PRESENT
AND FUTURE
APPROACHES TO
THE CONTROL OF
DYSLIPIDAEMIAS

S.I.Te.C.S.
Società Italiana di Terapia Clinica e Sperimentale

Ezetimibe and combination therapy

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Disclosure of potential conflicts of interest

Fees for lectures and / or advisory work from:	Amarin, Amgen, Amryt, Daiichi-Sankyo, Mylan, MSD, Novartis, Sanofi-Regeneron, Servier.

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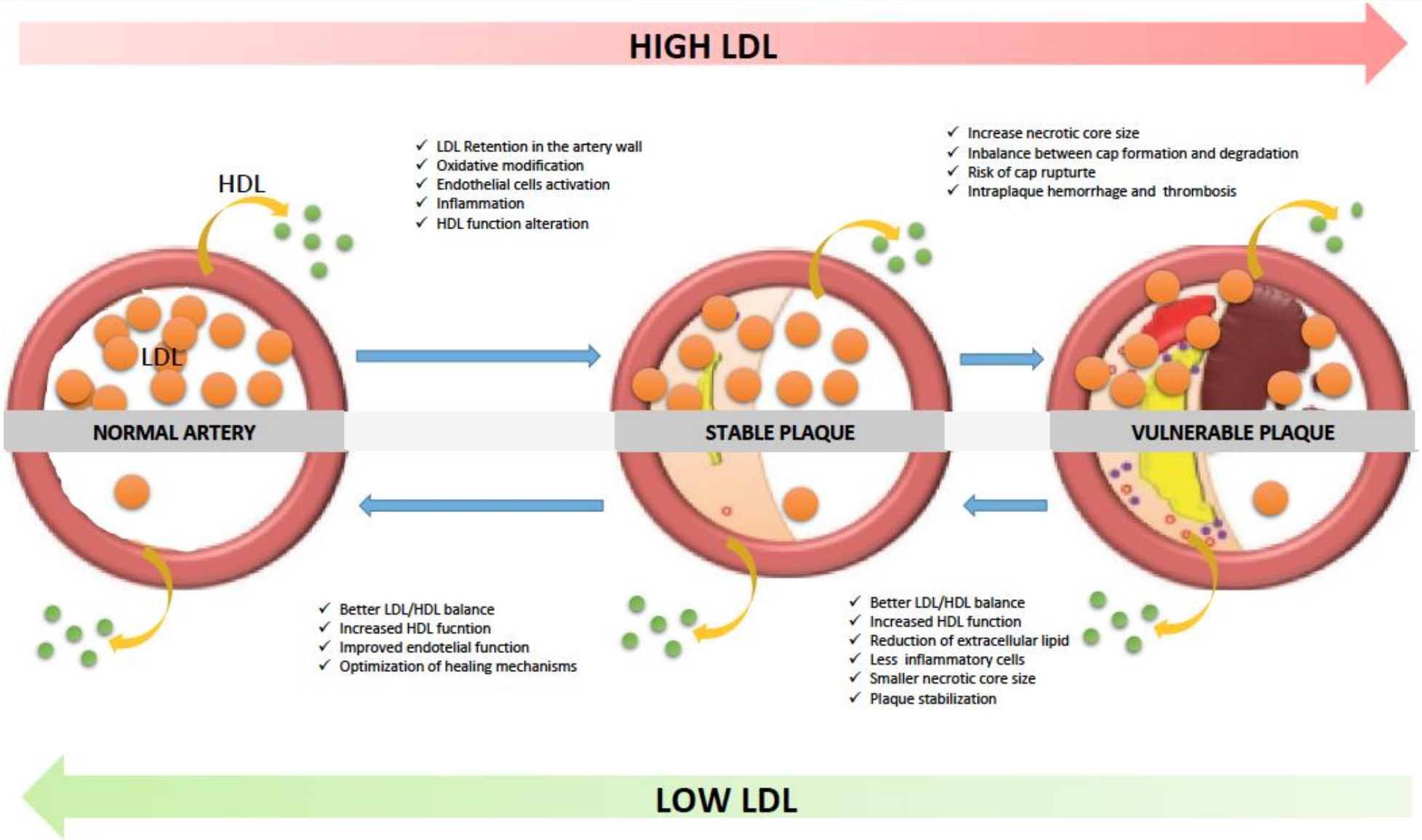
LDL-C LOWERING IS THE MAIN OBJECTIVE OF THERAPY
LDL-C is an etiological factor for atherosclerosis



Masana L 2019. Adapted from: Boren J, et al. Eur Heart J. 2020 [Epub ahead of print].

Atherosclerotic Plaque Disruption and Healing

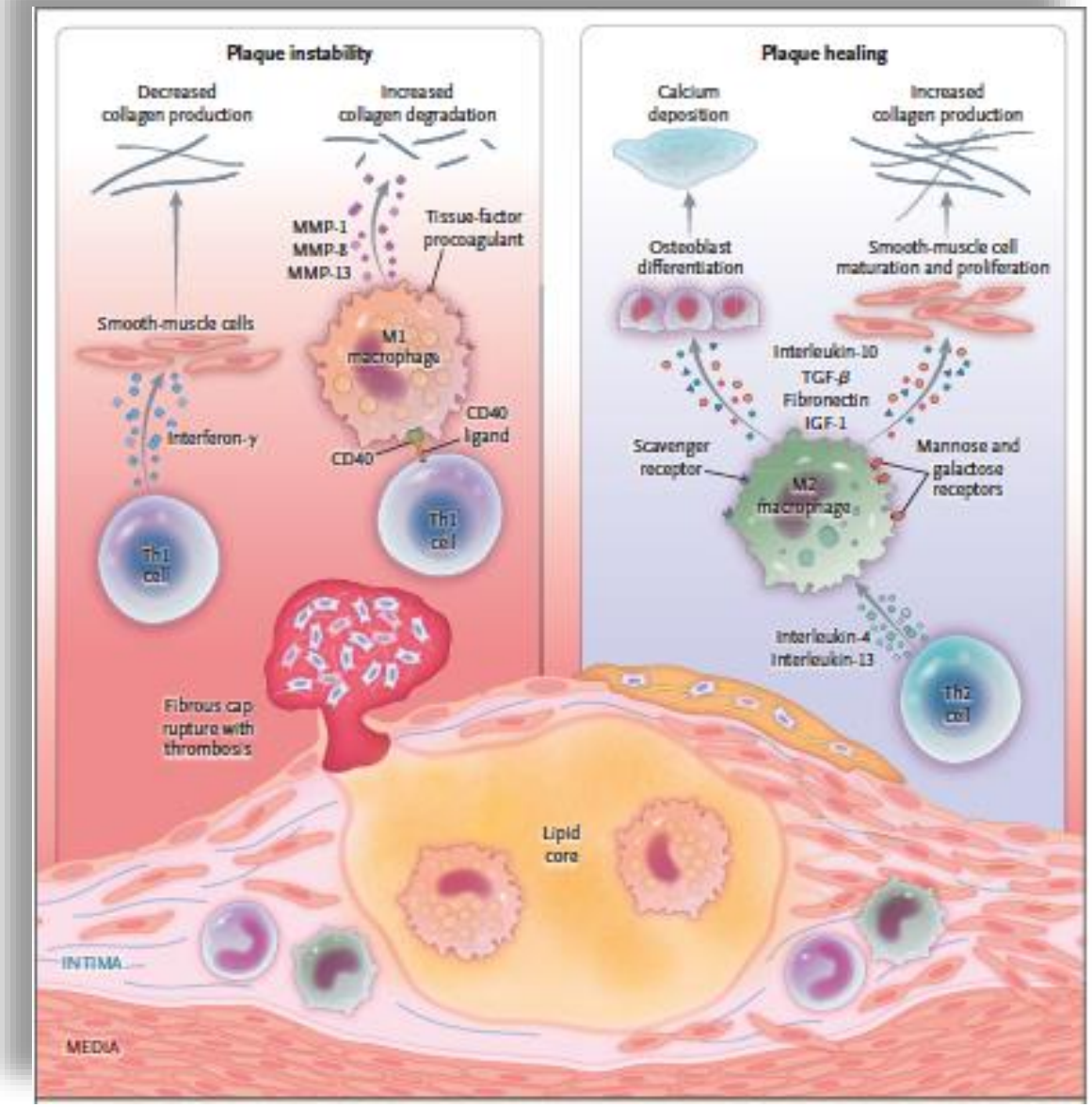
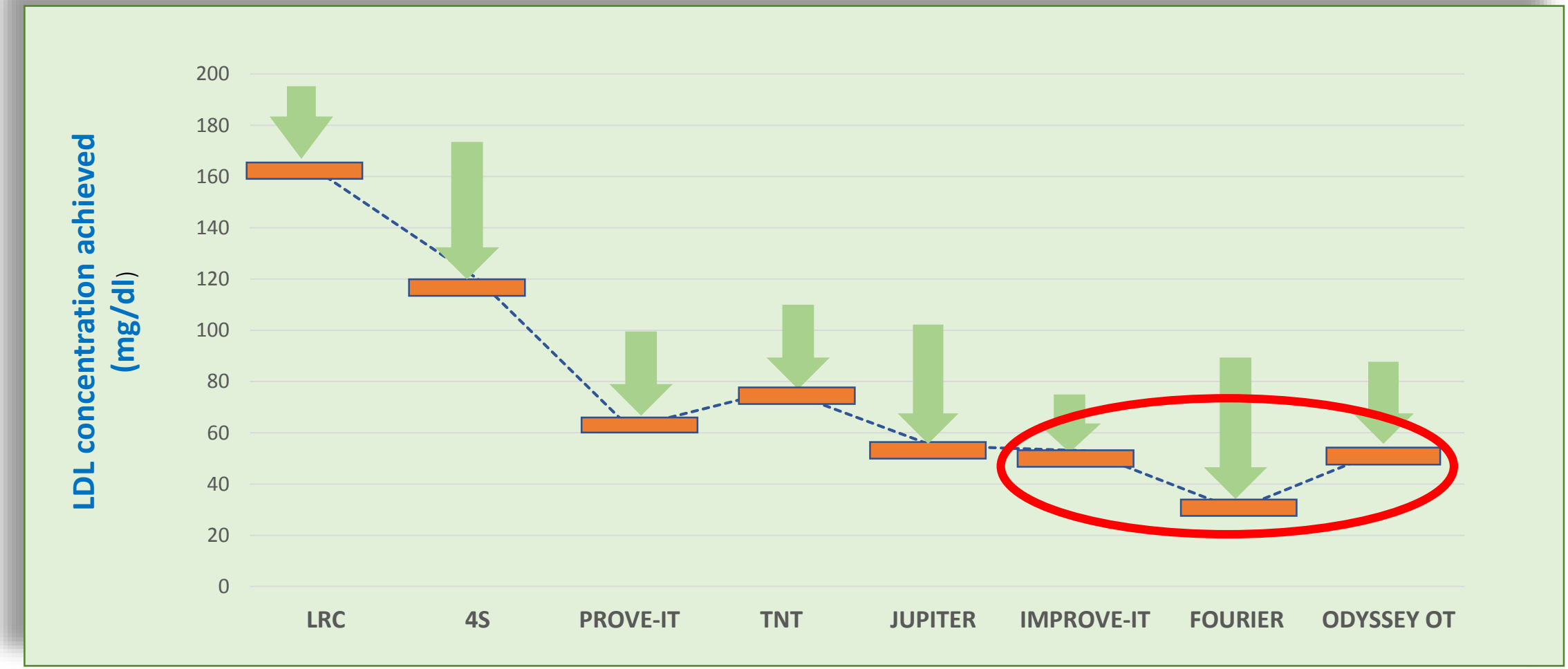


