Terapia di associazione nel paziente ad alto rischio cardiovascolare: dalle linee guida ESC al mondo reale. Come raggiungere i target?

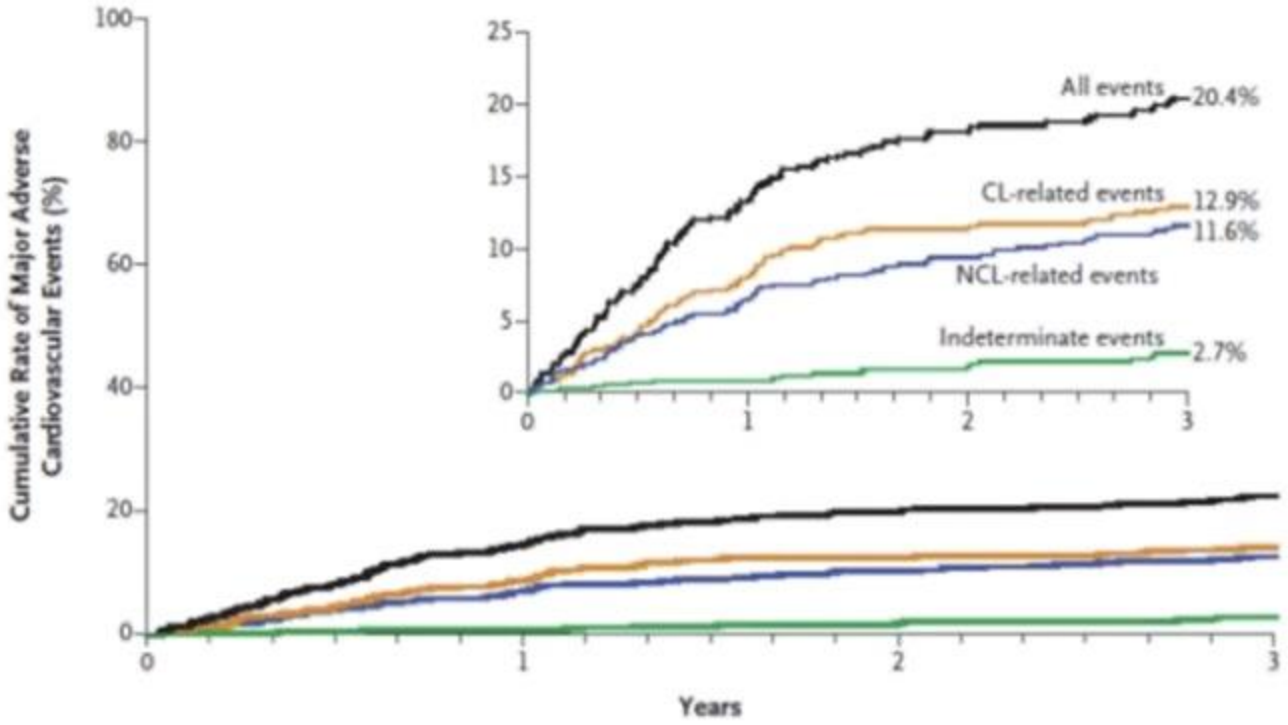
IPERCOLESTEROLEMIA

Dr. Luca Fileti

U.O. Cardiologia Ravenna

AUSL ROMAGNA

A Prospective Natural-History Study of Coronary Atherosclerosi

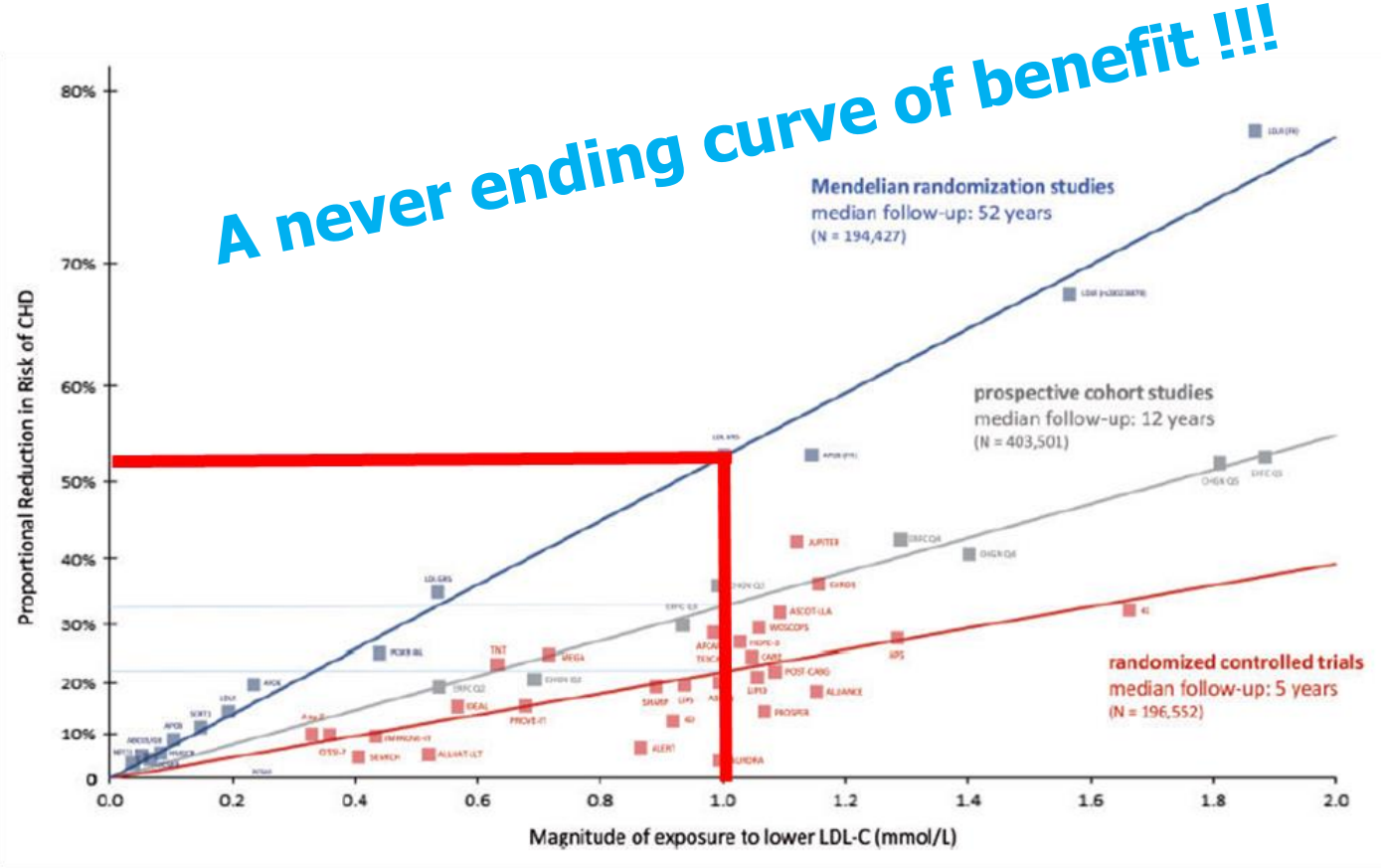


No. at Risk				
All patients	697	557	506	480
Patients with CL-related events	697	590	543	518
Patients with NCL-related events	697	595	553	521
Patients with indeterminate events	697	634	604	583

