TURIN,
October
25th-27th
2018
Starhotels
Majestic

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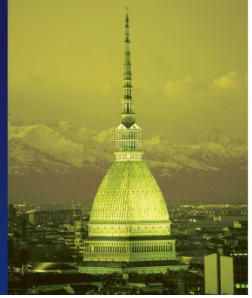
CARDIOLOGICHE
TORINESI



UNIVERSITÁ DEGLI STUDI DI TORINO

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

LDL is a Toxic

Gaetano M. De Ferrari

Direttore Scuola di Specializzazione in Malattie dell'Apparato Cardiovascolare, Università degli Studi di Pavia;
Direttore Unità Coronarica e Centro di Ricerca Clinica Cardiovascolare, Fondazione IRCCS Policlinico San Matteo, Pavia

OSPITALE DI S. MATTEO
PAVIA

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- Amgen
- Merck
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It All Started From A Rabbit

Centralbl. f. Allgemeine Pathologie u. Pathol. Anatomie Bd. XXIV. No. 1.
Ausgegeben am 15. Januar 1913.

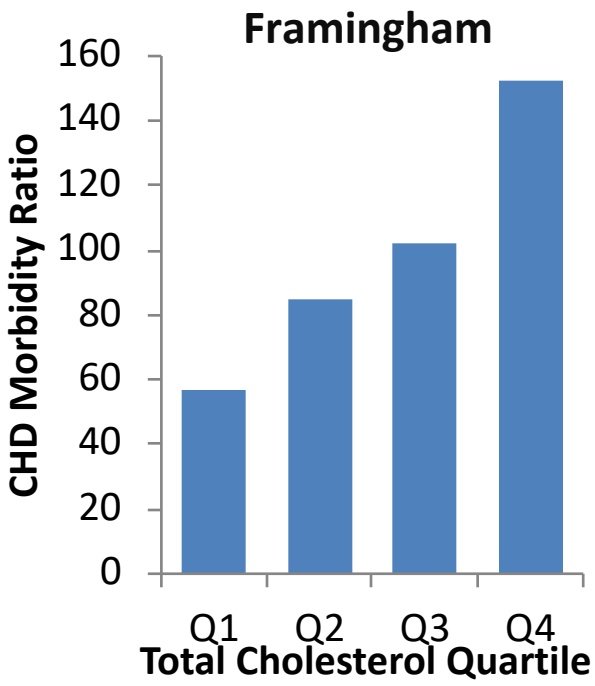
Originalmitteilungen.

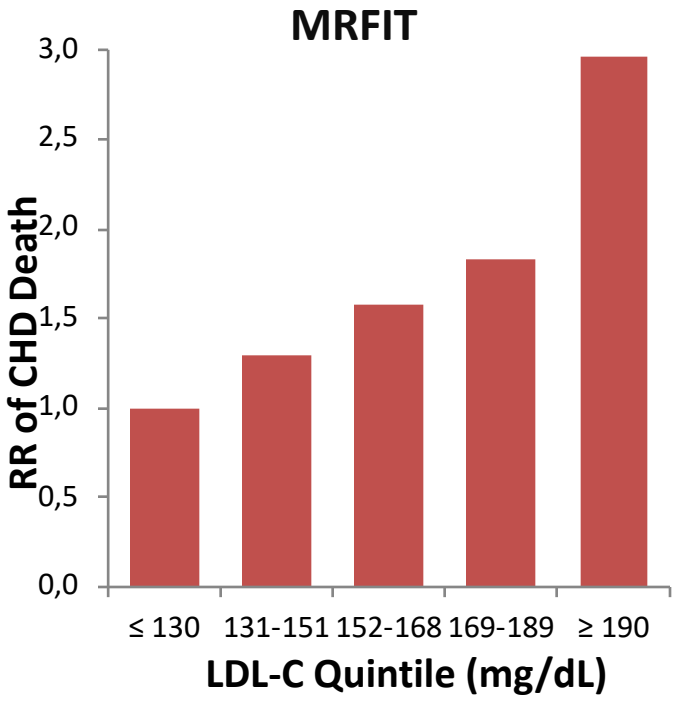
Nachdruck verboten.

Ueber experimentelle Cholesterinsteatose und ihre Bedeutung für die Entstehung einiger pathologischer Prozesse.

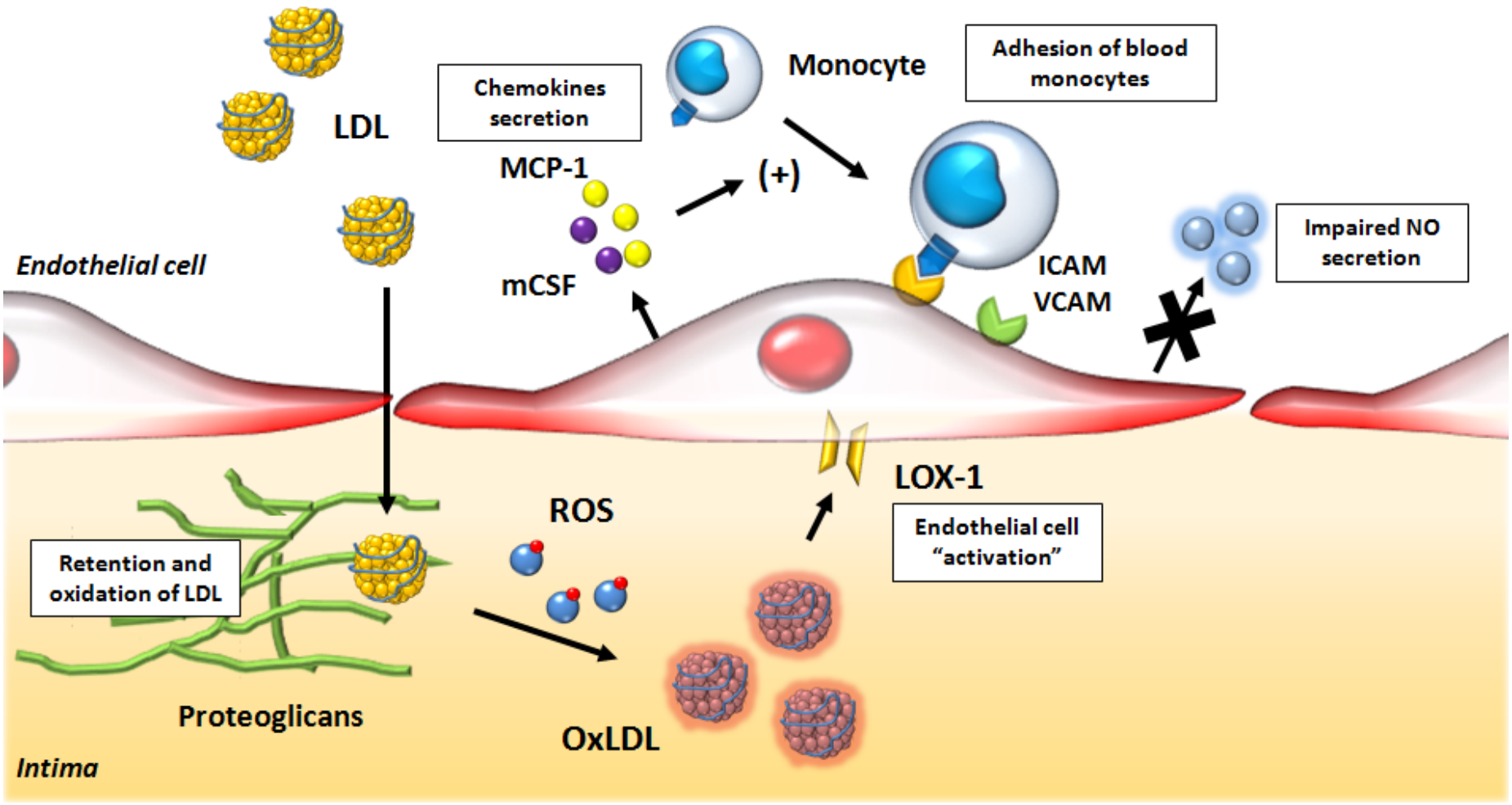
Von Dr. med. **N. Anitschkow** und Dr. **S. Chalatow.**
(Aus dem pathologisch-anatomischen Institut der Kaiserlichen militärmedizinischen Akademie zu St. Petersburg.)

