Colloque Paris:

Prévention cardiovasculaire en 2026 : évaluer, imager, traiter

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Hôpitaux Universitaires Genève

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UNIVERSITÉ DE GENÈVE

Work with industry

Royalties: UpToDate (minor).
Advisory / speaker: Amgen, Boehringer, NovoNordisk, Sanofi, Servier (minor).
Co-/PI of several clinical studies for the department (HORIZON, VICTORION-plaque, VICTORION-prevent, EMPA-activity, Collabree, MMT).

(Conflict of interest): other intersts

Unconditional support for **statins** (of any sort, preferentially potent statins such as rosuvastatin and atorvastatin)

Agenda

1. cholestérol
2. atteinte vasculaire subclinique
3. poids

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2. atteinte vasculaire subclinique
3. poids

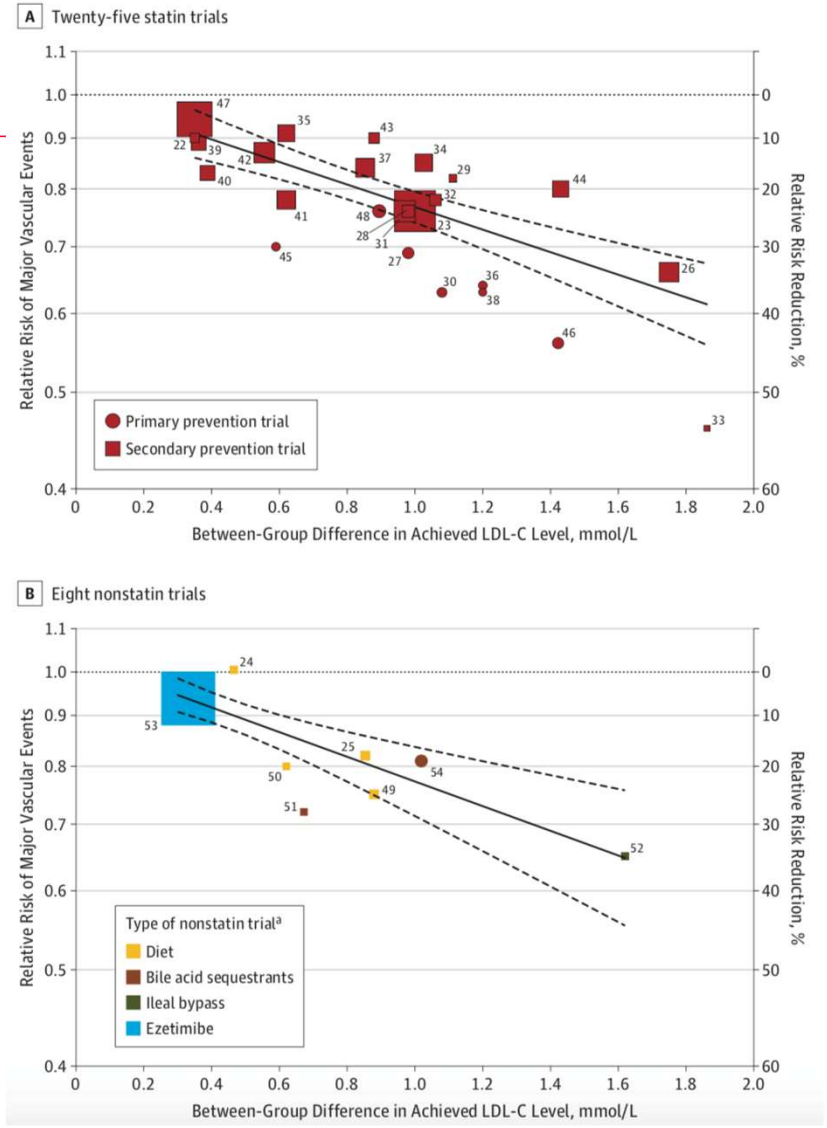
Impact of LDL lowering

Meta-analysis of 312,175 participants:

<u>For every “1mmol” reduction in LDL:</u> RR 0.8 for events

=

20% less events



Silvermann et al. JAMA. 2016;316(12):1289-1297.

Absolute and relative risk

Decrease of 1 mmol/l of LDL: relative risk 0.8 = 20% less events

this means

e.g. absolute risk of 20% -> absolute red. of 4% (=NNT ~25).

e.g. low risk patient: absolute risk of 1% -> absolute red. of 0.2% (=NNT ~500).

Conclusion: more benefit if higher risk !

Who are the patients at particularly high CV risk?

1. **After a first event or extensive ASCVD without event**

2. **Diabetics with target organ damage**

3. **Patients with severe renal failure**
   eGFR <30 ml/min

4. **Patients with familial hypercholesterolemia**

5. **Patients with SCORE2** >10%

The longer, the better

Baseline LDL-C (mmol/L)	Absolute reduction LDL-C (mmol/L)	Duration of treatment exposure [expected proportional risk reduction (%)]				
		5 years	10 years	20 years	30 years	40 years
7	3.5	58	68	81	89	93
7	3.0	53	62	76	85	90
7	2.5	46	56	70	79	86
7	2.0	39	48	61	71	79
7	1.5	31	39	51	61	69
5	2.5	46	56	70	79	86
5	2.0	39	48	61	71	79
5	1.5	31	39	51	61	69
5	1.0	22	28	38	46	54
3	1.5	31	39	51	61	69
3	1.0	22	28	38	46	54
3	0.5	12	15	21	27	32
2	1.0	22	28	38	46	54
2	0.5	12	15	21	27	32

Ference et al. Eur Heart J. 2018

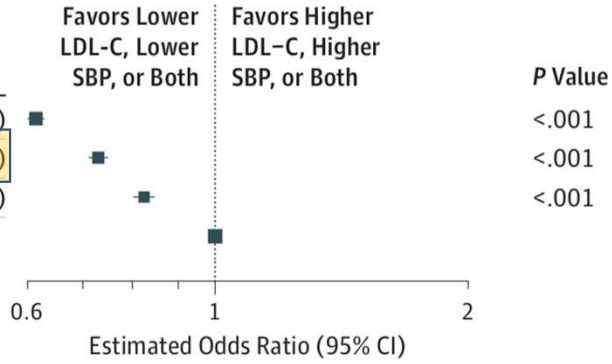
Genetically lower LDL in UK Biobank

438’952 participants

mean age 65y (40-80y), 54% female

A Associations for the observed difference in LDL-C and SBP vs reference group

	No. of Participants	No. of Events	Difference in LDL-C Score, mg/dL	Difference in SBP, mm Hg	Odds Ratio (95% CI)	*P* Value
Lower LDL-C and lower SBP	105528	4832	-13.9	-3.1	0.61 (0.59-0.64)	<.001
Lower LDL-C	109027	5784	-14.7	-0.1	0.73 (0.70-0.75)	<.001
Lower SBP	111097	6515	1.6	-2.9	0.82 (0.80-0.85)	<.001
Reference	113300	7849				



(14.7mg/dl = 0.38mmol/l)

Ference et al. JAMA. 2019;322(14):1381-1391.

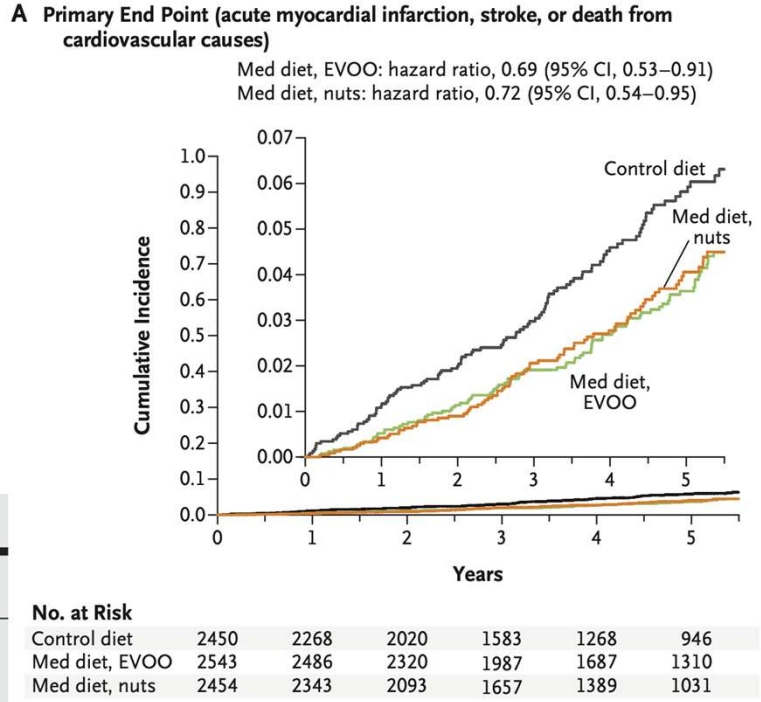
Cholesterol : “Lifestyle measures”

- Dietary approaches & physical exercise (Mediterranean diet, vegetarian diet, etc.): ***10%-15% (?)*** decrease of LDL.

Complex mechanisms: only the oxidized LDL is lower in PREDIMED:

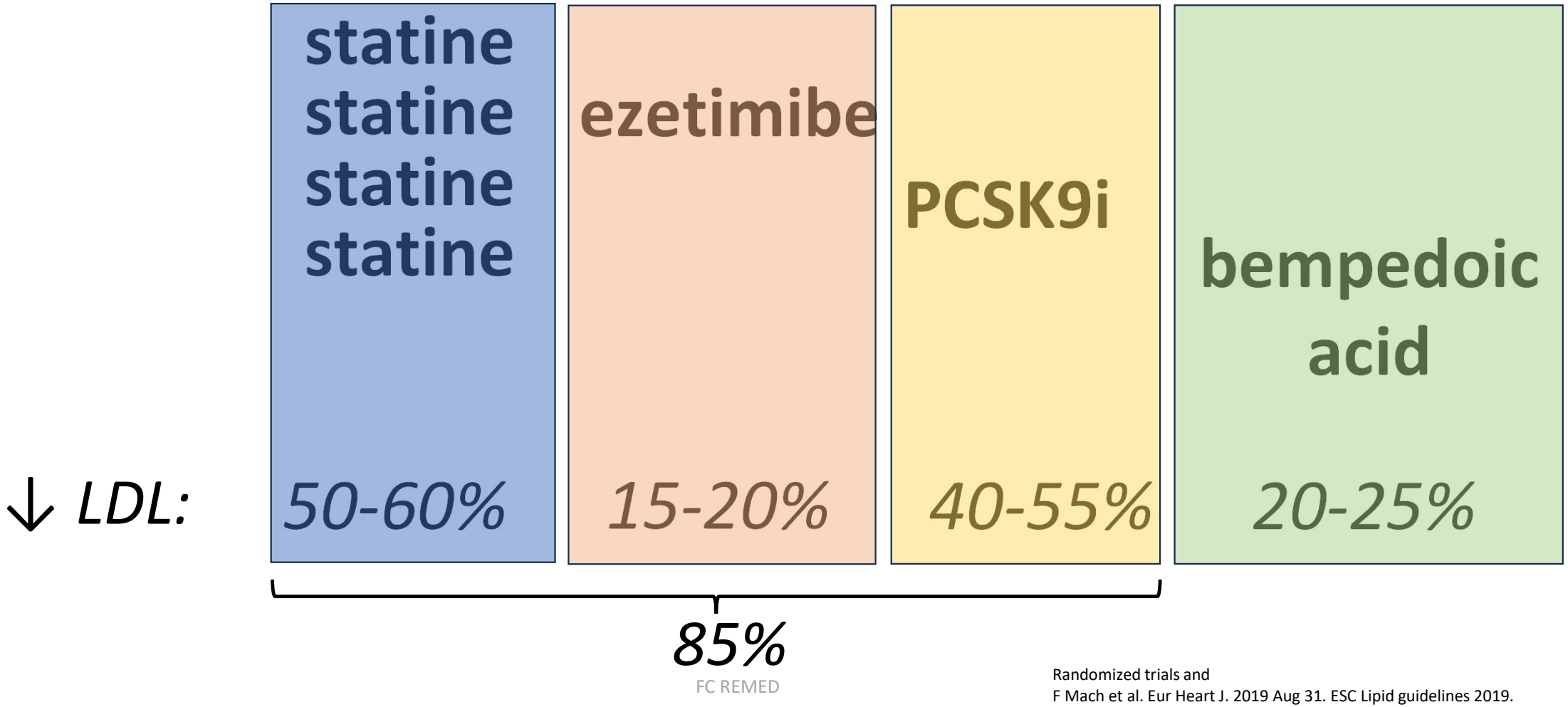
Table 4. Crude and Adjusted 3-Month Changes in OxLDL and GSH-Px Levels After Interventions

Model*	TMD + VOO, Mean (95% CI)	TMD + Nuts, Mean (95% CI)	Low-Fat Diet, Mean (95% CI)
Model 1			
OxLDL, U/L	−10.1 (−15 to −5.1)	−7.5 (−12 to −2.6)	−2.6 (−8.0 to 2.9)
GSH-Px, U/L	−16.4 (−44.6 to 11.8)	−10.4 (−35.9 to 15.1)	−20.1 (−50.6 to 10.4)



Estruch et al. N Engl J Med 2018;378:e34.
Fito et al. Arch Intern Med. 2007;167(11):1195-1203

Statin and non-statin LDL lowering potency



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Randomized trials and
F Mach et al. Eur Heart J. 2019 Aug 31. ESC Lipid guidelines 2019.

Case: M. C

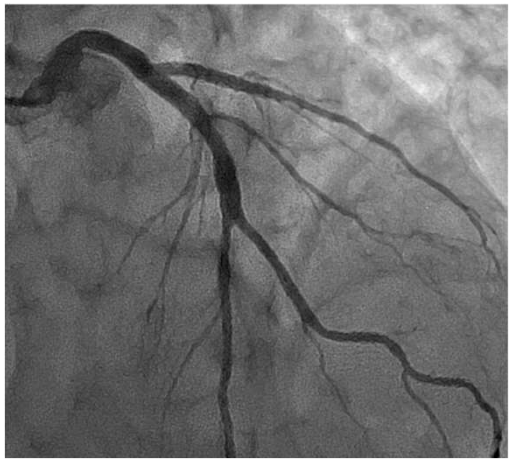
Male 50y.

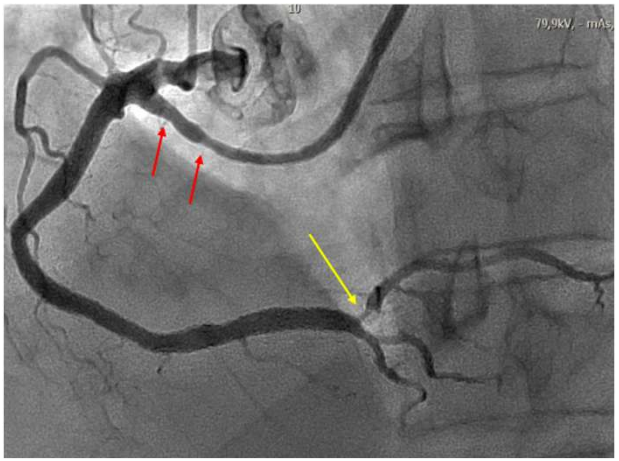
CC: Lipid counseling.

History:

- Three vessel disease: Elective stenting of D1 one year earlier, aberrant Cx.
- At encounter: Chest pain after cycling : NSTEMI -> stenting RVP.

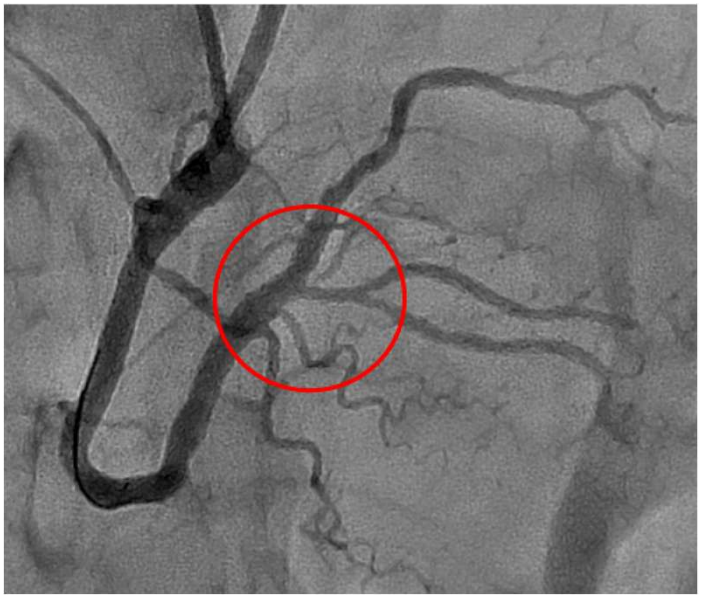
M. C : coronary angiogram





yellow: RVP lesion
red: aberrant Cx with atheroma

after stenting:



M. C, cont.

Other medical history:

- Transient stroke some years back.
- Arterial hypertension.
- Renal failure G3aA2 (creatinine 123umol/l, UACR 6,2mg/mmol).
- Fatty liver (no fibrosis); hypothyroidism (treated).

PE: BP 142/82mmHg, P 72/'; BMI: 25.8kg/m^2; cardiac & pulm. and vascular exam normal.

Family hist.: father with MI @60y, brother and 2 adult children in good CV health. **Habits:** biker.

M. C, cont.

Lab: native LDL 4,3mmol/l.

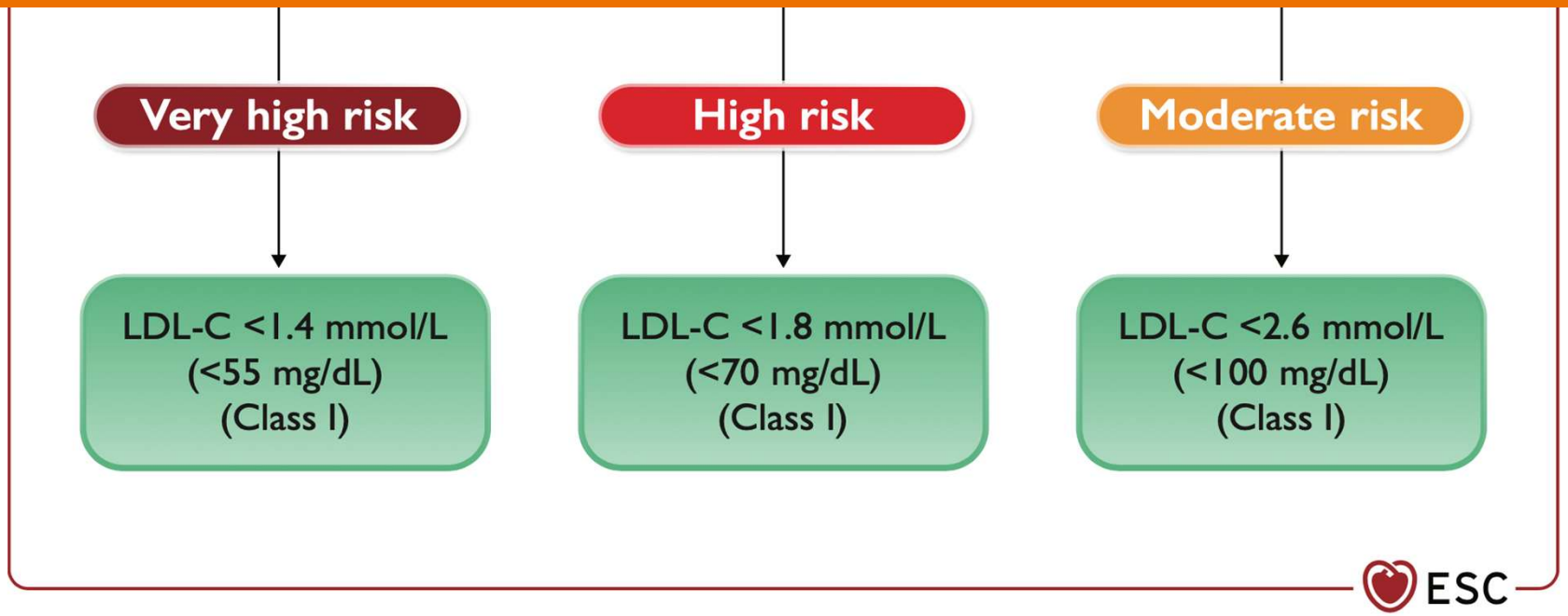
Statin intolerance:

- cutaneous eruption with atorvastatin.

With current treatment (ezetimibe only) LDL 3,9mmol/l, TG 2,3mmol/l, HDL 0.8mmol/l.

What next ?

LDL target depends on CV risk



Ference et al. JAMA. 2019;322(14):1381-1391.

Patients at highest CV risk and LDL target

- Patients with ASCVD who experience recurrent vascular events while taking maximally tolerated statin-based therapy
- Patients with polyvascular (e.g. coronary and peripheral) arterial disease

Class IIb

<1.0 mmol/L (<40 mg/dL)

Mach et al. European Heart Journal (2025) 46, 4359–4378.

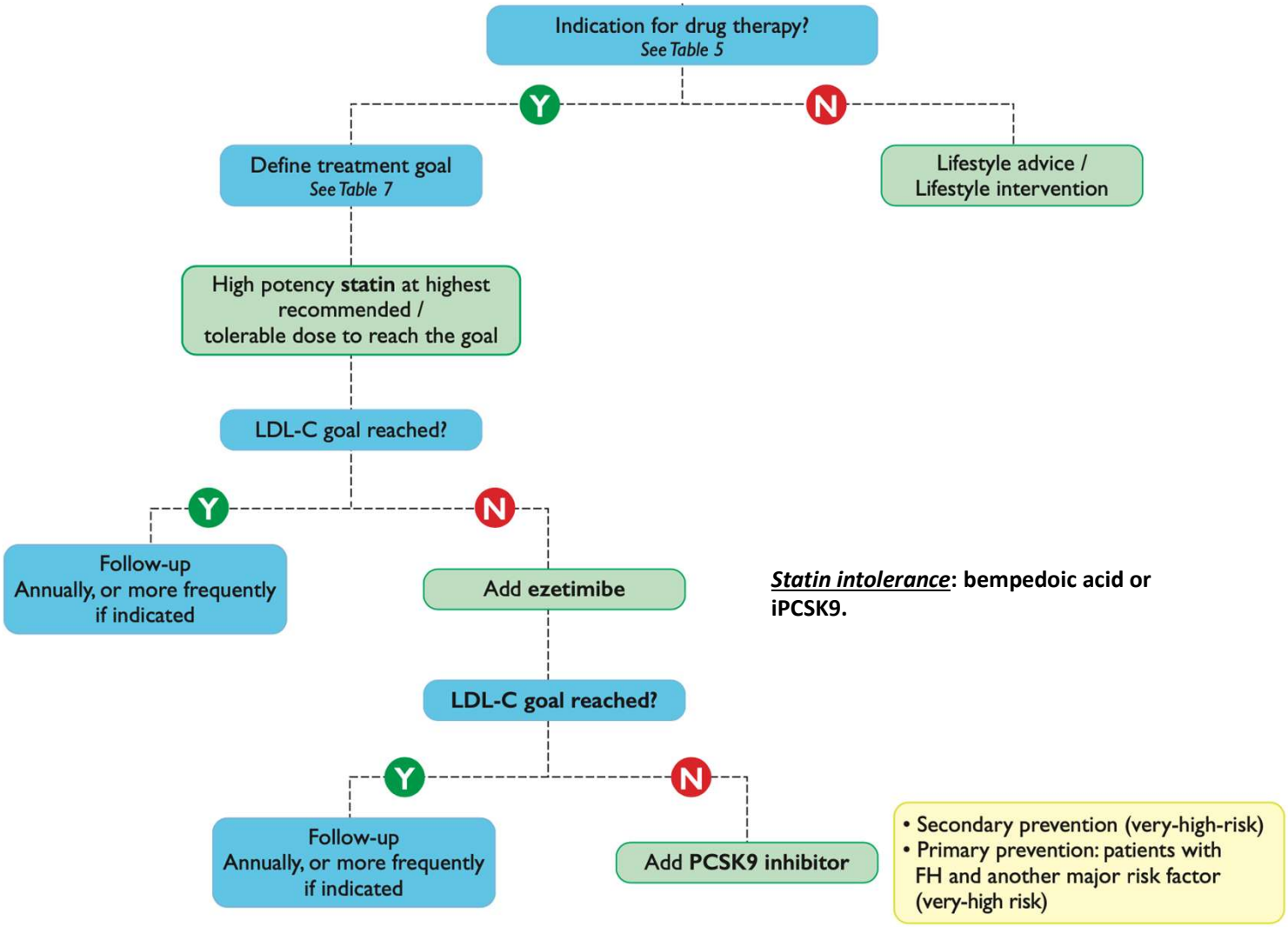
M. C, cont.

