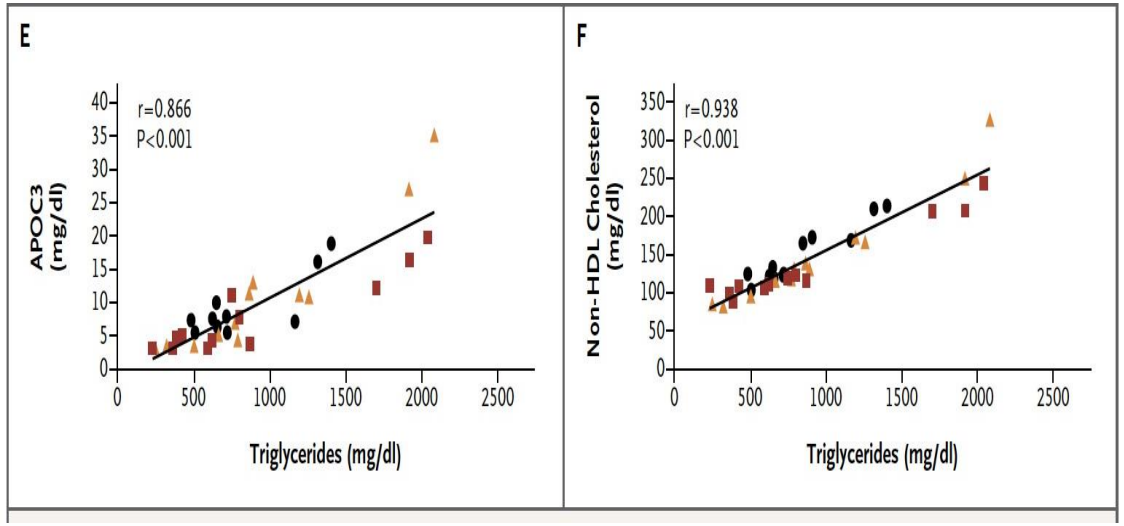


Gaudet D et al. *N Engl J Med* 2014; 371: 2200-6

L'inhibition de l'APOCIII par un ASO: preuve de concept



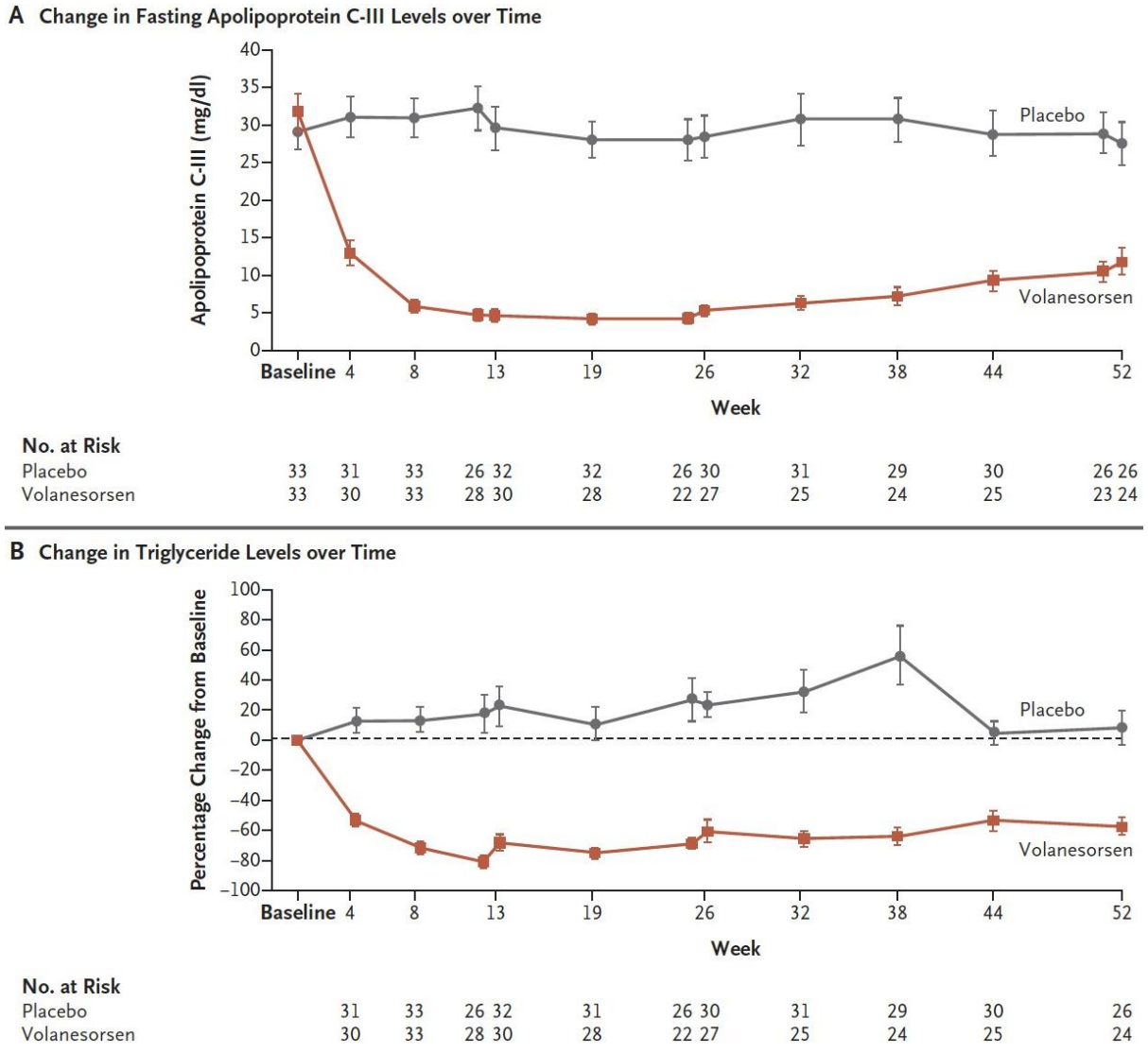
ASO anti APOCIII (ISIS 304801)
1 injection/sem