Table 1. Therapeutic Interventions That Might Enhance Atherosclerotic Plaque Healing.*

Therapy	Potential Favorable Effects on Plaque Healing
Lipid-lowering diet (e.g., low-cholesterol, low-fat diet)	Reduces expression and proteolytic activity of interstitial collagenase (MMP-1) Increases interstitial collagen content within fibrous cap Reduces oxidative stress Reduces endothelial-cell activation Reduces tissue factor expression and activity (reduces thrombotic potential)
Lipid-lowering drugs (e.g., statins, PCSK9 inhibitors)	Reduce expression and proteolytic activity of interstitial collagenase (MMP-1) Increase smooth-muscle cells and interstitial collagen within fibrous cap Reduce proliferation and activation of macrophages Reduce oxidative stress Reduce endothelial-cell activation Up-regulate endothelial progenitor cells and circulating angiogenic cells Reduce tissue factor expression and activity (reduce thrombotic potential) Reduce plasminogen activator inhibitor 1 levels (increase fibrinolytic potential)
Antiinflammatory drugs (e.g., interleukin-1β antagonists, colchicine)	Reduce expression of adhesion molecules and leukocyte recruitment on endothelial cells Reduce tissue factor expression (reduce thrombotic potential) Reduce fibrinogen and plasminogen activator inhibitor 1 levels (reduce thrombotic potential, increase fibrinolytic potential)
CD31-targeting therapies (e.g., agonist peptides, antibodies, recombinant proteins)	Polarize macrophages toward an alternative M2 phenotype
Epigenetic therapies targeting macrophage polarization (e.g., DNA methylation, histone modifications, miRNAs, lnc-RNAs)	Polarize macrophages toward an alternative M2 phenotype
PI3Kc–CXCL10 axis inhibitors	Increase re-endothelialization after vascular injury

Vergallo R et al. N Engl J Med. 2020. 383:
Vergallo R et al. European Heart Journal (2020) 00, 1–2

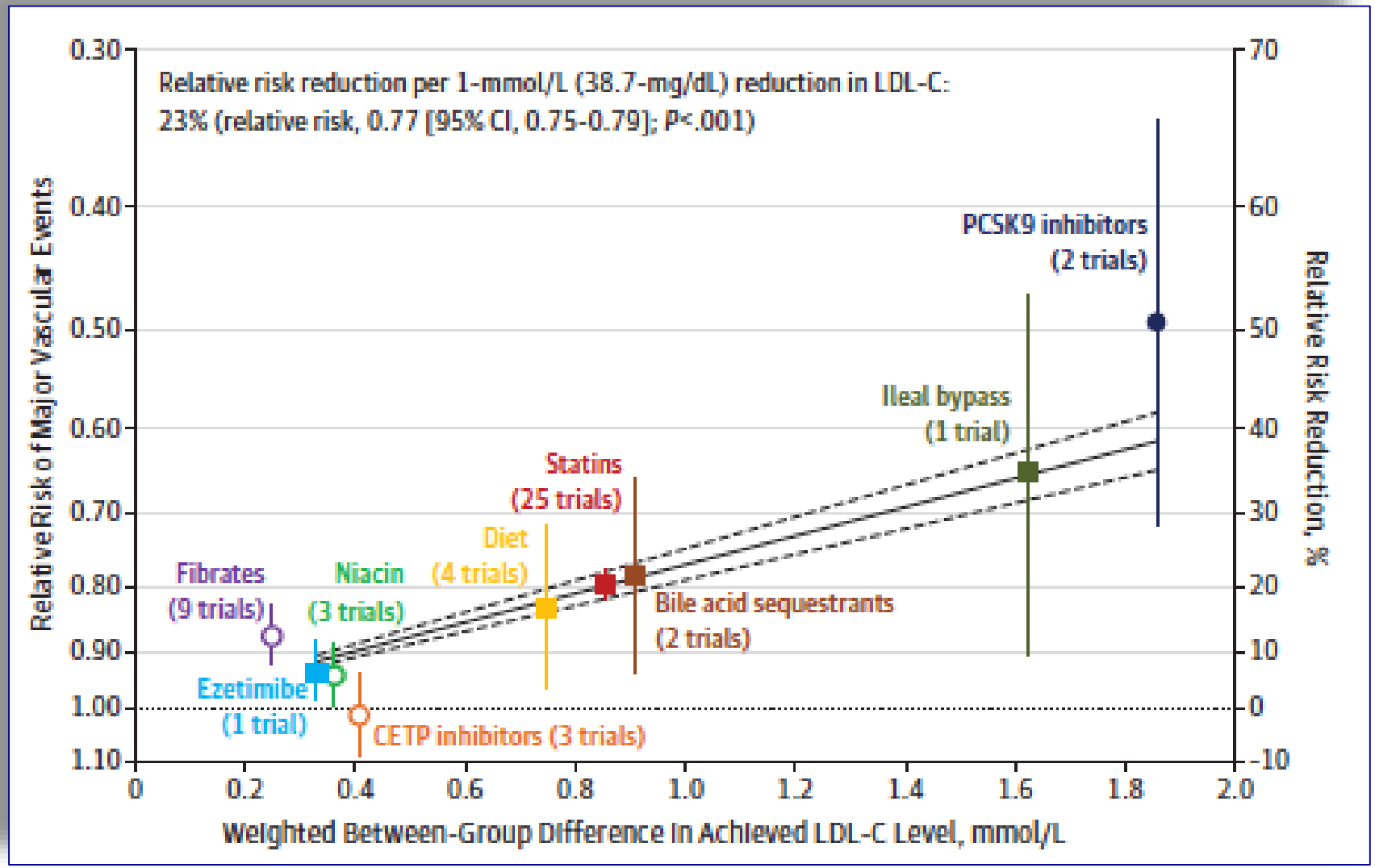
NEW EVIDENCES LEAD TO NEW GUIDELINES.
LDL-C concentrations obtained in the main lipid lowering Randomized Controlled Trials



Publication year	1984	1994	2004	2005	2008	2014	2017	2018

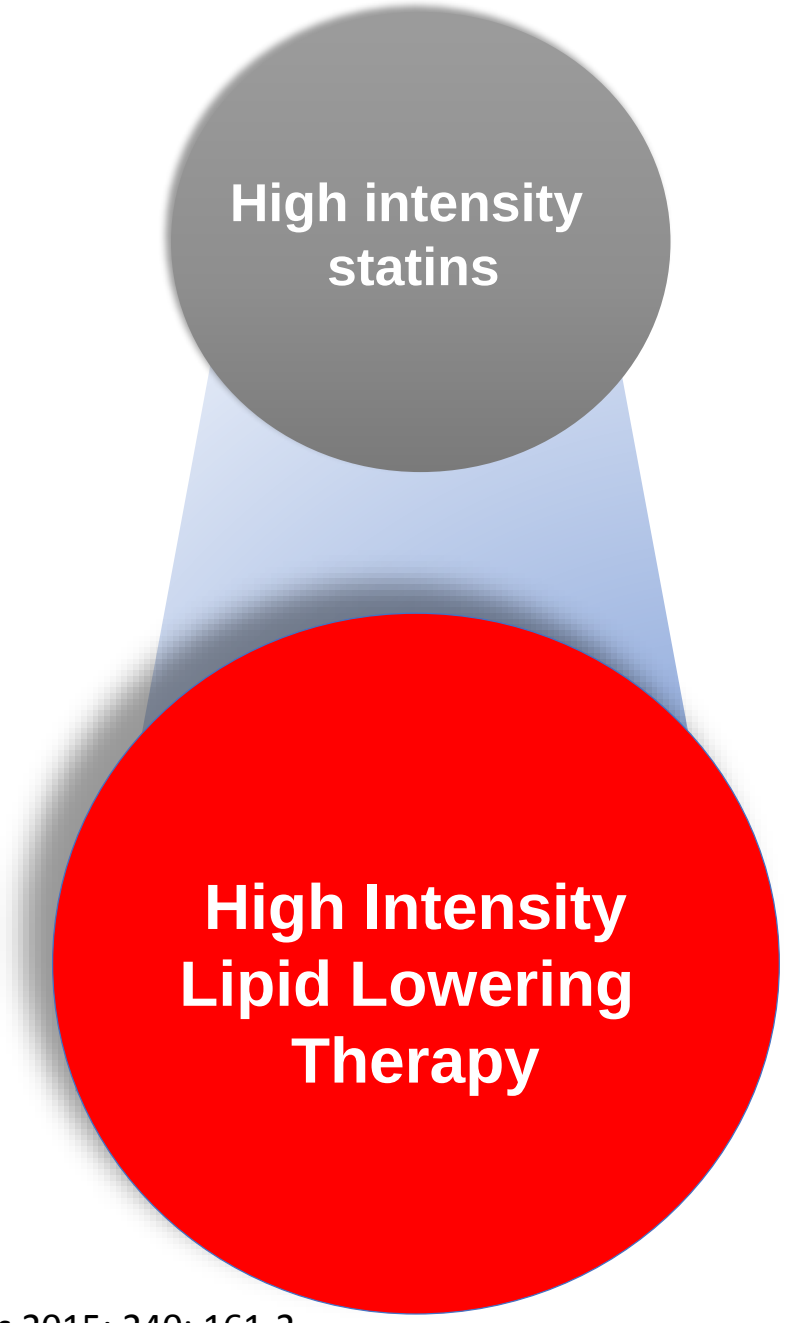
Adapted from Masana L et al. J Clin Lip 2018.