Rosuvastatin 10mg/d (small dose – in addition to ezetimibe)

Lab: LDL 1,83mmol/l

What next ?

Lipid-lowering therapy: treatment approach



***Statin intolerance*: bempedoic acid or iPCSK9.**

F. Mach, ESC lipid guidelines 2019

M. C, cont.

Adding evolocumab 140mg/2 weeks sc.

Lab after 4 weeks: LDL 0.9mmol/l

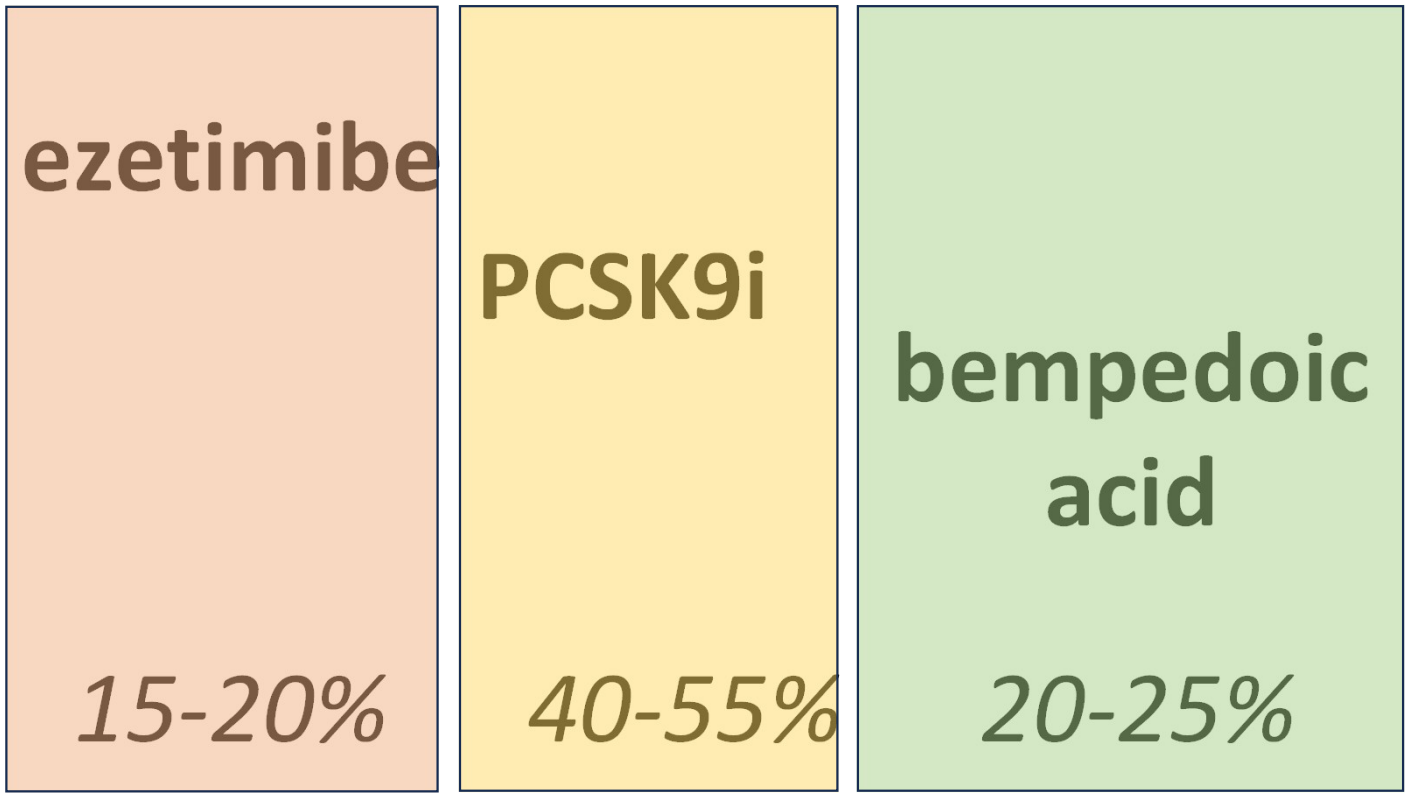
Is that too low ?

How safe are ultra-low LDL levels ?

- Different **randomized studies** (FOURIER-OLE, GLAGOV): no complication.
- **Observational studies**: no major signal.
- LDL levels **of the newborn**.
- **Genetic mutations that induce very low LDL levels** (e.g. inactivating PCSK9 mutations): normal life, normal intelligence, normal reproduction, normal stress response.

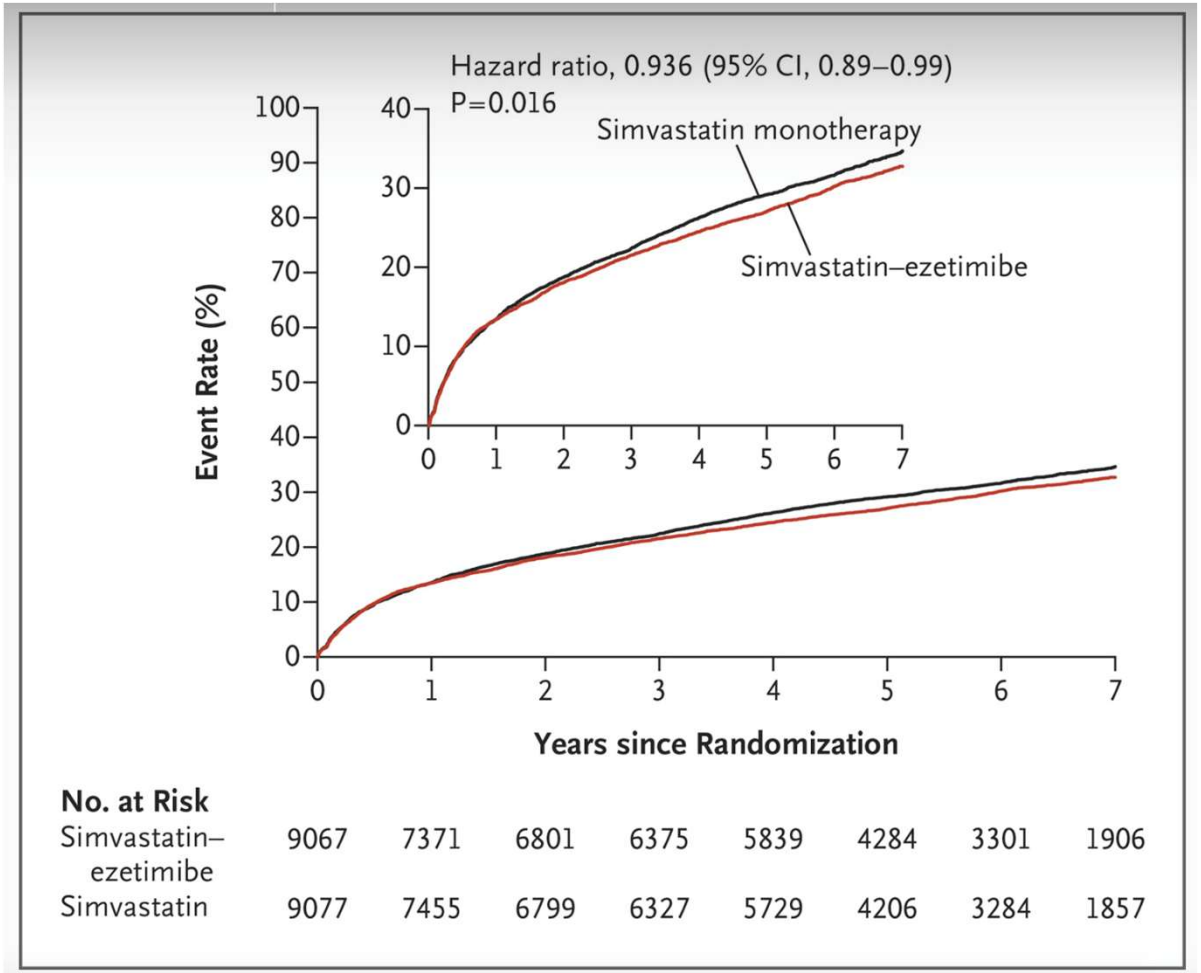
Gaba et al., Circulation 2023;147(16):1192-1203.
Meyer.., Ehret et al.Atherosclerosis 325,2021:63

Non-statin LDL lowering potency



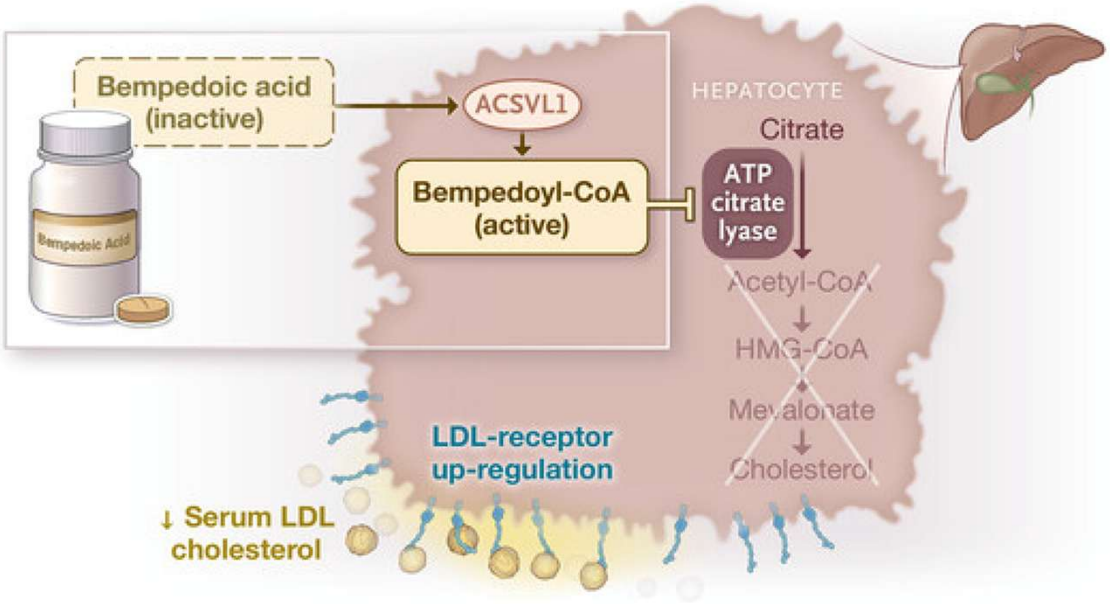
Randomized trials and
F Mach et al. Eur Heart J. 2019 Aug 31. ESC Lipid guidelines 2019.

Ezetimibe

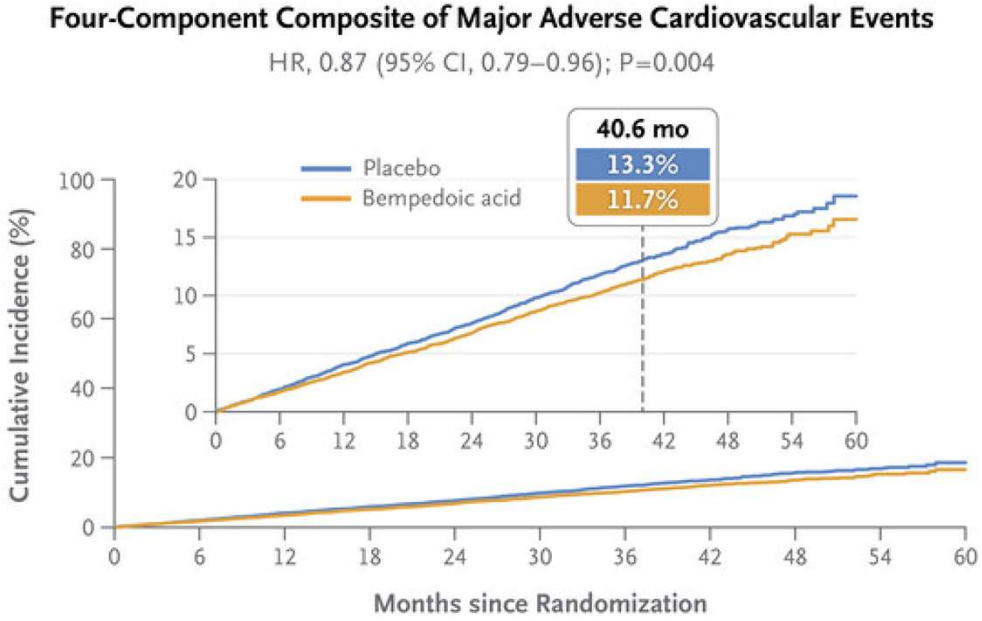


Cannon et al., N Engl J Med 2015;372:2387-2397

Bempedoic acid



In patients resistant to statins:



Nissen et al. N Engl J Med 2023;388:1353-1364

Bempedoic acid

Adverse Events

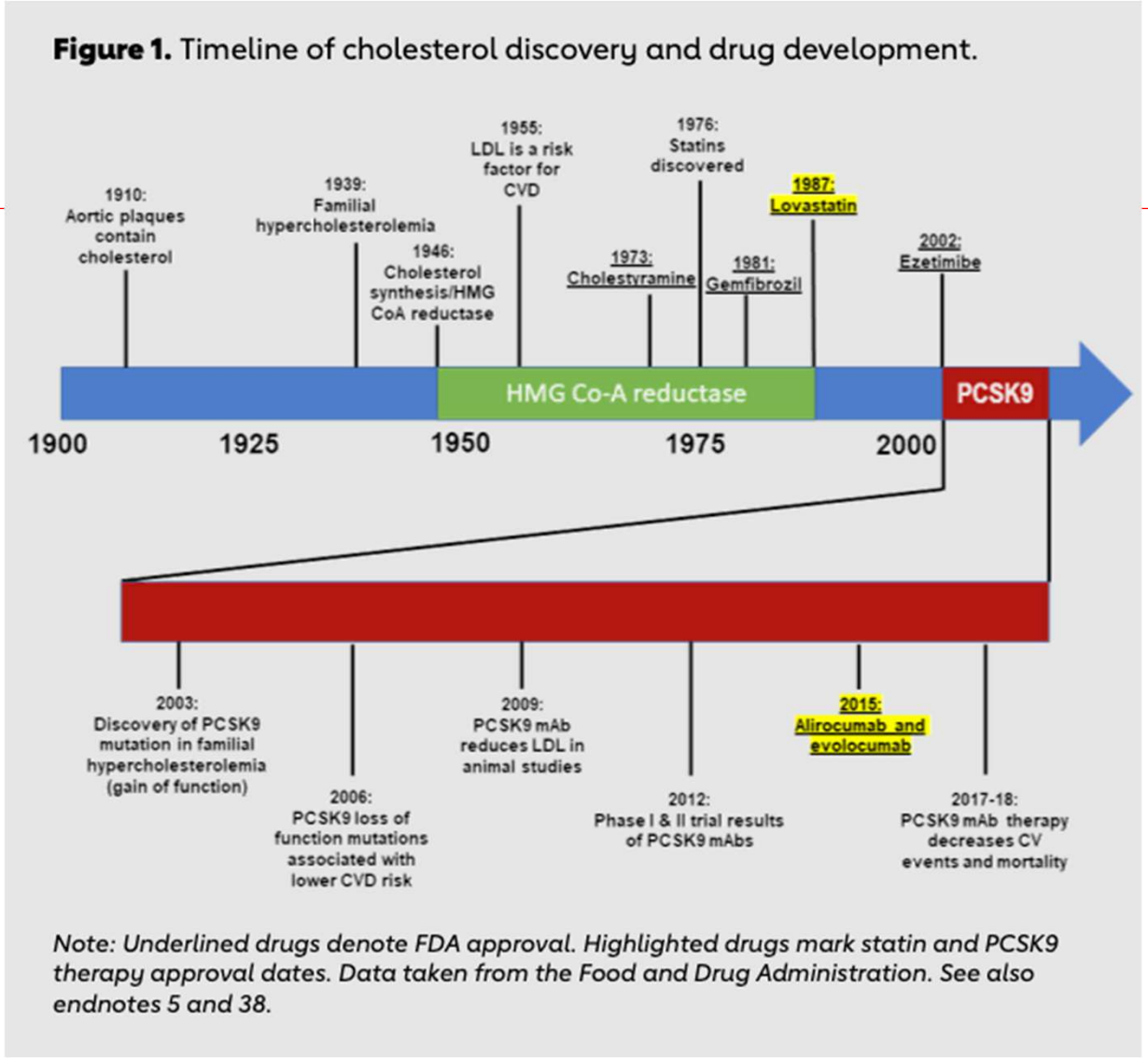
	Bempedoic acid (N=7001)	Placebo (N=6964)
	no. of patients (%)	
Any adverse event	6040 (86.3)	5919 (85.0)
Elevated hepatic enzymes	317 (4.5)	209 (3.0)
Renal impairment	802 (11.5)	599 (8.6)
Hyperuricemia	763 (10.9)	393 (5.6)
Gout	215 (3.1)	143 (2.1)
Cholelithiasis	152 (2.2)	81 (1.2)

Nissen et al. N Engl J Med 2023;388:1353-1364

Currently reimbursed non-statin drugs

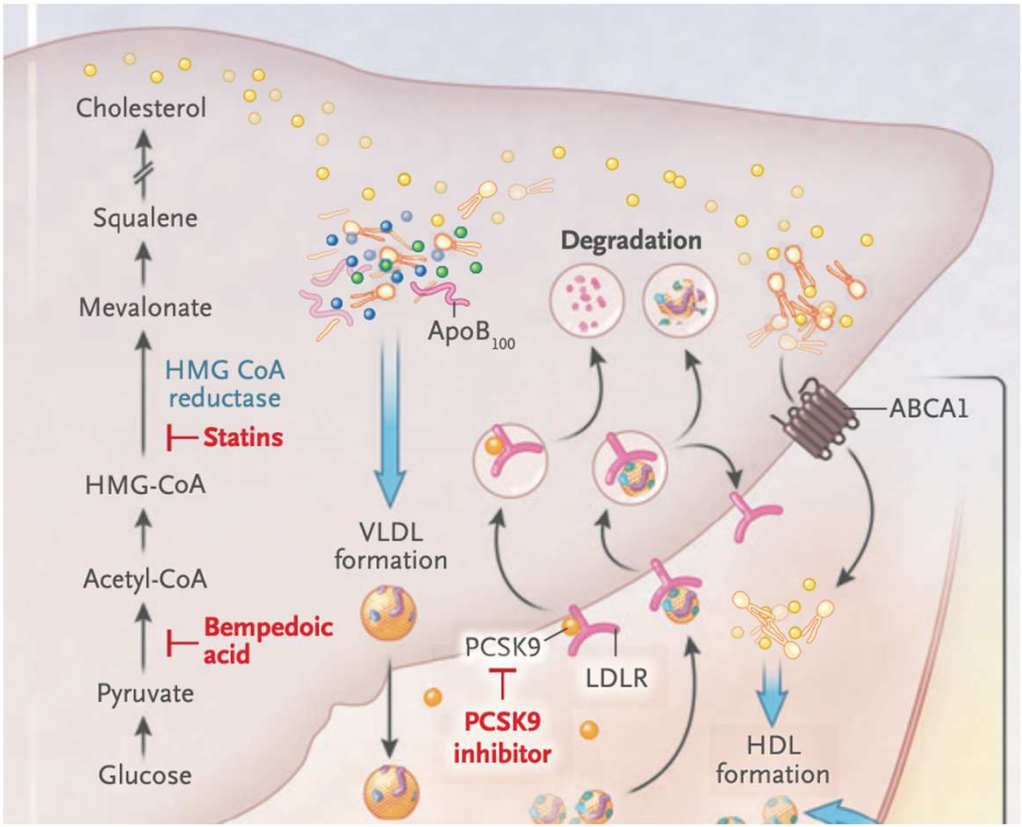
	Principal studies	LDL lowering	Indication restriction
ezetimibe		15-20%	none
bempedoic acid		20-25%	2nd prevent. + FH
PCSK9 inhibition		45-60%	2nd prevent. + FH

The iPCSK9 era



AHA Bridget et al. Innovations in Cardiovascular Health

Mechanism and history of iPCSK9



ORIGINAL ARTICLE

Sequence Variations in PCSK9, Low LDL, and Protection against Coronary Heart Disease

Jonathan C. Cohen, Ph.D., Eric Boerwinkle, Ph.D., Thomas H. Mosley, Jr., Ph.D., and Helen H. Hobbs, M.D.

N Engl J Med 2006; 354:1264-1272
N Engl J Med 2019;381:1557-67.

The iPCSK9: limitatio in CH

No need to ask the insurance for permission beforehand (?)

No need to try two statins any more.

Only two indications re-imbursed.

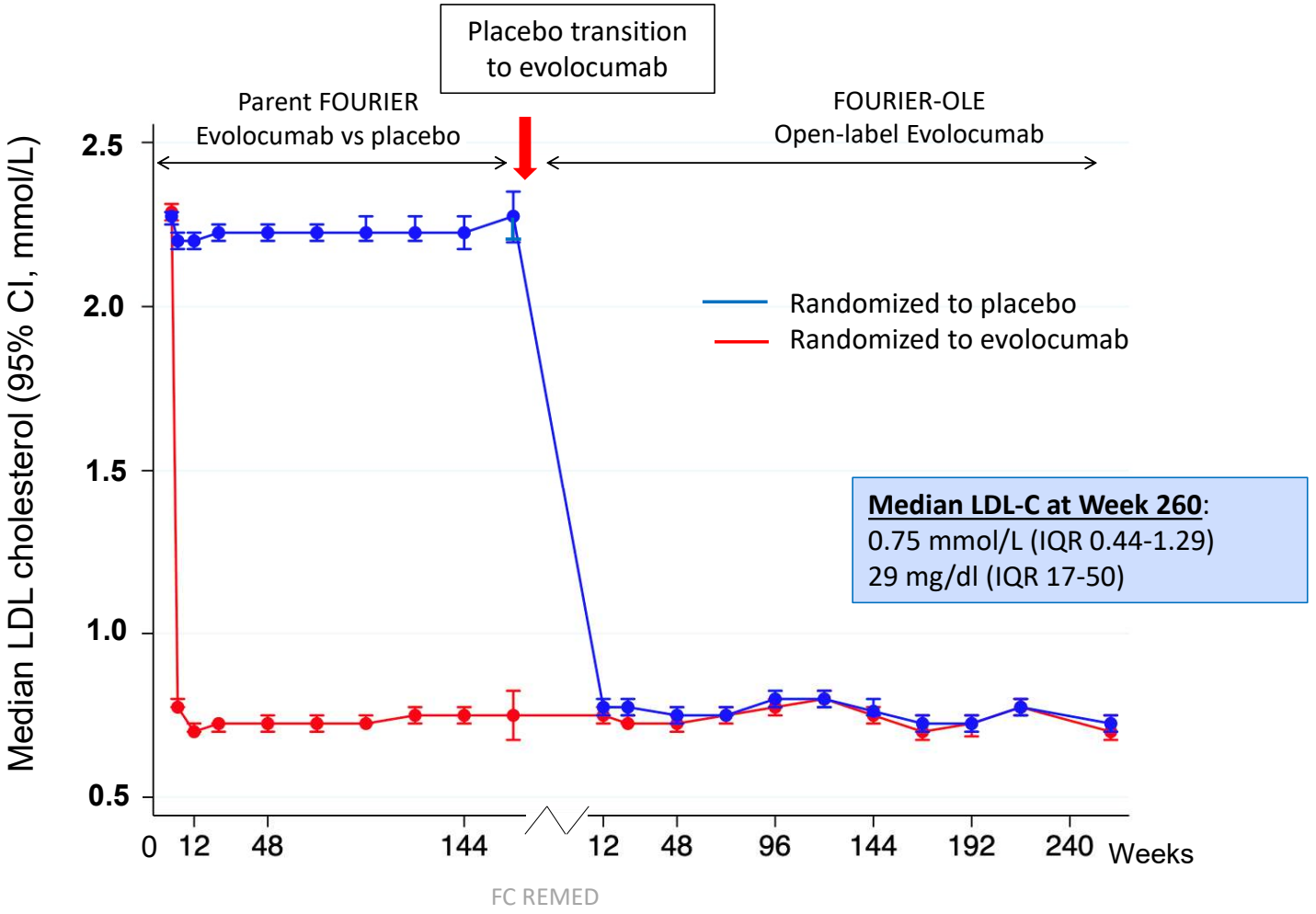
www.spezialitätenliste.ch; évolocumab 26/09/2024

Les iPCSK9

	alirocumab (Praluent)	evolocumab (Repatha)	Inclisiran (Leqvio)
baisse du LDL	environ 55%	environ 55%	environ 45%
application	1x/2 sem. sc.	1x/2 sem. sc.	1x/3 mois, puis 1x/6 mois
recul	~8 ans	~ 8 ans	~ 4 ans (études)
études outcome	oui	oui	non

- Très bonne acceptation par le patient avec éducation appropriée pour l'injection.
- Prix: semblable pour les 3, environ 5kCHF par an.