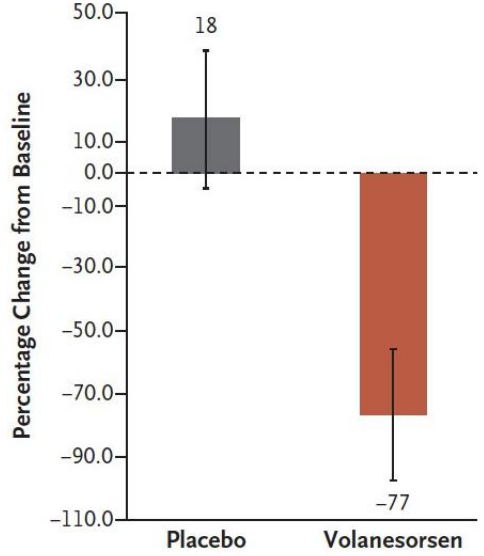


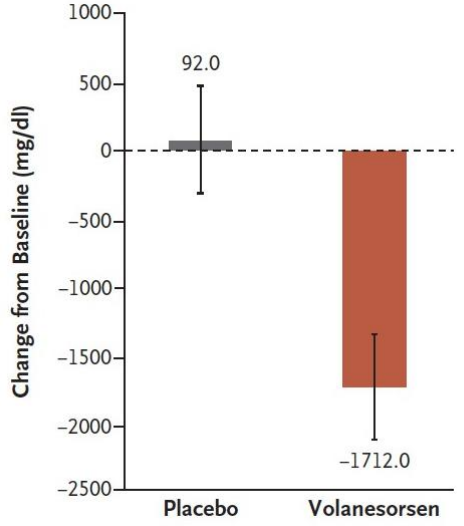
Gaudet D et al. *N Engl J Med* 2014; 371: 2200-6

ETUDE APPROACH: intérêt du volanesorsen dans la FCS

1 injection de 300 mg s/c toutes les semaines







Witztum JL et al. *N Engl J Med* 2019; 381: 531-42.

ETUDE APPROACH: intérêt du volanesorsen dans la FCS

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Placebo (N = 33)	Volanesorsen (N = 33)	All Patients (N = 66)
Mean age (range) — yr	46 (20–68)	47 (22–75)	46 (20–75)
Sex — no.			
Female	19	17	36
Male	14	16	30
Body-mass index†	24.1±4.7	25.9±6.5	25.0±5.7
Triglycerides — mg/dl	2152	2267	2209
History of pancreatitis — no. (%)	26 (79)	24 (73)	50 (76)
Baseline use of n–3 fatty acids, fibrates, or both — no. (%)	16 (48)	19 (58)	35 (53)
Genetic mutations — no. (%)			
LPL	24 (73)	17 (52)	41 (62)
APOA5	1 (3)	1 (3)	2 (3)
GPIHBP1	0	5 (15)	5 (8)
LMF1	0	1 (3)	1 (2)
APOC2	0	1 (3)	1 (2)
LPL/LMF-1	0	1 (3)	1 (2)
LPL/APOA5	1 (3)	0	1 (2)
Not identified‡	7 (21)	7 (21)	14 (21)

Witztum JL et al. *N Engl J Med* 2019; 381: 531-42.

ETUDE APPROACH: intérêt du volanesorsen dans la FCS

Table 3. Adverse Events.*

Adverse Event	Placebo (N=33)	Volanesorsen (N=33)
	number (percent)	
Injection-site reaction	0	20 (61)
Platelet count decreased	1 (3)	11 (33)
Abdominal pain	7 (21)	9 (27)
Fatigue	3 (9)	7 (21)
Headache	5 (15)	7 (21)
Nausea	2 (6)	6 (18)
Asthenia	3 (9)	5 (15)
Myalgia	1 (3)	5 (15)
Diarrhea	2 (6)	5 (15)
Epistaxis	0	5 (15)
Vomiting	3 (9)	5 (15)
Nasopharyngitis	7 (21)	5 (15)
Petechiae	0	4 (12)
Arthralgia	0	4 (12)
Pain in extremity	1 (3)	4 (12)
Thrombocytopenia	0	4 (12)
Diabetes mellitus	0	4 (12)

