Gestion des dyslipidémies en 2023

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SC-CH-AMG145-00823

2023 = 2019 ?

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

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The three chairpersons contributed equally to the document.

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ESC Committee for Practice Guidelines (CPG), National Cardiac Societies document reviewers and Author/Task Force Member affiliations: listed in the Appendix.

[1]Representing the EAS

2023 = 2022 ?

Anti-PCSK 9 : Changements en 2022

Remboursé en accompagnement d'un régime alimentaire et en complément d'une thérapie intensive à la dose maximale tolérée visant à réduire le LDL-C*:

Prévention Secondaire

Chez les patients après un événement cardiovasculaire ischémique athérosclérotique cliniquement manifeste

→ **LDL-C > 1.8 mmol/l**

Prévention Primaire

Chez les patients à partir de 10 ans atteints d'hypercholestérolémie familiale hétérozygote et homozygote

→ **LDL-C > 2.6 mmol/l**

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

* Repatha est remboursé si les valeurs de LDL-C ci-dessus n'ont pas pu être atteintes avec la dose maximale tolérée d'une thérapie intensive visant à réduire le LDL-C pendant au moins trois mois, consistant en l'essai d'au moins deux statines différentes avec ou sans ézétimibe (ou ézétimibe avec ou sans autre hypolipémiant en cas d'intolérance aux statines).

Les 3 critères supplémentaires

1. Objectif non atteint
   malgré 2 statines au maximal toléré pendant au moins 3 mois (avec ou sans ezetimibe)
2. Intolérance aux statines
3. Contrôle après 6 mois :
   Réduction d'au moins 40% ou < 1.4 mmol/l

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1. Pourquoi cibler le cholestérol ?
2. Quelles sont les « nouvelles » cibles ?
3. Pourquoi 1.4 mmol/l ?
4. Y parvient-on ?
5. Avec quelles armes (→2021) ?

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CVD is responsible for > 4 Million deaths in Europe each year

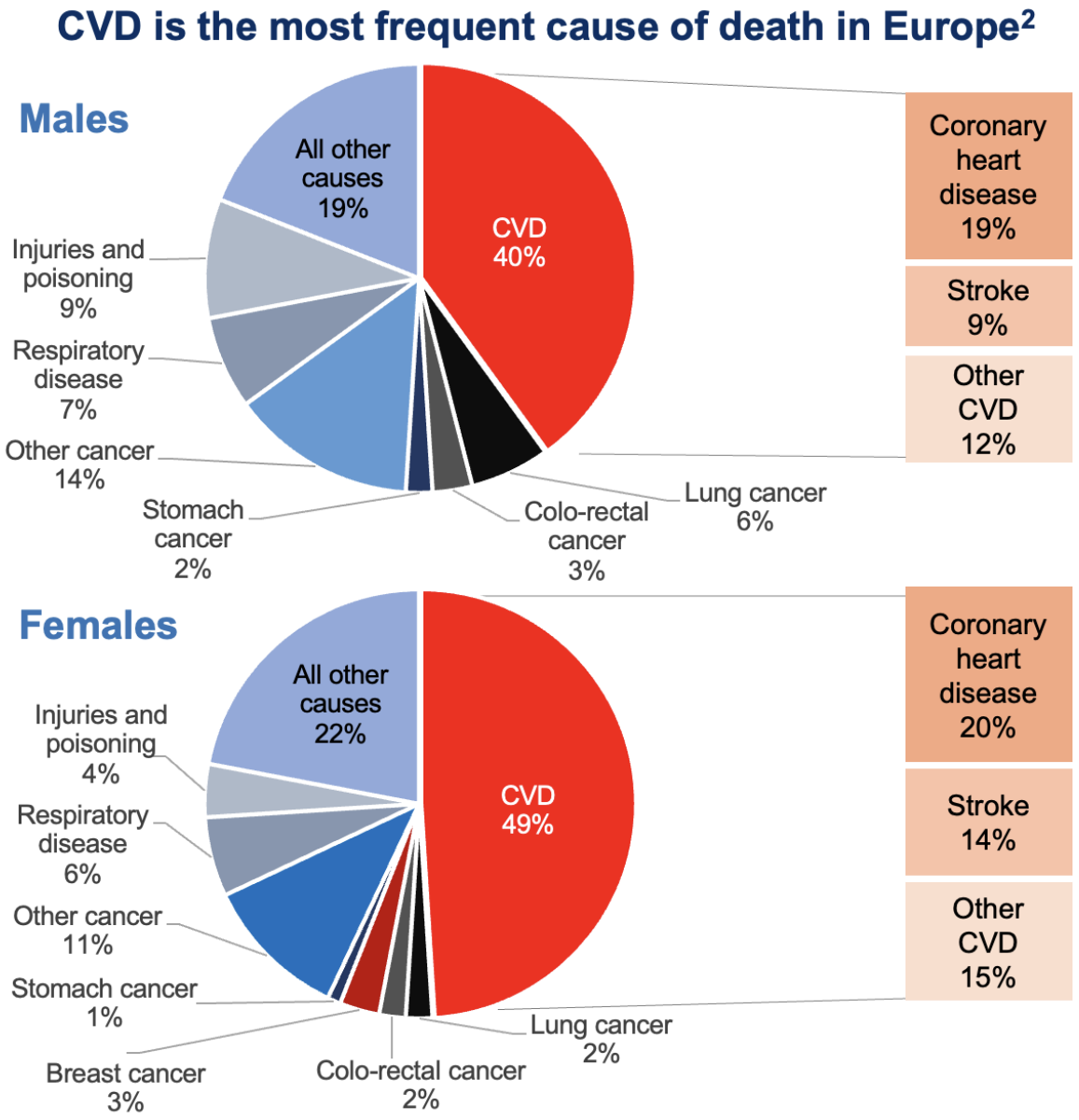


Figure adapted from Townsend, N. *et al*. Cardiovascular disease in Europe. *Eur Heart J*. 2016;*37:3232–3245.*

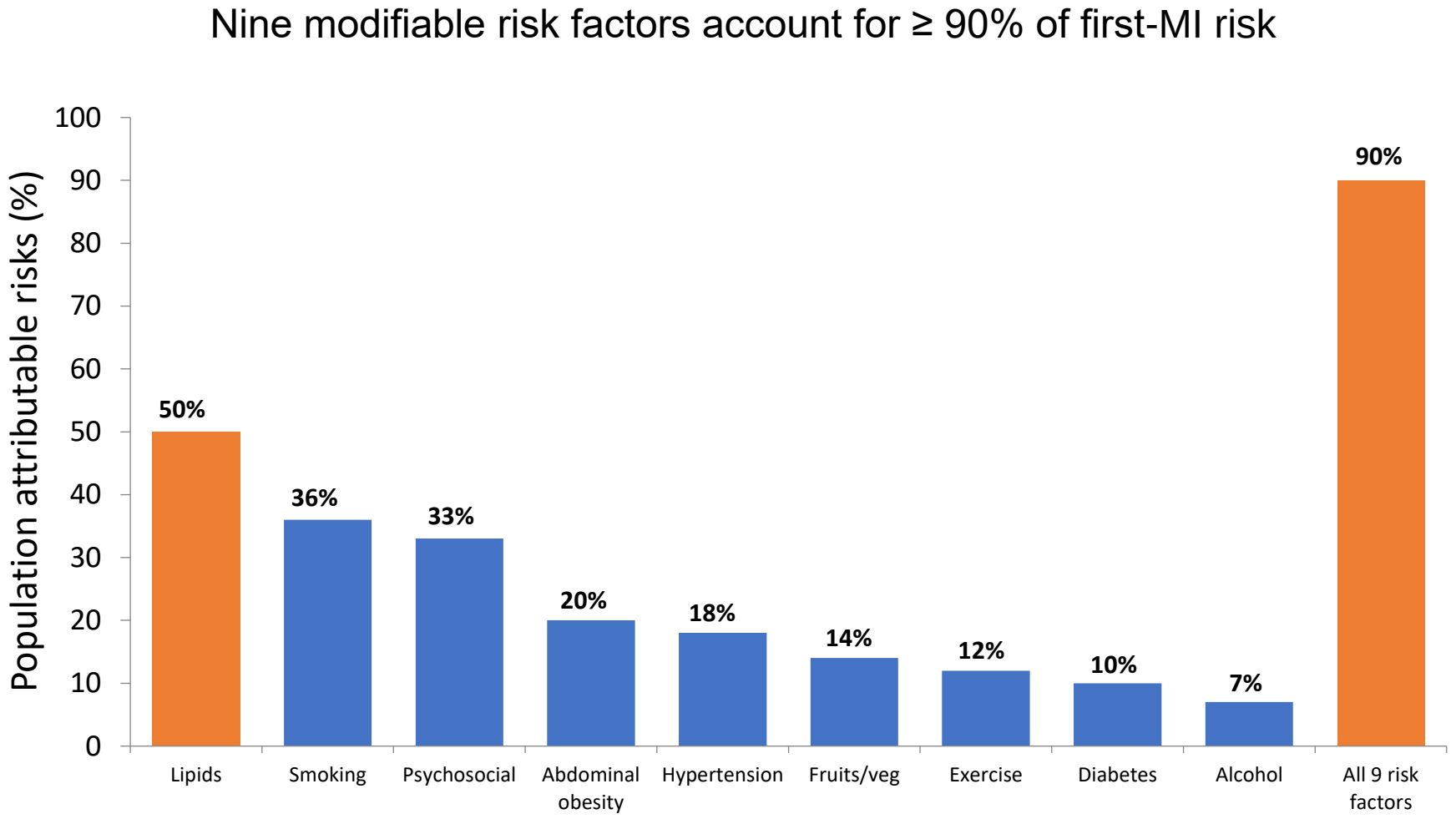
2018	Nombre de décès		Taux de mortalité[1]	
	Hommes	Femmes	Hommes	Femmes
Toutes les causes de décès	32 398	34 690	492,1	344,4
Maladies infectieuses	374	432	5,6	4,0
› Tumeurs malignes	9 545	7 815	149,1	101,1
Diabète sucré	574	578	8,3	5,1
Démence	2 004	4 450	26,3	33,5
› Maladies cardiovasculaires	9 418	11 178	134,6	91,4
Maladies de l'appareil respiratoire	2 395	2 228	33,8	21,1
Cirrhose du foie alcoolique	278	138	5,0	2,4
› Accidents et morts violentes	2 233	1 687	40,0	20,4

https://www.bfs.admin.ch/bfs/fr/home/statistiques/sante/etat-sante/maladies/cardiovasculaires.html

Maladies cardiovasculaires	9 418	11 178	134,6	91,4
Cardiopathies, toutes formes	7 438	8 627	106,3	69,1
Cardiopathies ischémiques	3 793	3 054	54,9	25,3

https://www.bfs.admin.ch/bfs/fr/home/statistiques/sante/etat-sante/maladies/cardiovasculaires.html

Lipids are a major modifiable risk factor for ASCVD



1. Yusuf S et al. Effect of potentially modifiable risk factors. INTERHEART study. Lancet 2004; 364: 937–52

N=15,152 patients and 14,820 controls in 52 countries. Presented from highest to lowest PAR (5%).

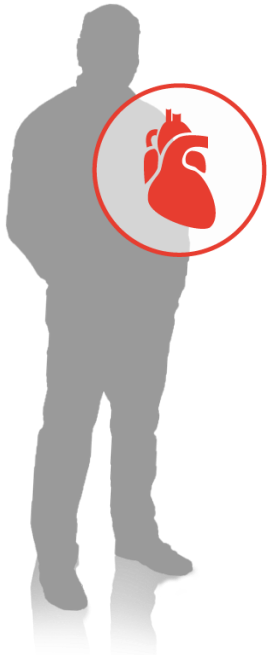
LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PAR = Population attributable risk, adjusted for all risk factors.

