CARDIO SCOPIE

iCANN LIFE SCIENCES

LDL-c, une cible à atteindre afin de réduire le risque CV de votre patient à haut et très haut risque

Symposium satellite Daiichi-Sankyo

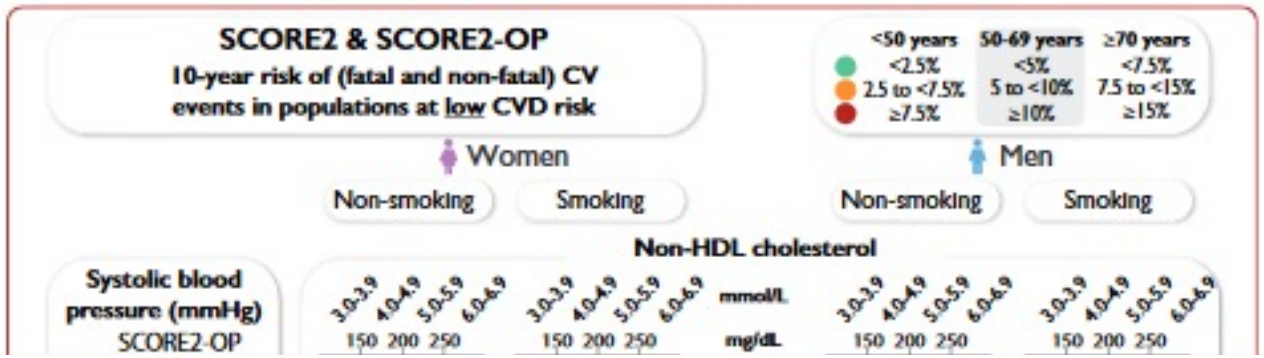
Prof. Fabian DEMEURE

CHU UCL Namur – site Godinne

CHU UCL NAMUR

CARDIO SCOPIE

Evaluation du risque CV



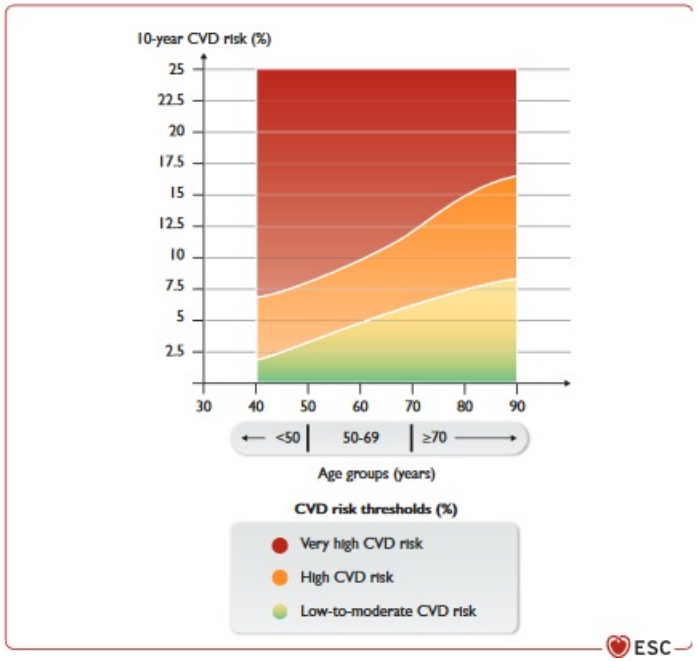
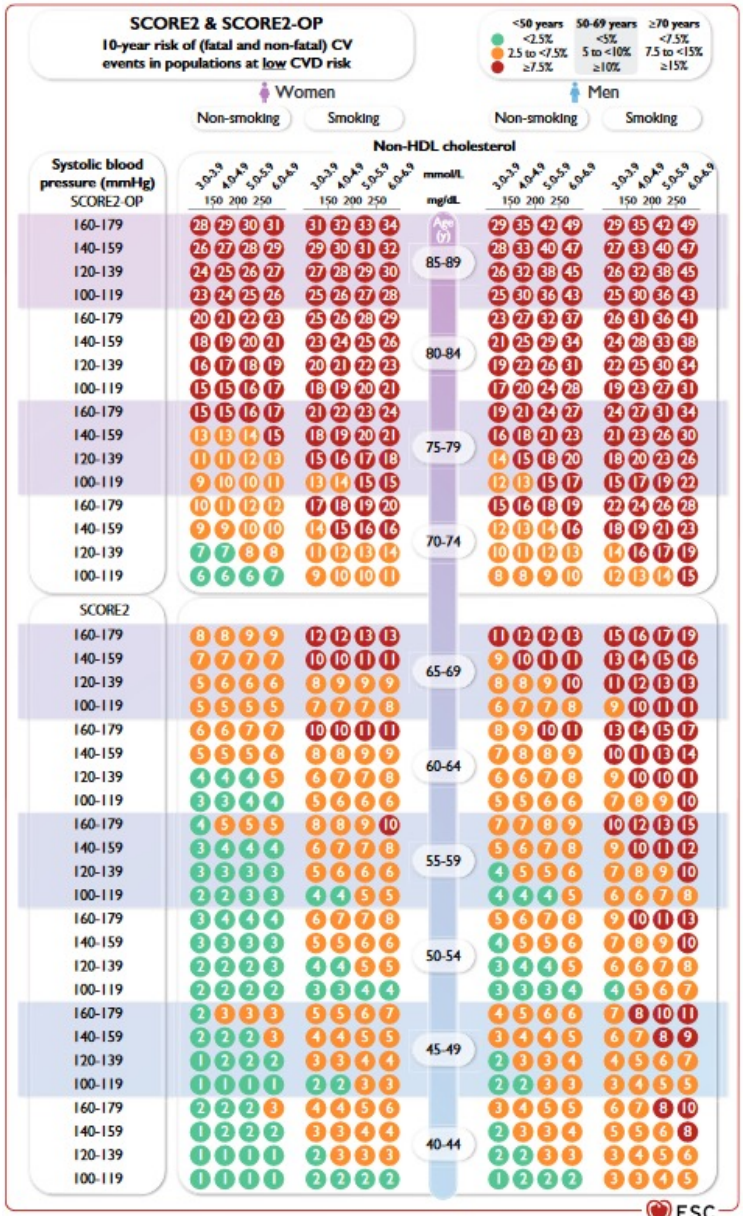


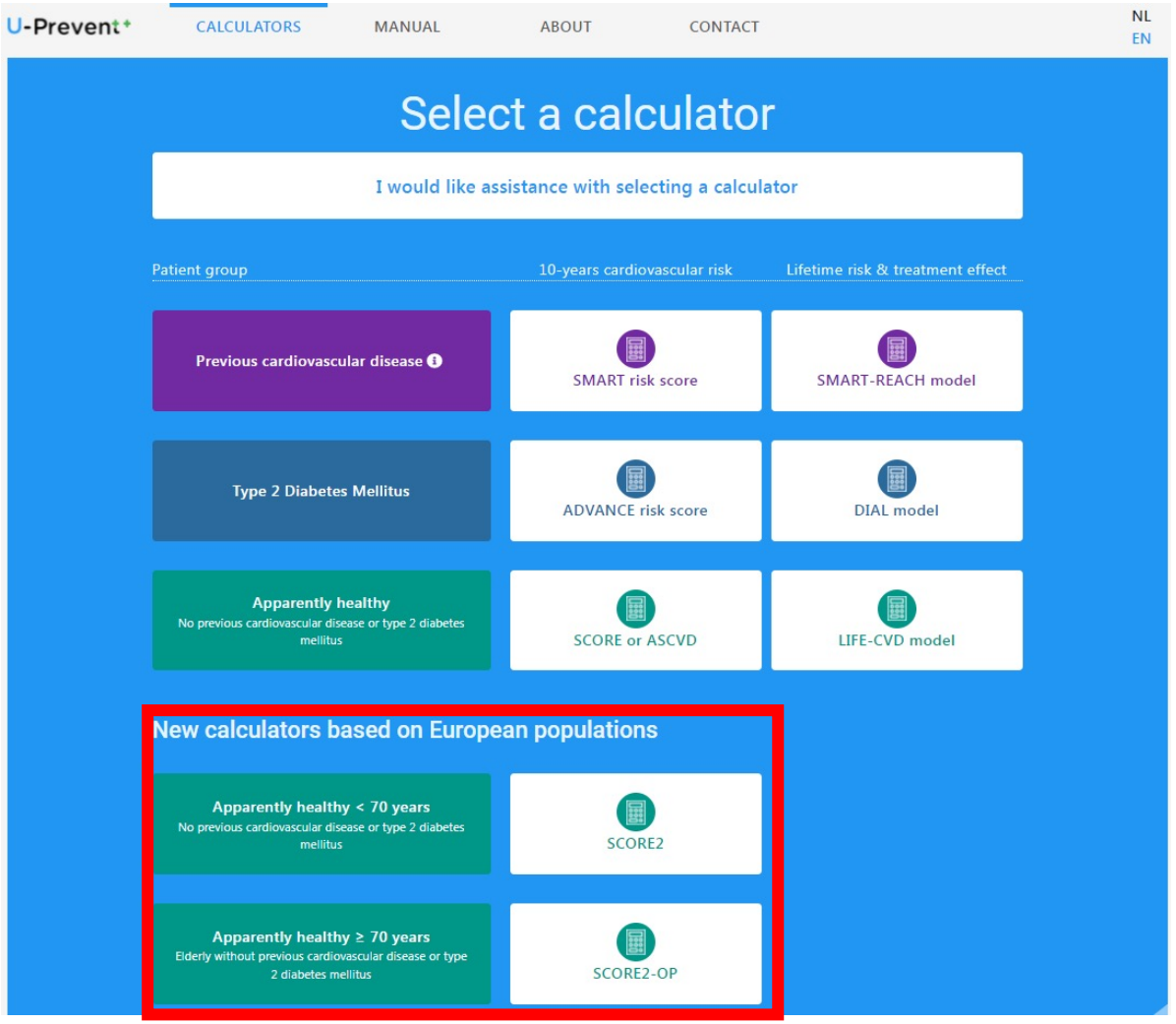
Table 5 Cardiovascular disease risk categories based on SCORE2 and SCORE2-OP in apparently healthy people according to age