LDL-C and CV Morbidity and Mortality

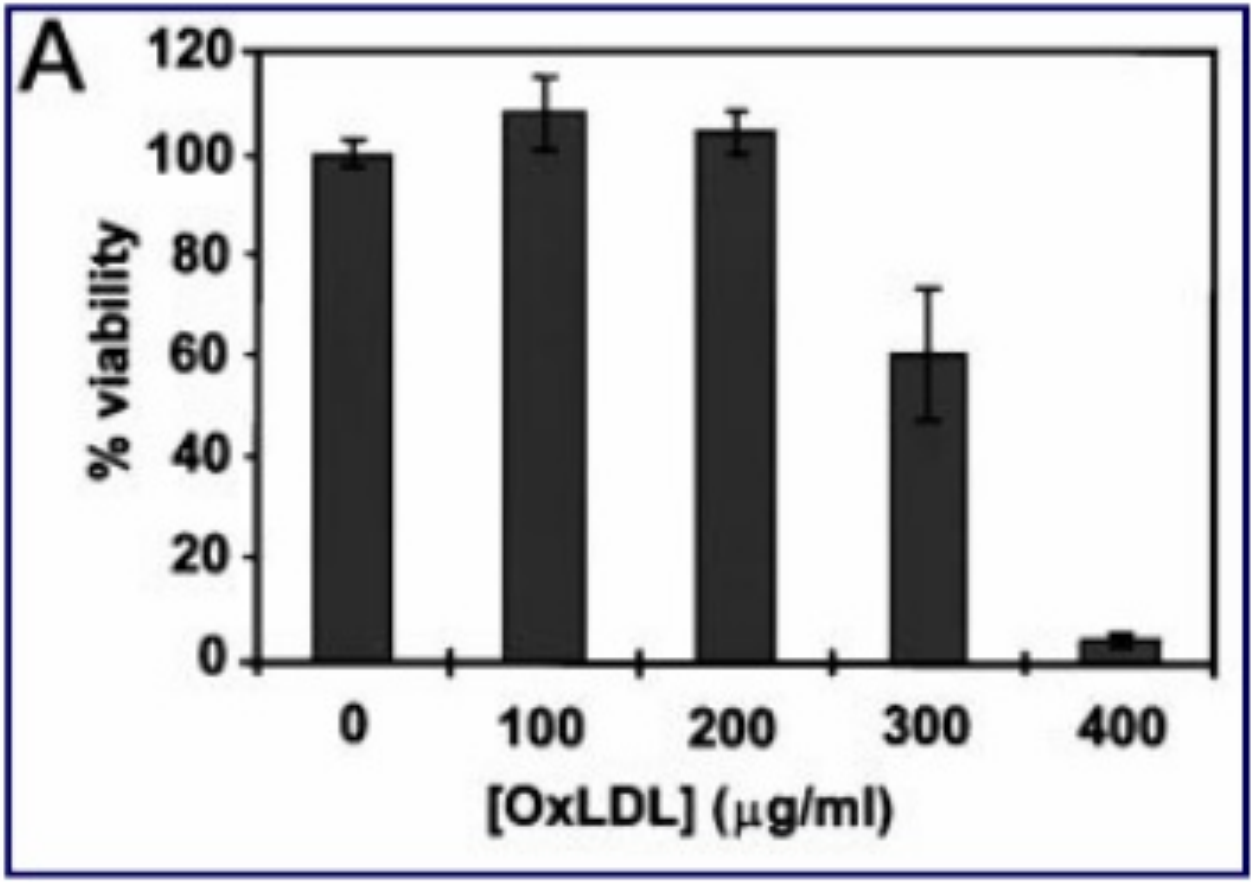




Kannel WB, et al. *Ann Intern Med.* 1971;74:1-12
MRFIT Research Group. *Prev Med.* 1986;15:254–273


LDL
Chemokines secretion
Monocyte
Adhesion of blood monocytes
MCP-1
(+)
Endothelial cell
mCSF
ICAM
VCAM
Impaired NO secretion
LOX-1
ROS
Endothelial cell "activation"
Retention and oxidation of LDL
Proteoglicans
OxLDL
Intima

Oxidized LDL is Toxic to Endothelial Cells



Sata M and Walsh K. J Biol Chem. 1998;273(50):33103-6

The Atherosclerotic Plaque is a Toxic Waste Superfund Site

Consensus EAS on LDL-C

European Heart Journal (2017) **38**, 2459–2472
doi:10.1093/eurheartj/ehx144

CURRENT OPINION

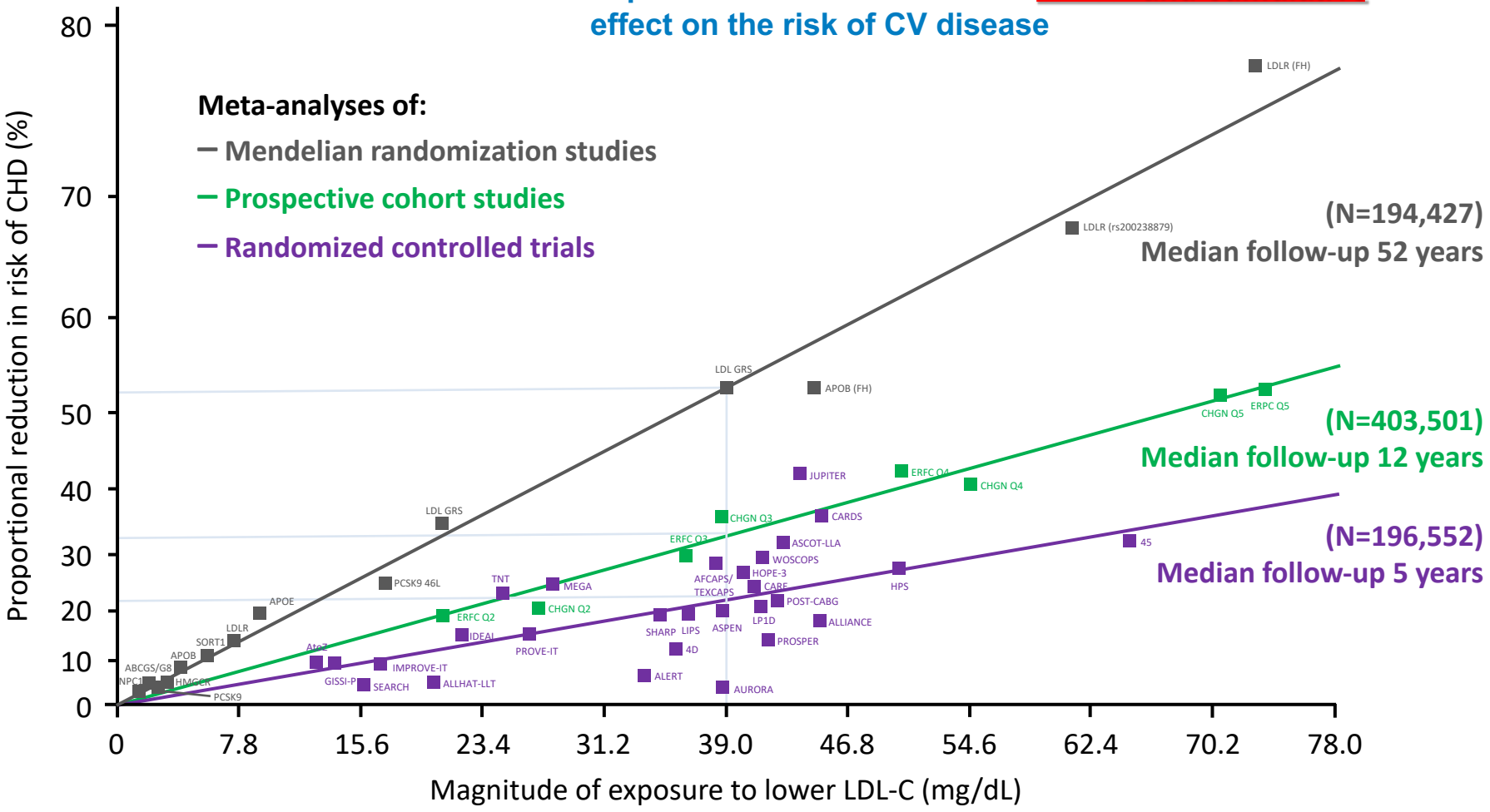
Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel

Brian A. Ference[1]*, Henry N. Ginsberg[2], Ian Graham[3], Kausik K. Ray[4], Chris J. Packard[5], Eric Bruckert[6], Robert A. Hegele[7], Ronald M. Krauss[8], Frederick J. Raal[9], Heribert Schunkert[10,11], Gerald F. Watts[12], Jan Borén[13], Sergio Fazio[14], Jay D. Horton[15,16], Luis Masana[17], Stephen J. Nicholls[18], Børge G. Nordestgaard[19,20,21], Bart van de Sluis[22], Marja-Riitta Taskinen[23], Lale Tokgözoğlu[24], Ulf Landmesser[25,26], Ulrich Laufs[27], Olov Wiklund[28,29], Jane K. Stock[30], M. John Chapman[31]†, and Alberico L. Catapano[32]†

Ference BA, et al. Eur Heart J. 2017;38:2459-2472

Log-linear Association per Unit Change in LDL-C and the Risk of CV Disease

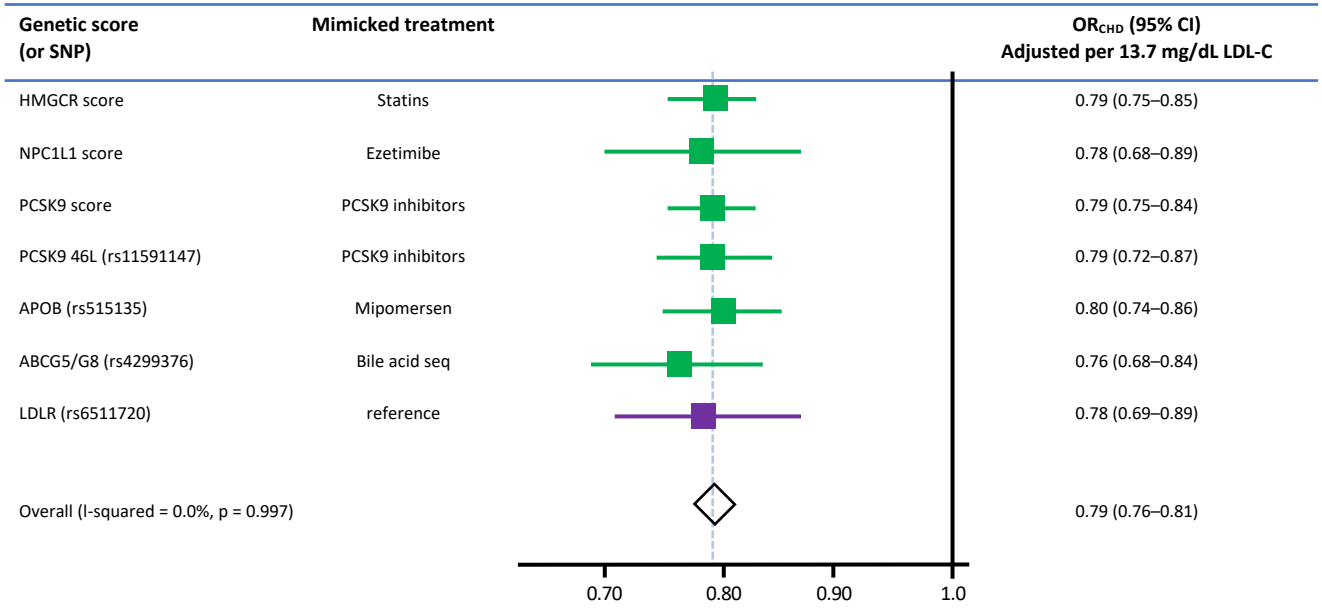
The increasingly steeper slope of the log-linear association with increasing length of follow-up time implies that LDL-C has both a causal and cumulative effect on the risk of CV disease



Ference BA, et al. Eur Heart J. 2017;38:2459-2472

Exposure to Lower LDL-C by Mechanism of LDL-C Lowering: Genetic Data

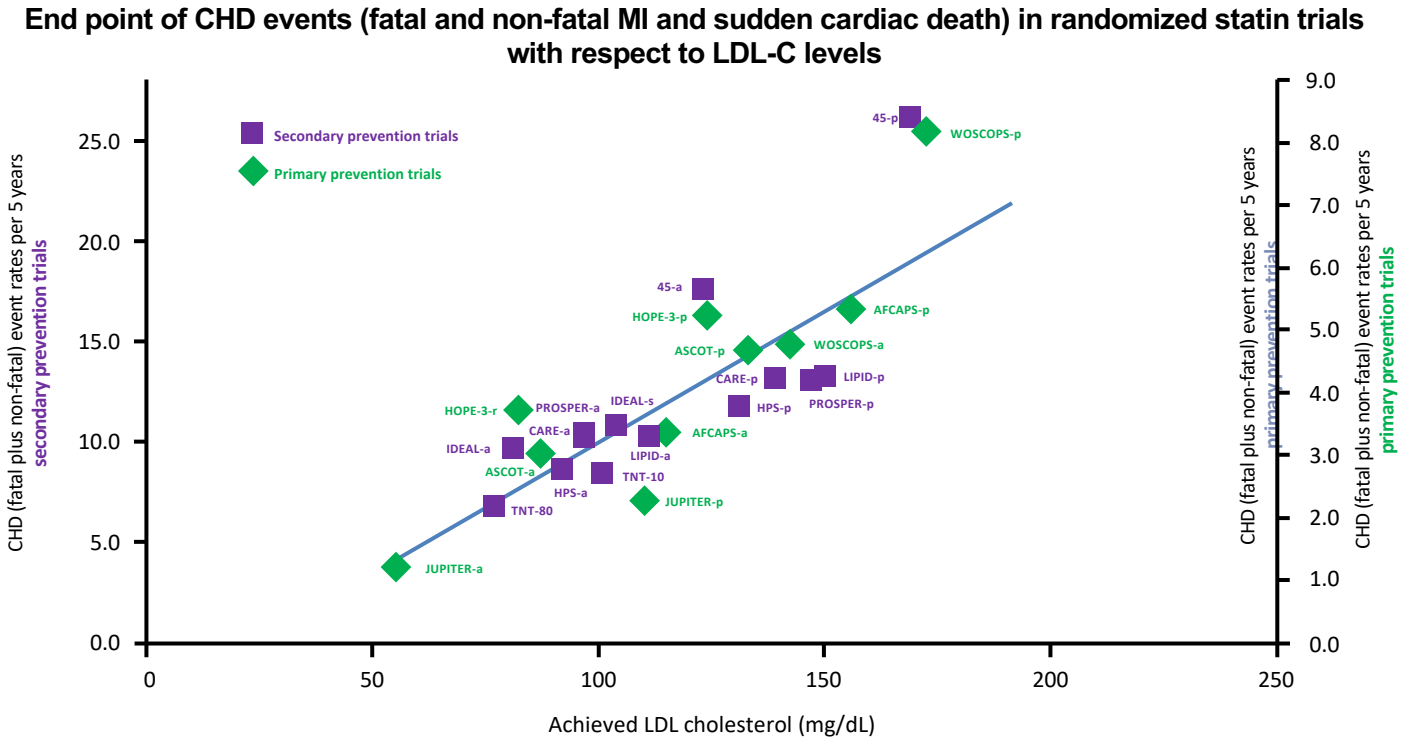
Effect of genetic variants or genetic scores combining multiple variants in the genes that encode for targets of LDL-C-lowering therapies in comparison with the effect of lower LDL-C mediated by variants in the LDL receptor gene



