METABOLISME ET DIABETE

QUOI de NEUF en 2023?

François DIEVART

ELSAN Clinique Villette, DUNKERQUE

Disclosures – Dr François Diévart

Consulting fees or fees for conferences

- Laboratoires pharmaceutiques : Alliance BMS-Pfizer, Amgen, Astra-Zeneca, Bayer Healthcare, Boerhinger Ingelheim, BMS, Bouchara-Recordati, Hikma, Lily, MSD, Novartis, Novo Nordisk, Organon, Pfizer, Sanofi, Servier

- Agences de communication en santé: Axis, CCC, DDB Healthcare, IDEAS, LEN Médical, Nex et Com, Re-Imagine, TBWA, Vivactis

Other

- Membre du conseil d'administration de la Société française de cardiologie (SFC),
- Membre du conseil d'administration du Collège national des cardiologues français (CNCF), president du comité scientifique du CNCF, membre (2019-2022) du Nucleus of the Council of cardiology practice de la Société européenne de cardiologie (ESC)
- Président du groupe Coeur, vaisseaux et métabolisme de la SFC, membre de la Société française d'hypertension artérielle, du GACI, de l'ESC, de l'EAPCI, de la HFA, secrétaire scientifique du CNCF
- Président du groupe Pharmacologie Clinique et thérapeutique de la SFC (2021-2018)
- Membre du conseil d'administration du Syndicat national des cardiologues (SNC)
- Membre des comités de rédaction ou de lecture de Réalités Cardiologiques, Le Cardiologue, Le Quotidien du Médecin, theHeart.org

PLAN

- Épidémiologie du LDL : jusqu'où le plus bas?
- Une étude « dérangeante » sur le score calcique à zéro ?
- Etude REPRIEVE : statines et SIDA
- Etude STOP-CA : statines et prévention cardiotoxicité anthracyclines
- Etude CLEAR-Outcomes: un nouvel arrivant
- Epidémiologie du diabète
- Diabète et maladies CV: de nouvelles recommandations
- Un regard vers le futur…

PLAN

- **Épidémiologie du LDL : jusqu'où le plus bas?**
- Une étude « dérangeante » sur le score calcique à zéro ?
- Etude REPRIEVE : statines et SIDA
- Etude STOP-CA : statines et prévention cardiotoxicité anthracyclines
- Etude CLEAR-Outcomes: un nouvel arrivant
- Epidémiologie du diabète
- Diabète et maladies CV: de nouvelles recommandations
- Un regard vers le futur…

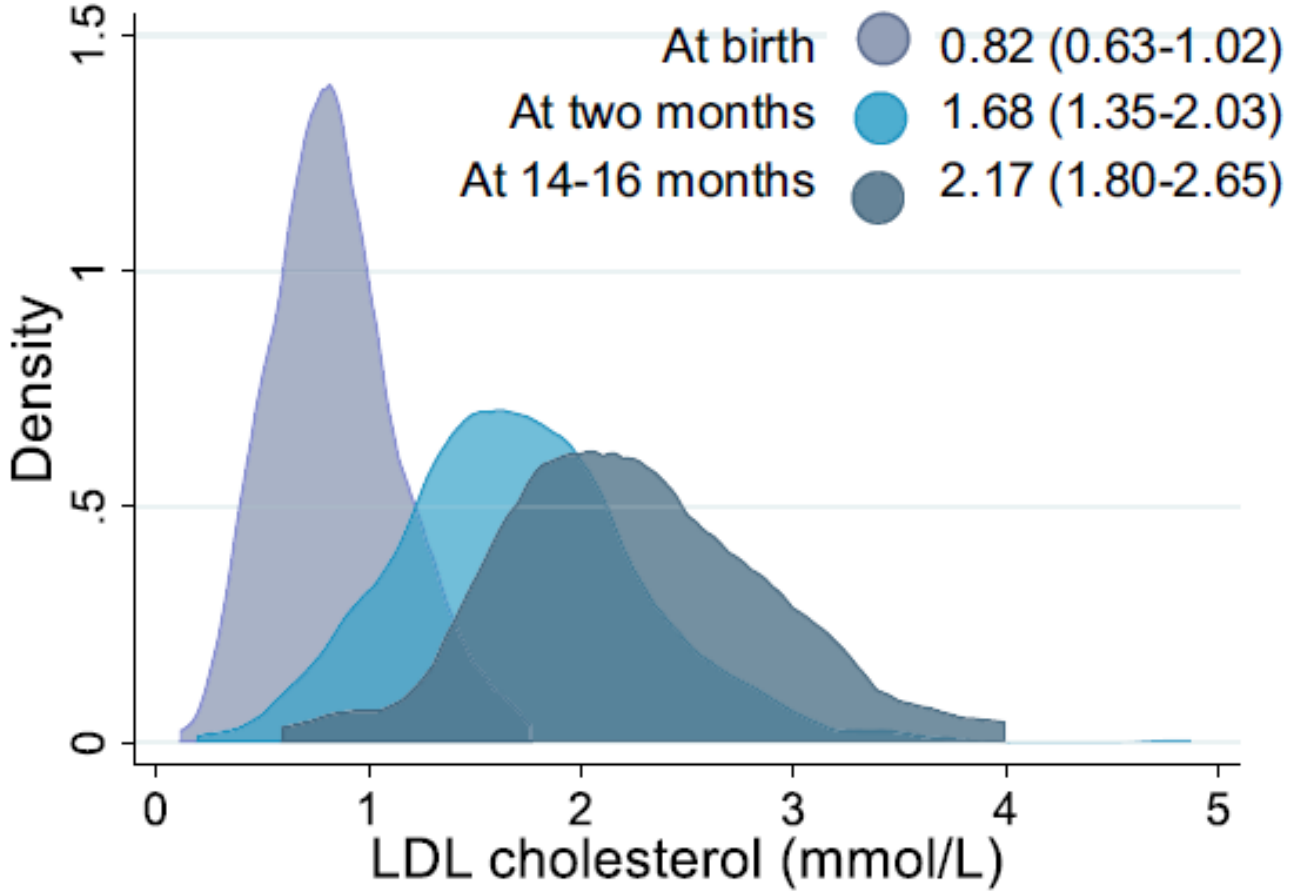
ESC European Society of Cardiology
European Heart Journal (2023) **00**, 1–11
https://doi.org/10.1093/eurheartj/ehad547

Significance of lipids, lipoproteins, and apolipoproteins during the first 14–16 months of life

Sofie Taageby Nielsen [1], Rikke Mohr Lytsen[1], Nina Strandkjær[2],

LDL-cholestérol

1 mmol/l = 0,39 g/l



= 0,32 g/l
= 0,65 g/l
= 0,84 g/l

ESC European Society of Cardiology

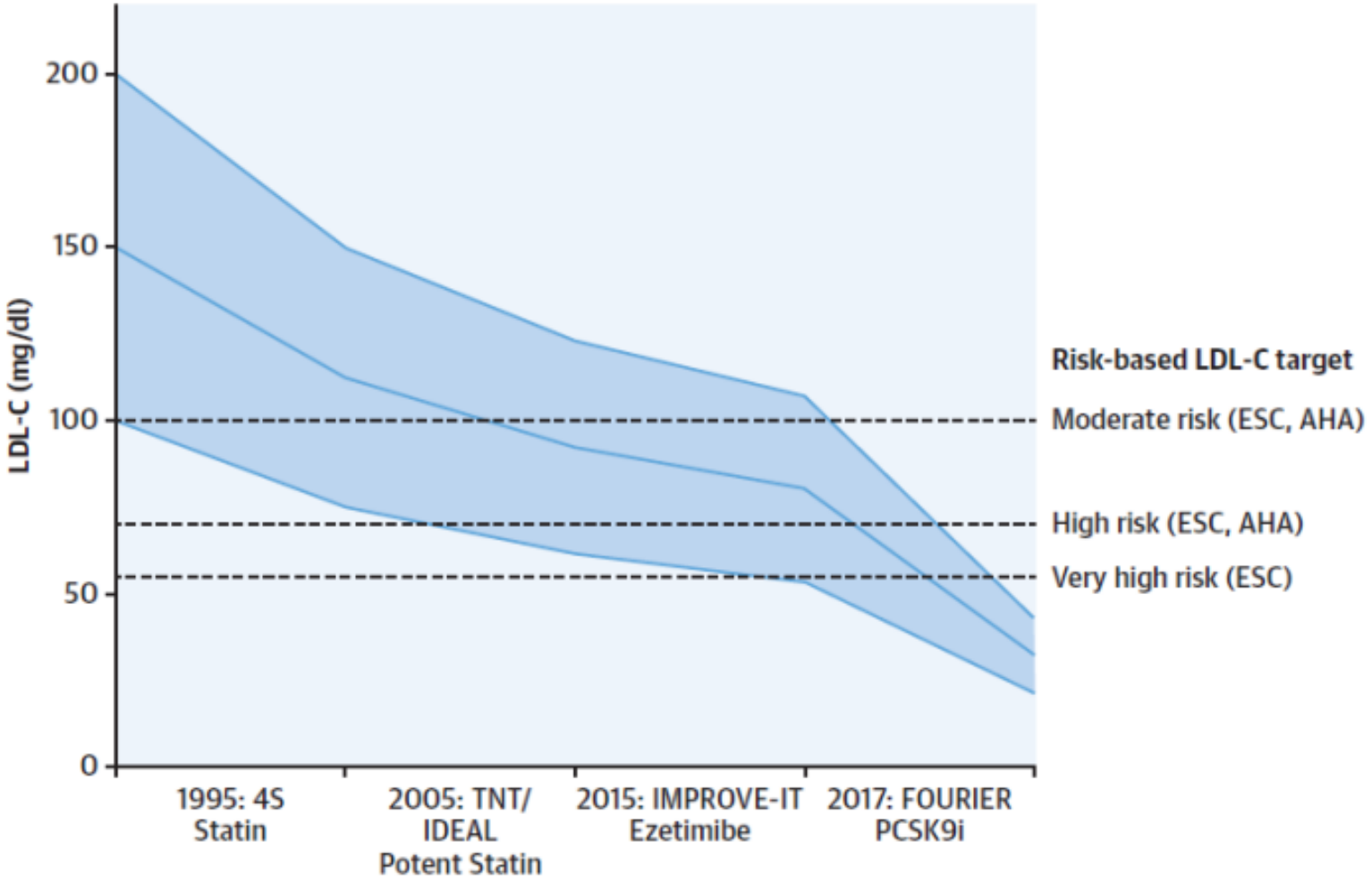
European Heart Journal - Cardiovascular Pharmacotherapy (2023) **9**, 138–147
https://doi.org/10.1093/ehjcvp/pvac049

ORIGINAL ARTICLE
Lipids

Safety and efficacy of very low LDL-cholesterol intensive lowering: a meta-analysis and meta-regression of randomized trials

Giuseppe Patti [1,2,*], Enrico Guido Spinoni [1], Leonardo Grisafi [1], Roxana Mehran [3] and Marco Mennuni [2]

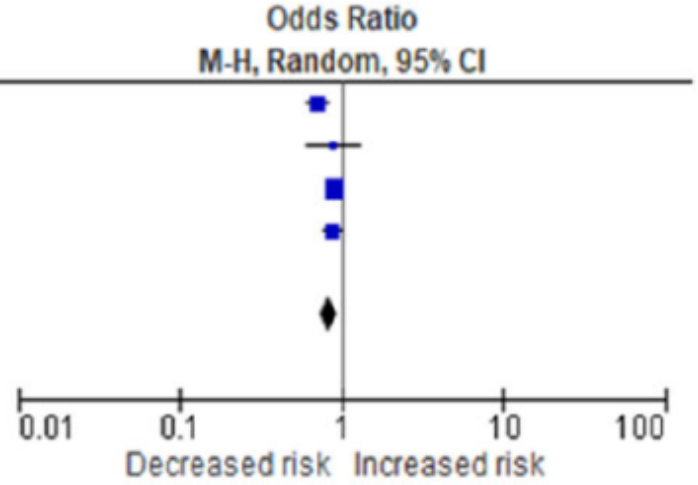
Baisser encore plus le LDL



A Primary composite efficacy endpoint, as defined in each trial

Study or Subgroup	Very low LDL level Events	Total	Control group Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
FOURIER	217	2669	1314	11866	26.2%	0.71 [0.61, 0.83]
PROVE IT - TIMI 22	39	193	324	1463	8.4%	0.89 [0.61, 1.29]
REVEAL	1640	15225	1803	15224	38.6%	0.90 [0.84, 0.96]
SPIRE 1 and 2	352	13720	397	13718	26.9%	0.88 [0.76, 1.02]
Total (95% CI)		**31807**		**42271**	**100.0%**	**0.84 [0.75, 0.95]**
Total events	2248		3838			

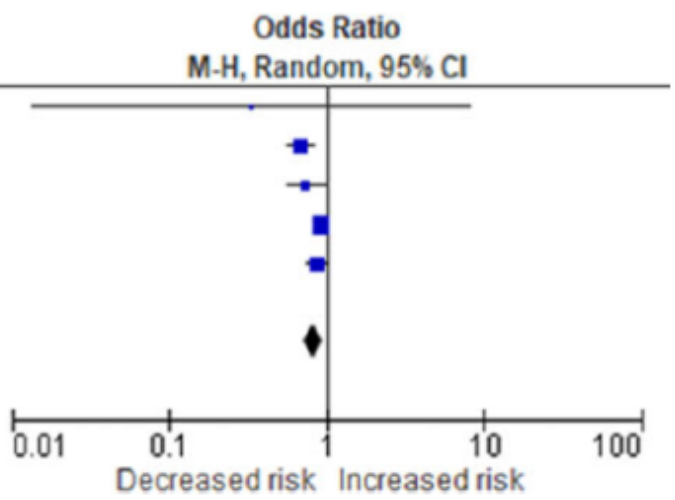
Heterogeneity: Tau² = 0.01; Chi² = 7.80, df = 3 (P = 0.05); I² = 62%
Test for overall effect: Z = 2.85 (P = 0.004)



B MACE

Study or Subgroup	Very low LDL level Events	Total	Control group Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
AMG 145	0	202	1	202	0.2%	0.33 [0.01, 8.19]
FOURIER	134	2669	843	11866	22.9%	0.69 [0.57, 0.83]
ODYSSEY OUTCOMES	90	3357	121	3357	15.3%	0.74 [0.56, 0.97]
REVEAL	1497	15225	1604	15224	35.6%	0.93 [0.86, 1.00]
SPIRE 1 and 2	293	13720	335	13718	26.0%	0.87 [0.74, 1.02]
Total (95% CI)		**35173**		**44367**	**100.0%**	**0.82 [0.72, 0.94]**
Total events	2014		2904			

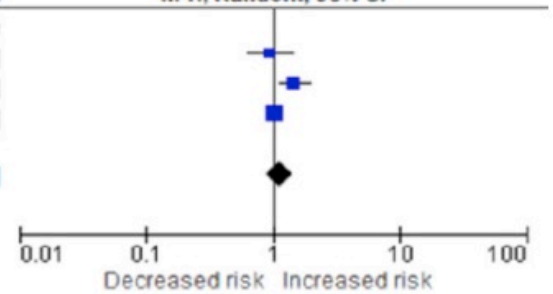
Heterogeneity: Tau² = 0.01; Chi² = 10.14, df = 4 (P = 0.04); I² = 61%
Test for overall effect: Z = 2.79 (P = 0.005)



Non-cardiovascular death

Study or Subgroup	Very low LDL level Events	Total	Control group Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
AMG 145	0	202	0	202		Not estimable
FOURIER	25	2669	231	23313	21.9%	0.94 [0.62, 1.43]
IMPROVE-IT	56	971	571	14310	31.6%	1.47 [1.11, 1.95]
REVEAL	602	15225	591	15224	46.5%	1.02 [0.91, 1.14]
Total (95% CI)		**19067**		**53049**	**100.0%**	**1.13 [0.87, 1.45]**
Total events	683		1393			

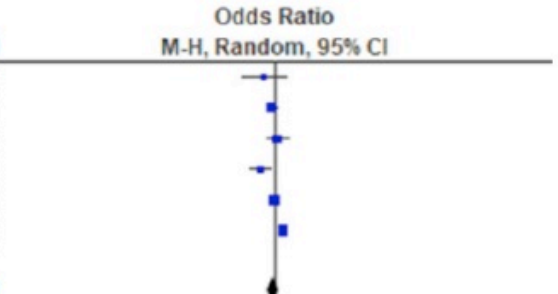
Heterogeneity: Tau² = 0.03; Chi² = 5.94, df = 2 (P = 0.05); I² = 66%
Test for overall effect: Z = 0.91 (P = 0.36)



A Any adverse events

Study or Subgroup	Very low LDL level Events	Total	Control group Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
AMG 145	94	202	103	202	5.7%	0.84 [0.57, 1.24]
FOURIER	614	2669	5492	23313	20.5%	0.97 [0.88, 1.07]
JUPITER	620	767	6509	8150	13.9%	1.06 [0.88, 1.28]
ODYSSEY Pooled data	610	839	1461	1894	14.0%	0.79 [0.66, 0.95]
REVEAL	8898	15225	8912	15224	23.4%	1.00 [0.95, 1.04]
SPIRE 1 and 2	4049	6285	8289	13697	22.6%	1.18 [1.11, 1.26]
Total (95% CI)		**25987**		**62480**	**100.0%**	**1.00 [0.90, 1.11]**
Total events	14885		30766			

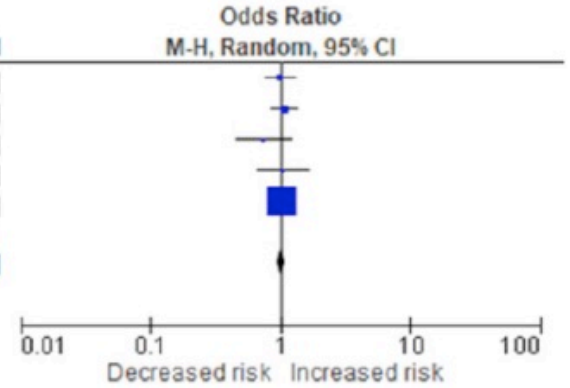
Heterogeneity: Tau² = 0.01; Chi² = 31.42, df = 5 (P < 0.00001); I² = 84%
Test for overall effect: Z = 0.08 (P = 0.94)



