Individual Treatment Strategy for Dyslipidemia in CAD

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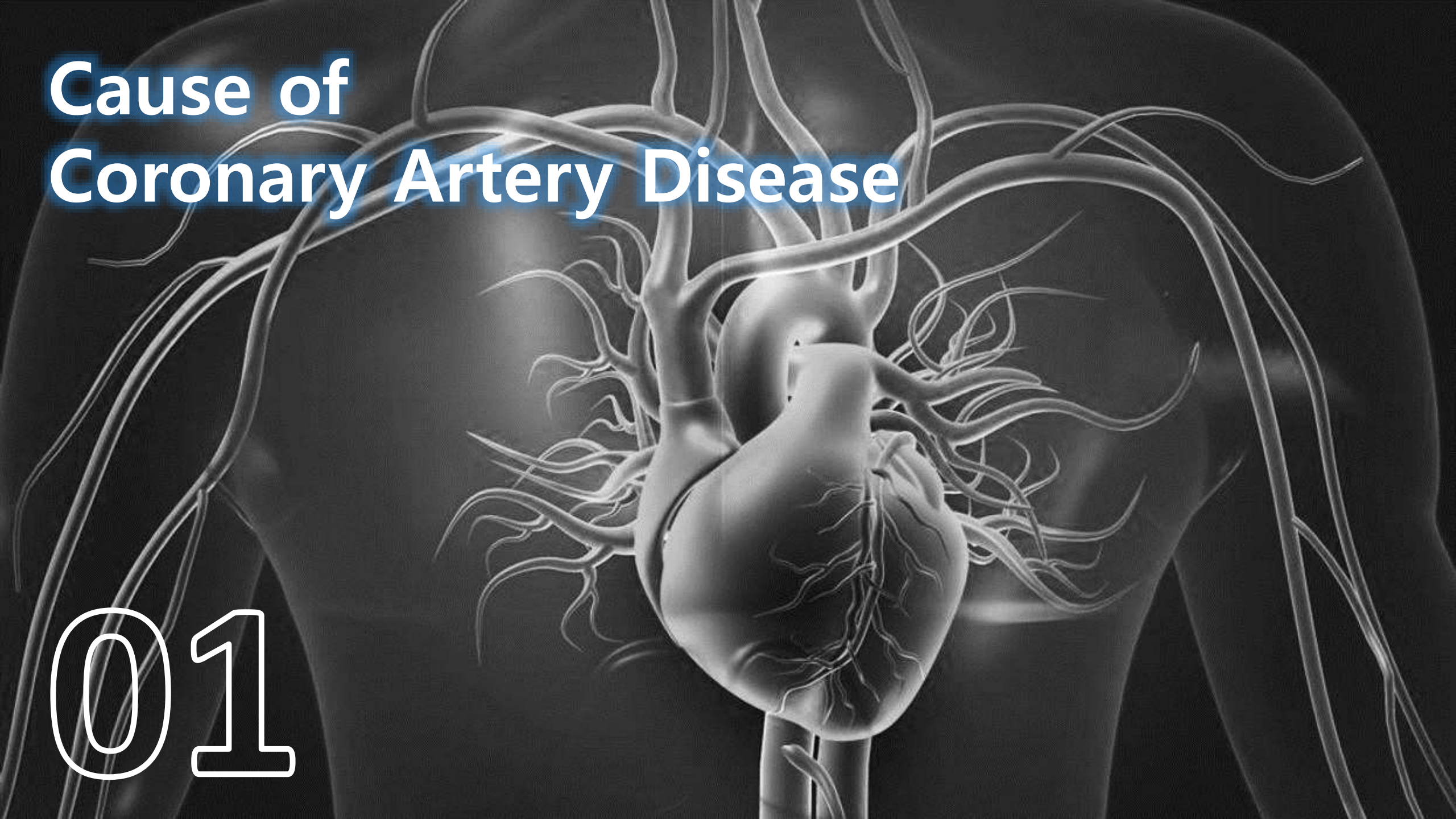
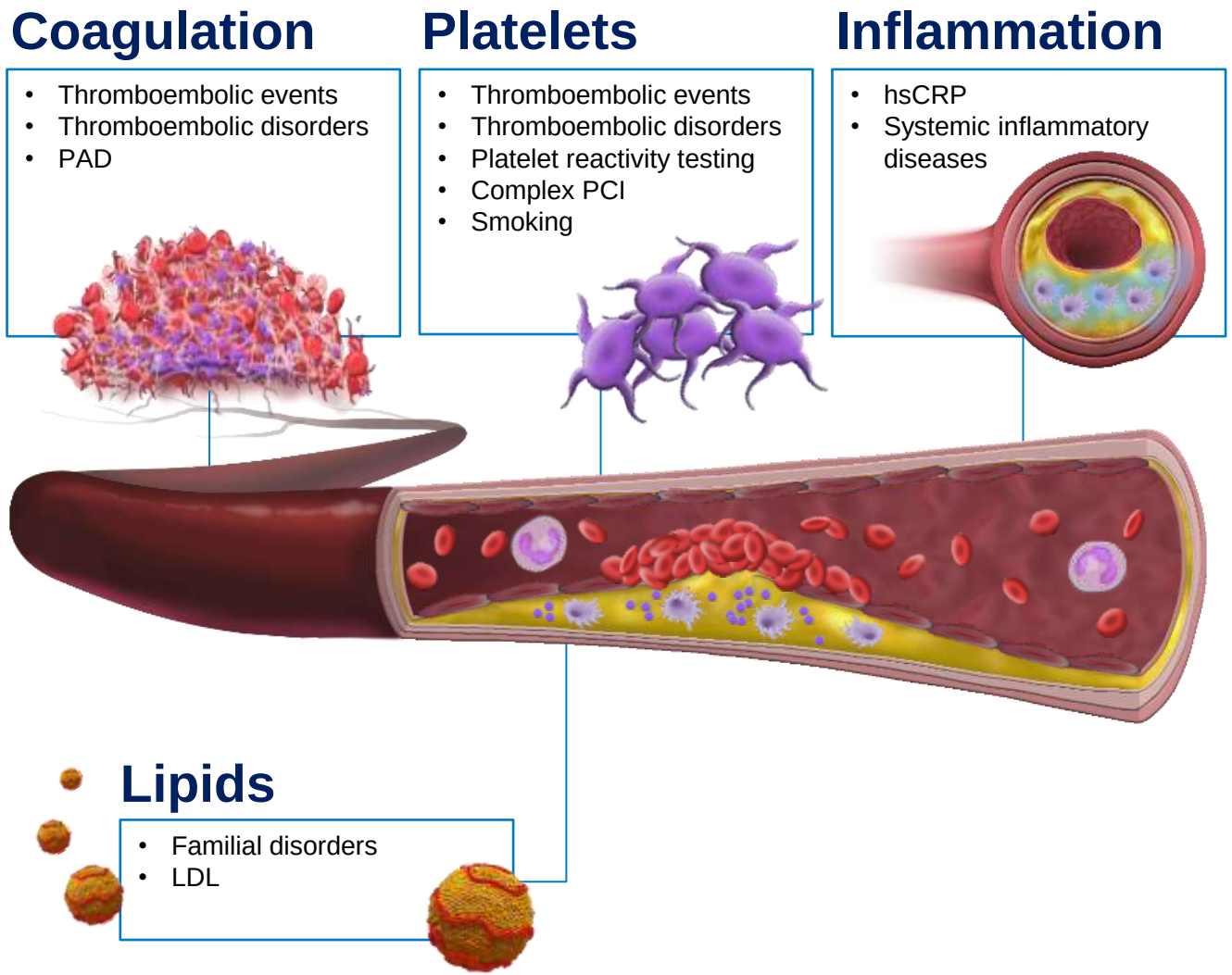

Cause of
Coronary Artery Disease
01

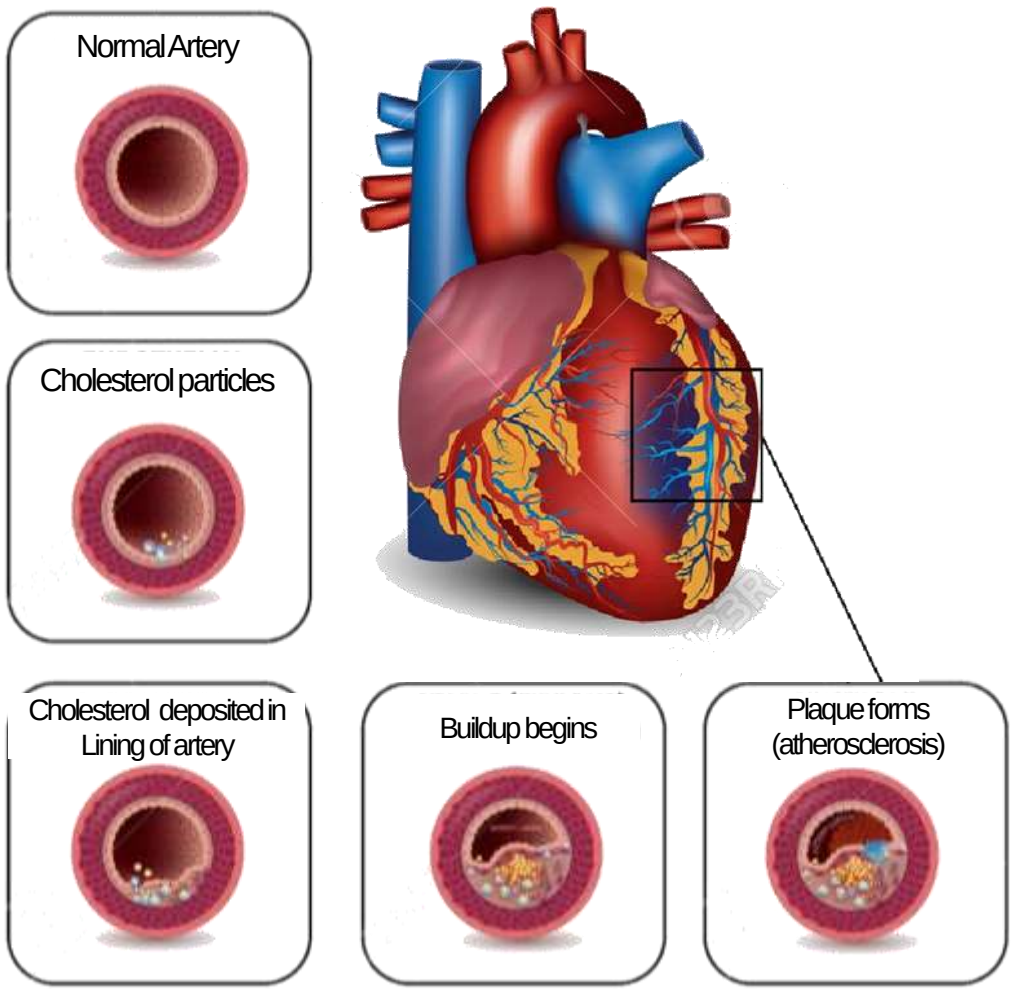
LDL cholesterol is building block of atherosclerosis

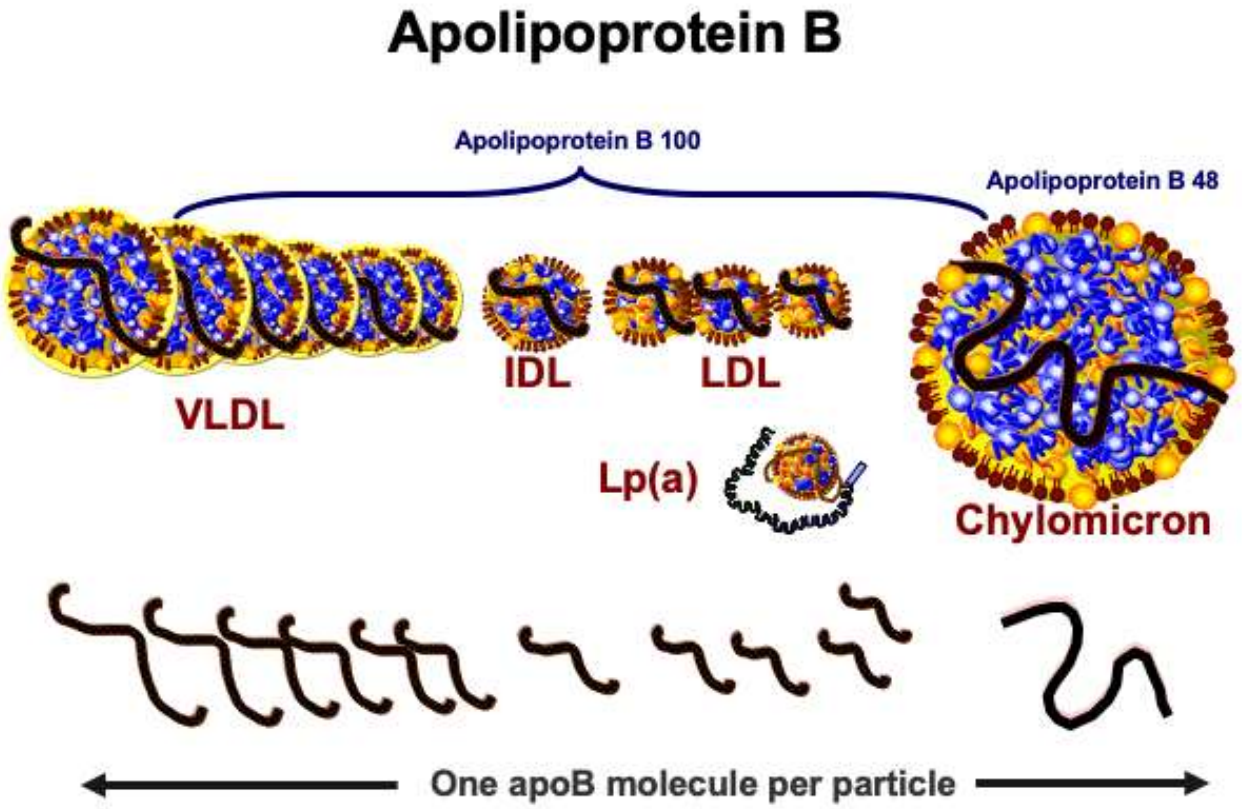
- Following ACS, patients have a high risk of subsequent ischemic events
- Each recurrent episode associates with increased mortality
- Heightened predisposition to atherothrombotic events may persist for years, suggesting pathobiology of recurrent events post-ACS differs from that of stable CAD with no prior ischemic events
- The goal is for optimal medical management and risk factor control that targets atherosclerotic burden as a whole

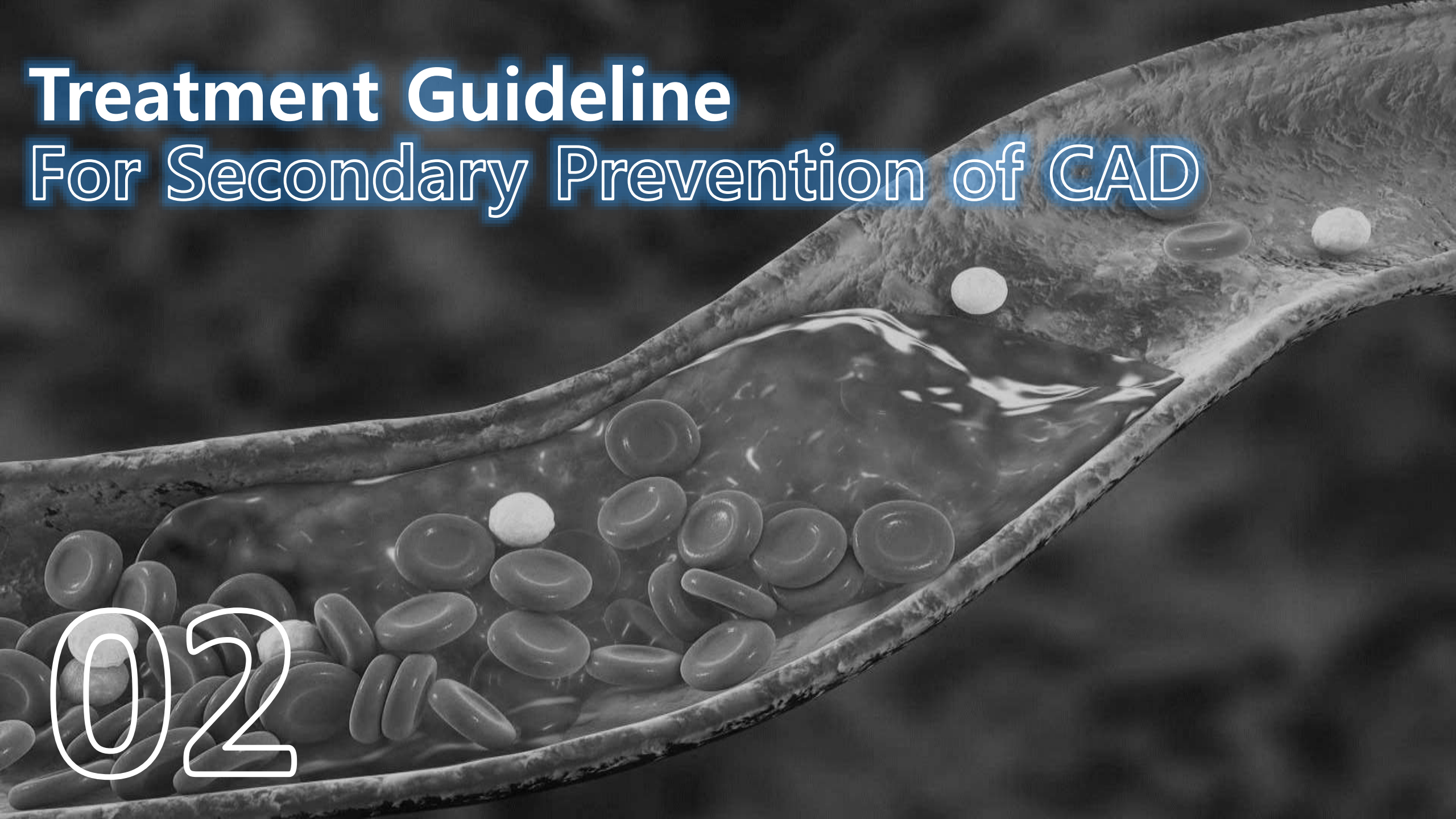


CAD = coronary artery disease; CHIP = clonal hematopoiesis of indeterminate potential; PAD = peripheral artery disease.
Gallone G, et al. *J Am Coll Cardiol.* 2018;72:2886-2903.

Atherosclerosis (=Cholesterol Disease)





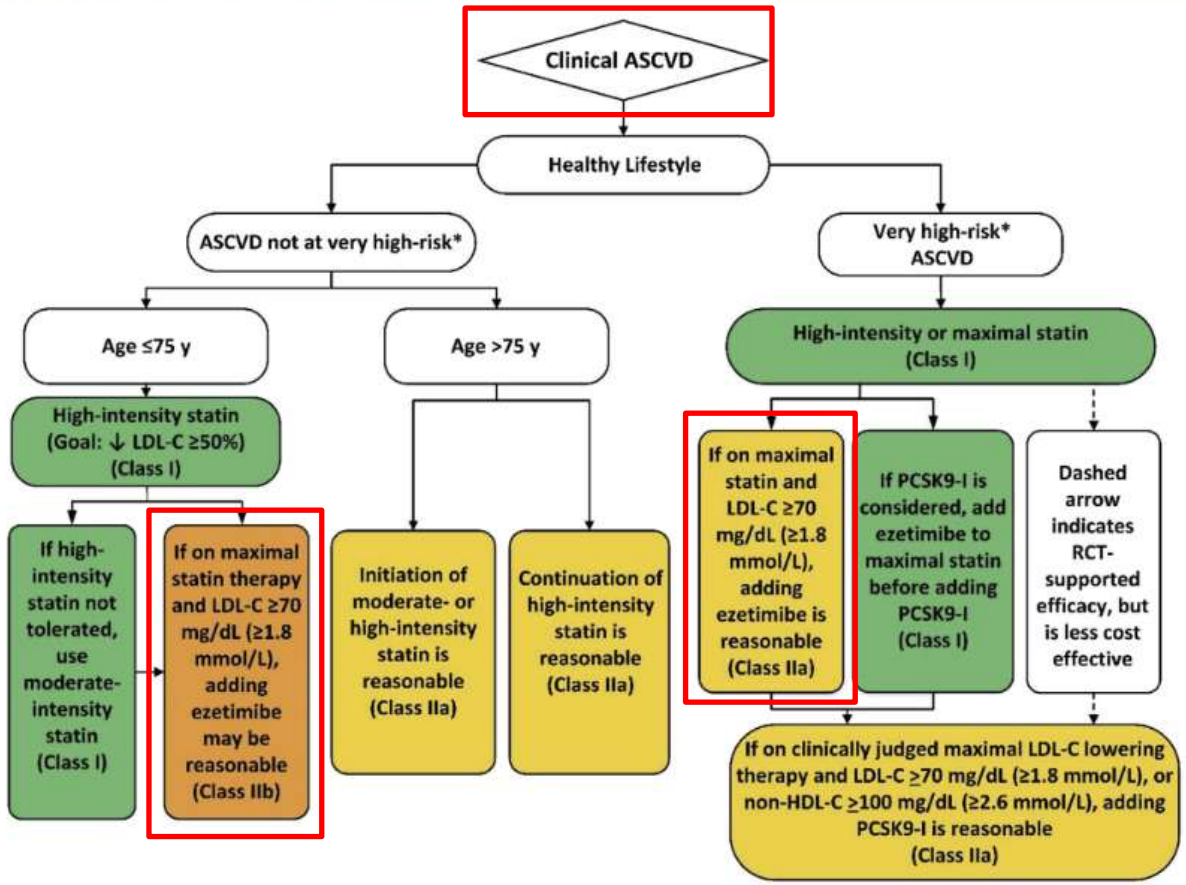


Treatment Guideline
For Secondary Prevention of CAD

02

2018 ACC/AHA Guideline
: Secondary Prevention in Patients With Clinical ASCVD

FIGURE 1 Secondary Prevention in Patients With Clinical ASCVD



Colors correspond to Class of Recommendation in Table 2. Clinical ASCVD consists of ACS, those with history of MI, stable or unstable angina or coronary other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD) including aortic aneurysm, all of atherosclerotic origin Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions (Table 4). ACS indicates acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; MI, myocardial infarction; and PCSK9-I, PCSK9 inhibitor.

