Terapia ipocolesterolemizzante: fino a dove possiamo andare?

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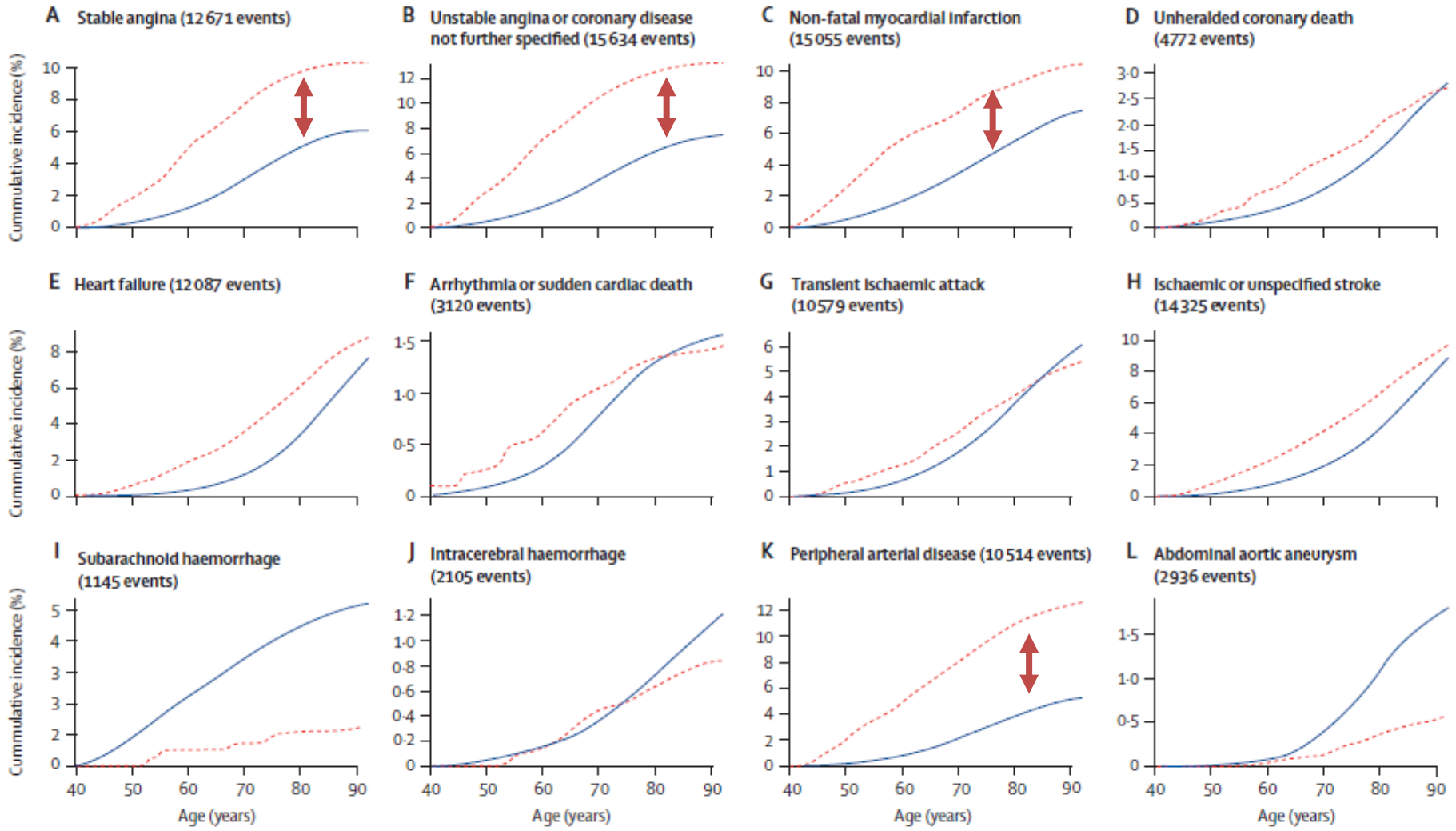
Fino a dove possiamo andare?

- Diabete, LDL-C e rischio CV: *burden of disease*
- Nuove linee guida, nuovi *target* (e nuovi problemi?)
- Le (tante) soluzioni terapeutiche

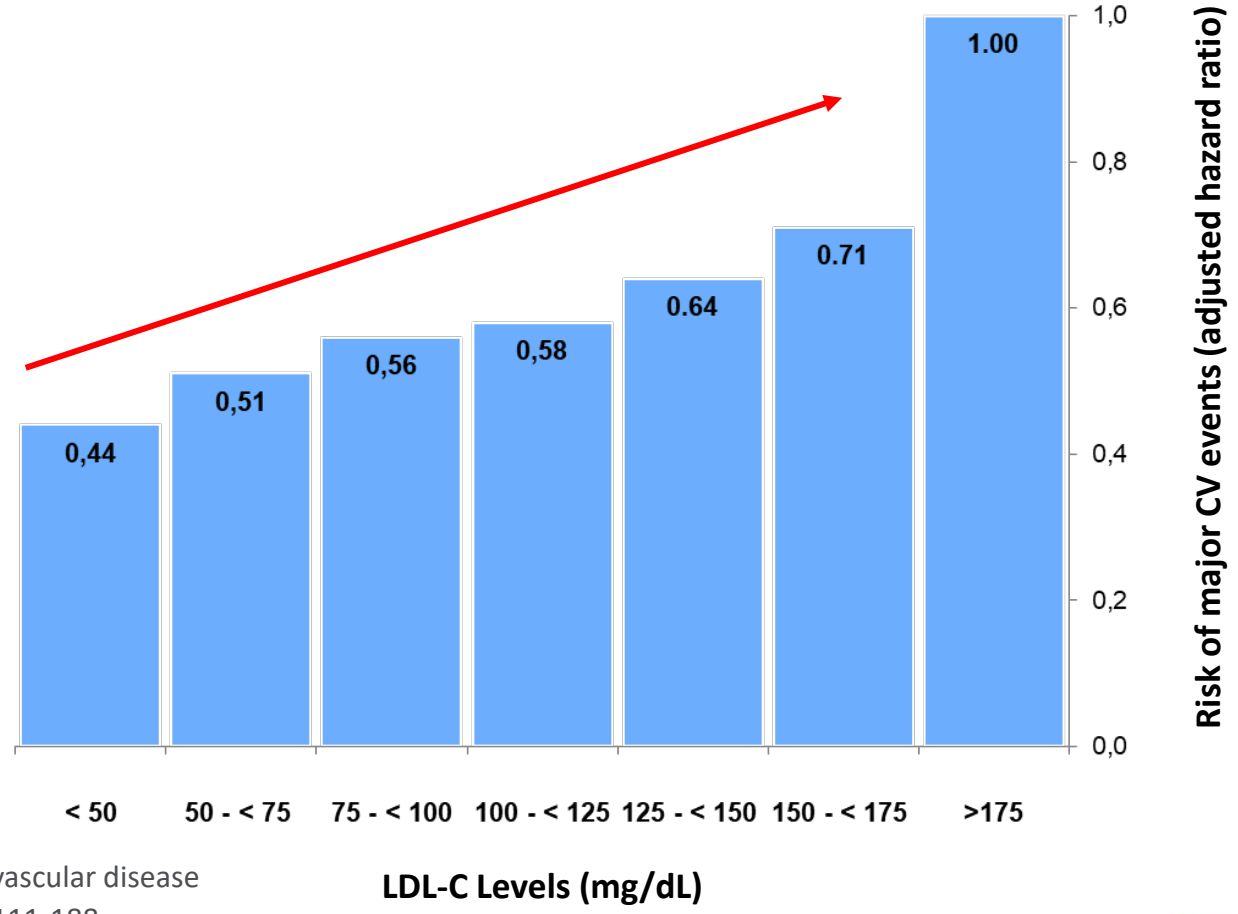
Cumulative incidence curves for first presentation of 12 cardiovascular diseases in patients aged ≥40 years, by diabetes status (1.9 million people cohort)



Shah AD et al. *Lancet Diabetes Endocrinol* 2015; 3:105-13.