Relative risk reduction is driven by LDL-C lowering



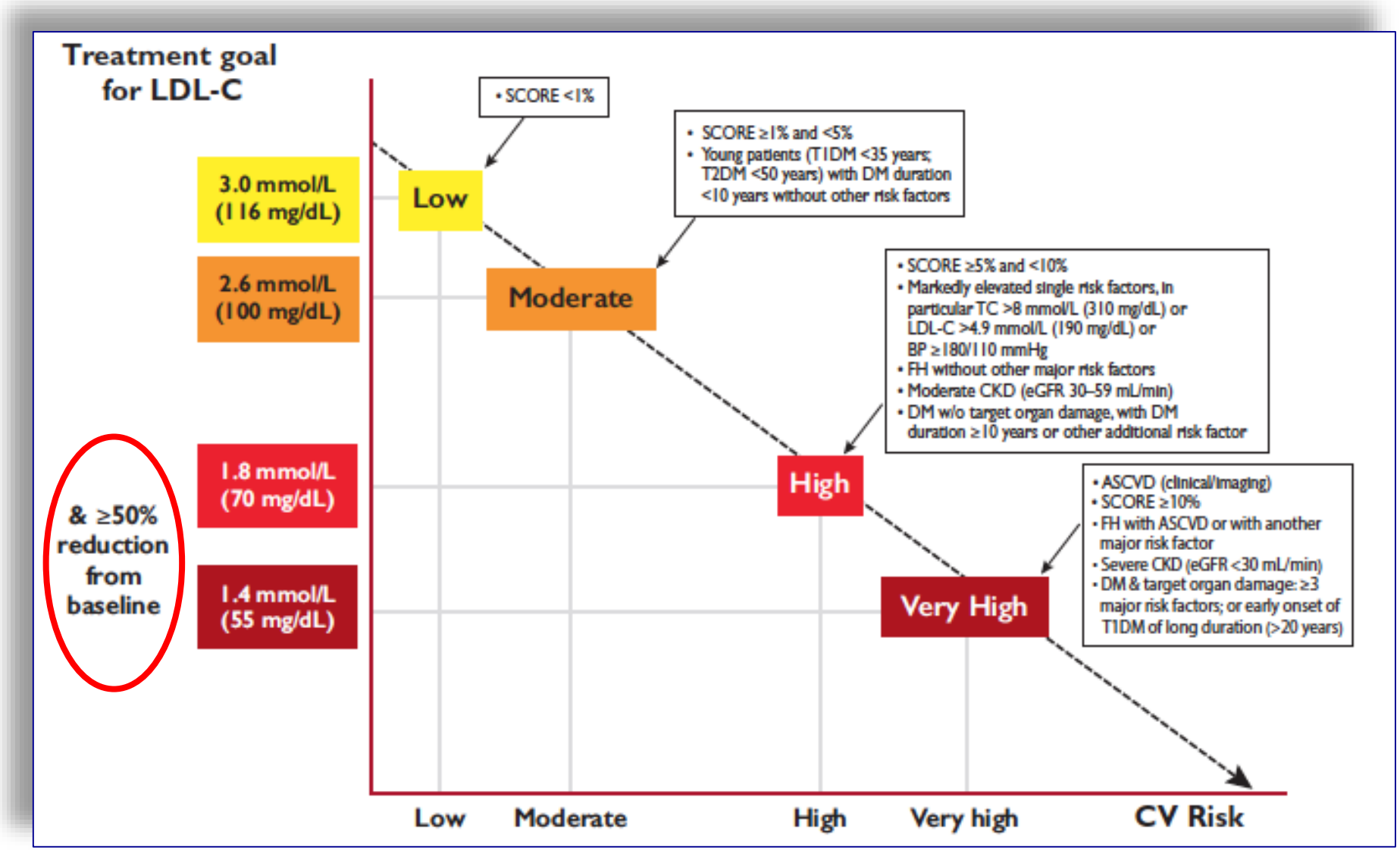
JAMA. 2016;316(12):1289-1297

NEW CONCEPT



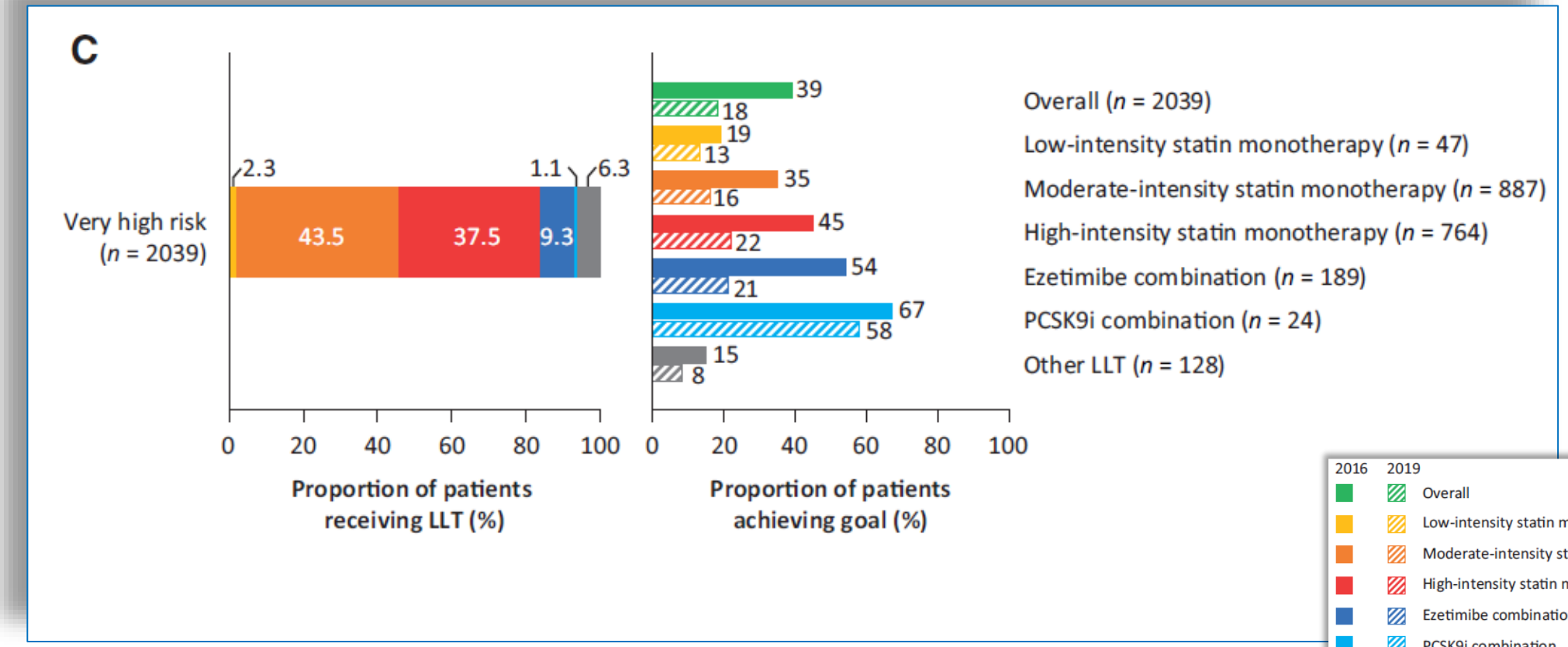
Masana L, Pedro-Botet J, Civeira F. Atherosclerosis 2015; 240: 161-2

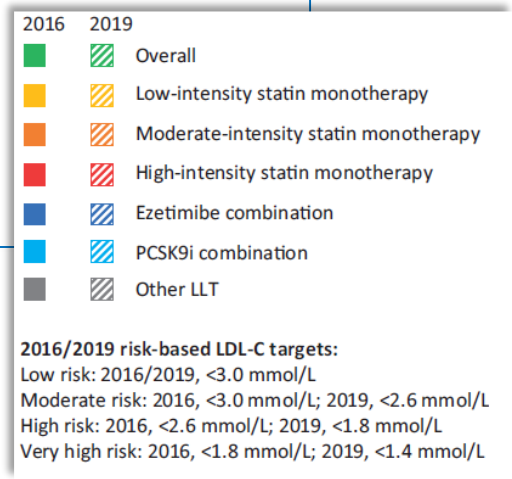
ESC/EAS 2019 guidelines: Treatment goals for LDL-C across cardiovascular risk categories



