

VENERDI' 1 MARZO

# PREVENZIONE SECONDARIA DELLA CARDIOPATIA ISCHEMICA. VA RIVISTO IL VALORE SOGLIA DI 70 MG/DL PER LA COLESTEROLEMIA LDL ?

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# Conoscere e Curare il Cuore

# 2019

**XXXVI Congresso di Cardiologia**  
del Centro per la Lotta contro l'Infarto - Fondazione Onlus

PROGRAMMA DEFINITIVO

Firenze, Fortezza da Basso  
28 febbraio, 1-2-3 marzo



**Prevenzione secondaria  
della cardiopatia ischemica  
Va rivisto il valore soglia  
di 70 mg/dl per la  
colesterolemia LDL ?**

Alberto Zambon  
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# DISCLOSURE SLIDE

Prof. A. Zambon reports having received grants, consulting fees and/or honoraria and delivering lectures for:

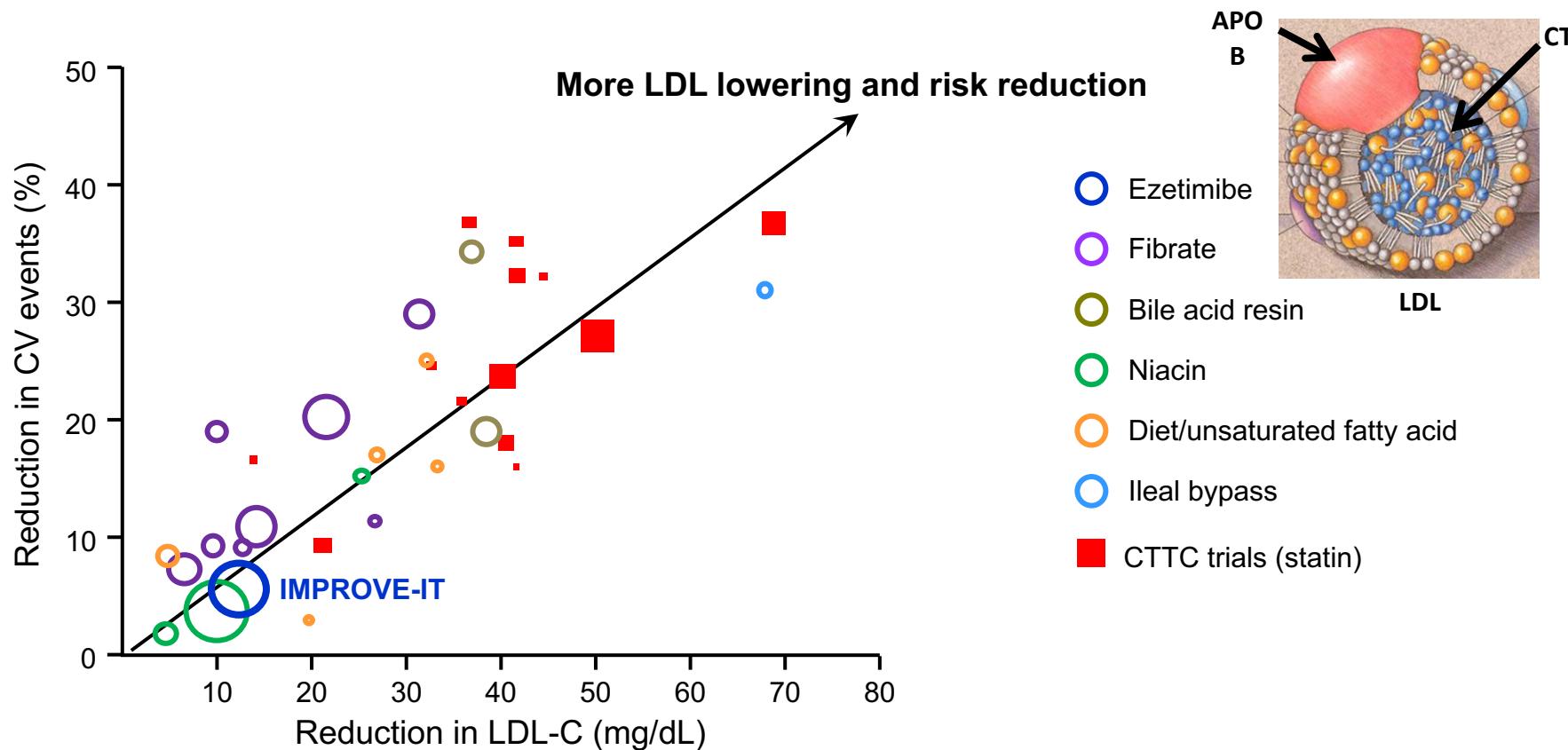
- Abbott
- AstraZeneca
- Merck Sharp & Dohme
- Amgen
- Sanofi
- Alfasigma
- Mylan
- Chiesi

# Va rivista la soglia di LDL-C<70 mg/dl?

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- Setting the stage
- The lower the LDL-C the better: Evidenze in era pre-PCSK9i
- PCSK9i Revolution: The lowest the LDL-C the best? Safe...Costs?
- In quali pazienti sarebbe opportuno rivedere (in basso) la soglia di LDL-C di <70 mg/dl
- Take Home message

# Every 39 mg/dl (1 mmol/L) reduction in LDL-C reduces annual CV risk by up to 28%, regardless of mechanism



**There is no evidence of any lower LDL-C threshold**

Data from studies of non-statin lipid-lowering medications superimposed upon data from the Cholesterol Treatment Trialists Collaboration (CTTC) 2005 meta-analysis. The IMPROVE-IT trial was adequately powered to show the efficacy on incremental LDL-C lowering on CV outcomes. [To convert, 100 mg/dL=2.59 mmol/L].

CV, cardiovascular; IMPROVE-IT, IMProved Reduction of Outcomes: Vytorin Efficacy International Trial; LDL-C, low-density lipoprotein cholesterol.

