The recent trend of dyslipidemia management focused on intensive & combination therapy

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Today’s Contents

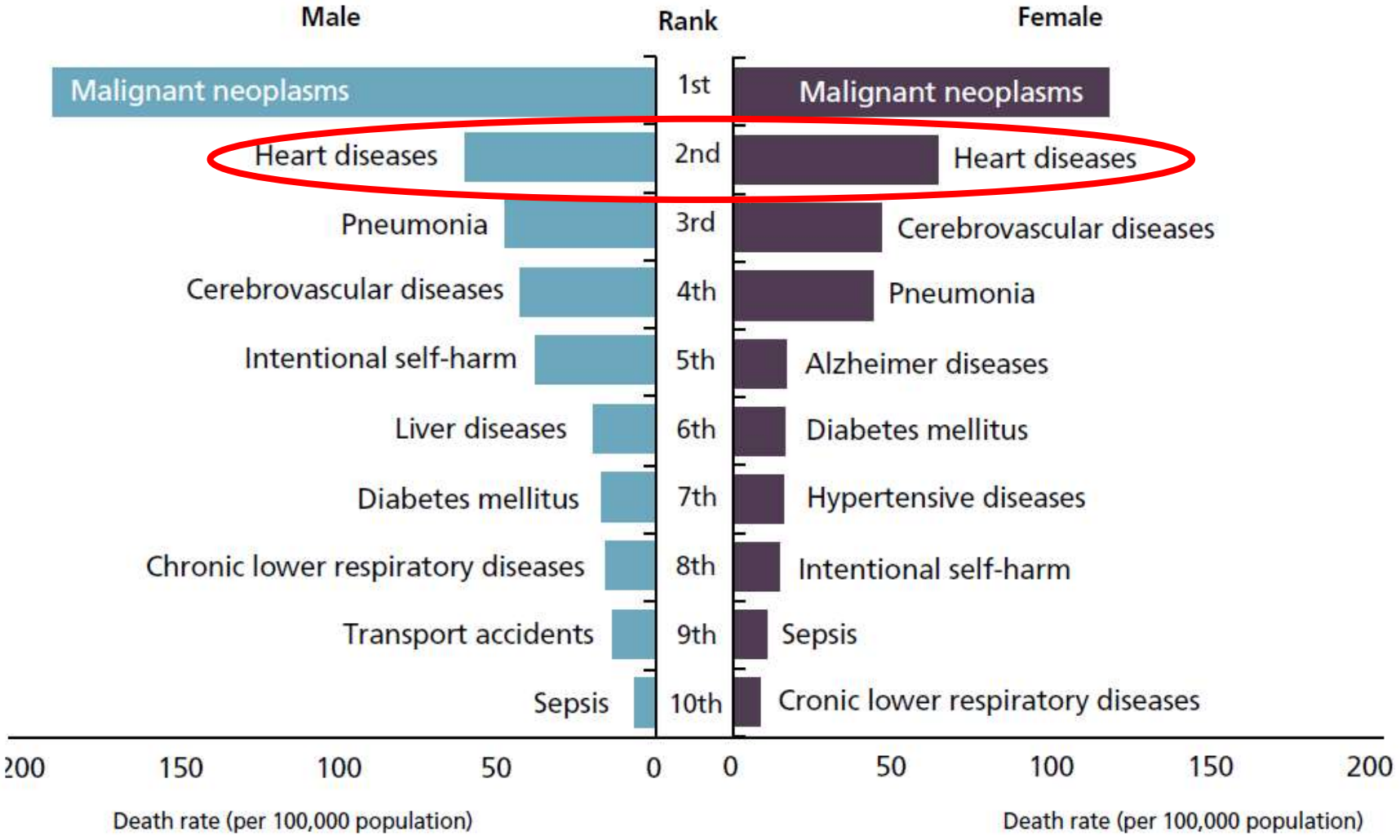
1. Current status of heart disease and the need for active LDL-C management

2. Latest guideline trend and Korean dyslipidemia guidelines

3. The ways to reach the goal

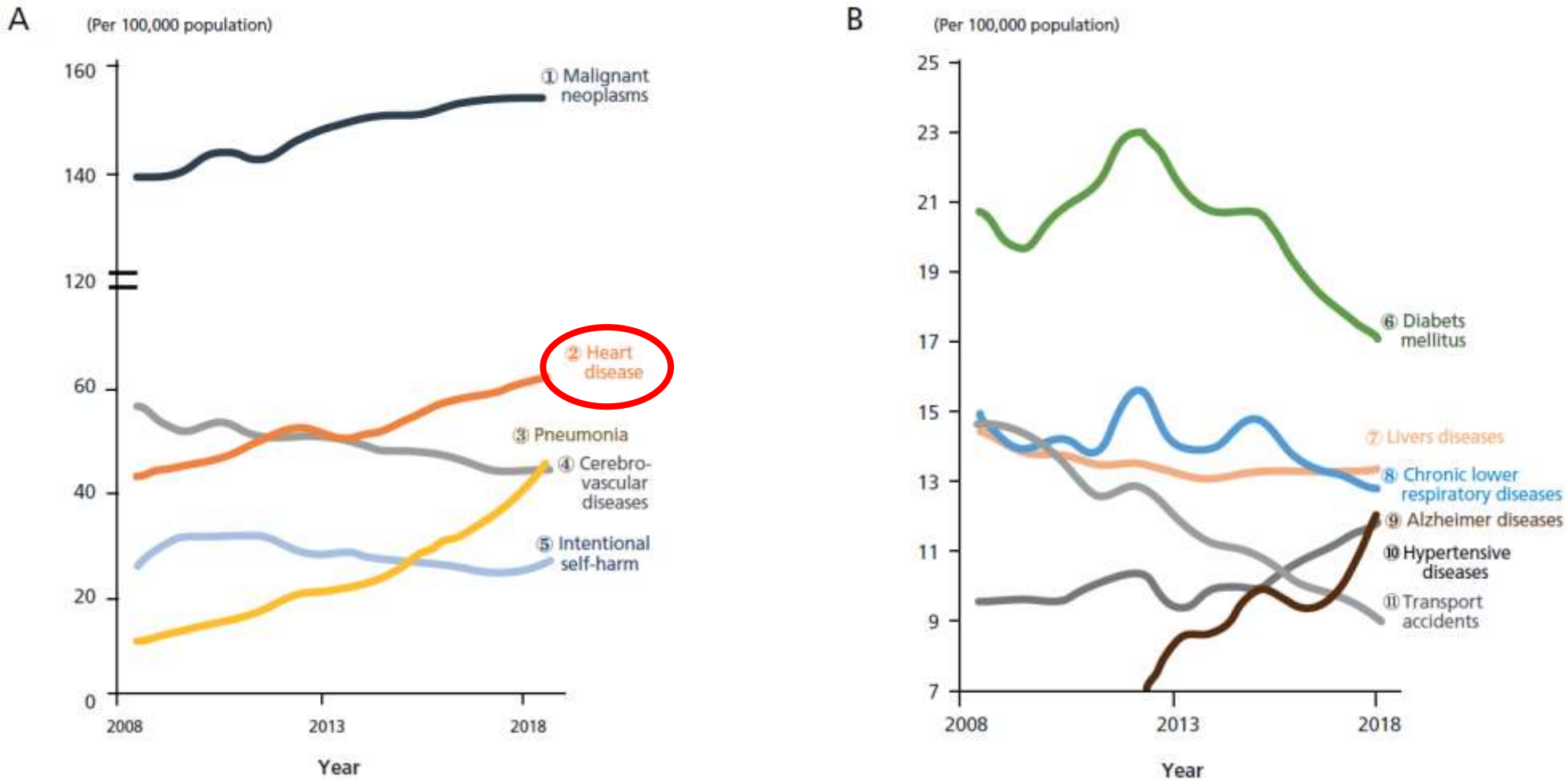
4. Treatment gaps

Heart disease is the second cause of death in Korea



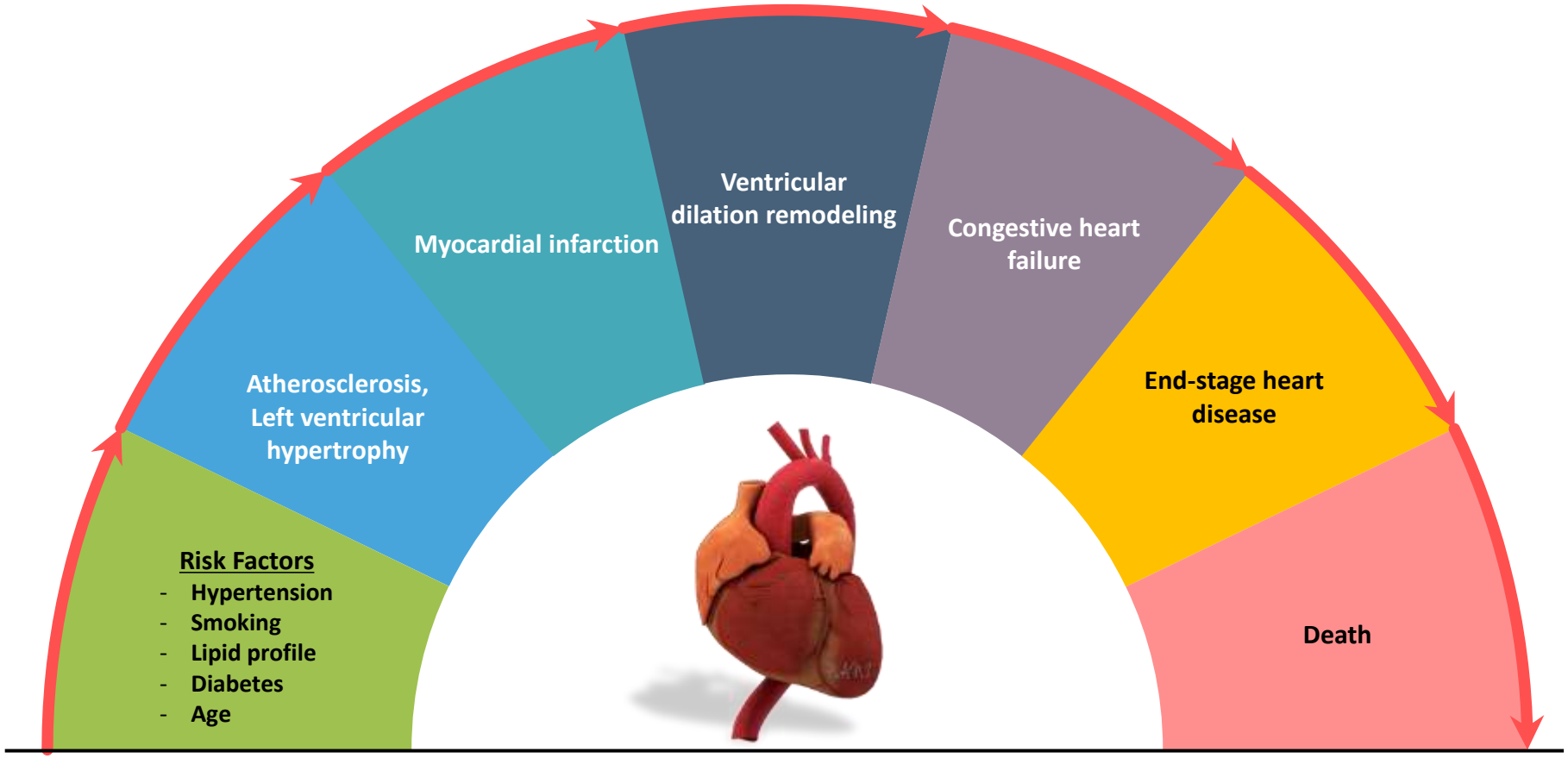
Reference : 2020 통계청_사망원인

Trends in death rates by major causes of death

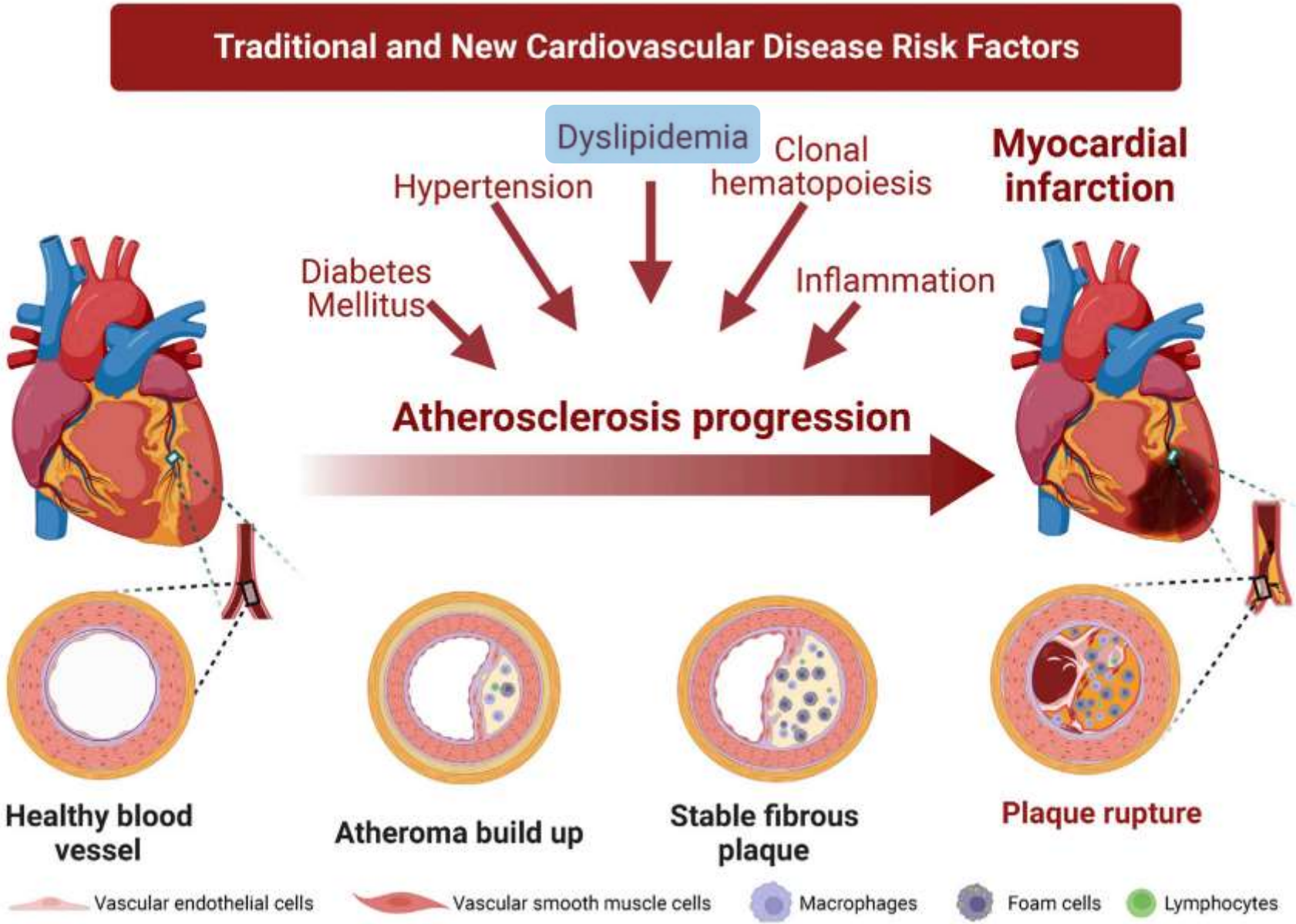


Reference : 2020 통계청_사망원인

A sequence of cardiovascular events, Cardiovascular Disease Continuum



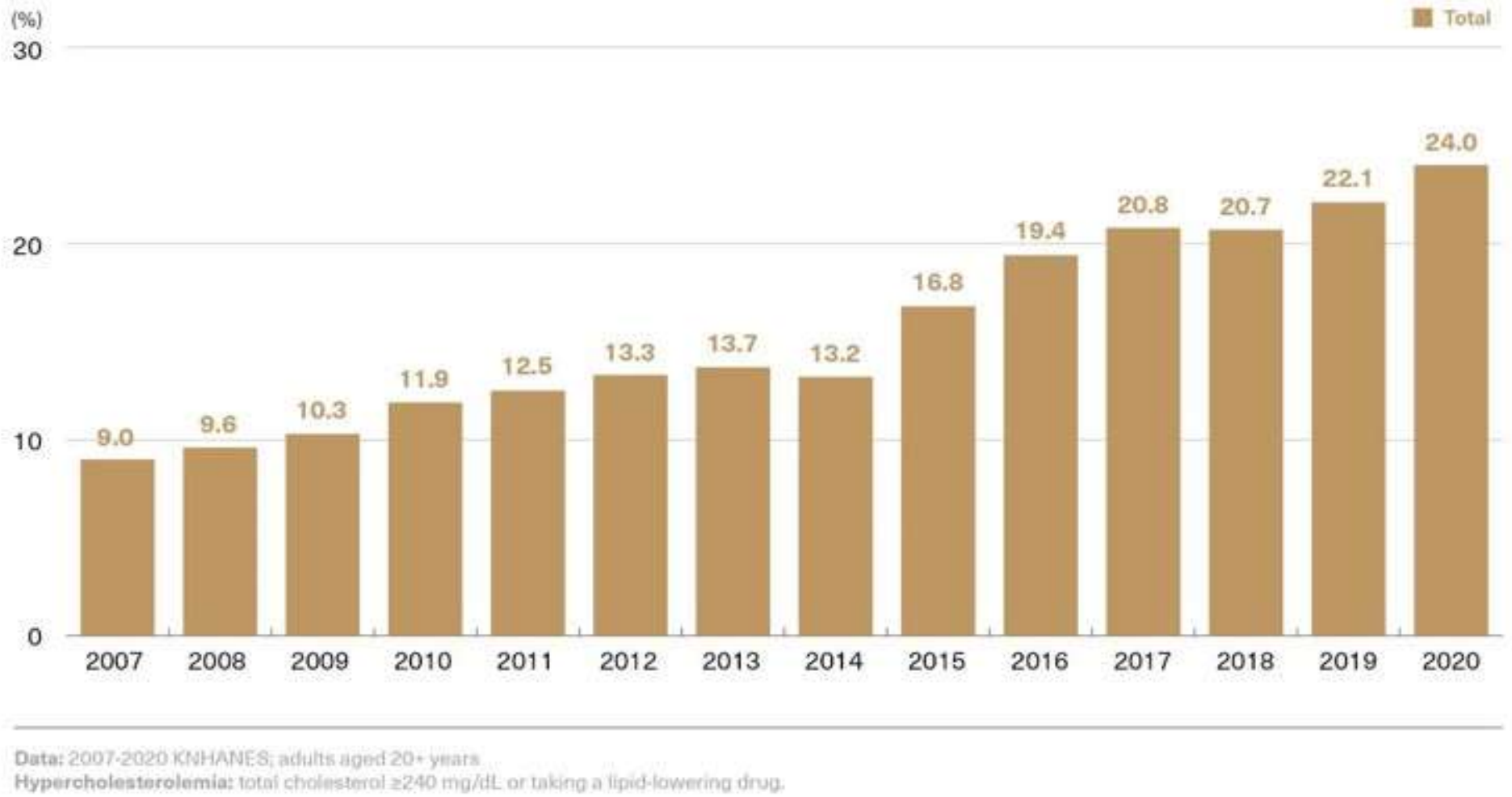
Ref. Dzau V et al. Am Heart J. 1991;121:1244-1263.