FOURIER-OLE: Long-Term Effect



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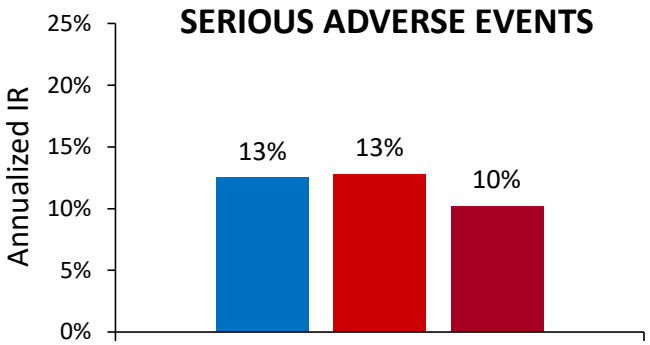
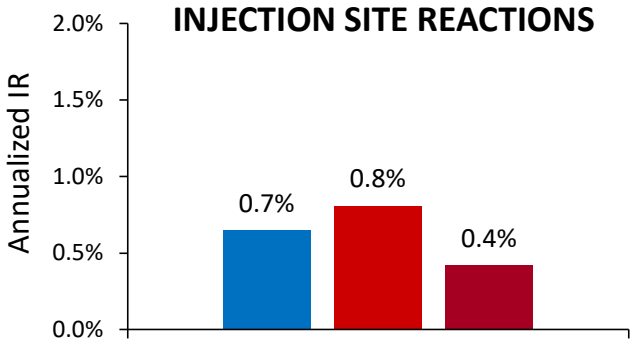
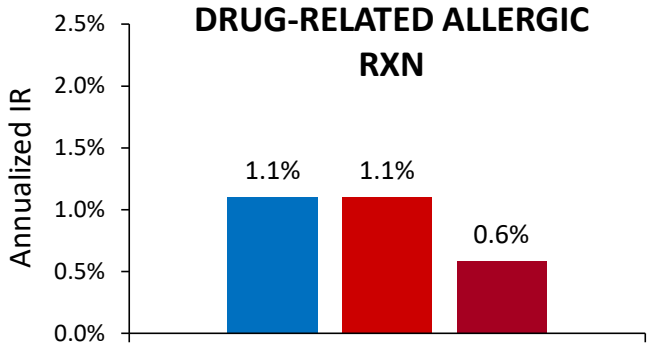
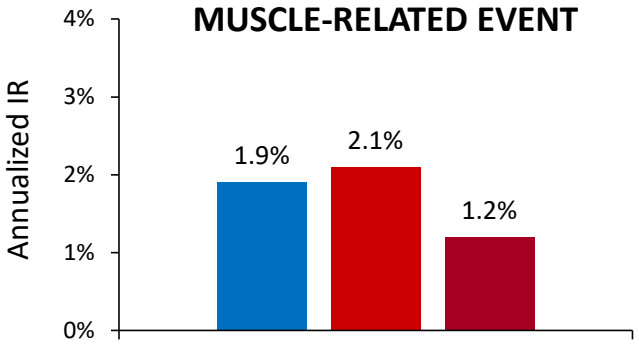
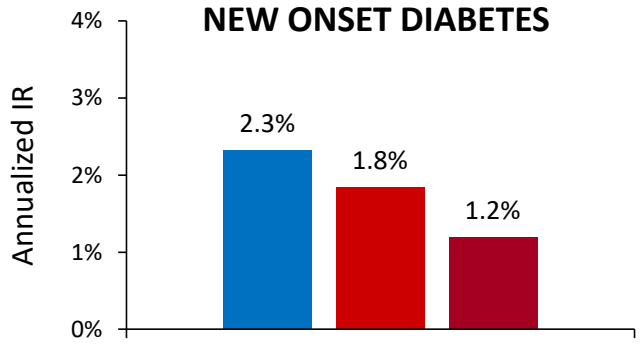
FOURIER-OLE: Long-Term Safety

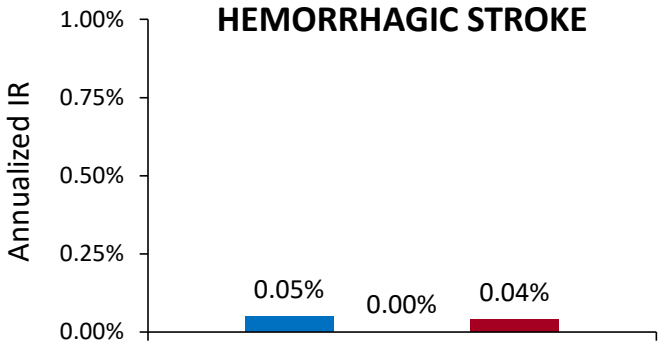


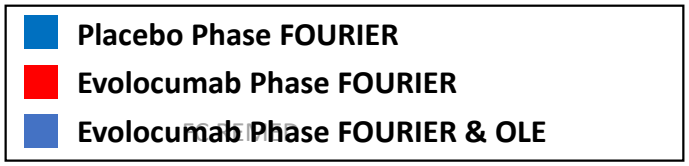






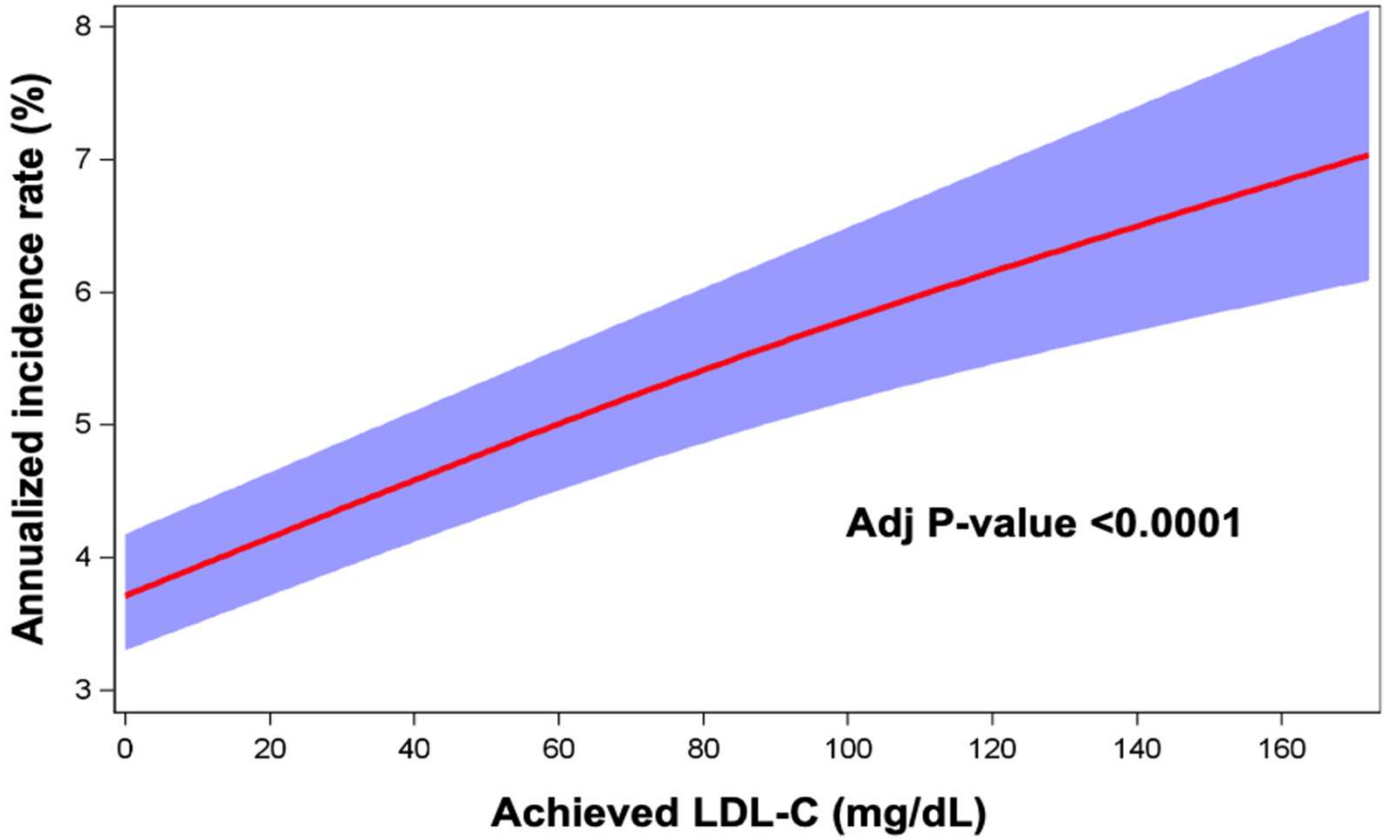






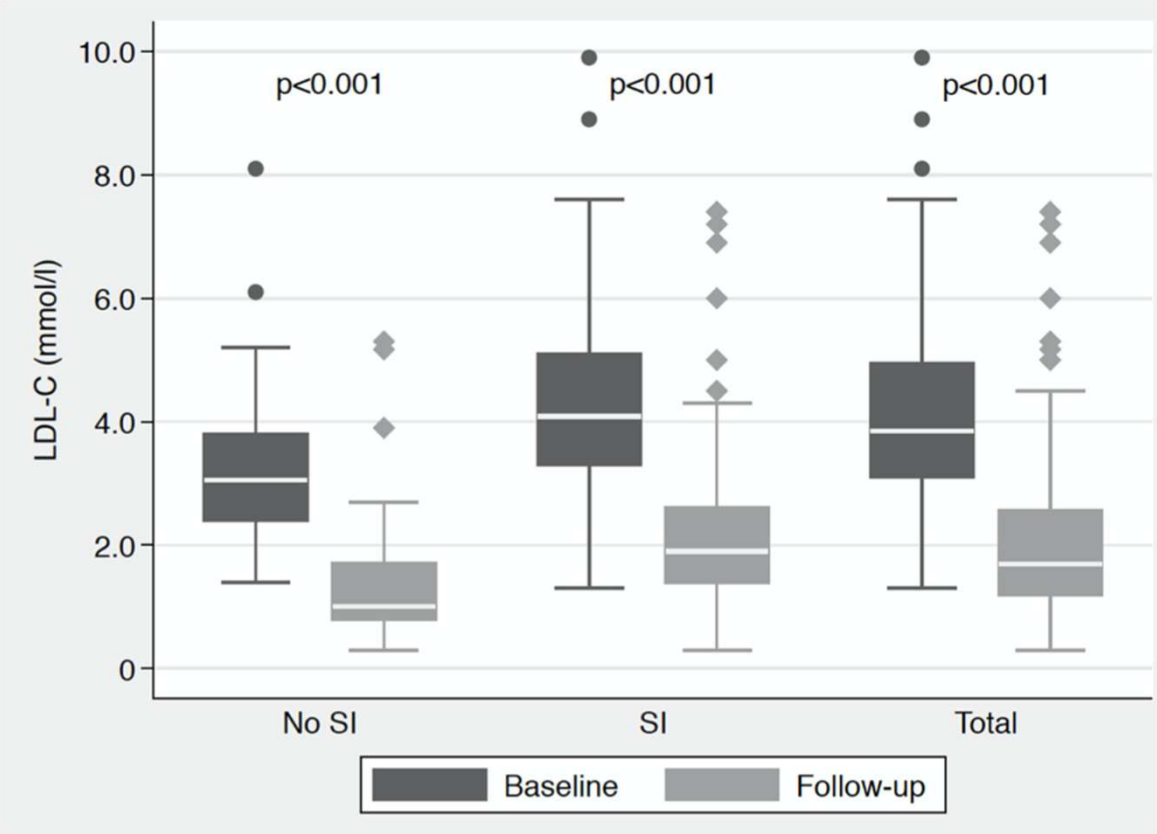
CV Outcomes and Achieved LDL-C

Primary endpoint: CV death, MI, stroke, coronary revascularization or hospitalization for unstable angina



Gaba P, et al. *Circulation*. 2023.

Importance d'utiliser les iPCSK9

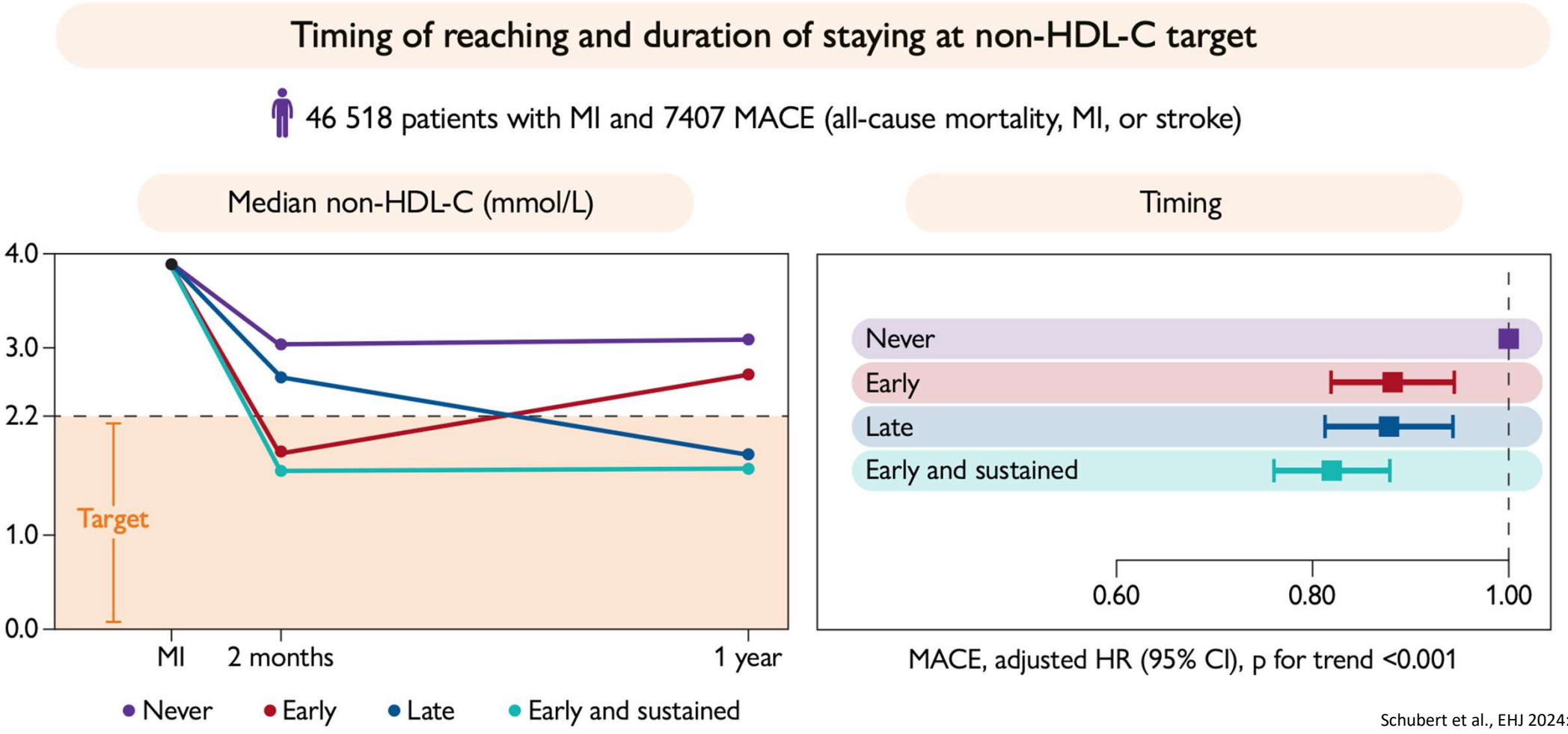


Etude Suisse représentative de pts traités par iPCSK9:

- Diminution LDL de 50-55%.
- 81% étaient intolérantes aux statines (!)

Sudano, … Ehret et al., Frontiers in CV Medicine, 2022

Outlook: are we giving medications too late ?



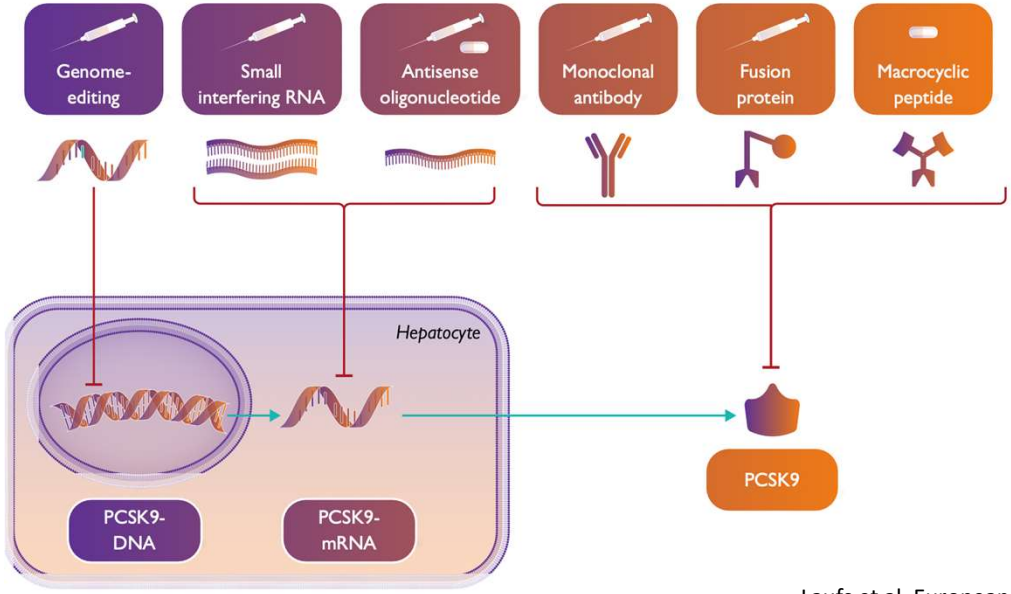
Schubert et al., EHJ 2024:.

Outlook for LDL: non-PCSK9 based

- **ANGPTL3 inibitor** evinacumab (hFH – soon other ?)
- microsomal triglyceride transfer protein inhibitor (**MTP inhibitor**): lomitapide

Outlook for LDL: PCSK9 based

- **oral PCSK9 inhibitors in 2026 (?)**
- **injectable PCSK9 inhibitors 1x/mois**
- **« single course programs »**, e.g. Verve (permanently turn off the PCSK9 gene in the liver to reduce disease-driving LDL-C)
- **many others**



Laufs et al. European Heart Journal (2023) 44, 4281–4283.

Agenda

1. cholestérol
2. atteinte vasculaire subclinique
3. poids

Case : Ms K

Female 62y.

CC: Cardiovascular risk counseling (referral by GP).

History: Fatigue, sleep disturbance, night sweats +++.

PE: BP 135/82mmHg, P 72/'; BMI: 25.7kg/m^2; cardiac & pulm. and vascular exam normal.

Ttt: None.

FH: Father with NSTEMI at 63 years, two brothers with HTN. One overweight daughter.

Case : Ms K, cont.

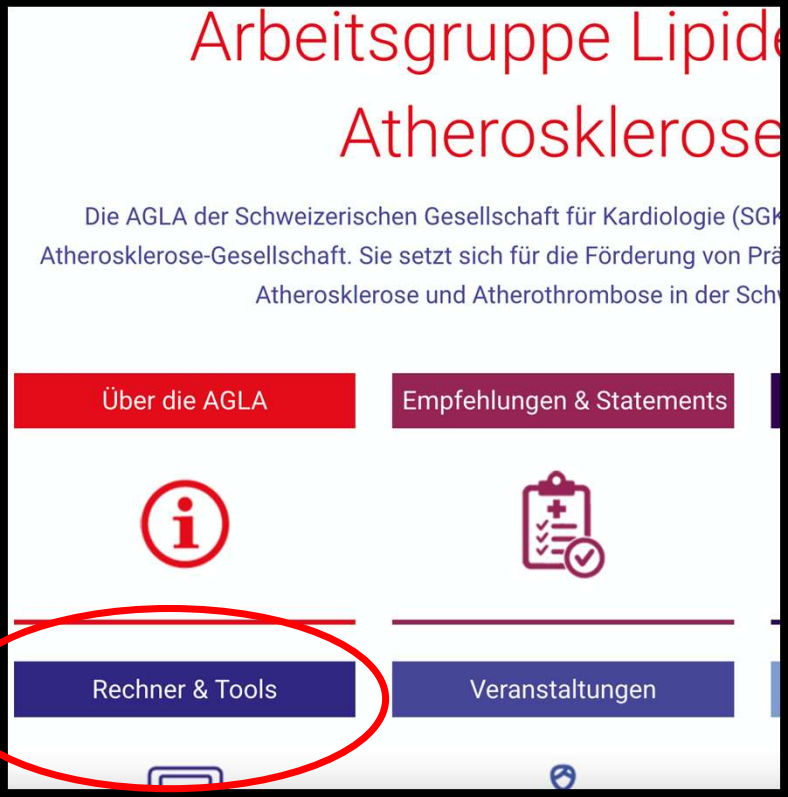
Psychosocial history: retired UN official, travels part of the year to Africa, lives with husband.

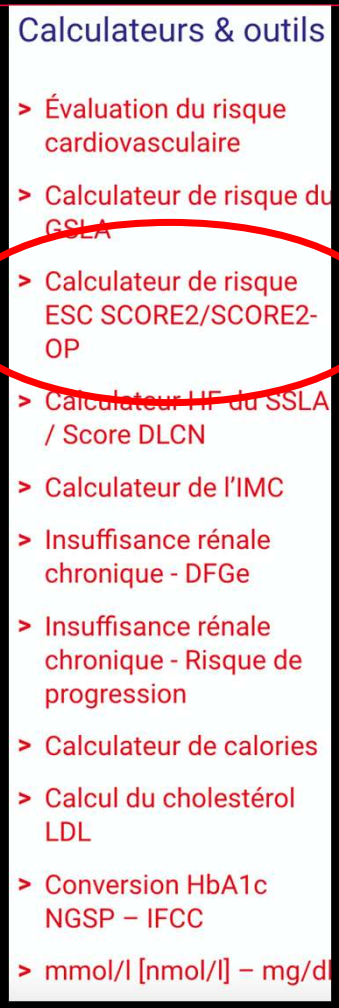
Lab: Hematology and electrolytes nl, LDL 4.3mmol/l, HDL 1.1mmol/L, triglycerides 2.1mmol/L. HbA1c 5.9%.

