La Saga PCSK9 …..
de l'identification d'un gene aux données cliniques

Patrick HENRY
Cardiologie – Hôpital Lariboisiere – AP-HP
Université Denis Diderot Paris VII
Paris - France

- Conflits d’intérêt pour cette presentation
  - Amgen
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- Press Release
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▸ Michael S. Brown
▸ Joseph L. Goldstein

All Nobel Prizes in Physiology or Medicine
All Nobel Prizes in 1985

The Nobel Prize in Physiology or Medicine 1985
Michael S. Brown, Joseph L. Goldstein

The Nobel Prize in Physiology or Medicine 1985

Michael S. Brown

Joseph L. Goldstein

The Nobel Prize in Physiology or Medicine 1985 was awarded jointly to Michael S. Brown and Joseph L. Goldstein *"for their discoveries concerning the regulation of cholesterol metabolism"*

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MLA style: "The Nobel Prize in Physiology or Medicine 1985". *Nobelprize.org*. Nobel Media AB 2013. Web. 28 Jan 2014. <http://www.nobelprize.org/nobel_prizes/medicine/laureates/1985/>

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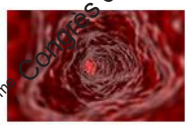
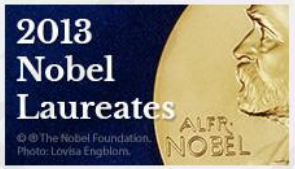
Facts on the Nobel



The Nobel Prize in



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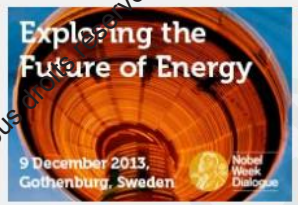

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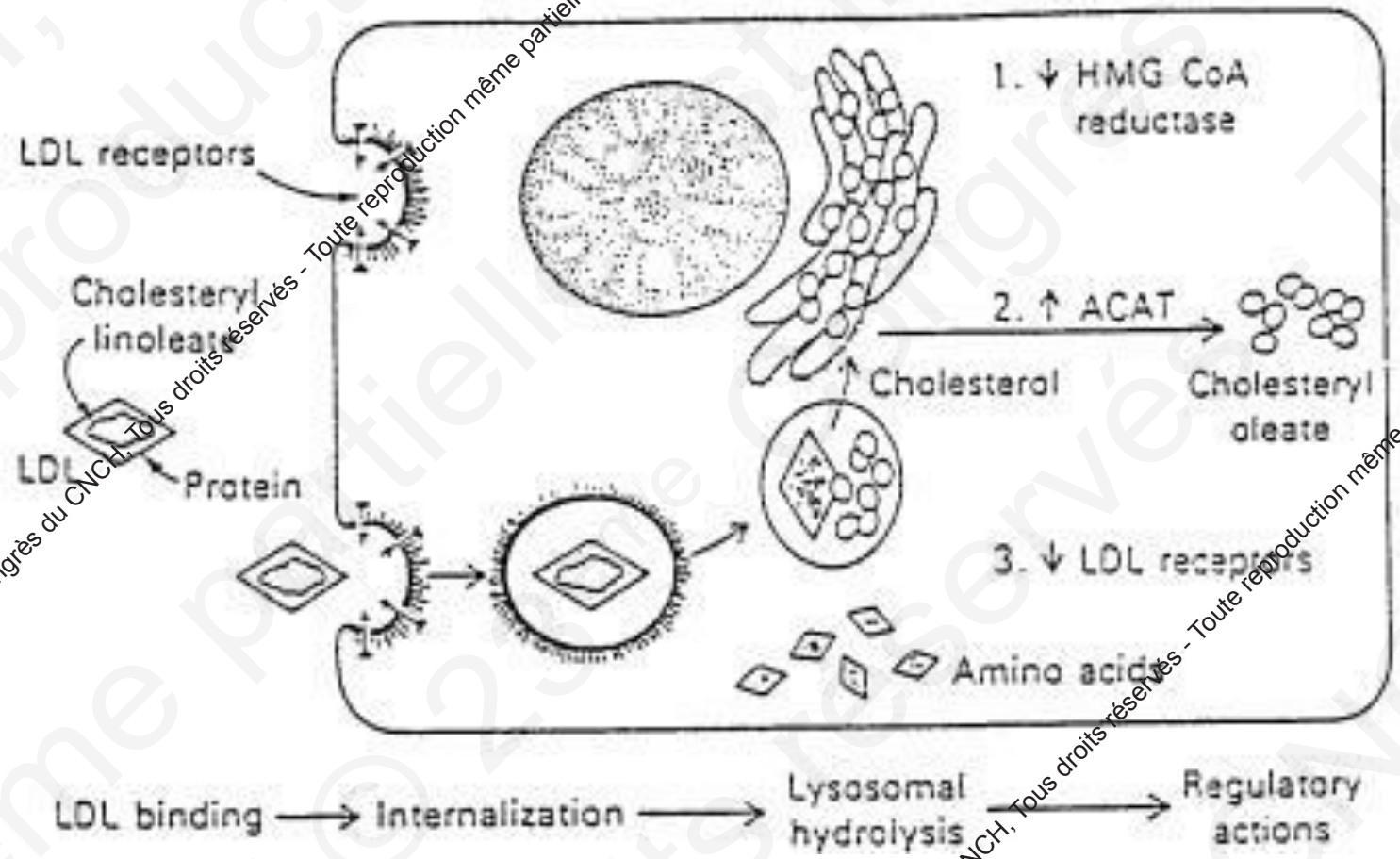


THE JOURNAL OF BIOLOGICAL CHEMISTRY

Author(s): Joseph L. Goldstein and Michael S. Brown

Title: Binding and Degradation of Low Density Lipoproteins by Cultured Human Fibroblasts: Comparison of Cells from Normal Subjects and from Patients with Homozygous Familial Hypercholesterolemia

Comments:

This is a most interesting paper and I wish I could recommend its acceptance without reservations.....

Page 2 .....

Page 3 .....

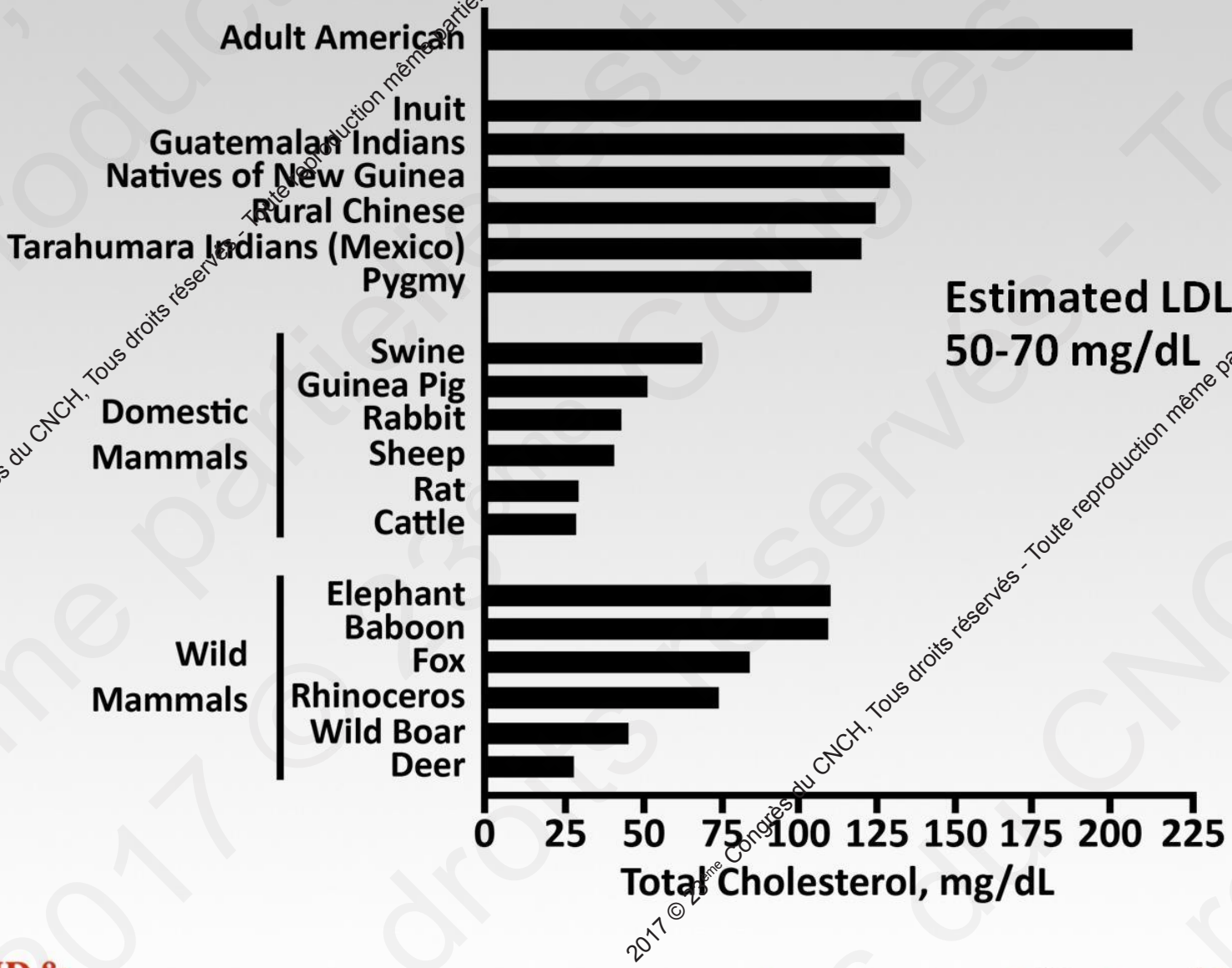
It is my considered opinion that publication of this paper with its incomplete observations would not serve medical science nor would it earn credit in the long run to its authors

Je considère que la publication de ce papier avec ses données incomplètes ne servira pas la science médicale ni ne permettra à ses auteurs une longue carrière

Kresge N et al. J. Biol. Chem. 2006;281:e25

jbc

Lipid-Lowering Goals: Back to Nature?



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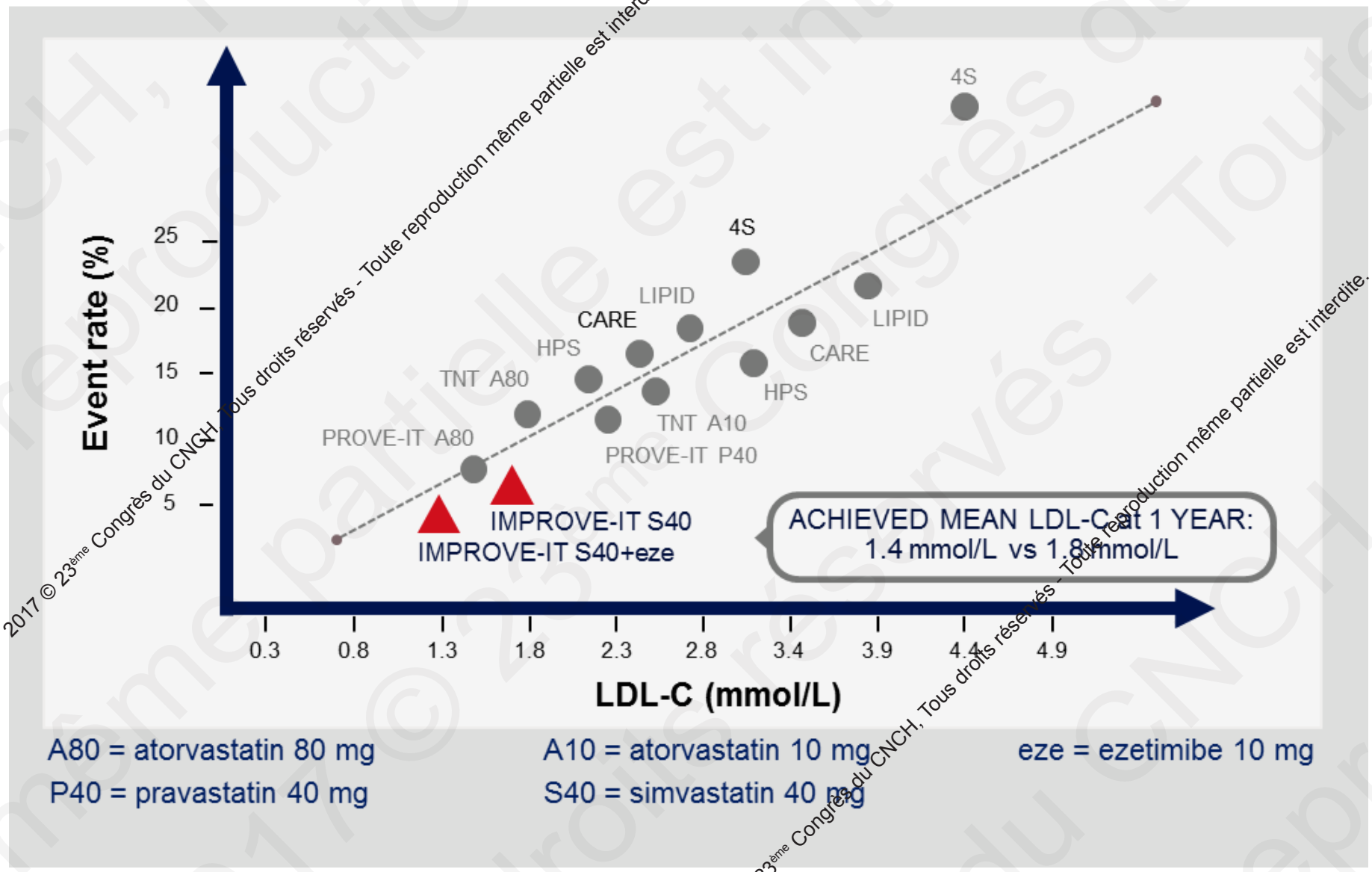
Hochholzer W, Giugliano RP.[8]



A80 = atorvastatin 80 mg
A10 = atorvastatin 10 mg
eze = ezetimibe 10 mg
P40 = pravastatin 40 mg
S40 = simvastatin 40 mg

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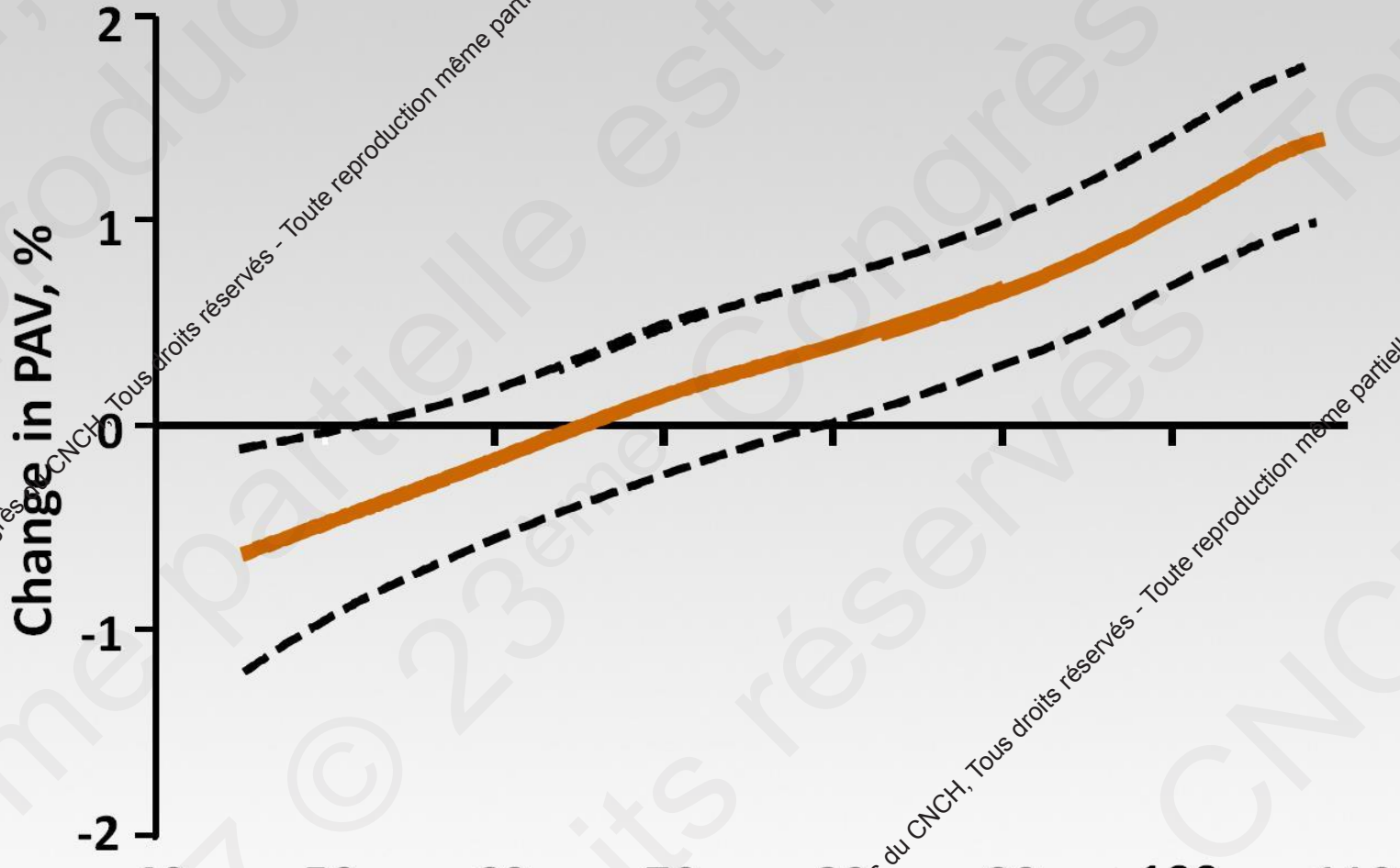
Impact of LDL-C on Plaque Progression



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Nicholls SJ, et al.[9]

JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Statins for Prevention of Cardiovascular Disease in Adults
Evidence Report and Systematic Review for the US Preventive Services Task Force

IMPORTANCE Cardiovascular disease (CVD), the leading cause of mortality and morbidity in the United States, may be potentially preventable with statin therapy.

OBJECTIVE To systematically review benefits and harms of statins for prevention of CVD to inform the US Preventive Services Task Force.

DATA SOURCES Ovid MEDLINE (from 1946), Cochrane Central Register of Controlled Trials (from 1991), and Cochrane Database of Systematic Reviews (from 2005) to June 2016.