Increased LDL-C Levels are a Proven and Direct Cause of CV Events

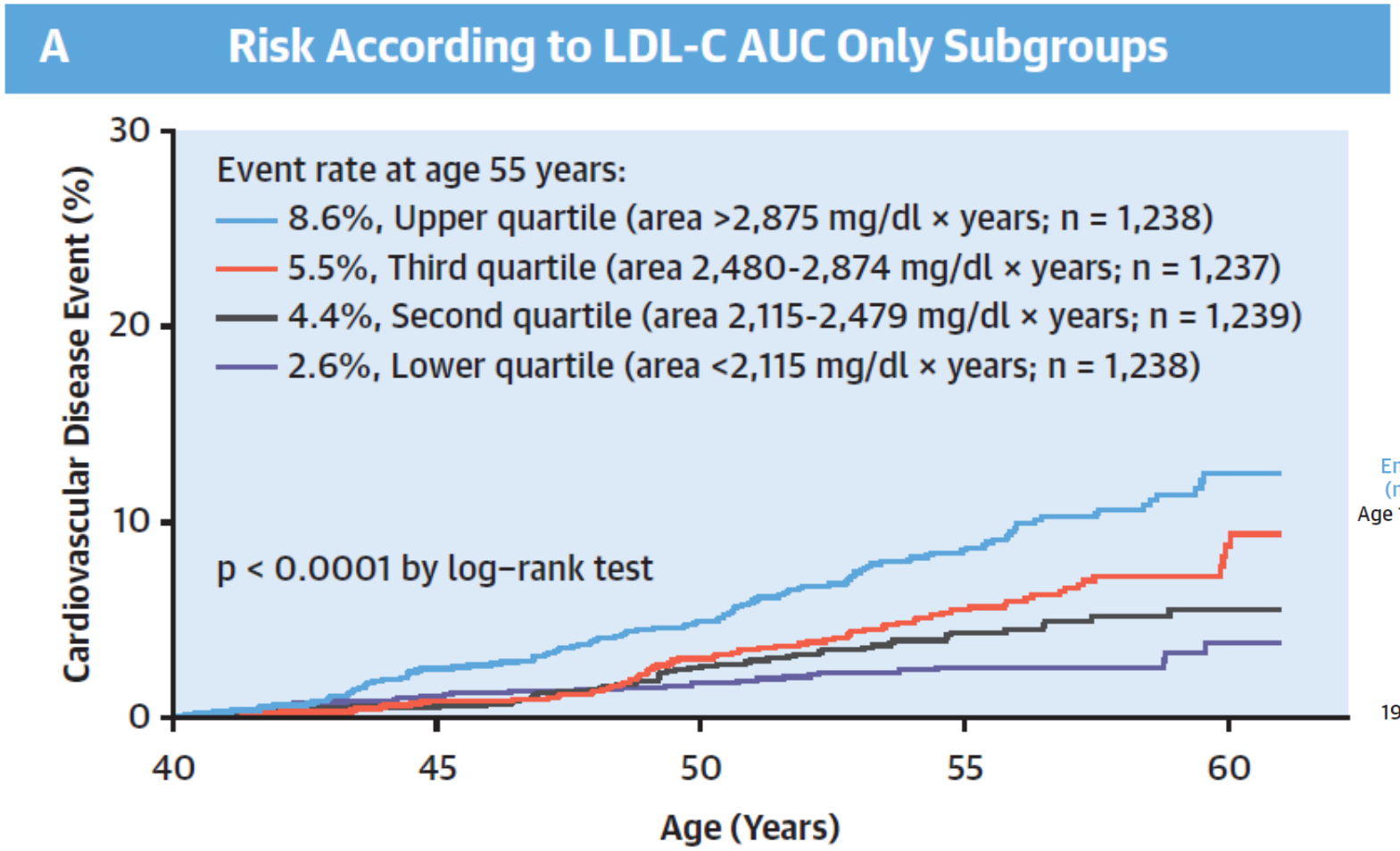
- Prospective studies, randomized trials, and Mendelian randomization studies have all shown that **raised LDL-C is a cause of ASCVD**[1–3]
- The cumulative arterial burden of LDL-C drives the development and progression of ASCVD[2]
- Patients who achieve **very low LDL-C levels have a lower risk** of major CV events than those who achieve moderately low levels[4]



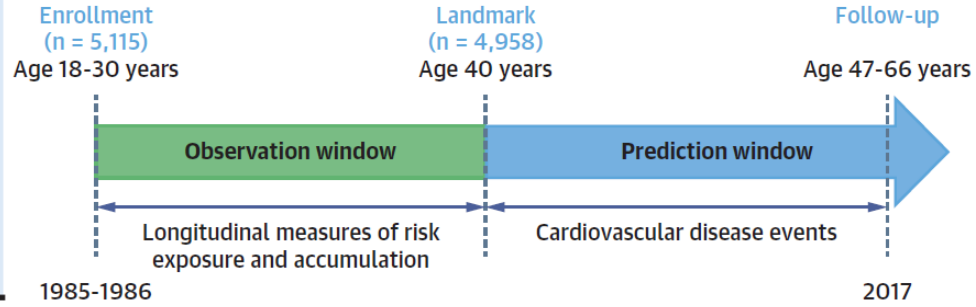
ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CVD, cardiovascular disease

1. ESC/EAS Guidelines for the management of dyslipidaemias. *Eur Heart J.* 2020; 41(1): 111-188.
2. Borén J et al. *Eur Heart J.* 2020; 0: 1-28.
3. Ference BA et al. *Eur Heart J*. 2017; 38(32): 2459–2472.
4. Boekholdt et al. *JACC* 2014;64: 485–494.

Cardiovascular events risk according to LDL-C exposure before the age of 40 years in the CARDIA study



- **Increased LDL-C AUC** was associated with increased **risk of an incident event** following the landmark age of 40 years.



Domansky MJ et al. *JACC* 2020; 76:1507–16.

Stepwise Selection of Risk Factors in 2,693 White Patients With NIDDM

United Kingdom Prospective Diabetes Study (UKPDS)

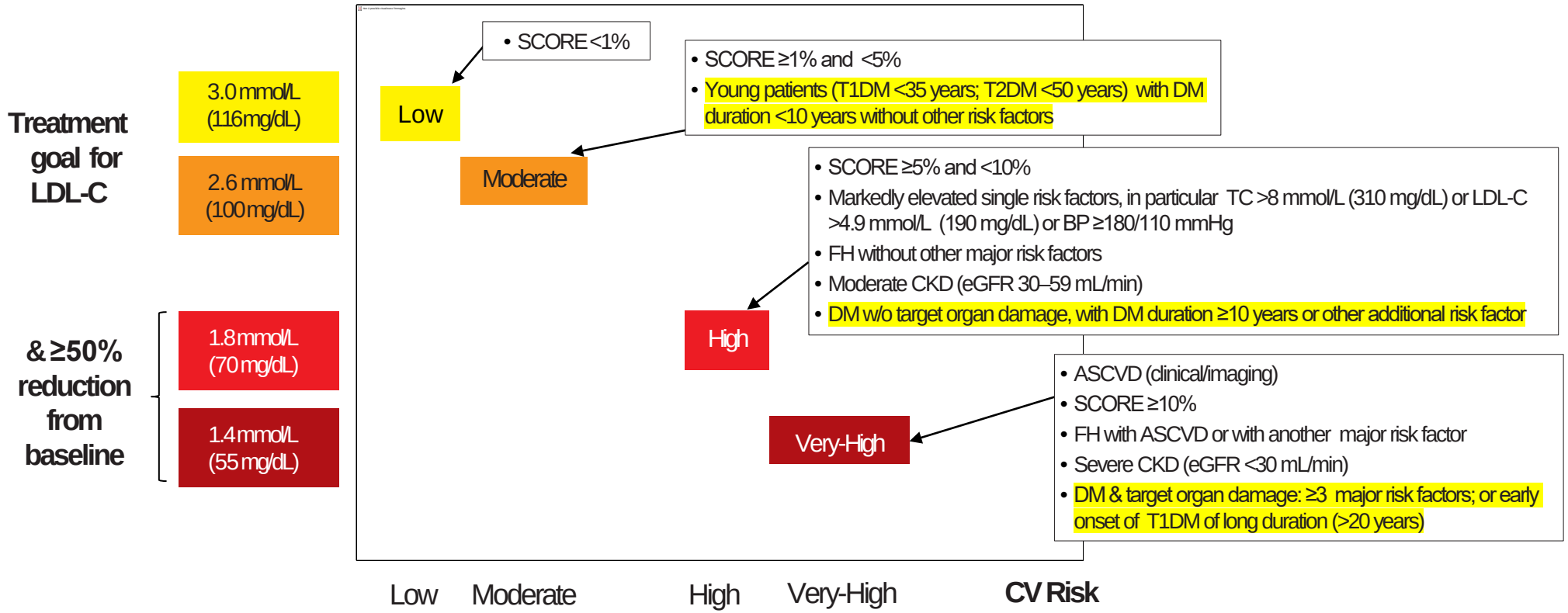
Coronary heart disease (n = 280)

Position in model	Variable	*P* value
1st	LDL-C	<0.0001
2nd	HDL-C	0.0001
3rd	Hemoglobin A_{1c}	0.0022
4th	Systolic blood pressure	0.0065
5th	Smoking	0.056

Turner RC et al. *BMJ* 1998; 316:823–828.

