Role of Combination Therapy in Lipid Management

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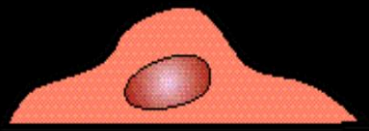
Does it matter how LDL-C is lowered?

Statin vs. LDL-C hypothesis

Some Potential Mechanisms of Statin Therapy

Cells in Atheroma

Endothelial cell

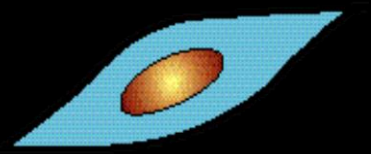


- Increases **NO** production[1]

Macrophage foam cell

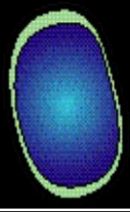
- Reduces **monocyte** recruitment and activation[2]

Smooth muscle cell



- Reduces **proliferation**[3]

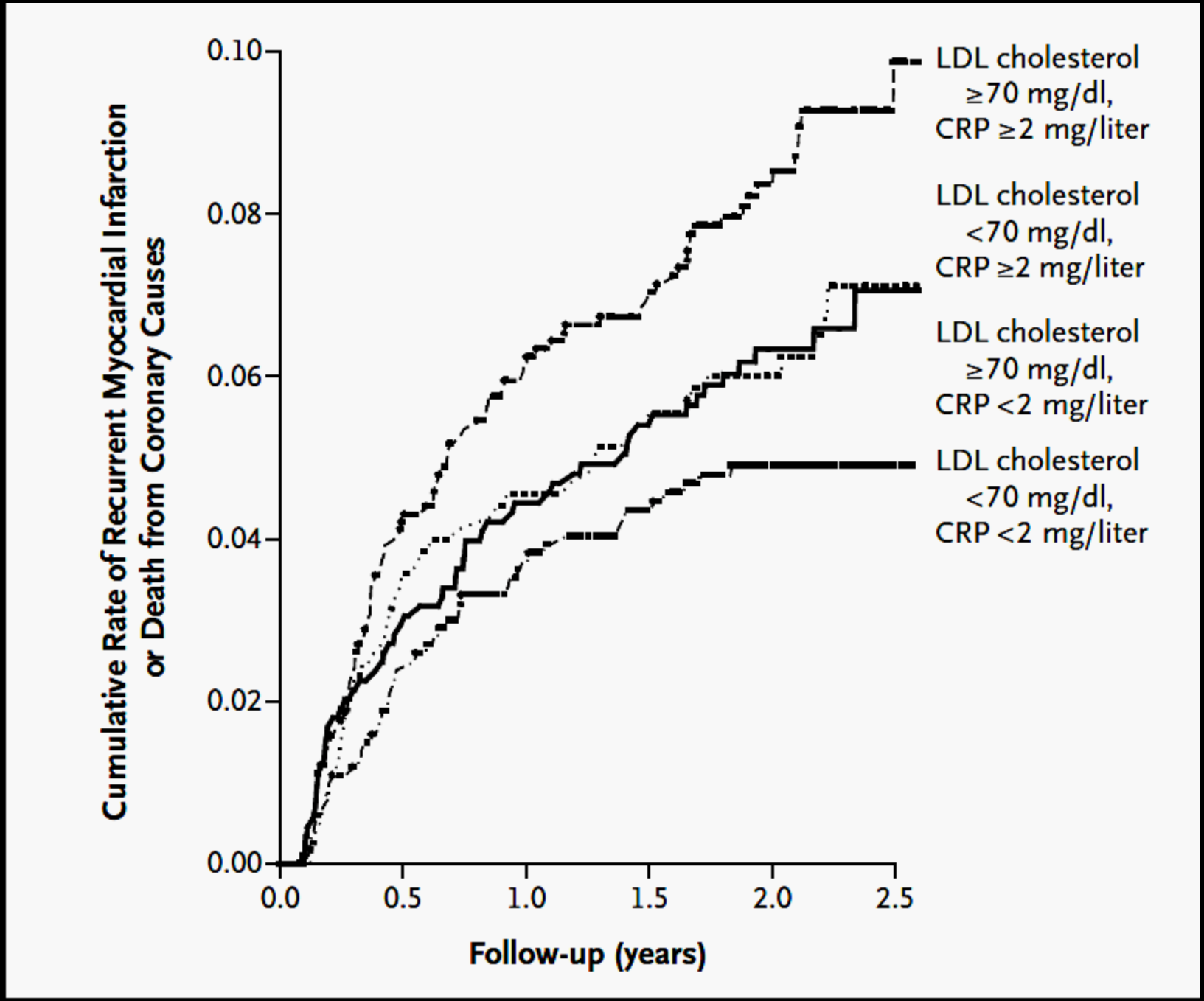
T-Lymphocyte



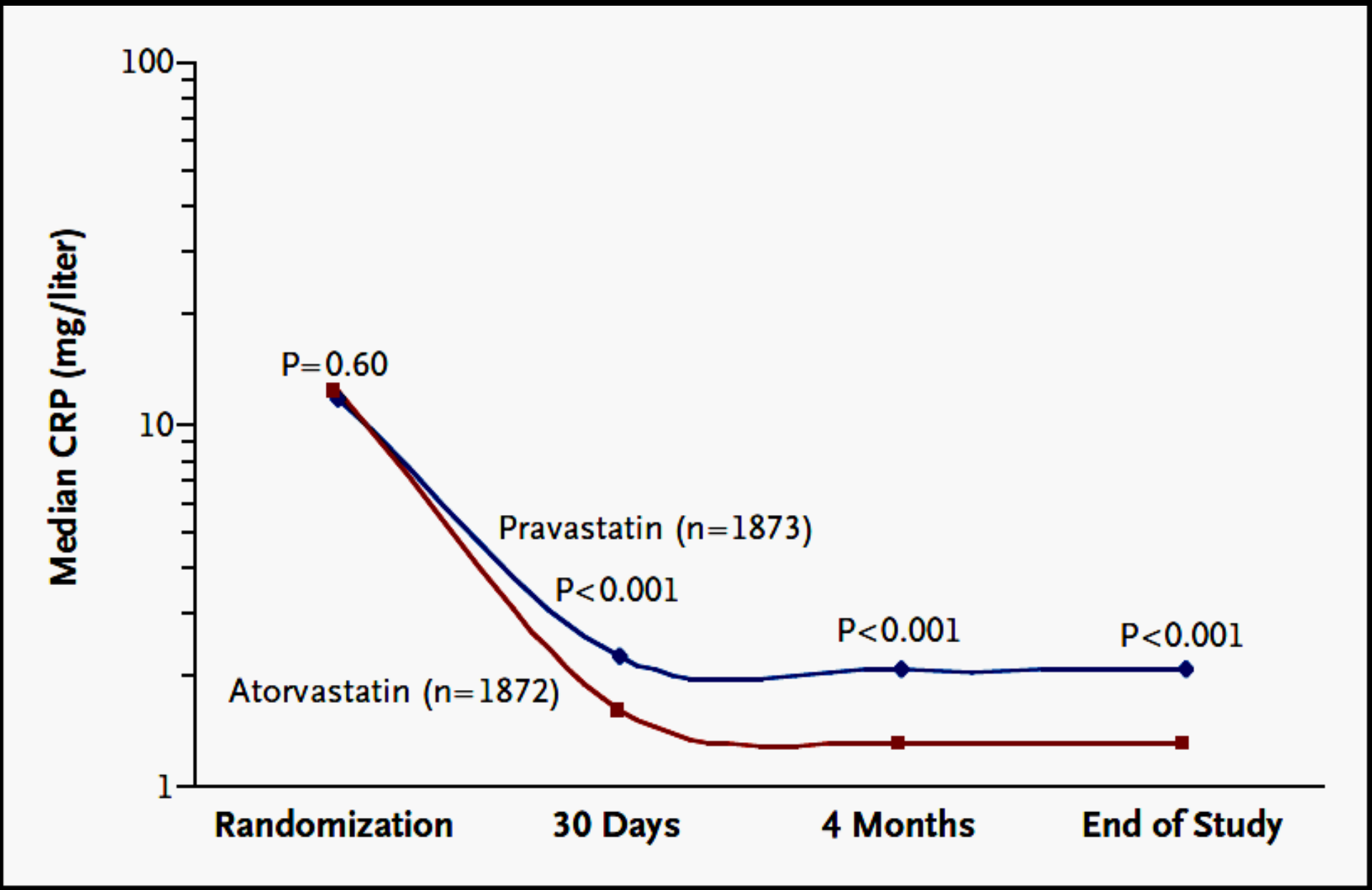
- Reduces activation by **cytokines**[4]

Net effect—improved endothelial function

1. Laufs U et al. *Circulation*. 1998;97:1129-1135.
2. Williams JK et al. *J Am Coll Cardiol*. 1998;31:684-691.
3. Bellosta et al. *Atherosclerosis*. 1998;137(suppl):S101-S109.
4. Tatsuno I et al. *Biochem Biophys Res Commun*. 1997;241:376-382.