A Cancer

Study or Subgroup	Very low LDL level Events	Total	Control group Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
FOURIER	64	2669	557	23313	7.3%	1.00 [0.77, 1.30]
IMPROVE-IT	87	971	1190	14310	9.7%	1.09 [0.86, 1.36]
JUPITER	19	767	269	8150	2.3%	0.74 [0.46, 1.19]
ODYSSEY Pooled data	29	839	63	1894	2.5%	1.04 [0.67, 1.63]
REVEAL	1323	15225	1295	15224	78.2%	1.02 [0.94, 1.11]
Total (95% CI)		**20471**		**62891**	**100.0%**	**1.02 [0.95, 1.10]**
Total events	1522		3374			

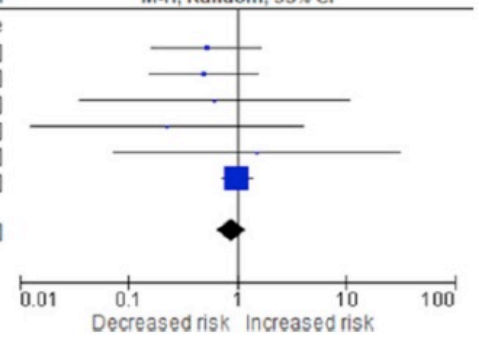
Heterogeneity: Tau² = 0.00; Chi² = 2.03, df = 4 (P = 0.73); I² = 0%
Test for overall effect: Z = 0.57 (P = 0.57)



B Haemorrhagic stroke

Study or Subgroup	Very low LDL level Events	Total	Control group Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
AMG 145	0	202	0	202		Not estimable
FOURIER	3	2669	50	23313	6.6%	0.52 [0.16, 1.68]
IMPROVE-IT	3	971	89	14310	6.7%	0.50 [0.16, 1.57]
JUPITER	0	767	8	8150	1.1%	0.62 [0.04, 10.82]
ODYSSEY OUTCOMES	0	730	6	2152	1.1%	0.23 [0.01, 4.02]
PROVE IT - TIMI 22	0	193	2	1463	1.0%	1.51 [0.07, 31.58]
REVEAL	72	15225	73	15224	83.6%	0.99 [0.71, 1.37]
Total (95% CI)		**20757**		**64814**	**100.0%**	**0.89 [0.66, 1.20]**
Total events	78		228			

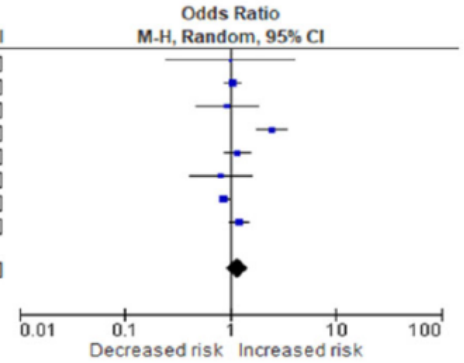
Heterogeneity: Tau² = 0.00; Chi² = 3.28, df = 5 (P = 0.66); I² = 0%
Test for overall effect: Z = 0.78 (P = 0.44)



A Diabetes mellitus

Study or Subgroup	Very low LDL level Events	Total	Control group Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
AMG 145	4	202	4	202	2.5%	1.00 [0.25, 4.05]
FOURIER	135	2669	1127	23313	17.3%	1.05 [0.87, 1.26]
GLAGOV	17	484	18	484	7.6%	0.94 [0.48, 1.85]
JUPITER	47	767	209	8150	14.2%	2.48 [1.79, 3.43]
ODYSSEY OUTCOMES	79	730	204	2152	15.3%	1.16 [0.88, 1.52]
ODYSSEY Pooled data	12	839	33	1894	7.7%	0.82 [0.42, 1.59]
REVEAL	807	15225	913	15224	18.6%	0.88 [0.80, 0.97]
SPIRE 1 and 2	139	6285	250	13697	16.7%	1.22 [0.99, 1.50]
Total (95% CI)		**27201**		**65116**	**100.0%**	**1.16 [0.91, 1.47]**
Total events	1240		2758			

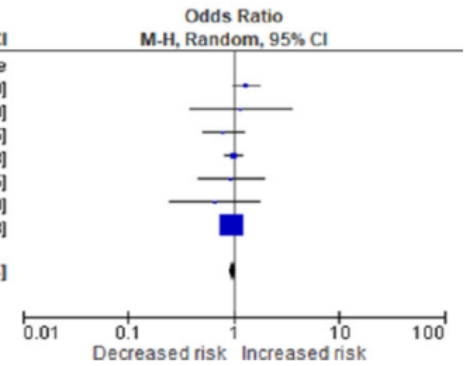
Heterogeneity: Tau² = 0.08; Chi² = 41.97, df = 7 (P < 0.00001); I² = 83%
Test for overall effect: Z = 1.21 (P = 0.23)



B Neurocognitive disorders

Study or Subgroup	Very low LDL level Events	Total	Control group Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
AMG 145	0	202	0	202		Not estimable
FOURIER	49	2669	325	23313	4.8%	1.32 [0.98, 1.79]
GLAGOV	7	484	6	484	0.4%	1.17 [0.39, 3.50]
IMPROVE-IT	20	971	370	14310	2.1%	0.79 [0.50, 1.25]
JUPITER	136	767	1431	8150	11.8%	1.01 [0.83, 1.23]
ODYSSEY OUTCOMES	10	730	31	2152	0.9%	0.95 [0.46, 1.95]
ODYSSEY Pooled data	5	839	17	1894	0.4%	0.66 [0.24, 1.80]
REVEAL	1503	15225	1566	15224	79.6%	0.96 [0.89, 1.03]
Total (95% CI)		**21887**		**65729**	**100.0%**	**0.97 [0.91, 1.04]**
Total events	1730		3746			

Heterogeneity: Tau² = 0.00; Chi² = 5.80, df = 6 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.83 (P = 0.41)

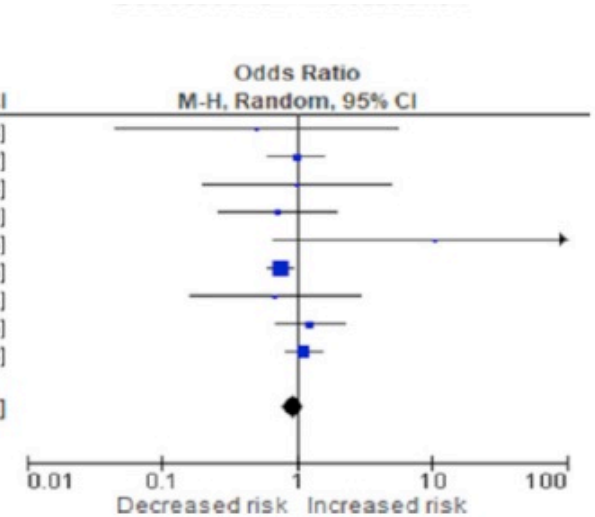


B Muscle disorders

Study or Subgroup	Very low LDL level Events	Total	Control group Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
AMG 145	1	202	2	202	0.6%	0.50 [0.04, 5.53]
FOURIER	18	2669	158	23313	13.2%	1.00 [0.61, 1.62]
GLAGOV	3	484	3	484	1.4%	1.00 [0.20, 4.98]
IMPROVE-IT	4	971	81	14310	3.5%	0.73 [0.27, 1.99]
JUPITER	1	767	1	8150	0.5%	10.64 [0.66, 170.25]
ODYSSEY Pooled data	116	839	328	1894	41.4%	0.77 [0.61, 0.96]
PROVE IT - TIMI 22	2	193	22	1463	1.7%	0.69 [0.16, 2.94]
REVEAL	25	15225	20	15224	9.5%	1.25 [0.69, 2.25]
SPIRE 1 and 2	63	6285	122	13697	28.2%	1.13 [0.83, 1.53]
Total (95% CI)		**27635**		**78737**	**100.0%**	**0.94 [0.77, 1.13]**
Total events	233		737			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 8.91$, $df = 8$ ($P = 0.35$); $I^2 = 10\%$

Test for overall effect: $Z = 0.69$ ($P = 0.49$)



PLAN

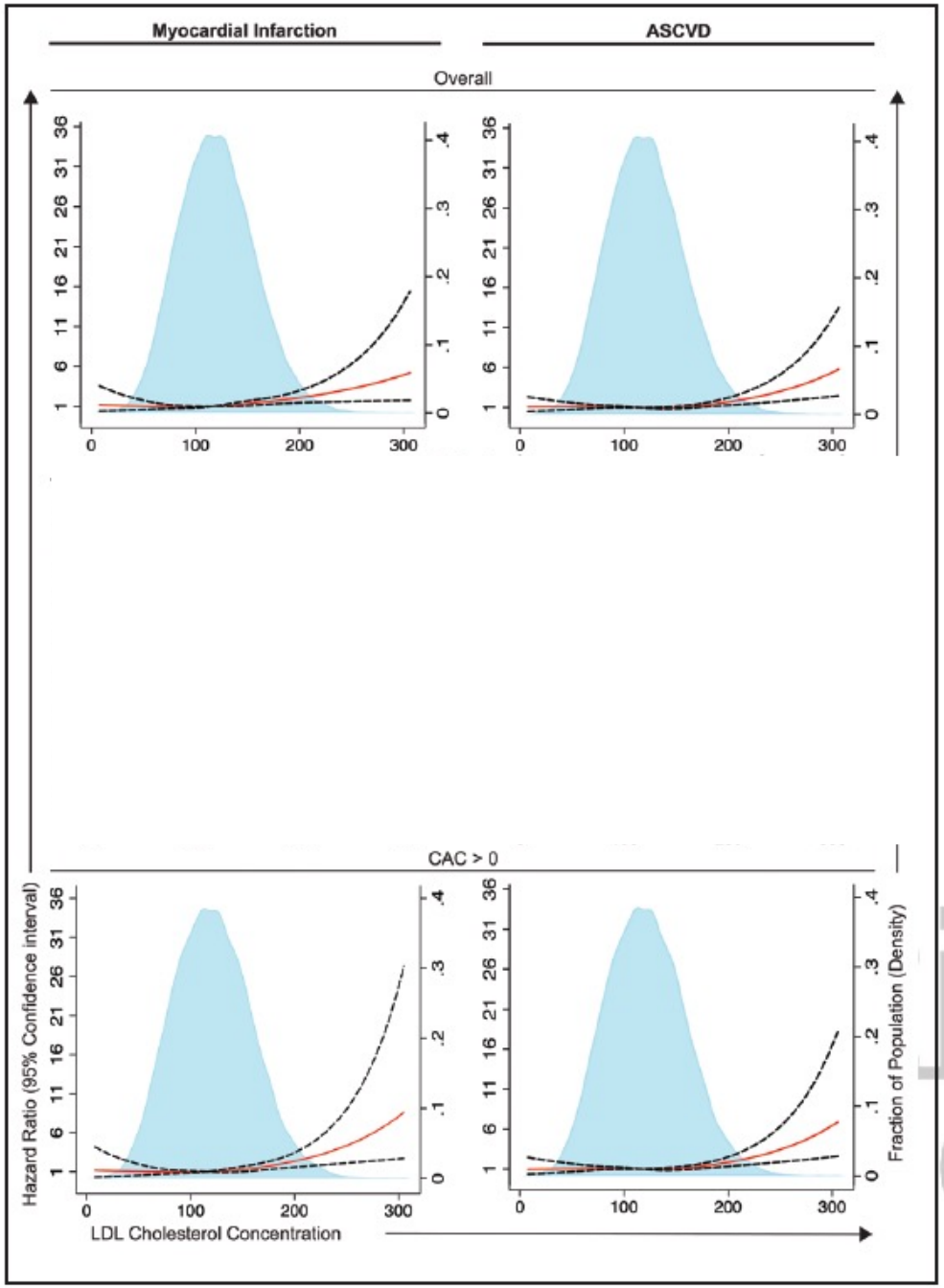
- Épidémiologie du LDL : jusqu'où le plus bas?
- **Une étude « dérangeante » sur le score calcique à zéro ?**
- Etude REPRIEVE : statines et SIDA
- Etude STOP-CA : statines et prévention cardiotoxicité anthracyclines
- Etude CLEAR-Outcomes: un nouvel arrivant
- Epidémiologie du diabète
- Diabète et maladies CV: de nouvelles recommandations
- Un regard vers le futur…

Circulation

ORIGINAL RESEARCH ARTICLE

Low-Density Lipoprotein Cholesterol Is Predominantly Associated With Atherosclerotic Cardiovascular Disease Events in Patients With Evidence of Coronary Atherosclerosis: The Western Denmark Heart Registry

Martin Bødtker Mortensen, MD, PhD*; Omar Dzaye, MD, MPH, PhD*; Hans Erik Bøtker, MD, DMSc;



research-article

Circulation

ORIGINAL RESEARCH ARTICLE

Low-Density Lipoprotein Cholesterol Is Predominantly Associated With Atherosclerotic Cardiovascular Disease Events in Patients With Evidence of Coronary Atherosclerosis: The Western Denmark Heart Registry

Être vieux avant d'être adulte?

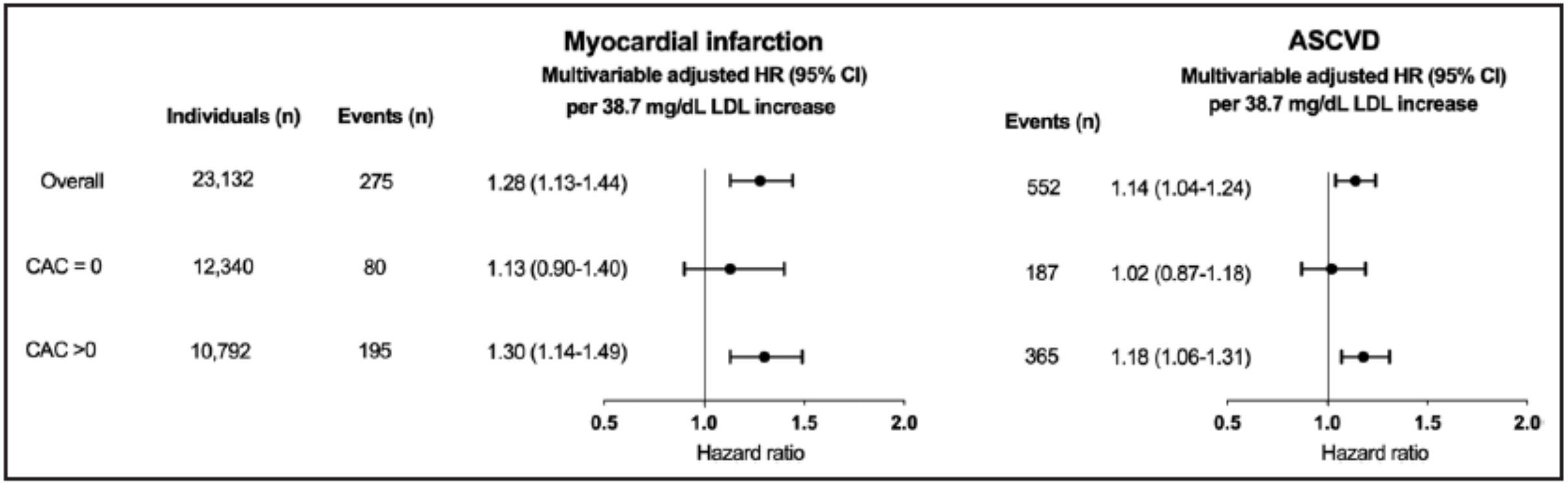


Figure 2. Association of 38.7 mg/dL higher low-density lipoprotein cholesterol level with development of myocardial infarction and atherosclerotic cardiovascular disease.

Analyses are shown in overall population and stratified by coronary artery calcium (CAC) groups in the Western Denmark Heart Registry.

PLAN

- Épidémiologie du LDL : jusqu'où le plus bas?
- Une étude « dérangeante » sur le score calcique à zéro ?
- **Etude REPRIEVE : statines et SIDA**
- Etude STOP-CA : statines et prévention cardiotoxicité anthracyclines
- Etude CLEAR-Outcomes: un nouvel arrivant
- Epidémiologie du diabète
- Diabète et maladies CV: de nouvelles recommandations
- Un regard vers le futur…

HIV + = risque CV x 2

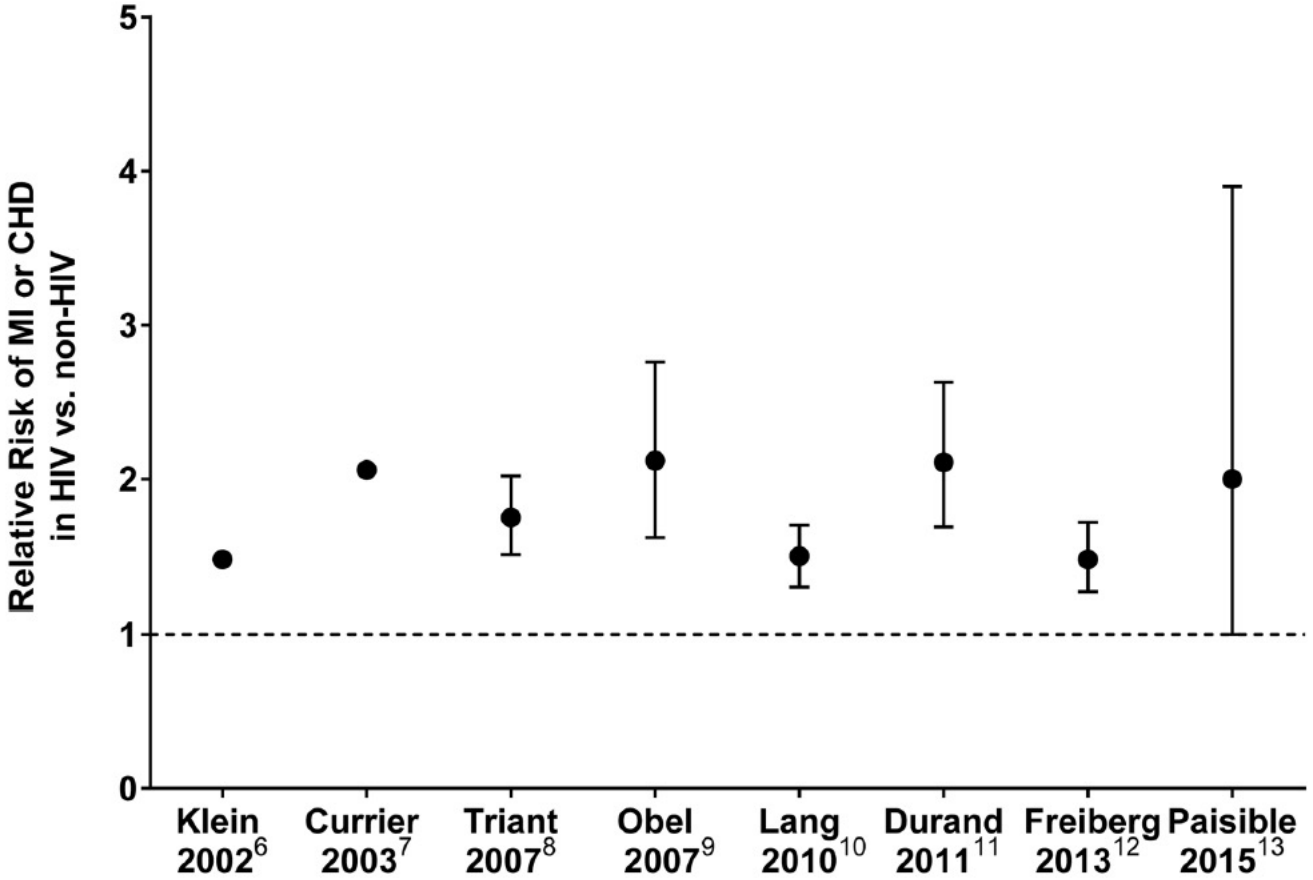


Figure 1. Summary of epidemiology studies investigating relative risk of cardiovascular disease in HIV patients vs. control subjects

Data are relative risk with 95% CI where available. Dotted line indicates relative risk of one.

