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EMA

EFMS

"Dyslipidemia Management: strike early, strike strong"

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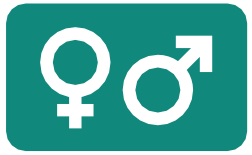
Coronary Heart Disease Risk factors:

NONMODIFIABLE

- Aging

- Gender



- Family History

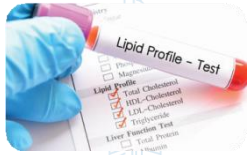
MODIFIABLE

- Atherogenic Diet

- Elevated Blood Pressure

- Diabetes

- Hyperlipidemia



- Obesity

- Physical Inactivity

- Smoking

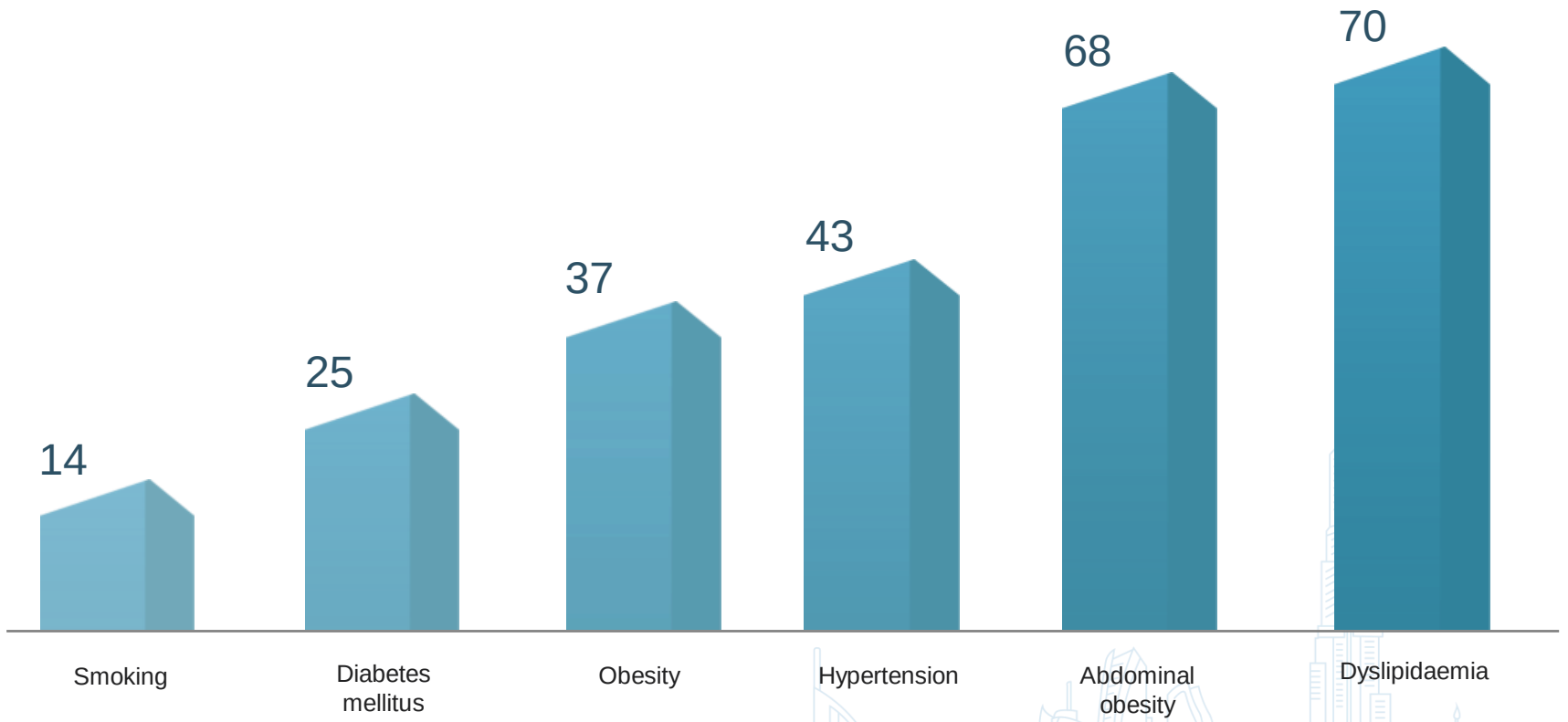
1. NCEP ATP III Expert Panel. Circulation. 2002;106:3143–3421.

Prevalence of cardiovascular risk factors in patients attending general practice clinics in Africa and the Middle East (AFME) cardiovascular epidemiological (ACE) study

ACE Study
AFME CARDIOVASCULAR EPIDEMIOLOGICAL STUDY

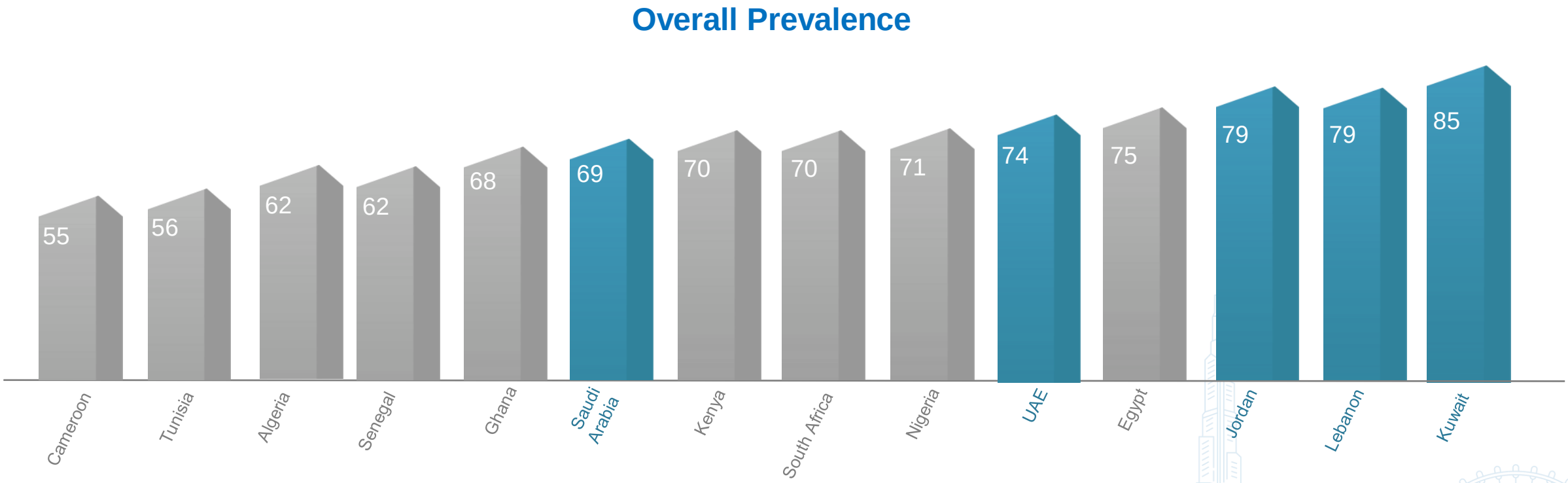
1- Alsheikh-Ali, A.A., et al., (2014). Cardiovascular risk factor burden in Africa and the Middle East: the Africa Middle East Cardiovascular Epidemiological (ACE) study. PLoS One; 9(8), pp. e102830.

Prevalence (%) – Overall results



1- Alsheikh-Ali, A.A., et al., (2014). Cardiovascular risk factor burden in Africa and the Middle East: the Africa Middle East Cardiovascular Epidemiological (ACE) study. PLoS One; 9(8), pp. e102830.

70% Overall Prevalence of Dyslipidaemia



1- Alsheikh-Ali, A.A., et al., (2014). Cardiovascular risk factor burden in Africa and the Middle East: the Africa Middle East Cardiovascular Epidemiological (ACE) study. PLoS One; 9(8), pp. e102830.

Note: This study was not designed to evaluate the CV risk factors of one country only.

Dyslipidemia *In UAE*

Dyslipidaemia prevalence and associated risk factors in the United Arab Emirates: a population-based study

BMJ Open

The overall dyslipidaemia prevalence was **72.5%**, with 42.8% of the participants showing high total cholesterol (TC) level, 29% showing high triglyceride (TG) level, 42.5% showing low (HDL-C) level, and **72.3%** showing high cholesterol ratio.

