# LDL-c bas un objectif ou une crainte?

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**Research contracts: AMGEN, Aegerion**
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# L'importance de la question du risque potentiel du LDL-c bas

- Les recommandations commencent à valider la diminution du seuil classique de LDL (extreme risk LDLc <0,50 g/l)
- Les nouvelles thérapeutiques peuvent entrainer des valeurs très basses de LDL-c
- Les études épidémiologiques classiques montrent qu'il existe un lien entre LDL-c bas et de nombreuses pathologies (globalement le LDL-c bas est associé à une surmortalité)
- Il existe une augmentation du risque hémorragique cérébral dans l'étude SPARCL
- La FDA demande une vigilance accrue quand il existe un LDL-c très bas

# Extreme risk in recent Guidelines

**Table 6**
**Atherosclerotic Cardiovascular Disease Risk Categories and LDL-C Treatment Goals**

| Risk category | Risk factors[a]/10-year risk[b] | Treatment goals | | |
|---|---|---|---|---|
| | | LDL-C (mg/dL) | Non-HDL-C (mg/dL) | Apo B (mg/dL) |
| Extreme risk | – Progressive ASCVD including unstable angina in patients after achieving an LDL-C <70 mg/dL<br>– Established clinical cardiovascular disease in patients with DM, CKD 3/4, or HeFH<br>– History of premature ASCVD (<55 male, <65 female) | <55 | <80 | <70 |
| Very high risk | – Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20%<br>– Diabetes or CKD 3/4 with 1 or more risk factor(s)<br>– HeFH | <70 | <100 | <80 |
| High risk | – ≥2 risk factors and 10-year risk 10-20%<br>– Diabetes or CKD 3/4 with no other risk factors | <100 | <130 | <90 |
| Moderate risk | ≤2 risk factors and 10-year risk <10% | <100 | <130 | <90 |
| Low risk | 0 risk factors | <130 | <160 | NR |


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# Baseline Low-Density Lipoprotein Cholesterol Levels and Outcome in Patients With Heart Failure

Gideon Charach, MD[a,*], Jacob George, MD[b], Arie Roth, MD[b], Ori Rogowski, MD[a], Dov Wexler, MD[a], David Sheps, MD[a], Itamar Grosskopf, MD[a], Moshe Weintraub, MD[a], Gad Keren, MD[b], and Ardon Rubinstein, MD[a]

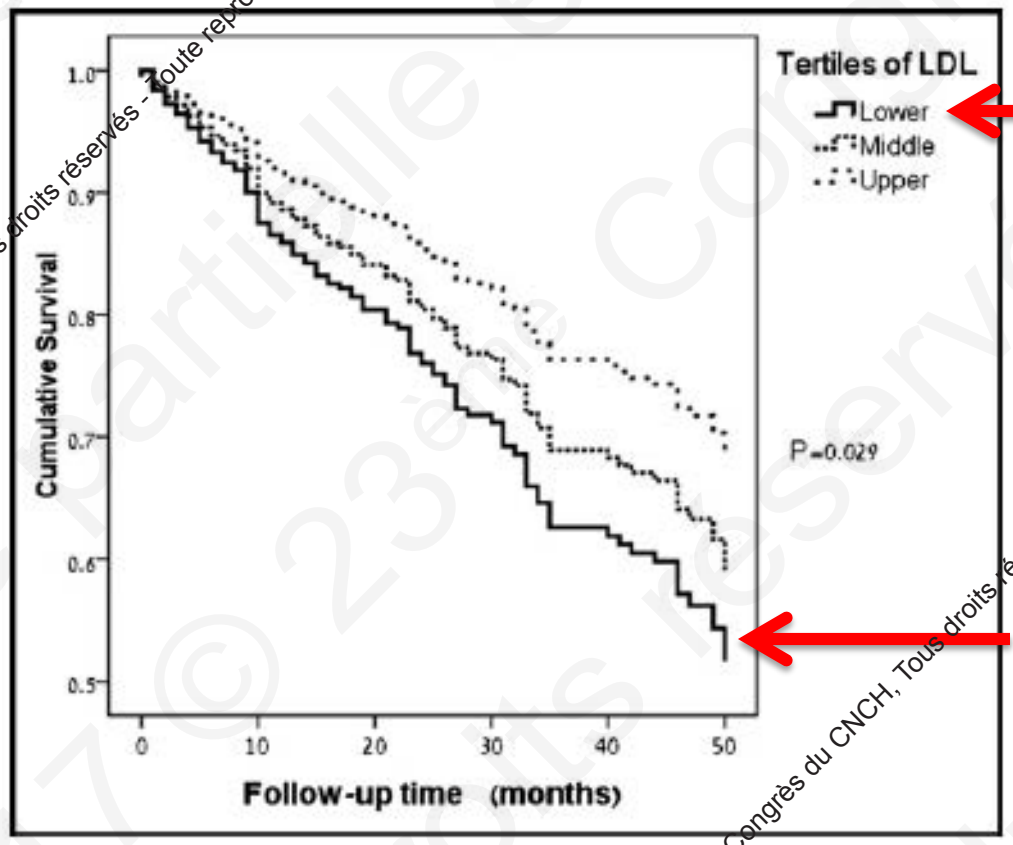


Figure 1. Cox regression curves comparing the lower tertile of LDL to the upper tertile, with adjustment for age, gender, the left ventricular ejection fraction, NYHA functional class, creatinine clearance, diabetes, and hypertension (for the entire cohort; n = 297).