Isabella Hetherington et al. Molecular Therapy. 2022

Crude prevalence of hypercholesterolemia

Nearly 1 out of 4 adults has hypercholesterolemia



1. 2022 fact sheet(KSoLA)

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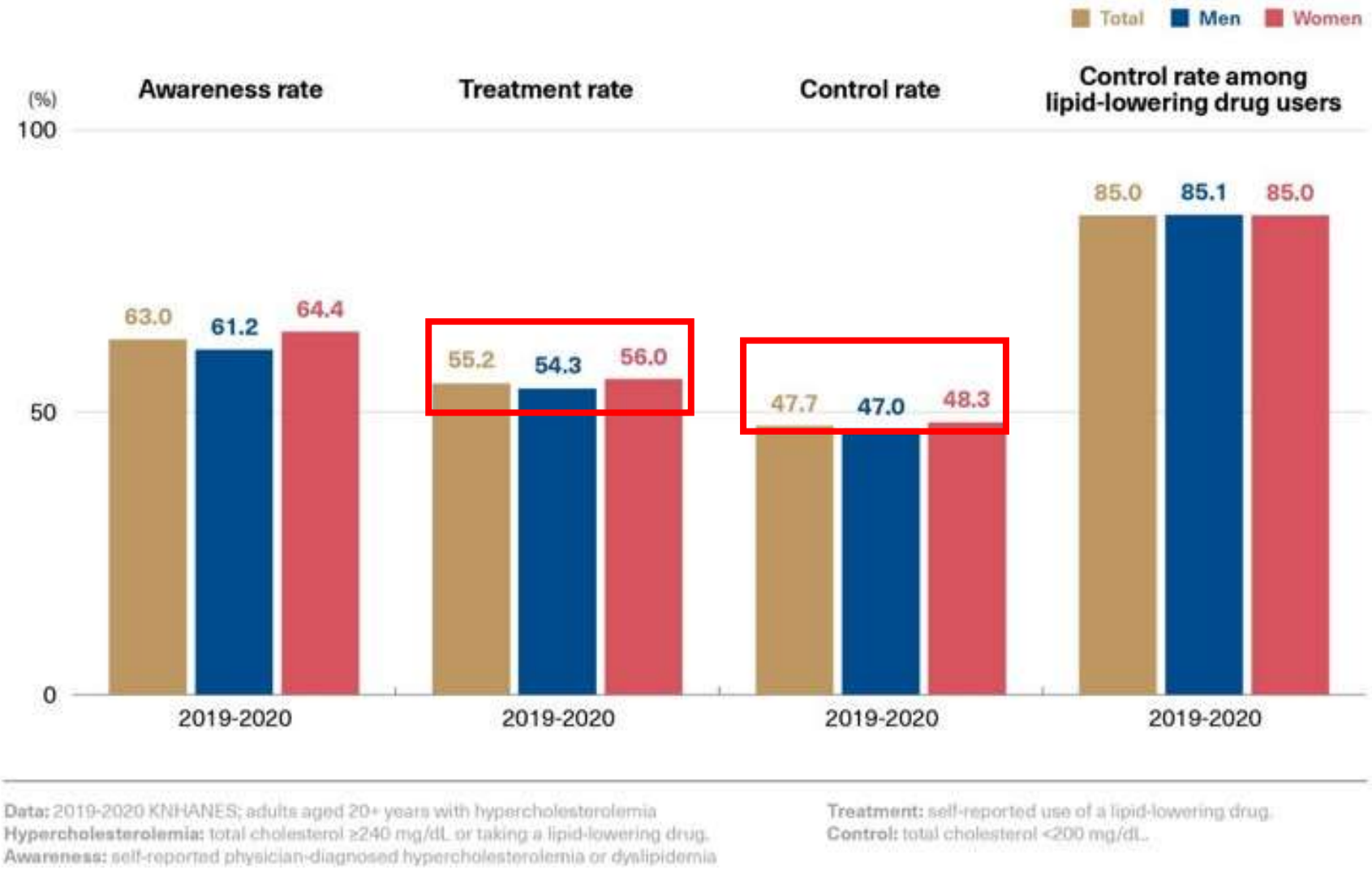
Summary of management of hypercholesterolemia



1. 2022 fact sheet(KSoLA)

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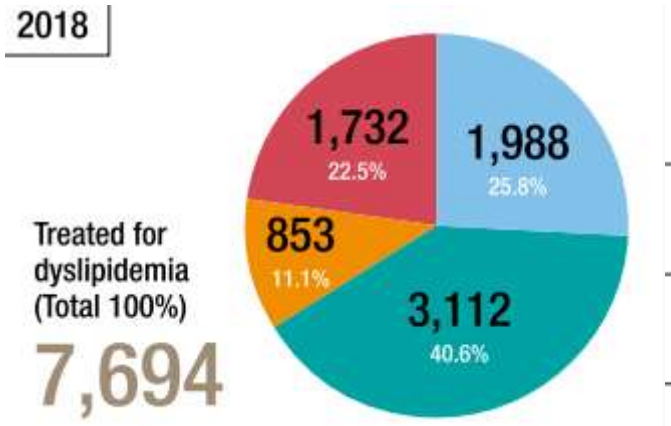
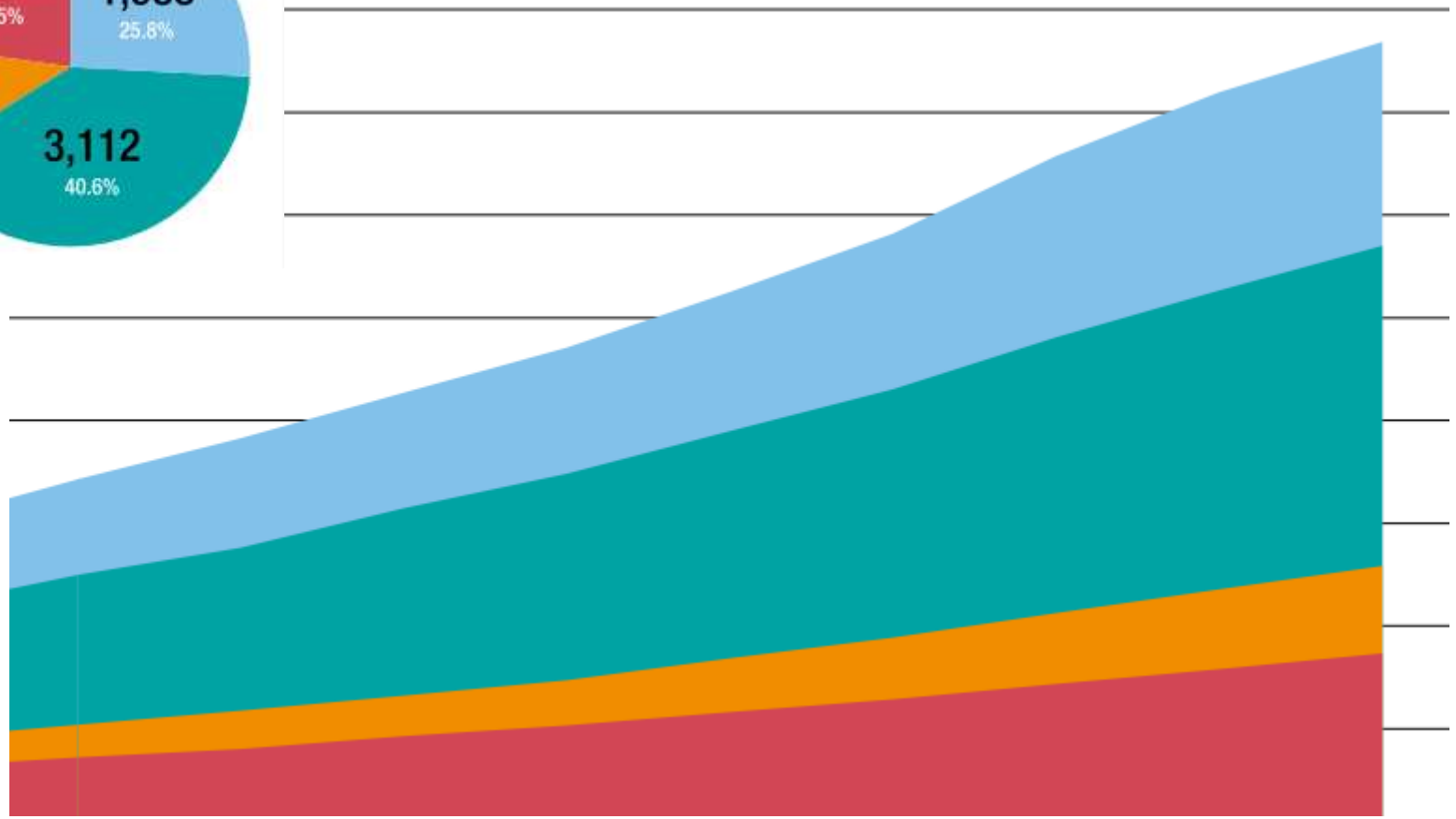
80% of patients with dyslipidemia is treated for HTN or DM



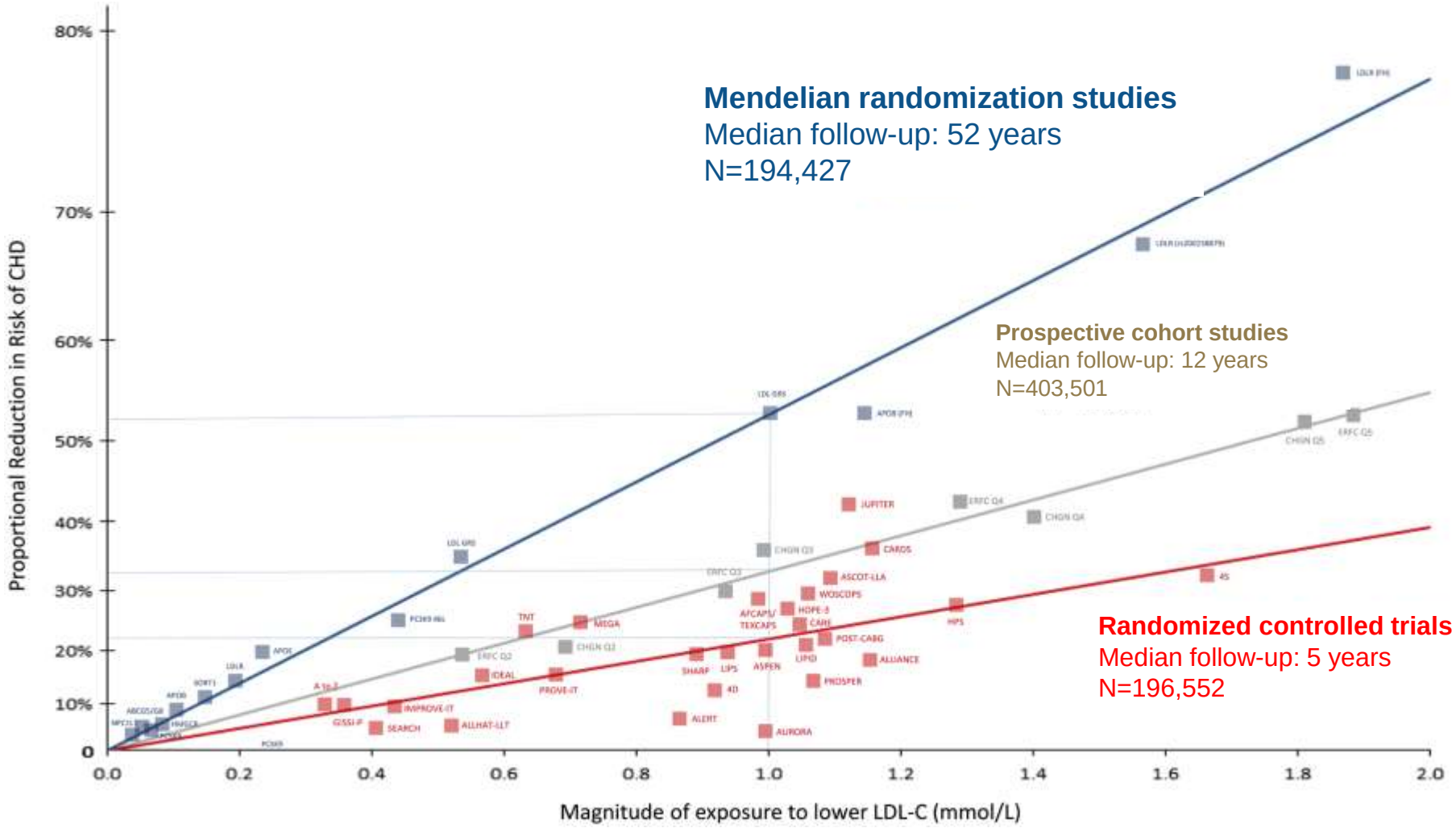
3/5 HTN, 1/3 DM, 4/5 HTN or DM



Dyslipidemia fact sheet 2020

The lower, the better

Evidence from meta-analyses of Mendelian randomization studies, prospective cohort studies, and randomized controlled trials unequivocally establishes that LDL causes ASCVD.



Ference BA *et al.*, Eur Heart J. 2017;38(32):2459-2472

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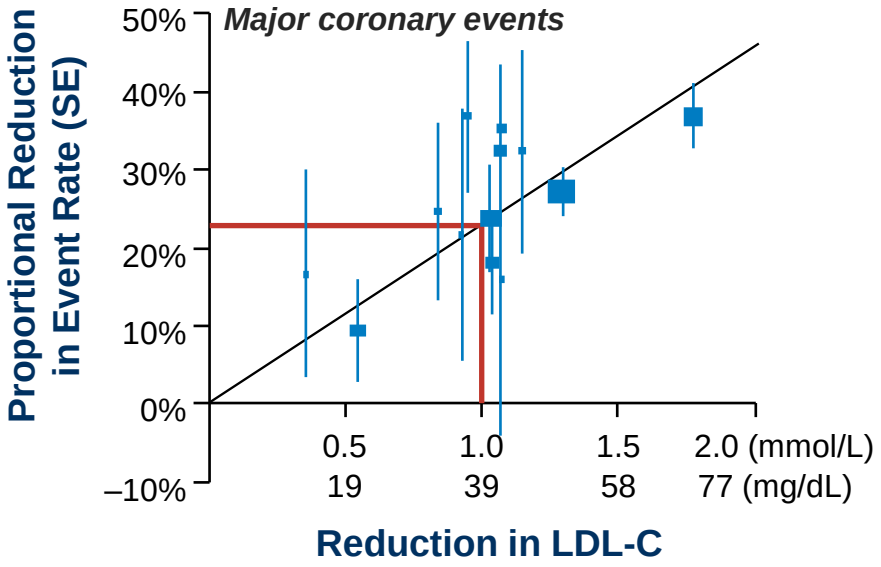
LDL-C Lowering Correlates With Relative Risk Reduction in CV Events

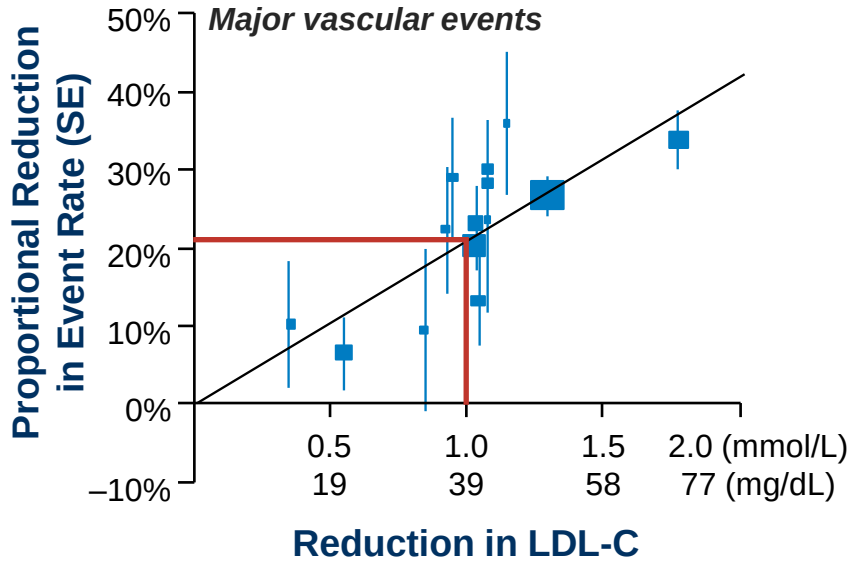
Meta-analysis of 14 Statin Trials (N = 90,056)

1 mmol/L (39 mg/dL) reduction in LDL-C was associated over 5 years with:

23% reduction *in major coronary events*



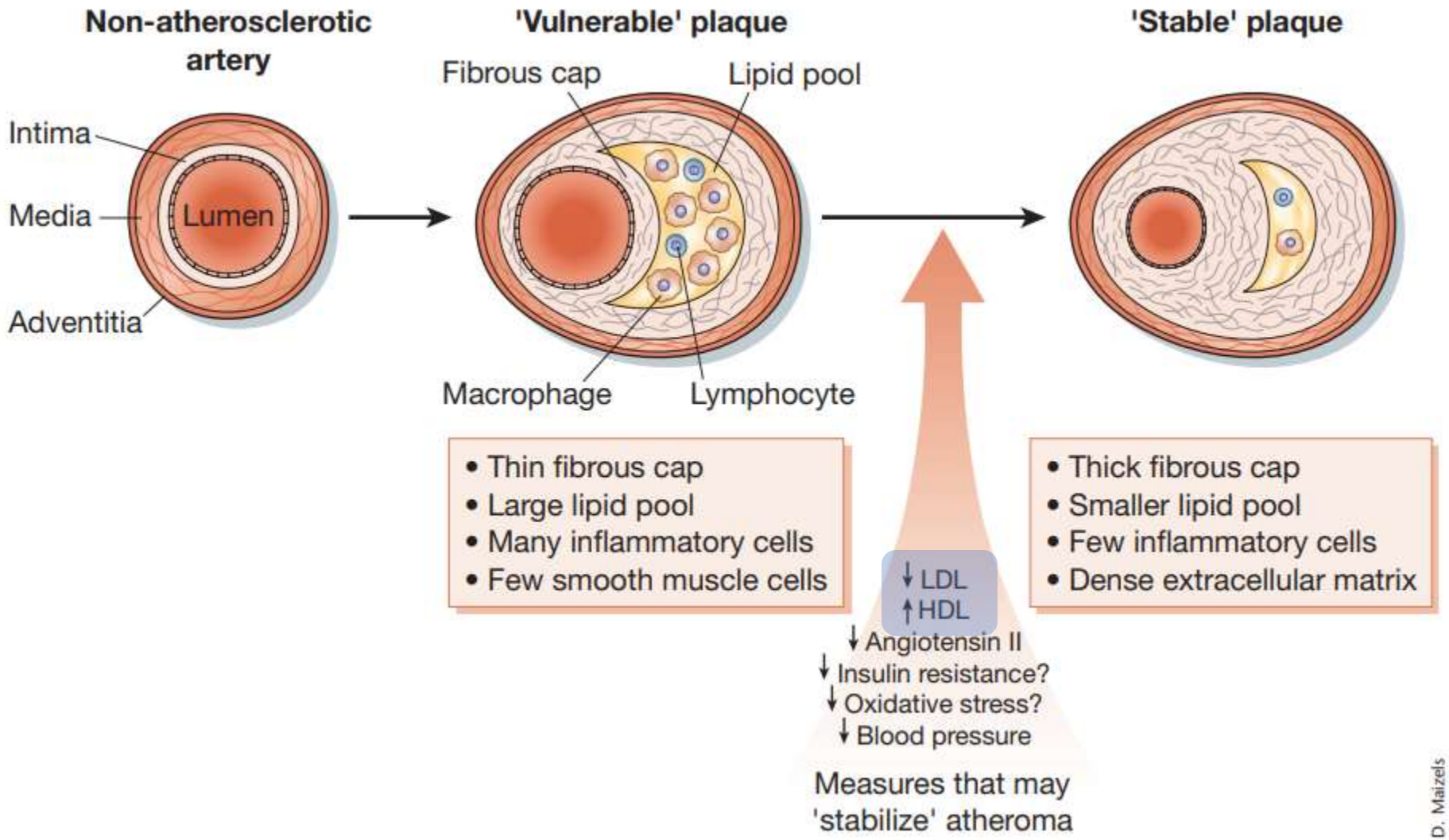
21% reduction *in major vascular events*



CHD = coronary heart disease; CV = cardiovascular; LDL-C = low-density lipoprotein cholesterol; SE = standard error.
Major coronary events = non-fatal myocardial infarction or CHD death.
Major vascular events = the combined outcome of major coronary event, non-fatal or fatal stroke, or coronary revascularization.