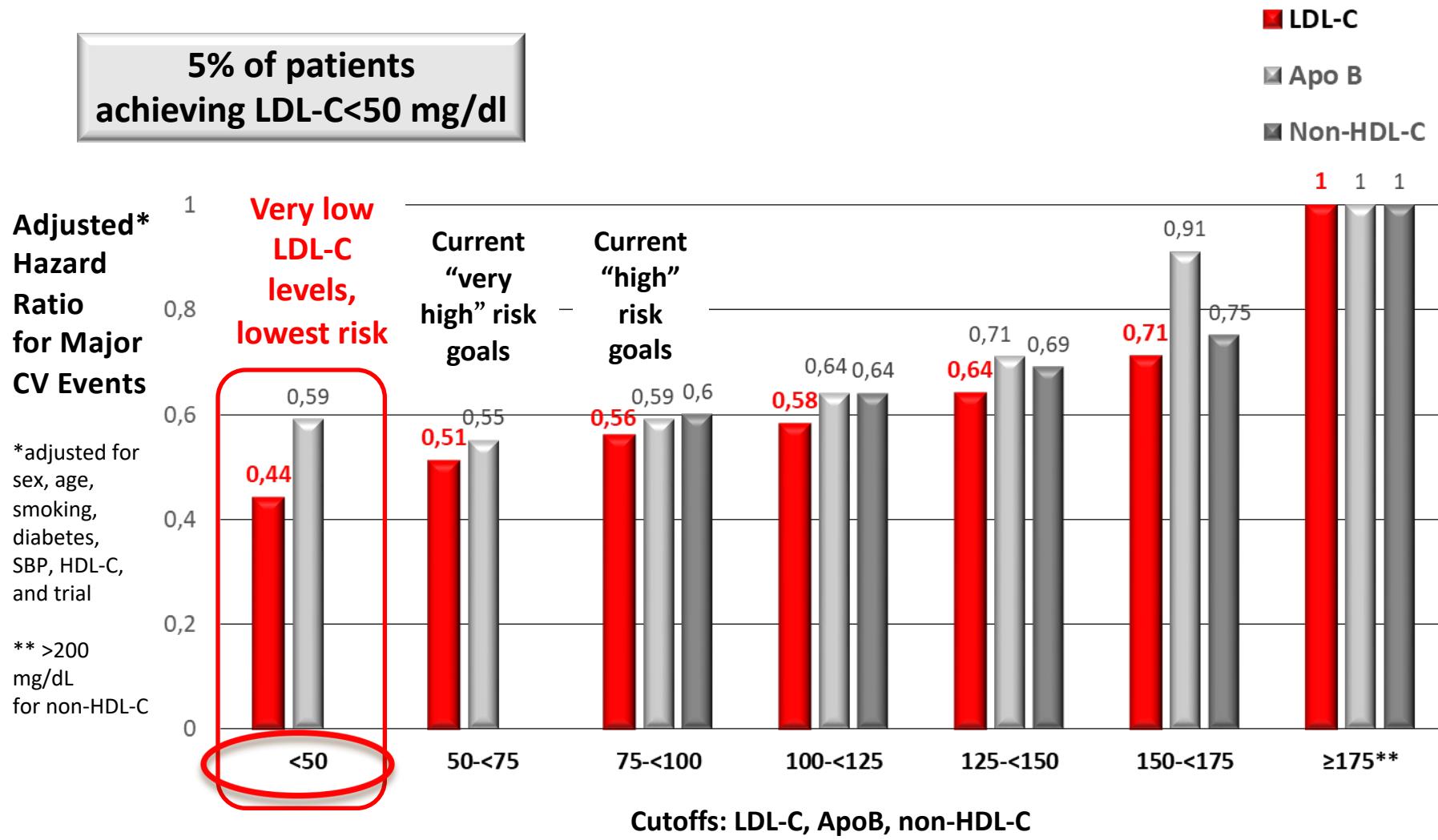
CTT Collaboration. Lancet 2005;366:1267–78; CTT Collaboration. Lancet 2010;376:1670–81;  
Cannon CP, et al. N Engl J Med 2015;372:2387–97.

# Va rivista la soglia di LDL-C<70 mg/dl?

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- **Setting the stage:** tanto più si riduce (in assoluto – mg/dl) il colesterolo LDL tanto più si riduce il rischio CV, indipendentemente dall'approccio terapeutico
- **The lower the LDL-C the better: evidenze in era pre-PCSK9i**

# Meta-analysis of 8 Statin Trials (Moderate- to High-Intensity Dosing): Patients Who Achieved Very Low LDL-C Levels Had Lower Risk for Major Cardiovascular Events



Abbreviations: apo, apolipoprotein; CV, cerebrovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

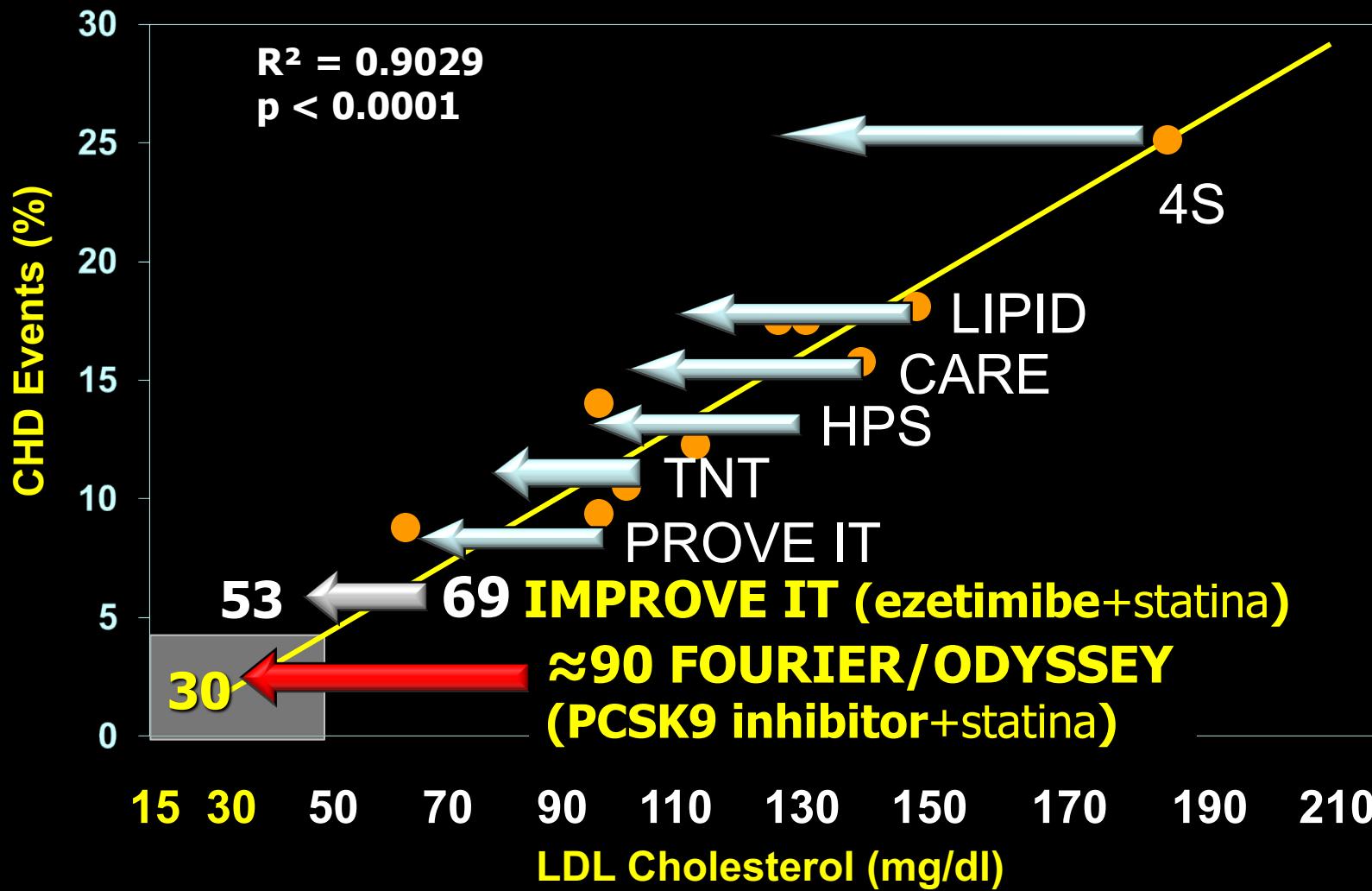
Boekholdt SM, et al. J Am Coll Cardiol. 2014;64(5):485-494.