	<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%



Evaluation du risque CV

www.U-prevent.com



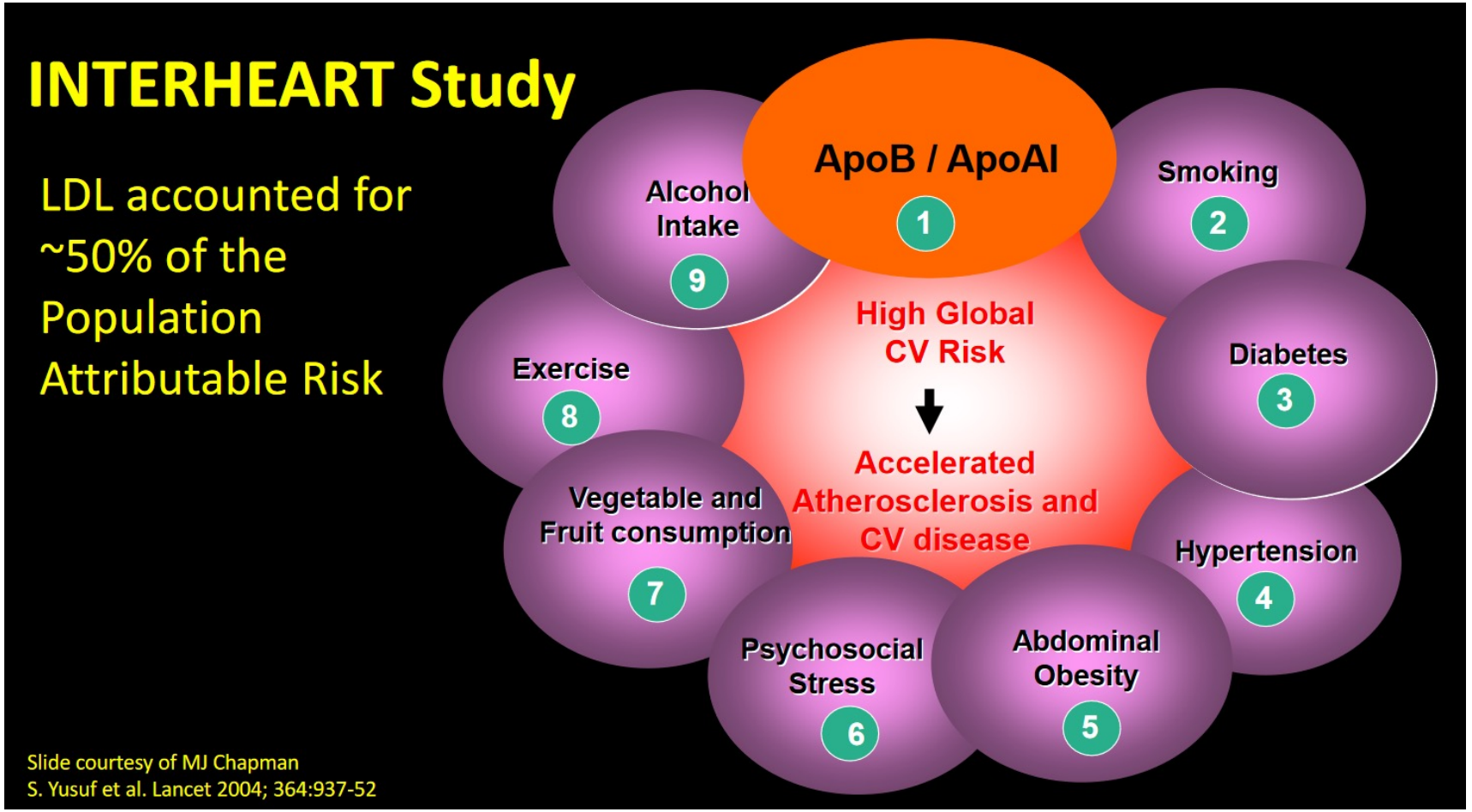
De nouvelles cibles en 2019

Risk category		LDL goals (starting with untreated LDL-C)		
		2016	2019	
Very-high-risk	1 B	<1.8 mmol/L (70 mg/dL) or >50% if LDL-C 1.8-3.5 (70-135 mg/dL)	**<1.4 mmol/L (55 mg/dL) and >50%↓**	1 A
High-risk	1 B	<2.6 mmol/L (100 mg/dL) or >50% if LDL-C 2.6-5.2 (100-200 mg/dL)	**<1.8 mmol/L (70 mg/dL) and >50%↓**	1 A
Moderate-risk	IIa C	<3.0 mmol/L (115 mg/dL)	**< 2.6 mmol/L (100 mg/dL)**	IIa A
Low-risk	IIa C	<3.0 mmol/L (115 mg/dL)	**< 3.0 mmol/L (116 mg/dL)**	IIb A

MORE INTENSIVE REDUCTION OF LDL-C ACROSS CV RISK CATEGORIES

Mach F, *et al. Eur Heart J.* 2019; 0:1-78
Catapano A, *et al. Eur Heart J.* 2016; 37, 2999-3058

Pourquoi cibler le LDL ?



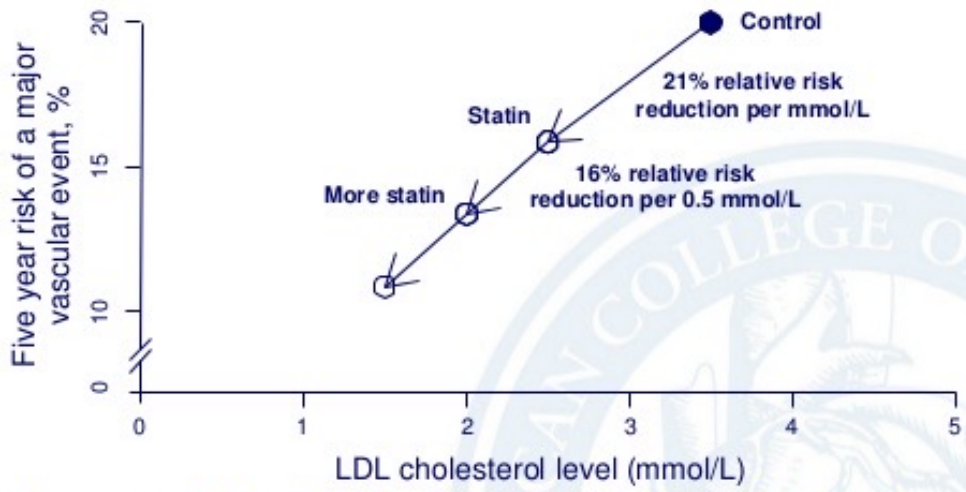
Présentation EAS 2017 - Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic and clinical studies. A Consensus Statement from the European Atherosclerosis Society Consensus Panel

Pourquoi modifier les cibles ?

HMG-CoA Reductase Inhibitor Evidence: Effect of Intensive Therapy

Cholesterol Treatment Trialists' (CTT) Collaboration

Meta-analysis of 169,138 patients randomized to at least 2 years of statin therapy



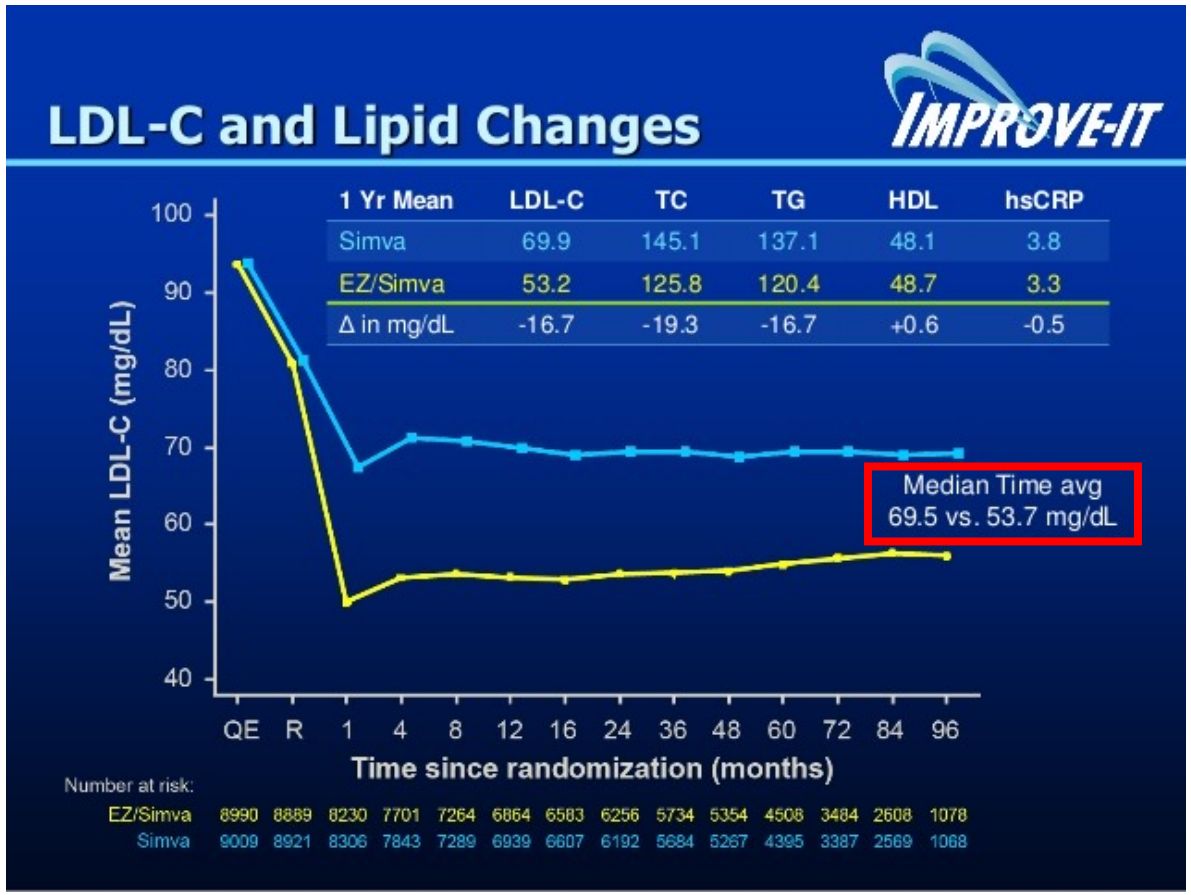
There is a proportionate reduction in CV events with greater LDL-cholesterol reduction