A Prospective Natural-History Study of Coronary AtherosclerosisGregg W. Stonen N.engl j med 364;3
neim 226 org january 20, 2011

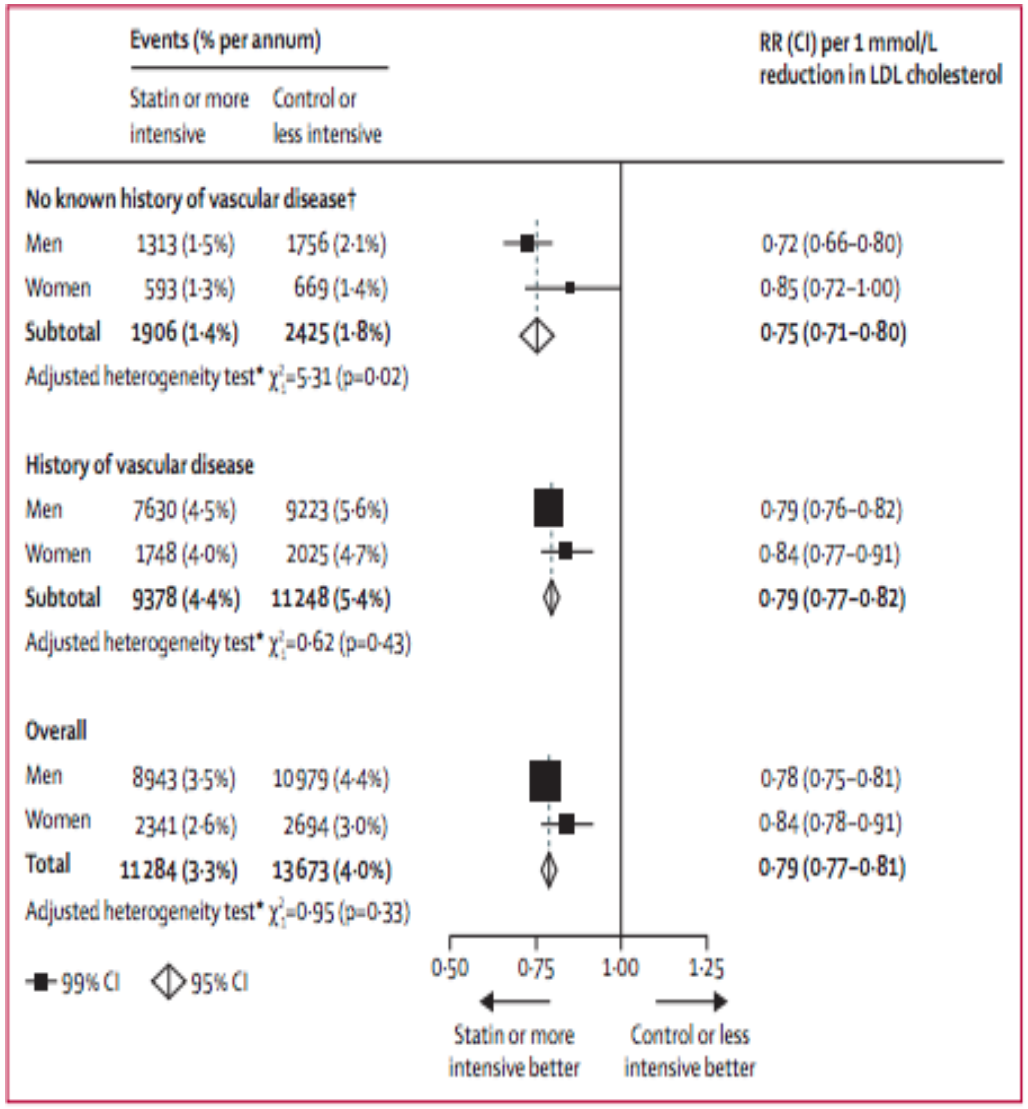
The importance of the target (Lowest is the Best)

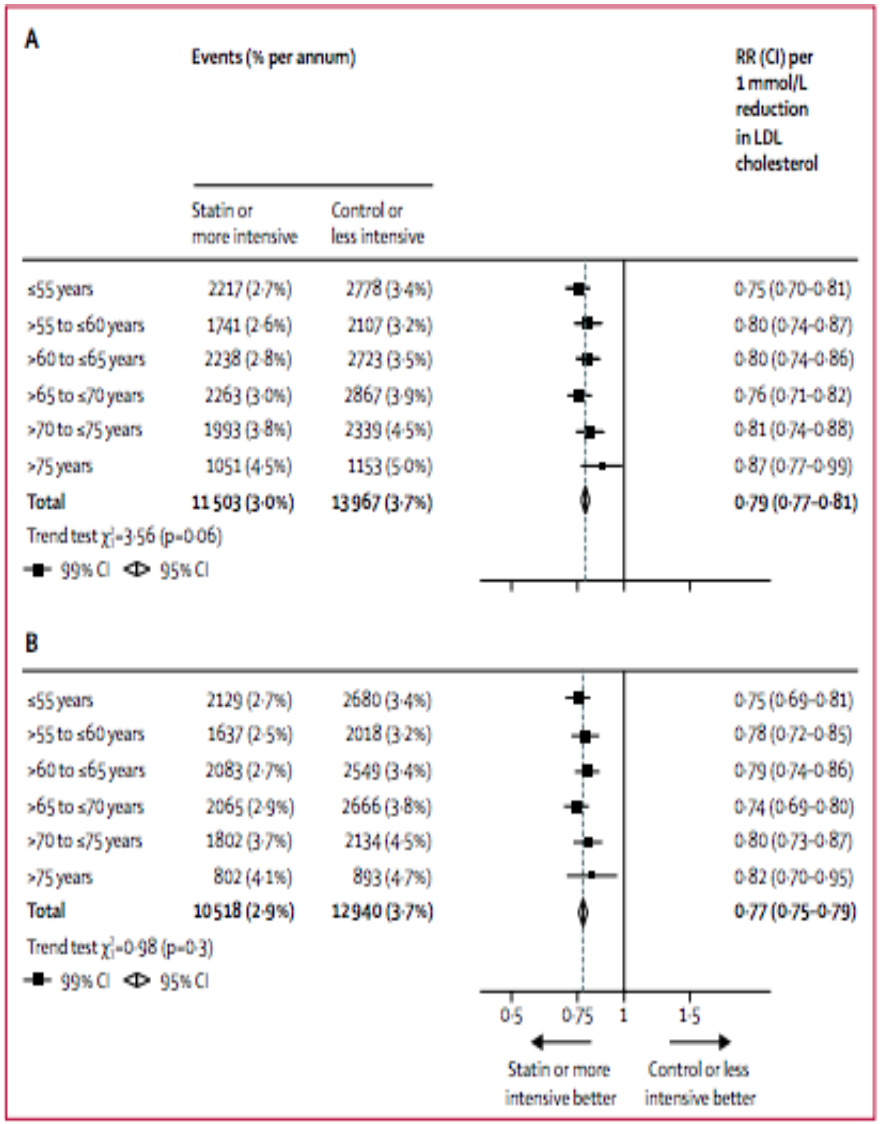
- Mendelian randomisation studies look at people who have lower LDL-C levels due to naturally occurring genetic variations
  - These studies show a continuous, linear relationship between levels of LDL-C and the risk of CHD[1,2]
- Prospective cohort studies and randomized controlled trials also show this linear relationship[1]
  - The linear relationship is steepest for Mendelian randomization studies because the beneficial effects of lower LDL-C levels are cumulative over a lifetime