Cholesterol Treatment Trialists' (CTT) Collaboration. *Lancet*. 2005;366:1267-1278.

Plaque stabilization by lipid lowering therapy

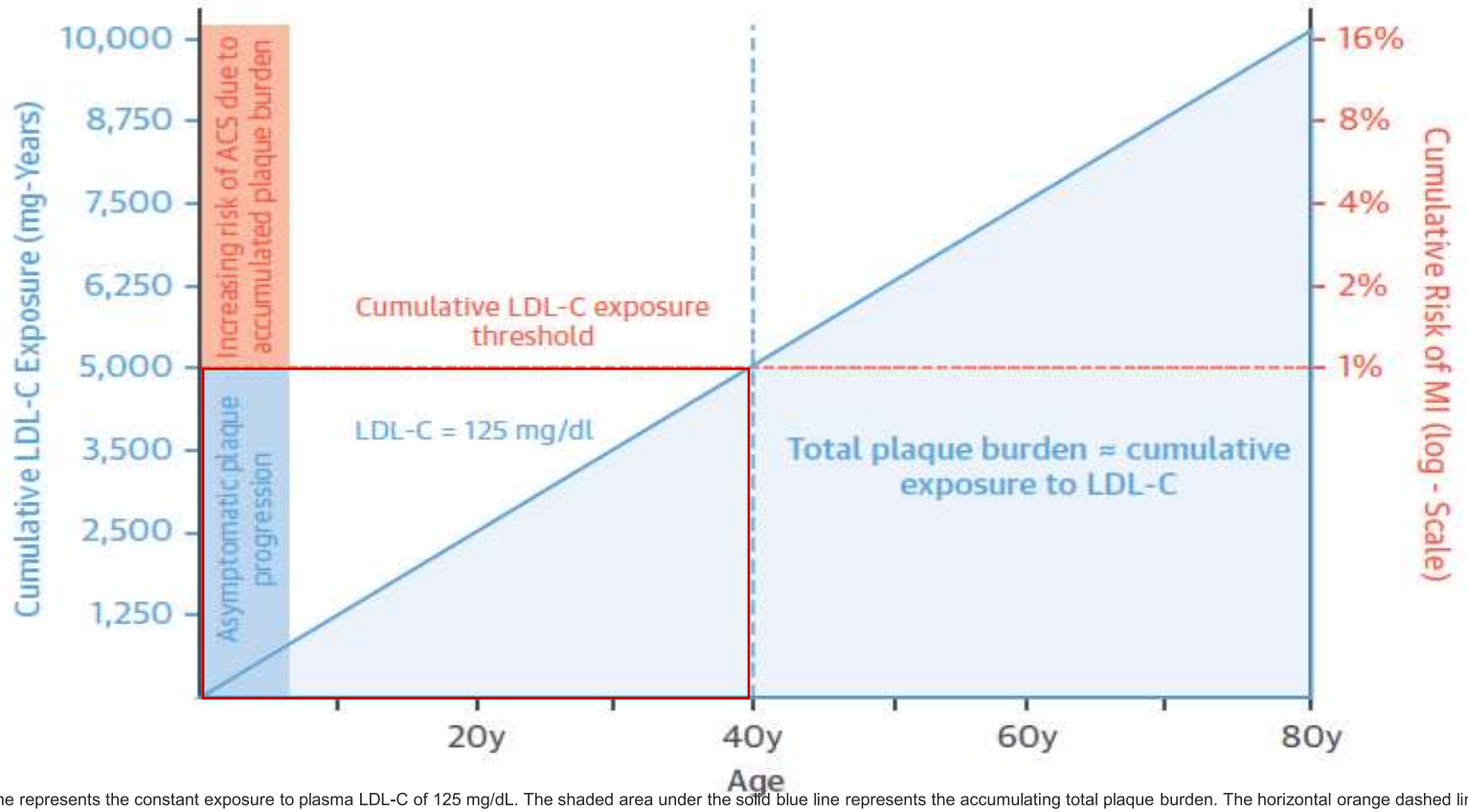


PETER LIBBY et al. Nat Med. 2002

The Earlier, the better

Once the Cumulative LDL Threshold Has Been Exceeded, the Risk of an ACS in Response to Continued Plaque Growth Increases Log-linearly

Effect of Cumulative Exposure to LDL-C on Plaque Burden and Risk of CVD



The solid blue line represents the constant exposure to plasma LDL-C of 125 mg/dL. The shaded area under the solid blue line represents the accumulating total plaque burden. The horizontal orange dashed line represents the cumulative LDL-C (= total plaque burden) needed to result in a measurable increase in the risk of MI. Beyond this threshold, if the plasma LDL-C remains constant, then both cumulative LDL-C exposure and total plaque burden increase linearly, but the risk of MI rises log-linearly and is shown on the right-hand side y-axis expressed on the log or "doubling scale". On average, 5,000 mg-years is the minimum threshold of a cumulative LDL-C exposure necessary to develop a sufficiently large total atherosclerotic plaque burden to increase the risk of experiencing a MI.
ACS, acute coronary syndrome; MI, myocardial infarction; LDL-C, low-density lipoprotein cholesterol; CVD, cardiovascular disease.

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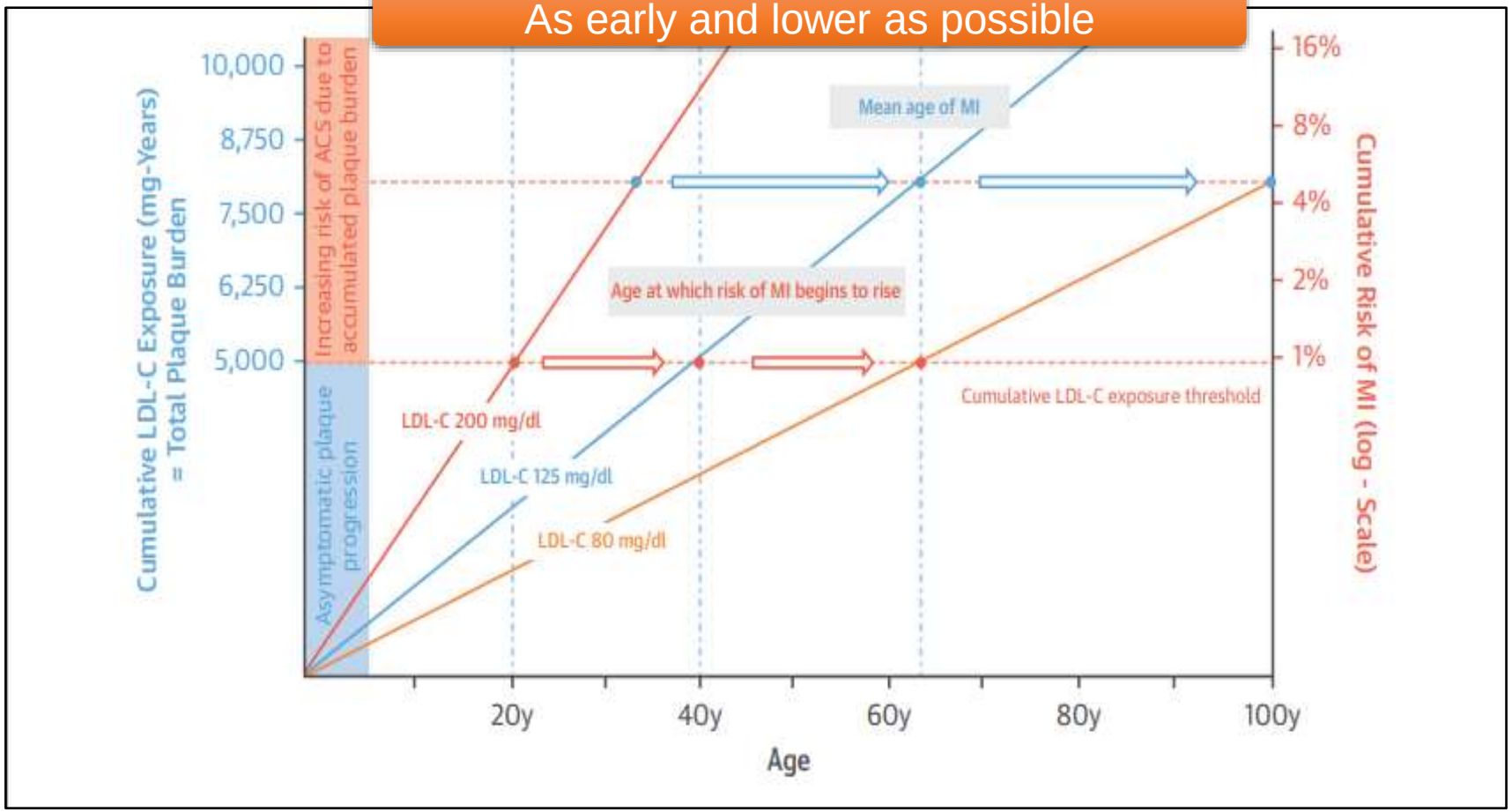
1. Ference BA, et al. *J Am Coll Cardiol.* 2018;72(10):1141-1156.

The Earlier, the better

Once the Cumulative LDL Threshold Has Been Exceeded, the Risk of an ACS in Response to Continued Plaque Growth Increases Log-linearly

As early and lower as possible



The **solid orange line** represents a low-density lipoprotein cholesterol (LDL-C) level of 200 mg/dl throughout life. The **solid blue line** represents a low-density lipoprotein cholesterol level of 125 mg/dl throughout life. The **yellow line** represents a low-density lipoprotein cholesterol level of 80 mg/dl throughout life. Cumulative low-density lipoprotein cholesterol exposure is derived by multiplying age by plasma low-density lipoprotein cholesterol. Cumulative risk of myocardial infarction (MI) is measured on the log ("doubling") scale. The **orange dots** represent the age at which persons with lifetime exposure to 200 mg/dl, 125 mg/dl, and 80 mg/dl, respectively, exceeds the 5,000 mg-years threshold of cumulative exposure to low-density lipoprotein cholesterol beyond which the cumulative lifetime risk of myocardial infarction exceeds 1%. The **blue dots** represent the average age that persons with lifetime exposure to 200 mg/dl, 125 mg/dl, and 80 mg/dl, respectively, experience a myocardial infarction (or approximately 8,000 mg-years of cumulative low-density lipoprotein cholesterol exposure). The figure shows that lower cumulative exposure to low-density lipoprotein cholesterol can slow plaque progression and delay the onset of myocardial infarction and other acute coronary syndromes (ACS). Abbreviations as in Figure 1.

Impact of Lipids on Cardiovascular Health (jacc.org)

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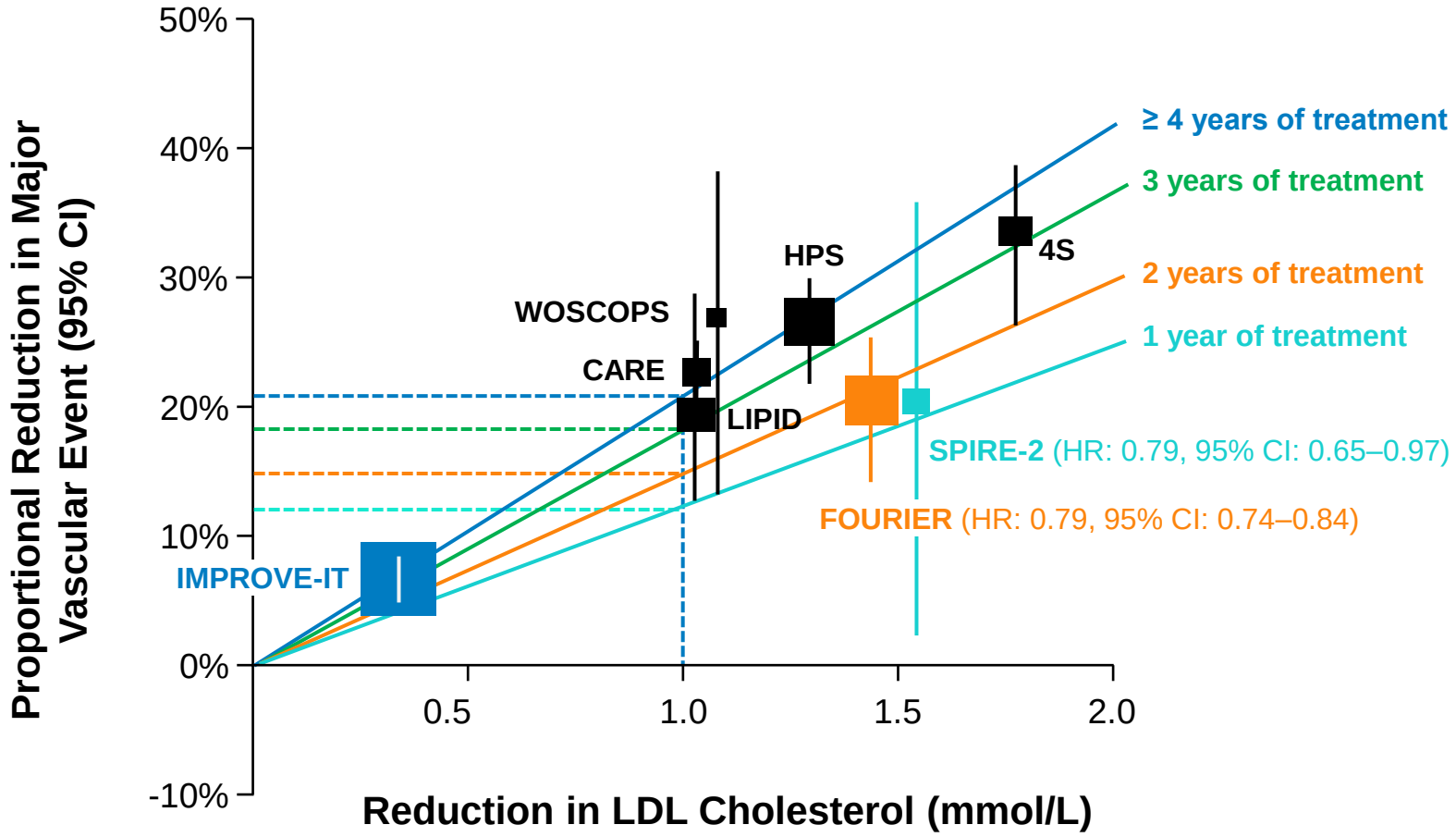
The longer & lower, the better

CTTC Regression for the Risk of Major CV Events by Reduction of LDL-C Considering Duration of Therapy in lipid lowering agent Trials



Major CV Events defined as CV death, MI, stroke or urgent revascularization. CTT regression line for reductions in CV risk is derived from meta-analysis of statin trials based on 5 years of treatment which allows for expected reductions in CV risk per mmol/L to be calculated for reduction of risk for various treatment durations. Boxes represent effect estimates, and lines represent 95% CI. Orange line represents 17% reduction in risk of major CV events per mmol/L reduction in LDL-C with statin as estimated by CTTC.

Ference BA, et al; *European Heart Journal* (2018) 39, 2540–2545

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The Earlier, the better

In the SWEDEHEART Registry, Greater LDL-C Reduction 6 to 10 Weeks Post-MI Is Associated With Lower Risk of CV Events

Kaplan–Meier curves of the cumulative incidence rates by quartile LDL-C change from index event to the cardiac rehabilitation visit. Outcomes are assessed after the cardiac rehabilitation visit.