# Va rivista la soglia di LDL-C<70 mg/dl?

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- Setting the stage: tanto più riduco (in assoluto – mg/dl) il colesterolo LDL tanto più riduco il rischio CV indipendentemente dall'approccio terapeutico
- Evidenze in era pre-PCSK9i: **anche per LDL-C<70 mg/dl riduzione di LDL-C associata a riduzione rischio eventi CV**
- **PCSK9i Revolution: The lowest the LDL-C the best? E' Sicuro...Costi?**

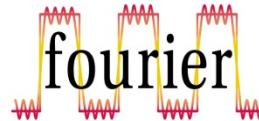
# Beyond The Statin ERA: For LDL: “The Lowest the Best”



Adapted and Updated from O’Keefe, J. et al., *J Am Coll Cardiol* 2004;43:2142-6.



# Further Details



# THE LANCET

Volume 390 · Number 10095 · Pages 625–714 · August 12–18, 2017

[www.thelancet.com](http://www.thelancet.com)

## Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial

Robert P Giugliano, Terje R Pedersen, Jeong-Gun Park, Gaetano M De Ferrari, Zbigniew A Gacjiong, Richard Ceska, Kalman Toth, Ioanna Gouni-Berthold, Jose Lopez-Miranda, François Schiele, François Mach, Brian R Ott, Estella Kanevsky, Armando Lira Pineda, Ransi Somaratne, Scott M Wasserman, Anthony C Keech, Peter S Sever, Marc S Sabatine, on behalf of the FOURIER Investigators

Thank you to all the patients, investigators, coordinators, steering  
and executive committee members of the FOURIER and  
EBBINGHAUS trials, TIMI CEC, Adverse Events and statistical  
teams, Cambridge Cognition, and the sponsor, Amgen

Article available at [www.thelancet.com](http://www.thelancet.com)

Slides available at [www.TIMI.org](http://www.TIMI.org)



An Academic Research Organization of  
Brigham and Women's Hospital and Harvard Medical School

# FOURIER: Patients by LDL-C Levels

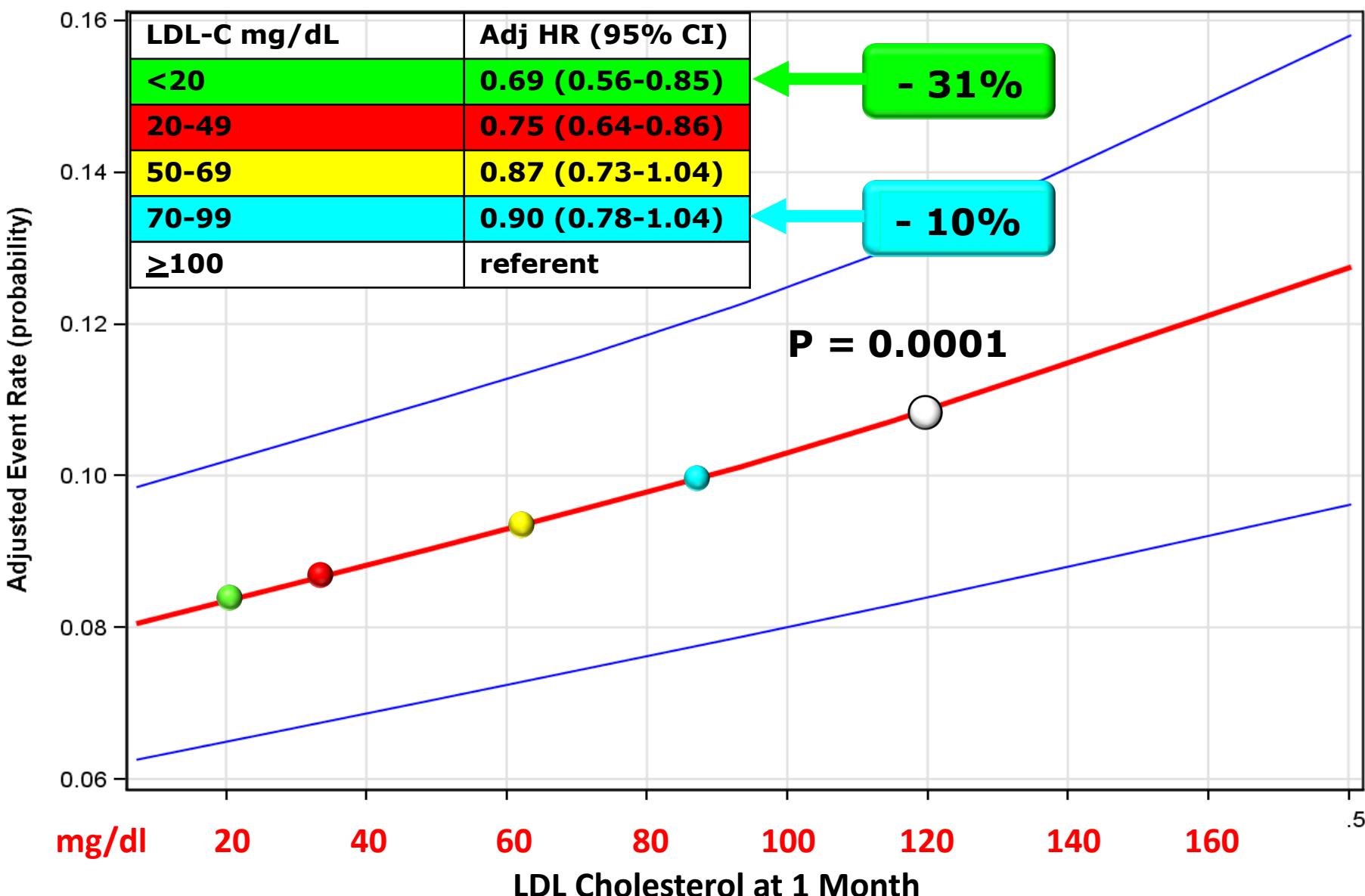
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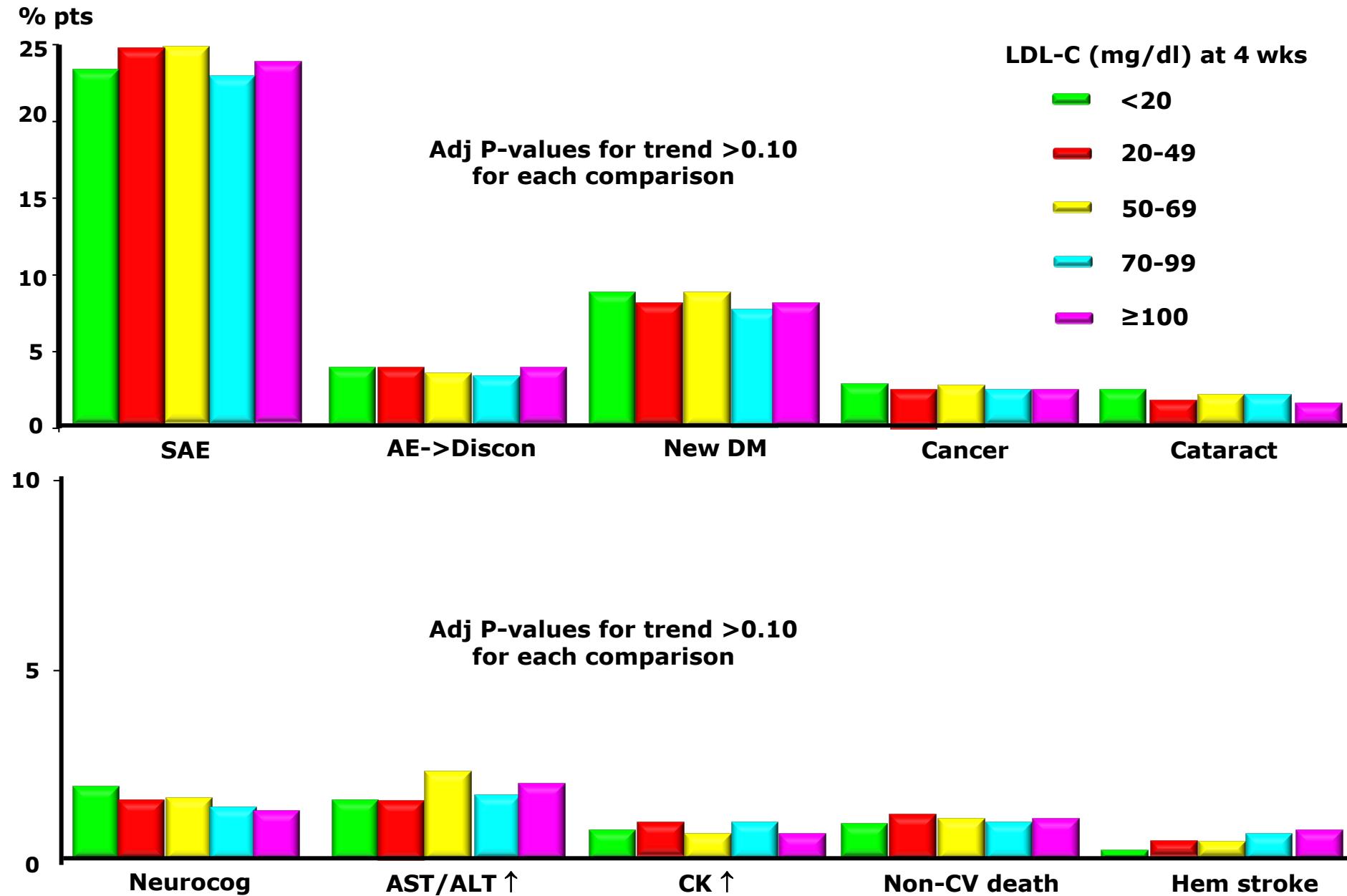
- LDL-C assessed at 4 wks (ultracentrifugation if <1 mM)
- Analyzed 5 groups by achieved LDL-C at 4 weeks
  - 1) <20 mg/dL (n=2669)
  - 2) 20- 49 mg/dL (n=8003)
  - 3) 50-69 mg/dL (n=3444)
  - 4) 70-99 mg/dL (n=7471)
  - 5) **≥100 mg/dL was the referent group** (n=4395)
- Pooled results across 2 Rx groups (evo, placebo)