The 2019 ESC/EAS Guidelines Recommend to Intensively Lower LDL-C to Reduce Cardiovascular Risk, Particularly in Uncontrolled Patients

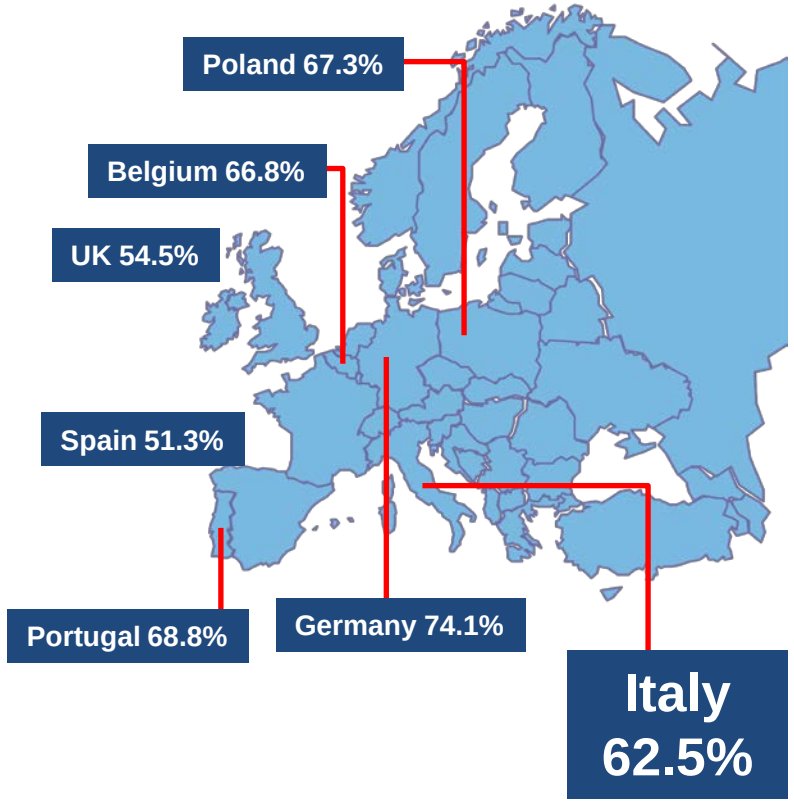
- The updated ESC/EAS Guidelines recommend an LDL-C reduction of ≥50% and LDL-C goals of <70 (1.8 mmol/L) and <55 mg/dL (1.4 mmol/L) in high- and very high-risk patients, respectively
- These goals are more stringent than previously because the greater the absolute LDL-C reduction, the greater the CV risk reduction



ESC/EAS Guidelines for the management of dyslipidaemias. *Eur Heart J.* 2020; 41: 111-188.

Unmet Need: Very High Risk Patients with LDL-C ≥70 mg/dL Across EUROPE

- Analysis of the hospital arm of the **EUROASPIRE V survey** of risk factors and management in **coronary heart disease patients** with/without diabetes
- Carried out in 27 European countries, 2016–17
- **Coronary patients followed up n=7,824**
- 84.3% of patients were receiving LLT
  - 49.9% were receiving high intensity LLT
  - 34.1% were receiving low/moderate intensity LLT
- Overall, 71.0% of coronary patients across Europe were not at LDL-C goal <1.8 mmol/L (<70 mg/dL)



Conclusions

- The majority of patients with CAD did not reach LDL-C goals recommended by the 2016 ESC/EAS guidelines
- The 2019 ESC/EAS guidelines recommend even lower LDL-C goals, so, in reality, the unmet need will be greater

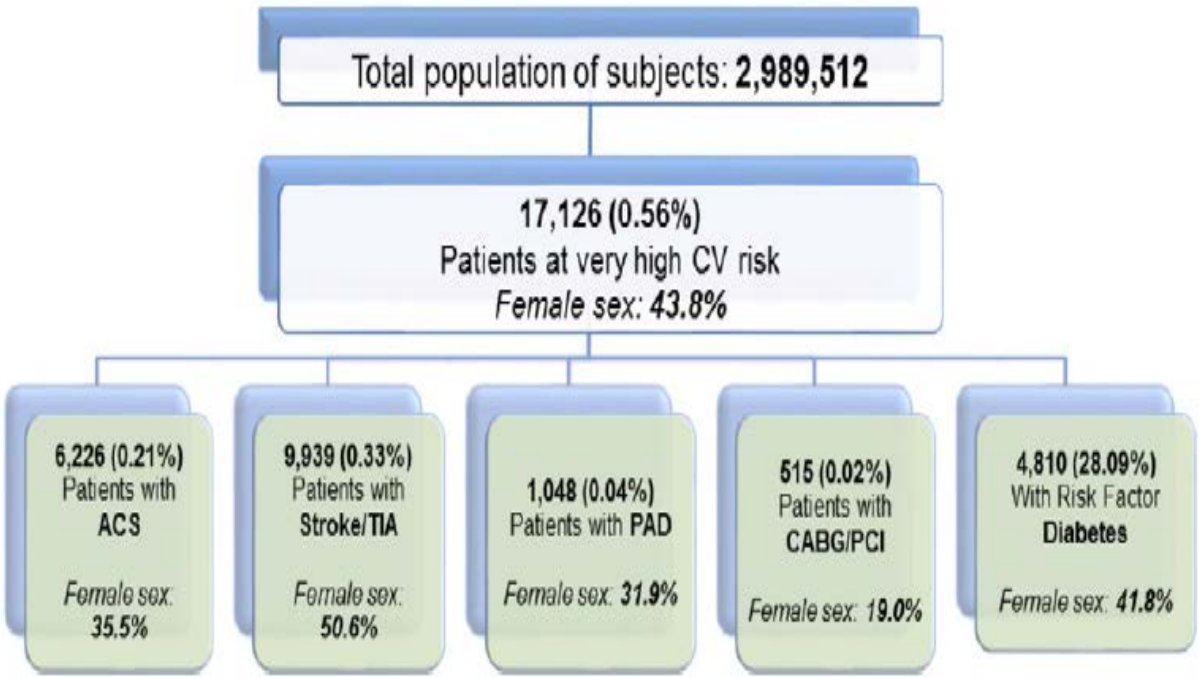
EUROASPIRE, European Action on Secondary and Primary Prevention by Intervention to Reduce Events

de Backer G et al. *Atherosclerosis.* 2019;285:135–146.

Prescription rate and continuity of treatment with statins is suboptimal in DM patients with recent CV events

Use of lipid lowering drugs in patients at very high risk of cardiovascular events: An analysis on nearly 3,000,000 Italian subjects of the ARNO Observatory

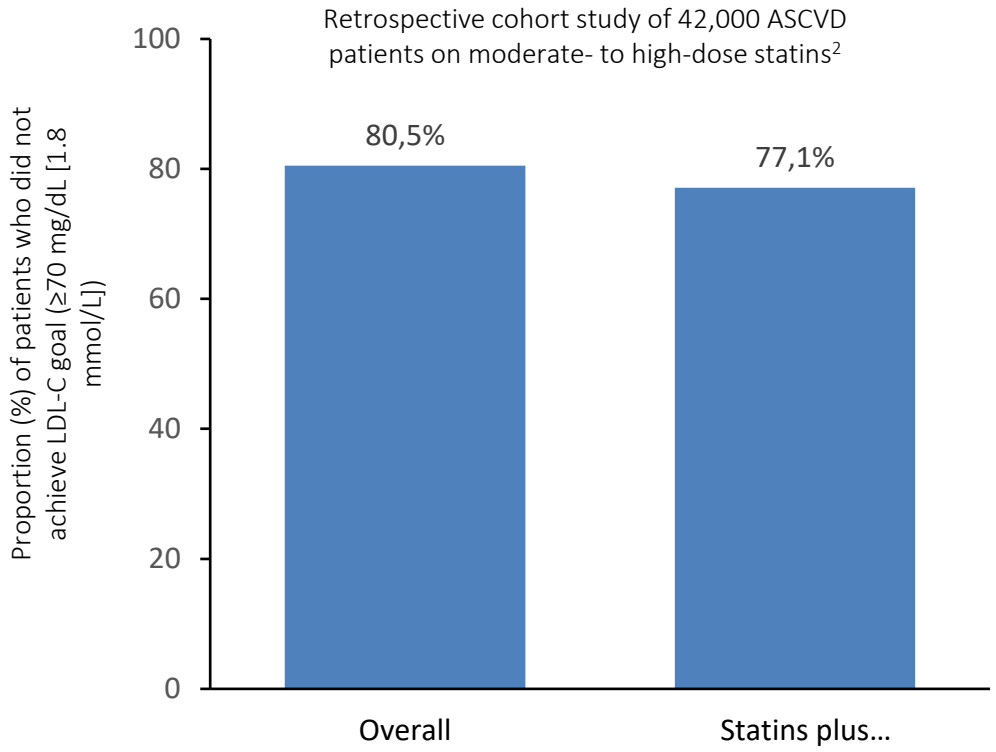
Aldo P. Maggioni [a,*], Silvia Calabria [b], Elisa Rossi [c], Nello Martini [d], on the behalf of the ARNO Observatory:



- **The rate of use of statins with/without ezetimibe** in the diabetics cohort was **68.5, 59.3 and 53.1%** during the first, the second and the third year of follow-up, respectively.
- In the subgroup of diabetics, **at least one readmission** over the first year of follow-up occurred in **59.6%** of patients. The total number of re-hospitalizations of diabetics was 6118. Of them, **56.9% was due to CV causes**

Maggioni AP et al. *Int J Cardiol* 2017; 246:62–67.

