

## ACHIEVING LDL-C GOALS IN HIGH AND VERY HIGH RISK PATIENTS

### Ezetimibe and combination therapy

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## Conflict of interest disclosures

Fees for Lectures and participation in Advisory boards from:

AMGEN

SANOFI

MSD

DAICHI

MYLAN

RECORDATI

## AIMS OF LIPID LOWERING THERAPY

Cardiovascular risk reduction



**LDL lowering**

Atherogenic dyslipidaemia  
Triglycerides / HDL

Pancreatitis risk reduction



**Triglycerides lowering**

Non Alcoholic Steatohepatitis



***Lipid lowering therapy***

## **ESC/EAS guidelines:**

Statins should be used in the highest tolerable doses to reach the LDL cholesterol target level before combination therapy

**High intensity Statin dose**



**Moderate Intensity Statin dose**



**Highest Intensity Tolerable Statin dose**



**Combination therapy**

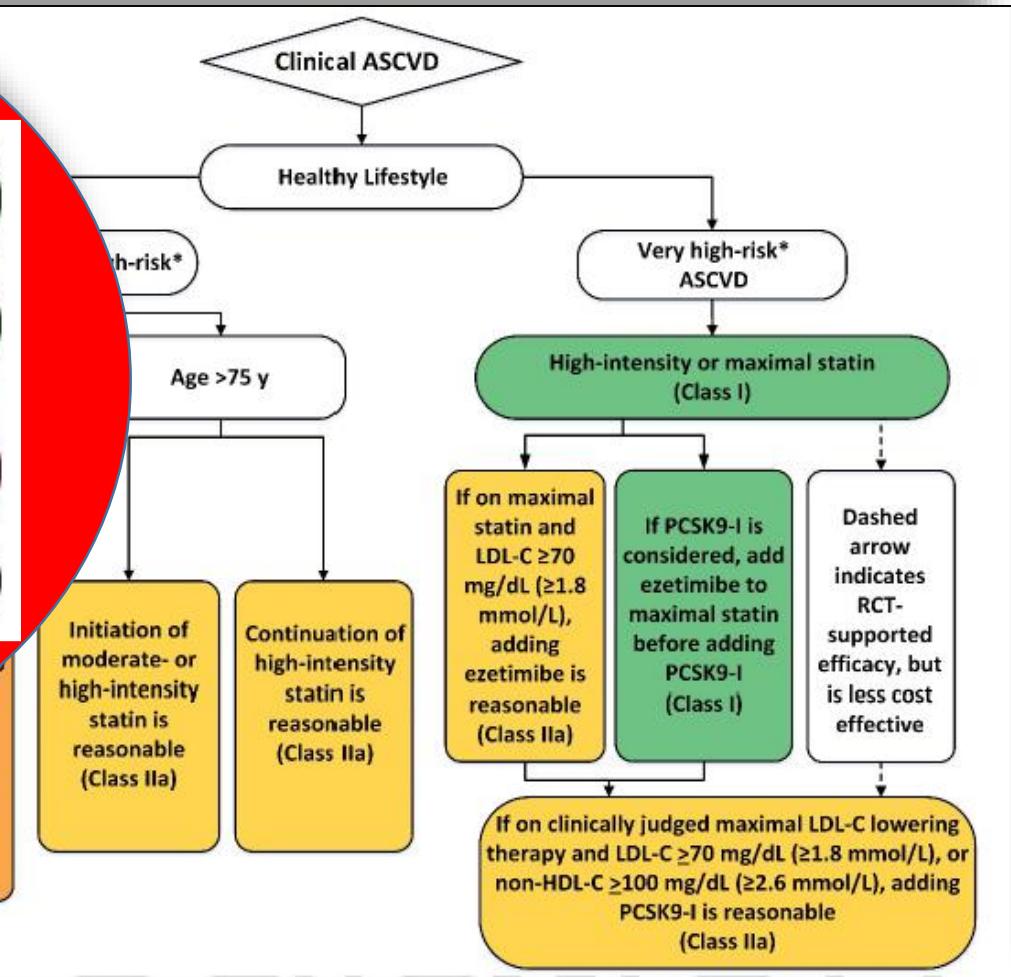
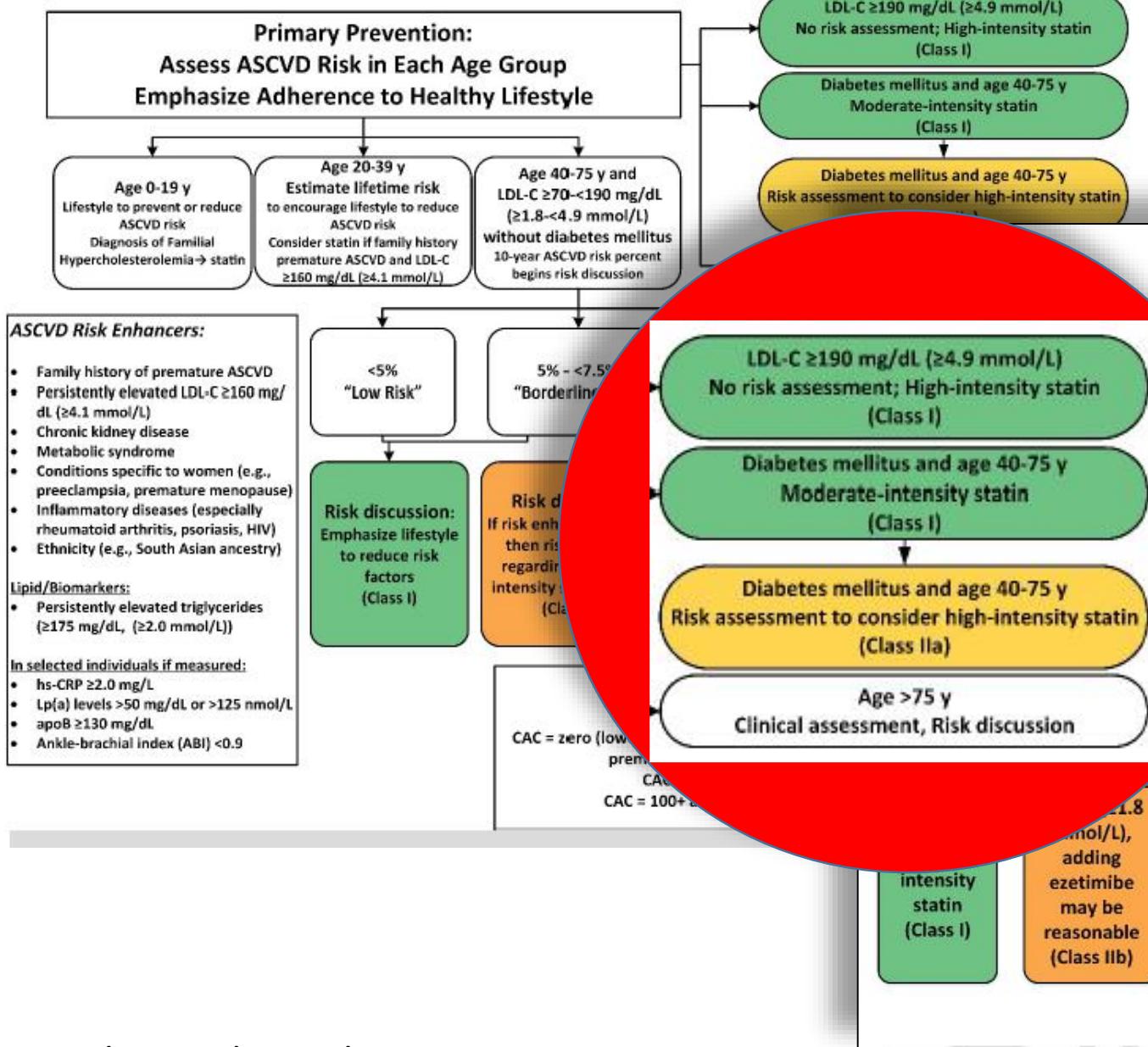