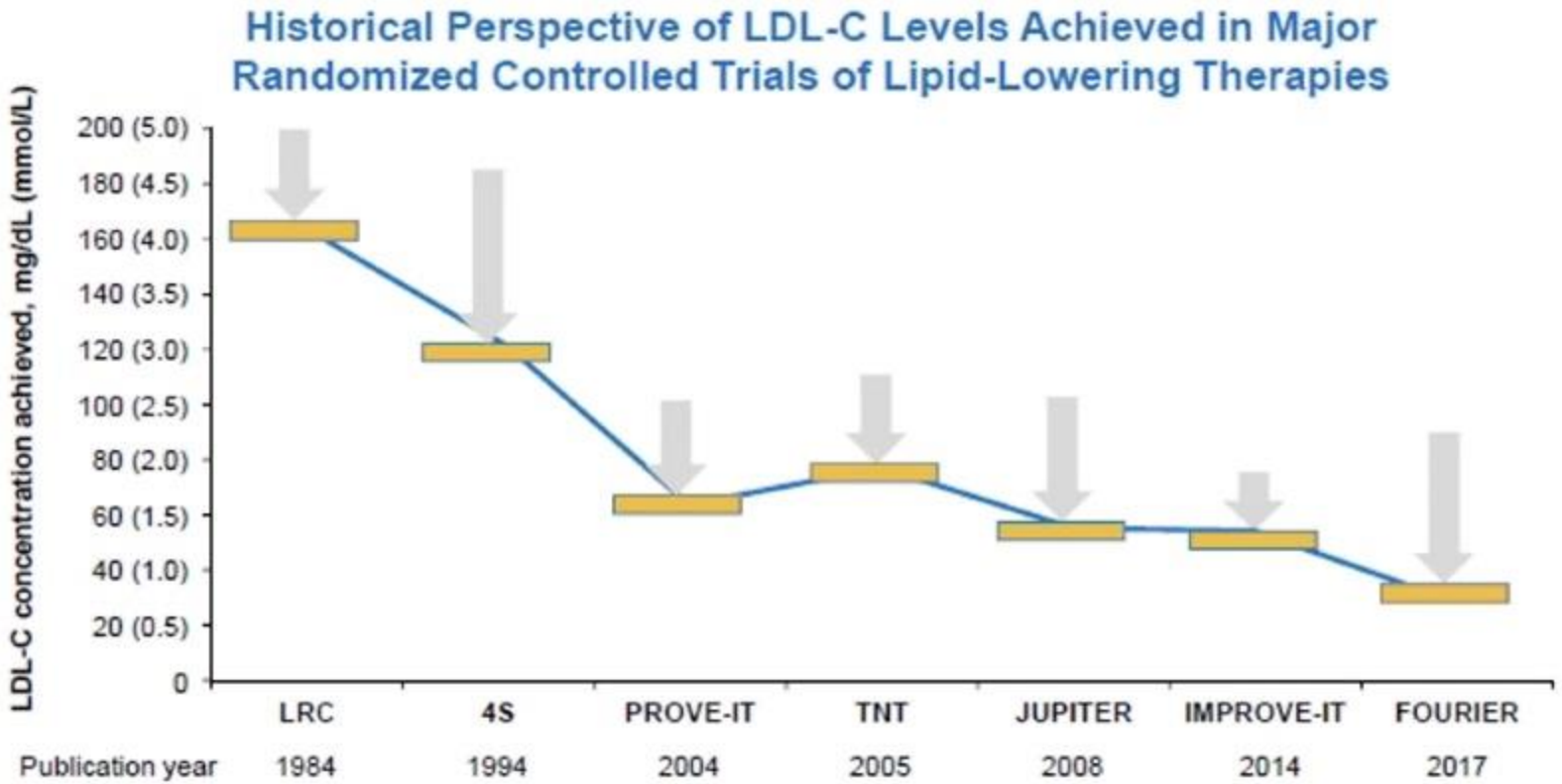
Ference BA et al. Eur Heart J. 2017; 38(32): 2459–2472.

The importance of the target (Lowest is the Best)