Recommendations for Statin Therapy Use in Patients With ASCVD
Referenced studies that support recommendations are summarized in Online Data Supplements 6 to 8 and in the Systematic Review Report.

COR	LOE	RECOMMENDATIONS
I	A	1. In patients who are 75 years of age or younger with clinical ASCVD,* high-intensity statin therapy should be initiated or continued with the aim of achieving a 50% or greater reduction in LDL-C levels (S4.1-1–S4.1-5).
I	A	2. In patients with clinical ASCVD in whom high-intensity statin therapy is contraindicated or who experience statin-associated side effects, moderate-intensity statin therapy should be initiated or continued with the aim of achieving a 30% to 49% reduction in LDL-C levels (S4.1-3, S4.1-6–S4.1-13).
I	B-NR	3. In patients with clinical ASCVD who are judged to be very high risk and considered for PCSK9 inhibitor therapy, maximally tolerated LDL-C lowering therapy should include maximally tolerated statin therapy and ezetimibe (S4.1-14, S4.1-15).
IIa	A[SR]	4. In patients with clinical ASCVD who are judged to be very high risk and who are on maximally tolerated LDL-C lowering therapy with LDL-C 70 mg/dL or higher (≥1.8 mmol/L) or a non-HDL-C level of 100 mg/dL or higher (≥2.6 mmol/L) it is reasonable to add a PCSK9 inhibitor following a clinician-patient discussion about the net benefit, safety, and cost (S4.1-15–S4.1-19).
IIa	B-R	5. In patients with clinical ASCVD who are on maximally tolerated statin therapy and are judged to be at very high risk and have an LDL-C level of 70 mg/dL or higher (≥1.8 mmol/L) it is reasonable to add ezetimibe therapy (S4.1-14, S4.1-15).
Value Statement: Low Value (LOE: B-NR)		6. At mid-2018 list prices, PCSK9 inhibitors have a low cost value (>$150,000 per QALY) compared to good cost value (<$50,000 per QALY) (Section 7 provides a full discussion of the dynamic interaction of different prices and clinical benefit) (S4.1-20–S4.1-22).
IIa	B-R	7. In patients older than 75 years of age with clinical ASCVD, it is reasonable to initiate moderate- or high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug–drug interactions, as well as patient frailty and patient preferences (S4.1-23–S4.1-31).
IIa	C-LD	8. In patients older than 75 years of age who are tolerating high-intensity statin therapy, it is reasonable to continue high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug-drug interactions, as well as patient frailty and patient preferences (S4.1-3, S4.1-10, S4.1-23, S4.1-26, S4.1-31–S4.1-36).
IIb	B-R	9. In patients with clinical ASCVD who are receiving maximally tolerated statin therapy and whose LDL-C level remains 70 mg/dL or higher (≥1.8 mmol/L) it may be reasonable to add ezetimibe (S4.1-15).
IIb	B-R	10. In patients with heart failure (HF) with reduced ejection fraction attributable to ischemic heart disease who have a reasonable life expectancy (3 to 5 years) and are not already on a statin because of ASCVD, clinicians may consider initiation of moderate-intensity statin therapy to reduce the occurrence of ASCVD events (S4.1-37).

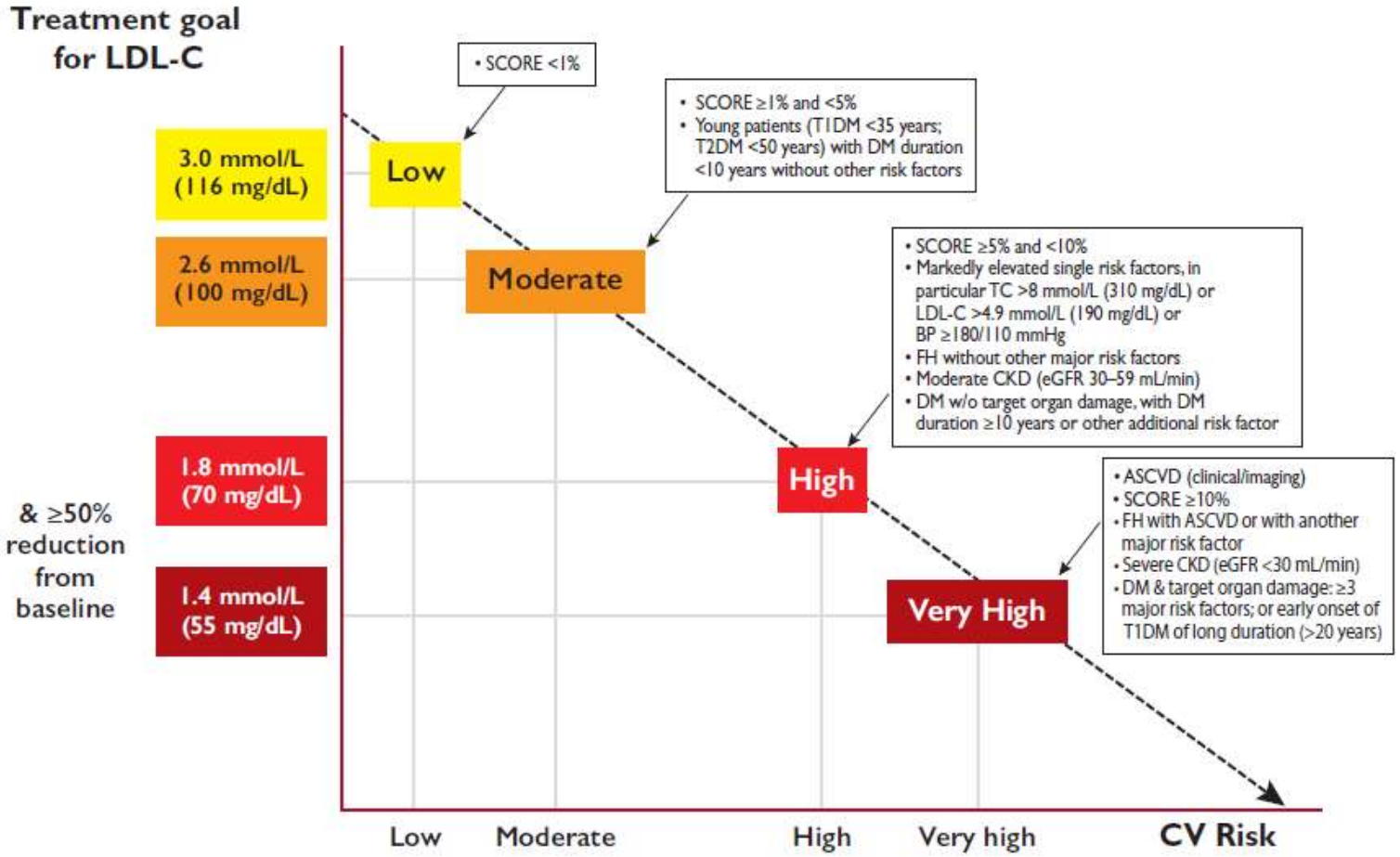
*Clinical atherosclerotic cardiovascular disease (ASCVD) includes acute coronary syndrome (ACS), those with history of myocardial infarction (MI), stable or unstable angina or coronary or other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD) including aortic aneurysm, all of atherosclerotic origin.

<Ref.> Grundy et al. 2018 Cholesterol Clinical Practice Guideline. JACC vol. 73, NO.24,2019 JUNE 25, 2019

2019 ESC/EAS guidelines: Cardiovascular Risk categories

Table 4 **Cardiovascular risk categories**

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.



<Ref.> Cosentino F, et al. Eur Heart J. 2020;41(2):255-323

2022 KSoLA guidelines: Recommendations for treatment goals

Risk category	LDL-C (mg/dL)	non-HDL-C (mg/dL)
Coronary artery disease[1)*]	< 55	< 85
Atherosclerotic stroke and transient ischemic attack* Carotid artery disease* Peripheral artery disease* Abdominal aortic aneurysm* Diabetes mellitus (duration ≥ 10 years or major risk factor† or target organ damage)[2)]	< 70	< 100
Diabetes mellitus (duration < 10 years and no major risk factors†)	< 100	< 130
Moderate risk (major risk factors† ≥ 2)	< 130	< 160
Low risk (major risk factors† ≤ 1)	< 160	< 190

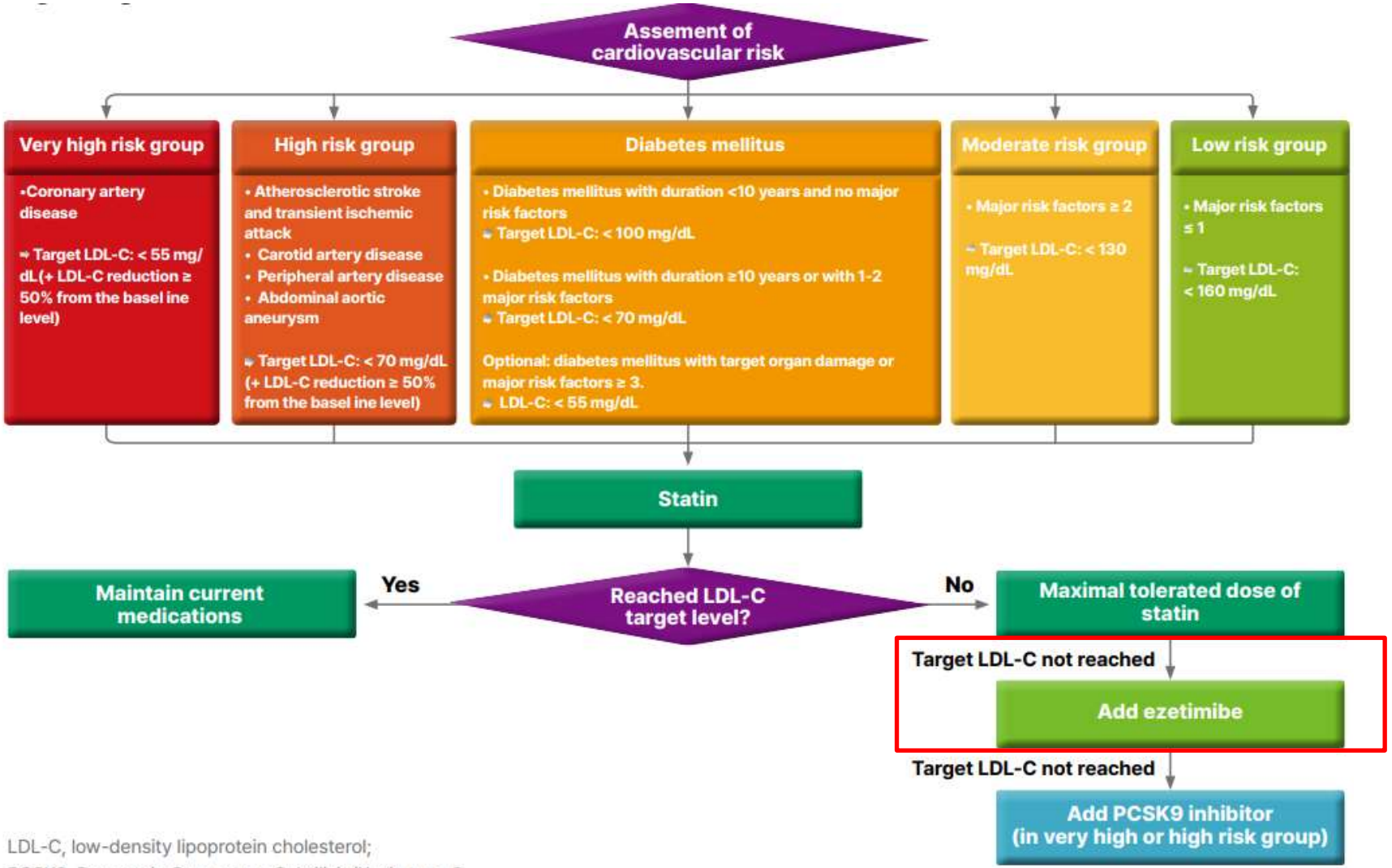
*It is also recommended to reduce LDL-C by ≥ 50% from the baseline level.
†Age (men ≥ 45 years, women ≥ 55 years), family history of premature ASCVD, hypertension, smoking, and low HDL-C level (< 40 mg/dL).

1) In patient with acute myocardial infarction, statin is recommended irrespective of LDL-C level.
2) In diabetes mellitus with target organ damage (albuminuria, CKD [eGFR <60 mL/min/1.73m^2], retinopathy, neuropathy, left ventricular hypertrophy) or major risk factors† ≥ 3: target LDL-C < 55 mg/dL (optional)

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

<Ref.> Korean Guidelines for the Management of Dyslipidemia 5th

2022 KSoLA guidelines
: Evidence-guided approach algorithm dyslipidemia treatment



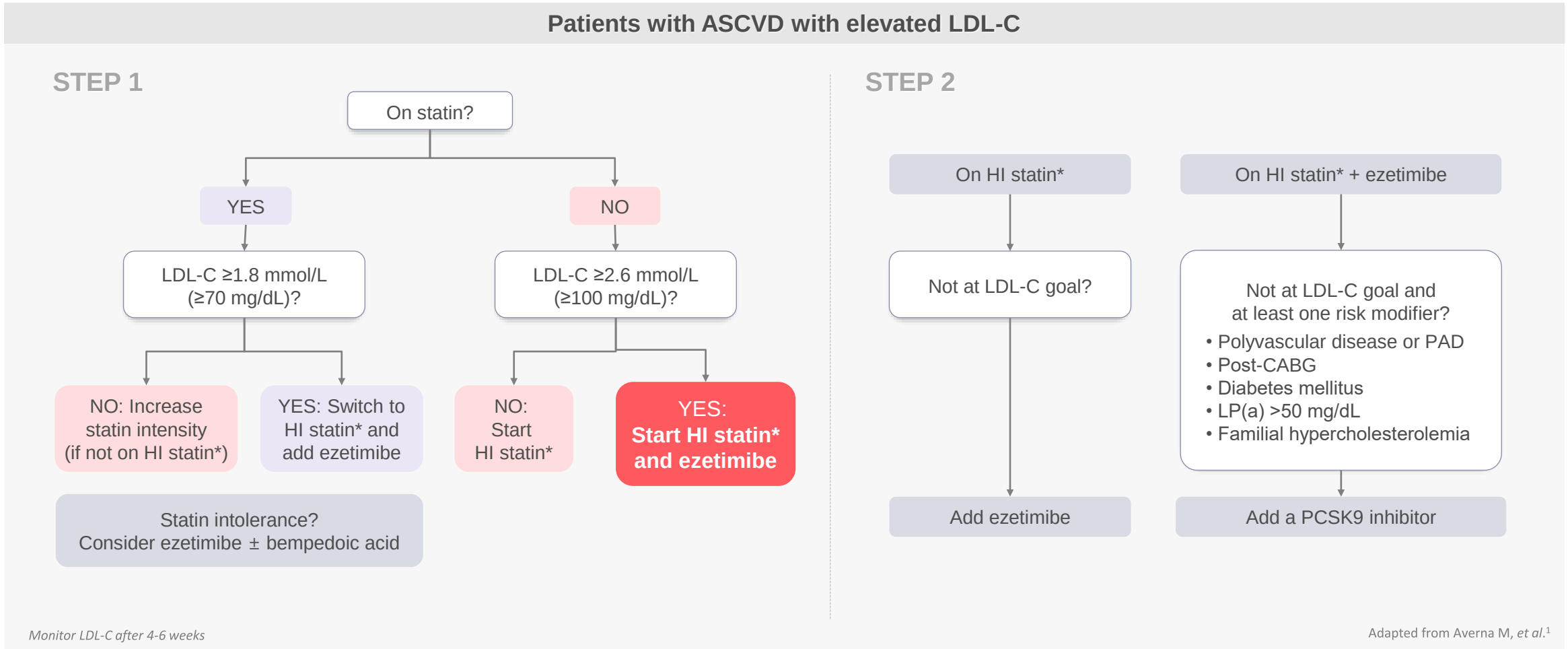
LDL-C, low-density lipoprotein cholesterol;
PCSK9, Proprotein Convertase Subtilisin/Kexin type 9.

<Ref.> Korean Guidelines for the Management of Dyslipidemia 5th

2021 EAS Task Force Statement

Patients with ASCVD with Elevated LDL-C

- 2021 EAS Task Force reinforces guideline recommendations for upfront high-intensity statin-ezetimibe combination therapy in ASCVD patients with baseline LDL-C levels ≥2.6 mmol/L (≥100 mg/dL).



* **HI statin** : High-intensity statin or maximally tolerated statin therapy

EAS : European Atherosclerosis Society, **ASCVD** : Atherosclerotic cardiovascular disease, **LDL-C** : Low-density lipoprotein cholesterol, **Lp(a)** : Lipoprotein (a), **PCSK9** : Proprotein convertase subtilisin/kexin type 9, **CABG** : Coronary artery bypass graft, **HI** : High-intensity, **PAD** : Peripheral artery disease

1. Averna M, *et al.* Practical guidance for combination lipid-modifying therapy in high- and very-high-risk patients: A statement from a European Atherosclerosis Society Task Force. *Atherosclerosis.* 2021 May;8259-99-109.

Acute LDL-C reduction post ACS: Strike Early, Strike Strong

ESC European Society of Cardiology
European Heart Journal: Acute Cardiovascular Care (2022) 11, 939–949
https://doi.org/10.1093/ehjacc/zuac123
REVIEW
Acute Coronary Syndromes

Acute LDL-C reduction post ACS: strike early and strike strong: from evidence to clinical practice. A clinical consensus statement of the Association for Acute CardioVascular Care (ACVC), in collaboration with the European Association of Preventive Cardiology (EAPC) and the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy

Konstantin A. Krychtiuk[1,2*†], Ingo Ahrens[3†], Heinz Drexel[4,5,6‡], Sigrun Halvorsen[7,8†], Christian Hassager[9†], Kurt Huber[10,11,12†], Donata Kurpas[13§], Alexander Niessner[1‡], Francois Schiele[14†], Anne Grete Semb[15§], Alessandro Sionis[16,17†], and Marc J. Claeys[18†]

Document reviewers: José Barrabes[19,20] (review coordinator), Santiago Montero[21], Peter Sinnaeve[22], Roberto Pedretti[23], and Alberico Catapano[24]

Table 2 Trial evidence supporting early and strong LDL-c reduction

Name	Design	Study population	Follow-up	Primary outcome	Primary results	Laboratory results
MIRACL[38]	Atorvastatin (80 mg) 1x/day vs. placebo initiated within the first 4 days after ACS (median 2.6 days)	Patients with unstable angina or non-Q-wave MI without planned revascularization $n = 3\,086$	16 weeks	Composite endpoint: death, non-fatal MI, cardiac arrest, recurrent unstable angina requiring rehospitalization	HR: 0.84 (0.70–1.00) $P = 0.048$	LDL-C: 72 mg/dL vs. 135 mg/dL
PROVE-IT TIMI-22[26]	Atorvastatin (80 mg) 1x/day vs. pravastatin (40 mg) 1x/day initiated within the first 10 days after ACS	ACS (AMI and unstable angina) $n = 4\,162$	Median of 24 months	Time to composite endpoint: Death, MI, stroke, unstable angina requiring hospitalization, any revascularization (PCI; CABG) beyond 1 month	HR: 0.84 (0.74–0.95) $P = 0.005$	LDL-C: 62 mg/dL vs 95 mg/dl
IMPROVE-IT[40]	Ezetimibe 10 mg & simvastatin (40 mg) 1x/day vs. Placebo & simvastatin (40 mg) 1x/day Randomization at a median of 5 days after index event	ACS $n = 18\,144$	Median 6 years	Composite endpoint: Death, non-fatal stroke or major coronary event (non-fatal MI, unstable angina requiring hospitalization or any revascularization beyond 1 month)	HR 0.94 (0.89–0.99) $P = 0.016$	LDL-C: 53.7 mg/dL vs. 69.5 mg/dL
ODYSSEY OUTCOMES[41]	Alirocumab & standard treatment vs. placebo & standard treatment Randomization at a median of 2.6 months after ACS	ACS $n = 18\,924$	Median 2.8 years	Composite endpoint: Death from coronary heart disease, non-fatal MI, all stroke, unstable angina requiring hospitalization	HR 0.85 (0.78–0.93) $P < 0.001$	LDL-C: 53 mg/dL vs. 92 mg/dL (at 48 months on treatment)

Primary outcomes given as hazard ratio (95% confidence interval)
ACS, acute coronary syndrome; MI, myocardial infarction; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; IVUS, intravascular ultrasound; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CV, cardiovascular.