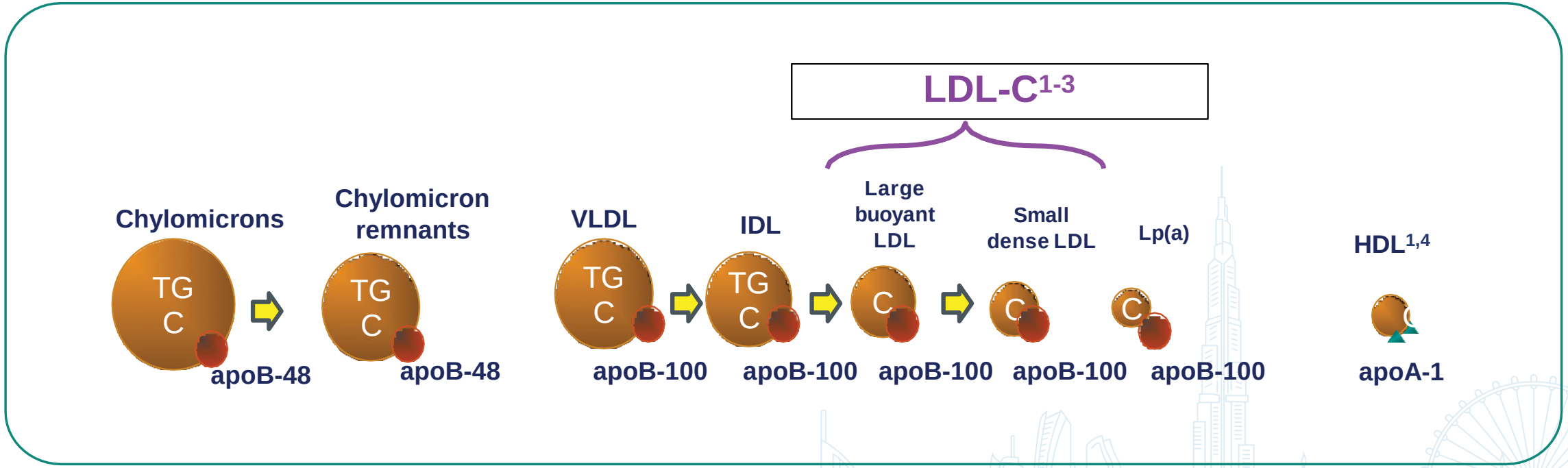
Results of the Dyslipidemia International Study (DYSIS)- Middle East: Clinical Perspective on the Prevalence and Characteristics of Lipid Abnormalities in the Setting of Chronic Statin Treatment

Results: The majority of patients (82.6%) were classified as being at very high risk of cardiovascular events, and 61.8% of all patients did not attain LDL-C target levels. Low high-density lipoprotein cholesterol levels and elevated triglyceride levels were noted in 55.5% and 48.5% of patients, respectively. Multivariate logistical regression modeling indicated that factors independently associated with LDL-C levels not being at goal were lifestyle choices, diabetes mellitus, ischemic heart disease, and blood pressure ≥ 140/90 mmHg.

1. Al Sifri SN, Almahmeed W, Azar S, Okkeh O, Bramlage P, et al. (2014) Results of the Dyslipidemia International Study (DYSIS)-Middle East: Clinical Perspective on the Prevalence and Characteristics of Lipid Abnormalities in the Setting of Chronic Statin Treatment. PLoS ONE 9(1): e84350. doi: 10.1371/journal.pone.00843506 cardiologists & 6 Endocrinologists from the UAE; December 2022. 8. Abdelgadir E. et al. Oman Medical Journal [2019], Vol. 34, No. 4: 290-296
2. Mahmoud I, Sulaiman N. BMJ Open 2019;9:e031969. doi:10.1136/bmjopen-2019-031969

LDL-C Is a Risk Factor for CHD

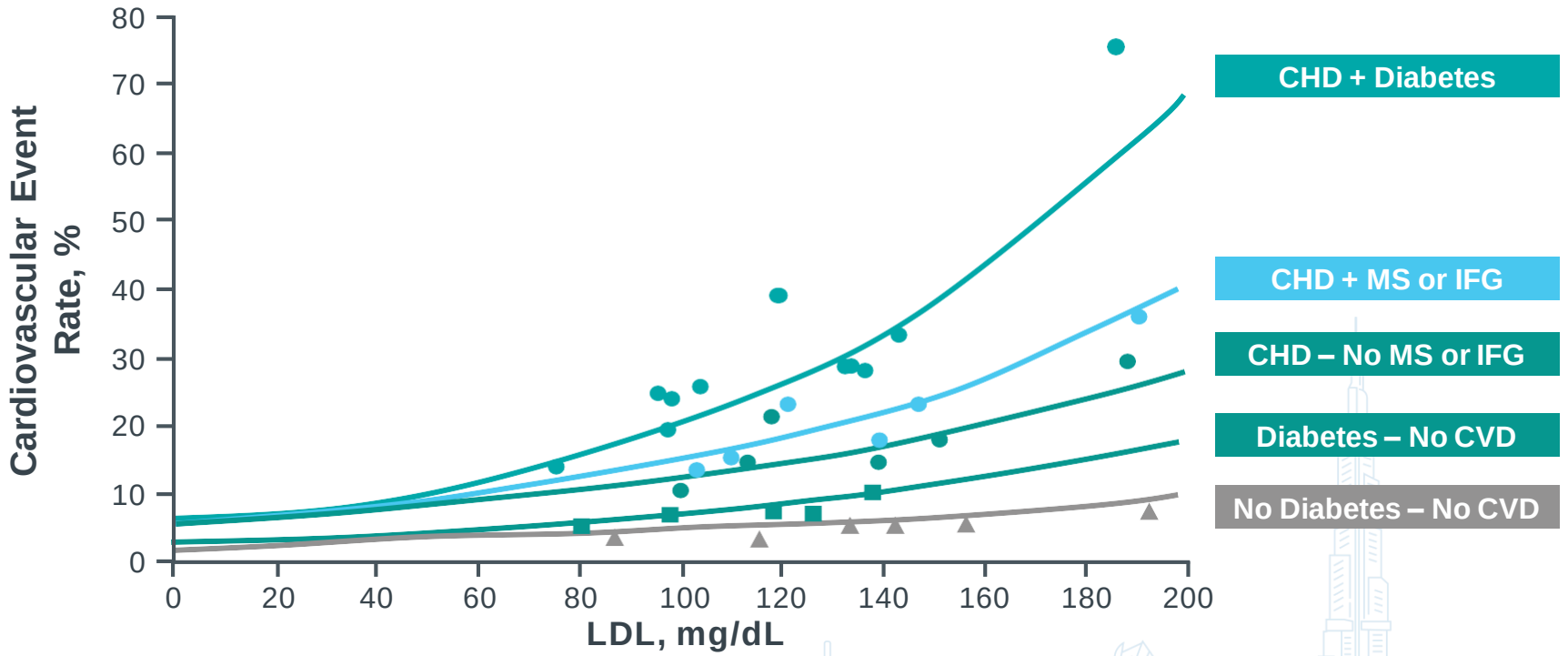
Multiple lines of evidence (animal studies, laboratory investigations, epidemiology, genetic forms of hypercholesterolemia, and controlled trials) indicate a strong causal association between elevated LDL-C and CHD[1]



CHD= coronary heart disease; TG = triglyceride; Apo = apolipoprotein; VLDL = very low-density lipoprotein; IDL = intermediate-density lipoprotein; Lp(a) = lipoprotein (a); C = cholesterol.

1. NCEP ATP III Expert Panel. Circulation. 2002;106:3143–3421. 2. Rana JS et al. Curr Opin Cardiol. 2010;25:622–626. 3. Chapman MJ et al. Eur Heart J Suppl. 2004;6(suppl A):A43–A48.
4. Barter P. In: Ballantyne CM. Clinical Lipidology: A Companion to Braunwald's Heart Disease. Saunders, an imprint of Elsevier Inc; 2009:387–395. 5. Walldius G et al. J Intern Med. 2004;255:188–205.

Risk Pattern for Subsequent CV Events Over a Range of LDL-C values [7]