STUDY SELECTION Randomized clinical trials of statins vs placebo, fixed-dose vs titrated statins, and higher- vs lower-intensity statins in adults without prior cardiovascular events.

DATA EXTRACTION AND SYNTHESIS One investigator abstracted data, a second checked data for accuracy, and 2 investigators independently assessed study quality using predefined criteria. Data were pooled using random-effects meta-analysis.

MAIN OUTCOMES AND MEASURES All-cause mortality, CVD-related morbidity or mortality, and harms.

RESULTS Nineteen trials (n = 71 344 participants [range, 95-17 802]; mean age, 51-66 years) compared statins vs placebo or no statin. Statin therapy was associated with decreased risk of all-cause mortality (risk ratio [RR], 0.86 [95% CI, 0.80 to 0.93]; I^2 = 0%; absolute risk difference [ARD], −0.40% [95% CI, −0.64% to −0.17%]), cardiovascular mortality (RR, 0.69 [95% CI, 0.54 to 0.88]; I^2 = 54%; ARD, −0.43% [95% CI, −0.75% to −0.11%]), stroke (RR, 0.71 [95% CI, 0.62 to 0.82]; I^2 = 0; ARD, −0.38% [95% CI, −0.53% to −0.23%]), myocardial infarction (RR, 0.64 [95% CI, 0.57 to 0.71]; I^2 = 0%; ARD, −0.81% [95% CI, −1.19 to −0.43%]), and composite cardiovascular outcomes (RR, 0.70 [95% CI, 0.63 to 0.78]; I^2 = 36%; ARD, −1.39% [95% CI, −1.79 to −0.99%]). Relative benefits appeared consistent in demographic and clinical subgroups, including populations without marked hyperlipidemia (total cholesterol level <200 mg/dL); absolute benefits were higher in subgroups at higher baseline risk. Statins were not associated with increased risk of serious adverse events (RR, 0.99 [95% CI, 0.94 to 1.04]), myalgias (RR, 0.96 [95% CI, 0.79 to 1.16]), or liver-related harms (RR, 1.10 [95% CI, 0.90 to 1.35]). In pooled analysis, statins were not associated with increased risk of diabetes (RR, 1.05 [95% CI, 0.91 to 1.20]), although statistical heterogeneity was present (I^2 = 52%), and 1 trial found high-intensity statins associated with increased risk (RR, 1.25 [95% CI, 1.05 to 1.49]). No trial directly compared titrated vs fixed-dose statins, and there were no clear differences based on statin intensity.

CONCLUSIONS AND RELEVANCE In adults at increased CVD risk but without prior CVD events, statin therapy was associated with reduced risk of all-cause and cardiovascular mortality and CVD events, with greater absolute benefits in patients at greater baseline risk.

Chou et al, JAMA 2016; 2008 - 24

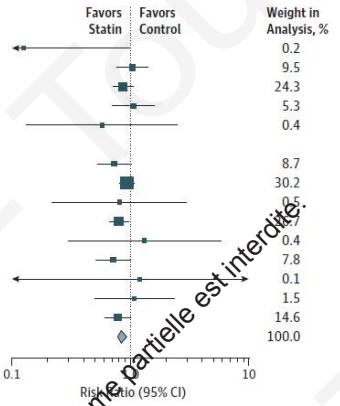
Primary prevention

Figure 3. Meta-analysis: Statins vs Placebo and All-Cause Mortality, Cardiovascular Mortality, and Incident Diabetes

A All-cause mortality

Study	Follow-up, y	Statins: Patients With Events, No./Total (%)	Control: Patients With Events, No./Total (%)	Risk Ratio (95% CI)	Weight in Analysis, %
ACAPS,[18] 1994	3	1/460 (0.22)	8/459 (1.7)	0.12 (0.02-0.99)	0.2
AFCAPS/TexCAPS,[19] 1998	5	80/3304 (2.4)	77/3301 (2.3)	1.04 (0.76-1.41)	9.5
ASCOT-LLA,[20] 2003	3	185/5168 (3.6)	212/5137 (4.1)	0.87 (0.71-1.05)	24.3
ASPEN,[21] 2006	4	44/959 (4.6)	41/946 (4.3)	1.06 (0.70-1.60)	5.3
Beishuizen et al,[23] 2004	2	3/103 (2.9)	4/79 (5.1)	0.58 (0.13-2.50)	0.4
Bone et al,[24] 2007	1	0/485 (0)	0/119 (0)	Not estimable	
CARDS,[26] 2004	4	61/1428 (4.3)	82/1410 (5.8)	0.73 (0.53-1.01)	8.7
HOPE-3,[14] 2016	6	334/6361 (5.3)	357/6344 (5.6)	0.93 (0.81-1.08)	30.2
HYRIM,[28] 2005	4	4/283 (1.4)	5/285 (1.8)	0.81 (0.22-2.97)	0.5
JUPITER,[29] 2008	2	198/8901 (2.2)	247/8901 (2.8)	0.80 (0.67-0.96)	4.7
KAPS,[30] 1995	3	4/214 (1.9)	3/212 (1.4)	1.32 (0.30-5.83)	0.4
MEGA,[31] 2006	5	55/3866 (1.4)	79/3966 (2.0)	0.71 (0.51-1.00)	7.8
METEOR,[32] 2007	2	1/700 (0.14)	0/281 (0)	1.21 (0.05-29.5)	0.1
Prevend-IT,[34] 2004	4	13/433 (3.0)	12/431 (2.8)	1.08 (0.50-2.34)	1.5
WOSCOPS,[35] 1995	5	106/3302 (3.2)	135/3293 (4.1)	0.78 (0.61-1.01)	14.6
Total (95% CI)		1089/35 967 (3.0)	1262/35 164 (3.6)	0.86 (0.80-0.93)	100.0

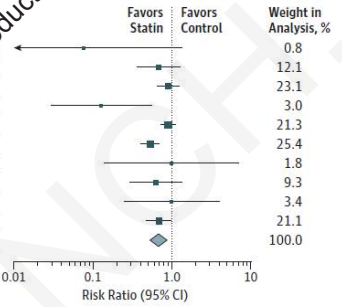
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_{13} = 11.07$, ($P = .60$); $I^2 = 0\%$
Test for overall effect: $Z = 3.63$ ($P < .003$)



B Cardiovascular mortality

Study	Follow-up, y	Statins: Patients With Events, No./Total (%)	Control: Patients With Events, No./Total (%)	Risk Ratio (95% CI)	Weight in Analysis, %
ACAPS,[18] 1994	3	0/460 (0)	6/459 (1.3)	0.08 (0.004-1.[illegible])	0.8
AFCAPS/TexCAPS,[19] 1998	5	17/3304 (0.51)	25/3301 (0.76)	0.68 (0.37-1.26)	12.1
ASCOT-LLA,[20] 2003	3	74/5168 (1.4)	82/5137 (1.6)	0.90 (0.[illegible]-1.23)	23.1
ASTRONOMER,[22] 2010	4	2/103 (1.9)	12/79 (15.2)	0.13 (0.03-0.55)	3.0
HOPE-3,[14] 2016	6	154/6361 (2.4)	171/6344 (2.7)	0.90 (0.72-1.11)	21.3
JUPITER,[29] 2008	2	83/8901 (0.93)	157/8901 (1.8)	0.53 (0.41-0.69)	25.4
KAPS,[30] 1995	3	2/214 (0.93)	2/212 (0.94)	0.99 (0.14-6.97)	1.8
MEGA,[31] 2006	5	11/3866 (0.28)	18/3966 (0.45)	0.63 (0.30-1.33)	9.3
Prevend-IT,[34] 2004	4	4/433 (0.92)	4/431 (0.[illegible])	1.00 (0.25-3.95)	3.4
WOSCOPS,[35] 1995	5	50/3302 (1.5)	73/3293 (2.2)	0.68 (0.48-0.98)	21.1
Total (95% CI)		397/32 112 (1.2)	550/32 123 (1.7)	0.69 (0.54-0.88)	100.0

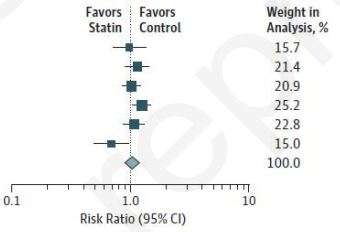
Heterogeneity: $\tau^2 = 0.06$; $\chi^2_9 = 19.46$, ($P = .02$); $I^2 = 54\%$
Test for overall effect: $Z = 3.00$ ($P = .003$)



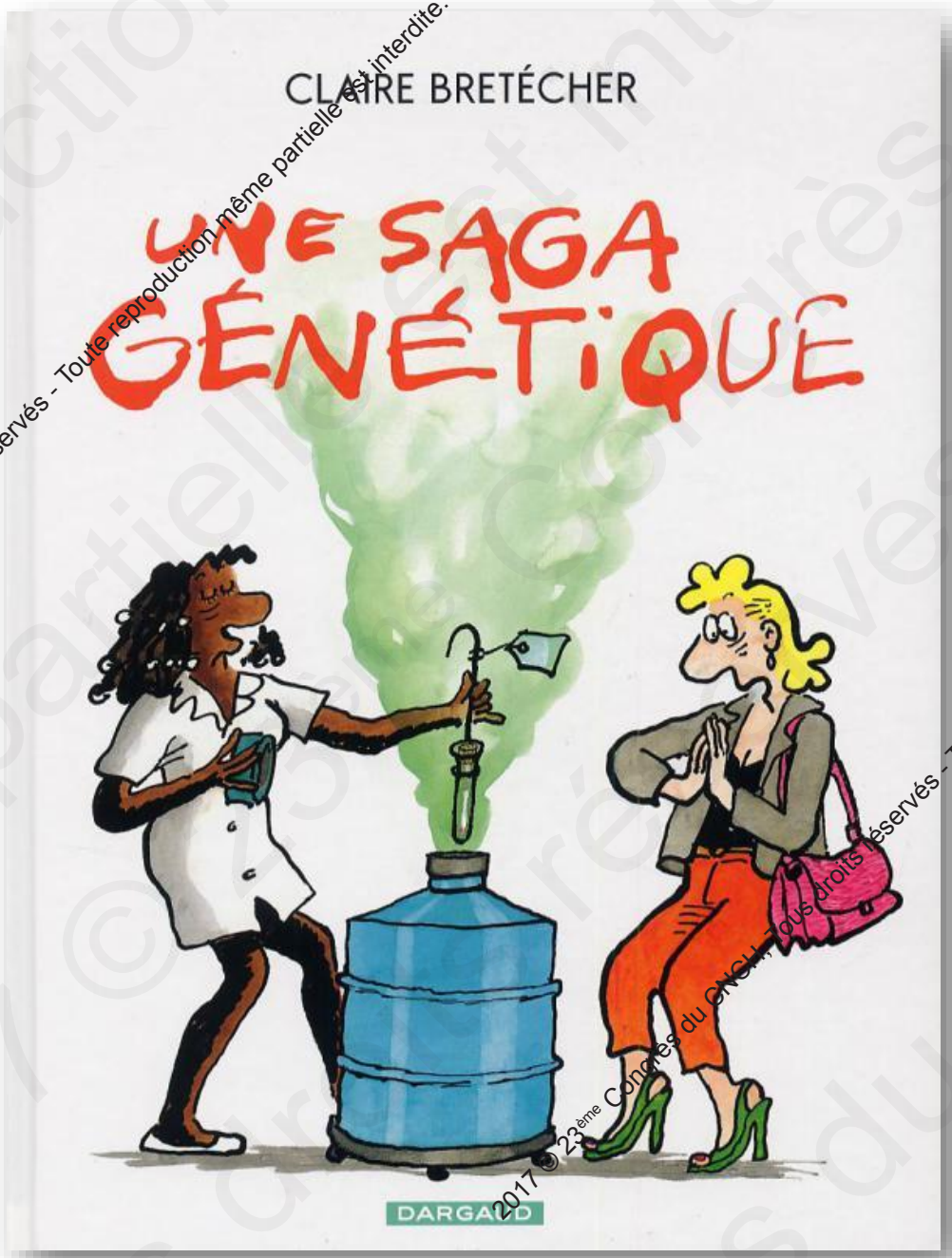
C Incident diabetes

Study	Follow-up, y	Statins: Patients With Events, No./Total (%)	Control: Patients With Events, No./Total (%)	Risk Ratio (95% CI)	Weight in Analysis, %
AFCAPS/TexCAPS,[19] 1998	5	72/3094 (2.3)	74/3117 (2.4)	0.98 (0.71-1.35)	15.7
ASCOT-LLA,[20] 2003	3	154/5168 (3.0)	134/5137 (2.6)	1.14 (0.91-1.44)	21.4
HOPE-3,[14] 2016	6	232/6361 (3.6)	226/6344 (3.6)	1.02 (0.86-1.23)	20.9
JUPITER,[29] 2008	2	270/8901 (3.0)	216/8901 (2.4)	1.25 (1.05-1.49)	25.2
MEGA,[31] 2006	5	172/3013 (5.7)	164/3073 (5.3)	1.07 (0.87-1.32)	22.8
WOSCOPS,[35] 1995	5	57/2999 (1.9)	82/2975 (2.8)	0.69 (0.49-0.96)	15.0
Total (95% CI)		957/29 536 (3.2)	896/29 547 (3.0)	1.05 (0.91-1.20)	100.0

Heterogeneity: $\tau^2 = 0.02$; $\chi^2_5 = 10.46$, ($P = .06$); $I^2 = 52\%$
Test for overall effect: $Z = 0.64$ ($P = .52$)



Size of data markers indicates weight of study in the pooled analysis.



Genome-Wide Scans for CAD and MI

	Ref	Study Population	Families	Age	1°Locus	Analysis Program	Gene
Pajukanta	4	Finnish	156	<55	2q21	MAPMAKER	ND
Francke	5	Mauritian	99	47	16p13	GENEHUNTER	ND
Broeckel	6	European	513	52	14	SOLAR	ND
Harrap	7	Australian	61	62	2q36	MAPMAKER	ND
Wang	8	American	428	44	1p34	SAGE	ND
Hauser	9	Euro-Amer	438	56	3q13	GENEHUNTER	ND
Helgadottir	10	Icelandic	296	--	13q12	ALLEGRO	ALOX5AP
Helgadottir	11	Icelandic	296	--	12q22	ALLEGRO	LTA4H
Brit Ht Found	12	British	1933	53	2p11	ALLEGRO	ND

Abbreviations: Brit Ht Found-British Heart Foundation, Euro-Amer-European-American, ND-not determined

(Lack of)
Validation of Genetic Markers for CAD

ORIGINAL CONTRIBUTION

Nonvalidation of Reported Genetic Risk Factors for Acute Coronary Syndrome in a Large-Scale Replication Study

Thomas M. Morgan, MD
Harlan M. Krumholz, MD, MS
Richard P. Lifton, MD, PhD
John A. Spertus, MD, MPH

Context Given the numerous, yet inconsistent, reports of genetic variants being associated with acute coronary syndromes (ACS), there is a need for comprehensive validation of ACS susceptibility genotypes.

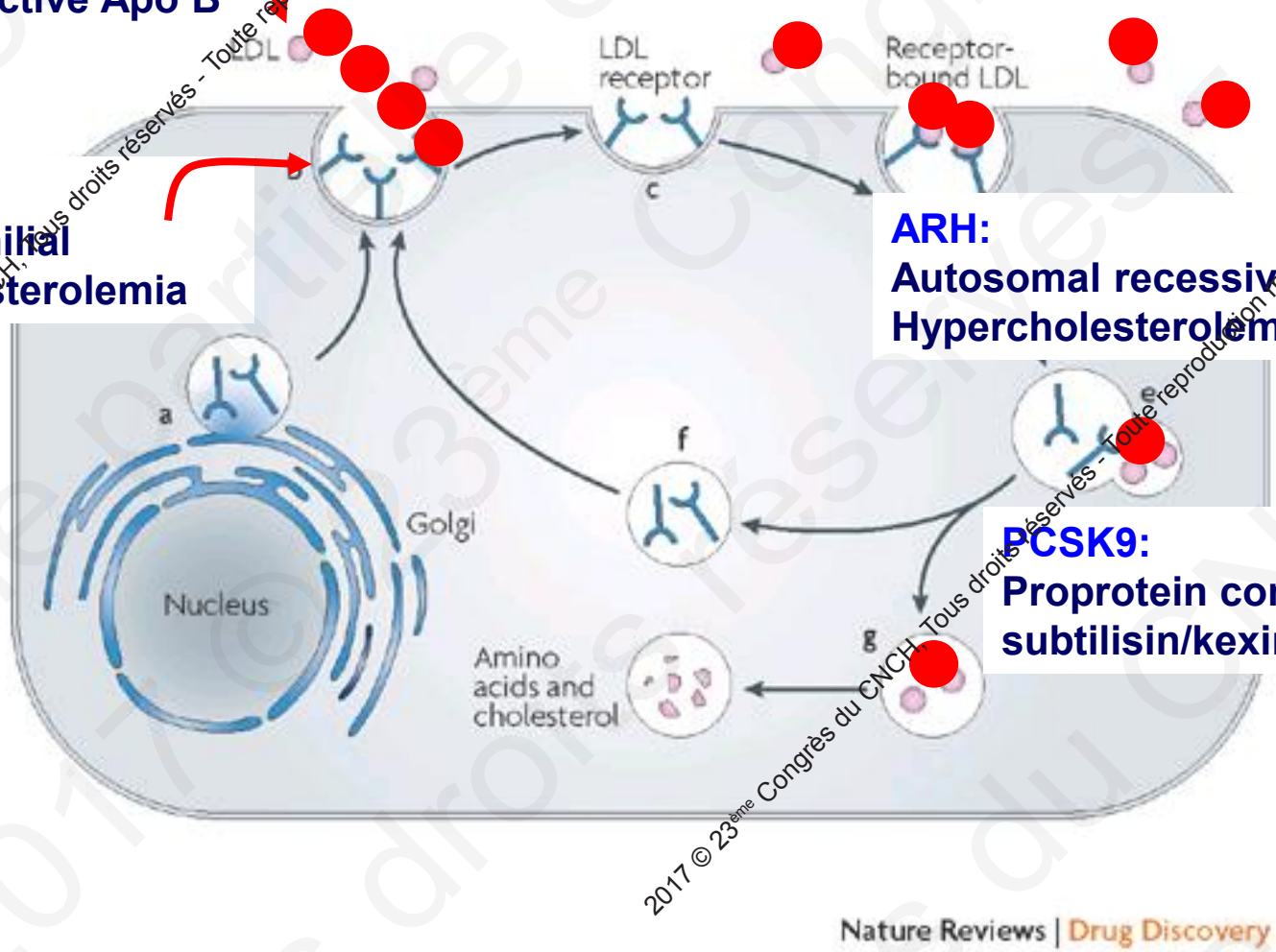
Objective To perform an extensive validation of putative genetic risk factors for ACS.