20% des patients avec un infarctus auront une récidive dans l'année[1-3]

After MI:

Risk of recurrence within a year

1 in 5[(1)]



After Stroke:

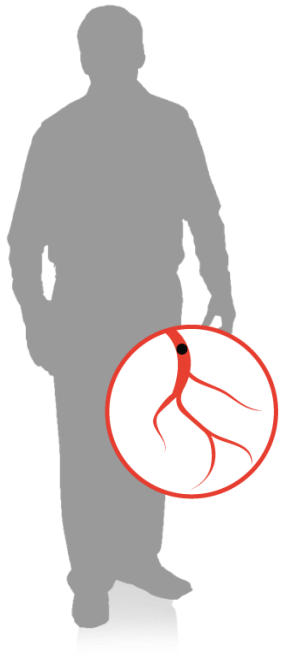
Risk of recurrence in 5 years

1 in 10[(2)]

Symptomatic PAD:

Risk of recurrence within a year

1 in 5[(3)]



SC-CH-AMG145-00641

1. Jernberg T et al. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. Eur Heart J. 2015;36(19):1163-70. 2. Amarenco P et al. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med. 2006;355(6):549-59. 3. Steg PG, Bhatt DL, Wilson PW, D'Agostino R Sr, Ohman EM, Röther J, Liau CS, Hirsch AT, Mas JL, Ikeda Y, Pencina MJ, Goto S; REACH Registry Investigators. MI = myocardial infarction

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Catégorie de risque	Cible
Risque très élevé	1.4 mmol/l
Risque élevé	1.8 mmol/l
Risque modéré	2.6 mmol/l
Risque faible	3 mmol/l

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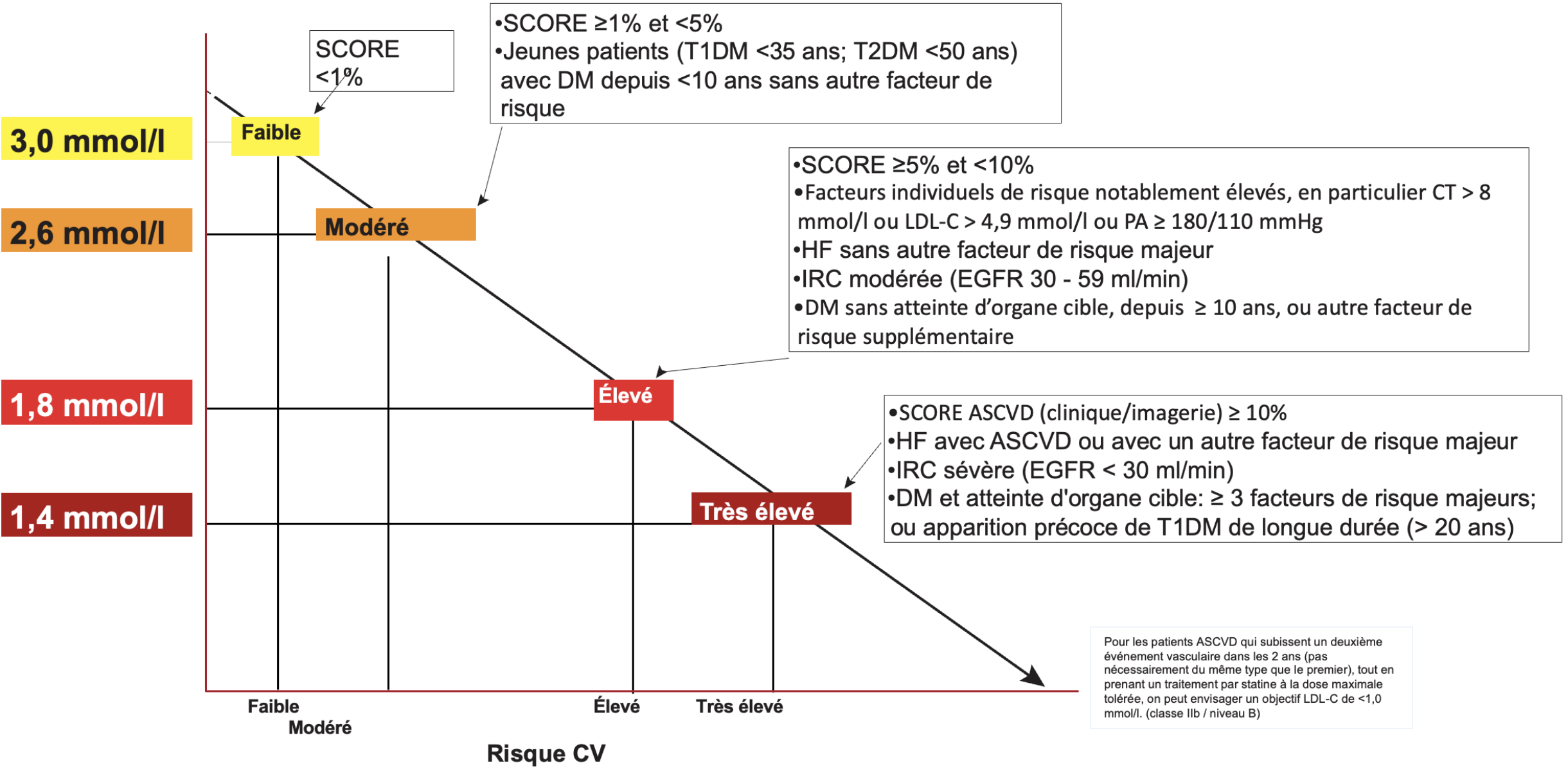

ASCVD = maladie cardiovasculaire athérosclérotique; PA = pression artérielle; IRC = insuffisance rénale chronique; CV = cardiovasculaire; DM = diabetes mellitus (diabète sucré); EGFR = récepteur du facteur de croissance épidermique; HF = hypercholestérolémie familiale; LDL-C = cholestérol des lipoprotéines 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.

1.4

1.8 → 1.4


POURQUOI
POURQUOI
POURQUOI
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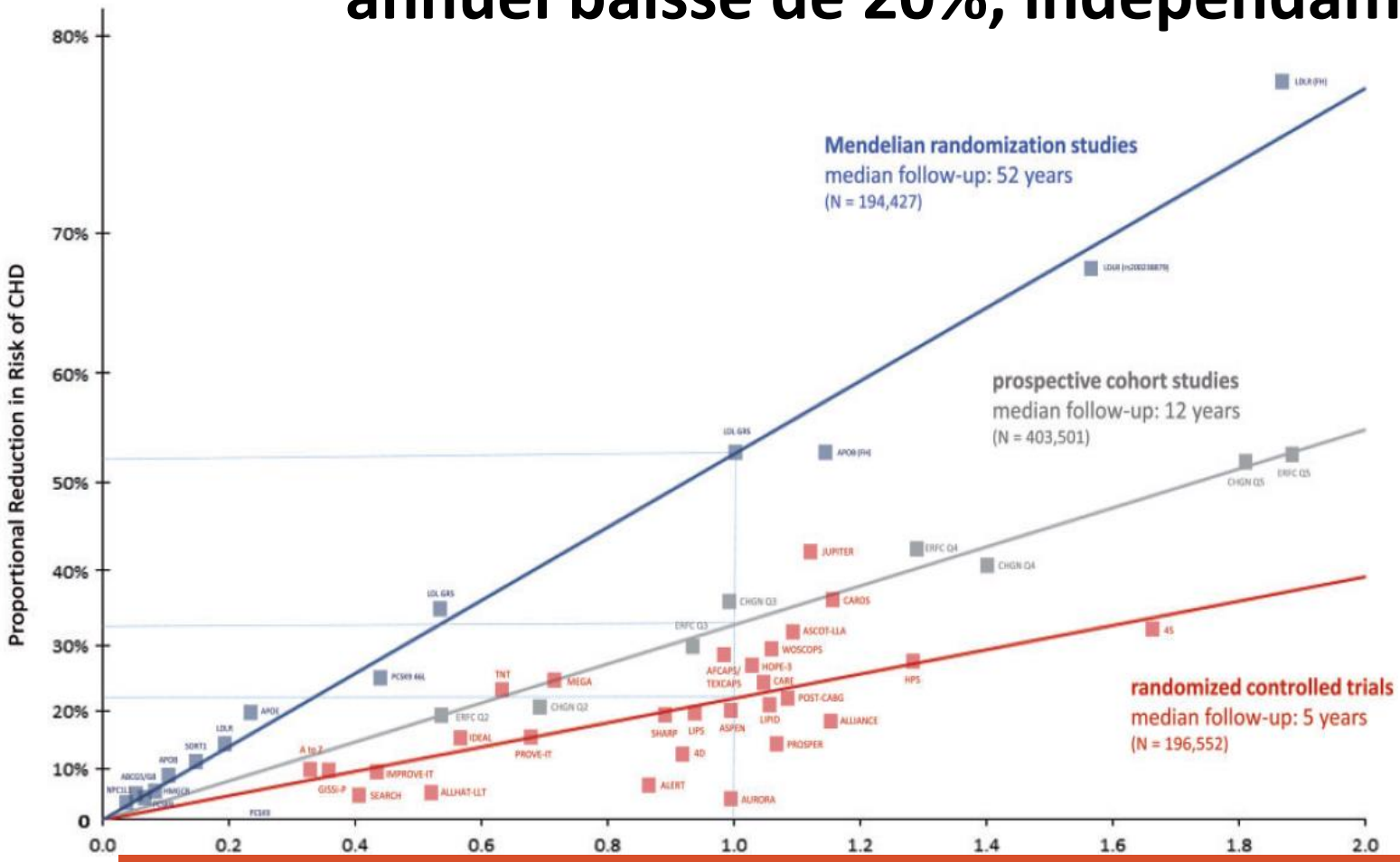
?????

Pour chaque réduction de 1 mmol/l du LDL-C, le risque CV annuel baisse de 20%, indépendamment du mécanisme[1-5]



Conclusion en cas de LDL-C peu élevé d'origine pharmacologique:
réduction d'env. 20% pour chaque unité (mmol/l) abaissée

Il existe un lien log-linéaire entre la concentration plasmatique de LDL-C et l'augmentation dose-dépendante des risques de signes d'événements ASCVD

CV, cardiovascular.

IMPROVE-IT, IMProved Reduction of Outcomes: Vytorin Efficacy International Trial; LDL-C, low-density lipoprotein cholesterol. CTT Collaboration. Lancet 2005:366;1267–78; CTT Collaboration. Lancet 2010;376:1670–81; Cannon CP, et al. N Engl J Med 2015;372:2387–97. Perk J, et al. Eur Heart J. 2012;33(13):1635–701;Ference BA, et al. European Heart Journal (2017) 0, 1–14. Ference BA, et al Engl J Med. 2016;375:2144–53

Catégorie de risque	Cible
Risque très élevé	**1.4**
Risque élevé	1.8
Risque modéré	2.6
Risque faible	3

Visseren Frank L J,Mach François et al.,European Heart Journal (2021) 00, 1111 doi:10.1093/eurheartj/ehab484
Recommandations GSLA 2023, 7ème édition, https://www.agla.ch/

Patients à très haut risque (1.4 mmol/l) :

1. Patients “ASCVD”
2. Diabétiques “sévères”
3. IRC sévère
4. Hypercholestéroémie familiale
5. Score SCORE >10%

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1. Patients “ASCVD”

Athero**S**clerotic **C**ardio**V**ascular **D**isease

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1. Patients “ASCVD”

Athero**S**clerotic **C**ardio**V**ascular **D**isease

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

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2. Diabétiques “sévères”

DM with

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

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3. IRC sévère

eGFR <30 ml/min

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4. Hypercholestéroémie familiale