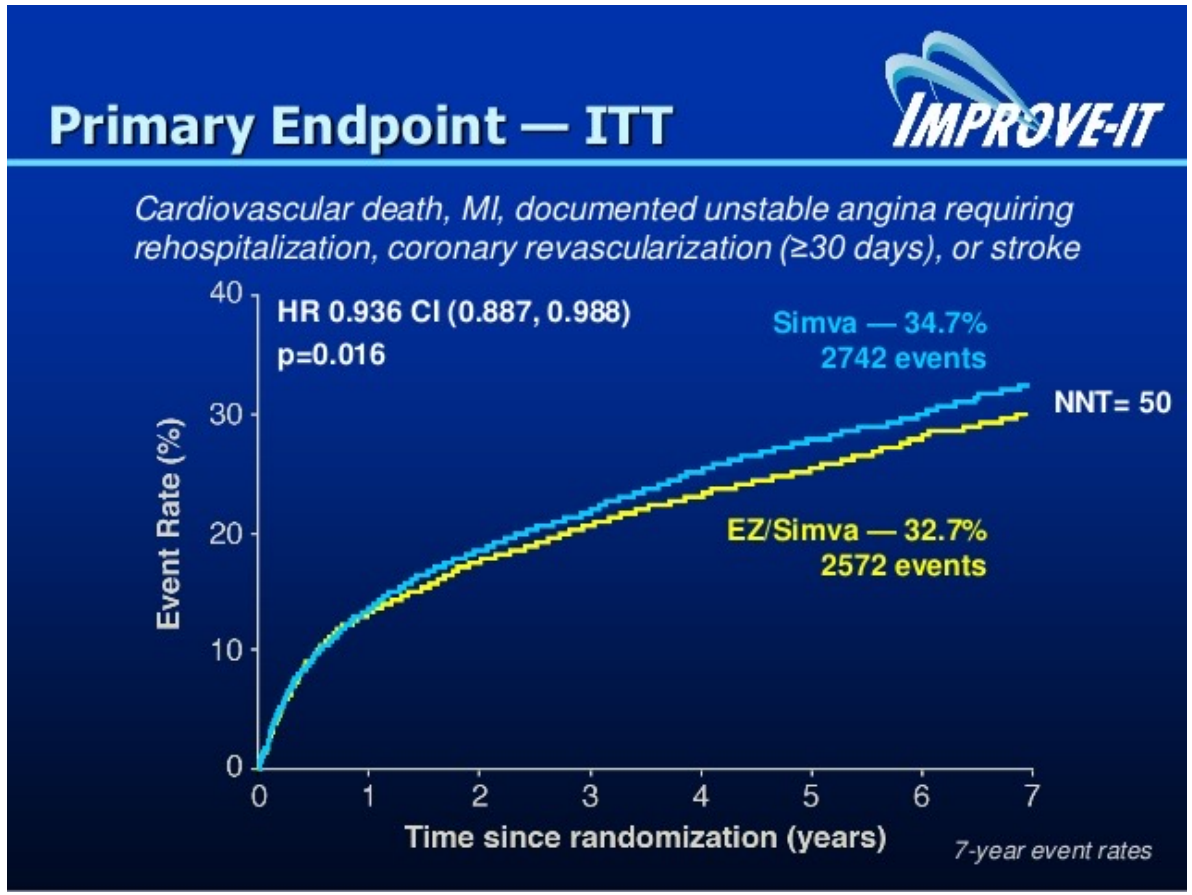
Helping Cardiovascular Professionals Learn. Advance. Heal.

CV=Cardiovascular, LDL=Low density lipoprotein

Source: Cholesterol Treatment Trialists' Collaboration. Lancet 2010;376:1670-1681

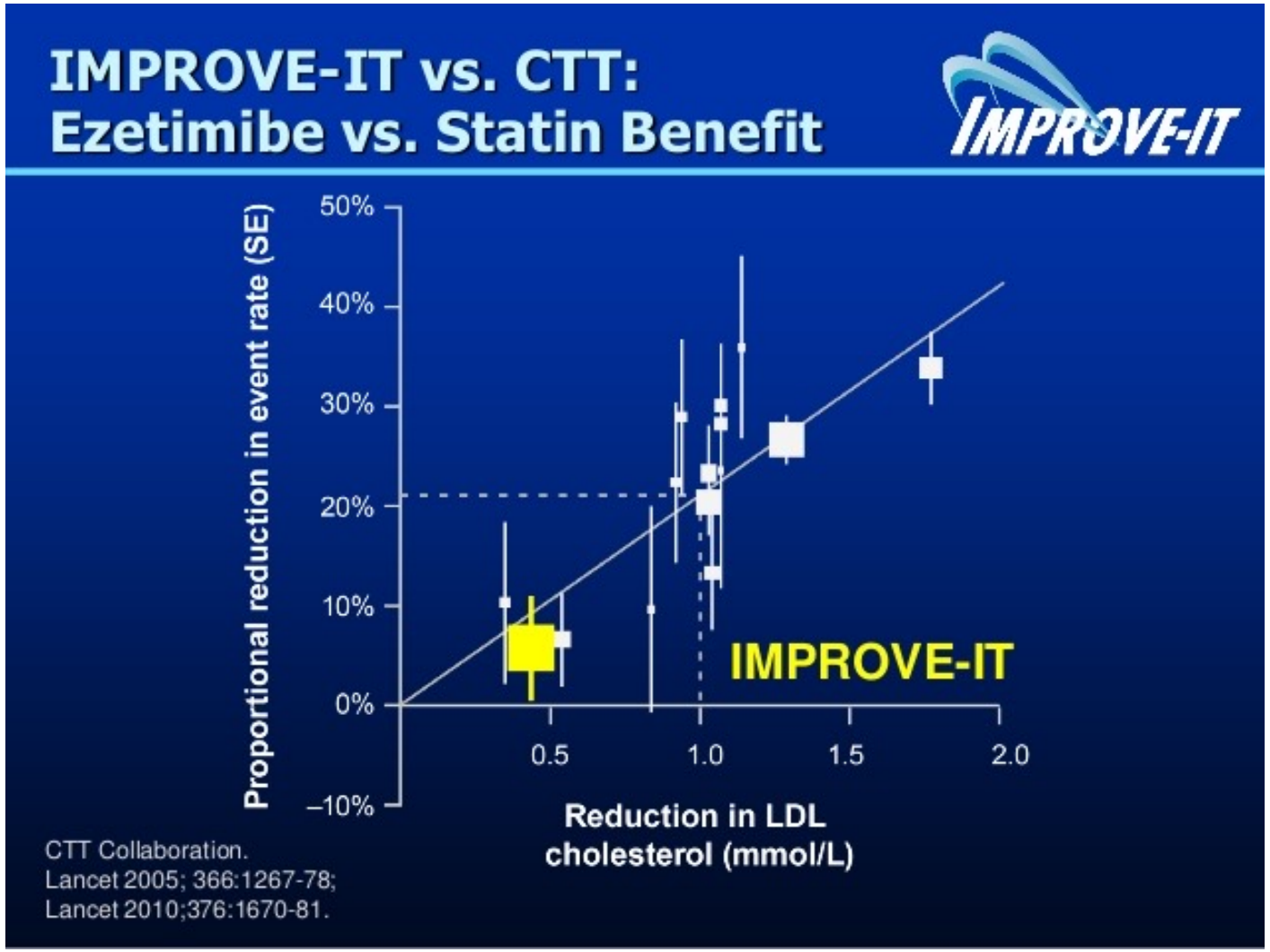
Pourquoi modifier les cibles ?





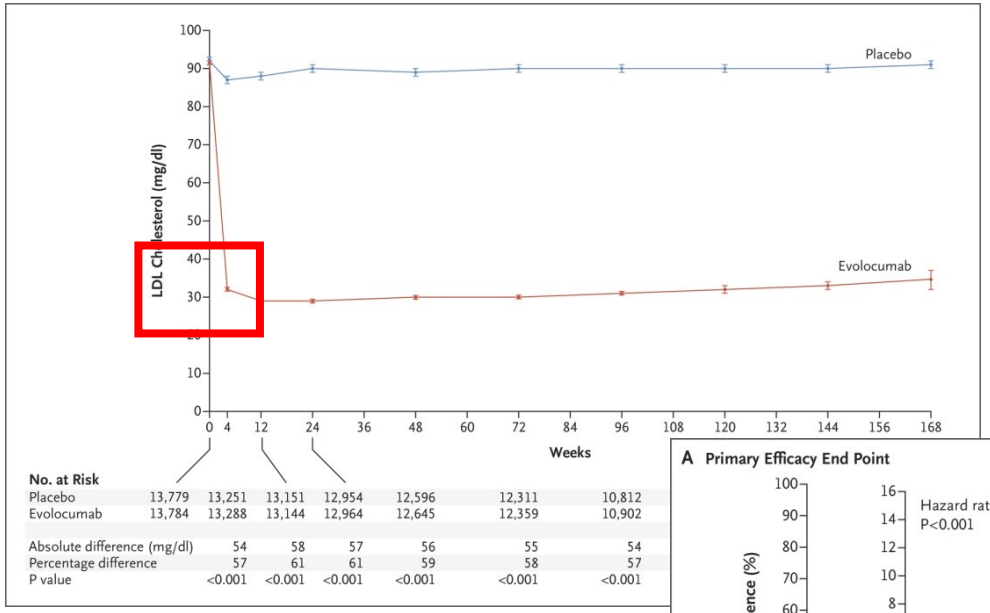
2% réduction risque absolu
6% réduction risque relatif

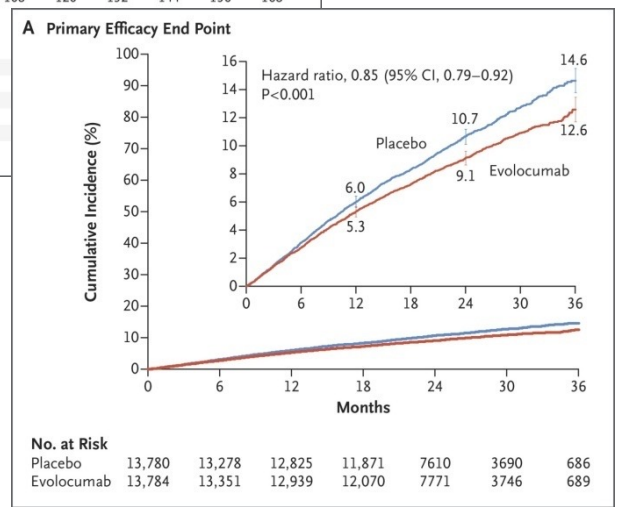
Pourquoi modifier les cibles ?