Additional LLTs are Needed to Complement Current Therapies to Help Uncontrolled Patients Achieve Their Goals

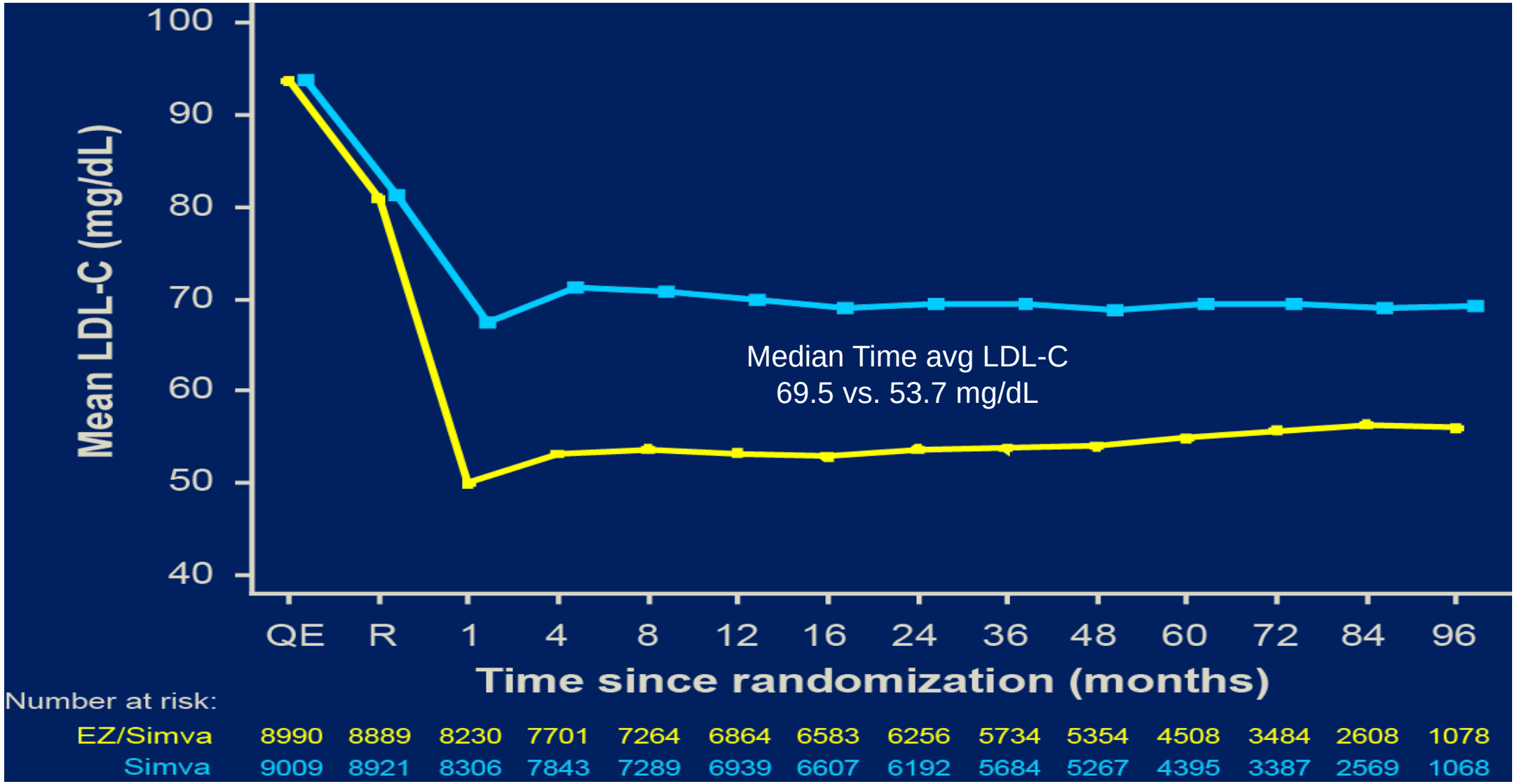


Intensity of lipid lowering treatment

Treatment	Average LDL-C reduction
Moderate intensity statin	≈ 30%
High intensity statin	≈ 50%
High intensity statin plus ezetimibe	≈ 65%
PCSK9 inhibitor	≈ 60%
PCSK9 inhibitor plus high intensity statin	≈ 75%
PCSK9 inhibitor plus high intensity statin plus ezetimibe	≈ 85%

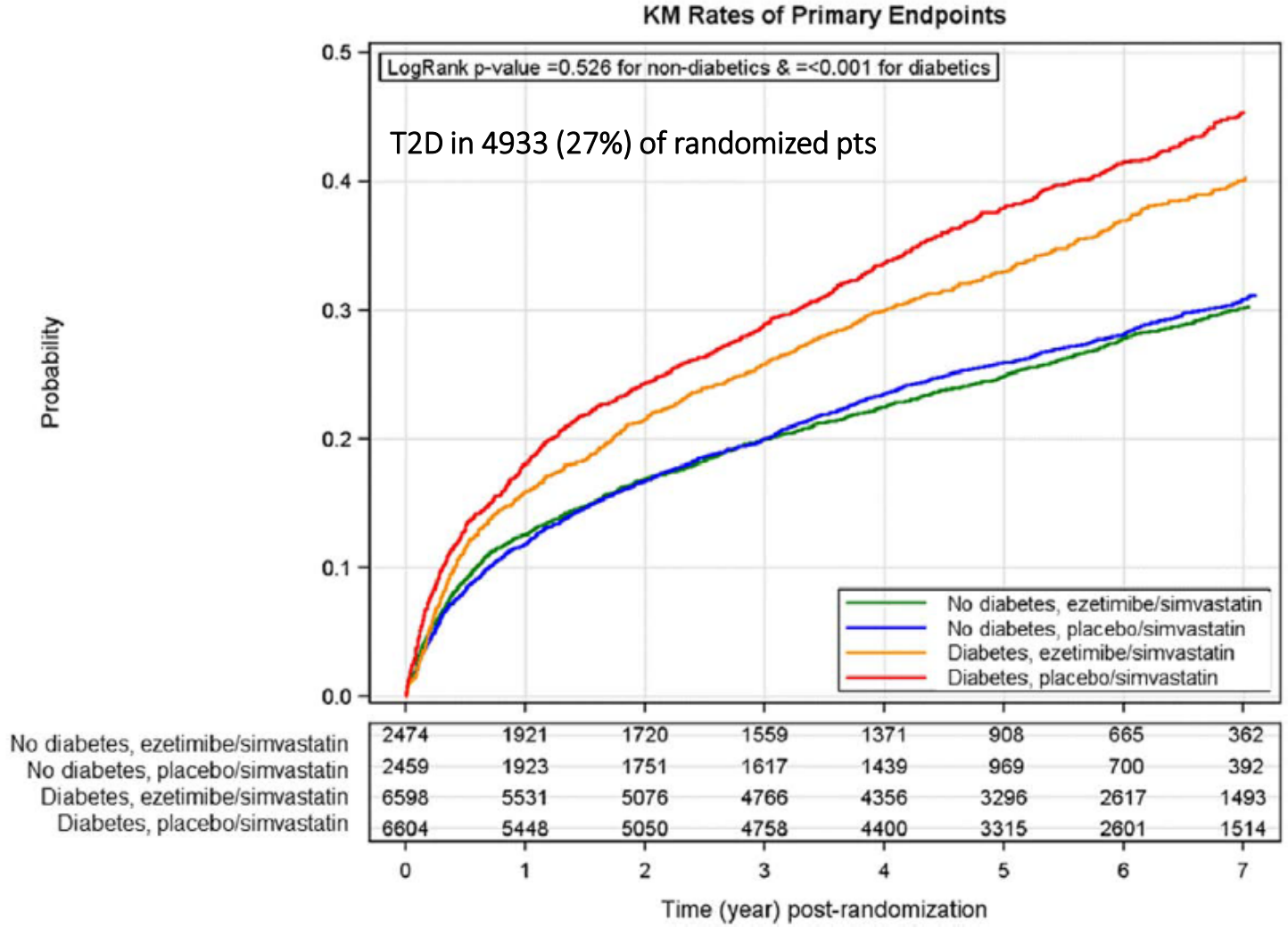
Figure adapted from Fox KM et al. *Clin Res Cardiol* 2018; 107: 380–388.