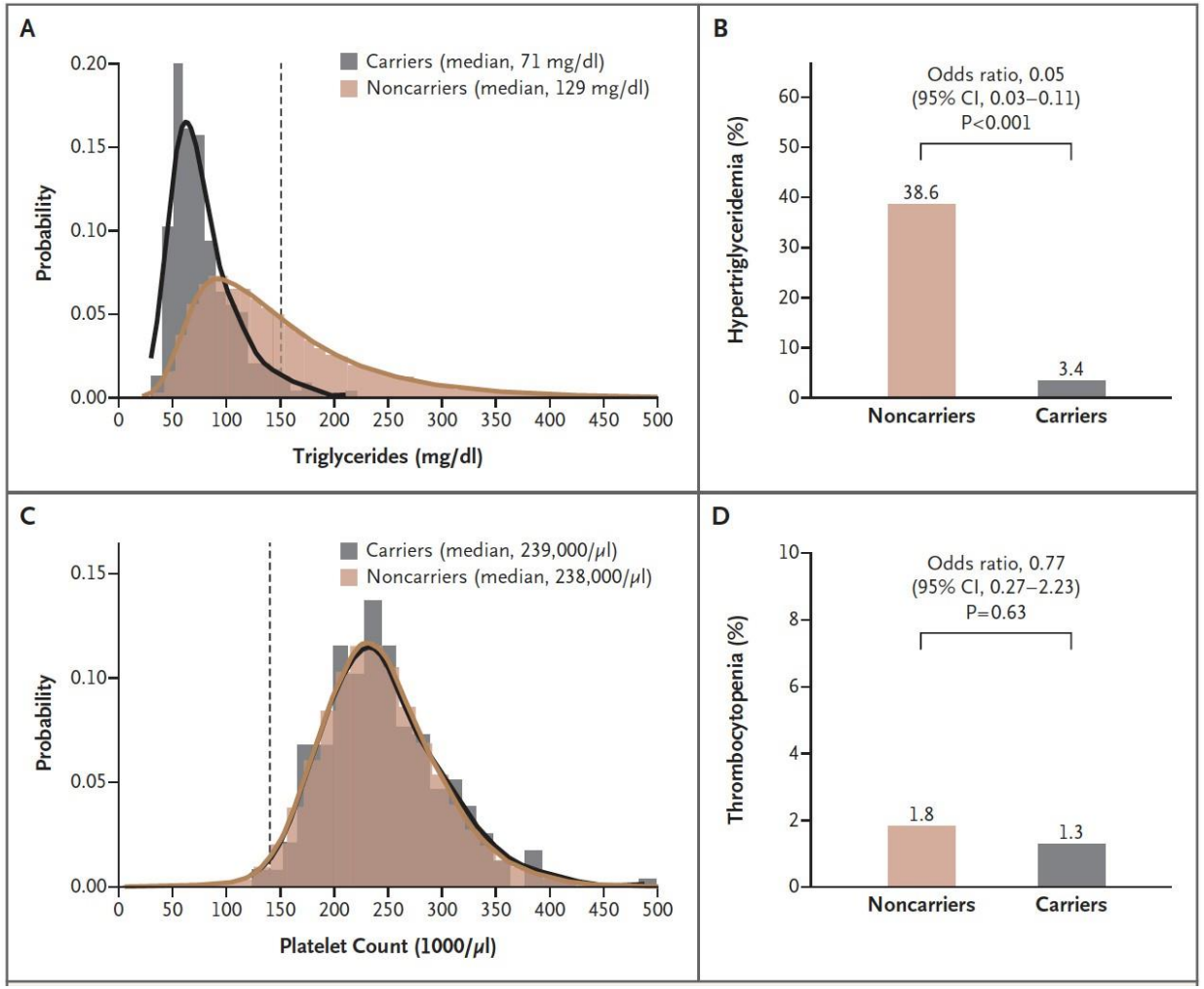
Table 4. Platelet Counts before and after Enhanced Platelet Monitoring.

Confirmed Platelet Count	Placebo (N=33)	Volanesorsen (N=33)*
	no. of patients (before/after)†	
<140,000/μl	8 (4/4)	25 (15/10)
<100,000/μl	0	16 (10/6)
100,000 to <140,000/μl	8 (4/4)	9 (5/4)
75,000 to <100,000/μl	0	6 (2/4)
50,000 to <75,000/μl	0	7 (5/2)
25,000 to <50,000/μl	0	1 (1/0)
0 to <25,000/μl	0	2 (2/0)‡

Witztum JL et al. *N Engl J Med* 2019; 381: 531-42.

La thrombopénie n'est pas un effet « on target » de l'inhibition de l'ApoC-III

Comparaison de patients avec ou sans une mutation inactivatrice de l'APO-CIII (UK Biobank)



Khetarpal SA et al. *N Engl J Med* 2019; 381: 2582-84.

COMMISSION DE LA TRANSPARENCE
AVIS
19 FEVRIER 2020

volanesorsen
WAYLIVRA 285 mg, solution injectable en seringue préremplie

Première évaluation

Avis favorable au remboursement uniquement chez les patients ayant un syndrome d'hyperchylomicronémie familial (SHCF) génétiquement confirmé, chez qui la réponse au régime alimentaire et au traitement visant à réduire les triglycérides a été insuffisante, et avec un antécédent de pancréatite.

La décision d'instauration de traitement par WAYLIVRA devra être prise lors de réunions de concertation pluridisciplinaires au sein des centres de référence des maladies rares du pancréas (PaRaDis) ou à défaut au sein d'une réunion de concertation pluridisciplinaire émanant de la NSFA (Nouvelle Société Française d'Athérosclérose) et ce compte tenu de la population spécifique susceptible de bénéficier de ce traitement au regard des données d'efficacité et du profil de tolérance, notamment concernant le risque de thrombopénie (le traitement s'accompagne d'une surveillance régulière de la numération plaquettaire).

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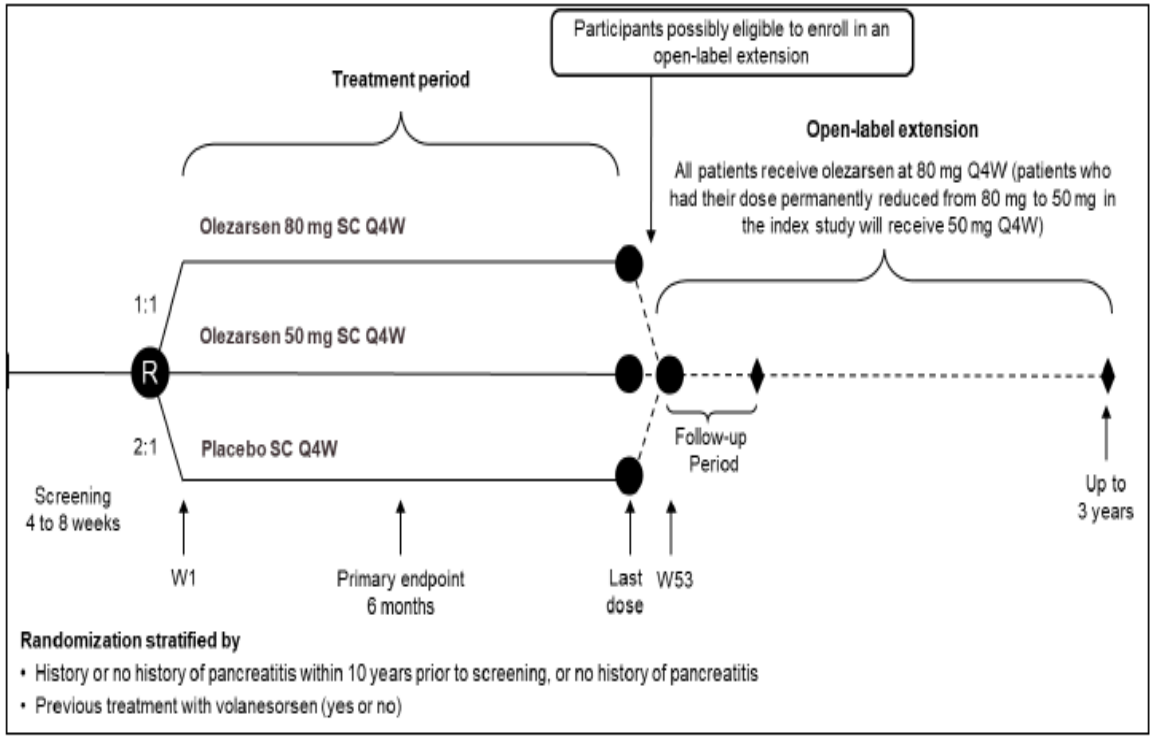
2ème génération d'ASO anti-apoC-III: olezarsen

