



**SOCIETE
LUXEMBOURGEOISE
DE CARDIOLOGIE**

LE TRAITEMENT DES DYSLIPEMIES

par

par Pierre Kutter et Laurent Visser
aucun conflit d'intérêt à déclarer

ESC/ EAS GUIDELINES 2016

Question aux auditeurs :

**Croyez-vous que le
cholestérol soit un facteur
de risque pour les maladies
cardiovasculaires ?**

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

The Task Force on the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)

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ANALYSE LIPIDES SANGUINES

Recommendations	Class ^a	Level ^b
TC is to be used for the estimation of total CV risk by means of the SCORE system.	I	C
LDL-C is recommended to be used as the primary lipid analysis for screening, risk estimation, diagnosis and management. HDL-C is a strong independent risk factor and is recommended to be used in the HeartScore algorithm.	I	C
TG adds information on risk and is indicated for risk estimation.	I	C
Non-HDL-C is a strong independent risk factor and should be considered as a risk marker, especially in subjects with high TG.	I	C
ApoB should be considered as an alternative risk marker whenever available, especially in subjects with high TG.	IIa	C
Lp(a) should be considered in selected cases at high-risk, in patients with a family history of premature CVD, and for reclassification in subjects with borderline risk.	IIa	C
The ratio apoB/apoA1 may be considered as an alternative analysis for risk estimation.	IIb	C
The ratio non-HDL-C/HDL-C may be considered as an alternative but HDL-C used in HeartScore gives a better risk estimation.	IIb	C

Table 4 Risk categories

Very high-risk

Subjects with any of the following:

- Documented cardiovascular disease (CVD), clinical or unequivocal on imaging. Documented CVD includes previous myocardial infarction (MI), acute coronary syndrome (ACS), coronary revascularisation (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)) and other arterial revascularization procedures, stroke and transient ischaemic attack (TIA), and peripheral arterial disease (PAD). Unequivocally documented CVD on imaging is what has been shown to be strongly predisposed to clinical events, such as significant plaque on coronary angiography or carotid ultrasound.
- DM with target organ damage such as proteinuria or with a major risk factor such as smoking, hypertension or dyslipidaemia.
- Severe CKD (GFR <30 mL/min/1.73 m²).
- A calculated SCORE $\geq 10\%$ for 10-year risk of fatal CVD.

**Prévention
secondaire**

**Prévention
primaire
élargie**

Score

**Hyper-
cholestérolémie
familiale**

**Diabète, HTA,
Insuffisance rénale
non compliquée**

Score

Score

Table 4 Risk categories

High-risk	Subjects with: <ul style="list-style-type: none">• Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP $\geq 180/110$ mmHg.• Most other people with DM (some young people with type 1 diabetes may be at low or moderate risk).• Moderate CKD (GFR 30–59 mL/min/1.73 m²).• A calculated SCORE $\geq 5\%$ and $<10\%$ for 10-year risk of fatal CVD.
Moderate-risk	SCORE is $\geq 1\%$ and $<5\%$ for 10-year risk of fatal CVD.
Low-risk	SCORE $<1\%$ for 10-year risk of fatal CVD.

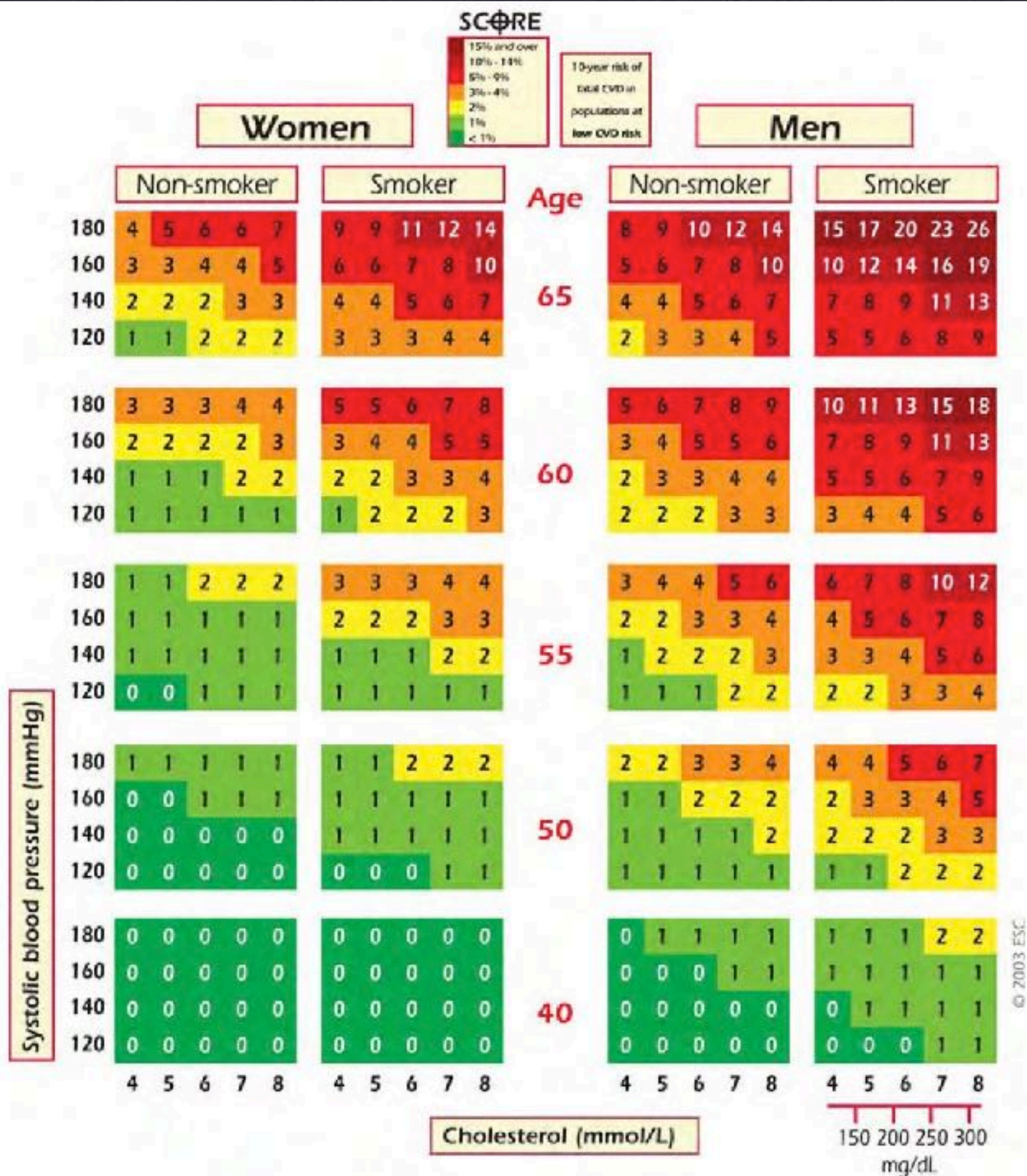


Table 5 Intervention strategies as a function of total cardiovascular risk and low-density lipoprotein cholesterol level

Total CV risk (SCORE) %	LDL-C levels				
	<70 mg/dL <1.8 mmol/L	70 to <100 mg/dL 1.8 to <2.6 mmol/L	100 to <155 mg/dL 2.6 to <4.0 mmol/L	155 to <190 mg/dL 4.0 to <4.9 mmol/L	≥190 mg/dL ≥4.9 mmol/L
<1	No lipid intervention	No lipid intervention	No lipid intervention	No lipid intervention	Lifestyle intervention, consider drug if uncontrolled
Class ^a /Level ^b	I/C	I/C	I/C	I/C	IIa/A
≥1 to <5	No lipid intervention	No lipid intervention	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled
Class ^a /Level ^b	I/C	I/C	IIa/A	IIa/A	I/A
≥5 to <10, or high-risk	No lipid intervention	Lifestyle intervention, consider 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
≥10 or very high-risk	Lifestyle intervention, consider drug	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
Class ^a /Level ^b	IIa/A	IIa/A	I/A	I/A	I/A

DÉCISION THÉRAPEUTIQUE

MESURES THÉRAPEUTIQUES

Smoking	No exposure to tobacco in any form.
Diet	Healthy diet low in saturated fat with a focus on whole grain products, vegetables, fruit and fish.
Physical activity	2.5–5 h moderately vigorous physical activity per week or 30–60 min most days.
Body weight	BMI 20–25 kg/m ² , waist circumference <94 cm (men) and <80 cm (women).
Blood pressure	<140/90 mmHg ^a
Lipids LDL-C is the primary target^c	Very high-risk: LDL-C <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline ^b is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL).
	High-risk: LDL-C <2.6 mmol/L (100 mg/dL) or a reduction of at least 50% if the baseline ^b is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL).
	Low to moderate risk: LDL-C <3.0 mmol/L (115 mg/dL).
	Non-HDL-C secondary targets are <2.6, 3.4 and 3.8 mmol/L (100, 130 and 145 mg/dL) for very high-, high- and moderate-risk subjects, respectively.
	HDL-C: no target, but >1.0 mmol/L (40 mg/dL) in men and >1.2 mmol/L (48 mg/dL) in women indicates lower risk.
	TG: no target but <1.7 mmol/L (150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.
Diabetes	HbA1c: <7% (<53 mmol/mol).