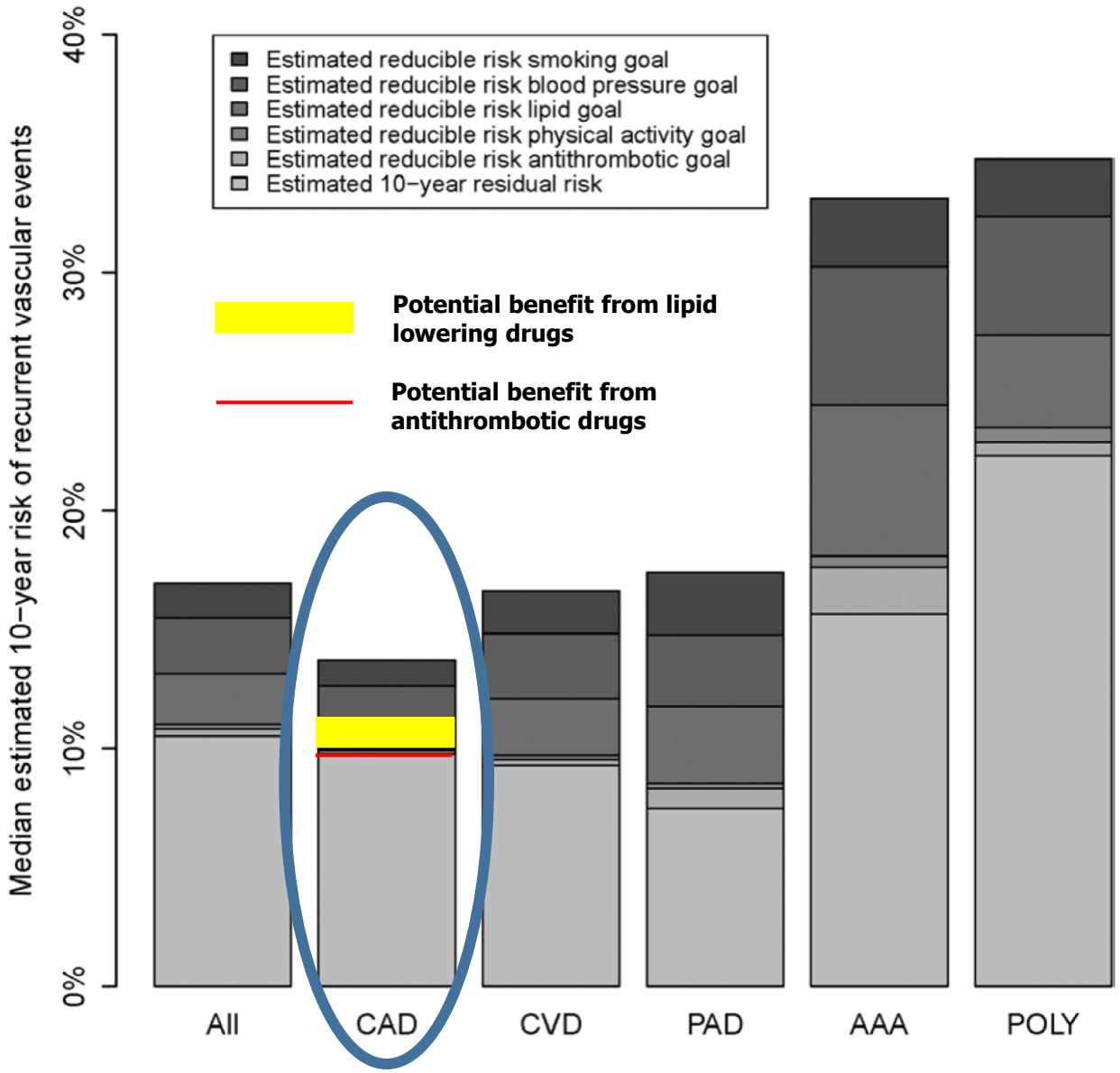




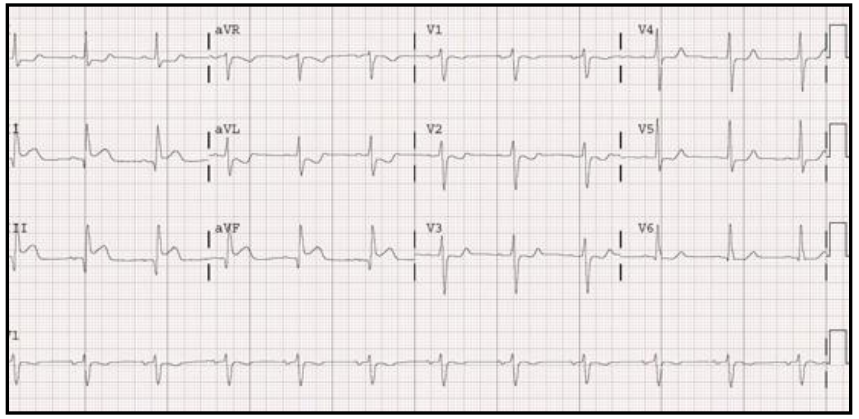
Evoluzione delle terapie ipolipidemizzanti nel corso degli anni per raggiungere livelli di C-LDL più bassi

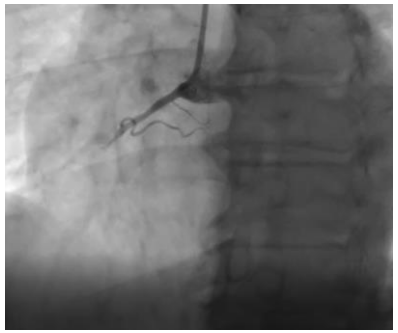


- Masana L, et al. J Clin Lipidol. 2018;12(2):292-299.e3.
- Braunwald E Featuring: Eugene Braunwald Eur Cardiol. 2019 Jul 11;14(2):130-133. doi: 10.15420/ecr.2019.14.2.CM1. eCollection 2019 Jul.



Estimated reduction in the 10-year risk





Aspirin 100 + Ticagrelor 90 x2 + Perindopril 10 + Atorvastatin 40 + Ezetimibe 10 + Physio-guided complete revasc

Beyond the acute event

Residual Inflammatory Risk

Residual Thrombotic Risk

Residual Metabolic (lipid) Risk

Lipid lowering agents (achieving the target) are the best available weapons to minimize residual risk

