Hypercholestérolémie:

Introduction

Intolérance aux statines

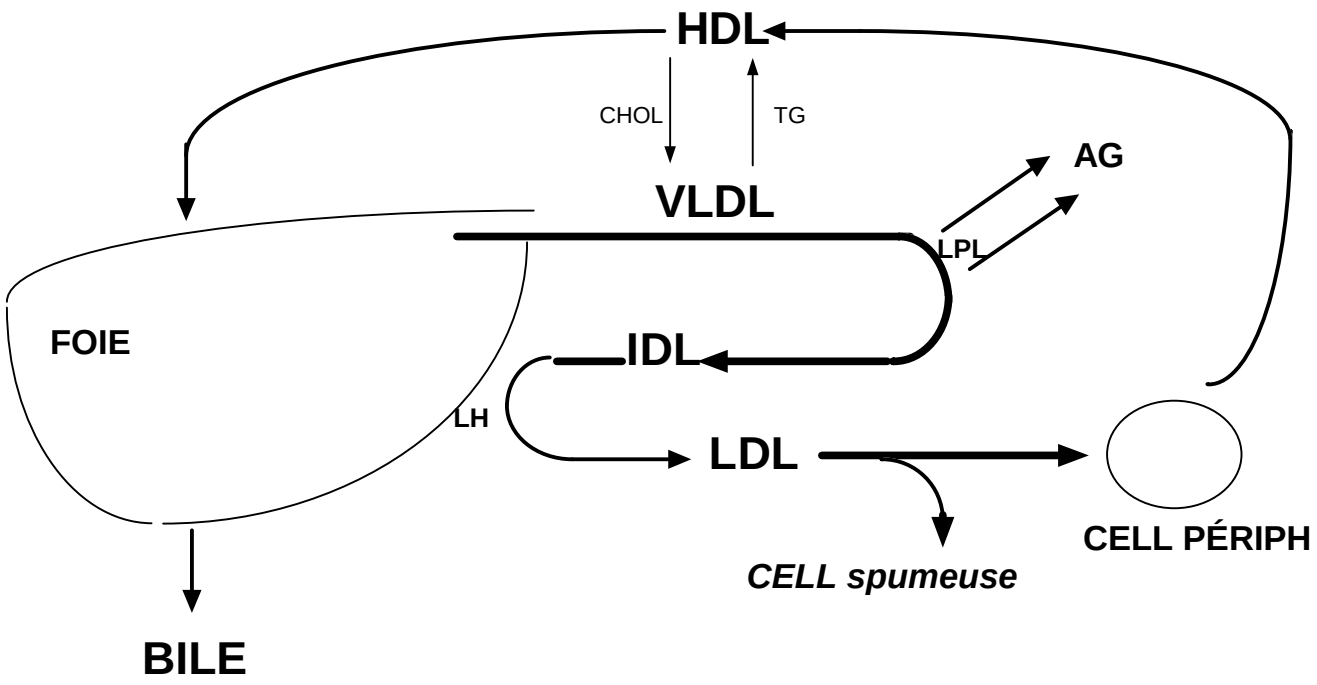
V Rigalleau 2014

Conflits d’intérêts

- **1996: prix de recherche en nutrition CIDEF* (50000 FF) pour le projet "Rôle des interactions lipides-glucides … »**
- **1999: prix de recherche en nutrition de l'Institut Appert (50000 FF) et subvention du conseil Régional d’Aquitaine (40000 FF) pour le projet "Effet des acides gras … »**
- **2011: Président comité de Titration essai GALAPAGOS (Sanofi-Aventis)**
- Bourses : Servier, Roche, Merck-Lipha
- Partenariats : Bayer, GSK, Novo, Lilly, Pfizer, Takeda, Scherring-Plough, MSD, Novartis

- * CIDEF: Comité Interprofessionnel de la Dinde en France

Métabolisme lipidique à jeun



(acides biliaires)

Métabolisme des lipoprotéines à jeun: « Règles »

- 1 pas de CM
- 2 TG : aller simple / Cholestérol: aller-retour
- 3 Toute élévation des TG est une élévation des VLDL, contenant 1g cholestérol/5g TG
- 4 L'échange HDL-VLDL fait que la plupart des HTG s'accompagnent d 'une baisse du HDL-C
- 5 Le cholestérol athérogène vient des LDL;
  LDLC = CT-(HDLC + TG/5) selon Friedwald

Interprétation de l ’EAL

- 1 TG>10g --> HTG urgente (diététique)
- 2 TG>4g --> HTG : diététique, fibrate
- **3 LDL-C≥1,6g (sans FR ni ATCD CV) --> Hchol**
  - **diététique**
  - **Décompte des FRCV pour indication médicamenteuse**
- 4 TG> 1,5 g/L--> HTG

Intolérance aux statines

Vrai/Faux ?

Les atteintes musculaires sont rares dans les essais.

On peut aussi avoir des douleurs sans statine

?

Prevalence of Musculoskeletal Pain and Statin Use

Catherine Buettner, MD, MPH[1,4], Roger B. Davis, ScD[1,3,4], Suzanne G. Leveille, PhD[1,4], Murray A. Mittleman, MD, DrPH[2,4,5], and Kenneth J. Mukamal, MD, MPH, MA[1,4]

J Gen Intern Med 2008

MEASUREMENTS AND MAIN RESULTS: Prevalence and adjusted odds ratios (OR) of any musculoskeletal pain and musculoskeletal pain in 4 different anatomical regions (neck/upper back, upper extremities, lower back, and lower extremities) by statin use during the last 30 days. Among statin users (n=402), 22.0% (95% CI 18.0–26.7%) reported musculoskeletal pain in at least 1 anatomical region during the last 30 days, compared with 16.7% (95%CI 15.1–18.4%) of those who did not use a statin. Compared to persons who did not use statins, those who used statins had multivariable-adjusted odds ratios (95%CI; p value) of 1.50 (1.07–2.11; p=.01) for any musculoskeletal pain, 1.59 (1.04–2.44, p=.03) for lower back pain, and 1.50 (1.02–2.22, p=.03) for lower extremity pain.