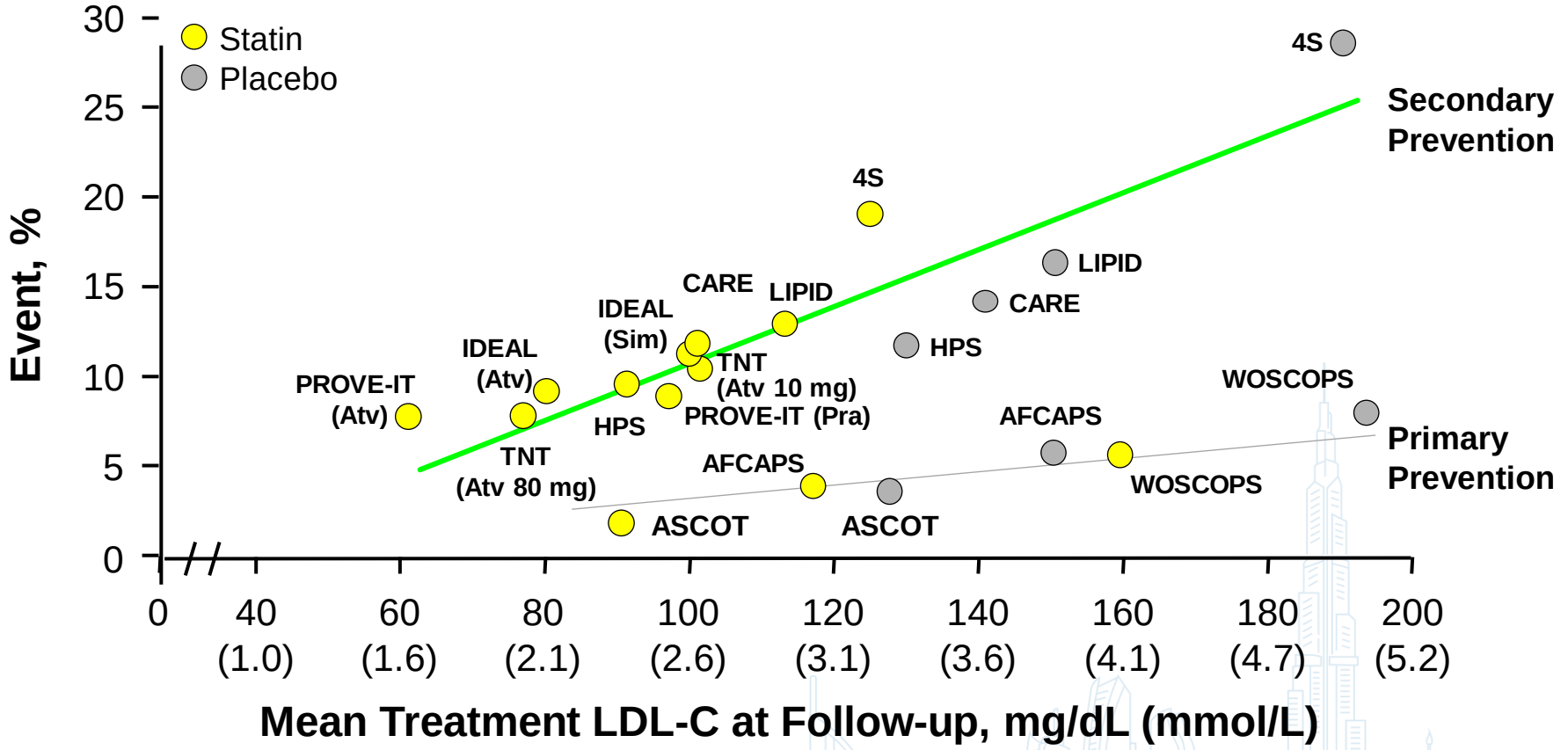


Adapted with permission from Robinson JG et al.1

CV = cardiovascular; CHD = coronary heart disease; MS = metabolic syndrome; IFG = impaired fasting glucose; CVD = CV disease.

7. Robinson JG et al. Am J Cardiol. 2006;98:1405–1408.

Relationship Between LDL-C and CV Incidence



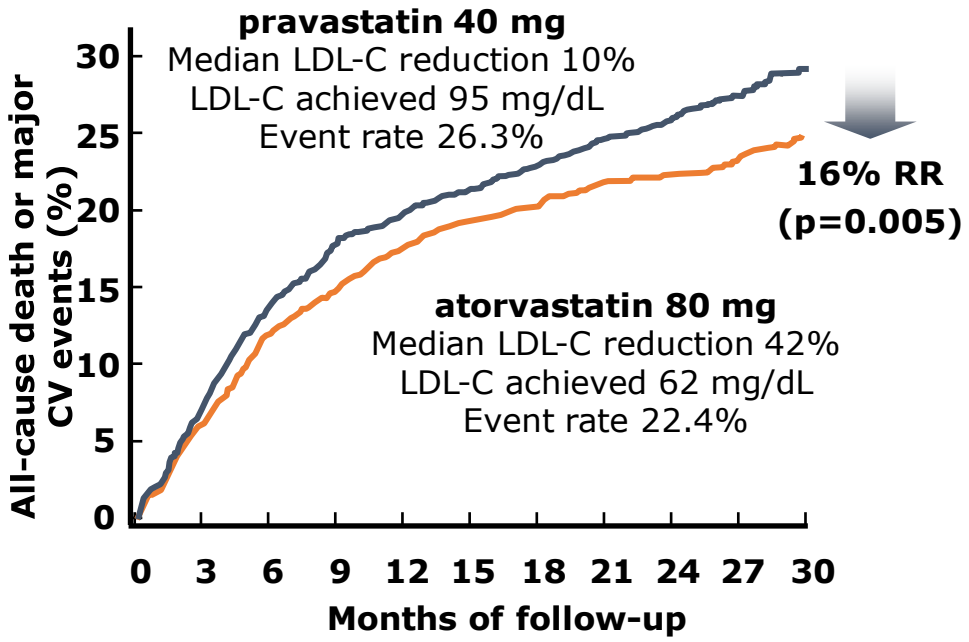
Atv = atorvastatin; Pra = pravastatin; Sim = simvastatin; PROVE-IT = Pravastatin or AtorVastatin Evaluation and Infection Therapy; IDEAL = Incremental Decrease in Endpoints through Aggressive Lipid Lowering; ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial; AFCAPS = Air Force Coronary Atherosclerosis Prevention Study; WOSCOPS = West of Scotland Coronary Prevention Study

Adapted from Rosenson RS. Expert Opin Emerg Drugs. 2004;9:269–279; LaRosa JC, et al. N Engl J Med. 2005;352:1425–1435; Pedersen TR, et al. JAMA. 2005;294:2437–2445.

Intensive LDL-C Lowering Improves Patient Outcomes

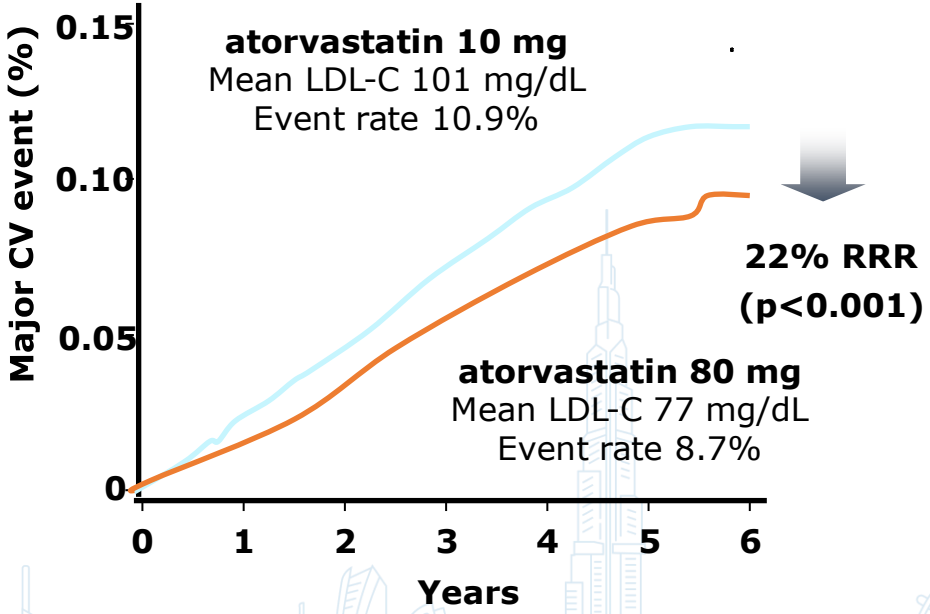
PROVE-IT[1]

All-cause death or major cardiovascular events in all randomised subjects



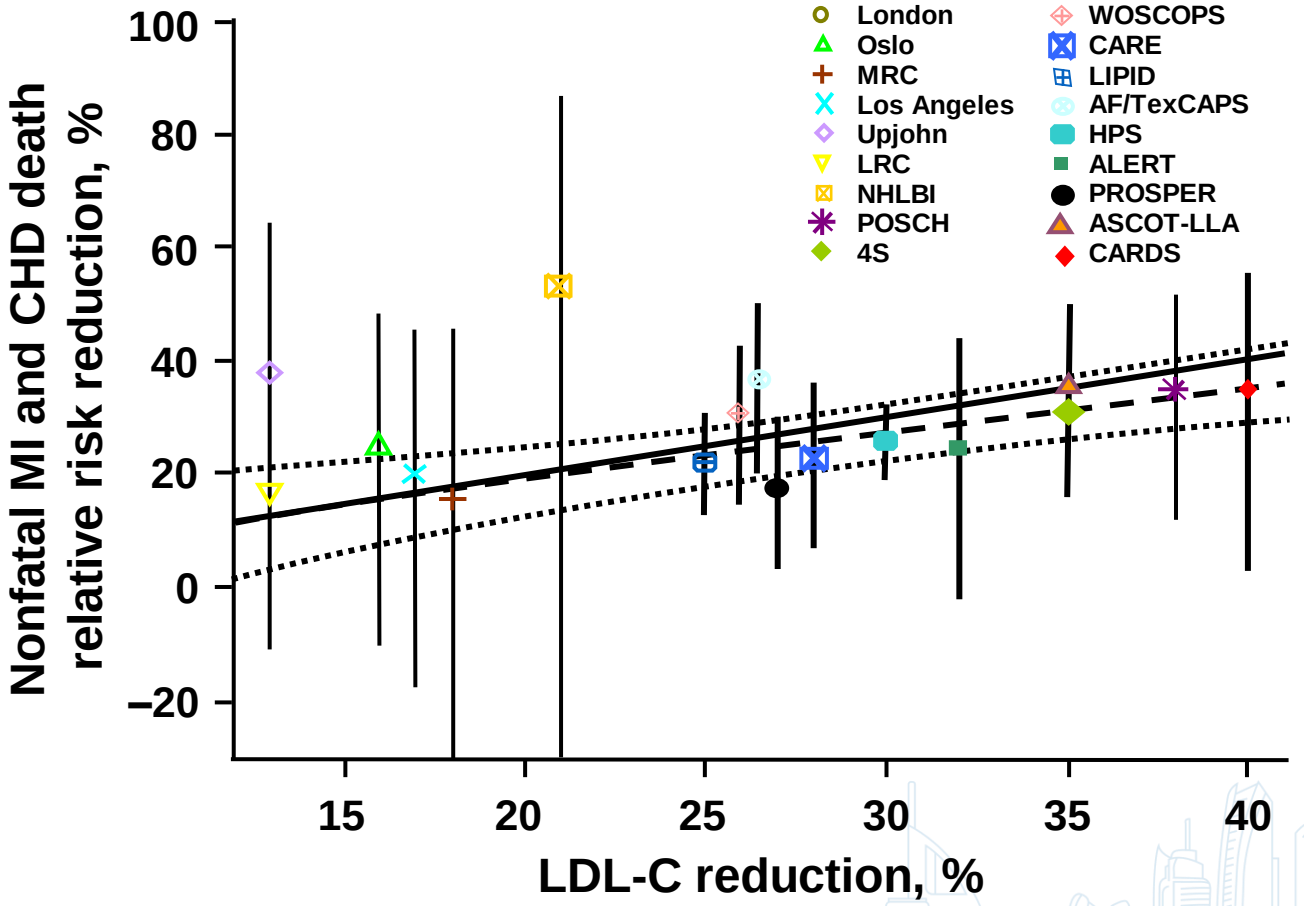
TNT[2]