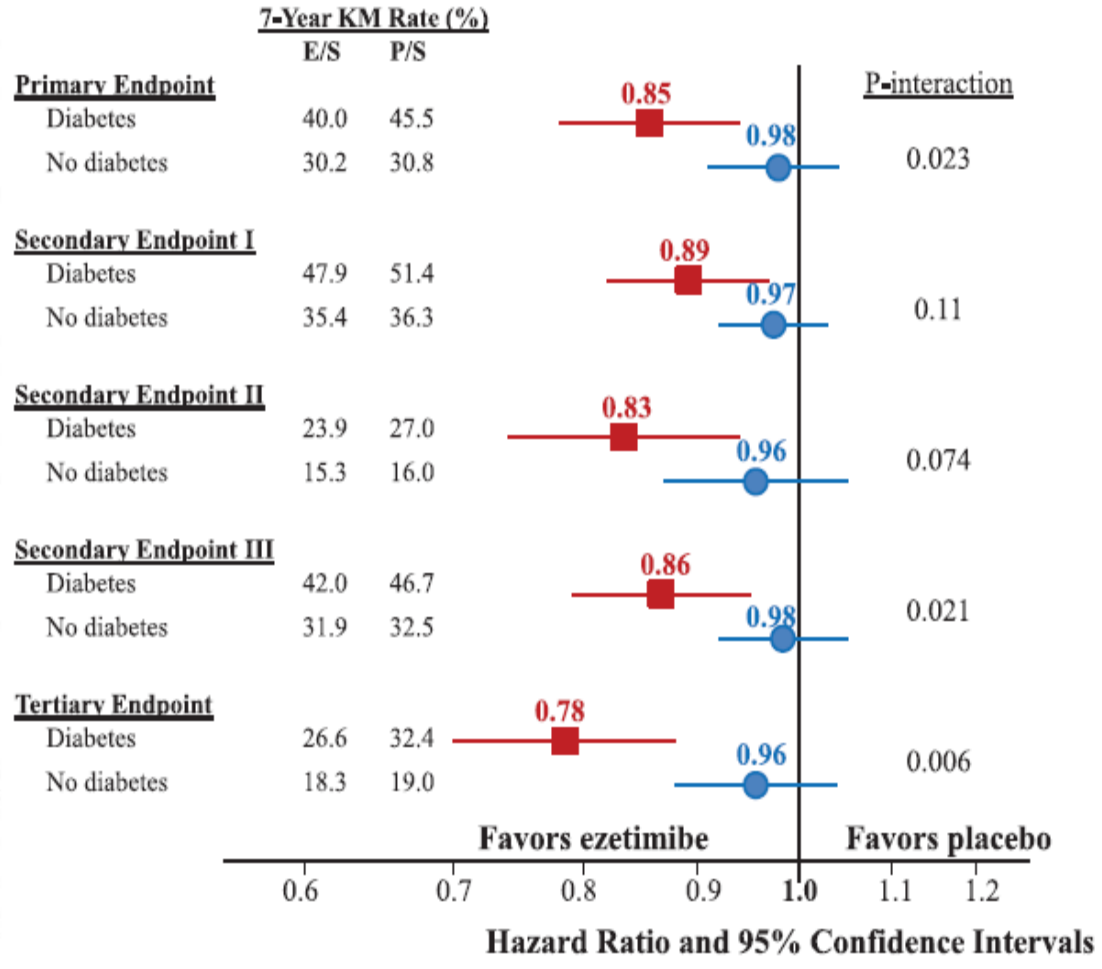
LDL-C reduction in the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT)



Cannon CP et al. *NEJM* 2015; 372:2387-97.

Benefit of Adding Ezetimibe to Statin on Cardiovascular Outcomes and Safety in Patients With Versus Without Diabetes Mellitus (IMPROVE-IT)





Giugliano RP et al. *Circulation* 2018;137:1571–1582.

CV Outcomes Trials with PCSK-9 Inhibitors

The ODYSSEY OUTCOMES Trial: Topline Results

Alirocumab in Patients After Acute Coronary Syndrome

Gregory G. Schwartz, Michael Szarek, Deepak L. Bhatt, Vera Bittner, Rafael Diaz, Jay Edelberg, Shaun G. Goodman, Corinne Hanotin, Robert Harrington, J. Wouter Jukema, Guillaume Lecorps, Angèle Moryusef, Robert Pordy, Matthew Roe, Harvey D. White, Andreas Zeiher,
Ph. Gabriel Steg
On behalf of the ODYSSEY OUTCOMES Investigators and Committees

American College of Cardiology – 67th Scientific Sessions
March 10, 2018

ODYSSEY OUTCOMES

ClinicalTrials.gov: NCT01663402

Cardiovascular Efficacy & Safety of Evolocumab in Diabetes, and Risk of Development of Diabetes:

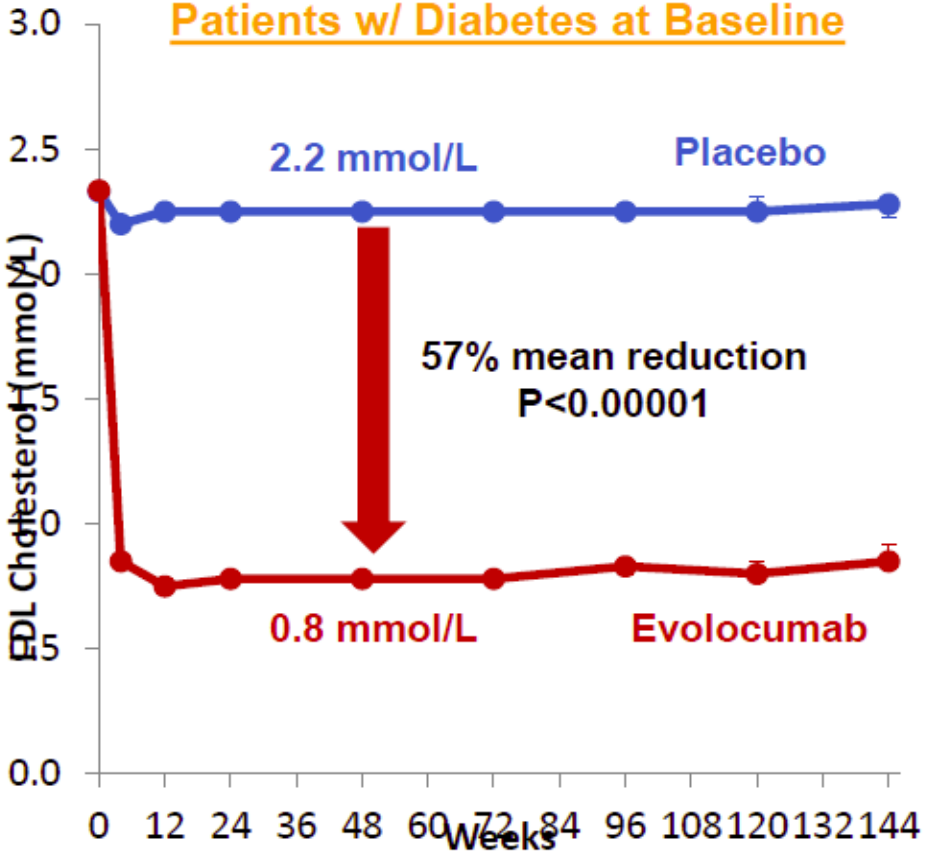
An Analysis from the FOURIER Trial

MS Sabatine, LA Leiter, SD Wiviott, RP Giugliano, P Deedwania, GM De Ferrari, SA Murphy, JF Kuder, AC Keech, PS Sever, and TR Pedersen, for the FOURIER Steering Committee & Investigators