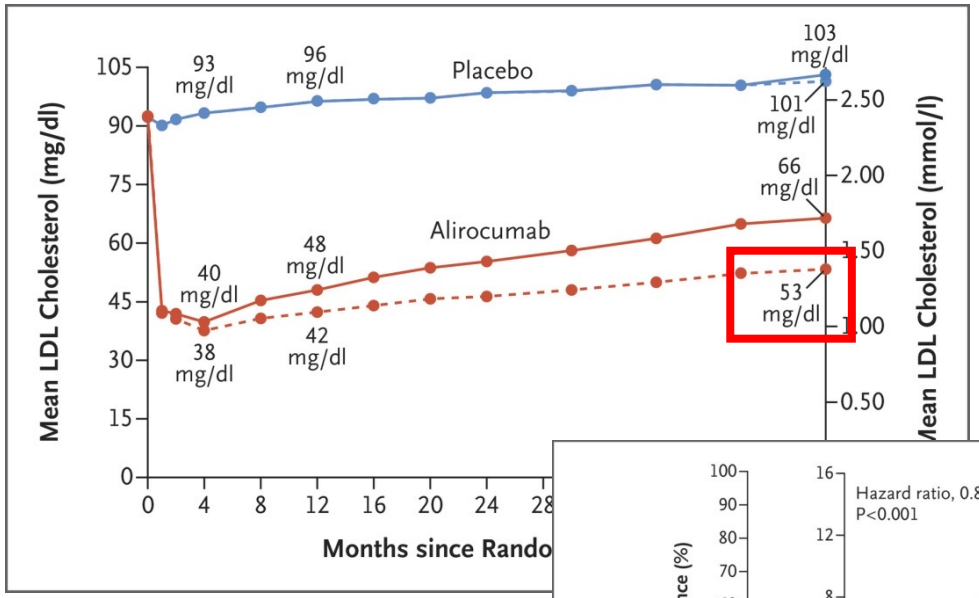
Pourquoi modifier les cibles ?

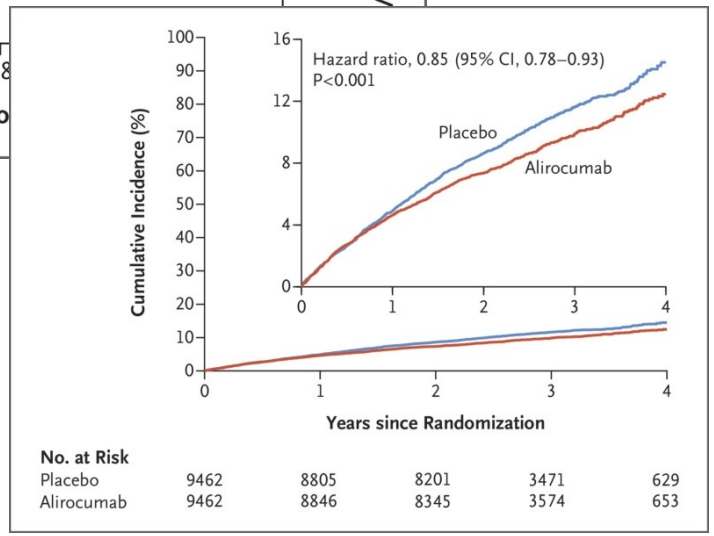
FOURIER



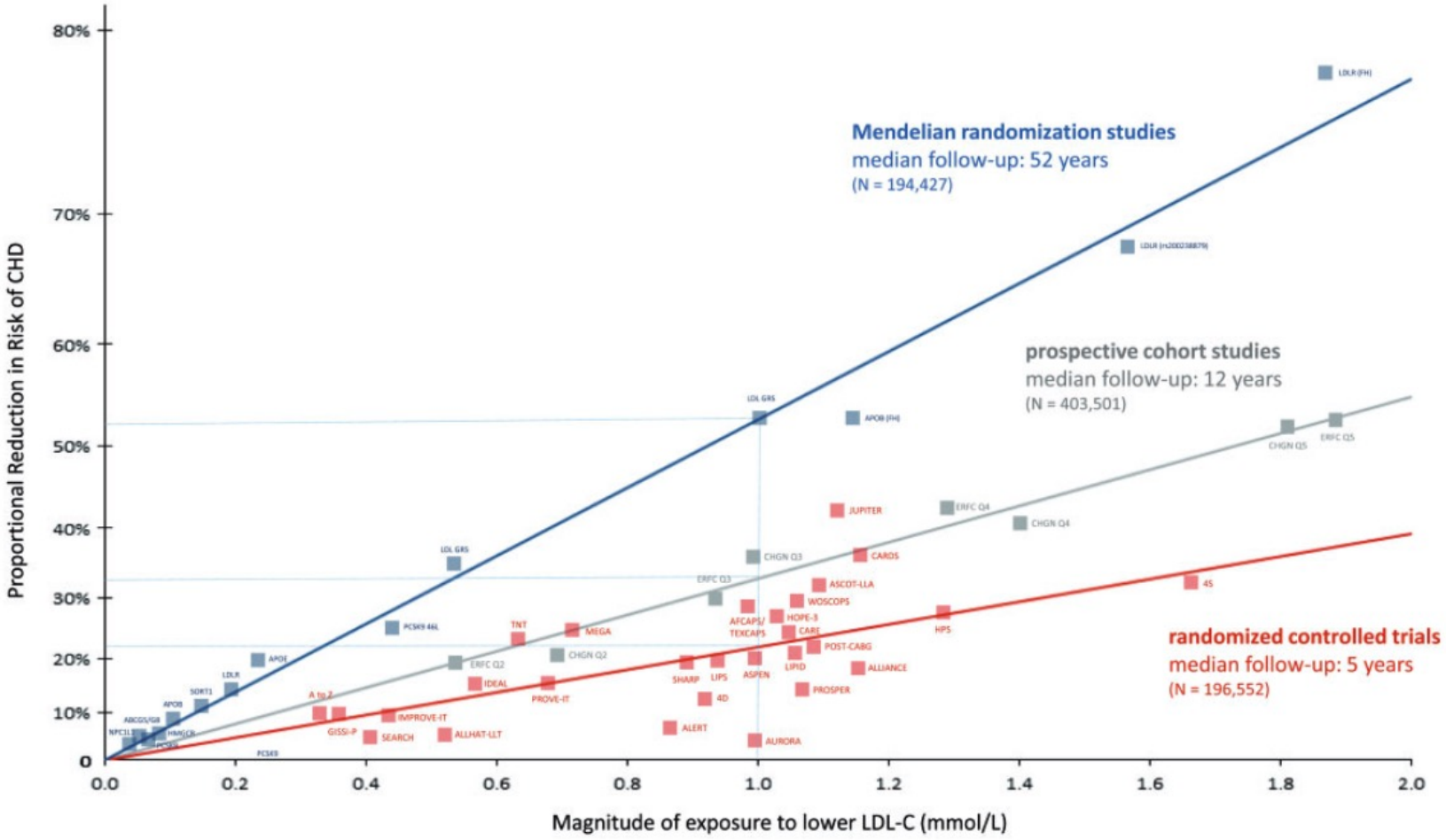


ODYSSEY Outcomes





« The lower the better »

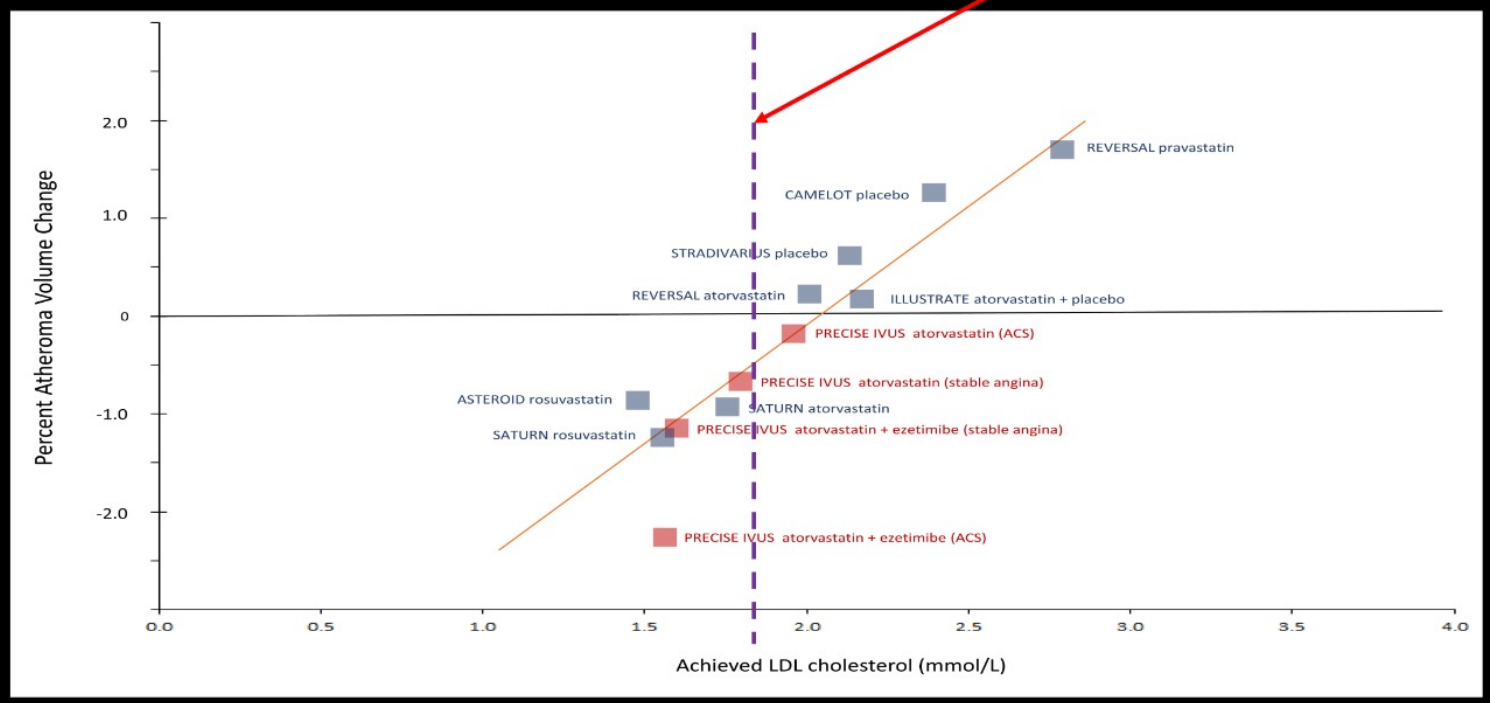


Ference et al. Eur Heart J 2017 Aug 21;38(32):2459-2472.