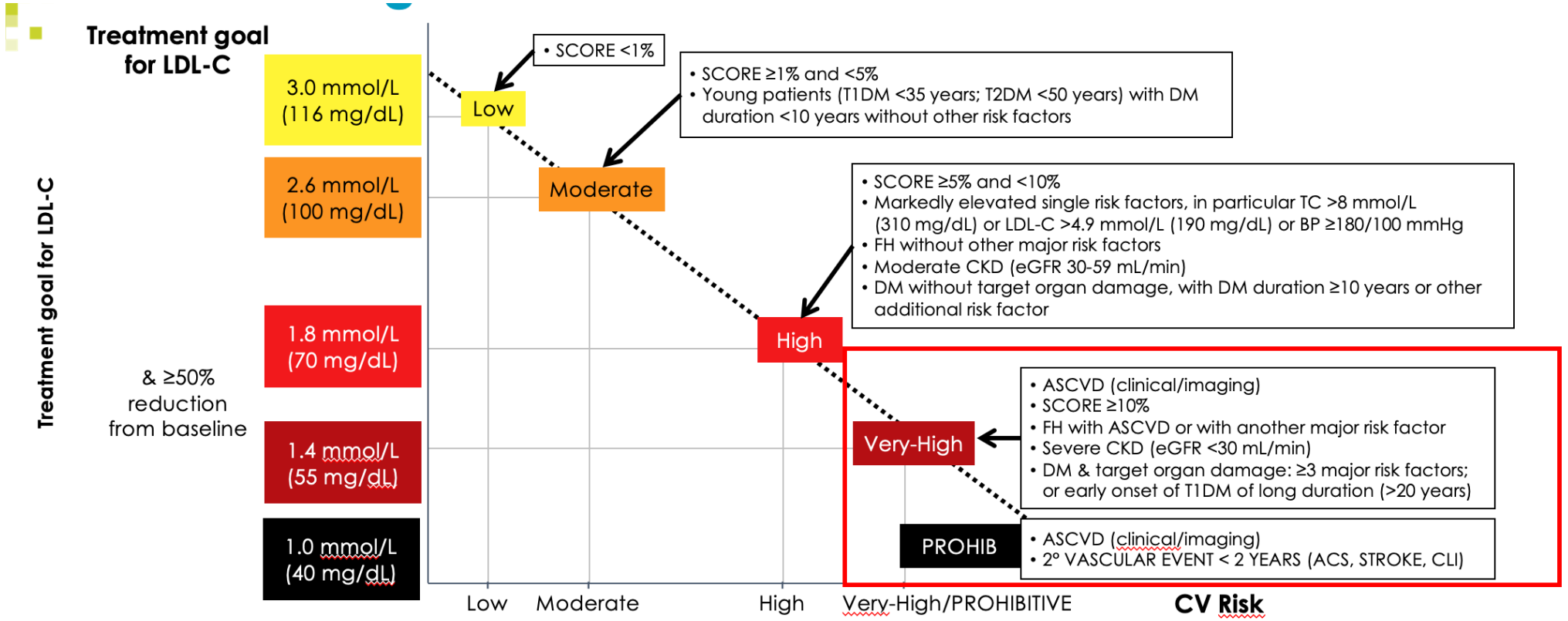
Our background

Atherosclerotic cardiovascular disease

Very-high-risk	People with any of the following: Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound. DM with target organ damage,[a] or at least three major risk factors, or early onset of T1DM of long duration (>20 years). Severe CKD (eGFR <30 mL/min/1.73 m^2). A calculated SCORE ≥10% for 10-year risk of fatal CVD. FH with ASCVD or with another major risk factor.
High-risk	People with: Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP ≥180/110 mmHg. Patients with FH without other major risk factors. Patients with DM without target organ damage,[a] with DM duration ≥10 years or another additional risk factor. Moderate CKD (eGFR 30–59 mL/min/1.73 m^2). A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1 % and <5% for 10-year risk of fatal CVD.
Low-risk	Calculated SCORE <1% for 10-year risk of fatal CVD.

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

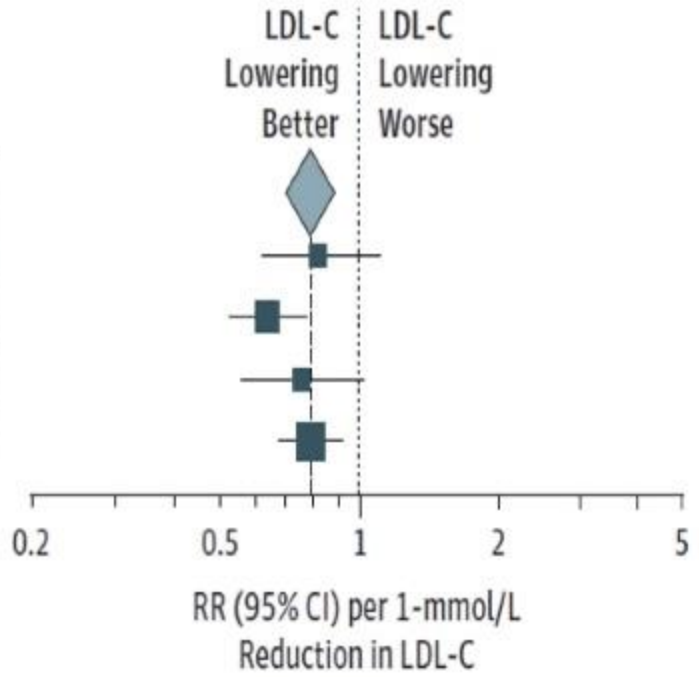
The updated ESC/EAS Guidelines recommend an LDL-C reduction of ≥50% and LDL-C goals of <70 and <55 mg/dL in high- and very high-risk patients, respectively



MODIFICATO *from: Mach F, et al. Eur Heart J 2019. doi:10.1093/eurheartj/ehz455.*

Raggiungere livelli di C-LDL pari a 0.5 mmol/L o 20 mg/dL determina una ulteriore riduzione del rischio cardiovascolare

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)



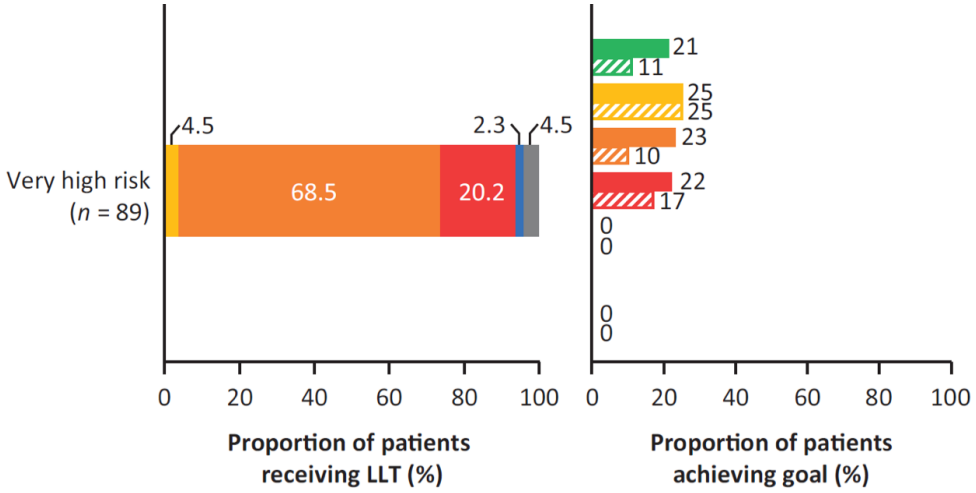
Consistent clinical benefit from further LDL-C lowering in patient populations starting as low as a median of 1.6 mmol/L (63mg/dL) and achieving levels as low as a median of 0.5 mmol/L (21 mg

- Sabatine MS, et al. JAMA Cardiol. 2018;3(9):823-828.

QUANTO

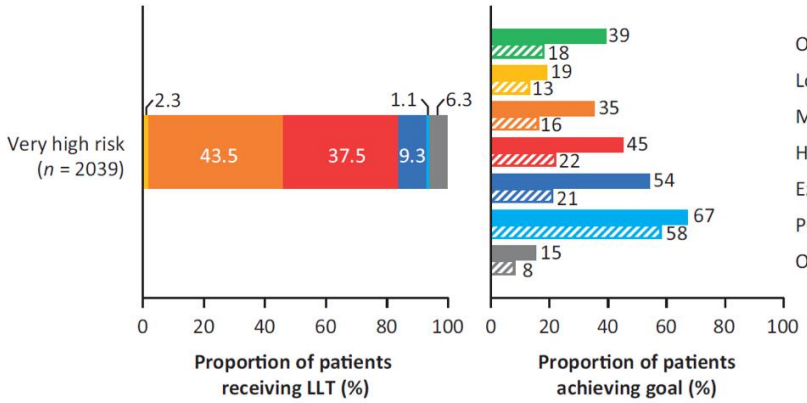
Patients at target across the world

Primary prevention



Overall (*n* = 89)
Low-intensity statin monotherapy (*n* = 4)
Moderate-intensity statin monotherapy (*n* = 61)
High-intensity statin monotherapy (*n* = 18)
Ezetimibe combination (*n* = 2)
PCSK9i combination (*n* = 0)
Other LLT (*n* = 4)