Lancet Diabetes Endocrinol. 2016 July ; 4(7): 598–610. doi:10.1016/S2213-8587(15)00388-5.

Physiopathologie complications CV dans HIV +

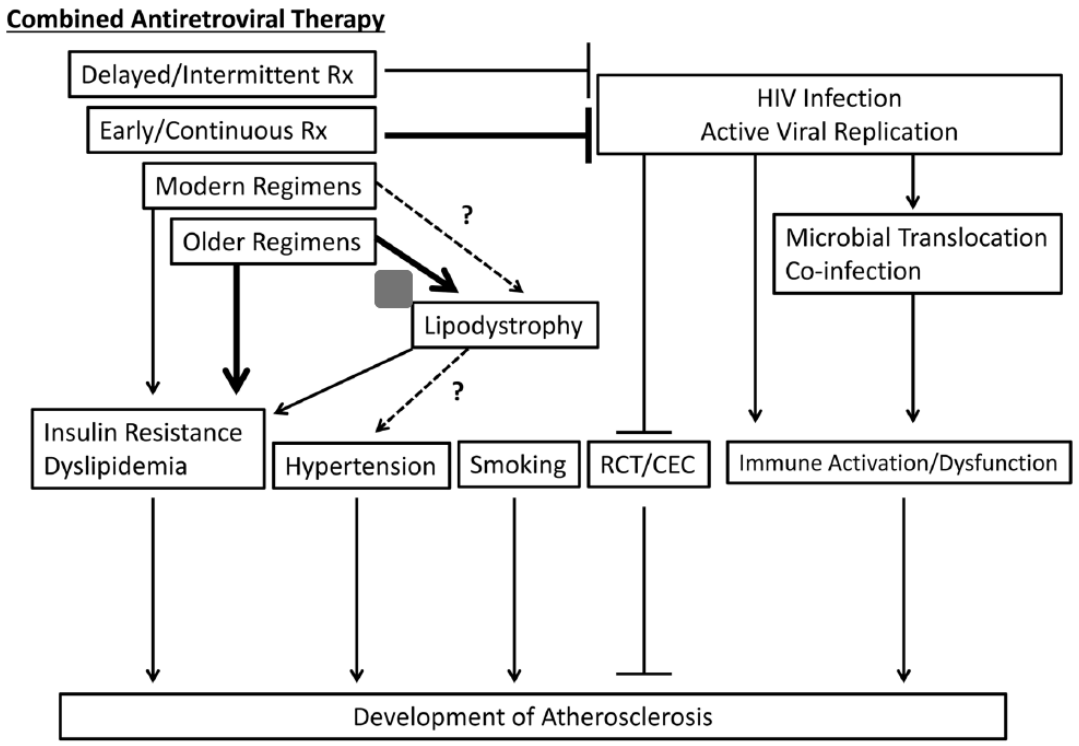


Figure 2. Pathophysiology of atherosclerosis in HIV-infected individuals
RCT = reverse cholesterol transport, CEC = cholesterol efflux capacity, Rx = treatment

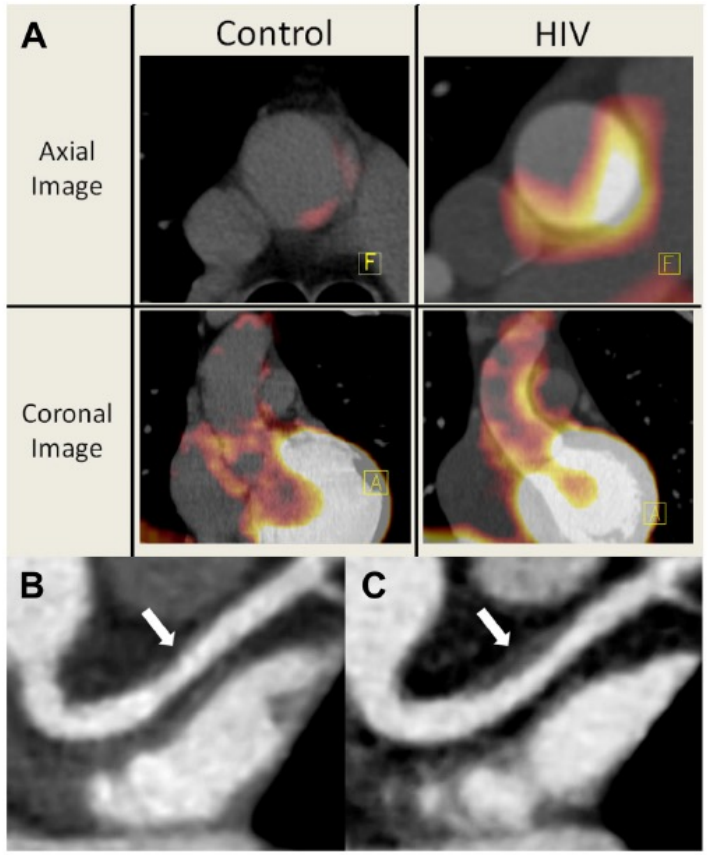


Figure 3. FDG/PET and Coronary Computed Tomography Angiography Images of Arterial Inflammation and Non-Calcified Plaque Progression in HIV patients

Lancet Diabetes Endocrinol. 2016 July ; 4(7): 598–610. doi:10.1016/S2213-8587(15)00388-5.

HIV + et risque CV : le problème

- x 2 quand HIV + vs HIV –

- sous-estimé par les équations de risque
  - car probable part inflammatoire donc mal corrélé aux FdR traditionnels

- Antirétroviraux majorent les FdR traditionnels

- Excès de risque non prévenu par la suppression du virus

Une statine peut-elle diminuer le risque CV
chez des patients HIV + “estimés à faible risque CV”?

Etude REPRIEVE

Randomized Trial to Prevent Vascular Events in HIV

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 24, 2023 VOL. 389 NO. 8

Pitavastatin to Prevent Cardiovascular Disease in HIV Infection

Steven K. Grinspoon, M.D., Kathleen V. Fitch, M.S.N., Markella V. Zanni, M.D., Carl J. Fichtenbaum, M.D., Triin Umbleja, M.S., Judith A. Aberg, M.D., Edgar T. Overton, M.D., Carlos D. Malvestutto, M.D., M.P.H.,

Critère d'inclusion :

- infection HIV à risque CV faible à modéré
- 40 à 75 ans
- traitement en cours par antirétroviraux

N = 7 769

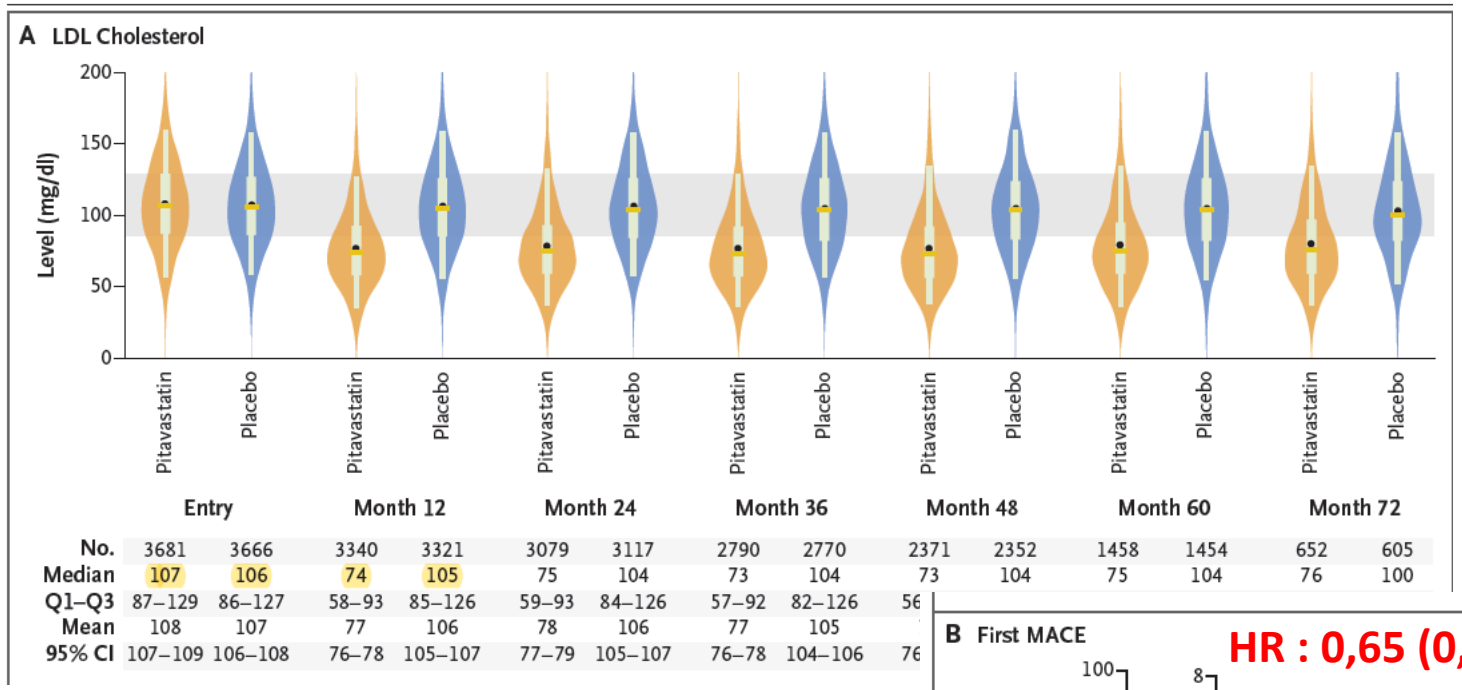
Pitavastatine 4 mg/J vs placebo

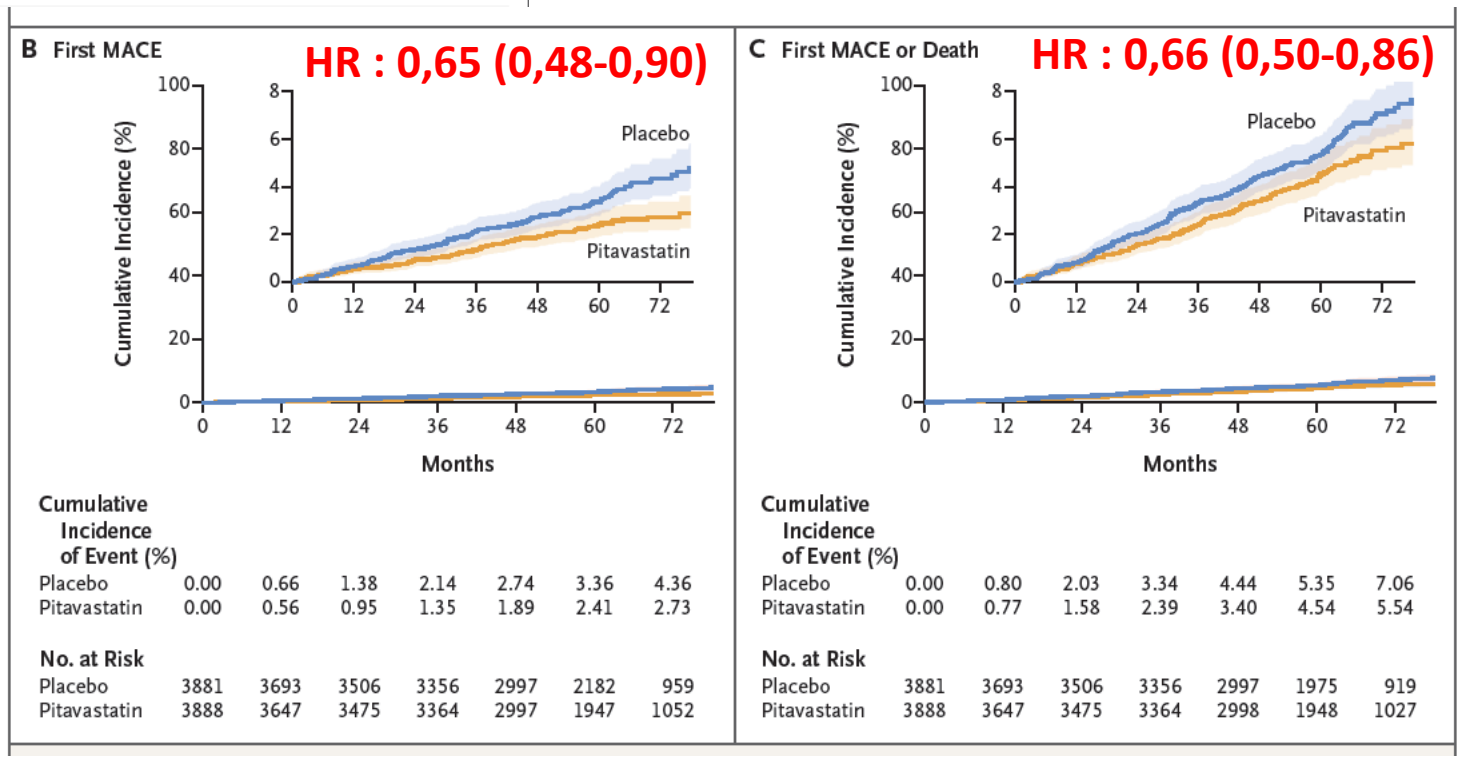
Critère primaire : décès CV, IDM, hospitalisation pour angor instable, AVC, AIT, ischémie artérielle, revascularisation ou décès toute cause

Durée Moyenne: 5,1 ans (arrêt premature pour efficacité)

Table 1. Characteristics of the Participants at Baseline.*

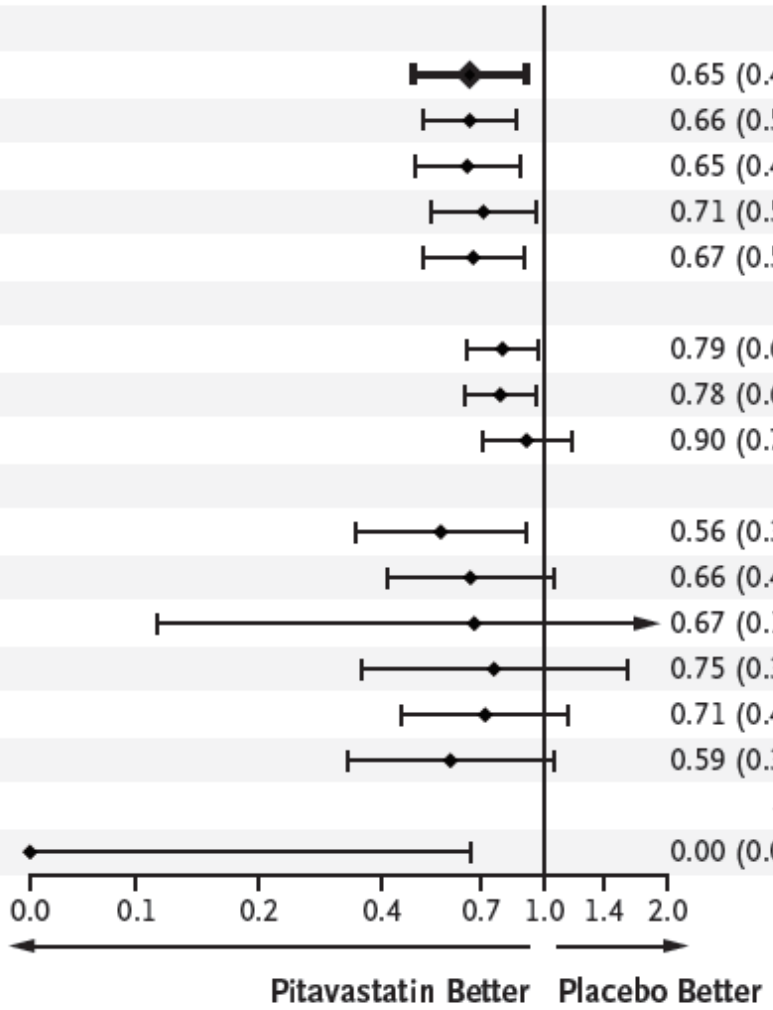
Characteristic	Pitavastatin (N = 3888)	Placebo (N = 3881)	Total (N = 7769)
Region of global burden of disease — no. (%)			
High income	2044 (52.6)	2051 (52.8)	4095 (52.7)
Latin America or Caribbean	709 (18.2)	714 (18.4)	1423 (18.3)
Southeast or East Asia	304 (7.8)	286 (7.4)	590 (7.6)
South Asia	246 (6.3)	258 (6.6)	504 (6.5)
Sub-Saharan Africa	585 (15.0)	572 (14.7)	1157 (14.9)
Age			
Median (IQR) — yr	50 (45–55)	50 (45–55)	50 (45–55)