- **Conjugaison à un résidu GalNAc** => espacement des injections et diminution des doses (50-80 mg/4 sem)

BALANCE: Etude de phase 3 chez les patients avec une hyperchylomicronémie

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Olezarsen, 80 mg (N=22)	Olezarsen, 50 mg (N=21)	Placebo (N=23)
Age — yr	47.7±13.3	43.2±12.1	44.0±14.7
Sex — no. (%)			
Female	11 (50)	15 (71)	12 (52)
Male	11 (50)	6 (29)	11 (48)
Race and ethnic group — no. (%)†			
White	17 (77)	17 (81)	22 (96)
Hispanic or Latino	1 (5)	3 (14)	3 (13)
Asian	3 (14)	3 (14)	0
Native Hawaiian or Pacific Islander	0	1 (5)	0
Other	2 (9)	0	1 (4)
Weight — kg	68.4±16.7	61.2±11.6	67.8±16.1
Body-mass index‡	25.1±6.0	22.4±3.5	24.2±4.1
History of acute pancreatitis in the previous 10 years — no. (%)	17 (77)	15 (71)	15 (65)
No. of episodes of acute pancreatitis per patient in the previous 10 years§	4.8±7.5	4.1±4.4	6.6±16.5
Type 1 or 2 diabetes mellitus — no. (%)	7 (32)	3 (14)	6 (26)
Hypertension — no. (%)	4 (18)	3 (14)	6 (26)
Tobacco user — no. (%)	2 (9)	3 (14)	0
Current thrombocytopenia — no. (%)¶	2 (9)	4 (19)	4 (17)
Laboratory measures — mg/dl			
Triglyceride level			
Mean	2613±1499	2684±1235	2596±1256
Median (range)	2086 (683–6898)	2679 (779–5965)	2493 (334–5436)