Mach F et al. European Heart Journal (2019) 00, 178

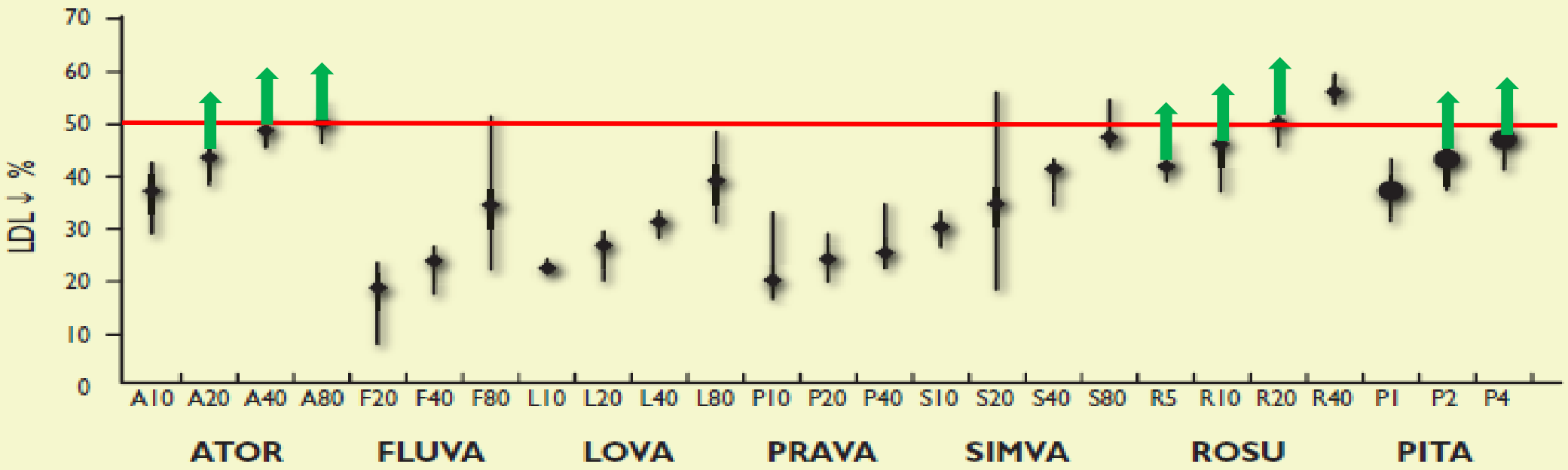
Proportion of high cardiovascular risk patients achieving the LDL-C targets according lipid lowering therapy . The DA VINCI study





Ray K et al, Eur J Prev Card , 2020 . doi:10.1093/eurjpc/zwaa047

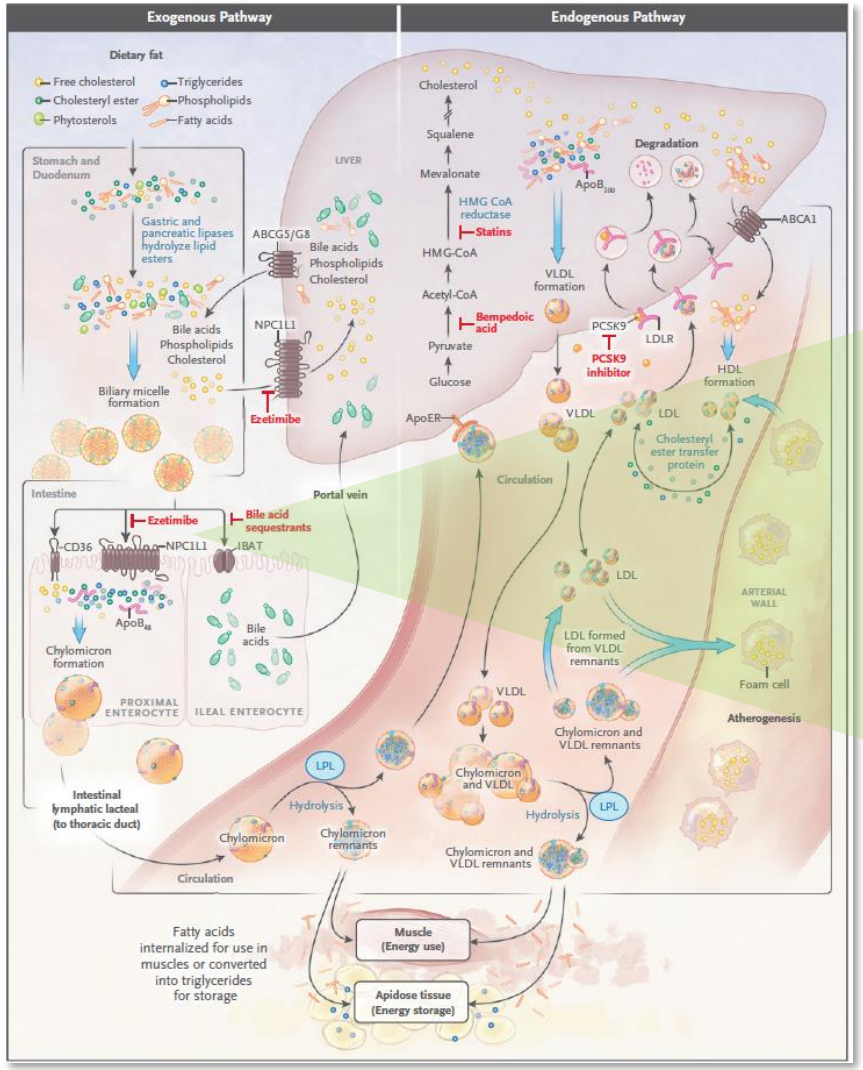
And , at least 50% REDUCTIÓN !!!

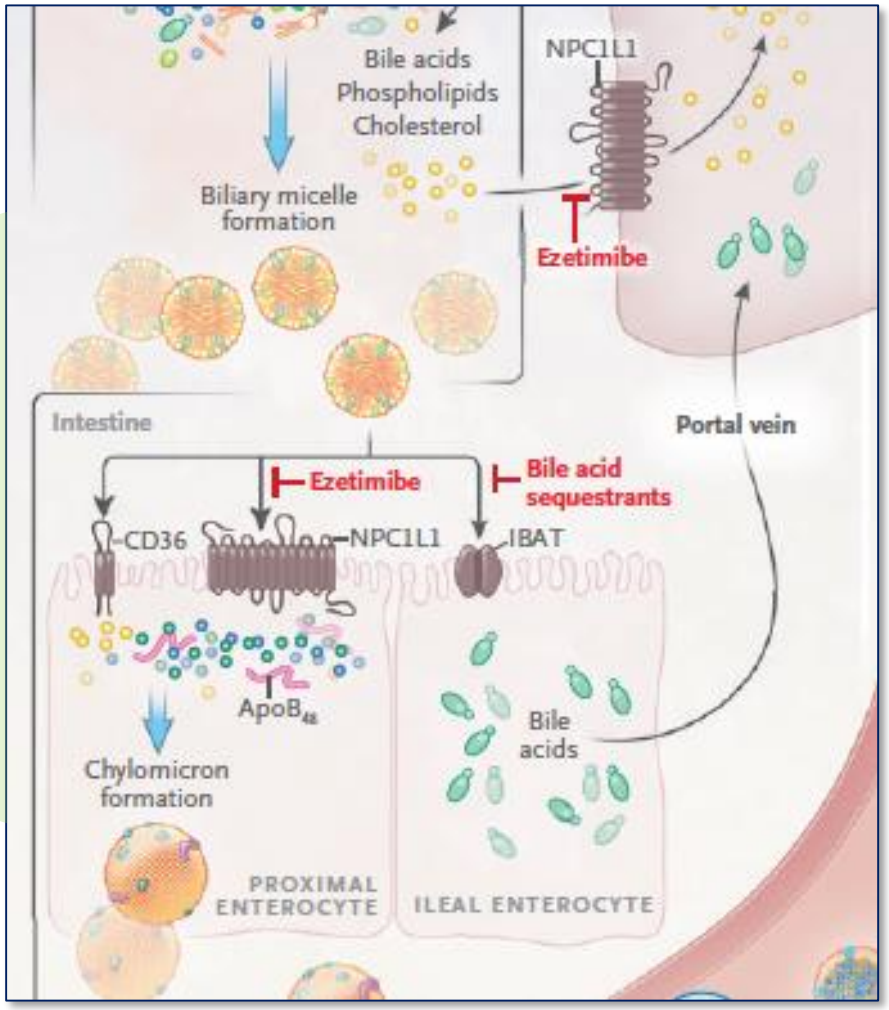


Weng TC, *et al. J Clin Pharm Ther* . 2010;35:139-151
Mukhtar RY, *et Al. Int J Clin Pract* . 2015;59(2):239-252