# FOURIER: CV DEATH, MI, or STROKE



# SAFETY EVENTS



# Efficacy and Safety of Further Lowering of Low-Density Lipoprotein Cholesterol in Patients Starting With Very Low Levels

## A Meta-analysis

Marc S. Sabatine, MD, MPH; Stephen D. Wiviott, MD; KyungAh Im, PhD;  
Sabina A. Murphy, MPH; Robert P. Giugliano, MD, SM

**The magnitude of clinical benefit of further LDL-C lowering in patients already with very low LDL-C levels remains debated**

**OBJECTIVE** To evaluate efficacy and safety of further lowering LDL-C levels in patient populations presenting with **median LDL-C levels of 1.8 mmol/L (70 mg/dL) or less**.

Trial	No. of Participants	Type of Intervention	Drug	Achieved LDL-C, mmol/L		Median Duration of Follow-up, y	Overall No. of Major Vascular Events
				Control Arm	Experimental Arm		
CTTC (<2 mmol/L)	NR	HMGCR inhibitor (statin)	Various	1.7 <sup>a</sup>	NR	4.9 <sup>b</sup>	1922
IMPROVE-IT	18 144	NPC1L1 inhibitor	Ezetimibe	1.8 <sup>c</sup>	1.4	6.0	5104
FOURIER (<1.8 mmol/L)	2034	PCSK9 inhibitor	Evolocumab	1.7 <sup>d</sup>	0.5	2.1	184
REVEAL	30 449	CETP inhibitor	Anacetrapib	1.6 <sup>e</sup>	1.4	4.1	4282

CTTC, Cholesterol Treatment Trialists Collaboration;

CETP, cholesteryl ester transfer protein;

FOURIER, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk;

IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial;

HMGCR, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase;

LDL-C, low-density lipoprotein cholesterol; NPC1L1, Niemann-Pick C1-Like

# Efficacy and Safety of Further Lowering of Low-Density Lipoprotein Cholesterol in Patients Starting With Very Low Levels

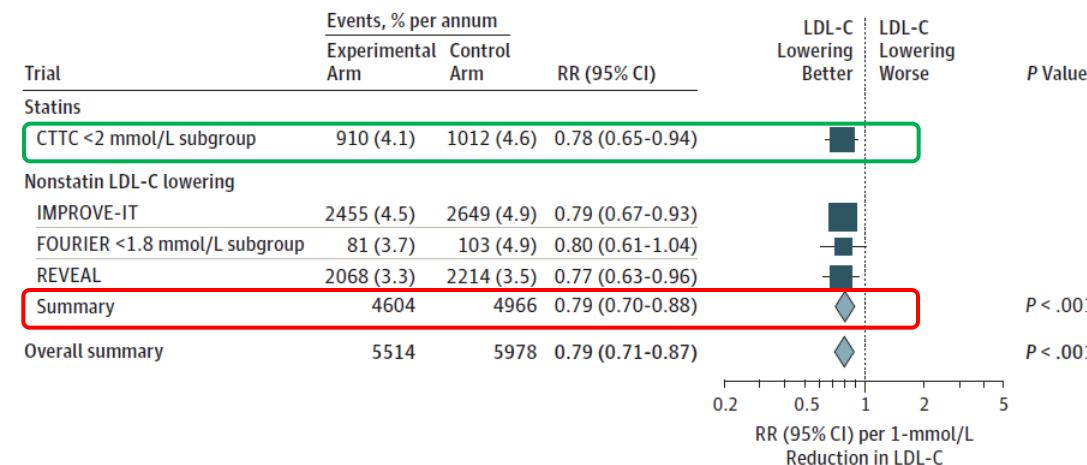
## A Meta-analysis

JAMA Cardiol. doi:10.1001/jamacardio.2018.2258  
Published online August 1, 2018.