## Several lipid lowering therapies failed to show overall cardiovascular benefit when added-on statins



# 2018 Cholesterol Clinical Practice Guidelines

## AHA/ACC



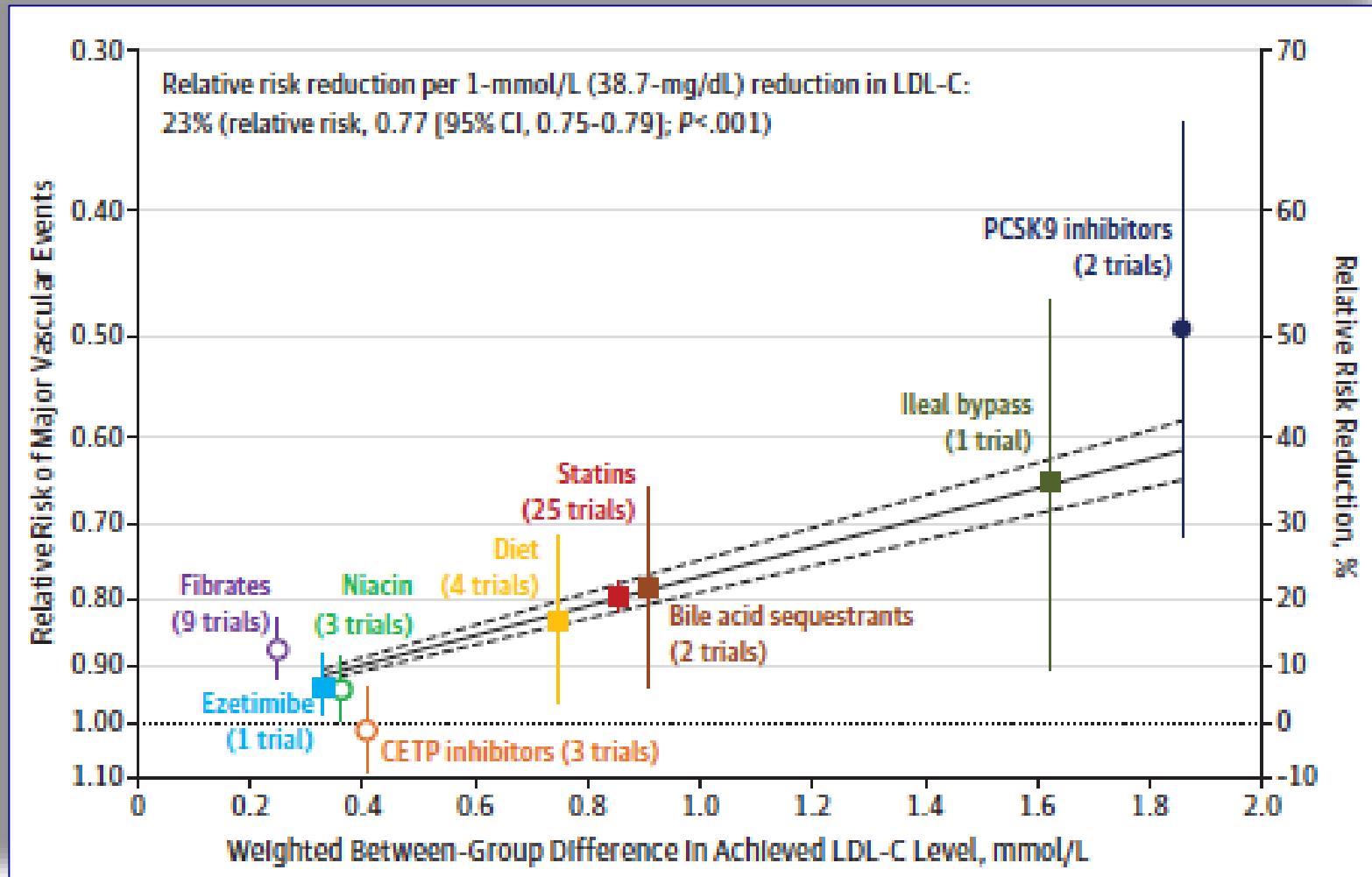


**LDL**  
**STATINS**

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

## Lowering LDL-C and Cardiovascular Risk Reduction Among Different Therapeutic Interventions





Invited commentary

IMPROVE-IT clinical implications. Should the “high-intensity cholesterol-lowering therapy” strategy replace the “high-intensity statin therapy”?



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High-intensity  
statin therapy

