Collège National des Cardiologues des Hôpitaux

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Cholesterol Burden
ou
Quel risque cumulé à l'exposition au cholestérol ?

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Disclosure of potential conflicts of interest

Research contracts:	None
Consulting:	Abbott, Akcea/Ionis, Amarin, Amgen, AstraZeneca, Daïchi-Sankyo, Kowa, Merck and Co, Mylan, Pfizer, Sanofi/Regeneron and Servier
Employment in industry:	None
Stockholder of a healthcare company:	None
Owner of a healthcare company:	None
Participation in Clinical Trials:	ODYSSEY Programme (Sanofi/Regeneron) TESLA/TAUSSIG/VESALIUS (Amgen) Evinacumab (Regeneron)

Cholesterol Burden

- ☑ Cholestérol et athérosclérose
- ☑ Données épidémiologiques
- ☑ Données génétiques

  Modèle : hypercholestérolémie familiale (HF)

- ☑ Implications thérapeutiques

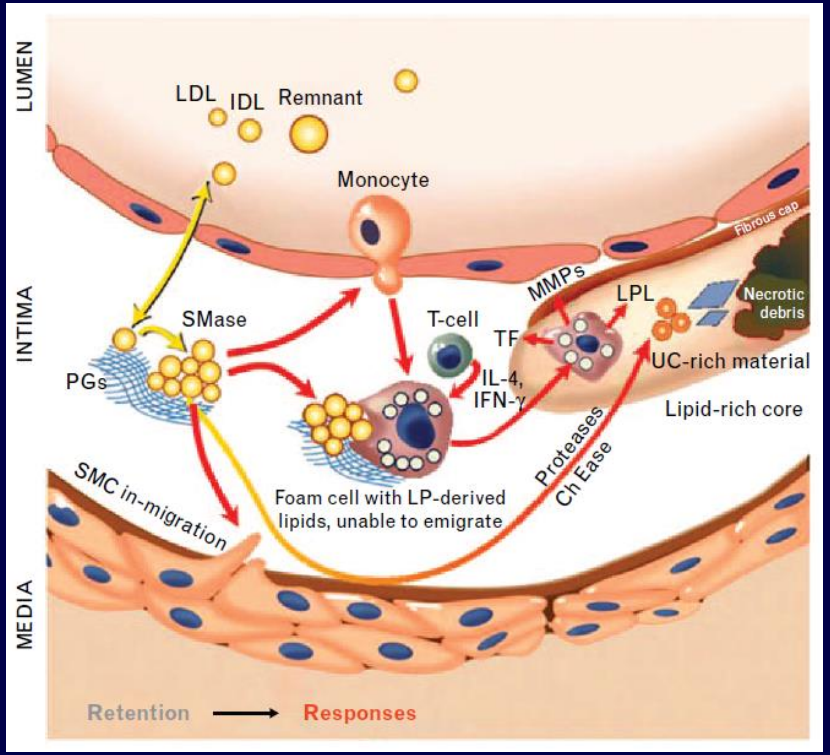
Evaluation du « Cholesterol burden »

2 éléments essentiels à prendre en compte :

- ✓ l'ensemble du cholestérol athérogène
  - ➔ lipoprotéines riches en apoB
- ✓ la durée d'exposition
  - ➔ peu utilisée en pratique

expression : g-ans (g/l-ans)

Influx of apo-B-lipoproteins into the artery wall

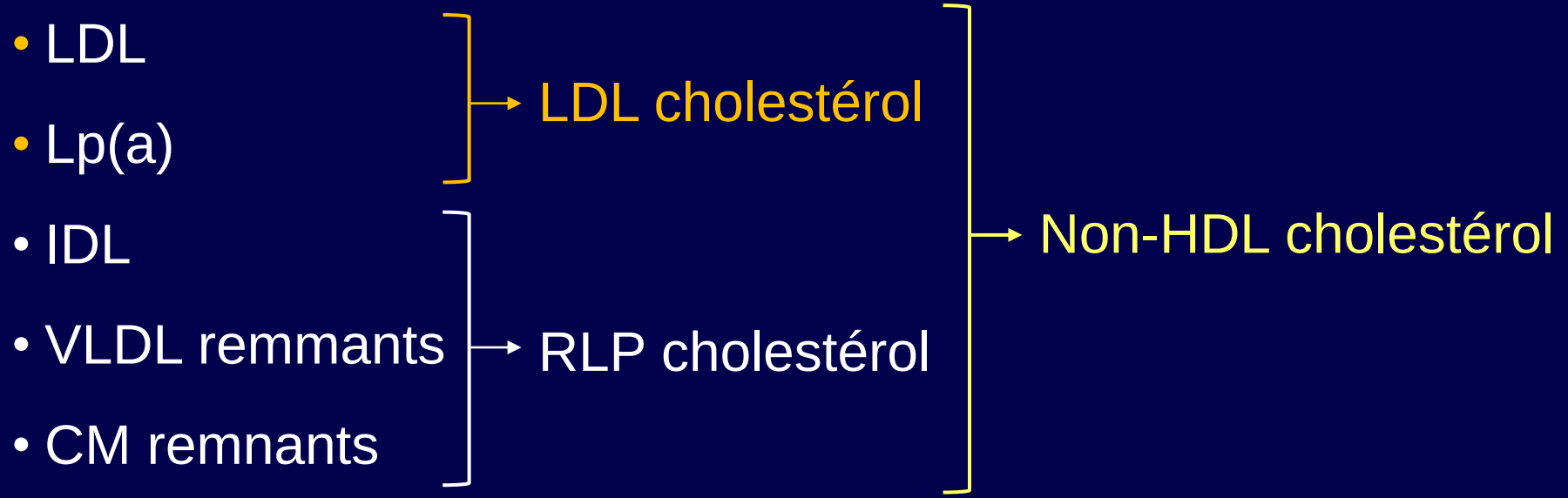


ApoB-lipoproteins up to only ≈ 70 nm in diameter (remnants, IDL, LDL, Lp(a)) can efficiently cross an intact endothelium (the smaller ones pass more readily than the larger ones)