A LDL Cholesterol
Level (mg/dl)
200
150
100
50
0
Pitavastatin
Placebo
Entry
Month 12
Month 24
Month 36
Month 48
Month 60
Month 72
No. 3681 3666 3340 3321 3079 3117 2790 2770 2371 2352 1458 1454 652 605
Median 107 106 74 105 75 104 73 104 73 104 75 104 76 100
Q1–Q3 87–129 86–127 58–93 85–126 59–93 84–126 57–92 82–126 56
Mean 108 107 77 106 78 106 77 105
95% CI 107–109 106–108 76–78 105–107 77–79 105–107 76–78 104–106 76


B First MACE
HR : 0,65 (0,48-0,90)
Cumulative Incidence (%)
Placebo
Pitavastatin
Months
Cumulative Incidence of Event (%)
Placebo 0.00 0.66 1.38 2.14 2.74 3.36 4.36
Pitavastatin 0.00 0.56 0.95 1.35 1.89 2.41 2.73
No. at Risk
Placebo 3881 3693 3506 3356 2997 2182 959
Pitavastatin 3888 3647 3475 3364 2997 1947 1052
C First MACE or Death
HR : 0,66 (0,50-0,86)
Cumulative Incidence (%)
Placebo
Pitavastatin
Months
Cumulative Incidence of Event (%)
Placebo 0.00 0.80 2.03 3.34 4.44 5.35 7.06
Pitavastatin 0.00 0.77 1.58 2.39 3.40 4.54 5.54
No. at Risk
Placebo 3881 3693 3506 3356 2997 1975 919
Pitavastatin 3888 3647 3475 3364 2998 1948 1027

A Estimated Treatment Effect

Subgroup	Pitavastatin (N=3888)	Placebo (N=3881)	Hazard Ratio (95% CI)
	no./1000 person-yr (no. of events)		
Primary outcome and supporting analyses			
First MACE	4.81 (89)	7.32 (136)	0.65 (0.48 to 0.90)
First MACE including vital status follow-up	4.75 (90)	7.22 (137)	0.66 (0.50 to 0.86)
First confirmed MACE	3.83 (71)	5.92 (110)	0.65 (0.48 to 0.87)
First MACE (as-treated analysis)	4.44 (77)	6.25 (107)	0.71 (0.53 to 0.95)
First MACE (per-protocol analysis)	4.54 (80)	6.77 (120)	0.67 (0.50 to 0.89)
Secondary outcomes and supporting analyses			
First MACE or death	9.18 (170)	11.63 (216)	0.79 (0.65 to 0.96)
First MACE or death including vital status follow-up	9.13 (173)	11.70 (222)	0.78 (0.64 to 0.95)
Death from any cause	6.17 (116)	6.83 (129)	0.90 (0.70 to 1.16)
Individual components of MACE			
First cardiac ischemia or myocardial infarction	1.40 (26)	2.51 (47)	0.56 (0.34 to 0.90)
First cerebrovascular event (stroke or TIA)	1.56 (29)	2.36 (44)	0.66 (0.41 to 1.05)
First peripheral arterial ischemia	0.11 (2)	0.16 (3)	0.67 (0.11 to 4.02)
Death from cardiovascular causes	0.64 (12)	0.85 (16)	0.75 (0.36 to 1.59)
Death from cardiovascular or undetermined causes	1.60 (30)	2.24 (42)	0.71 (0.45 to 1.14)
First cardiac catheterization or revascularization	0.97 (18)	1.66 (31)	0.59 (0.33 to 1.05)
First carotid or cerebrovascular revascularization	0.00 (0)	0.00 (0)	—
First peripheral arterial revascularization	0.00 (0)	0.32 (6)	0.00 (0.00 to 0.66)



Event type		Total (N=225)	Pitavastatin (N=89)	Placebo (N=136)
All Cerebrovascular Events (Stroke or TIA) — no. (%)		**72 (32)**	**29 (33)**	**43 (32)**
Stroke	Ischemic	43 (19)	15 (17)	28 (21)
	Hemorrhagic	10 (4)	2 (2)	8 (6)
	Undetermined	2 (1)	1 (1)	1 (1)
Transient Ischemic Attack (TIA)		17 (8)	11 (12)	6 (4)
All Cardiac Ischemia or MI Events — no. (%)		**71 (32)**	**25 (28)**	**46 (34)**
Myocardial Infarction	Type 1	50 (22)	16 (18)	34 (25)
	Type 2	13 (6)	7 (8)	6 (4)
Unstable Angina		8 (4)	2 (2)	6 (4)
All Deaths — no. (%)		**63 (28)**	**28 (31)**	**35 (26)**
CV Death	Sudden Cardiac Death	16 (7)	8 (9)	8 (6)
	Cardiovascular Causes	1 (0)	1 (1)	0 (0)
	Cardiovascular Hemorrhage	1 (0)	0 (0)	1 (1)
	Heart Failure	1 (0)	1 (1)	0 (0)
Undetermined		44 (20)	18 (20)	26 (19)

REPRIEVE: effets indésirables

Table 2. Adverse Events.

Event	Pitavastatin (N=3888)		Placebo (N=3881)		Incidence Rate Ratio (95% CI)*
	No. with Event	Incidence Rate (95% CI) *no./100 person-yr*	No. with Event	Incidence Rate (95% CI) *no./100 person-yr*	
Nonfatal serious adverse event	695	4.16 (3.86–4.48)	694	4.13 (3.84–4.45)	1.01 (0.91–1.12)
Diabetes mellitus†	206	1.13 (0.99–1.30)	155	0.84 (0.72–0.99)	1.35 (1.09–1.66)
Myalgia, muscle weakness, or myopathy of grade ≥3 or treatment-limiting‡	91	0.49 (0.40–0.61)	53	0.28 (0.22–0.37)	1.74 (1.24–2.45)
Rhabdomyolysis of grade ≥3 or treatment-limiting	3	0.02 (0.01–0.05)	4	0.02 (0.01–0.06)	0.75 (0.17–3.37)§
Alanine aminotransferase elevation of grade ≥3	11	0.06 (0.03–0.11)	8	0.04 (0.02–0.08)	1.38 (0.56–3.43)§
Any adverse event¶	1304	8.88 (8.41–9.38)	1256	8.37 (7.92–8.84)	1.06 (0.98–1.15)

REPRIEVE: statines quand HIV +

- 50 ans en moyenne: 0,5 % d'IDM ou d'AVC par an
- Possible de réduire ce risque de 40 % avec une statine diminuant de 35 % le LDL
- Validation de la pitavastatine en matière de rapport bénéfice-risque
- NB: à explorer complément d'étude évaluant l'inflammation coronaire et les paramètres d'activation immune et inflammatoire

PLAN

- Épidémiologie du LDL : jusqu'où le plus bas?
- Une étude « dérangeante » sur le score calcique à zéro ?
- Etude REPRIEVE : statines et SIDA
- **Etude STOP-CA : statines et prévention cardiotoxicité anthracyclines**
- Etude CLEAR-Outcomes: un nouvel arrivant
- Epidémiologie du diabète
- Diabète et maladies CV: de nouvelles recommandations
- Un regard vers le futur…

JAMA | Original Investigation

Atorvastatin for Anthracycline-Associated Cardiac Dysfunction
The STOP-CA Randomized Clinical Trial

Tomas G. Neilan, MD, MPH; Thiago Quinaglia, MD, PhD; Takeshi Onoue, MD; Syed S. Mahmood, MD, MPH; Zsofia D. Drobni, MD; Hannah K. Gilman, BS; Amanda Smith, MS; Julius C. Heemelaar, MD; Priya Brahmbhatt, BS; Jor Sam Ho, MPH; Supraja Sama, BS; Jakub Svoboda, MD; Donna S. Neuberg, ScD; Jeremy S. Abramson, MD; Ephraim P. Hochberg, MD; Jefferey A. Barnes, MD, PhD; Philippe Armand, MD; Eric D. Jacobsen, MD; Caron A. Jacobson, MD; Austin I. Kim, MD; Jacob D. Soumerai, MD; Yuchi Han, MD; Robb S. Friedman, MD; Ann S. Lacasce, MD; Bonnie Ky, MD; Dan Landsburg, MD; Sunita Nasta, MD; Raymond Y. Kwong, MD; Michael Jerosch-Herold, PhD; Robert A. Redd, MS; Lanqi Hua, MS; James L. Januzzi, MD; Aarti Asnani, MD;

The STOP-CA Trial

Statins TO Prevent the Cardiotoxicity associated with Anthracyclines

Méthode: ETC, double aveugle, multicentrique

Intervention : **atorvastatine vs placebo**

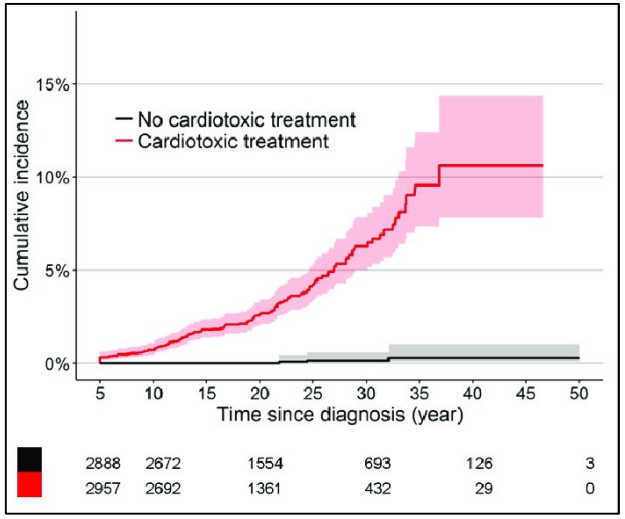
Critère évalué : dysfonction cardiaque

Population évaluée : lymphome traité par anthracyclines

Anthracyclines – Cardiac Toxicity

- Cardiac injury with anthracyclines (e.g., doxorubicin, epirubicin, idarubicin) **begins with the 1st cycle of chemotherapy**.[1]

- Depending on the population, time from therapy, and the diagnostic criteria, there is an **up to ~10-15-fold increased risk of heart failure with anthracyclines**.[2, 3]

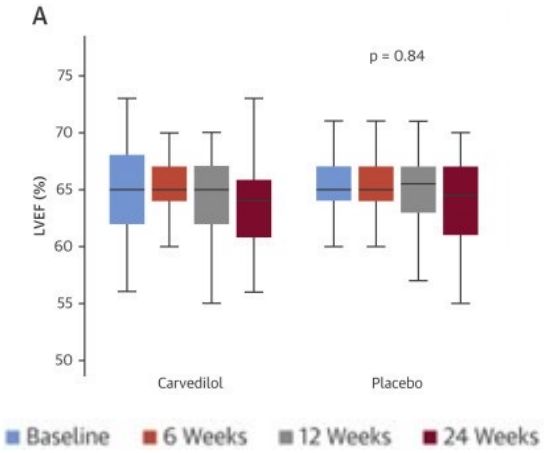


Ewer MS, Journal of Clinical Oncology, 1984;[1] Lieke Feijen EAM, Journal of the American Heart Association, 2019;[2] Larsen CM, JAMA Network Open, 2023;[3]

What Primary Prevention Strategies have been Tested?

- There is one cardioprotectant (dexrazoxane, Zinecard) approved by the FDA to reduce anthracycline-associated cardiotoxicity with limited widespread use due to potential secondary effects.

- Other therapies, principally neurohormonal blockade, have been tested with modest effects or have been limited by hemodynamic factors.[1, 2, 3, 4, 5]



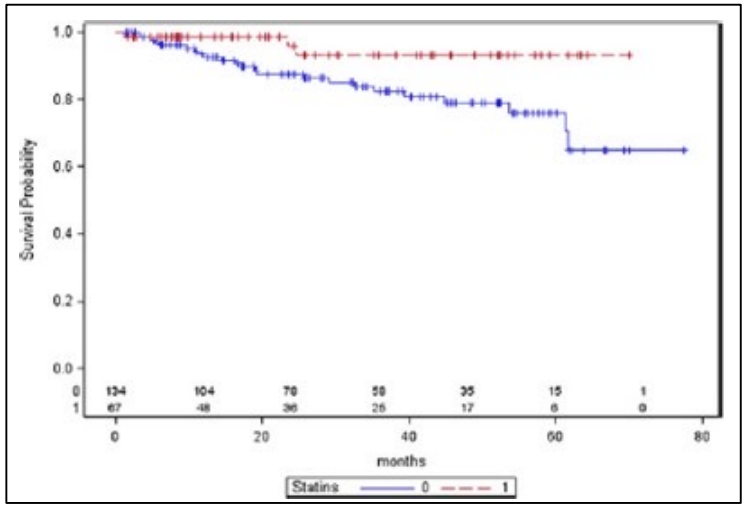
Bosch X, Journal of the American College of Cardiology, 2013;[1] Gulati G, European Heart Journal, 2016;[2] Avila MS, Journal of the American College of Cardiology, 2018;[3] Pituskin, E, Journal of Clinical Oncology, 2016;[4] Guglin M, Journal of the American College of Cardiology, 2019;[5]

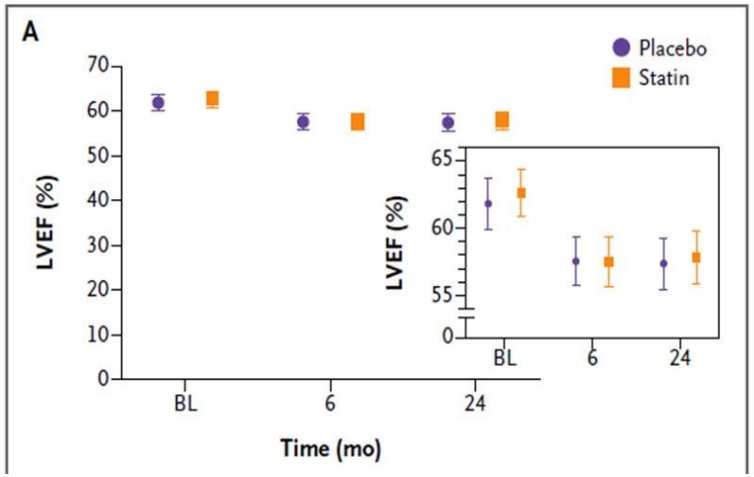
Why Statins/Atorvastatin?

- Experimental data,[1,2] retrospective studies,[3,4] and a small randomized trial [5] have reported either attenuation of anthracycline-associated LV dysfunction or a lower rate of heart failure.

HOWEVER

- A recent multicenter randomized trial of atorvastatin vs placebo did not show preservation of the LVEF at 24 months.[6] The 24-month LVEF was 58% in both the atorvastatin and placebo group.

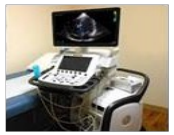




Riad, A, Cancer Research, 2009;[1] Ramanjaneyulu SV, Journal of Physiology and Biochemistry, 2013;[2] Seicean S, Journal of the American College of Cardiology, 2013;[3] Abdel-Qadir H, Journal of the American Heart Assoc, 2021;[4], Acar Z, Journal of the American College of Cardiology, 2011;[5] Hundley WG, New England Journal of Medicine Evidence, 2022;[6]

STOP-CA Primary Study Procedures and Intervention

Pretreatment


Randomized to atorvastatin or placebo for 12 months
40mg/j

First chemotherapy infusion

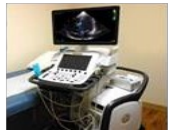
• Complete blood count
• AST and ALT
• Basic metabolic profile
• Glucose
• + non-fasting lipid profile at 0 and 3 months

1 month safety labs

3-month safety labs

6-month safety labs

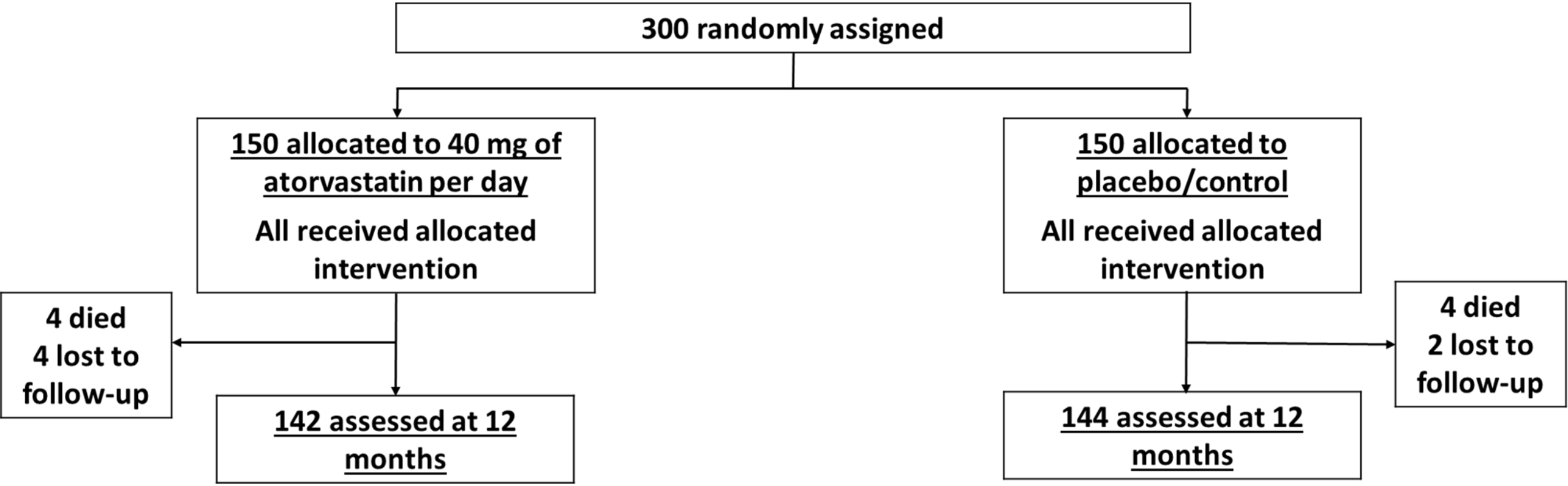
12-months


STOP-CA trial

- **Primary outcome: proportion who had a decline in the LVEF of ≥ 10% to less than 55%.**