European Heart Journal doi:10.1093/eurheartj/ehw106

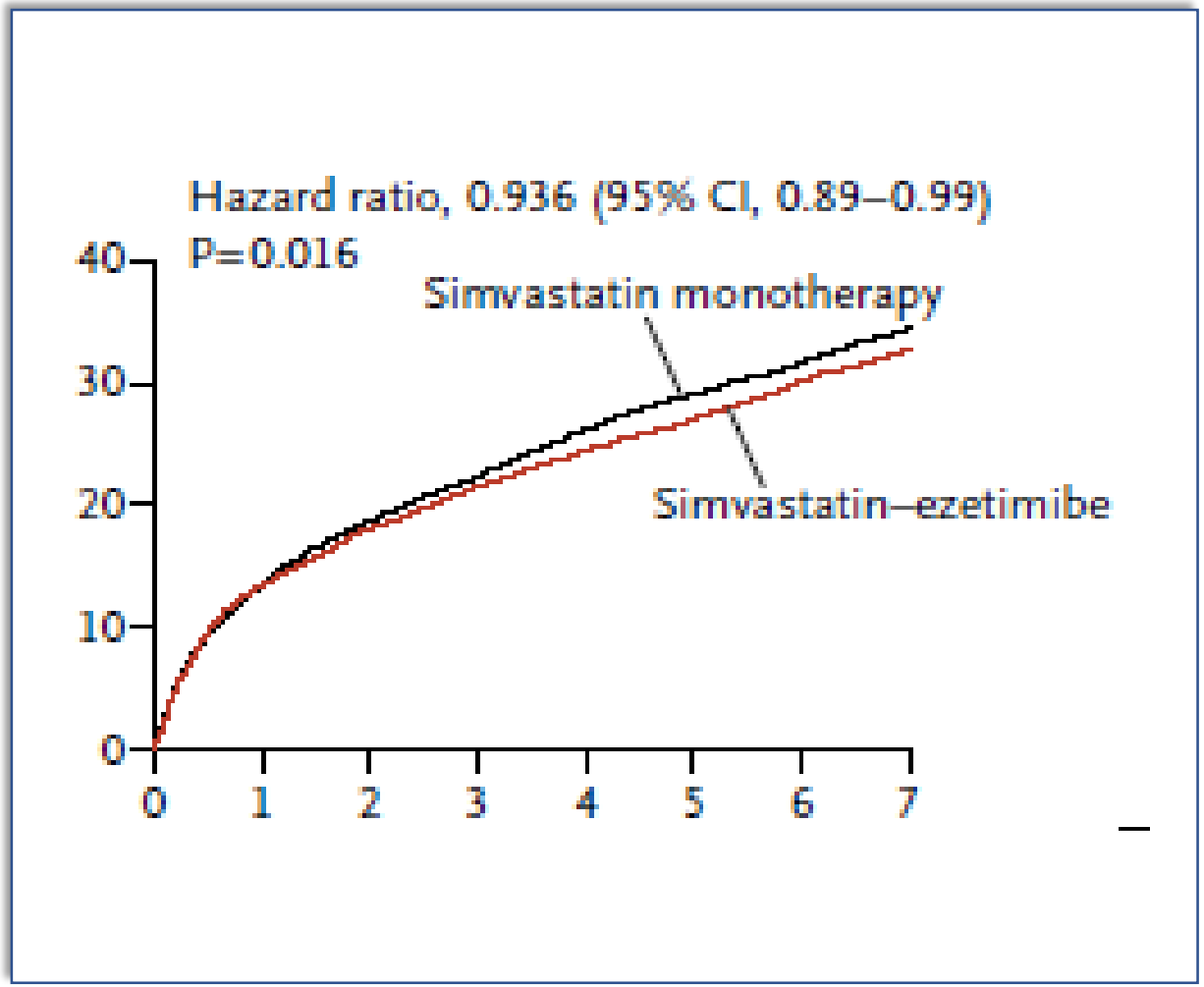
Ezetimibe: Selective Inhibitor of cholesterol transporter NPC1L1