Morgan T et al. JAMA 2007;297:1551

Molecular Causes of Familial Hypercholesterolemia (FH)

ApoB:
Familial defective Apo B

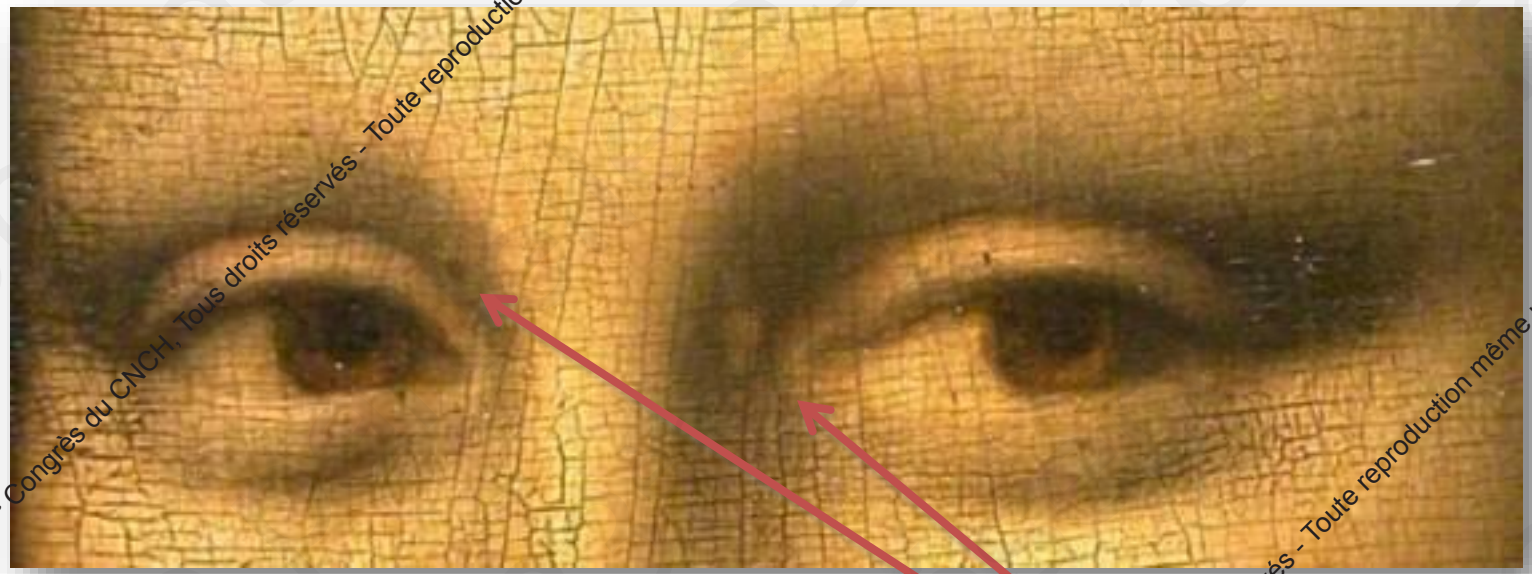
LDL-R:
Primary familial hypercholesterolemia



ARH:
Autosomal recessive familial Hypercholesterolemia

PCSK9:
Proprotein convertase subtilisin/kexin type 9

Léonard de Vinci
Mona Lisa
1510



Léonard de Vinci
Mona Lisa
1510

Xanthelasma ?

Léonard de Vinci
Mona Lisa
1510

Xanthome ?

Protein Science (1997), 6:501–523. Cambridge University Press. Printed in the USA.

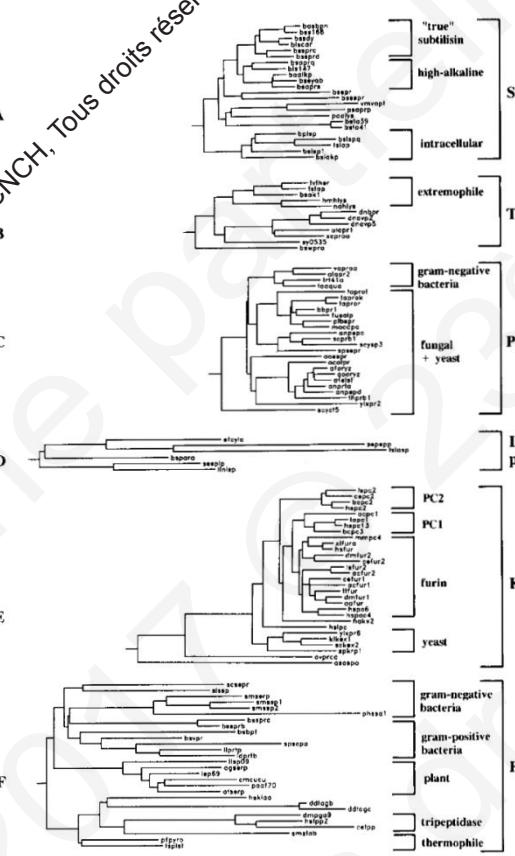
REVIEW

Subtilases: The superfamily of subtilisin-like serine proteases

ROLAND J. SIEZEN[1] AND JACK A.M. LEUNISSEN[2]

[1]Department of Biophysical Chemistry, NIZO, P.O. Box 20, 6710BA Ede, The Netherlands
[2]CAOS/CAMM Center, University of Nijmegen, Toernooiveld, 6525ED, Nijmegen, The Netherlands

(RECEIVED August 22, 1996; ACCEPTED November 5, 1996)



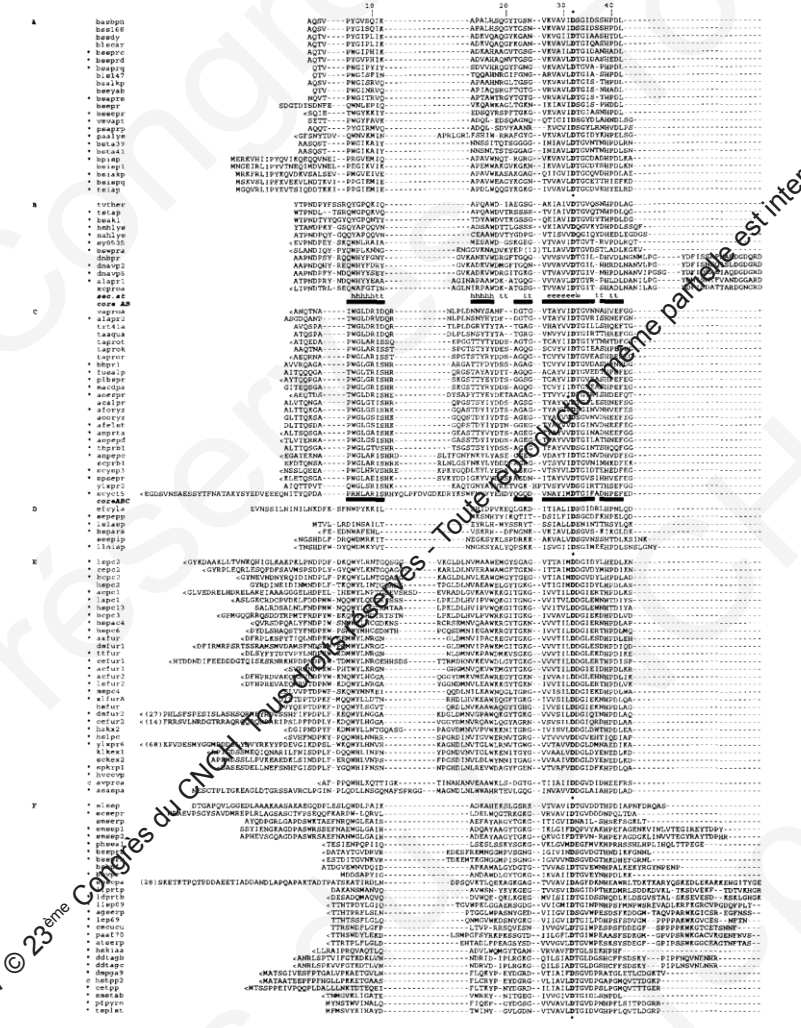


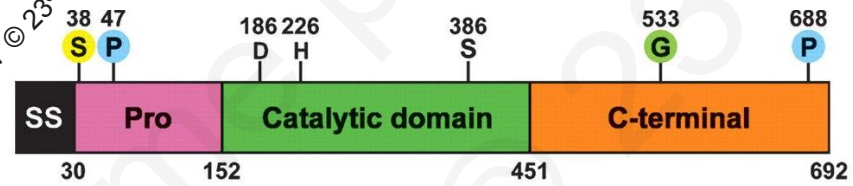
Fig. 2. *Continues on following pages.*

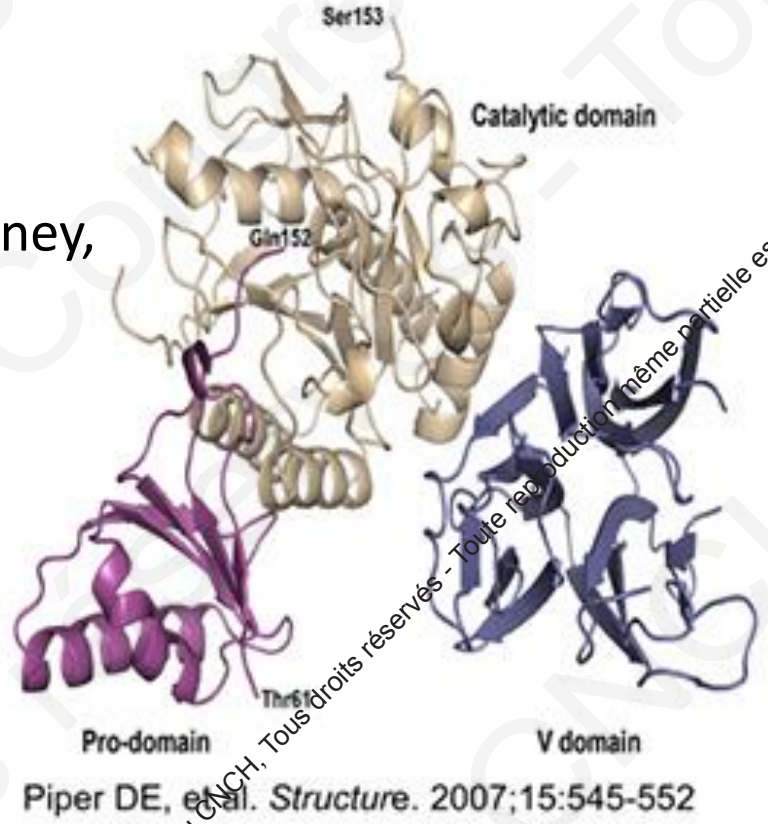
PCSK9

PCSK9 = Proprotein convertase subtilisin/kexin type 9

Human PCSK9 gene :

- chromosome 1p32.3
- expressed in several organs (liver, kidney, intestine)





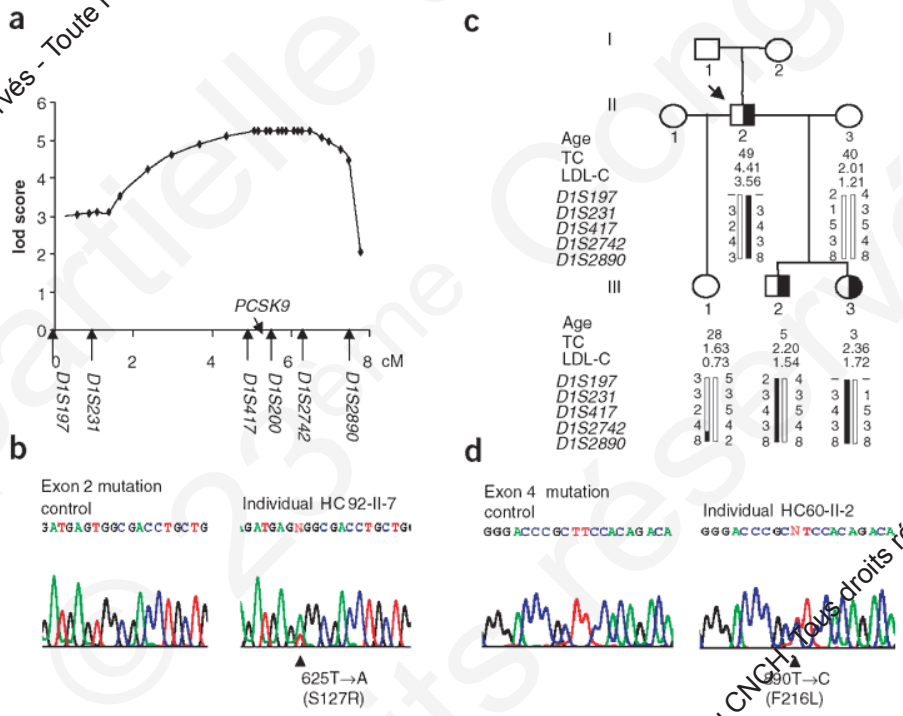
Piper DE, et al. *Structure*. 2007;15:545-552

Mayne J, Dewpura T, Raymond A, et al. Novel loss-of-function PCSK9 variant is associated with low plasma LDL cholesterol in a French-Canadian family and with impaired processing and secretion in cell culture. Clin Chem 2011;57:1415—23

Abifadel M, Varret M, Rabès JP, Allard D, Ouguerram K, Devillers M, Cruaud C, Benjannet S, Wickham L, Erlich D, Derré A, Villéger L, Farnier M, Beucler I, Bruckert E, Chambaz J, Chanu B, Lecerf JM, Luc G, Moulin P, Weissenbach J, Prat A, Krempf M, Junien C, Seidah NG, Boileau C.

Mutations in PCSK9 cause autosomal dominant hypercholesterolemia.

Nat Genet. 2003 Jun;34(2):154-6.



… We report two mutations in the gene PCSK9 (encoding proprotein convertase subtilisin/kexin type 9) that cause ADH. PCSK9 encodes NARC-1 (neural apoptosis regulated convertase), a newly identified human subtilase that is highly expressed in the liver and contributes to cholesterol homeostasis.

ADH : autosomal dominant hypercholesterolemia

PCSK9 genetic overview

Gain of function

LDL

Mortality CAD

Loss of function

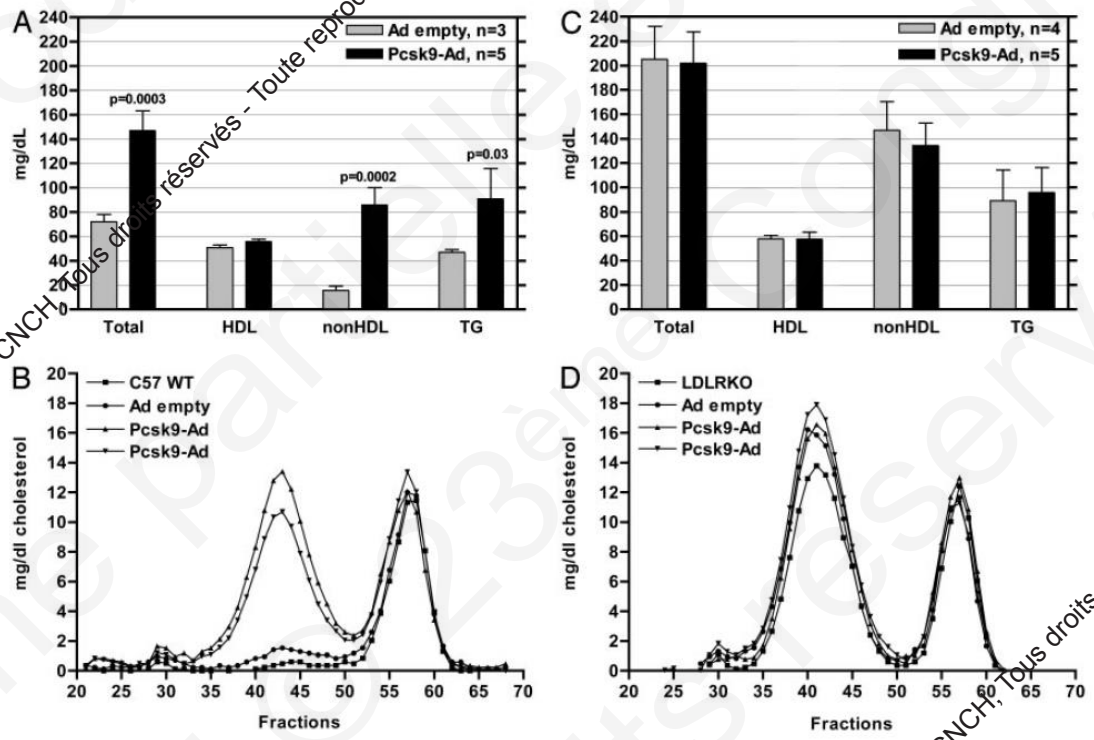
LDL

Mortality CAD

Adenoviral-mediated expression of Pcsk9 in mice results in a low-density lipoprotein receptor knockout phenotype

Kara N. Maxwell and Jan L. Breslow

Laboratory of Biochemical Genetics and Metabolism, The Rockefeller University, 1230 York Avenue, New York, NY 10021



LDL receptor Knock-out

Fig. 2. Overexpression of Pcsk9 increases LDL cholesterol levels in an LDLR-dependent manner. (*A*) Plasma was isolated from wild-type male C57BL/6 mice injected with Ad empty and Pcsk9-Ad, and HDL and non-HDL plasma fractions were separated by ultracentrifugation. Cholesterol levels in these fractions were measured by enzymatic assay. Overexpression of Pcsk9 caused an increase in total and non-HDL cholesterol with no change in HDL cholesterol levels. (*B*) Plasma was pooled from at least two wild-type animals (C57 WT), animals injected with Ad empty, and animals injected with Pcsk9-Ad; plasma was fractionated by FPLC; and cholesterol was measured by enzymatic assay. Two runs of Pcsk9-Ad-injected mice are shown to demonstrate reproducibility. Wild-type mice and mice injected with Ad empty had mainly HDL-derived cholesterol (fractions 52–62). Mice injected with Pcsk9-Ad had similar levels of HDL-derived and very-low-density lipoprotein-derived cholesterol, but they had high levels of LDL-derived cholesterol (fractions 35–50). (*C*) LDLR knockout mice were injected with Ad empty and Pcsk9-Ad. LDLR knockout mice injected with Ad empty had elevated total cholesterol and non-HDL cholesterol with no change in HDL cholesterol levels. Overexpression of Pcsk9 did not cause a further increase in total or non-HDL cholesterol levels in LDLR knockout mice. (*D*) FPLC analysis demonstrated that the lipoprotein profile of LDLR knockout mice injected with Pcsk9-Ad was indistinguishable from that of uninjected LDLR knockout mice (LDLRKO) and LDLR knockout mice injected with Ad empty.