Major cardiovascular events in all randomised subjects



. Cannon C et al. N Engl J Med 2004;350:1495-1504
2. LaRosa JC et al. N Engl J Med 2005;352:1425-1435

Lowering LDL-C by Interventions Other Than Statins Also Reduced the Risk for CHD [1]



Interventions:

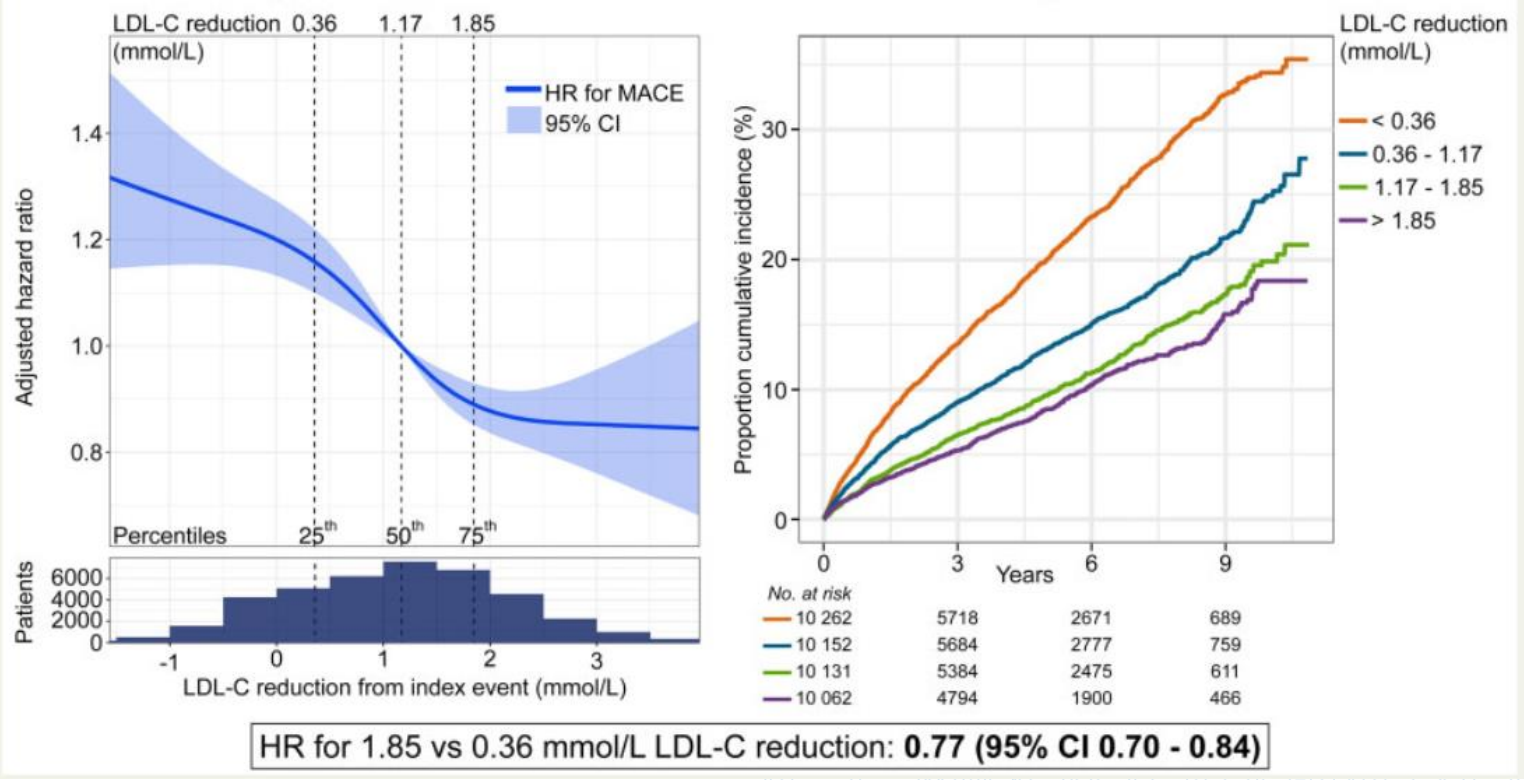
- Statins
- Diet
- Surgery
- Bile acid sequestrants

MI = myocardial infarction.

1. Adapted with permission from Robinson JG et al. J Am Coll Cardiol. 2005;46:1855–1862

Lower is better , Earlier and larger % reduction is better .

40 607 patients with acute MI from SWEDEHEART registry: Larger LDL-C reduction (1.85 mmol/L, 75th percentile) ***at 6 weeks***, compared with a smaller reduction (0.36 mmol/L, 25th percentile) had lower hazard ratios (HR) for all outcomes 0.77 (0.70–0.84); all-cause mortality 0.71 (0.63–0.80); CV mortality 0.68 (0.57–0.8



Schubert ***European Heart Journal*** (2021) 42, 243–252

Statin Therapy

High-Intensity Statin Therapy	Moderate-Intensity Stain Therapy	Low-Intensity Statin Therapy
LDL–C ↓ ≥50%	**LDL–C ↓ 30% to <50%**	**LDL–C ↓ <30%**
Atorvastatin (40†)–80 mg **Rosuvastatin 20** *(40)* **mg**	**Atorvastatin 10** ***(20) mg*** **Rosuvastatin (***5***) *10 mg*** **Simvastatin 20–40 mg‡** **Pravastatin 40** ***(80) mg*** **Lovastatin 40 mg** *Fluvastatin XL 80 mg* **Fluvastatin 40 mg bid** *Pitavastatin 2–4 mg*	*Simvastatin 10 mg* **Pravastatin 10–20 mg** **Lovastatin 20 mg** *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

Lifestyle modification remains a critical component of ASCVD risk reduction, both prior to and in concert with the use of cholesterol lowering drug therapies.

Statins/doses that were not tested in randomized controlled trials (RCTs) reviewed are listed in *italics*
†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL
‡Initiation of or titration to simvastatin 80 mg not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.

- Stone NJ, et al. *J Am Coll Cardiol*. 2013: doi:10.1016/j.jacc.2013.11.002. Available at: http://content.onlinejacc.org/article.aspx?articleid=1770217. Accessed November 13, 2013.