The effect of LDL-C on the risk of cardiovascular events is approximately the same per unit change in LDL-C for any mechanism that lowers LDL-C via up-regulation of the LDL receptor

Ference BA, et al. Eur Heart J. 2017;38:2459-2472

Association Between Achieved LDL-C Level and Absolute CHD Event Rate



Achieved LDL-C in primary and secondary prevention trials in stable CHD patients was related to the end point of CHD events proportioned to 5 years assuming linear rates with time

CHD = coronary heart disease; MI = myocardial infarction

Ference BA, et al. Eur Heart J. 2017;38:2459-2472

Class 1 Evidence for LDL-C and ASCVD

Bradford-Hill criterion	Evidence grade	Summary of the evidence
Plausibility	1	LDL and other apolipoprotein (apo) B-containing lipoproteins (very low-density lipoprotein, their remnants, intermediate-density lipoprotein and lipoprotein (a)) are directly implicated in the initiation and progression of ASCVD; experimentally induced elevations in plasma LDL and other apo-B containing lipoproteins lead to atherosclerosis in all mammalian species studied
Strength	1	Monogenic and polygenic-mediated lifelong elevations in LDL lead to markedly higher lifetime risk
Biological gradient	1	Monogenic lipid disorders, prospective cohort studies, Mendelian randomization studies, and randomized intervention trials uniformly demonstrate a dose-dependent, log-linear association between the absolute magnitude of exposure to LDL and risk of ASCVD
Temporal sequence	1	Monogenic lipid disorders and Mendelian randomization studies demonstrate that exposure to elevated LDL precedes the onset of ASCVD
Specificity	1	Mendelian randomization studies and randomized intervention trials both provide unconfounded randomized evidence that LDL is associated with ASCVD independent of other risk factors
Consistency	1	Over 200 studies involving more than 2 million participants with over 20-million person-years of follow-up and more that 150,000 cardiovascular events consistently demonstrate a dose-dependent log-linear association between the absolute magnitude of exposure to LDL and risk of ASCVD
Coherence	1	Monogenic lipid disorders, prospective cohort studies, Mendelian randomization studies, and randomized intervention trials all show a dose-dependent, log-linear association between the absolute magnitude of exposure to LDL and risk of ASCVD
Reduction in risk with intervention	1	More than 30 randomized trials involving over 200,000 participants and 30,000 ASCVD events evaluating therapies specifically designed to lower LDL (including statins, ezetimibe, and PCSK9 inhibitors) consistently demonstrate that reducing LDL-C reduces the risk of ASCVD events proportional to the absolute reduction in LDL-C

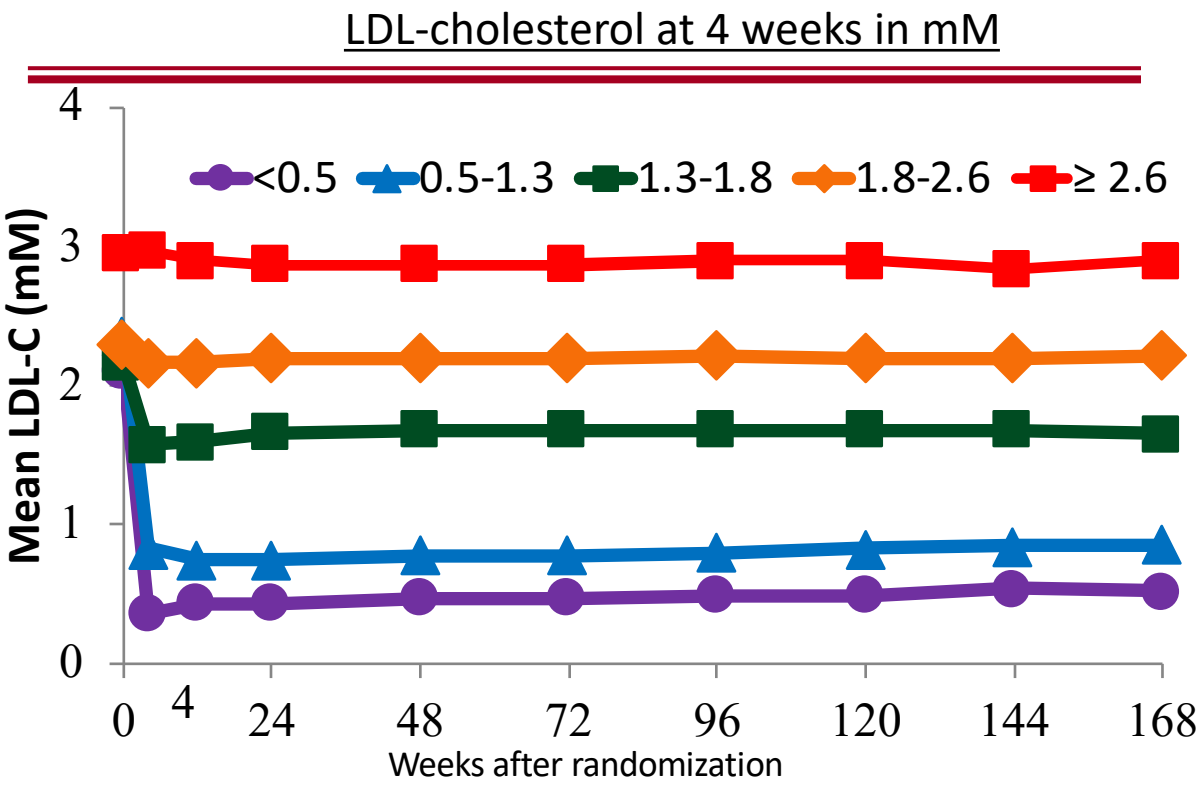
Criteria are graded by a modification of the quality criteria adopted by the European Society of Cardiology system.
For reference, see https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Guidelines-development/Writing-ESC-Guidelines (Accessed June 2017). These are defined as follows:
Class 1: Evidence and/or general agreement that the criterion for causality is fulfilled
Class 2: Conflicting evidence and/or a divergence of opinion about whether the criterion indicated causality
Class 3: Evidence or general agreement that the criterion for causality is not fulfilled

Ference BA, et al. Eur Heart J. 2017;38:2459-2472

What About Extreme Reductions of LDL?