- Secondary outcome: proportion who had a decline in the LVEF of ≥ 5% to less than 55%

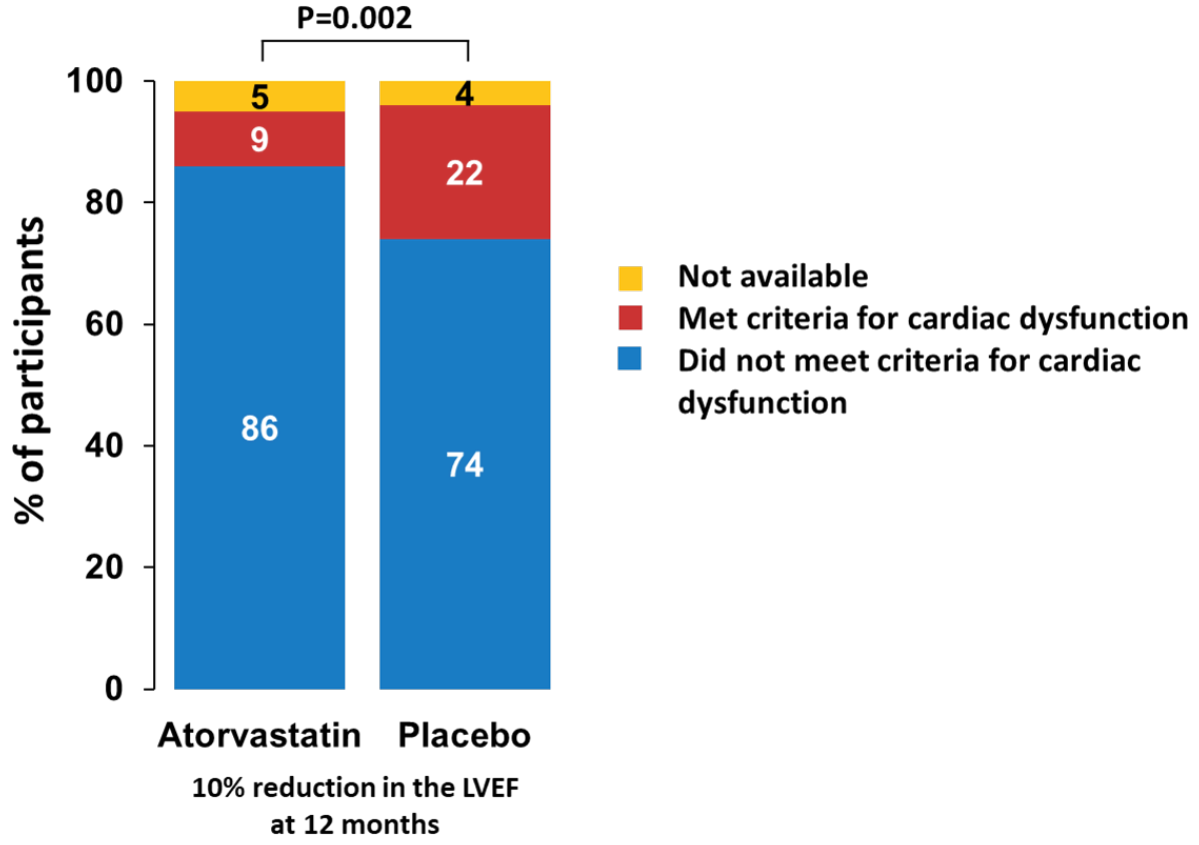


STOP-CA Primary Endpoint Results

proportion who had a decline in the LVEF of ≥ 10% to less than 55%

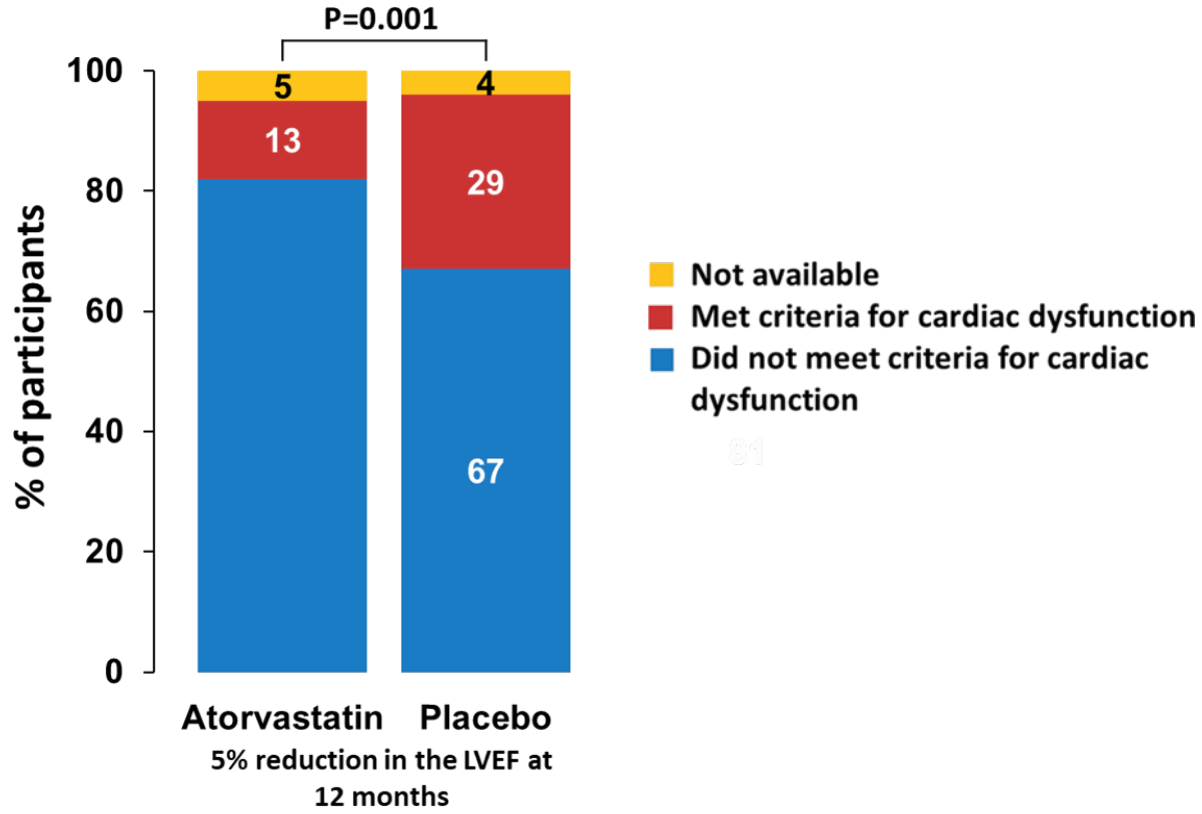
Incidence at 12 months

- **9 % in the atorvastatin group**
- **22 % in the placebo group**
- **P=0.002**



STOP-CA Secondary Endpoint Results

- Decline in the LVEF of ≥ 5% from prior to chemotherapy to a final value of < 55% at 12 months:
  - 64 participants (21%) in the entire cohort
  - 13% in the atorvastatin group
  - 29% in the placebo group
  - P=0.001



STOP-CA : en synthèse

- La façon d'évaluer le critère primaire peut expliquer le résultat: n'est-il pas le mieux adapté?
- Le bénéfice est là mais, sur un critère intermédiaire (la FEVG)
- La population : **lymphome et anthracyclines** : donc OK pour ces patients

Nécessité de plus d'études et d'un suivi plus long

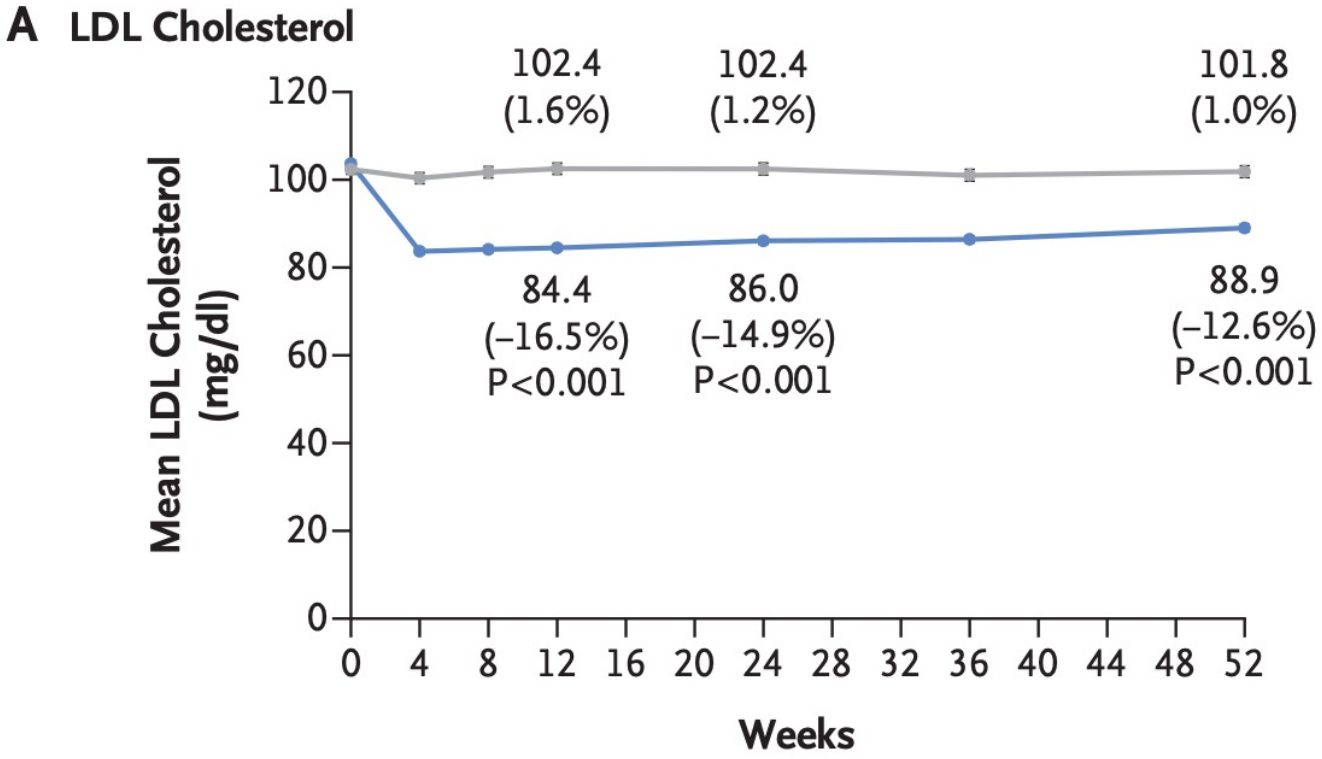
PLAN

- Épidémiologie du LDL : jusqu'où le plus bas?
- Une étude « dérangeante » sur le score calcique à zéro ?
- Etude REPRIEVE : statines et SIDA
- Etude STOP-CA : statines et prévention cardiotoxicité anthracyclines
- **Etude CLEAR-Outcomes: un nouvel arrivant**
- Epidémiologie du diabète
- Diabète et maladies CV: de nouvelles recommandations
- Un regard vers le futur…

Bempedoic acid reduces LDL-C by 15%

CLEAR-HARMONY

- Oral, once-daily, prodrug
- Inhibits ATP-citrate lyase
- Clinical ASCVD (97%) or heFH
- 2,330 patients, LDL-C >70
- 99% statin, 7% ezetimibe
- BA 180 mg daily vs. placebo
- 52 weeks



CLEAR Outcomes Trial Design

Statin intolerance

- Intolerance to 2 or more statins **or** 1 statin if **unwilling to attempt** a second statin or advised by physician to not attempt second statin
  Very low dose statin therapy permitted (< lowest approved dose).

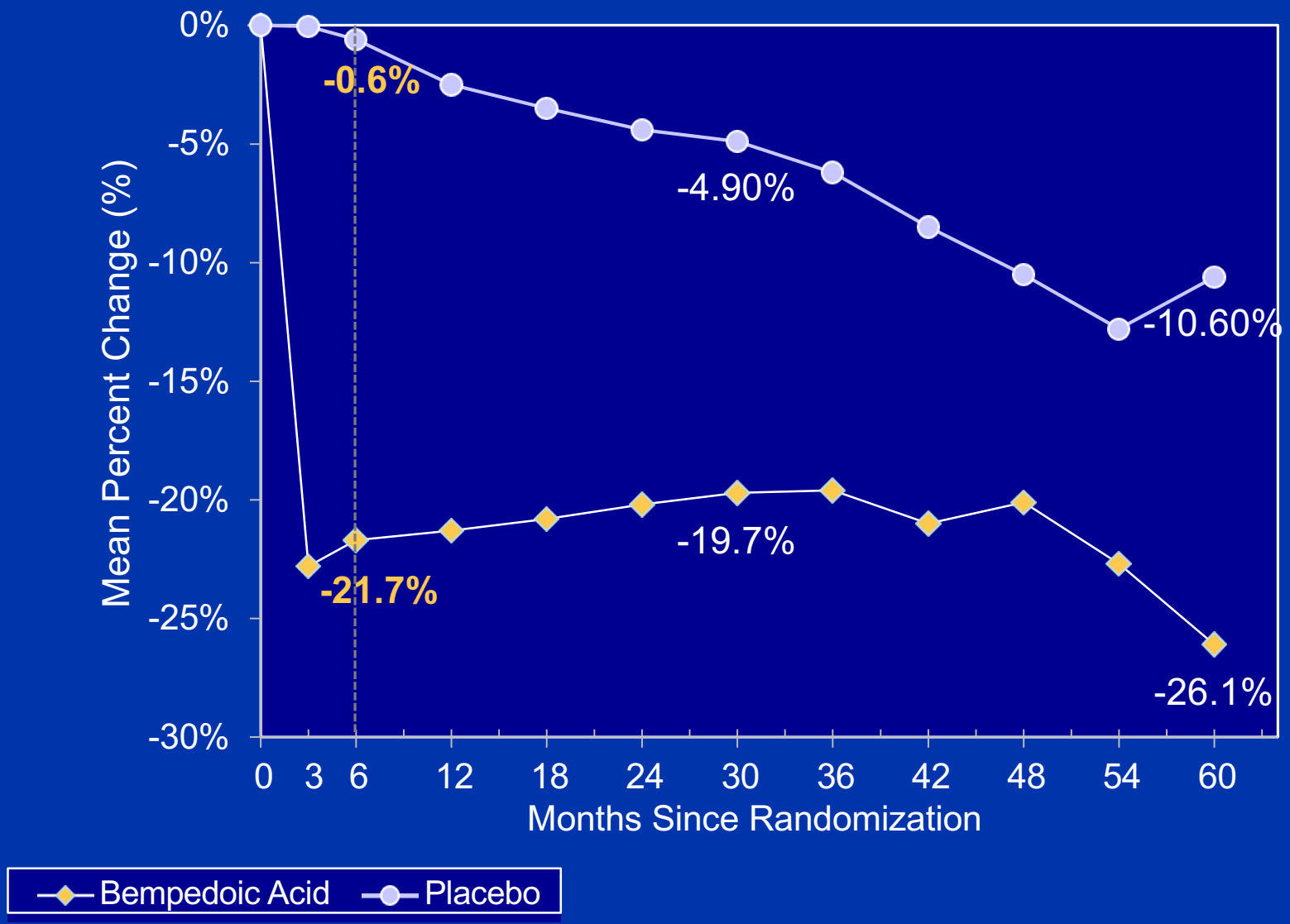
Primary or secondary prevention patients with LDL-C ≥ 100 mg/dL