Recommendations	Class^a	Level^b	Ref^c
Prescribe statin up to the highest recommended dose or highest tolerable dose to reach the goal.	I	A	62, 64, 68
In the case of statin intolerance, ezetimibe or bile acid sequestrants, or these combined, should be considered.	IIa	C	239, 256, 257
If the goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered.	IIa	B	63
If the goal is not reached, statin combination with a bile acid sequestrant may be considered.	IIb	C	
In patients at very high-risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered.	IIb	C	115, 116

TRAITEMENT MÉDICAMENTEUX HYPERCHOLESTÉROLÉMIE

Recommendations	Class^a	Level^b	Ref^c
LDL-C is recommended as the primary target for treatment.	I	A	64, 68
TC should be considered as a treatment target if other analyses are not available.	Ila	A	64, 123
Non-HDL-C should be considered as a secondary treatment target.	Ila	B	103
ApoB should be considered as a secondary treatment target, when available.	Ila	B	103, 124
HDL-C is not recommended as a target for treatment.	III	A	92, 93
The ratios apoB/apoA1 and non-HDL-C/HDL-C are not recommended as targets for treatment.	III	B	103

TRAITEMENT MÉDICAMENTEUX HYPERCHOLESTÉROLÉMIE

Molécules/ Familles	Effet biologique	Réduction risque Cardiovasculaire
Séquestrants biliaires	↓TC, ↓LDL-C, ↑HDL-C	?
Fibrates	↓TC, ↓LDL-C, ↑↑HDL-C, ↓TG	?
Ezetimib	↓TC, ↓LDL-C, ↑HDL	+
Levure riz rouge	↓TC, ↓LDL-C	?
Phytostérols	↓TC, ↓LDL-C	-
Acides gras polyinsaturés	↓TG	-
Acide nicotinique	↓TC, ↓LDL-C, ↑↑HDL-C, ↓TG	-
Statines	↓↓TC, ↓↓LDL-C, ↑HDL-C	+++

TRAITEMENT MÉDICAMENTEUX HYPERCHOLESTÉROLÉMIE

MYOTOXICITÉ

10-15% myalgies ou douleurs diffuses

5% myosite confirmée (augmentation CK)

1-3/100.000 patients-années rhabdomyolyse

HÉPATOTOXICITÉ

0,5-2% augmentation modérée SGOT 3x

DIABÈTE

+ 0,2% risque total hyperglycémie

NÉPHROTOXICITÉ (-)

NEUROTOXICITÉ (-)

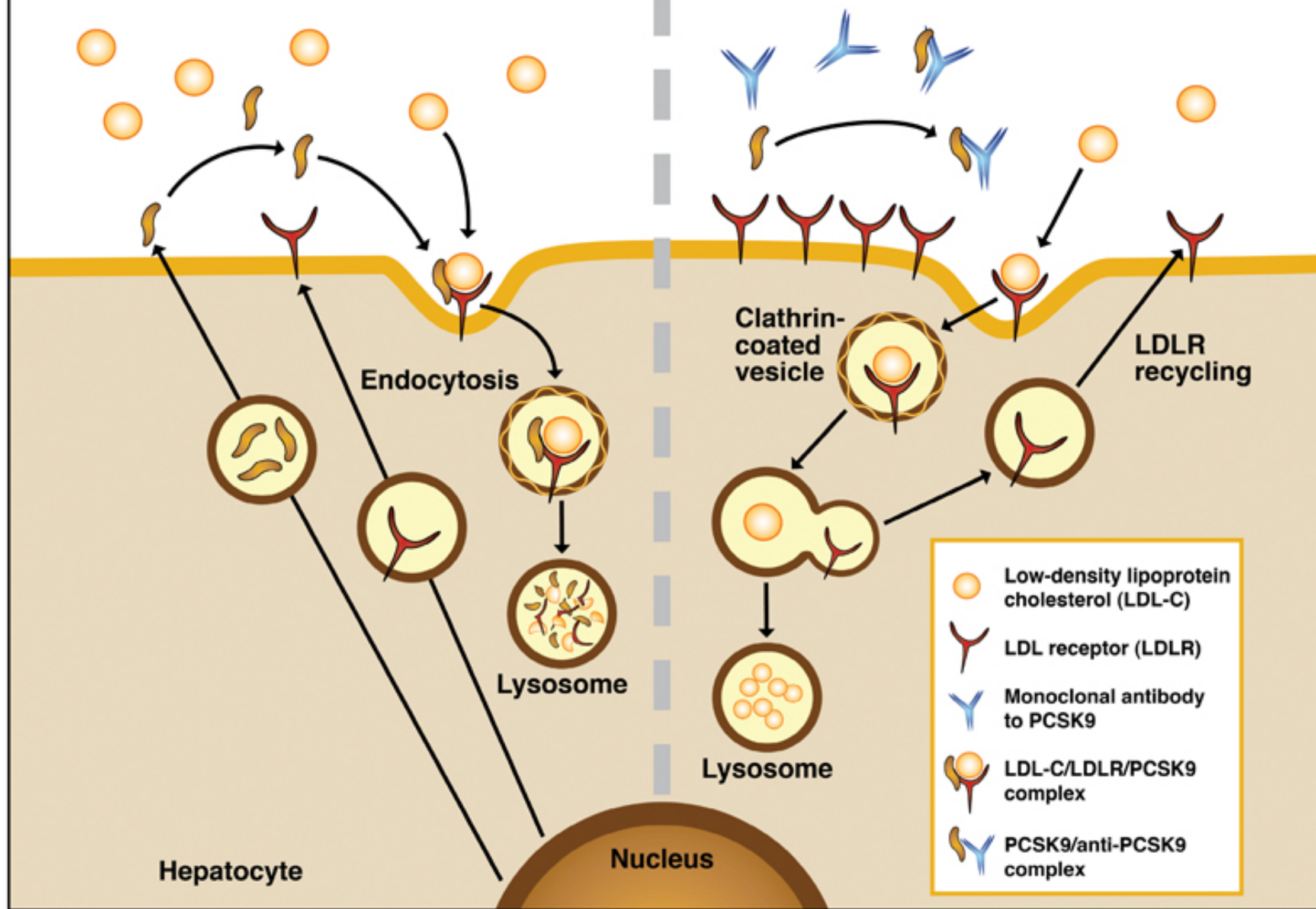
NÉOPLASIE (-)

MONITORING EFFETS SECONDAIRES DES STATINES

2 NOUVEAUTÉS

A. Hypercholesterolemia

B. Monoclonal Antibodies to PCSK9



INHIBITEURS PCSK9

HYPERCHOLESTÉROLÉMIE FAMILIALE

- (Homozygote avec expression résiduelle LDL-R)
- Hétérozygote insuffisamment contrôlée par statines
 - Monothérapie
 - Association Statines, Ezetimib

PATIENTS A TRÈS HAUT RISQUE

- intolérant aux statines

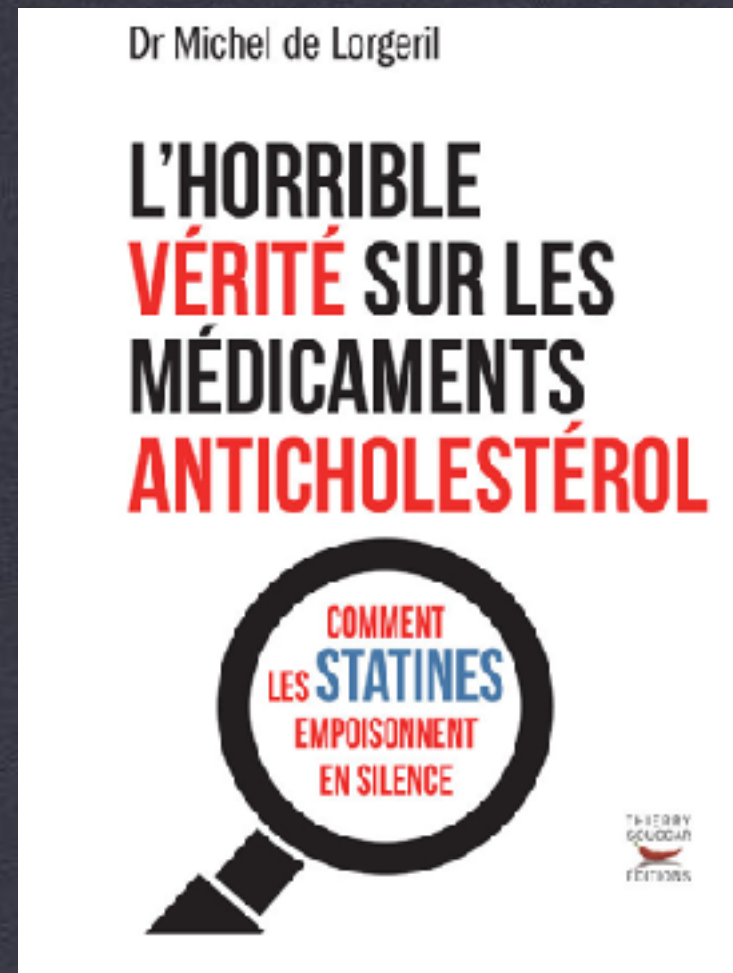
INDICATIONS INHIBITEURS PCSK9

**SI ON PARLAIT DU
CHOLESTÉROL**

Depuis +/- 1950 controverse féroce sur l'action du cholestérol,
« Lipid theory »

- **Pro** ➡ **+/- 90% de l'opinion dans les publications scientifiques**
 - ➡ Le cholestérol est un des principaux facteurs de risque cardio-vasculaires responsable de l'artériosclérose
 - ➡ Le régime pauvre en graisse saturées / cholestérol et le traitement par statines sont les mesures efficaces de prévention
- **Contra** ➡ **+/- 90% de l'opinion dans les médias grand public**
 - ➡ Le cholestérol est une molécule précieuse pour la santé
 - ➡ Le régime pauvre en graisse saturées / cholestérol est inefficace
 - ➡ Les statines sont des médicaments inutiles et toxiques

LIPID THEORY



INFLUENCE DES MÉDIAS SUR LA DÉCISION THÉRAPEUTIQUE

Le Camp de Contra avance les hypothèses alternatives suivantes :

- L'artériosclérose est un processus naturel de vieillissement des artères
- La surconsommation des sucres est responsable de la maladie artérielle
- L'augmentation de l'homocystéine est responsable de la maladie artérielle
- Le régime méditerranéen est protecteur