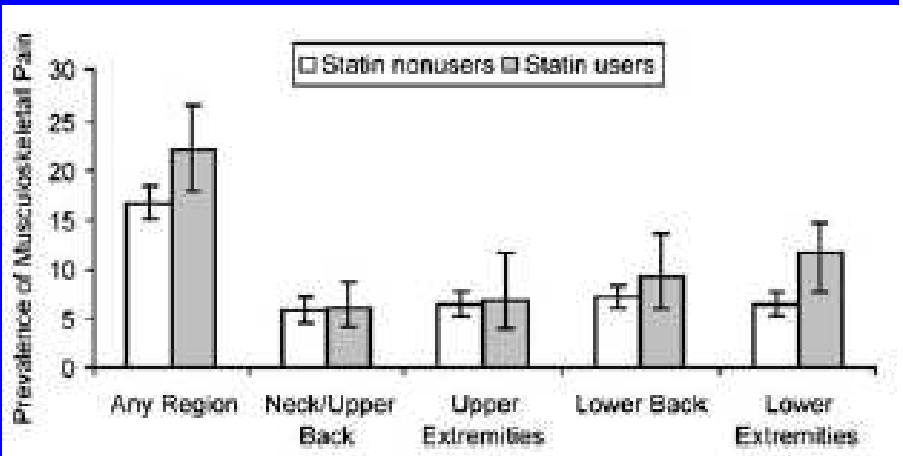


Figure 1. Unadjusted weighted prevalence estimates (percent) and 95% confidence intervals of any musculoskeletal pain and musculoskeletal pain at 4 different anatomical regions according to statin use (p=.01, p=.86, p=.80, p=.26, p=.03, respectively).

Il y a des douleurs sous statines,

mais le rapport:
bénéfice cardiovasculaire /
risque musculaire
est TOUJOURS favorable
dans les essais

?

Weighing the Benefits of High-Dose Simvastatin against the Risk of Myopathy

Amy Egan, M.D., M.P.H., and Eric Colman, M.D.

NEJM 2011

- Essai SEARCH: (*Lancet 2010*)
  - 80mg vs 20mg Simva après infarctus
  - 24,5% vs 25,7% evts CV à 7 ans (p=0,10)
  - 52 (0,9%) vs 1 myopathies (douleur, faiblesse, CK x10)
  - 22 vs 0 rhabdomyolyses
  - Risque ++ la 1ère année (ensuite ÷5)

Key Components of Recent Safety-Labeling Changes for Simvastatin

1. Use of the 80-mg dose of simvastatin should be restricted to patients who have been taking it for a long time (e.g., 12 months or more) without signs or symptoms of clinically significant toxic effects on muscle.
2. Patients who are currently taking an 80-mg dose of simvastatin without adverse effects but who need to begin taking an interacting drug that is contraindicated or is associated with a dose cap for simvastatin should be switched to an alternative statin with less potential for a drug–drug interaction.
3. Patients in whom the LDL cholesterol goal cannot be achieved with a 40-mg dose of simvastatin should instead be given other appropriate LDL cholesterol–lowering therapy (e.g., a more potent statin that poses a lower risk of myopathy, such as atorvastatin or rosuvastatin).

Drug Interactions Associated with Increased Risk of Myopathy and Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Itraconazole	Contraindicated with simvastatin
Ketoconazole	
Posaconazole	
Erythromycin	
Clarithromycin	
Telithromycin	
HIV protease inhibitors	
Nefazodone	
Gemfibrozil	
Cyclosporine	
Danazol	
Amiodarone	Do not exceed 10 mg of simvastatin daily
Verapamil	
Diltiazem	
Amlodipine	Do not exceed 20 mg of simvastatin daily
Ranolazine	
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 qt daily)

Les statines sont de bons médicaments.

Chez quelques patients malchanceux elles ont une toxicité musculaire, avec l ’une ou l ’autre des statines.

?

The muscle-specific ubiquitin ligase atrogin-1/MAFbx mediates statin-induced muscle toxicity

Jun-ichi Hanai,[1] Peirang Cao,[1] Preeti Tanksale,[1] Shintaro Imamura,[2,3] Eriko Koshimizu,[3,4] Jinghui Zhao,[5] Shuji Kishi,[3] Michiaki Yamashita,[2] Paul S. Phillips,[6] Vikas P. Sukhatme,[1] and Stewart H. Lecker[1]

JCI 2007

Dénutrition, cancer, sepsis diabète, ins rénale,cardiaque

Atrophy related genes : « Atrogens »

Protéasome

Perte musculaire

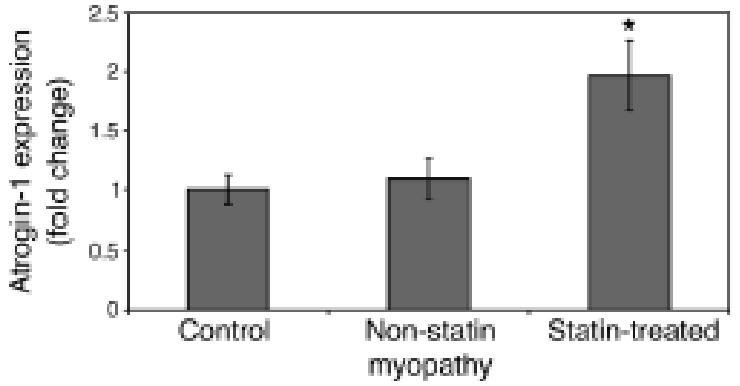


Figure 1
Atrogin-1 is induced in human biopsy samples from patients with statin-induced muscle injury. Total RNA was extracted from human quadriceps muscle biopsies, and *atrogin-1* mRNA was quantitated by real-time PCR as described in Methods. *$P = 0.017$, difference between groups by 1-way ANOVA.