Borén et al. Curr Opin Lipidol 2016; 27: 473-83

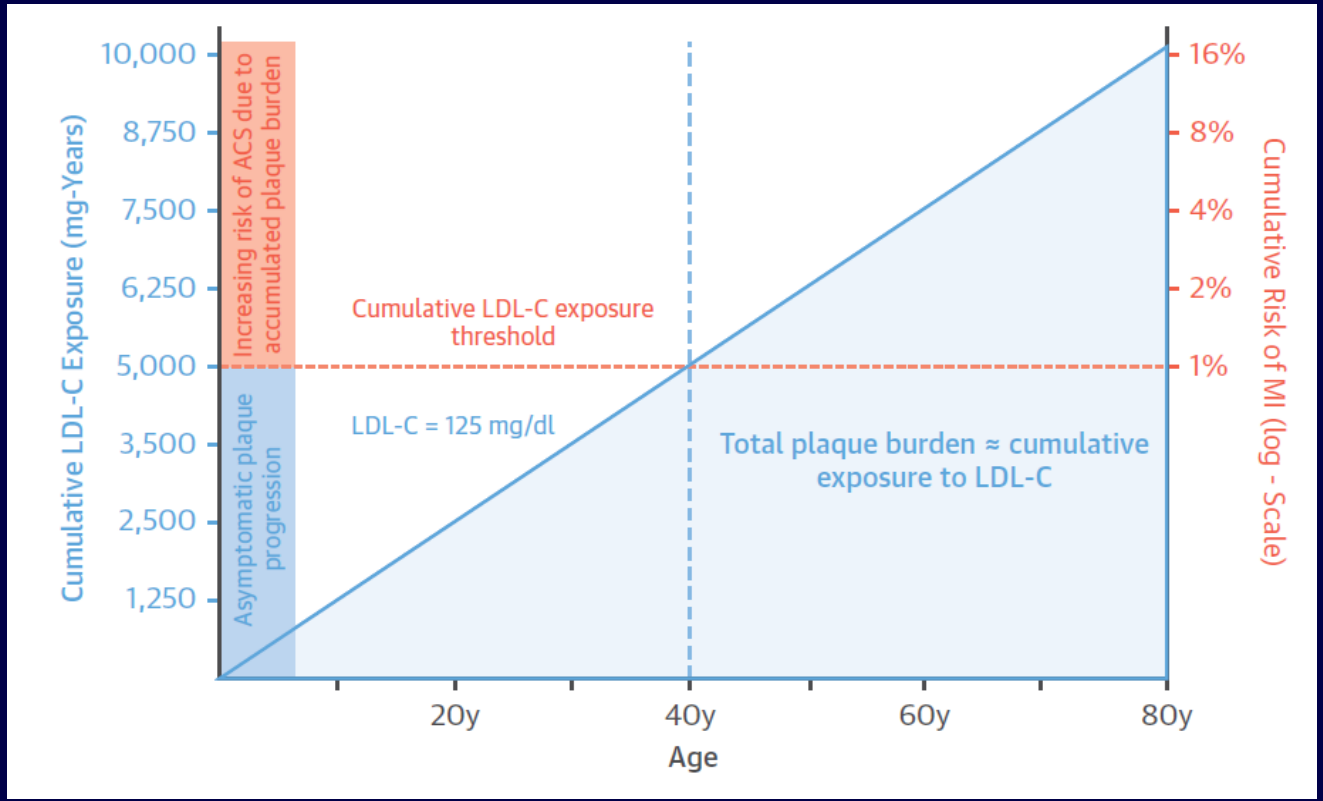
Cholestérol des lipoprotéines riches en apoB

(pas trop larges)



CM: chylomicrons; RLP: remnant

Effect of cumulative exposure to LDL on plaque burden and risk of cardiovascular disease



Ference et al. J Am Coll Cardiol 2018; 72: 1141-56

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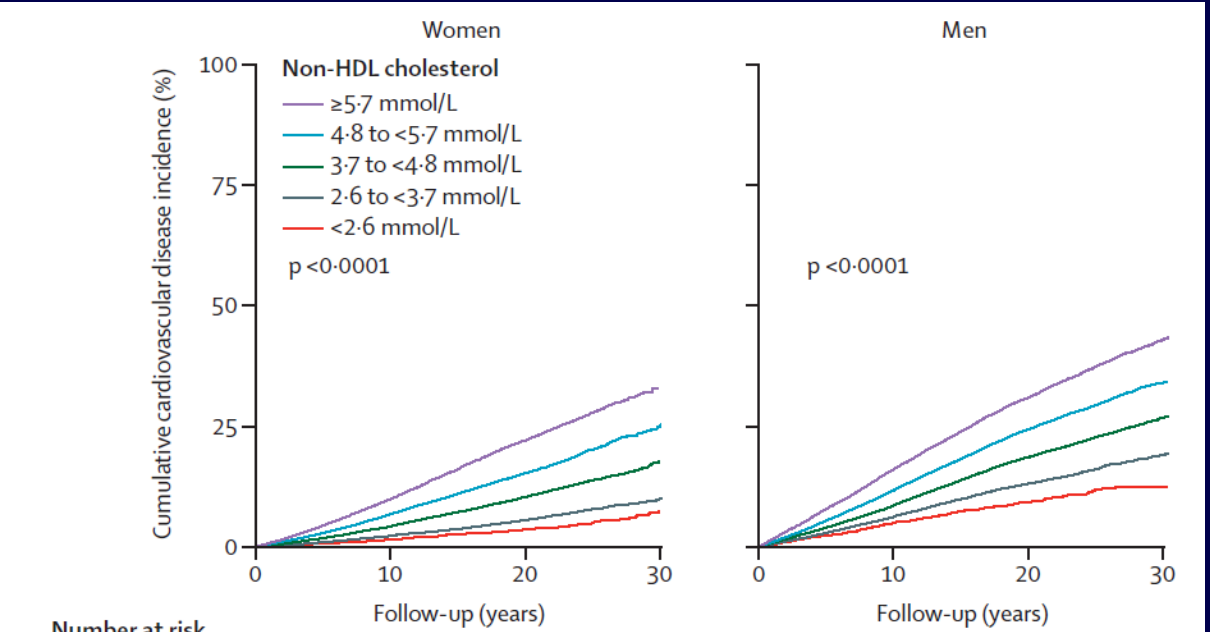
Application of non-HDL cholesterol for population-based cardiovascular risk stratification: results from the Multinational Cardiovascular Risk Consortium