Observational study using the SWEDEHEART registry, a nationwide MI quality registry

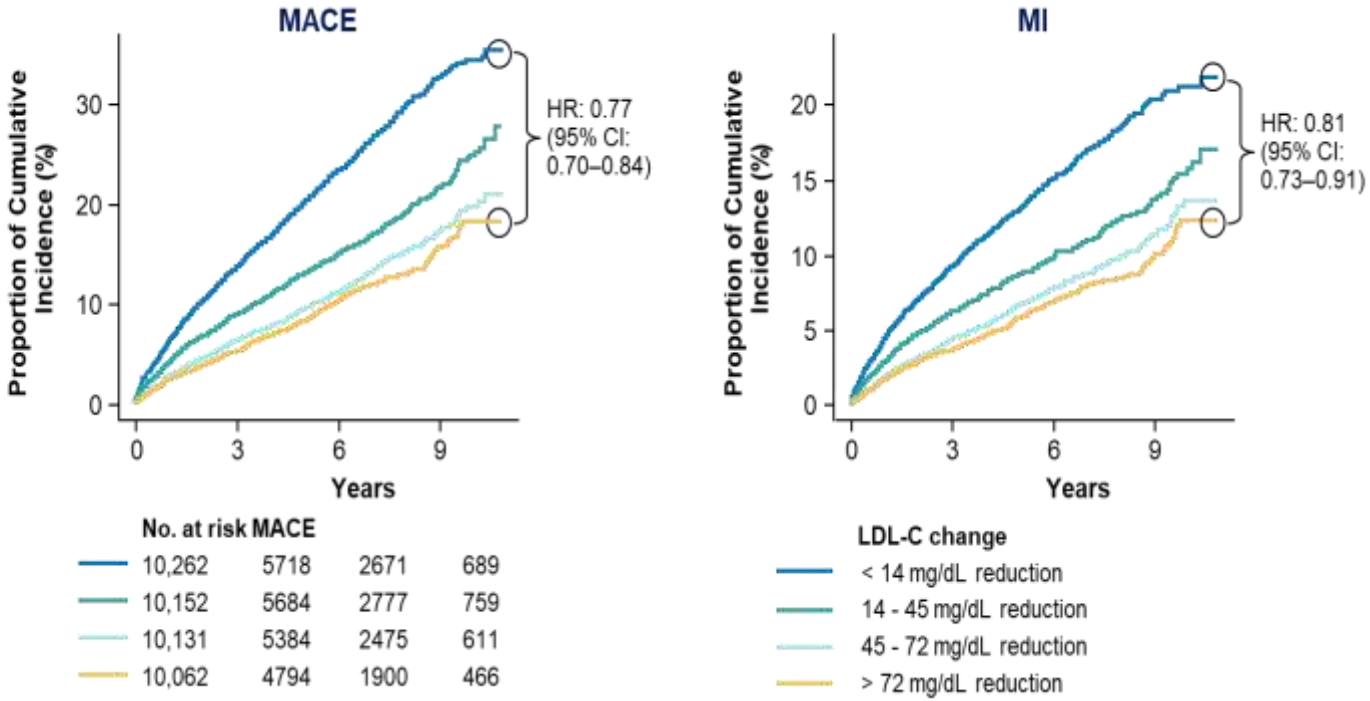
N = 40,607

Population: 30–74 years of age admitted for MI in Sweden 2006–2016, alive at follow-up in cardiac rehab 6–10 weeks post-discharge

Follow-up: Maximum 11 years, median: 3.8 years

LDL-C measured within 24 hours of admission and 6–10 weeks post-discharge

Prior to hospitalization: 77% were not on statin, mean LDL-C: 120 mg/dL



Numbers at risk shown for MACE. MACE, major adverse cardiovascular event is the composite outcome of cardiovascular mortality, myocardial infarction, and ischemic stroke.

Schubert J, et al. *European Heart Journal* (2021) 42, 243–252

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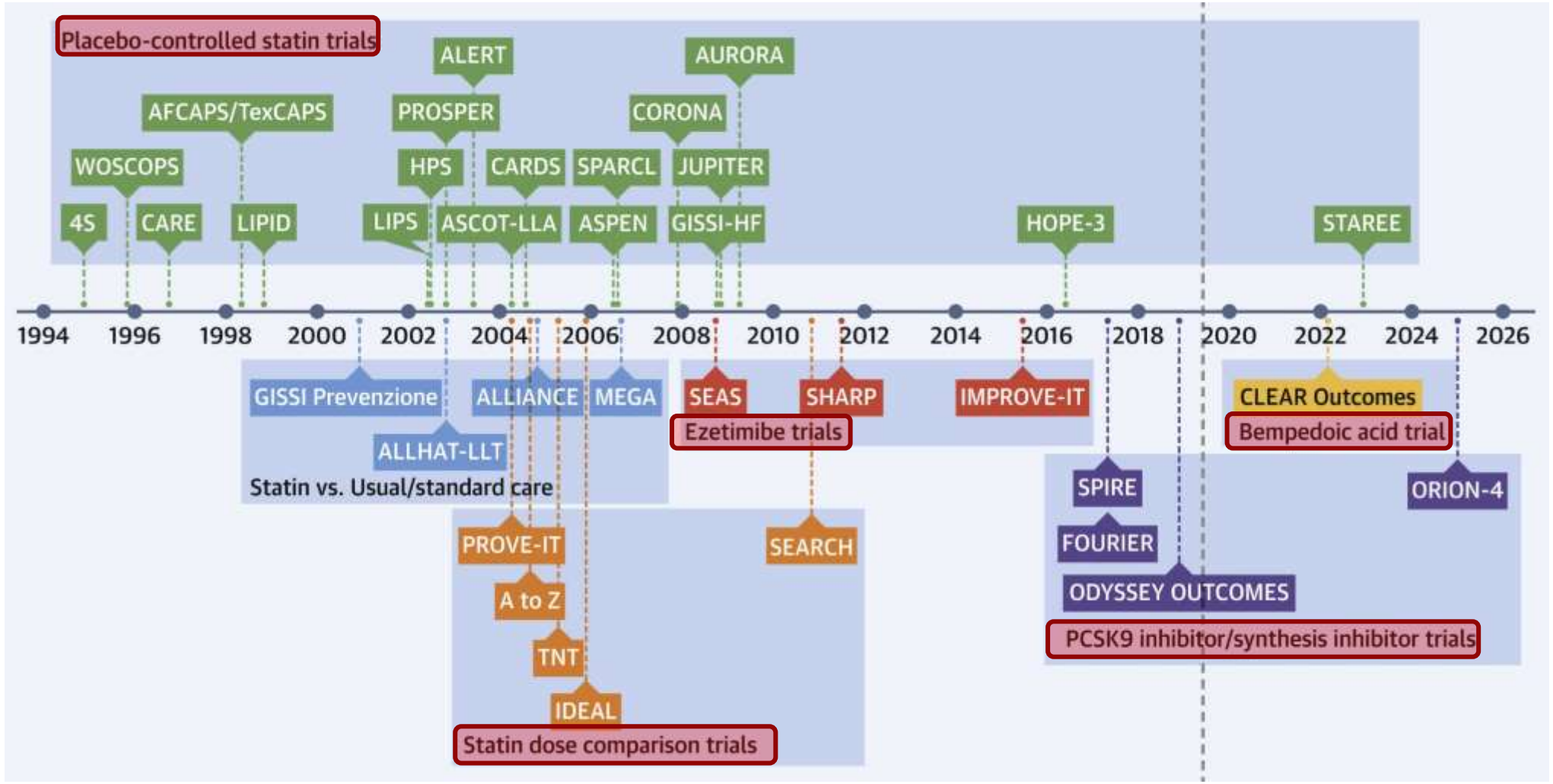
Timeline of Completed & Ongoing LDL Cholesterol–Lowering Cardiovascular Outcome Trials



1.Journal of the American College of Cardiology Volume 75, Issue 16, 28 April 2020, Pages 1945-1955

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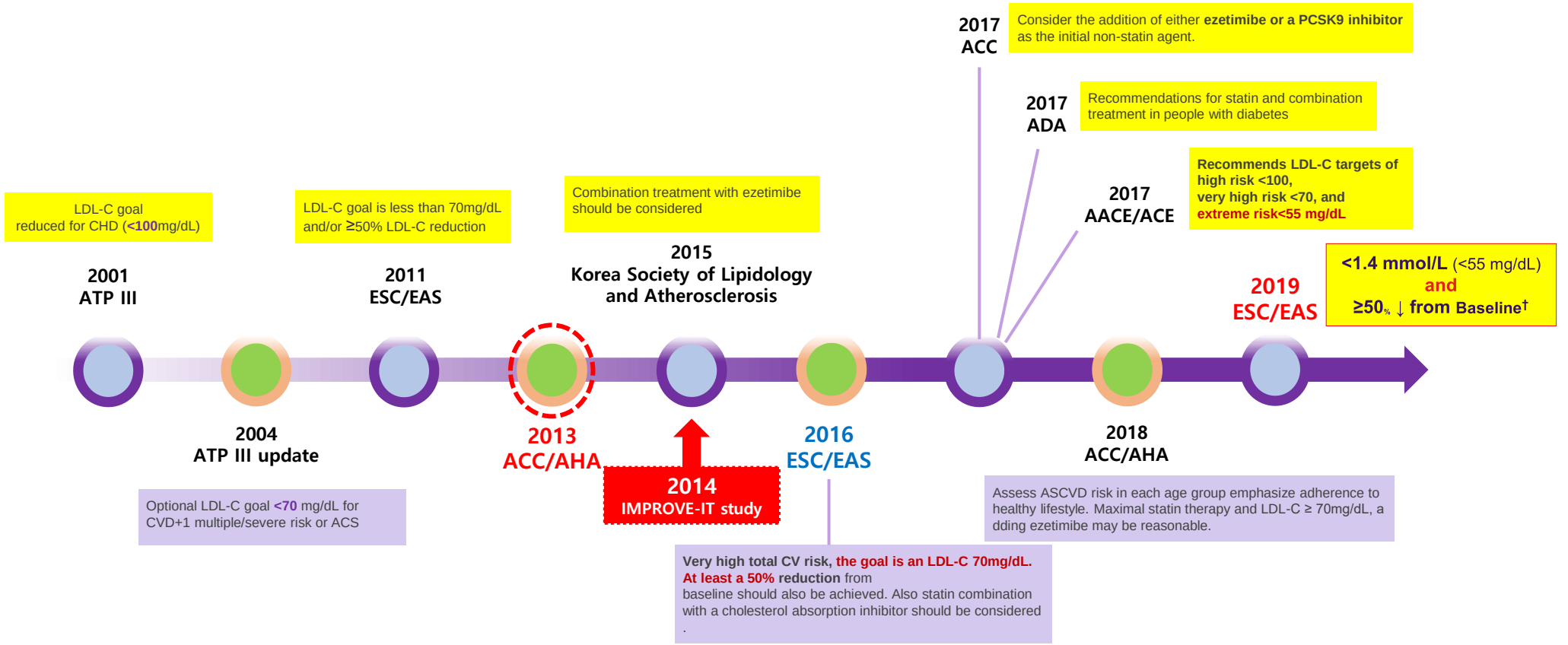
Changes in major dyslipidemia guidelines:
Emphasis on the need for a strong control



ESC : The European Society of Cardiology, EAS : The European Atherosclerosis Society, AACE : The American Association of Clinical Endocrinologists, ACE : American College of Endocrinology, ACC : The American College of Cardiology, AHA : American Heart Association, IMPROVE-IT : The Improved Reduction of Outcomes: Vytorin Efficacy International Trial, NCEP ATP Ⅲ : National Cholesterol Education Program Adult Treatment Panel. Ⅲ
1.Talwalkar P. G, *et al.* Journey in guidelines for lipid management : From adult treatment panel(ATP)- Ⅰ to ATP-Ⅲ and what to expect in ATP-Ⅳ. Indian *J Endocrinol Metab*. 2013 Jul;17(4):628-35 **2.** 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. *J Am Coll Cardiol* . 2014;63:2889-2934**. 3.** Korea Society of Lipidology and Atherosclerosis. 2015 Korean Guidelines for the Management of Dyslipidemia. **4.** Cannon CP, *et al.* IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372(25):2387–2397. **5.** Catapano AL, *et al.* 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. *Eur Heart J.* 2016 Aug;23(11):NP1-NP96. **6.** Garber AJ, *et al*. Consensus statement by the American association of clinical endocrinologists and American college of endocrinology on the comprehensive type 2 diabetes management algorithm-2017 executive summary. *Endocr Pract.* 2017 Feb;23(2):207-238.

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2019 ESC/EAS dyslipidemia guideline
Recommended treatment goals for LDL-lowering therapy:
main change from 2016 to 2019

Risk category‡	LDL-C goals (starting with untreated LDL-C)	
	2016[2]	2019[1]
Very-high-risk	<1.8 mmol/L (<70 mg/dL) or ≥50% ↓ if Baseline LDL-C* 1.8-3.5 mmol/L (70-135 mg/dL)	**<1.4 mmol/L** (<55 mg/dL) **and ≥50% ↓ from Baseline†**
High-risk	<2.6 mmol/L (<100 mg/dL) or ≥50% ↓ if Baseline LDL-C* 2.6-5.2 mmol/L (100-200 mg/dL)	**<1.8 mmol/L** (<70 mg/dL) **and ≥50% ↓ from Baseline†**
Moderate-risk	<3.0 mmol/L (<115 mg/dL)	**<2.6 mmol/L** (<100 mg/dL)
Low-risk	<3.0 mmol/L (<115 mg/dL)	**<3.0 mmol/L** (<116 mg/dL)

*The term "baseline LDL-C" refers to the level in a subject not taking any lipid lowering medication.[2]
†The term 'baseline' refers to the LDL-C level in a person not taking any LDL-C-lowering medication. In people who are taking LDL-C-lowering medication (s), the projected baseline (untreated) LDL-C levels should be estimated, based on the average LDL-C-lowering efficacy of the given medication or combination of medications.[1]
‡**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 (microalbuminuria, retinopathy, or neuropathy) 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. **High-risk** People with Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP ≥180/110 mmHg. Patients with FH without other major risk factors. Patients with DM without target organ damage (microalbuminuria, retinopathy, or neuropathy), with DM duration ≥10 years or another additional risk factor. Moderate CKD (eGFR 30-59 mL/min/1.73 m^2). A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD. **Moderate-risk** Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1 % and <5% for 10-year risk of fatal CVD. **Low-risk** Calculated SCORE <1% for 10-year risk of fatal CVD.
ESC : European Society of Cardiology, **EAS** : European Atherosclerosis Society, **LDL-C** : Low-density lipoprotein cholesterol

1. Baigent C, *et al.* 2019 ESC/EAS guidelines for the management of dyslipidaemias : lipid modification to reduce cardiovascular risk. *Eur Heart J.* 2019:1-78.
2. Catapano AL, *et al.* 2016 ESC/EAS Guidelines for the management of dyslipidaemias. *Eur Heart J.* 2016;37:2999–3058.

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2019 ESC/EAS Guidelines for the treatment goals of Dyslipidemias

- **2016**

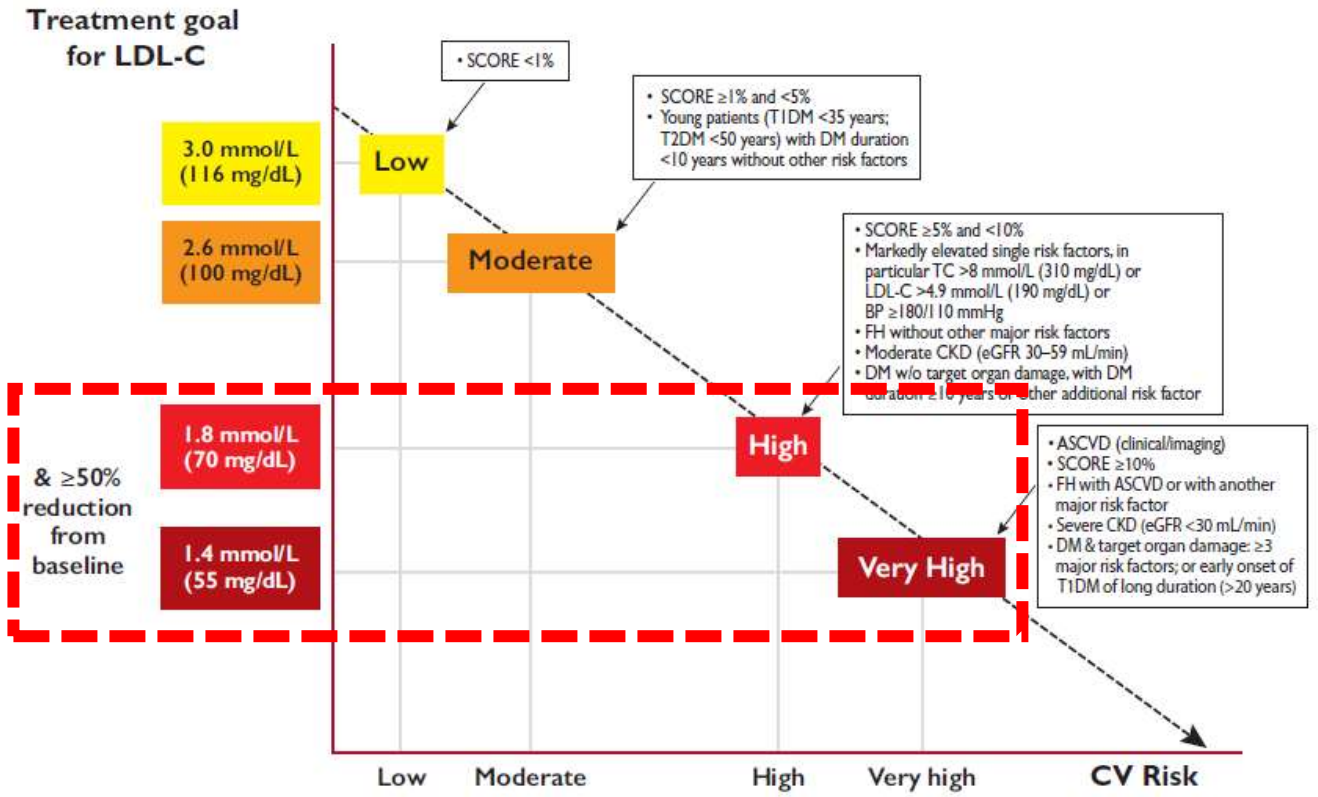
For High risk

In patients at HIGH CV risk[d], an LDL-C goal of <2.6 mmol/L (100 mg/dL), or a reduction of at least 50% if the baseline LDL-C[e] is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL) is recommended.	I

For Very High risk

Recommendations	Class[a]
In patients at VERY HIGH CV risk[d], an LDL-C goal of <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C[e] is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.	I

- **2019** Lower LDL-C is better;



1. Baigent C, *et al.* 2019 ESC/EAS guidelines for the management of dyslipidaemias : lipid modification to reduce cardiovascular risk. *Eur Heart J.* 2019:1-78
2. https://www.acc.org/latest-in-cardiology/articles/2019/09/09/13/08/key-takeaways-comparing-lipid-guidelines-across-the-pond

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Three Key Concepts of Lipid-lowering Strategies to Reduce Cardiovascular Diseases in 2019 ESC/EAS Guidelines

1. Mach F, *et al.* European Heart Journal (2019) 00, 1-78

AHA : the American Heart Association, **ACC** : the American College of Cardiology, **AACVPR**: American Association of Cardiovascular and Pulmonary Rehabilitation, **AAPA** : American Association Academy of Physician Assistants, **ABC** : Association of Black Cardiologists, **ACPM**: American College of Preventive Medicine, **ADA** : American Diabetes Association, **AGS**: American Geriatrics Society, **APhA** : American Pharmacists Association, **ASPC** :American Society for Preventive Cardiology, **NLA** : National Lipid Association, **PCNA** : Preventive Cardiovascular Nurses Association

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2022 Korean guidelines update(5th)

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.