# L'association du LDL-c bas à la morbi-mortalité est non causale dans la majorité des cas

- **De nombreuses conditions entrainent une baisse du cholestérol: dénutrition, baisse de poids, insuffisance cardiaque, pathologies neurologiques, hépatopathies… (« healthy worker effect » en épidémiologie)**

- **L'effet disparait après ajustement *ad hoc***
- **L'effet est souvent à court terme**


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| |
|---|
| General Allergic Adverse Events |
| Neuromuscular Adverse Events |
| Neurocognitive Disorders |
| Musculoskeletal Events |
| Creatine kinase levels >fivefold above normal range |
| Neurological Events |
| Psychiatric Disorders |
| Depression, suicide |
| Diabetes |
| New diagnosis |
| Worsening glycaemic status |
| Diabetic complications |
| Endocrine Deficiencies |
| Sex steroids |
| Adrenal corticoid deficiencies |
| Fat-soluble vitamin Deficiencies |
| Vitamin A, D, E and K levels |
| Disorders associated with deficiencies of fat-soluble vitamins |
| Hepatic Disorders |
| ALT/AST >threefold above normal range with and without elevated bilirubin |
| Ophthalmologic Events |
| Cataracts |
| Retinopathies |
| Infections |
| Cancers |

# Monitoring of AEs of Special Interest as requested by FDA in Patients With PCSK9 ABs and LDL-C Levels <0.65 mmol/L(25 mg/dL)





Journal of Internal Medicine, 2017, 281; 534–553

# Etude sur le risque de maladie d'Alzheimer et de maladie de Parkinson

1) Is LDLc at baseline associated prospectively with disease?
2) Are scores of LDL-c lowering alleles of PCSK9 R46L (rs11591147), R237W (rs148195424), I474V (rs562556), and E670G (rs505151), and HMGCR (rs17238484) associated with low LDLc?
3) Are LDL-c lowering alleles associated directly with risk of diseases, as an indication of a causal effect of low LDLc on risk of disease
4) Is the causal effect of low LDLc levels consistent with the corresponding observational associations using instrumental variable analysis.