<Ref.> European Heart Journal: Acute Cardiovascular Care (2022) 11, 939–949

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Acute LDL-C reduction post ACS: Strike Early, Strike Strong

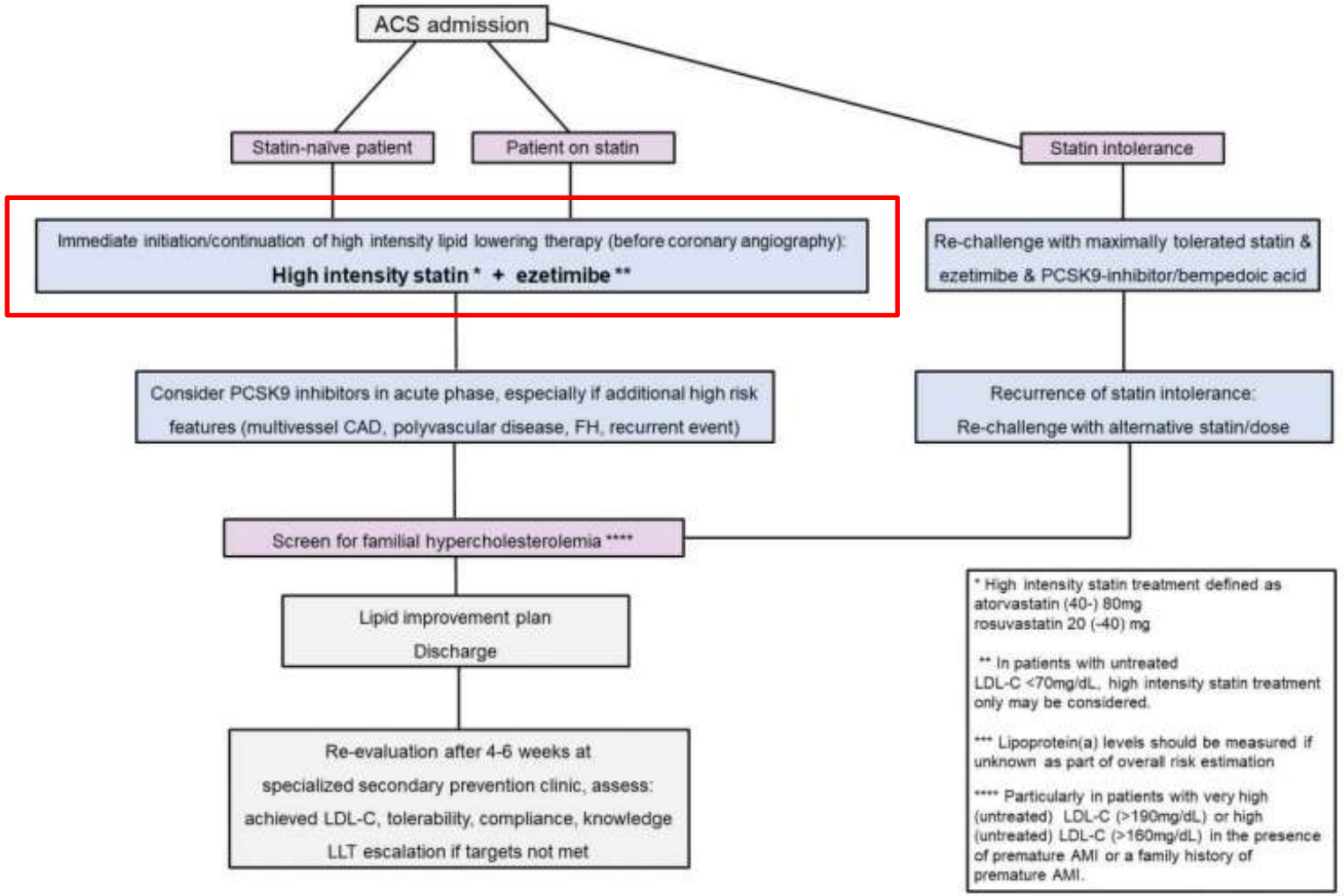

Figure 1 Proposed lipid-lowering algorithm after ACS. A combination therapy consisting of a high-intensity statin and ezetimibe, preferably as a combination pill, should be initiated as soon as possible, preferably before coronary angiography, irrespective of LDL-C levels or pre-existing statin therapy. A lipid panel should be obtained as early as possible. Treatment with PCSK9 inhibitors in the acute phase may be discussed, especially in patients exhibiting additional high-risk features such as multivessel coronary disease, polyvascular disease or familial hypercholesterolemia. In patients experiencing a second major vascular event while treated with a high-intensity statin, current ESC guidelines suggest a LDL-C goal of <40 mg/dL for which a PCSK9 inhibitor would be necessary in most patients. All patients, particularly those with very high untreated LDL-C of >190 mg/dL or >160 mg/dL in the presence of premature AMI or family history of premature AMI, should be screened for FH. All patients should be discharged with a clear lipid improvement plan and be re-evaluated after 4–6 weeks in a specialized secondary prevention clinic and achieved LDL-C, treatment tolerability, compliance and knowledge about disease and therapies should be assessed. Lipid-lowering therapy should be escalated if goals are not met. In patients with known statin intolerance, statin treatment should be re-initiated at the maximally tolerated dose in combination with ezetimibe and a PCSK-9 inhibitor. If PCSK9 inhibitors are not available, bempedoic acid may represent an alternative. In case of a recurrence of symptoms suggestive of recurrent statin intolerance, re-challenge with an alternative statin should be attempted. In patients prescribed a PCSK9 inhibitor in the acute phase for fast LDL-C goal achievement and/or stabilization of the remaining coronary vasculature, de-escalation of triple therapy (high-intensity statin, ezetimibe and PCSK9 inhibitor) should be discussed during follow-up. ACS, acute coronary syndrome; PCSK9, proprotein convertase subtilisin/kexin type 9; CAD, coronary artery disease; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; AMI, acute myocardial infarction; ESC, European Society of Cardiology.

<Ref.> European Heart Journal: Acute Cardiovascular Care (2022) 11, 939–949

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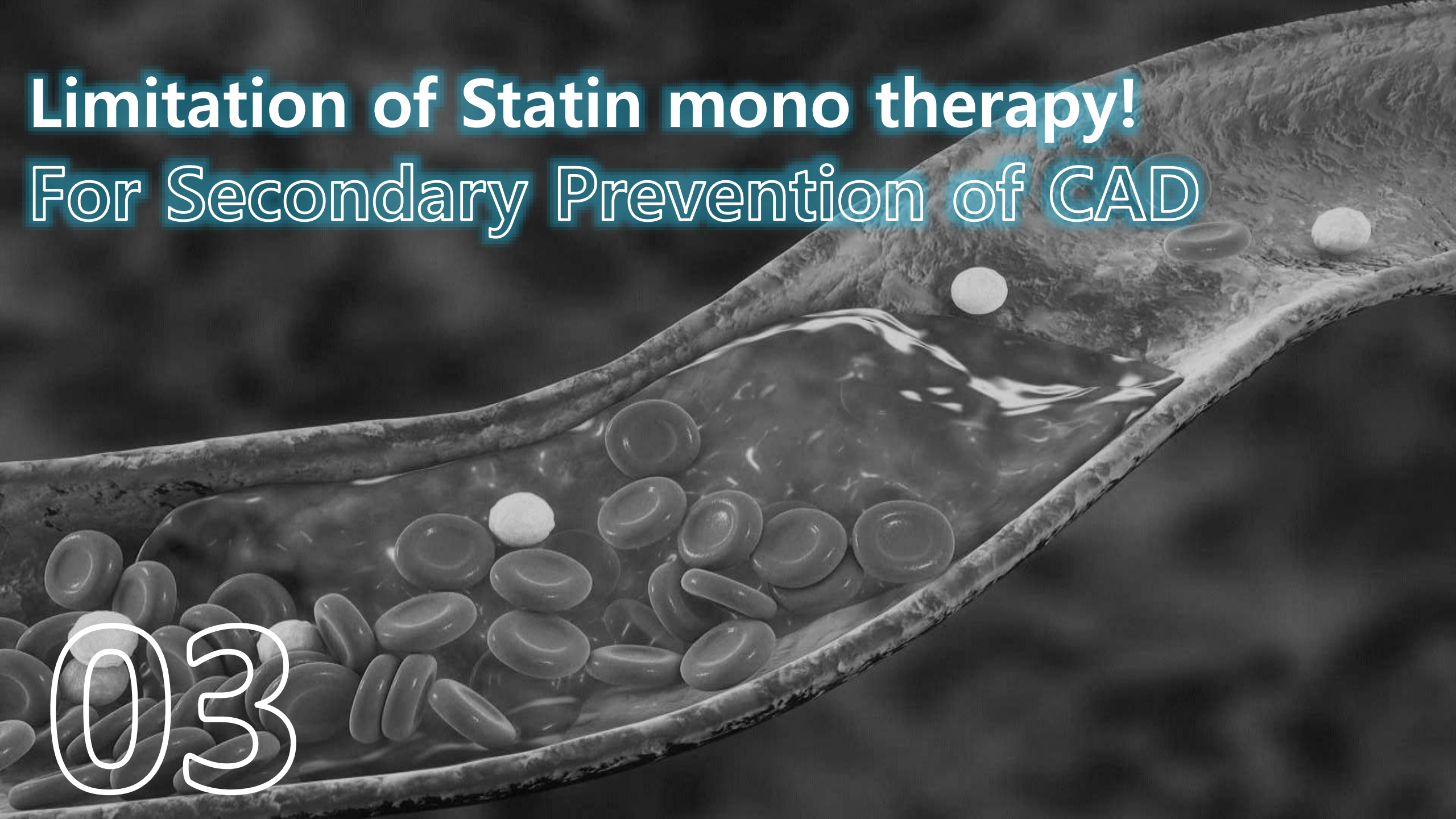

Limitation of Statin mono therapy!
For Secondary Prevention of CAD
03

LDL-C target goal attainment by CV risk group

A retrospective cohort study using the NHS-National Health Examination Cohort (NHIS-HEALS) database

National Health Insurance Service—National Health Screening Cohort enrollees (n=514,866)

↓

Patients who received health examination with LDL-C measurement between January 1, 2007, and December 31, 2011 (n=414,088)

↓

Patients without any missing values in major risk factors (n=312,622)

↓

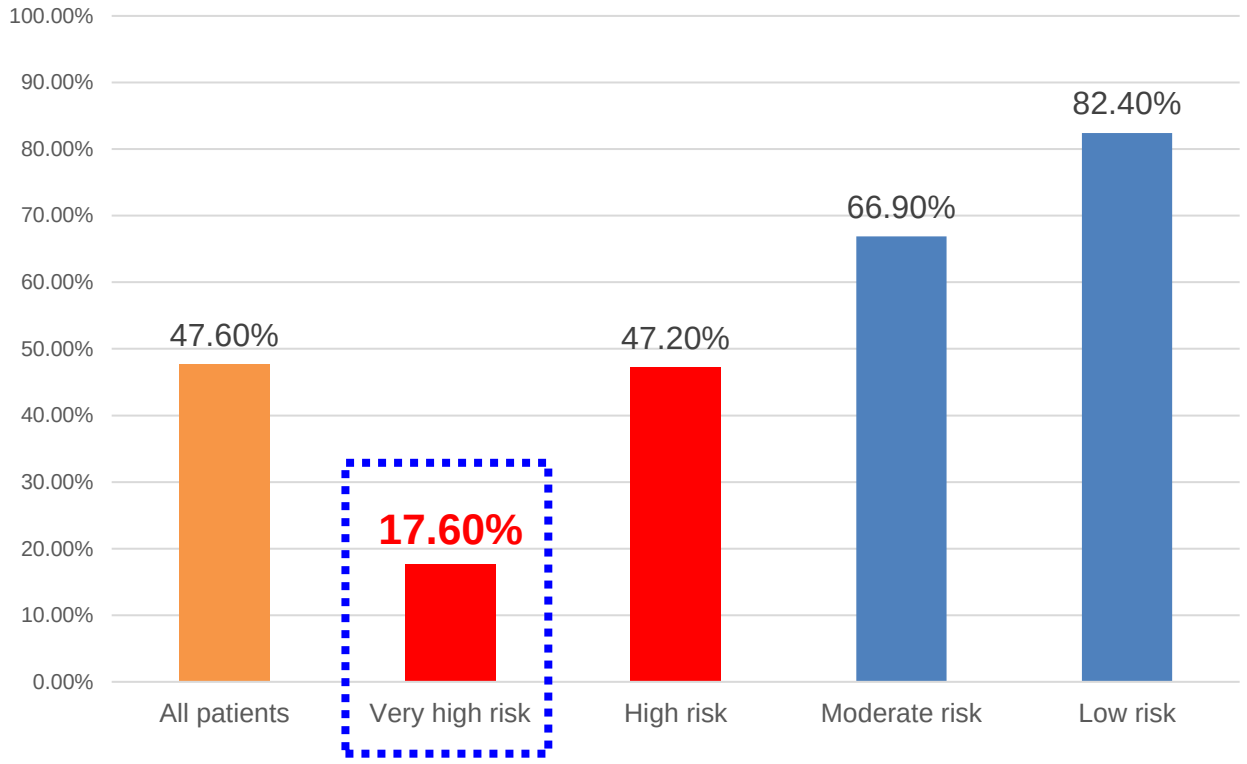
Patients with at least one diagnosis of dyslipidemia during the one year before the index date (n=69,942)

↓

Patients who achieved LDL-C goal (n=33,270)

Patients who did not achieve LDL-C goal (n=36,672)

LDL-C Target Achievement Rate



Patients (n=69,942), retrospective cohort study, using the National Health Insurance Service–National Health Screening Cohort (NHIS-HEALS) database from 2006 to 2013.

Percentage of patients by risk group : Very high risk 36.7%, High risk 22.5%, Moderate risk 20.1%, Low risk 20.6%, as defined by the 2015 Korean guidelines

Ref.> Kim S. et al. PLoS One. 2020:15(1):e0228472

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LDL-C goal attainment status and comparison of cardiovascular events

CV events	LDL-C goal achievers		LDL-C goal non-achievers		*P*-value[a]
	Number of events	Rates per 100 PYs	Number of events	Rates per 100 PYs	
Total CV events[b]	11,560	11.93	19,890	24.35	<0.0001
All-cause death	539	0.56	718	0.88	<0.0001
CV death	39	0.04	73	0.09	<0.0001
Acute coronary syndrome[c]	1,764	1.82	3,021	3.70	<0.0001
Ischemic stroke	1,686	1.74	3,584	4.39	<0.0001
Peripheral artery disease	7,571	7.81	12,567	15.38	<0.0001

CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; PY, person-year.

[a]*P*-values for differences between rates of LDL-C goal achievers and non-achievers.

[b]Total CV events included all-cause death, acute coronary syndrome, ischemic stroke, and peripheral artery disease.

[c]Acute coronary syndrome is a composite of myocardial infarction and unstable angina.

increasing risk by 2.5 times

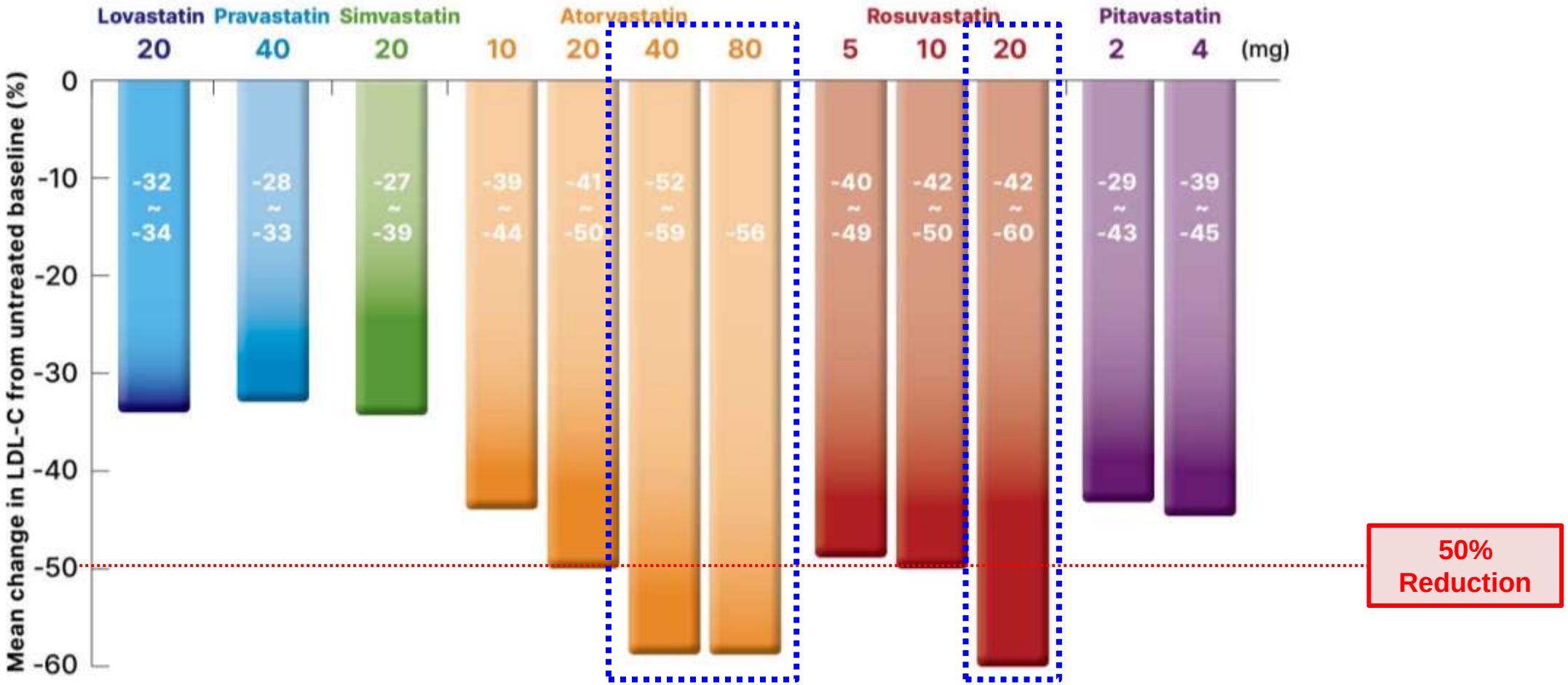
Patients (n=69,942), retrospective cohort study, using the National Health Insurance Service–National Health Screening Cohort (NHIS-HEALS) database from 2006 to 2013.

Percentage of patients by risk group : Very high risk 36.7%, High risk 22.5%, Moderate risk 20.1%, Low risk 20.6%,

Ref.> Kim S. et al. PLoS One. 2020:15(1):e0228472

Limitations of Statin treatment (LDL-C lowering)

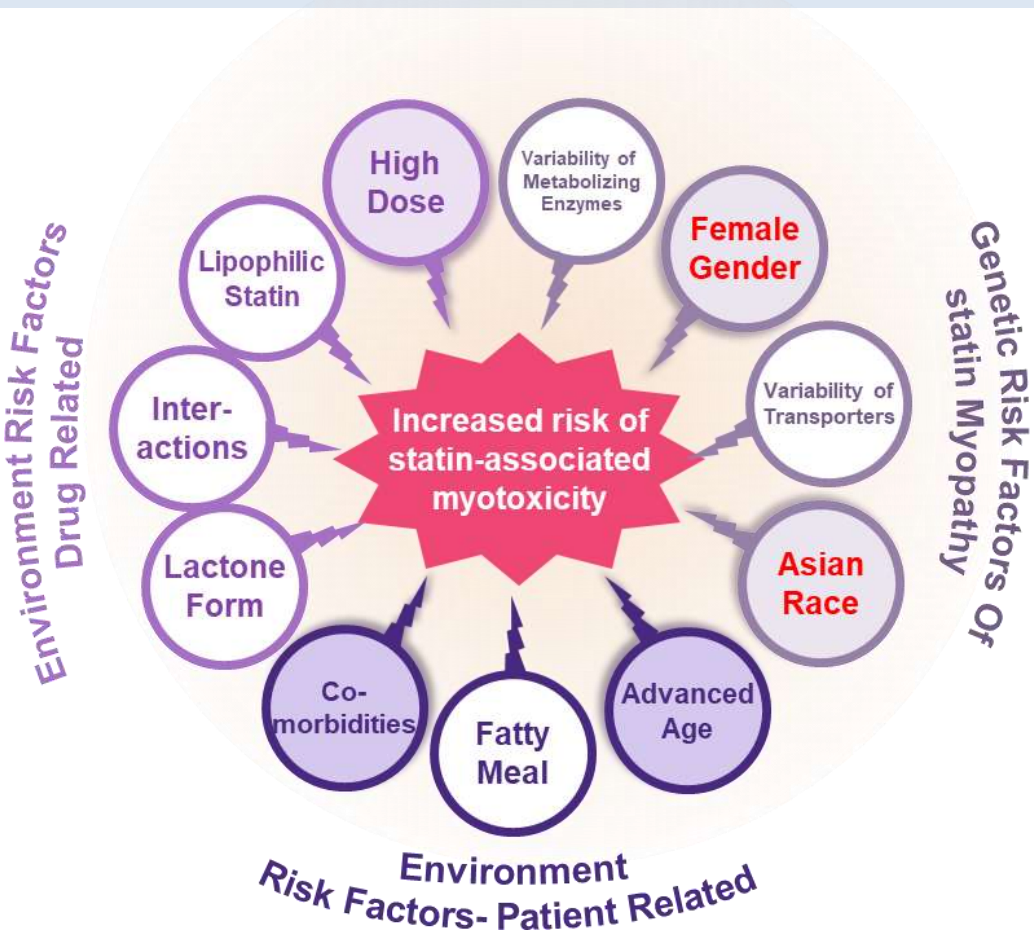
To achieve a reduction of 50% or more compared to baseline in high-risk/very-high-risk patients, high doses of ATV 40mg and RSV 20mg or more are recommended, as statin monotherapy has limitations in controlling LDL-C



<Ref.> Korean Guidelines for the Management of Dyslipidemia 5th

Limitations of Statin treatment (side effect)

Statin-related Muscle Symptoms (SAMS): Risk Factors



New diabetes by High dose statin

Subgroup	Low dose statins Cases	Low dose statins Controls	High dose statins Cases	High dose statins Controls	Rate ratio (95% CI)	Weight (%)	Rate ratio (95% CI)
≤120 days of current therapy							
Alberta	26	159	31	306		6.3	0.57 (0.30 to 1.07)
CPRD	30	282	50	495		7.9	0.96 (0.55 to 1.69)
Manitoba	9	113	52	425		3.9	1.89 (0.85 to 4.20)
Marketscan	86	773	195	1452		33.0	1.29 (0.98 to 1.70)
Nova Scotia	9	46		56		1.1	0.20 (0.04 to 0.91)
Ontario	62	758	197	1696		23.8	1.52 (1.10 to 2.11)
Quebec	57	550	123	959		18.7	1.40 (0.97 to 2.02)
Saskatchewan	17	137	69	442		5.3	1.31 (0.66 to 2.60)
Total	296	2818	720	5831		100.0	1.26 (1.07 to 1.47)