INFLUENCE DES MÉDIAS SUR LA DÉCISION THÉRAPEUTIQUE

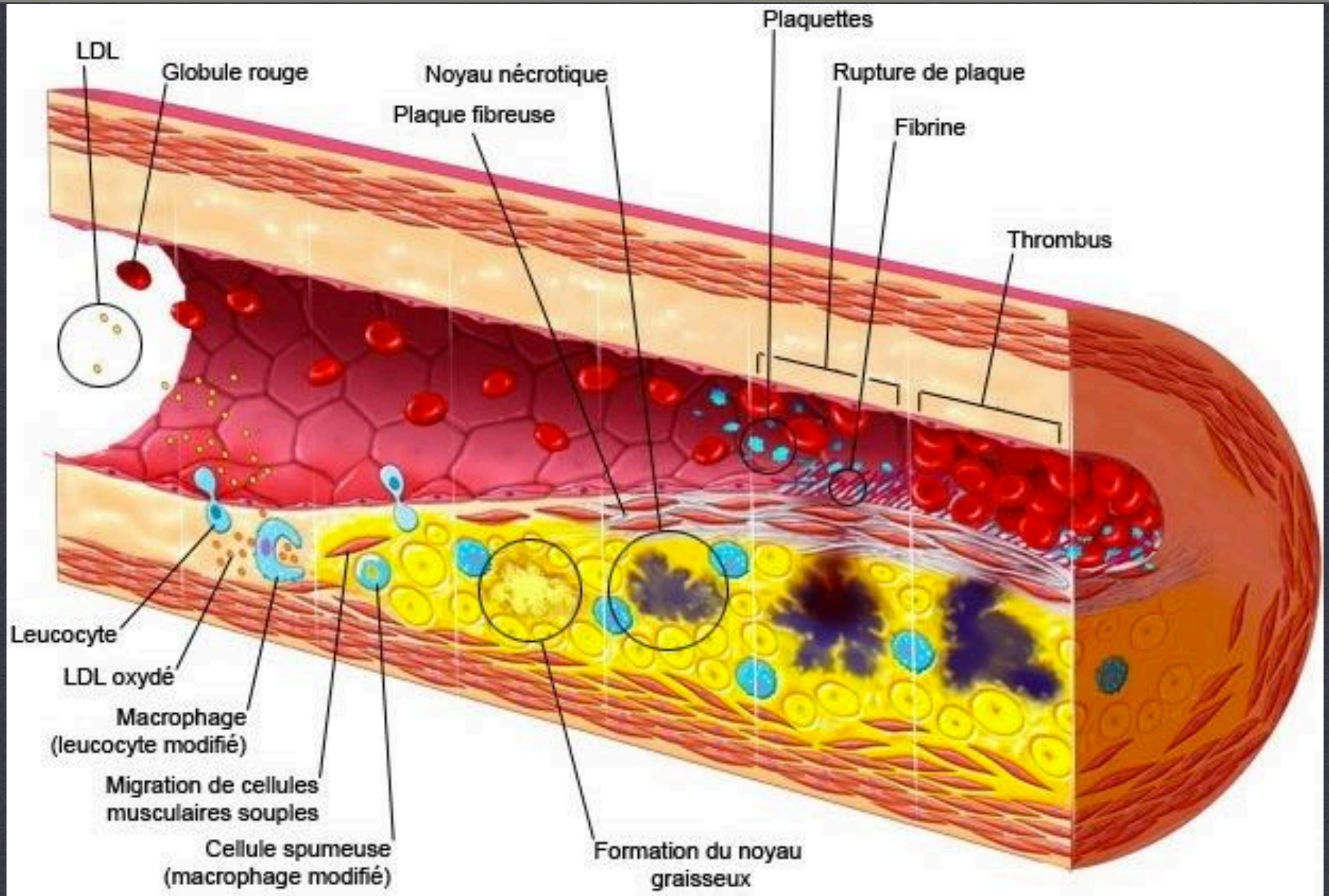
Les patient vont s'adresser à vous après avoir été informé par les médias grand publique, bien rédigées, messages cohérents, mais non nuancées

Risque

- ➡ Rupture de confiance avec médecins traitants
- ➡ Semer le doute auprès des professionnels de santé

INFLUENCE DES MÉDIAS SUR LA DÉCISION THÉRAPEUTIQUE

BASES DE « LIPID THEORY »



1880 RUDOLF VIRCHOW CHOLESTÉROL DANS LES PLAQUES
HISTOIRE LIPID THEORY

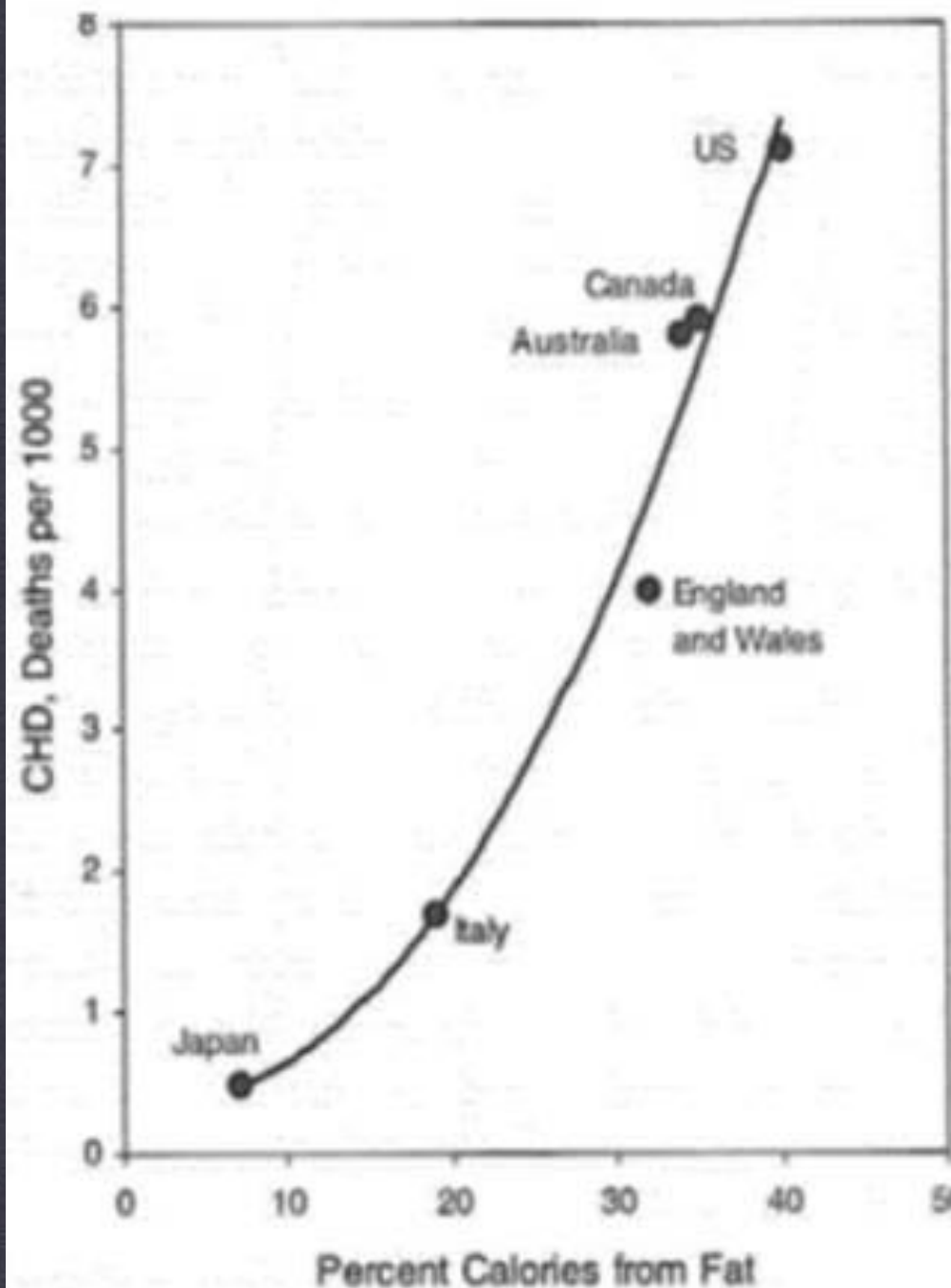


Figure 1A. Correlation between the total fat consumption as a percent of total calorie consumption, and mortality from coronary heart disease in six countries. Data from Keys.¹