PNAS 2004

Sequence Variations in *PCSK9*, Low LDL, and Protection against Coronary Heart Disease

Jonathan C. Cohen, Ph.D., Eric Boerwinkle, Ph.D., Thomas H. Mosley, Jr., Ph.D., and Helen H. Hobbs, M.D.

ABSTRACT

BACKGROUND

A low plasma level of low-density lipoprotein (LDL) cholesterol is associated with reduced risk of coronary heart disease (CHD), but the effect of lifelong reductions in plasma LDL cholesterol is not known. We examined the effect of DNA-sequence variations that reduce plasma levels of LDL cholesterol on the incidence of coronary events in a large population.

METHODS

We compared the incidence of CHD (myocardial infarction, fatal CHD, or coronary revascularization) over a 15-year interval in the Atherosclerosis Risk in Communities study according to the presence or absence of sequence variants in the proprotein convertase subtilisin/kexin type 9 serine protease gene (*PCSK9*) that are associated with reduced plasma levels of LDL cholesterol.

RESULTS

Of the 3363 black subjects examined, 2.6 percent had nonsense mutations in *PCSK9*; these mutations were associated with a 28 percent reduction in mean LDL cholesterol and an 88 percent reduction in the risk of CHD (P=0.008 for the reduction; hazard ratio, 0.11; 95 percent confidence interval, 0.02 to 0.81; P=0.03). Of the 9524 white subjects examined, 3.2 percent had a sequence variation in *PCSK9* that was associated with a 15 percent reduction in LDL cholesterol and a 47 percent reduction in the risk of CHD (hazard ratio, 0.50; 95 percent confidence interval, 0.32 to 0.79; P=0.003).

CONCLUSIONS

These data indicate that moderate lifelong reduction in the plasma level of LDL cholesterol is associated with a substantial reduction in the incidence of coronary events, even in populations with a high prevalence of non–lipid-related cardiovascular risk factors.

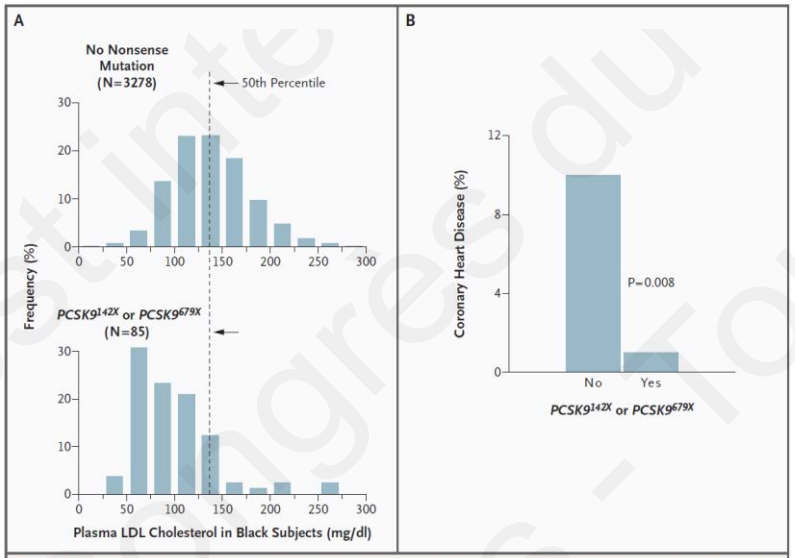


Figure 1. Distribution of Plasma LDL Cholesterol Levels (Panel A) and Incidence of Coronary Heart Disease (Panel B), among Black Subjects, According to the Presence or Absence of a *PCSK9*^{142X} or *PCSK9*^{679X} Allele.

In Panel A, the distribution of plasma LDL cholesterol levels at baseline among 3278 black subjects who did not have a *PCSK9*^{142X} or *PCSK9*^{679X} allele (top) is compared with the distribution of levels among the 85 black subjects who had one of these two alleles (bottom). Panel B shows the percentage of participants from these two groups who had no evidence of coronary heart disease at baseline and in whom coronary heart disease developed during the 15-year follow-up period. To convert values for LDL cholesterol to millimoles per liter, multiply by 0.02586.

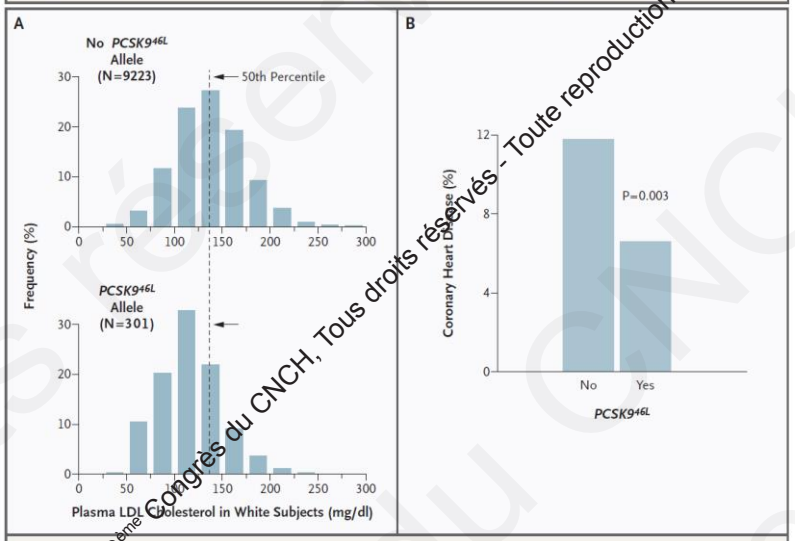
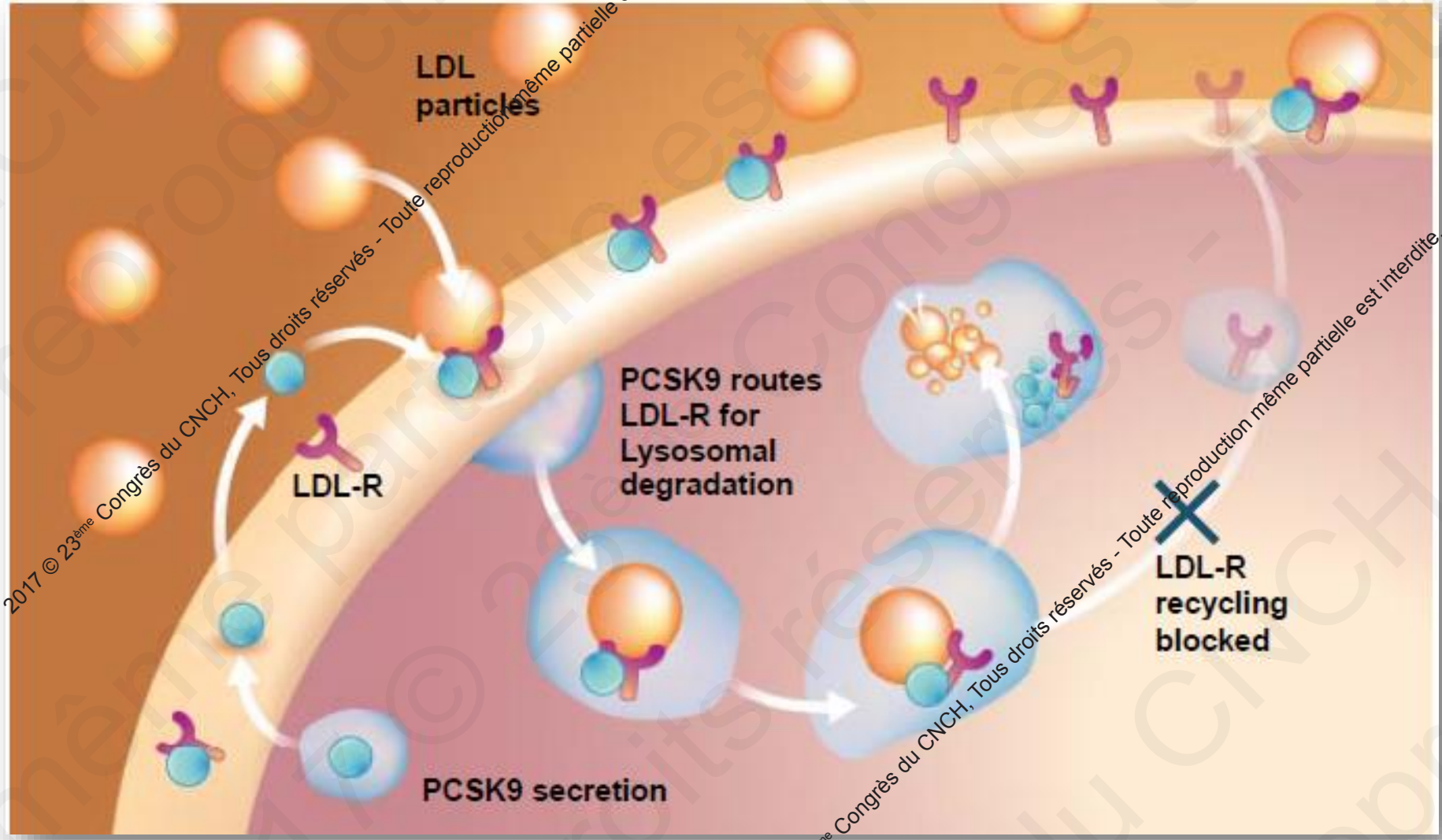
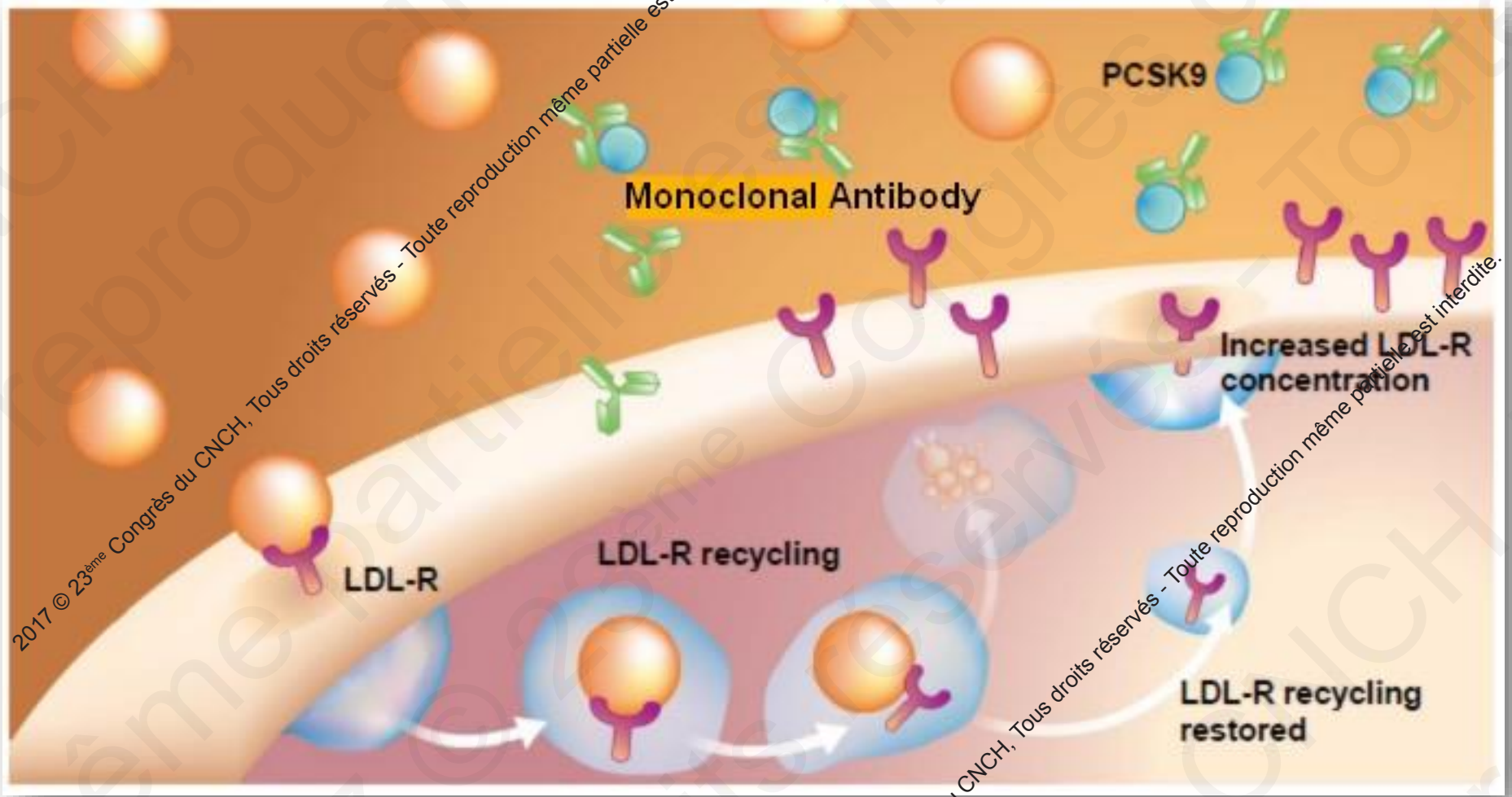


Figure 2. Distribution of Plasma LDL Cholesterol Levels (Panel A) and Incidence of Coronary Events (Panel B) among White Subjects, According to the Presence or Absence of a *PCSK9*^{46L} Allele.

In Panel A, the distribution of plasma LDL cholesterol levels at baseline among 9223 white subjects who did not have a *PCSK9*^{46L} allele (top) is compared with the distribution of levels among the 301 white subjects who were either heterozygous or homozygous for this allele (bottom). Panel B shows the percentage of participants from these two groups who had no evidence of coronary heart disease at baseline and in whom coronary heart disease developed during the 15-year follow-up period. To convert values for LDL cholesterol to millimoles per liter, multiply by 0.02586.

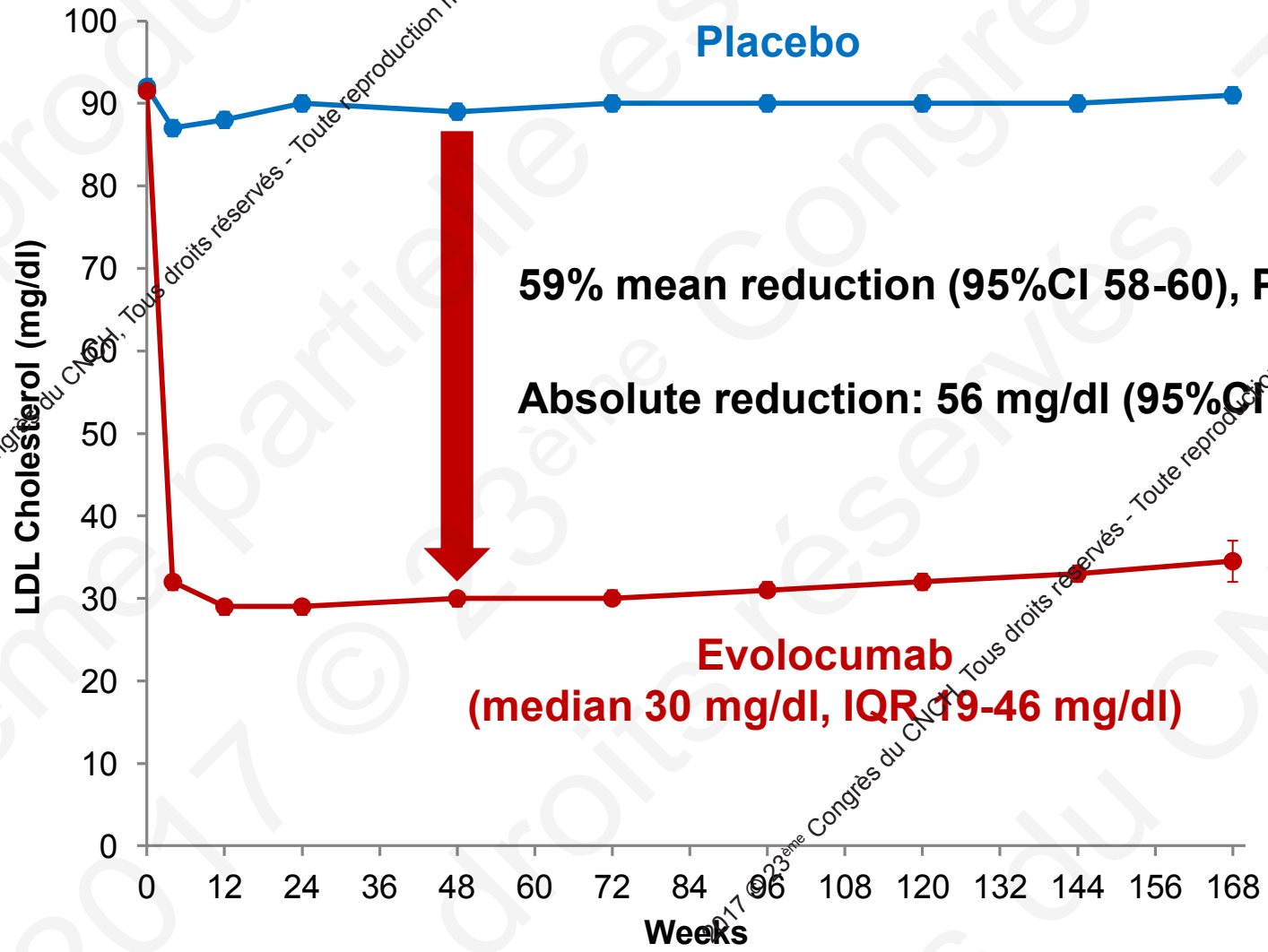


PCSK9: From discovery to therapeutic Applications – Michel Farnier - Archives of Cardiovascular Disease (2014) 107, 58—66