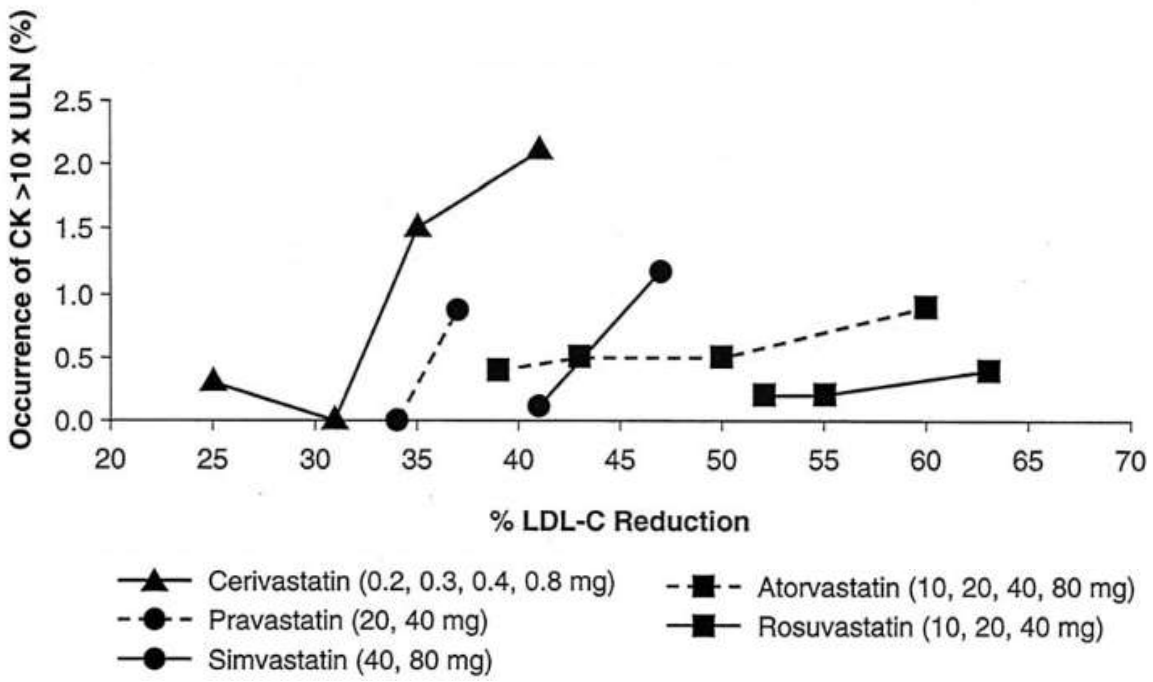
Test for heterogeneity: χ^2=15.22, df=7, P=0.03, I^2=54%

Test for overall effect: z=2.84, P=0.004

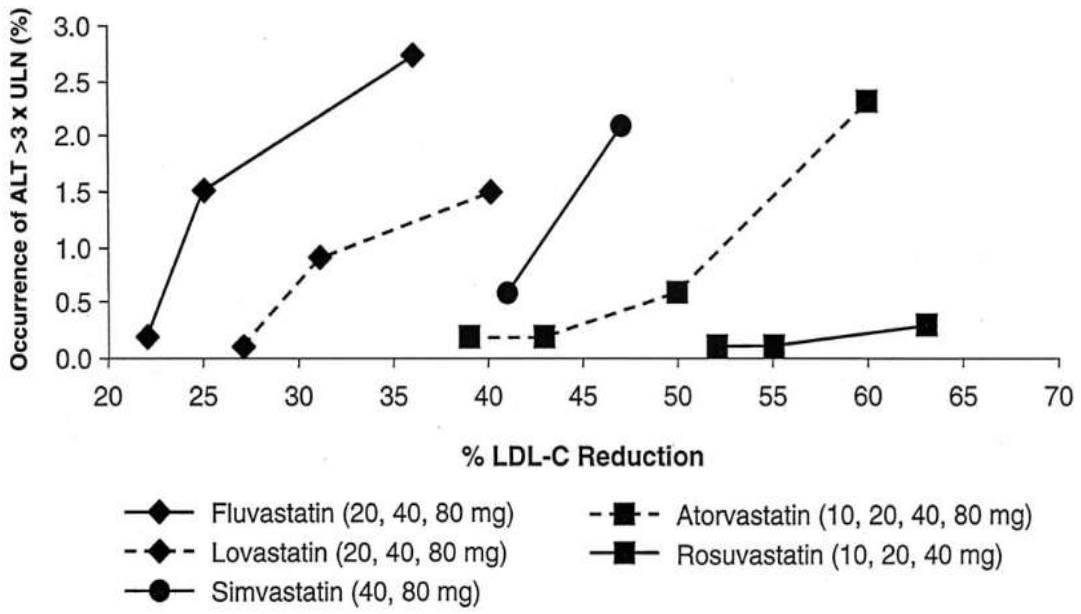
<Ref.> Taha DA, et al. Transl Res. 2014;164(2):85-109. / Dormuth CR, et al. BMJ. 2014;348:g3244.

Limitations of Statin treatment (side effect)

Creatine kinase elevations > 10times ULN

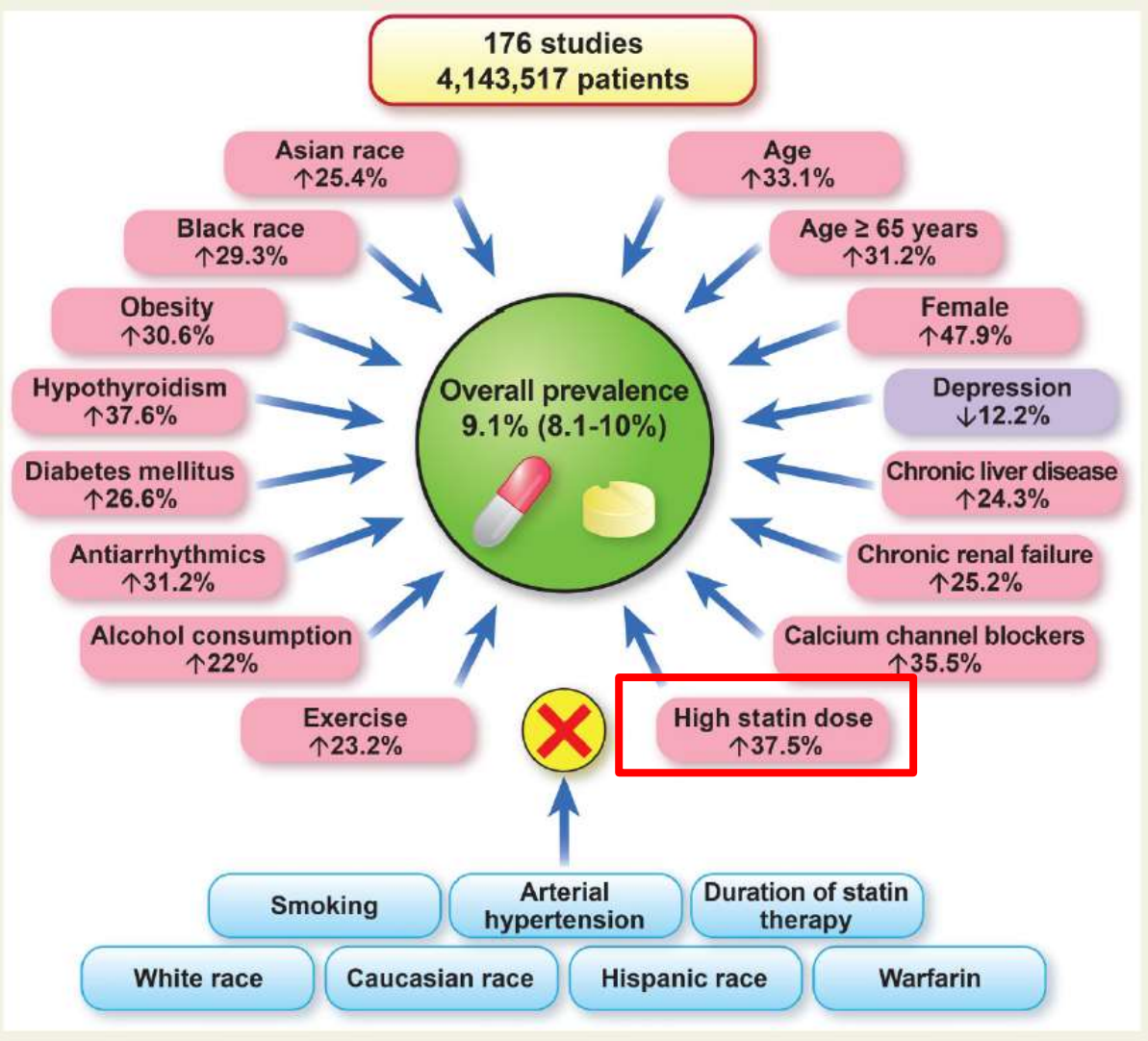


Alanine amino transferase elevations > 3times ULN



<Ref.> Brewer HB Jr. Am J Cardiol. 2003;92(4B):23K-29K.

Limitations of Statin treatment (Statin intolerance)



Methods and results: We searched several databases up to 31 May 2021, for studies that reported the prevalence of SI. The primary endpoint was overall prevalence and prevalence according to a range of diagnostic criteria [National Lipid Association (NLA), International Lipid Expert Panel (ILEP), and European Atherosclerosis Society (EAS)] and in different disease settings. The secondary endpoint was to identify possible risk factors for SI. A random-effects model was applied to estimate the overall pooled prevalence. A total of 176 studies [112 randomized controlled trials (RCTs); 64 cohort studies] with 4 143 517 patients were ultimately included in the analysis. The overall prevalence of SI was 9.1% (95% confidence interval 8.0-10%). The prevalence was similar when defined using NLA, ILEP, and EAS criteria [7.0% (6.0-8.0%), 6.7% (5.0-8.0%), 5.9% (4.0-7.0%), respectively]. The prevalence of SI in RCTs was significantly lower compared with cohort studies [4.9% (4.0-6.0%) vs. 17% (14-19%)]. The prevalence of SI in studies including both primary and secondary prevention patients was much higher than when primary or secondary prevention patients were analysed separately [18% (14-21%), 8.2% (6.0-10%), 9.1% (6.0-11%), respectively]. Statin lipid solubility did not affect the prevalence of SI [4.0% (2.0-5.0%) vs. 5.0% (4.0-6.0%)]. Age [odds ratio (OR) 1.33, P = 0.04], female gender (OR 1.47, P = 0.007), Asian and Black race (P < 0.05 for both), obesity (OR 1.30, P = 0.02), diabetes mellitus (OR 1.26, P = 0.02), hypothyroidism (OR 1.37, P = 0.01), chronic liver, and renal failure (P < 0.05 for both) were significantly associated with SI in the meta-regression model. Antiarrhythmic agents, calcium channel blockers, alcohol use, and increased statin dose were also associated with a higher risk of SI.
Conclusion: Based on the present analysis of >4 million patients, the prevalence of SI is low when diagnosed according to international definitions. These results support the concept that the prevalence of complete SI might often be overestimated and highlight the need for the careful assessment of patients with potential symptoms related to SI.

<Ref.> European Heart Journal (2022) 43, 3213–3223

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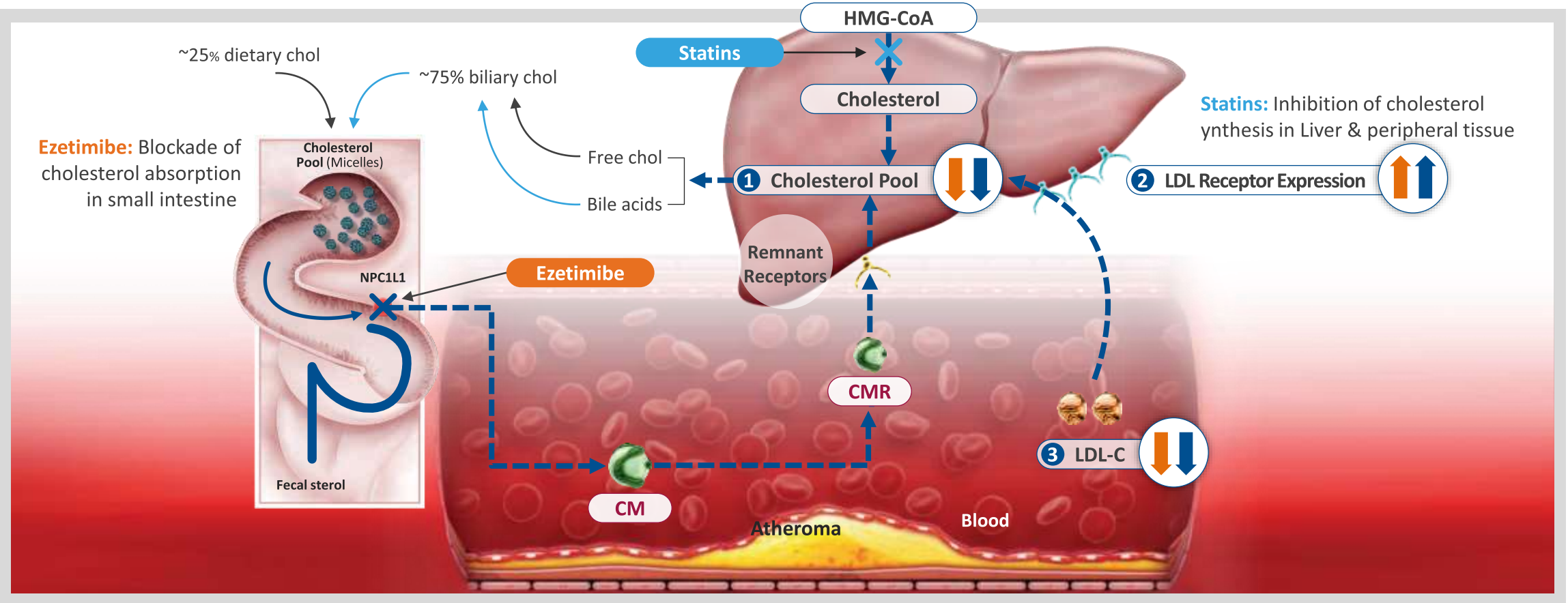
Benefit of Statin+Ezetimibe combination!
For Secondary Prevention of CAD
04

Ezetimibe and Statins have complementary mechanisms of action

Together, Ezetimibe in combination with a statin provides:

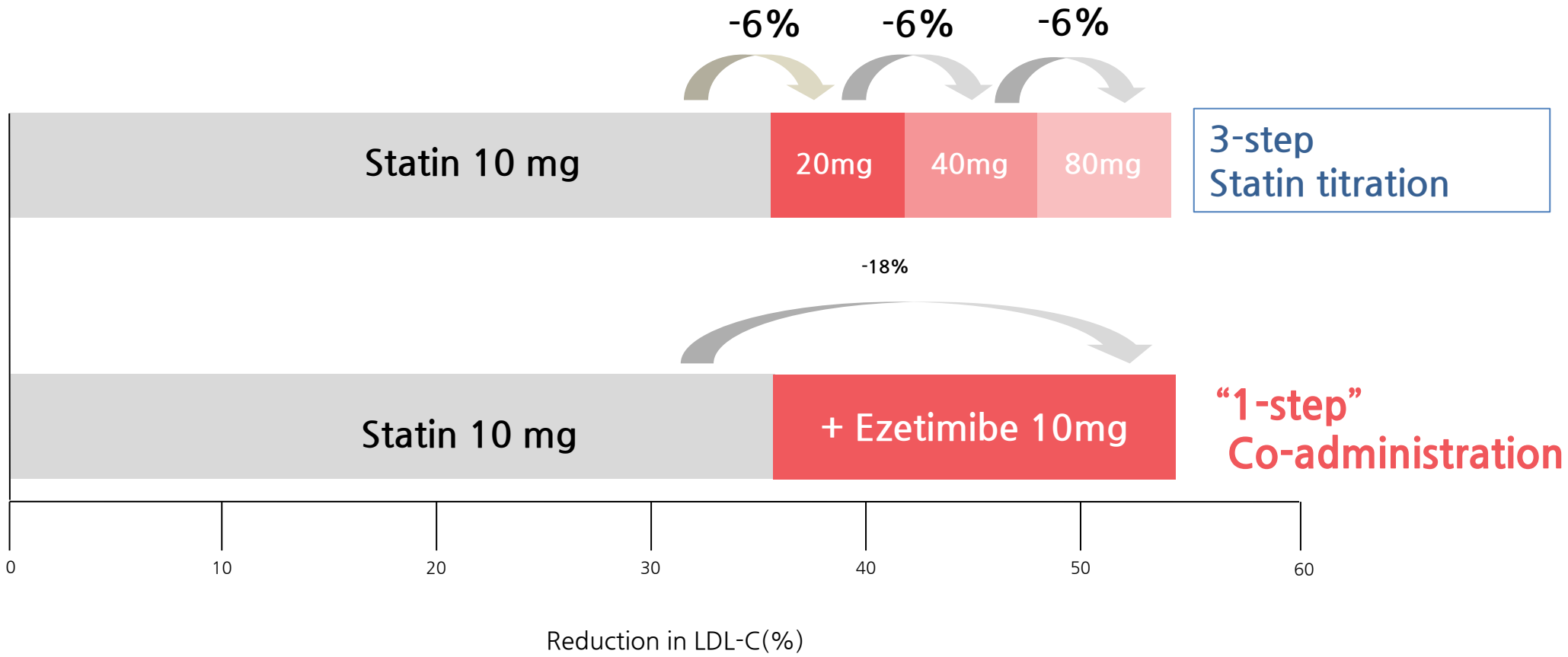
❶ Reduction of hepatic cholesterol ❷ Upregulation of hepatic LDL receptor expression ❸ Increased clearance of plasma LDL-C



NPC1L1=Niemann-Pick C1-like 1; HMG-CoA=3-hydroxy-3-methylglutaryl acetyl coenzyme A; CMR = chylomicron remnant.

<Ref.> 1.Grigore L et al. Vas Health Risk Manag. 2008;4:267-278. 2. Bays HE, et al. Expert Rev Cardiovasc Ther. 2008;6(4):447-470.

LDL-C lowering : Statin up-titration vs Statin + Ezetimibe



<Ref.> Bays H, et al. Expert Opin Pharmacother. 2003;4(5):779-790.