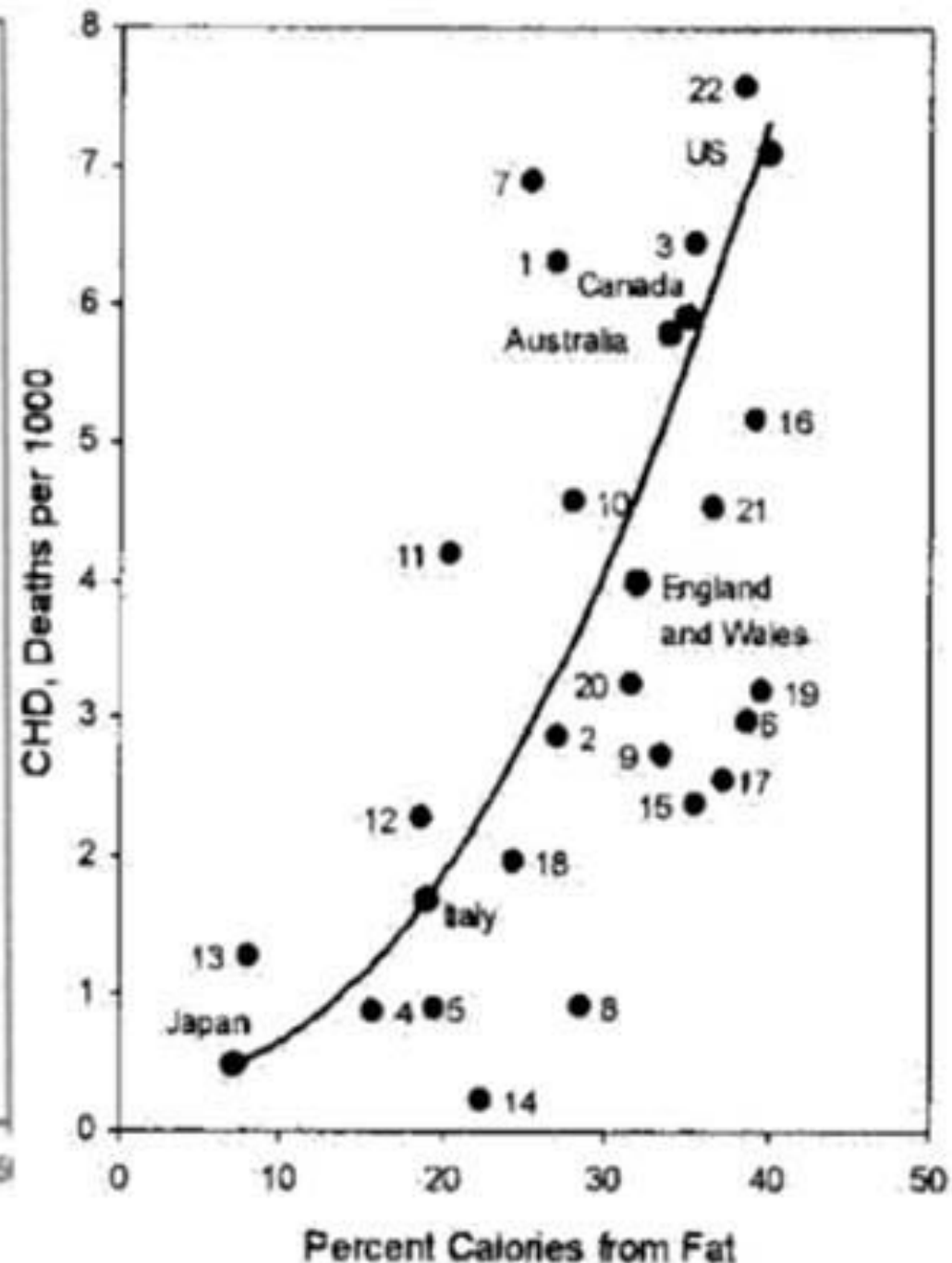
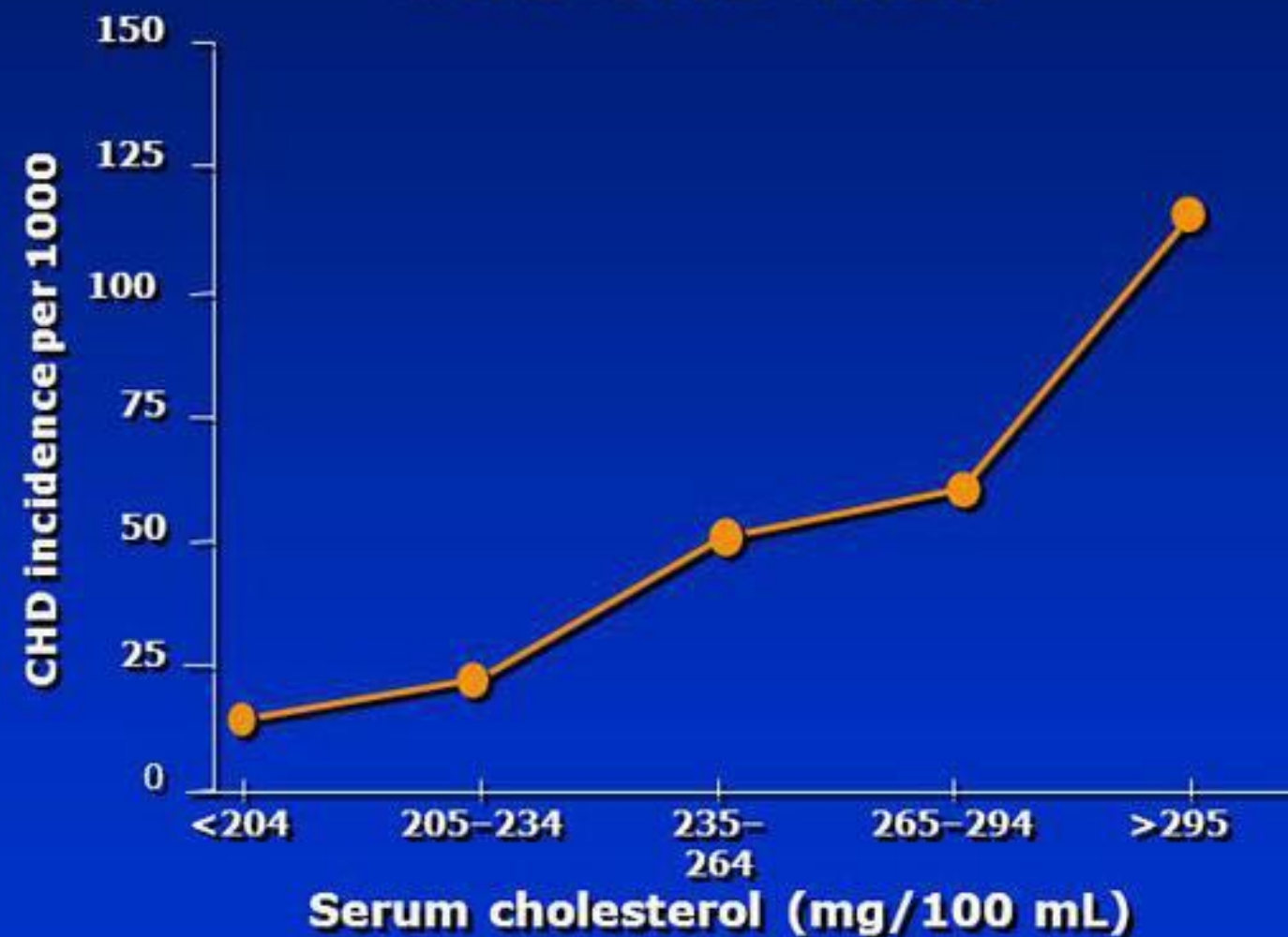


Figure 1B - as 1A but with all countries where data were available when Keys published. 1 Australia 2 Italy 3 Canada 4 Ceylon 5 Chile 6 Denmark 7 Finland 8 France 9 W. Germany 10 Ireland 11 Israel 12 Italy 13 Japan 14 Mexico 15 Holland 16 New Zealand 17 Norway 18 Portugal 19 Sweden 20 Switzerland 21 Great Britain 22 USA. Data from Yerushalamy and Hilleboe.

1953 SIX COUNTRIES STUDY

HISTOIRE LIPID THEORY

The Framingham Study: Relationship Between Cholesterol and CHD Risk

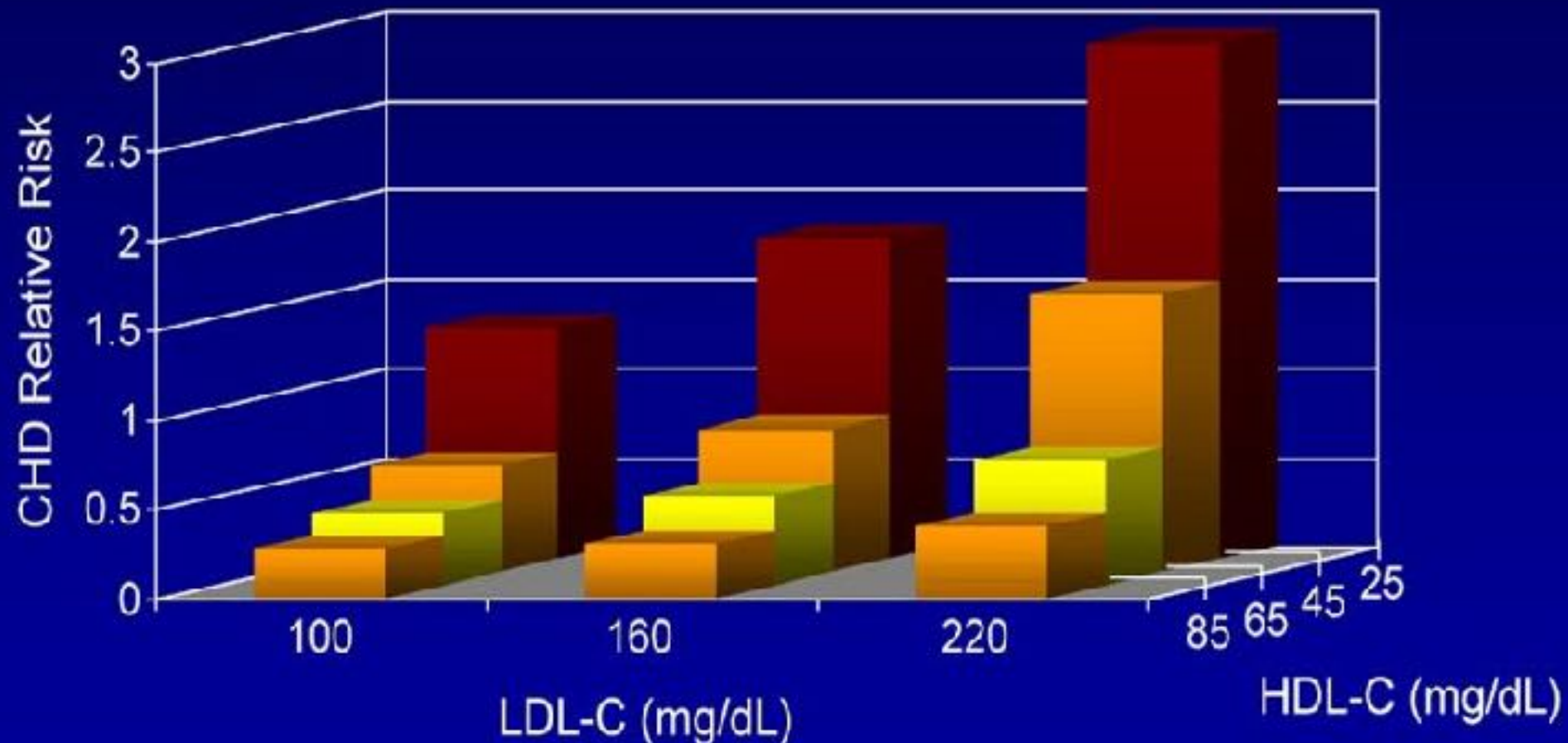


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Adapted from Castelli WP. *Am J Med* 1984;76:4-12