Ridker PM, et al. N Engl J Med 2005;352:20-8



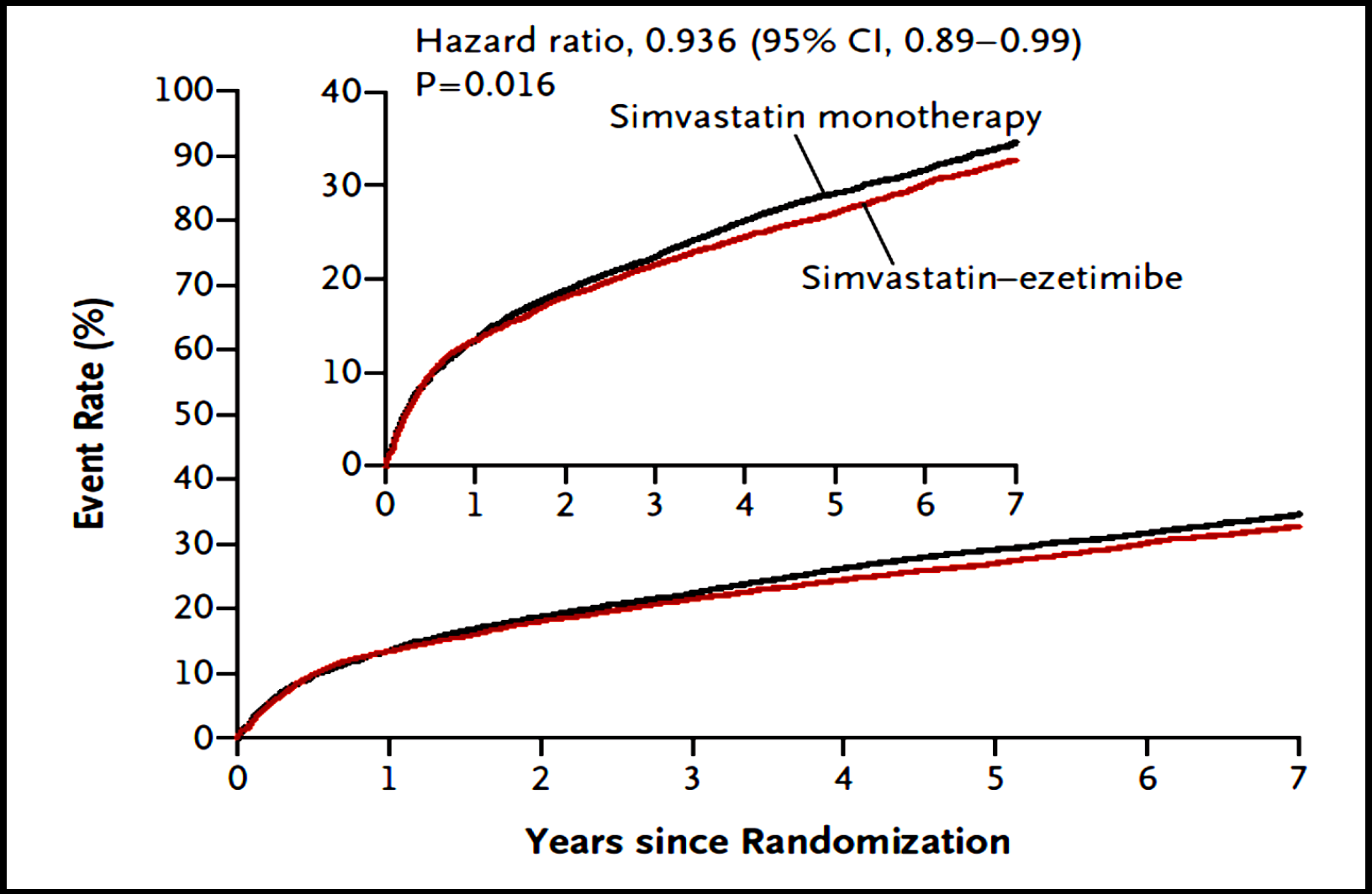
Ridker PM, et al. N Engl J Med 2005;352:20-8

Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

Christopher P. Cannon, M.D., Michael A. Blazing, M.D., Robert P. Giugliano, M.D., Amy McCagg, B.S., Jennifer A. White, M.S., Pierre Theroux, M.D., Harald Darius, M.D., Basil S. Lewis, M.D., Ton Oude Ophuis, M.D., Ph.D., J. Wouter Jukema, M.D., Ph.D., Gaetano M. De Ferrari, M.D., Witold Ruzyllo, M.D., Paul De Lucca, Ph.D., KyungAh Im, Ph.D., Erin A. Bohula, M.D., D.Phil., Craig Reist, Ph.D., Stephen D. Wiviott, M.D., Andrew M. Tershakovec, M.D., M.P.H., Thomas A. Musliner, M.D., Eugene Braunwald, M.D., and Robert M. Califf, M.D., for the IMPROVE-IT Investigators*

N Engl J Med 2015. DOI: 10.1056/NEJMoa1410489

Cardiovascular outcomes associated with LDL-C lowered to 70 mg/dl vs 54 mg/dl



Cannon CP, et al. N Engl J Med 2015. DOI: 10.1056/NEJMoa1410489

Study	Drugs	n	LDL-C placebo (mg/dl)	LDL-C treatment (mg/dl)	Hazard ratio
IMPROVE-IT	Simvastatin ± ezetimibe	18,144	69.5	53.7	0.936 (P = 0.016)
FOURIER	Statin ± evolocumab	27,564	86	30	0.85 (P<0.001)
ODYSSEY OUTCOMES	Statin ± alirocumab	18,924	97.3*	51.3*	0.85 (P<0.001)