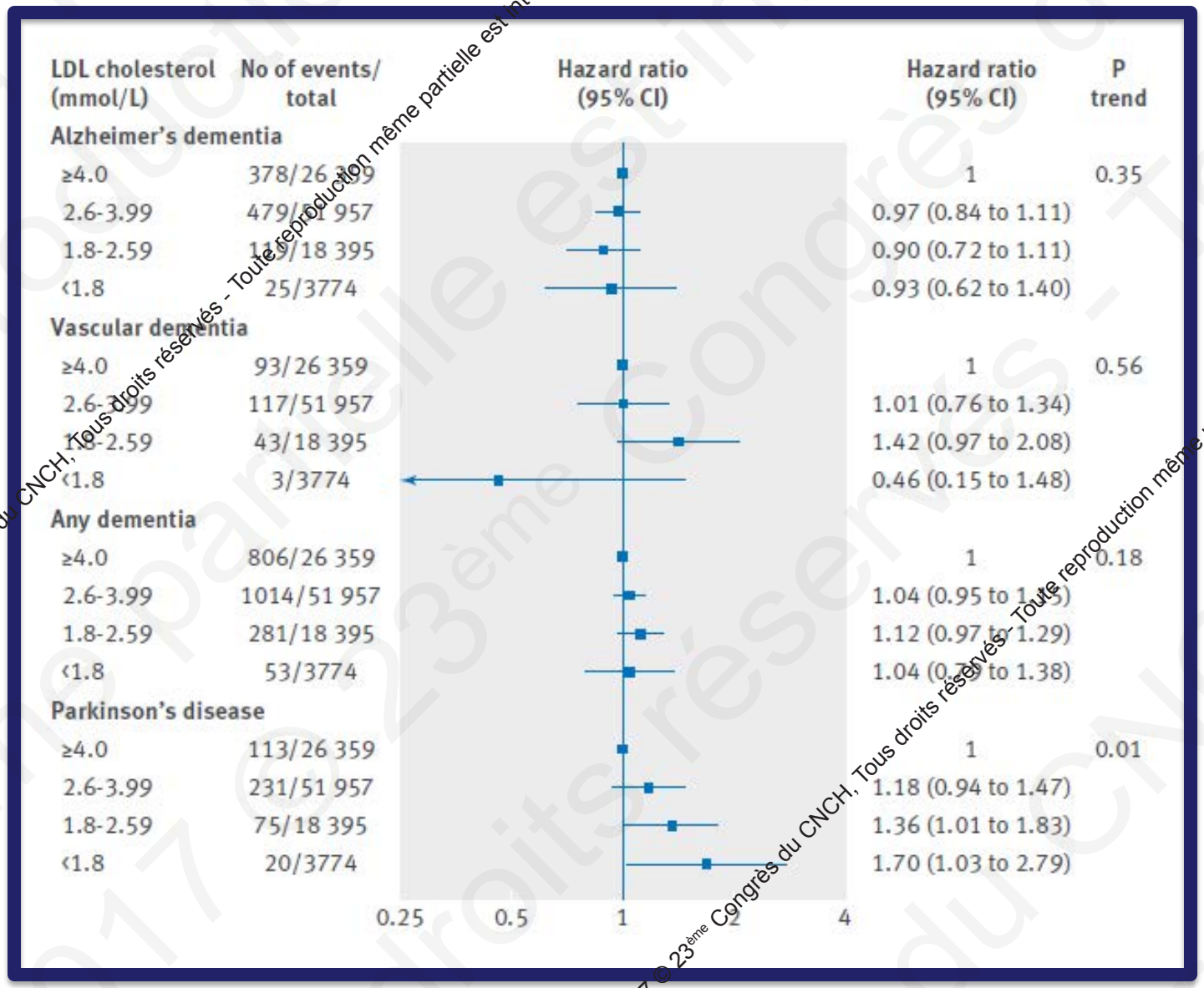


Of 111 194 participants 4087 (3.7%) had LDLc < 1.8 mmol/L, During follow-up, 1001 participants developed Alzheimer's disease, 256 vascular dementia, 2154 any dementia, and 460 Parkinson's disease.



Benn et al BMJ 2017

# Low LDL-c at baseline and risk of disease



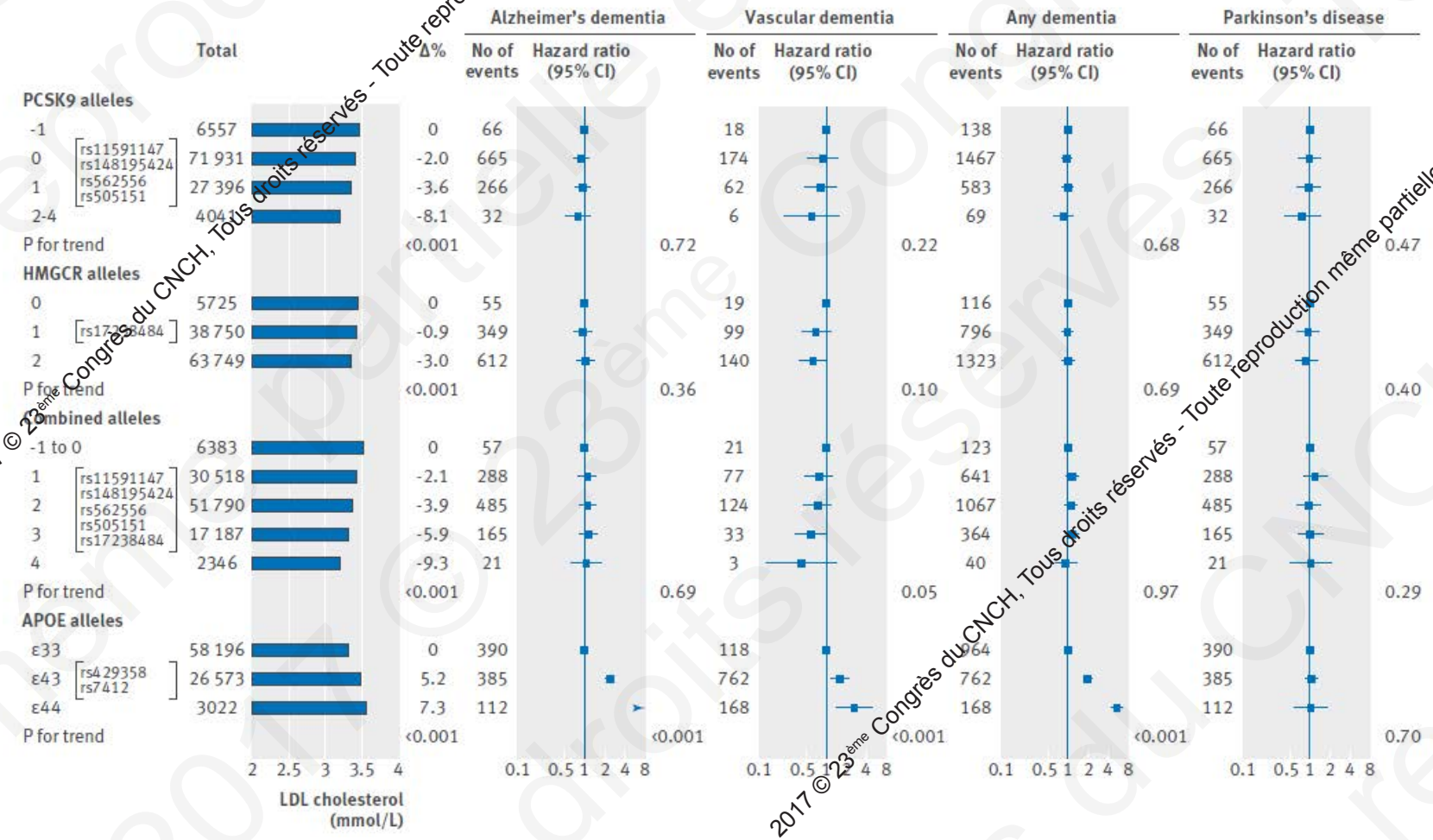



**Adjusted for age sex, birth year, smoking, alcohol, physical inactivity, income, education, and menopause for women**

**Benn et al BMJ 2017**

# Low LDL-c: genetic analysis

- **Prospective risk as a function of *PCSK9,HMGCR*, and combined alleles adjusted for age, sex, and birth year**
- **Positive control of study power: apoE and dementia.**