1948 FRAMINGHAM STUDY
HISTOIRE LIPID THEORY

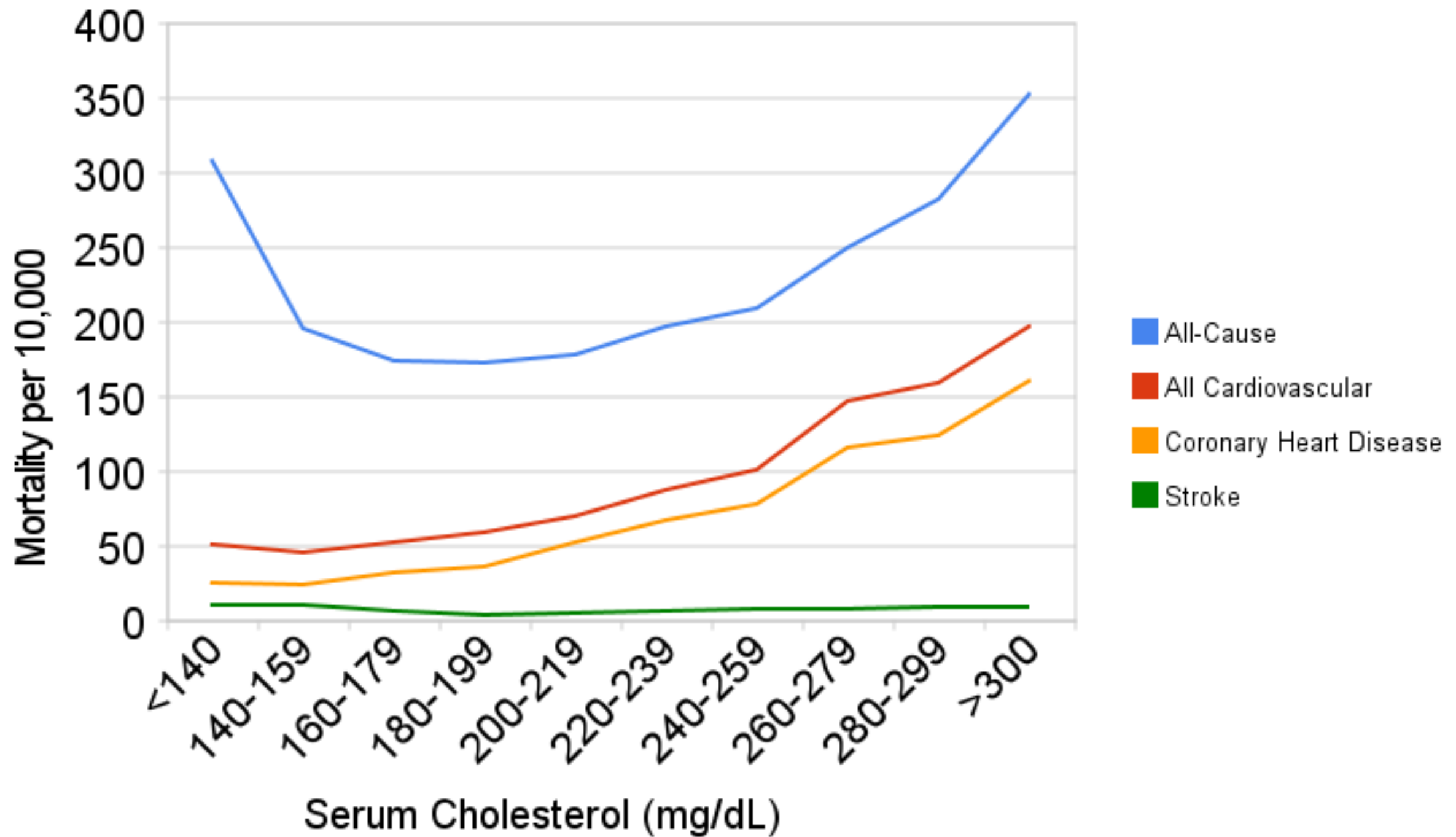
Framingham Heart Study: Risk of CAD in Men Aged 50–70 by LDL-C and HDL-C Levels



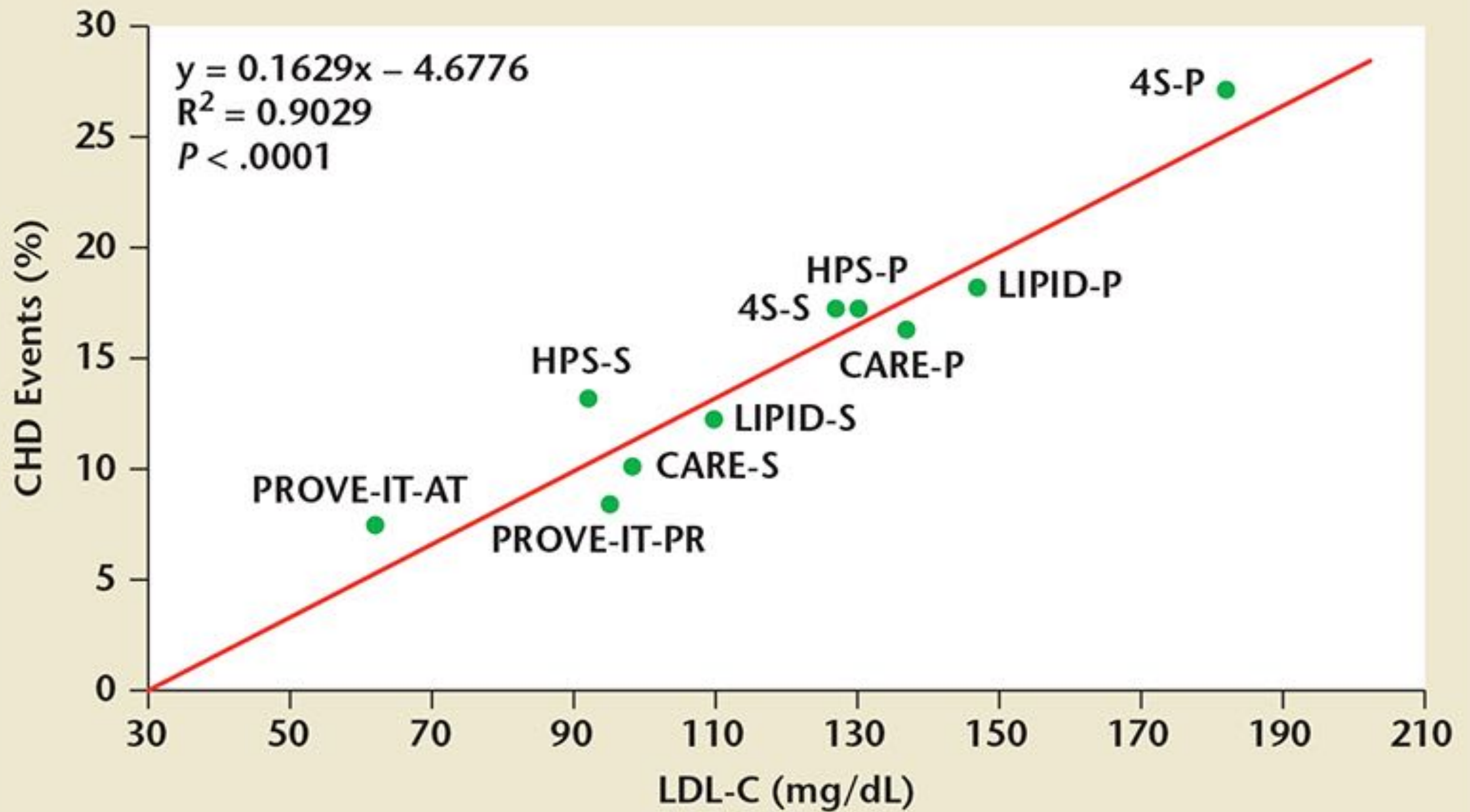
Castelli W. *Can J Cardiol*. 1988;4(suppl A):5A-10A.

1948 FRAMINGHAM STUDY
HISTOIRE LIPID THEORY

MRFIT: Mortality in 350,977 men aged 35-57



1971 MRFIT
HISTOIRE LIPID THEORY



ETUDES INTERVENTIONNELLES
HISTOIRE LIPID THEORY

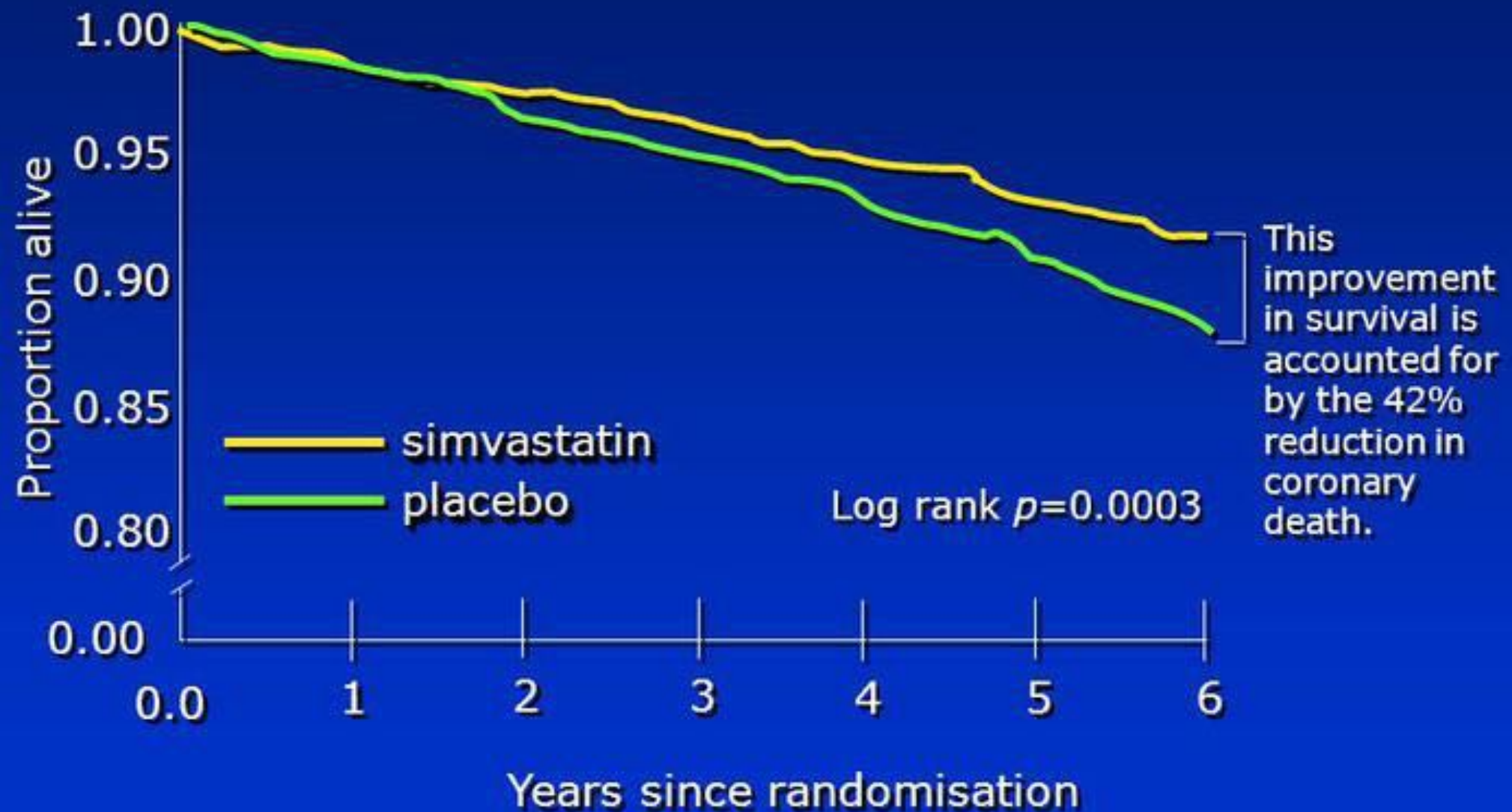


DÉCOUVERTE DES STATINES

- 1971 Akira Endo découvre par hasard par fermentation du *Penicillium citrinum* la Mevastatin, effet inhibant puissant sur HMG Co reductase mais hépatotoxique
- 1978 MSD découvre par fermentation de *Aspergillus terreus* la Lovastine
- 1987 Lovastine mise sur le marché
- 1988 Simvastatine mise sur le marché