Avec ASCVD ou autre FRCV

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5. Score SCORE >10%

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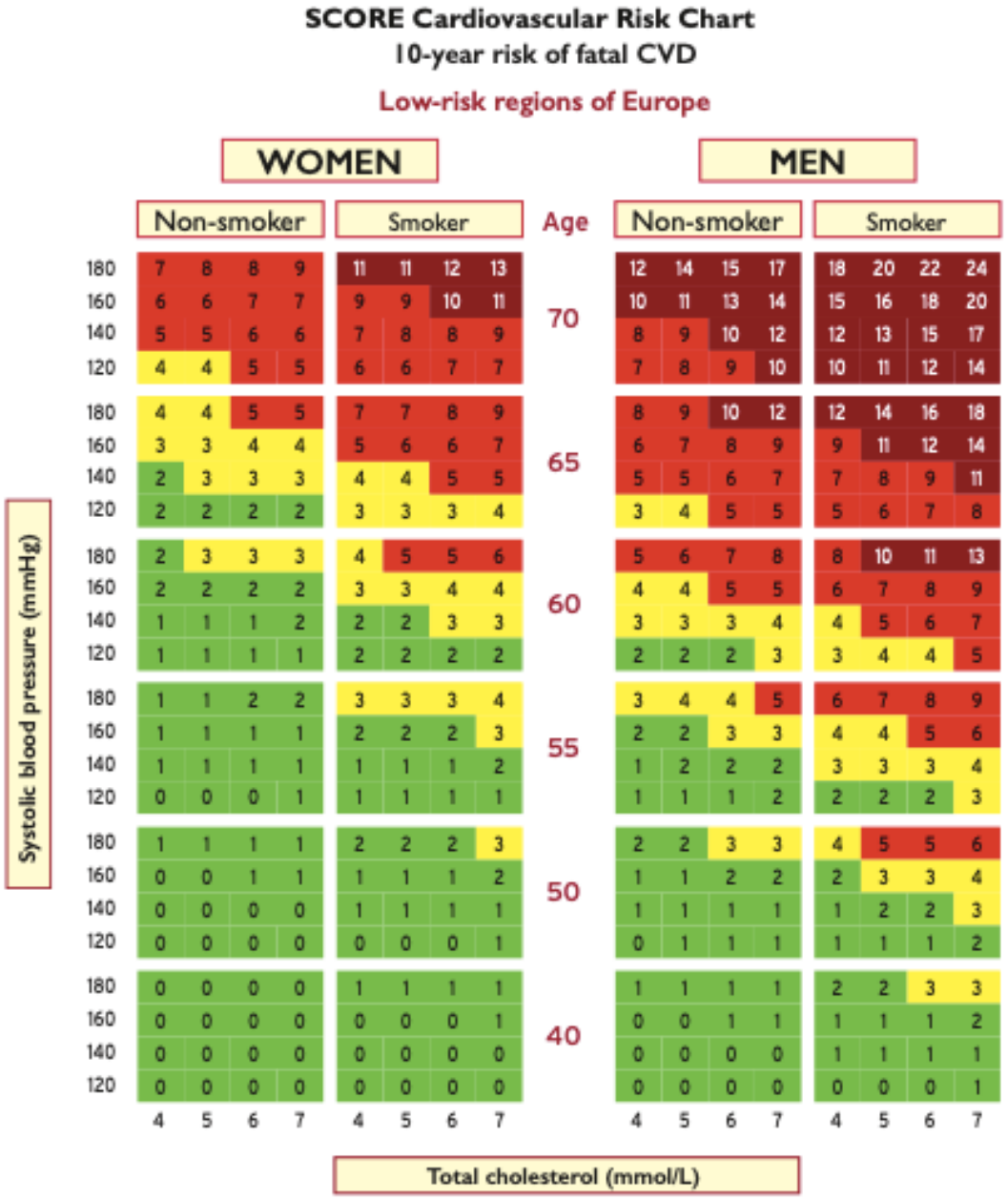

0 % : LOW RISK
1-4 % : MODERATE RISK
5-9% : HIGH RISK
10-… : VERY HIGH RISK

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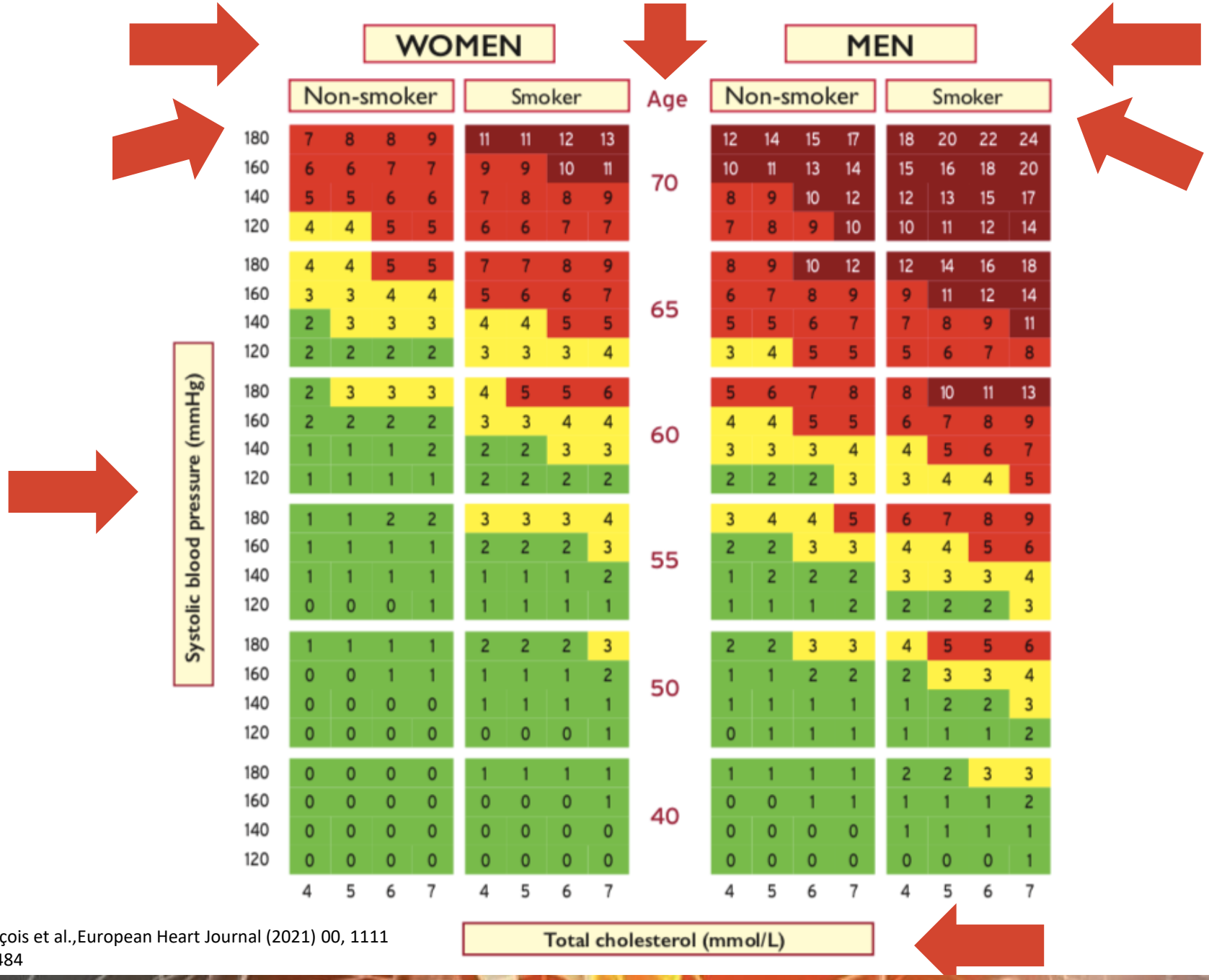

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Femme

60 ans

~~Fumeuse~~

TA : 140

Chol. : 4

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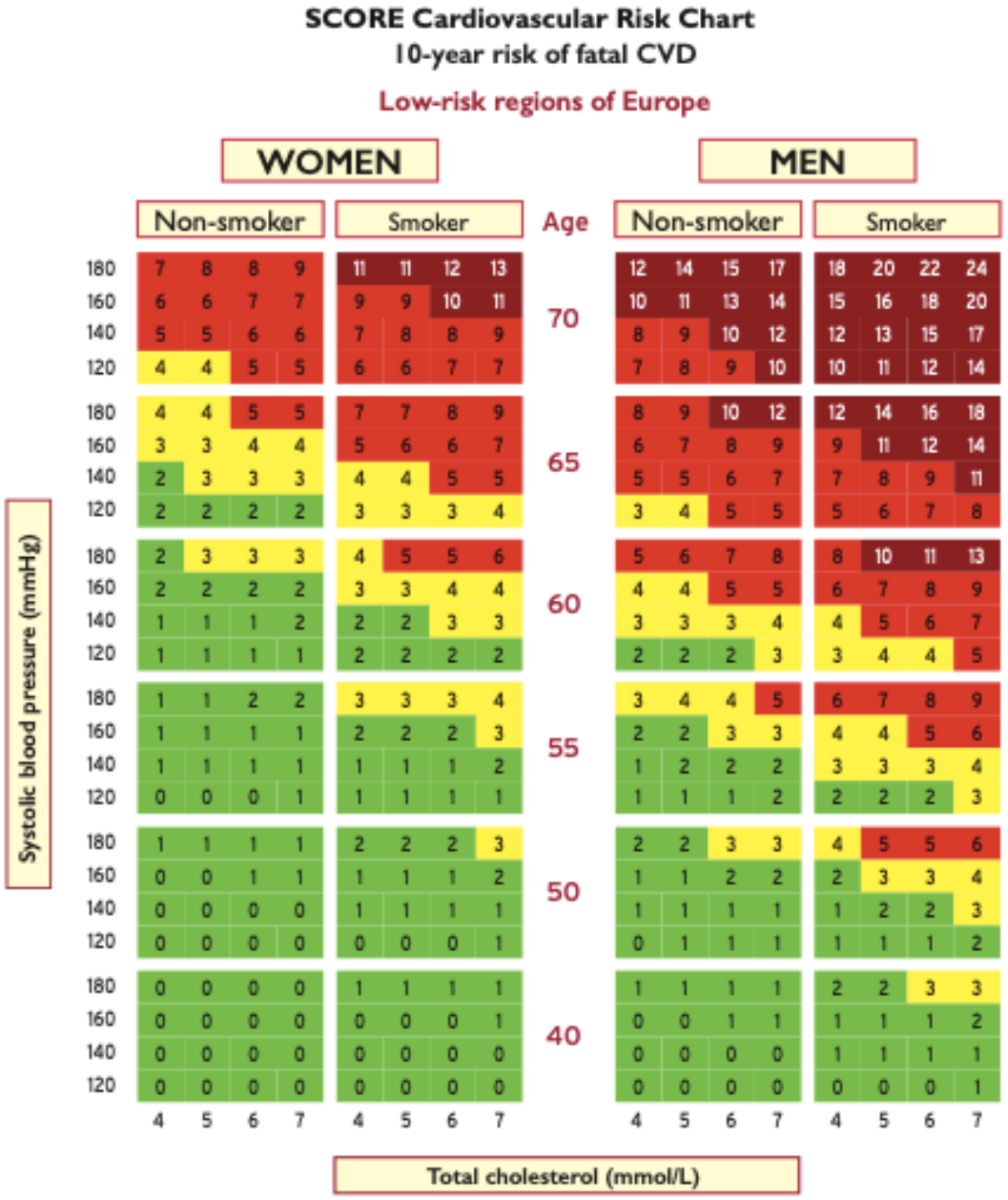

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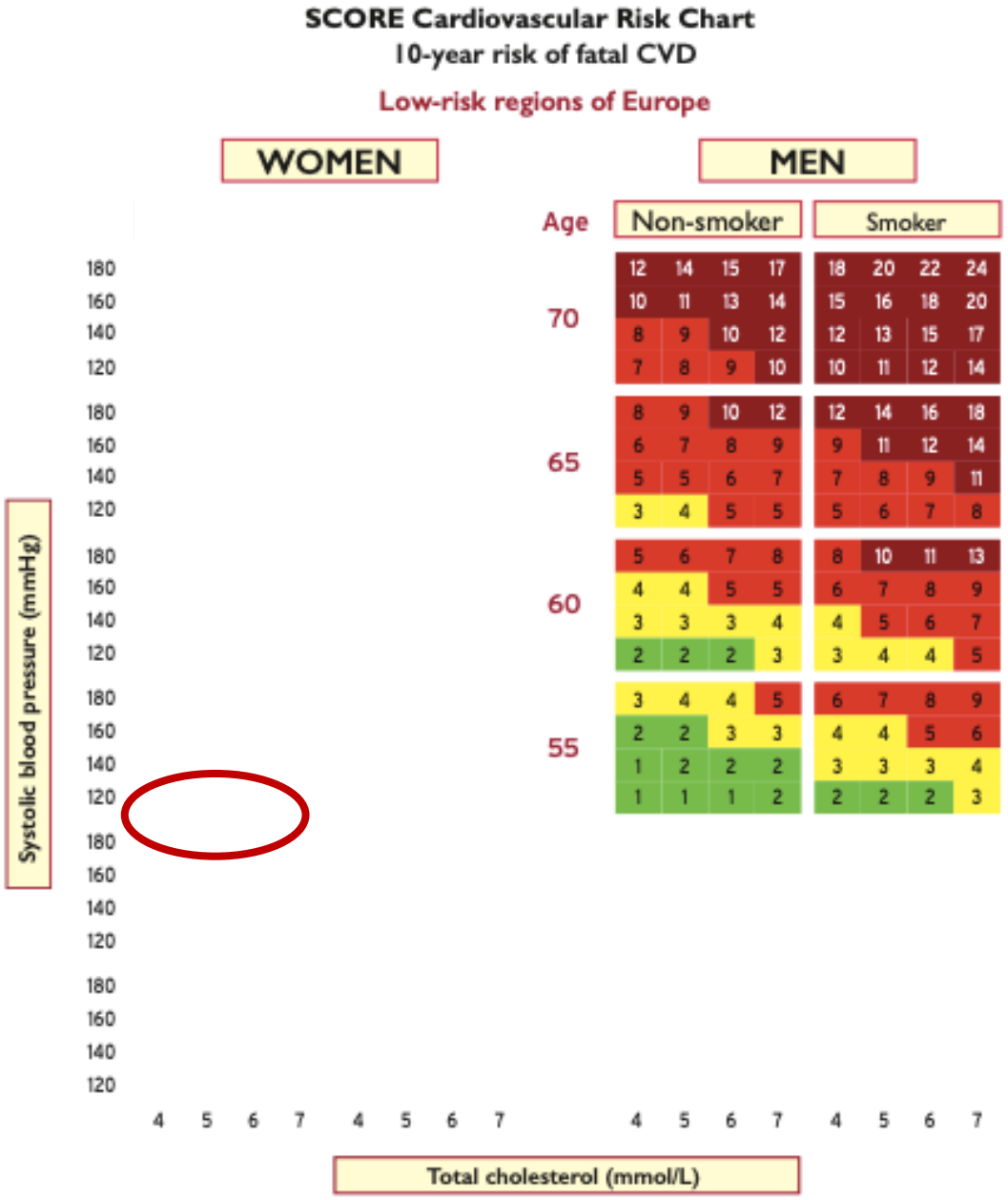