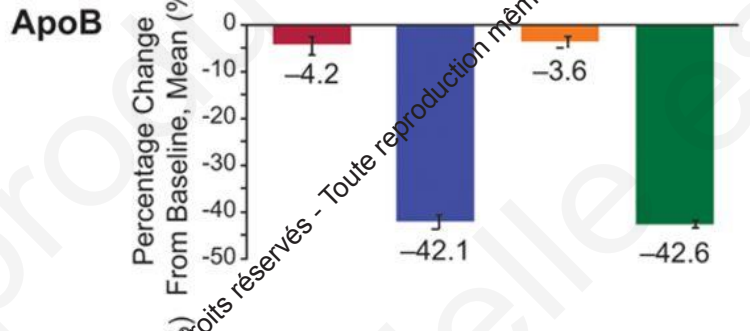


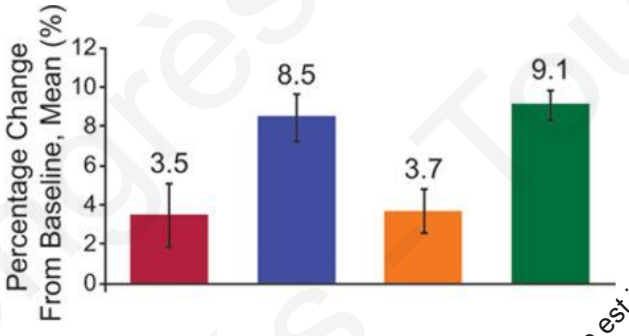
PCSK9: From discovery to therapeutic Applications – Michel Farnier - Archives of Cardiovascular Disease (2014) 107, 58—66

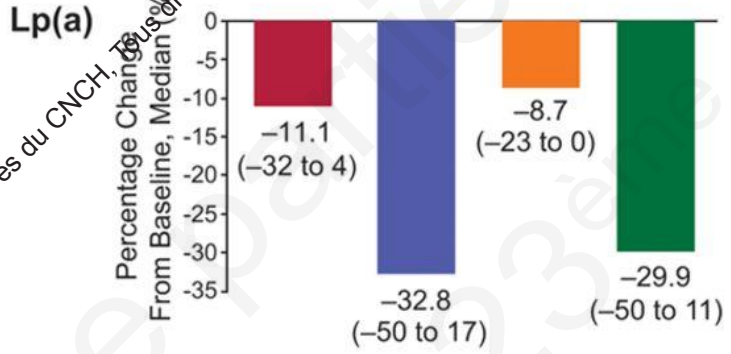
LDL Cholesterol

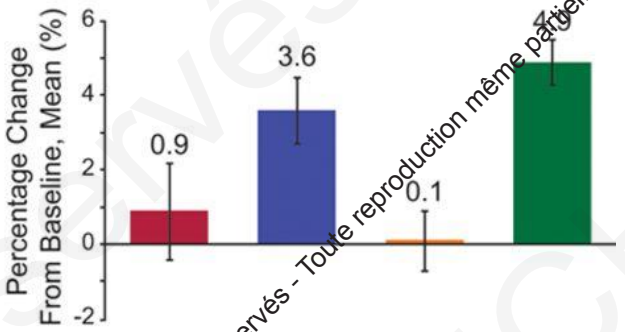


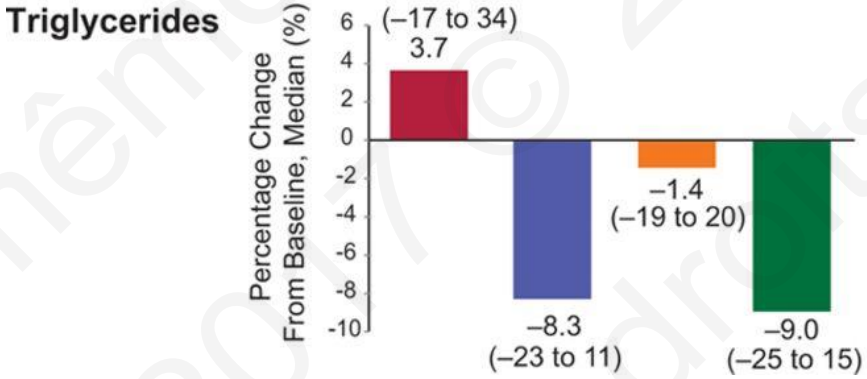
Percentage change from phase 2 parent study baseline at week 52 in apolipoprotein B (ApoB), lipoprotein(a) [Lp(a)], triglycerides, high-density lipoprotein cholesterol (HDL-C), and apolipoprotein A1 (ApoA1).

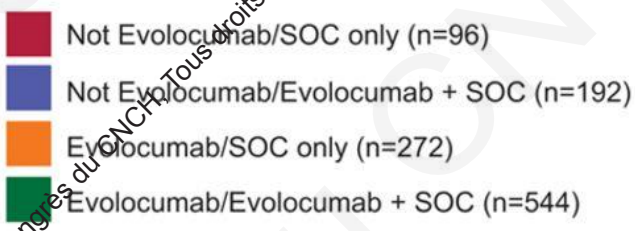












CRP

Michael J. Koren et al. Circulation. 2014;129:234-243

LDL and PCSK9 in JUPITER trial

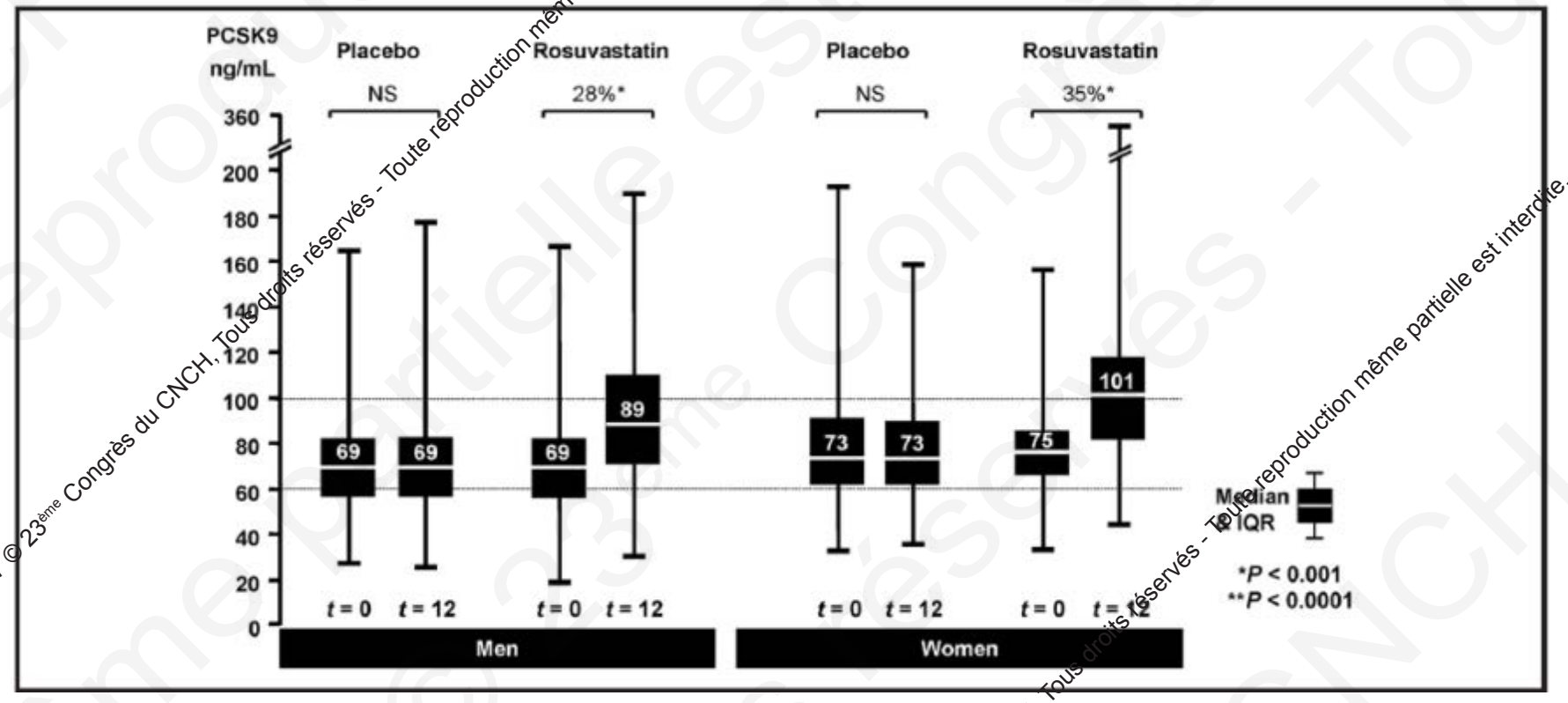
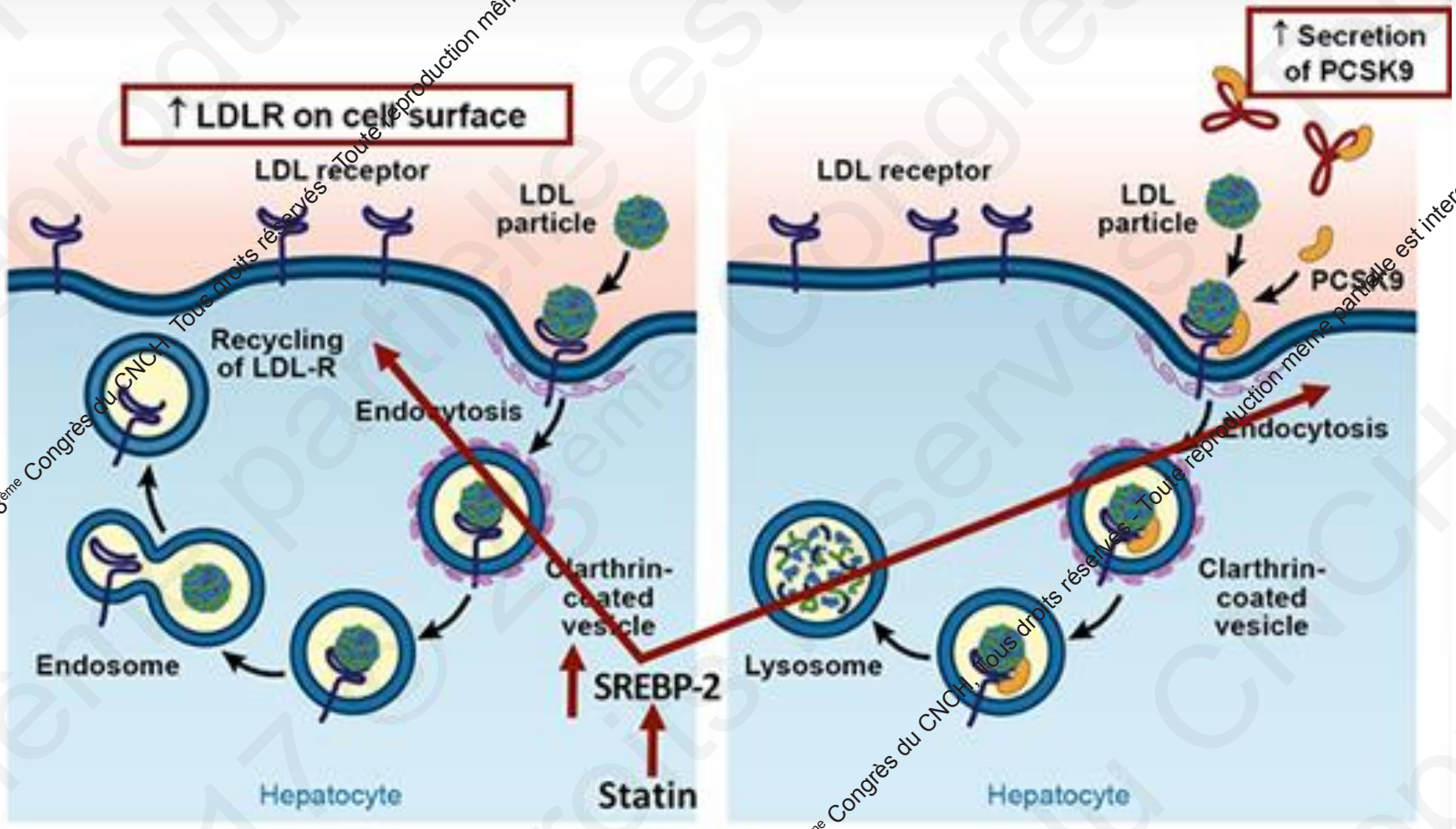


Figure 1. Stability of PCSK9 concentrations over 1 year in the JUPITER placebo arm vs the rosuvastatin arm. PCSK9 concentrations in men and women at baseline and over 1 year.
Vertical bars, minimum and maximum values; box, interquartile range (IQR); horizontal bar, median; NS, nonsignificant; t=0, baseline values; t=12, 1-year values. *P<0.0001.

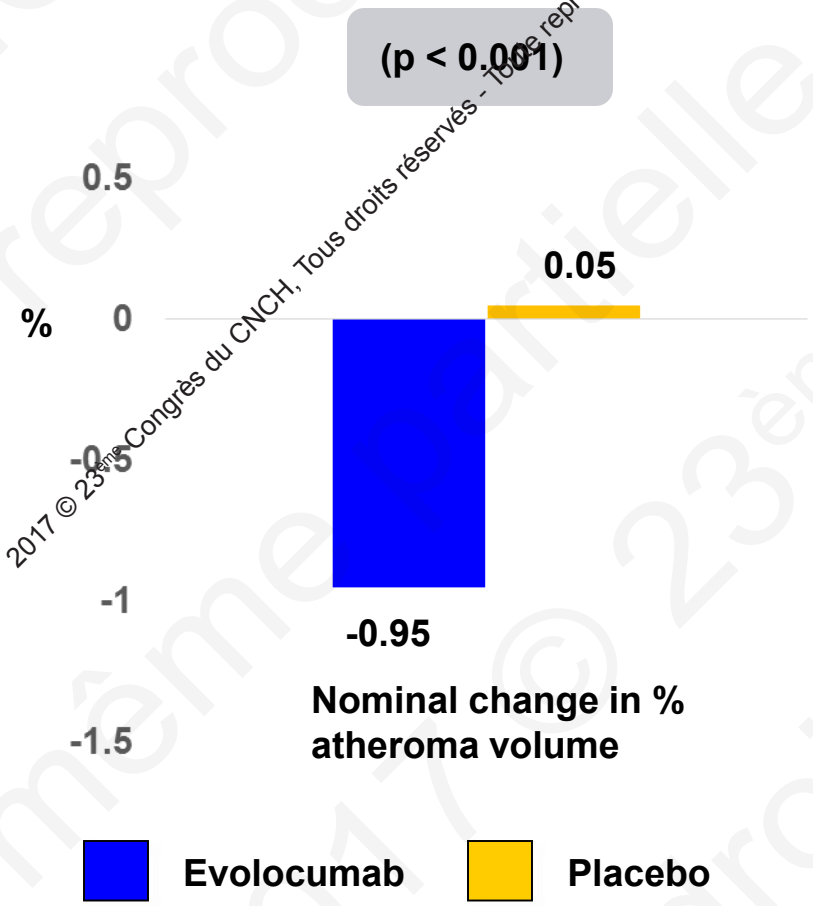
Impact of Statin Therapy on PCSK9



Lambert G, et al. *J. Lipid Res.* 2012;53:2515-2524.

GLAGOV

Trial design: Patients with CAD and elevated LDL cholesterol on statin therapy were randomized to subcutaneous evolocumab (n = 484) vs. subcutaneous placebo (n = 486).