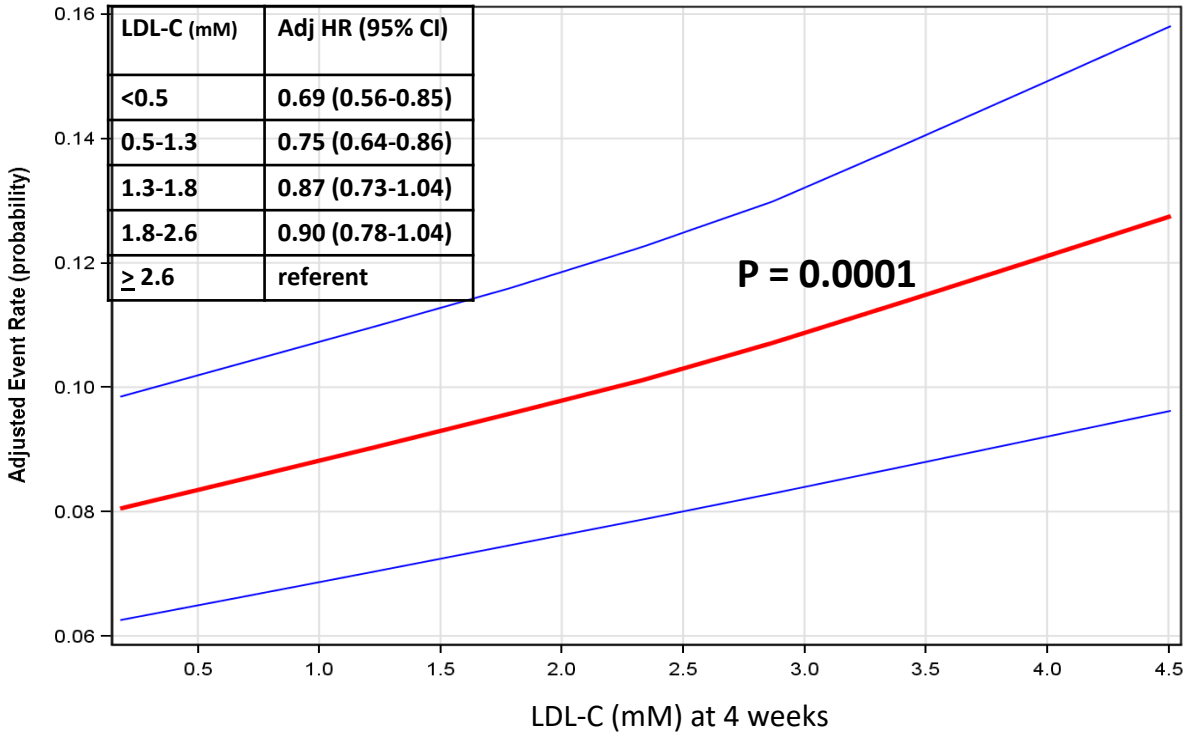
Should we Suggest it to our Patients?

LDL-C Over Time



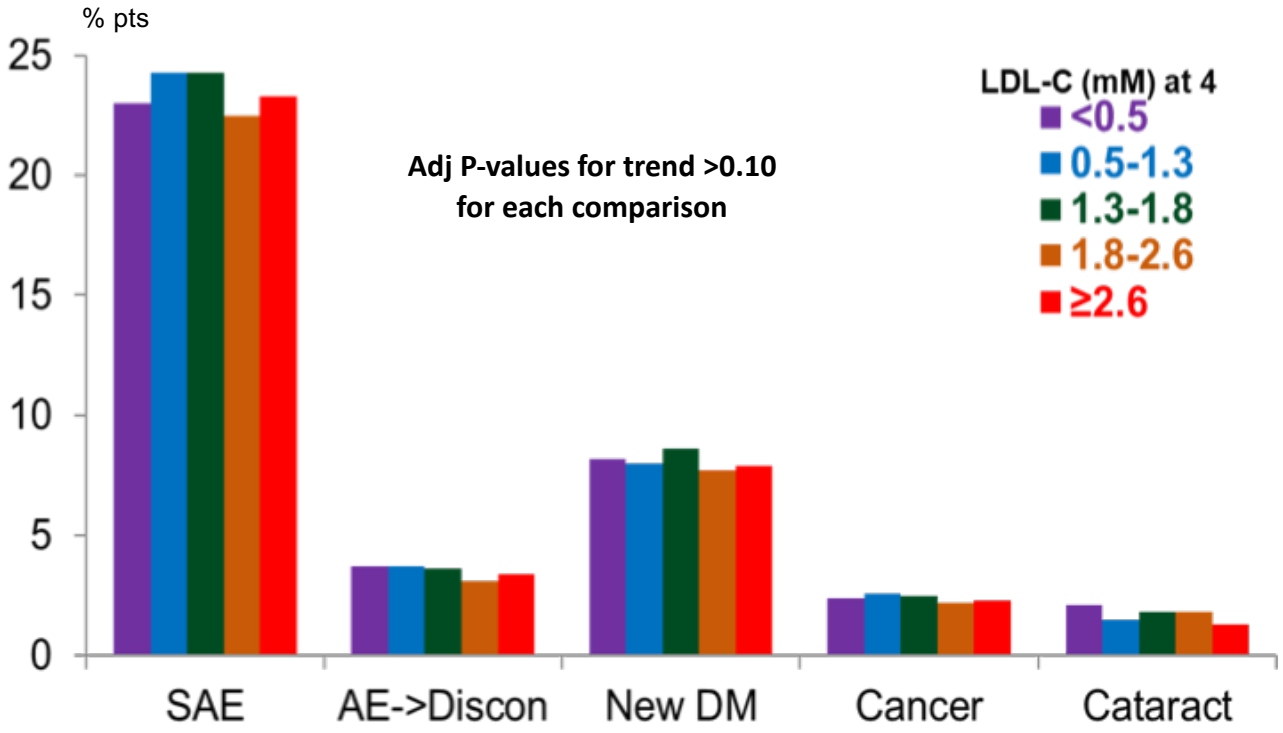
Giugliano RP, ESC Congress 2017, Barcelona 8/28/2017