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Les preuves du 1.4 mmol/L

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

Table 5 Intervention strategies as a function of total cardiovascular risk and untreated low-density lipoprotein cholesterol levels

	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

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	≥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**

Visseren Frank L J,Mach François et al.,European Heart Journal (2021) 00, 1111
doi:10.1093/eurheartj/ehab484

Table 5 Intervention strategies as a function of total cardiovascular risk and untreated low-density lipoprotein cholesterol levels

	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							
	Class[a]/Level[b]	IIa/A					
	≥10, or at very-high risk due to a risk condition (see *Table 4*)	**Lifestyle advice**					
	Class[a]/Level[b]	IIa/B					

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Primary prevention							
	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

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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

Visseren Frank L J,Mach François et al.,European Heart Journal (2021) 00, 1111 doi:10.1093/eurheartj/ehab484

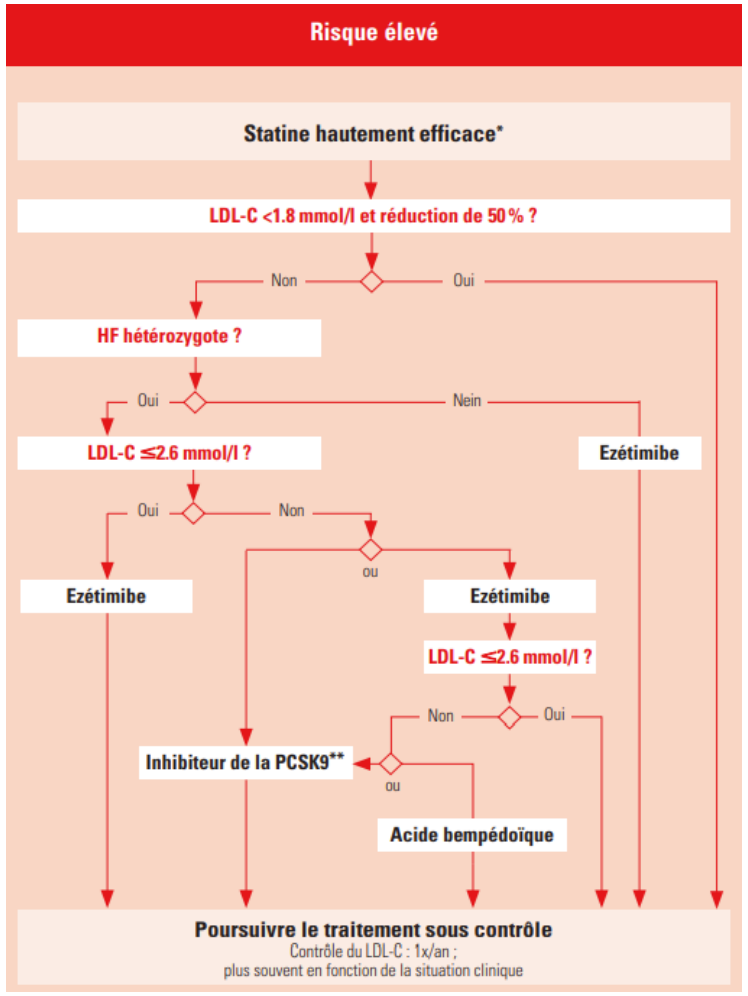
GSLA 2023: stratégies de traitement

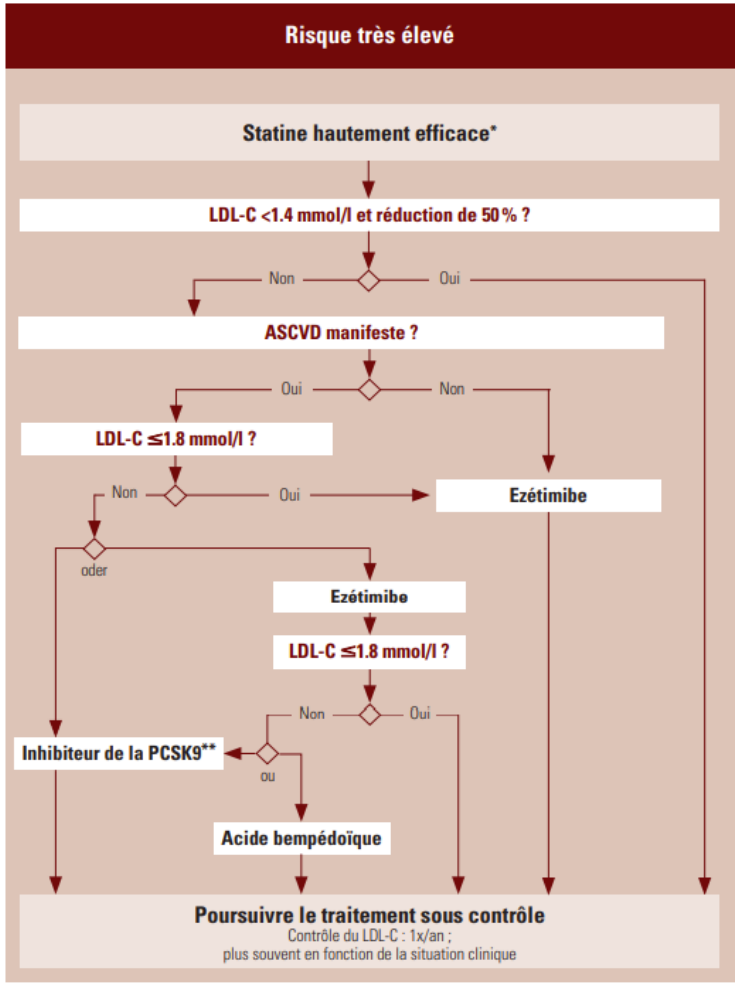
Risque faible
Valeur cible : LDL-C <2.6 mmol/l

Pas de traitement pharmaceutique systématique
Conseils d'hygiène de vie

Risque modéré
Valeur cible : LDL-C <2.6 mmol/l

Envisager une statine
Conseils d'hygiène de vie





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

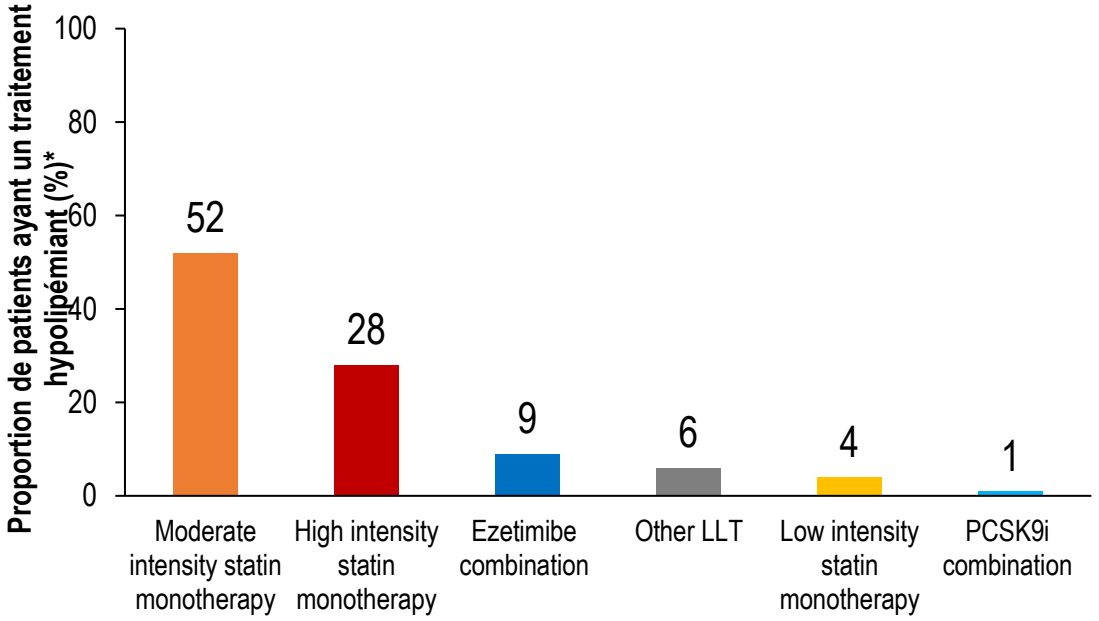
1. Recommandations GSLA 2023, 7ème édition, https://www.agla.ch/

Programme

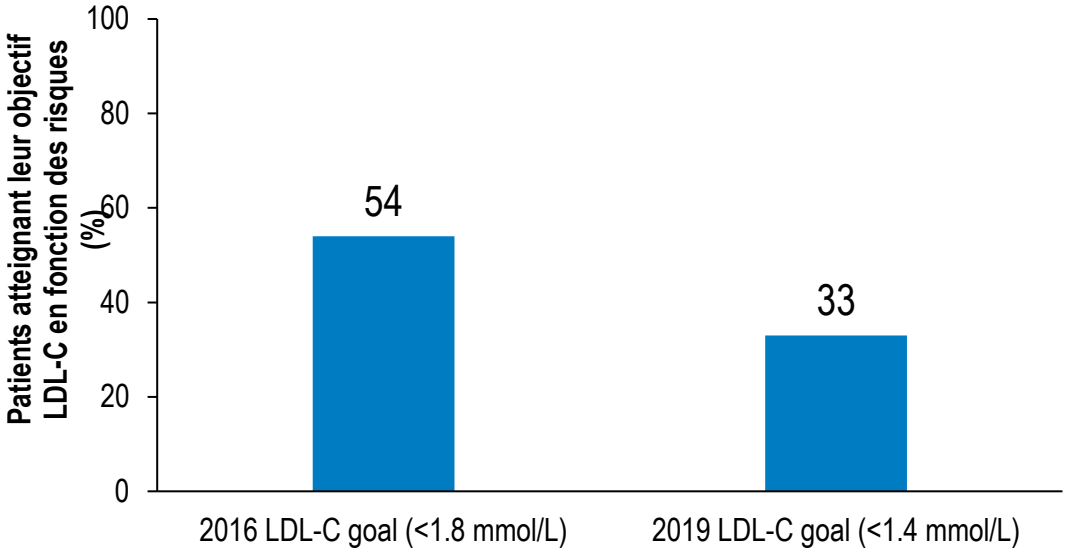
1. Pourquoi cibler le cholestérol ?
2. Quelles sont les « nouvelles » cibles ?
3. Pourquoi 1.4 mmol/l ?
4. **Y parvient-on ?**
5. Avec quelles armes (→2021) ?

DAVINCI: décrit la mise en œuvre des recommandations européennes pour les traitements hypolipémiants[1]

Seuls 28% des patients ont reçu de fortes doses de statines en monothérapie, 9% une association avec l'ézétimibe, 1% une association de PCSK9i



Seuls 33% des patients ont atteint les valeurs cibles de LDL-C ESC 2019 avec une plus faible probabilité d'atteindre l'objectif en cas de risque élevé



La mise en place des directives 2019 va nécessiter un changement dans les pratiques, en particulier chez les patients à très haut risque, ainsi que le recours à des traitements combinés.