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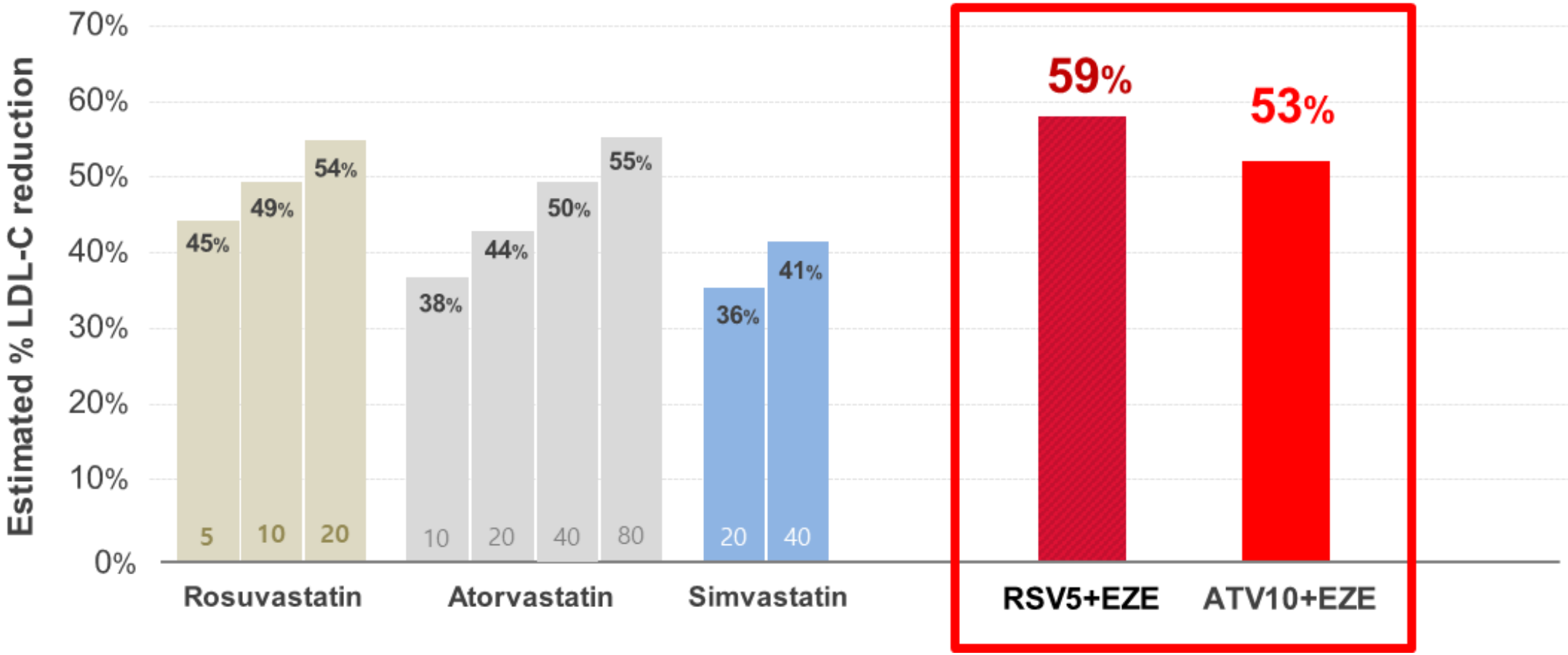
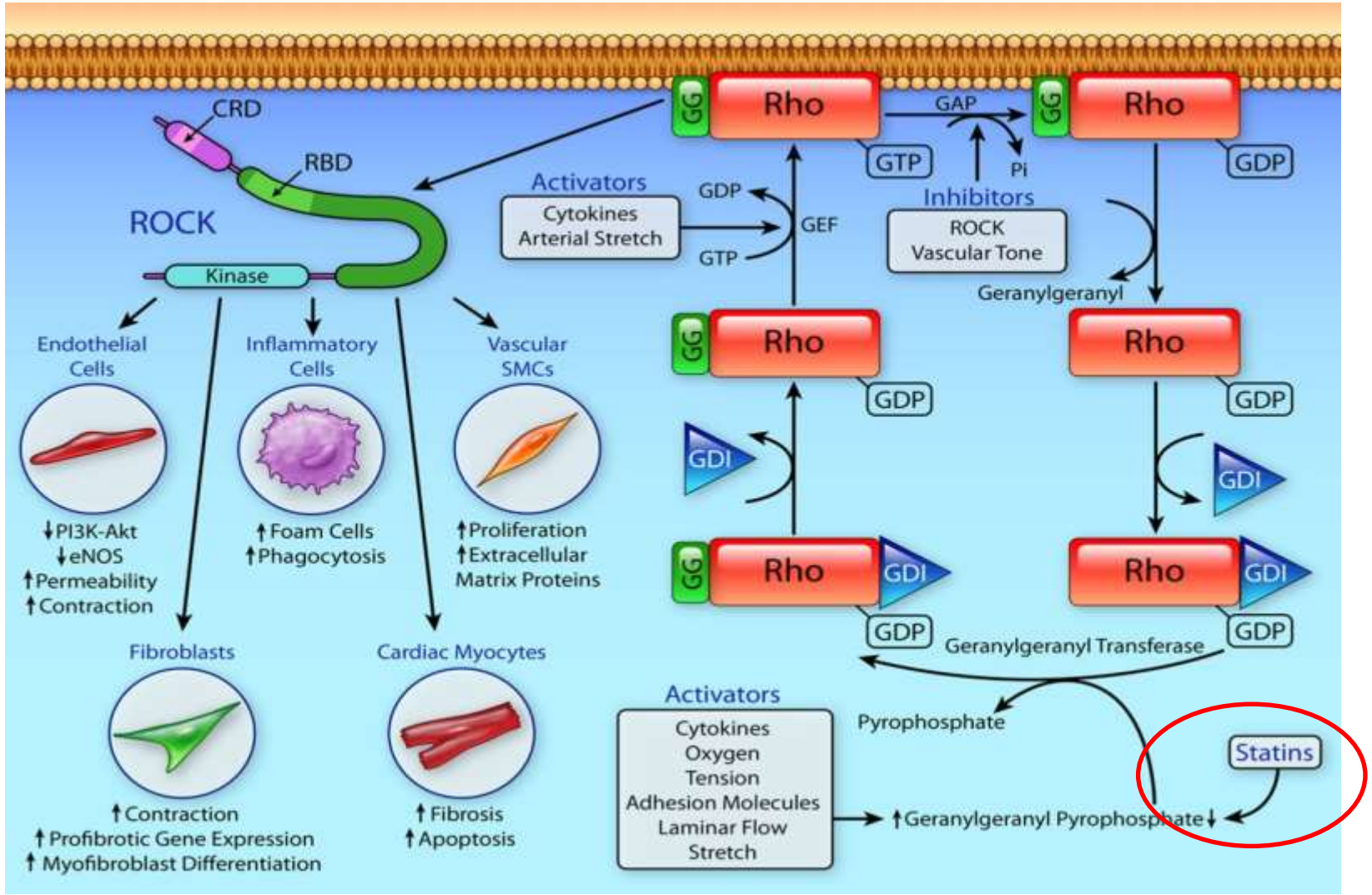
LDL-C lowering : Statin up-titration vs Statin + Ezetimibe



Method : Eligible patients (n=17,830), initially on statin monotherapy who were 18 years with baseline and follow-up LDL-C values, no concomitant use of other lipid-lowering therapy, and on lipid-lowering therapy for 42 days, were identified between November 1, 2002 and September 30, 2009. The percent change from baseline in LDL-C levels and the odds ratios for attainment of LDL-C,1.8 and 2.6 mmol/L (70 and 100 mg/dL) were estimated using an analysis of covariance and logistic regression, respectively, adjusted for various baseline factors.

<Ref.> Foody JM, et al. Vasc Health Risk Manag 2013;9:719-727.

Pleiotropic Effects of Statins Beyond LDL-C

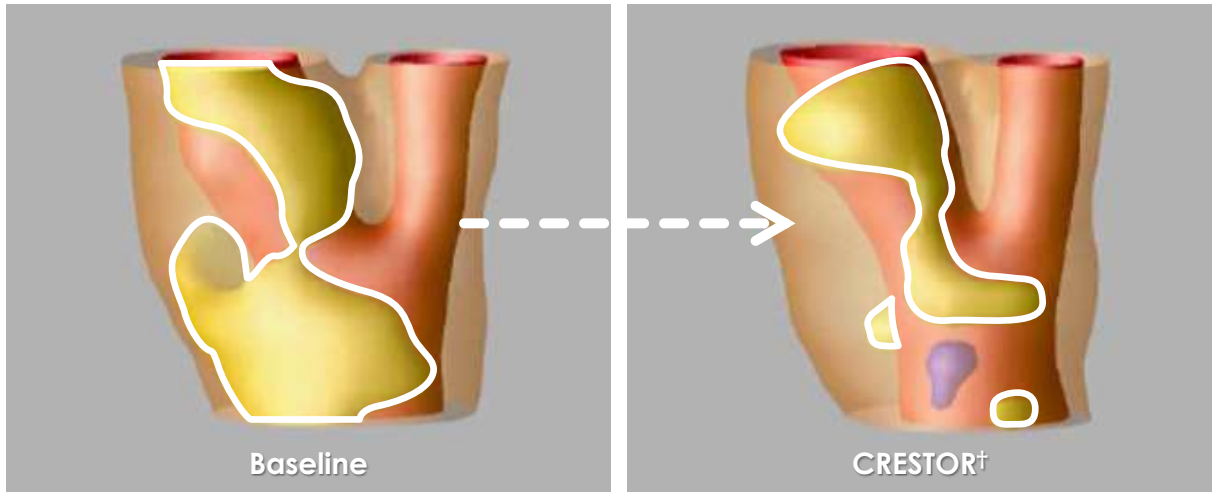


- ✓**Statins have demonstrated the inhibition of leukocyte ROCK activity in humans independent of LDL reduction.**
- ✓**ROCK inhibition is a candidate for mediating statin pleiotropy because of ROCK's effects on the CV system.**
- ✓**ROCK inhibition by statins occurs through cholesterol-independent mechanisms.**

Ref.> Oesterle A, et al. Circ Res. 2017 Jan 6;120(1):229-243.

Patients Showing Plaque Regression (ORION)

Plaque Composition Changes After 2 Years of Rosuvastatin Treatment
(3D rendering of MRI images)[1]



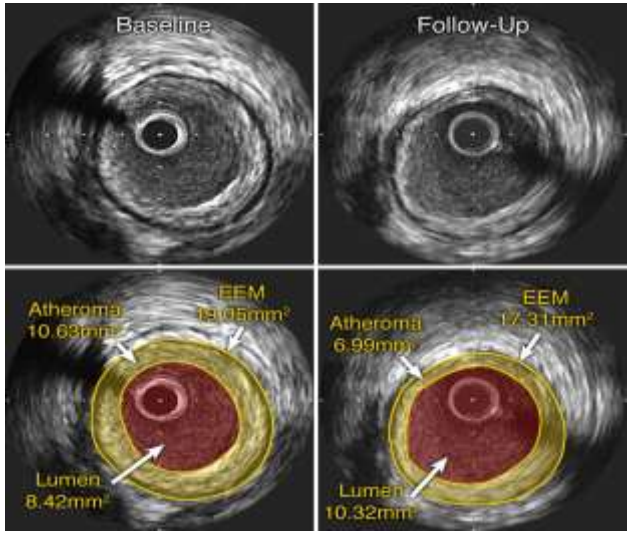
Yellow: lipid rich necrotic core (LRNC), Red: vessel lumen, Light orange: outer wall
Purple: calcification, MRI: magnetic resonance imaging,† Personal communication

ORION, Outcome of Rosuvastatin treatment on carotid artery atheroma: a magnetic resonance imaging ObservatioN

- ✓ **Methods**: A randomized double-blind study comparing the effects of low dose of rosuvastatin and high dose of carotid plaque reduction in patients with hypercholesterolemia with asymptomatic carotid artery disease. Comparison of changes in volume and composition of carotid artery plaques after 24 months of random assignment of low dose (5 mg) or high dose (40/80 mg) of rosuvastatin in 43 individuals.
- ✓ **Result**: After 24 months, 33 patients had matched serial MRI scans to compare by reviewers blinded to clinical data, dosage, and temporal sequence of scans. Low-density lipoprotein cholesterol was significantly reduced from baseline in both the low- and high-dose groups (38.2% and 59.9%, respectively, both P < .001). At 24 months, there were no significant changes in carotid plaque volume for either dosage group. In all patients with a lipid-rich necrotic core (LRNC) at baseline, the mean proportion of the vessel wall composed of LRNC (%LRNC) decreased by 41.4% (P = .005).

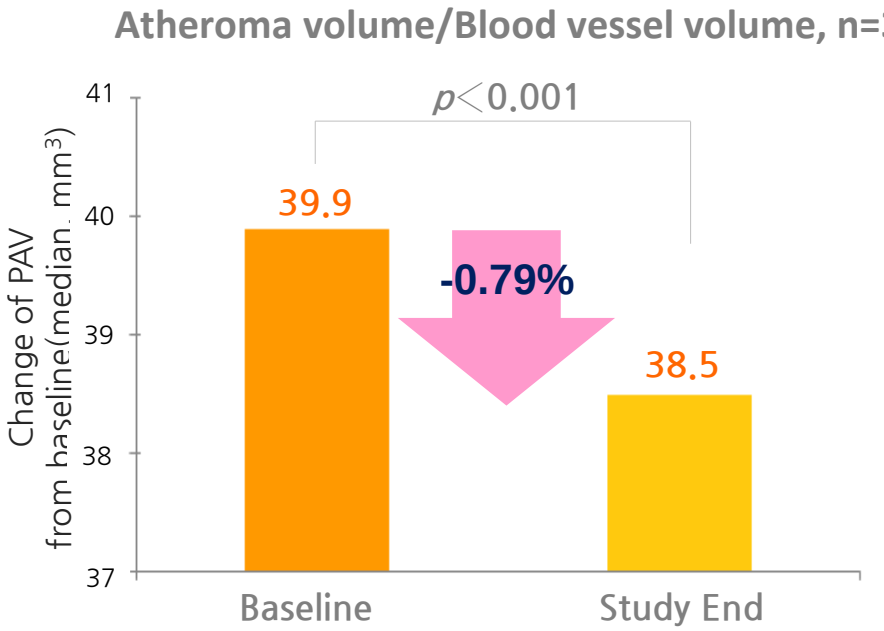
Ref.> Underhill HR, et al. Effect of rosuvastatin therapy on carotid plaque morphology and composition in moderately hypercholesterolemic patients: a high-resolution magnetic resonance imaging trial. Am Heart J 2008;155:584.e1- 8.

Patients Showing Plaque Regression (ASTEROID)

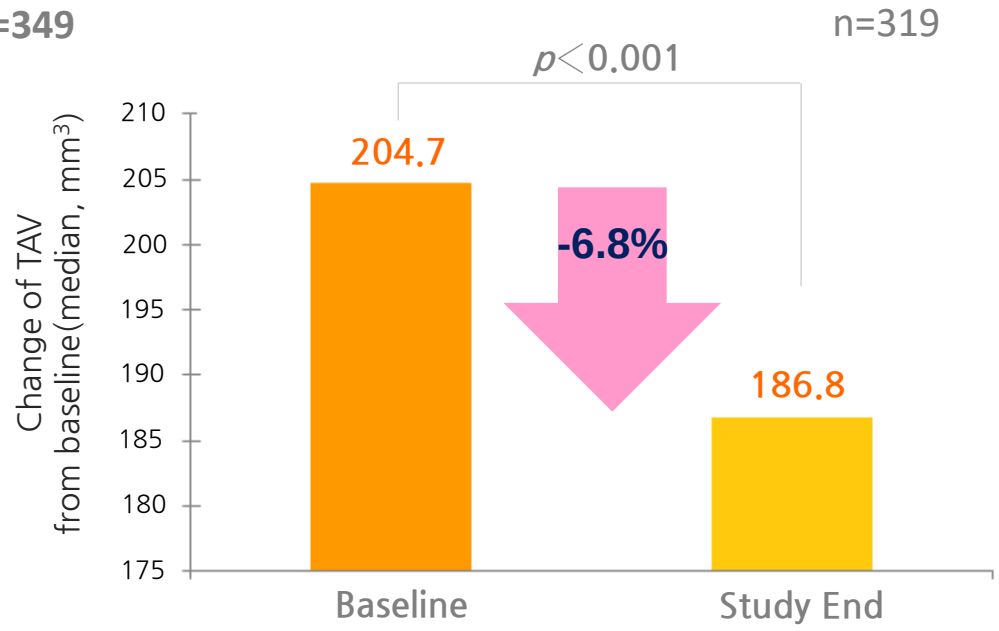


Regression of atheroma p<0.001

<Percent Atheroma Volume>



<Total Atheroma Volume>

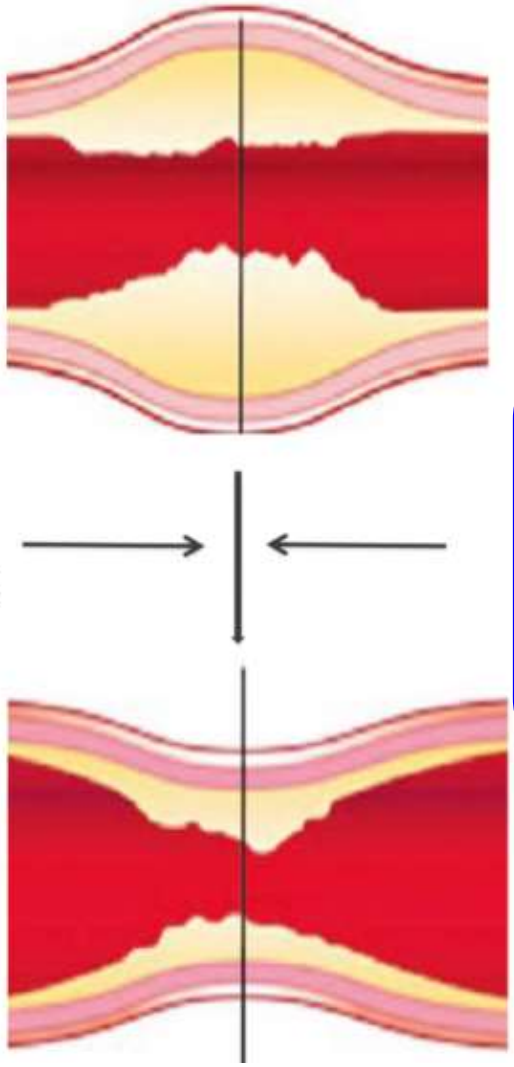


ASTEROID, A Study To Evaluate the Effect of ROsuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden

- ✓ **Methods**: Prospective, open-label blinded end-points trial was performed at 53 community and tertiary care centers in the United States, Canada, Europe, and Australia. A motorized IVUS pullback was used to assess coronary atheroma burden at baseline and after 24 months of treatment. Each pair of baseline and follow-up IVUS assessments was analyzed in a blinded fashion. Between November 2002 and October 2003, 507 patients had a baseline IVUS examination and received at least 1 dose of study drug. After 24 months, 349 patients had evaluable serial IVUS examinations.
- ✓ **Result**:The mean (SD) baseline low-density lipoprotein cholesterol (LDL-C) level of 130.4 (34.3) mg/dL declined to 60.8 (20.0) mg/dL, a mean reduction of 53.2% (P<.001). Mean (SD) high-density lipoprotein cholesterol (HDL-C) level at baseline was 43.1 (11.1) mg/dL, increasing to 49.0 (12.6) mg/dL, an increase of 14.7% (P<.001). The mean (SD) change in PAV for the entire vessel was -0.98% (3.15%), with a median of -0.79% (97.5% CI, -1.21% to -0.53%) (P<.001 vs baseline). The mean (SD) change in atheroma volume in the most diseased 10-mm subsegment was -6.1 (10.1) mm3, with a median of -5.6 mm3 (97.5% CI, -6.8 to -4.0 mm3) (P<.001 vs baseline). Change in total atheroma volume showed a 6.8% median reduction; with a mean (SD) reduction of -14.7 (25.7) mm3, with a median of -12.5 mm3 (95% CI, -15.1 to -10.5 mm3) (P<.001 vs baseline). Adverse events were infrequent and similar to other statin trials.

Ref.> Nissen SE, et al. JAMA. 2006;295(13):1556-1565.

Beneficial effects of statins & ezetimibe on plaque growth



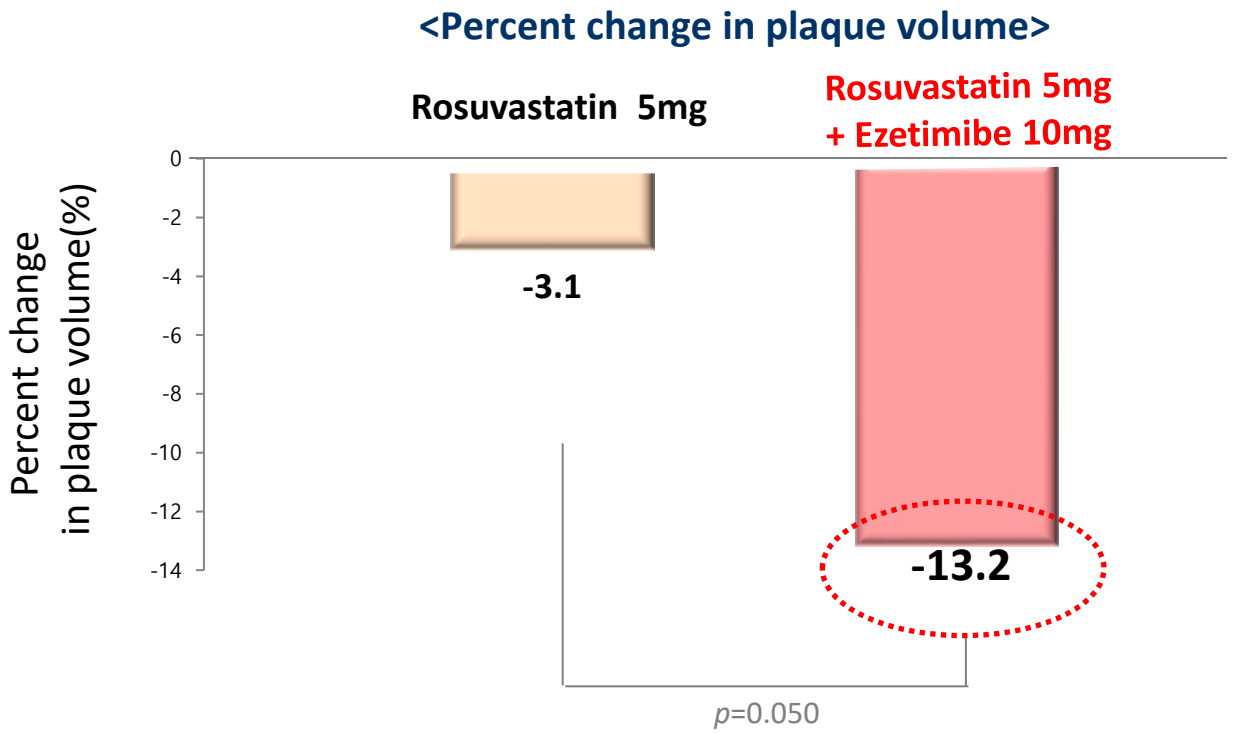
Statins

LDL-C reduction
Anti-oxidant effects
Anti-inflammatory effects
Anti-thrombotic effects
CC dissolution

Ezetimibe

- LDL-C reduction
- Anti-oxidant effects
- Sterol reduction
- vSMc proliferation inhibition
- CC reduction

Regression of Coronary Atherosclerosis : Statin vs Statin+Ezetimibe (1)



✓ **Methods**: The aim of this study was to investigate the add-on effect of ezetimibe to a statin on coronary atherosclerosis evaluated by intravascular ultrasound (IVUS).In this prospective randomized open-label study, a total of 51 patients with stable coronary artery disease (CAD) requiring percutaneous coronary intervention (PCI) were enrolled, and assigned to a combination group (n = 26, rosuvastatin 5 mg/day + ezetimibe 10 mg/day) or a monotherapy group (n = 25, rosuvastatin 5 mg/day). Volumetric IVUS analyses were performed at baseline and 6 months after the treatment for a non-PCI site.

Ref.> Masuda J, et al. Int Heart K. 2015;56(3):278-285.