**Benn et al BMJ 2017**

# Les données permettant l'analyse des effets potentiels d'un LDL-c bas

**Les études épidémiologiques et les études GWAS**

**Les données des essais thérapeutiques**

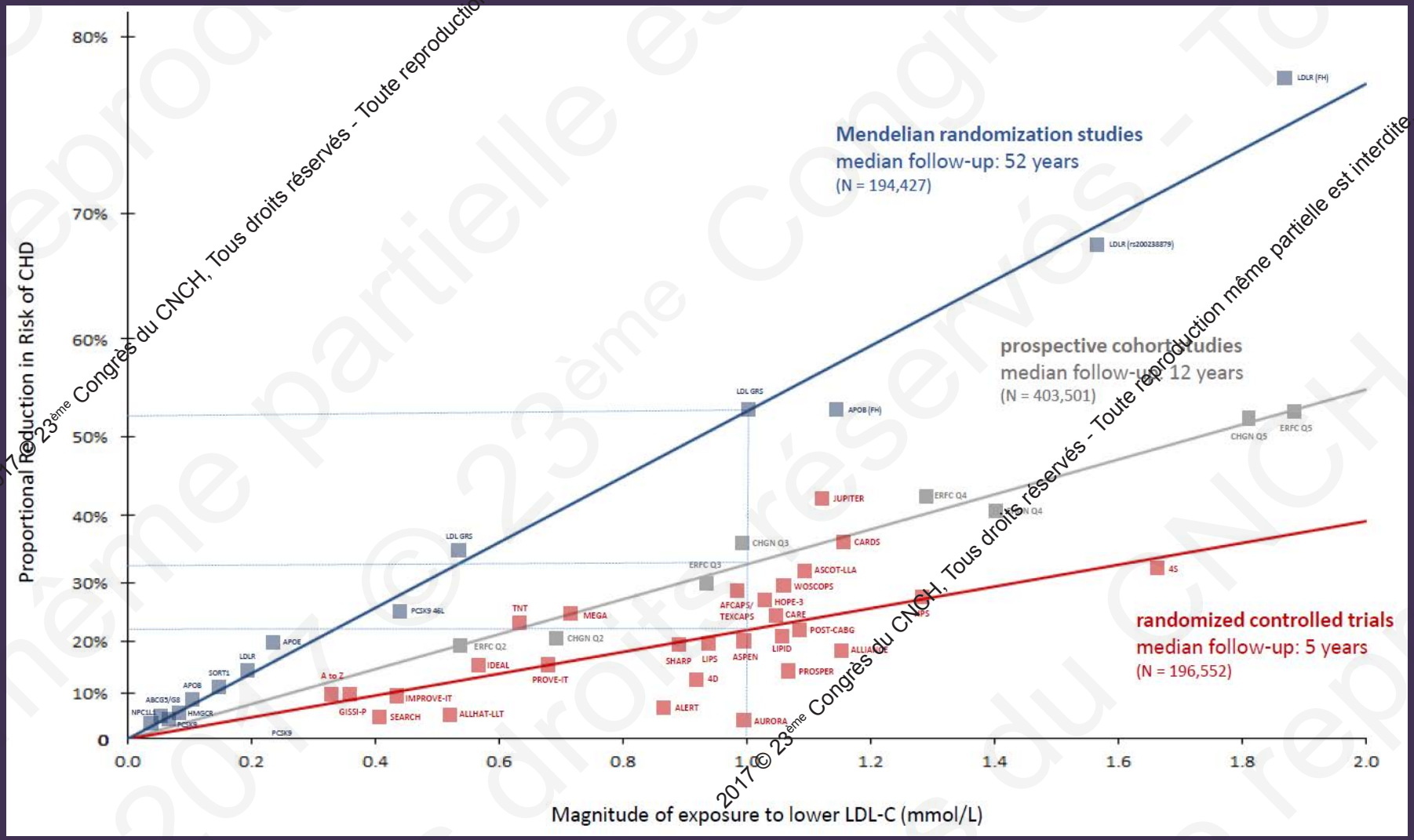
**Les analyses dans les sous groupes avec LDL très bas des essais thérapeutiques**