« The lower the better »

Evidence from IVUS Studies

Progression of coronary atherosclerotic plaque volume can be arrested at achieved LDL-C levels of ~1.8 mmol/L (70 mg/dL)



European Heart Journal. doi:10.1093/eurheartj/ehx144.

Présentation EAS 2017 - Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic and clinical studies. A Consensus Statement from the European Atherosclerosis Society Consensus Panel

Qui traiter ?

2019 Guidelines ESC/EAS
on dyslipidemia

	Total CV risk (SCORE) %	Untreated LDL-C levels					
		<1.4 mmol/L (55 mg/dL)	1.4 to <1.8 mmol/L (55 to <70 mg/dL)	1.8 to <2.6 mmol/L (70 to <100 mg/dL)	2.6 to <3.0 mmol/L (100 to <116 mg/dL)	3.0 to <4.9 mmol/L (116 to <190 mg/dL)	≥4.9 mmol/L (≥190 mg/dL)
Primary prevention	<1, low-risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	I/C	I/C	I/C	I/C	IIa/A	IIa/A
	≥1 to <5, or moderate risk (see *Table 4*)	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	I/C	I/C	IIa/A	IIa/A	IIa/A	IIa/A
	≥5 to <10, or high-risk (see *Table 4*)	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	IIa/A	IIa/A	IIa/A	I/A	I/A	I/A
	≥10, or at very-high risk due to a risk condition (see *Table 4*)	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	IIa/B	IIa/A	I/A	I/A	I/A	I/A
Secondary prevention	Very-high-risk	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	IIa/A	I/A	I/A	I/A	I/A	I/A

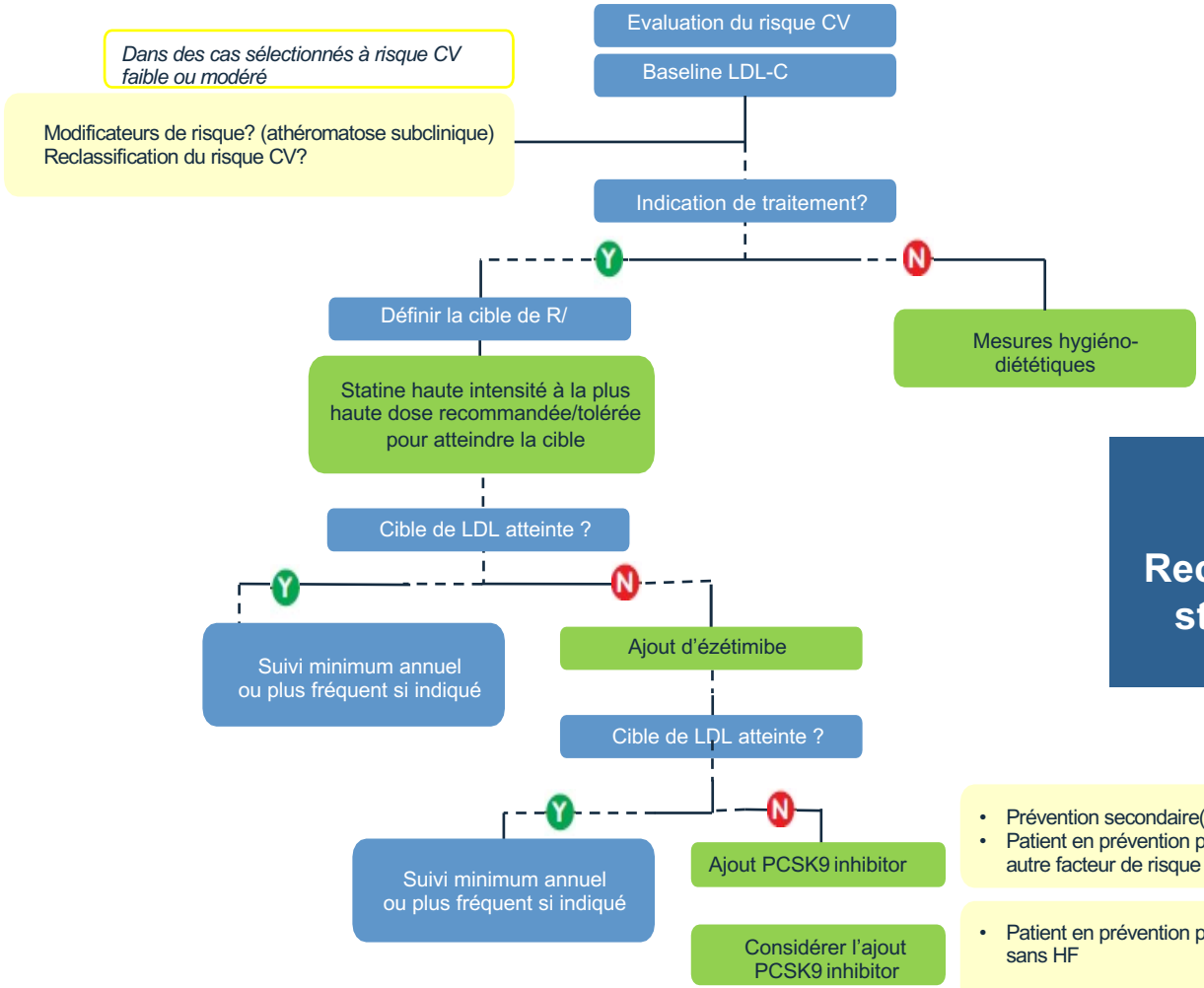
Avec quel traitement ?

- Statine à haute intensité ou à la dose maximale tolérée afin d'atteindre la cible (Classe IA)
- Ajout d'ézétimibe si cible non atteinte (Classe IB)
- Si prévention secondaire et cible non atteinte, ajout inhibiteur PCSK9 (Classe IA)
- FH à très haut risque, ajout inhibiteur PCSK9

Quelles cibles ?

Risque CV	Très haut	Haut	Modéré	Bas
LDL mg/dL	< 55 Et ↙≥50%	< 70 Et ↙≥50%	< 100	< 116
Non-HDL mg/dL	< 85	< 100	< 130	
ApoB mg/dL	< 65	< 80	< 100	
TG mg/dL	< 150			
HbA1c	< 7%			

Algorithme du traitement pharmacologique pour abaisser le LDL cholestérol



Nouveauté des guidelines ESC/EAS 2019

Reconnaissance de l'association statine/Ezetimibe comme 2ème étape

Avec quel traitement ?

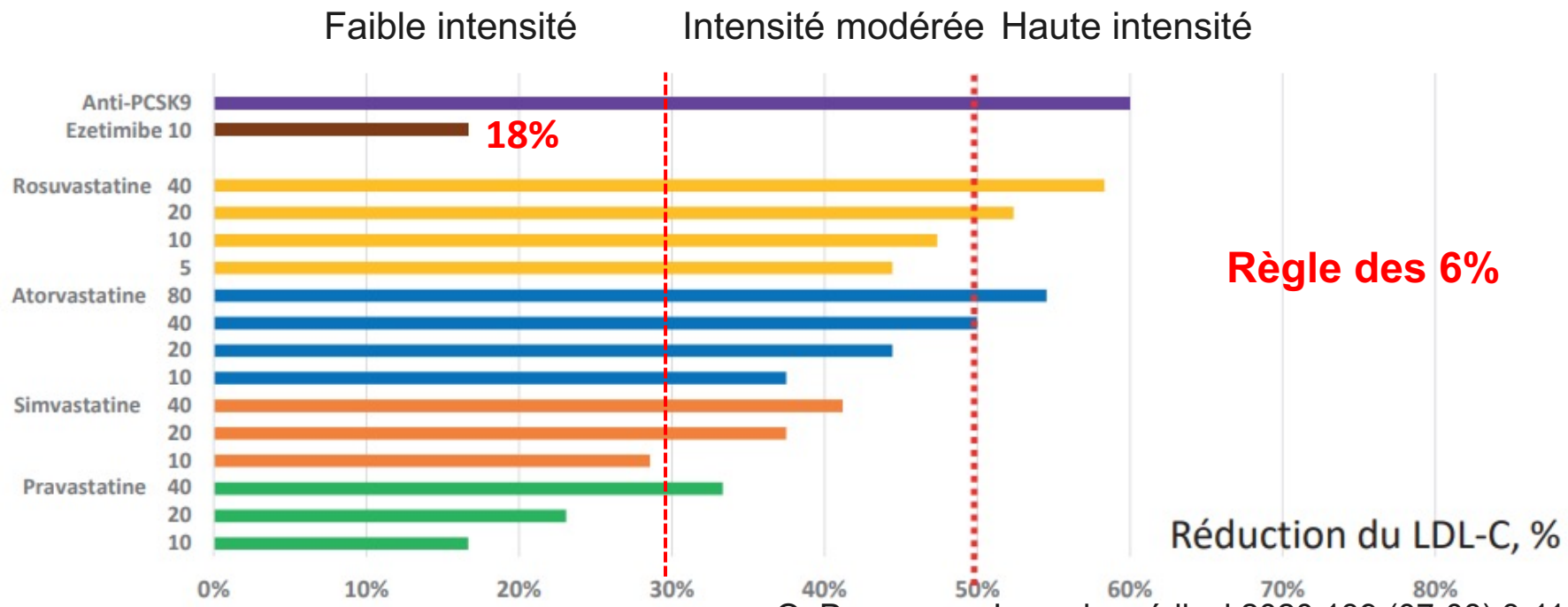
High-Intensity Statin	Moderate-Intensity Statin	Low-Intensity Statin
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg	Simvastatin 10 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg	Pravastatin 10–20 mg
	Simvastatin 20–40 mg	Lov mg
	Pravastatin 40–80 mg	Fluva 20–40 mg
	Lova 0 mg	Pita mg
	Fluv XL 80 mg	
	Flu 0 mg bid	
	Pitavastatin 2–4 mg	

Effet attendu des traitements

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%

Effet attendu des traitements



O. Descamps, Louvain médical 2020;139 (07-08):3-11

Quelle statine ?