HISTOIRE DU TRAITEMENT CONTRE LE CHOLESTÉROL

4S: Total Mortality

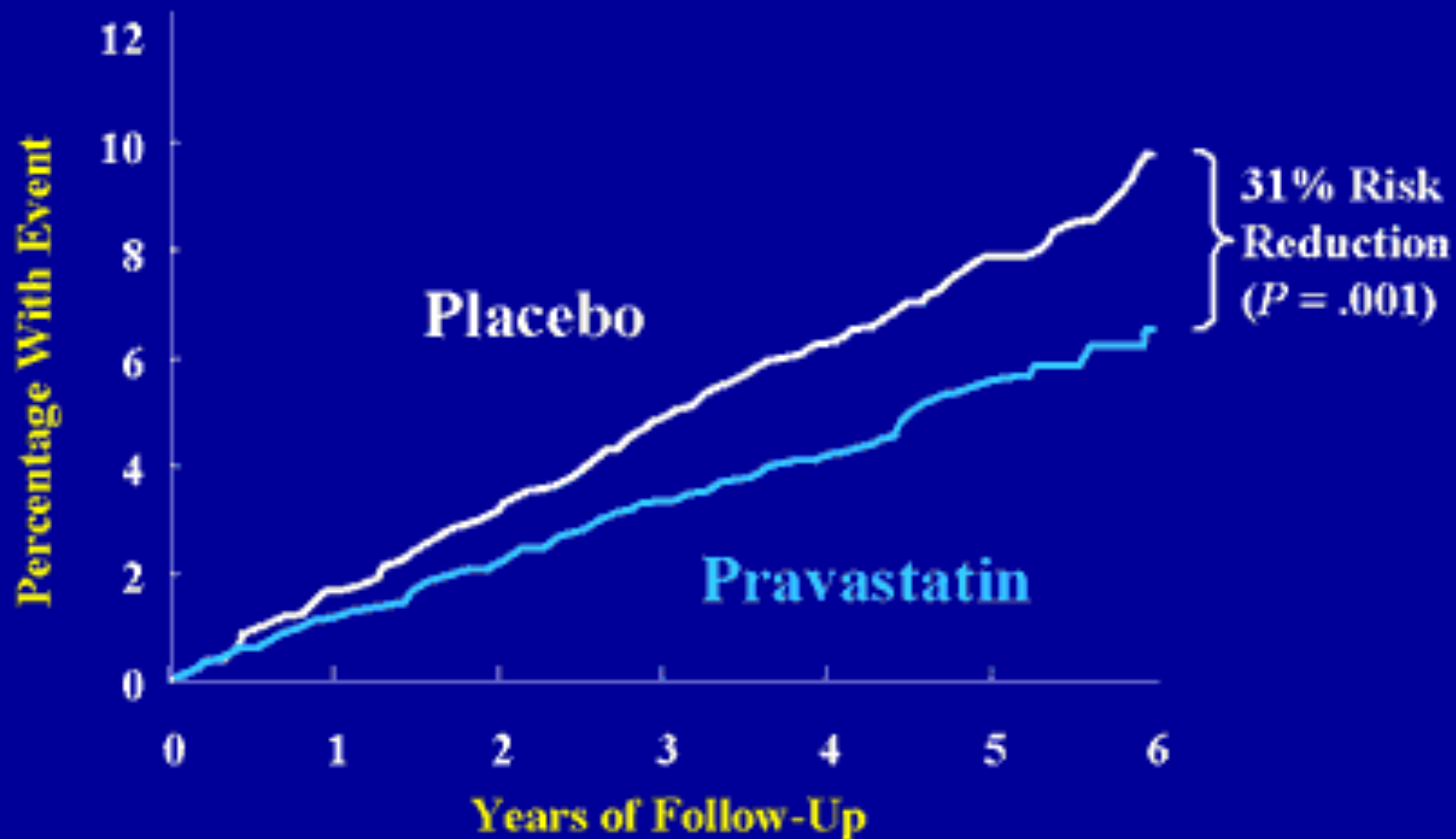


 MyShared

The Scandinavian Simvastatin Survival Study Group. *Lancet* 1994;**344**:1383-1389

HISTOIRE DU TRAITEMENT CONTRE LE CHOLESTÉROL

WOSCOPS Primary End Point: Nonfatal MI or CHD Death



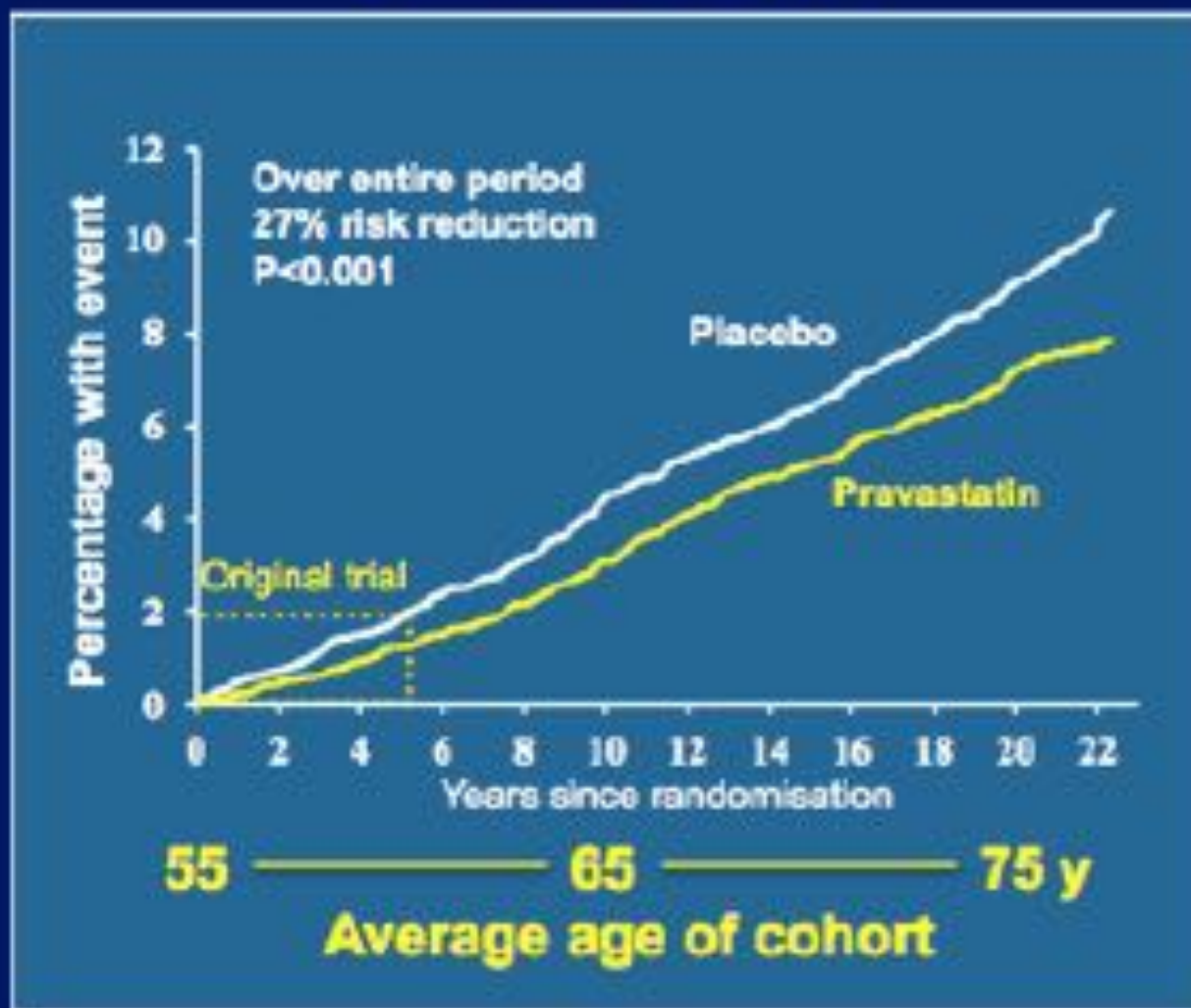
Adapted from Shepherd J, et al. *N Engl J Med*. 1995;333:1301-1307.