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Regression of Coronary Atherosclerosis : Statin vs Statin+Ezetimibe (2)

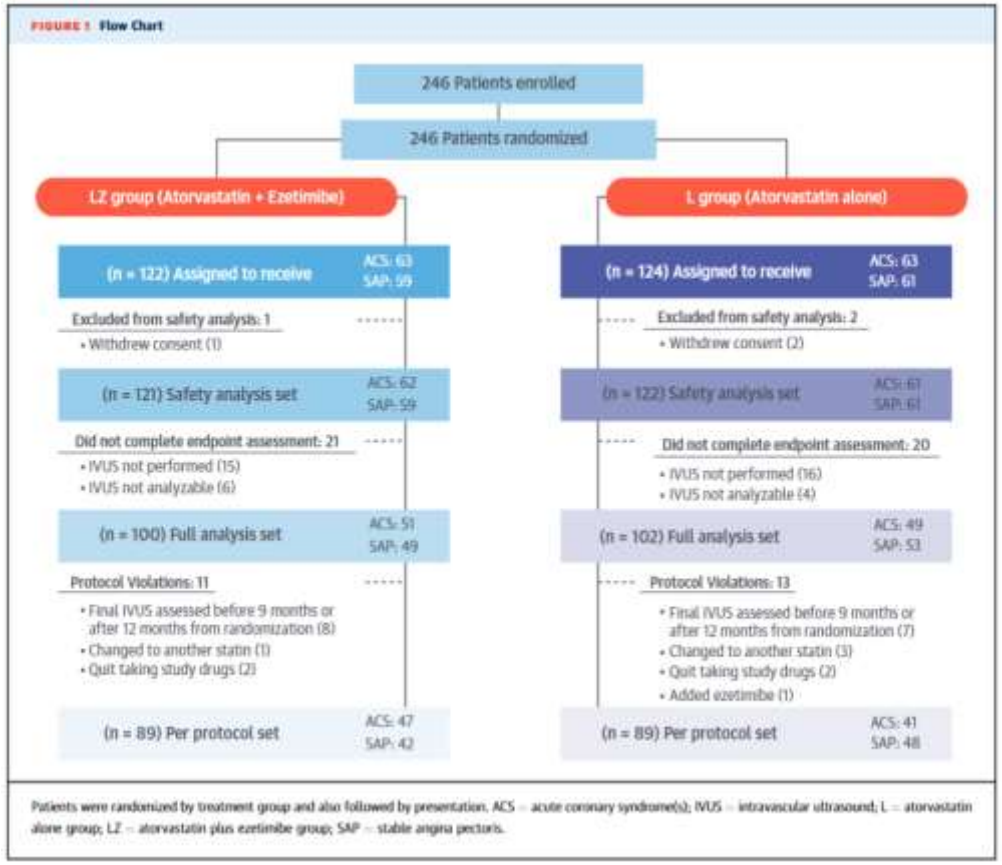


TABLE 2 Baseline and Follow-Up Laboratory Data

	Baseline		Follow-Up		Percent Change (%)		
	LZ Group (n = 100)	L Group (n = 102)	LZ Group (n = 100)	L Group (n = 102)	LZ Group (n = 100)	L Group (n = 102)	p Value
TC, mg/dl	177.3 ± 32.4	172.7 ± 32.6	129.4 ± 22.0	138.7 ± 26.2	-25 ± 17	-18 ± 18	0.006
HDL-C, mg/dl	41.1 ± 9.5	40.0 ± 10.3	45.6 ± 11.9	43.3 ± 11.5	14 ± 26	11 ± 25	0.5
LDL-C, mg/dl	109.8 ± 25.4	108.3 ± 26.3	63.2 ± 16.3	73.3 ± 20.3	-40 ± 18	-29 ± 24	<0.001
Triglycerides, mg/dl	114 (81 to 158)	116 (92 to 159)	92 (76 to 120)	111 (87 to 139)	-14 (-33 to 18)	-9 (-33 to 25)	0.3
Lipoprotein (a), mg/dl	21.5 (12.5 to 37.5)	18.0 (10.0 to 30.5)	17.0 (8.0 to 36.0)	14.0 (7.0 to 30.5)	-12 (-42 to 17)	-20 (-50 to 7)	0.1
Apolipoprotein A-I, mg/dl	112.8 ± 20.2	112.6 ± 21.6	128.1 ± 25.0	123.7 ± 24.5	15 ± 21	11 ± 17	0.2
Apolipoprotein B, mg/dl	96.9 ± 20.6	94.0 ± 19.2	62.5 ± 13.0	69.0 ± 16.1	-34 ± 16	-26 ± 20	0.001
Free fatty acid, μEq/l	402 (281 to 574)	431 (278 to 610)	384 (218 to 541)	376 (223 to 627)	-7 (-50 to 59)	-11 (-56 to 68)	0.8
MDA-LDL, U/l	122.9 ± 39.9	121.8 ± 40.5	81.8 ± 24.1	95.1 ± 30.8	-27.7 ± 27.0	-15.3 ± 38.5	0.1
RLP-C, mg/dl	3.8 (2.7 to 4.8)	3.5 (2.7 to 5.1)	2.6 (2.1 to 3.5)	3.1 (2.4 to 4.5)	-28 (-48 to 3)	-17 (-37 to 17)	0.02
sdLDL-C, mg/dl	32.7 ± 15.6	30.5 ± 11.8	20.6 ± 8.6	22.5 ± 10.1	-28.5 ± 33.5	-21.4 ± 35.0	0.2
Insulin, μIU/ml	6.8 (4.3 to 10.1)	7.3 (4.9 to 9.6)	7.9 (4.9 to 12.6)	8.4 (5.4 to 12.5)	15 (-33 to 73)	22 (-18 to 51)	0.99
HbA_{1c}, %	5.4 (5.1 to 6.3)	5.5 (5.3 to 6.3)	5.6 (5.2 to 6.0)	5.7 (5.4 to 6.1)	3 (-2 to 5)	2 (-4 to 4)	0.2
Total adiponectin, μg/ml	4.7 (3.4 to 7.0)	4.1 (2.7 to 5.7)	6.2 (3.9 to 8.3)	5.0 (3.3 to 7.2)	28 (-4 to 64)	19 (-5 to 63)	0.4
HMW adiponectin, μg/ml	1.9 (1.0 to 3.1)	1.4 (0.8 to 2.6)	2.3 (1.2 to 4.3)	1.6 (0.9 to 2.9)	24 (-25 to 74)	19 (-25 to 86)	0.9
Lathosterol, μg/ml	1.1 (0.7 to 2.3)	1.3 (0.7 to 2.1)	1.0 (0.8 to 1.4)	0.6 (0.4 to 0.9)	-15 (-53 to 45)	-53 (-71 to -22)	<0.001
Campesterol, μg/ml	4.4 (3.3 to 5.7)	3.7 (2.8 to 5.0)	2.3 (1.8 to 2.9)	4.9 (3.5 to 6.4)	-46 (-61 to -30)	22 (-5 to 61)	<0.001
Sitosterol, μg/ml	2.2 (1.7 to 3.0)	2.0 (1.5 to 2.7)	1.3 (1.0 to 1.9)	2.4 (1.8 to 3.4)	-39 (-53 to -20)	31 (-6 to 67)	<0.001
Lathosterol, μg/100 mg TC	68 (43 to 109)	73 (44 to 116)	81 (59 to 108)	49 (33 to 66)	14 (-28 to 68)	-36 (-57 to 2)	<0.001
Campesterol, μg/100 mg TC	252 (199 to 321)	215 (165 to 281)	183 (143 to 228)	362 (258 to 451)	-30 (-43 to -10)	53 (24 to 82)	<0.001
Sitosterol, μg/100 mg TC	129 (98 to 174)	113 (91 to 152)	101 (78 to 145)	178 (131 to 264)	-15 (-34 to 9)	60 (27 to 106)	<0.001
Campesterol/Lathosterol	3.7 (2.2 to 6.5)	2.8 (2.0 to 5.0)	2.2 (1.5 to 3.6)	7.5 (4.3 to 12.5)	-40 (-66 to 10)	167 (48 to 267)	<0.001
hs-CRP, mg/l	3.0 (1.0 to 14.9)	3.7 (1.2 to 8.1)	0.4 (0.2 to 1.3)	0.3 (0.2 to 0.8)	-89 (-97 to -59)	-86 (-95 to -70)	0.9

Values are mean ± SD or median (IQR).
HDL-C = high-density lipoprotein cholesterol; HMW = high molecular weight; hs-CRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; MDA-LDL = malondialdehyde-modified LDL; RLP-C = remnant like particles cholesterol; sdLDL-C = small-dense LDL-C; TC = total cholesterol; other abbreviations as in Table 1.

PRECISE-IVUS, Plaque Regression With Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound

✓ **Methods**: prospective, randomized, controlled, multicenter study. Eligible patients who underwent PCI were randomly assigned to atorvastatin alone or atorvastatin plus ezetimibe (10 mg) daily. Atorvastatin was uptitrated witha treatment goal of low-density lipoprotein cholesterol (LDL-C) <70 mg/dl. Serial volumetric intravascular ultrasound was performed at baseline and again at 9 to 12 months to quantify the coronary plaque response in 202 patients

Ref.> Tsujita, K. et al. J Am Coll Cardiol. 2015; 66: 495-507

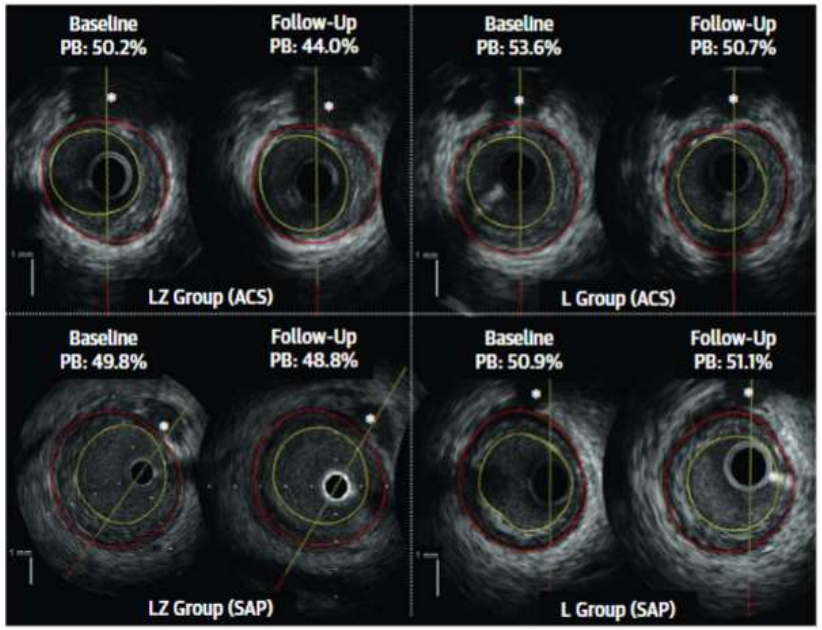
Regression of Coronary Atherosclerosis : Statin vs Statin+Ezetimibe (2)

TABLE 3 Demonstration of Coronary Plaque Progression/Regression

	Baseline			9-12 Months Follow-Up		
	LZ Group (n = 100)	L Group (n = 102)	p Value	LZ Group (n = 100)	L Group (n = 102)	p Value
Plaque volume, mm^3	72.6 (37.6 to 117.4)	76.3 (45.5 to 128.4)	0.5	69.6 (35.0 to 107.2)	77.3 (45.4 to 126.2)	0.2
Percent atheroma volume, %	51.3 ± 10.8	50.9 ± 11.4	0.8	49.3 ± 10.3	50.4 ± 11.6	0.5
TAV_{norm}, mm^3	89.6 (65.8 to 118.8)	84.8 (61.5 to 112.7)	0.7	85.4 (65.5 to 110.0)	87.2 (60.1 to 111.8)	0.6
Vessel volume, mm^3	144.4 (78.5 to 218.6)	159.8 (97.7 to 244.4)	0.3	141.8 (70.0 to 222.3)	155.7 (101.4 to 241.6)	0.2
Lumen volume, mm^3	70.4 (34.5 to 117.1)	79.4 (47.5 to 116.6)	0.3	65.8 (36.5 to 113.8)	79.1 (47.7 to 115.3)	0.2
Lesion length, mm	10.1 (5.6 to 14.6)	12.4 (7.5 to 16.0)	0.11	9.7 (5.8 to 14.5)	11.9 (7.2 to 15.9)	0.10

	Absolute Change				
	LZ Group (n = 100)	p Value Compared With Baseline	L Group (n = 102)	p Value Compared With Baseline	p Value Between Groups
Plaque volume, mm^3	-3.9 (-10.6 to 0.0)	<0.001	-1.0 (-6.8 to 5.7)	0.4	0.001
Percent atheroma volume, %	-1.4 (-3.4 to -0.1)	<0.001	-0.3 (-1.9 to 0.9)	0.03	0.001
ACS cohort	-2.3 (-3.7 to -0.5)	<0.001	-0.2 (-1.3 to 0.5)	0.2	<0.001
SAP cohort	-1.2 (-2.2 to -0.1)	0.001	-0.7 (-2.3 to 1.1)	0.08	0.2
TAV_{norm}, mm^3	-5.3 (-12.4 to 0.1)	<0.001	-1.2 (-5.7 to 3.3)	0.1	<0.001
Vessel volume, mm^3	-4.1 (-12.6 to 3.1)	0.001	-0.6 (-11.8 to 10.6)	0.9	0.04
Lumen volume, mm^3	-0.3 (-4.9 to 4.0)	0.4	0.8 (-5.6 to 6.9)	0.5	0.4

FIGURE 3 Plaque Progression/Regression



IVUS images of the same cross sections at baseline and follow-up show outlined leading edges of lumen **(yellow line)** and external elastic membrane **(red line)**. Note the substantial reduction in plaque area observed for the cross-sectional images, especially in the LZ group versus the L group.*Side branches show same position and shape. PB = plaque burden; other abbreviations as in Figures 1 and 2.

PRECISE-IVUS, Plaque Regression With Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound

- ✓ **Methods**: prospective, randomized, controlled, multicenter study. Eligible patients who underwent PCI were randomly assigned to atorvastatin alone or atorvastatin plus ezetimibe (10 mg) daily. Atorvastatin was uptitrated witha treatment goal of low-density lipoprotein cholesterol (LDL-C) <70 mg/dl. Serial volumetric intravascular ultrasound was performed at baseline and again at 9 to 12 months to quantify the coronary plaque response in 202 patients

Ref.> Tsujita, K. et al. J Am Coll Cardiol. 2015; 66: 495-507

Regression of Coronary Atherosclerosis : Statin vs Statin+Ezetimibe (3)

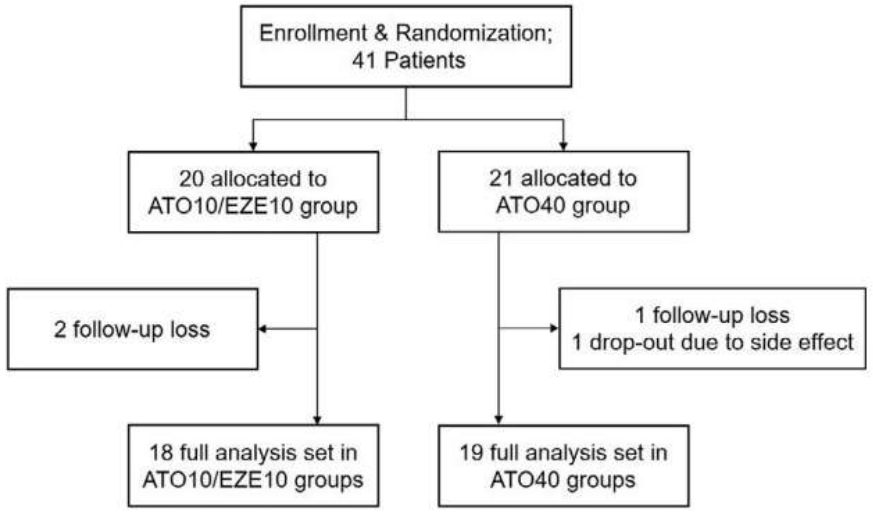


Figure 1. Flow chart of the study procedure.

Table 2
Baseline and follow-up laboratory data

Variables	ATO10/EZE10 (n = 18)			ATO40 (n = 19)		
	Baseline	Follow-up	p value	Baseline	Follow-up	p value
Total cholesterol (mg/dL)	171.0 ± 34.7	123.2 ± 19.5	0.030	167.2 ± 36.5	125.6 ± 28.0	0.004
HDL-C (mg/dL)	38.7 ± 13.3	38.2 ± 15.2	0.928	44.7 ± 13.5	44.2 ± 10.8	0.779
LDL-C (mg/dL)	107.0 ± 31.5	60.5 ± 19.0	0.019	100.6 ± 30.7	57.8 ± 20.7	0.001
Triglycerides (mg/dL)	109.0 (69.5, 193.5)	101.0 (55.0, 121.8)	0.173	107.0 (90.8, 152.3)	102.0 (54.8, 149.5)	0.722
Apolipoprotein A-I (mg/dL)	115.8 ± 23.5	110.3 ± 27.3	0.639	132.6 ± 23.7	140.2 ± 20.0	0.286
Apolipoprotein B (mg/dL)	91.7 ± 23.6	58.7 ± 13.9	0.008	86.9 ± 19.0	57.7 ± 18.9	0.002
Ratio B/A-I	0.83 ± 0.30	0.57 ± 0.23	0.061	0.67 ± 0.17	0.41 ± 0.11	<0.001
Fasting glucose (mg/dL)	93.0 (90.8, 122.0)	101.5 (70.5, 114.3)	0.916	104.0 (93.8, 136.8)	107.5 (97.8, 119.8)	0.756
HbA1c (%)	5.8 (5.2, 6.3)	5.9 (5.4, 6.2)	0.461	5.9 (5.7, 7.1)	6.0 (5.5, 6.4)	0.315
hs-CRP (mg/dL)	0.050 (0.018, 0.105)	0.025 (0.010, 0.113)	0.018	0.070 (0.063, 0.278)	0.025 (0.010, 0.130)	0.003

Percent change between baseline and follow-up

Variables	*ATO10/EZE10 (n = 18)*	*ATO40 (n = 19)*	*p value*
Total cholesterol	−25.3 ± 20.9	−23.1 ± 16.7	0.725
HDL-C	3.6 ± 39.9	0.5 ± 12.9	0.750
LDL-C	−39.5 ± 23.4	−38.1 ± 21.3	0.726
Triglycerides	−25.6 (−47.2, 10.8)	−30.8 (−38.1, 11.2)	0.301
Apolipoprotein A-I	−2.8 ± 23.7	7.3 ± 16.5	0.140
Apolipoprotein B	−33.6 ± 17.7	−32.3 ± 20.2	0.837
Ratio B/A-I	−28.2 ± 22.9	−36.8 ± 16.5	0.197
hs-CRP	−50.0 (−66.7, 5.0)	−60.8 (−83.1, 2.3)	0.285

Values are mean ± standard deviation, or median (interquartile range).
HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol.

✓ **Methods**: prospective, open-label, randomized, singlecenter study with blind endpoint evaluation. In patients aged ≥19 years with suspected stable angina pectoris, coronary angiography was performed and culprit lesions with severe stenosis were treated with a percutaneous coronary intervention using the standard techniques. After the successful angioplasty, patients with an intermediate nonculprit lesion were enrolled. The intermediate non-culprit lesion (target lesion) was defined as a NIRS-IVUS feasible native coronary lesion with 30% to 60% angiographic diameter stenosis and 2.0 mm to 4.0 mm in diameter by visual estimation and located > 10 mm apart from the Department of Cardiology, Gil Medical Center, Gachon University College of Medicine, Incheon, Republic of Korea. The target lesion was evaluated using a combined NIRS-IVUS imaging system (Infraredx, a Nipro Company, Burlington, MA, United States). Patients were required to have an LDL-C level >70 mg/dL at baseline regardless of the use of previous lipid-lowering agents

Ref.> J Am Coll Cardiol. 2015 Aug, 66 (5) 508–510

Regression of Coronary Atherosclerosis : Statin vs Statin+Ezetimibe (3)

Table 3
Baseline and follow-up near-infrared spectroscopy-intravascular ultrasonography data

	ATO10/EZE10 (n = 18)			ATO40 (n = 19)		
Variables	Baseline	Follow-up	p value	Baseline	Follow-up	p value
Vessel volume (mm^3)	158.9 (116.2, 227.9)	156.5 (113.6, 211.8)	0.265	184.5 (122.9, 233.0)	180.8 (120.8, 232.3)	0.155
Lumen volume (mm^3)	89.3 (53.3, 124.2)	83.9 (55.0, 117.0)	0.412	100.7 (73.2, 133.5)	93.9 (74.6, 126.5)	0.213
Plaque volume (mm^3)	69.6 (52.9, 127.2)	66.2 (48.6, 123.9)	0.024	79.6 (68.7, 119.8)	76.9 (65.2, 111.1)	0.013
Percent atheroma volume (%)	45.9 ± 6.4	42.7 ± 6.3	0.022	44.8±4.8	41.0 ± 4.8	0.018
Normalized total atheroma volume (mm^3)	81.8 (58.9-111.3)	78.7 (53.8-104.0)	0.012	91.7 (68.8-129.8)	87.2 (64.0-110.6)	0.010
Lesion length (mm)	10.6 ± 2.8	10.5 ± 2.9	0.882	11.4 ± 4.1	11.5 ± 3.8	0.901
LCBI	30.0 (2.0, 57.0)	29.0 (3.0, 55.0)	0.753	54.0 (9.0, 97.0)	50.0 (9.0, 93.0)	0.354
$maxLCBI_{4mm}$	95.0 (39.0, 243.0)	91.0 (43.0, 250.0)	0.680	100 (87.0, 288.0)	104 (81.0, 300.0)	0.773