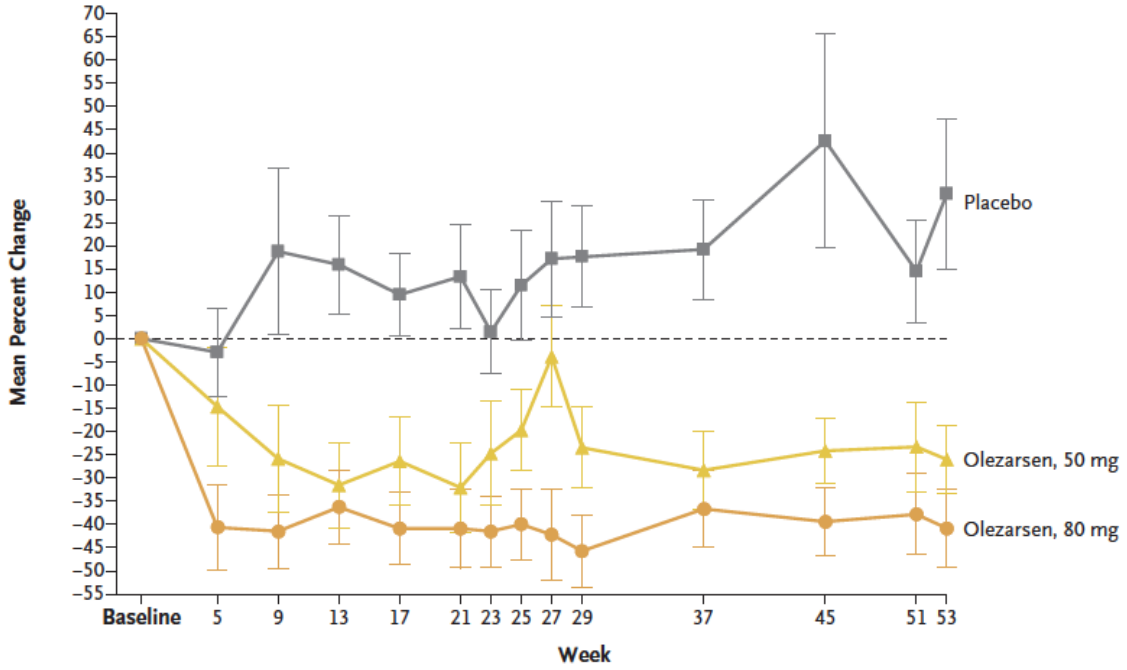


Stroes ESG et al. *N Engl J Med* 2024; 390: 1781-92

2ème génération d'ASO anti-apoC-III: olezarsen

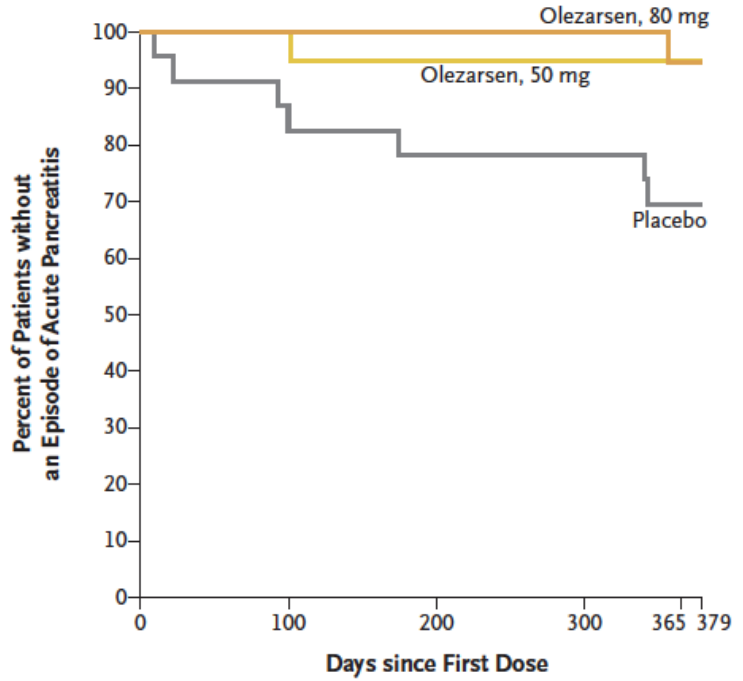
BALANCE: Etude de phase 3 chez les patients avec une hyperchylomicronémie

A Change in Fasting Plasma Triglyceride Levels



No. of Patients														
Placebo	23	23	21	21	22	22	19	21	19	21	22	20	19	20
Olezarsen, 50 mg	21	19	18	20	19	15	17	19	18	18	18	19	18	19
Olezarsen, 80 mg	22	21	20	21	20	20	15	19	16	20	18	19	15	17

Pancréatites aigües



No. at Risk					
Placebo	23	19	18	18	14 5
Olezarsen, 50 mg	21	20	19	19	17 5
Olezarsen, 80 mg	22	20	20	19	18 9

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Stroes ESG et al. *N Engl J Med* 2024; 390: 1781-92

2ème génération d'ASO anti-apoC-III: olezarsen

BALANCE: Etude de phase 3 chez les patients avec une hyperchylomicronémie

Table 2. Adverse Events That Occurred during the Treatment Period.*

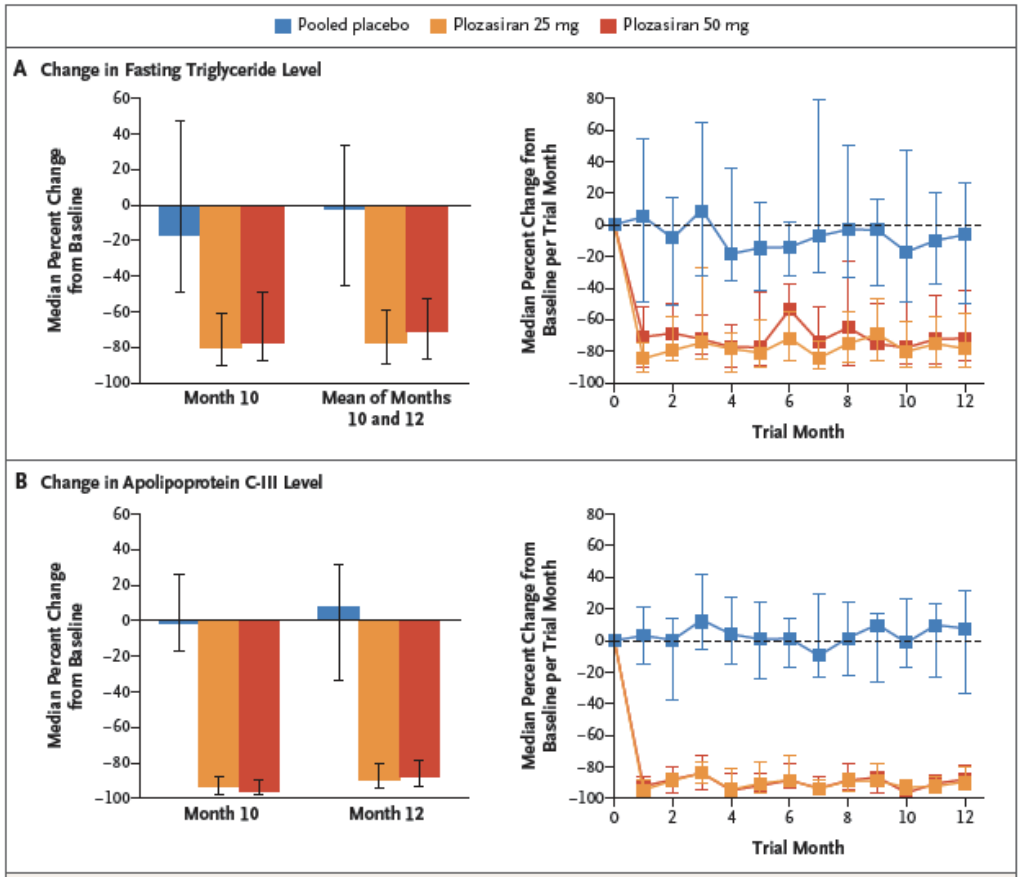
Event	Olezarsen, 80 mg (N=22)	Olezarsen, 50 mg (N=21)	Placebo (N=23)
Adverse event — no. of patients/no. of events (% of patients)			
Any adverse event	19/110 (86)	18/133 (86)	22/141 (96)
Adverse event related to the trial drug or placebo			
Any severity	7/25 (32)	6/29 (29)	5/7 (22)
Mild	3/16 (14)	6/29 (29)	3/5 (13)
Moderate	4/9 (18)	0	0
Severe	0	0	2/2 (9)
Any adverse event leading to discontinuation of the trial drug or placebo	2/7 (9)	1/1 (5)	0
Any serious adverse event	3/3 (14)	4/4 (19)	9/21 (39)
Any serious adverse event related to trial drug	0	0	0
Any adverse event leading to death	0	1/1 (5)	0
Most frequent adverse event†			
Coronavirus disease 2019	3/3 (14)	6/6 (29)	8/8 (35)
Abdominal pain	4/5 (18)	3/5 (14)	8/14 (35)
Diarrhea	2/2 (9)	1/1 (5)	6/12 (26)
Headache	1/3 (5)	4/7 (19)	3/4 (13)
Pancreatitis	1/1 (5)	2/2 (10)	4/5 (17)
Fatigue	1/1 (5)	1/3 (5)	4/4 (17)
Adverse event of interest — no. of patients (%)			
Reduction in platelet count‡	0	0	0
≥1 Injection-site reaction in a patient	3 (14)	3 (14)	2 (9)
≥1 Influenza-like illness in a patient§	1 (5)	1 (5)	0
≥1 Hypersensitivity adverse event in a patient	0	1 (5)	3 (13)
Narrow FMQ for anaphylactic reaction	0	0	0
Narrow FMQ for hepatic failure	0	0	0
Abnormal hepatic laboratory value			
ALT level ≥3×ULN	0	0	2 (9)
AST level ≥3×ULN	1 (5)	0	1 (4)
Total bilirubin level ≥2×ULN	0	0	0
GGT level ≥2×ULN	2 (9)	6 (29)	6 (26)
ALP level ≥2×ULN	0	0	1 (4)
INR ≥1.5×ULN	2 (9)	0	1 (4)
Patients with ≥1 renal impairment–related adverse event according to narrow or broad SMQ for acute renal failure	0	0	2 (9)