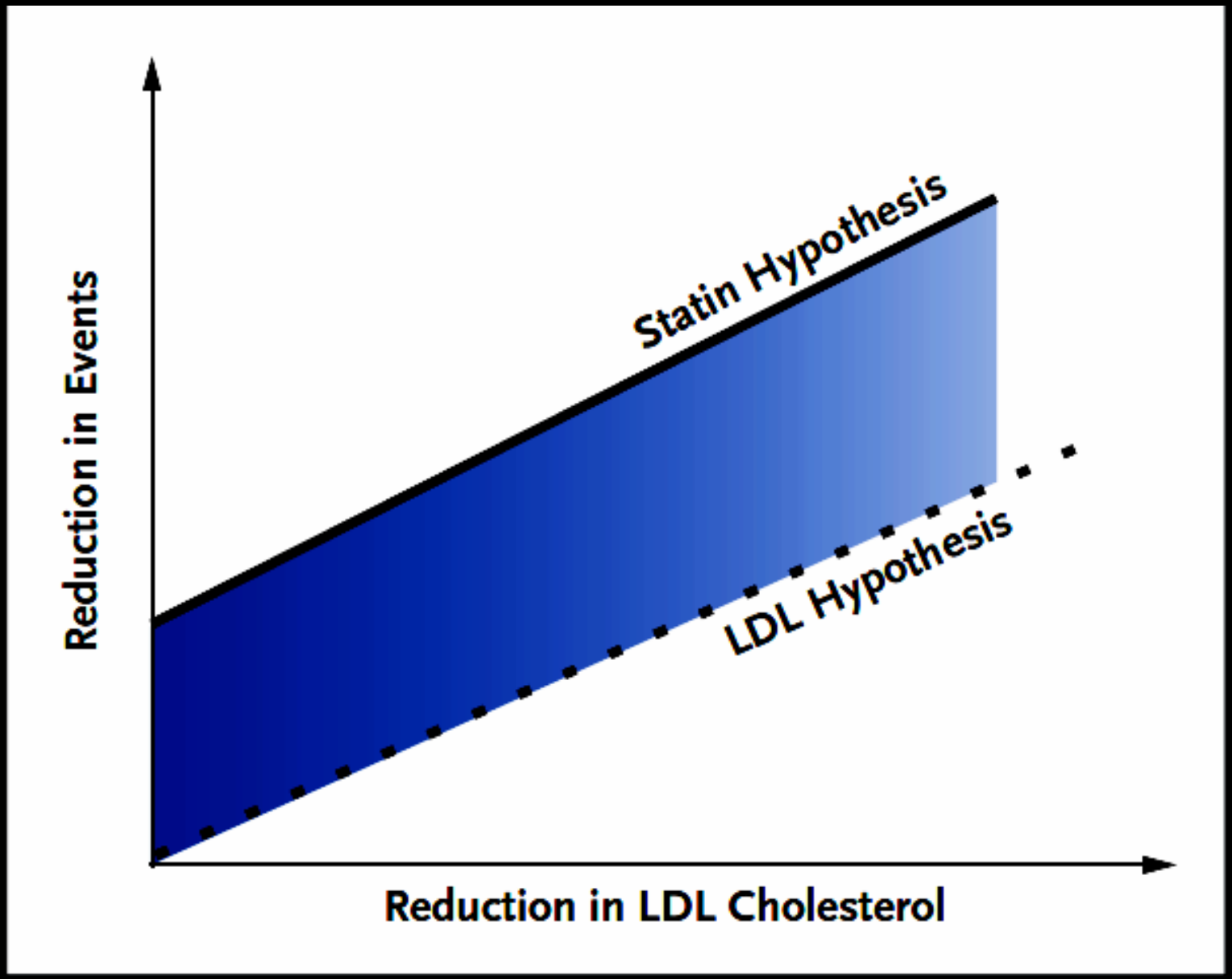
*** Mean of LDL-C level at 4, 12, and 48 months after randomization**

Ridker PM, et al. Lancet 2009; 373: 1175–82

Sabatine MS, et al. N Engl J Med 2017. DOI: 10.1056/NEJMoa1615664

Schwartz GG, et al. N Engl J Med 2018. DOI: 10.1056/NEJMoa1801174

Conclusion



Jarcho JA, Keaney JF. N Engl J Med 2015;372,2448–2450.

Lower LDL-C Is Better

But

How Low Should We Go?

Risk level	LDL-C target (mg/dl)	
	ESC 2016	ESC 2019
Very high	↓50% and <70	↓50% and <55*
High	↓50% and <100	↓50% and <70
Moderate	<115	<100
Low		<116

* <40 mg/dl may be considered for patients with ASCVD who experience a second vascular event within 2 years

Catapano AL, et al. Eur Heart J 2016;37:2999-3058
Mach F, et al. Eur Heart J 2019. doi:10.1093/eurheartj/ehz455

For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin-based therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered	IIb	B

Safety of low LDL cholesterol concentrations. There are no known adverse effects of very low LDL-C concentrations [e.g. <1 mmol/L (40 mg/dL)].

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

LDL-C level: how low should we go?

Study, year	Drug	LDL-C	Side-effects
Robinson, 2017	Alirocumab	<25 mg/dl	Cataract
Everett, 2014	Rosuvastatin	<30 mg/dl	DM, hematuria, insomnia, hepatic steatosis
Sabatine, 2017	Evolocumab	30 mg/dl	Relatively save
Cannon, 2015	Ezetimibe/ simvastatin	54 mg/dl	Relatively save

Robinson JG, et al. J Am Coll Cardiol 2017;69:471–82
Everett BM, et al. Am J Cardiol 2014;114:1682–9
Sabatine MS, et al. N Engl J Med 2017. DOI: 10.1056/NEJMoa1615664
Cannon CP, et al. N Engl J Med 2015;372:2387–97

IMPROVE-IT Study: Prespecified Safety End Points

End Point	Simvastatin Monotherapy (N=9077)	Simvastatin–Ezetimibe (N=9067)	P Value
	no. of patients (%)		
ALT, AST, or both ≥3× ULN	208 (2.3)	224 (2.5)	0.43
Cholecystectomy	134 (1.5)	133 (1.5)	0.96
Gallbladder-related adverse events	321 (3.5)	281 (3.1)	0.10
Rhabdomyolysis	18 (0.2)	13 (0.1)	0.37
Myopathy	10 (0.1)	15 (0.2)	0.32
Rhabdomyolysis or myopathy	28 (0.3)	27 (0.3)	0.90
Rhabdomyolysis, myopathy, myalgia with creatine kinase elevation ≥5× ULN	58 (0.6)	53 (0.6)	0.64
Cancer†	732 (10.2)	748 (10.2)	0.57
Death from cancer†	272 (3.6)	280 (3.8)	0.71

Cannon CP, et al. N Engl J Med 2015. DOI: 10.1056/NEJMoa1410489

Strategy to Achieve LDL-C Target

Not all patients will have their LDL-C target be achieved with high intensity statins

High – Moderate - and Low - Intensity Statin

High intensity statin therapy (mg)	Moderate intensity statin therapy (mg)	Low intensity statin therapy (mg)
Daily dose lowers LDL-C on average, by approx. ≥50%	Daily dose lowers LDL-C on average, by approx. 30% to <50%	Daily dose lowers LDL-C on average, by approx. <30%
Atorvastatin 40-80 Rosuvastatin 20-40	Atorvastatin 10-20 Rosuvastatin 5-10 Simvastatin 20-40 Pravastatin 40-80 Lovastatin 40 Fluvastatin Xl 80 Fluvastatin 40 bid Pitavastatin 2-4	Simvastatin 10 Pravastatin 10-20 Lovastatin 20 Fluvastatin 20-40 Pitavastatin 1