Marc S. Sabatine, MD, MPH; Stephen D. Wiviott, MD; KyungAh Im, PhD;

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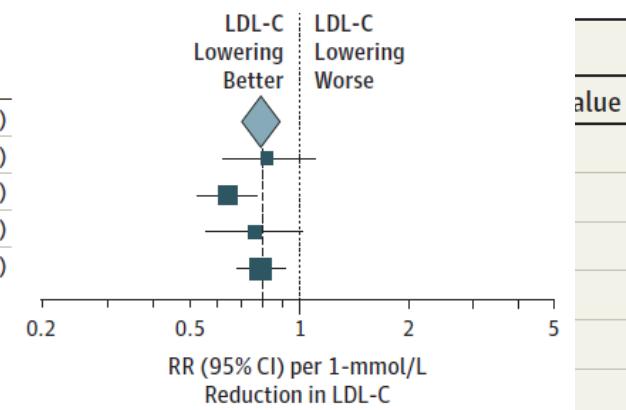
**A** Meta-analysis of effect of 1-mmol/L LDL-C lowering on the risk of major vascular events



**Δ LDL-C 39 mg/dl = - 21% Major Vascular Events in patients with Baseline LDL-C 70 mg/dl**

**Table 7** Safety Outcomes in Trials of Nonstatin Therapy

Safety Outcome	Patients With Events, No.		
	Experimental Arm	Control Arm	RR (95% CI)
Major vascular events	4604	4966	0.79 (0.70-0.88)
Coronary heart death	836	891	0.82 (0.62-1.10)
Myocardial infarction	1671	1930	0.64 (0.53-0.77)
Ischemic stroke	737	804	0.76 (0.56-1.02)
Coronary revascularization	3003	3228	0.79 (0.68-0.92)



# PCSK9 inhibitor valuation: A science-based review of the two recent models

Seth J. Baum<sup>1</sup>  | Christopher P. Cannon<sup>2</sup>

- The **newer**, more **costly** therapies should be **targeted** to those who will **benefit most**, and only after other less expensive therapies have failed to meet risk-reduction goals.
- Rather than using models to block access for patients, **payers** should work jointly with **clinicians**, who can identify those patients who will benefit most.
- In so doing, we will assure the most cost-effective use of this important new class of drugs

# Va rivista la soglia di LDL-C<70 mg/dl?

- Setting the stage: tanto più riduco (in assoluto – mg/dl) il colesterolo LDL tanto più riduco il rischio CV indipendentemente dall'approccio terapeutico
- Evidenze in era pre-PCSK9i: **anche per LDL-C<70 mg/dl più basso LDL-C minor rischio eventi CV**
- **The lowest the LDL-C the best: Sicuro** (ad oggi)...**Costi maggiori**
- **Quali sono i pazienti a rischio CV estremo e potenziale massimo**  
**beneficio CV da soglia più bassa di LDL-C (es. LDL-C<50 mg/dl)?**

The ***TIMI Risk Score for Secondary Prevention (TRS 2P)*** is a simple 9-point risk stratification tool for post-ACS patients

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TRS 2°P Risk Indicators
CHF
HTN
Age $\geq 75$
DM
Prior Stroke
Prior CABG
PAD
eGFR $< 60$
Current Smoking



# ASCVD Risk Categories and LDL-C Treatment Goals

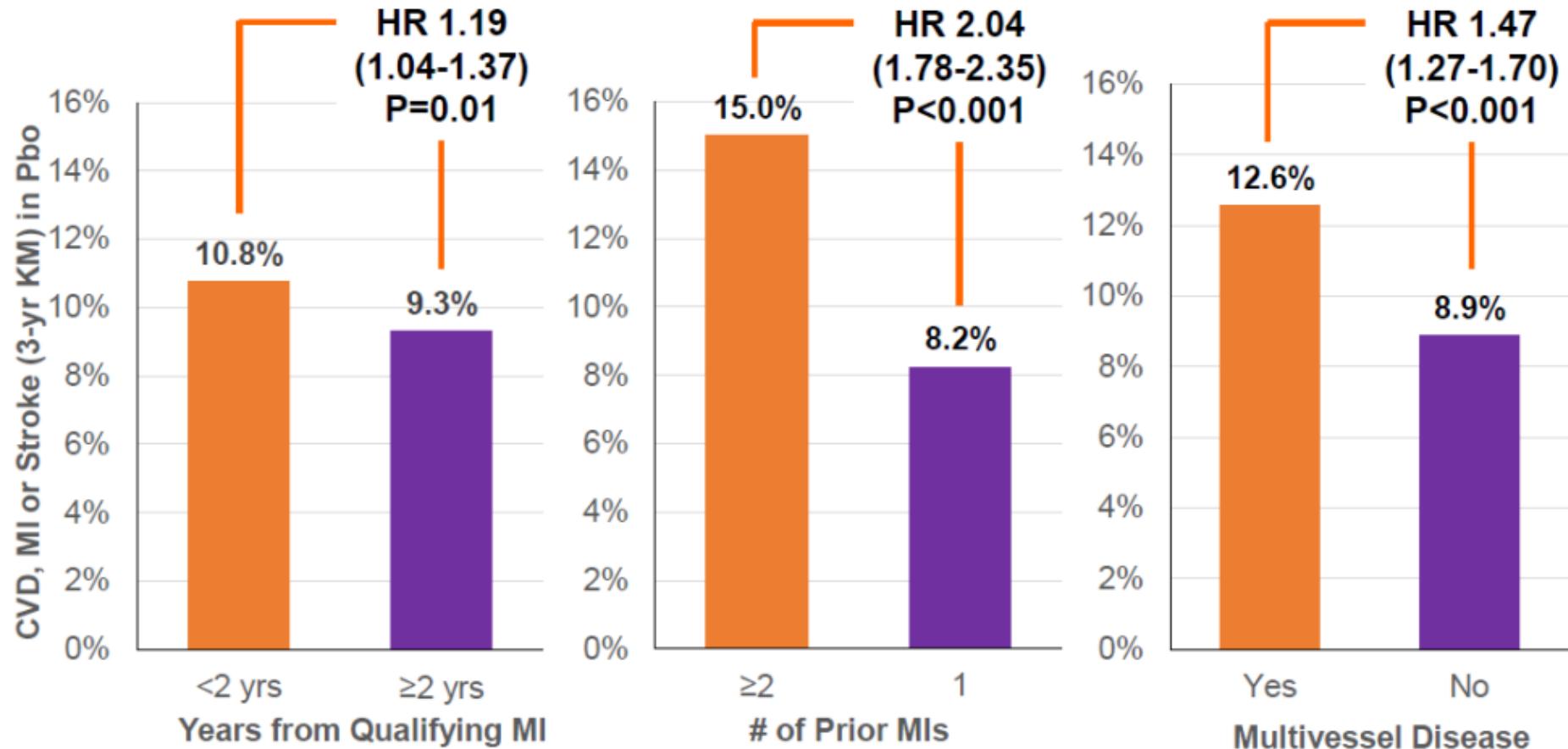
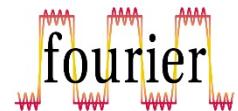
Risk category	Risk factors/10-year risk	Treatment goals		
		LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme risk	<ul style="list-style-type: none"> <li>– Progressive ASCVD including unstable angina in individuals after achieving an LDL-C &lt;70 mg/dL</li> <li>– Established clinical cardiovascular disease in individuals with DM, stage 3 or 4 CKD, or HeFH</li> <li>– History of premature ASCVD (&lt;55 male, &lt;65 female)</li> </ul>	<55	<80	<70
Very high risk	<ul style="list-style-type: none"> <li>– Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk &gt;20%</li> <li>– DM <u>or</u> stage 3 or 4 CKD with 1 or more risk factor(s)</li> <li>– HeFH</li> </ul>	<70	<100	<80
High risk	<ul style="list-style-type: none"> <li>– ≥2 risk factors and 10-year risk 10%-20%</li> <li>– DM or stage 3 or 4 CKD with no other risk factors</li> </ul>	<100	<130	<90
Moderate risk	≤2 risk factors and 10-year risk <10%	<100	<130	<90
Low risk	0 risk factors	<130	<160	NR