Secondary prevention



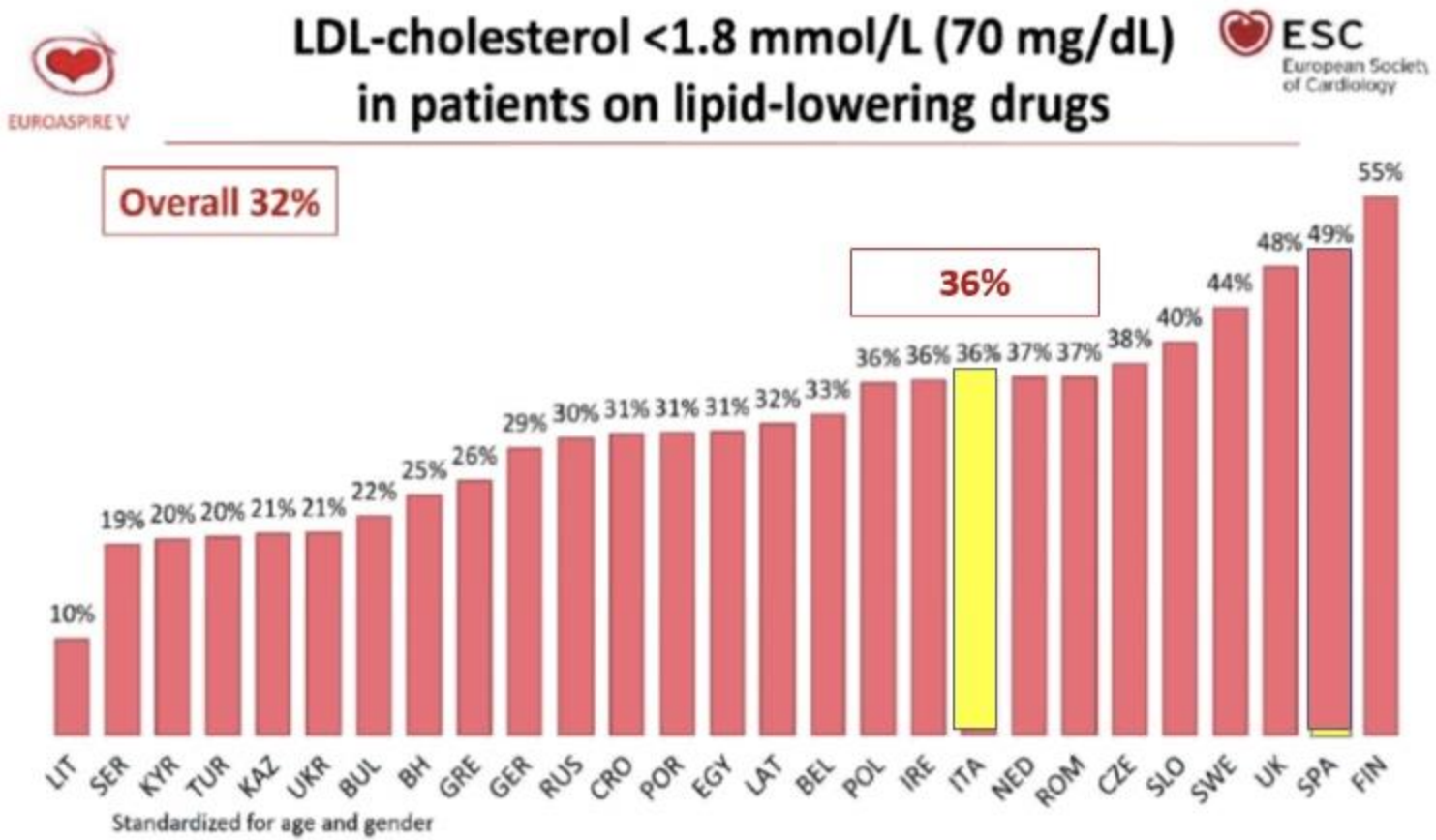
Overall (*n* = 2039)
Low-intensity statin monotherapy (*n* = 47)
Moderate-intensity statin monotherapy (*n* = 887)
High-intensity statin monotherapy (*n* = 764)
Ezetimibe combination (*n* = 189)
PCSK9i combination (*n* = 24)
Other LLT (*n* = 128)

2016 2019
Overall
Low-intensity statin monotherapy
Moderate-intensity statin monotherapy
High-intensity statin monotherapy
Ezetimibe combination
PCSK9i combination
Other LLT

2016/2019 risk-based LDL-C targets:
Low risk: 2016/2019, <3.0 mmol/L
Moderate risk: 2016, <3.0 mmol/L; 2019, <2.6 mmol/L
High risk: 2016, <2.6 mmol/L; 2019, <1.8 mmol/L
Very high risk: 2016, <1.8 mmol/L; 2019, <1.4 mmol/L