→ Bempedoic Acid 180 mg/day

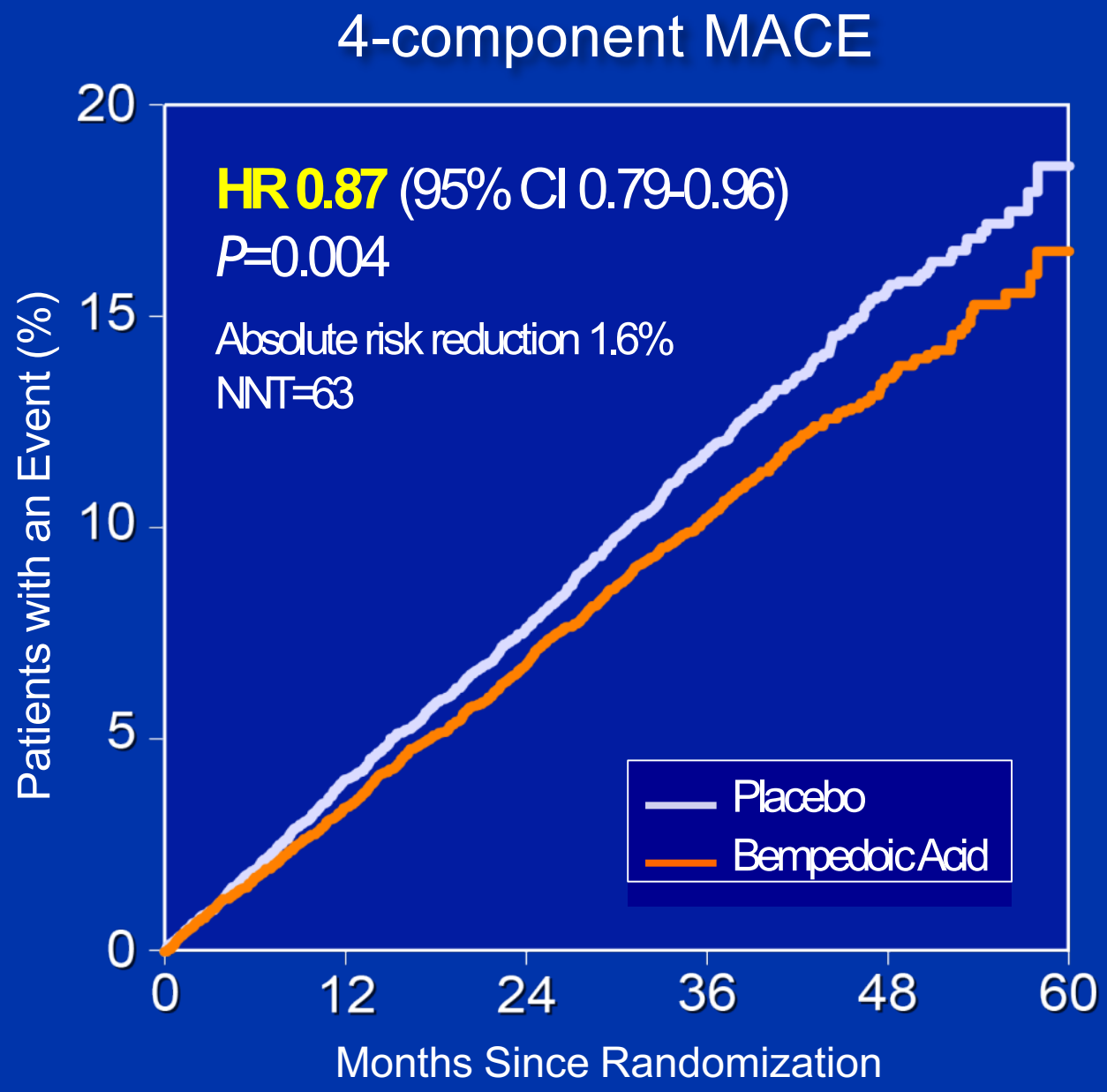
→ Matching Placebo

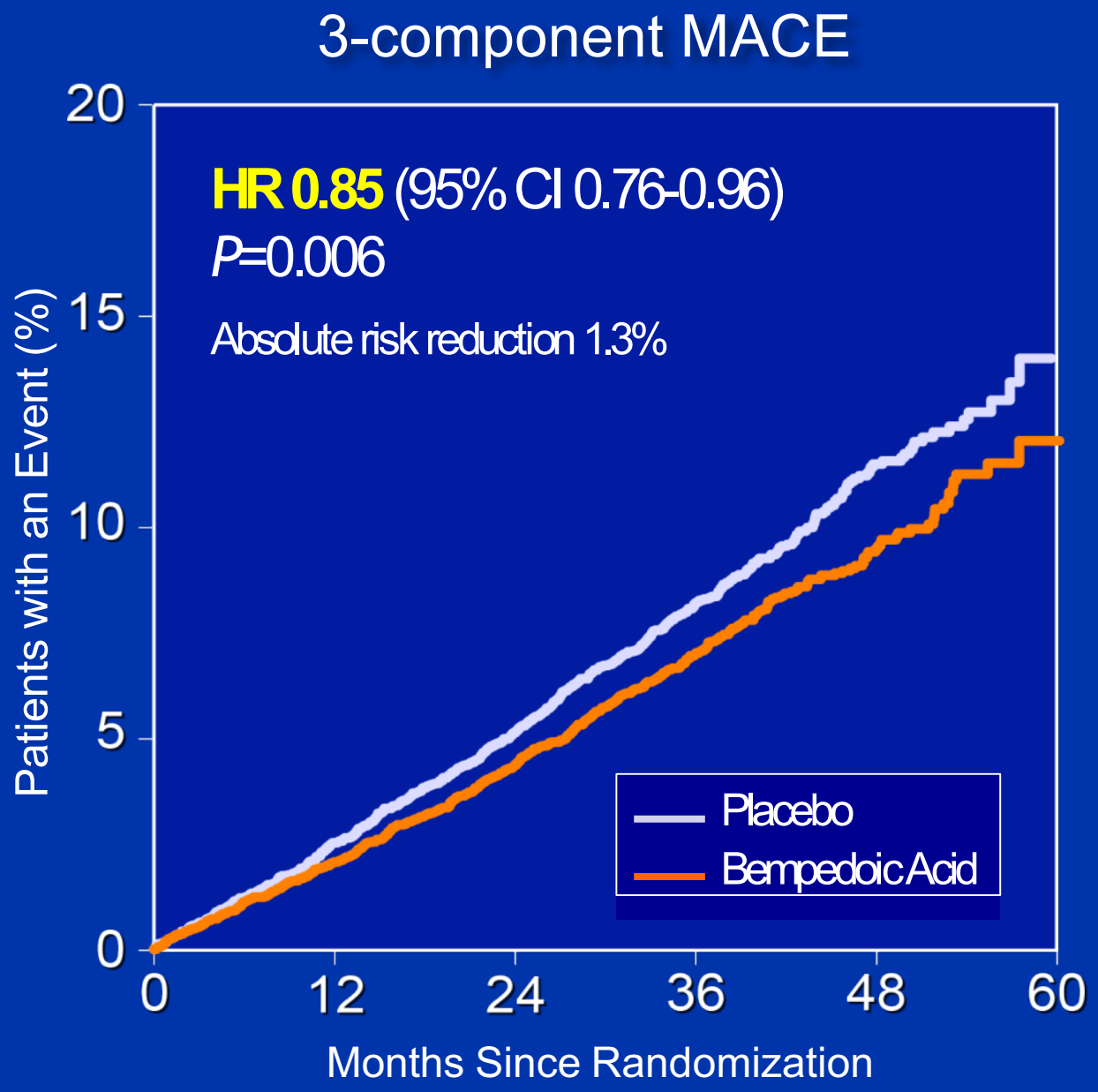
- ≥1,620 primary 4-component MACE
- ≥810 key secondary 3-component MACE
- ≥24 months follow up

Percent Change in LDL-C over Time



Primary and First Key Secondary Cardiovascular End Points





Investigator-Reported Adverse Effects

Characteristic	Bempedoic Acid N=7001	Placebo N=6964
Serious Treatment Emergent Adverse event	25.2%	24.9%
Adverse event leading to drug discontinuation	10.8%	10.4%
Any muscle disorder	15.0%	15.4%
New onset diabetes	16.1%	17.1%
Elevated hepatic enzymes	4.5%	3.0%
Prespecified renal events	11.5%	8.6%
Gout	3.1%	2.1%
Cholelithiasis	2.2%	1.2%
Adjudicated tendon rupture	1.2%	0.9%

Bempedoic acid

- Agit sur la synthèse du cholestérol via ATP-citrate lyase ou ACL, en amont de l'HMG-CoA
- Action hypocholestérolémiante et anti-inflammatoire

	LDL reduction
Alone	20 %
+ ezetimibe	38 %
+ ezetimibe + atorvastatine 10 mg	60 %

PLAN

- Épidémiologie du LDL : jusqu'où le plus bas?
- Une étude « dérangeante » sur le score calcique à zéro ?
- Etude REPRIEVE : statines et SIDA
- Etude STOP-CA : statines et prévention cardiotoxicité anthracyclines
- Etude CLEAR-Outcomes: un nouvel arrivant
- **Epidémiologie du diabète**
- Diabète et maladies CV: de nouvelles recommandations
- Un regard vers le futur…

Epidémiologie du diabète

Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021

*GBD 2021 Diabetes Collaborators**

Summary

Background Diabetes is one of the leading causes of death and disability worldwide, and affects people regardless of country, age group, or sex. Using the most recent evidentiary and analytical framework from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD), we produced location-specific, age-specific, and sex-specific estimates of diabetes prevalence and burden from 1990 to 2021, the proportion of type 1 and type 2 diabetes in 2021, the proportion of the type 2 diabetes burden attributable to selected risk factors, and projections of diabetes prevalence

Lancet 2023; 402: 203–34
Published Online
June 22, 2023
https://doi.org/10.1016/
S0140-6736(23)01301-6

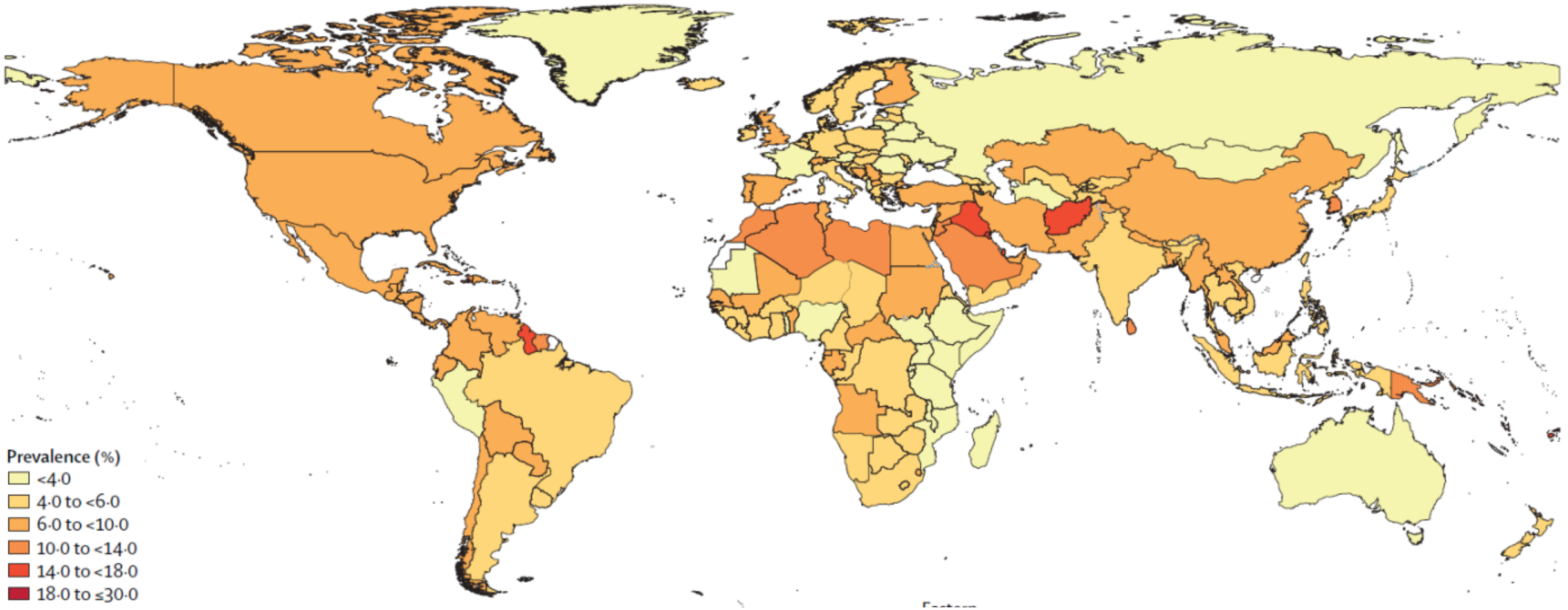
Epidémiologie du diabète

En 2021

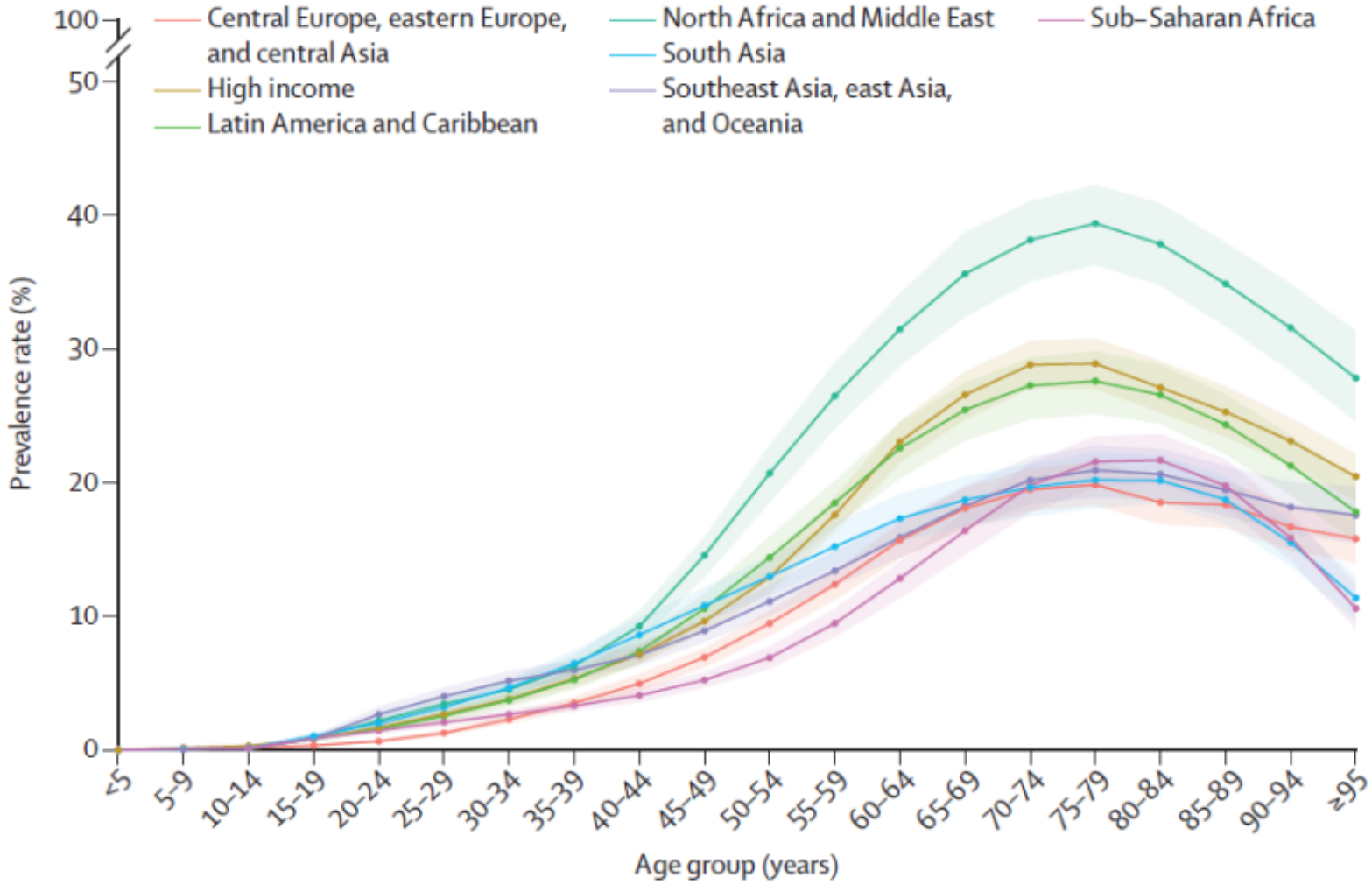
- **529 millions** de diabétiques dans le monde
- Diabète de type 2 dans **96 %** des cas

- **Prévalence globale : 6,1 %**
  - Afrique-moyen-Orient : 9,3 % (Qatar : 76,1 % chez les plus de 75 ans)
  - Océanie: 12,3 %
  - Prévalence globale projetée en 2050 : 10 %

Epidémiologie du diabète
Prévalence selon la région du monde



Epidémiologie du diabète
Prévalence par âge selon la région du monde



PLAN

- Épidémiologie du LDL : jusqu'où le plus bas?
- Une étude « dérangeante » sur le score calcique à zéro ?
- Etude REPRIEVE : statines et SIDA
- Etude STOP-CA : statines et prévention cardiotoxicité anthracyclines
- Etude CLEAR-Outcomes: un nouvel arrivant
- Epidémiologie du diabète
- **Diabète et maladies CV: de nouvelles recommandations**
- Un regard vers le futur…

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes

Official ESC Guidelines slide set

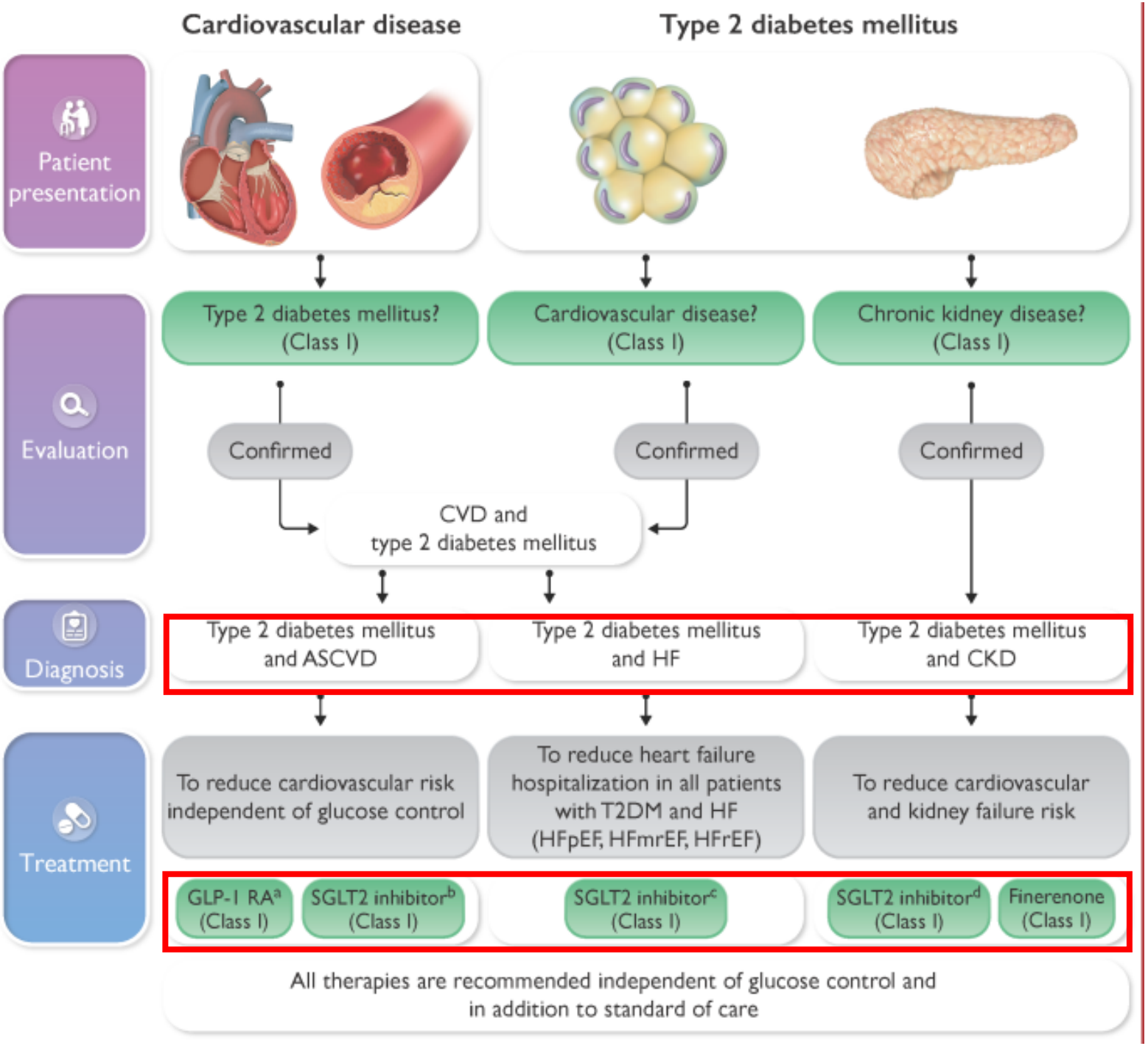
ESC
European Society of Cardiology

DIABETE

- Et insuffisance cardiaque
- Et Maladie rénale chronique
- Et Maladie athérothrombotique
- Aucun