Abbreviations: ACS, acute coronary syndrome; apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DM, diabetes mellitus; HeFH, heterozygous familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NR, not recommended.

Barter PJ, et al. *J Intern Med*. 2006;259:247-258; Boekholdt SM, et al. *J Am Coll Cardiol*. 2014;64(5):485-494; Brunzell JD, et al. *Diabetes Care*. 2008;31:811-822; Cannon CP, et al. *N Engl J Med*. 2015;372(25):2387-2397; Grundy SM, et al. *Circulation*. 2004;110:227-239; Heart Protection Study Collaborative Group. *Lancet*. 2002;360:7-22; Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497; Lloyd-Jones DM, et al. *Am J Cardiol*. 2004;94:20-24; McClelland RL, et al. *J Am Coll Cardiol*. 2015;66(15):1643-1653; NHLBI. NIH Publication No. 02-5215. 2002; Ridker PM, et al. *J Am Coll Cardiol*. 2005;45:1644-1648; Ridker PM, et al. *JAMA*. 2007;297(6):611-619; Sever PS, et al. *Lancet*. 2003;361:1149-1158; Shepherd J, et al. *Lancet*. 2002;360:1623-1630; Smith SC Jr, et al. *Circulation*. 2006;113:2363-2372; Stevens RJ, et al. *Clin Sci*. 2001;101(6):671-679; Stone NJ. *Am J Med*. 1996;101:4A40S-48S; Weiner DE, et al. *J Am Soc Nephrol*. 2004;15(5):1307-1315.



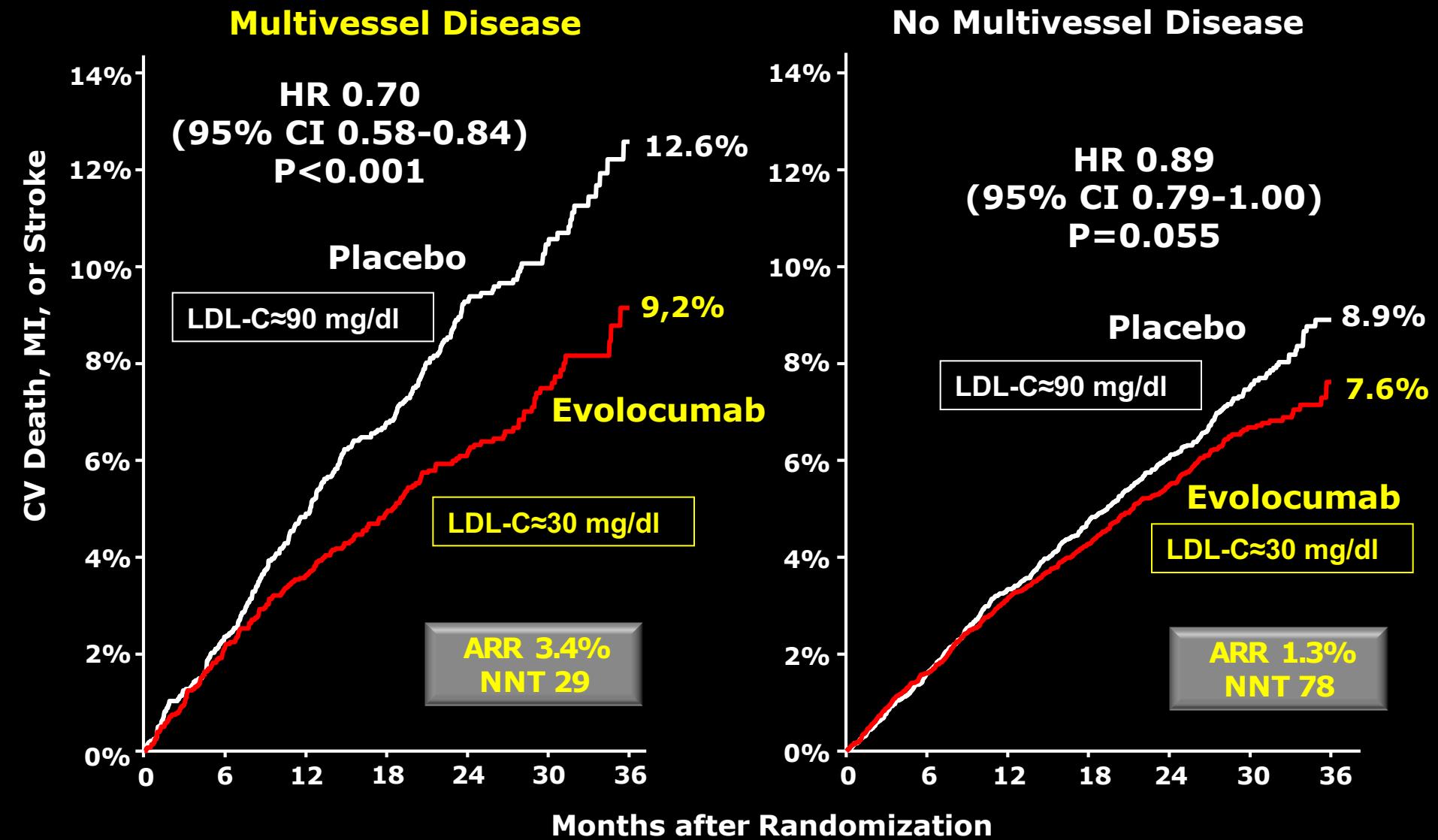
# Risk of CV Death, MI or Stroke With Each Risk Factors