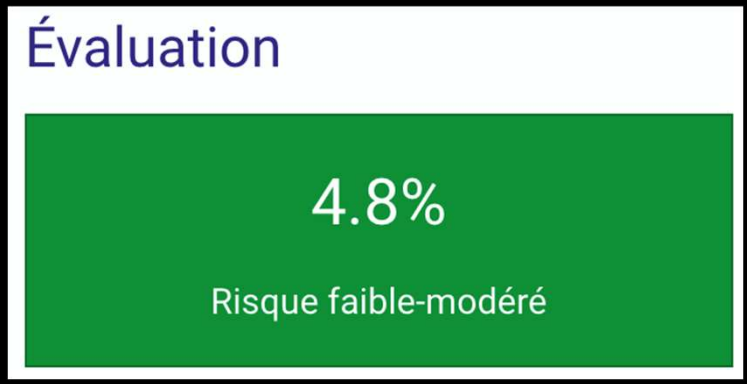
Urines: albumin 72mg/l, creatinine 19.3mmol/l.

Patient Ms K:

SCORE2 (www.agla.ch)







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New CV risk categories

	<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%

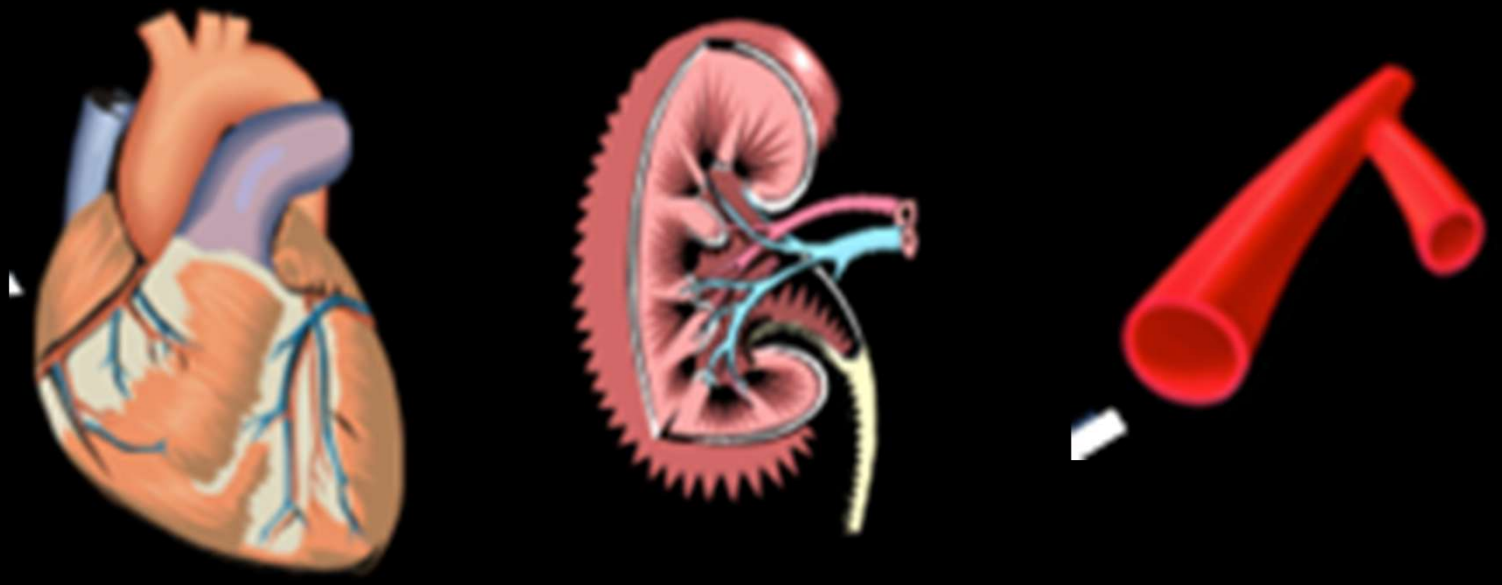
Visseren et al. European Heart Journal, 2021:3227

Screening recommendations

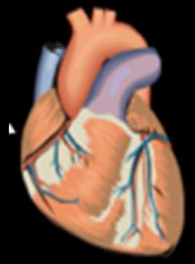
Recommendations	Class[a]	Level[b]
Systematic global CVD risk assessment is recommended in individuals with any major vascular risk factor (i.e. family history of premature CVD, FH, CVD risk factors such as smoking, arterial hypertension, DM, raised lipid level, obesity, or comorbidities increasing CVD risk).	I	C
Systematic or opportunistic CV risk assessment in the general population in men >40 years of age and in women >50 years of age or postmenopausal with no known ASCVD risk factors may be considered.[9]	IIb	C

Visseren et al. European Heart Journal, 2021:3227

How to detect subclinical atherosclerosis



Heart



ECG: what marker for LVH?

- ECG sensitivity for LVH **low**.
- ECG LVH is **independent predictor of CV events**.
- Study on 958 hypertensives**: simplified Cornell predicts** LVH and CV events as well as other indices.

	AUC
RaVL (mm)	0.721
SV3 (mm)	0.556
Sokoloff (mm)	0.521
QRS duration (ms)	0.557
Cornell (mm)	0.669
Cornell product (mm × ms)	0.670
Product Sokoloff × QRS (mm × ms)	0.544
Product RaVL × QRS (mm × ms)	0.726

Sokolow-Lyon index (SV1+RV5 > 3.5mV)

Modified Sokolow-Lyon index (largest S+R >3.5mV)

Cornell voltage (>244mV*ms)

Simplified Cornell (RaVL >1.1mV)

Manchia et al., Journal of Hypertension 2013, 31:1281–1357
Levy et al., Circulation 1994; 90:1786–1793
Gosse et al., J Hypertens. 2012 May;30(5):990-6

Kidney

Albuminuria

	24h urines	UACR
moderately increased microalbuminuria ("microalbuminuria")	30 - 300 mg/day	3.4 to 34 mg/mmol
severely increased microalbuminuria ("macroalbuminuria")	>300mg/day	>34 mg/mmol

UACR = urinary albumin creatinine ration =
u. albumin/u. creat.
= is in mg/mmol

UpToDate 2017

Albuminuria: potent predictor of CV risk

Very high CV risk	Patients with T2DM with: • Clinically established ASCVD or • Severe TOD or • 10-year CVD risk ≥20% using SCORE2-Diabetes
High CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: • 10-year CVD risk 10 to <20% using SCORE2-Diabetes
Moderate CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: • 10-year CVD risk 5 to <10% using SCORE2-Diabetes
Low CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: • 10-year CVD risk <5% using SCORE2-Diabetes

Severe TOD defined as eGFR <45 mL/min/1.73 m2 irrespective of albuminuria; or eGFR 45– 59 mL/min/1.73 m2 and microalbuminuria (UACR 30–300 mg/g; stage A2); or proteinuria (UACR >300 mg/g; stage A3); or presence of microvascular disease in at least three different sites [e.g. microalbuminuria (stage A2) plus retinopathy plus neuropathy].

Marx et al. European Heart Journal (2023) 44, 4043–4140

Vessels

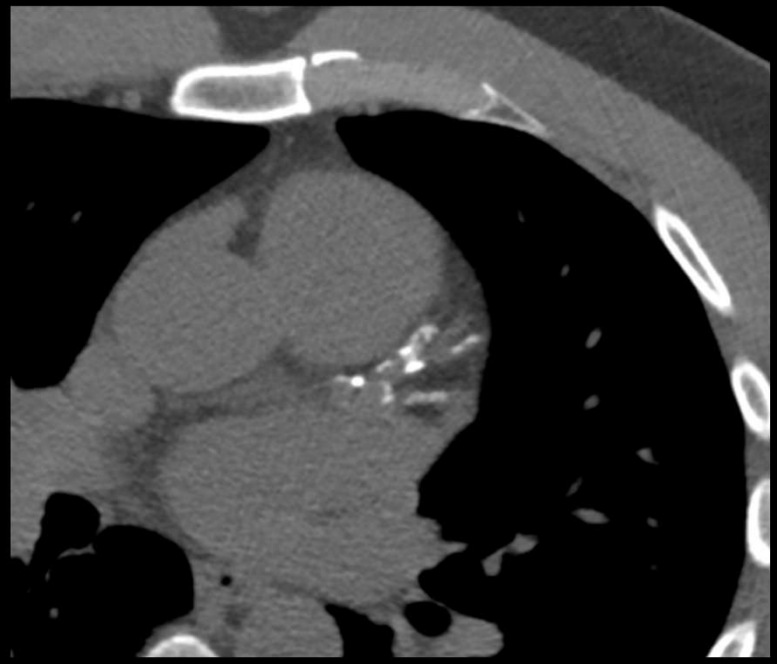
Investigations vasculaires

Recherche de plaques carotidiennes:
avantages: non-irradiant, peu couteux (?)
desavantages: moins bonne prediction que le SCC

Score calcique coronarien (SCC):
avantages: meilleure prediction d'évennements que l'US carotidien
desavantages: irradiant, couteux

Score calcique coronarien

Score calcique coronarien: p.e. 402UA



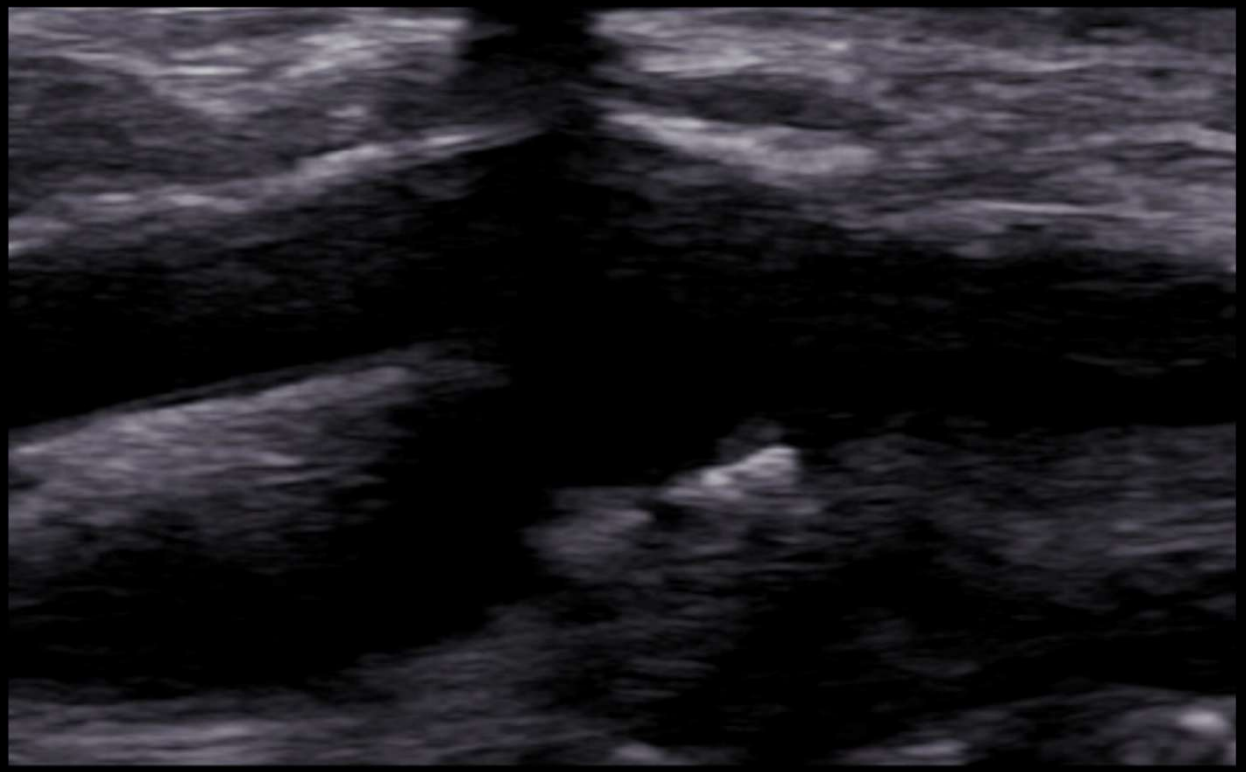
(0 UA: power of 0!

0-100: mild

100-400:moderate

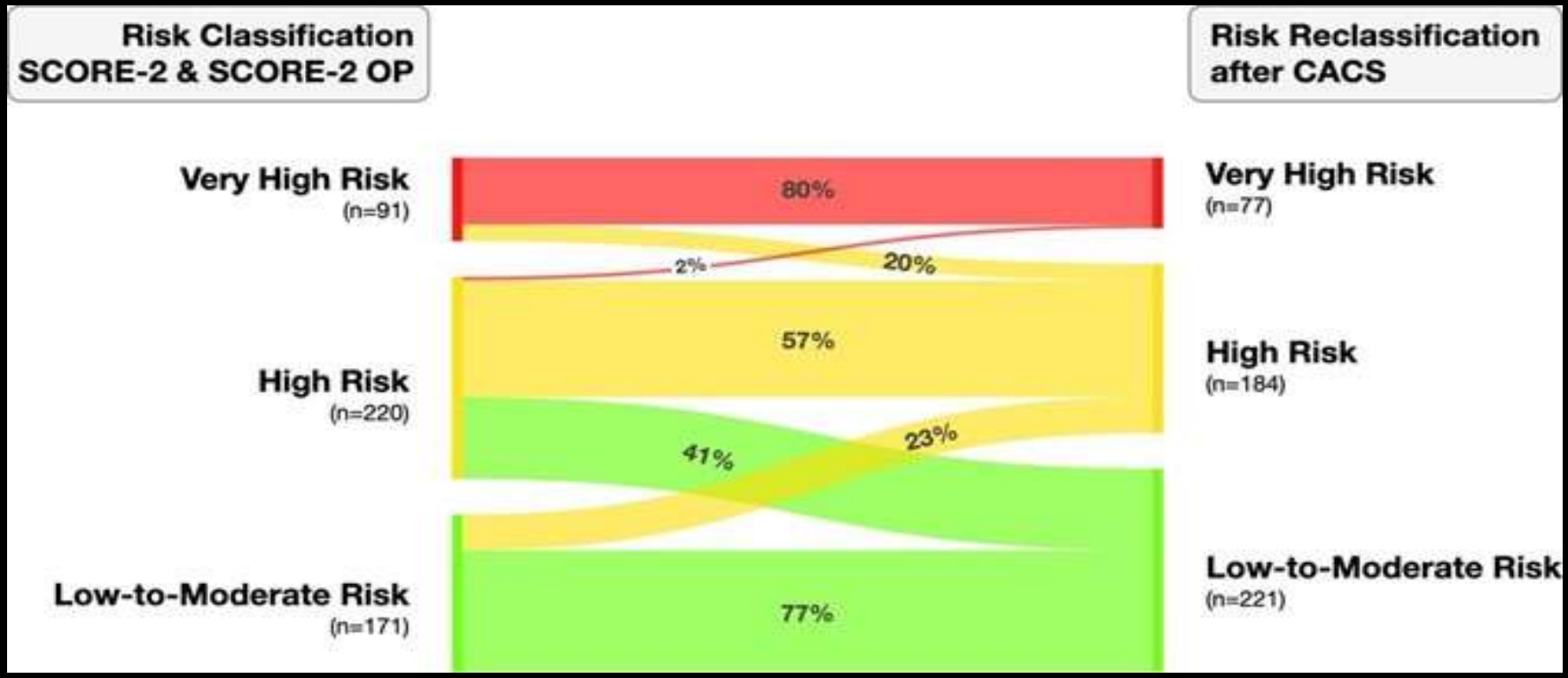
>400UA: sévère)

Recherche de plaques carotidiennes/fémorales



Improvement of classification by coronary calcium score

- "Some" reclassification of CV risk



Paiva et al. European Heart Journal, Volume 43, Supp 2022: 544

Recommendation clinique

CAC scoring may be considered to improve risk classification around treatment decision thresholds. Plaque detection by carotid ultrasound is an alternative when CAC scoring is unavailable or not feasible.[103,104]	IIb	B

Visseren et al. European Heart Journal, 2021:3227

Case : Ms K, cont.

SCC: 0UA

Plaques carotidiennes: absence

→ **Risque cardiovasculaire calculé (4.1%) sur-estimé.**

→ **Tout le monde est rassuré.**

Agenda

1. cholestérol
2. atteinte vasculaire subclinique
3. poids

Signification de l’obésité pour la cardiologie préventive

- **« Cible facile » pour reduire le risque CV**
- **Risque cardiovasculaire** chez le patient obèse.

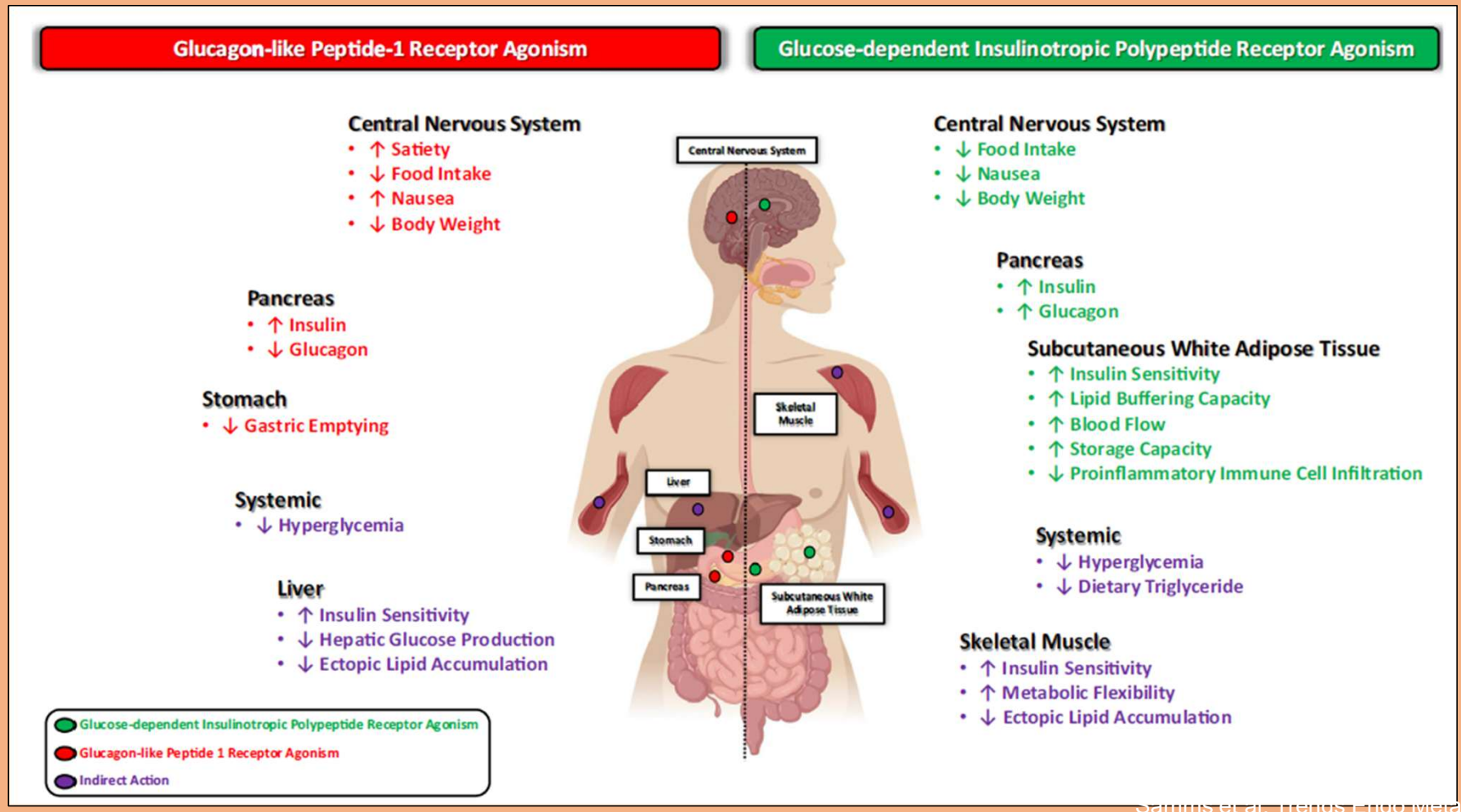
Cardiovascular effects of bariatric surgery

coronary artery disease	0.68 (0.52-0.91), p = 0.008
myocardial infarction	0.53 (0.44-0.64), p < 0.01
heart failure	0.45 (0.37-0.55), p < 0.01
cerebrovascular accident	0.68 (0.59-0.78), p < 0.01
cardiovascular mortality	0.48 (0.40-0.57), p < 0.01
atrial fibrillation	0.81 (0.65-1.01), p = 0.07

hazard ratios are indicated

Chandrakumar et al. Cureus. 2023 Feb 7;15(2):e34723

Actions agonistes GLP-1 et GIP



Samms et al. Trends Endo Metabo 2020

Large outcome studies with GLP-1 agonists in non-diabetics ?