**Les données physiopathologiques**

**Les hypoLDLémies génétiques**

# LDL-c et maladies cardiovasculaires

## Meta-analyse des essais d'intervention, de l'épidémiologie prospective et de la génétique



# Meta-analyse des études randomisées statine et maladie d'Alzheimer

**Comparison 1. Incidence of dementia**

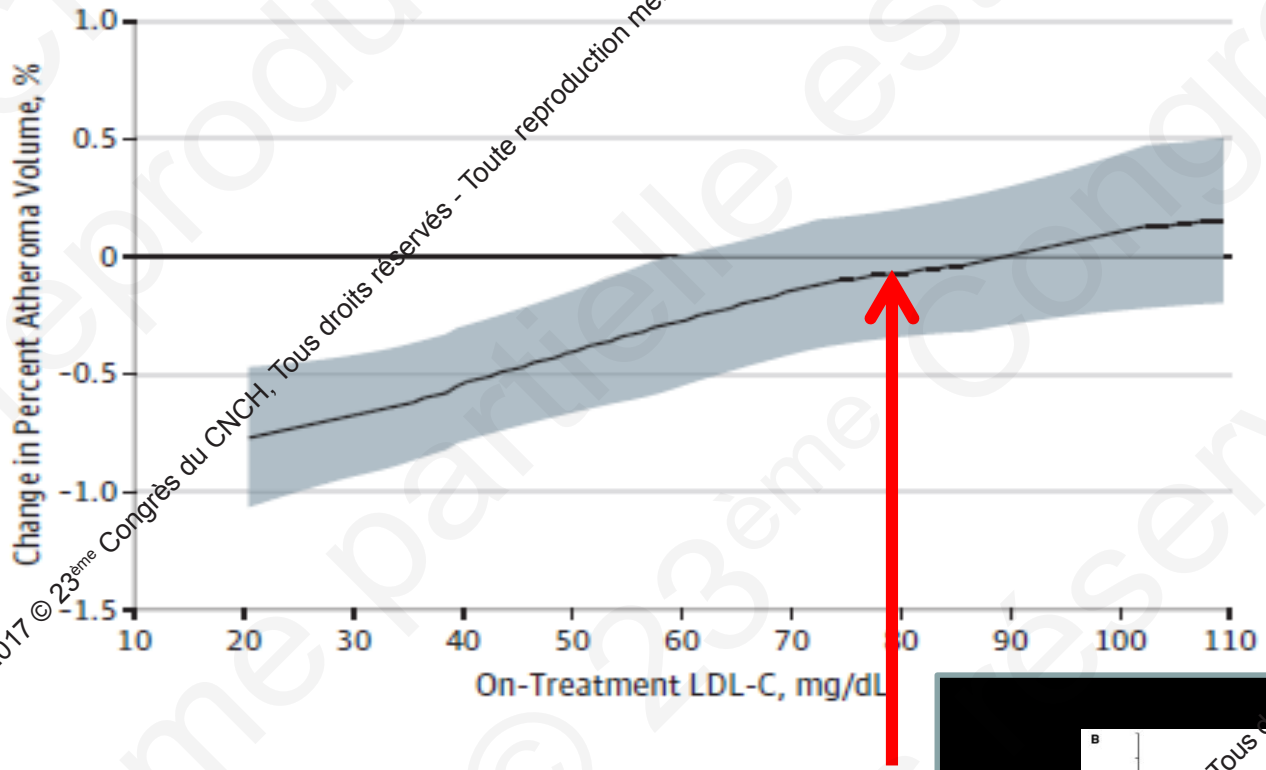
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Number of cases of dementia | 1 | 20536 | Odds Ratio (M-H, Fixed, 95% CI) | 1.00 [0.66, 1.65] |

**Comparison 2. Cognitive change from baseline**

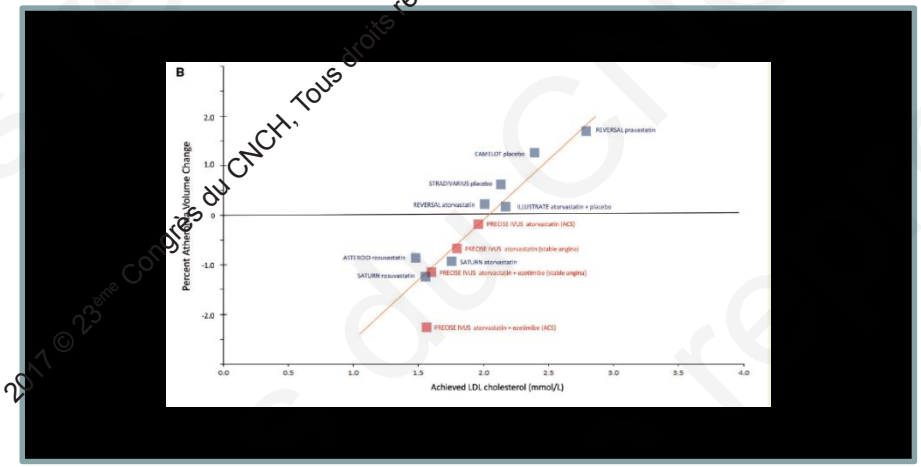
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Change in Mini Mental State Examination | 1 | 5804 | Mean Difference (Fixed, 95% CI) | 0.06 [-0.04, 0.16] |
| 2 Stroop test (seconds) | 1 | 5804 | Mean Difference (Fixed, 95% CI) | 0.8 [-0.38, 1.98] |
| 3 Picture-Word Learning Task | 1 | 5804 | Mean Difference (Fixed, 95% CI) | 0.02 [-0.12, 0.16] |
| 4 Letter Digit | 1 | 5804 | Mean Difference (Fixed, 95% CI) | -0.01 [-0.25, 0.23] |