HISTOIRE DU TRAITEMENT CONTRE LE CHOLESTÉROL

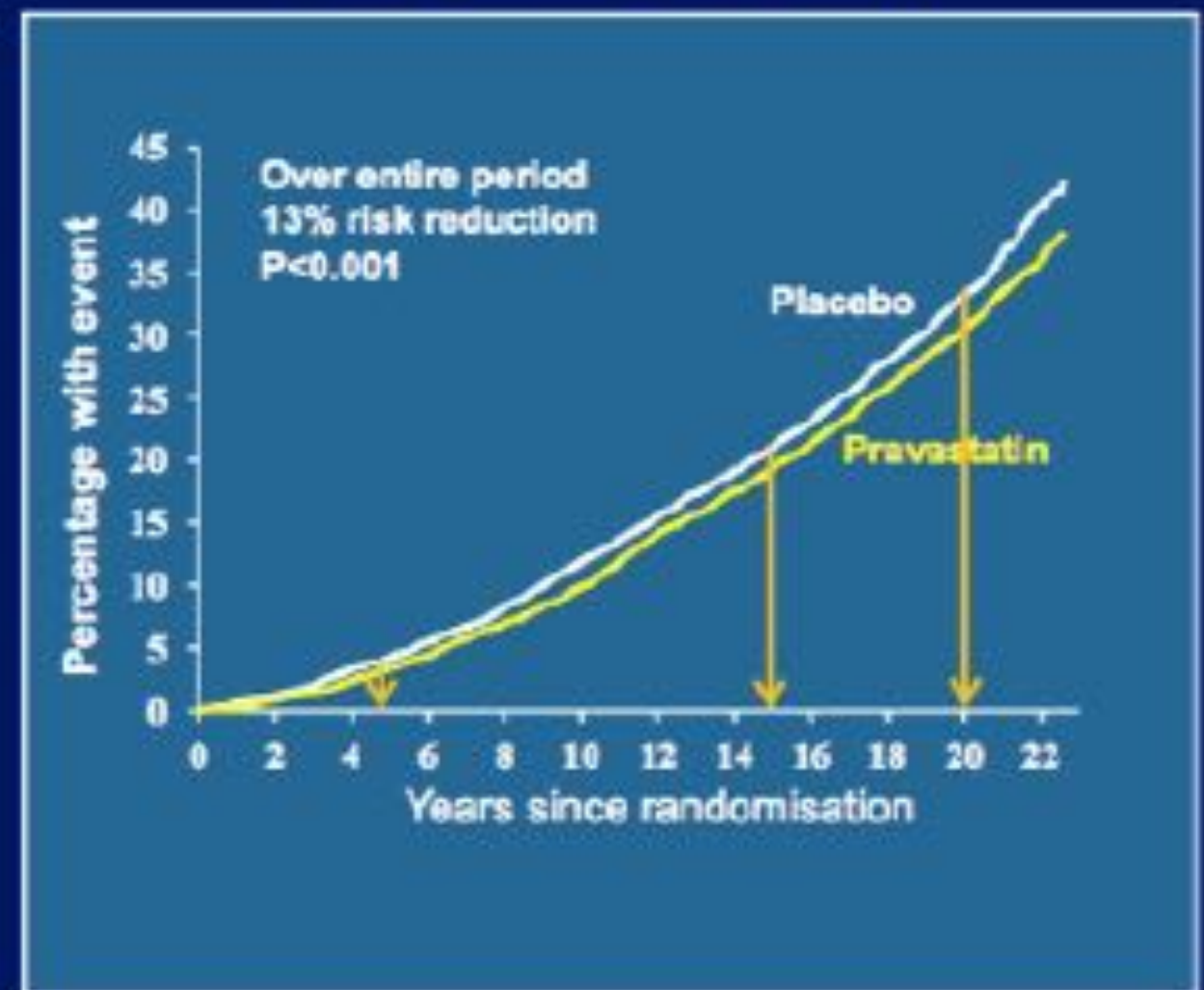
Long term follow up in statin studies

WOSCOPS experience

CHD mortality

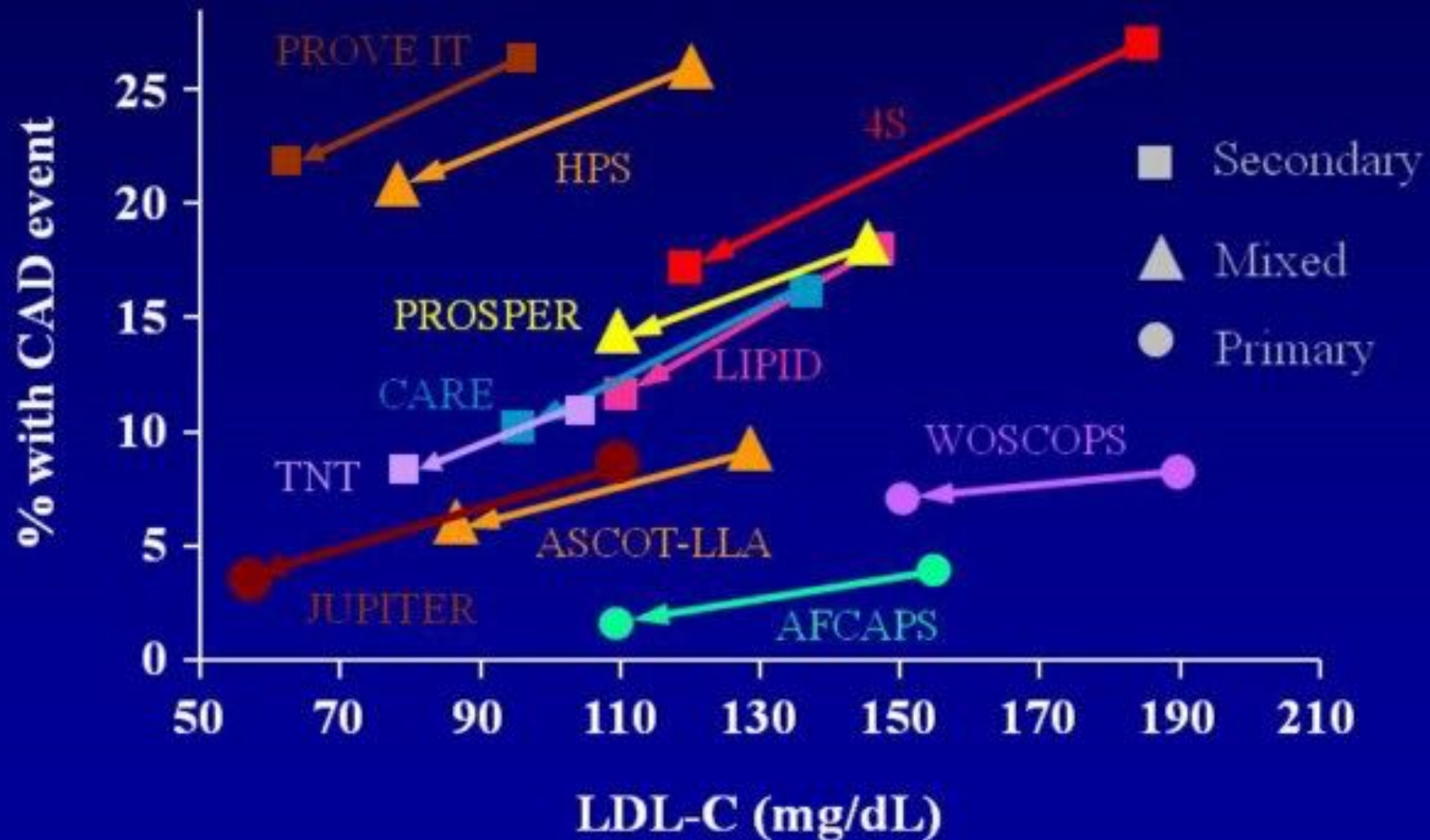


All-cause mortality



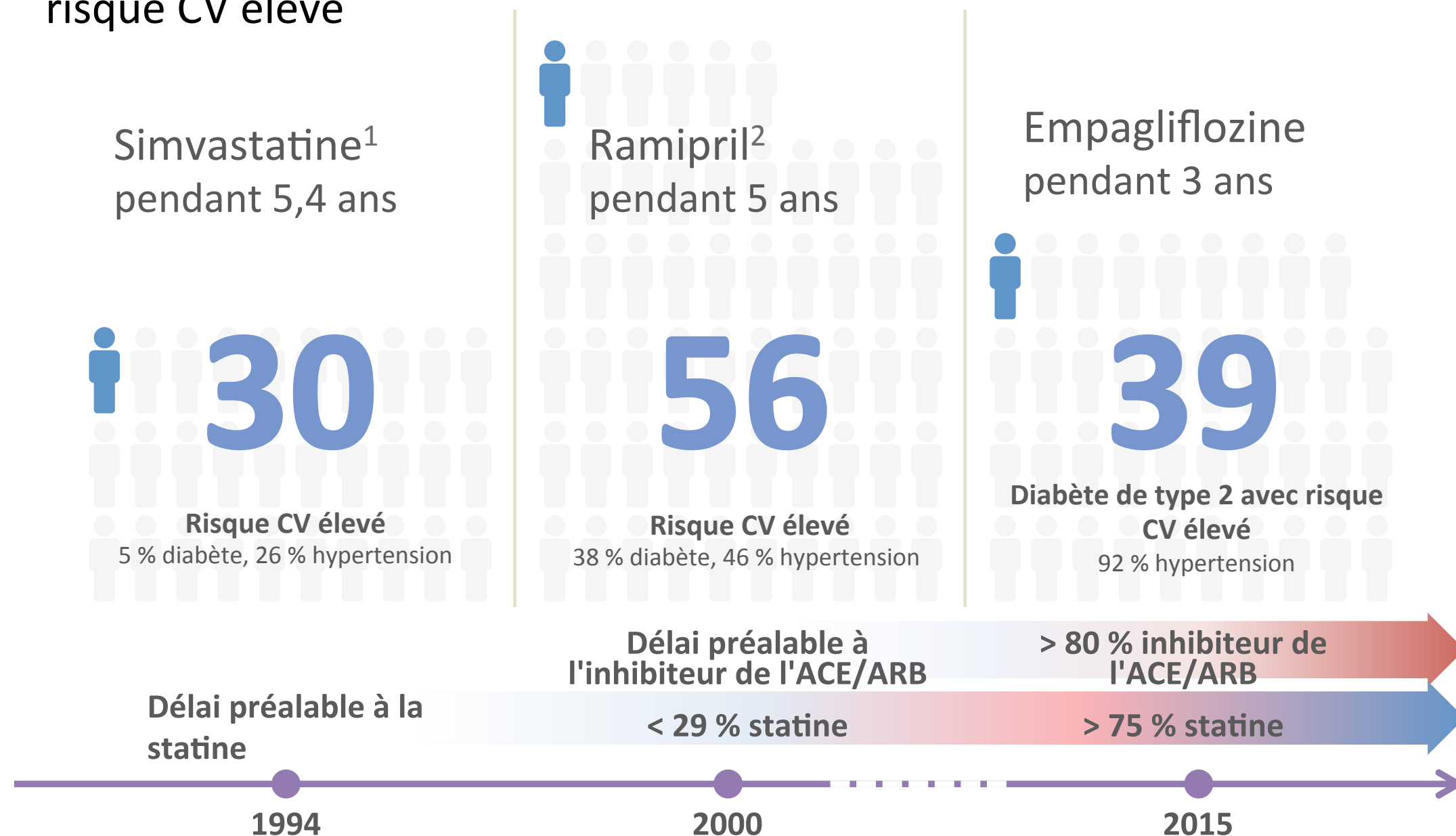
HISTOIRE DU TRAITEMENT CONTRE LE CHOLESTÉROL

Major Statin Trials



HISTOIRE DU TRAITEMENT CONTRE LE CHOLESTÉROL

Nombre de sujets à traiter afin de prévenir un cas de décès dans toutes les études importantes réalisées sur des patients présentant un risque CV élevé



1. 4S investigateur. Lancet 1994 ; 344 : 1383-89, <http://www.trialresultscenter.org/study2590-4S.htm>;