The DA VINCI study EJ CVP 2020

EUROASPIRE V

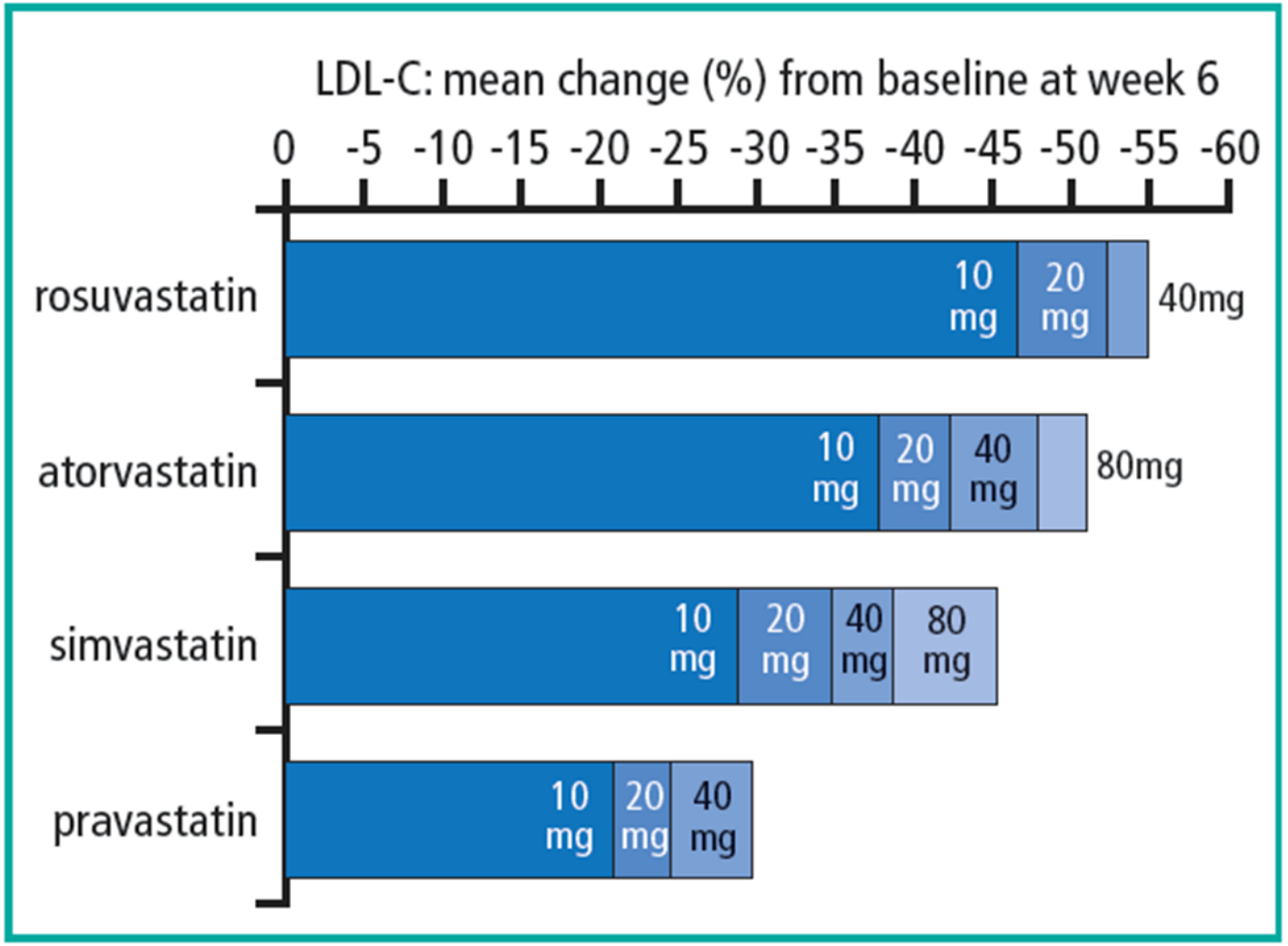


EAS 2018 De Backer; courtesy A. Castro

Why ?!?

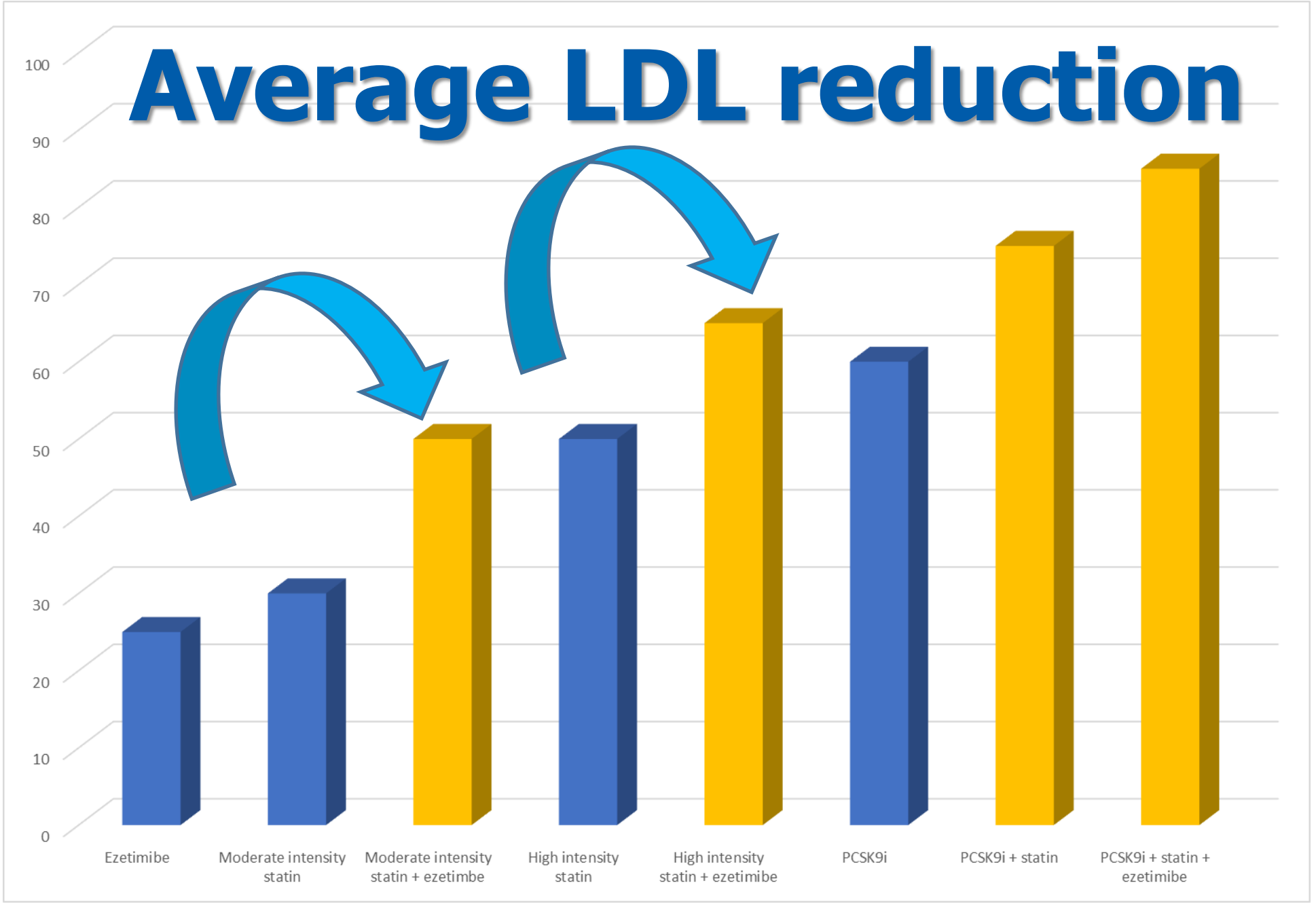
- Side effects
- Poor compliance
- Inertia in prescription
- Regulatory restrictions
- Limitations of one-drug strategy