Setting the Stage in dyslipidemia management

CV Risk, Target and Pharmacological Approaches to Achieve the goal

ESC European Society of Cardiology
European Heart Journal (2021) **42**, 3227–3337
doi:10.1093/eurheartj/ehab484

ESC GUIDELINES

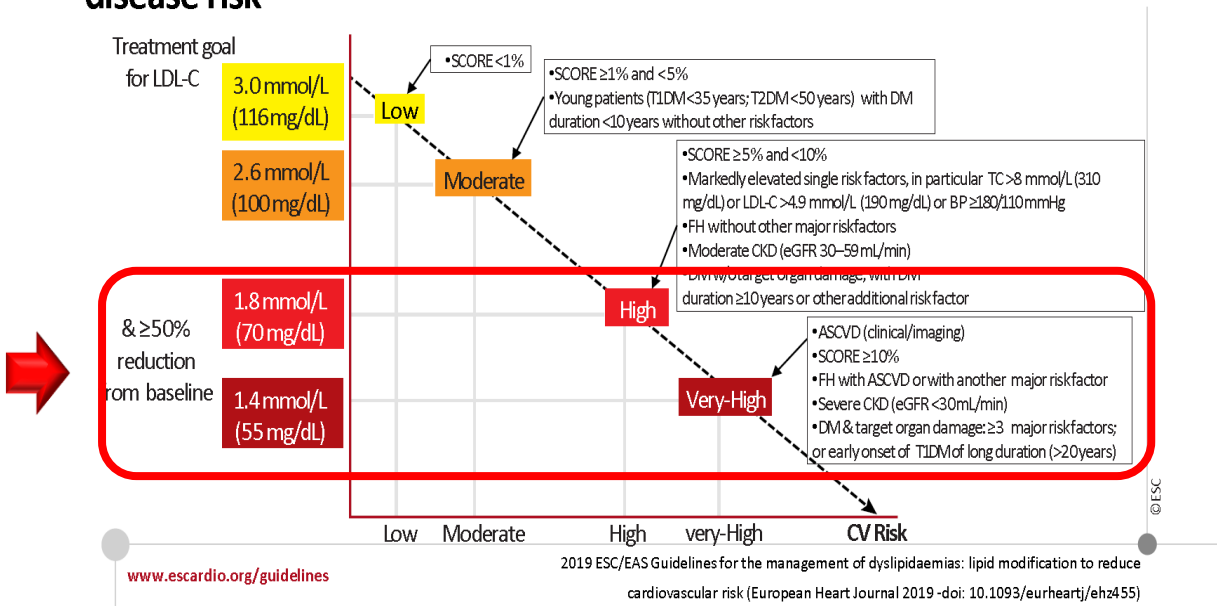
2021 ESC Guidelines on cardiovascular disease prevention in clinical practice

PATIENT CATEGORIES AND CV DISEASE RISK.

Patient category	Subgroups	Risk categories
Patients with type 2 diabetes mellitus		
Patients with type 1 DM above 40 years of age may also be classified according to these criteria	Patients with well controlled short-standing DM (e.g. <10 years), no evidence of TOD and no additional ASCVD risk factors	Moderate-risk
	Patients with DM without ASCVD and/or severe TOD, and not fulfilling the moderate risk criteria.	High-risk
	Patients with DM with established ASCVD and/or severe TOD:[87,93-95] • eGFR <45 mL/min/1.73 m² irrespective of albuminuria • eGFR 45-59 mL/min/1.73 m² and microalbuminuria (ACR 30 -300 mg/g) • Proteinuria (ACR >300 mg/g) • Presence of microvascular disease in at least 3 different sites (e.g. microalbuminuria plus retinopathy plus neuropathy)	Very high-risk

Treatment goals for low-density lipoprotein cholesterol (LDL-C) across categories of total cardiovascular disease risk

EAS ESC European Society of Cardiology



www.escardio.org/guidelines

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

- **Large majority of our patients (T2D) at very high/high risk of CVD**
- **LDL-C Primary lipid goal for CVD management**
- **>50% LDL-C reduction recommended by the ESC guidelines for dyslipidemia (2019) and CVD prevention (2021) recommend :**
  - **Use a hierarchical order: statins, ezetimibe and PCSK9i.**
  - **Use a strategy of stepwise intensification to reach the LDL-c target.**

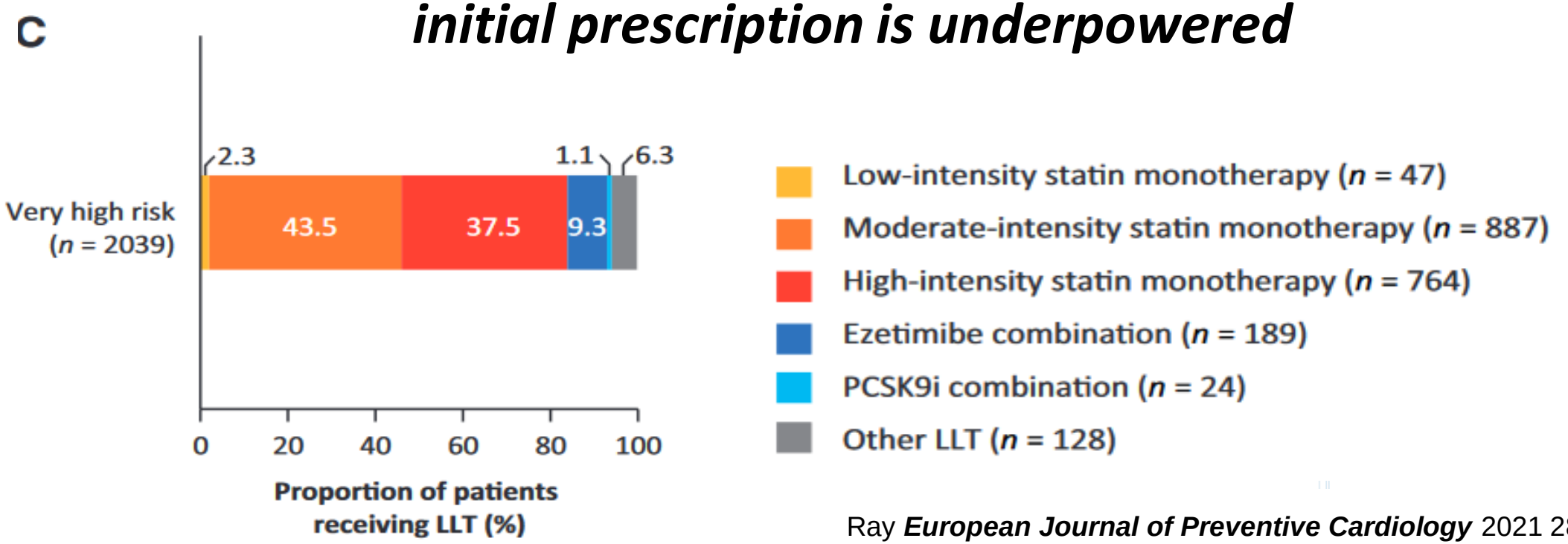
ESC 2021 – Recommendations for pharmacological LDL-C lowering

	Class	Level
It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the LDL-C goals for specific risk group	I	A
If the goals are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended	I	B
For primary prevention patients at very high risk, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor may be considered.	IIb	C
For secondary prevention patients not achieving their goals on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor is recommended.	I	A
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), ezetimibe should be considered	IIa	B

European Heart Journal (2021) 42, 3227-3337 - doi:10.1093/eurheartj/ehab484

Real life with the current strategy:

initial prescription is underpowered



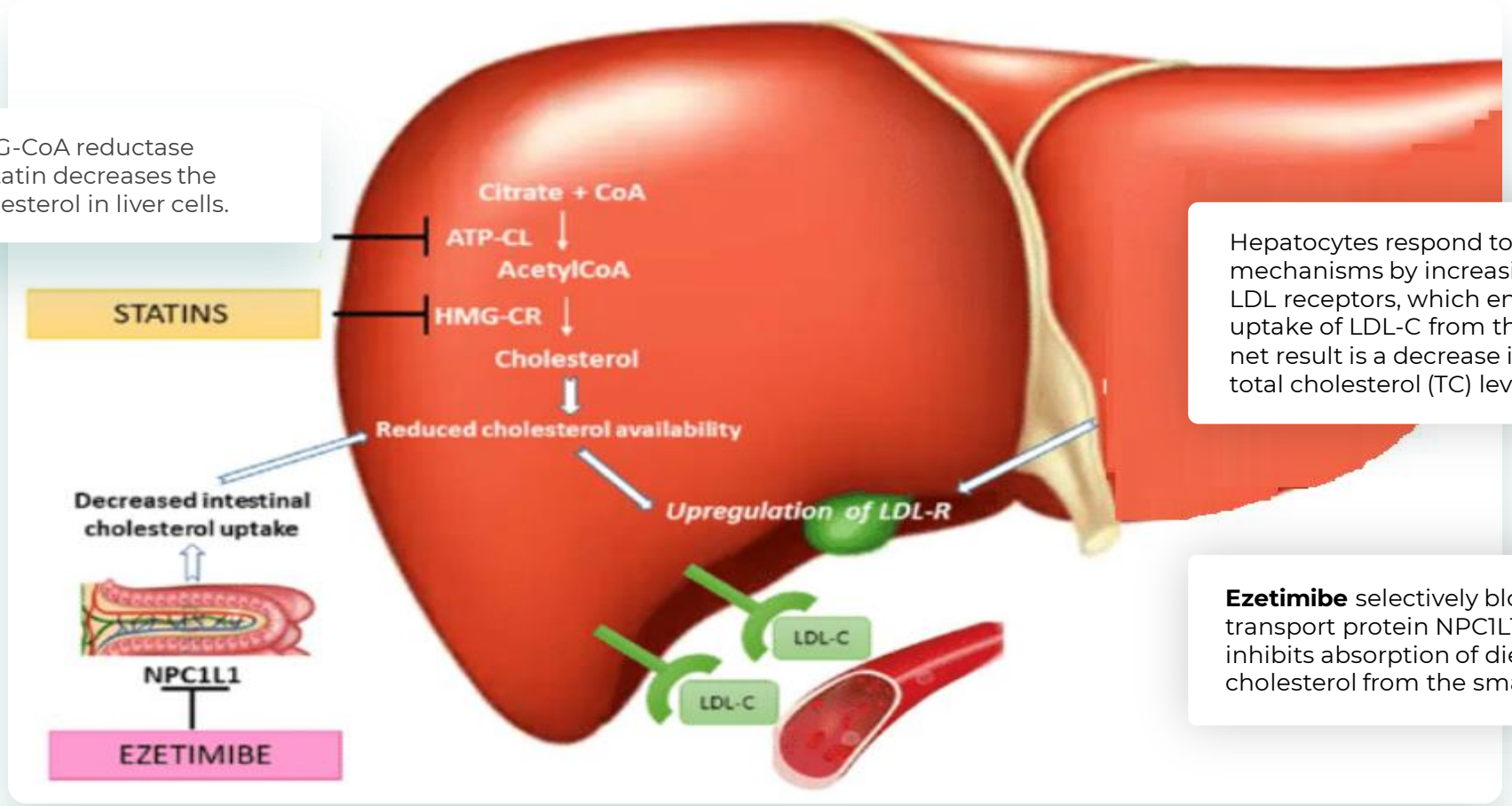
Ray ***European Journal of Preventive Cardiology*** 2021 28, 1279–1289