CV Death, MI, or Stroke



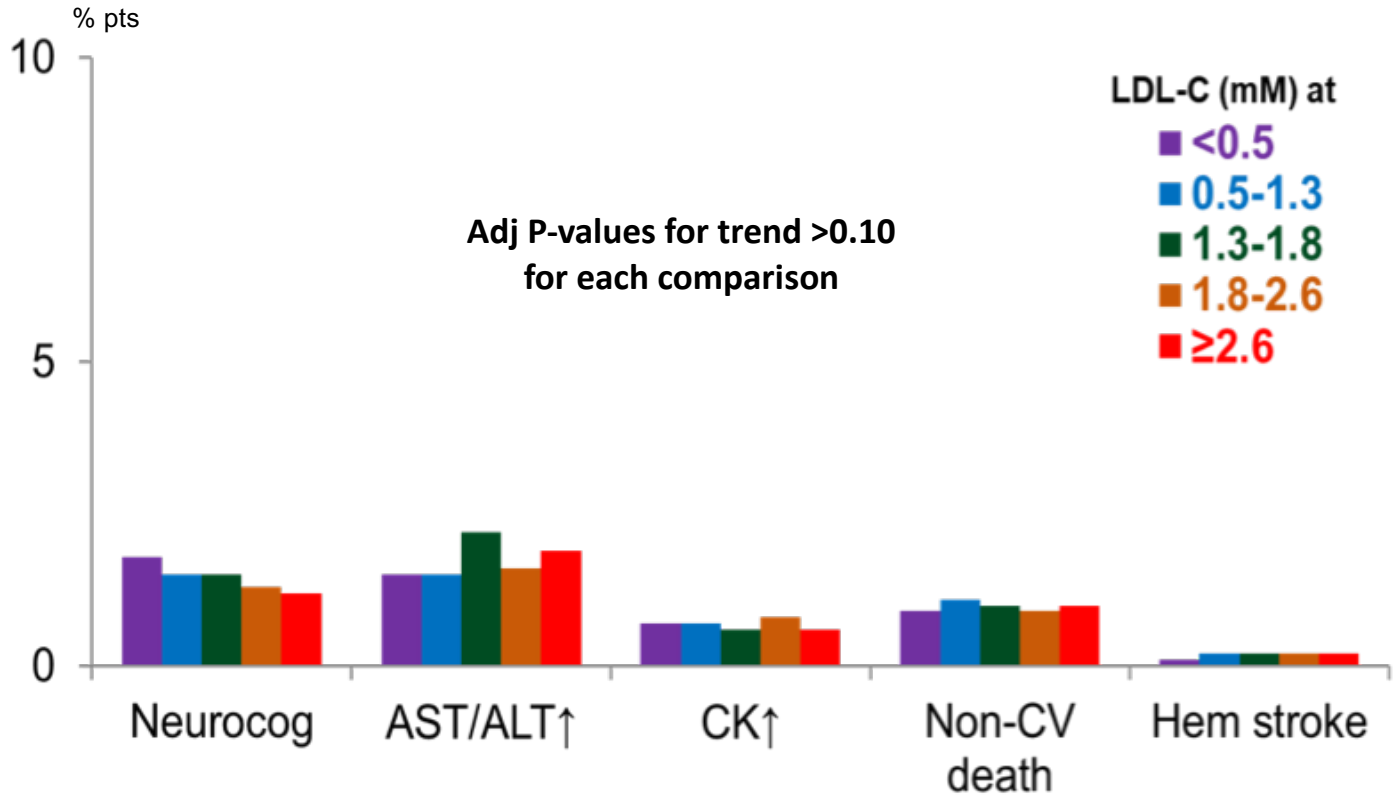
Giugliano RP, ESC Congress 2017, Barcelona 8/28/2017

Safety Events - 1



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

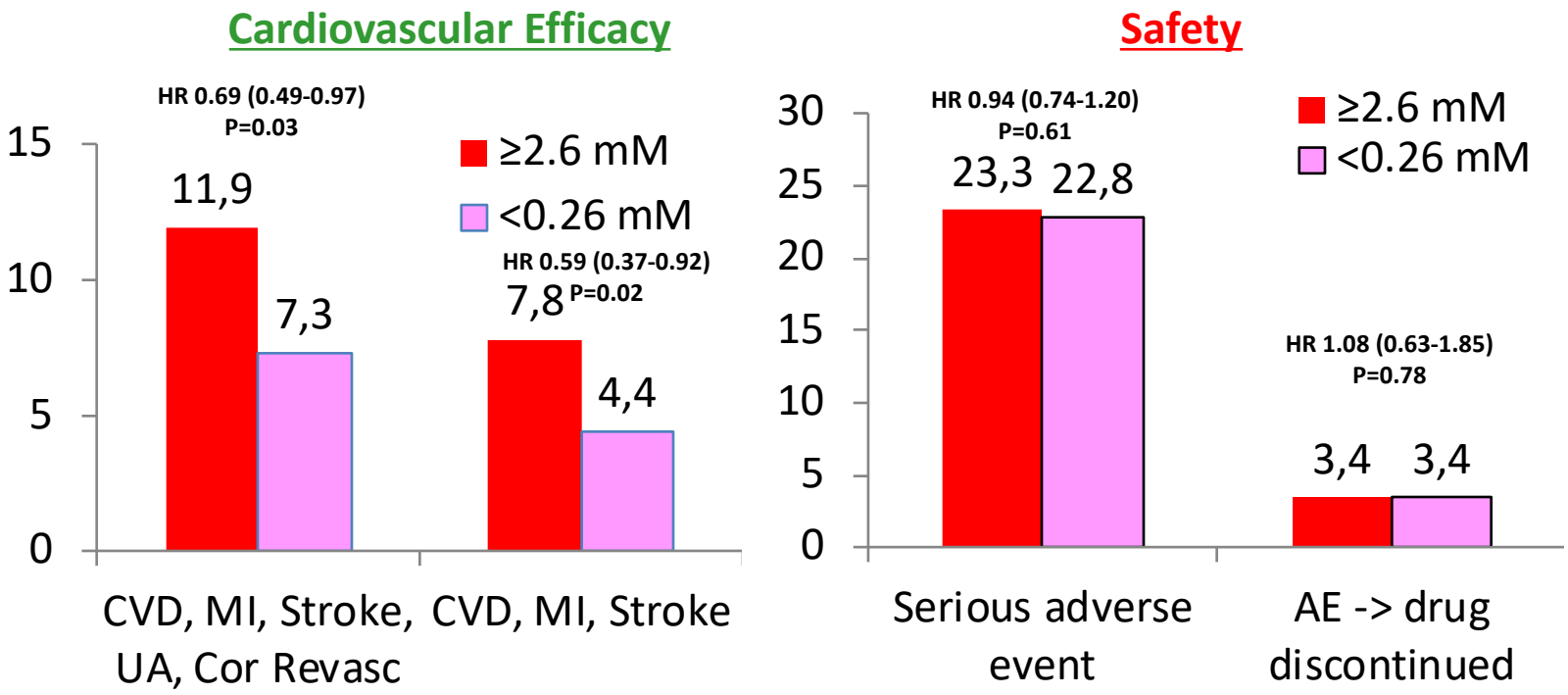
Safety Events - 2



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

Exploratory Analysis Pts with LDL-C <0.26 mM (<10 mg/dL) at 4 wks

N=504: Median [IQR] LDL-C 0.18 [0.13-0.23] mM = 7 [5-9] mg/dL

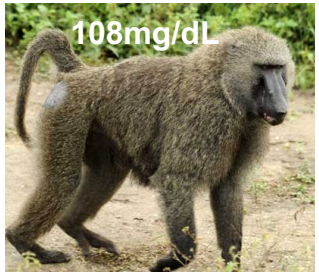


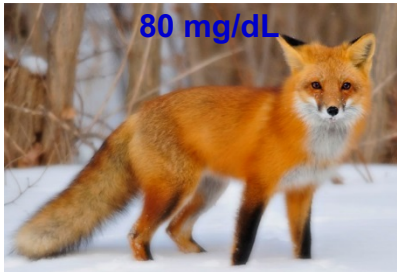
Giugliano RP, ESC Congress 2017, Barcelona 8/28/2017

Take home message

Let’s go back to the Rabbit !