STEP & SELECT clinical programs

- STEP 1: semaglutide + livestyle in o&o (N=1’961) NEJM 2021
- STEP 2: semaglutide in DM2 o&o (N=1’210) Lancet 2021
- STEP 3: semaglutide + intensive livestyle intervention in o&o (N=611) JAMA 2021
- STEP 4: semaglutide max dose + livestlyle in o&o (N=803) JAMA 2021
- SELECT: CV outcomes in 2nd prev. of semaglutide in o&o (N=17’604) NEJM 2023
- STEP-HFpEF: HFpEF outcomes of semaglutide (N=529) NEJM 2023

o&o: overweight & obesity

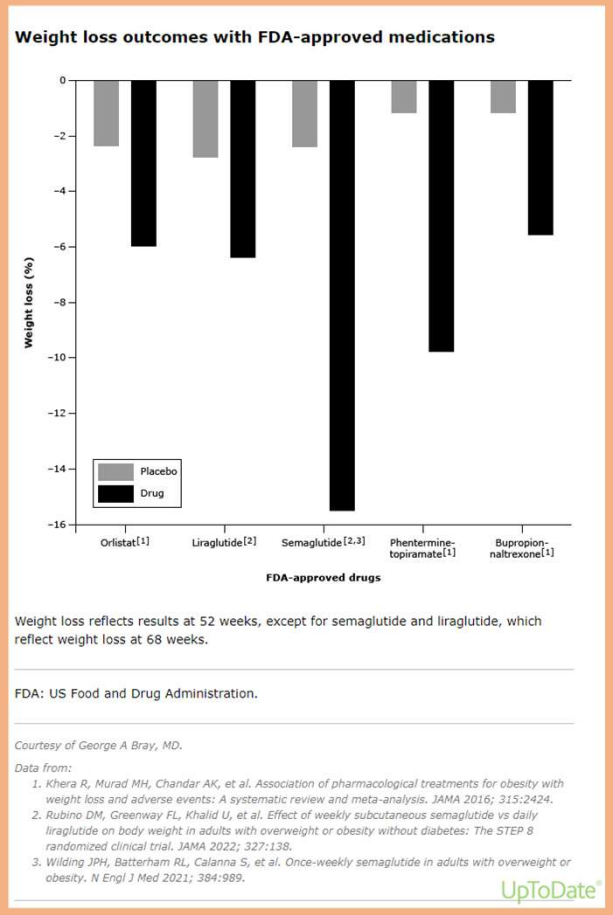
Semaglutide Treatment Effect in People with Obesity (STEP)

Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT)

Perte de poids avec les agonistes GLP-1/GIP

- semaglutide : -14.9%* (STEP-1 NEJM 2021; 384:989-1002)
- liraglutide: -7.9%* (SCALE NEJM 2015; 373:11-22)
- tirzepatide: -20.9%* (SURMOUNT-1 NEJM 2022; 387:205-216)

*weight reduction with highest dose

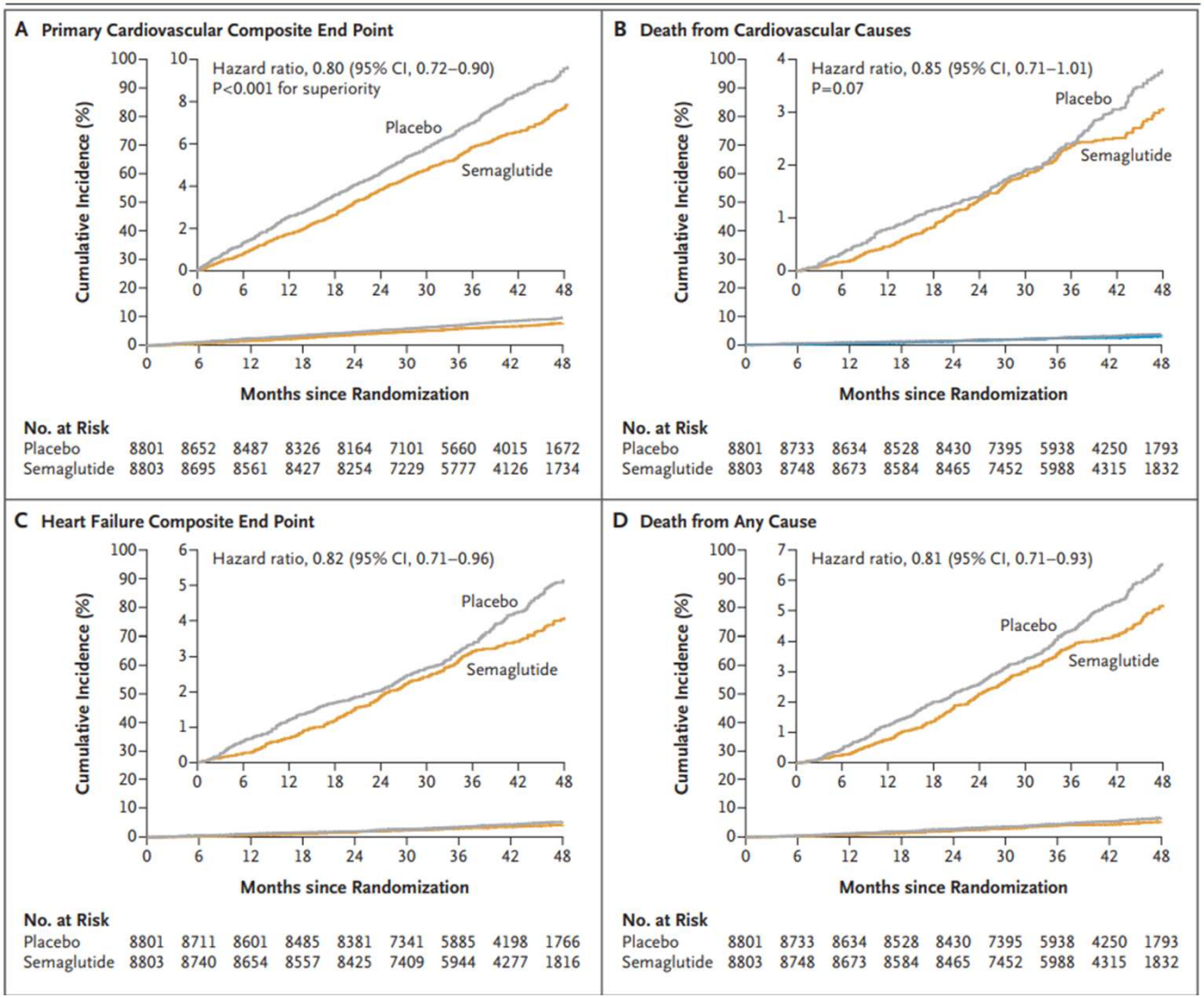


Etude SELECT

- RCT avec > de 17’604 participants.
- Patients de > 45 ans sans diabète avec BMI ≥27kg/m2 avec antécédent maladie CV.
- Placebo vs semaglutide 2.4 mg 1x/semaine.
- Critères de jugement : endpoint composite CV (mort de cause CV, IM non-fatal, AVC non-fatal).

Lincoff et al. N Engl J Med 2023;389:2221-2232

Etude SELECT



Lincoff et al. N Engl J Med 2023;389:2221-2232

Résumé d'impact du semaglutide sur des paramètres cardiovasculaires

paramètre	sémaglutide	placébo	étude
poids	-16%	-5.7%	STEP3
tension artérielle systolique	-5.6mmHg	-1.6mmHg	STEP3
LDL	-5.25%	-3.14%	N Engl J Med 2023;389:2221
triglycérides	-18.3%	-3.2%	N Engl J Med 2023;389:2221
CRP	-59.6	-22.9%	STEP3

Autres effets du sémaglutide dépendants et indépendants (?) du poids

- Prédiabète -> diabète.
- Fibrillation auriculaire.
- Mort subite.
- Cardiac valve stenosis.
- Thromboembolisme.
- Perméabilité intestinale.
- Apnées du sommeil.
- Stéatose hépatique.
- Fonction articulaire.
- Dépression.
- Consommation d'alcool.
- Cognition.
- Fonction rénale.

Ehret et al., Revue Médicale Suisse, en révision.

Semaglutide: effect on smoking and addiction

Annals of Internal Medicine®

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Original Research | 30 July 2024

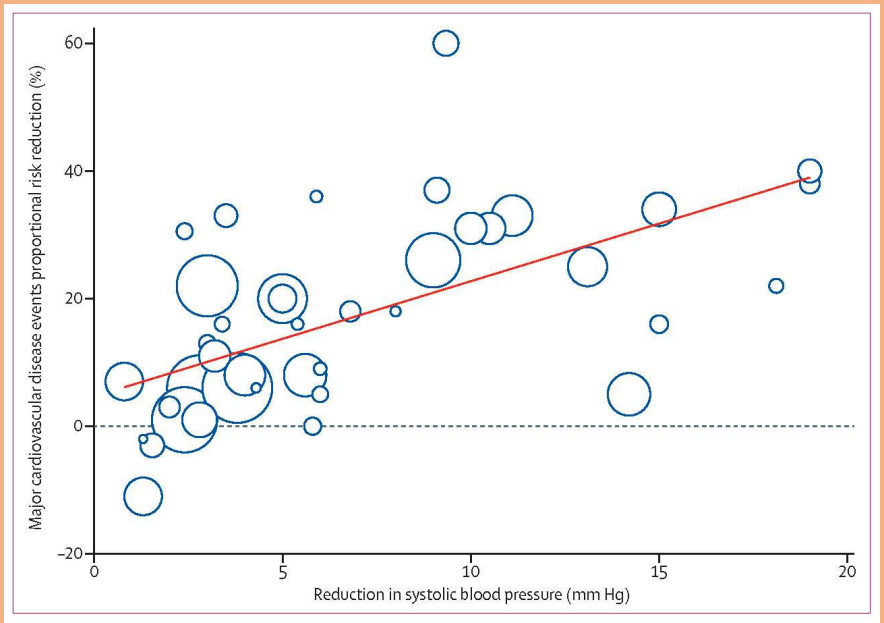
Association of Semaglutide With Tobacco Use Disorder in Patients With Type 2 Diabetes: Target Trial Emulation Using Real-World Data

Authors: William Wang, Nora D. Volkow, MD , Nathan A. Berger, MD , Pamela B. Davis, MD, PhD , David C. Kaelber, MD, PhD, MPH , and Rong Xu, PhD | AUTHOR, ARTICLE, & DISCLOSURE INFORMATION

Agenda

1. cholestérol
2. atteinte vasculaire subclinique
3. Poids
4. Tension artérielle

Impact of BP lowering



Meta-analysis of 123 RCT with a total of 613,815 participants

For every 10mmHg reduction in SBP:

- RR 0.8 (0.77-0.83) for major CV events
- RR 0.83 (0.78-0.88) for coronary events
- RR 0.73 (0.68-0.77) for stroke
- RR 0.72 (0.67-0.78) for heart failure

Lancet. 2016 Mar 5;387(10022):957-67

Resumé

- Lowering LDL is an opportunity !
- “The lower the better.”
- Not only LDL !

Cardiologie Préventive
Service de cardiologie / HUG

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




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

End of slides.

Case

Female 32y, no relevant medical history.

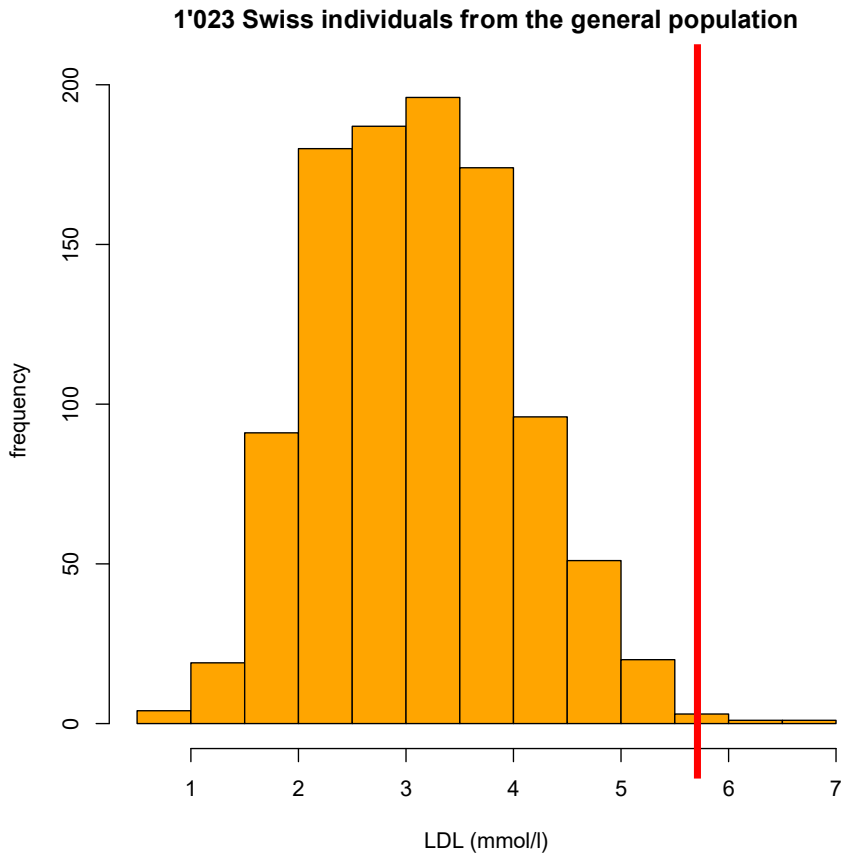
History: No known CV risk factors except obesity (BMI 33.7kg/m2).

PE: BP 120/76mmHg, P 72/'; BMI: 33.7kg/m^2; cardiac & pulm. and vascular exam normal.

Lab: Hematology and e'lytes nl, LDL 5.8mmol/l, HDL 1.1mmol/L, triglycerides 1.9mmol/L.

Who treats this patient with LLT (in add. to lifestyle) ?

Case

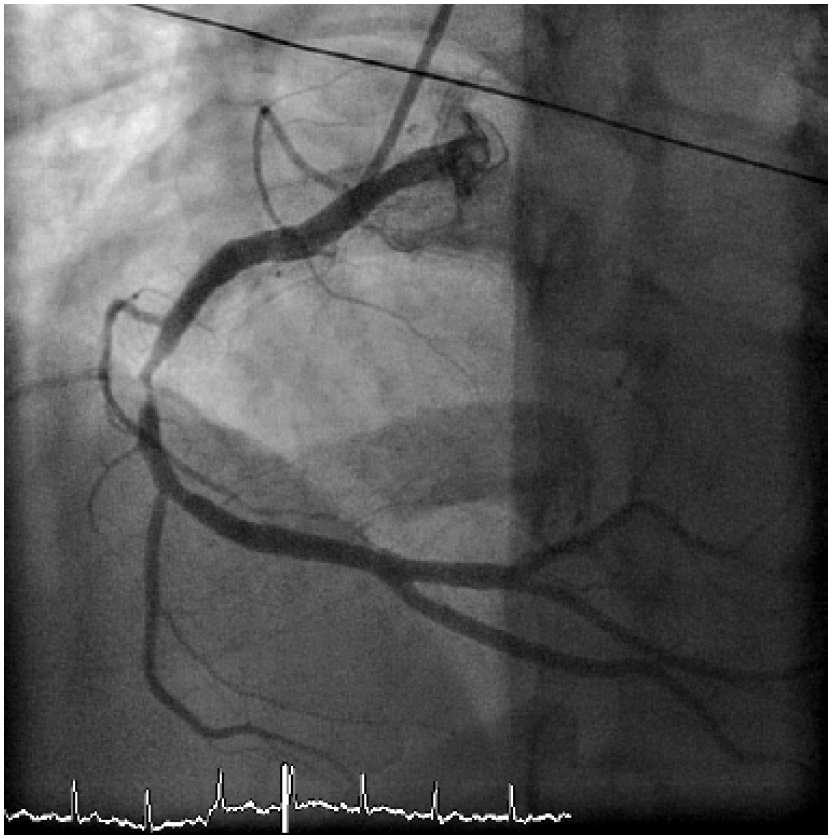


Who treats this patient with LLT ?

Ehret et al., unpublished

Case

STEMI on mono-vessel CAD (RCA).



Who treats this patient with LLT ?

Case: family screening: heterozygous familial hypercholesterolemia

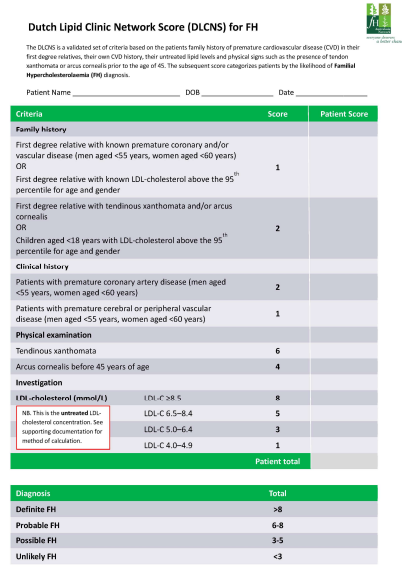
Laboratory nl for 2nd causes of dyslipidemia.

mother: LDL 5.8, lp(a) 970mg/l

male 11y: LDL 7.0, HDL 1.4, trigl. 0.7, lp(a) 486mg/l

male 9y: LDL 2.8, HDL 1.5, trigl. 0.5, lp(a) 287mg/l

female 8y: LDL 6.2, HDL 1.5, trigl. 0.8, lp(a) 58mg/l



Dutch Lipid Clinic Network Score (DLCNS) for FH

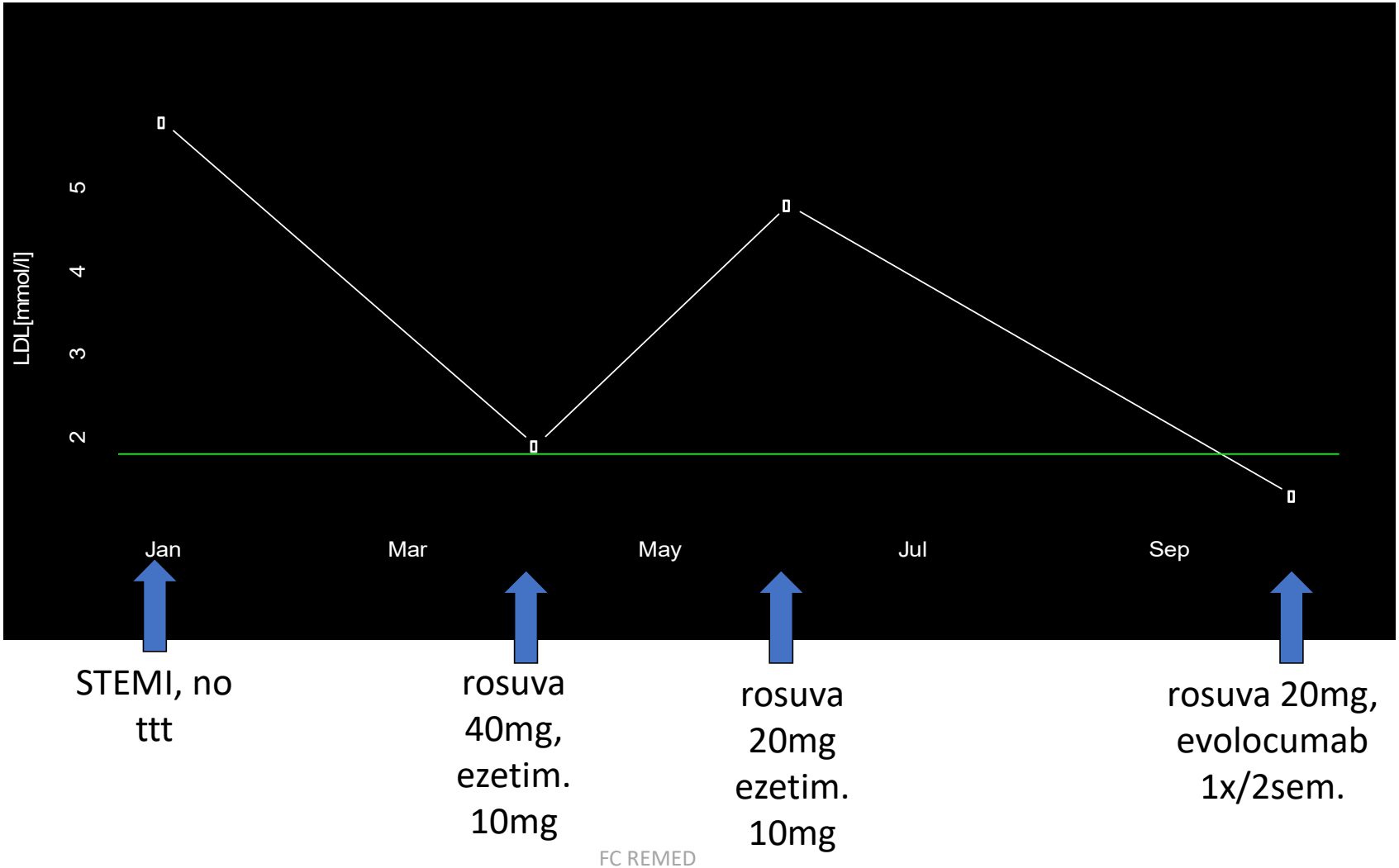
The DLCNS is a validated set of criteria based on the patients family history of premature cardiovascular disease (CVD) in their first degree relatives, their own CVD history, their untreated lipid levels and physical signs such as the presence of tendon xanthomata or arcus cornealis prior to the age of 45. The subsequent score categorizes patients by the likelihood of **Familial Hypercholesterolaemia (FH)** diagnosis.

Patient Name _____ DOB _____ Date _____

Criteria		Score	Patient Score
Family history			
First degree relative with known premature coronary and/or vascular disease (men aged <55 years, women aged <60 years) OR First degree relative with known LDL-cholesterol above the 95th percentile for age and gender		1	
First degree relative with tendinous xanthomata and/or arcus cornealis OR Children aged <18 years with LDL-cholesterol above the 95th percentile for age and gender		2	
Clinical history			
Patients with premature coronary artery disease (men aged <55 years, women aged <60 years)		2	
Patients with premature cerebral or peripheral vascular disease (men aged <55 years, women aged <60 years)		1	
Physical examination			
Tendinous xanthomata		6	
Arcus cornealis before 45 years of age		4	
Investigation			
LDL-cholesterol (mmol/l)	LDL-C ≥8.5	8	
NB. This is the **untreated** LDL-cholesterol concentration. See supporting documentation for method of calculation.	LDL-C 6.5–8.4	5	
	LDL-C 5.0–6.4	3	
	LDL-C 4.0–4.9	1	
		Patient total	

Diagnosis	Total
Definite FH	>8
Probable FH	6-8
Possible FH	3-5
Unlikely FH	<3

Patient trajectory



Limitatio iPCSK9 (mAB or iRNA)

iPCSK9 is reimbursed in Switzerland using the following LDL criteria
+ maximal tolerated lipid therapy + dietary approaches + control of other CV risk factors

	LDL thresholds for reimbursement
Secondary prevention In patients who have clinically apparent atherosclerosis	**LDL-C > 1.8 mmol/l**
Primary prevention >10 years and heterozygous or homozygous familial hypercholesterolemia	**LDL-C > 2.6 mmol/l**

1) Spezialitätenliste des Bundesamt für Gesundheit (BAG), http://www.spezilitätenliste.ch

Objectives of PCSK9i (and other LLT)

1. ***Clinical***: **reduce the number of events (FOURIER-OLE)**
2. ***Safe*** **and comfortable treatment (FOURIER-OLE)**
3. ***Subclinical***: **(HUYGENS, PACMAN-AMI)**
   - **decrease plaque progression / induce regression**
   - **stabilize plaque**
4. **Future uses (?):**
   - **very early use after myocardial infarction ? (EVOPACS)**
   - **aortic stenosis ? (not discussed here)**

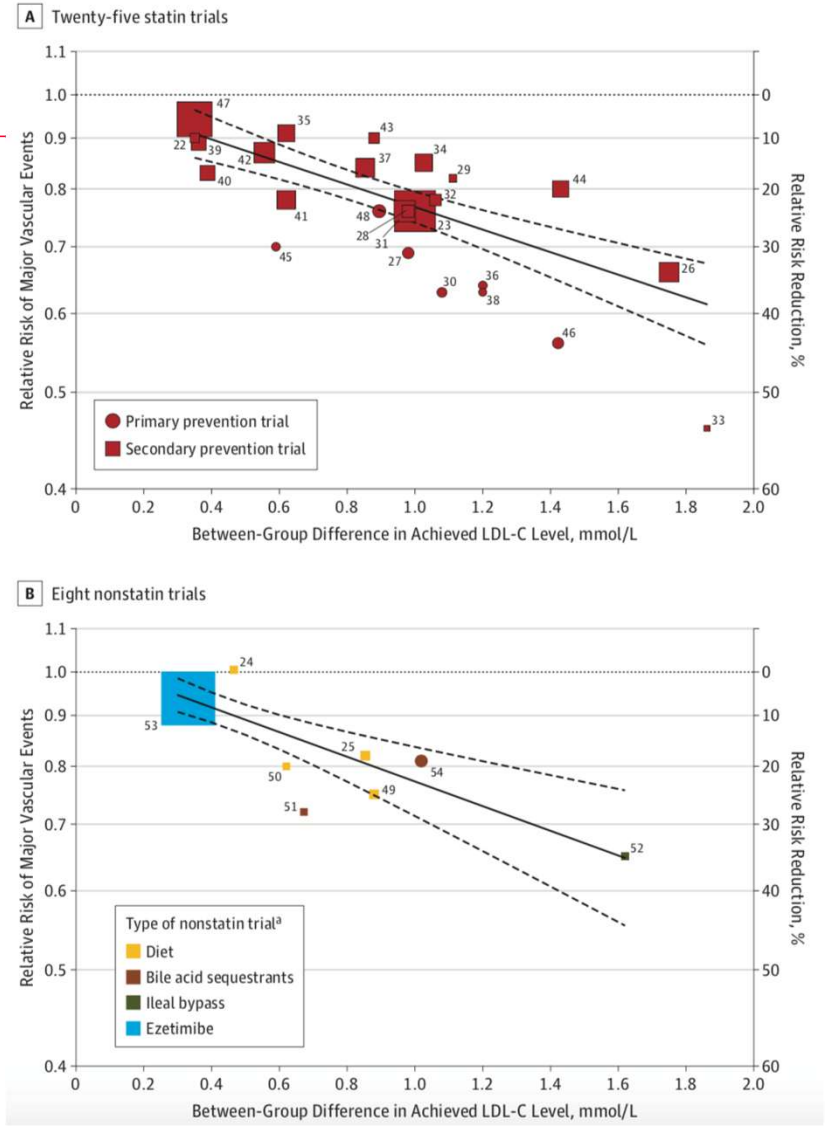
Impact of LDL lowering

Meta-analysis of 312,175 participants:

<u>For every “1mmol” reduction in LDL:</u> RR 0.8 for events

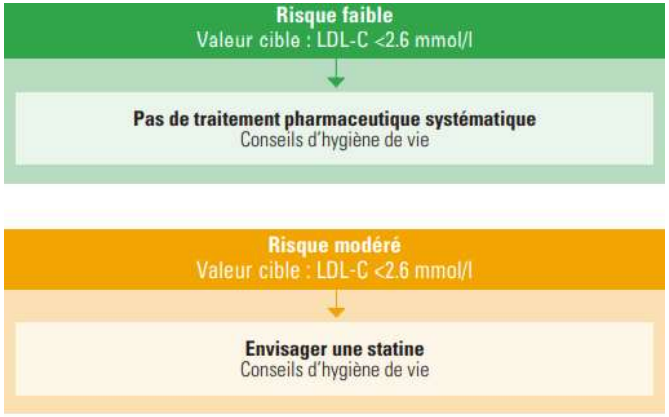
=

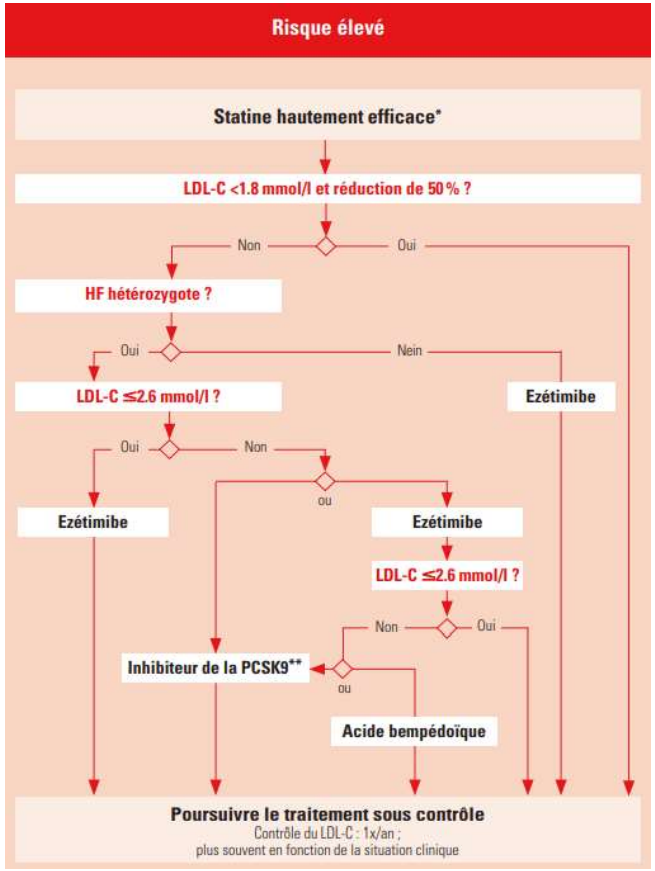
20% less events

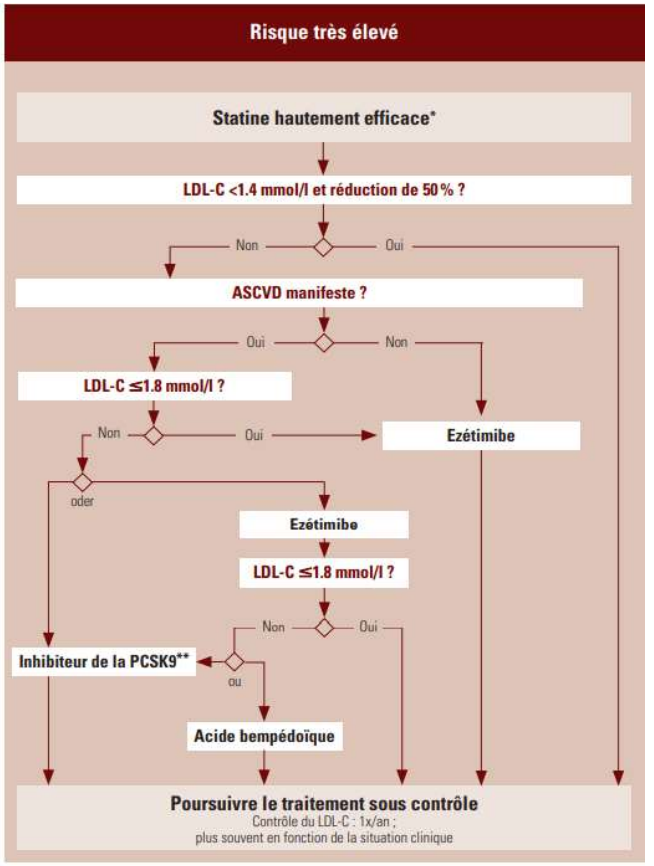


Silvermann et al. JAMA. 2016;316(12):1289-1297.

How to get there ? (AGLA 2023)[1]







*Rosuvastatine, pitavastatine, atorvastatine
**Evolocumab, alirocumab, inclisiran

1. Recommandations GSLA 2023, 7ème édition, https://www.agla.ch/

Les schémas de traitement représentés ci-dessus tiennent compte de la limitation de l'OFSP concernant les inhibiteurs de la PCSK9. C'est pourquoi, ils diffèrent de l'indication PCSK9 des lignes directrices de l'ESC/EAS. Voir limitation OFSP concernant l'utilisation des inhibiteurs de la PCSK9 à la p. 37. *atorvastatine, rosuvastatine **evolocumab, alirocumab #sont considérés comme facteurs de risque: diabète sucré, Lp(a) >50 mg/dl (>120 nmol/l), PA ≥180/110 mmHg

Evidence for efficacy of LDL-lowering therapies down to below 1.4 mmol/L (55 mg/dL)

Source of evidence	Mean reduction in LDL cholesterol; mmol/L [mg/dL]	Outcome	RR (95% CI) [per mmol/L]
CTT meta-analysis[1] (high-intensity vs standard statin; subgroup <2.0 mmol/L)	1.71 [66] vs 1.32 [50]	MI, CHD death, stroke, coronary revascularisation	0.71 (0.56–0.91)
IMPROVE-IT[2] (ezetimibe plus statin vs statin)	1.80 [70] vs 1.40 [54]	CV death, MI, stroke, UA, coronary revascularisation	0.94 (0.89–0.99)
FOURIER[3] (evolocumab plus high-dose statin ± ezetimibe vs high-dose statin ± ezetimibe)	2.37 [92] vs 0.78 [30]	CV death, MI, stroke, UA, coronary revascularisation	0.85 (0.79–0.92)
ODYSSEY OUTCOMES[4] (alirocumab plus high-dose statin ± ezetimibe vs high-dose statin ± ezetimibe)	2.37 [92] vs 1.37 [53]	MI, CHD death, stroke, UA	0.85 (0.78–0.93)

CHD = coronary heart disease; CV = cardiovascular; MI = myocardial infarction; UA = unstable angina.
1.CTT Collaboration. Lancet 2010;376:1670–81; 2. Cannon CP, et al. N Engl J Med 2015;372:2387–97;
3. Sabatine MS, et al. N Engl J Med 2017;376:1713–22; 4. Schwartz GG, et al. N Engl J Med 2018;379:2097–107

Very high CV risk patients have the greatest benefit: who are they ?

1. **Documented ASCVD**, either **clinical** or **unequivocal on imaging.**
   - Previous ACS (MI or unstable angina); Stable angina; Coronary revascularisation (PCI, CABG, and other arterial revascularisation procedures); Stroke and TIA; Peripheral arterial disease.
   - Significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound

2. **"Severe" diabetics**

   DM with
   - target organ damage, or at least three major risk factors or early onset of T1DM of long duration (>20 years)

3. **Severe renal failure**

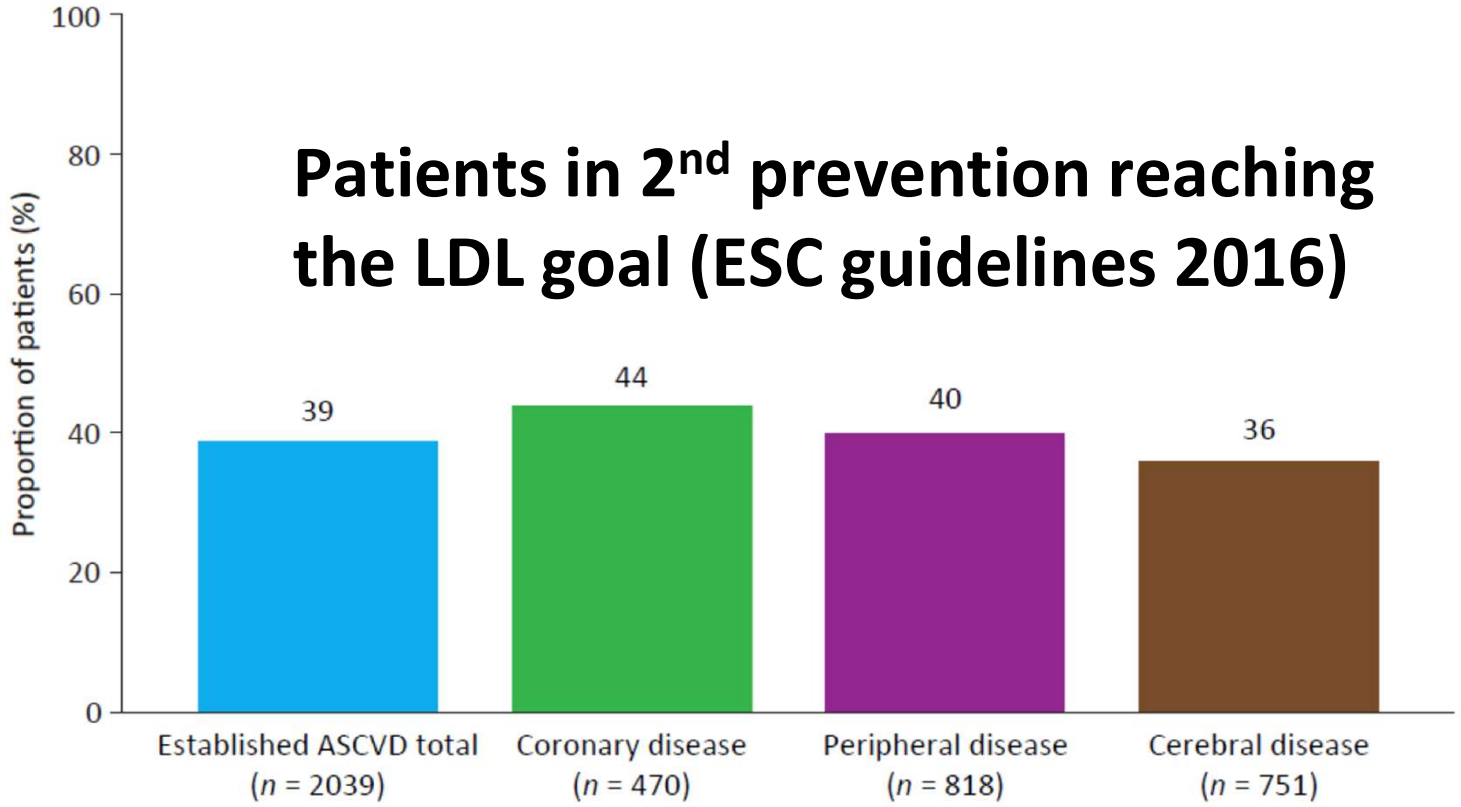
   eGFR <30 ml/min

4. **Familial hyperchol. (high risk) or with another CV risk factor (very high risk)**

5. **Score**

   SCORE2 >10%

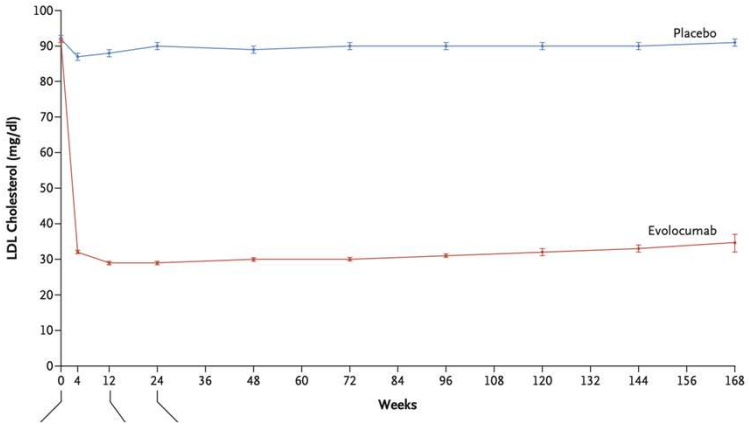
Do we get there ? Not yet !



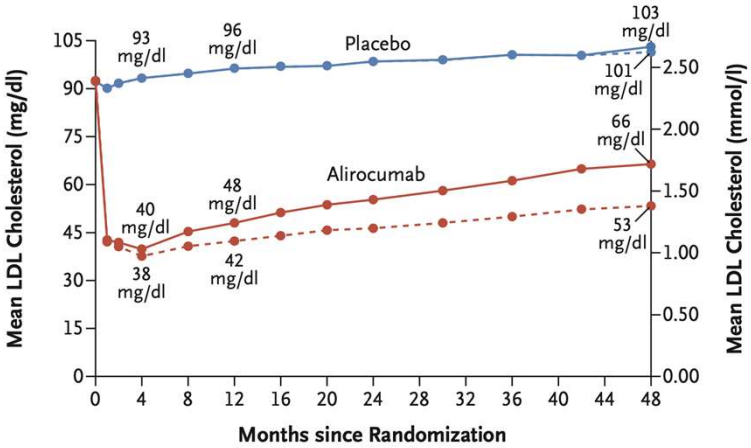
Ray et al. Eur J Prev Cardiol. 2020 Aug 28

LDL-lowering by PCSK9i

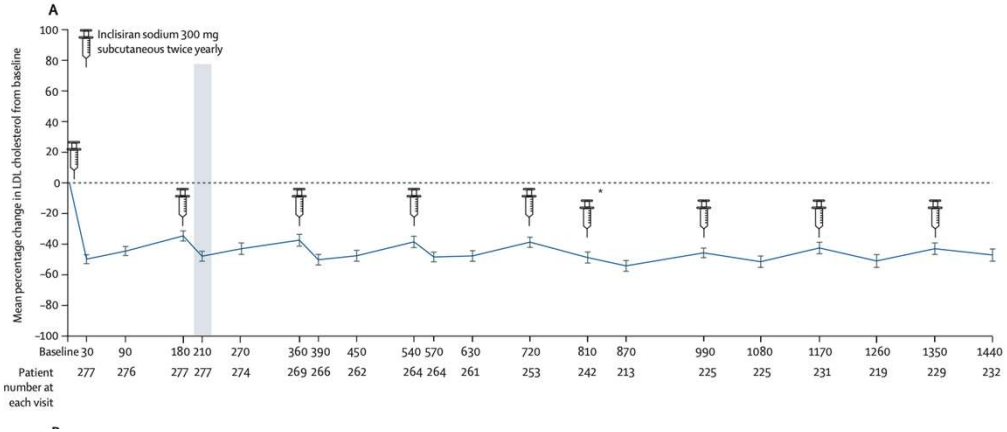
FOURIER TRIAL



ODYSSEY OUTCOMES TRIAL

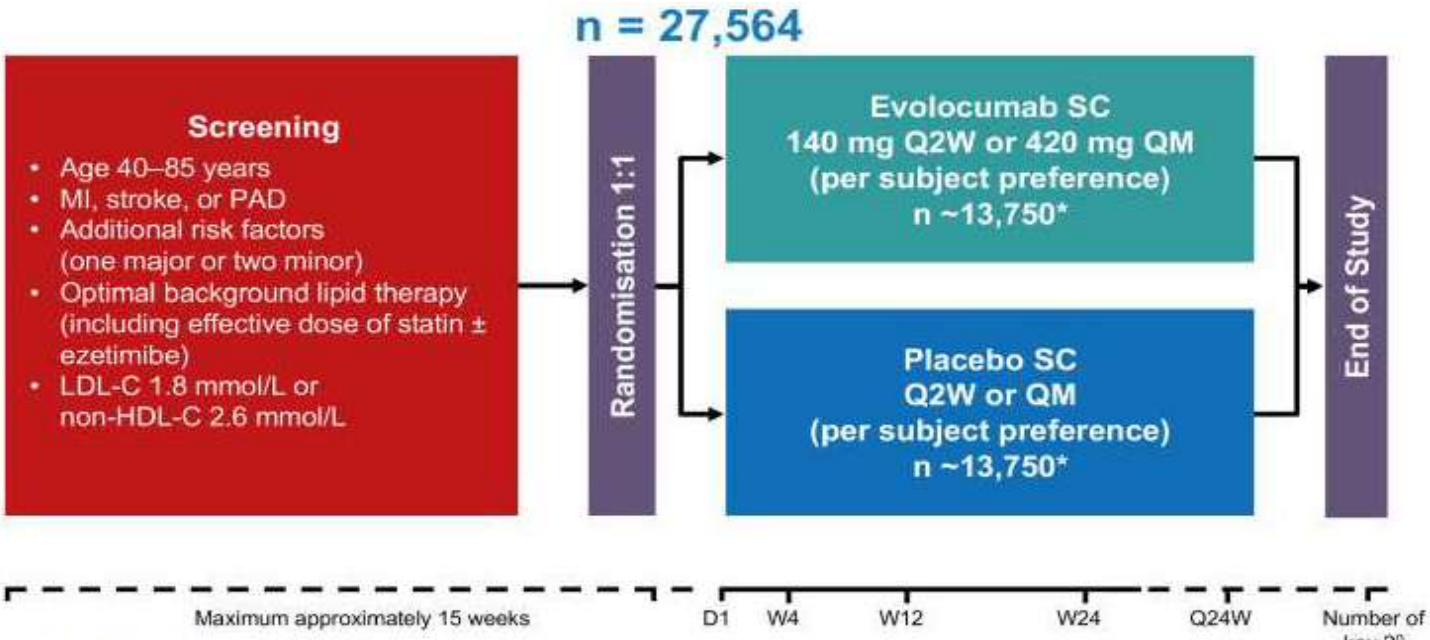


ORION TRIAL 1+3 TRIALS



N Engl J Med 2017; 376:1713-1722 and N Engl J Med 2018; 379:2097-2107 Ray et al. Lancet Diabetes Endocrinol 2023; 11: 109–19

FOURIER outcomes
Evolocumab outcomes trial study design[1]



Primary endpoint (MACE+):
Major CV event (CV death, MI, stroke, hospitalisation for unstable angina or coronary revascularisation)

Key secondary endpoint (MACE):
CV death, MI or stroke

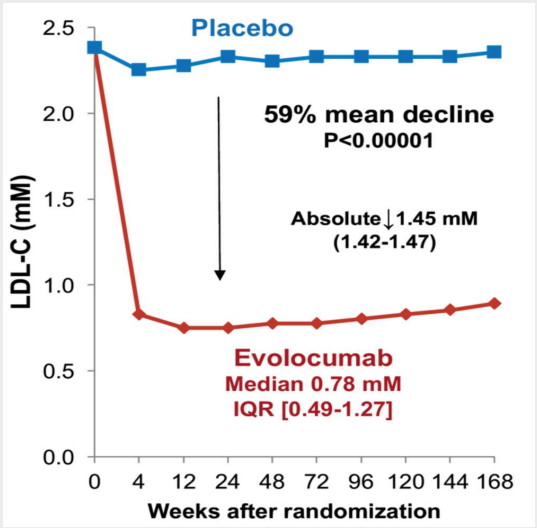
- **Secondary prevention (clinically evident ASCVD) with baseline LDL-C >1.8 mmol/L**

*Patients on optimized regimen of lipid-lowering therapy. D, day; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PAD, peripheral artery disease; Q2W, once every two weeks; SC, subcutaneous; W, week. 1. Sabatine MS, et al. Am Heart J. 2016;173:94–101.

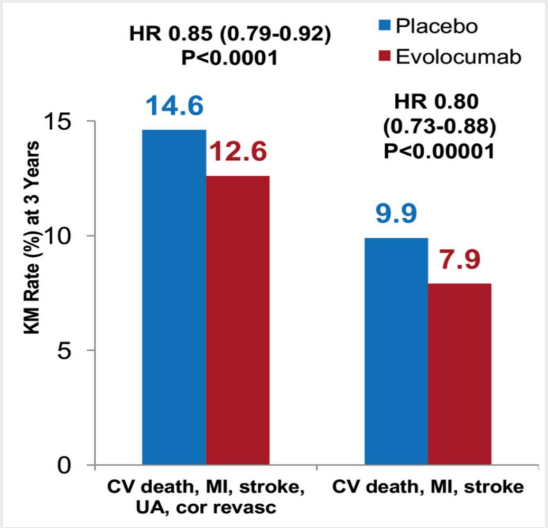
FOURIER Outcomes

Results of primary and secondary endpoints

LDL-C decline: mean 59 %, median: 0.8 mmol/L



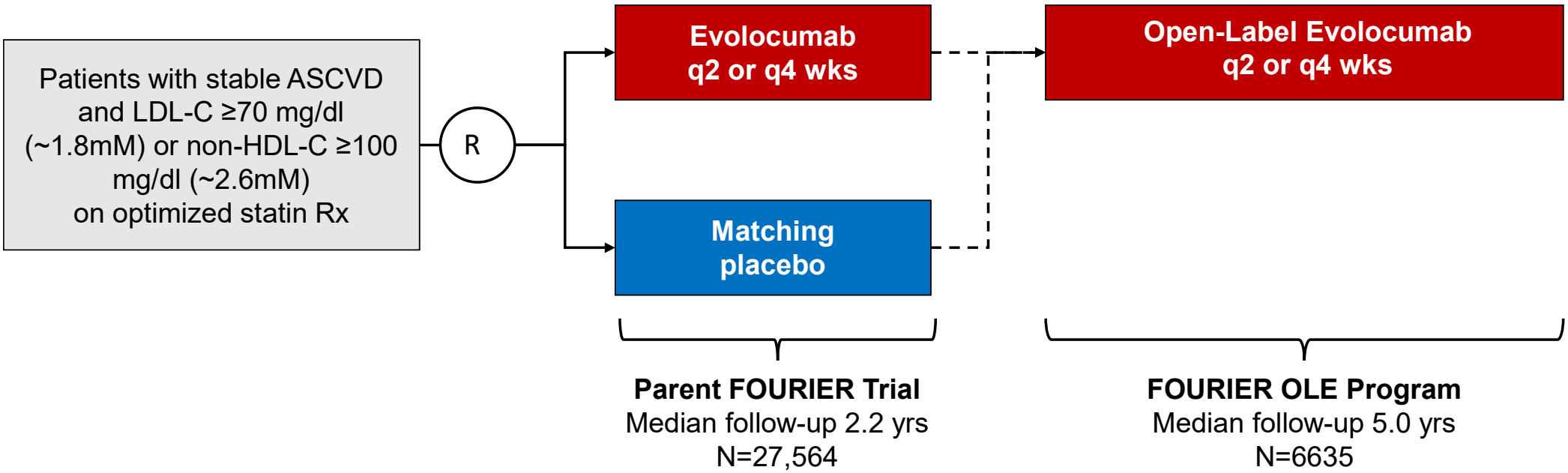
Primary endpoint: ARR 2%, RRR 15 %
Key secondary endpoint: ARR 2%, RRR 20 %



Evolocumab reduced LDL by 59% and reduced CV outcomes more than statins alone

Study duration 2.2. years. Baseline statin use 99%. ARR, absolute risk reduction, CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction. RRR, relative risk reduction.
Sabatine MS, et al. N Engl J Med 2017;376:1713–22.