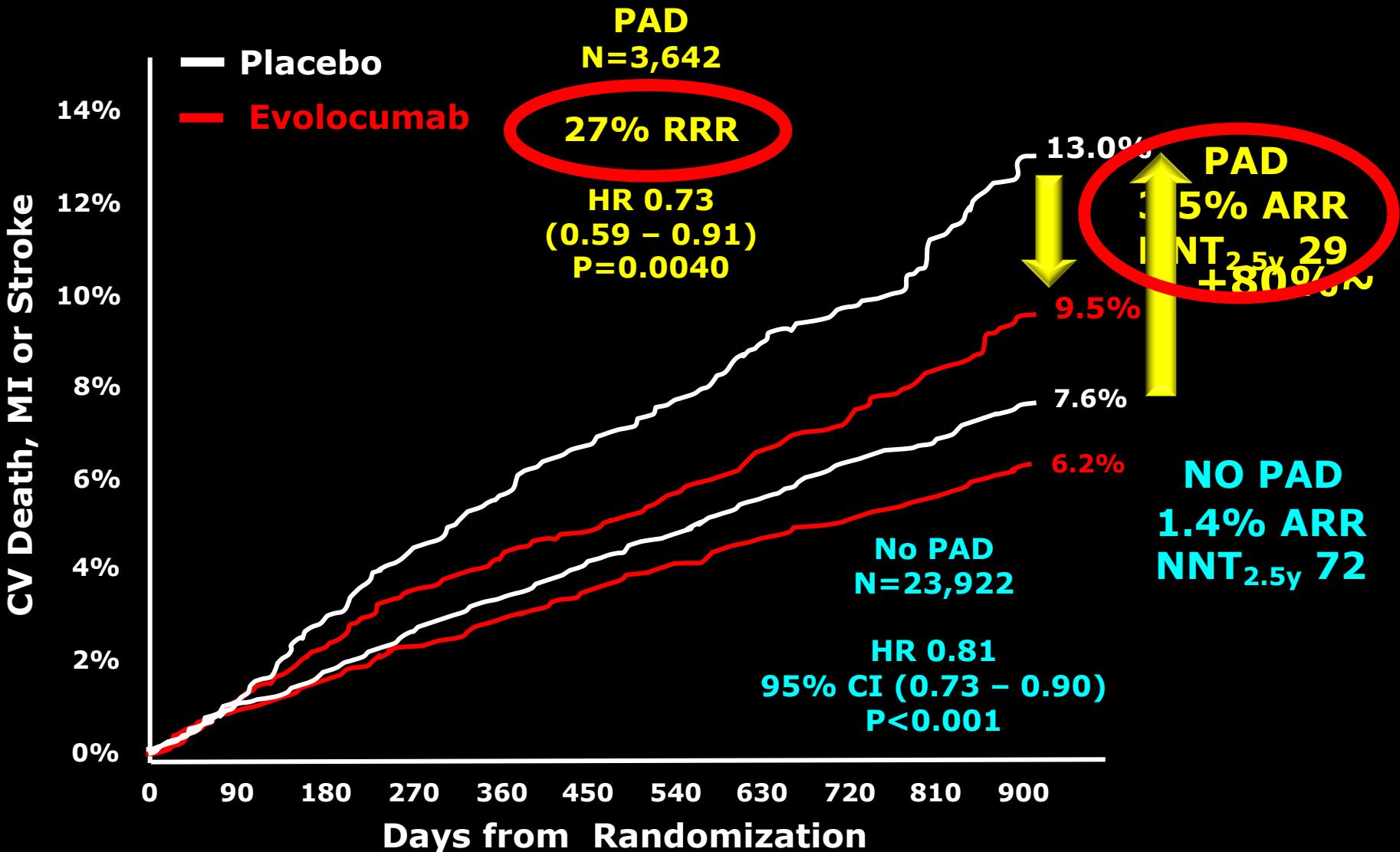
Analyses in placebo arm



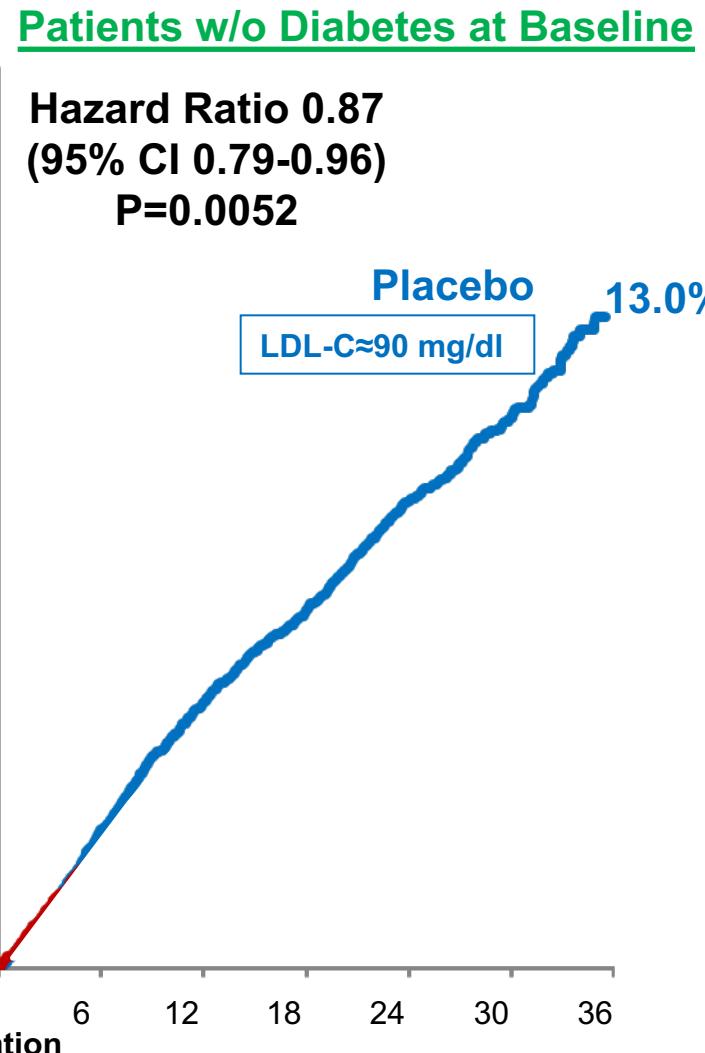
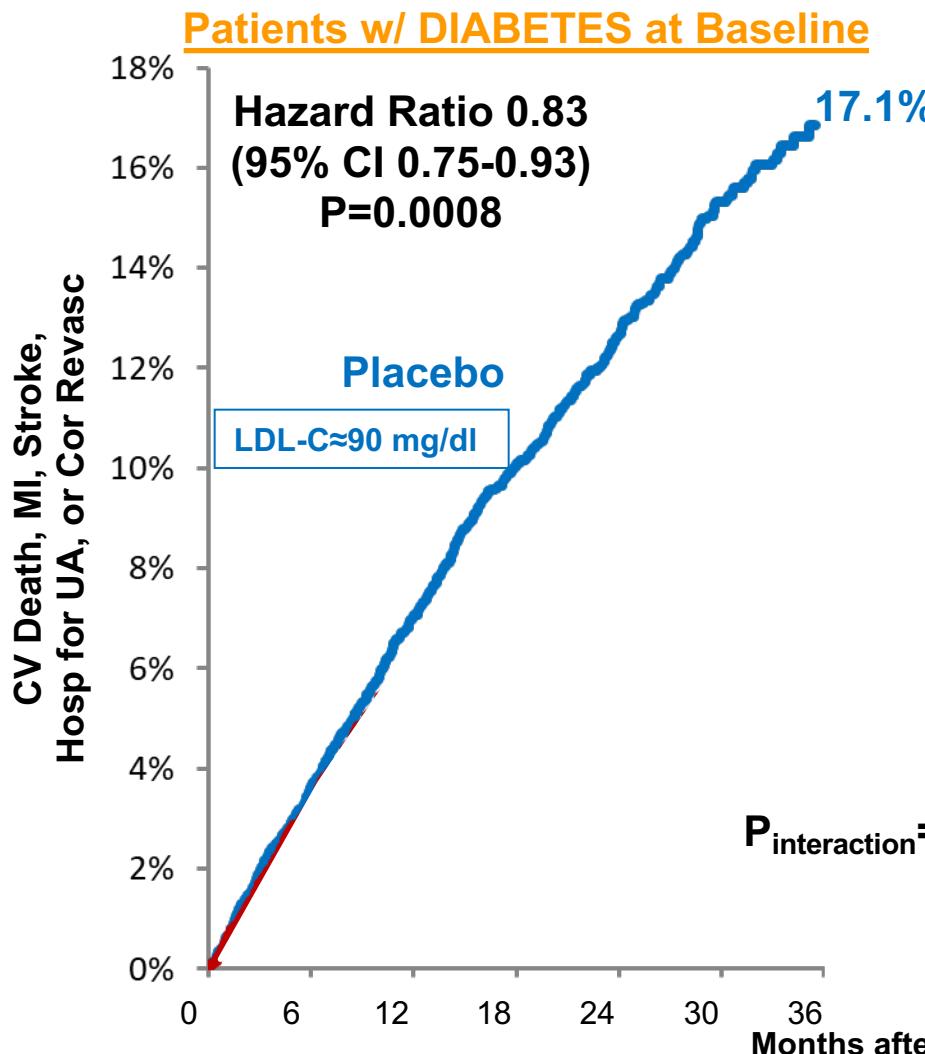
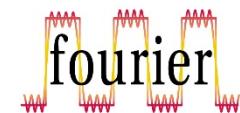
# BENEFIT OF EVOLOCUMAB BASED ON MULTIVESSEL DISEASE