Lancet 2019; 394: 2173–83

Fabian J Brunner, Christoph Waldeyer*, Francisco Ojeda, Veikko Salomaa, Frank Kee, Susana Sans, Barbara Thorand, Simona Giampaoli, Paolo Brambilla, Hugh Tunstall-Pedoe, Marie Moitry, Licia Iacoviello, Giovanni Veronesi, Guido Grassi, Ellisiv B Mathiesen, Stefan Söderberg, Allan Linneberg, Hermann Brenner, Philippe Amouyel, Jean Ferrières, Abdonas Tamosiunas, Yuriy P Nikitin, Wojciech Drygas, Olle Melander, Karl-Heinz Jöckel, David M Leistner, Jonathan E Shaw, Demosthenes B Panagiotakos, Leon A Simons, Maryam Kavousi, Ramachandran S Vasan, Robin P F Dullaart, S Goya Wannamethee, Ulf Risérus, Steven Shea, James A de Lemos, Torbjørn Omland, Kari Kuulasmaa, Ulf Landmesser, Stefan Blankenberg, on behalf of the Multinational Cardiovascular Risk Consortium†*

Interpretation Non-HDL cholesterol concentrations in blood are strongly associated with long-term risk of atherosclerotic cardiovascular disease. We provide a simple tool for individual long-term risk assessment and the potential benefit of early lipid-lowering intervention. These data could be useful for physician–patient communication about primary prevention strategies.

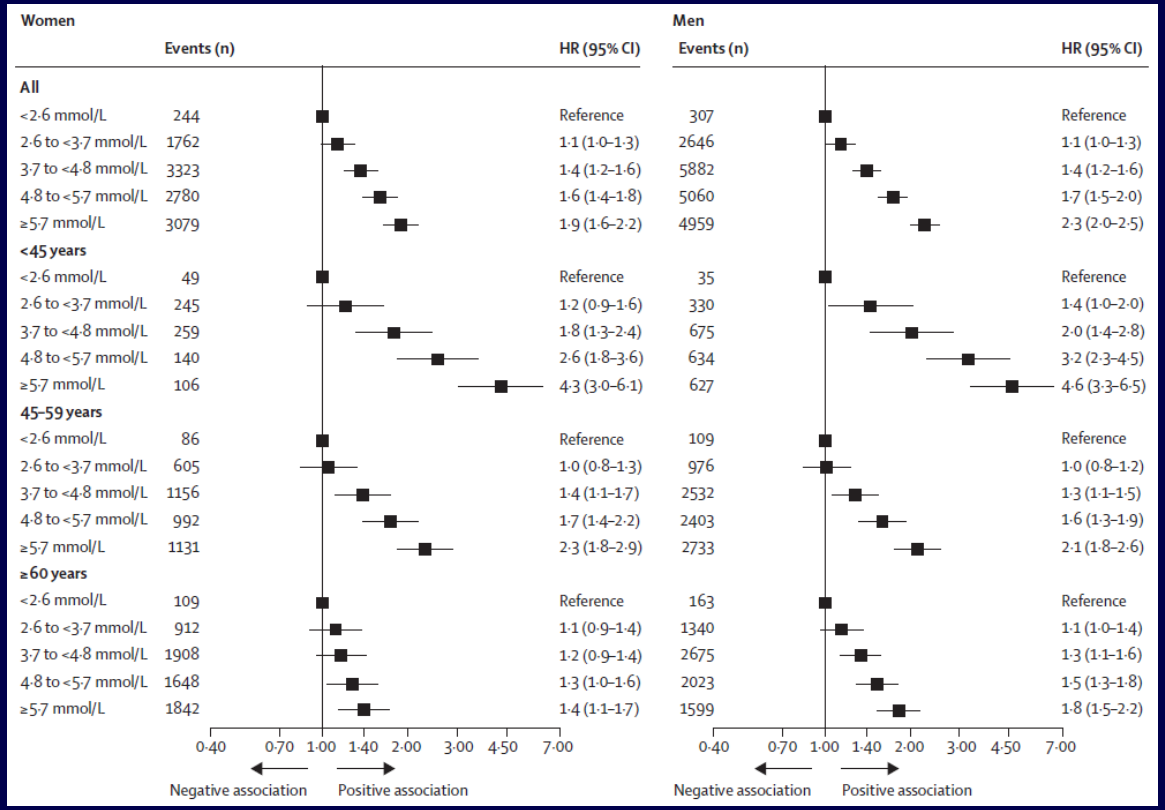
Incidence of cardiovascular disease across non-HDL-C thresholds



Number at risk								
≥5·7 mmol/L	19101	11502	3758	39	29955	17871	4036	349
4·8 to <5·7 mmol/L	26054	15534	5374	104	40190	24087	5605	358
3·7 to <4·8 mmol/L	47516	28175	10061	395	60083	34694	8810	703
2·6 to <3·7 mmol/L	46249	27712	10299	1005	37918	20743	5798	597
<2·6 mmol/L	10216	5801	2034	321	5878	2940	895	129

Brunner et al. Lancet 2019; 394: 2173-83

Age-specific and sex-specific association of non-HDL-C and cardiovascular disease