Stroes ESG et al. *N Engl J Med* 2024; 390: 1781-92

siRNA anti-apoC-III: l'exemple du Plozasiran

Etude PALISADE: Etude de phase 3 chez les patients avec une hyperchylomicronémie familiale
1 injection s/c tous les 3 mois

Variable	Placebo (N=25)	Plozasiran, 25 mg (N=26)	Difference, 25-mg Dose vs. Placebo (95% CI)†	Plozasiran, 50 mg (N=24)	Difference, 50-mg Dose vs. Placebo (95% CI)†
	median (IQR)		*percentage points*	*median (IQR)*	*percentage points*
Triglycerides					
Baseline value — mg/dl	2053 (1435 to 2755)	2008 (1204 to 3361)		1902 (1434 to 2948)	
Percent change from baseline					
Month 10	-17 (-49 to 47)	-80 (-90 to -61)	-59 (-90 to -28)	-78 (-88 to -49)	-53 (-83 to -22)
Mean at months 10 and 12	-3 (-45 to 33)	-78 (-89 to -59)	-60 (-92 to -28)	-71 (-87 to -53)	-51 (-84 to -18)
Apolipoprotein C-III					
Baseline value — mg/dl	39 (29 to 50)	39 (27 to 44)		30 (18 to 37)	
Percent change from baseline					
Month 10	-1 (-17 to 27)	-93 (-98 to -88)	-91 (-108 to -73)	-96 (-98 to -90)	-93 (-109 to -77)
Month 12	8 (-34 to 31)	-89 (-94 to -80)	-87 (-113 to -61)	-88 (-93 to -79)	-88 (-112 to -63)



Watts GF et al. *N Engl J Med* 2024; online 02 Sep 2024

siRNA anti-apoC-III: l'exemple du Plozasiran

Etude PALISADE: Etude de phase 3 chez les patients avec une hyperchylomicronémie familiale
1 injection s/c tous les 3 mois