Donald M. Lloyd-Jones DM, Morris PB, et al. JACC 2016;68:92-125

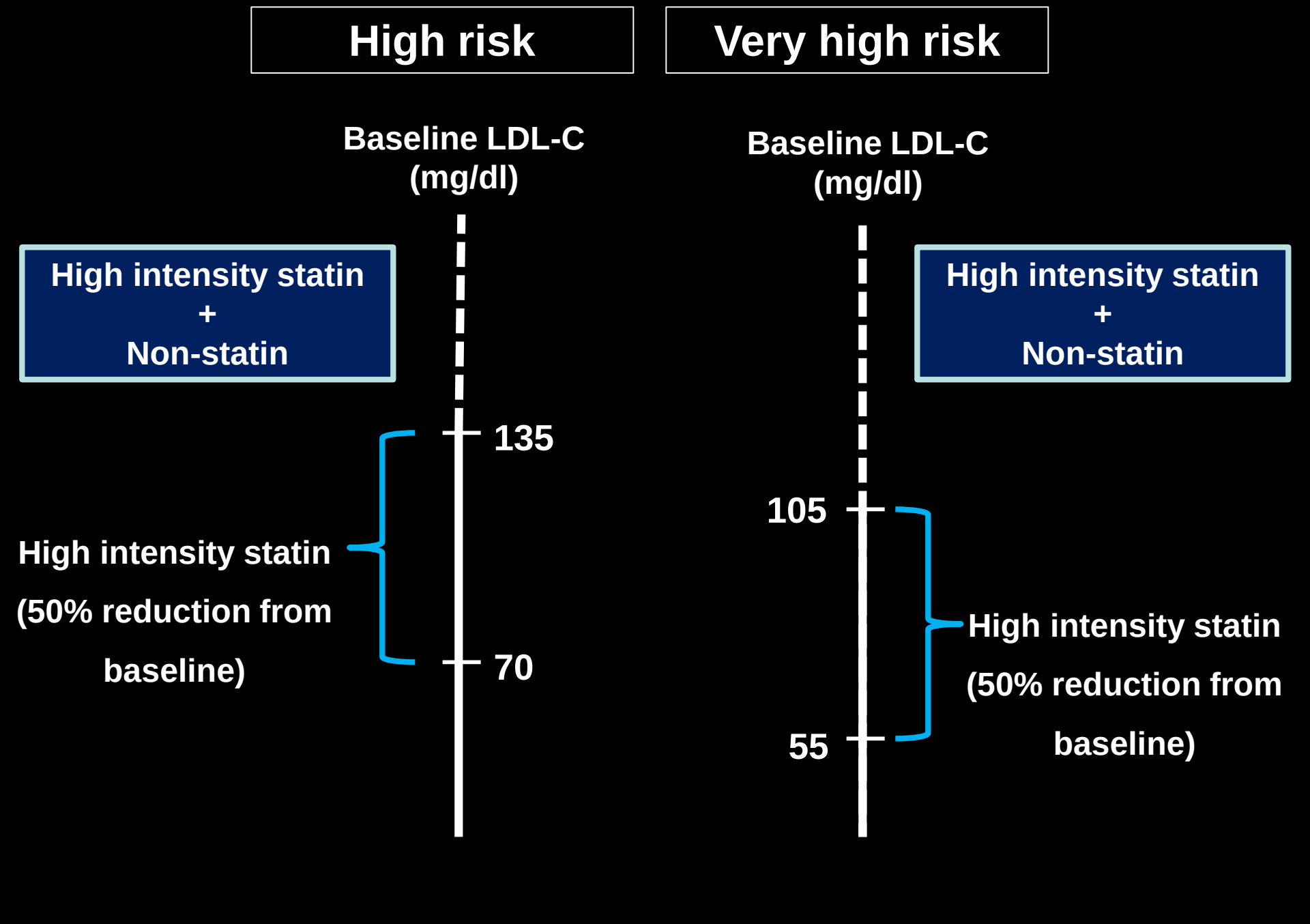
Intensity of lipid lowering treatment

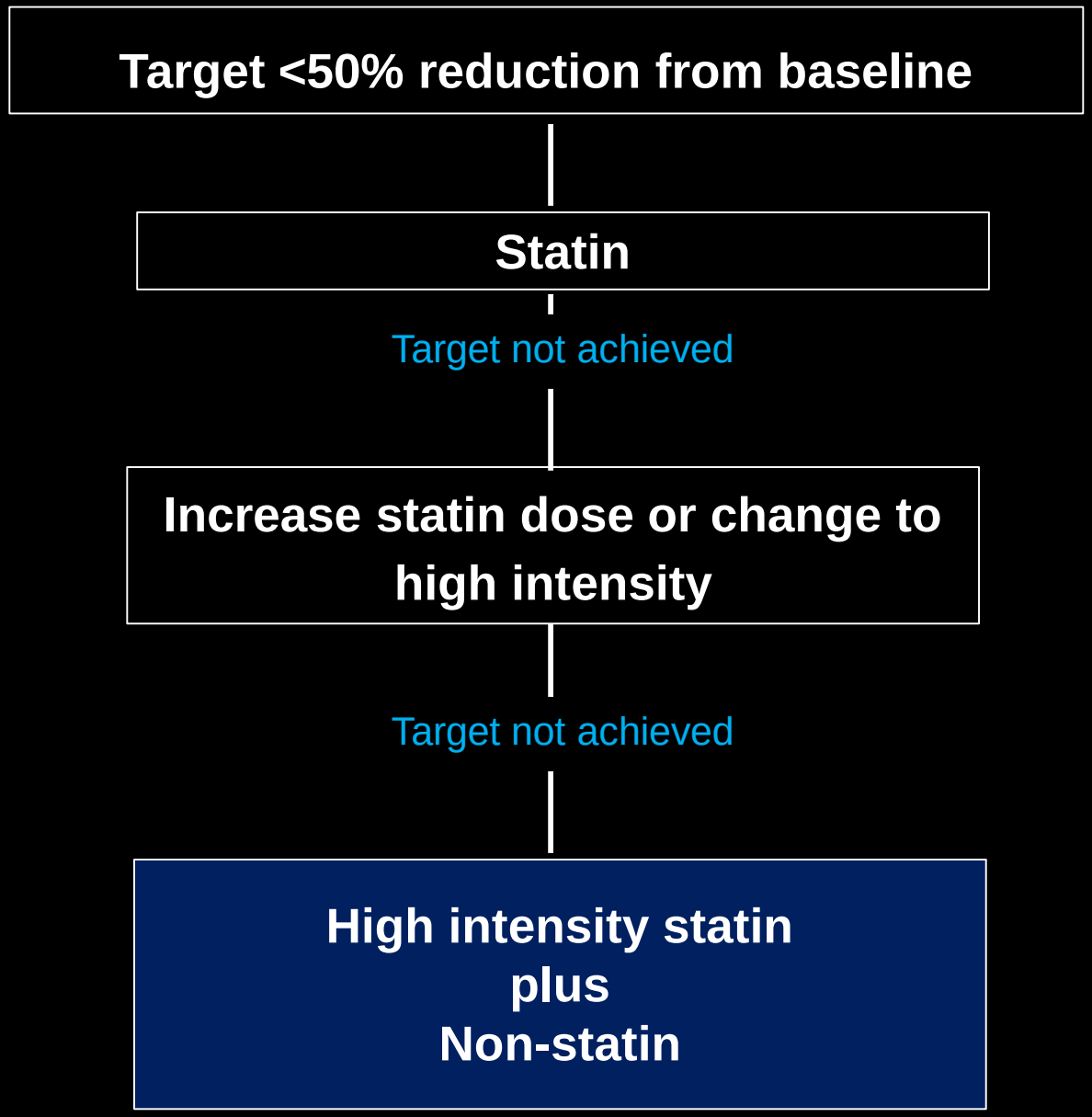
Treatment	Average LDL-C reduction
Moderate intensity statin	≈ 30%
High intensity statin	≈ 50%
High intensity statin plus ezetimibe	≈ 65%
PCSK9 inhibitor	≈ 60%
PCSK9 inhibitor plus high intensity statin	≈ 75%
PCSK9 inhibitor plus high intensity statin plus ezetimibe	≈ 85%