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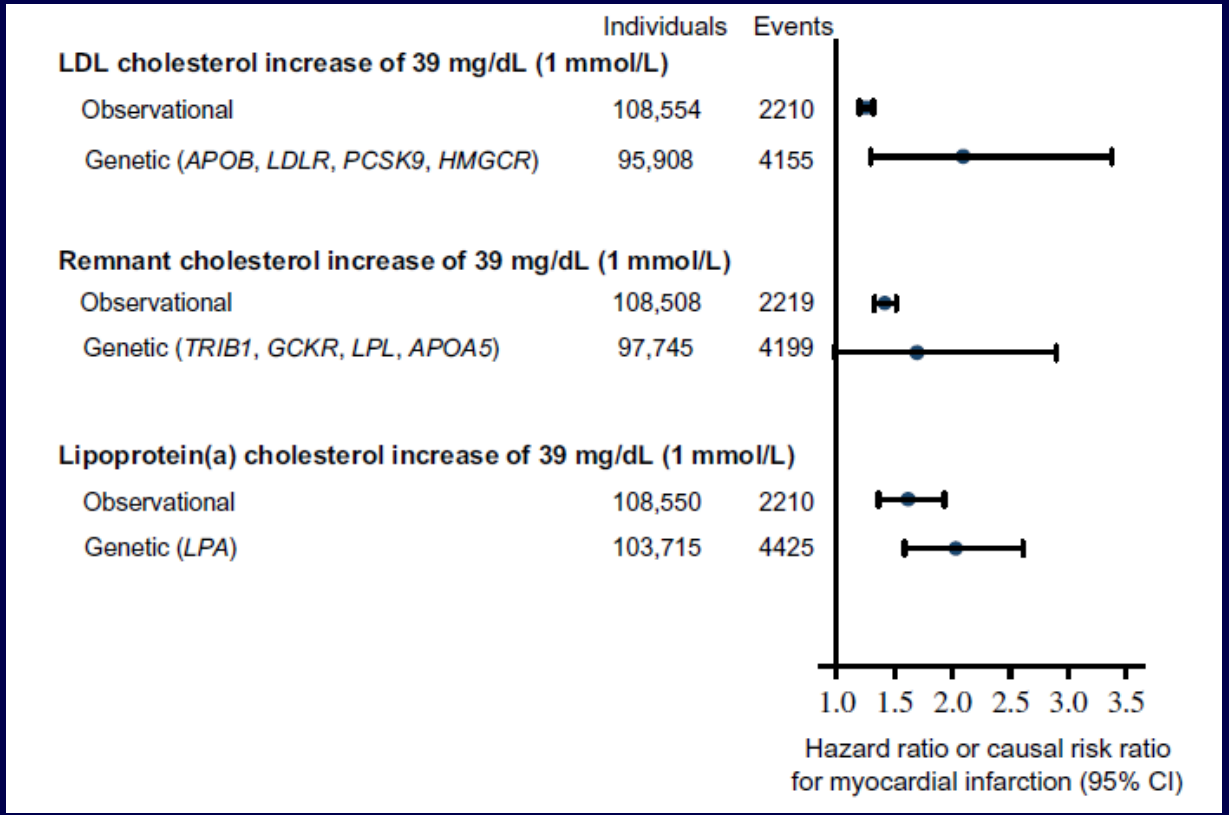
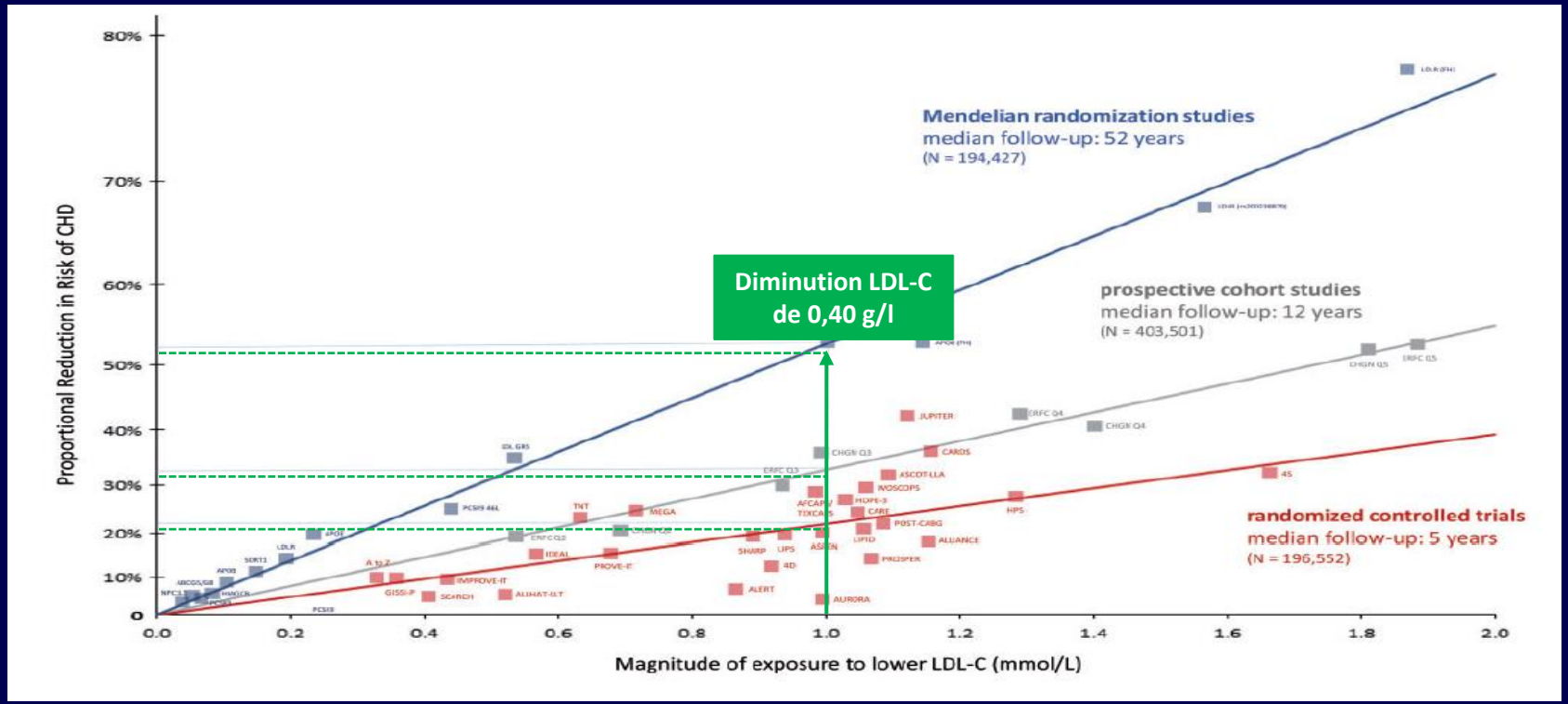
Comparison of risk of MI by 1 mmol/L (39 mg/dL) higher levels of LDL-C, RLP-C and Lp(a)-cholesterol from observational and genetic studies