Average LDL reduction



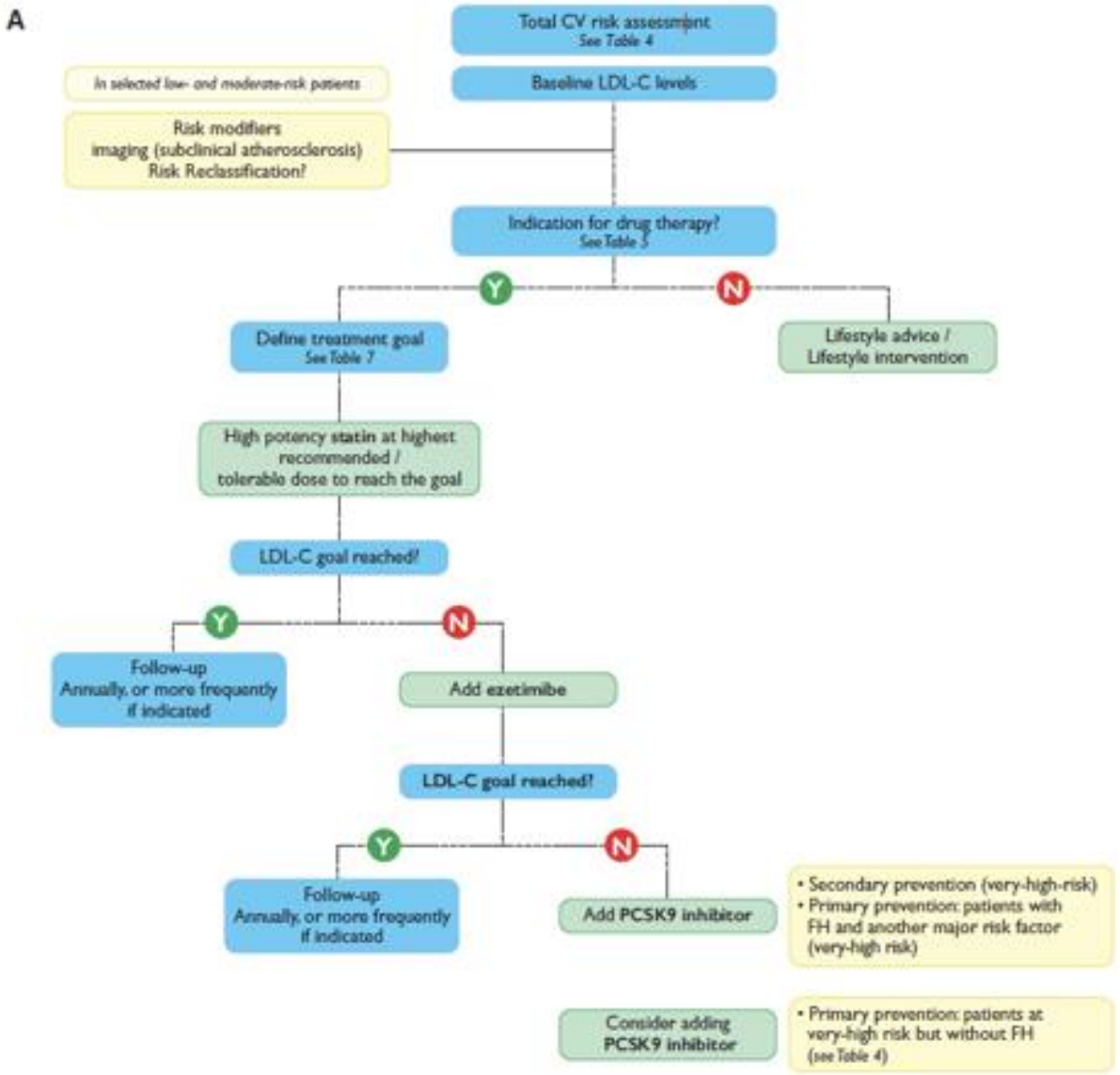
The benefit that we can reach increasing statin dose is limited

Average LDL reduction

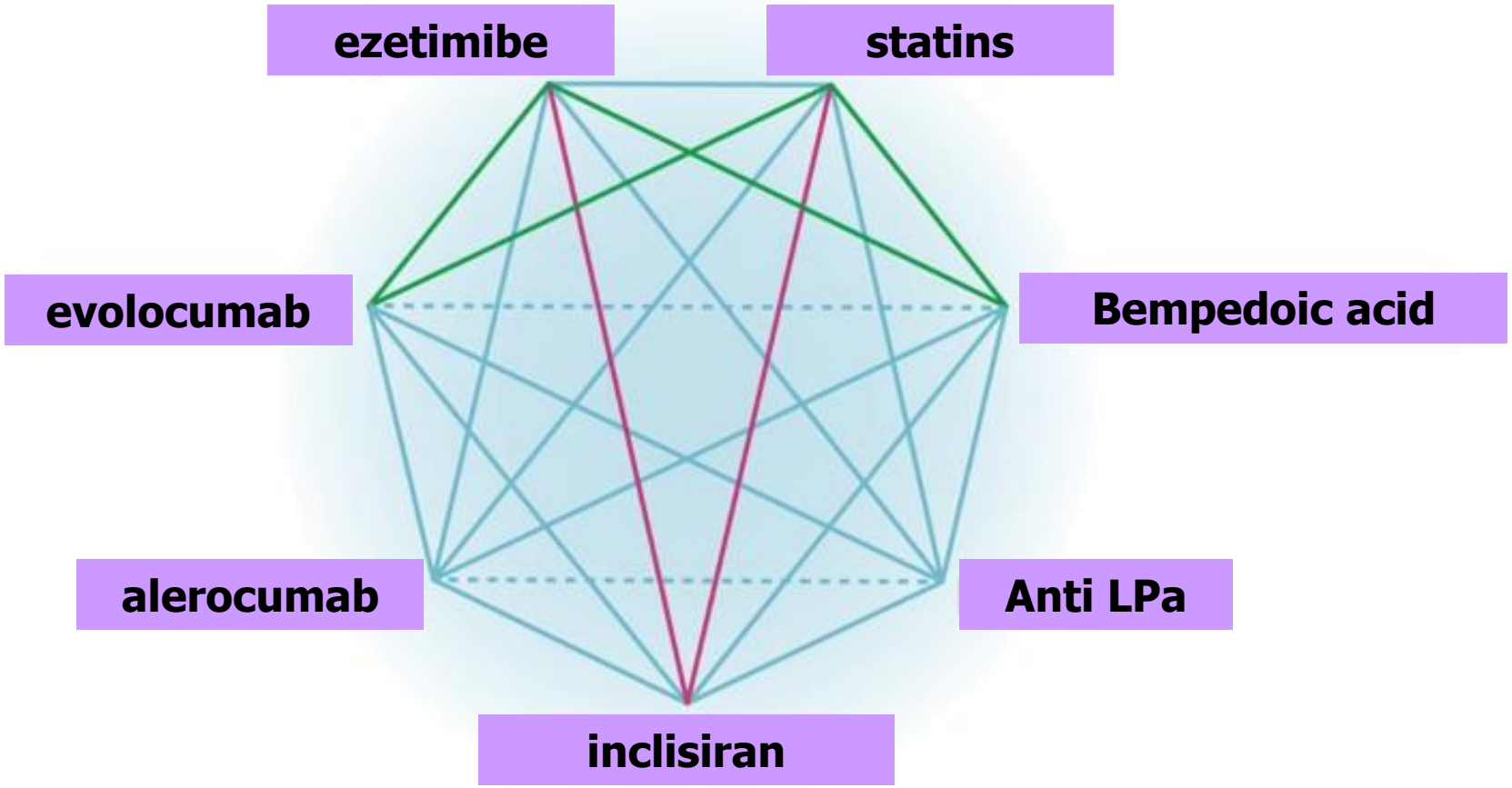


Add-on is the best way to achieve the target

- Pharmacological therapy to lower LDL starts with maximally tolerated statin therapy
- It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the goals for the specific level of risk
- If the goals are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended



Find the tailored combination for your patient



Lipid lowering drugs

Expected clinical benefit of LLT on LDL-C

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%

High intensity (reduction ≥50%)

Atorvastatin 40-80 mg

Rosuvastatin 20-40 mg

Moderate intensity (reduction 30-50%)

Atorvastatin 10-20 mg

Rosuvastatin 5-10 mg

Simvastatin 20-40 mg

From Mach F et al. Eur Heart J 2020;41:111-88

Conclusions

- **Available evidence strongly supports the LDL reduction below 55 mg/dl**
- **A one-drug strategy permits to achieve the target in few patients (around 40%)**
- **The add-on strategy is the best choice to achieve the target**
- **The combination statin + ezetimibe is not enough in many patients**