DIABETE

- **Et insuffisance cardiaque**
- **Et Maladie rénale chronique**
- **Et Maladie athérothrombotique**
- Aucun



Chez tout diabétique

A toute consultation

Rechercher des éléments pour

- une maladie athérothrombotique
- une insuffisance cardiaque
- une maladie rénale chronique

Car il y a des traitements qui améliorent le pronostic

DIABETE

- **Et insuffisance cardiaque**
- Et Maladie rénale chronique
- Et Maladie athérothrombotique
- Aucun

New recommendations (9)

Recommendations	Class	Level
Heart failure and diabetes		
Evaluation for heart failure in diabetes		
If HF is suspected, it is recommended to measure BNP/NT-proBNP.	I	B
Systematic survey for HF symptoms and/or signs of HF is recommended at each clinical encounter in all patients with diabetes.	I	C
Diagnostic tests in all patients with suspected heart failure		
12-lead ECG is recommended.	I	C
Transthoracic echocardiography is recommended.	I	C
Chest radiography (X-ray) is recommended.	I	C
Routine blood tests for comorbidities are recommended, including full blood count, urea, creatinine and electrolytes, thyroid function, lipids, and iron status (ferritin and TSAT).	I	C

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

New recommendations (11)

Recommendations	Class	Level
Other treatments indicated in selected patients with HFrEF (NYHA class II–IV) and diabetes		
Hydralazine and isosorbide dinitrate should be considered in self-identified Black patients with diabetes and LVEF ≤35% or with an LVEF <45% combined with a dilated LV in NYHA class III–IV despite treatment with an ACE-I (or ARNI), a beta-blocker, and an MRA, to reduce the risk of HF hospitalization and death.	IIa	B
Digoxin may be considered in patients with symptomatic HFrEF in sinus rhythm despite treatment with sacubitril/valsartan or an ACE-I, a beta-blocker, and an MRA, to reduce the risk of hospitalization.	IIb	B
Heart failure treatments in patients with diabetes and LVEF >40%		
Empagliflozin or dapagliflozin are recommended in patients with T2DM and LVEF >40% (HFmrEF and HFpEF) to reduce the risk of HF hospitalization or CV death.	I	A

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

DIABETE

- Et insuffisance cardiaque
- **Et Maladie rénale chronique**
- Et Maladie athérothrombotique
- Aucun

New recommendations (13)

Recommendations	Class	Level
Chronic kidney disease and diabetes		
Intensive LDL-C lowering with statins or a statin/ezetimibe combination is recommended.	I	A
A SGLT2 inhibitor (canagliflozin, empagliflozin, or dapagliflozin) is recommended in patients with T2DM and CKD with an eGFR ≥20 mL/min/1.73 m^2 to reduce the risk of CVD and kidney failure.	I	A
Finerenone is recommended in addition to an ACE-I or ARB in patients with T2DM and eGFR >60 mL/min/1.73 m^2 with a UACR ≥30 mg/mmol (≥300 mg/g), or eGFR 25–60 mL/min/1.73 m^2 and UACR ≥3 mg/mmol (≥30 mg/g) to reduce CV events and kidney failure.	I	A
Low-dose ASA (75–100 mg o.d.) is recommended in patients with CKD and ASCVD.	I	A

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

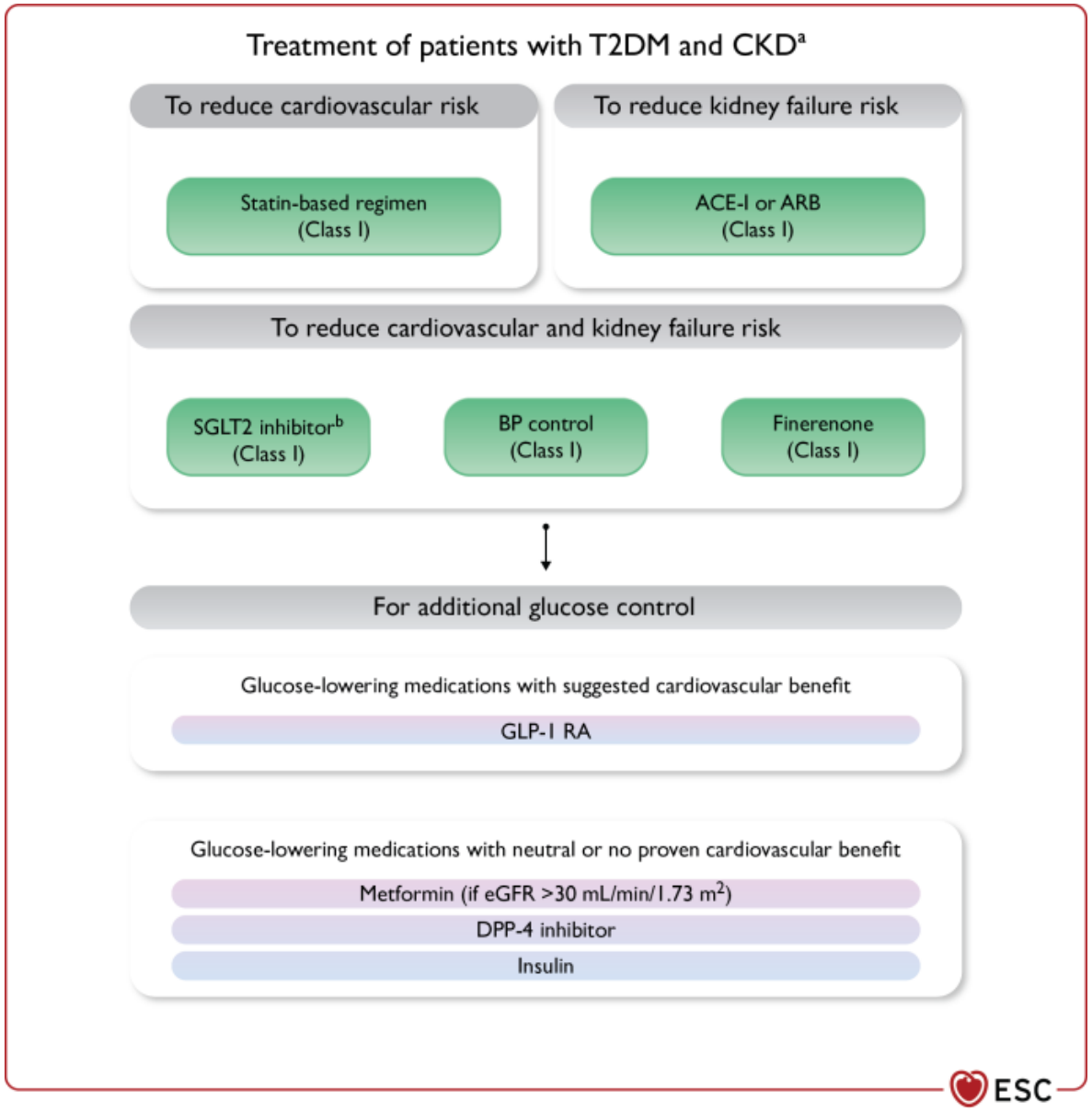
Revised recommendations (9)

2019	Class	Level	2023	Class	Level
Chronic kidney disease and diabetes					
Treatment with the GLP-1 RAs liraglutide and semaglutide is associated with a lower risk of renal endpoints, and should be considered for diabetes treatment if eGFR is >30 mL/min/1.73 m^2.	**IIa**	**B**	A GLP-1 RA is recommended at an eGFR >15 mL/min/1.73 m^2 to achieve adequate glycaemic control, due to low risk of hypoglycaemia and beneficial effects on weight, CV risk, and albuminuria.	**I**	**A**

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

Figure 18

Pharmacological management to reduce cardiovascular or kidney failure risk in patients with type 2 diabetes and chronic kidney disease



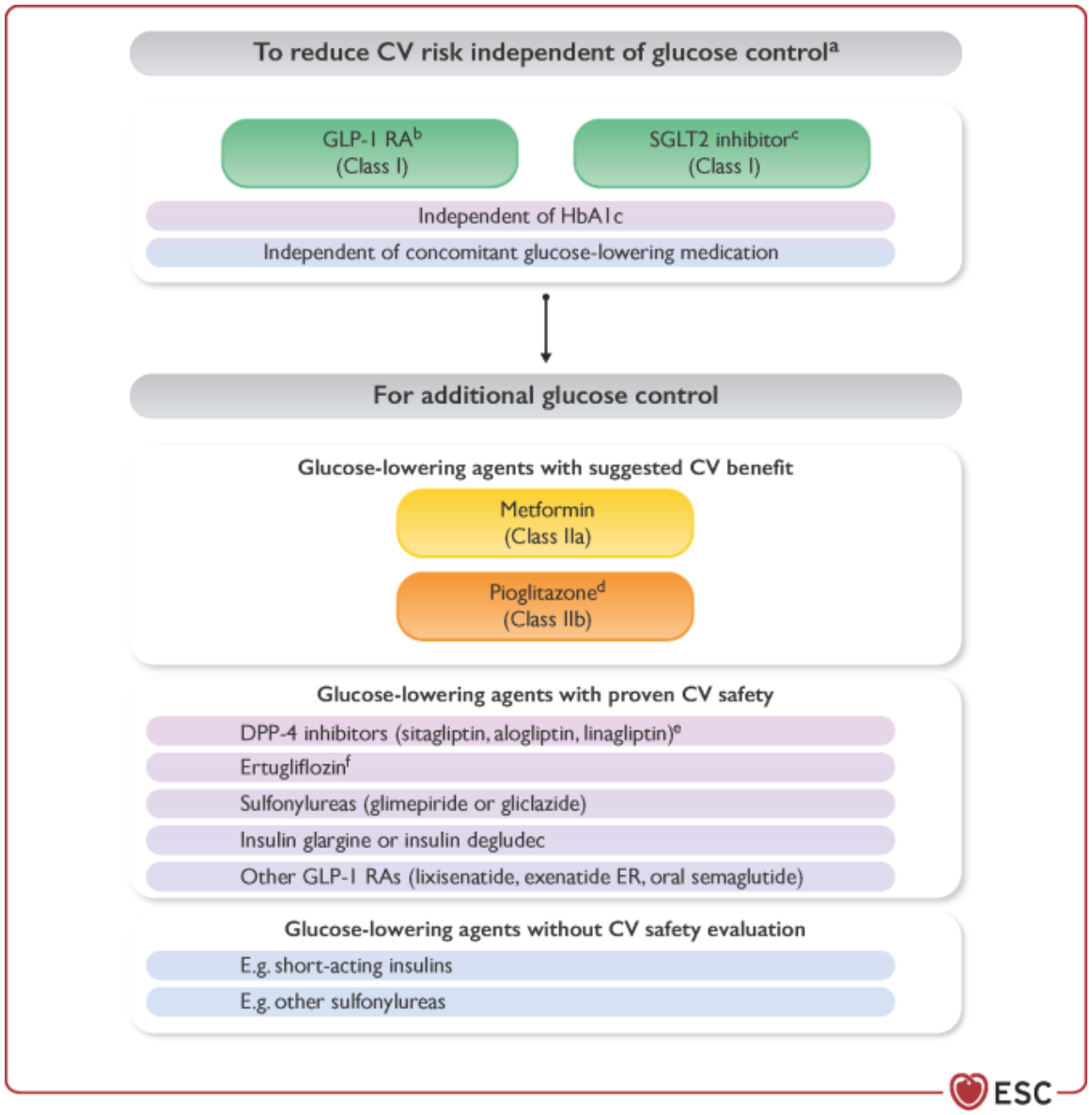
2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

DIABETE

- Et insuffisance cardiaque
- Et Maladie rénale chronique
- **Et Maladie athérothrombotique**
- Aucun

Figure 8

Glucose-lowering treatment for patients with type 2 diabetes and atherosclerotic cardiovascular disease to reduce cardiovascular risk



2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

DIABETE

- Et insuffisance cardiaque
- Et Maladie rénale chronique
- Et Maladie athérothrombotique
- **Aucun**

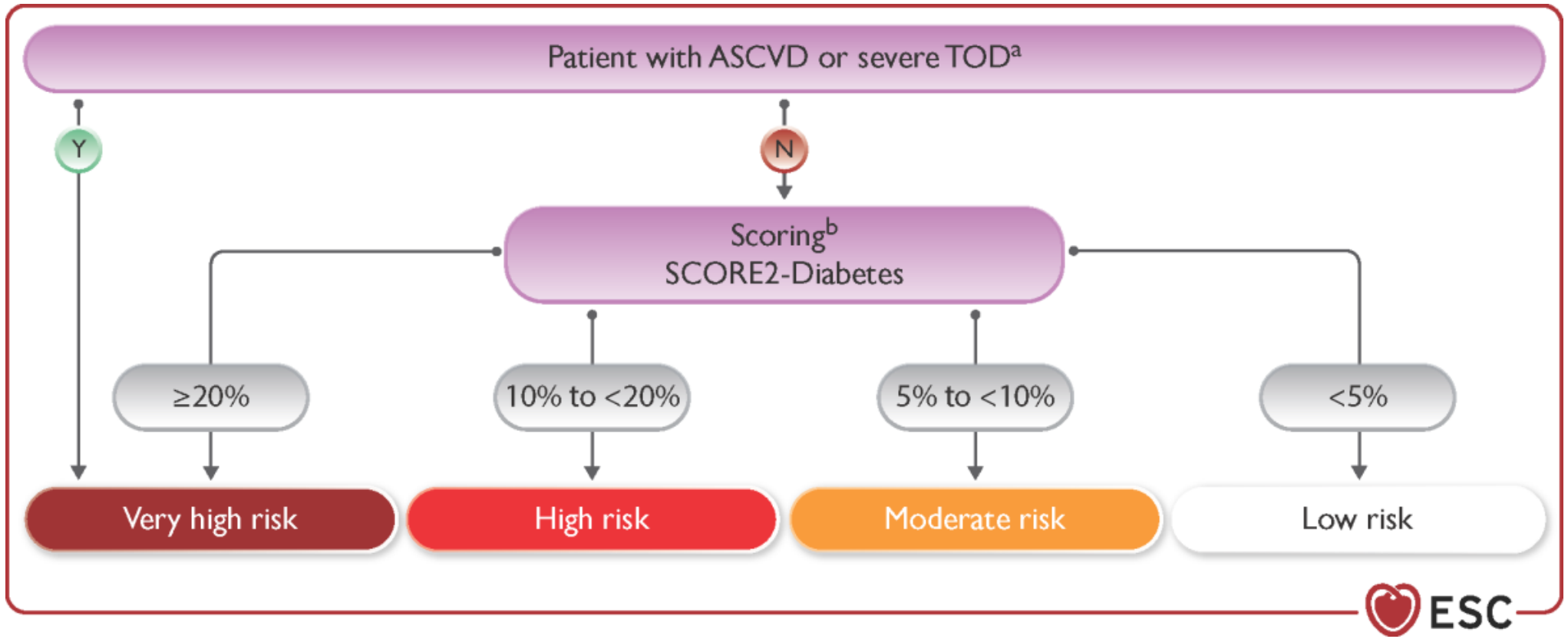
New recommendations (1)

Recommendations	Class	Level
Cardiovascular risk assessment in diabetes		
In patients with T2DM without symptomatic ASCVD or severe TOD, it is recommended to estimate 10-year CVD risk via SCORE2-Diabetes.	I	B
Weight reduction in patients with diabetes		
It is recommended that individuals living with overweight or obesity aim to reduce weight and increase physical exercise to improve metabolic control and overall CVD risk profile.	I	A
Glucose-lowering medications with effects on weight loss (e.g. GLP-1 RAs) should be considered in patients with overweight or obesity to reduce weight.	IIa	B
Bariatric surgery should be considered for high and very high risk patients with BMI ≥35 kg/m^2 (≥Class II) when repetitive and structured efforts of lifestyle changes combined with weight-reducing medications do not result in maintained weight loss.	IIa	B