1. 2022 Korean guidelines for the management of dyslipidemia(KSoLA)

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2022 Korean guidelines update(5th) change

2018 4th

Risk categories		LDL-C (mg/dL)	non-HDL-C (mg/dL)
Very high	Coronary artery disease	< 70 (or ≥50%)	< 100
	Atherosclerotic stroke and transient ischemic attack		
	Peripheral artery disease		
High	Carotid artery disease	< 100	< 130
	Abdominal aortic aneurysm		
	Diabetes mellitus		
Moderate risk	major risk factor ≥2	< 130	< 160
Low risk	major risk factor ≤1	< 160	< 190

2022 5th

임상상황	LDL-C (mg/dL)	non-HDLC (mg/dL)
✓ Coronary artery disease*	<55 (and ≥50%)	<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 factor)	<100	<130
✓ Moderate risk(major risk factor ≥ 2)	<130	<160
✓ Low risk (major risk factor ≤ 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.
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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.

1. 2022 Korean guidelines for the management of dyslipidemia(KSoLA)

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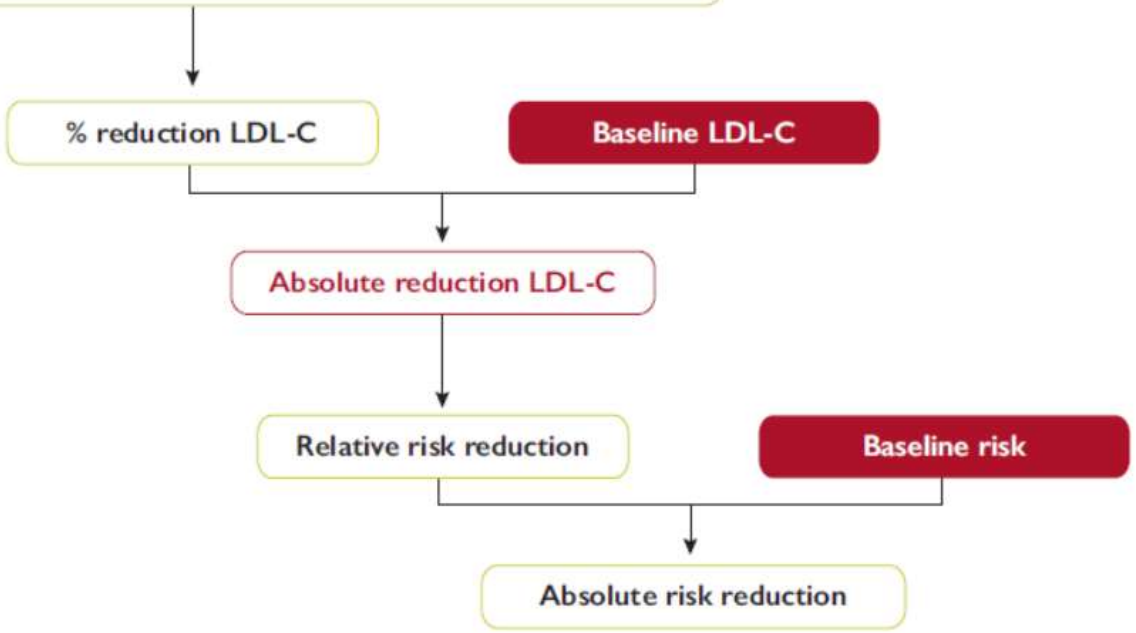
Intensity of lipid lowering therapy

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%



2019 Guidelines on Dyslipidaemias (Management of) ESC Clinical Practice Guidelines

2013 ACC/AHA Blood Cholesterol Guideline
Focus on ASCVD Risk Reduction : Statin Therapy Intensity

High- Moderate- and Low-Intensity Statin Therapy[1]

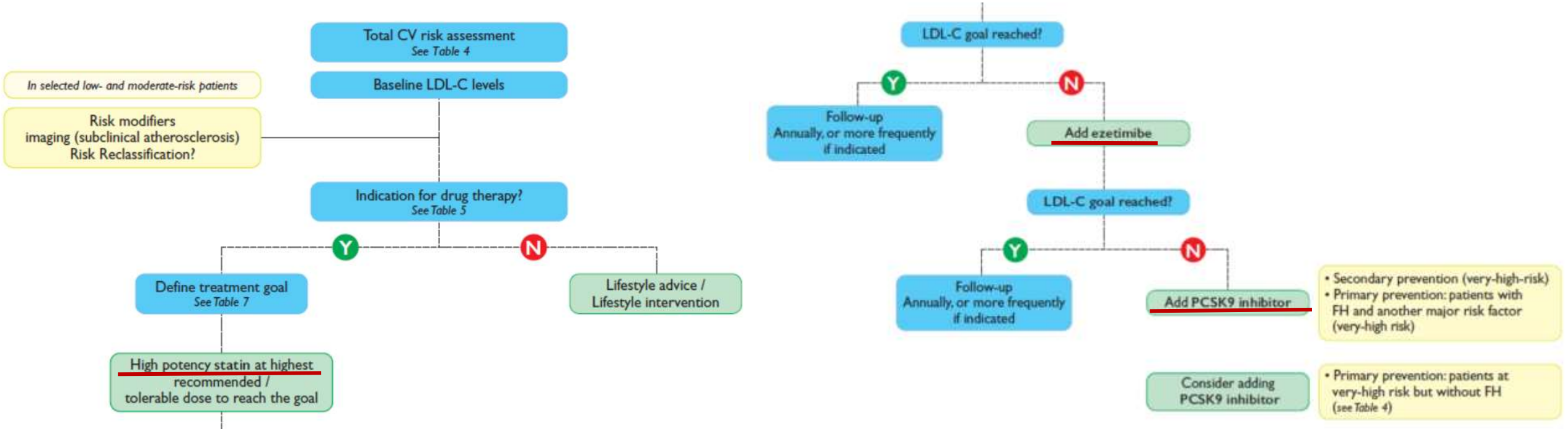
High intensity therapy	Moderate	Low
Daily dose lowers LDL-C on average, by approximately ≥ 50%	Daily dose lowers LDL-C on average, by approximately 30% to < 50%	Daily dose lowers LDL-C on average, by < 30%
• **Atorvastatin(40)-80 mg** • **Rosuvastatin 20** *(40)* **mg**	• **Atorvastatin 10** *(20)* **mg**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

Adapted from Stone NJ, *et al.*[1]

* Specific statins and doses are noted in bold that were evaluated in RCTs demonstrated a reduction in major cardiovascular events.
Statins and doses that are approved by the U.S. FDA but were not tested in the RCTs reviewed are listed in italics.
ACC : American College of Cardiology, AHA : American Heart Association, ASCVD : Atherosclerotic cardiovascular disease, LDL-C : Low-density lipoprotein cholesterol, FDA : Food and Drug Adminstration.

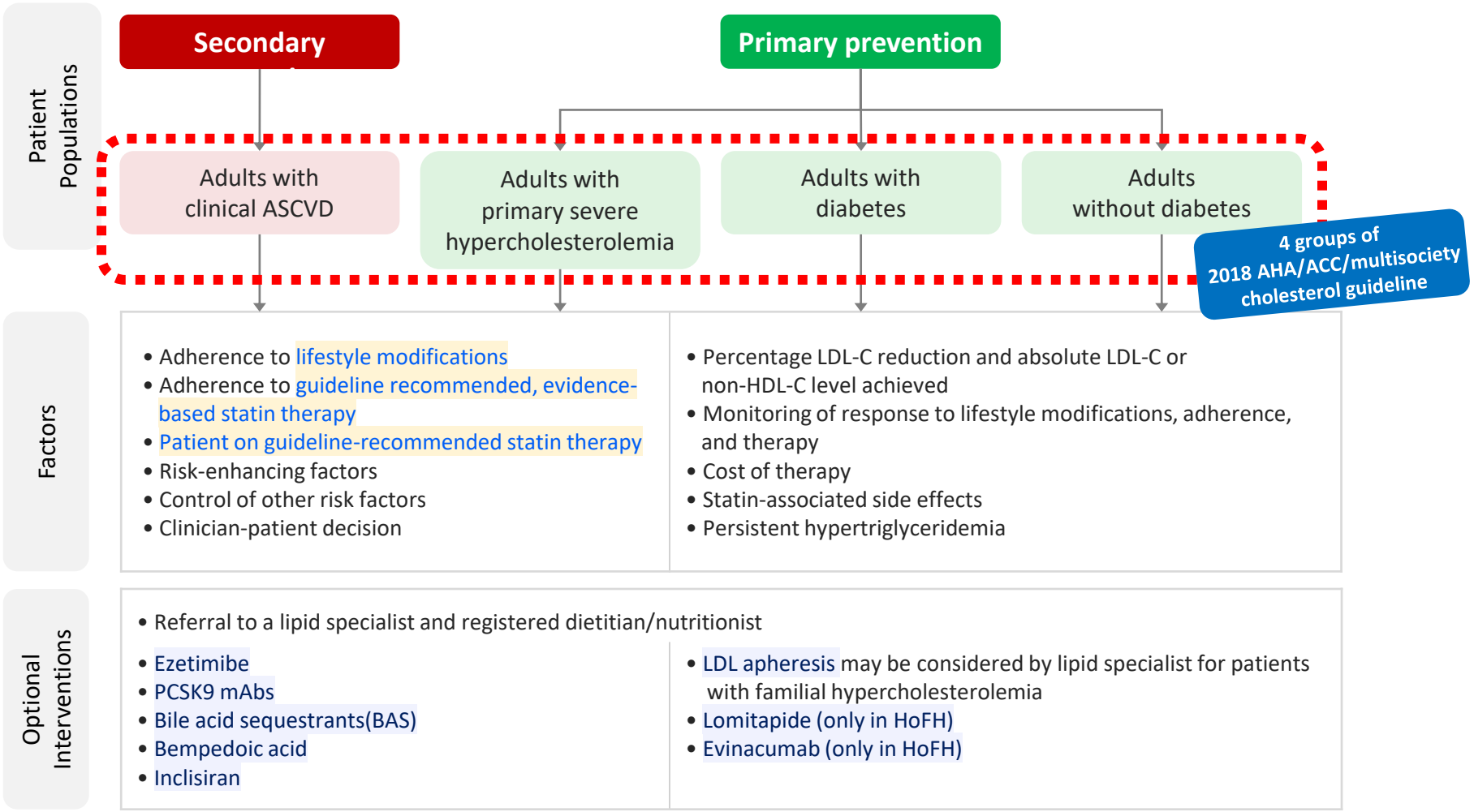
1. Stone NJ, *et al.* 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;1-84.

Treatment algorithm for pharmacological LDL-C lowering



2019 Guidelines on Dyslipidaemias (Management of) ESC Clinical Practice Guidelines

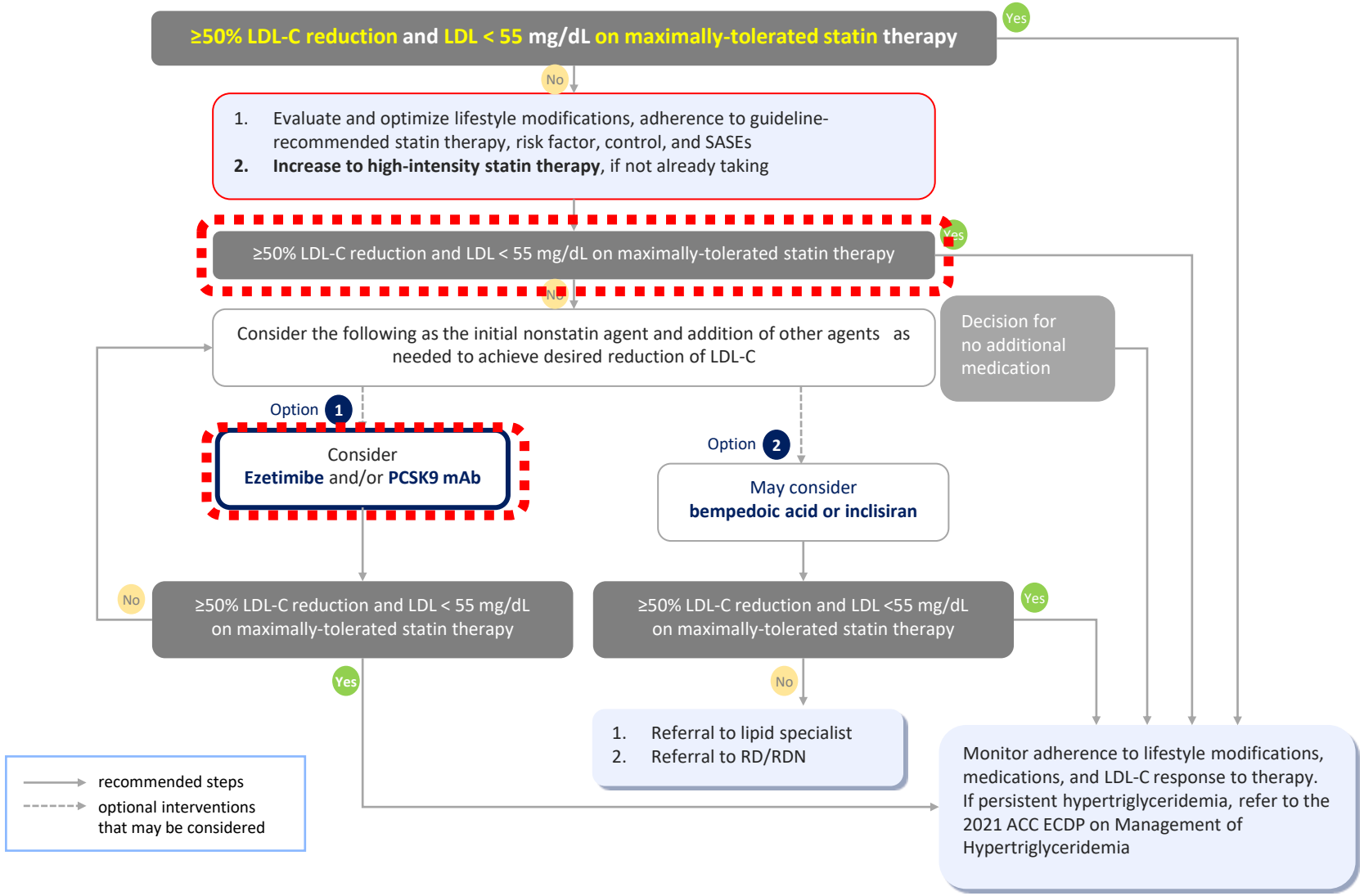
Patient Populations, Factors & Interventions to Consider



*2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk, ** LDL-C ≥190 mg/dL
PCSK9 mAb includes alirocumab and evolocumab. ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; PCSK9 mAb, proprotein convertase subtilisin/kexin type 9 monoclonal antibodies

Ref. Lloyd-Jones DM, et al. J Am Coll Cardiol. 2022 Oct 4;80(14):1366-1418.

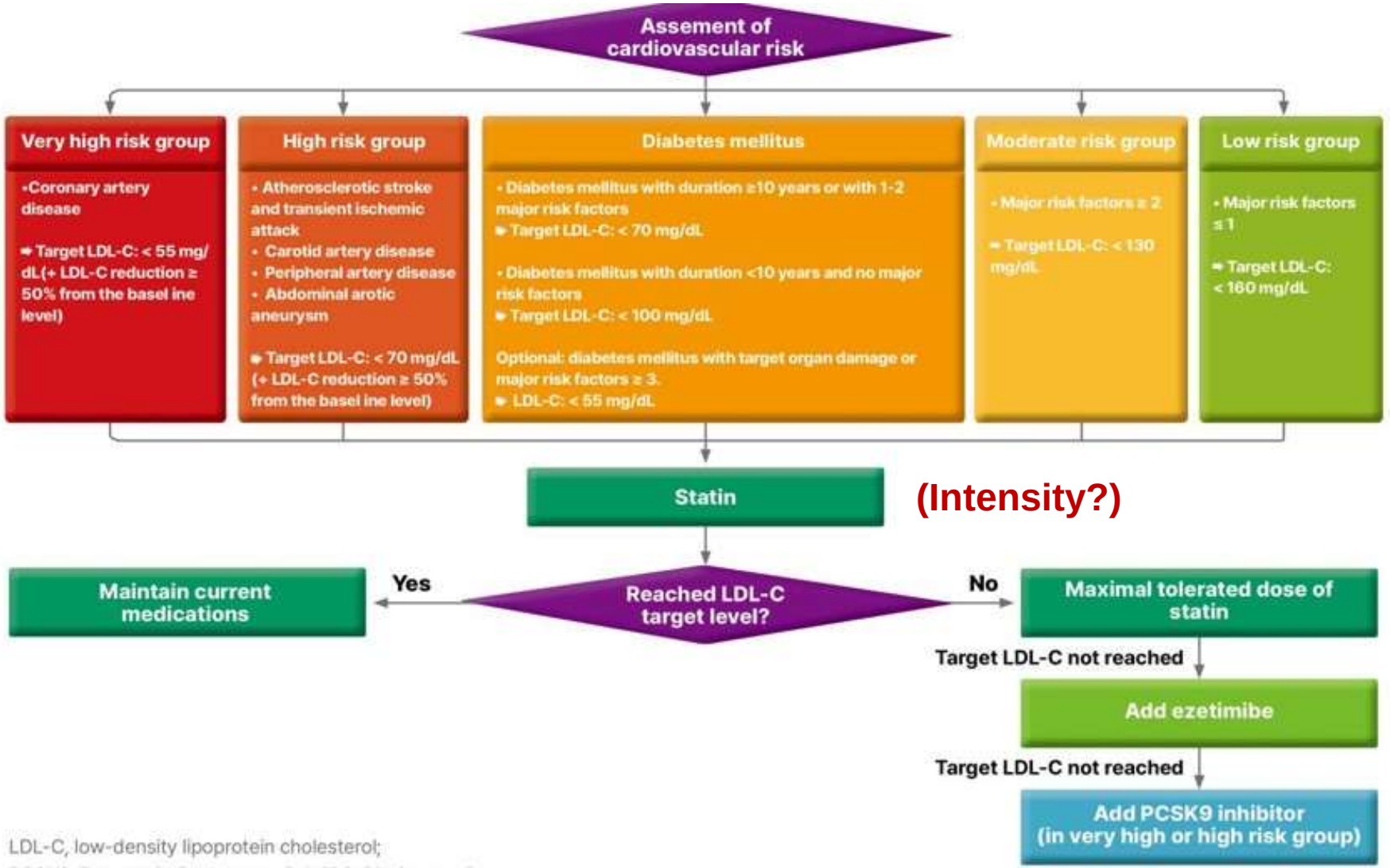
ASCVD at very high risk on statin therapy



ASCVD: atherosclerotic cardiovascular disease, ECDP: Expert Consensus Decision Pathway, LDL-C: low density lipoprotein cholesterol, PCSK9: mAb, proprotein convertase subtilisin/kexin type 9 monoclonal antibody, RD/RDN: registered dietitian/registered dietitian nutritionist, SASE: statin-associated side effect

Ref. Lloyd-Jones DM, et al. J Am Coll Cardiol. 2022 Oct 4;80(14):1366-1418.