Indication for High-Intensity Statin	Choose atorvastatin or rosuvastatin.	Atorvastatin 40-80 mg Rosuvastatin 20-40 mg
Previous Myalgias with Statin Therapy	Choose hydrophilic statin.	Rosuvastatin Pravastatin
Issues with Adherence	Choose long half-life statin.	Atorvastatin Rosuvastatin
CYP3A4 Drug Interactions	AVOID simvastatin, lovastatin, atorvastatin.	Pravastatin Rosuvastatin*
Impaired Renal Function	Use caution with rosuvastatin.	Atorvastatin Fluvastatin

Place des fibrates ?

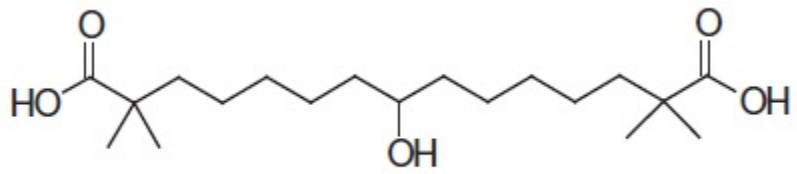
- Réduction du risque CV semble proportionnel au degré de baisse du non-HDL cholestérol (taux élevé de TG et faible de HDL)
- Probable réduction d'évènements mais pas en mortalité (CV ou totale)
- Données bien moins robustes qu'avec les statines
- Place ? => hyperTG après statine (IIb)

Mais que proposer de plus ?

Acide bempedoïque

Nilemdo

Nustendi en association fixe avec l'ézétimibe

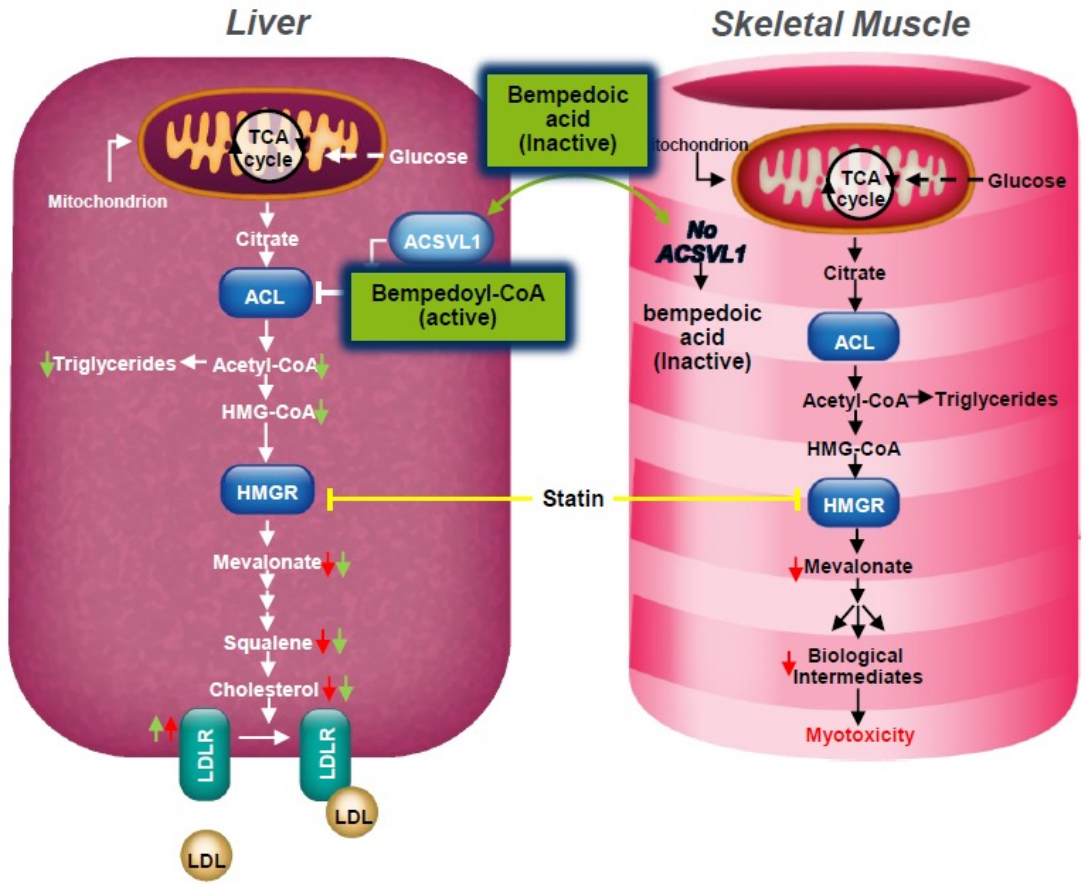


- 8-hydroxy-2,2,14,14-tetramethylpentadecanedioicacid
- ETC-1002
- developed by Esperion Therapeutics Inc.
- Commercialisé en Europe par Daiichi-Sankyo

Acide bempedoïque

- Pro-drogue (ACSVL1)
- ACSVL1 non présent dans le muscle
- Même voie que les statines mais plus haut sur la voie (inhibiteur de l'ATP-citrate lyase (ACL))

- Po 180 mg/j



Acide bempedoïque (Nilemdo)

Bempedoic acid: overview CLEAR program phase III

High-very high risk
(ASCVD and/or HeFH)
Statin Add-On

- **CLEAR Wisdom** (047): Efficacy (N=779)[1]
  LDL-C ≥ 100 mg/dL — **12-week LDL-C / 52-week safety**
- **CLEAR Harmony** (040): Safety (N=2230)[2]
  LDL-C ≥ 70 mg/dL — **52-week safety/ 12-week LDL-C**
- **CLEAR Harmony OLE** (050): Open-label extension (N=1452)[3] — **1.5-year safety**

Moderate-high risk
(ASCVD and/or HeFH or primary prevention)
Statin intolerant
(Low, very low or no statin)

- **CLEAR Serenity** (046): Statin intolerant (N=345)[4]
  LDL-C ≥ 100 mg/dL (sec prev)
  LDL-C ≥ 130 mg/dL (prim prev) — **24-week safety / 12-week LDL-C**
- **CLEAR Tranquility** (048)[5]
  Statin intolerant + Ezetimibe (N=269)
  LDL-C ≥ 100 mg/dL — **12-week LDL-C**

Moderate-high risk
(ASCVD and/or HeFH or primary prevention)
Statin Add-On

- **Study 053**[6]
  BA + EZE FDC (N=382)
  LDL-C ≥ 100 mg/dL (sec prev)
  LDL-C ≥ 130 mg/dL (prim prev) — **12-week safety / 12-week LDL-C**

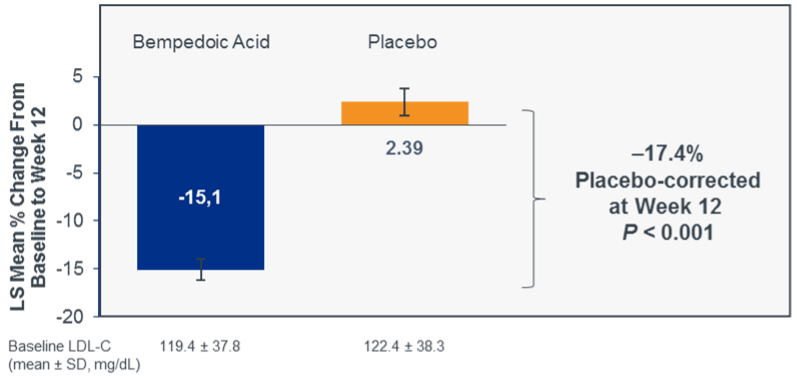
ASCVD = atherosclerotic cardiovascular disease; BA = bempedoic acid; EZE = ezetimibe; HeFH = heterozygous familial hypercholesterolemia

1. Goldberg et al. JAMA. 2019 Nov 12;322(18):1780-1788
2. Ray et al. NEJM. 2019 Mar 14;380(11):1022-1032
3. Ballantyne et al. Poster presented at ESC congress 2020 (Aug 29-Sept 1)
4. Laufs et al. J Am Heart Assoc. 2019 Apr 2;8(7):e011662
5. Ballantyne et al. Atherosclerosis. 2018 Oct;277:195-203
6. Ballantyne et al. Eur J Prev Cardiol. 2020 Apr;27(6):593-603

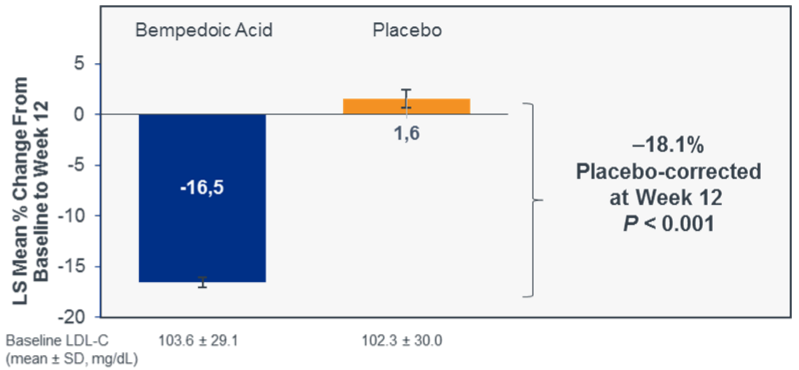
Acide bempedoïque (Nilemdo)

Bempedoic acid monotherapy: LDL-C lowering between 17.4% and 28.5%

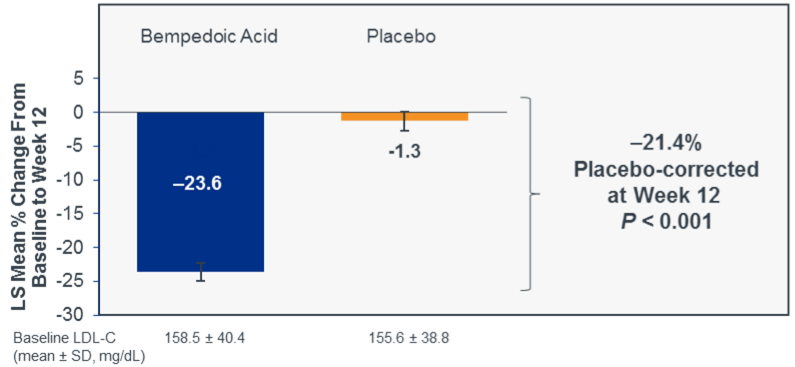
CLEAR Wisdom[1]