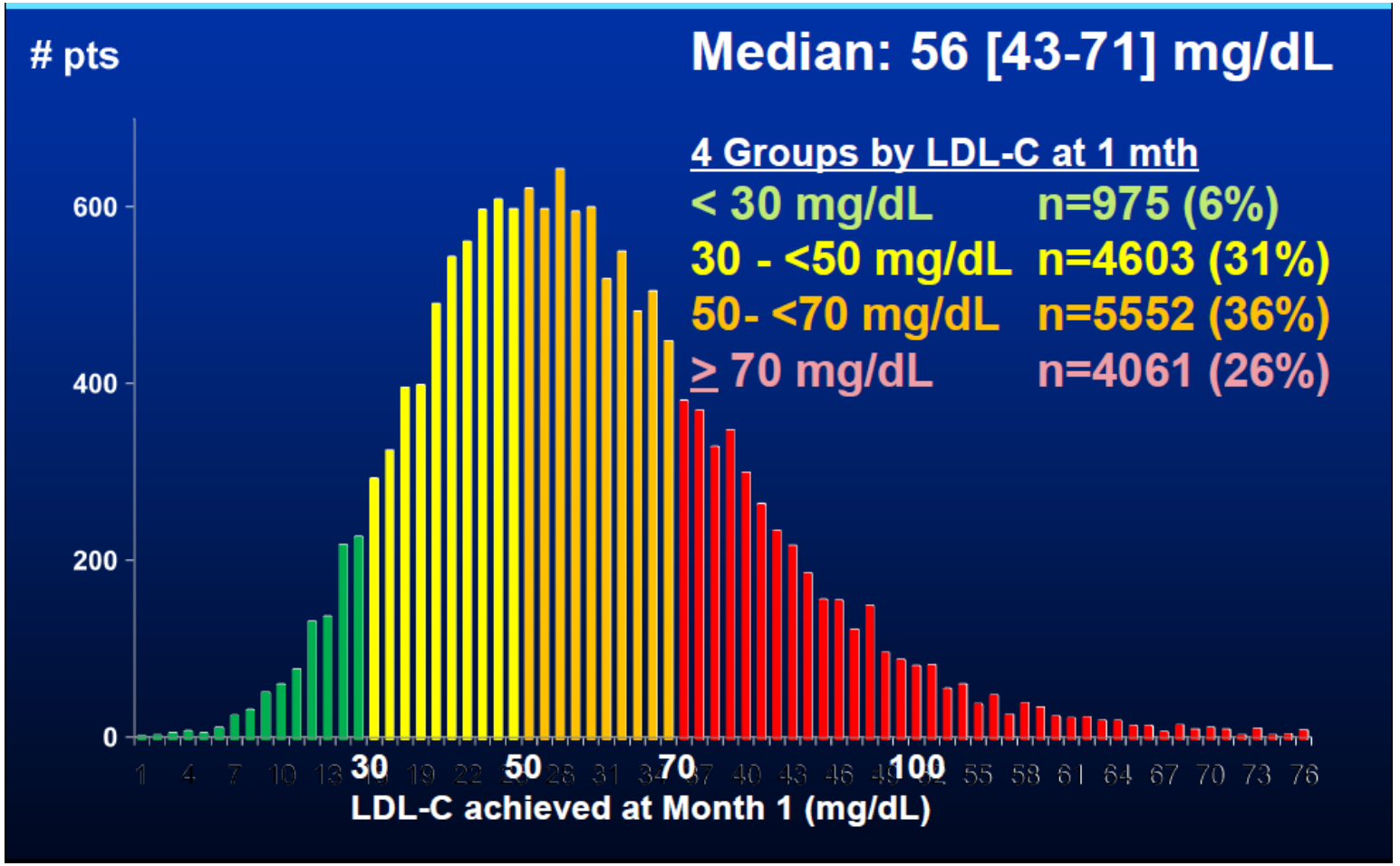
Total Cholesterol Levels in Different Mammals