High intensity  
cholesterol-lowering  
therapy

Triglycerides lowering

Statins

Cholesterol lowering

Fibrates

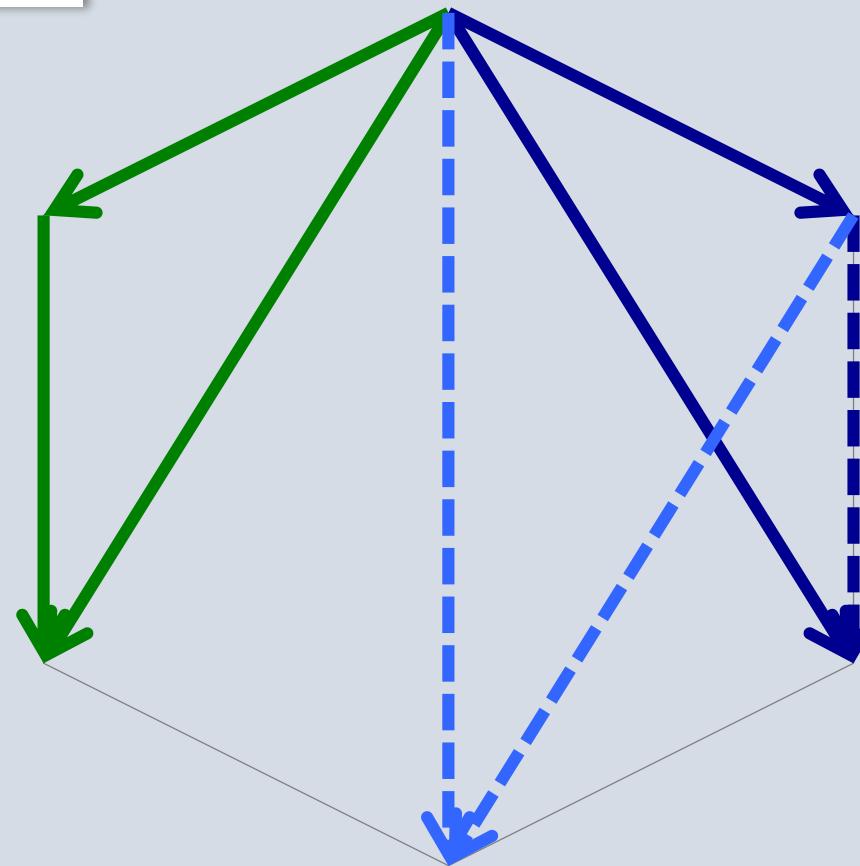
Omega-3  
Fatty Acids

Niacin

Ezetimibe

PCSK9 inhibitors

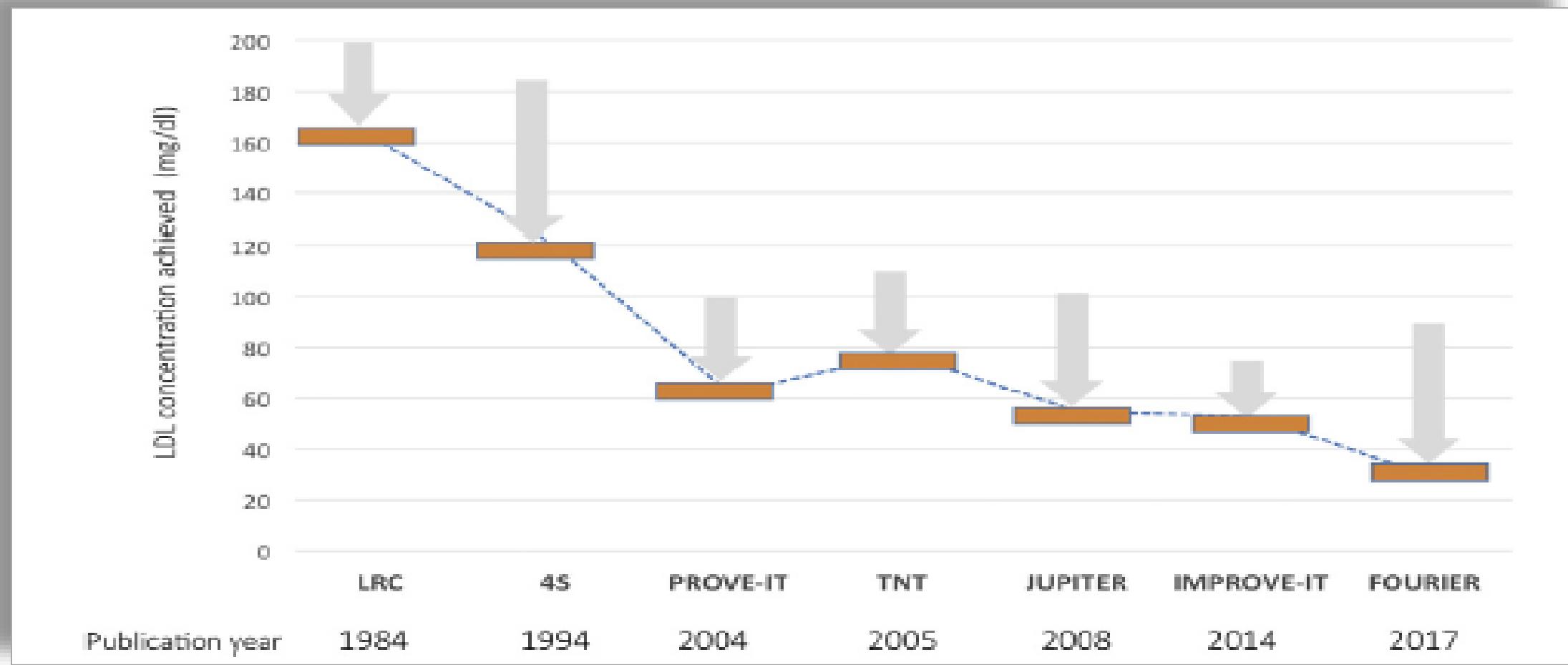
Resins



## Classification of cholesterol-lowering therapy according to LDL cholesterol reduction intensity

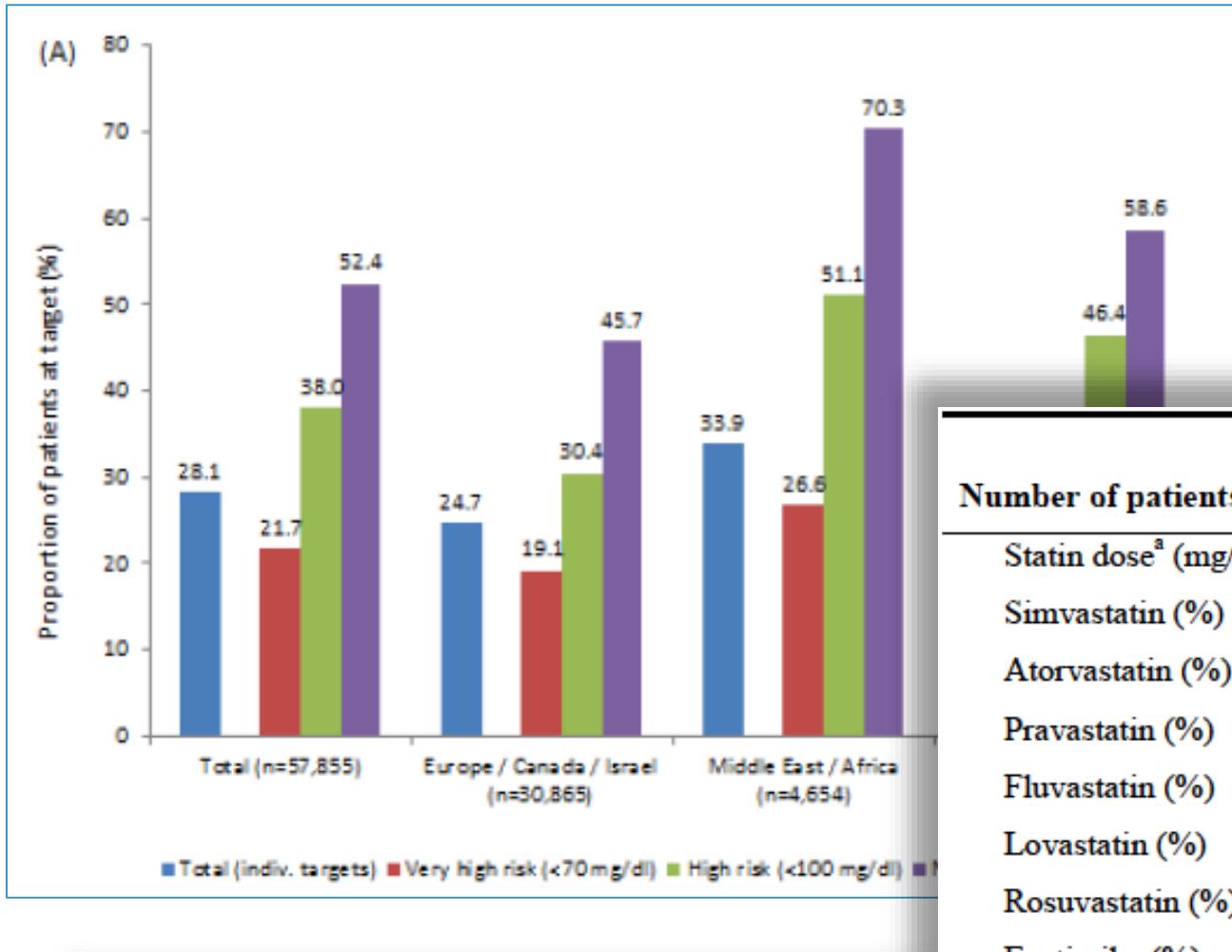
Low-intensity cholesterol-lowering therapy (LICLT) ↓ LDLc < 30%	Mild-intensity cholesterol-lowering therapy (MICLT) ↓ LDLc 30–49%	
Simvastatin 10 mg Pravastatin 10–20 mg Lovastatin 10–20 mg Fluvastatin 40 mg Pitavastatin 1 mg Ezetimibe 10 mg	<b>High-intensity cholesterol-lowering therapy (HICLT) ↓ LDLc 50–60%</b>  Atorvastatin 40–80 mg Rosuvastatin 20–40 mg Simvastatin 20–40 mg + Ezetimibe 10 mg Pravastatin 40 mg + Ezetimibe 10 mg Lovastatin 40 mg + Ezetimibe 10 mg Fluvastatin 80 mg + Ezetimibe 10 mg Pitavastatin 2–4 mg + Ezetimibe 10 mg Atorvastatin 10–20 mg + Ezetimibe 10 mg  Rosuvastatin 5–10 mg + Ezetimibe 10 mg	<b>Very-high-intensity cholesterol-lowering therapy (VHICLT) ↓ LDLc &gt; 60%</b>  Atorvastatin 40–80 mg + Ezetimibe 10 mg Rosuvastatin 20–40 mg + Ezetimibe 10 mg

## LDL VALUES ACHIEVED IN DIFFERENT RANDOMIZED CONTROLLED TRIALS



# FACT: Very few CVD patients achieve LDL targets worldwide

DYSIS STUDY: 57,885 patients involved. Overall only 28.1 % of patients reached their risk-based target.



In patients at very high CV risk  
the mean distance to LDL target  
is about 1 mmol/L

Number of patients (%)	Total	Very high risk
	57,885 (100%)	44,015 (76.0%)
Statin dose <sup>a</sup> (mg/day)	33.5 ± 25.1	35.2 ± 26.3
Simvastatin (%)	42.1 (24,341/57,885)	41.0 (18,065/44,015)
Atorvastatin (%)	37.2 (21,561/57,885)	39.0 (17,171/44,015)
Pravastatin (%)	5.3 (3,057/57,885)	4.8 (2,115/44,015)
Fluvastatin (%)	2.8 (1,635/57,885)	2.8 (1,233/44,015)
Lovastatin (%)	0.7 (396/57,885)	0.6 (275/44,015)
Rosuvastatin (%)	11.7 (6,744/57,885)	11.4 (5,037/44,015)
Ezetimibe (%)	1.8 (3,891/57,507)	7.2 (3,135/43,734)