Results

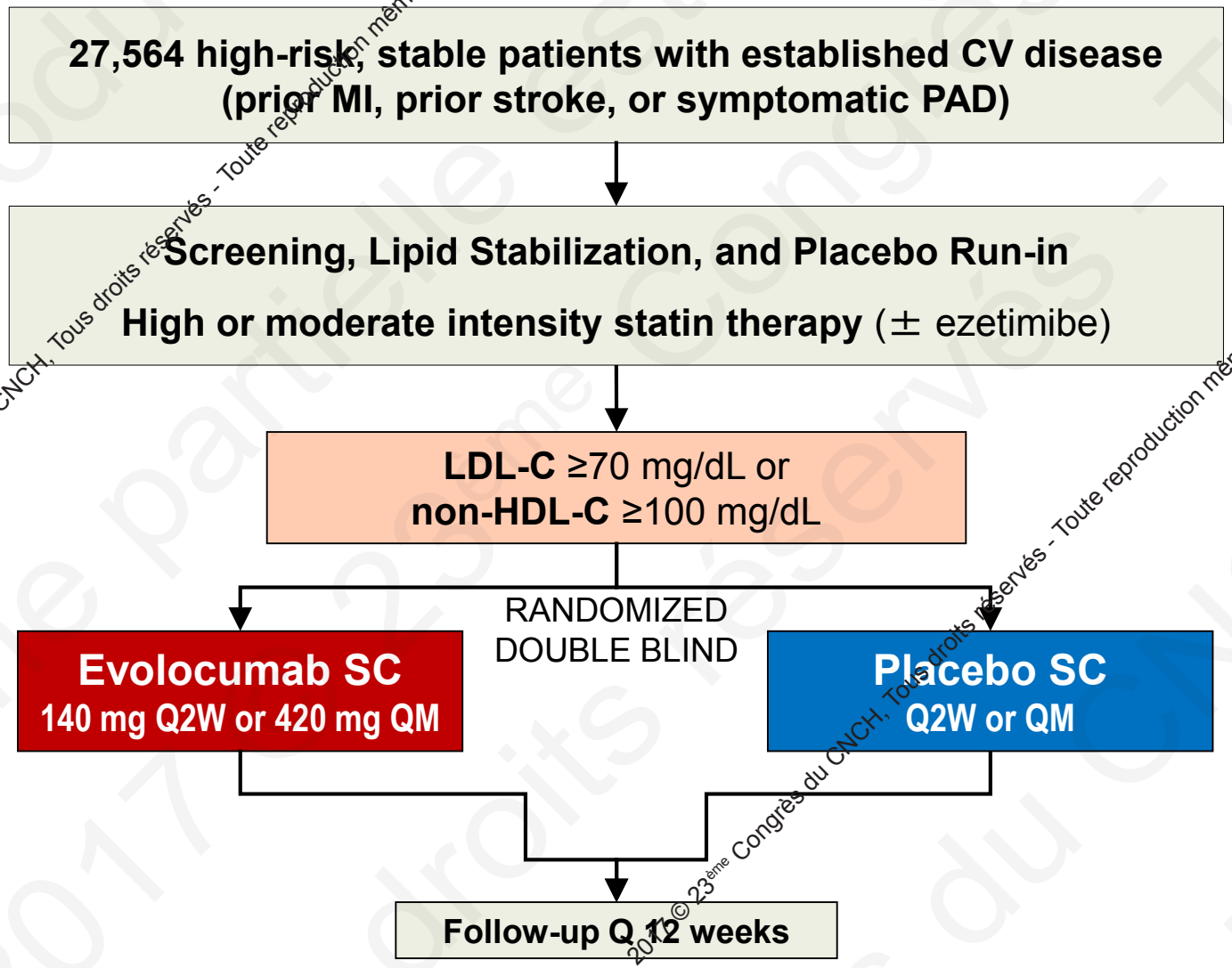
- Nominal change in percent atheroma volume at 78 weeks: -0.95% in the evolocumab group vs. 0.05% in the placebo group (p < 0.001 for between-group comparison)
- Patients with plaque regression: 64.3% with evolocumab vs. 47.3% with placebo (p < 0.001)
- Major adverse cardiac events: 12.2% with evolocumab vs. 15.3% with placebo

Conclusions

- Among patients with angiographic evidence of CAD on chronic statin therapy, the PCSK9 inhibitor evolocumab resulted in a greater change in percent atheroma volume and a greater proportion of patients with plaque regression

Nicholls SJ, et al. JAMA 2016;316:2373-84

Trial Design



Sabatine MS et al. *Am Heart J* 2016;173:94-101

Endpoints

- **Efficacy**
  - **Primary: CV death, MI, stroke, hosp. for UA, or coronary revasc**
  - **Key secondary: CV death, MI or stroke**
- **Safety**
  - **AEs/SAEs**
  - **Events of interest incl. muscle-related, new-onset diabetes, neurocognitive**
  - **Development of anti-evolocumab Ab (binding and neutralizing)**
- **TIMI Clinical Events Committee (CEC)**
  - **Adjudicated all efficacy endpoints & new-onset diabetes**
  - **Members unaware of treatment assignment & lipid levels**

Sabatine MS et al. *Am Heart J* 2016;173:94-101

Baseline Characteristics

Characteristic	Value
Age, years, mean (SD)	**63 (9)**
Male sex (%)	**75**
Type of cardiovascular disease (%)	
Myocardial infarction	**81**
Stroke (non-hemorrhagic)	**19**
Symptomatic PAD	**13**
Cardiovascular risk factor (%)	
Hypertension	**80**
Diabetes mellitus	**37**
Current cigarette use	**28**

Median time from most recent event ~3 yrs

Pooled data; no differences between treatment arms

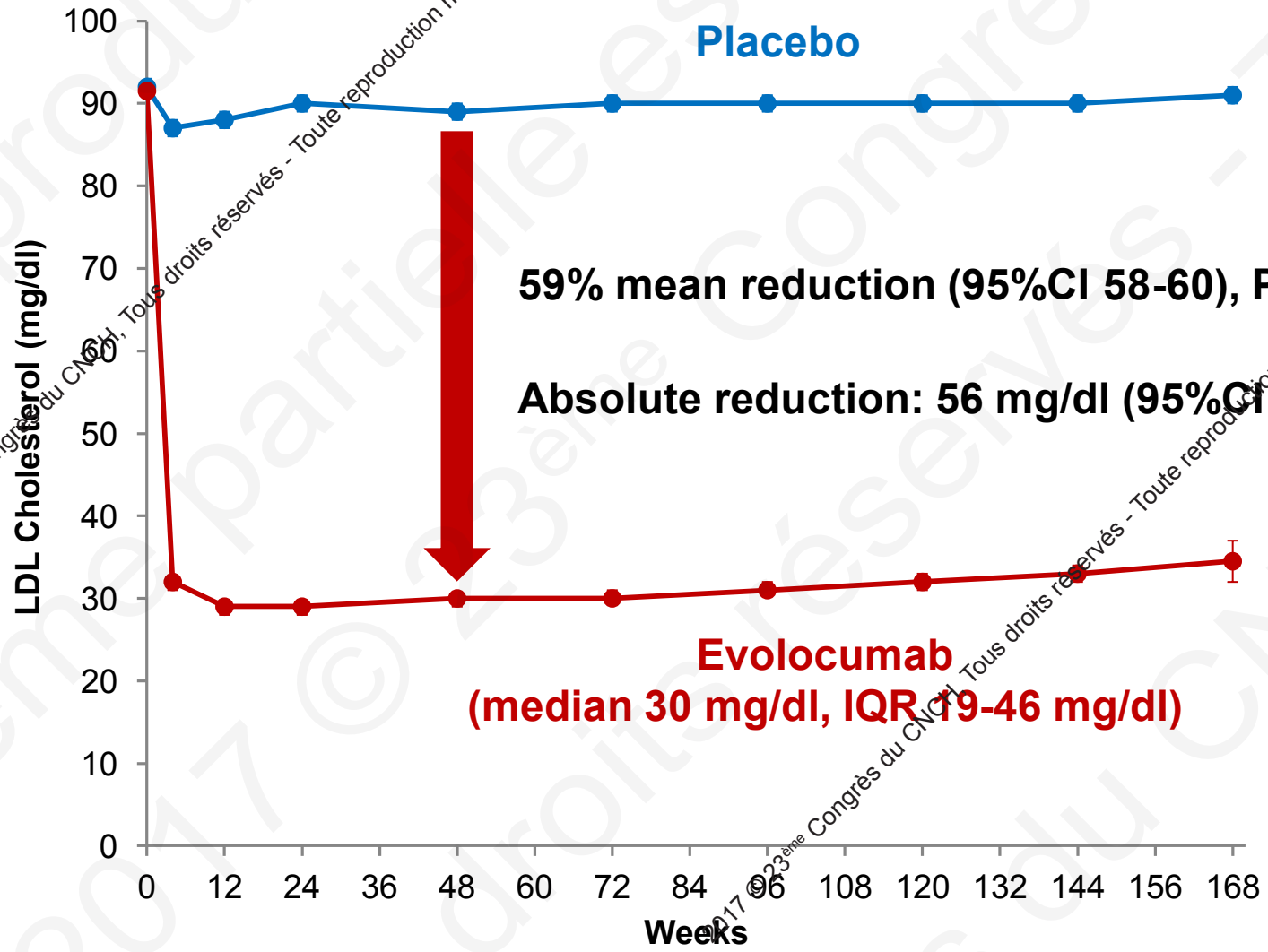
Lipid Lowering Therapy & Lipid Levels at Baseline

Characteristic	Value
Statin use (%)*	
High-intensity	**69**
Moderate-intensity	**30**
Ezetimibe use (%)	**5**
Median lipid measures (IQR) – mg/dL	
LDL-C	**92 (80-109)**
Total cholesterol	**168 (151-189)**
HDL-C	**44 (37-53)**
Triglycerides	**133 (100-182)**

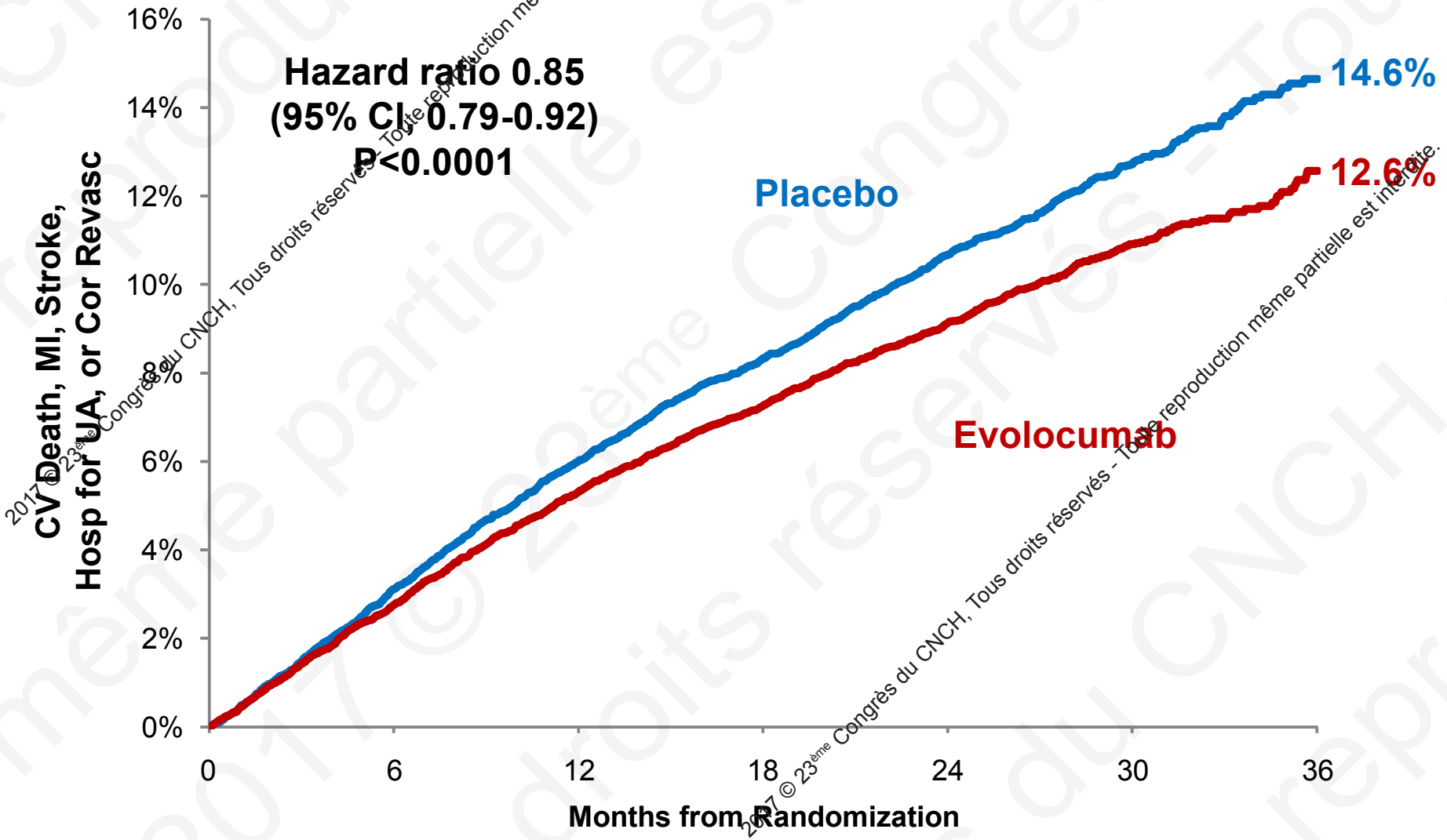
*Per protocol, patients were to be on atorva ≥20 mg/d or equivalent.
1% were on low intensity or intensity data were missing.
Statin intensity defined per ACC/AHA 2013 Cholesterol Guidelines.

Pooled data; no differences between treatment arms

LDL Cholesterol



Primary Endpoint



Types of CV Outcomes

fourier

Endpoint	Evolocumab (N=13,784)	Placebo (N=13,780)	HR (95% CI)
	3-yr Kaplan-Meier rate		
CVD, MI, stroke, UA, or revasc	**12.6**	**14.6**	**0.85 (0.79-0.92)**
CV death, MI, or stroke	**7.9**	**9.9**	**0.80 (0.73-0.88)**
Cardiovascular death	**2.5**	**2.4**	**1.05 (0.88-1.25)**
MI	**4.4**	**6.3**	**0.73 (0.65-0.82)**
Stroke	**2.2**	**2.6**	**0.79 (0.66-0.95)**
Hosp for unstable angina	**2.2**	**2.3**	**0.99 (0.82-1.18)**
Coronary revasc	**7.0**	**9.2**	**0.78 (0.71-0.86)**
Urgent	3.7	5.4	0.73 (0.64-0.83)
Elective	3.9	4.6	0.83 (0.73-0.95)
Death from any cause	**4.8**	**4.3**	**1.04 (0.91-1.19)**

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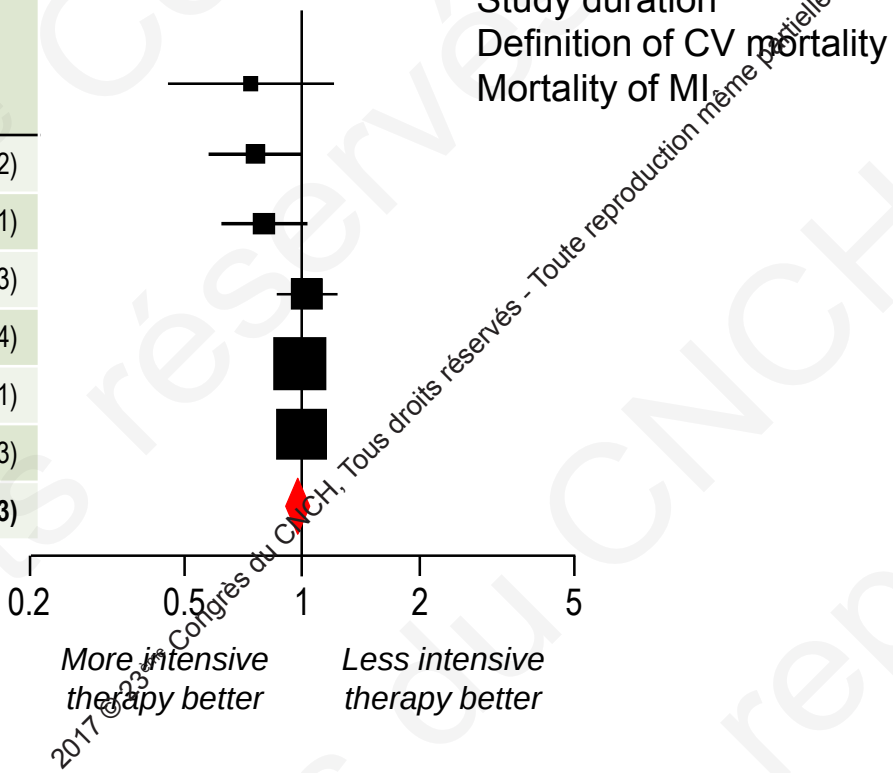
More Intensive LDL-C Lowering & CV Death

No clear benefit on CV mortality

Trial	Year	# of CV Deaths: More Intensive Rx Arm	# of CV Deaths: Less Intensive Rx Arm	HR (95% CI)
PROVE-IT TIMI 22	2004	27	36	0.74 (0.45-1.22)
A2Z	2004	86	111	0.76 (0.57-1.01)
TNT	2005	101	127	0.80 (0.61-1.03)
IDEAL	2005	223	218	1.03 (0.85-1.24)
SEARCH	2010	565	572	0.99 (0.88-1.11)
IMPROVE-IT	2015	538	537	1.00 (0.89-1.13)
Summary		**1540**	**1601**	**0.96 (0.90-1.03)**

NEJM 2004;350:1495-504
JAMA 2004;292:1307-16
NEJM 2005;352:1425-35
JAMA 2005;294:2437-45
Lancet 2010;376:1658-69
NEJM 2015;372:2387-97



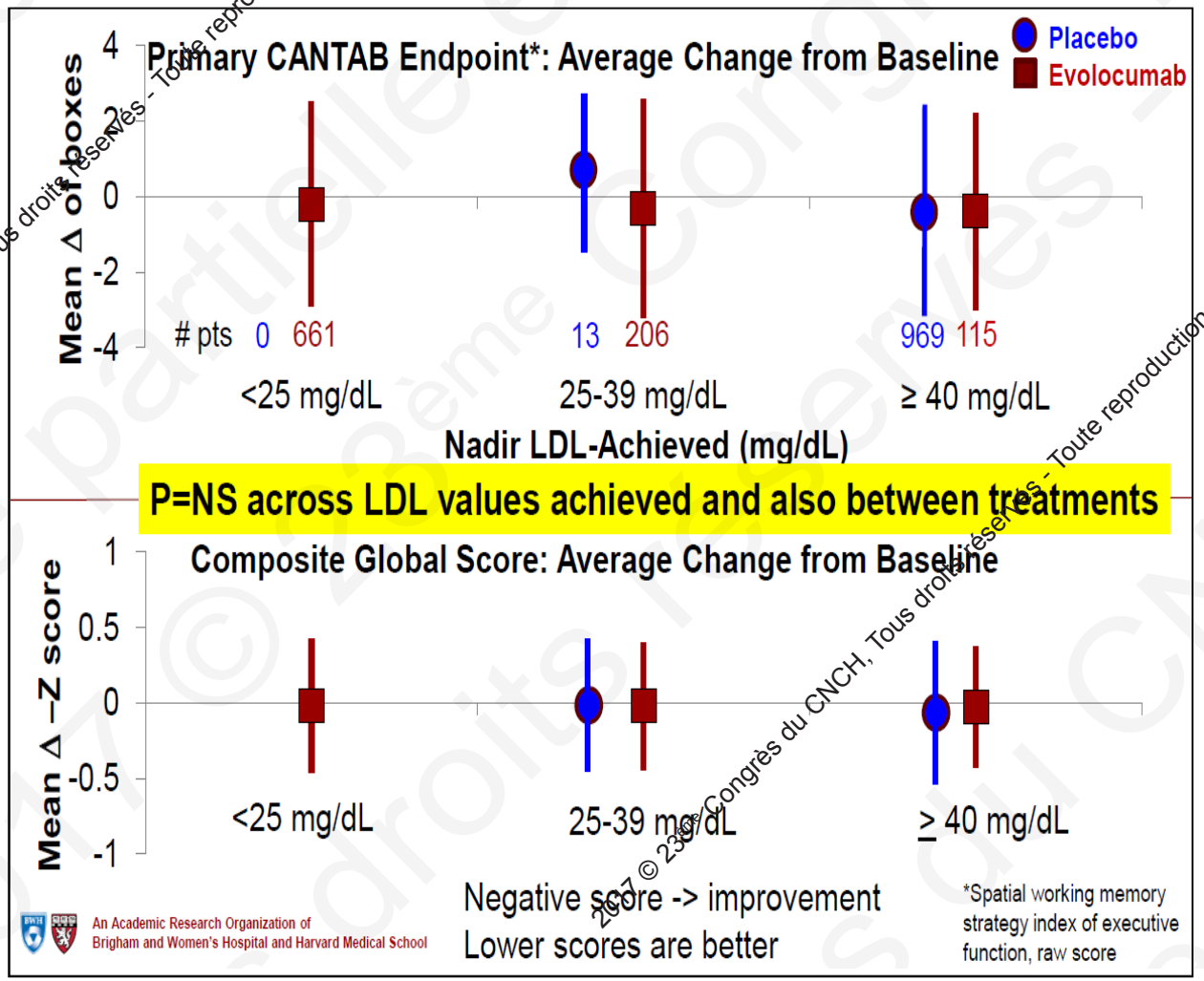
Safety

	Evolocumab (N=13,769)	Placebo (N=13,756)
Adverse events (%)		
Any	77.4	77.4
Serious	24.8	24.7
Allergic reaction	3.1	2.9
Injection-site reaction	2.1	1.6
Treatment-related and led to d/c of study drug	1.6	1.5
Muscle-related	5.0	4.8
Cataract	1.7	1.8
Diabetes (new-onset)	8.1	7.7
Neurocognitive	1.6	1.5
Laboratory results (%)		
Binding Ab	0.3	n/a
Neutralizing Ab	*none*	n/a

New-onset diabetes assessed in patients without diabetes at baseline; adjudicated by CEC

Un LDL-c très bas est associé à un déclin cognitif ?