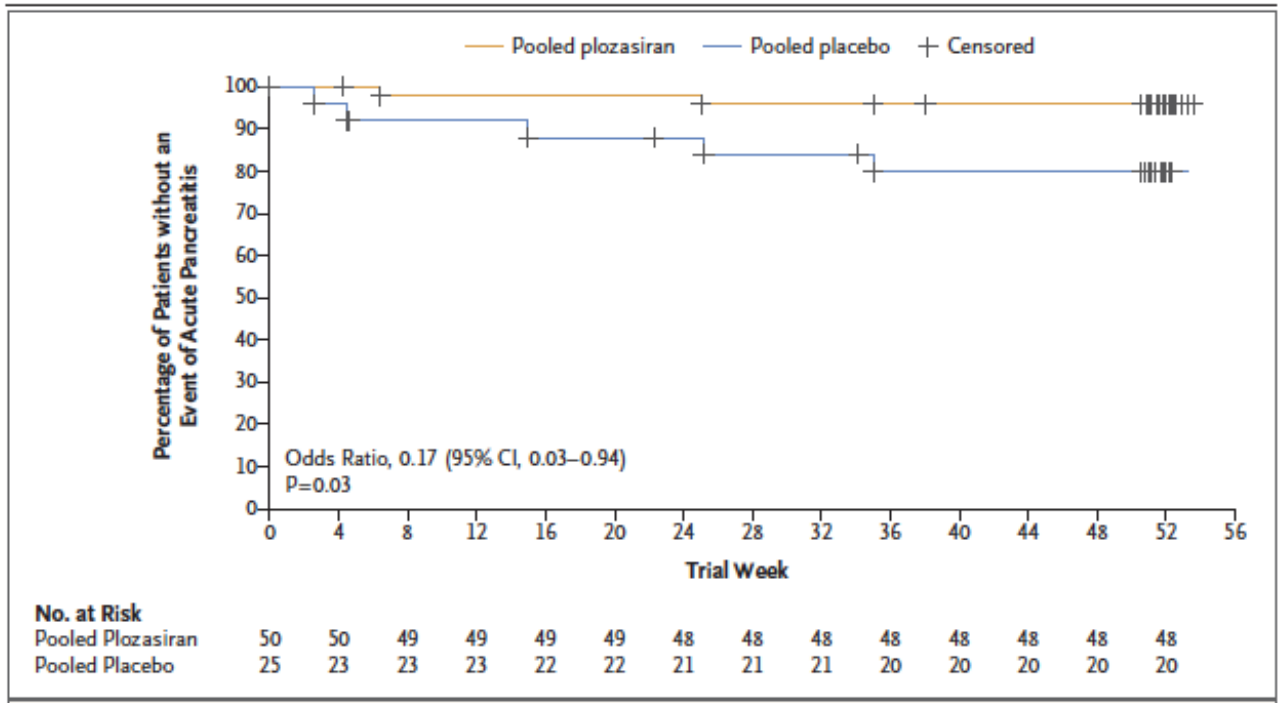


Figure 2. Acute Pancreatitis.
Shown is a Kaplan–Meier plot of the time until the first positively adjudicated events of acute pancreatitis in the full analysis population of 75 patients with persistent chylomicronemia.

Table 3. Adverse Events.*

Adverse Event	Plozasiran, 25 mg (N=26)	Plozasiran, 50 mg (N=24)	Placebo (N=25)
Any event — no.	23	20	20
Most common event — no. (%)			
Abdominal pain	7 (27)	6 (25)	5 (20)
Covid-19	5 (19)	7 (29)	0
Nasopharyngitis	5 (19)	2 (8)	3 (12)
Headache	3 (12)	5 (21)	2 (8)
Nausea	4 (15)	3 (12)	2 (8)
Back pain	3 (12)	2 (8)	2 (8)
Upper respiratory tract infection	3 (12)	2 (8)	2 (8)
Diarrhea	1 (4)	4 (17)	2 (8)
Severe event — no. (%)	3 (12)	3 (12)	5 (20)
Serious event — no. (%)	5 (19)	2 (8)	7 (28)
Premature discontinuation — no. (%)	3 (12)	2 (8)	6 (24)
Laboratory values			
Glycated hemoglobin — %			
Baseline	5.7±0.9	5.6±1.2	6.1±1.3
Month 12	6.0±1.0	5.8±1.6	6.2±1.2
Platelet count†			
Baseline	204.4±70.4	192.9±50.7	217.9±80.5
Change from baseline at month 10	28.7±61.2	−4.4±48.2	25.9±38.2
Change from baseline at month 12	−4.3±40.8	−8.7±50.8	8.6±47.5

Watts GF et al. *N Engl J Med* 2024; online 02 Sep 2024

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Le futur: l'édition génomique (CRISPR/Cas9) in vivo

Article

In vivo CRISPR base editing of *PCSK9* durably lowers cholesterol in primates

https://doi.org/10.1038/s41586-021-03534-y

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Check for updates

nature
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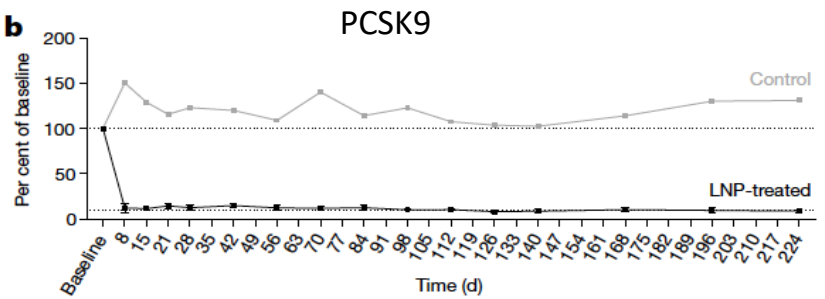
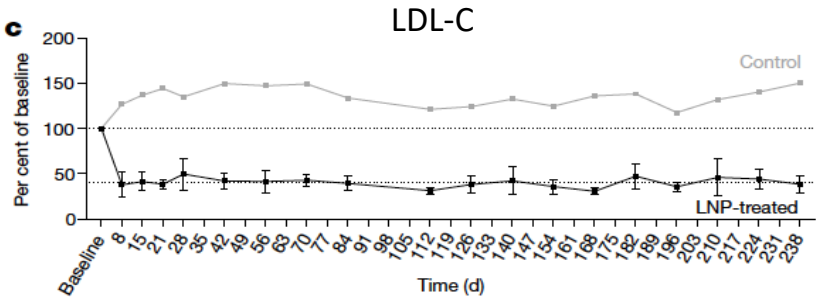
Kiran Musunuru[1,2,3], Alexandra C. Chadwick[4], Taiji Mizoguchi[4], Sara P. Garcia[4], Jamie E. DeNizio[4], Caroline W. Reiss[4], Kui Wang[4], Sowmya Iyer[4], Chaitali Dutta[4], Victoria Clendaniel[4], Michael Amaonye[4], Aaron Beach[4], Kathleen Berth[4], Souvik Biswas[4], Maurine C. Braun[4], Huei-Mei Chen[4], Thomas V. Colace[4], John D. Ganey[4], Soumyashree A. Gangopadhyay[4], Ryan Garrity[4], Lisa N. Kasiewicz[4], Jennifer Lavoie[4], James A. Madsen[4], Yuri Matsumoto[4], Anne Marie Mazzola[4], Yusuf S. Nasrullah[4], Joseph Nneji[4], Huilan Ren[4], Athul Sanjeev[4], Madeleine Shay[4], Mary R. Stahley[4], Steven H. Y. Fan[5], Ying K. Tam[5], Nicole M. Gaudelli[5], Giuseppe Ciaramella[5], Leslie E. Stolz[4], Padma Malyala[4], Christopher J. Cheng[4], Kallanthottathil G. Rajeev[4], Ellen Rohde[4], Andrew M. Bellinger[4] & Sekar Kathiresan[4,6]