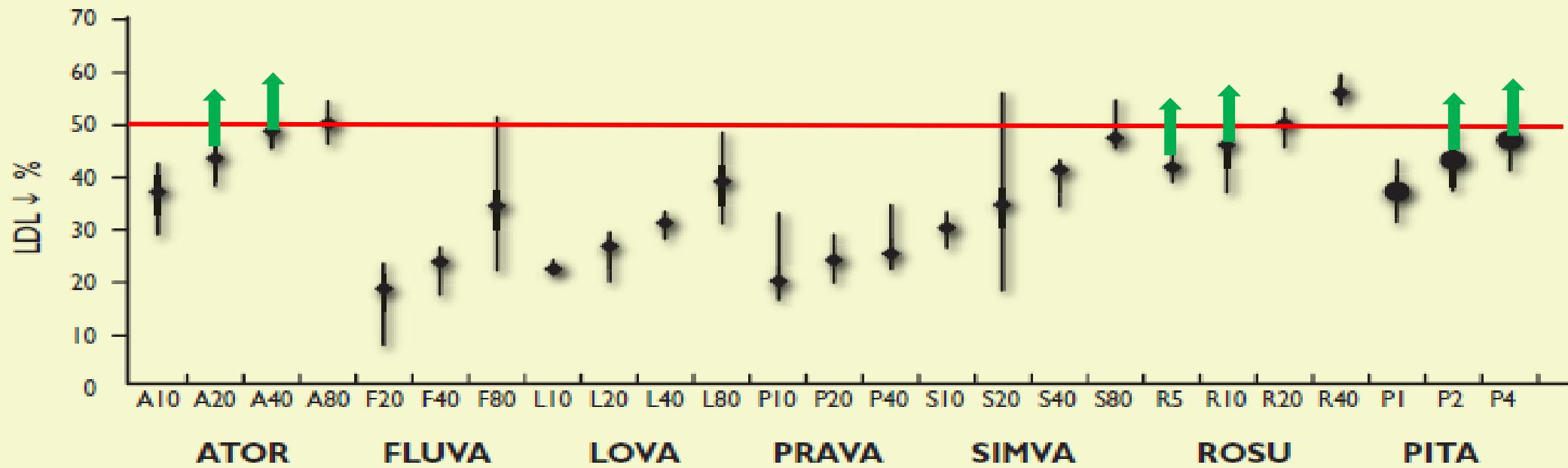
## Clinical decision before a patient treated with a statin at a medium / standard dose that has not reached the therapeutic objectives

Doubling statin dose

Switch to a more  
powerful statin

Combination  
therapy





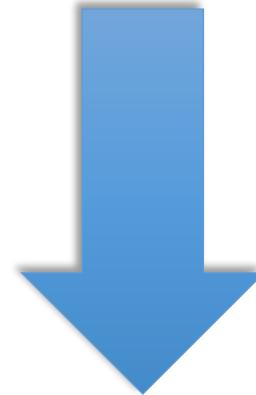
Weng TC, et al. *J Clin Pharm Ther*. 2010;35:139-151

Mukhtar RY, et Al. *Int J Clin Pract*. 2005;59(2):239-252

**50 plus 20 = ?**

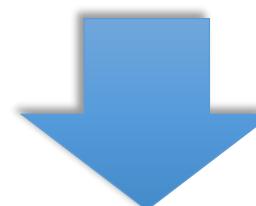
Atorvastatin 80 mg/day (50% LDL lowering effect):

200 mg/dl



100 mg/dl

Ezetimibe 10 mg/day (20% LDL lowering effect):