La lovastatine abime la chair de Zebrafish

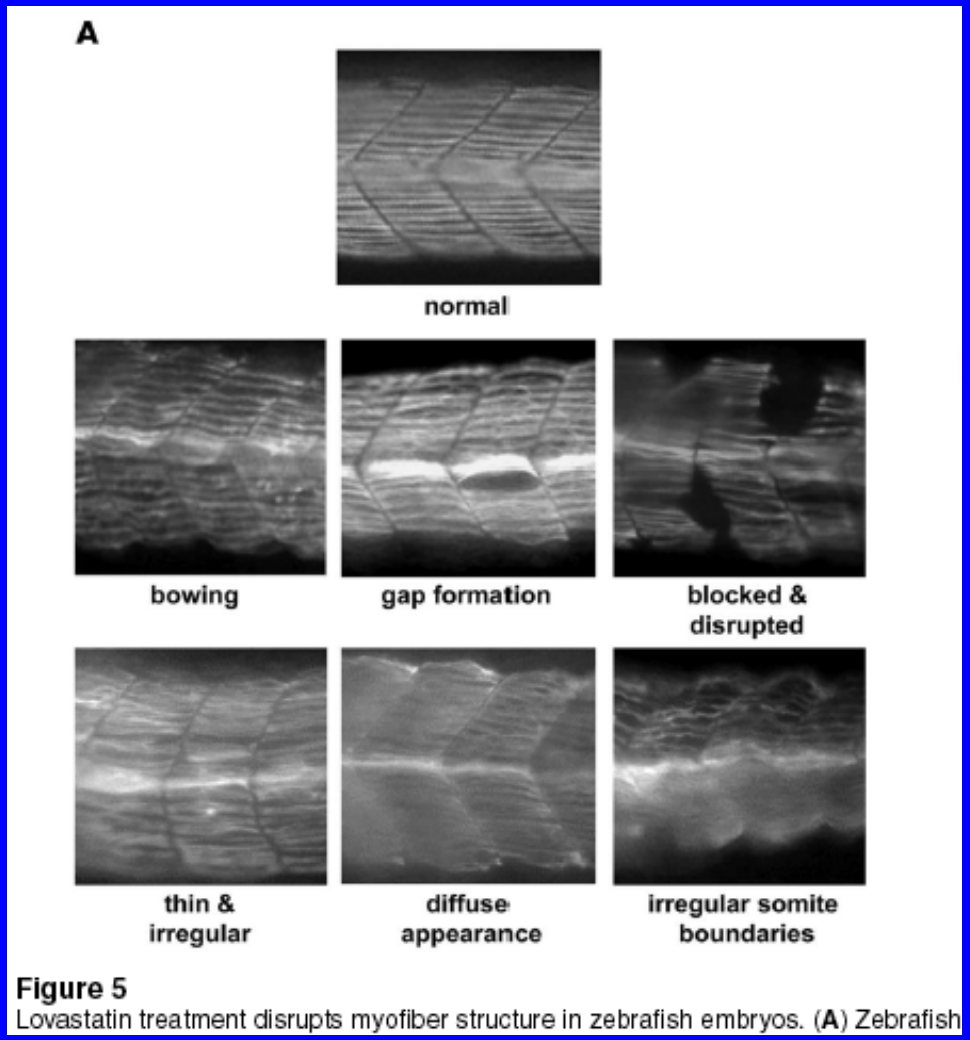