(data from individuals in the Copenhagen General Population Study)

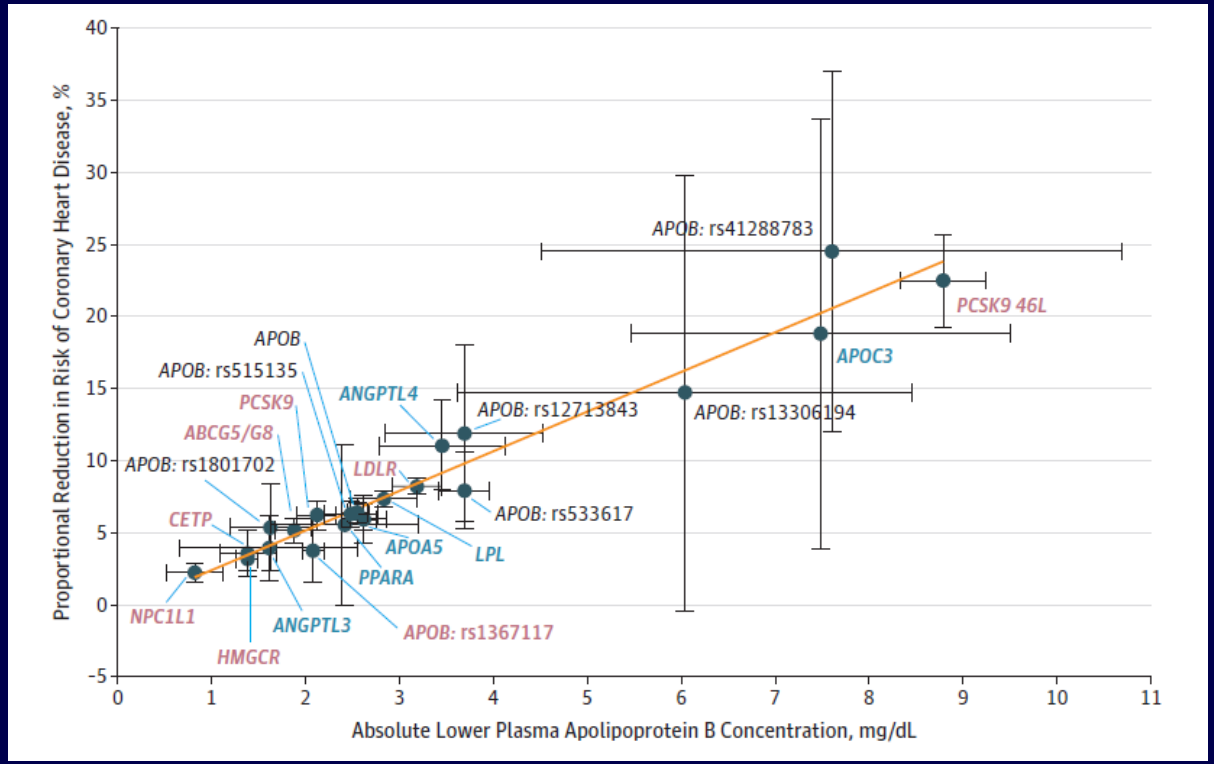
Borén et al. Eur Heart J 2020: online

Log-linear association per unit change in LDL-C and the risk of cardiovascular disease as reported in meta-analyses of Mendelian randomization studies, prospective epidemiologic cohort studies, and randomized trials



Ference et al. Eur Heart J 2017; 38: 2459-72

Association between ApoB differences and lower risk of CHD for each genetic variant



blue: TG genes (LPL pathway)

red: LDL genes (LDL-R pathway)

Ference et al. JAMA 2019; 321: 364-73

(Am J Cardiol 1996;77:575–580)

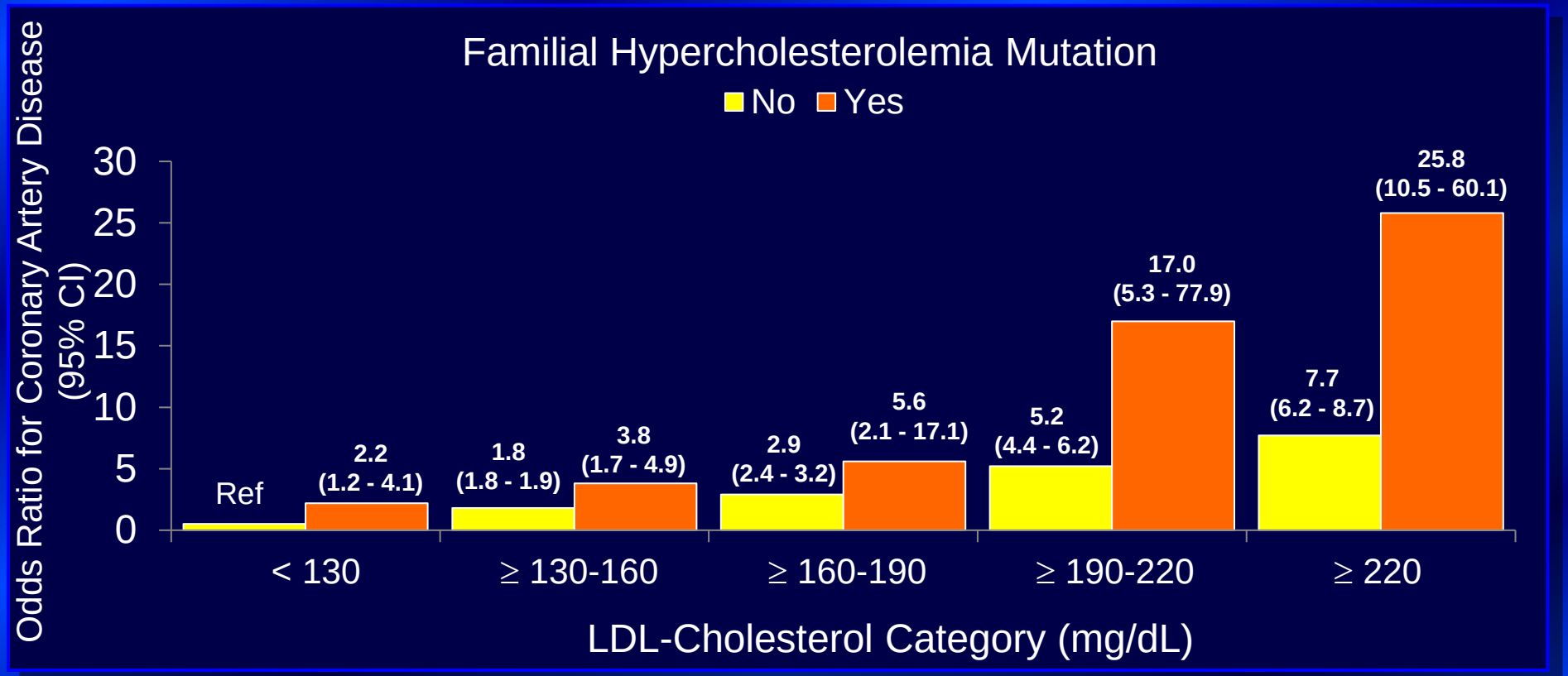
Relation of Cholesterol-Year Score to Severity of Calcific Atherosclerosis and Tissue Deposition in Homozygous Familial Hypercholesterolemia