McGuinness et al. COCHRANE 2016

# Relation entre LDL-c sous traitement et changement du volume d'athérome dans GLAGOV








**Glagov JAMA 2016**
**Eur Heart J Aout 2017**

# Tolérance du traitement dans l'étude GLAGOV

Table 4. Clinical and Biochemical Adverse Events in the Safety Population

| Parameter | No. (%) Placebo (n = 484) | Evolocumab (n = 484) |
|---|---|---|
| Cardiovascular events[a] | | |
| Death | 4 (0.8) | 3 (0.6) |
| Nonfatal myocardial infarction | 14 (2.9) | 10 (2.1) |
| Nonfatal stroke | 3 (0.6) | 2 (0.4) |
| Hospitalization for unstable angina | 4 (0.8) | 3 (0.6) |
| Coronary revascularization | 66 (13.6) | 50 (10.3) |
| First major adverse cardiovascular event | 74 (15.3) | 59 (12.2) |
| Clinically important adverse events | | |
| Injection site reaction | 0 | 2 (0.4) |
| Myalgia | 28 (5.8) | 34 (7.0) |
| Neurocognitive events[b] | 6 (1.2) | 7 (1.4) |
| New diagnosis diabetes mellitus[b] | 18 (3.7) | 17 (3.6) |
| Abnormality in laboratory value[c] | | |
| Aspartate or alanine aminotransferase >3× ULN | 2 (0.5) | 2 (0.5) |
| Total bilirubin >2× ULN | 2 (0.5) | 1 (0.3) |
| Creatine phosphokinase >5× ULN | 3 (0.7) | 3 (0.7) |
| Creatinine >ULN | 5 (1.0) | 3 (0.6) |
| Antievolocumab binding antibody | NA | 1 (0.2) |
| Antievolocumab neutralizing antibody | NA | 0 |

**Glagov JAMA 2016**
**Eur Heart J Aout 2017**

# FOURIER

- Randomized, double-blind. Median duration of FU 2.2 years
- 27,564 patients with ACVD and LDL c ≥ 70 mg/dL upon statin
- Evolocumab (140 mg every 2 weeks or 420 mg monthly) or PCB.
- Primary efficacy end point: CV death + MI + stroke + hospitalization for UA + coronary revascularization.
- Reduction in LDL-c 59%, (baseline 92 mg/dl)

- **Reduction of primary end point (n = 1344 [9.8%] vs n = 1563 [11.3%]; HR 0.85; 95% CI 0.79 to 0.92, P<0.001**
- **Results consistent across key subgroups,**

- No significant difference between the study groups with regard to AEs, with the exception of injection-site reactions (evolo 2.1% vs. 1.6% for pcb)

# Adverse events in FOURIER

**Table 3. Adverse Events and Laboratory Test Results.**

| Outcome | Evolocumab (N=13,769) | Placebo (N=13,756) |
|---|---|---|
| Adverse events — no. of patients (%) | | |
| Any | 10,664 (77.4) | 10,644 (77.4) |
| Serious | 3410 (24.8) | 3404 (24.7) |
| Thought to be related to the study agent and leading to discontinuation of study regimen | 226 (1.6) | 201 (1.5) |
| Injection-site reaction* | 296 (2.1) | 219 (1.6) |
| Allergic reaction | 420 (3.1) | 393 (2.9) |
| Muscle-related event | 682 (5.0) | 656 (4.8) |
| Rhabdomyolysis | 8 (0.1) | 11 (0.1) |
| Cataract | 228 (1.7) | 242 (1.8) |
| Adjudicated case of new-onset diabetes† | 677 (8.1) | 644 (7.7) |
| Neurocognitive event | 217 (1.6) | 202 (1.5) |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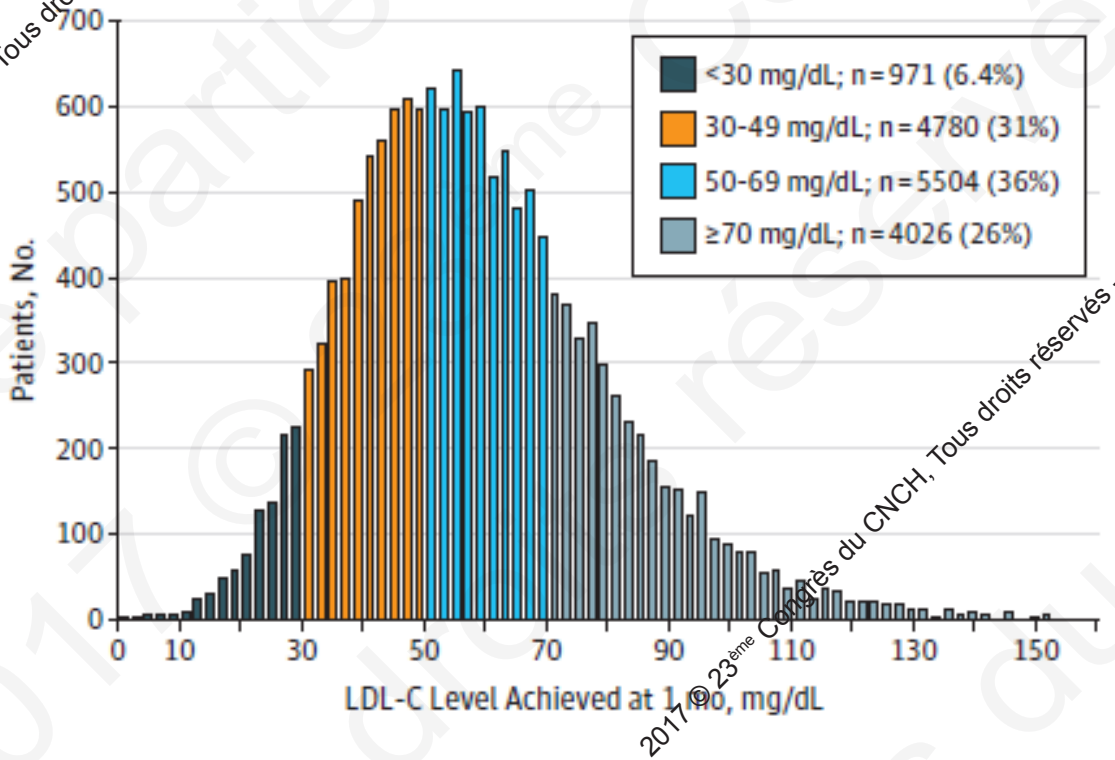
JAMA Cardiology | Original Investigation