- **Ebbinghaus**: absence de déclin cognitif décelable par le Cambridge Neuropsychological Test Automated Battery, en 2 ans, sur 770 pts, avec Evolocumab, quelque soit le niveau de LDL-C.



Bocozizumab - Spire

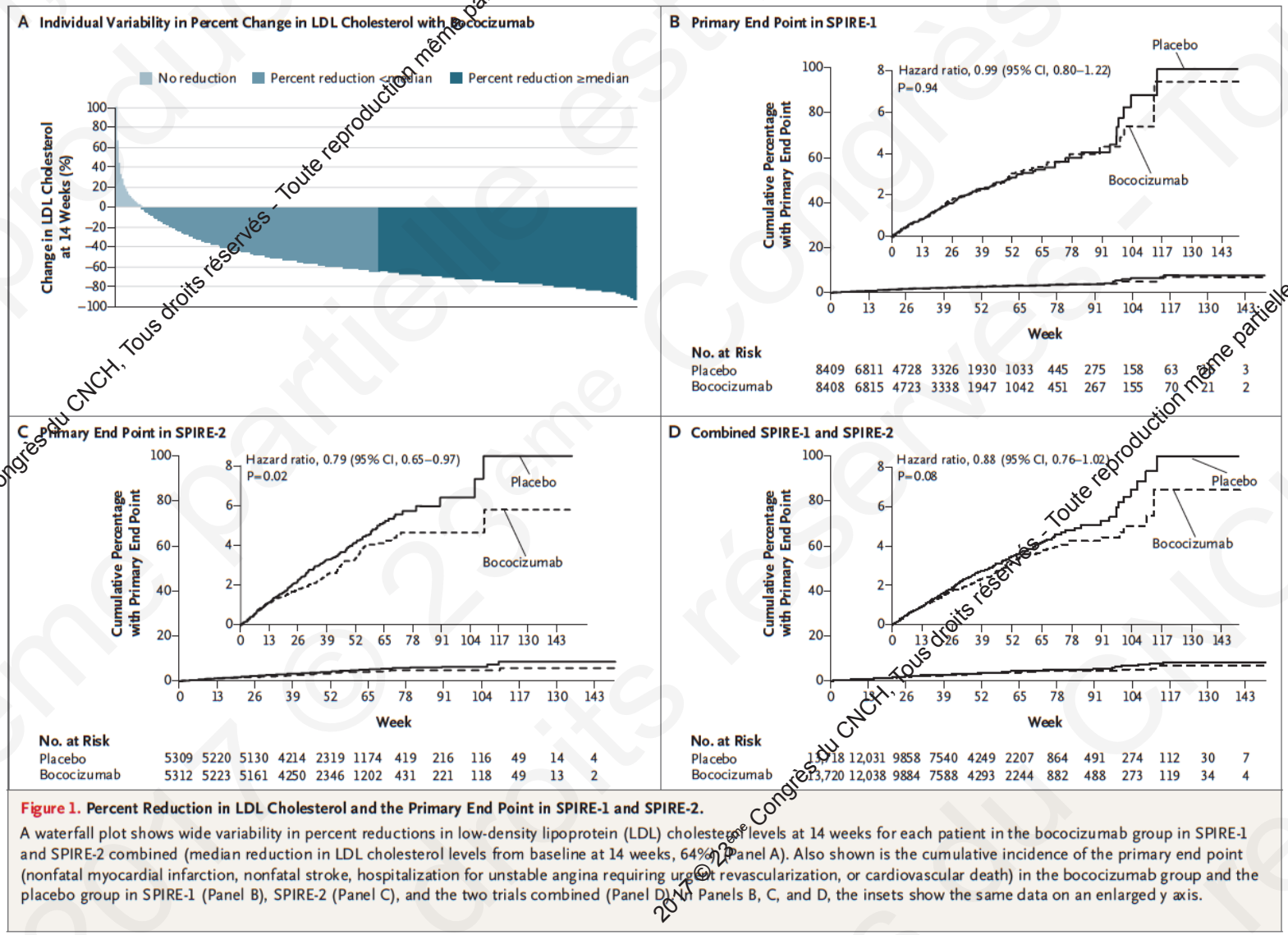
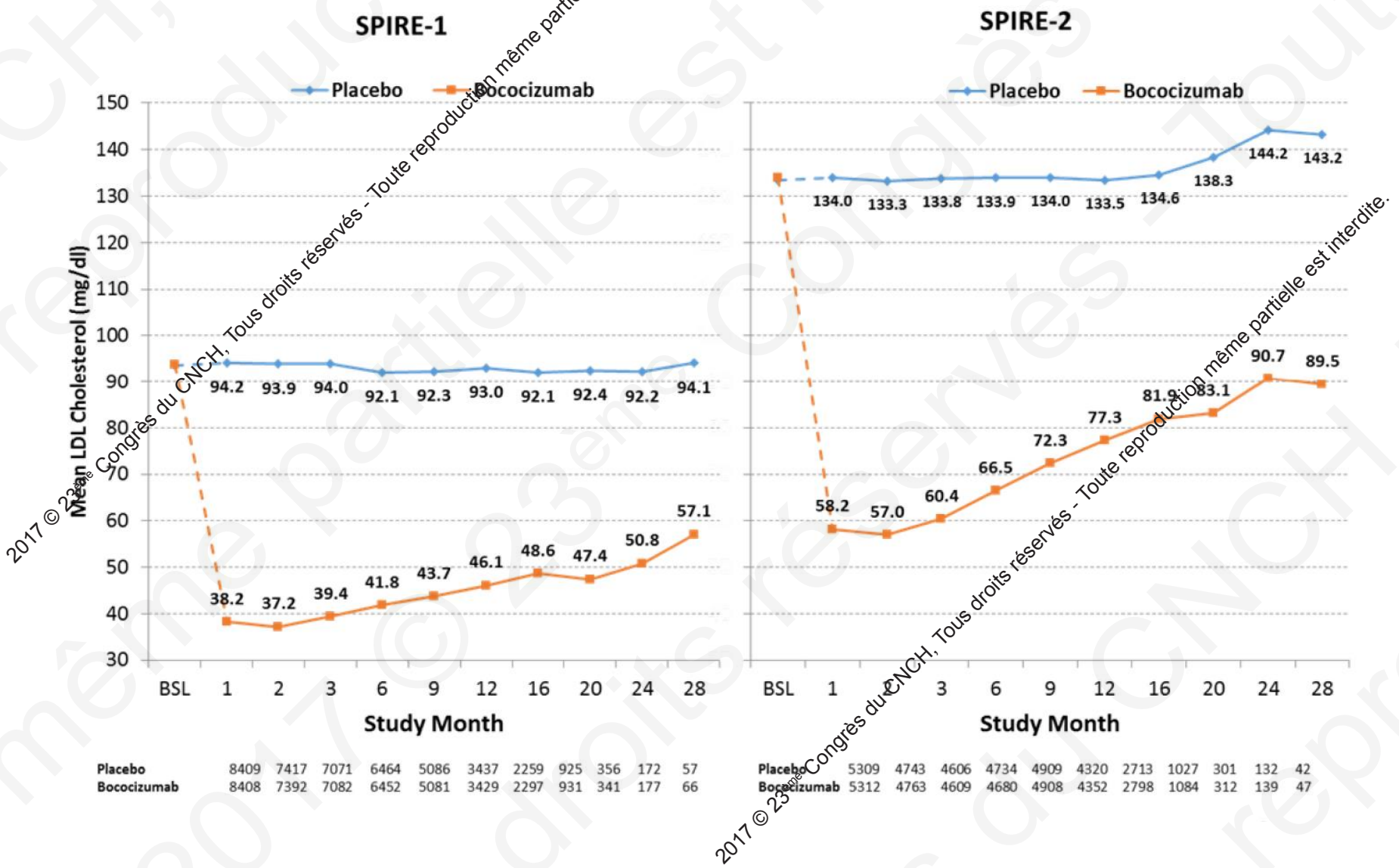


Figure 1. Percent Reduction in LDL Cholesterol and the Primary End Point in SPIRE-1 and SPIRE-2.

A waterfall plot shows wide variability in percent reductions in low-density lipoprotein (LDL) cholesterol levels at 14 weeks for each patient in the bococizumab group in SPIRE-1 and SPIRE-2 combined (median reduction in LDL cholesterol levels from baseline at 14 weeks, 64%) (Panel A). Also shown is the cumulative incidence of the primary end point (nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death) in the bococizumab group and the placebo group in SPIRE-1 (Panel B), SPIRE-2 (Panel C), and the two trials combined (Panel D). In Panels B, C, and D, the insets show the same data on an enlarged y axis.

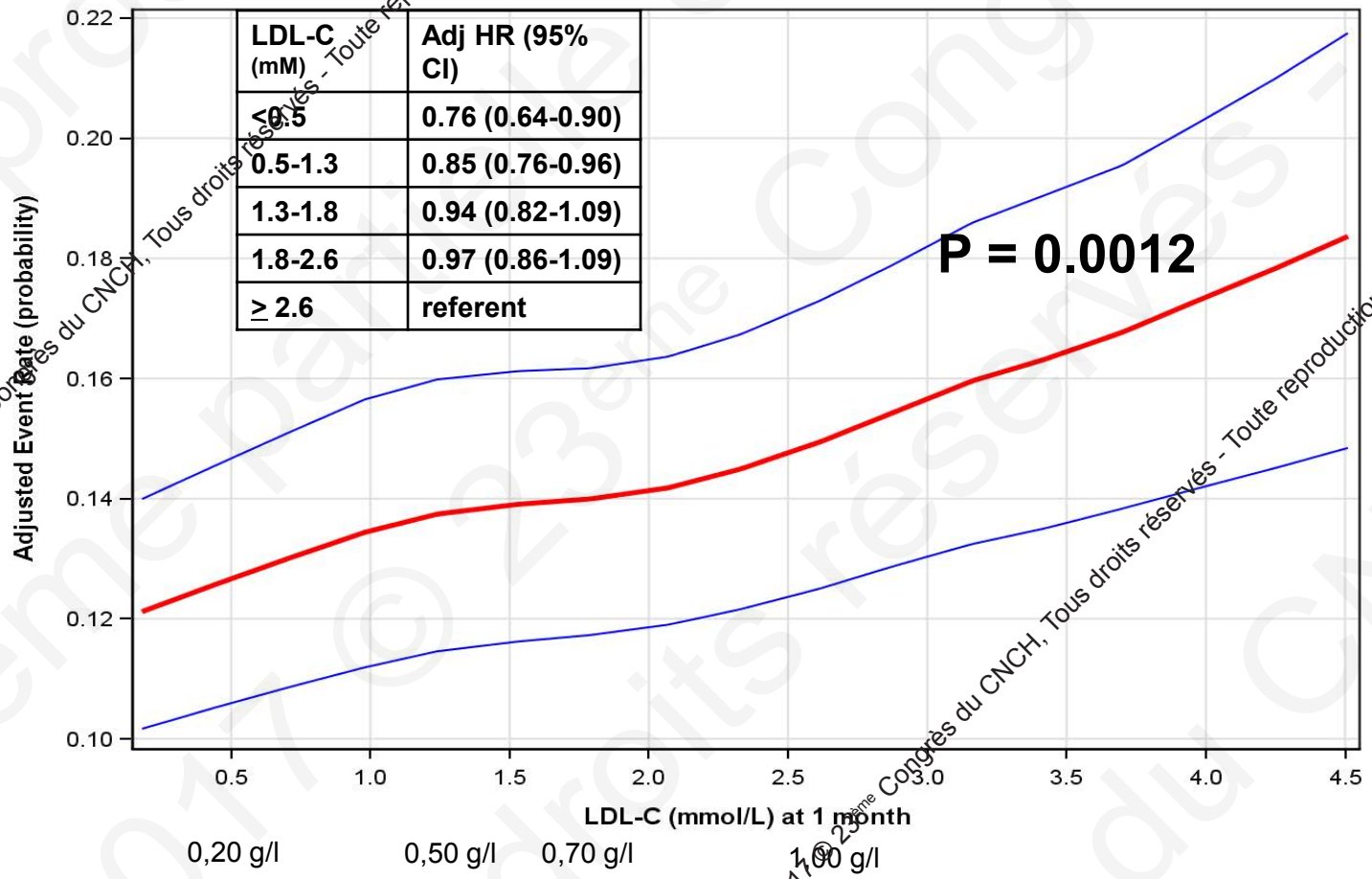
Ridker et al, NEJM 2017

Bocozizumab - Spire



Ridker et al, NEJM 2017

MACE / LDL at 4 weeks

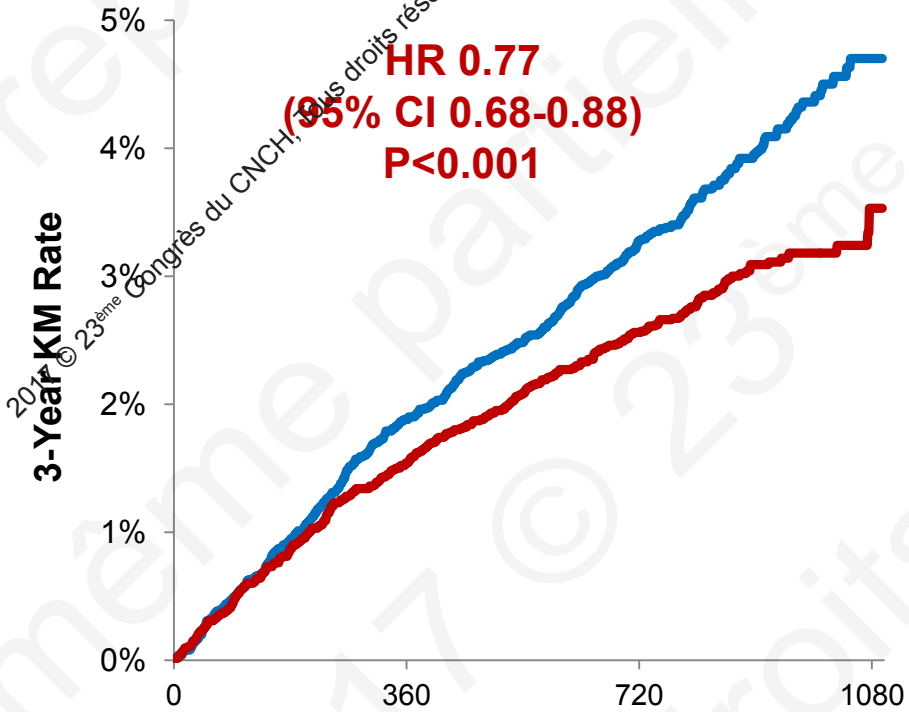


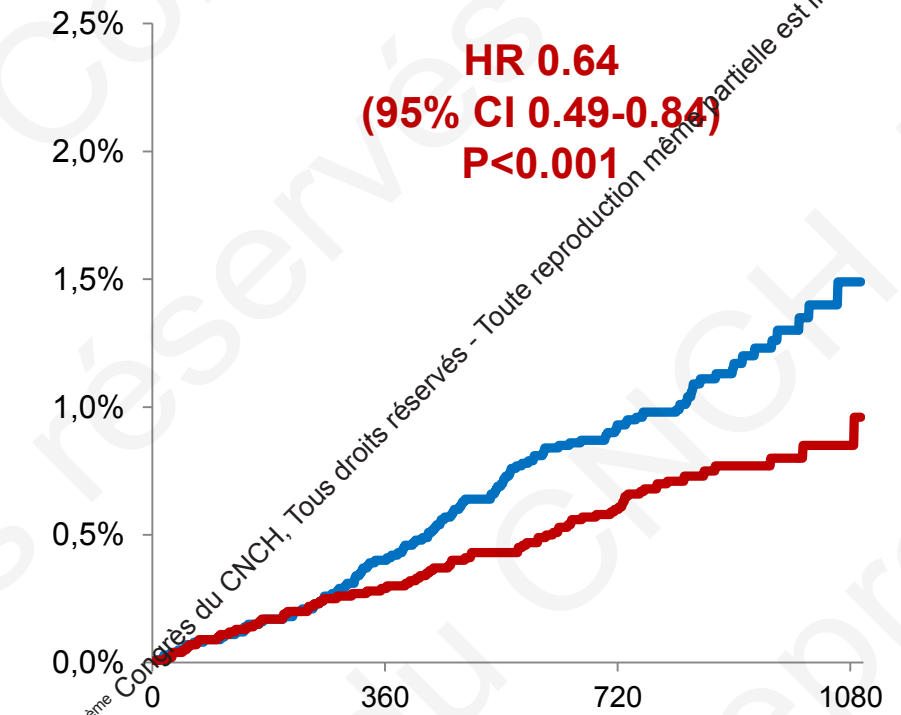
LDL-C (mM)	Adj HR (95% CI)
<0.5	0.76 (0.64-0.90)
0.5-1.3	0.85 (0.76-0.96)
1.3-1.8	0.94 (0.82-1.09)
1.8-2.6	0.97 (0.86-1.09)
≥ 2.6	referent