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

Figure 3

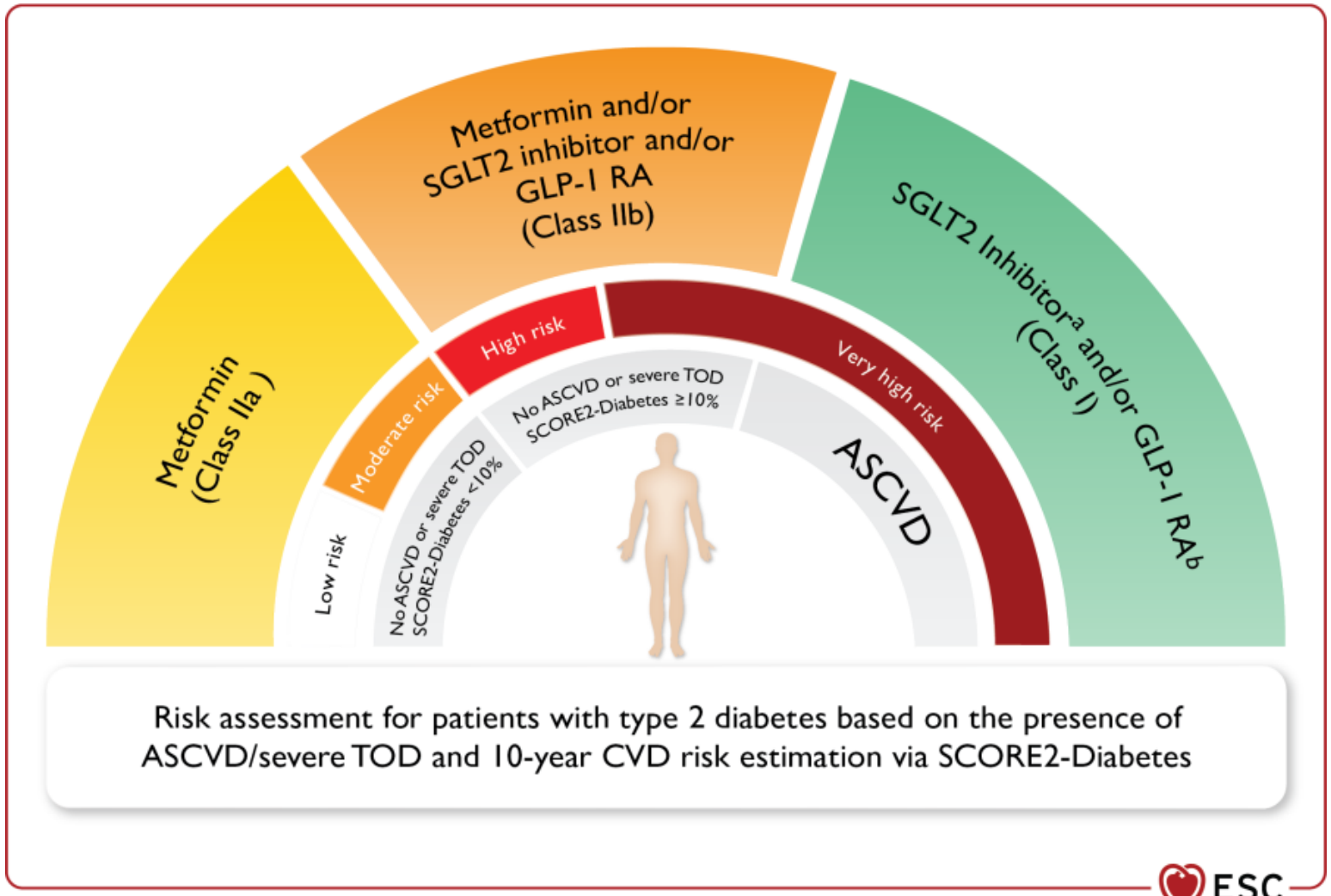
Cardiovascular risk categories in patients with type 2 diabetes



2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

Figure 7

Glucose-lowering treatment for patients with type 2 diabetes to reduce cardiovascular risk based on the presence of ASCVD/severe target-organ damage and 10-year cardiovascular disease risk estimation via SCORE2-Diabetes



2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

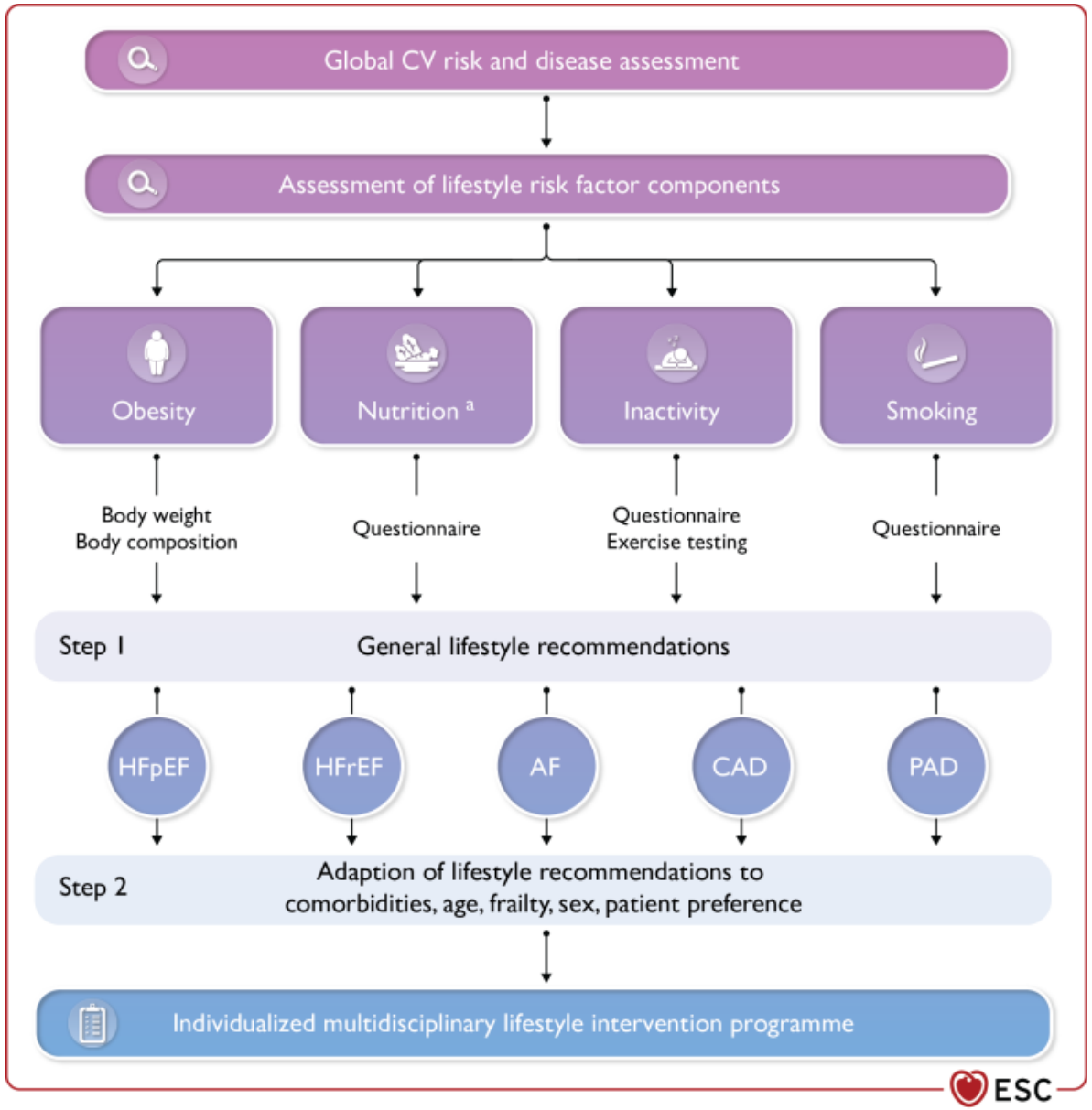
Recommendation for glucose-lowering treatment for patients with type 2 diabetes without ASCVD or severe TOD to reduce cardiovascular risk

Recommendations	Class	Level
In patients with T2DM without ASCVD or severe TOD at low or moderate risk, treatment with metformin should be considered to reduce CV risk.	IIa	C
In patients with T2DM without ASCVD or severe TOD at high or very high risk, treatment with metformin may be considered to reduce CV risk.	IIb	C
In patients with T2DM without ASCVD or severe TOD but with a calculated 10-year CVD risk≥10%, treatment with a SGLT2 inhibitor or GLP-1 RA may be considered to reduce CV risk.	IIb	C

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

Figure 13

Assessment of lifestyle risk-factor components and stepwise lifestyle recommendations in patients with diabetes

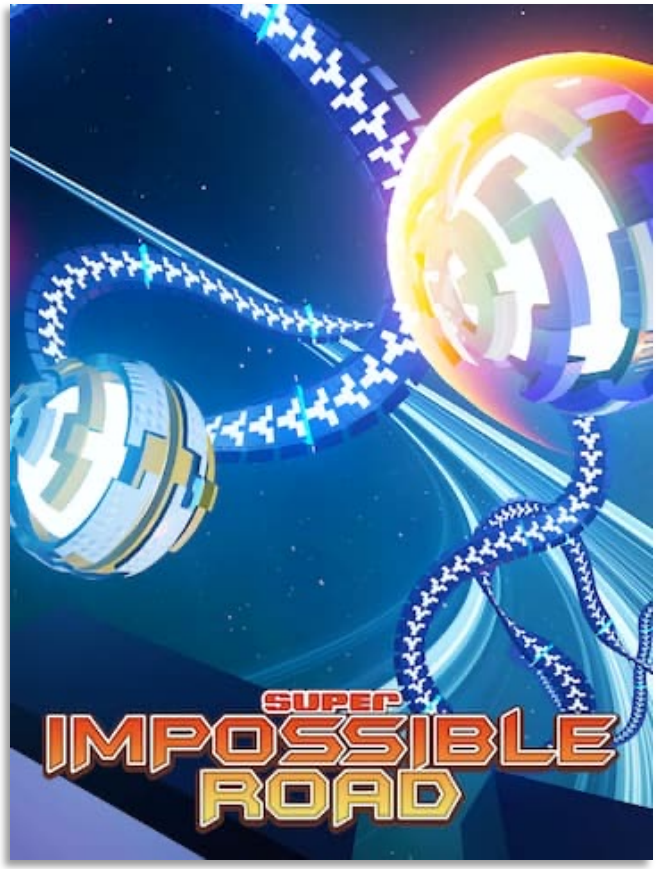


2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)

PLAN

- Épidémiologie du LDL : jusqu'où le plus bas?
- Une étude « dérangeante » sur le score calcique à zéro ?
- Etude REPRIEVE : statines et SIDA
- Etude STOP-CA : statines et prévention cardiotoxicité anthracyclines
- Etude CLEAR-Outcomes: un nouvel arrivant
- Epidémiologie du diabète
- Diabète et maladies CV: de nouvelles recommandations
- **Un regard vers le futur…**

Les méthodes: vers une action sur les **gènes**

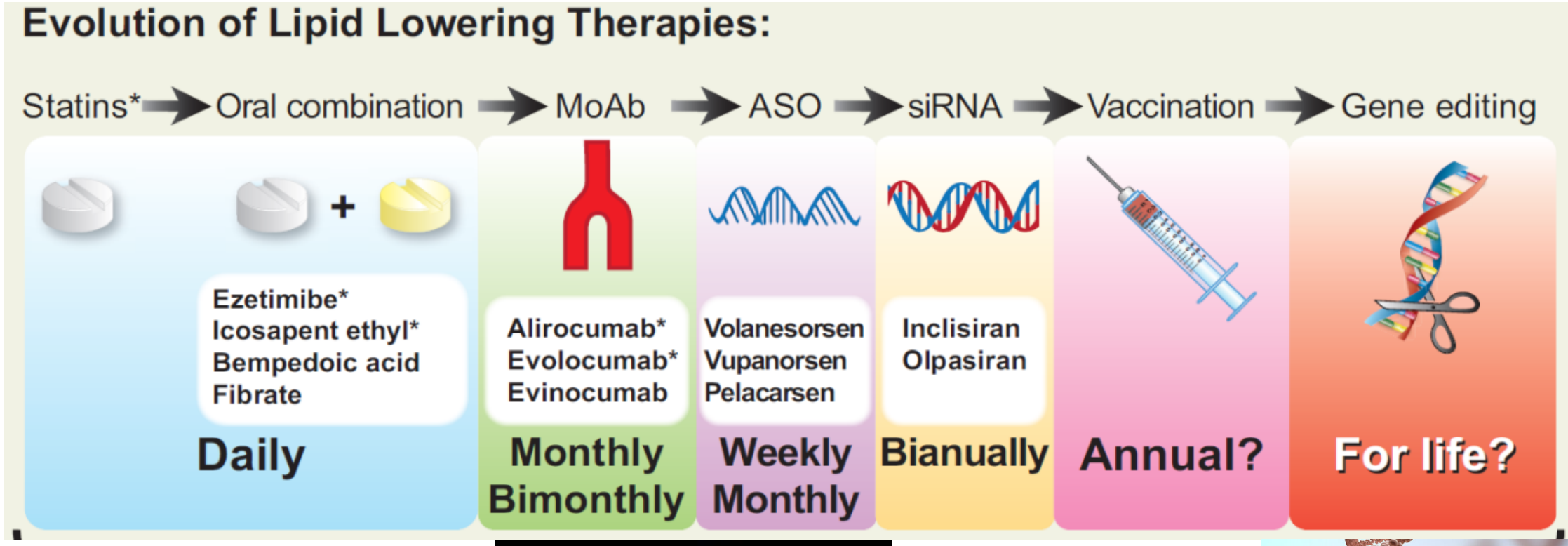


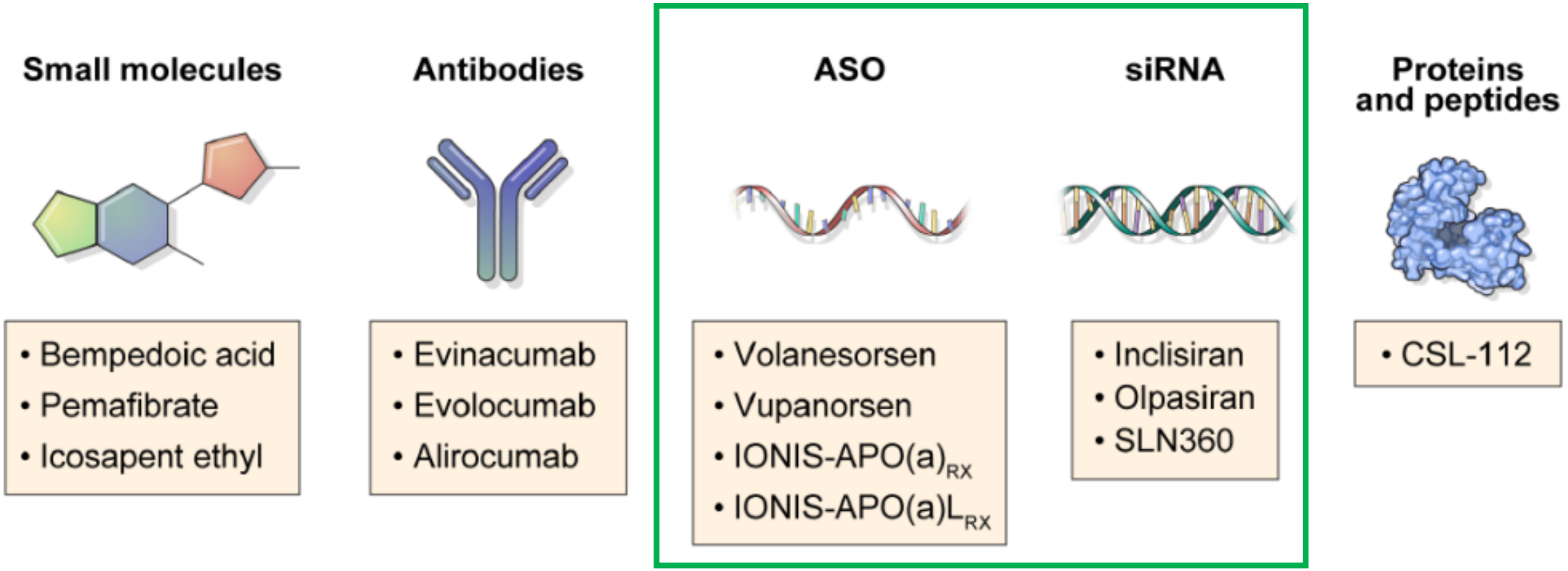
Le plein de nouveautés

Name	Drug Target	Phase	Indication/In Use For	Effect on LDL-C	Known Safety Issues
Statins	HMGCR	Approved	All patients	20% to 50%	Rhabdomyolysis
Ezetimibe	NPC1L1	Approved	All patients	~23%	Not known
PCSK9i antibody	PCSK9	Approved	Secondary prevention; FH	~47%	Not known
Mipomersen	ApoB100 mRNA	Approved, FDA only	HoFH	26%	Liver toxicity, injection-site reactions, flu-like symptoms
Lomitapide	MTP	Approved, with registry	HoFH	40% to 50%	Liver toxicity, GI side effects
Bempedoic acid	ACL	Approved/phase 4	Statin-intolerance; 3rd agent after statin/ezetimibe	17% to 21%	Gout, tendon rupture
Inclisiran	PCSK9 mRNA	Phase 3	NA	~50%	Mild injection-site reactions
Evinacumab	ANGPTL3	Phase 3	NA	~49%	Elevated liver enzymes
AKCEA-ANGPTL3-L_{Rx}	ANGPTL3 mRNA	Phase 2	NA	~33%	Not known yet
ARO-ANG3	ANGPTL3 mRNA	Phase 1	NA	Up to 42%	Not known yet
Obicetrapib	CETP	Phase 2	NA	Up to 45%	Not known yet

ACL = ATP citrate lyase; ANGPTL3 = angiopoetin-like 3 protein; apoB = apolipoprotein B; CETP = cholesteryl ester transfer protein; FDA = Food and Drug Administration; HMGCR = 3-hydroxy-3-methylglutaryl coenzyme reductase; HoFH = homozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein; MTP = microsomal triglyceride transfer protein; NPC1L1 = Niemann-Pick-like protein 1C1; PCSK9i = proprotein convertase subtilisin kexin type 9 inhibiting.

Les méthodes





Diverse classes of lipid-lowering agents. ASO, antisense oligonucleotide; siRNA, small interfering RNA.

Synthèse

- **LDL à la naissance**: **0,32 g/l**
- Bénéfice d'un LDL à **moins de 0,40 g/l en prévention secondaire**
- **Score calcique = 0** : corrélation LDL-CAD non établie

- **HIV + = statines**
- Lymphome et anthracyclines: utilité d'une statine d'emblée
- **Acide bempédoïque: traitement prochainement disponible**

- France : moins de 4 % de diabétiques
- **Diabète: toujours rechercher athérothrombose, IC et MRC**

- Avenir: ARN et ADN cibles thérapeutiques