DAVINCI – Mise à jour Congrès ESC 2020: Étude observationnelle longitudinale menée en Europe sur le traitement hypolipémiant proposé dans les soins primaires et secondaires. Cette étude incluait 5888 patients recevant un traitement hypolipémiant en soins primaires (n = 3000) et en soins secondaires (n = 2888) dans 18 pays de l'UE et sur 128 sites. LDL-C = cholestérol des lipoprotéines de faible densité

1. Ray KK et al., EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care: the DAVINCI study. *European Journal of Preventive Cardiology* 2020

DAVINCI: parmi les patients à très haut risque avec ASCVD avérée, l'objectif était plus souvent atteint chez ceux qui bénéficiaient d'un traitement combiné

DAVINCI – Mise à jour Congrès ESC 2020: Étude observationnelle longitudinale menée en Europe sur le traitement hypolipémiant proposé dans les soins primaires et secondaires. Cette étude incluait 5888 patients recevant un traitement hypolipémiant en soins primaires (n = 3000) et en soins secondaires (n = 2888) dans 18 pays de l'UE et sur 128 sites. LDL-C = cholestérol des lipoprotéines de faible densité

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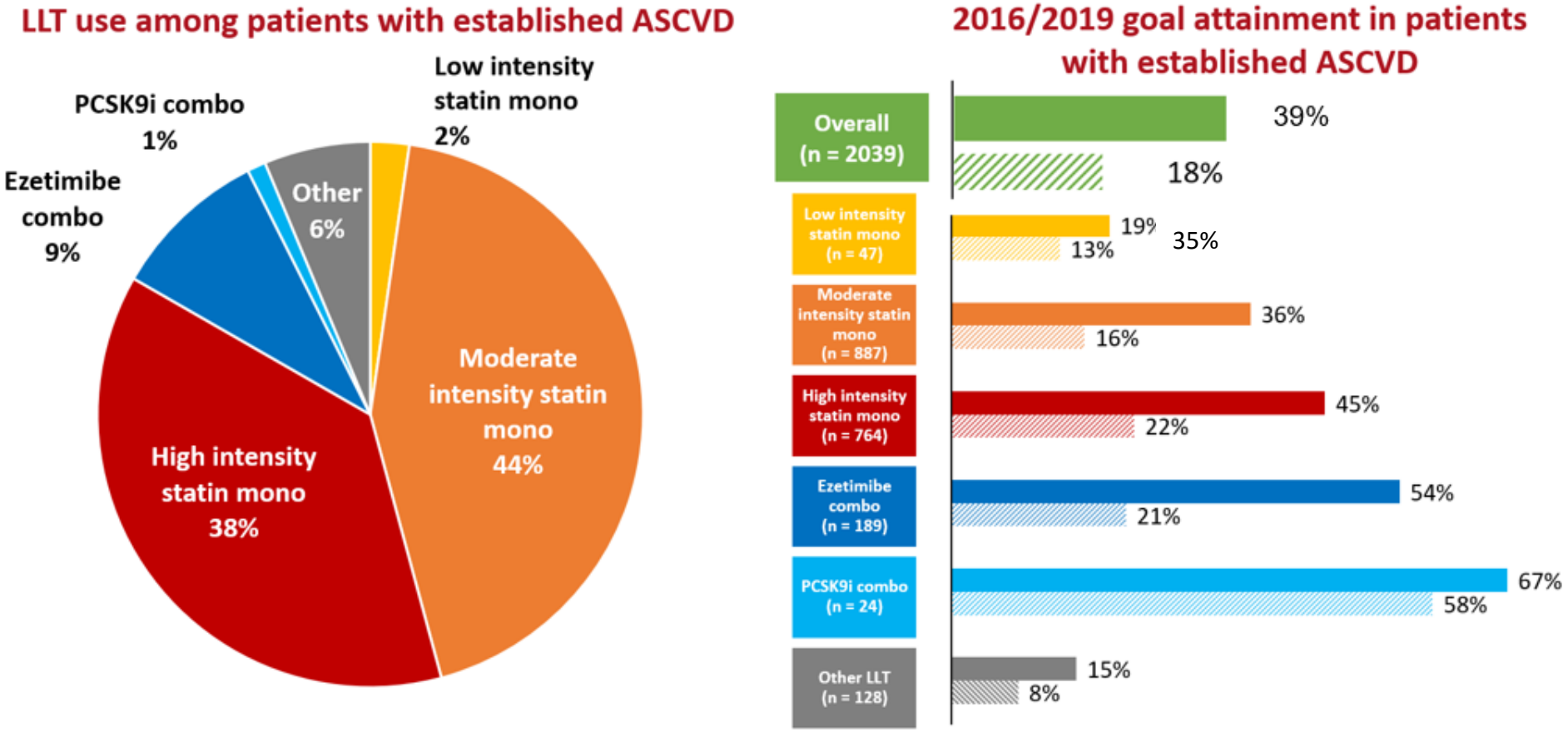
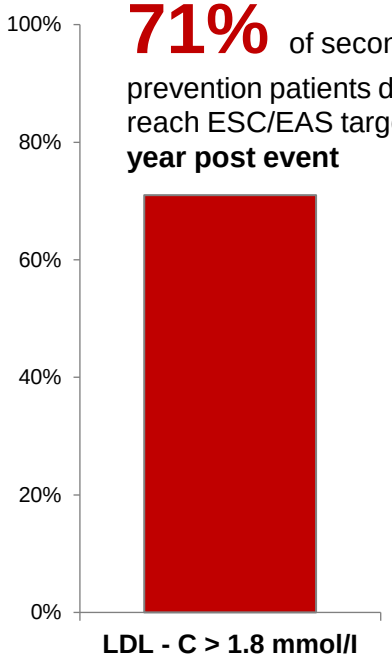


Chez les patients à très haut risque, l'objectif 2019 de 1,4 mmol/l a été atteint pour environ la moitié d'entre eux comparé à 2016 (18% vs 39%).

LDL-C target* achievement of very high-risk CV patients is insufficient[1-2]

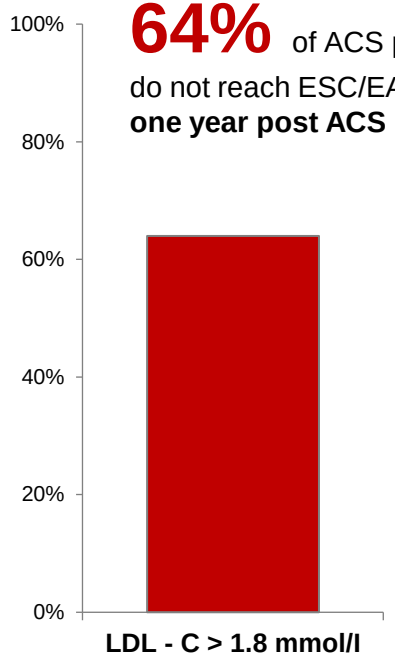
EUROASPIRE V[1]

71% of secondary prevention patients do not reach ESC/EAS target **one year post event**



SPUM-ACS[2]

64% of ACS patients do not reach ESC/EAS target **one year post ACS**



AVERAGE LDL-C IS 2.2 MMOL/L[2]

In Switzerland two thirds of post-ACS patients do not reach the ESC/EAS 2016 target.

1. De Backer G, EAS2018 Late Breaking Clinical Trial Online May 8, 2018: https//www.eas-society.org/news/399857/EAS2018-Late-Breaking-Clinical-Trial-EUROASPIRE-V.htm
2. Gencer, Koskinas et al. J Am Heart Association 2017;6:e006537. Data from SPUM-ACS: A prospective, multi-center cohort study of consecutive patients hospitalized with ACS in Switzerland. *If target defined as <1.8 mmol/L. SPUM-ACS = Special Program University Medicine-Acute Coronary Syndromes / Participating academic centers from Switzerland: Bern, Geneva, Lausanne, and Zurich. EUROASPIRE = Survey in secondary prevention (1 year post-index event); EUROASPIRE VI: N=7998, year 2012–2013. EUROASPIRE V: N=8261, year 2016. ACS = Acute Coronary Syndrome; SPUM-ACS = (Special Program University Medicine-Acute Coronary Syndromes).

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«Puissance» du traitement

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%

+ Inclisiran

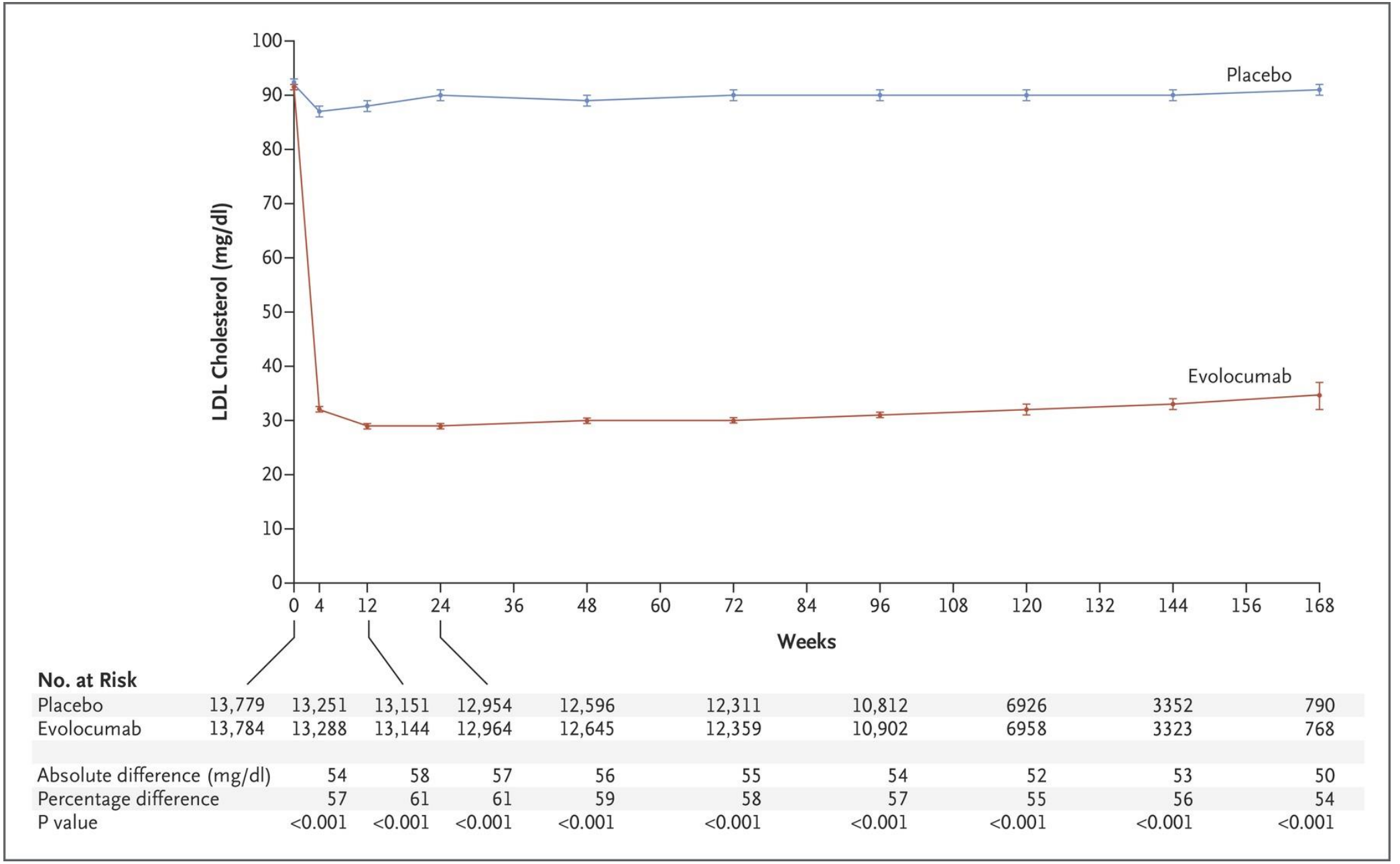
+ Acide Bembedoïque

Mach F, et al. *Eur Heart J.* 2019. doi:10.1093/eurheartj/ehz455. [Epub ahead of print.].