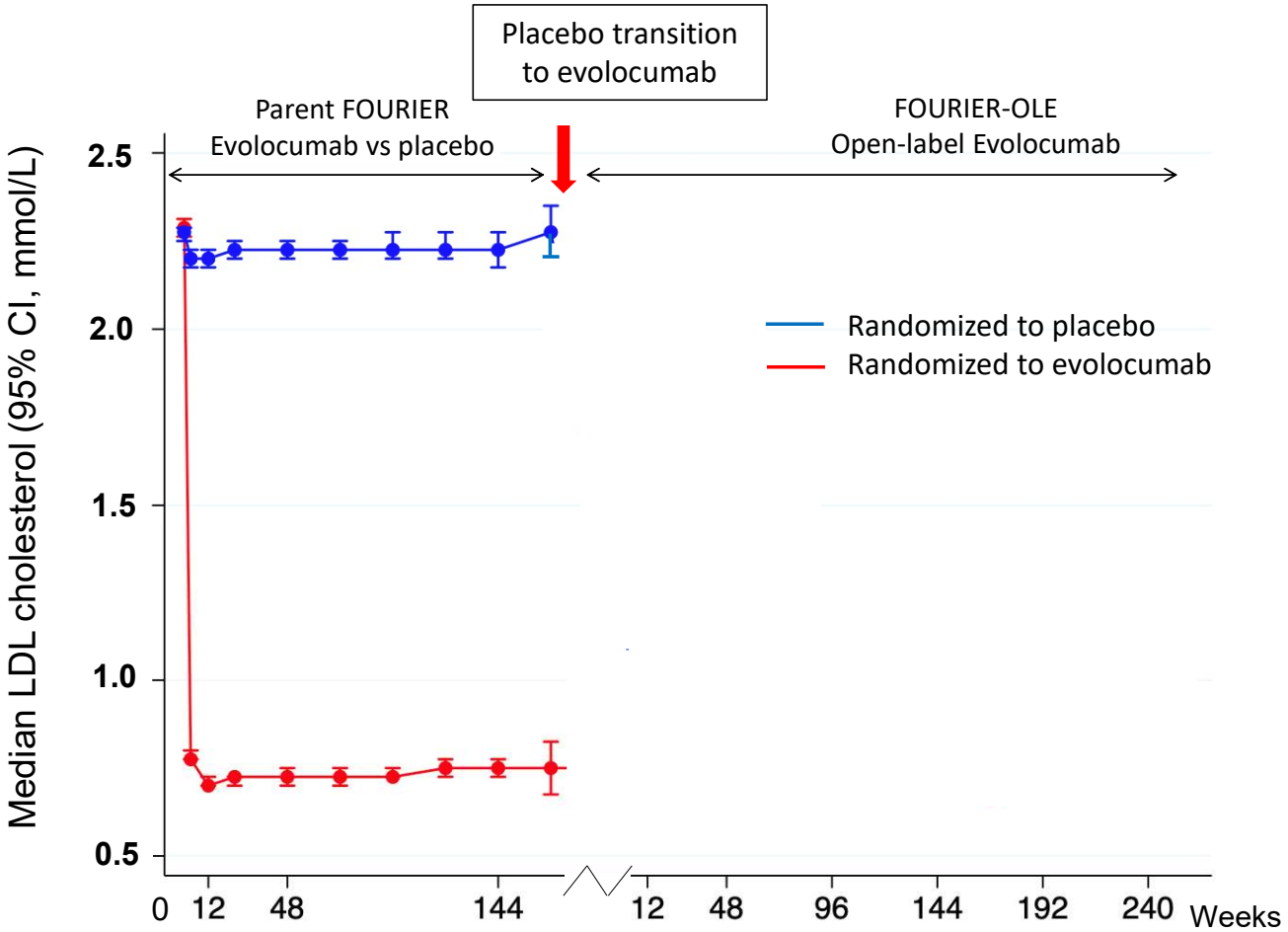
FOURIER-OLE: Study design



O'Donoghue ML, et al. *Circulation*. 2022;146:1109-1119.

US & Eastern Europe: NCT02867813
Western Europe: NCT03080935

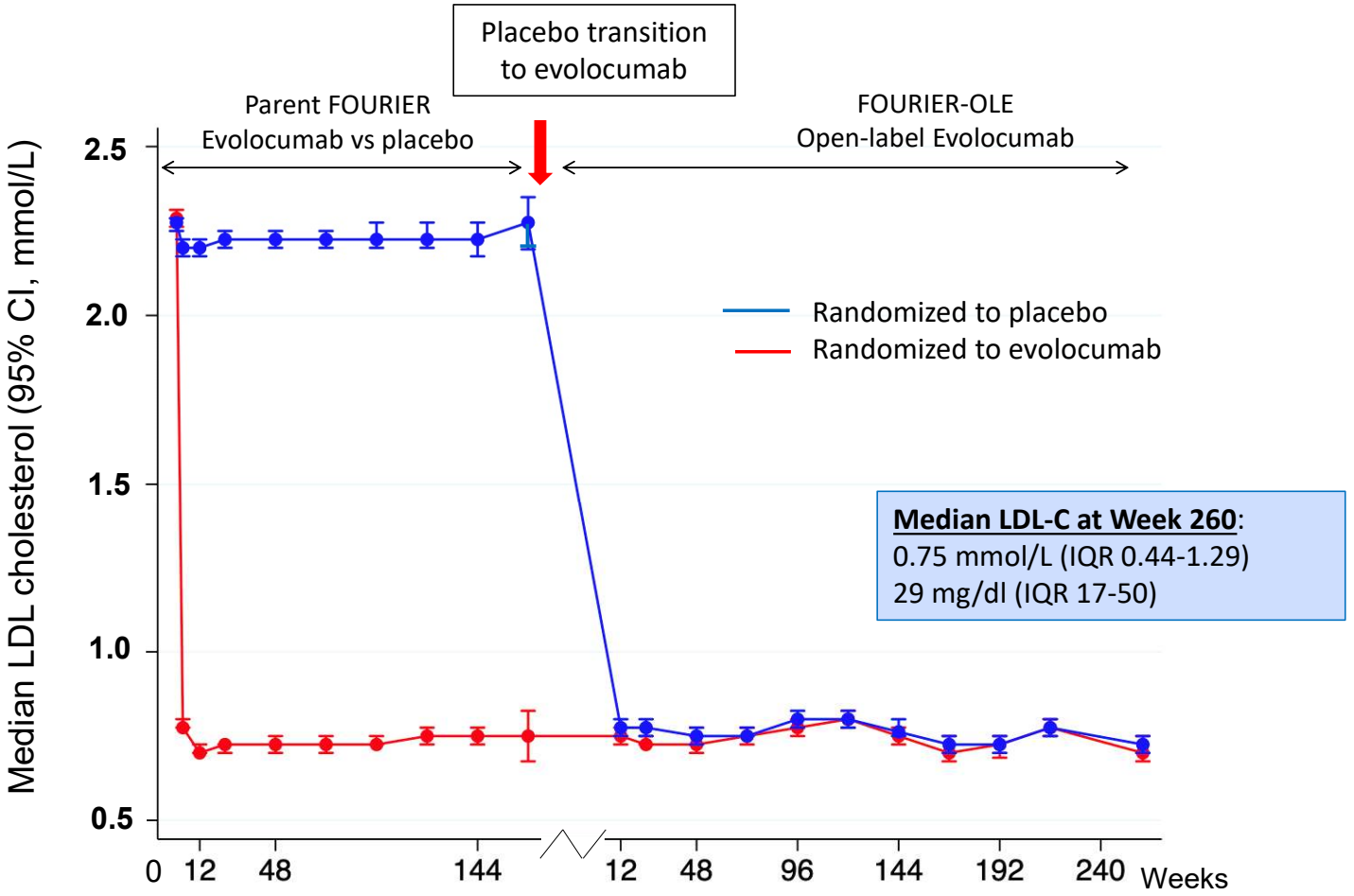
FOURIER-OLE : Effect on LDL-C



FC REMED

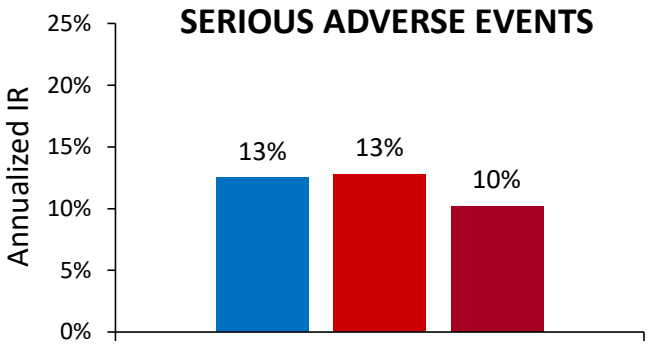
O'Donoghue ML, et al. *Circulation*. 2022;146:1109-1119.

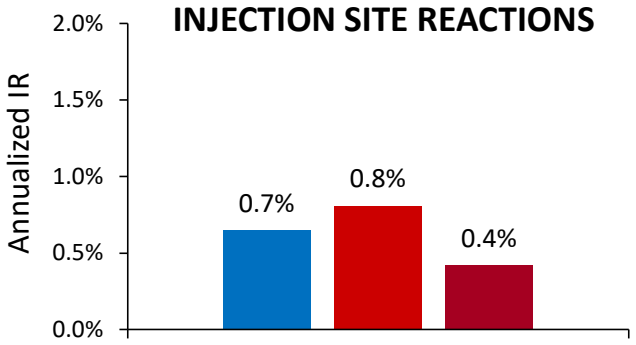
FOURIER-OLE : Effect on LDL-C

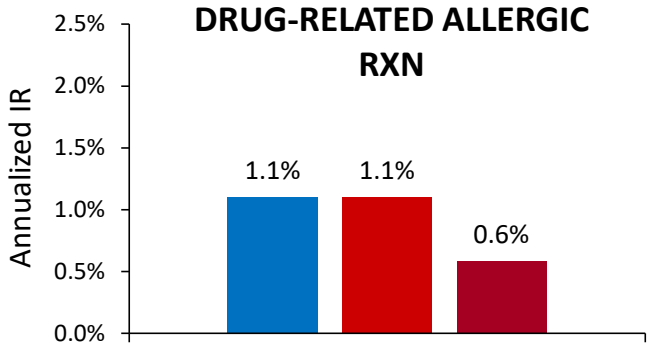


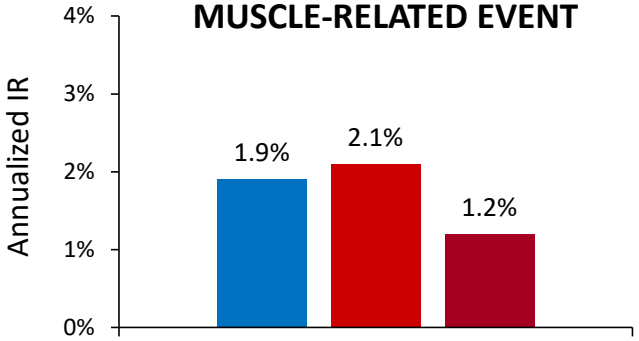
O'Donoghue ML, et al. *Circulation*. 2022;146:1109-1119.

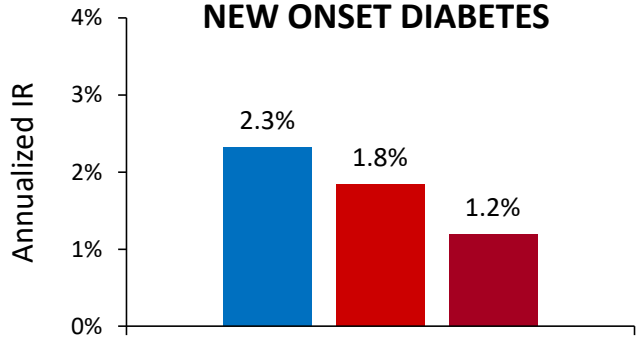
FOURIER-OLE : Long-term safety

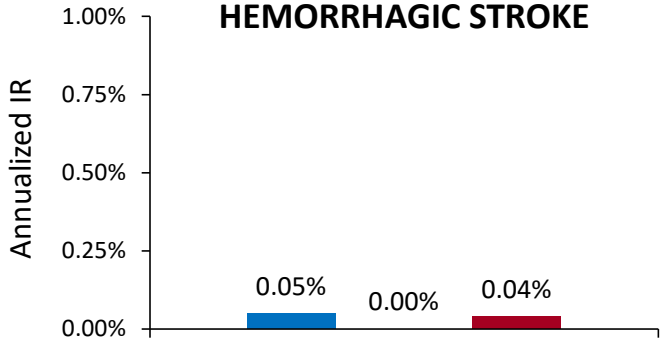


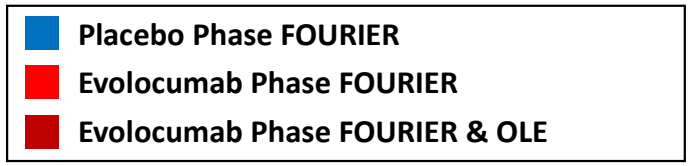






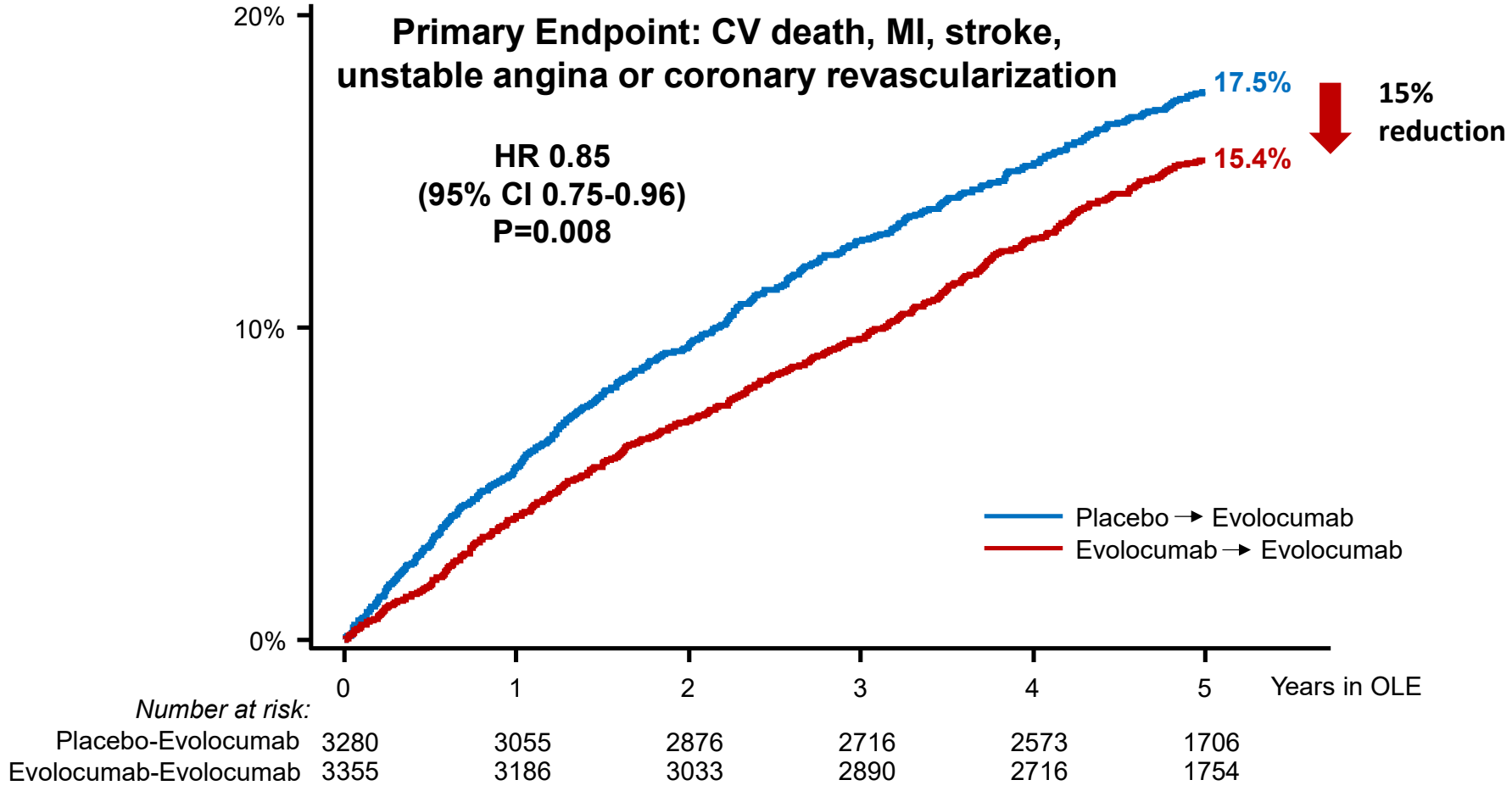






O'Donoghue ML, et al. *Circulation*. 2022;146:1109-1119.

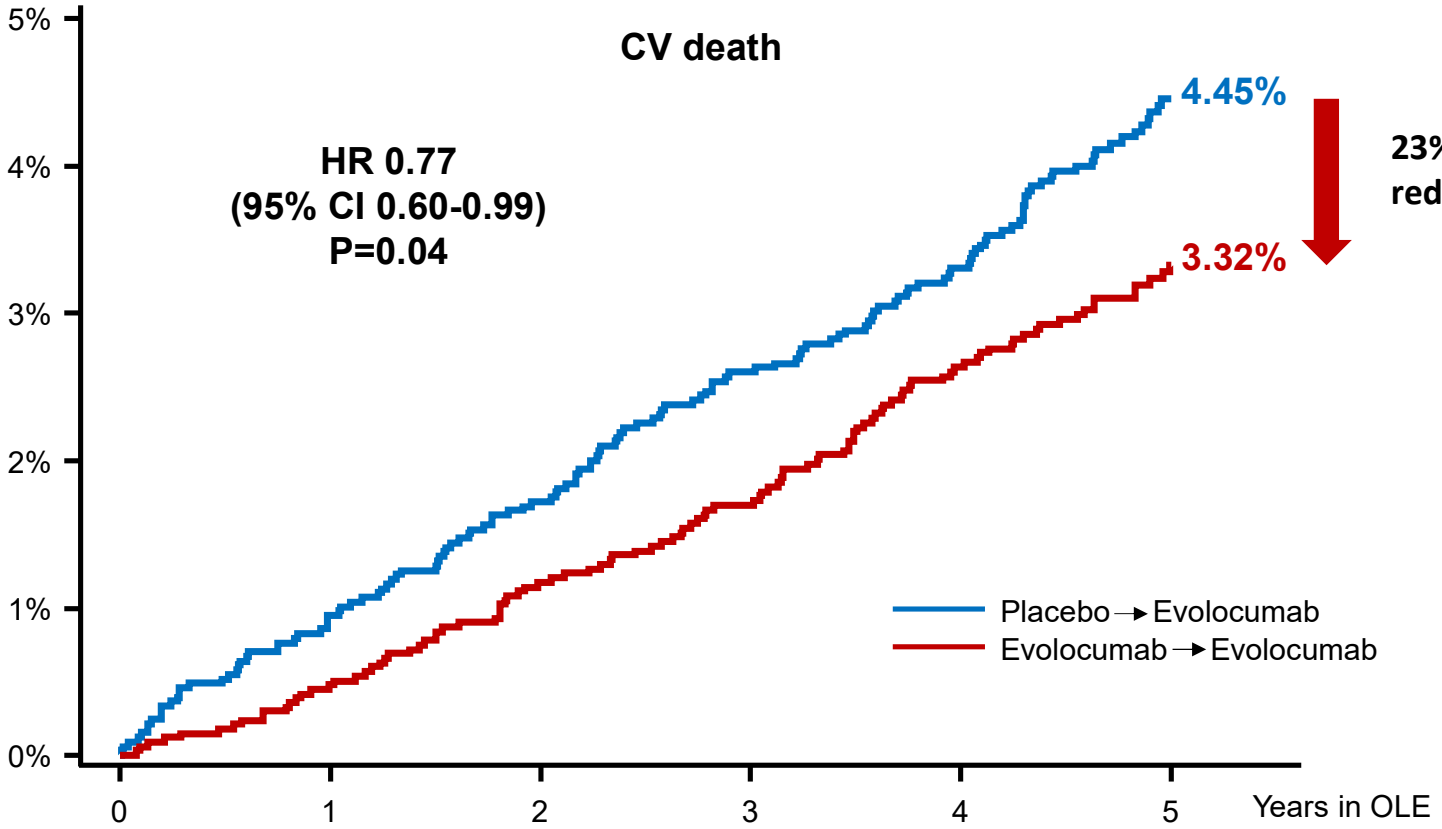
FOURIER-OLE : Primary endpoint



O'Donoghue ML, et al. *Circulation*. 2022;146:1109-1119.

These are exploratory endpoints and p-values not adjusted for multiplicity.

FOURIER-OLE : cardiovascular death



Number at risk:

Placebo-Evolocumab	3280	3223	3155	3081	2991	2049
Evolocumab-Evolocumab	3355	3314	3244	3173	3080	2069

O'Donoghue ML, et al. *Circulation*. 2022;146:1109-1119.

These are exploratory endpoints and p-values not adjusted for multiplicity.