DA VINCI (***European Observational Study***): subset of patients at very high risk:

- 18% of the patients are at LDL-c target
- ***Statins: 37.5% at high intensity***
- Combination statin ezetimibe: 9.3%
- Combination statin PCSK9i: 1%

Complementary mechanisms of action of **statins and ezetimibe** have an additive **cholesterol-lowering effect**

By blocking HMG-CoA reductase activity, rosuvastatin decreases the synthesis of cholesterol in liver cells.



Hepatocytes respond to both of these mechanisms by increasing synthesis of LDL receptors, which enhances the re-uptake of LDL-C from the circulation. The net result is a decrease in serum LDL-C and total cholesterol (TC) levels.

Ezetimibe selectively blocks the cholesterol transport protein NPC1L1 in the gut and inhibits absorption of dietary and biliary cholesterol from the small intestine.

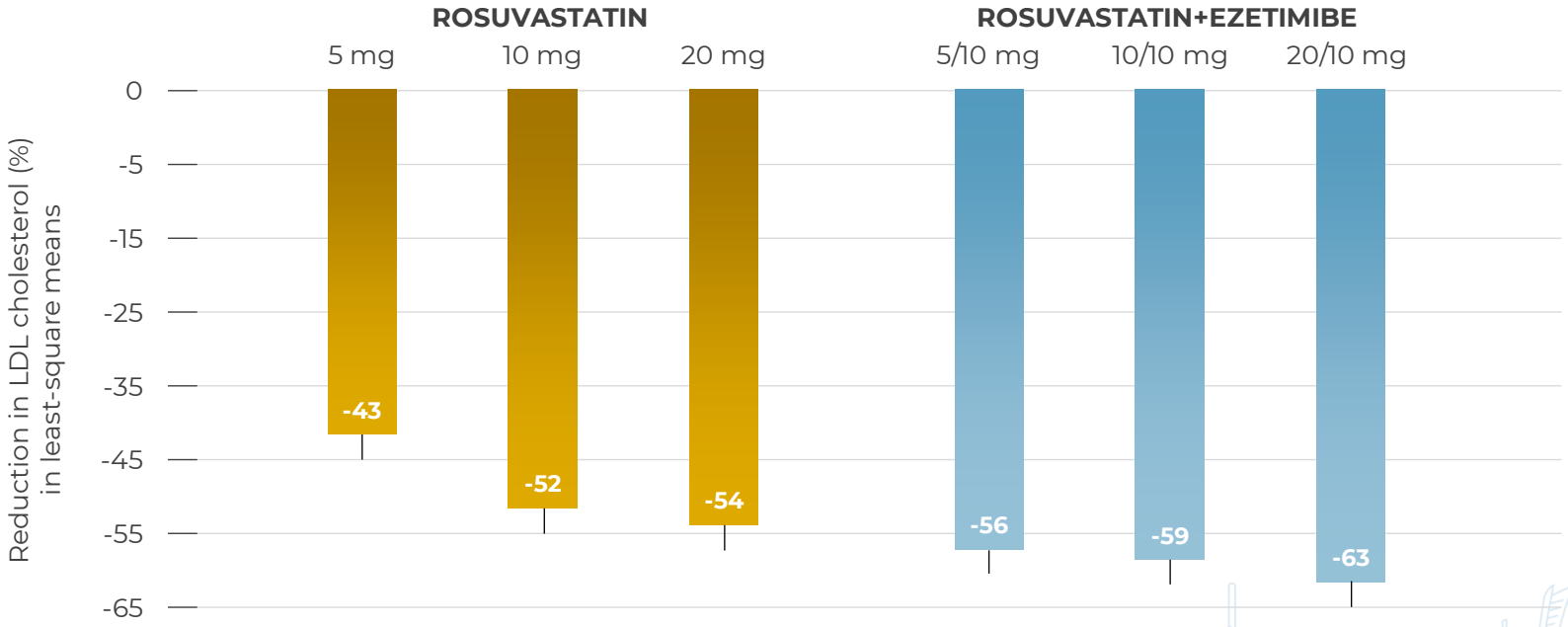
CoA, coenzyme A; ATP-CL, ATP citrate lyase; HMG-CR, HMG-CoA reductase; NPC1L1, Niemann-Pick C1-Like 1; LDL-C, low-density lipoprotein cholesterol; LDL-R, LDL receptors.

1. Lamb YN. *Am J Cardiovasc Drugs*. 2020;20(4):381-392.
2. Maddalena Rossi et al, Am J Cardiovasc Drugs . 2022 Mar;22(2):141-155.

Rosu/Eze combination provides superior efficacy to Rosu alone in lowering LDL-C in **patients with primary hypercholesterolemia**

MRS-ROZE Trial

Comparison of the percentage changes in LDL-C between monotherapy and combination therapy for 8 weeks (primary end point)



High efficacy with

63%

LCL-C reduction[1]

Kim KJ et al. *Cardiovasc Ther*. 2016;34:371-382.

Change in paradigm: *first line combination statin + ezetimibe*

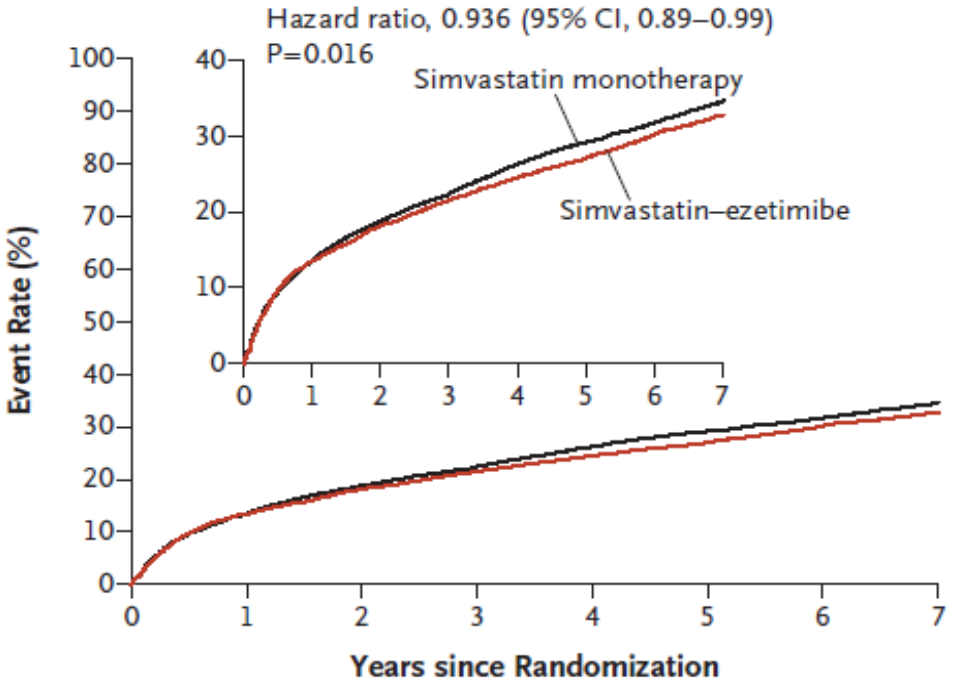
Two clinical trials with early combination of statin + ezetimibe

IMPROVE-IT:

Statin moderate intensity vs +ezetimibe

18144 pt (10 days post-ACS)

LDL-c 54 mg (simva plus ezetimibe) vs 69 mg/dL(simva)