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

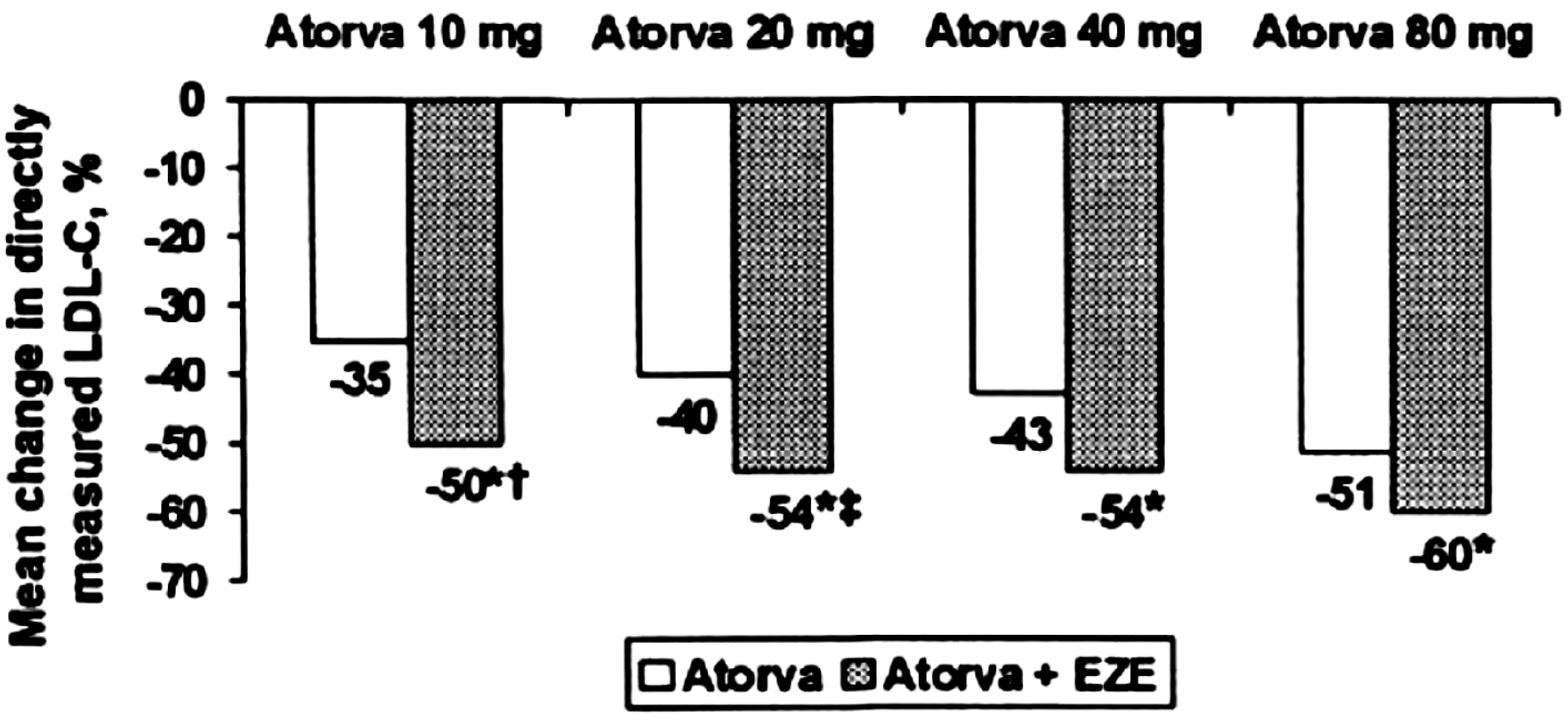
Strategy to Achieve LDL-C Target

The role of combination therapy of high intensity statins and ezetimibe


High risk
Very high risk
Baseline LDL-C (mg/dl)
Baseline LDL-C (mg/dl)
High intensity statin + Non-statin
High intensity statin + Non-statin
135
70
105
55
High intensity statin (50% reduction from baseline)
High intensity statin (50% reduction from baseline)


Target <50% reduction from baseline
Statin
Target not achieved
Increase statin dose or change to high intensity
Target not achieved
High intensity statin
plus
Non-statin

Effect of Ezetimibe Coadministered With Atorvastatin



*corresponding dose of atorvastatin alone

†atorvastatin (20 mg or 40 mg) alone

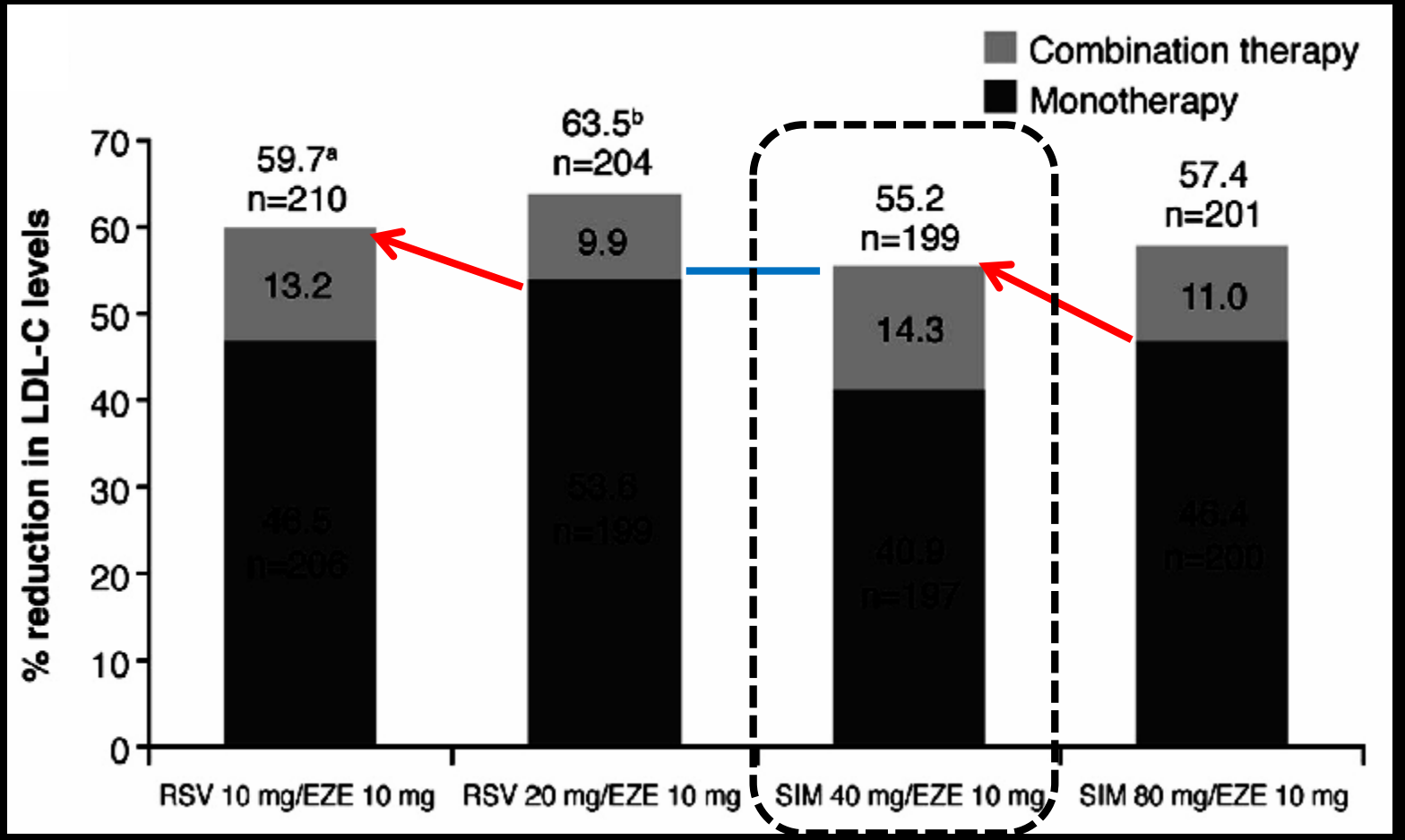
‡atorvastatin (40 mg) alone

Ballantyne CM, et al. Circulation. 2003;107:2409-15

Strategy to Achieve LDL-C Target

The role of combination therapy of moderate intensity statin (simvastatin) and ezetimibe