2. HOPE investigator N Engl J Med 2000;342:145-53, <http://www.trialresultscenter.org/study2606-HOPE.htm>

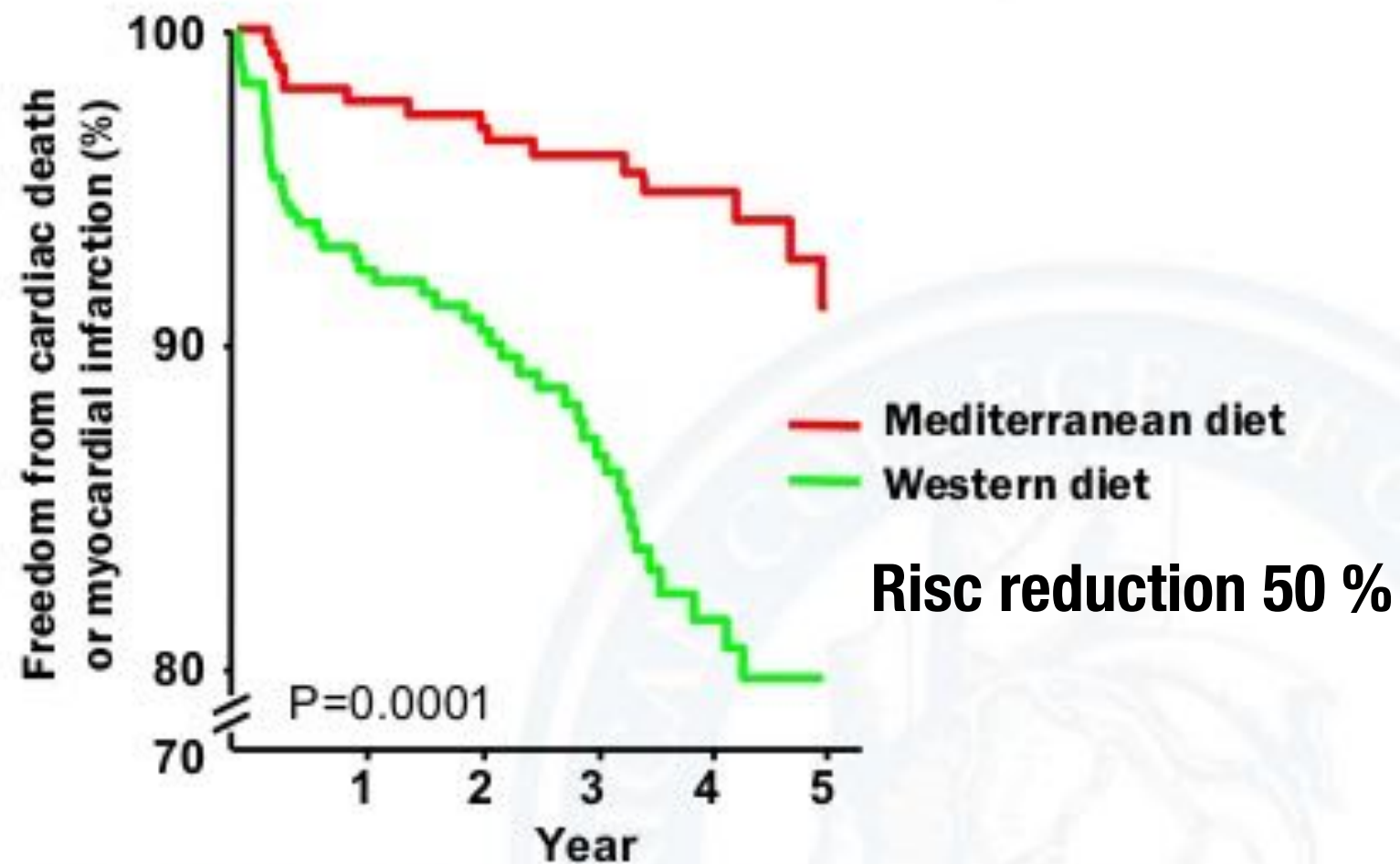
The Lyon Diet Heart Study

“Mediterranean-type diet”	Control study “Low Fat” Diet
More bread, More root vegetables, Green vegetables, More fish, Fruit every day, Reduced red meat Margarine instead of butter, Olive oil on salad, Wine in moderation	Less fiber American style diet Less fruits and vegetables
30% fat 8% saturated fat 203 mg/cholesterol a day More oleic acid fat	34% fat! 12% saturated fat 312 mg/day of cholesterol

Diet Evidence: Secondary Prevention

Lyon Diet Heart Study

605 patients following a myocardial infarction randomized to a Mediterranean* or Western** diet for 4 years



A Mediterranean diet reduces cardiovascular events



*Helping Cardiovascular Professionals
Learn. Advance. Heal.*

*High in polyunsaturated fat and fiber,
**High in saturated fat and low in fiber

Source: De Lorgeril M et al. *Circulation* 1999;99:779-785

RELATION RÉGIME / MALADIE CORONARIENNE

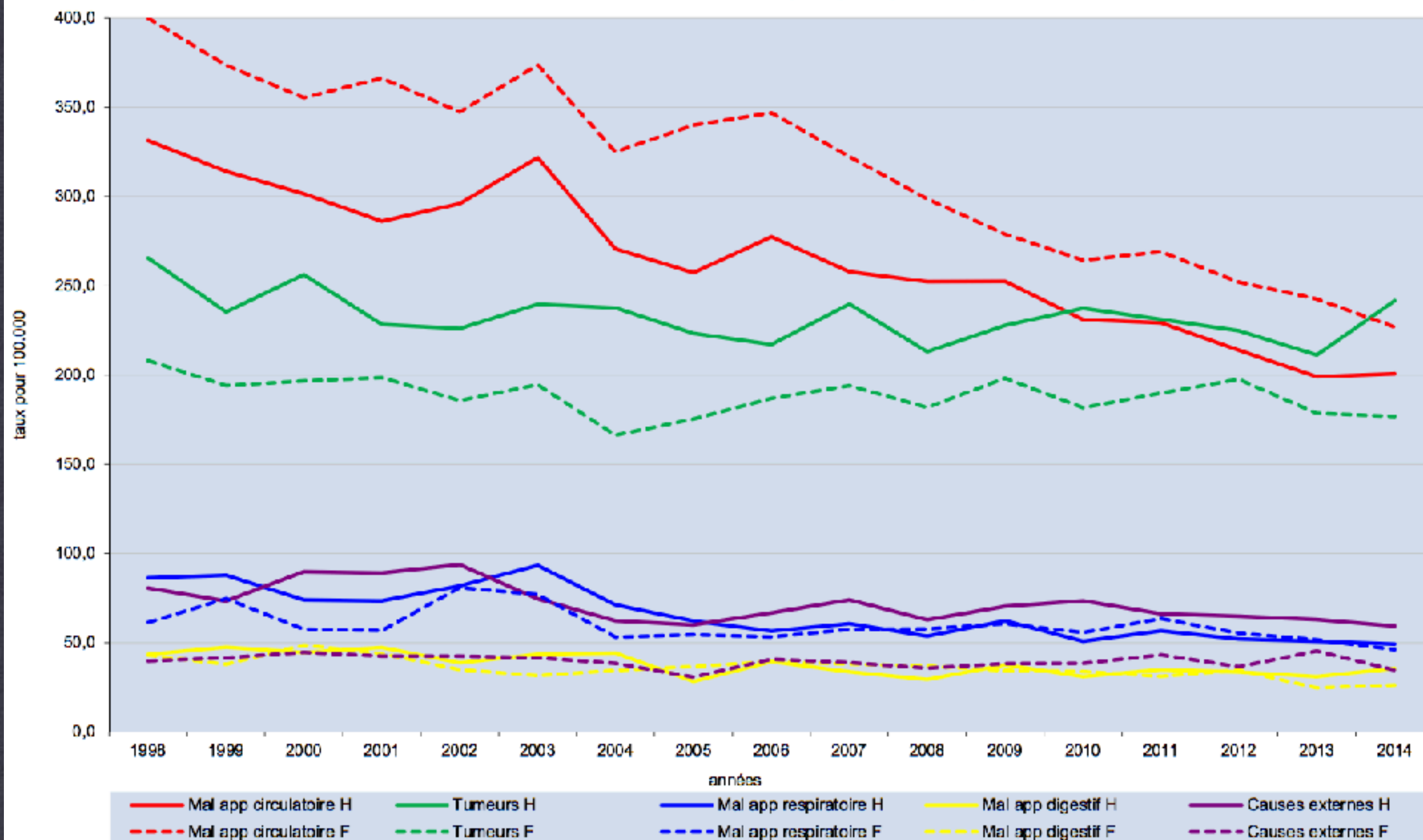
Entretiens que le camp des Pro et Contra se déchirent sur la « Lipid theory » depuis bientôt 70 ans, avec un débat porté actuellement sur la place publique

Les médecins traitants ?

- ➔ Ils ont conseillé un régime pauvre en cholestérol et en acides gras saturés
- ➔ Ils ont prescrit mondialement des milliards de doses de statines en 30 ans (aussi sur la pression marketing des firmes)
- ➔ Le résultat global est impressionnant
 - Réduction de la morbi-mortalité cardiovasculaire
 - Pas de majoration de morbi-mortalité d'autres causes

HISTOIRE DU TRAITEMENT CONTRE LE CHOLESTÉROL

Evolution du taux brut de mortalité selon la cause et le sexe, pour principaux chapitres ICD, de 1998 à 2014



**STATEC : RÉDUCTION DE 45% DE LA MORTALITÉ CARDIOVASCULAIRE EN 15 ANS
SUCCÈS DE LA MÉDECINE CARDIOVASCULAIRE AU LUXEMBOURG**

Entretemps que les camps des Pro et Contra se déchirent sur la « Lipid theory » depuis bientôt 70 ans, avec un débat porté actuellement sur la place publique

Les sociétés de cardiologie ?

Les guidelines ?

- ➡ Ils adhèrent aux grandes lignes de la lipid theory
- ➡ Pourtant les recommandations sont plus prudentes et nuancées
- ➡ Ils intègrent quelques éléments du camps des Contra

HISTOIRE DU TRAITEMENT CONTRE LE CHOLESTÉROL

Traiter les dyslipémies

Il vaut mieux savoir que croire

DÉCISION THÉRAPEUTIQUE

- réfléchi en accord avec les Guidelines ESC/EAS
- non influencé par les médias
- pondérer bénéfices / prix
 - en fonction de la catégorie de risque
 - en fonction coût financier, contrainte, effets secondaires

MESSAGES ESSENTIELS

COMMUNICATION AVEC LE PATIENT

- clarifier que les médecins traitants ont une relation thérapeutique avec le patient et qu'ils sont directement responsable de leurs actes et conseils (alors que les opinions prononcés dans les médias ne sont pas responsables)
- éducation thérapeutique du patient sur l'hygiène de vie
- discussion honnête et crédible des pro et contra d'une mesure préventive pour le cholestérol

MESSAGES ESSENTIELS