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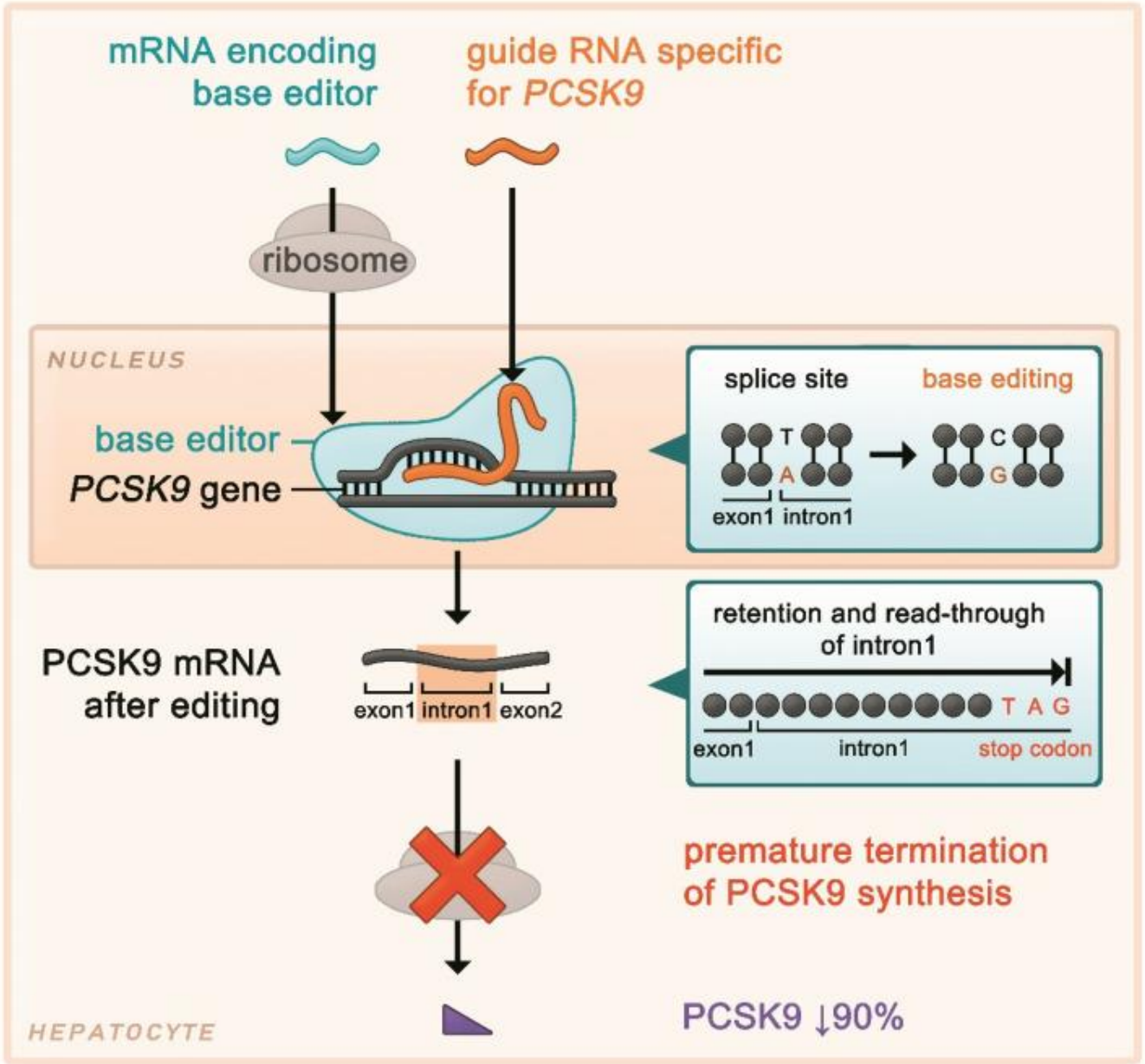

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Release Details

Verve Therapeutics Announces Updates on its PCSK9 Program

Apr 2, 2024

PDF VERSION

Heart-1 clinical trial demonstrated LDL-C reduction of up to 73% at 0.45 mg/kg of VERVE-101

Company to pause enrollment in Heart-1 clinical trial following asymptomatic Grade 3 transient ALT elevation and thrombocytopenia seen in the sixth participant enrolled in 0.45 mg/kg dose cohort

Verve to prioritize development of VERVE-102, which uses a different LNP delivery system than VERVE-101; Clinical Trial Applications have been cleared by the U.K. MHRA and Health Canada; initiation of Heart-2 clinical trial of VERVE-102 is expected in 2Q 2024, consistent with existing PCSK9 program guidance

Cash runway remains into late 2026

https://ir.vervetx.com/news-releases/news-release-details/verve-therapeutics-announces-updates-its-pcsk9-program

CONCLUSION

Les thérapies ciblant l'ARNm en lipidologie: une révolution en marche

- Des **cibles** identifiées et validées par la génétique: PCSK9, ANGPTL3, APOC-III…
- Des données solides pour le traitement des maladies génétiques et/ou rares: **HF** & **FCS**
- Un espoir pour les maladies cardiovasculaires (PCSK9 et Lp(a)): attendre les résultats des CVOTs en cours
- Un **nouveau mode d'administration**: 1 injection / 3 à 6 mois =>meilleure compliance?
- Un coût de production en baisse : siRNA << mAbs
- Il faut rester prudent pour l'édition génomique à large échelle dans les maladies chroniques : la technologie risque d'avancer plus vite que la connaissance biologique

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MERCI POUR VOTRE ATTENTION

CEDRA
CENTRES D'EXPERTISE DES DYSLIPIDEMIES RARES

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