Anti PCSK9 :

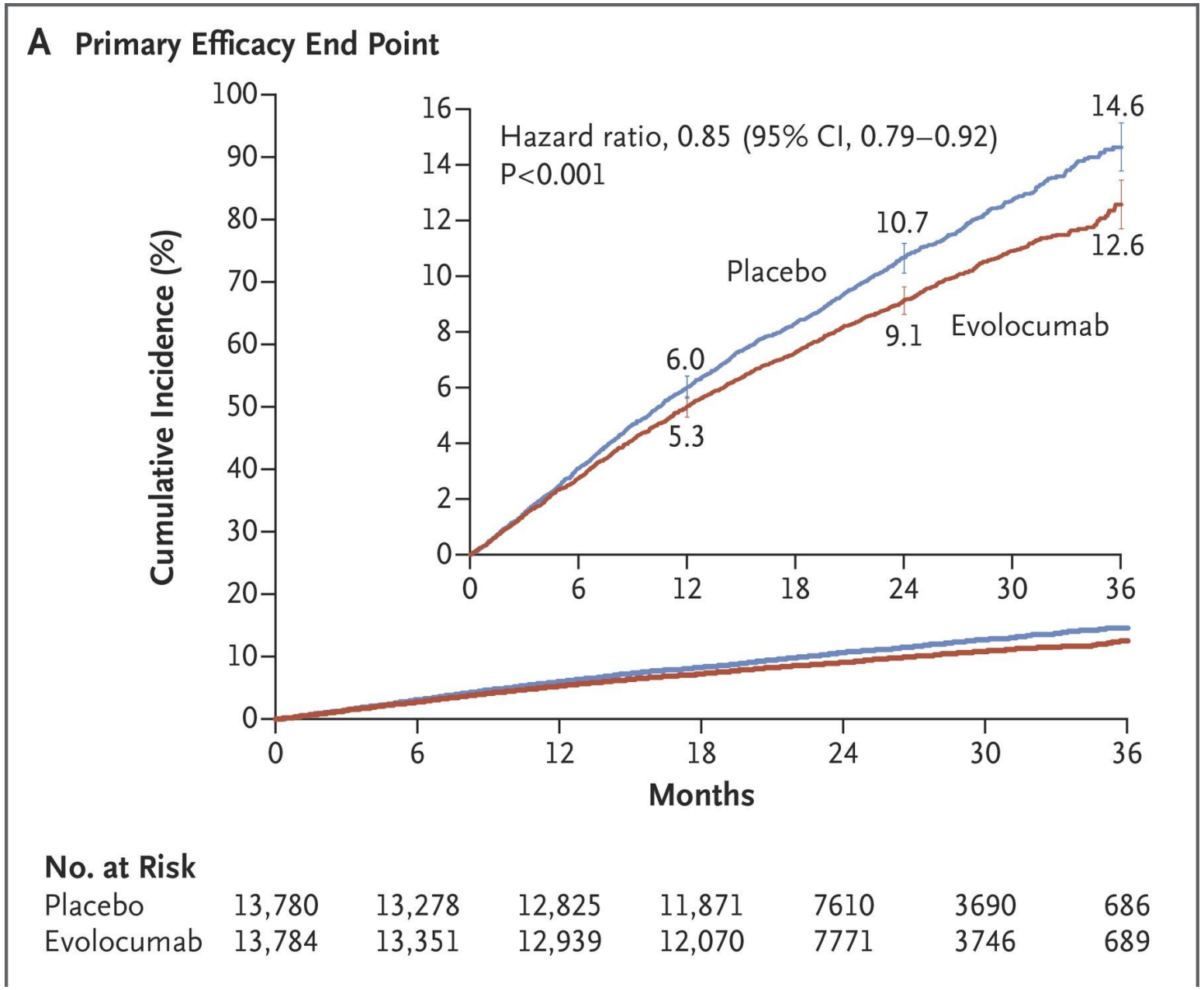
- **Evolocumab**
- **Alirocumab**

Mach F, et al. *Eur Heart J.* 2019. doi:10.1093/eurheartj/ehz455. [Epub ahead of print.].



No. at Risk									
Placebo	13,779	13,251	13,151	12,954	12,596	12,311	10,812	6926	3352	790
Evolocumab	13,784	13,288	13,144	12,964	12,645	12,359	10,902	6958	3323	768
Absolute difference (mg/dl)		54	58	57	56	55	54	52	53	50
Percentage difference		57	61	61	59	58	57	55	56	54
P value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

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.



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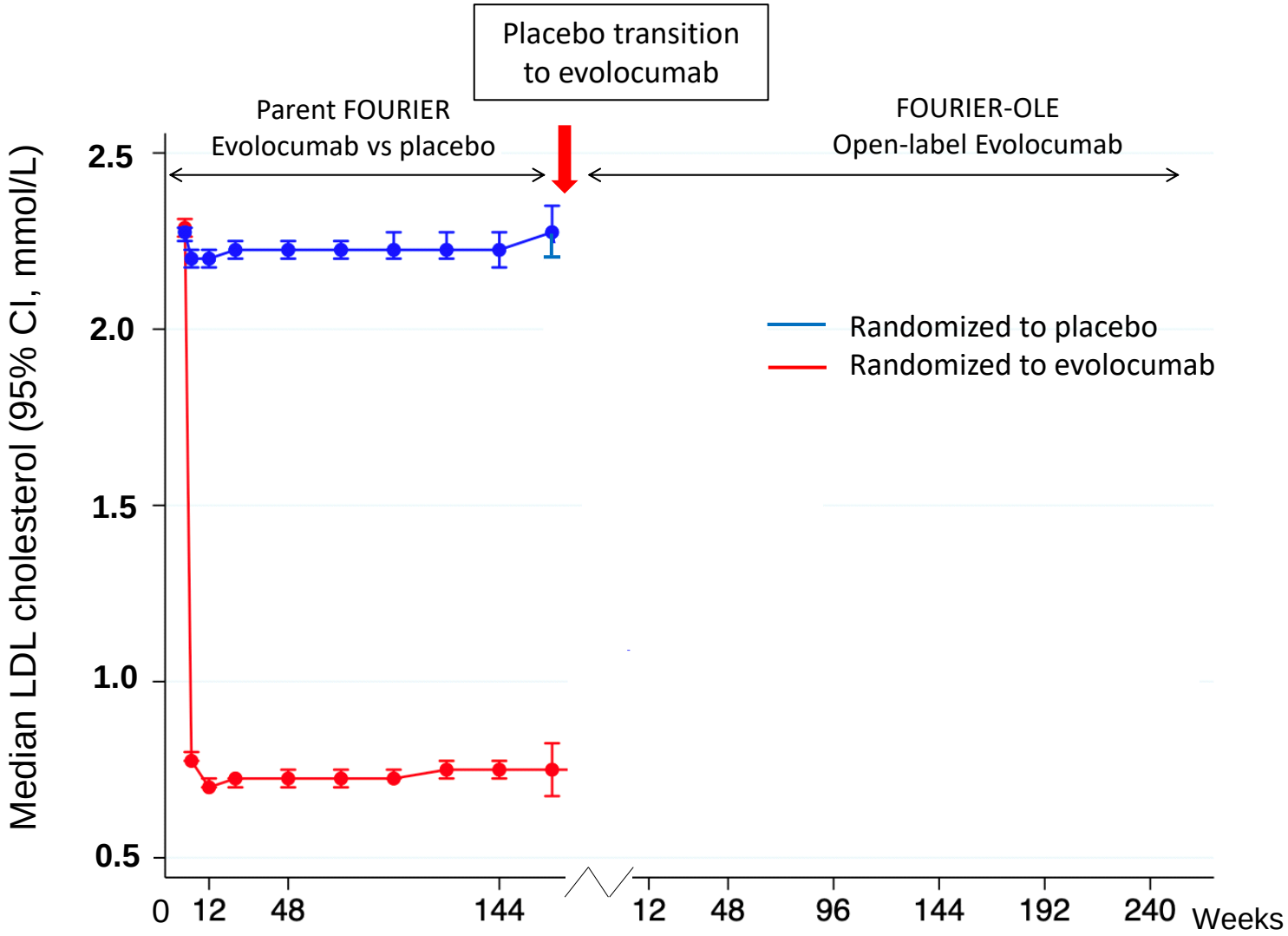
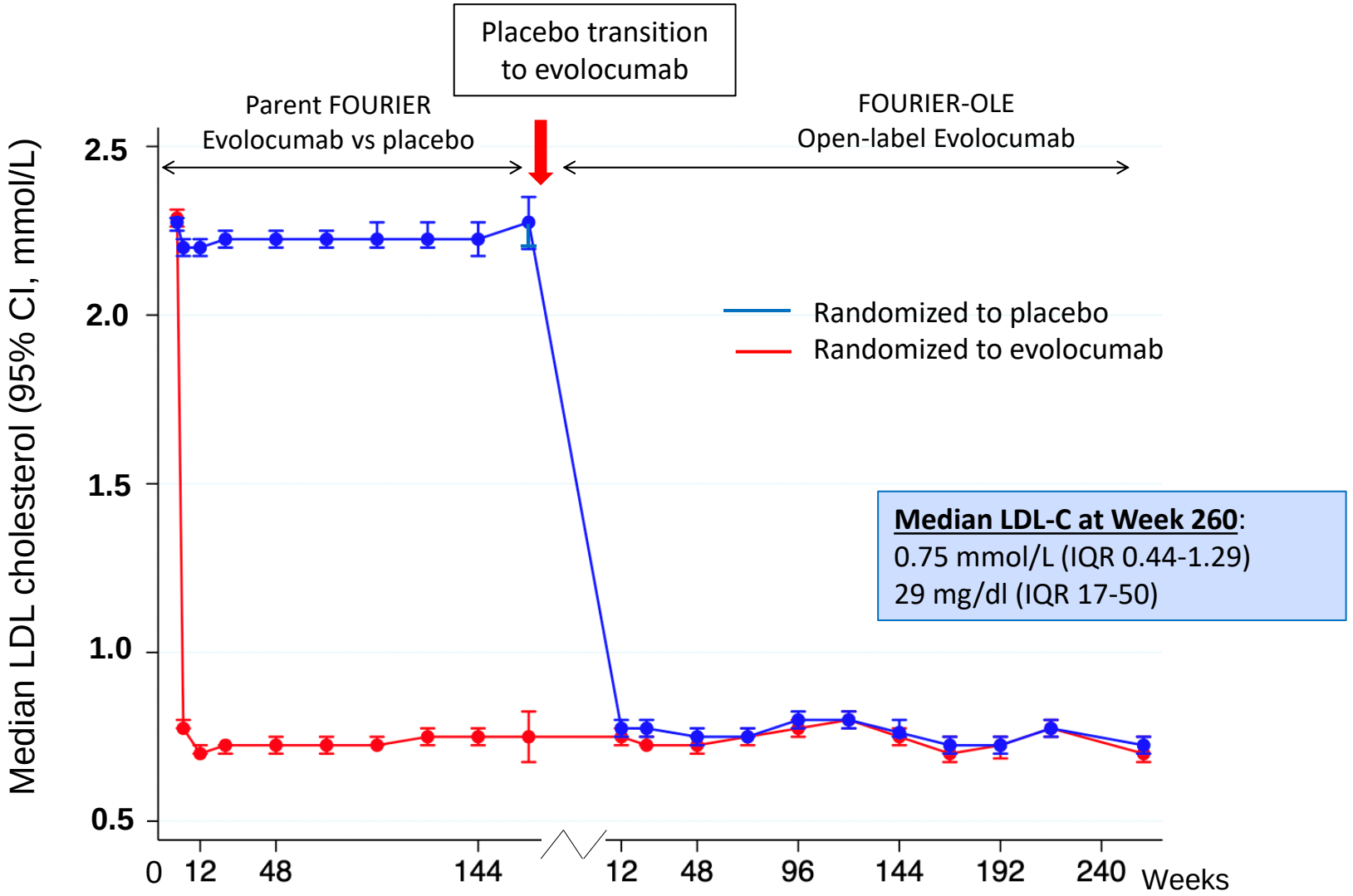
fourier - OLE