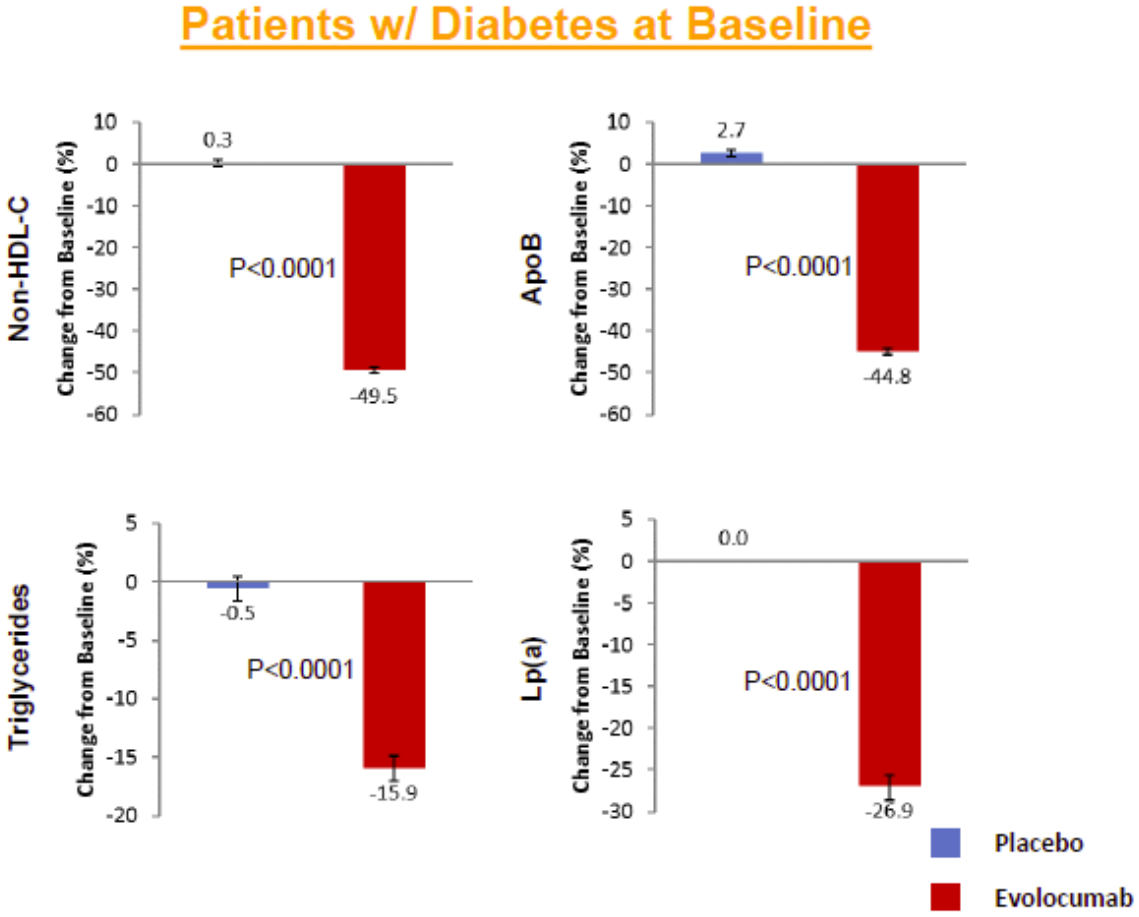
European Association for the Study of Diabetes – 53rd Annual Meeting
Clinical Trial Update
September 15, 2017

The FOURIER Study: Diabetes Subgroup

LDL-C Reduction



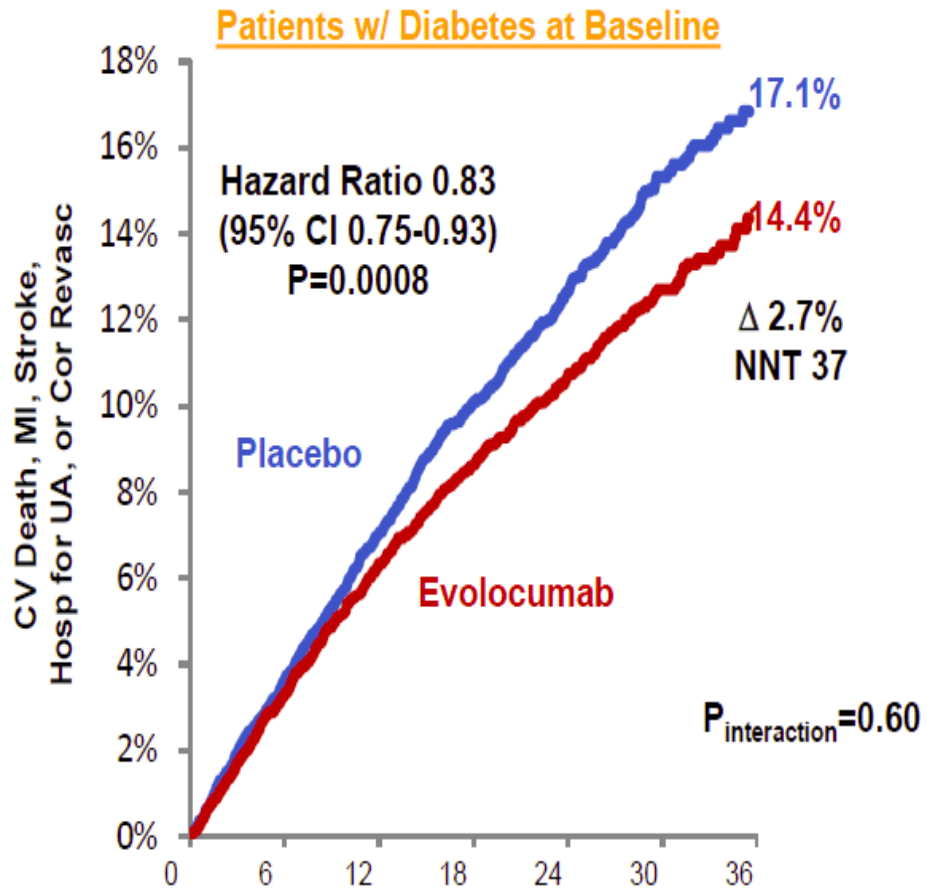
Other Lipid Parameters



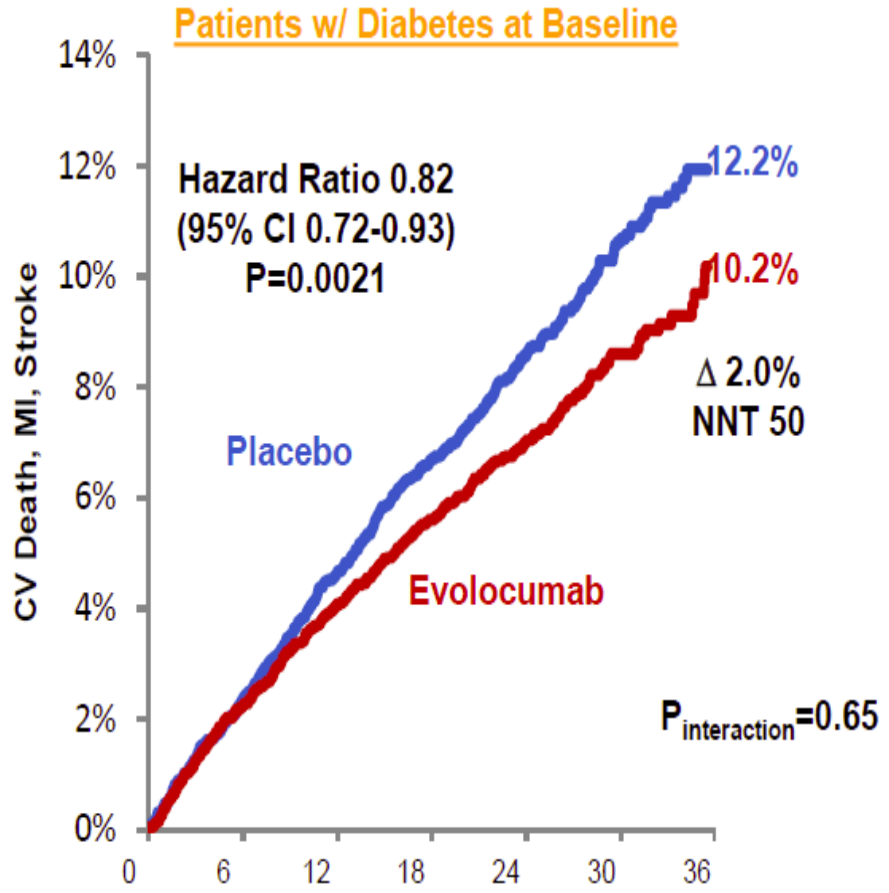
Sabatine MS et al. *Lancet Diabetes Endocrinol*. 2017;5:941-950