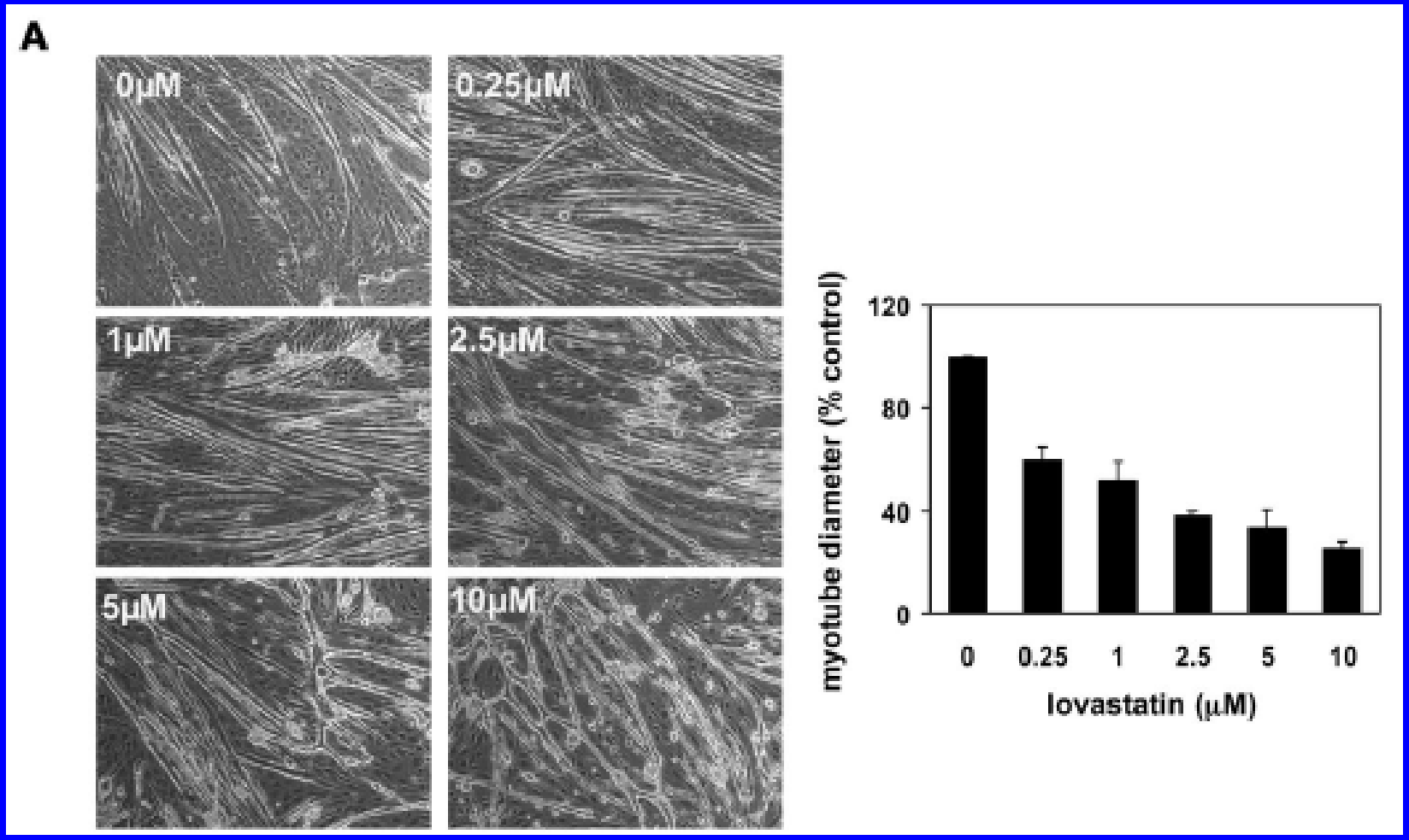
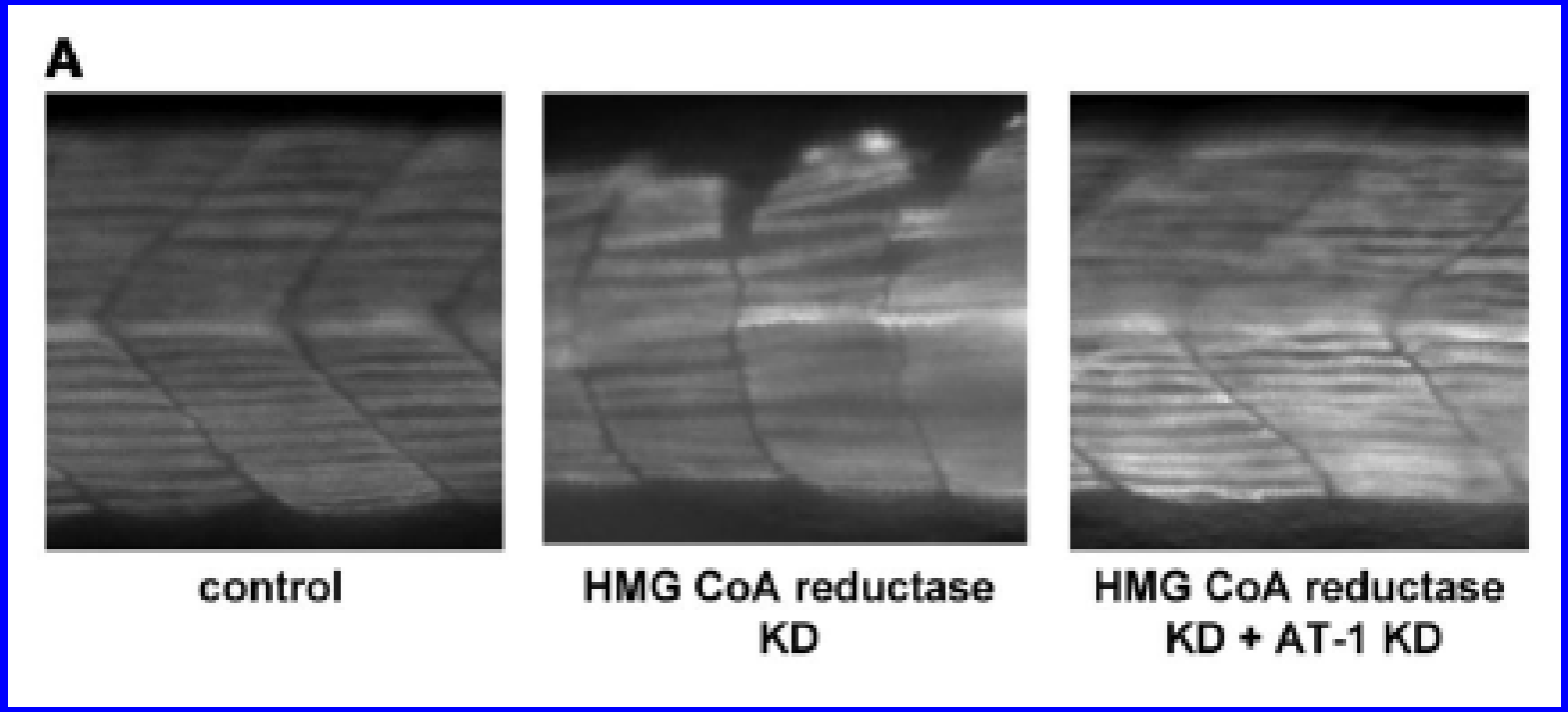