0,20 g/l 0,50 g/l 0,70 g/l 1,00 g/l

Giugliano RP, ESC Congress 2017, Barcelona 8/28/2017

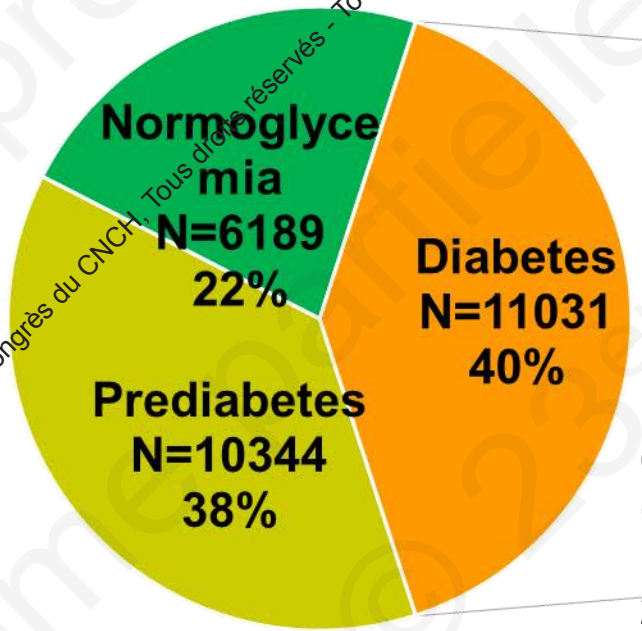
Effect of Evolocumab by MI Type: NSTEMI and STEMI





Days from Randomization

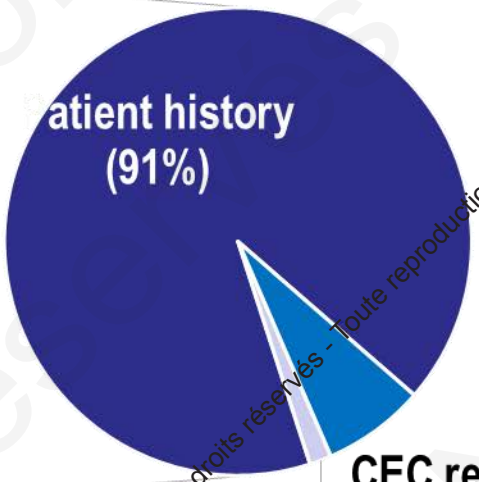
Diabetes at Baseline



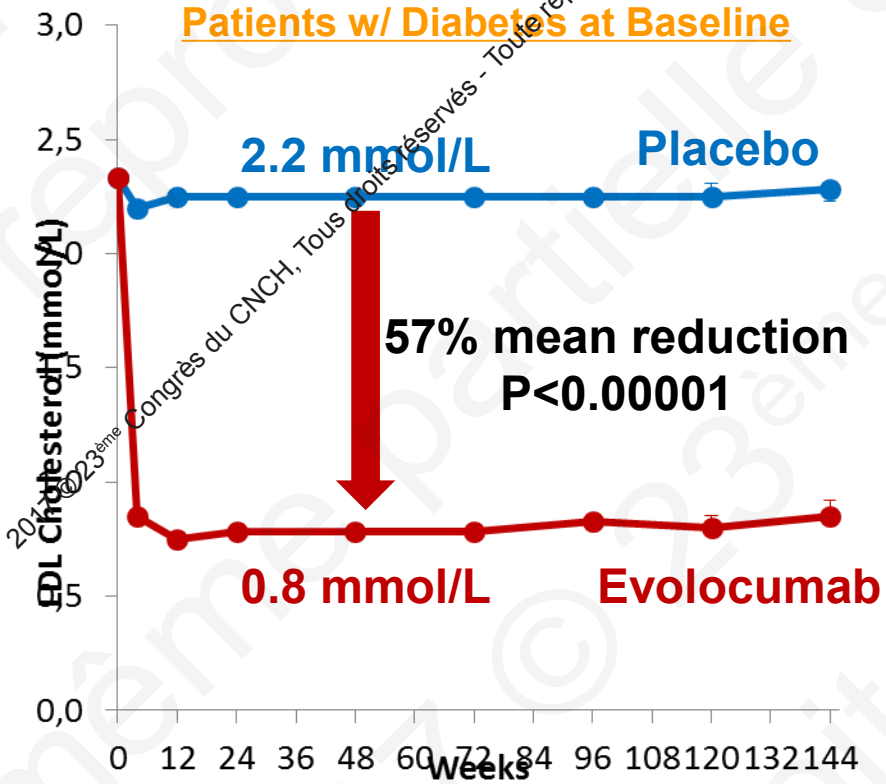
Median duration 5.7 y (IQR 1.9-11.9)

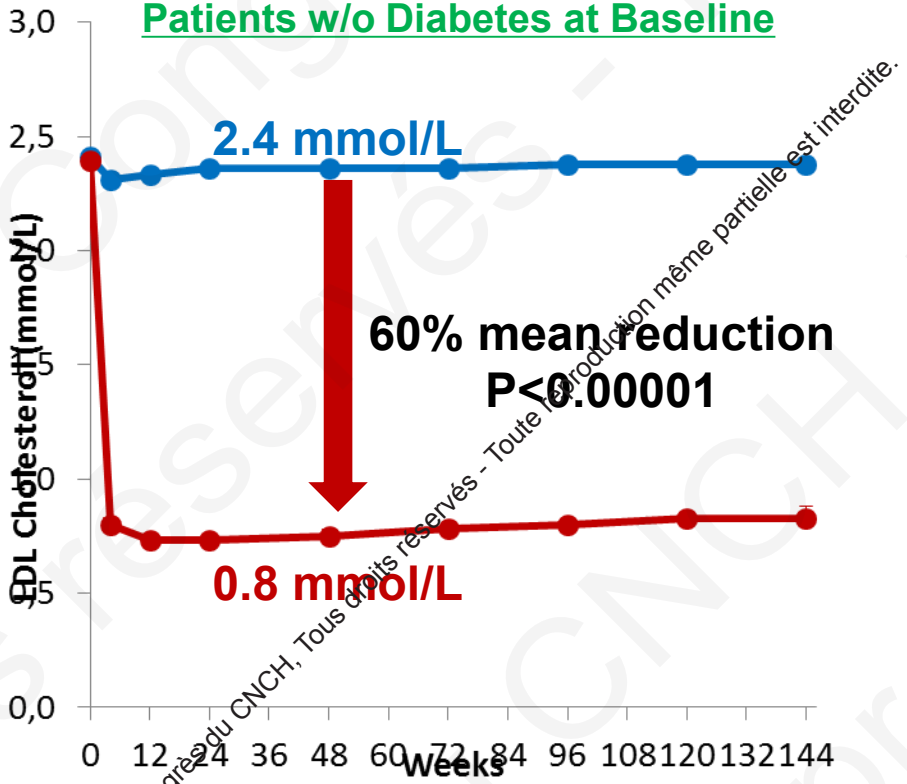
25% taking insulin

Diagnosis of diabetes:

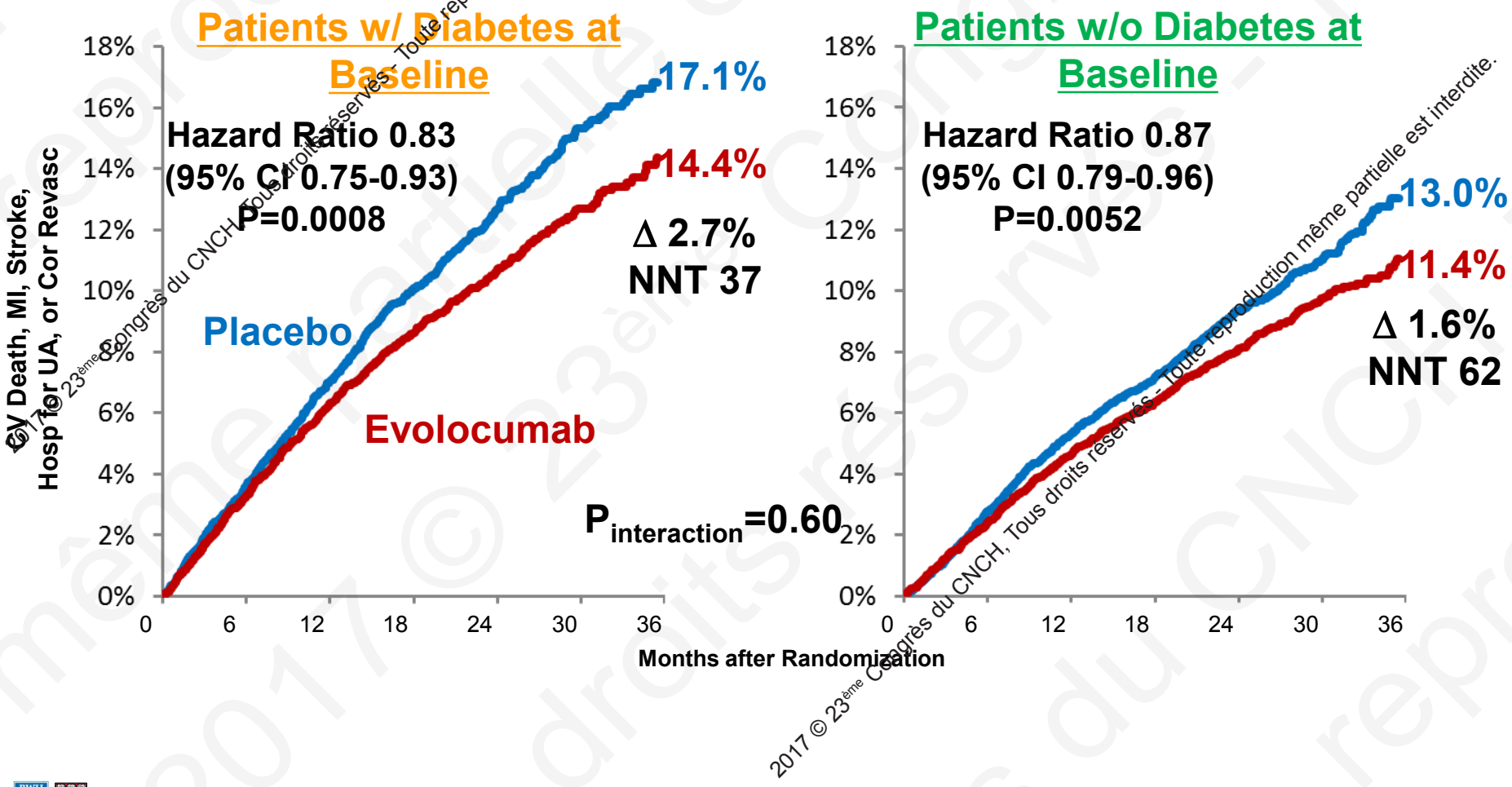


LDL-C Reduction with Evolocumab

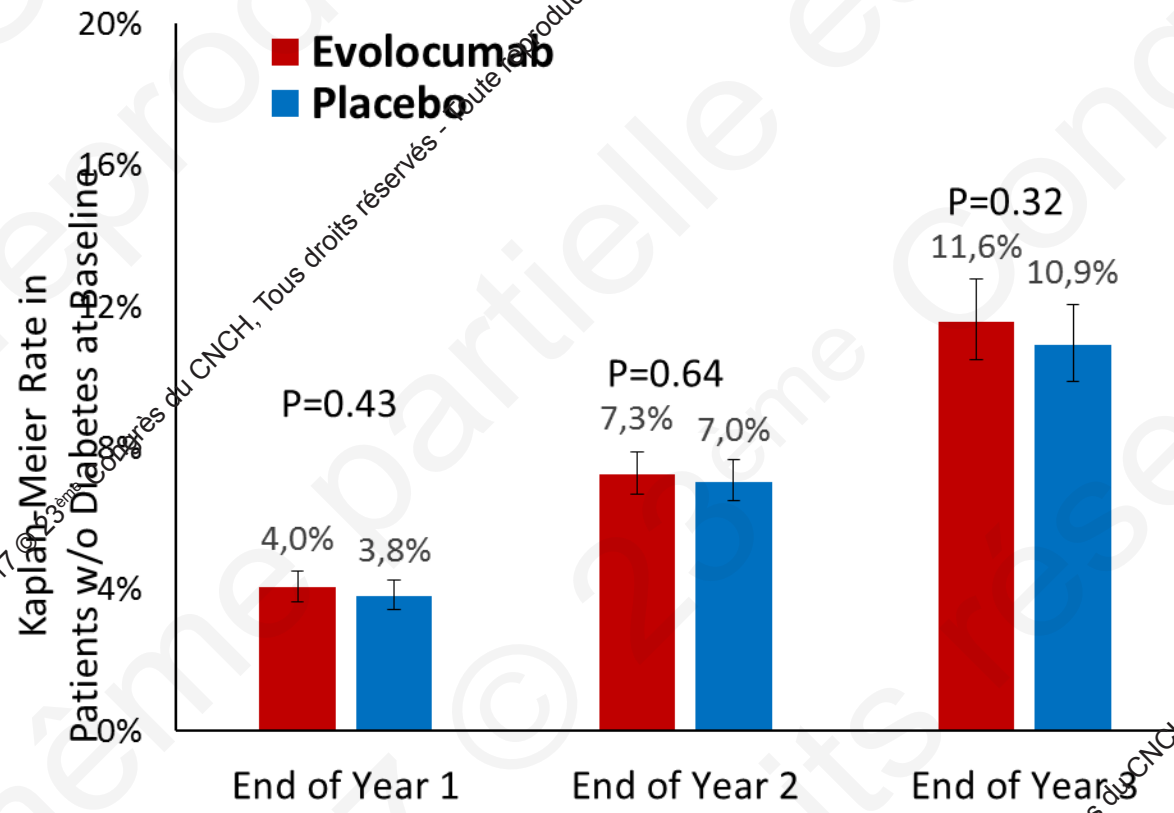




Effect of Evolocumab on Primary Endpoint



New-Onset Diabetes



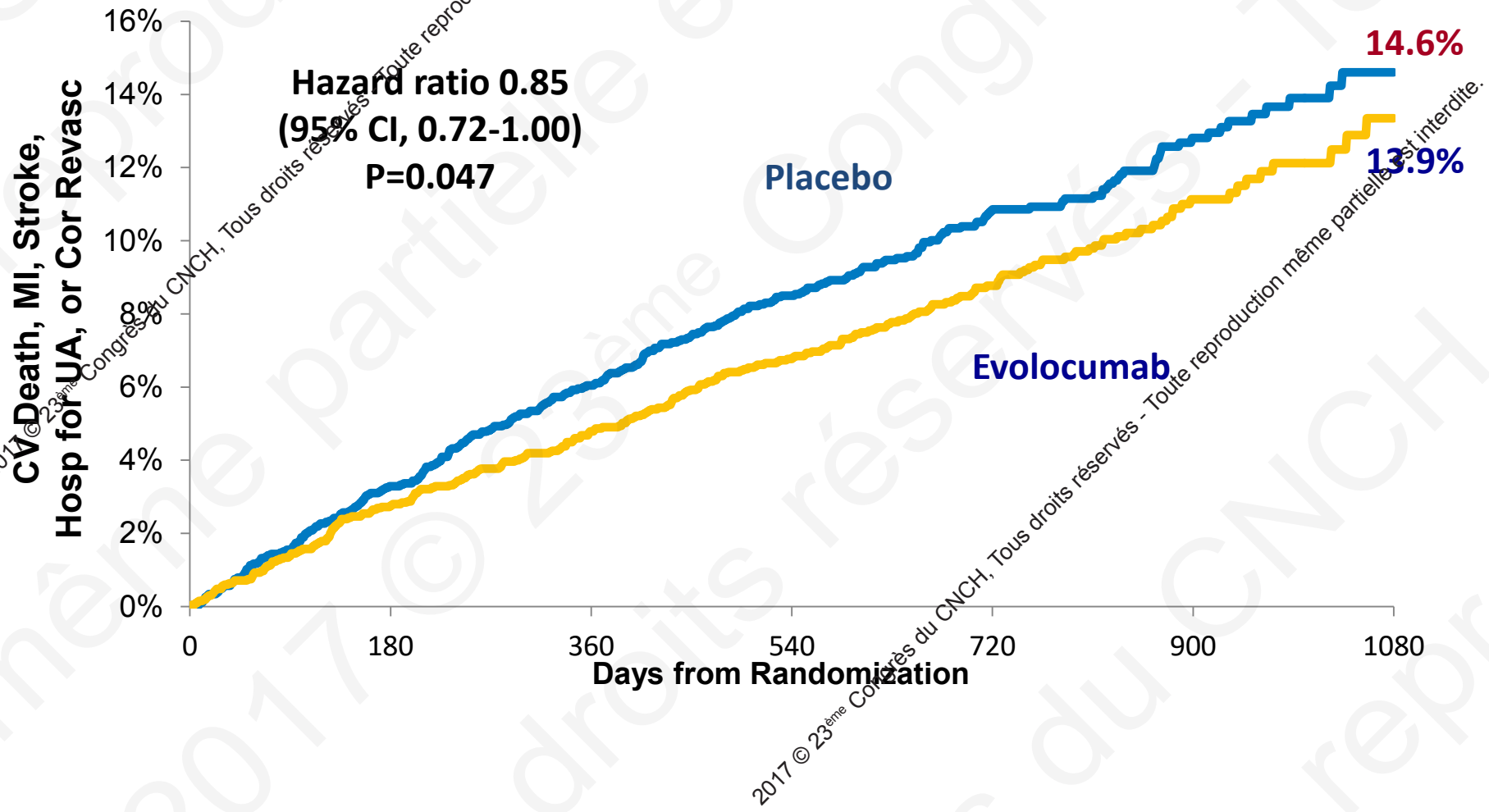
In all patients w/o diabetes at baseline (1294 incident cases in 16,510 patients):

HR 1.05 (95% CI 0.94-1.17)

In patients w/ prediabetes at baseline (1163 incident cases in 10,338 patients):

HR 1.00 (95% CI 0.89-1.13)

Hx Stroke Cohort: Primary Endpoint



Safety in Cohort With Stroke

Event	Evolocumab n	Placebo n	p-value
Neurocognitive AE	53	53	0.942
Headache	93	115	0.097
Arthralgia	121	99	0.159
Fatigue	65	52	0.255
New onset diabetes	114	106	0.640
AST or ALT >3X ULN	36	44	0.339
Cataract	55	44	0.254

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CV Death, MI or Stroke in Patients with and without Peripheral Artery Disease