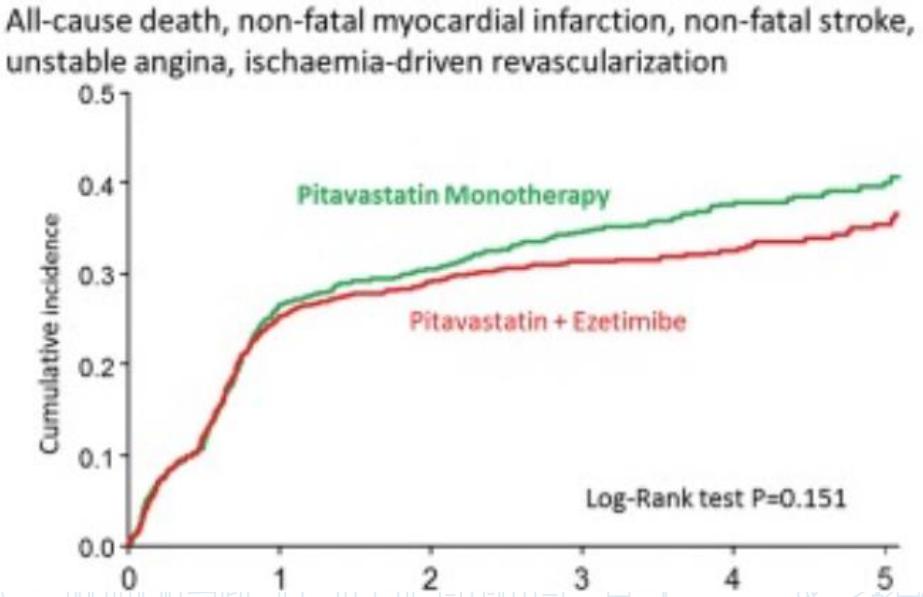
Cannon *NEJM.* 2015;372:2387–97;

HIJ-PROPER :

Pitavastatin 2mg vs + ezetimibe

1734 pts (72h post-ACS).

LDL-c 65.1 mg (pita plus ezetimibe) vs 84.6 mg/dL(pita)



Hagivara ***Eur Heart J*** . 2017 38:2264-2276

Great reduction in LDL-C and atherosclerotic plaque **volume with rosuvastatin/ezetimibe combination in patients with CAD requiring coronary intervention**

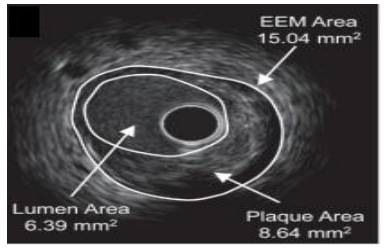
Masuda TRIAL

Baseline and Follow-up Biochemical Values

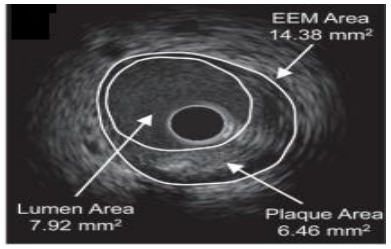
	RSV5 group (*n*=19)			EZT10/RSV5 group (*n*=21)			*P*		
	Baseline	Follow-up	%change	Baseline	Follow-up	%change	Time *effect P*	Group *effect P*	Interaction *effect P*
Total cholesterol, mg/dL	194.0 (35.6)	142.8 (25.5)**	-25.2 (13.8)	204.4 (33.7)	129.5 (24.1)**	-35.8 (13.7)	0.449	0.857	0.048
Triglycerides, mg/dL	144.9 (4.8)	125.0 (4.9)	-4.6 (15.3)	129.7 (5.1)	84.1 (5.1)	-17.5 (14.5)	0.328	0.075	0.029
LDL-C, mg/dL	**123.0 (27.0)**	**75.1 (21.4)****	**-36.8 (18.9)**	**131.8 (25.6)**	**57.3 (20.2)****	**-55.8 (18.9)**	**0.449**	**0.452**	**0.015**
HDL-C, mg/dL	47.1 (12.5)	49.1 (16.1)	4.3 (19.1)	53.1 (11.8)	57.5 (15.2)	8.8 (19.1)	0.980	0.101	0.490
Non-HDL-C, mg/dL	47.1 (12.5)	92.8 (24.7)**	-34.8 (17.9)	151.4 (29.4)	74.3 (23.4)**	-50.3 (17.9)	0.262	0.360	0.037
sd-LDL, mg/dL	146.2 (35.6)	18.6 (8.0)**	-34.4 (17.0)	28.1 (8.3)	13.0 (7.1)**	53.8 (16.8)	0.763	0.242	0.037
MDA-LDL, U/L	128 (41.6)	88.8 (32.9)*	-28.6 (21.6)	131.8 (36.9)	76.8 (29.1)**	-38.6 (21.4)	0.833	0.688	0.242
LDL-C/HDL-C ratio	2.7 (0.7)	1.6 (0.6)**	-38.4 (19.6)	2.6 (0.6)	1.1 (0.6)**	-58.2 (28.7)	0.131	0.088	0.043
hs-CRP, mg/dL	0.077 (0.006)	0.034 (0.006)	-14.4 (30.4)	0.092 (0.006)	0.037 (0.006)	-18.8 (28.7)	0.144	0.797	0.764
Hemoglobin A1c, %	6.5 (1.0	6.6 (1.3)	2.3 (9.9)	6.4 (0.9)	6.6 (1.2)	2.6 (9.8)	0.669	0.965	0.898

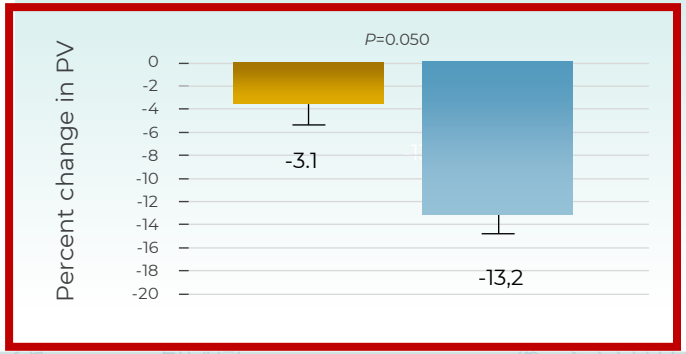
Rosu/Eze group

Baseline



Follow-up





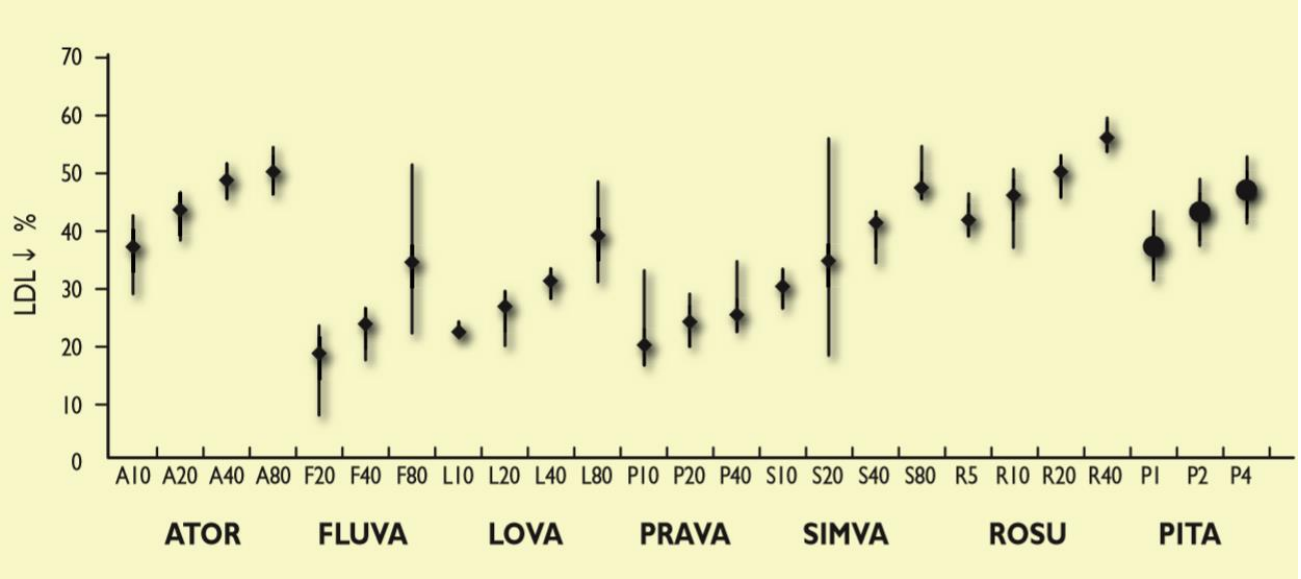
Powerful LDL-C–lowering effect of combination (rosuvastatin + ezetimibe) **(-55.8%)** vs monotherapy group **(-36.8%; P=0.004)** and significant, greater reduction in coronary plaque volume **(-13.2% vs -3.1%, respectively, P=0.050)** in patients with stable CAD