Michelle L. O'Donoghue et al., https://doi.org/10.1161/CIRCULATIONAHA.122.061620Circulation. 2022;146:1109–1119

fourier - OLE



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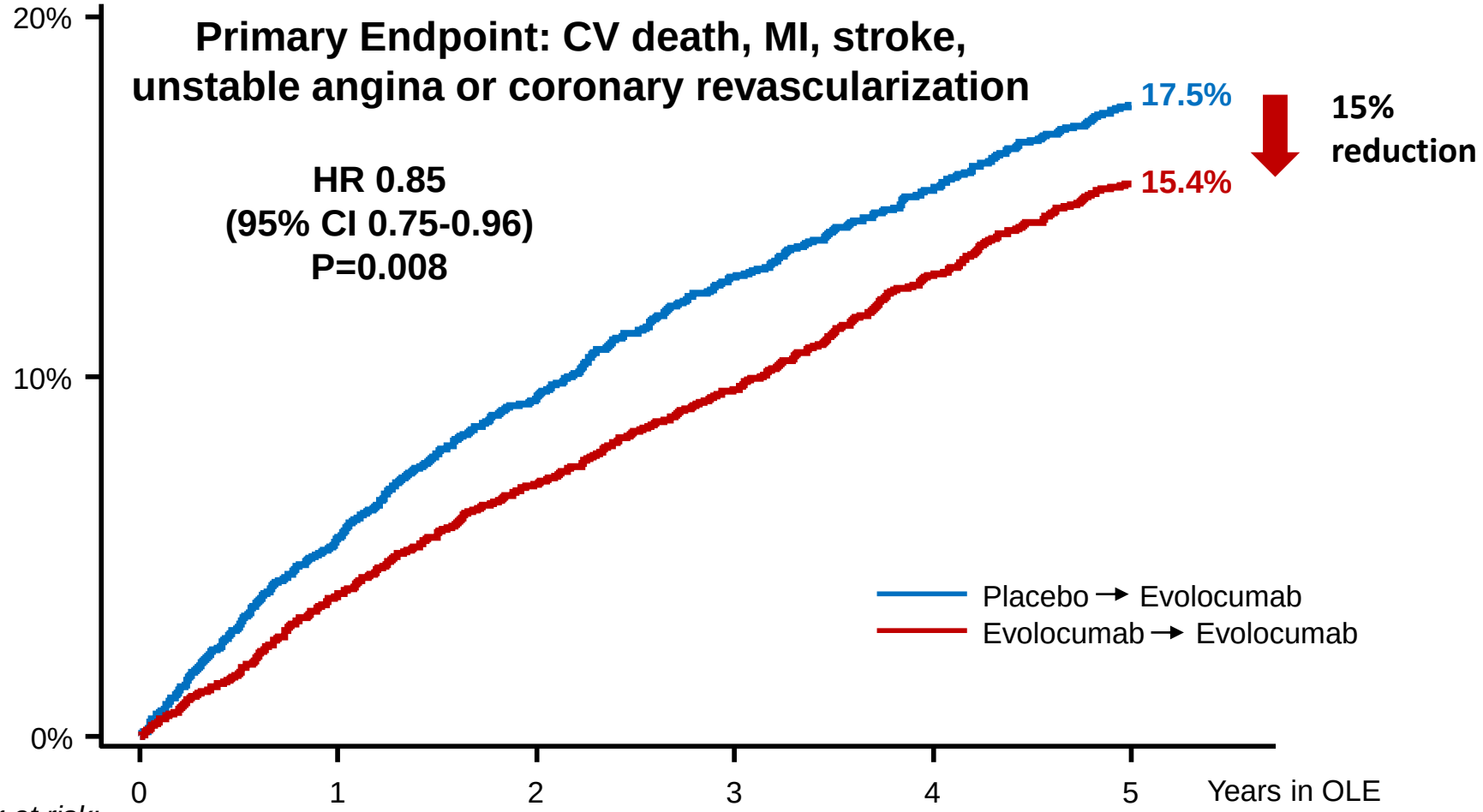

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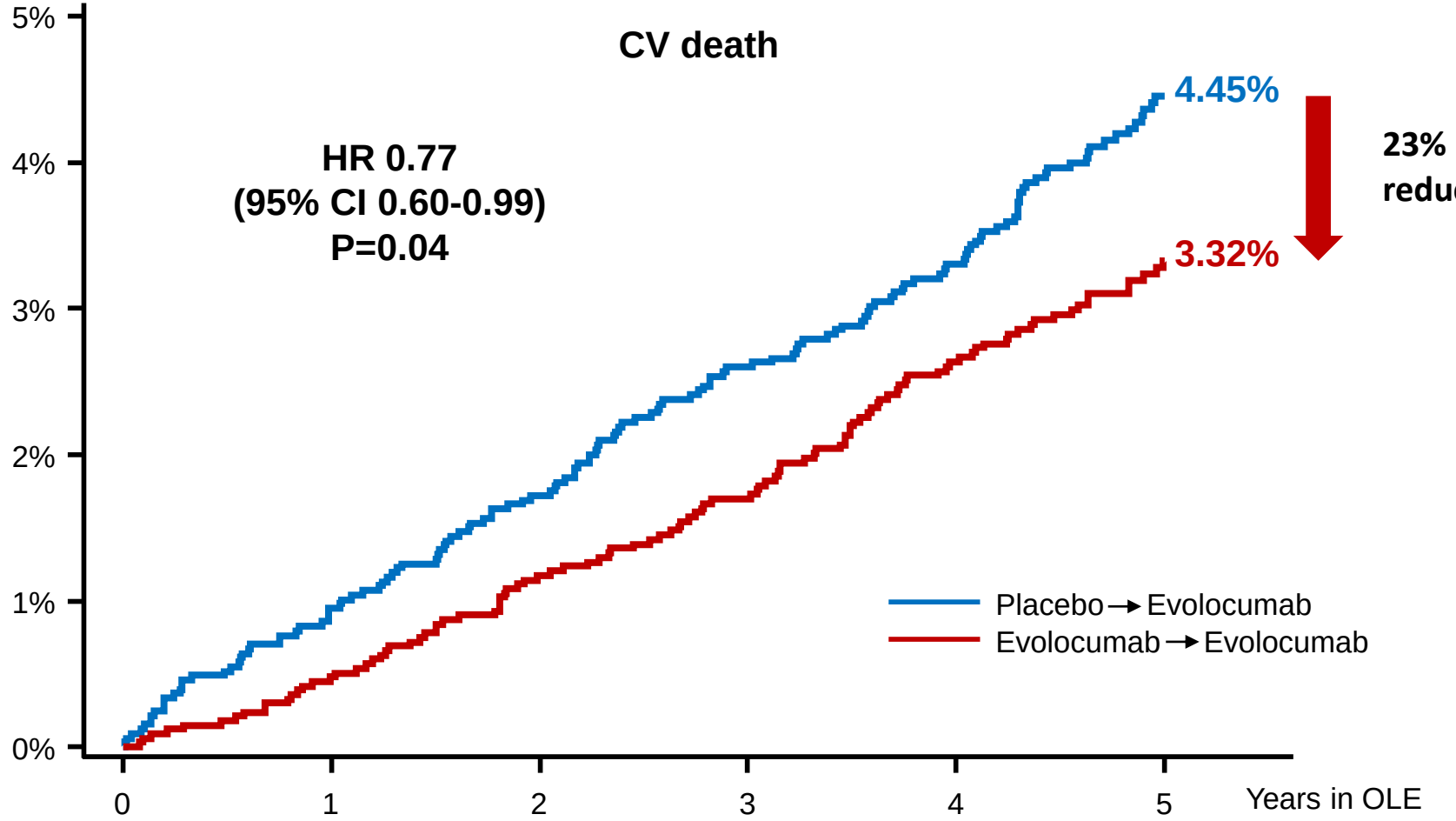


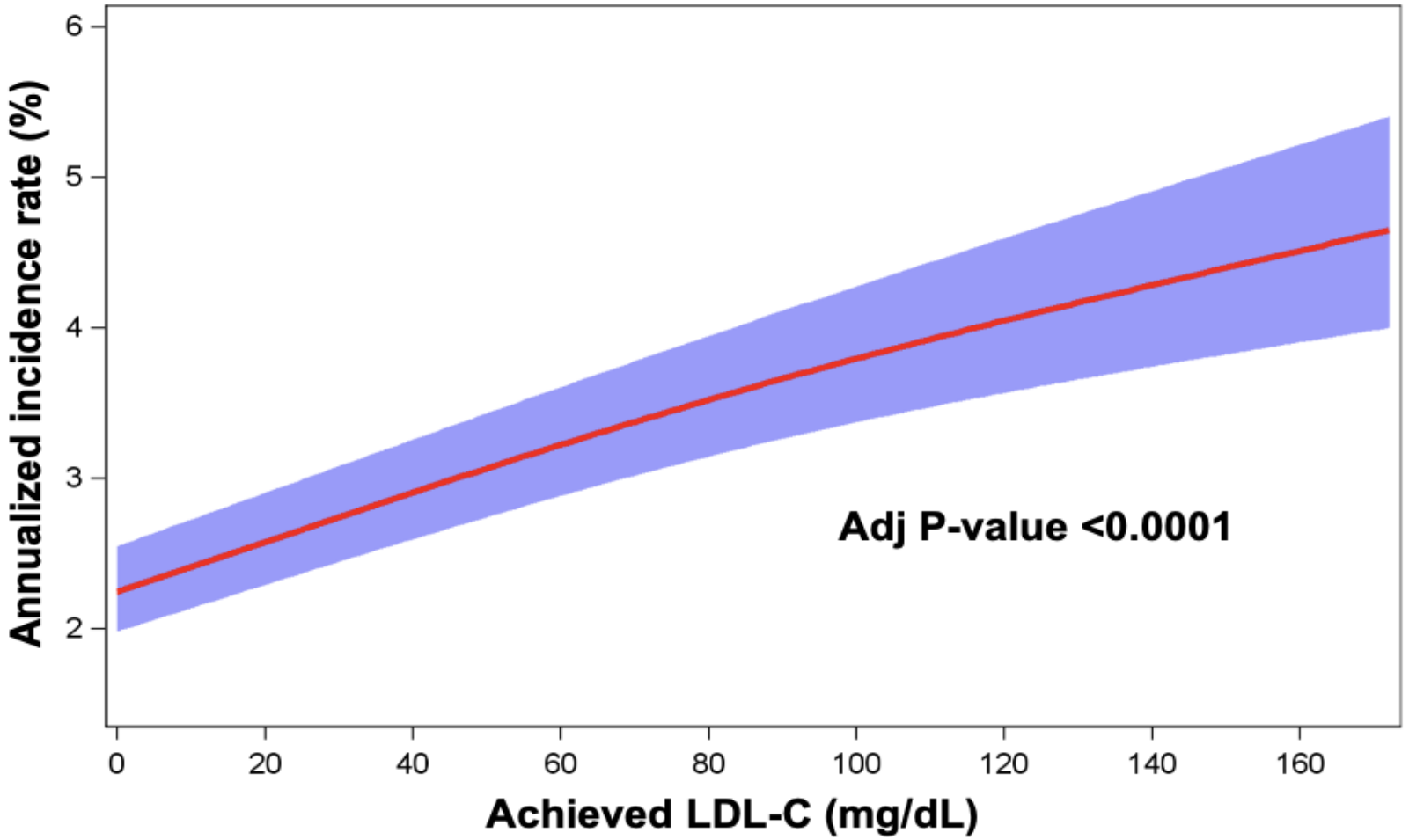
Number at risk:

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

Michelle L. O'Donoghue et al., https://doi.org/10.1161/CIRCULATIONAHA.122.061620Circulation. 2022;146:1109–1119