Absolute change between baseline and follow-up

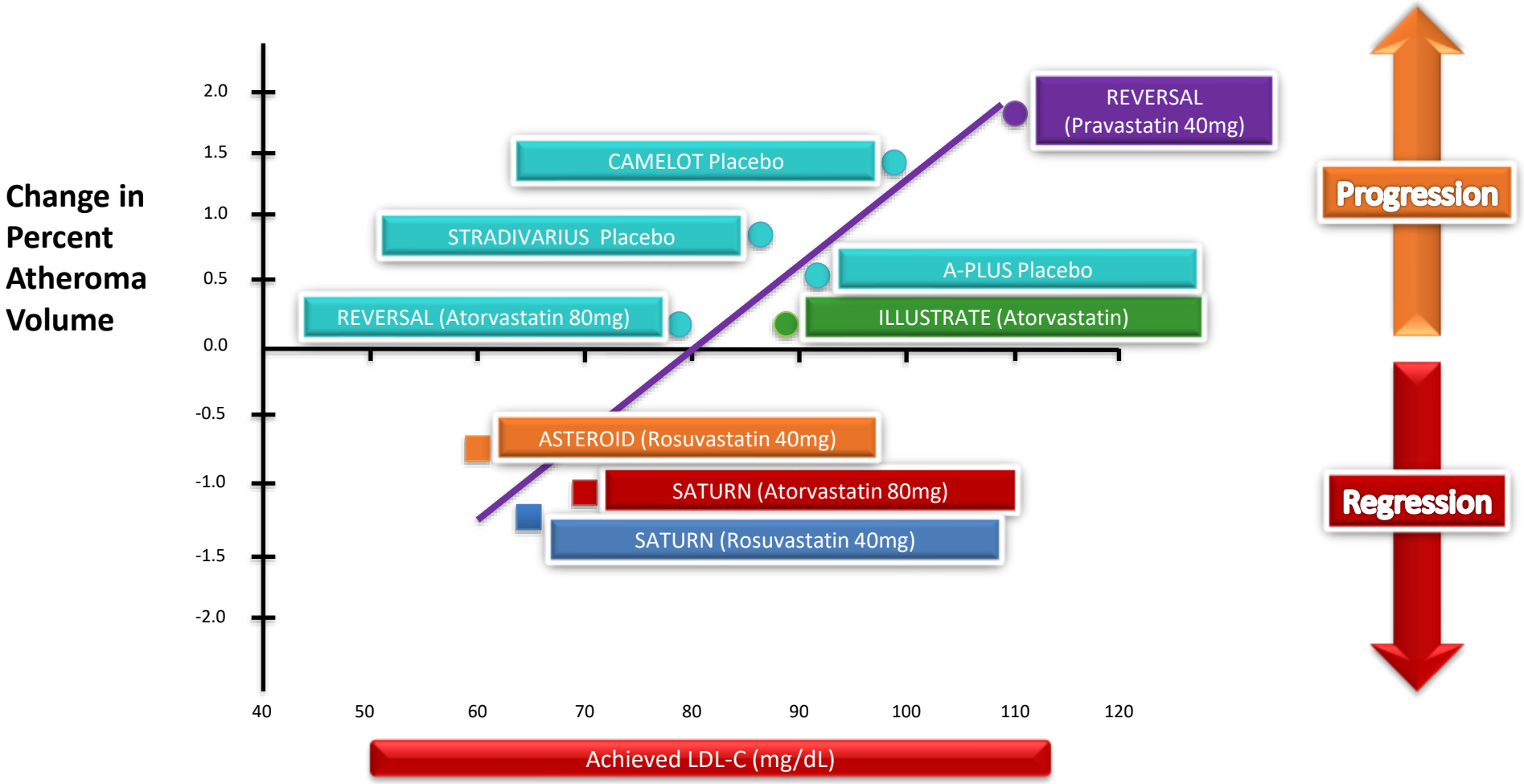
Variables	*ATO10/EZE10 (n = 18)*	*ATO40 (n = 19)*	*p value*
Vessel volume (mm^3)	−3.6 (−10.5, 5.2)	−4.7 (−13.6, 5.0)	0.724
Lumen volume (mm^3)	−0.2 (−5.8, 4.4)	−1.9 (−3.3, 2.2)	0.375
Plaque volume (mm^3)	−3.2 (−12.2, 0.9)	−3.9 (−15.2, −0.7)	0.328
Percent atheroma volume (%)	−2.9 (−5.7, −0.1)	−3.2 (−5.1, −0.6)	0.285
Normalized total atheroma volume (mm^3)	−4.1 (−14.3, 0.1)	−5.0 (−10.7, −0.4)	0.479
LCBI	−1.9 (−12.4, 9.2)	−4.0 (−20.0, 15.0)	0.845
$maxLCBI_{4mm}$	−5.2 (−33.4, 29.5)	2.2 (−54.2, 45.2)	0.328

Values are mean ± standard deviation, or median (interquartile range).
LCBI, lipid core burden index.

✓ **Methods**: prospective, open-label, randomized, singlecenter study with blind endpoint evaluation. In patients aged ≥19 years with suspected stable angina pectoris, coronary angiography was performed and culprit lesions with severe stenosis were treated with a percutaneous coronary intervention using the standard techniques. After the successful angioplasty, patients with an intermediate nonculprit lesion were enrolled. The intermediate non-culprit lesion (target lesion) was defined as a NIRS-IVUS feasible native coronary lesion with 30% to 60% angiographic diameter stenosis and 2.0 mm to 4.0 mm in diameter by visual estimation and located > 10 mm apart from the Department of Cardiology, Gil Medical Center, Gachon University College of Medicine, Incheon, Republic of Korea. The target lesion was evaluated using a combined NIRS-IVUS imaging system (Infraredx, a Nipro Company, Burlington, MA, United States). Patients were required to have an LDL-C level >70 mg/dL at baseline regardless of the use of previous lipid-lowering agents

Ref.> J Am Coll Cardiol. 2015 Aug, 66 (5) 508–510

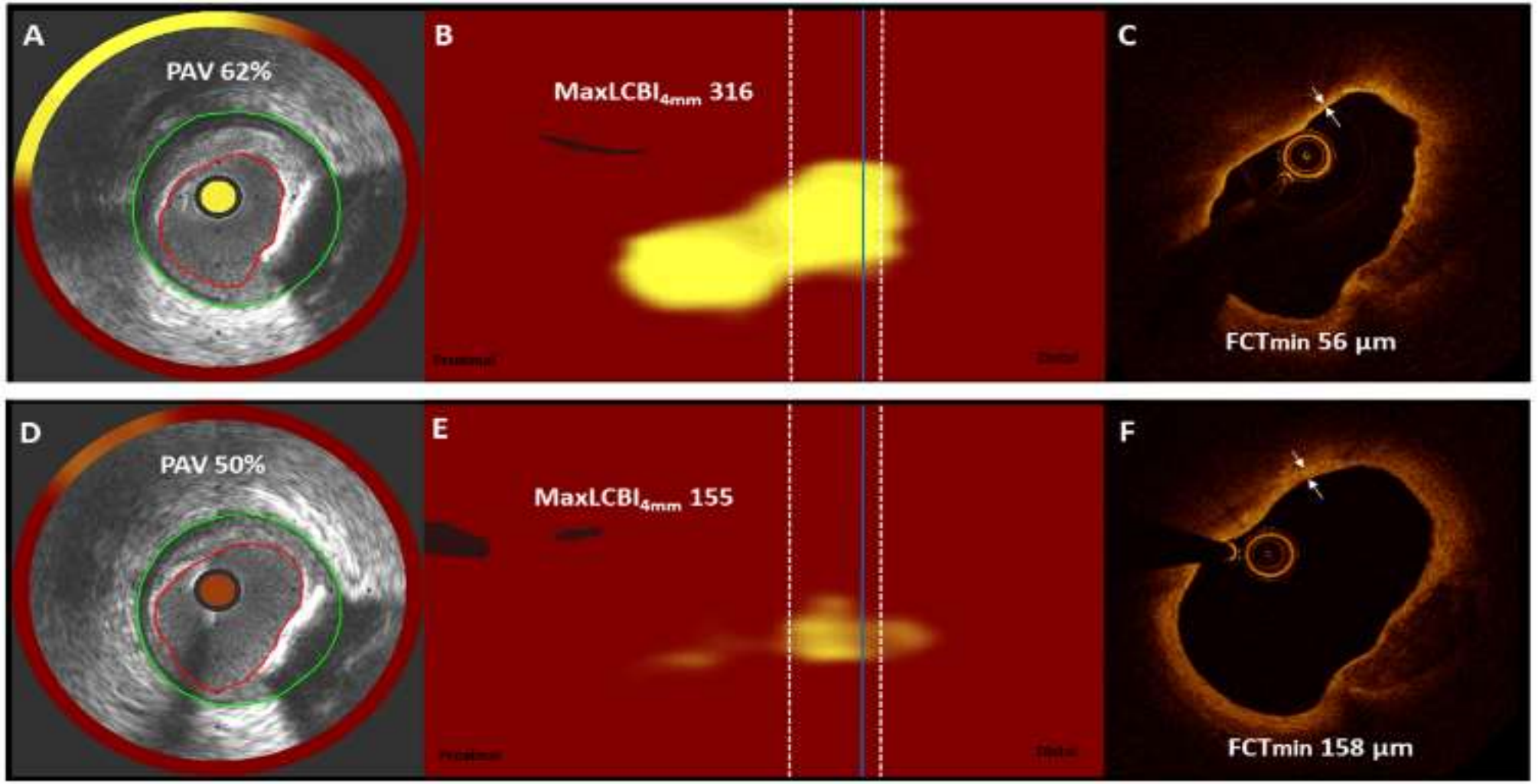
Relationship between achieved LDL-C and Change in Atheroma volume



Case Example PCSK9i (Alirocumab) & Statin Group

BASELINE

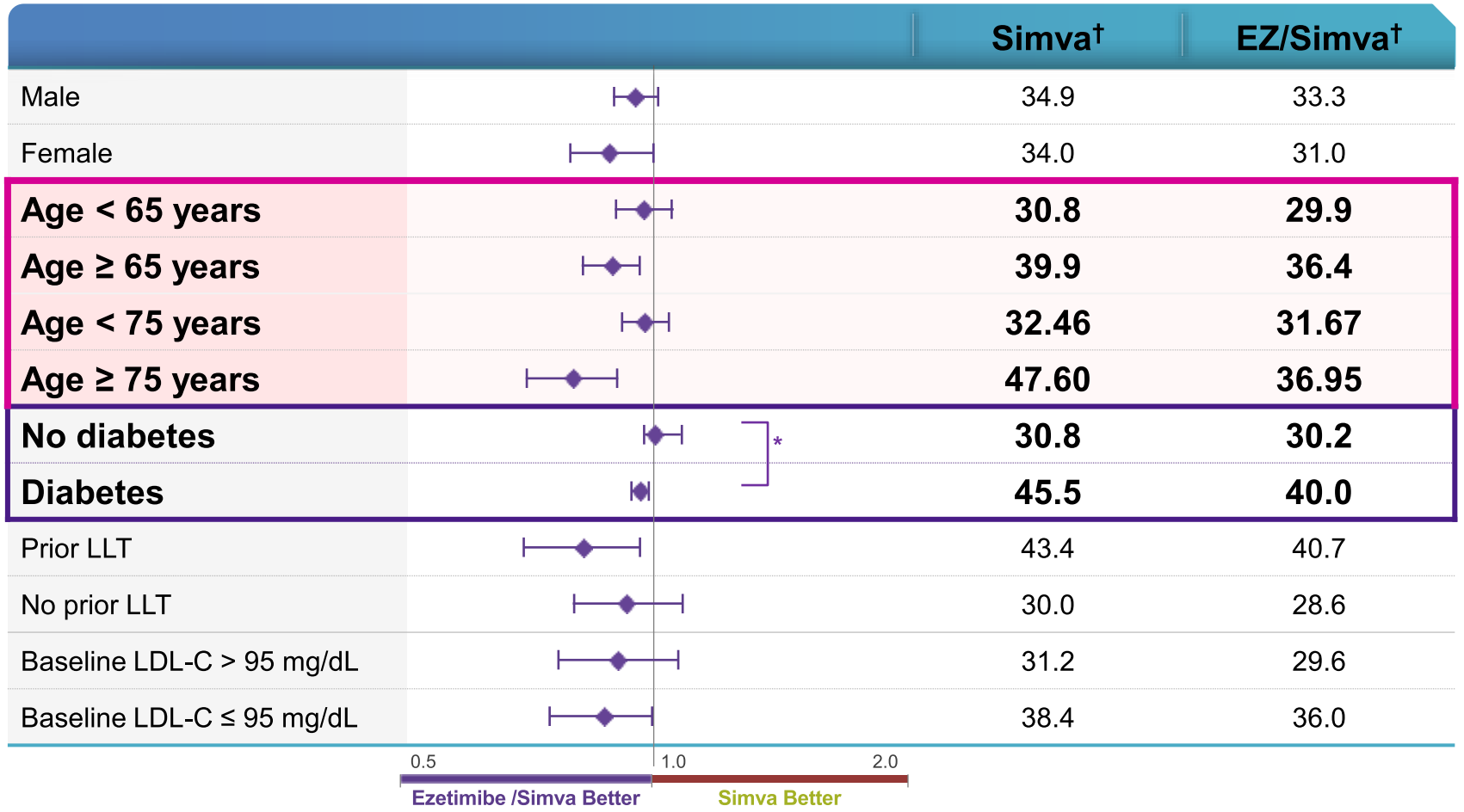
52 WEEKS



SNUH SEOUL NATIONAL UNIVERSITY BUNDANG HOSPITAL

[IMROVE-IT sub-analysis]
The CV benefit of Ezetimibe add-on therapy in elderly patients

Major Prespecified Subgroups



†7-year event rates, *p-interaction = 0.023, otherwise > 0.05

LLT : Lipid lowering treatment, **LDL-C** : Low density lipoprotein Cholesterol, DM : diabetes mellitus, **CV** : Cardiovascular, **EZ/Simva** : Ezetimibe/Simvastatin

1. Cannon, *et al.* Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *The New England Journal of Medicine.* 2015;372(25):2387–2397. **2.** Cannon CP, *et al.* Ezetimibe added to statin therapy after acute coronary syndromes. Supplementary Appendix. *N Engl J Med.* 2015;372:2387-97.

[IMPROVE-IT : Long-term Safety]
Simva/Eze vs. Simva after ACS Among Patients ≥75 Years Starting EZE/ATV Combo

Table 2. Safety End Points According to Age at Randomization and Treatment

	Patient Age Group by Treatment, No. (%)					
	<65 y		65-74 y		≥75 y	
	Simvastatin Monotherapy (n = 5129)	Simvastatin-Ezetimibe (n = 5044)	Simvastatin Monotherapy (n = 2520)	Simvastatin-Ezetimibe (n = 2653)	Simvastatin Monotherapy (n = 1428)	Simvastatin/Ezetimibe (n = 1370)
Liver-related events						
ALT or AST level or both ≥3 × ULN	108 (2.1)	128 (2.5)	51 (2.0)	60 (2.3)	49 (3.4)	36 (2.6)
Gallbladder-related adverse events	169 (3.3)	138 (2.7)	105 (4.2)	100 (3.8)	47 (3.3)	44 (3.2)
Muscle-related events						
Rhabdomyolysis	6 (0.1)	5 (0.1)	9 (0.4)	5 (0.2)	3 (0.2)	3 (0.2)
Myopathy	4 (0.1)	7 (0.1)	5 (0.2)	7 (0.3)	1 (0.1)	1 (0.1)
Myalgia	52 (1.0)	53 (1.1)	34 (1.3)	25 (0.9)	16 (1.1)	11 (0.8)
Myalgia with CK	17 (0.3)	16 (0.3)	9 (0.4)	5 (0.2)	5 (0.4)	5 (0.4)
Myopathy/rhabdomyolysis/myalgia with CK	27 (0.5)	28 (0.6)	22 (0.9)	16 (0.6)	9 (0.6)	9 (0.7)
Any cancer	368 (7.2)	378 (7.5)	335 (13.3)	339 (12.8)	212 (14.8)	192 (14.0)
Cataracts	106 (2.1)	116 (2.3)	134 (5.3)	151 (5.7)	85 (6.0)	81 (5.9)
Cognitive impairment	110 (2.1)	107 (2.1)	61 (2.4)	72 (2.7)	68 (4.8)	64 (4.7)

Ref> Bach RG, et al. JAMA Cardiol. doi:10.1001/jamacardio.2019.2306

[RACING] Long-term efficacy and Safety : Moderate intensity statin with Ezetimibe vs High intensity statin

- **Objective**

: this RACING trial sought to compare 3-year clinical efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients who are at very high risk for cardiovascular diseases. We sought to establish that adding ezetimibe to moderate-intensity statin could be an effective treatment for lowering cholesterol.

prospective, multicenter, open, randomized study, phase 4 clinical trial

Clinical CVD, Age 19-80 (n=3,780)

Moderate Intensity Statin + Ezetimibe
(ROS/EZE10/10mg) (N=1,890)

High Intensity Statin (Rosuvastatin 20mg) (N=1,890)

Non inferior

Regular clinical visits

Day 0 | 2 months | 6 months | 12 months | 24 months | 36 months

Randomization

Laboratory study

Primary Endpoint

Composite of CV death, major CV events* or nonfatal stroke within 3 years

*Any revascularization and hospitalization for CV events

Secondary Endpoint

- **Proportion of patients with LDL-C <70 mg/dL at 1, 2, and 3 years**
- **Composite of all death, major CV event, or nonfatal stroke**
- **Discontinuation or dose-reduction of study drug by intolerance**
- **Clinical adverse events**

LDL-C, low density lipoprotein cholesterol; CV, cardiovascular; CVD, cardiovascular disease.

Ref> Kim BK, Hong SJ, Lee YJ, et al. Long-term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease (RACING): a randomised, open-label, non-inferiority trial. Lancet. 2022 Jul 30;400(10349):380-390.

[RACING] Long-term efficacy and Safety : Moderate intensity statin with Ezetimibe vs High intensity statin

The primary endpoint occurred in **172 patients (9·1%) in the combination therapy** group and **186 patients (9·9%) in the high-intensity statin monotherapy** group (absolute difference −0·78%; 90% CI −2·39 to 0·83)

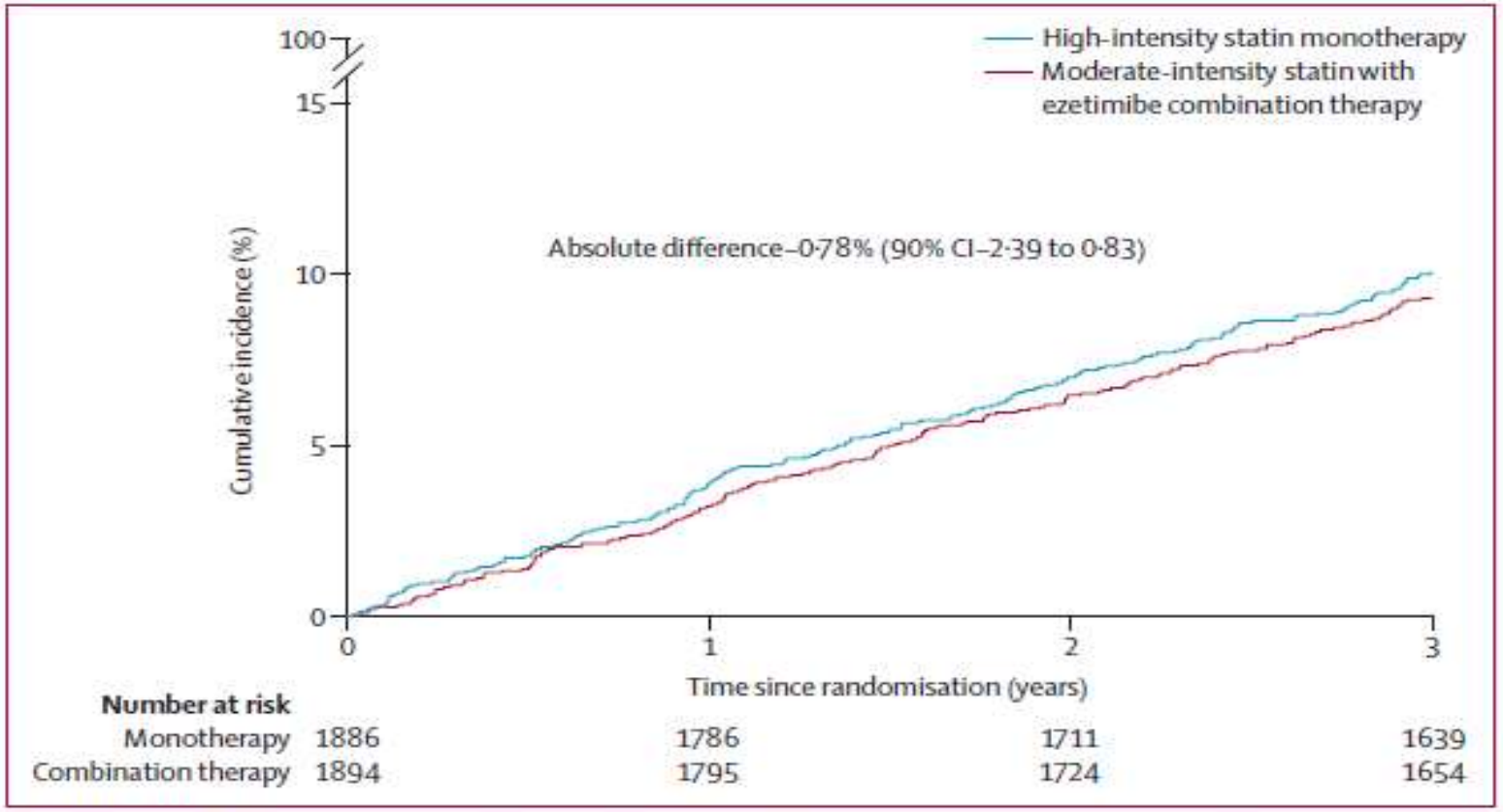


Figure 2: **Kaplan-Meier curves of the primary endpoint of the intention-to-treat population**

Ref> Kim BK, Hong SJ, Lee YJ, et al. Long-term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease (RACING): a randomised, open-label, non-inferiority trial. Lancet. 2022 Jul 30;400(10349):380-390.