Figure 5
Lovastatin treatment disrupts myofiber structure in zebrafish embryos. (**A**) Zebrafish

Lésions des myotubes en culture sous lovastatine



la chair de Zebrafish KO pour l'HMG CoA réductase est abimée



Les myotubes de souris KO pour l ’atrogine résistent à la lovastatine

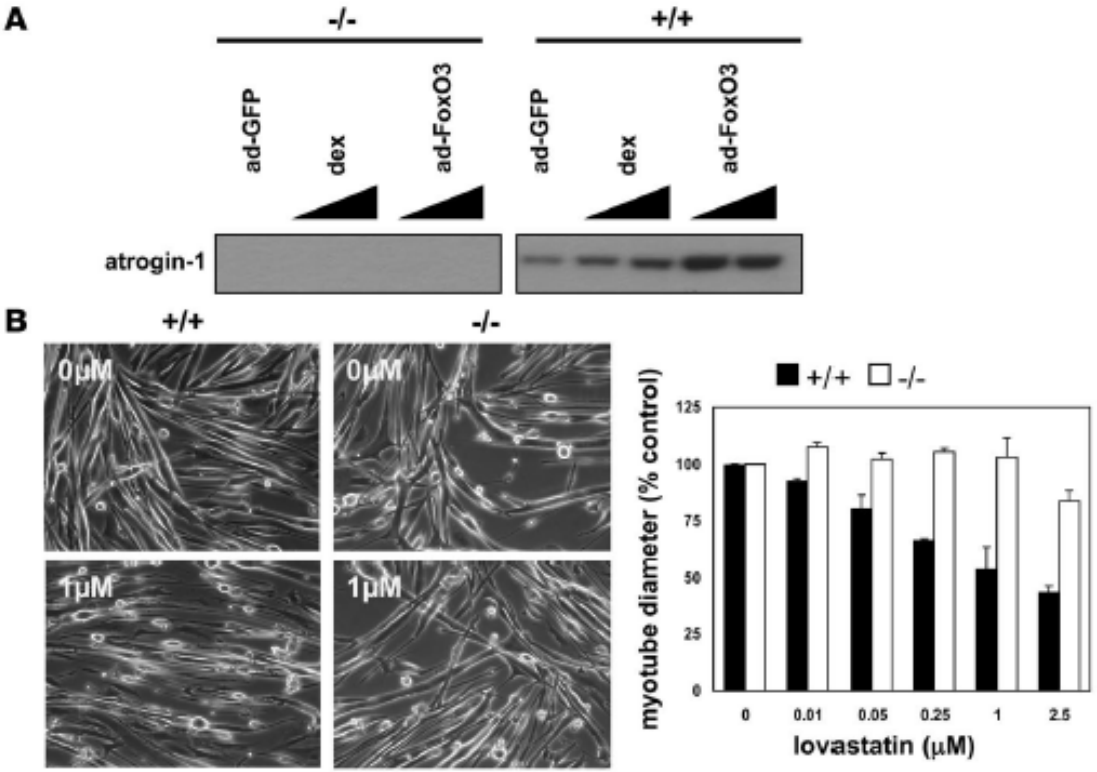
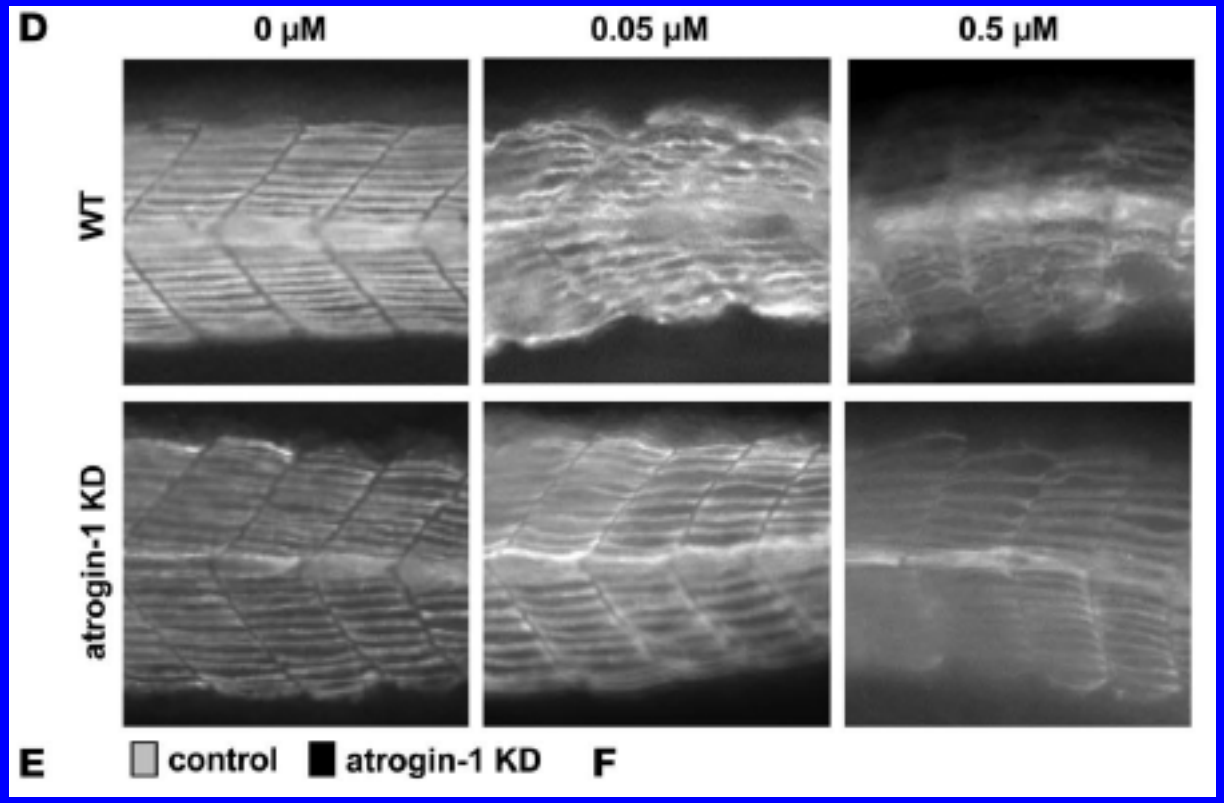


Figure 4
Myotubes from *atrogin-1* null (–/–) mice are resistant to lovastatin-induced damage. (**A**) Atrogin-1 protein expression is absent in *atrogin-1* null (–/–) myotubes. Myoblasts derived from *atrogin-1* knockout mice (–/–) and corresponding wild type (+/+) littermates were differentiated into myotubes. Cultures were stimulated to express atrogin-1 with dexamethasone (5 μM) or infected with constitutively active FoxO3- or GFP-expressing adenovirus (45). Atrogin-1 expression was detected by Western blotting as in Figure 3. (**B**) Myotubes from *atrogin-1* null (–/–) and wild-type (+/+) mice were treated with lovastatin at the indicated concentrations for 48 hours. Myotube morphology was examined, and diameter was measured. Original magnification, ×100.

La chair de Zebrafish KO pour l ’atrogine résiste à la lovastatine



Les statines peuvent
entrainer des myalgies.

Ce sont surtout certains patients,
difficiles,
qui s'en plaignent.

?

SLCO1B1 Variants and Statin-Induced Myopathy — A Genomewide Study

NEJM 2008

The SEARCH Collaborative Group*

METHODS

We carried out a genomewide association study using approximately 300,000 markers (and additional fine-mapping) in 85 subjects with definite or incipient myopathy and 90 controls, all of whom were taking 80 mg of simvastatin daily as part of a trial involving 12,000 participants. Replication was tested in a trial of 40 mg of simvastatin daily involving 20,000 participants.