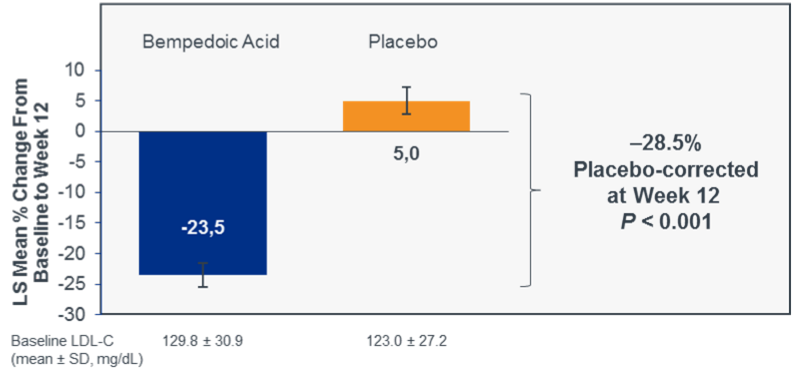
CLEAR Harmony[2]



CLEAR Serenity[3]



CLEAR Tranquility[4]

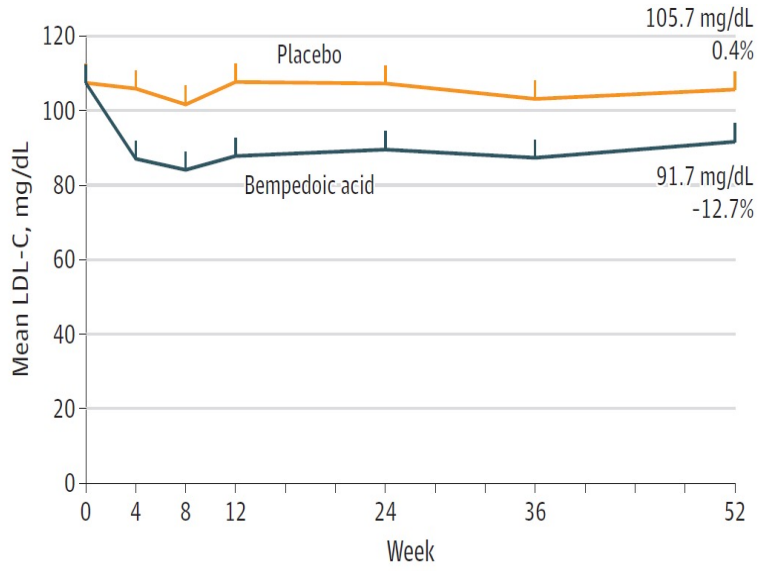


LS = least-squares; SD = standard deviation

1. Goldberg et al. JAMA. 2019 Nov 12;322(18):1780-1788
2. Ray et al. NEJM. 2019 Mar 14;380(11):1022-1032
3. Laufs et al. J Am Heart Assoc. 2019 Apr 2;8(7):e011662
4. Ballantyne et al. Atherosclerosis. 2018 Oct;277:195-203

Acide bempedoïque (Nilemdo)

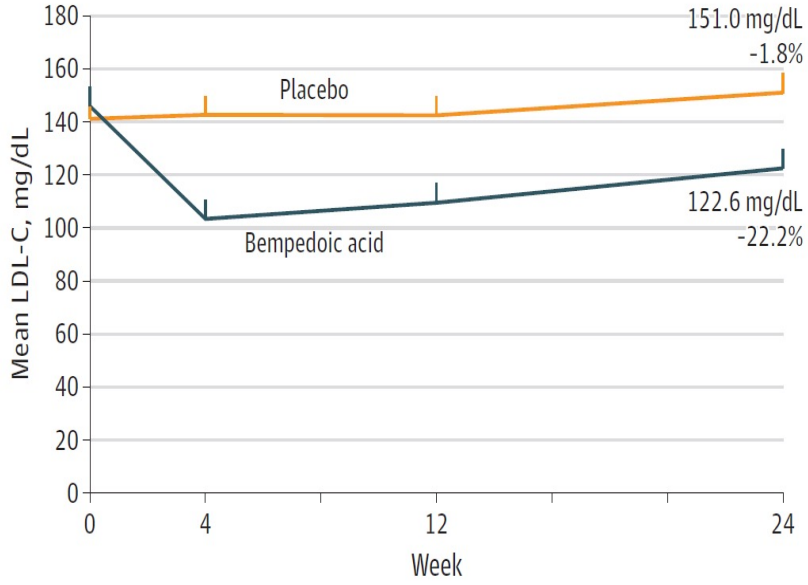
ASCVD or HeFH receiving statins pool



No. at risk

BA	2010	1934	1922	1882	1491	1831
PBO	999	980	978	954	756	922

Statin-intolerant pool



No. at risk

BA	415	409	399	217
PBO	199	191	189	106

- Mean LDL-C levels over time by treatment group. Data are observed mean (SE) values through week 52 in the pool of patients with ASCVD or HeFH or both receiving a maximally tolerated statin, and through week 24 in the pool of patients with statin intolerance
- ASCVD = atherosclerotic cardiovascular disease; BA = bempedoic acid; HeFH = heterozygous familial hypercholesterolemia; PBO = placebo
- Adapted from Banach et al. JAMA Cardiol 2020 Jul 1;5(10):1-12

Acide bempedoïque (Nilemdo)

Bempedoic acid pooled analysis: treatment emergent adverse events in all patients

Overview of TEAEs	Bempedoic acid (n = 2424)	Placebo (n = 1197)	P value
TEAEs of special interest[c]			
Myalgia	118 (4.9)	63 (5.3)	0.63
Muscle spasms	89 (3.7)	31 (2.6)	0.09
Pain in extremity	75 (3.1)	21 (1.8)	0.02
Muscular weakness	13 (0.5)	7 (0.6)	0.82
New-onset or worsening diabetes	96 (4.0)	67 (5.6)	0.03
Blood uric acid level increase	51 (2.1)	6 (0.5)	<0.001
Hyperuricemia	40 (1.7)	7 (0.6)	0.007
Gout	33 (1.4)	5 (0.4)	0.008
Blood creatinine level increase	19 (0.8)	4 (0.3)	0.12
Glomerular filtration rate decrease	16 (0.7)	1 (<0.1)	0.02
Hepatic enzyme (ALT or AST) level increase	67 (2.8)	15 (1.3)	0.004
>3 Times the upper reference limit	18 (0.7)	3 (0.3)	0.10
>5 Times the upper reference limit	6 (0.2)	2 (0.2)	>0.99
Neurocognitive disorder	16 (0.7)	9 (0.8)	0.83

[c]TEAEs of special interest were identified a priori (except for tendon rupture) and were derived from nonclinical findings or clinical data for bempedoic acid, adverse events associated with other lipid-lowering therapies, and anticipated adverse events among patients requiring lipid-lowering therapy

ALT = alanine aminotransferase; AST = aspartate aminotransferase; TEAE = treatment-emergent adverse event

Adapted from Banach et al. JAMA Cardiol 2020 Jul 1;5(10):1-12

Acide bempedoïque (Nilemdo)

Overview of TEAEs	Bempedoic acid (n = 2424)	Placebo (n = 1197)	P value
TEAEs of special interest[c]			
Hemoglobin decrease	69 (2.8)	22 (1.8)	0.07
Anemia	60 (2.5)	19 (1.6)	0.09
Hemoglobin level decrease	9 (0.4)	3 (0.3)	0.76
Hematocrit decrease	2 (<0.1)	3 (0.3)	0.34
Tendon rupture[d]	6 (0.2)	0	0.19
Most common TEAEs leading to discontinuation[e]			
Myalgia	31 (1.3)	21 (1.8)	0.30
Muscle spasm	18 (0.7)	3 (0.3)	0.10
Headache	11 (0.5)	3 (0.3)	0.57
Diarrhea	11 (0.5)	1 (<0.1)	0.12

[c]TEAEs of special interest were identified a priori (except for tendon rupture) and were derived from nonclinical findings or clinical data for bempedoic acid, adverse events associated with other lipid-lowering therapies, and anticipated adverse events among patients requiring lipid-lowering therapy

ALT = alanine aminotransferase; AST = aspartate aminotransferase; TEAE = treatment-emergent adverse event

Adapted from Banach et al. JAMA Cardiol 2020 Jul 1;5(10):1-12

Acide bempedoïque (Nilemdo)

Analyse des 3623 patients inclus dans le programme d'étude. Les effets secondaires sont :

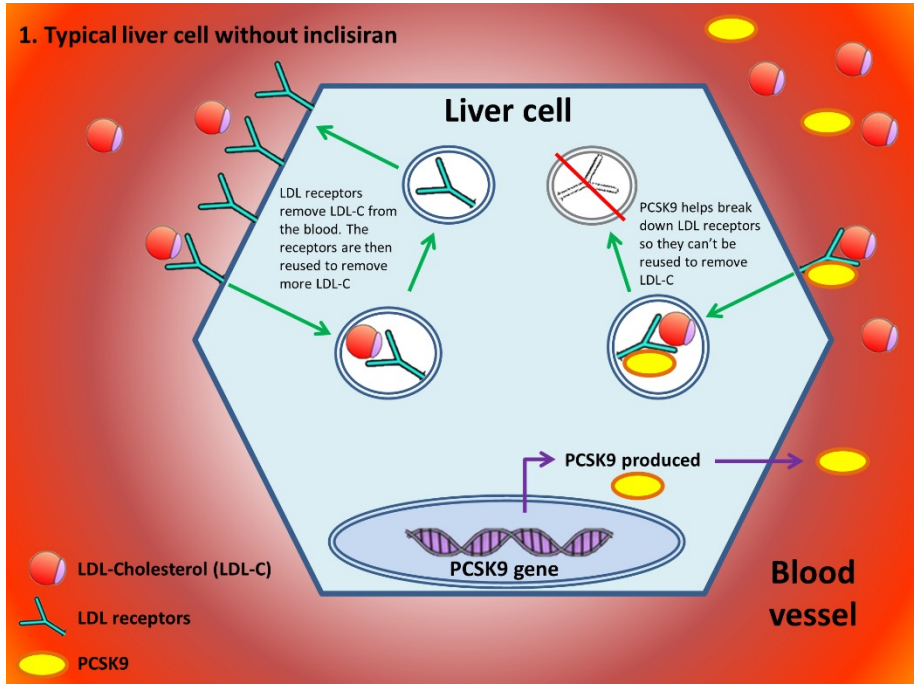
- Augmentation de l'acide urique sanguin
- Risque majoré de goutte (1,4% vs 0,4%)
- Diminution de la GFR
- Augmentation des enzymes hépatiques