80 mg/dl

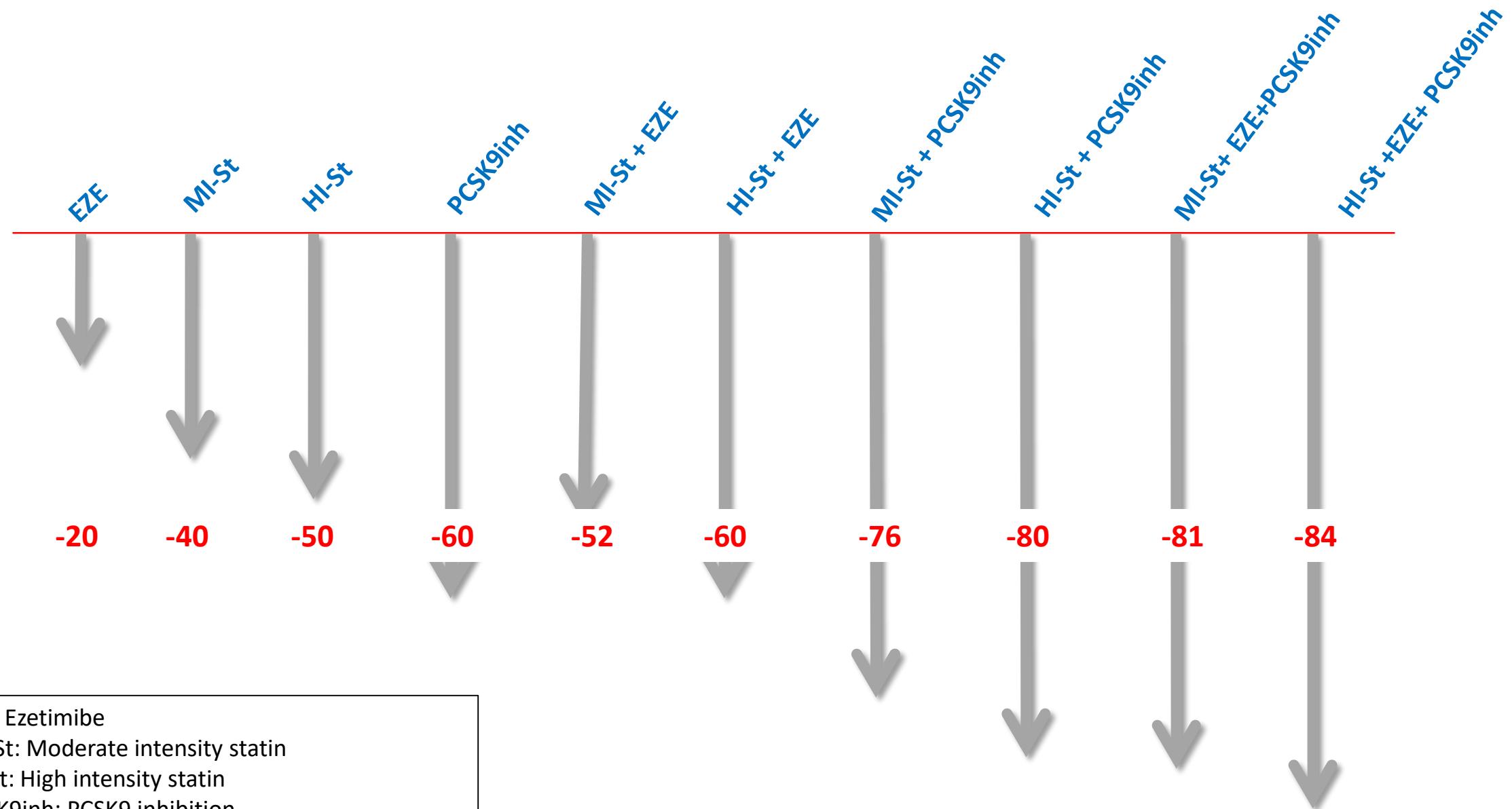


**120 mg/dl  
reduction**

**60%**

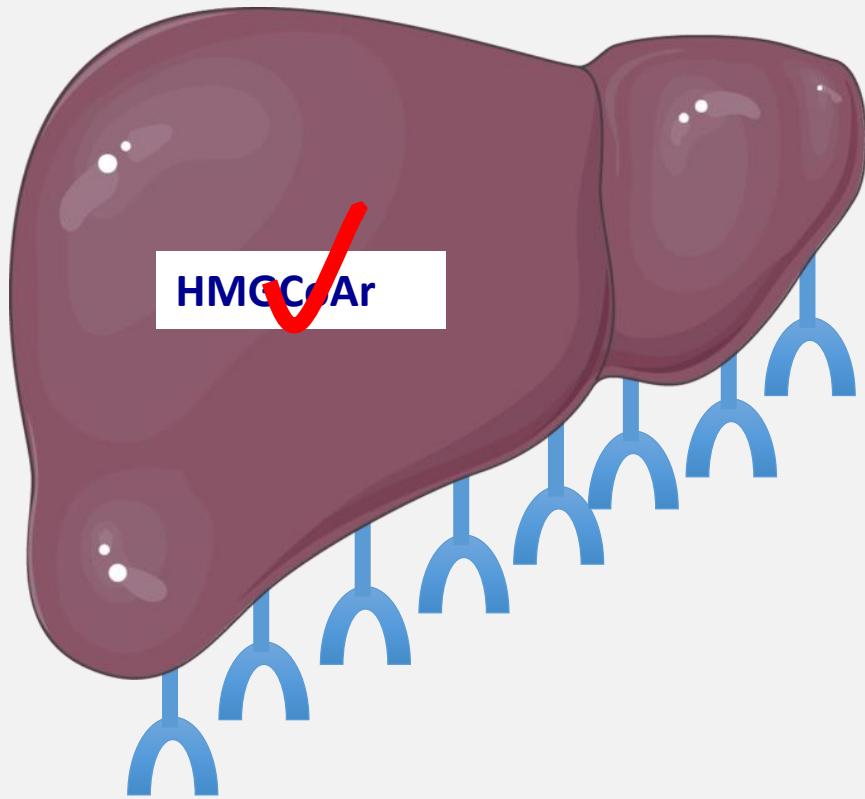
**50 PLUS 20 EQUALS 60**

## Expected LDL % reduction according lipid lowering therapy combination

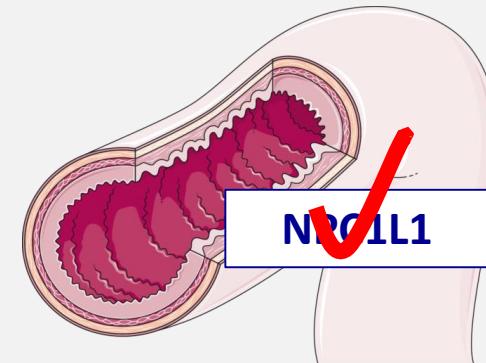


## LIPID LOWERING COMBINATION THERAPY = SINERGY

**STATINS**



**EZETIMIBE**



**PCSK9 INH**

## RISK

Side effects

Myopathy

Diabetes

Transaminases  
elevation



## BENEFIT

CV diseases  
reduction

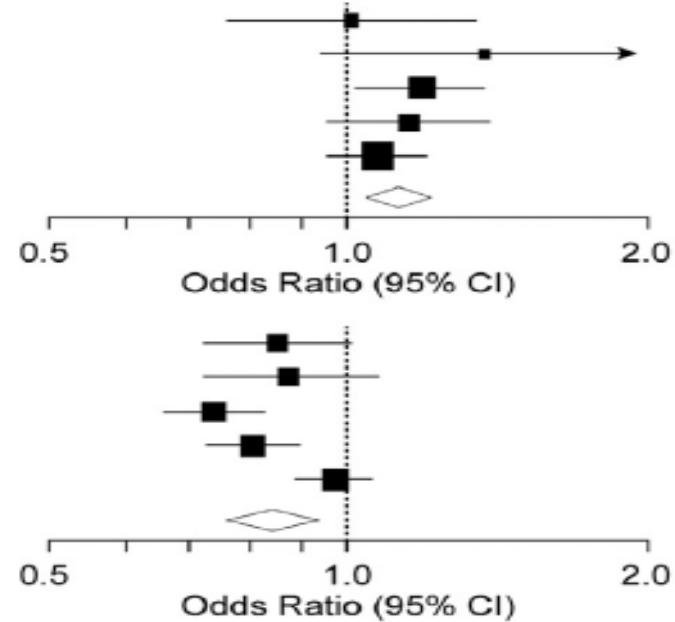
Increased  
survival

# The use of statins in people at risk of developing diabetes mellitus: Evidence and guidance for clinical practice

The diabetogenic effects of statins appear to be dose-related.

	Cases/Total, No. (%)		
	Intensive Dose	Moderate Dose	OR (95% CI)
<b>Incident Diabetes</b>			
PROVE IT_TIM 22, 2004	101/1707 (5.9)	99/1688 (5.9)	1.01 (0.76-1.34)
A to Z, 2004	65/1768 (3.7)	47/1736 (2.7)	1.37 (0.94-2.01)
TNT, 2005	418/3798 (3.7)	358/3797 (9.4)	1.19 (1.02-1.38)
IDEAL, 2005	240/3737 (6.4)	209/3724 (5.6)	1.15 (0.95-1.40)
SEARCH, 2010	625/5398 (11.6)	587/5399 (10.9)	1.07 (0.95-1.21)
Pooled odds ratio	1449/16408 (8.8)	1300/16344 (8.0)	1.12 (1.04-1.22)
Heterogeneity; $I^2=0\%$ ; $P=.60$			

	Intensive Dose	Moderate Dose	OR (95% CI)
<b>Incident CVD</b>			
PROVE IT_TIM 22, 2004	315/1707 (18.4)	355/1688 (21.0)	0.85 (0.72-1.01)
A to Z, 2004	212/1768 (12.0)	234/1736 (13.5)	0.87 (0.72-1.07)
TNT, 2005	647/3798 (17.0)	830/3797 (21.9)	0.73 (0.65-0.82)
IDEAL, 2005	776/3737 (20.8)	917/3724 (24.6)	0.80 (0.72-0.89)
SEARCH, 2010	1184/5398 (21.9)	1214/5399 (22.5)	0.97 (0.88-1.06)