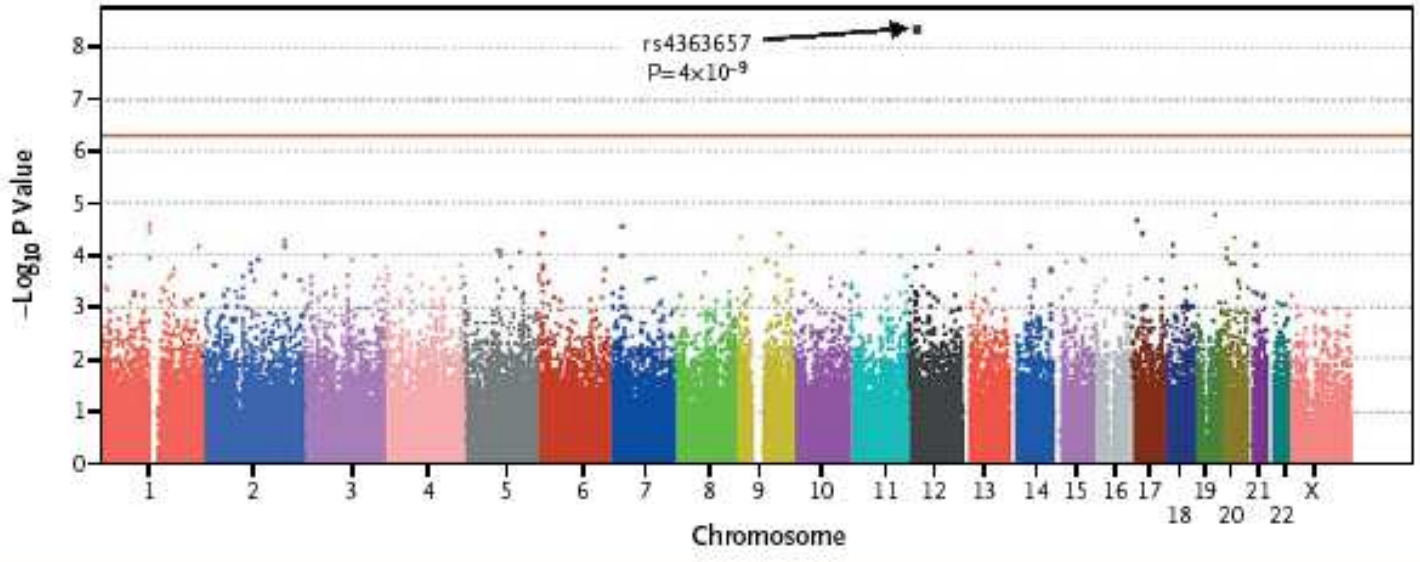
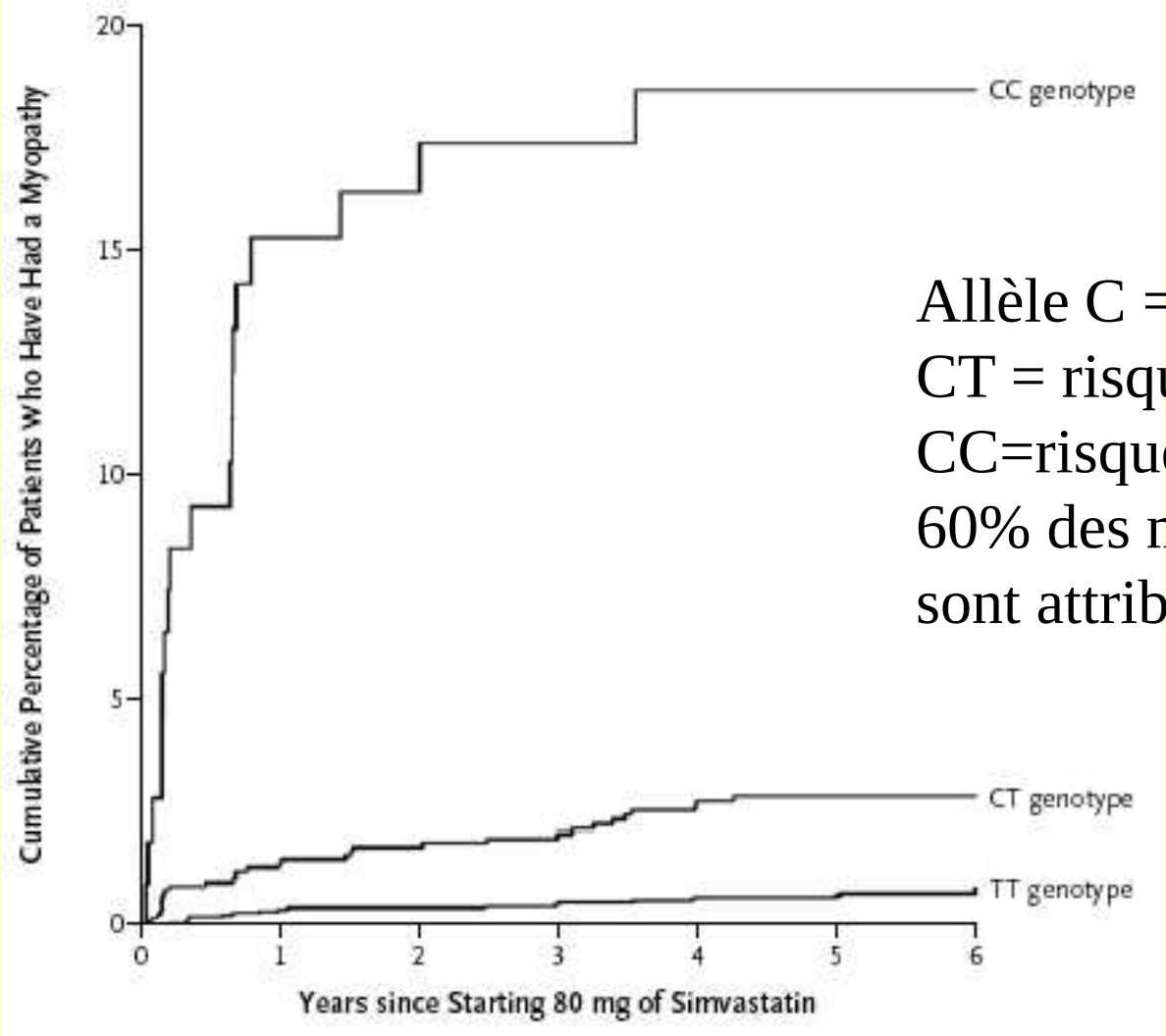


Figure 1. Results of Tests for a Trend in the Association between Myopathy and Each SNP Measured in the Genome-wide Association Study.