[RACING] Long-term efficacy and Safety : Moderate intensity statin with Ezetimibe vs High intensity statin

Moderate intensity statin with Ezetimibe has a higher proportion of patients who achieved LDL cholesterol concentration of less than 70 mg/dL

	Moderate-intensity statin with ezetimibe combination therapy	High-intensity statin monotherapy	Absolute differences in proportions, % (95% CI)
1 year			
Number of patients	1675	1673	..
Number of patients with LDL cholesterol concentrations <70 mg/dL	1217 (73%)	923 (55%)	17·5 (14·2 to 20·7)
LDL cholesterol concentration (mg/dL)	58 (47–71)	67 (55–80)	..
2 years			
Number of patients	1558	1539	..
Number of patients with LDL cholesterol concentrations <70 mg/dL	1168 (75%)	924 (60%)	14·9 (11·6 to 18·2)
LDL cholesterol concentration (mg/dL)	57 (45–70)	65 (53–79)	..
3 years			
Number of patients	1349	1315	..
Number of patients with LDL cholesterol concentrations <70 mg/dL	978 (72%)	759 (58%)	14·8 (11·1 to 18·4)
LDL cholesterol concentration (mg/dL)	58 (47–71)	66 (54–80)	..

Data are number of patients (%) or median (IQR).

Table 3: Proportions of the patients with LDL cholesterol concentrations <70 mg/dL in the intention-to-treat population

Ref> Kim BK, Hong SJ, Lee YJ, et al. Long-term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease (RACING): a randomised, open-label, non-inferiority trial. Lancet. 2022 Jul 30;400(10349):380-390.

[RACING] Long-term efficacy and Safety : Moderate intensity statin with Ezetimibe vs High intensity statin

	Moderate-intensity statin with ezetimibe combination therapy (n=1846)	High-intensity statin monotherapy (n=1832)	Absolute difference (95% CI)
Serious adverse events			
Death	26 (1·4%)	22 (1·2%)	0·21 (−5·88 to 1·01)
Adverse events			
Discontinuation or dose reduction of study drug due to intolerance	88 (4·8%)	150 (8·2%)	−3·42 (−5·07 to −1·80)
Reported symptoms			
Dizziness or general weakness	10	21	..
Chest discomfort or headache	7	12	..
Gastrointestinal symptoms	4	9	..
Urticaria or itching sensation	6	7	..
Myalgia	7	22	..
Other	5	3	..
Physician discretion			
Liver enzyme elevation	15	32	..
Creatine kinase elevation	25	33	..
Fasting glucose concentration elevation	5	6	..
Other	4	5	..
New-onset diabetes	145 (7·9%)	159 (8·7%)	−0·82 (−2·65 to 1·00)
New-onset diabetes with anti-diabetic medication initiation	95 (5·1%)	107 (5·8%)	..
Muscle-related adverse events	21 (1·1%)	34 (1·9%)	0·69 (−2·22 to 0·82)
Myalgia	17 (0·9%)	29 (1·6%)	0·66 (−1·46 to 1·06)
Myopathy	2 (0·1%)	4 (0·2%)	−0·11 (−0·50 to 0·25)
Myonecrosis*	11 (0·6%)	13 (0·7%)	0·11 (−0·72 to 0·48)
Mild	8	9	..
Moderate	2	3	..
Severe including rhabdomyolysis	1	1	..
Gallbladder-related adverse events	13 (0·7%)	7 (0·4%)	0·32 (−0·22 to 0·89)
Major bleeding	17 (0·9%)	13 (0·7%)	0·21 (−0·44 to 0·87)
Cancer diagnosis	37 (2·0%)	28 (1·5%)	0·48 (−0·43 to 0·14)
New-onset neurocognitive disorder	4 (0·2%)	2 (0·1%)	0·11 (−0·25 to 0·50)
Cataract surgery	19 (1·0%)	21 (1·1%)	−0·12 (−0·86 to 0·62)

Data are n (%). These events were adverse events of special interest in this study. ULN=upper limit of normal. *Severity of myonecrosis was classified by an elevation of creatine kinase concentration compared with either baseline concentration or the ULN: mild >3 times ULN; moderate ≥10 times ULN; severe ≥50 times ULN.

Table 4: **Secondary safety endpoint of the safety population**

Discontinuation or dose reduction of study medication owing to adverse events or intolerance occurred in **88 patients (4·8%) in the combination therapy** group and **150 patients (8·2%) in the high-intensity statin monotherapy group (p<0·0001).**

Ref> Kim BK, Hong SJ, Lee YJ, et al. Long-term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease (RACING): a randomised, open-label, non-inferiority trial. Lancet. 2022 Jul 30;400(10349):380-390.

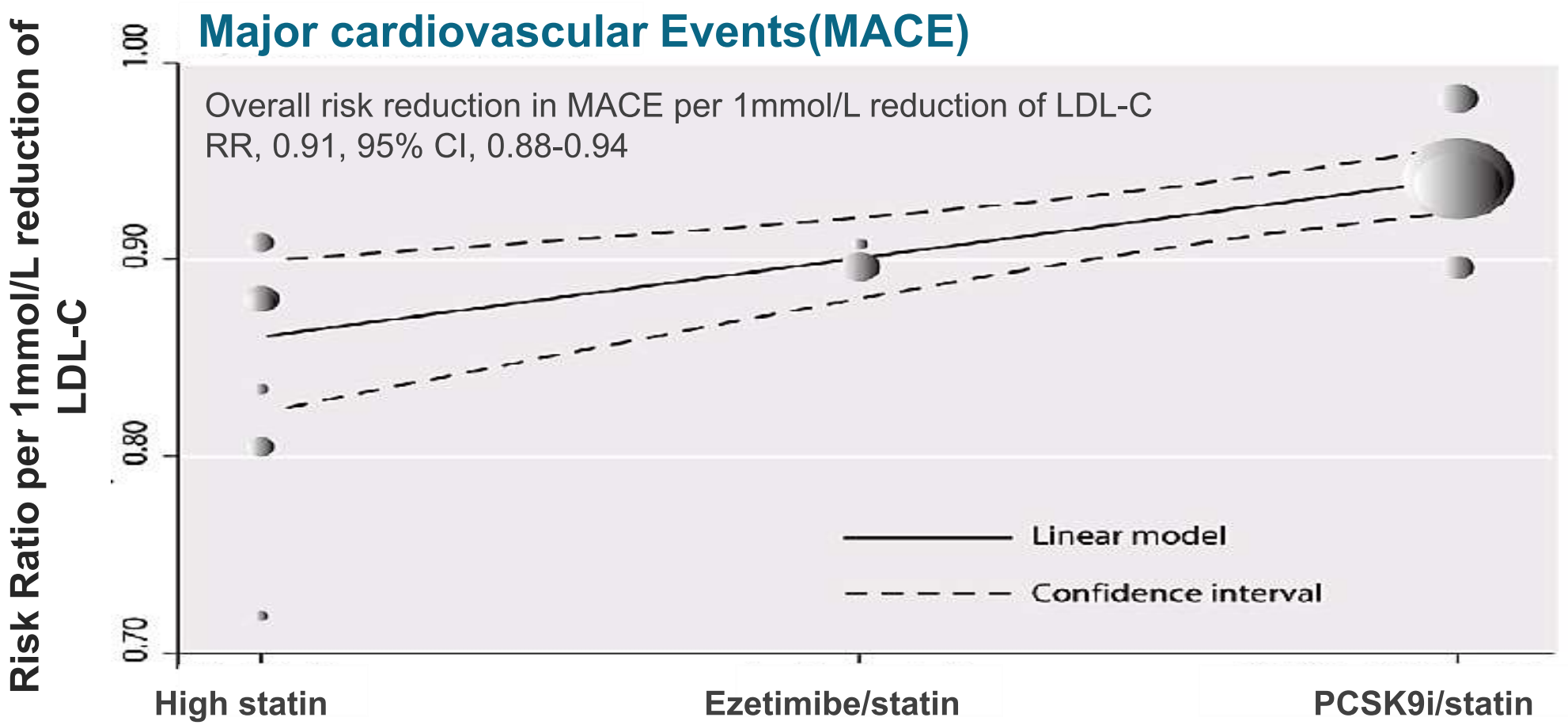
High-dose statin vs. ezetimibe-statin vs. PCSK9i-statin

- **6 trials: high-dose statins**
- **2 trials: ezetimibe-statin**
- **4 trial: PCSK9 inhibitor-statin**

Study and date	More intensive lipid-lowering			Less-intensive lipid-lowering			Background statin therapy, %
	Intervention	Baseline LDL-C	Achieved LDL	Intervention	Baseline LDL-C	Achieved LDL	
PROVE-IT (2004)[3]	Atorvastatin 80 mg	106.0	62.0	Pravastatin 40 mg	106.0	95.0	25.2
A to Z (2004)[4]	Simvastatin 40–80 mg	112.0	66.0	Simvastatin 20 mg[a]	111.0	81.0	0.0
TNT (2005)[5]	Atorvastatin 80 mg	97.0	77.0	Atorvastatin 10 mg	98.0	101.0	0.0
IDEAL (2005)[6]	Atorvastatin 80 mg	121.6	81.0	Simvastatin 20 mg	121.4	104.0	75.5
SEARCH (2010)[7]	Simvastatin 80 mg	96.7	83.1	Simvastatin 20 mg	96.7	96.7	NR
IMPROVE-IT (2015)[8]	Simvastatin 40 mg+ Ezetimibe 10 mg	93.8	53.7	Simvastatin 40 mg	93.8	69.5	34.5
ODYSSEY LONG TERM (2015)[15]	Alirocumab 150 mg[b]	122.7	58.5	Placebo	121.9	126.4	99.9
HIJ-PROPER (2017)[16]	Pitavastatin 2 mg+ Ezetimibe 10 mg	134.8	65.1	Pitavastatin 2 mg	135.6	84.6	17.5
SPIRE2 (2017)[17]	Bococizumab 150 mg[c]	133.9	93.0	Placebo	133.4	136.2	83.2
FOURIER (2017)[9]	Evolocumab 140 mg or 420 mg[d]	92.0	30.0	Placebo	92.0	92.0	99.8[e]
ODYSSEY OUTCOMES (2018)[19]	Alirocumab q2 weeks	87.0	42.3	Placebo	87.0	96.4	89.0[e]
REAL-CAD (2018)[18]	High-dose pitavastatin	87.7	73.7	Low-dose pitavastatin	88.1	89.4	90.9

Ref. Wang S et al. Circ J. 2019 May 24;83(6):1356-1367.

High-dose statin vs. ezetimibe-statin vs. PCSK9i-statin



Ref. Wang S et al. Circ J. 2019 May 24;83(6):1356-1367.

Absolute LDL cholesterol reduction vs. Statin matters?

Intensive LDL cholesterol-lowering treatment beyond current recommendations for the prevention of major vascular events: a systematic review and meta-analysis of randomised trials including 327 037 participants

Nelson Wang, Jordan Fulcher, Nishan Abeysuriya, Laura Park, Shejil Kumar, Gian Luca Di Tanna, Ian Wilcox, Anthony Keech, Anthony Rodgers, Sean Lal

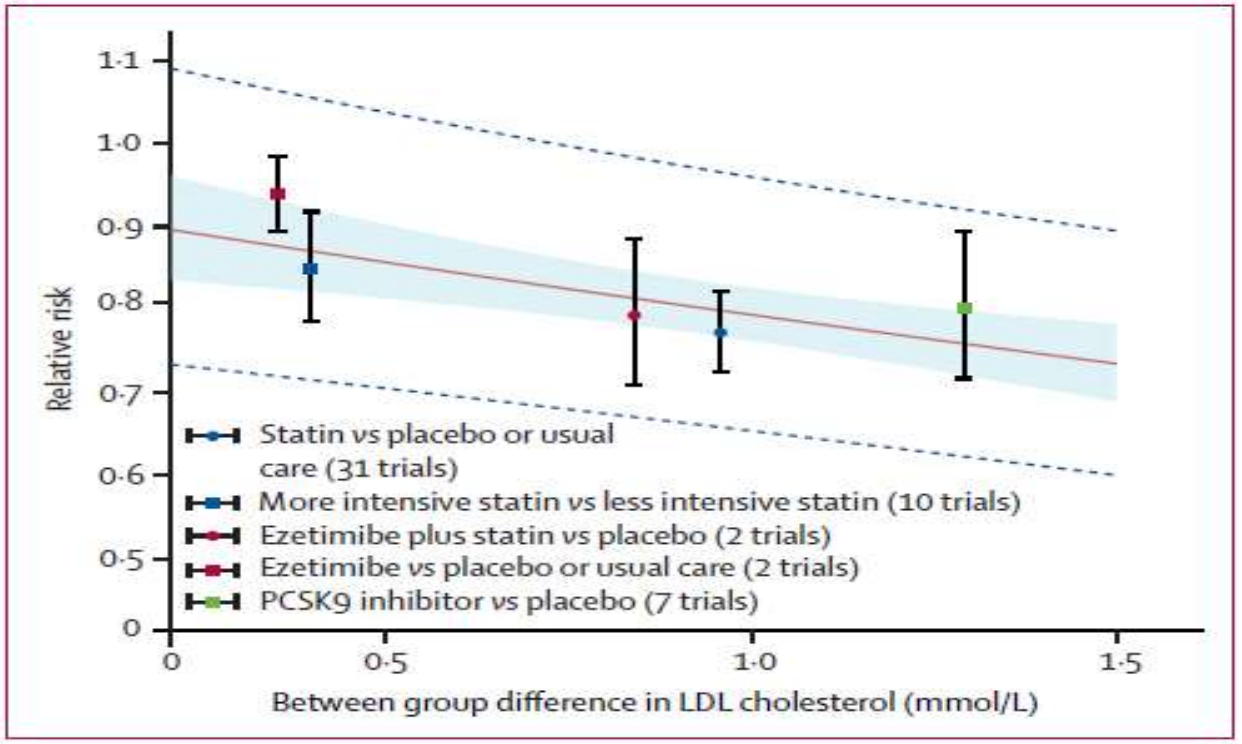
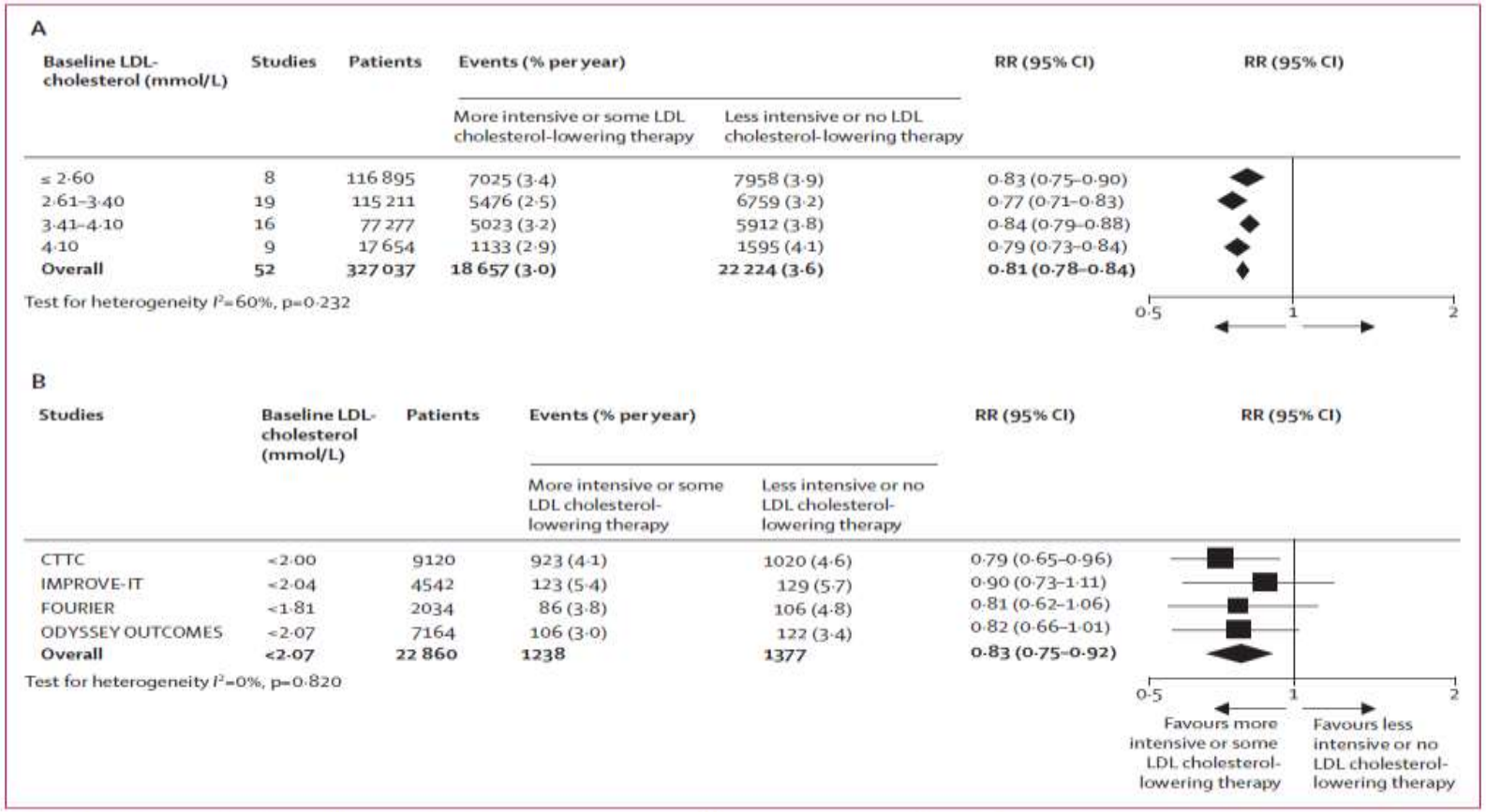


Figure 1: Meta-regression plot showing relative risk of major vascular events according to extent of LDL cholesterol lowering with various drug classes of LDL cholesterol-lowering therapy

We found that reductions in major vascular events were independent of drug class, which suggests that the benefits from statins, ezetimibe, and PCSK9 inhibitors are probably derived from the cholesterol-lowering effects of these drugs. Notably, the extent of LDL cholesterol reduction was the strongest independent predictor of major vascular events risk reduction.

Ref. Lancet Diabetes Endocrinol 2020; 8: 36–49

Absolute LDL reduction matters regardless of starting LDL level



A

Baseline LDL-cholesterol (mmol/L)	Studies	Patients	Events (% per year)		RR (95% CI)
			More intensive or some LDL cholesterol-lowering therapy	Less intensive or no LDL cholesterol-lowering therapy	
≤ 2·60	8	116 895	7025 (3·4)	7958 (3·9)	0·83 (0·75–0·90)
2·61–3·40	19	115 211	5476 (2·5)	6759 (3·2)	0·77 (0·71–0·83)
3·41–4·10	16	77 277	5023 (3·2)	5912 (3·8)	0·84 (0·79–0·88)
4·10	9	17 654	1133 (2·9)	1595 (4·1)	0·79 (0·73–0·84)
Overall	**52**	**327 037**	**18 657 (3·0)**	**22 224 (3·6)**	**0·81 (0·78–0·84)**

Test for heterogeneity I^2=60%, p=0·232

B

Studies	Baseline LDL-cholesterol (mmol/L)	Patients	Events (% per year)		RR (95% CI)
			More intensive or some LDL cholesterol-lowering therapy	Less intensive or no LDL cholesterol-lowering therapy	
CTTC	<2·00	9120	923 (4·1)	1020 (4·6)	0·79 (0·65–0·96)
IMPROVE-IT	<2·04	4542	123 (5·4)	129 (5·7)	0·90 (0·73–1·11)
FOURIER	<1·81	2034	86 (3·8)	106 (4·8)	0·81 (0·62–1·06)
ODYSSEY OUTCOMES	<2·07	7164	106 (3·0)	122 (3·4)	0·82 (0·66–1·01)
Overall	**<2·07**	**22 860**	**1238**	**1377**	**0·83 (0·75–0·92)**

Test for heterogeneity I^2=0%, p=0·820

Figure 2: Relative risk of major vascular events per 1 mmol/L reduction in LDL cholesterol, by baseline LDL-cholesterol concentration
(A) Meta-analysis according to baseline LDL cholesterol concentration. (B) Meta-analysis of subgroups of patients with LDL cholesterol less than 2·07 mmol/L (80 mg/dL). Squares represent individual studies, with the size proportional to the weight in the meta-analysis. Diamonds represent pooled results. RR=relative risk.

Interpretation For each 1 mmol/L LDL cholesterol lowering, the risk reduction of major vascular events is independent of the starting LDL cholesterol or the presence of diabetes or chronic kidney disease. Patients at lower cardiovascular risk and younger age might have a similar relative reduction in risk with LDL-cholesterol lowering therapies and future studies should investigate the potential benefits of earlier intervention.

Ref. Lancet Diabetes Endocrinol 2020; 8: 36–49

Daewoong Pharmaceutical's Product information

Add-on
Ezetimibe

Atorvastatin+Ezetimibe

Safe and Effective Treatment for Dyslipidemia

Litorvazet Tab

Litorvazet tab [Ezetimibe / Atorvastatin]
10/10, 10/20, 10/40mg

Rosuvastatin+Ezetimibe

CREZET

CREZET tab [Ezetimibe / Rosuvastatin]
10/2.5mg, 10/5mg, 10/10mg, 10/20mg

Conclusion

- **LDL-C** is a **major risk factor for Coronary Artery Disease** and requires aggressive management
- Guidelines suggest **more aggressive control of LDL cholesterol** in CAD patients
- **Statins** are recommended as **a first-line treatment for CAD patients**, as they have been shown to reduce LDL-C levels, have pleiotropic effects, and have demonstrated cardiovascular disease prevention effects. However, **statins have limitations** in **achieving LDL-C target levels** in CAD patients, and **the risk of side effects** may increase with the use of high doses to achieve target levels.
- **Combination therapy of statins and ezetimibe** has demonstrated **superior LDL-C-lowering** efficacy compared to statin monotherapy, with **higher LDL-C target attainment rates** and additional **CVD prevention** effects in CAD patients. Moreover, the **medication adherence** rate was even improved with the single pills.