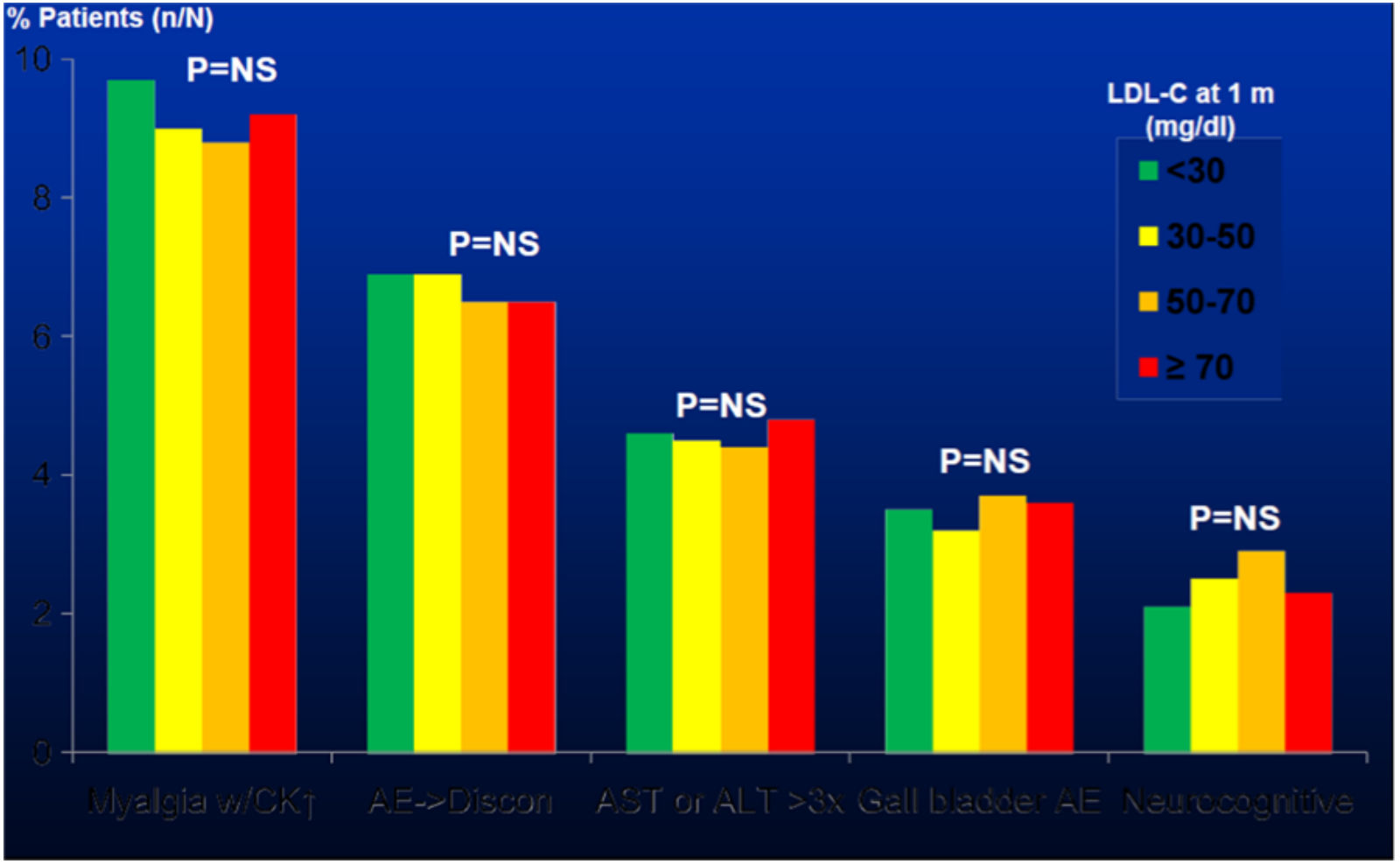




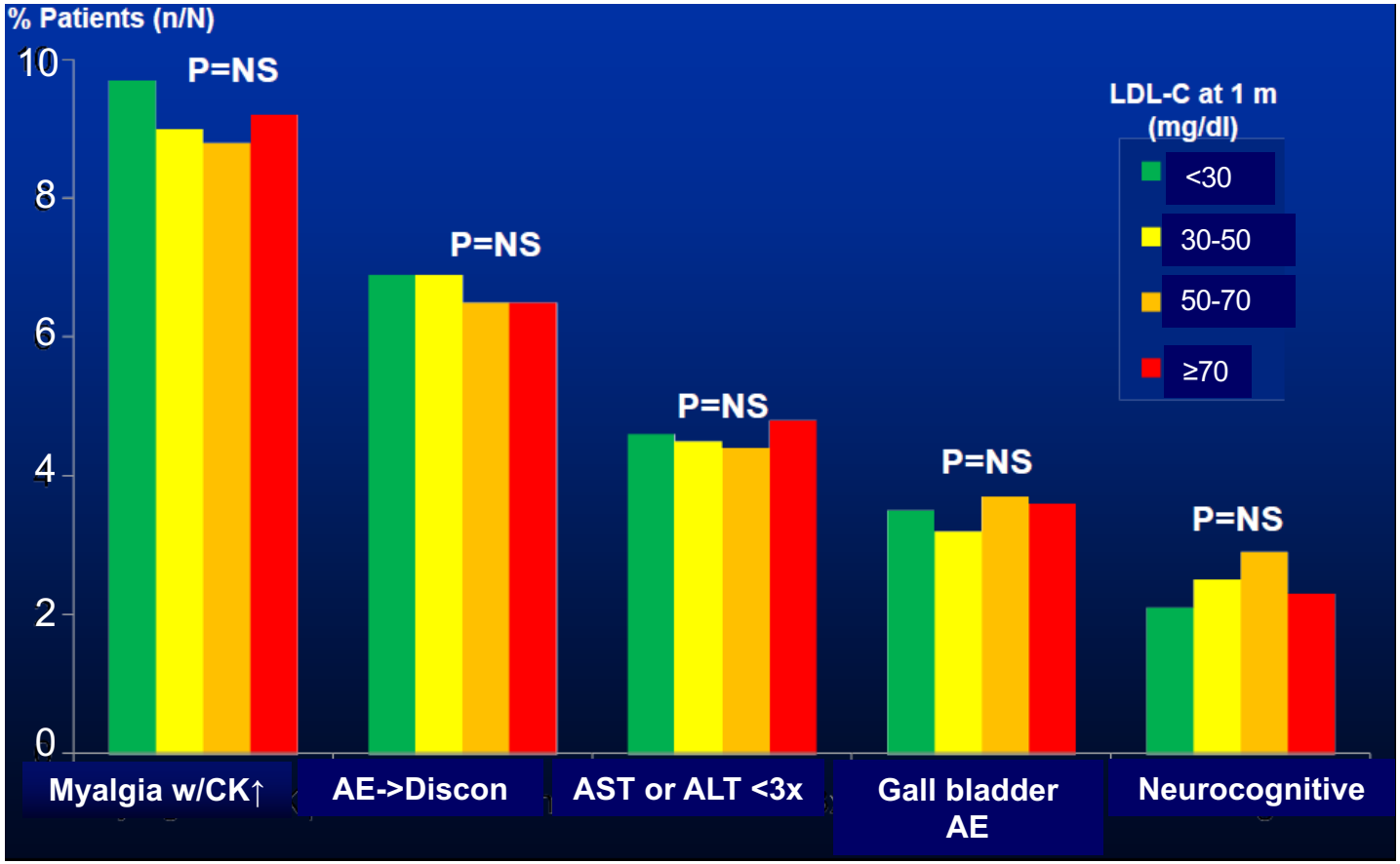
Data from: Hochholzer W and Giugliano RP. Ther Adv Cardiovasc Dis 2010;4(3):185-91

Achieved LDL-C at 1 Month

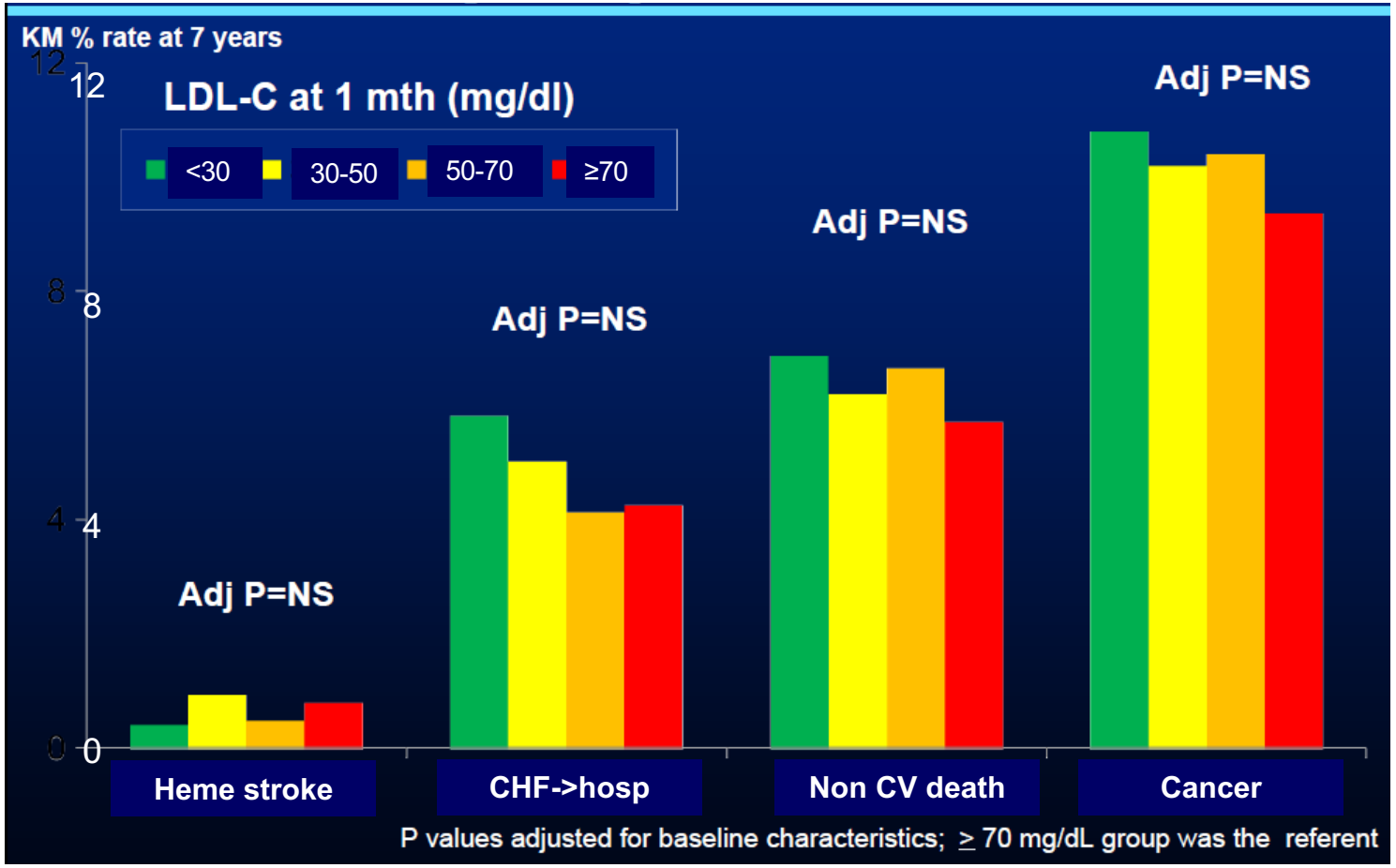



% Patients (n/N)
10
8
6
4
2
0
P=NS
P=NS
P=NS
P=NS
P=NS
LDL-C at 1 m (mg/dl)
<30
30-50
50-70
≥ 70
Myalgia w/CK↑
AE->Discon
AST or ALT >3x
Gall bladder AE
Neurocognitive

Safety Events



Clinical Safety Endpoints



Safety Events
LDL-C * Treatment Interactions

	Interaction P-value (Month 1 LDL*Trt)
Myalgias with CK elevation	0.74
AE leading to discontinuation	0.93
AST or ALT >3x ULN	0.28
Gall bladder adverse event	0.75
Neuropsychiatric adverse event	0.37
Hemorrhagic stroke	0.42
Hospitalization for CHF after day 30	0.33
Non-cardiovascular death	0.94
Cancer	0.64

No differences in safety by treatment group across each of the 4 achieved 1 month LDL-C groups