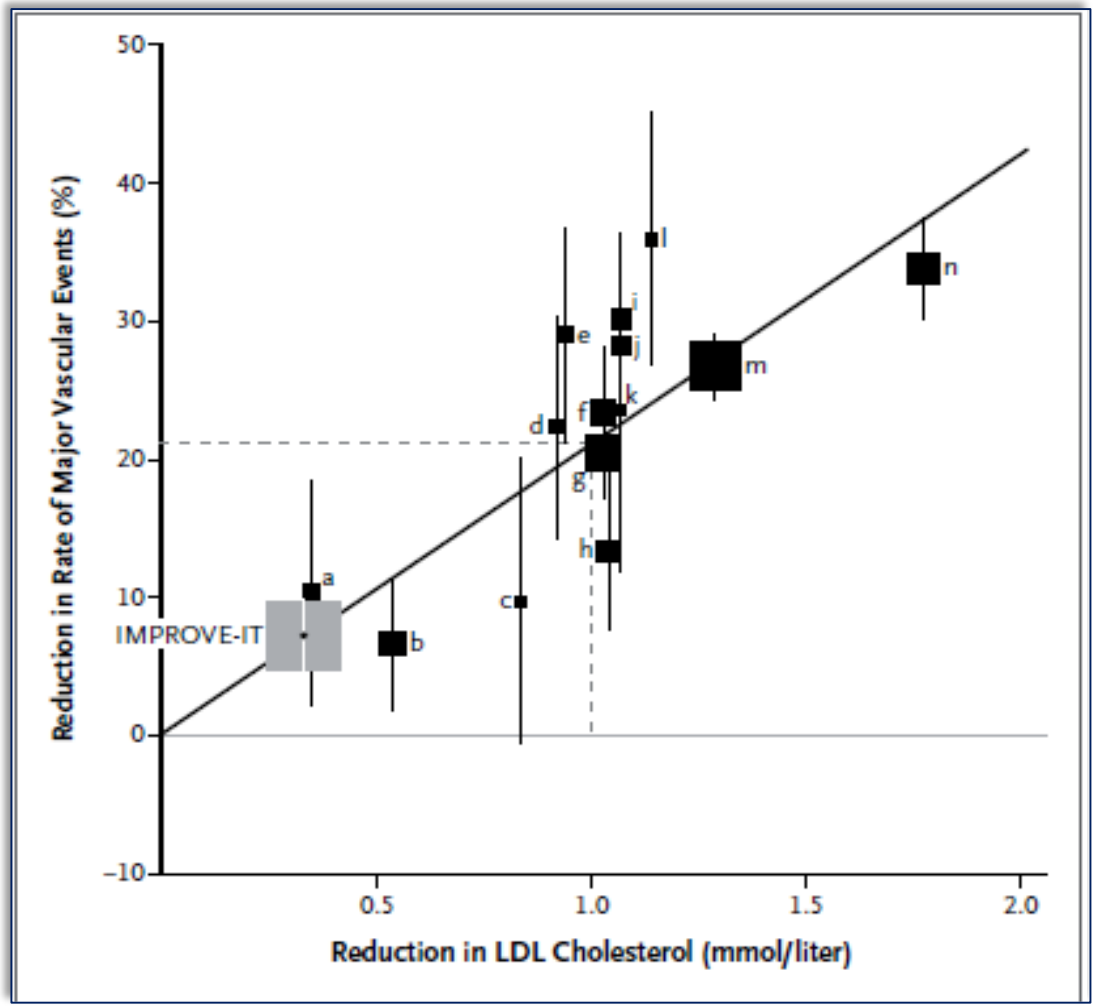


Michos ED et al NEJM 2019; 381:1557-67

IMPROVE-IT TRIAL



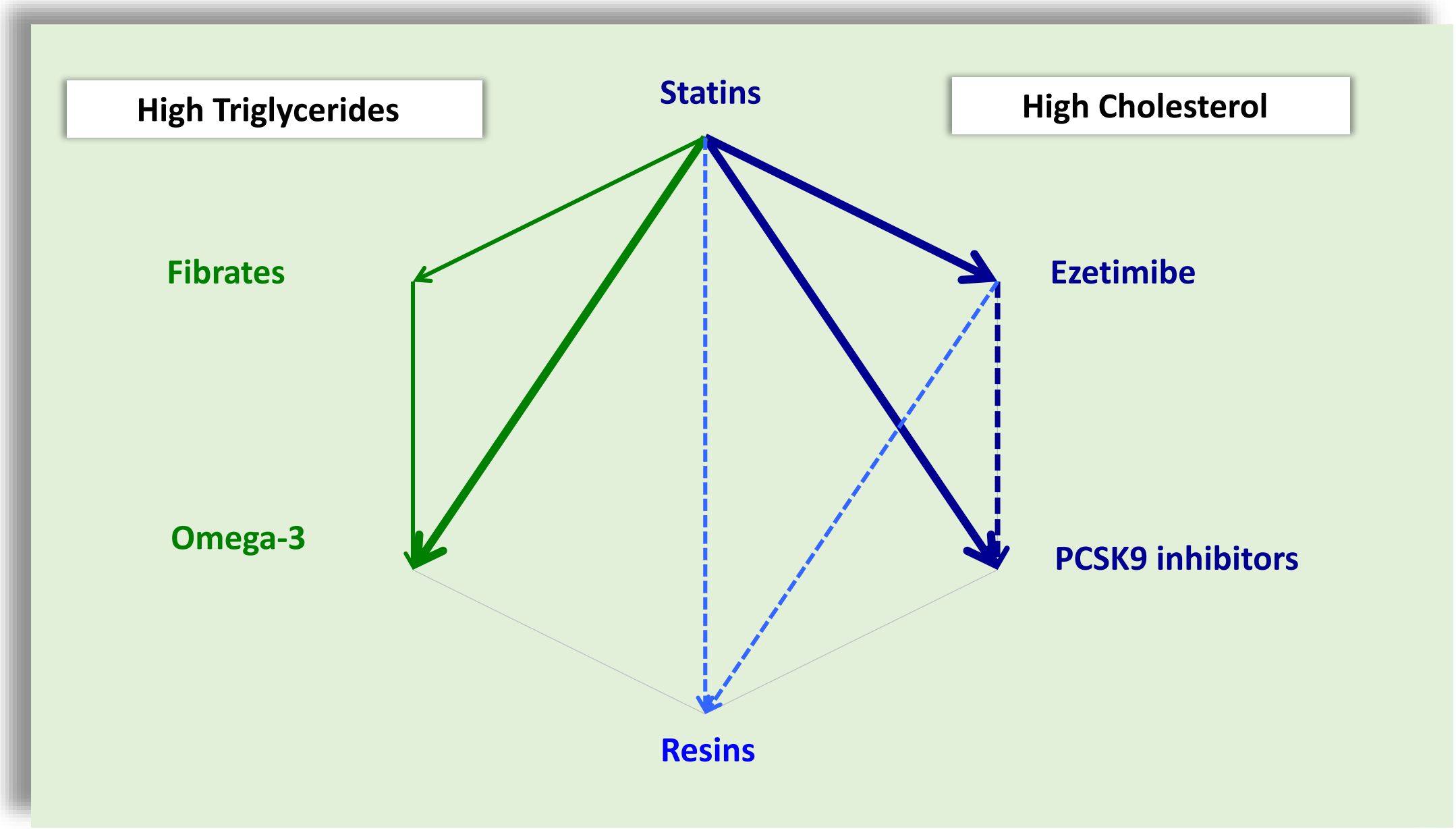
First non statin LLD to show CV benefit



Risk reduction according LDL decrease

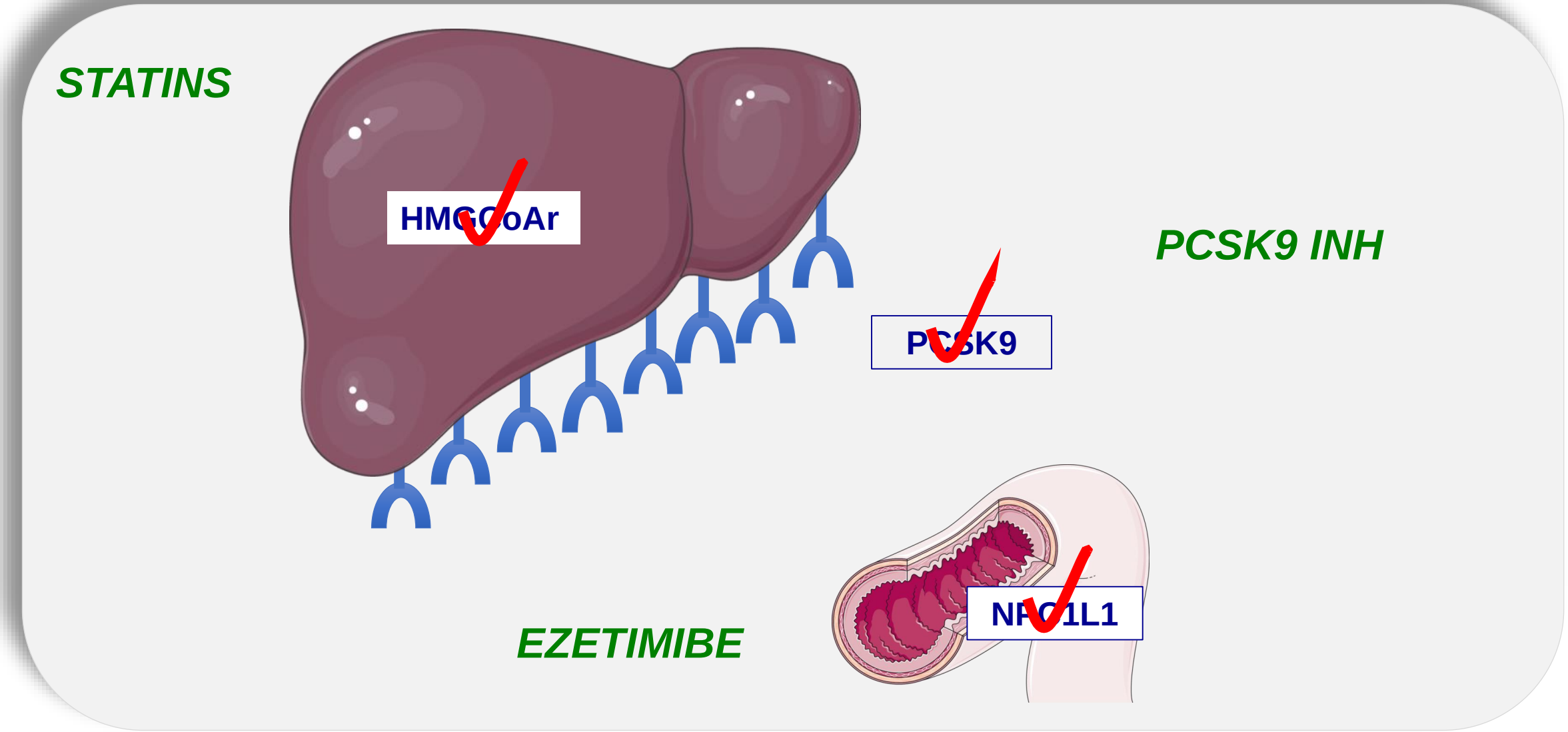
Cannon CJ N Engl J Med 2015;372:2387-97.

Evidence-based combined lipid lowering therapies (Thick arrows I,A,B)