Hartmut H.-J. Schmidt, MD, Suvimol Hill, MD, Erini V. Makariou, MD, Irwin M. Feuerstein, MD, Klaus A. Dugi, MD, and Jeffrey M. Hoeg, MD

- 17 patients, mean age : 28, mean baseline TC: 780 mg/dL, LDL-C: 676 mg/dL, mean chol-years 15 643 mg-yr/dL

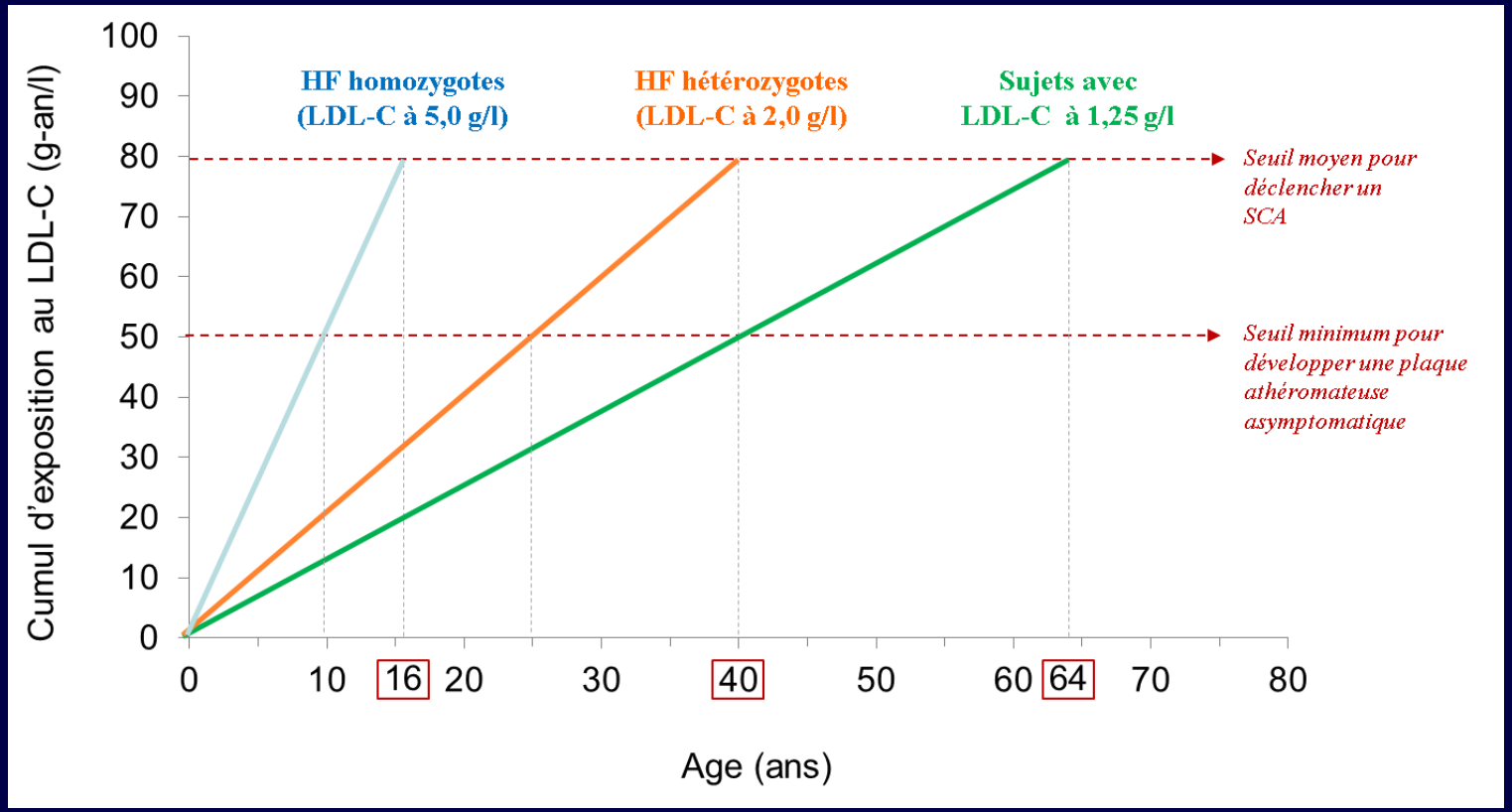
- tous les patients avec un score > 166 g-ans/l avaient des lésions coronaires
- d'où un patient avec un CT à 3 g/l aurait des lésions coronaires à environ 55 ans

For a given observed LDL, FH Mutation Carriers are at Increased Coronary Risk



Khera et al. J Am Coll Cardiol 2016; 67: 2578-89

Exposition cumulée au cholestérol et risque d'athérosclérose asymtomatique ou de SCA



HF: hypercholestérolémie familiale

Adapted from Ference et al. J Am Coll Cardiol 2018; 72: 1141-56.