SLCO1B1 code un transporteur OATPC qui régule la captation hépatique des statines



Allèle C = 15% de la population
CT = risque X4,5
CC=risque X17
60% des myopathies sous Simva sont attribuables à l ’allèle C

L ’intolérance aux statines existe.

Mais c ’est un petit problème.

?

Needed: Pragmatic Clinical Trials for Statin-Intolerant Patients

Patricia Maningat, M.D., and Jan L. Breslow, M.D.

NEJM 2011

- 20% en pratique courante
  - 5% dans les essais
- Essais randomisés contrôlés ≠ vie réelle:
  - sujets âgés, femmes, alcooliques, polypathologies
  - « Statin induced myopathy »: douleur, CKx10
- Adhérence aux statines à 2 ans:
  - 40% en prévention 2aire, 25% en prévention 1aire

Les fibrates n ’ont pas fait leur preuves concernant les complications cardio vasculaires à long terme.

Mais ils sont mieux tolérés

?

Statin Induced Myopathy and Myalgia: Time Trend Analysis and Comparison of Risk Associated with Statin Class from 1991–2006

Mariam Molokhia[1]*, Paul McKeigue[2], Vasa Curcin[3], Azeem Majeed[4]

Table 7. Case-crossover comparison of myopathy/myalgia based on 16,591 users extracted from the THIN database (1991–2006): Event rates using 26 week cut off for exposure.

Class of Drug	Exposed Events	Un-exposed Events	Rate Ratio 26 weeks	Standard error of RR
	350 p-years	**446 p-yrs**		
Atorvastatin	1401	83	15.2 (12.2–19.0)	0.11
Cerivastatin	59	7	24.7 (11.3–54.1)	0.40
Fluvastatin	92	9	33.3 (16.8–66.0)	0.35
Pravastatin	361	30	25.8 (17.8–37.4)	0.19
Rosuvastatin	128	9	9.9 (5.0–19.4)	0.34
Simvastatin	1825	98	19.5 (15.9–23.9)	0.10
All statins	**3866**	**236**	**19.1(16.7–21.8)**	0.07
Ever use of statin with the following fibrate				
Bezafibrate	82	14	25.4 (14.4–44.8)	0.29
Fenofibrate all	39	2	9.0 (2.2–37.1)	0.73
Ciprofibrate	15	4	40.5 (13.4–122.0)	0.56
All fibrates	136	20	**27.1 (17.0–43.4)**	0.24
ALL statins & fibrates (95% CI)	**4002**	**256**	**19.9 (17.6–22.6)**	**0.06**

significant. Analyses of fibrates prescribed alone showed an overall risk for myalgia/myopathy with all fibrate class (without statin co-prescriptions) was 12.8 (95% CI 6.3–25.9), however this was based on much smaller numbers, and the CI were overlapping for fibrates that had ever been prescribed following statin therapy.

Effects of Medical Therapies on Retinopathy Progression in Type 2 Diabetes

The ACCORD Study Group and ACCORD Eye Study Group*

NEJM 2010

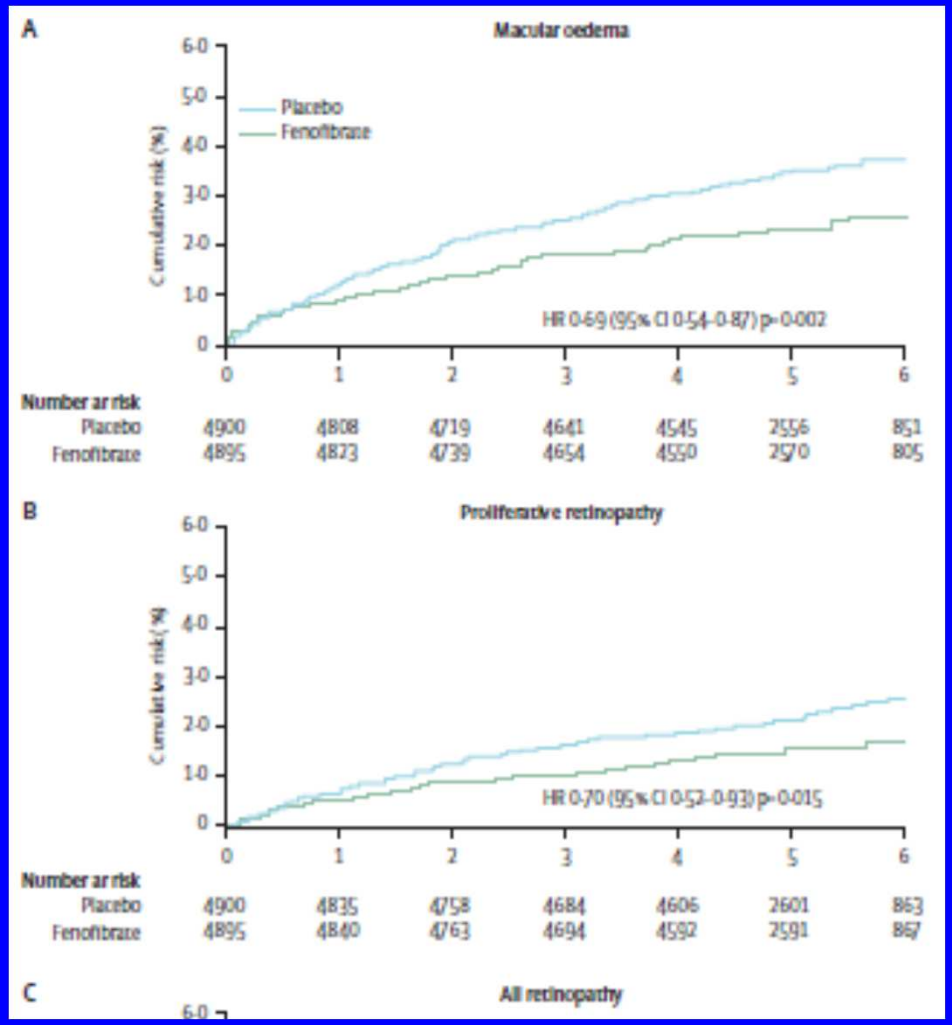
Table 2. Effects of Intensive Glycemic Control, Fenofibrate, and Intensive Blood-Pressure Control on Progression of Diabetic Retinopathy and Moderate Vision Loss.*