2022 Korean guidelines update(5th)



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

1. 2022 Korean guidelines for the management of dyslipidemia(KSoLA)

ORGANON

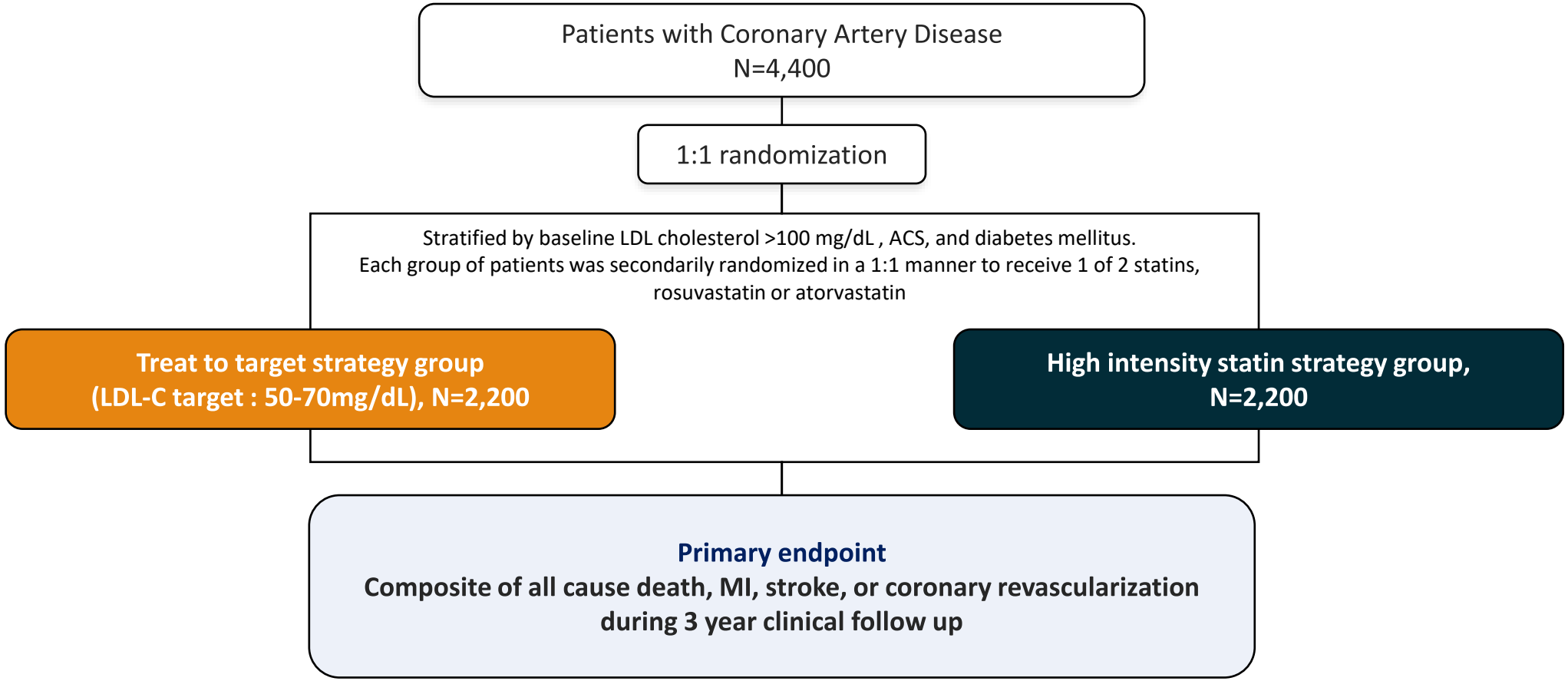
How to lower LDL

High intensity statin therapy vs Treat to target therapy

Patients with coronary artery disease
Treat-to-Target strategy vs. High-Intensity statin therapy

LODESTAR trial

(Low-Density Lipoprotein Cholesterol- Targeting Statin Therapy Versus Intensity-Based Statin Therapy in Patients With Coronary Artery Disease)

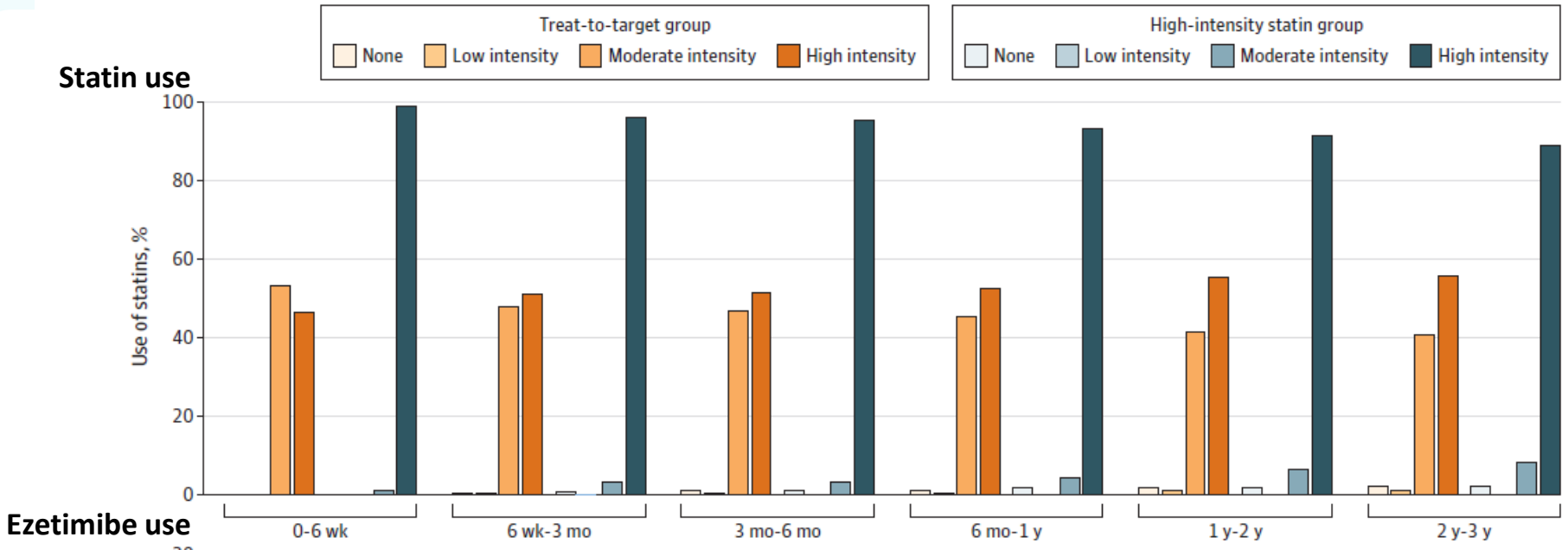


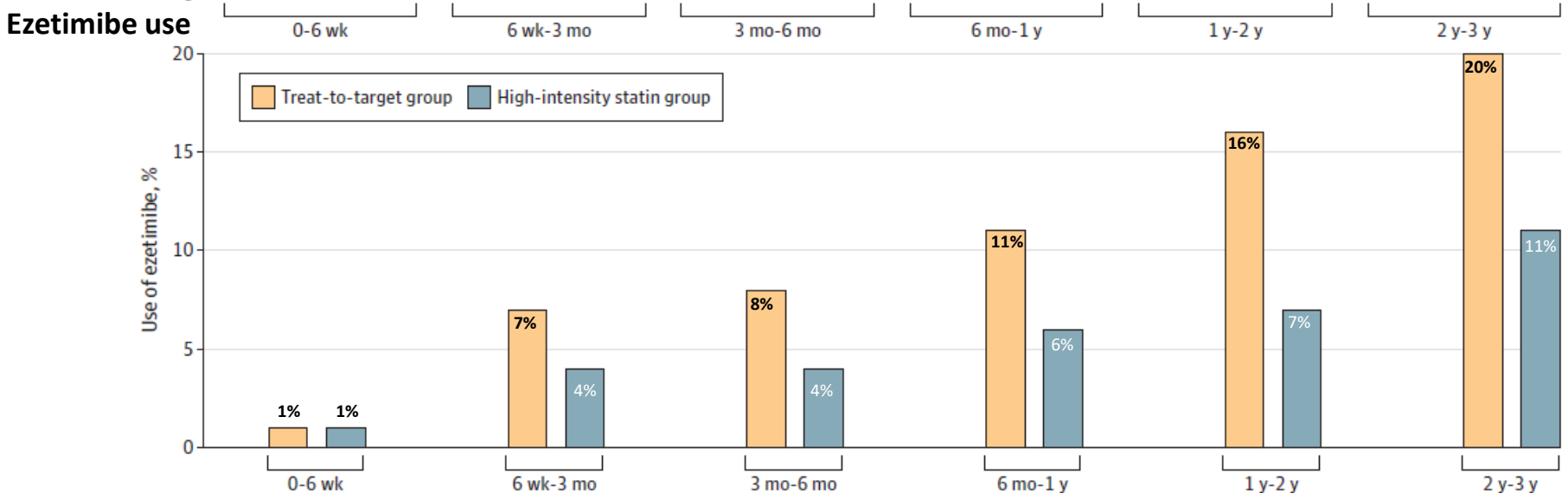
ACS, acute coronary syndrome; MI, myocardial infarction

Ref. Hong SJ, et al. JAMA. 2023 Mar 6;e232487.

LODESTAR trial

Lipid-lowering therapy during the study period





Overall period	Treat to Target group	High intensity group
Moderate intensity statin	43%	6%
High intensity statin	54%	92%

Ezetimibe was used more in the treat-to-target group from 6months, mostly as a combination therapy with high-intensity statin therapy

Ref. Hong SJ, et al. JAMA. 2023 Mar 6;e232487.

LODESTAR trial

Patients with LDL-C below 70 mg/dL

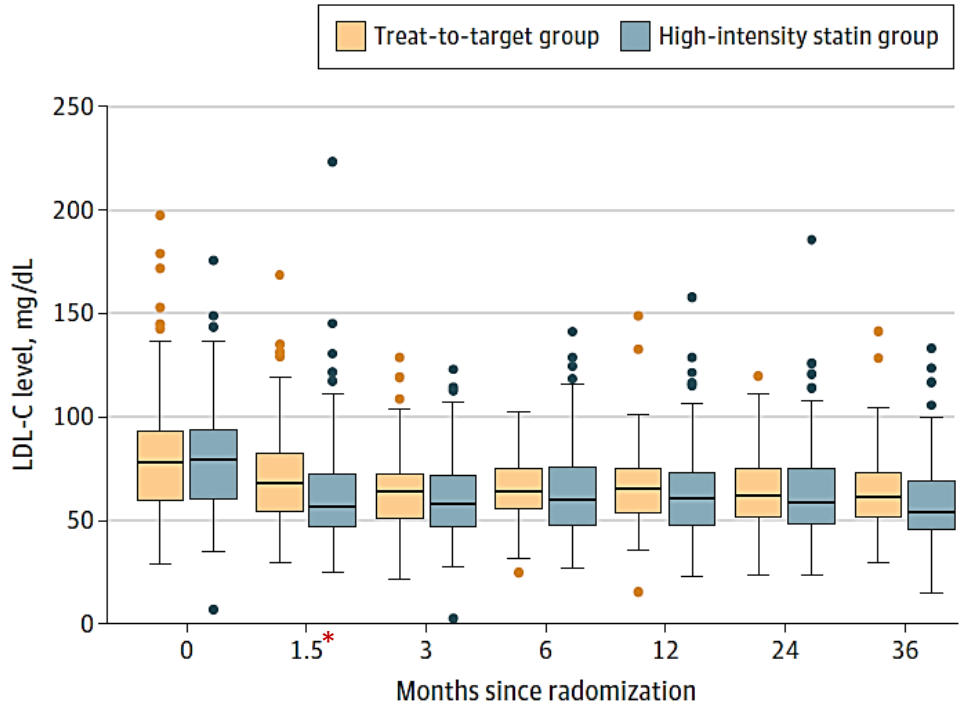
	Treat-to-target	High-intensity statin	Absolute Difference (95% confidence interval)	P Value
At randomization	712/2200 (32.4)	655/2200 (29.8)	2.6 (-0.1 to 5.3)	.06
At 6 weeks	890/1598 (55.7)	987/1601 (61.6)	-6.0 (-9.4 to -2.5)	<.001
At 3 months	261/441 (59.2)	267/397 (67.3)	-8.1 (-15.6 to -5.3)	.02
At 6 months	620/1074 (57.7)	653/1092 (59.8)	-2.1 (-5.8 to 1.7)	.33
At 1 year	1038/1862 (55.7)	1092/1854 (58.9)	-3.2 (-6.3 to 0.0)	.05
At 2 years	1005/1654 (60.8)	1015/1679 (60.4)	0.3 (-3.0 to 3.6)	.86
At 3 years	908/1560 (58.2)	927/1554 (59.7)	-1.4 (-4.9 to 2.0)	.41

Ref. Hong SJ, et al. JAMA. 2023 Mar 6;e232487.

LODESTAR trial

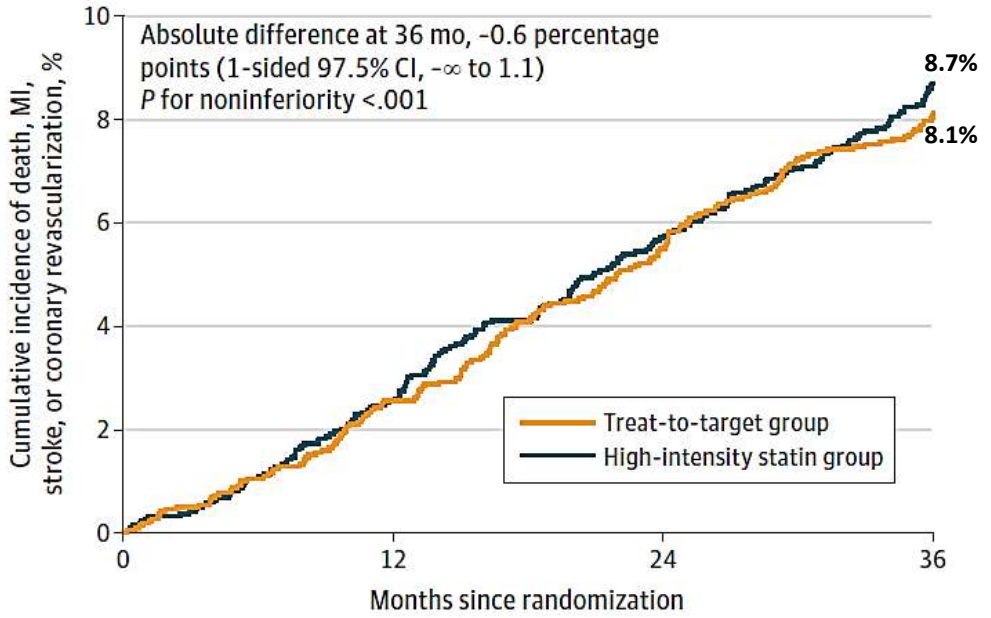
LDL-C levels and Cumulative incidence of primary end point

Distribution of LDL-C levels



The mean LDL-C level for 3 years
Treat-to-target group: - 69.1 mg/dL
High-intensity statin group: 68.4 mg/dL
(*P*=0.21).

Cumulative incidence of the primary end point



Absolute difference, –0.6 percentage points
[upper boundary of the 1-sided 97.5%CI, 1.1 percentage points]
P < 0.001 for noninferiority

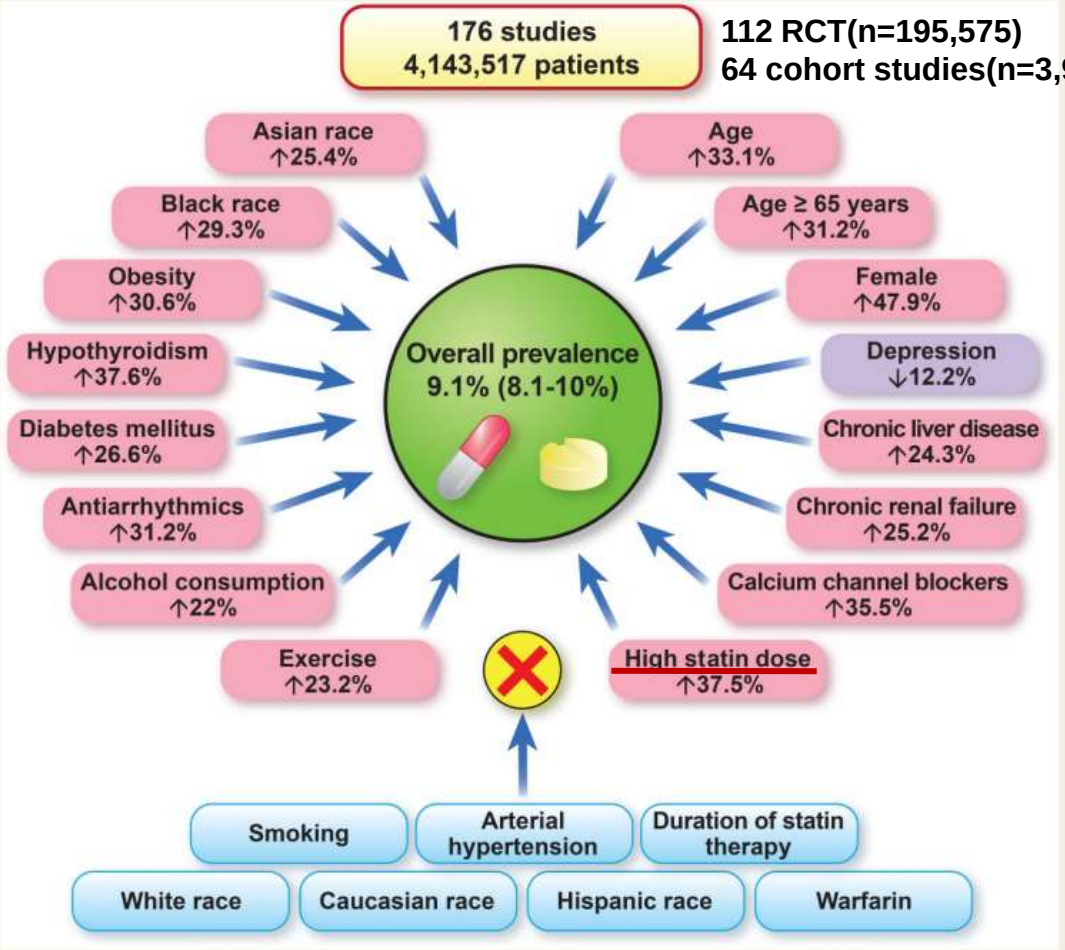
*P<0.001 at 1. 5 months (6 weeks)

Ref. Hong SJ, et al. JAMA. 2023 Mar 6;e232487.