# Long-term Safety and Efficacy of Achieving Very Low Levels of Low-Density Lipoprotein Cholesterol
## A Prespecified Analysis of the IMPROVE-IT Trial

Robert P. Giugliano, MD, SM; Stephen D. Wiviott, MD; Michael A. Blazing, MD; Gaetano M. De Ferrari, MD; Jeong-Gun Park, PhD; Sabina A. Murphy, MPH; Jennifer A. White, MD; Andrew M. Tershakovec, MD, MPH; Christopher P. Cannon, MD; Eugene Braunwald, MD



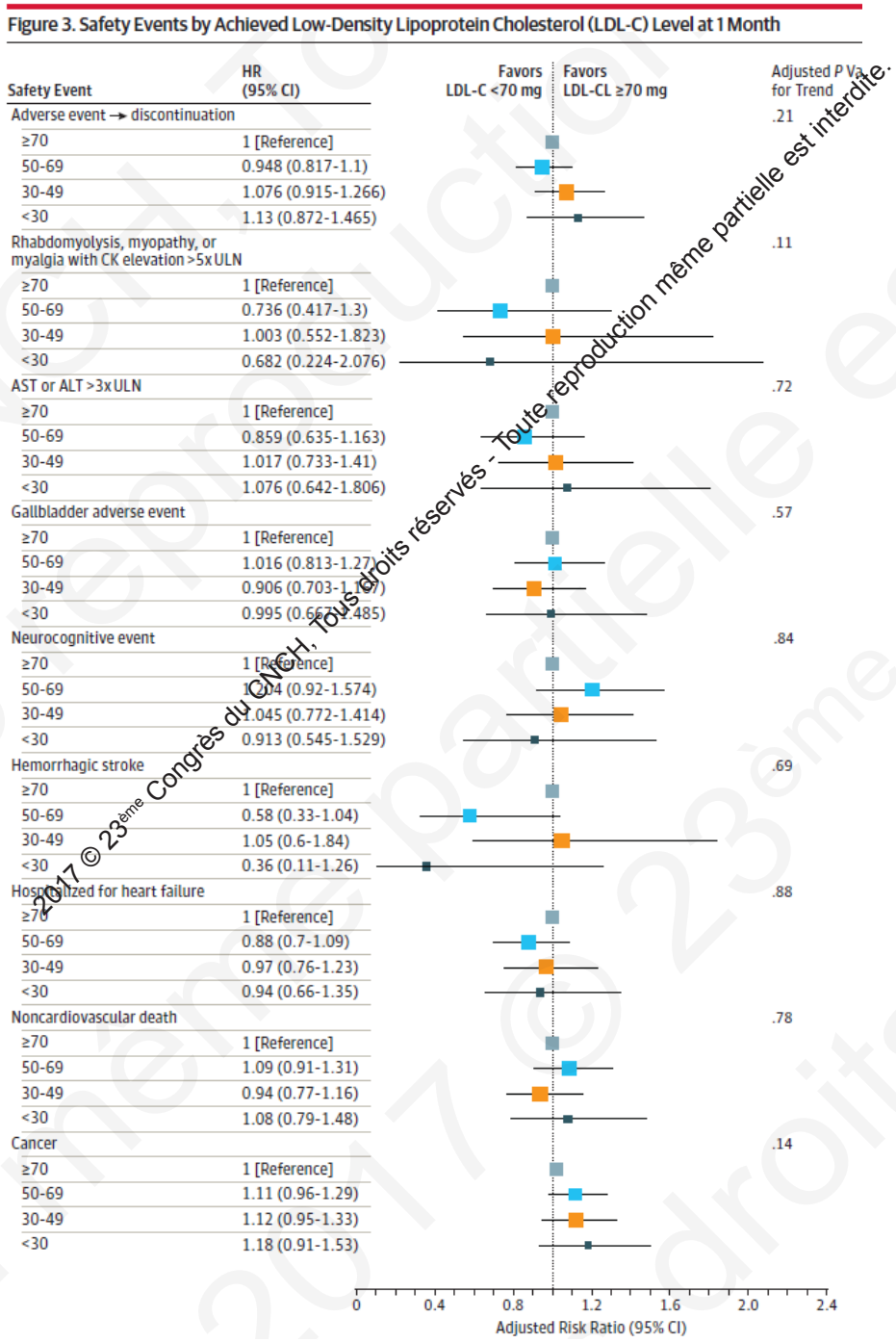
**Figure 1. Distribution of Achieved Calculated Low-Density Lipoprotein Cholesterol (LDL-C) Level at 1 Month Among Patients Who Did Not Have a Primary Efficacy or Prespecified Safety Event Prior to the Sample**