Pooled odds ratio	3134/16408 (19.1)	1214/16344 (22.5)	0.84 (0.75-0.94)
Heterogeneity; $I^2=74\%$ ; $P=.004$			



# Statin-associated muscle symptoms: impact on statin therapy

## EAS Consensus Panel

### **Box 2 Factors that influence the pharmacokinetics of statins and risk for statin-associated muscle symptoms (SAMS)**

- Pre-existing risk factors and co-morbidities: see Box 1
- High-dose statin therapy
- Polypharmacy
- Drug–drug interactions: concomitant use of certain drugs including gemfibrozil, macrolides, azole antifungal agents, protease inhibitors, and immunosuppressive drugs such as cyclosporine, and inhibitors of CYP450 isoenzymes, OATP 1B1, or P-gp, can affect the metabolism of statins, increase their circulating levels and, consequently, the risk for SAMS.
- Pharmacogenetic considerations may be relevant (see Overview of the pathophysiology of statin-induced myopathy)

CYP450, cytochrome P450; OATP 1B1, organic anion-transporting polypeptide 1B1; P-gp, P-glycoprotein 1.

LDL-C is a causal factor of atherosclerosis

Cardiovascular disease relative risk is reduced proportionally to LDL-C decrease regardless of therapy used

The efficacy of combination therapy (statins, ezetimibe and PCSK9 inhibitors) is science-evidence based

Combination therapy increases lipid lowering efficacy, reduces side effects associated to high-intensity statin regimes leading to higher adherence to therapy and event reduction

**The concept of “high-intensity statin therapy” should be changed by “high-intensity cholesterol lowering therapy”**