The FOURIER Study: Diabetes Subgroup

Primary Endpoint

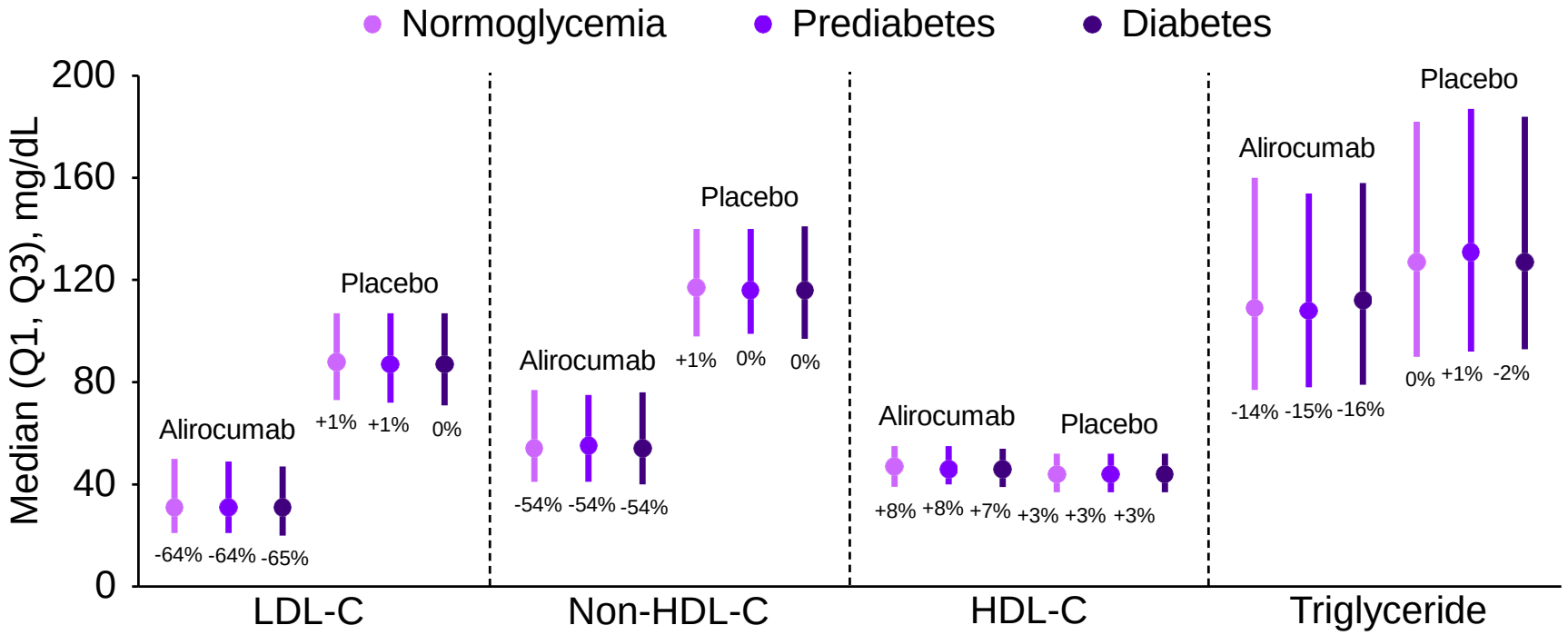


Secondary Endpoints



Sabatine MS et al. *Lancet Diabetes Endocrinol*. 2017;5:941-950

Lipids at 16 Weeks After Randomization In the ODYSSEY OUTCOMES



Median percent change from baseline presented below each bar
Intention-to-treat analysis

Ray KK et al. *Lancet Diabetes Endocrinol.* 2019;7:618-628

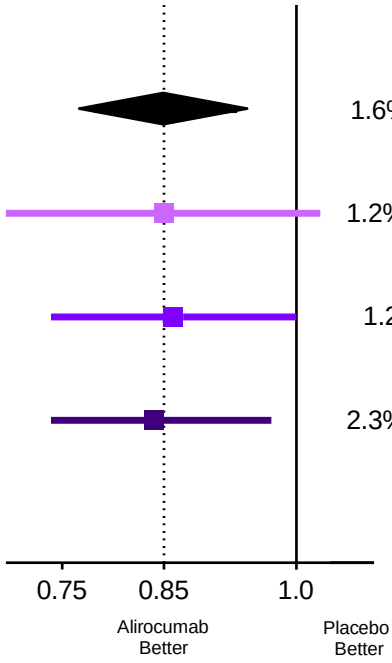
Relative and Absolute Risk Reduction with Alirocumab By Glucometabolic Status

Treatment × baseline glucometabolic status:

Subgroup	MACE Incidence Alirocumab n/N (%)	MACE Incidence Placebo n/N (%)	HR (95% CI)	ARR (95% CI)
Overall	903/9462 (9.5)	1052/9462 (11.1)	0.85 (0.78, 0.93)	1.6% (0.7%, 2.4%)
Normoglycemia	192/2639 (7.3)	220/2595 (8.5)	0.85 (0.70, 1.03)	1.2% (-0.3%, 2.7%)
Prediabetes	331/4130 (8.0)	380/4116 (9.2)	0.86 (0.74, 1.00)	1.2% (0%, 2.4%)
Diabetes	380/2693 (14.1)	452/2751 (16.4)	0.84 (0.74, 0.97)	2.3% (0.4%, 4.2%)

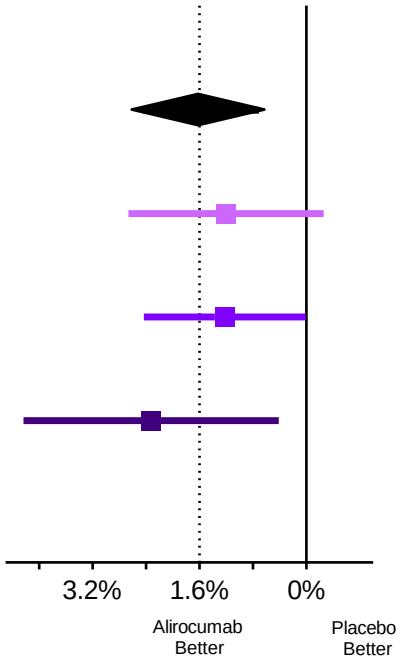
Relative risk reduction

$P_{interaction} = 0.98$



Absolute risk reduction

$P_{interaction} = 0.0019$



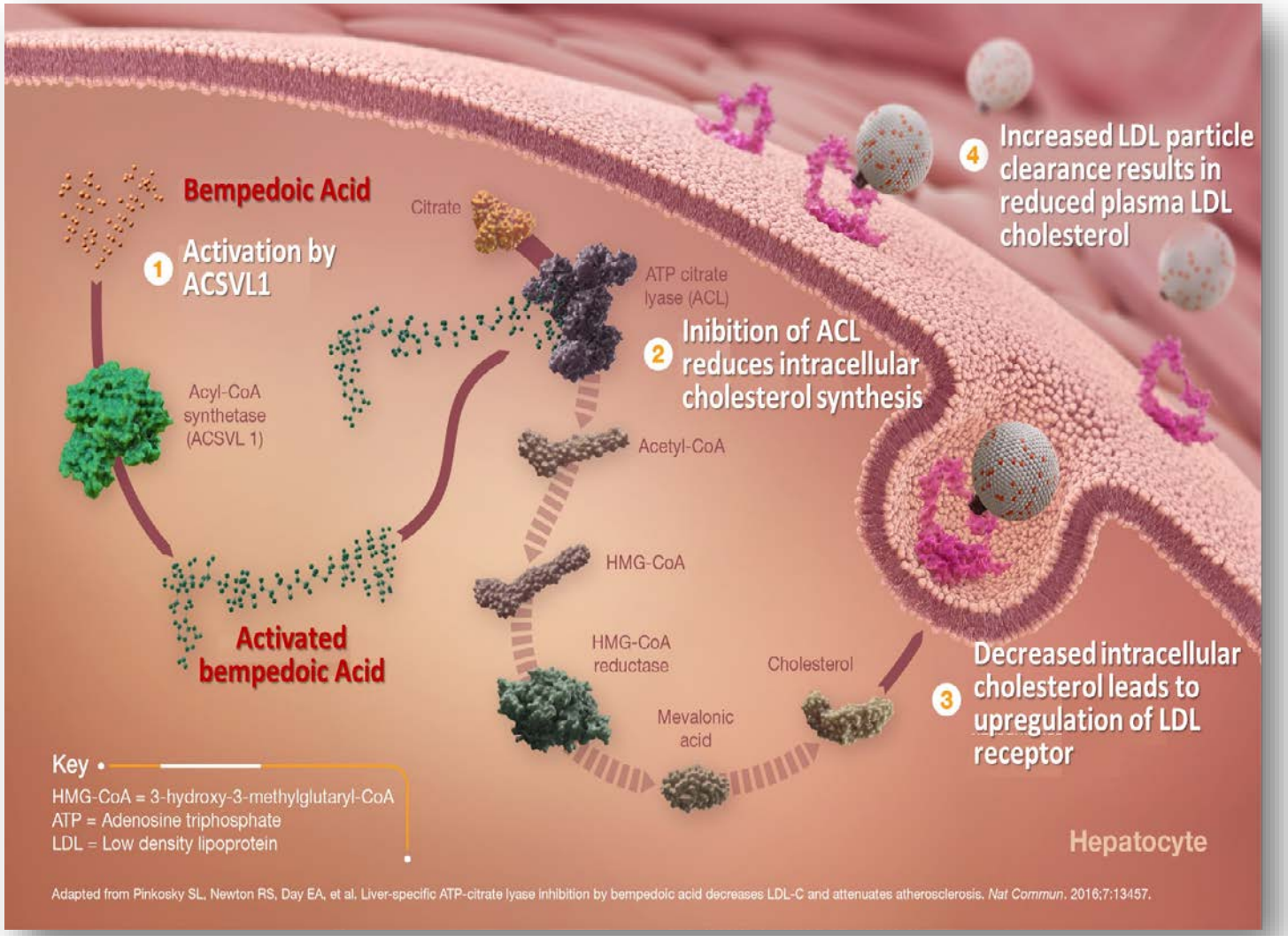
Median (Q1, Q3) follow-up: 2.8 (2.3, 3.4) years

Ray KK et al. *Lancet Diabetes Endocrinol.* 2019;7:618-628

The Mechanism of Action of Bempedoic Acid is Complementary, yet Distinct from Statins and Other LLTs