Efficacy of Combination of Ezetimibe and Statins in Lowering LDL-C at 12 weeks



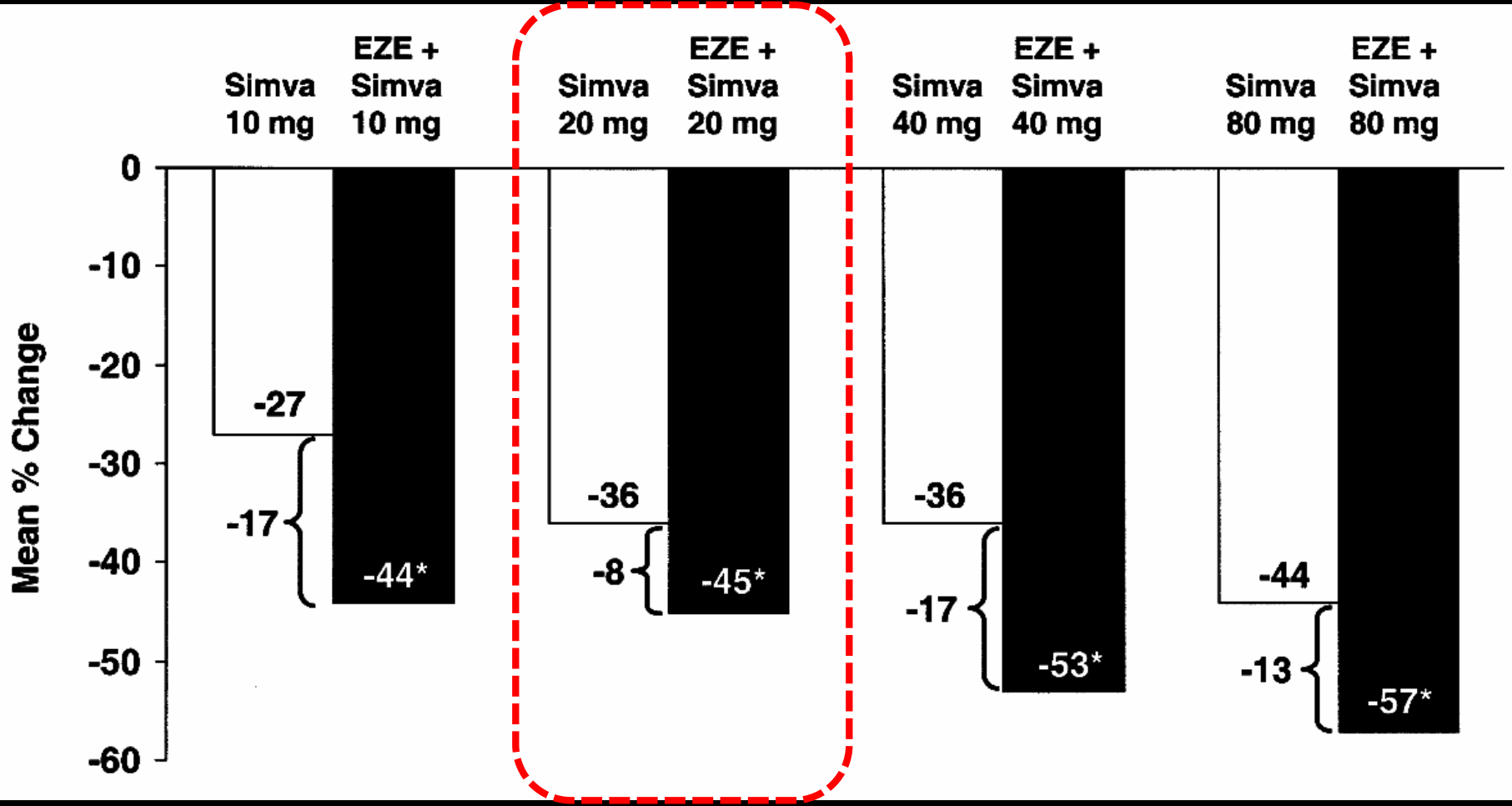
RSV, rosuvastatin; EZE, ezetimibe; SIM, simvastatin

[a] p = 0.002 vs. SIM 40 mg/EZE 10 mg,

[b] p < 0.001 vs. SIM 40 mg/EZE 10 mg and SIM 80 mg/EZE 10 mg,

Ballantyne CM, et al. Atherosclerosis. 2014;232:86–93.