CV Outcomes and Achieved LDL-C

Key secondary endpoint: CV death, MI, or stroke



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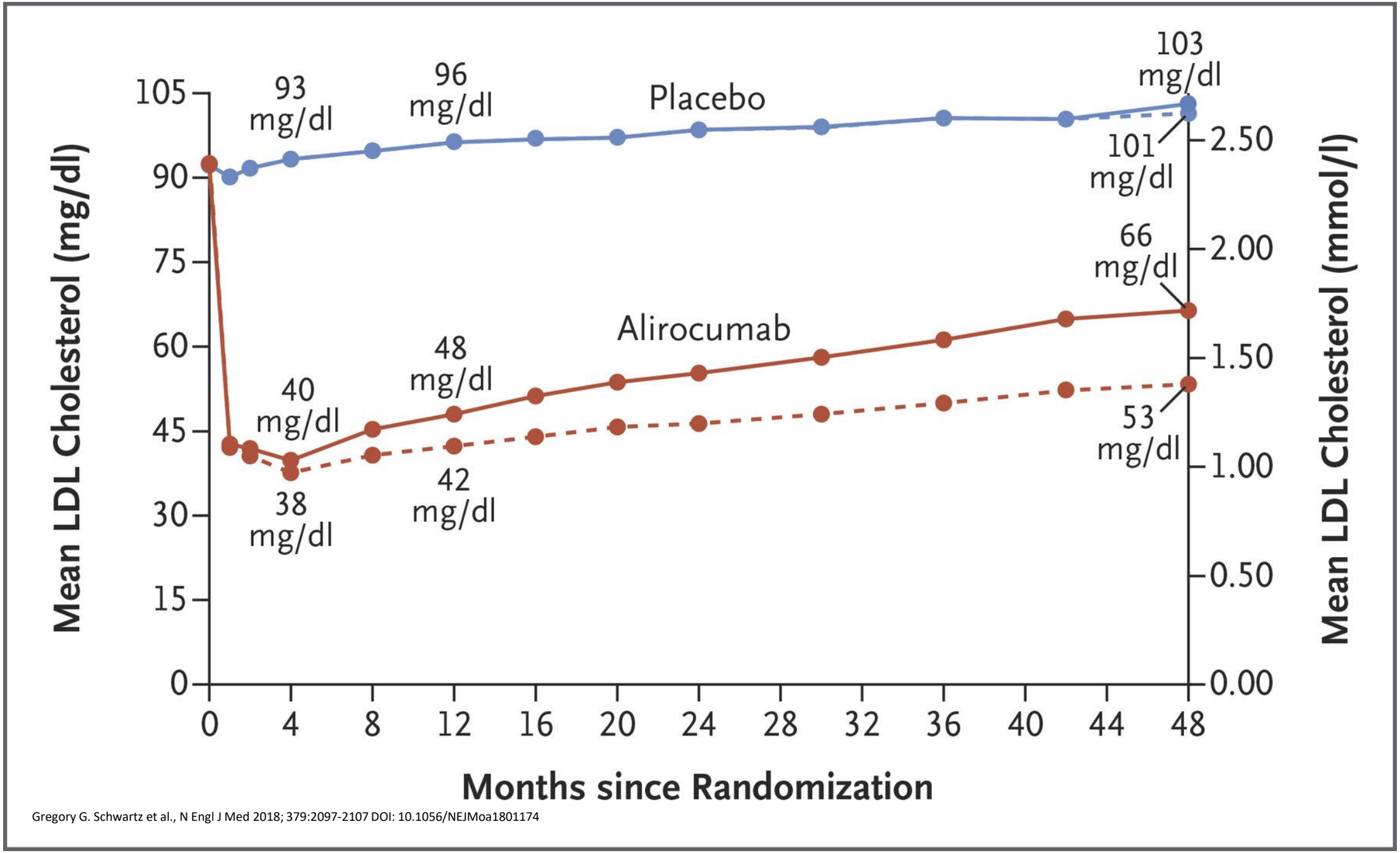
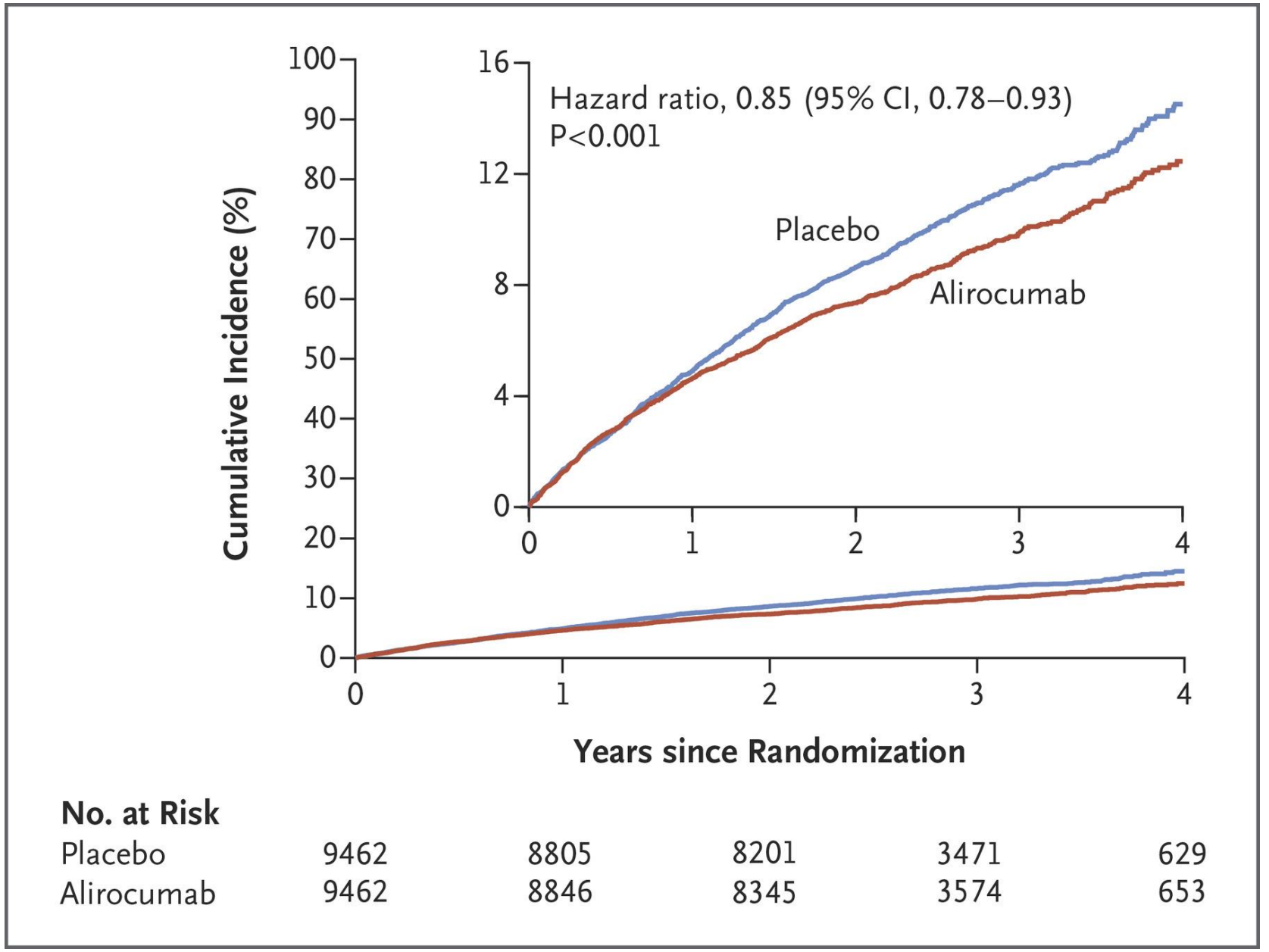


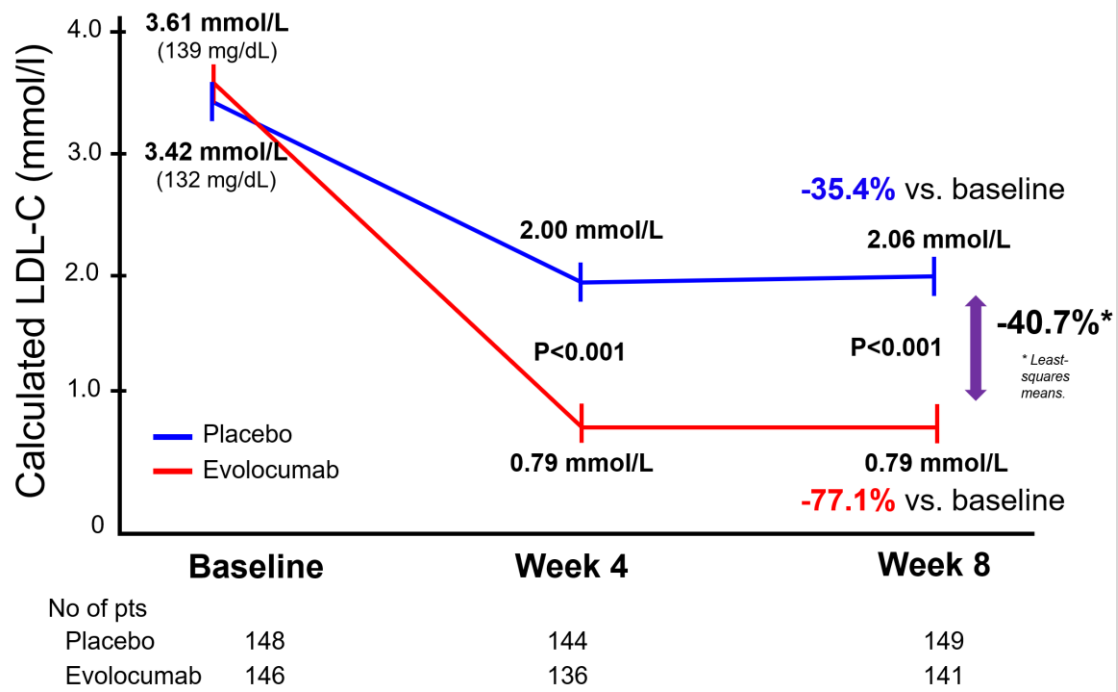
Gregory G. Schwartz et al., N Engl J Med 2018; 379:2097-2107 DOI: 10.1056/NEJMoa1801174



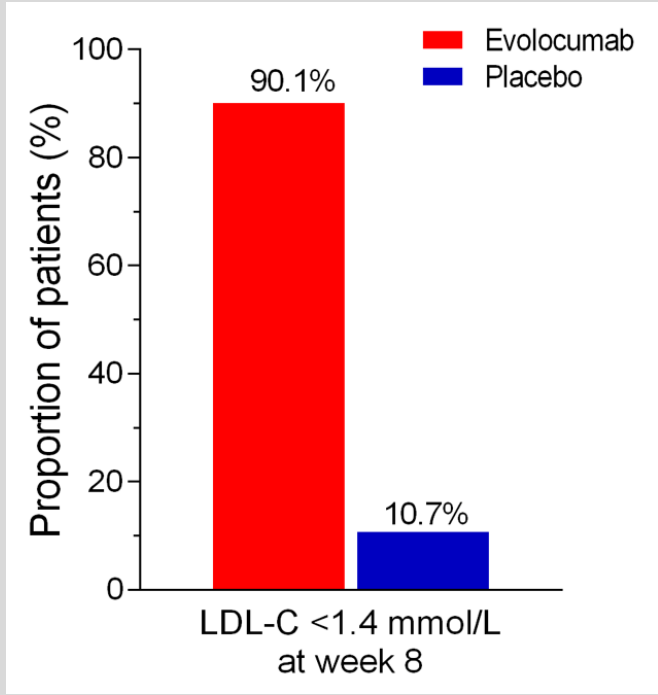
Gregory G. Schwartz et al., N Engl J Med 2018; 379:2097-2107 DOI: 10.1056/NEJMoa1801174

Le traitement reçu dans un contexte de SCA montre que l'évolocumab permet d'atteindre l'objectif LDL-C de 1,4 mmol/l à >90%[1]

Critère d'évaluation principal: % de variation du LDL-C à 8 semaines[1]



Cible LDL-C < 1,4 mmol/l[1,2]



L'évolocumab utilisé pour la réduction précoce des taux de LDL-C chez les patients atteints de SCA (EVOPACS). n = 308. Étude multicentrique, randomisée, en double aveugle et contrôlée contre placebo. Sites de l'étude: Berne, Genève, Lugano, Bâle, Fribourg, Zürich, Lausanne. Conception de l'étude: évolocumab SC 420mg + atorvastatine 40mg QD comparé au placebo SC + atorvastatine 40mg QD. Patients avec ACS STEMI <24 h ou NSTE-ACS <72 h. LDL-C au screening: > 1,8 mmol/l avec statines hautement dosées; > 2.3 mmol/l avec statines faiblement à modérément dosées; > 3.2 mmol/l sans statines. Intensité du traitement par statine en début d'étude (LDL-C): aucune statine 78% (3,7 mmol/l), statines faiblement à modérément dosées 11% (2.9 mmol/l), statines hautement dosées (atorva). ≥40mg; rosuva. ≥ 20mg; simva. 80mg) 10% (2,3 mmol/l).

1. Koskinas KC, et al. Evolocumab for Early Reduction of LDL Cholesterol Levels in Patients With Acute Coronary Syndromes (EVOPACS). J Am Coll Cardiol. 2019 Nov 19;74(20):2452-2462.]; 2. ESC/EAS 2019 Dyslipidemia Guidelines Mach F, et al. Eur Heart J 2019.

Merci beaucoup !

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