**Giugliano RP et al. JAMA cardiol March 2017**

# IMPROVE-IT et LDL-c bas



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**Giugliano RP et al. JAMA Cardiol March 2017**

# Monitoring of AEs of Special Interest in Patients With PCSK9 ABs and LDL-c Levels <0.65 mmol/L (25 mg/dL).



**Table 2** *Adverse events (%) in clinical trials of alirocumab- and evolocumab-treated patients [2, 43, 44].*

| | Alirocumab | | Alirocumab | Evolocumab | | Evolocumab |
|---|---|---|---|---|---|---|
| | Alirocumab group (total) | Standard of Care | LDL-C < 0.65 mmol $L^{-1}$ on 2 occasions | Evolocumab Group | Standard of Care | LDL-C < 0.65 mmol $L^{-1}$ on 2 occasions |
| Any | 81.0 | 82.5 | 75.7 | 69.2 | 64.8 | NR |
| Local site reaction | 5.9 | 4.2 | 3.8 | 4.3 | NR | NR |
| Muscle-reported | 6.4 | 6.0 | NR | 6.4 | 6.0 | 4.9 |
| Neurocognitive | 1.2 | 0.5 | 0.5 | 0.9 | 0.3 | 0.5 |
| Cataracts | 1.0 | 1.0 | 1.9 | NR | NR | NR |
| Alanine aminotransferase /aspartate aminotransferase or both | 1.8, 1.4 | 2.1, 2.3 | NR | 1.0 | 1.2 | 0.9 |
| Creatine kinase >fivefold above normal | 3.7 | 4.9 | NR | 0.61 | 1.0 | 0.4 |

NR. Not reported.

# Les données permettant l'analyse des effets potentiels d'un LDL-c bas

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Les hypoLDLémies génétiques

# Hypolipidémies génétiques

| Maladie | Transmission | Protéine mutée | Biologie |
|---|---|---|---|
| Hypo-beta lipoprotéinémie | Codominant* | Apo B | ApoB <5em percentile<br>LDL-C 20- 50 mg/dL |
| Rétention de Chylomicrons | Récessif | SAR1B | LDL-C et HDL-C diminué de 50%<br>Triglycerides normaux |
| Hypolipidémie familiale combinée | Codominant | ANGPTL3 | Panhypolipidémie |
| - | Codominant* | LOF PCSK9 | Heterozygous – faible réduction du LDL-C<br>Homozygote – LDL-C ~15 mg/dl |
| Abeta lipoprotéinemie | Récessif | MTP | Triglycérides < 30 mg/dl<br>Cholestérol < 30 mg/dl)<br>LDL et apoB indétectable |

Exceptionnelles formes homozygotes. Hypo-bêta homozygote tableau proche de l'abêta et PCSK9 homozygote pas de signe clinique

# Hypolipidémies génétiques

| Maladie | Protéine mutée | Clinique | | | MCV |
|---|---|---|---|---|---|
| | | Stéatose | Malabsorption | Autre | |
| Hypo-bêta lipoprotéinémie | Apo B | oui | non | | Diminuée |
| Rétention de Chylomicrons | SAR1B | non | oui | | Non documenté |
| Hypolipidémie familiale combinée | ANGPTL 3 | non | non | | Diminuée |
| - | LOF PCSK9 | non | non | | Diminuée |
| Abêta lipoprotéinemie | MTP | oui | oui | Déficit vit lipoS* | Non documenté |

* S cérébelleux, rare++ déficit vitamine K avec risque hémorragique

# Conclusion

- **Les recommandations commencent à valider la diminution du seuil classique de LDL (extreme risk LDL-c <0,50 g/l)**
- **Il n'existe actuellement aucun argument démontrant qu'il existe un risque associé au LDL-c très bas (30 mg/dL)**
- **Il reste nécessaire d'avoir des données sur le long terme et dans des populations fragiles (ex. sujets âgés)**