FOURIER-OLE : sub-analyses based on achieved LDL levels: safety

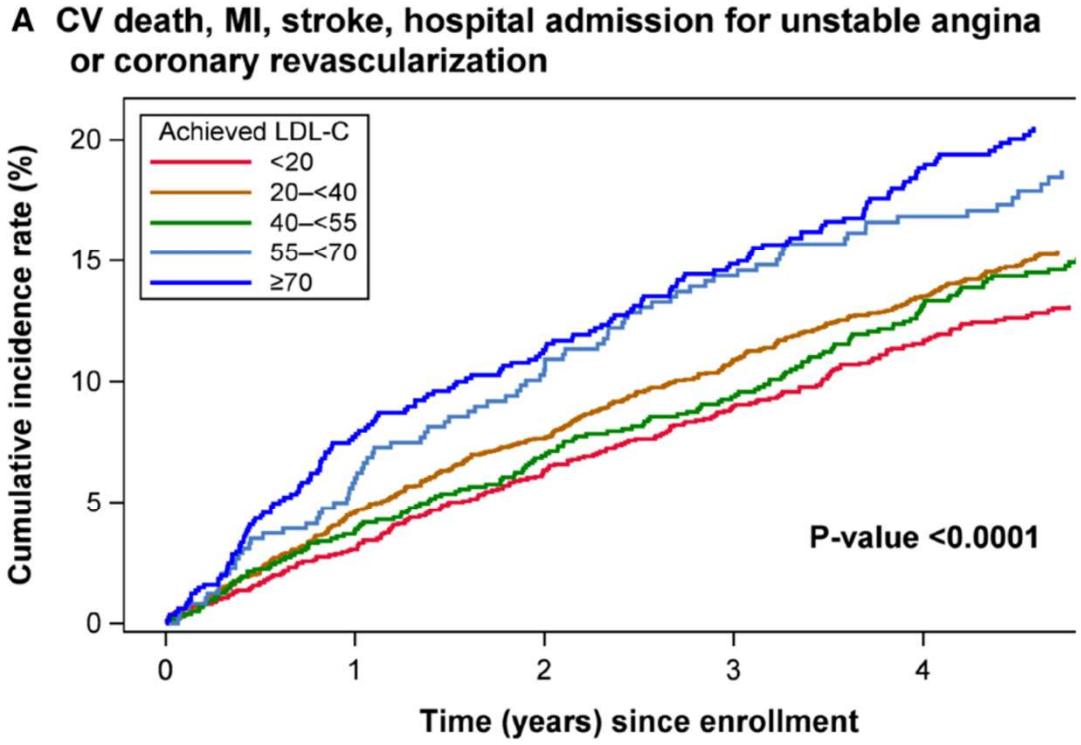
Table 4. Safety Outcomes According to Achieved LDL-C Level in FOURIER-OLE

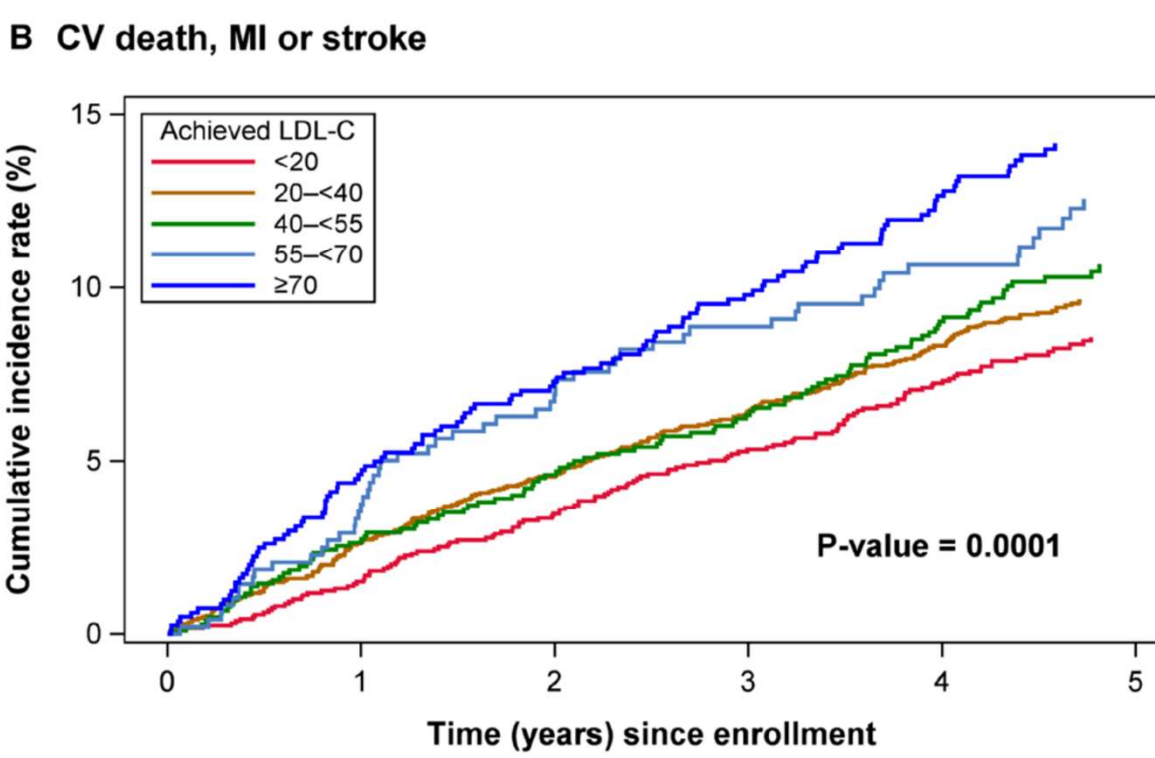
Safety outcomes	Achieved LDL-C level, mg/dL					Adjusted *P* trend
	<20 (n=1604)	20–<40 (n=2627)	40–<55 (n=1031)	55–<70 (n=486)	≥70 (n=811)	
Serious adverse events	12.15 (10.34, 14.27)	12.64 (10.89, 14.67)	12.65 (10.70, 14.97)	12.90 (10.63, 15.65)	12.18 (10.27, 14.43)	0.88
Neurocognitive events	0.50 (0.25, 0.98)	0.53 (0.28, 1.00)	0.53 (0.27, 1.07)	0.30 (0.12, 0.73)	0.43 (0.21, 0.89)	0.35
Cataract-related adverse events	0.82 (0.47, 1.44)	0.87 (0.51, 1.49)	0.91 (0.51, 1.62)	0.33 (0.14, 0.79)	0.64 (0.35, 1.20)	0.11
New or progressive malignancy	1.83 (1.26–2.66)	1.76 (1.23–2.50)	1.73 (1.17–2.57)	1.89 (1.21–2.96)	1.36 (0.89–2.10)	0.23
New-onset diabetes*	0.66 (0.32, 1.39)	0.52 (0.25, 1.05)	0.46 (0.20, 1.02)	0.45 (0.18, 1.12)	0.43 (0.20, 0.95)	0.13
Hemorrhagic stroke†	0.06 (0.02, 0.15)	0.09 (0.05, 0.17)	0.07 (0.02, 0.20)	–	0.06 (0.01, 0.23)	0.55
Muscle-related events	0.67 (0.38, 1.18)	0.62 (0.36, 1.07)	0.69 (0.38, 1.24)	0.76 (0.39, 1.46)	0.56 (0.30, 1.05)	0.84
Noncardiovascular death	1.33 (0.87, 2.04)	1.14 (0.76, 1.71)	1.65 (1.07, 2.56)	2.32 (1.46, 3.67)	1.49 (0.94, 2.36)	0.04
All-cause mortality	2.65 (1.98, 3.56)	2.87 (2.20, 3.76)	3.72 (2.77, 5.00)	4.30 (3.10, 5.98)	3.93 (2.92, 5.29)	0.0001

No safety signal even with extremely low LDL levels (<0.5mmol/l)

Gabs et al., Circulation. 2023;147:1192–1203

FOURIER-OLE : sub-analyses based on achieved LDL levels: outcomes



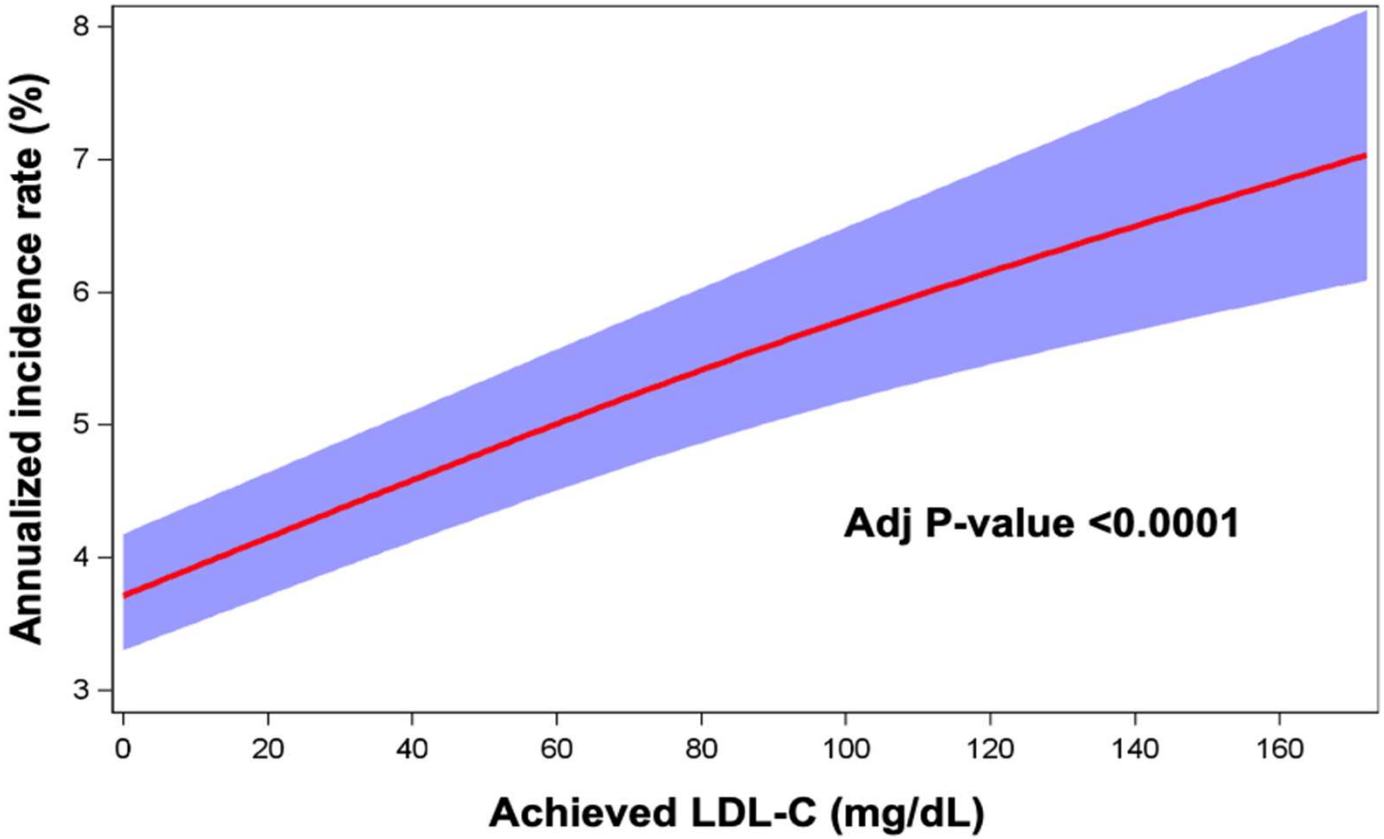


Results show graded outcomes with achieved LDL as marker.

Gabs et al., Circulation. 2023;147:1192–1203

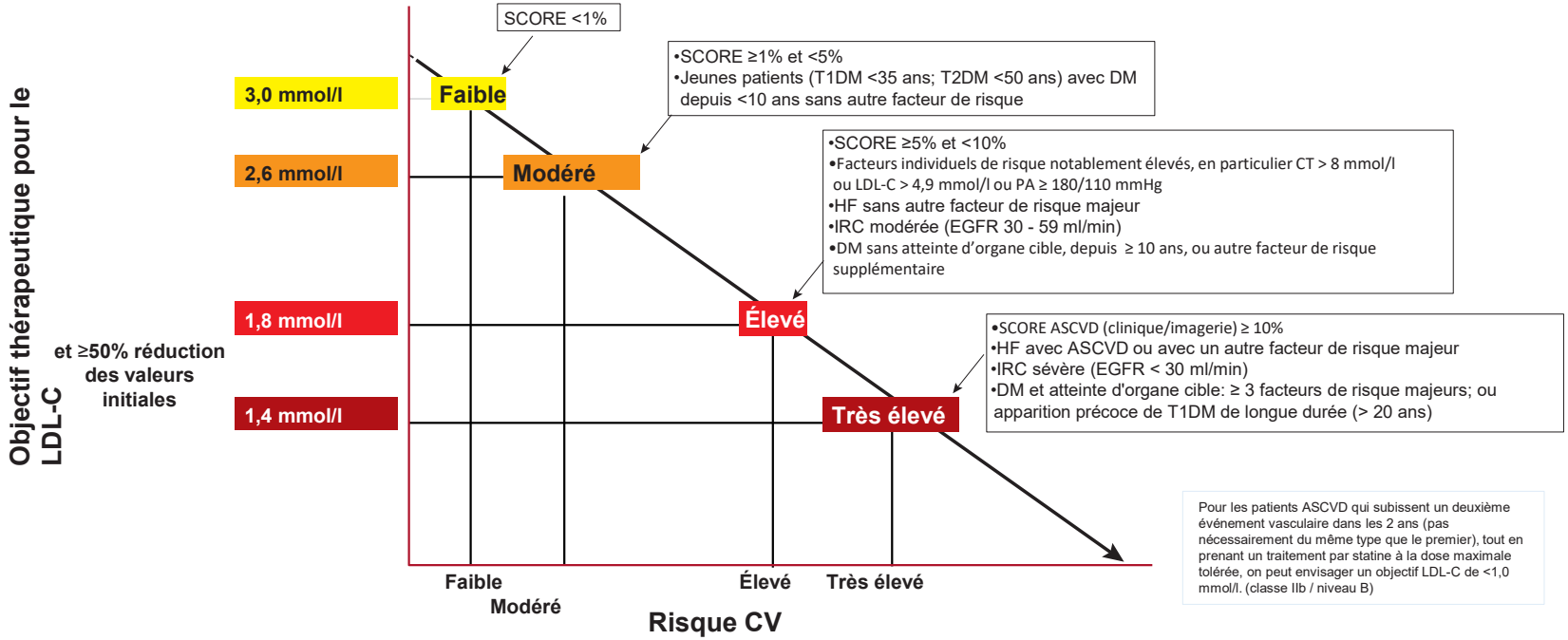
FOURIER-OLE : achieved LDL and outcomes: the lower the better (!)

Primary endpoint: CV death, MI, stroke, coronary revascularization or hospitalization for unstable angina



Gabs et al., Circulation. 2023;147:1192–1203

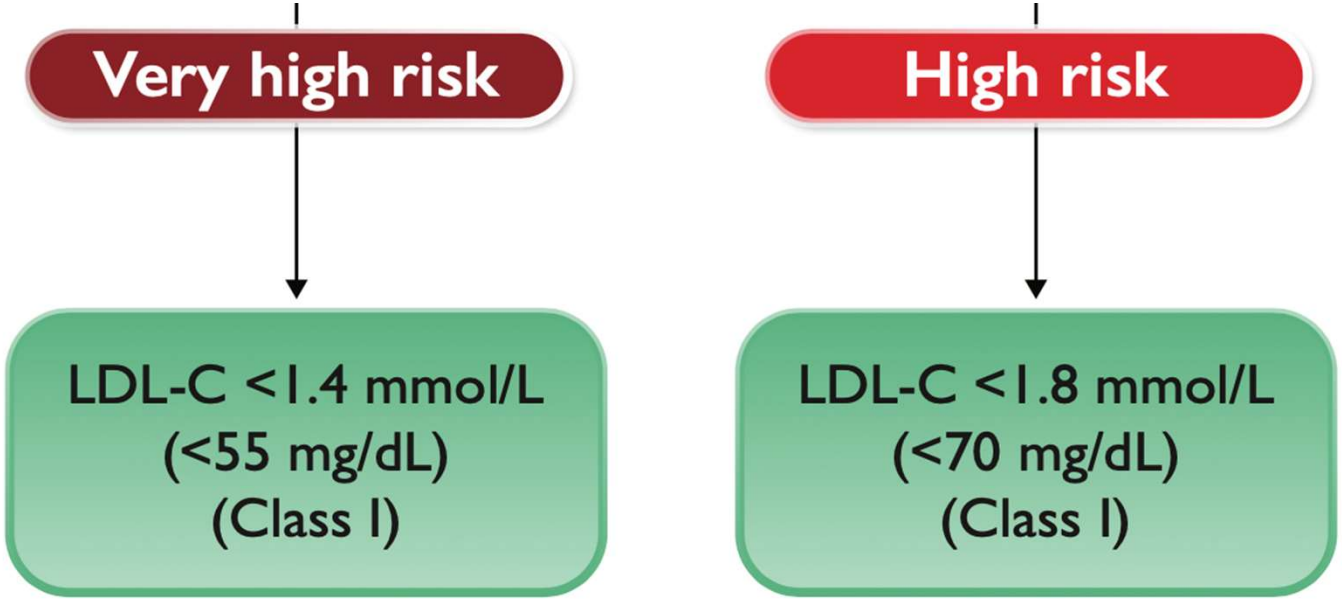
Directives ESC/EAS 2019: la nouvelle valeur cible de LDL-C recommandée est 1,4 mmol/l pour les patients à très haut risque[1]



Un taux trop élevé de LDL-C est une cause potentielle d'ASCVD; la réduction proportionnelle du risque dépend de la réduction absolue du LDL-C.

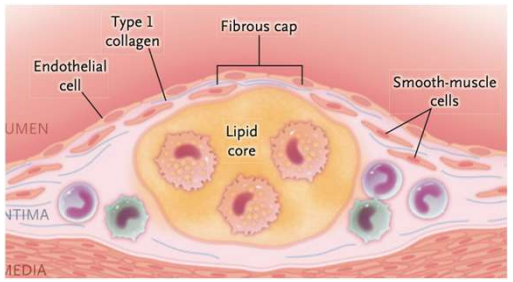
ASCVD = maladie cardiovasculaire athérosclérotique; PA = pression artérielle; IRC = insuffisance rénale chronique; CV = cardiovasculaire; DM = diabetes mellitus (diabète sucré); EGFR = récepteur du facteur de croissance épidermique; HF = hypercholestérolémie familiale; LDL-C = cholestérol des lipoprotéines de basse densité; SCORE = estimation systématique du risque coronarien; T1DM = DM de type 1; T2DM = DM de type 2; CT = cholestérol total. Adapté d'après: 1. Adapted from Mach F, et al. Mach F, et al. Eur Heart J. 2020 Jan 1;41(1):111-188. doi: 10.1093/eurheartj/ehz455.

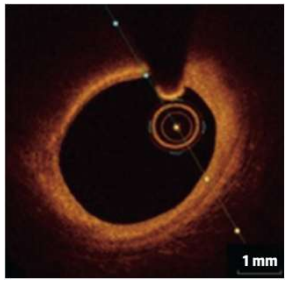
LDL target depends on CV risk

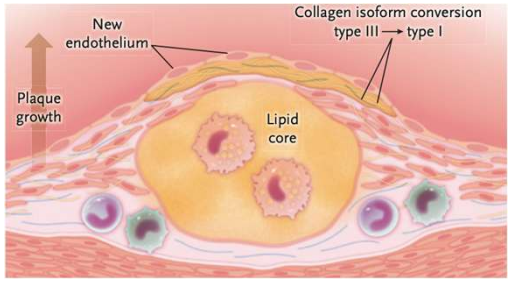


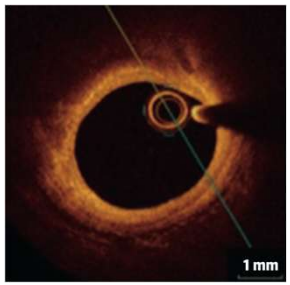
HUYGENS and PACMAN-AMI (iPCSK9 and plaque regression/stabilisation)

	HUYGENS			PACMAN	
	evolo	placebo		aliro	placebo
no. of participants	80	81		131	135
LDL @ 1 year	0.8	2.2		0.6	1.9
plaque volume	-2.3%	-0.6%		-2.1%	-0.9%
gain in fibrous cap thickness	+43um	+22um		+63um	+33um







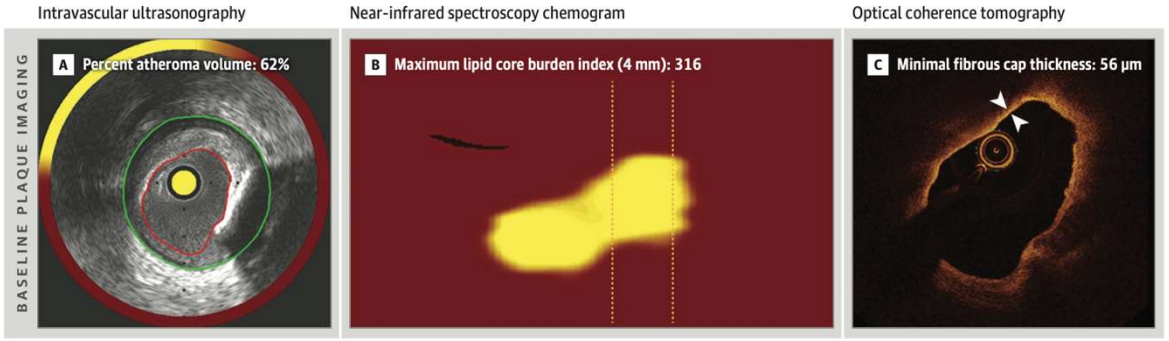


Vergallo et al. NEJM 383;9:846
Nicholls et al., J Am Coll Cardiol Img 2022;15:1308–1321
Raeber et al., JAMA. 2022;327(18):1771-1781

Si le LDL est baissé rapidement après un évènement: modification des plaques

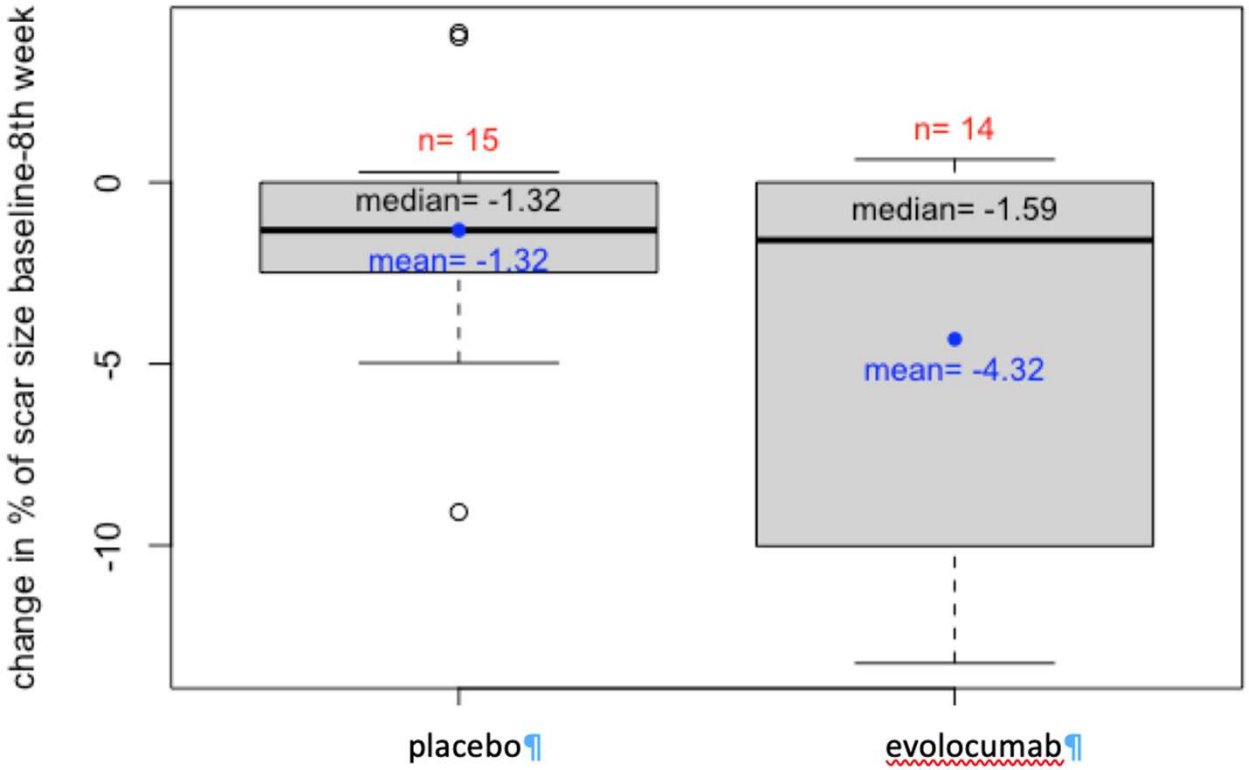
300 patients en prév. 2nd Suisses traités par alirocumab ou placebo (+ statine) durant 52 semaines:

changement de volume d'athérome −2.13% avec alirocumab vs −0.92% avec placebo (différence, −1.21% [95% CI, −1.78% to −0.65%], P < .001).



Raeber et al. JAMA. 2022;327(18):1771-1781

Very early use of iPCSK9 after MI (EVOPACS)



Ehret et al. manuscript in preparation

« Gene-deletion » of PCSK9: Verve-101

Overall findings showed that three patients receiving the highest two VERVE-101 doses (0.45 mg/kg and 0.6 mg) saw the greatest reductions in LDL-C and PCSK9 protein levels. The two patients in the 0.45 mg/kg group saw reductions in LDL-C by 39% and 48%, respectively, and in PCSK9 by 47% and 59%. The one patient in the 0.6 group experienced a reduction in LDL-C of 55% and in PCSK9 of 84%. Bellinger noted that the LDL change has been durable up to six months so far, with follow-up ongoing.

Bellinger, AHA 2023