# CV DEATH, MI OR STROKE IN PATIENTS WITH AND WITHOUT PERIPHERAL ARTERY DISEASE



# Effect of Evolocumab on Primary Endpoint in Pts with Diabetes



# SUMMARY

## Va rivista la soglia di LDL-C<70 mg/dl?

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- ✓ Beneficio su eventi CV dipende da quanto si riduce LDL-C e non da «come» lo si riduce;
- ✓ Studi con PCSK9i confermano la relazione lineare tra riduzione LDL-C e benefici CV sino a livelli di **LDL-C<20 mg/dl**
- ✓ Buona sicurezza e tollerabilità anche a livelli di LDL-C  $\leq$  30 mg/dl
  - Eventi avversi simili vs placebo, inclusi DM & eventi neurocognitivi
  - No eventi avversi per LDL-C <0.5 mM (<20 mg/dL) dopo 2.2 anni

# **CONCLUSIONI**

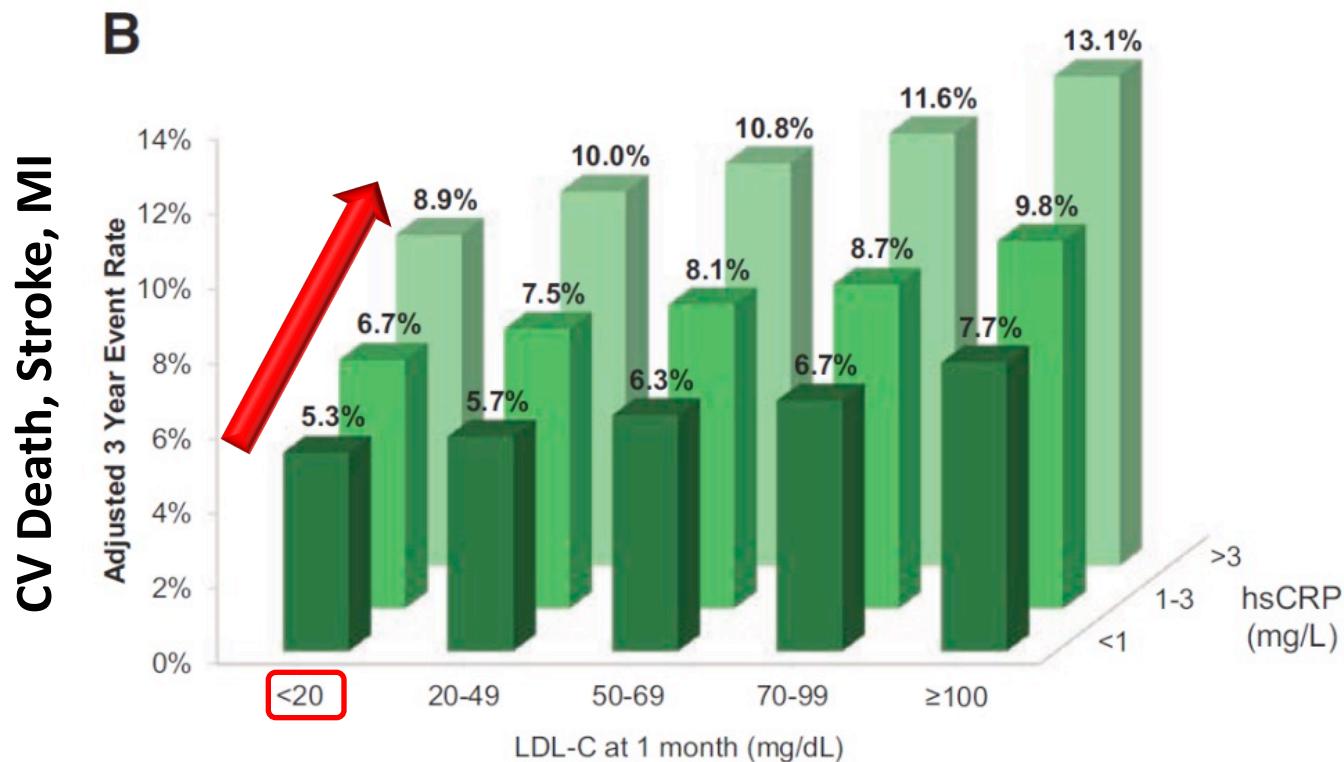
**LDL Lowering<70 mg/dl or LDL Eradication <50 mg/dl (or more)?**

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- ✓ Bilancio costi/benefici della riduzione del LDL-C:

ORIGINAL RESEARCH ARTICLE

## Inflammatory and Cholesterol Risk in the FOURIER Trial





IT'S A  
LONG, LONG  
WAY TO  
TIPPERARY

**IT'S STILL A LONG, LONG WAY TO TIPPERARY!!!**