Masana L et al . Curr Card Reports 2020; Sept

LIPID LOWERING COMBINATION THERAPY = SINERGY



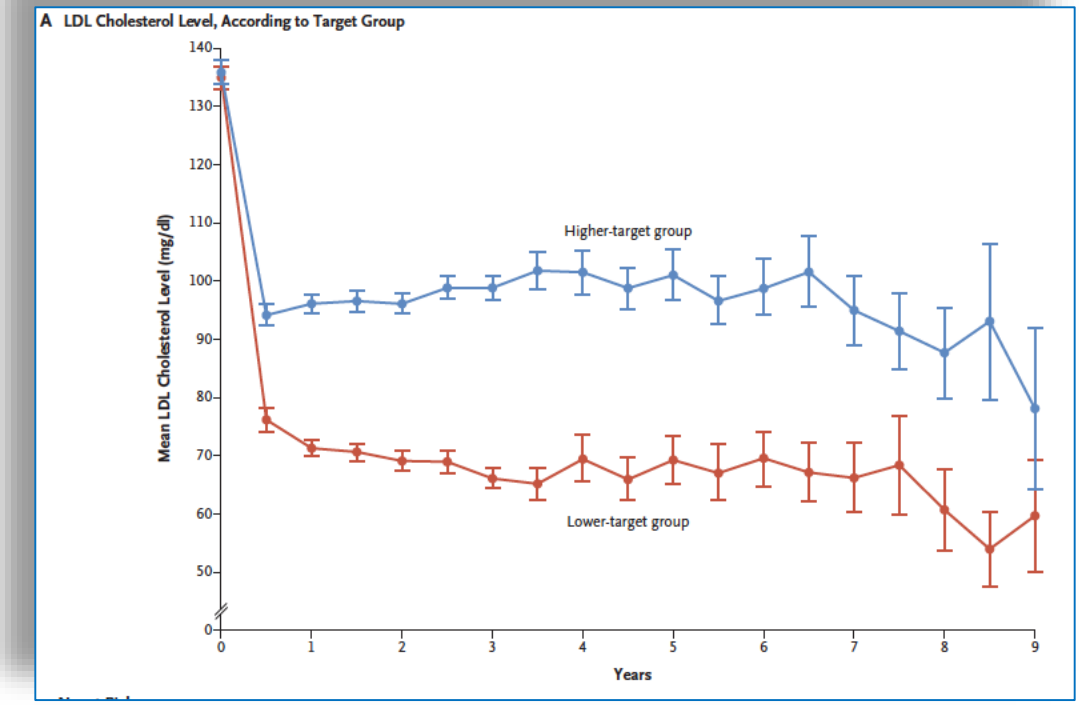
Masana L . EAS 2019 Maastrich

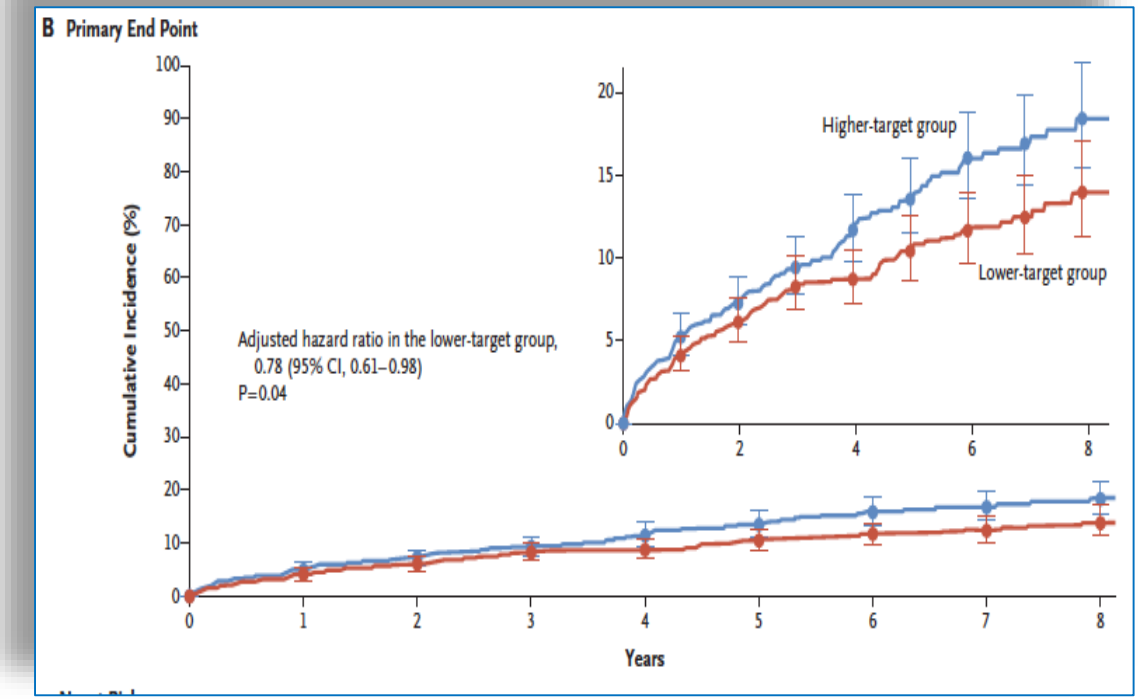
	Low intensity cholesterol lowering therapy <- 30%	Mild intensity cholesterol lowering therapy >30%<50%	High intensity cholesterol lowering therapy >50%<60%	Very high intensity cholesterol lowering therapy >60%<80%*	Extremely high intensity cholesterol lowering therapy >80%<85%
Oral Monotherapy	Simvastatin 10 Pravastatin 10-20 Lovastatin 10-20 Fluvastatin 40 Pitavastatin 1 Ezetimibe 10	Atorvastatin 10-20 Rosuvastatin 5-10 Simvastatin 20-40 Pravastatin 40 Lovastatin 40 Fluvastatin 80 Pitavastatin 2-4	Atorvastatin 40-80 Rosuvastatin 20-40		
Oral combination therapy		Simvastatin 10 + Ezetimibe 10 Pravastatin 20 + Ezetimibe 10 Lovastatin 20 + Ezetimibe 10 Fluvastatin 40 + Ezetimibe 10 Pitavastatin 1 + Ezetimibe 10	Atorvastatin 10-20 + Ezetimibe 10 Rosuvastatin 5-10 + Ezetimibe 10 Simvastatin 20-40 + Ezetimibe 10 Pravastatin 40 + Ezetimibe 10 Lovastatin 40 + Ezetimibe 10 Fluvastatin 80 + Ezetimibe 10 Pitavastatin 2-4 + Ezetimibe 10	Atorvastatin 40-80 + Ezetimibe 10 Rosuvastatin 20-40 + Ezetimibe 10	
Oral + subcutaneous combination therapy		Alirocumab 75		Alirocumab 150 Evolocumab 140 Atorvastatin 10-20 + Alirocumab/Evolocumab* Rosuvastatin 5-10 + Alirocumab/Evolocumal Simvastatin 40 + Alirocumab/Evolocumab	Atorvastatin 40-80 + Alirocumab/Evolocumab Rosuvastatin 20-40 + Alirocumab/Evolocumab Atorvastatin 40-80 + Ezetimibe 10 + Alirocumab/Evolocumab Rosuvastatin 20-40 + Ezetimibe 10 + Alirocumab/Evolocumab

Masana L et al . Curr Card Reports 2020; Sept

A Comparison of Two LDL Cholesterol Targets after Ischemic Stroke

2860 patients after TIA and ischemic stroke were enrolled and followed for a median of 3.5 years



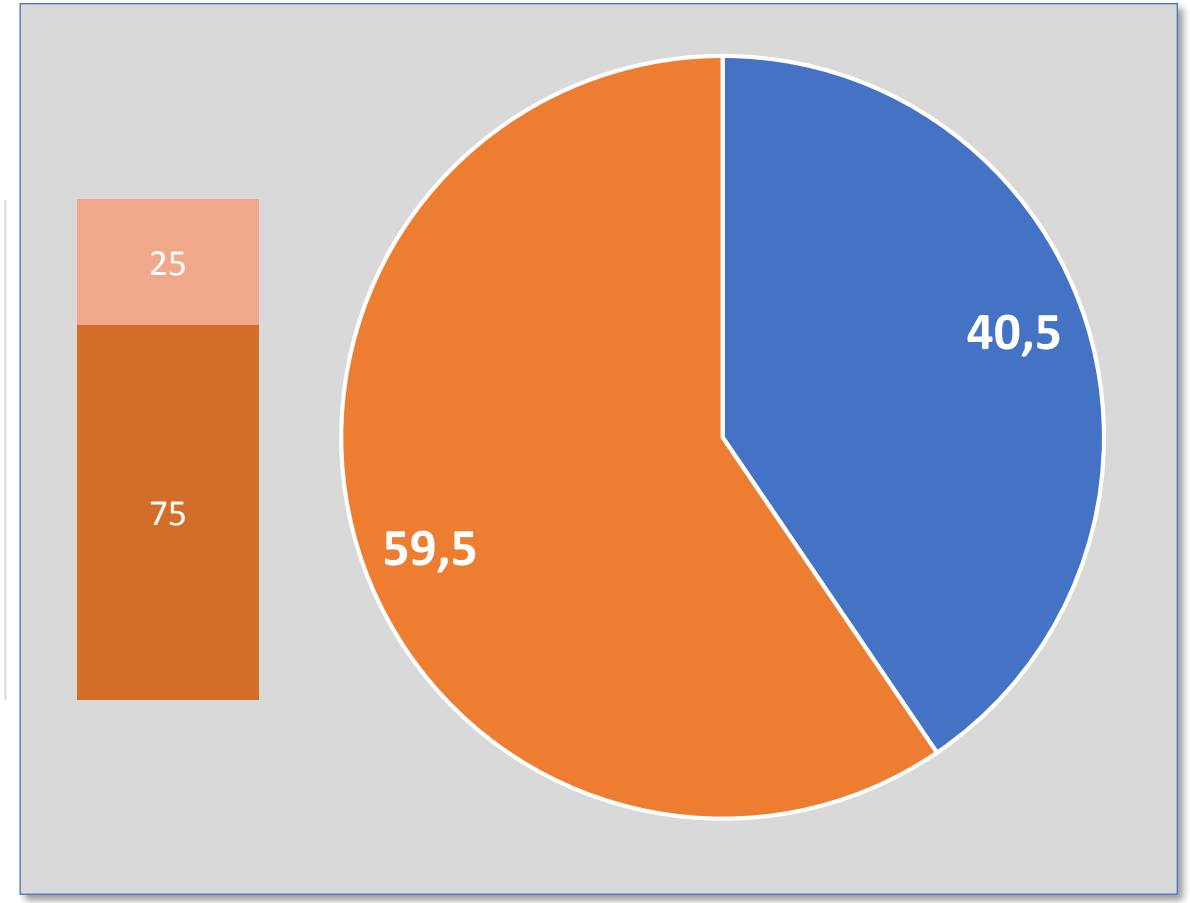


Primary end-point:
Ischemic stroke, myocardial infarction, urgent coronary or carotid revascularization, or death from cardiovascular causes.