- Activated primarily in the liver, bempedoic acid inhibits the ACL enzyme in the well-known cholesterol synthesis pathway, **upstream of the statin target**

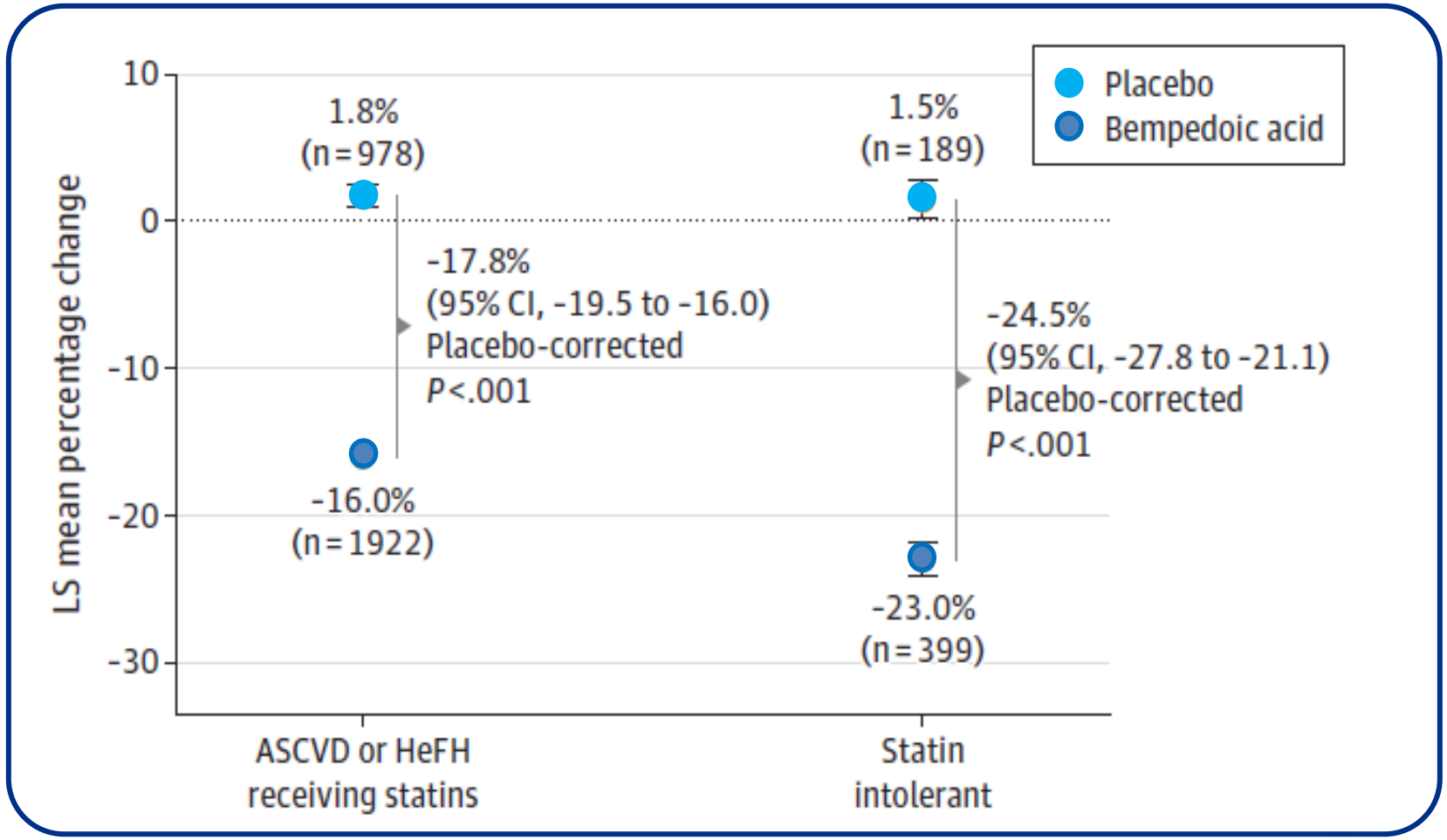
- Upregulation of the LDL receptor results in an increased uptake and removal of LDL particles by the liver



Adapted from Pinkosky et al. *Nature Communications*. 2016; 7:13457 | DOI: 10.1038/ncomms13457

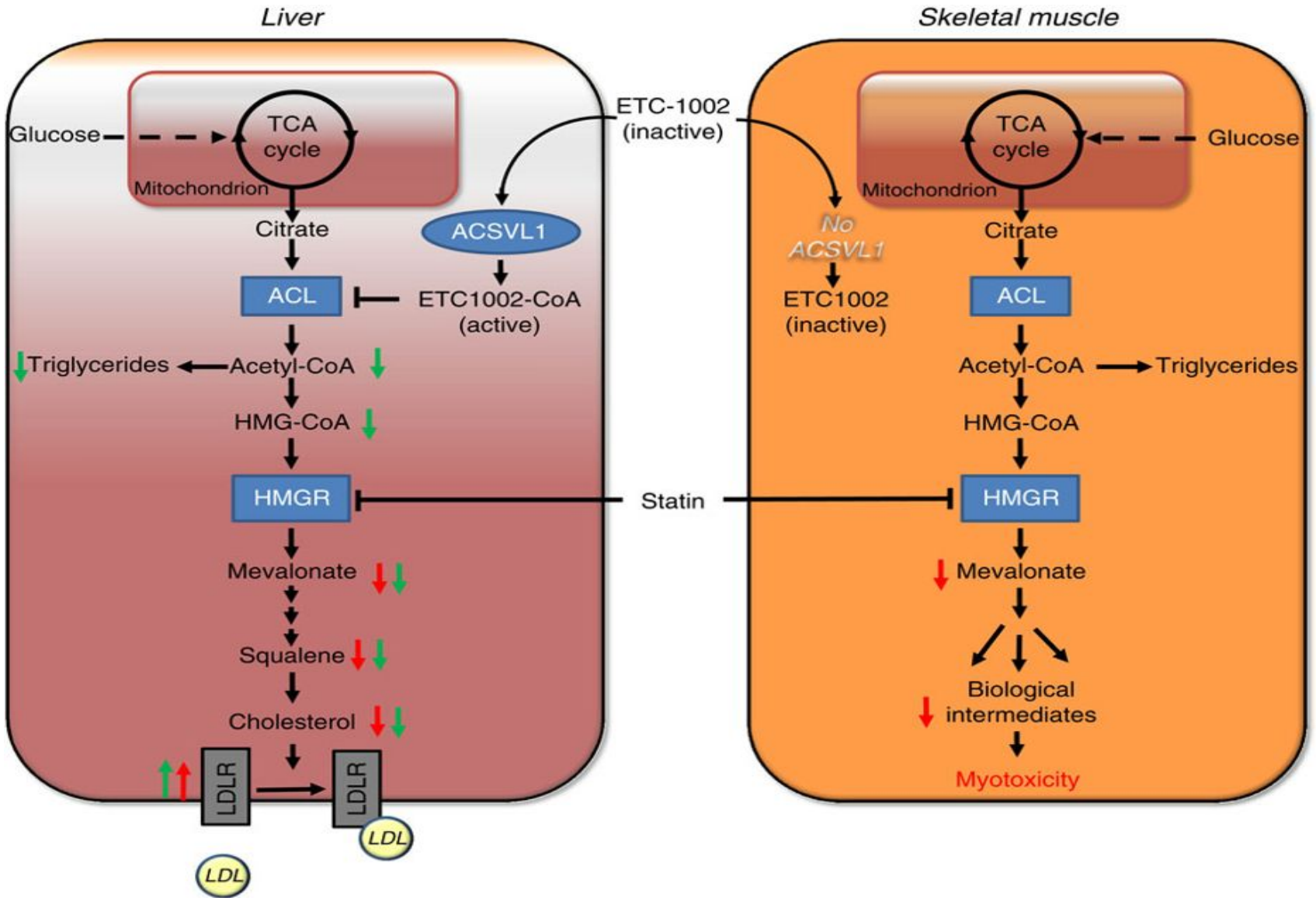
Bempedoic Acid Reduction in LDL-C vs Placebo on top of Maximally Tolerated Statins with or without Other Oral LLT

- Compared with placebo, treatment with bempedoic acid was associated with **significantly lower LDL-C levels at week 12** in both pools



Banach M. et al., JAMA Cardiology, published online July 1, 2020. doi:10.1001/jamacardio.2020.2314

Bempedoic Acid is not Activated in the Skeletal Muscle



Pinkosky S et al. Nat Commun. 2016;7:13457. doi: 10.1038/ncomms1345

Fino a dove possiamo andare?

- LDL-C va ridotto **aggressivamente** nel paziente con DM (solide evidenze da RCTs, studi osservazionali, registri amministrativi…)
- Molte opzioni/alternative terapeutiche, **tutte efficaci e sicure**
- **Ostacoli:**
  - Inerzia terapeutica
  - Non aderenza, persistenza in terapia
  - Difficile accesso ad alcune cure