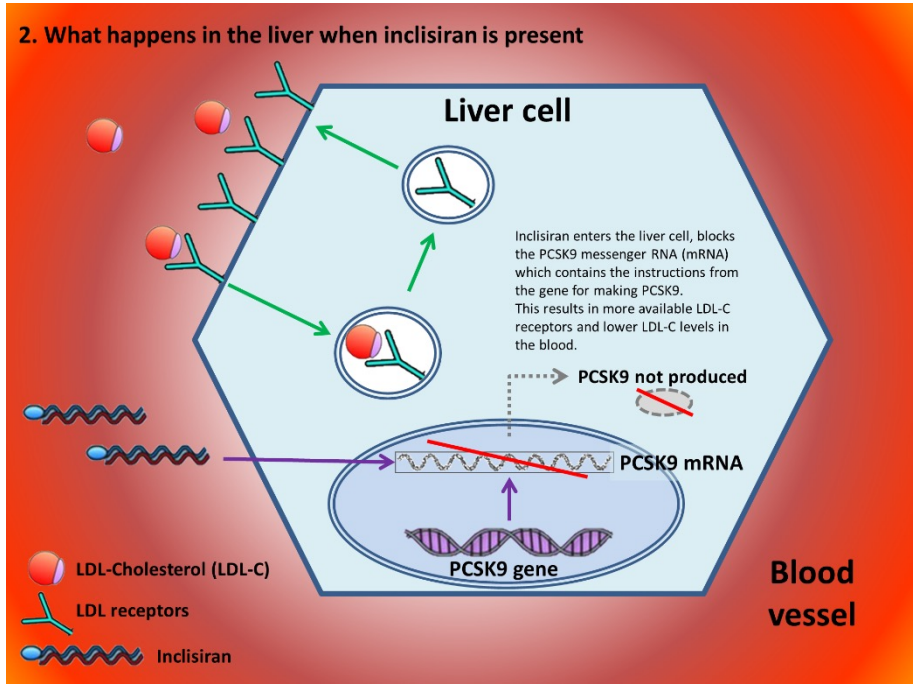
Réduction du LDL de **17.4 - 28.5% vs placebo**

En cas d'association avec la simvastatine celle-ci doit être à 20 mg maximum

Inclisiran (Leqvio)

Inclisiran – siRNA réduisant la production hépatique du PCSK9

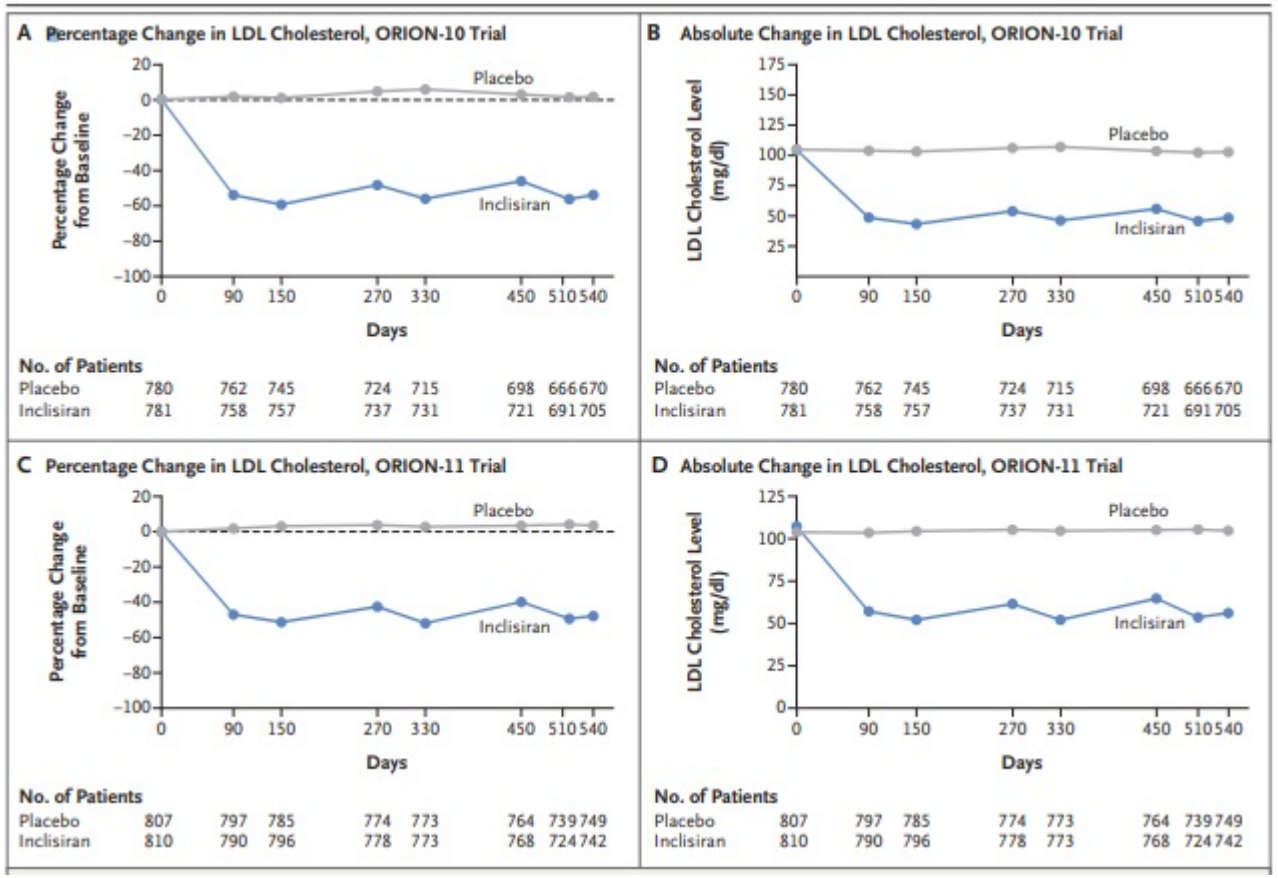




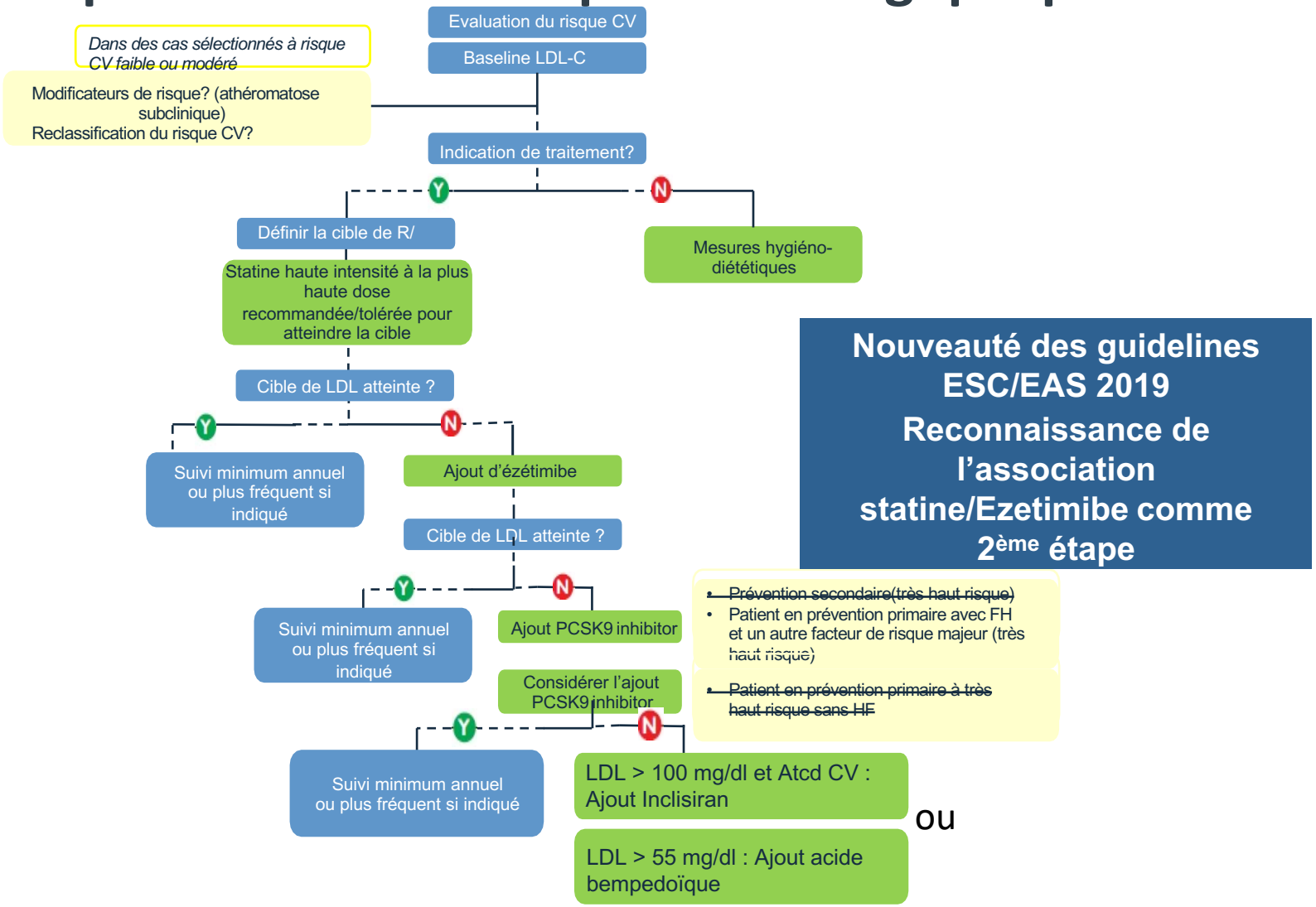
Inclisiran (Leqvio)

Programme études ORION

50% baisse du LDL
on top R/ optimal



Algorithme “adapté” du traitement pharmacologique pour abaisse le LDL cholestérol



CARDIO
SCOPIE

THANK YOU