Problems of maximal dose of high intensity statin

Statin intolerance

Prevalence of statin intolerance



Ibadete Bytyçi et al. Eur Heart J 2022

Statin intolerance diagnostic criteria by

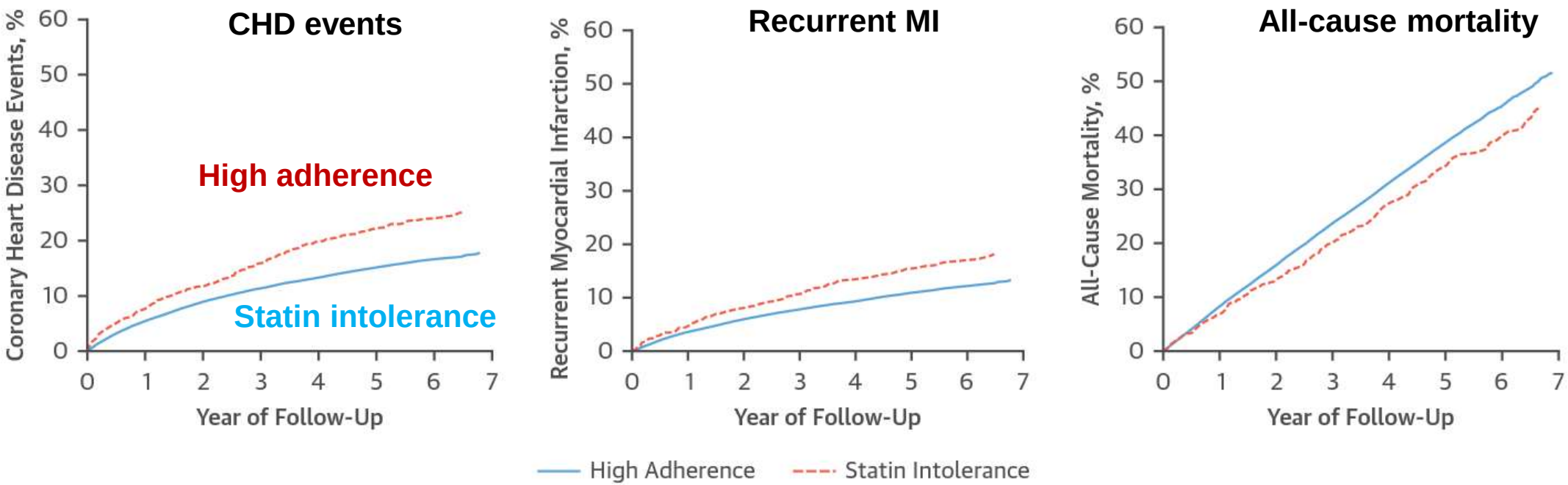
NLA: adverse effects relating to the quality of life, leading to decisions to decrease or stop the use of an otherwise Beneficial drug

ILEP: inability to tolerate a dose of statin required to reduce a person's CV risk sufficiently from their baseline risk and could result from different statin-related side effects.

EAS: assessment of the probability of SAMS considering the nature of the muscle symptoms, the elevation in CK levels, and their temporal association with statin initiation, discontinuation, and re-challenge

CCWG & LLAC: significant symptoms & biomarker Abnormalities that is documented by challenge/dechallenge /re-challenge using ≥2 statins that is not due to drug interactions or untreated risk factors for intolerance

Statin Intolerance and Risk of Coronary Heart Events



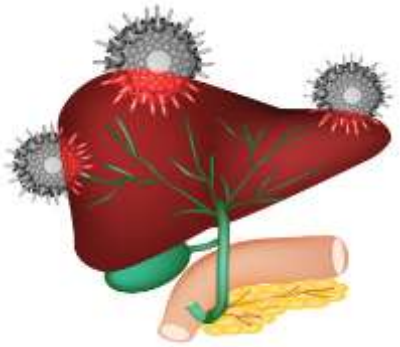
Statin intolerance

1. Statin **discontinuation** with the initiation of ezetimibe therapy;
2. Initiation of **ezetimibe therapy within 7 days** before or any time after downtitrating statin dose;
3. An inpatient or outpatient claim for **rhabdomyolysis** (defined by ICD-9-CM code 728.88 in any position), followed by statin down-titration or discontinuation;
4. An inpatient or outpatient claim for "**adverse effect of an antihyperlipidemic agent**" (defined by ICD-9-CM diagnostic code E942.2 in any position), followed by statin down-titration or discontinuation; and
5. Fills for **≥ 3 types of statins**.

Maria-Corina Serban. et al. J Am Coll Cardiol. 2017

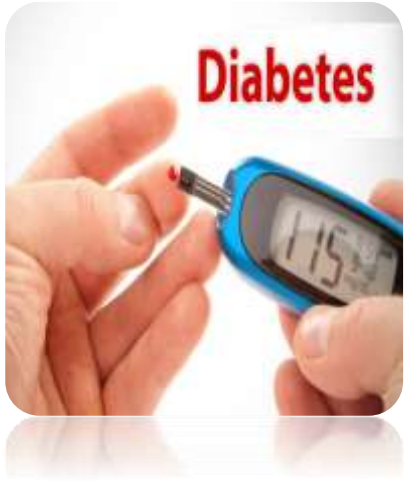
Concerns of high intensity statin therapy

Liver
hepatic toxicity[1]



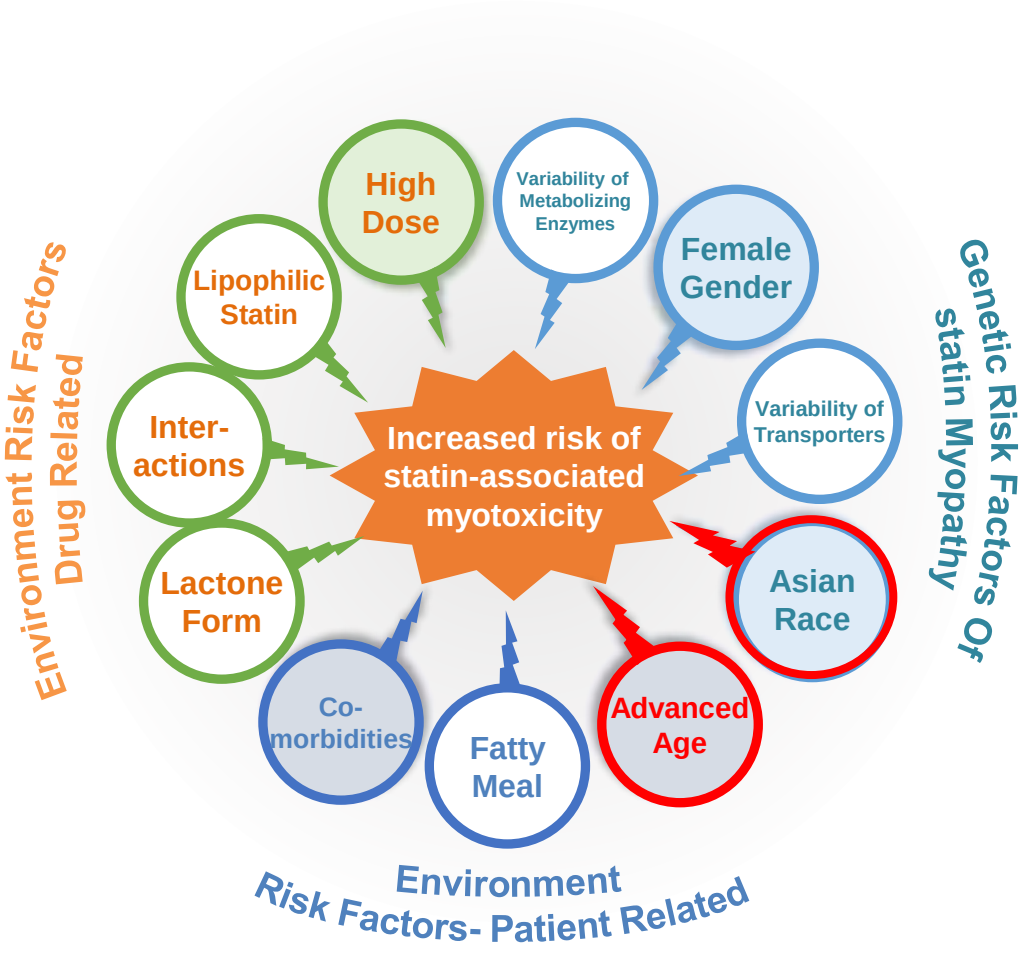
Myopathy
muscle pain[2]

New onset DM[3]



Ref> 1. Data from prescribing information for atorvastatin, lovastatin, simvastatin – *20 mg includes pts on 40 mg (37%).
2. Bruckert et. al, Cardiovascular Drugs and Therapy, 2005;19:403-414
3. BMJ 2014;348:g3244

Risk factors for statin myotoxicity



MC adverse effects of statins
(10–29% in observational studies, 1-2% in RCT)

very common reason for stopping statin therapy

Myalgia, **cramps** & weakness

bilateral & large muscle groups
(thighs, calves, hip flexors or proximal upper extremities)

appear shortly after **starting** statin or **increasing** dose
resolve quickly after cessation of statin

SAMS(statin ass muscle symptoms)
Myopathy: 1/1,000, CK > 10XULN
Rhabdomyolysis: 1/10,000, CK >10XULN

coenzyme Q10↓ > mitochondrial ATP depletion
isoprenoid biosynthesis↓ > mitochondria-dependent apoptosis

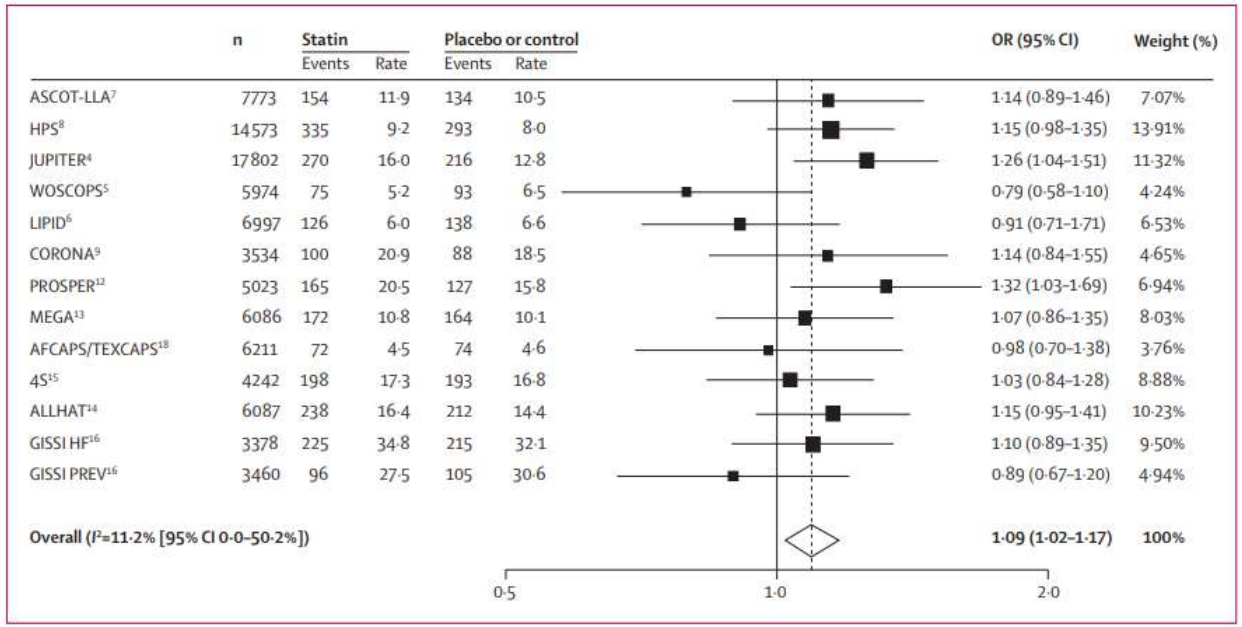
Taha A, et al. Translational Research 2014;164:85–109

Bhavin B. Adhyaru et al. Nat Rev Cardiol. 2018

Statins and risk of incident diabetes

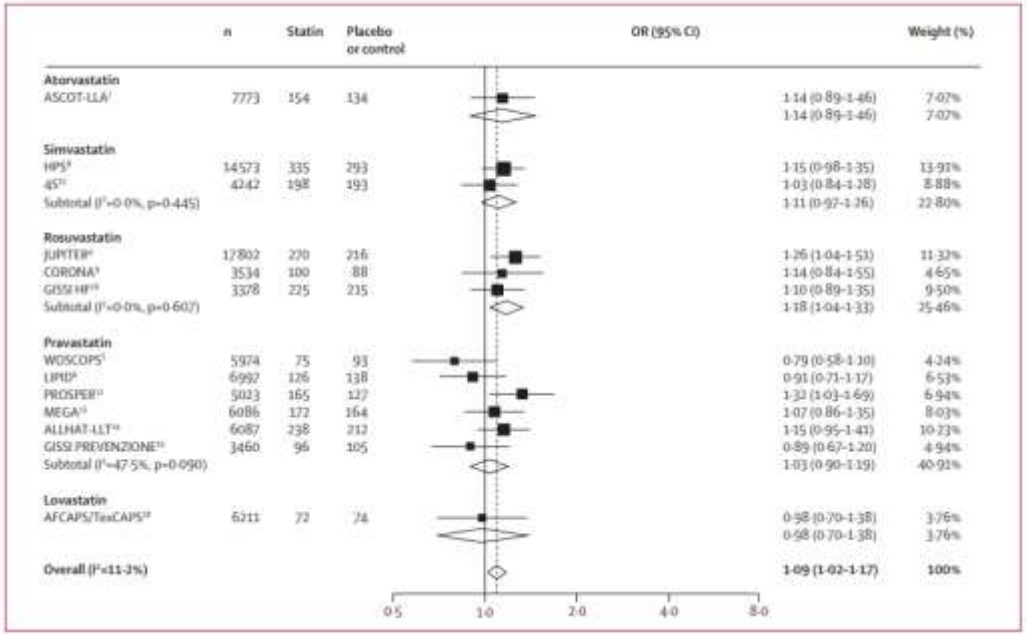
13 statin RCT, n=91,140

Association between statin therapy & incident DM in 13 major CV trials



	n	Statin Events	Statin Rate	Placebo or control Events	Placebo or control Rate	OR (95% CI)	Weight (%)
ASCOT-LLA[7]	7773	154	11·9	134	10·5	1·14 (0·89–1·46)	7·07%
HPS[8]	14573	335	9·2	293	8·0	1·15 (0·98–1·35)	13·91%
JUPITER[4]	17802	270	16·0	216	12·8	1·26 (1·04–1·51)	11·32%
WOSCOPS[5]	5974	75	5·2	93	6·5	0·79 (0·58–1·10)	4·24%
LIPID[6]	6997	126	6·0	138	6·6	0·91 (0·71–1·71)	6·53%
CORONA[9]	3534	100	20·9	88	18·5	1·14 (0·84–1·55)	4·65%
PROSPER[12]	5023	165	20·5	127	15·8	1·32 (1·03–1·69)	6·94%
MEGA[13]	6086	172	10·8	164	10·1	1·07 (0·86–1·35)	8·03%
AFCAPS/TEXCAPS[18]	6211	72	4·5	74	4·6	0·98 (0·70–1·38)	3·76%
4S[15]	4242	198	17·3	193	16·8	1·03 (0·84–1·28)	8·88%
ALLHAT[14]	6087	238	16·4	212	14·4	1·15 (0·95–1·41)	10·23%
GISSI HF[16]	3378	225	34·8	215	32·1	1·10 (0·89–1·35)	9·50%
GISSI PREV[16]	3460	96	27·5	105	30·6	0·89 (0·67–1·20)	4·94%
Overall (I^2=11·2% [95% CI 0·0–50·2%])						**1·09 (1·02–1·17)**	**100%**

Association between different statins & development of DM

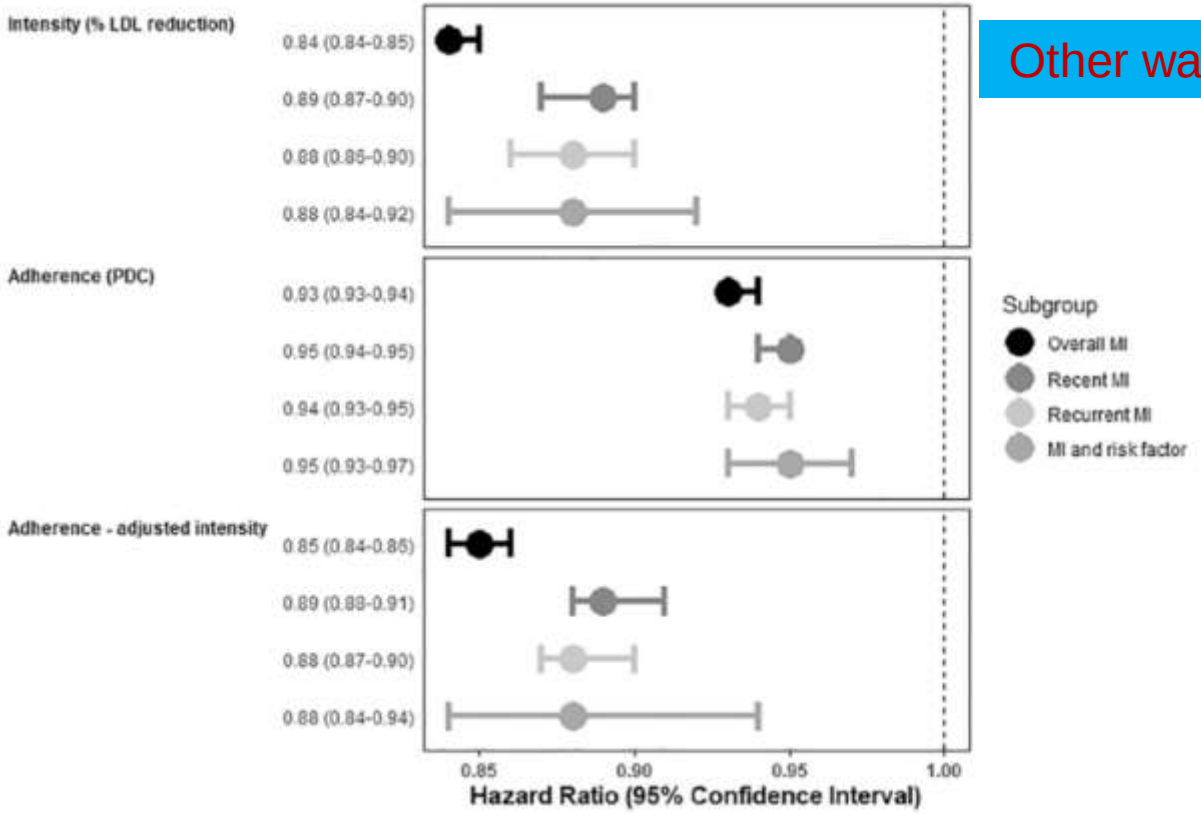


Naveed Sattar. et al. Lancet. 2010

Disadvantage of high intensity statin

Effective Lipid lowering therapy(LLT) : intensity X adherence

maximal tolerated dose of high intensity statin
Intensity↑(effect↓ & side effect↑) & adherence↓ > Ineffective LLT