Ezetimibe Coadministration With Simvastatin: Percentage Change in LDL-C

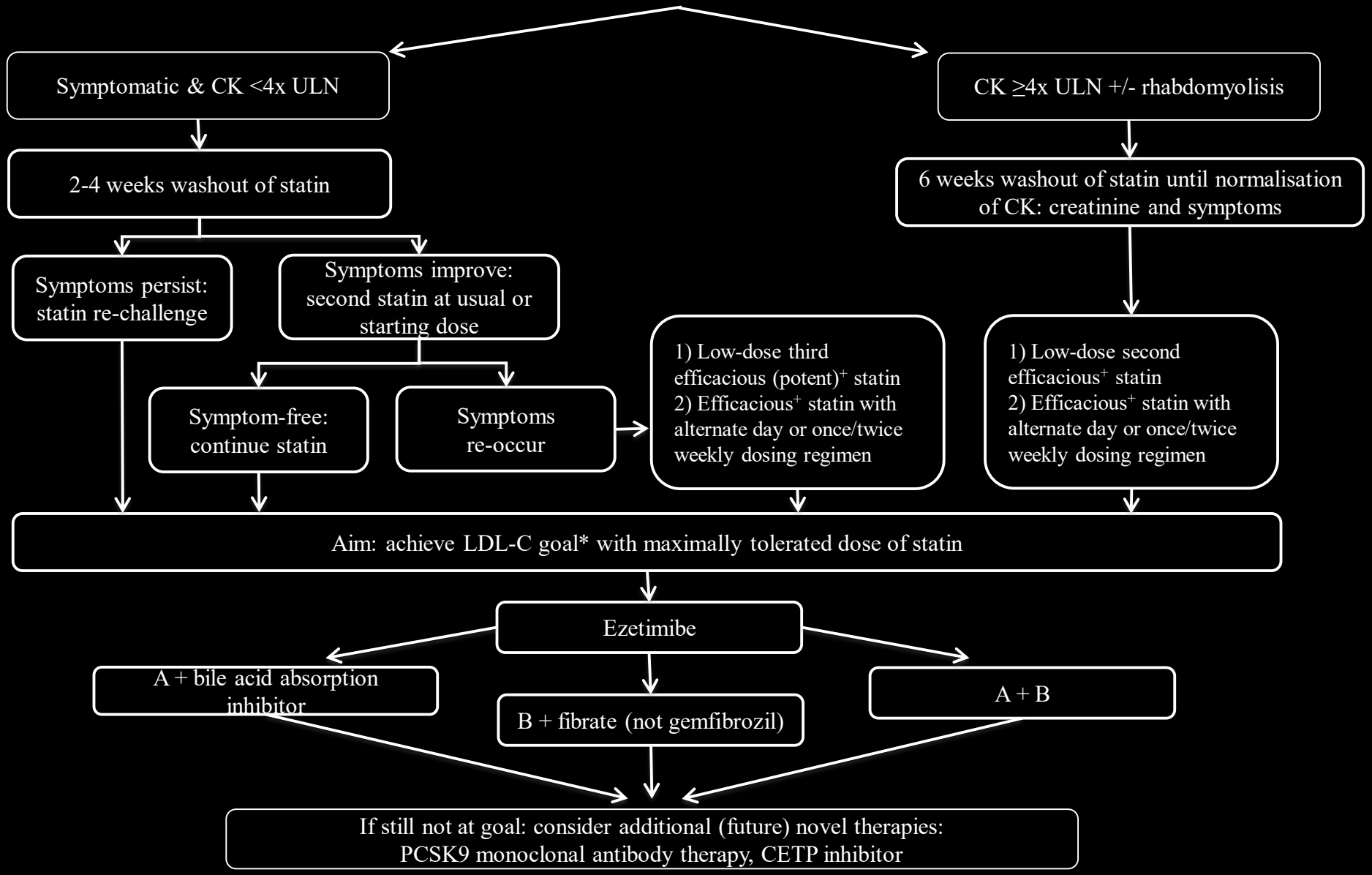


Davidson MH, et al. J Am Coll Cardiol 2002;40:2125–2134

Strategy to Achieve LDL-C Target

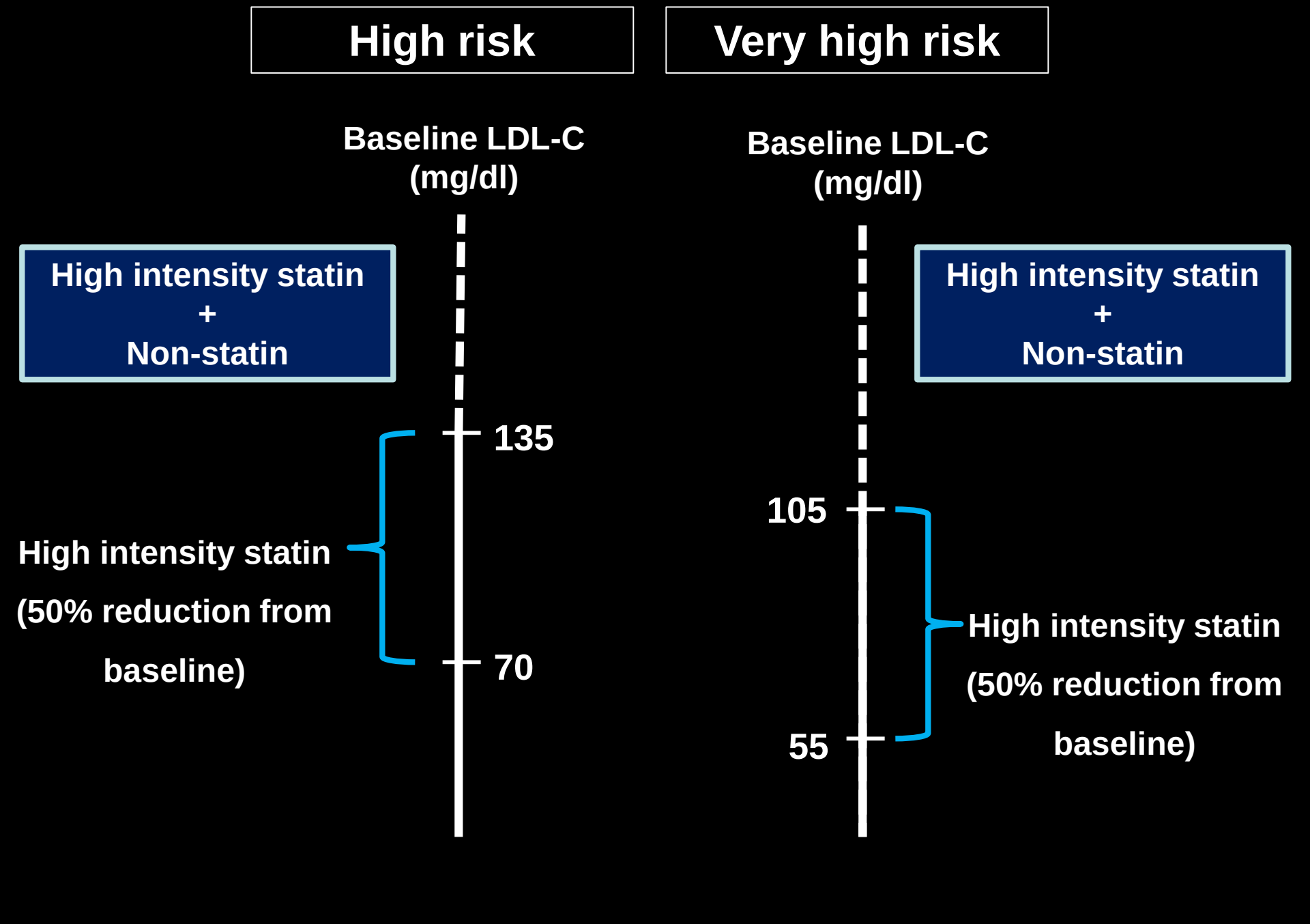
The role of combination therapy of low intensity statins and ezetimibe

Consider if Statin-Attributed **Muscle Symptoms** Favour Statin Continuation/Reinitiation



Catapano AL, et al. Eur Heart J 2016;37:2999-3058

Take-Home Message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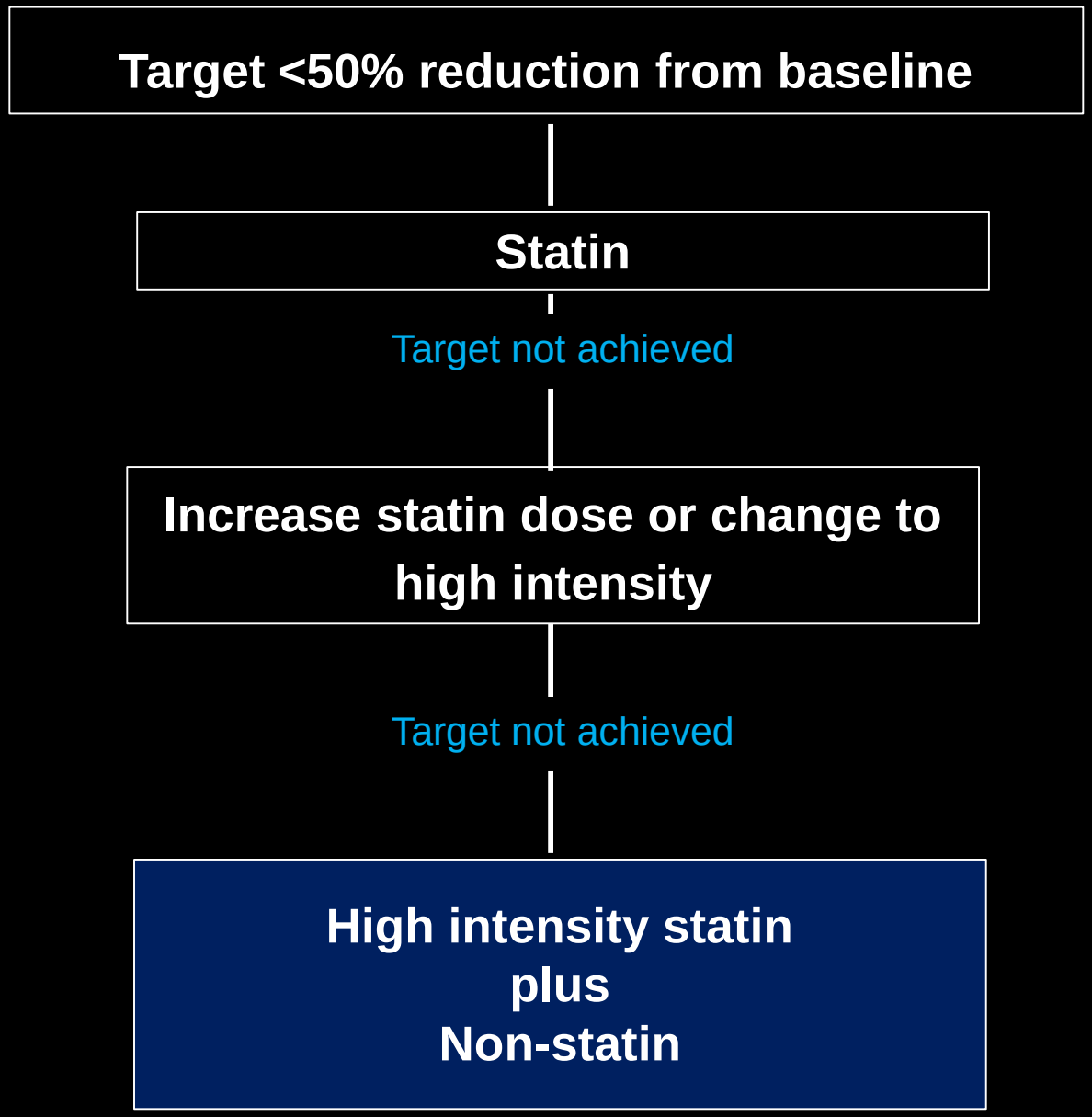
Very high risk
Baseline LDL-C (mg/dl)
Baseline LDL-C (mg/dl)
High intensity statin + Non-statin
High intensity statin + Non-statin
135
70
105
55
High intensity statin (50% reduction from baseline)
High intensity statin (50% reduction from baseline)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Statin
Target not achieved
Increase statin dose or change to high intensity
Target not achieved
High intensity statin
plus
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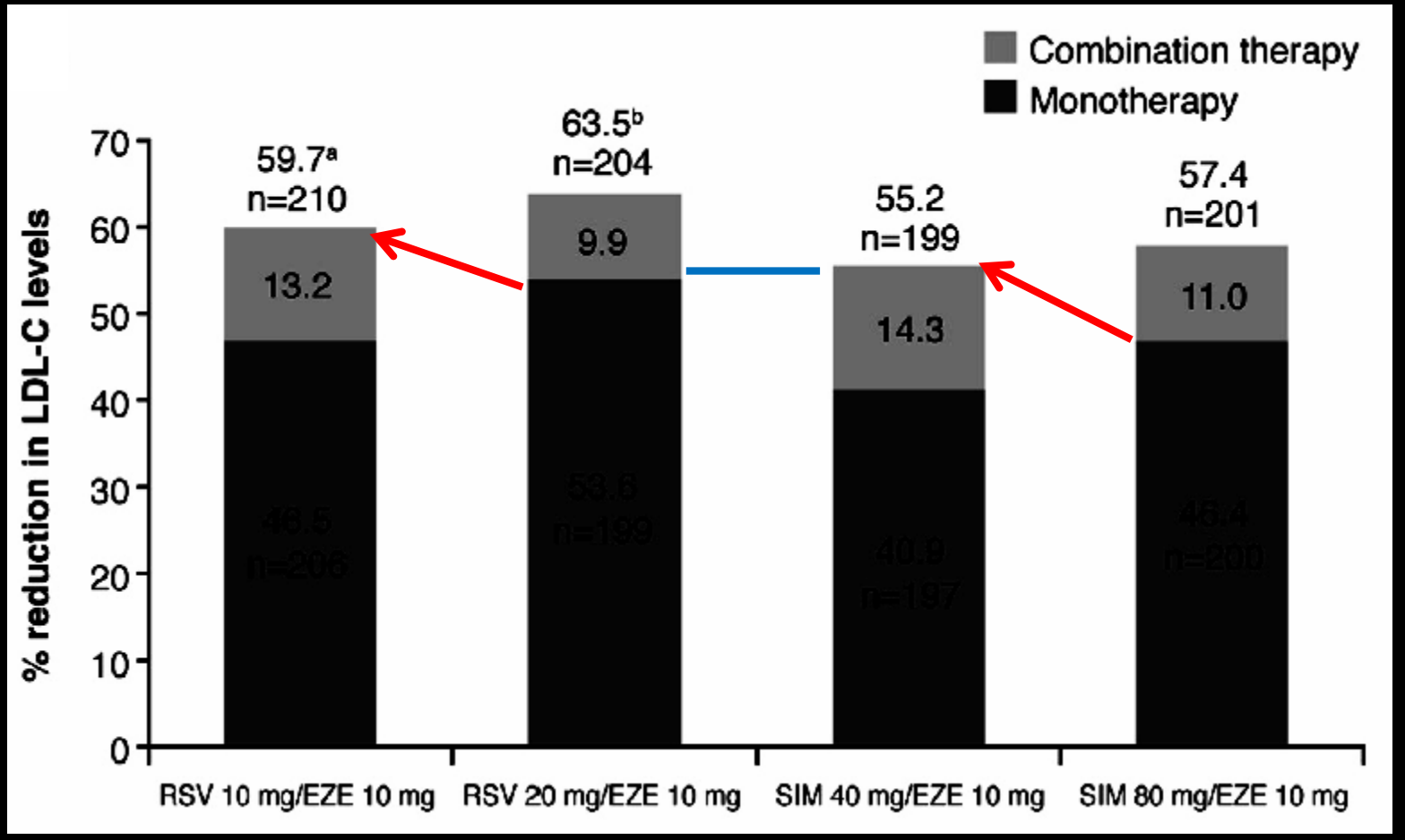
Efficacy of Combination of Ezetimibe and Statins in Lowering LDL-C at 12 weeks