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Implications thérapeutiques

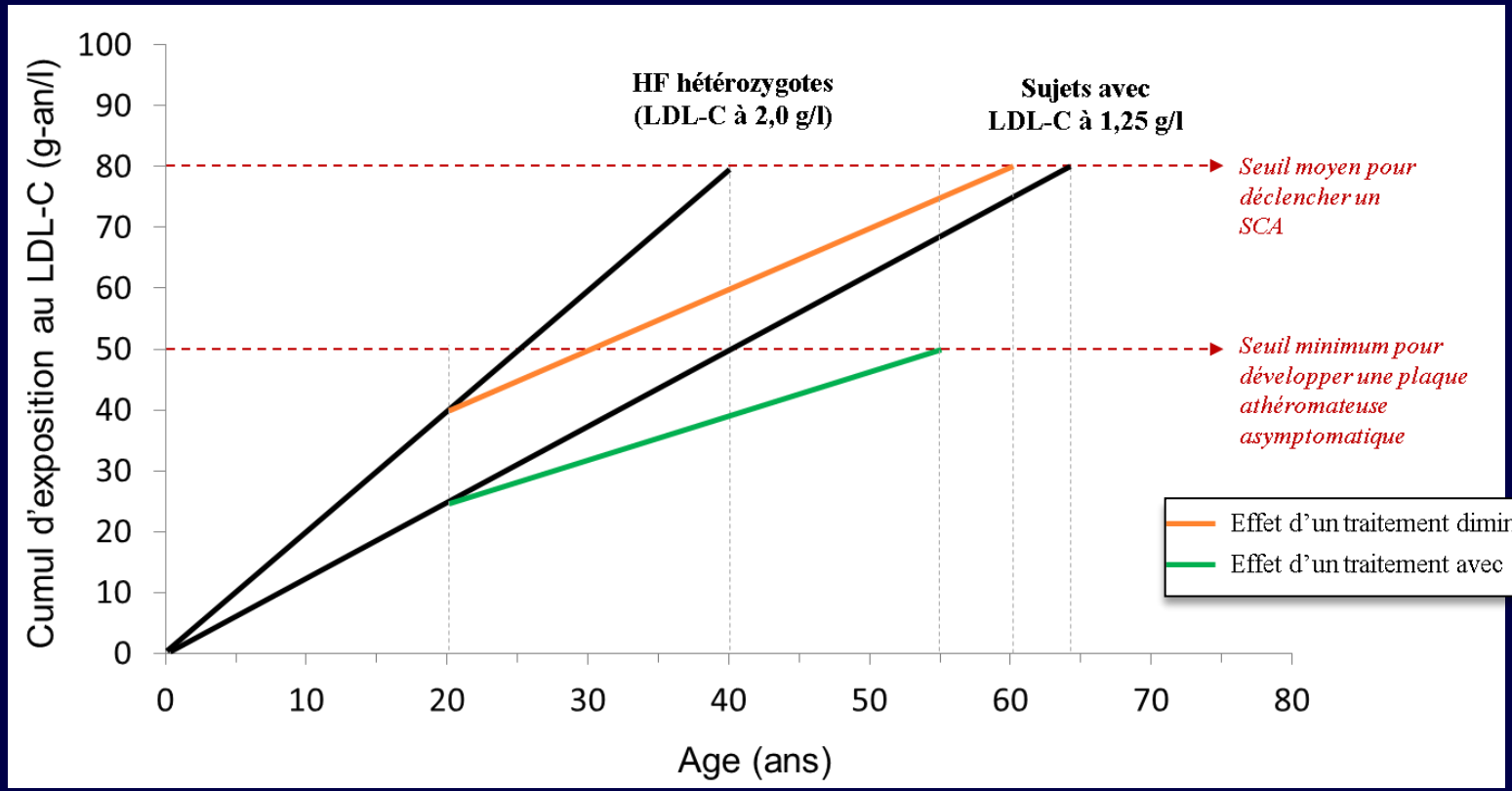
- ☑ Arguments pour traiter tôt en prévention primaire
- ☑ Arguments pour traiter plus fort, en particulier en prévention secondaire

La durée de l'exposition à un taux élevé de LDL-C (ou Non-HDL-C) conditionne le pronostic

Conséquences pratiques

- Dépister tôt :
  dès l'âge adulte et dès l'enfance (8-10 ans) en cas de HF
- pas de calcul de risque par SCORE / Framingham avant 40 ans
  sujets jeunes sont « classés » à bas risque sur 10 ans
- Présence de HF ➡ Haut risque

Illustration de stratégies d'intervention en prévention primaire (illustrant l'intérêt de traiter tôt)



Adapted from Ference et al. J Am Coll Cardiol 2018; 72: 1141-56.

Lancet Diabetes Endocrinol
2020; 8: 36–49

Intensive LDL cholesterol-lowering treatment beyond current recommendations for the prevention of major vascular events: a systematic review and meta-analysis of randomised trials including 327 037 participants

Nelson Wang, Jordan Fulcher, Nishan Abeysuriya, Laura Park, Shejil Kumar, Gian Luca Di Tanna, Ian Wilcox, Anthony Keech, Anthony Rodgers, Sean Lal

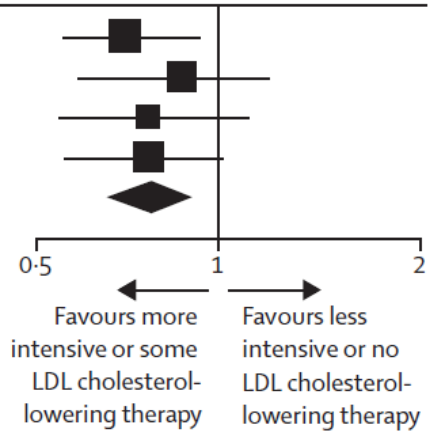
Interpretation For each 1 mmol/L LDL cholesterol lowering, the risk reduction of major vascular events is independent of the starting LDL cholesterol or the presence of diabetes or chronic kidney disease. Patients at lower cardiovascular risk and younger age might have a similar relative reduction in risk with LDL-cholesterol lowering therapies and future studies should investigate the potential benefits of earlier intervention.