Treatment	Progression of Diabetic Retinopathy	Adjusted Odds Ratio (95% CI)	P Value	Moderate Vision Loss	Adjusted Hazard Ratio (95% CI)	P Value
	no./total no. (%)			*no./total no. (%)*		
Glycemia therapy		0.67 (0.51–0.87)	0.003		0.88 (0.77–1.01)	0.06
Intensive	104/1429 (7.3)			409/1715 (23.8)		
Standard	149/1427 (10.4)			457/1737 (26.3)		
Dyslipidemia therapy†		0.60 (0.42–0.87)	0.006		0.95 (0.79–1.14)	0.57
With fenofibrate	52/806 (6.5)			227/956 (23.7)		
With placebo	80/787 (10.2)			233/950 (24.5)		
Antihypertensive therapy		1.23 (0.84–1.79)	0.29		1.17 (0.96–1.42)	0.12
Intensive	67/647 (10.4)			221/798 (27.7)		
Standard	54/616 (8.8)			185/748 (24.7)		

* Moderate vision loss was defined as loss of visual acuity by three or more lines in either eye.
† Dyslipidemia therapy consisted of simvastatin plus either fenofibrate or placebo.

Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial

A C Keech, P Mitchell, P A Summanen, J O'Day, T M E Davis, M S Moffitt, M-R Taskinen, R J Simes, D Tse, E Williamson, A Merrifield, L T Laatikainen, M C d'Emden, D C Crimet, R L O'Connell, P G Colman, for the FIELD study investigators*

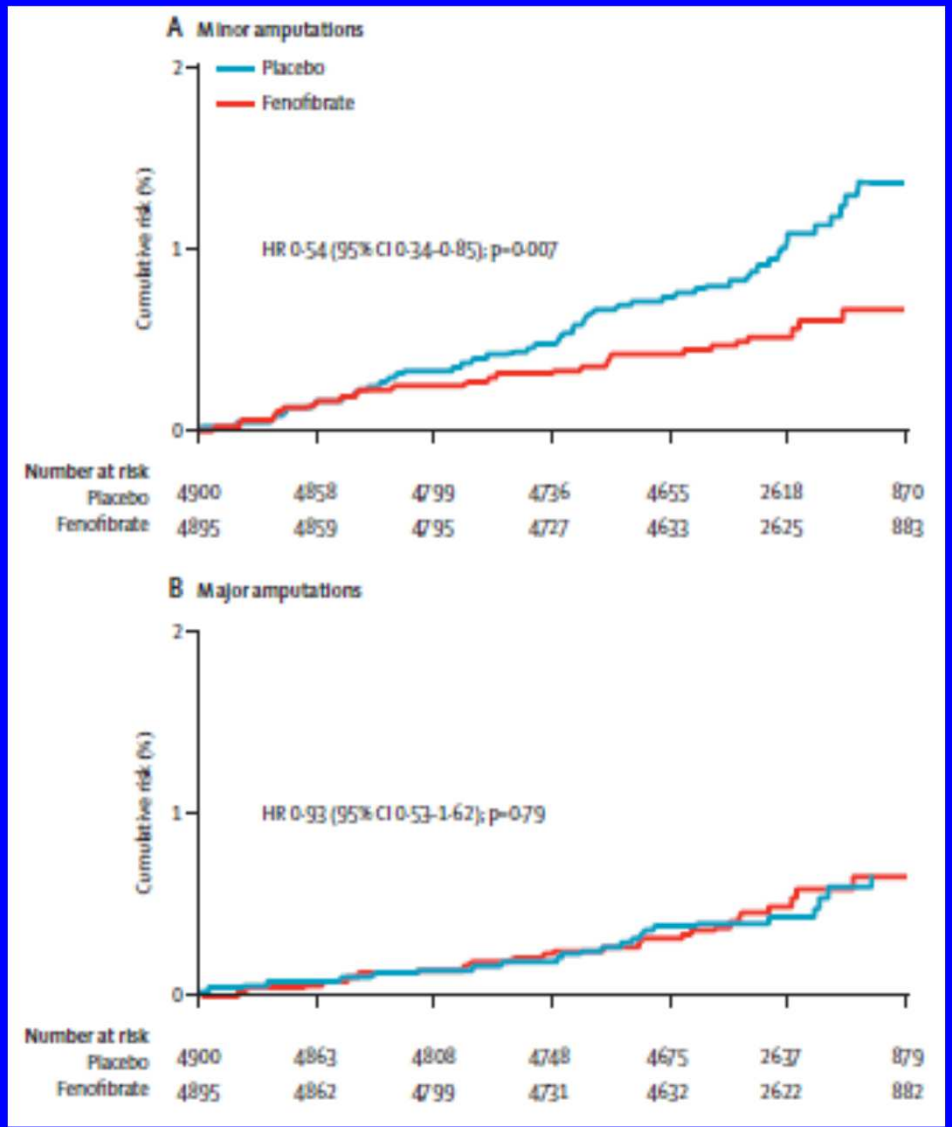


Lancet 2007

Effect of fenofibrate on amputation events in people with type 2 diabetes mellitus (FIELD study): a prespecified analysis of a randomised controlled trial

Kushwin Rajamani, Peter G Colman, Li Ping Li, James D Best, Merryn Voysey, Michael C D'Emden, Markku Laakso, John R Baker, Anthony C Keech, on behalf of the FIELD study investigators

Lancet 2009



Conclusions:
l ’intolérance aux statines

- Est un vrai problème
- Fait partie de leur activité
- Limite leur utilisation
- Est génétiquement déterminée
- Aucun des patients traités par lipaphérèses à Bordeaux n ’arrive à prendre une statine