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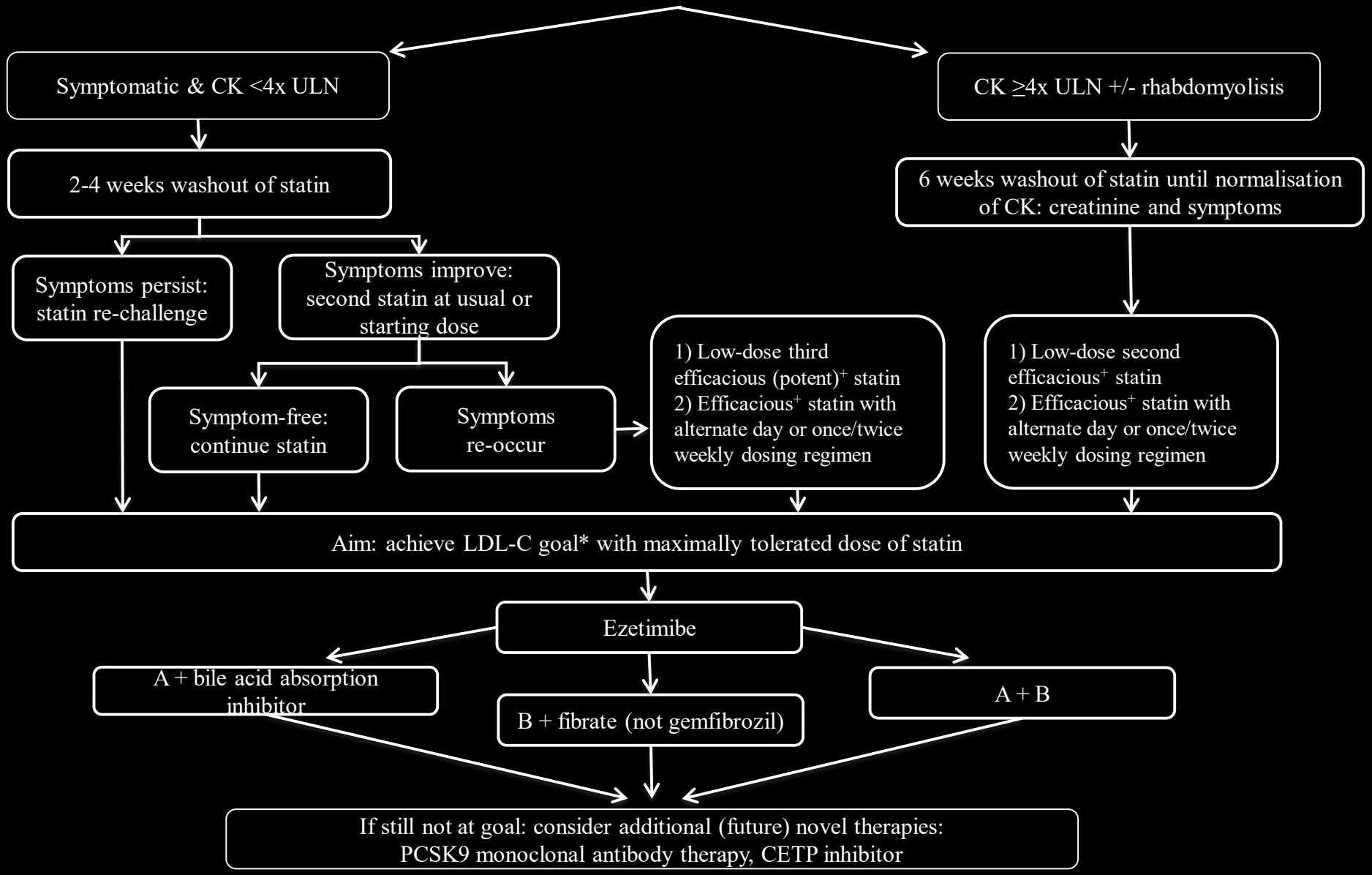
Consider if Statin-Attributed **Muscle Symptoms** Favour Statin Continuation/Reinitiation



Catapano AL, et al. Eur Heart J 2016;37:2999-3058