Relative risk of major vascular events per 1mmol/L reduction in LDL-C, by baseline LDL-C concentration

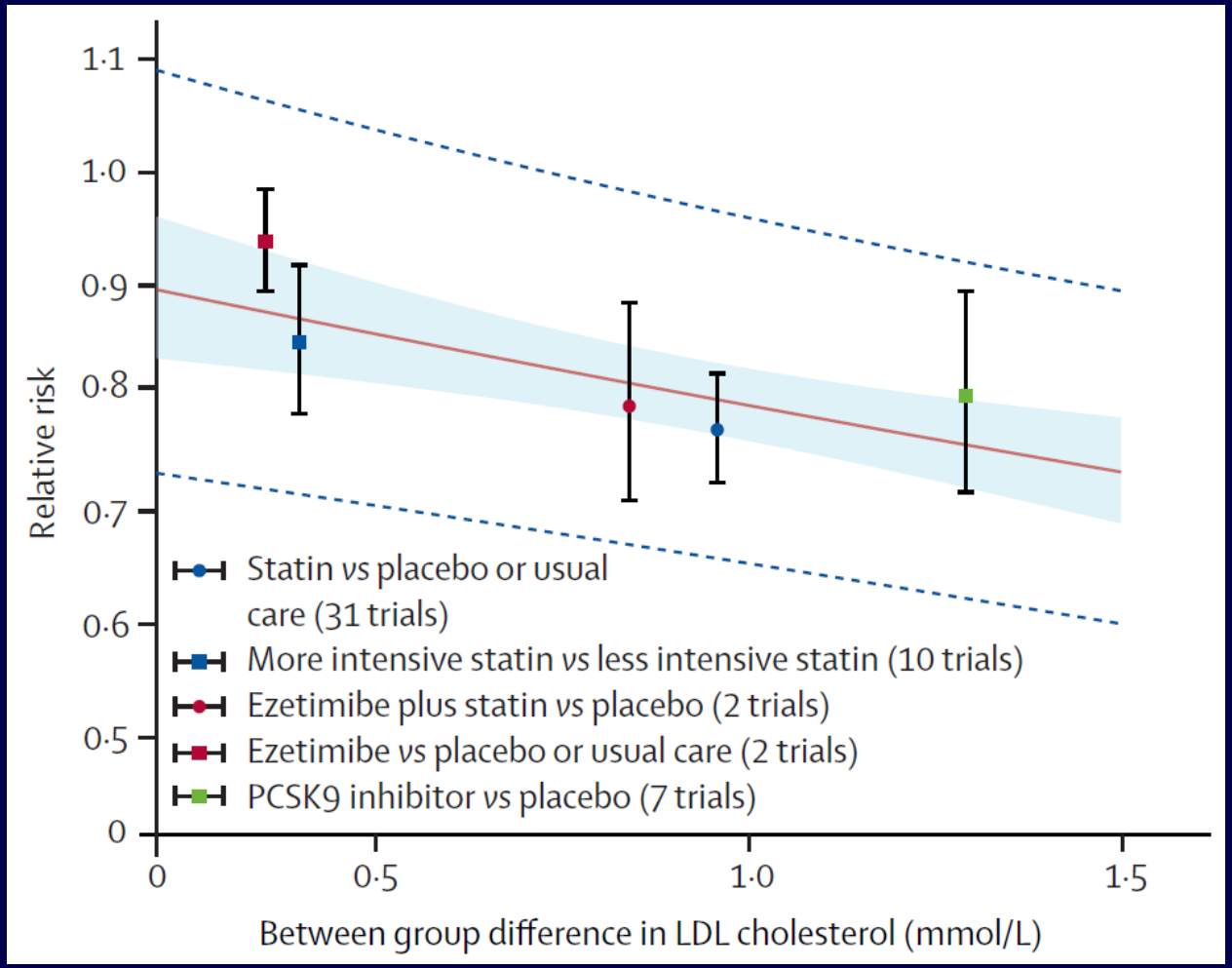
Meta-analysis of subgroups of patients with LDL-C less than 2,07 mmol/L (80 mg/dL)

Studies	Baseline LDL-cholesterol (mmol/L)	Patients	Events (% per year)		RR (95% CI)
			More intensive or some LDL cholesterol-lowering therapy	Less intensive or no LDL cholesterol-lowering therapy	
CTTC	<2·00	9120	923 (4·1)	1020 (4·6)	0·79 (0·65–0·96)
IMPROVE-IT	<2·04	4542	123 (5·4)	129 (5·7)	0·90 (0·73–1·11)
FOURIER	<1·81	2034	86 (3·8)	106 (4·8)	0·81 (0·62–1·06)
ODYSSEY OUTCOMES	<2·07	7164	106 (3·0)	122 (3·4)	0·82 (0·66–1·01)
Overall	**<2·07**	**22 860**	**1238**	**1377**	**0·83 (0·75–0·92)**

Test for heterogeneity I^2=0%, p=0·820



Wang et al. Lancet Diabetes Endocrinol 2020; 8: 36-49



Meta-regression plot showing relative risk of major vascular events according to extent of LDL-C lowering with various drug classes of LDL-C-lowering therapy

Wang et al. Lancet Diabetes Endocrinol 2020; 8: 36-49

Take Home Messages : En pratique

- ☑ Dépister le plus tôt possible
- ☑ Evaluer (si possible) la durée d'exposition
- ☑ Dépister les lésions infra-cliniques
- ☑ Pour sujets haut / très haut risque, traiter rapidement, fort, longtemps

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