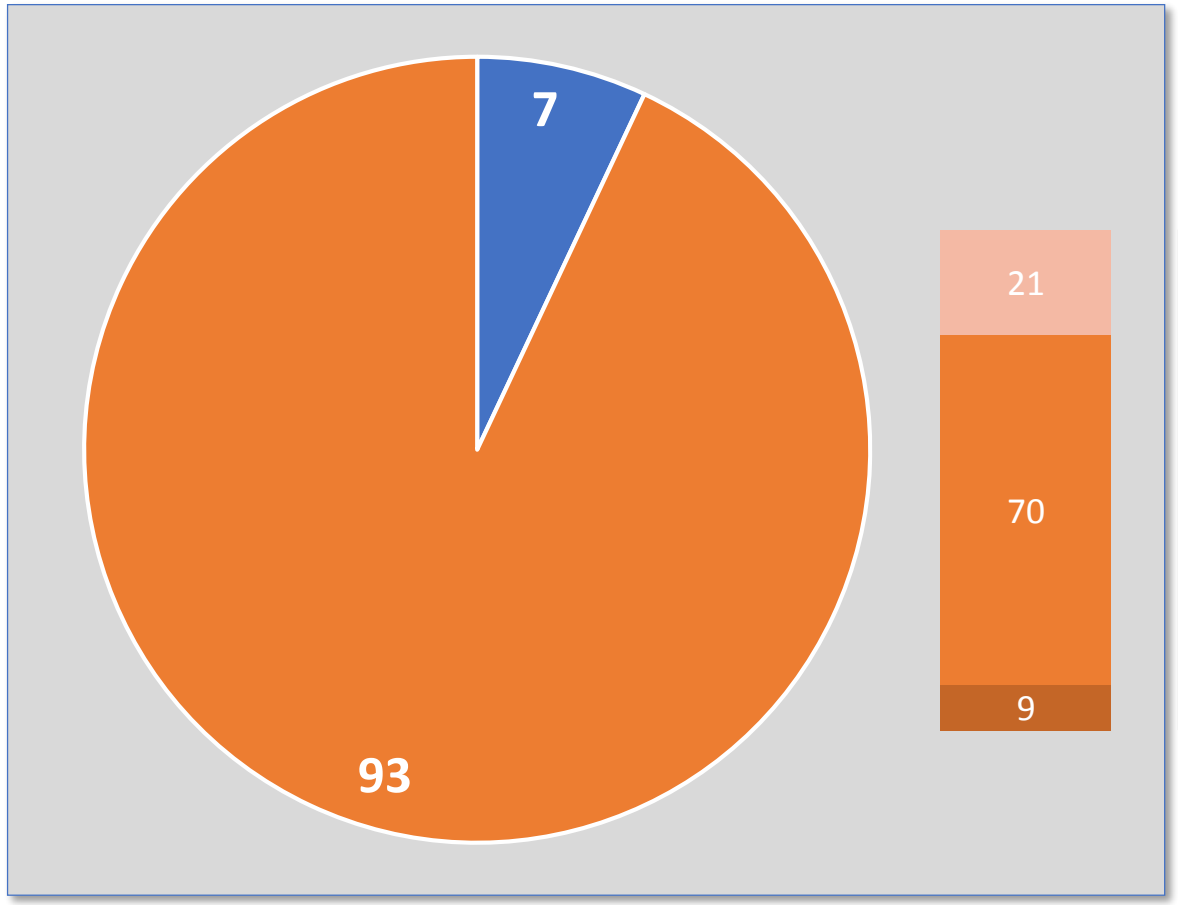
Amarenco P et al. NEJM 2019

Three out of five patients in the <70 mg/dl group were on combination therapy

OBJ < 70 mg/dl



OBJ : 90-110 mg/dl



STATIN + EZETIMIBE

STATIN

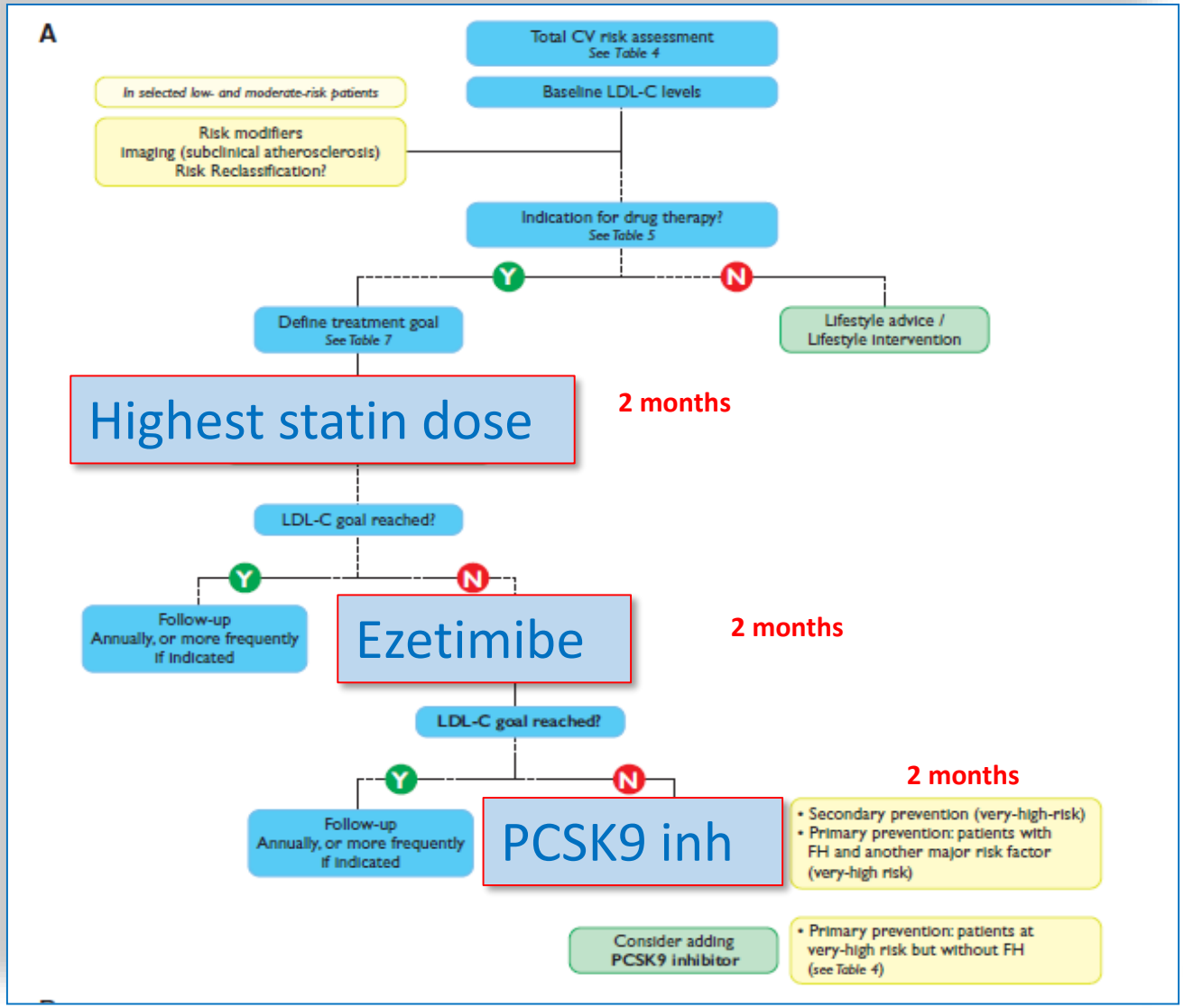
HIGH INTENSITY

MODERATE INTENSITY

LOW INTENSITY

Adapted from Amarenco P et al. NEJM 2019 (supplemental material)

2019 ESC/EAS dyslipidemia guidelines: STEP BY STEP THERAPY STRATEGY



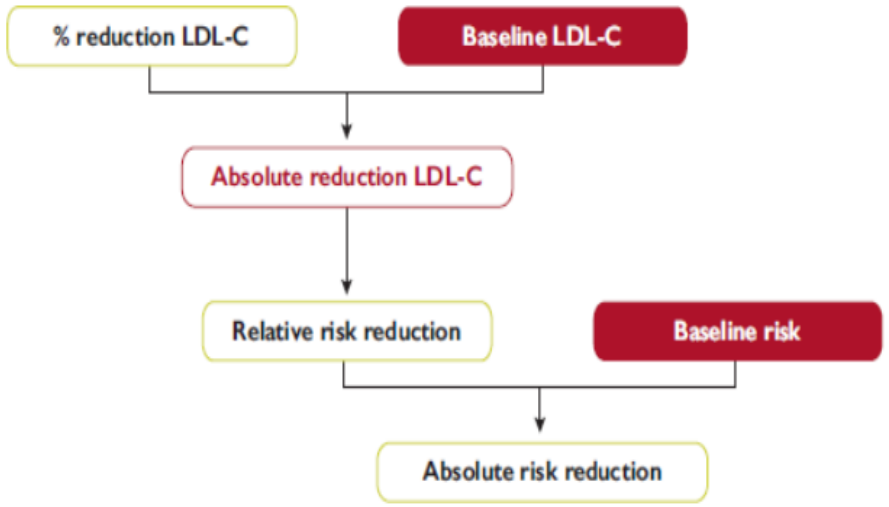
Class[a]	Level[b]
I	A
I	B
I	A

Mach F, et al. European Heart Journal. 2019;00:1–78

2019 ESC/EAS dyslipidemia guidelines: PLANNING THERAPY STARTEGY

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%



Mach F, et al. European Heart Journal. 2019;00:1–78

DISEASE	CLINICAL CONDITIONS	CV RISK CATEGORY	LDL-C TARGET	CLASS/ LEVEL OF EVIDENCE	LIPID LOWERING THERAPY RECOMMENDED*
Atherosclerotic cardiovascular disease	Coronary heart disease. Ischemic stroke. Peripheral artery disease or Unequivocal image of ASCVD	Very High	<55 mg/dl and 50% reduction	I,A	Very High Intensity Oral combination therapy (if target not attained add PCSK9 inhibitors)**
Type 2 diabetes	organ damage or 3 additional risk factors	Very High	<55 mg/dl and 50% reduction	I,C	Very High Intensity Oral combination therapy
	> 10 y of duration or up to two additional risk factors	High	<70 mg/dl and 50% reduction	I,A	High Intensity Oral combination therapy (If basal LDL-C < 140 mg/dl high intensity statin monotherapy can also be effective)
	age < 50 y and duration < 10 y and no additional risk factors	Moderate	< 100 mg/dl	IIa,A	High Intensity statin monotherapy or combination therapy.
Type 1 diabetes	long duration (> 20 y)	Very High	<55 mg/dl and 50% reduction	I,C	Very High Intensity Oral combination therapy
	> 10 y of duration or up to two additional risk factors	High	<70 mg/dl and 50% reduction	I,A	High Intensity Oral combination therapy (If basal LDL-C < 140 mg/dl high intensity statin monotherapy can also be effective)
	age < 35 y, and duration < 10 y and no additional risk factors	Moderate	< 100 mg/dl	IIa,A	High Intensity statin monotherapy or combination therapy.

Masana L et al . Curr Card Reports 2020; Sept

DISEASE	CLINICAL CONDITIONS	CV RISK CATEGORY	LDL-C TARGET	CLASS/ LEVEL OF EVIDENCE	LIPID LOWERING THERAPY RECOMMENDED*
Chronic kidney disease.	eGFR < 30 ml/min/m²	Very High	<55 mg/dl and 50% reduction	I,C	Very High Intensity Oral combination therapy
	eGFR >30 <60 ml/min/m²	High	<70 mg/dl and 50% reduction	I,A	High Intensity Oral combination therapy (If basal LDL-C < 140 mg/dl high intensity statin monotherapy can also be effective)
Familial Hypercholesterolemia	ASCVD or 1 additional major risk factor	Very High	<55 mg/dl and 50% reduction	IIa,C	Very High Intensity Oral combination therapy (if target not attained add PCSK9 inhibitors)***
	without additional risk factors	High	<70 mg/dl and 50% reduction	I,A	Very High Intensity Oral combination therapy
Severe Single Risk Factor	LDL-C above 190 mg/dl	High	<70 mg/dl and 50% reduction	I,A	Very High Intensity Oral combination therapy
	Blood pressure above 180/110	High	<70 mg/dl and 50% reduction	I,A	High Intensity Oral combination therapy (If basal LDL-C < 140 mg/dl high intensity statin monotherapy can also be effective)
Combination of risk factors	SCORE >- 10	Very High	<55 mg/dl and 50% reduction	I,C	Very High Intensity Oral combination therapy
	SCORE >-5<10	High	<70 mg/dl and 50% reduction	I,A	High Intensity Oral combination therapy (If basal LDL-C < 140 mg/dl high

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Take-Home Messages

LDL-C is a causal factor for atherosclerosis.

Cardiovascular risk reduction is driven by LDL-C reduction, regardless of LLT used

In patients at high / very high CV risk, therapy should be based in the high intensity lipid lowering therapy, taking advantage of all available drugs

Planning therapy and personalized medicine are crucial to achieve targets.