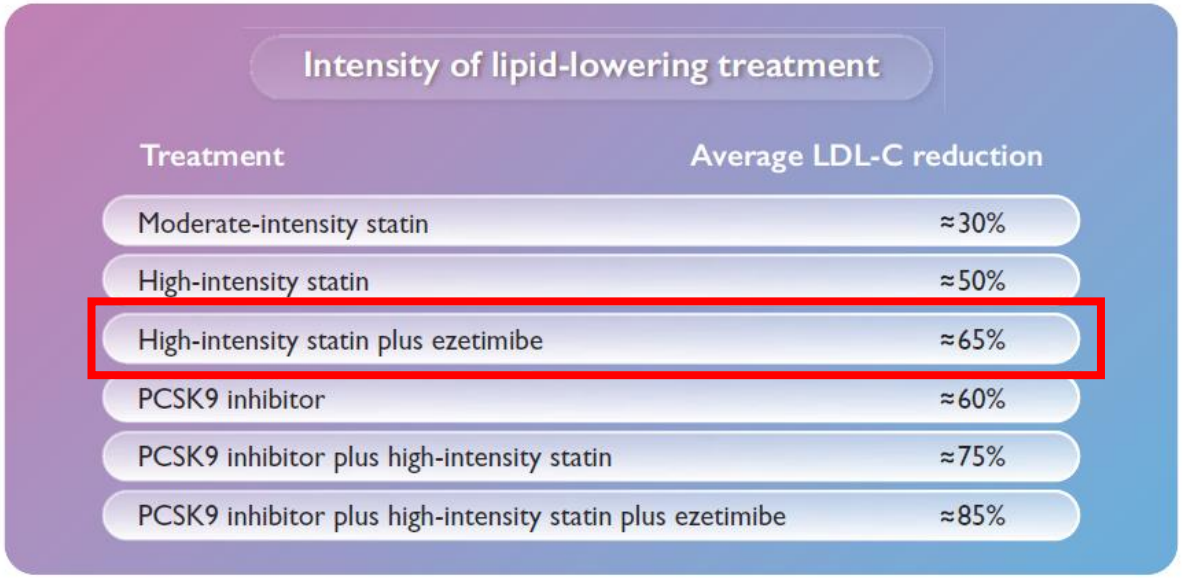
Masuda J et al. *Int Heart J.* 2015;56(3):278-285. doi:10.1536/ihj.14-311.

Change in paradigm:

Avoid unnecessary steps

Despite individual variations, the capacity of LDL-c reduction by statins monotherapy and LLT combinations is predictable





Weng ***J Clin Pharm Ther*** 2010; 35:139-151

Visseren F, et al. *Eur Heart J*. 2021;00:1–107

"Treat to Target" = select the initial prescription likely to reach the LDL-c target.

For example, to lower LDL-c <55 mg/dL, use high intensity statins + ezetimibe when baseline LDL-c is > 110mg/dL

Paradigm shift in dyslipidemia management - moving from a sequential treatment strategy to the upfront use of combinations

New EAS Statement supporting upfront combinations of high-intensity statin/ezetimibe and fixed-dose combinations (FDCs)

Upfront combinations

2.1.3. ***Why upfront combination treatment with a statin and ezetimibe?***

Patients with ASCVD, particularly those at enhanced risk with additional risk moderators, **or FH without ASCVD and high LDL-C levels**, are unlikely to attain LDL-C goal with intense statin monotherapy.

Therefore, this Task Force recommends upfront combination high-intensity statin-ezetimibe treatment in the patients. This approach has particular advantages in avoiding repeated follow-up, allowing patients to be on target as early as possible , with favorable impact on cardiovascular outcome.

In FDCs

Proportion of patients at LDL-C goal by 3-fold [28]. **The availability of a fixed combination of ezetimibe and high dose of a more efficacious statin will likely improve patient adherence.** For patients with statin.

Averna M et al. *Atherosclerosis*. 2021;325:99-109. doi:10.1016/j.atherosclerosis.2021.03.039.

ESC position paper on statins adherence and implementation of new lipid-lowering medications: barriers to be overcome

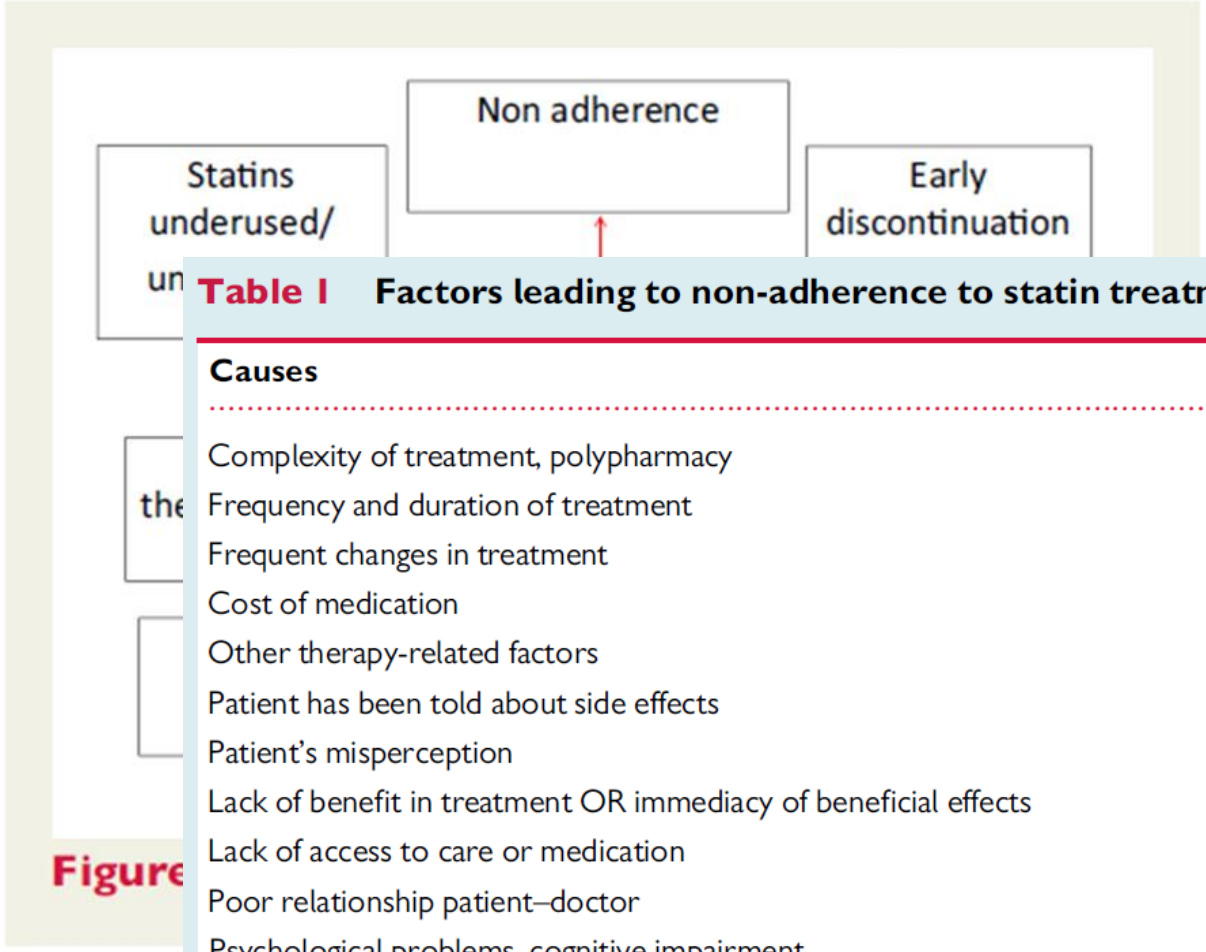


Table I **Factors leading to non-adherence to statin treatment**

Causes	Suggested strategies to improve adherence
Complexity of treatment, polypharmacy	Single pill administration
Frequency and duration of treatment	
Frequent changes in treatment	
Cost of medication	
Other therapy-related factors	
Patient has been told about side effects	Improve patient awareness and doctor–patient relationship
Patient's misperception	Increase availability of medical support
Lack of benefit in treatment OR immediacy of beneficial effects	
Lack of access to care or medication	
Poor relationship patient–doctor	
Psychological problems, cognitive impairment	Role of caregivers
Inadequate follow-up or discharge planning	Implementation of treatment plan
Statin-specific, documented side effects	Therapeutic interchange

Drexel H et al. European Hea
ww.escardio.org/guidelines . doi:10.1093/eurjcvp/pvz079

ESC position statement – Statin plus Ezetimibe

- Adherence decreases with increasing number of pills
- Combination therapies present different advantages
  - May have a synergistic effect
  - May have less adverse events and thus better tolerated.
  - Simplified drug regimen usually leads to better adherence and, potentially, better outcomes and costs reduction for the healthcare.
- Fixed combination with **statin and ezetimibe** in the same pill is one of the best strategies in terms of initial efficacy and adherence, which is a major determinant of good outcomes

Take home messages

Dyslipidemia is highly prevalent and the commonest modifiable CVD risk factor in AfME

ESC guidelines advocate starting LLT with lifestyle measures/statins with a stepwise increase to reach the targets.

However, majority of our patients do not attain lipid goals – *possibly due to:*

- *Underpowered initial statin intensity*
- *No intensification of LLT*
- *Low uptake of LLT combinations*

Change in paradigm from statins to earlier LLT combination may result better LDL-C reduction, more patients at target and effective CV prevention

Consider combination statin (HI) + ezetimibe as first line, particularly in very high risk patients

Thank You