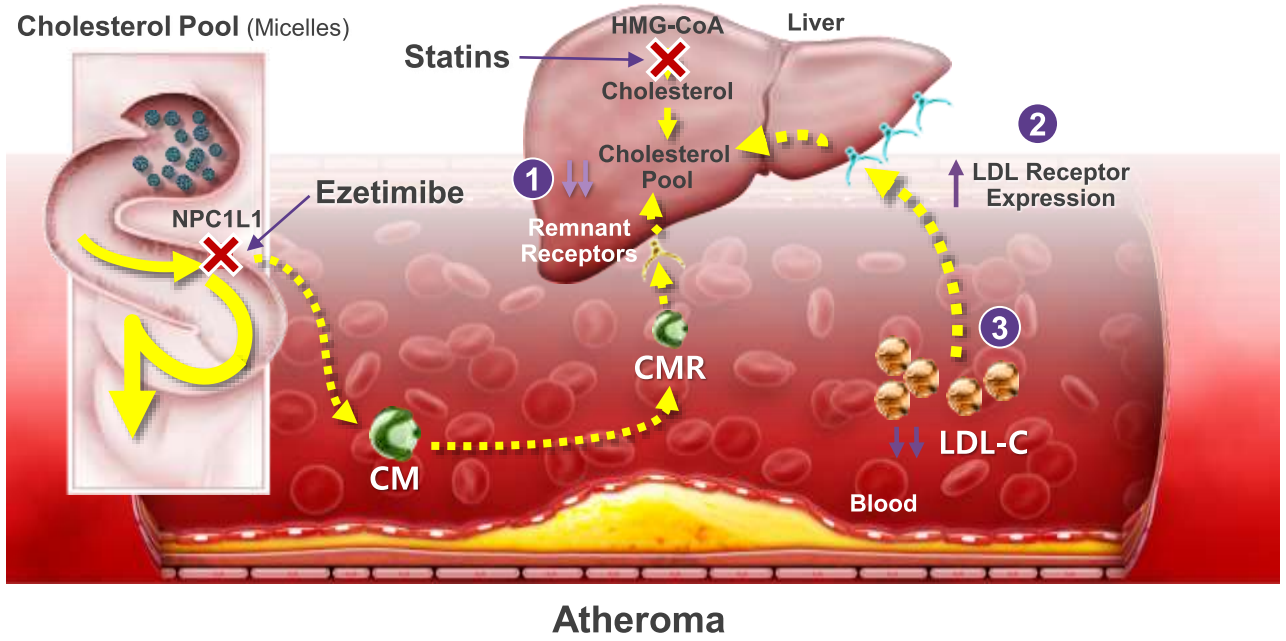
Other ways of increasing LLT intensity & adherence!

François Schiele et al. Int J Cardiol. 2021

Ezetimibe & statins have complementary mechanisms of action

Together, ezetimibe in combination with a statin provides[1]:

1. Reduction of hepatic cholesterol
2. Increased LDL receptor expression
3. Increased clearance of plasma LDL-C



NPC1L1 : Niemann-Pick C1-like 1, LDL-C : Low-density lipoprotein cholesterol, HMG-CoA : 3-hydroxy-3-methylglutaryl acetyl coenzyme A, CMR : Chylomicron remnant.

1. Grigore L, *et al.* Combination therapy in cholesterol reduction: focus on ezetimibe and statins. *Vas Health Risk Manag*. 2008;4:267-278.

Cholesterol absorption is increased during statin treatment

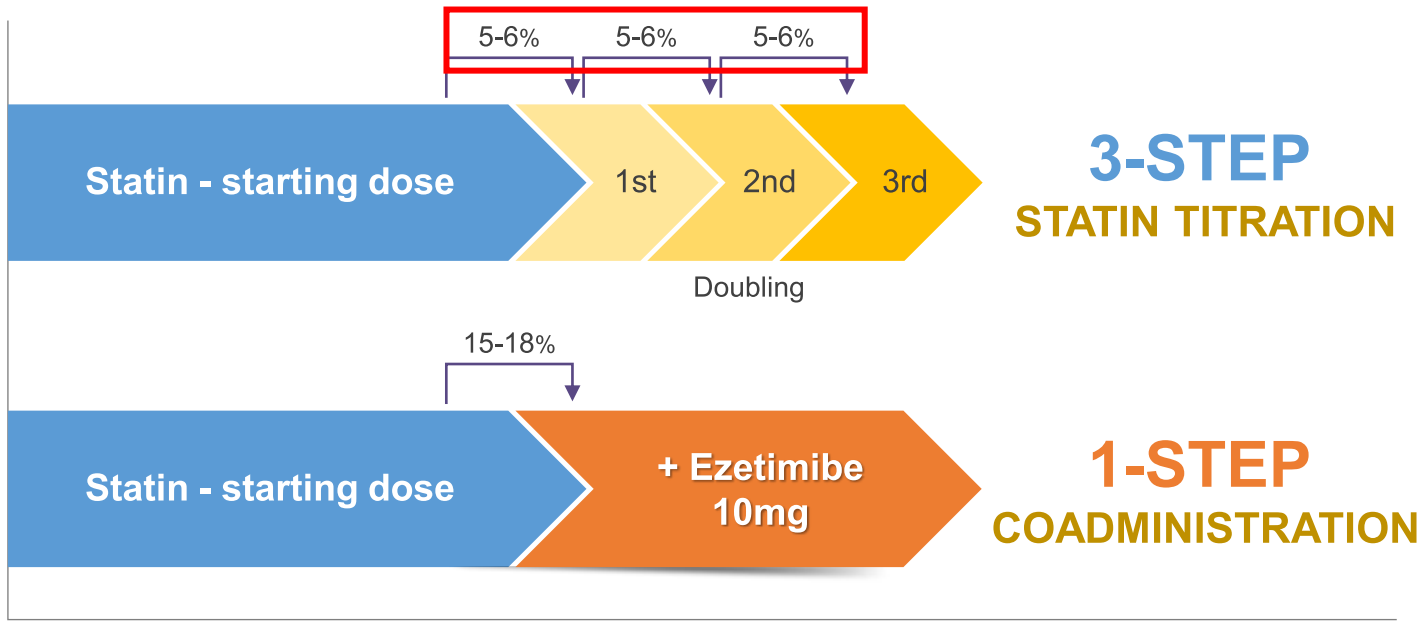
Type II DM Men atorvastatin 80mg for 6 month

Variables	Before	During	Change (%)
Cholesterol absorption (%)	26 ± 2	53 ± 5	+103 ± 1*
Fecal neutral sterols (mg d^{-1})	894 ± 104	480 ± 62	−46 ± 3*
Fecal bile acids (mg d^{-1})	424 ± 84	371 ± 89	−2 ± 21
Fecal total steroids (mg d^{-1})	1391 ± 149	851 ± 119	−34 ± 10*
Cholesterol synthesis (mg d^{-1})	1078 ± 269	551 ± 105	−42 ± 8*
Cholesterol turnover (mg d^{-1})	1143 ± 117	699 ± 106	−37 ± 9*
Dietary cholesterol (mg d^{-1})	241 ± 49	300 ± 33	+40 ± 19
Absorbed (mg d^{-1})	65 ± 16	153 ± 8	+187 ± 57*
Intestinal cholesterol (mg d^{-1})	1208 ± 139	1016 ± 87	−18 ± 8
Absorbed (mg d^{-1})	314 ± 43	536 ± 69	+82 ± 32*
Dietary sitosterol (mg d^{-1})	232 ± 33	195 ± 14	−10 ± 12

T A Miettinen et al Eur J Clin Invest. 2003

Ezetimibe add-on therapy was comparable to 3-step statin up-titration in % LDL-C reduction[1]

Percent change from baseline (mean[SE]) **in low-density lipoprotein cholesterol** (LDL-C)



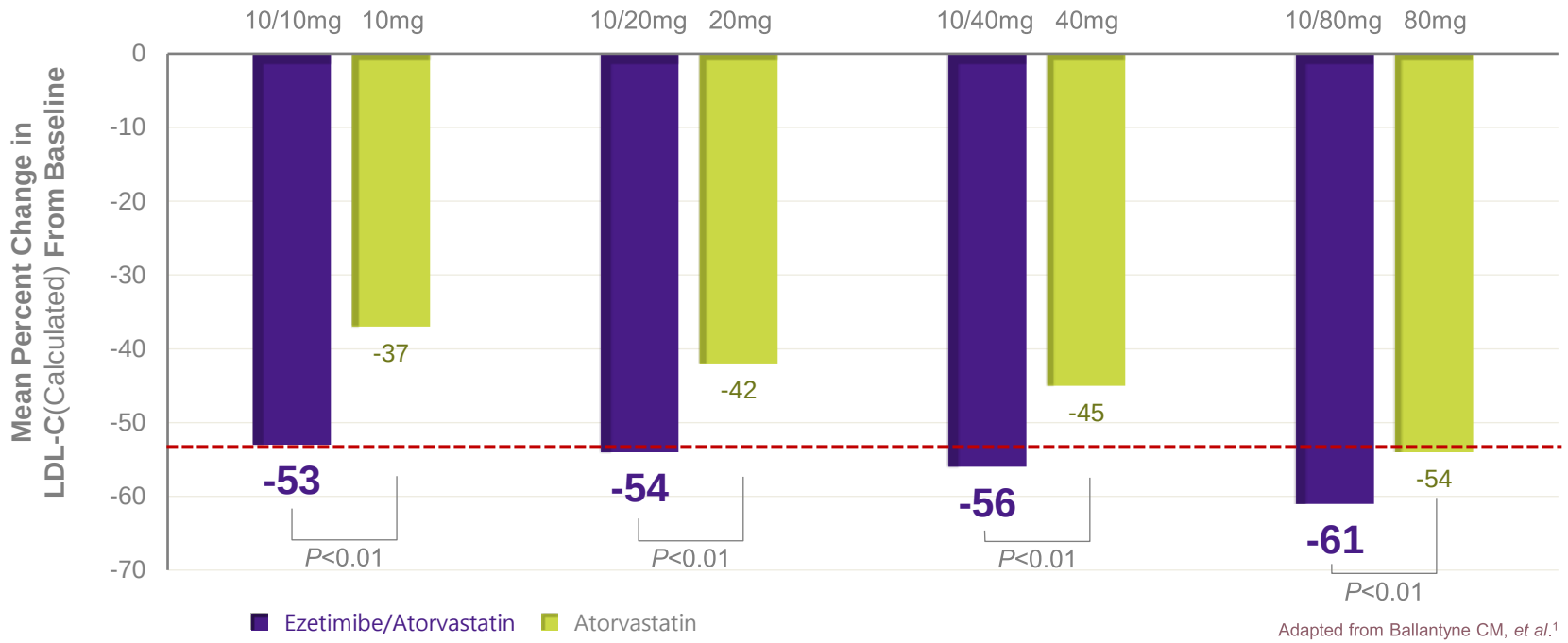
LDL-C : Low-density liopoprotein cholesterol

1. Harold E, *et al*. A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Factorial Design Study to Evaluate the Lipid-Altering Efficacy and Safety Profile of the Ezetimibe/Simvastatin Tablet Compared with Ezetimibe and Simvastatin Monotherapy in Patients with Primary Hypercholesterolemia. *Clin Ther*. 2004;26:1758-1773.

Starting Atozet® provided significantly greater calculated LDL-C reduction compared with corresponding Atorvastatin doses[1,#]

This double-blind study was conducted 628 primary hypercholesterolemia patients without diabetes mellitus for 12 weeks.[1]

Mean percent change in calculated LDL-C from baseline[1]



Adapted from Ballantyne CM, *et al*.[1]

Mean baseline LDL-C was 182 mg/dL (~4.7 mmol/L) for ezetimibe /atorvastatin arms (n=255) and 181 mg/dL (~4.7 mmol/L) for atorvastatin arms (n=248).
Primary endpoint result : 에제티미브/아토르바스타틴 병용 투여는 아토르바스타틴 단독 투여 대비 baseline으로부터 direct LDL-C를 유의하게 보다 더 감소시켰습니다. (-54.5% vs. -42.4%,p <0.01).
LDL-C : Low density lipoprotein cholesterol
study design A 12-week, double-blind study (N=628) evaluating the LDL-C–lowering efficacy of add on ezetimibe compared with atorvastatin alone in patients with primary hypercholesterolemia. Patients were randomized to receive atorvastatin 10mg (n=60), 20mg (n=60), 40mg (n=66), or 80mg (n=62), respectively, or ezetimibe plus atorvastatin 10/10mg (n=65), 10/20mg (n=62), 10/40mg (n=65), or 10/80mg (n=63), respectively. The primary end point was the percent change from baseline of LDL-C at study end in the treatment group receiving add on ezetimibe and the atorvastatin alone treatment group.
1. Ballantyne CM *et al*. The effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia. *Circulation.* 2003;107: 2409–2415.

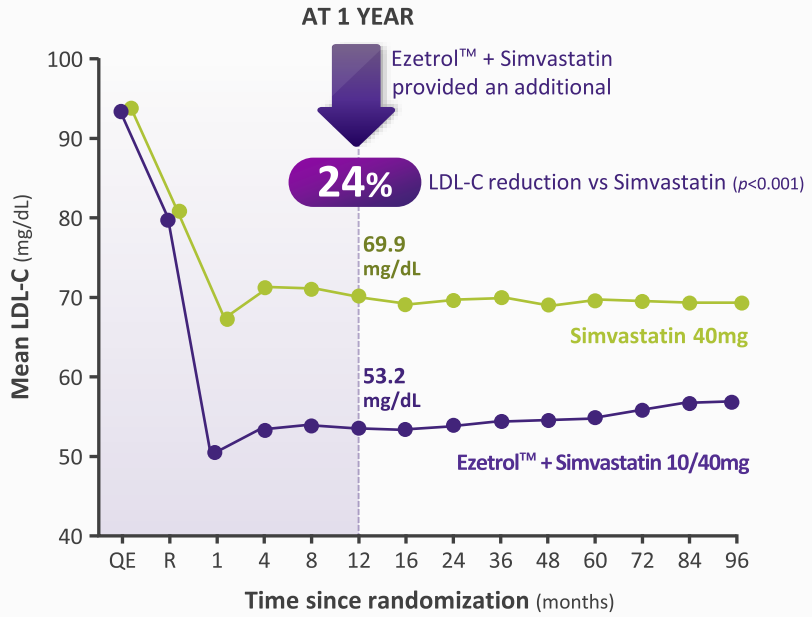
IMPROVE-IT trial

18,144 patients stabilized post ACS ≤ 10 days: LDL-C 50–125*mg/dL
(or 50–100**mg/dL if prior lipid-lowering Rx)

- **Ezetrol™/simvastatin 10/40 mg**
- **Simvastatin 40 mg**

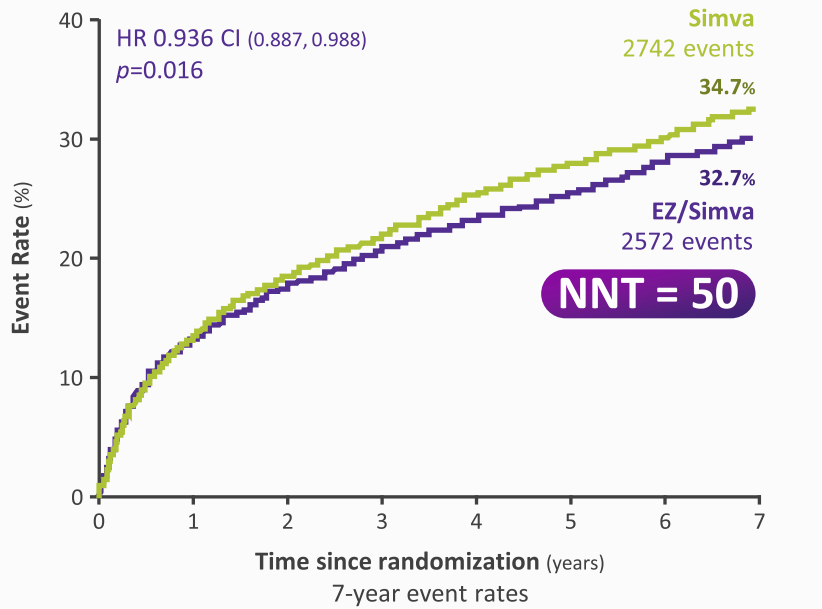
Primary Endpoint:
CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization)**, or stroke**
Duration: Minimum 2½--year follow-up (at least 5250 events)

Change of LDL-cholesterol[4,5]



Adapted from Cannon CP, *et al.*

Primary Endpoint[4]



Adapted from Cannon CP, *et al.*

* 3.2mM, ** 2.6mM

ACS : Acute Coronary Syndrome, MI : Myocardial infarction, HR : Hazzard Ratio, UA : Unstable angina, LDL-C : Low density lipoprotein-cholesterol, CI : Confidence interval, NNT : Number needed to be treated, CV : Cardiovascluar

1. Cannon CP, *et al*. Rationale and design of IMPROVE-IT. *AHJ*. 2008;156:826-32 2. Califf RM, *et al*. Premature Release of Data from Clinical Trials of Ezetrol™. *New England Journal of Medicine*. 2009;361:712-717
3. Blazing MA, *et al*. Evaluating cardiovascular event reduction with Ezetrol™ as an adjunct to simvastatin in 18,144 patients after acute coronary syndromes: Final baseline characteristics of the IMPROVE-IT study population. *AHJ*. 2014;168:205-12 4. Cannon CP, Blazing MA, Giugliano RP, *et al*; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372(25):2387–2397
5. Cannon CP, *et al*. *N Engl J Med*. 2015;372(25):2387–2397; IMPROVEIT Main Study Results. http://www.timi.org/index.php?page=improve-it-timi-40-slide-sets. Accessed July 20, 2015.

How to lower LDL

High intensity statin monotherapy vs Moderate intensity statin ezetimibe combination

Moderate intensity statin+EZ vs High intensity statin

Articles

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

Byeong-Keuk Kim, Sung-Jin Hong*, Yong-Joon Lee, Soon Jun Hong, Kyeong Ho Yun, Bum-Kee Hong, Jung Ho Heo, Seung-Woon Rha, Yun-Hyeong Cho, Seung-Jun Lee, Chul-Min Ahn, Jung-Sun Kim, Young-Guk Ko, Donghoon Choi, Yangsoo Jang, Myeong-Ki Hong, on behalf of the RACING investigators†*

Moderate intensity statin+EZ vs High intensity statin

RACING trial

Moderate intensity statin+ezetimibe vs high dose statin

ASCVD(previous MI, ACS, history of coronary revascularisation or other arterial revascularisation procedures, ischaemic stroke, or PAD)

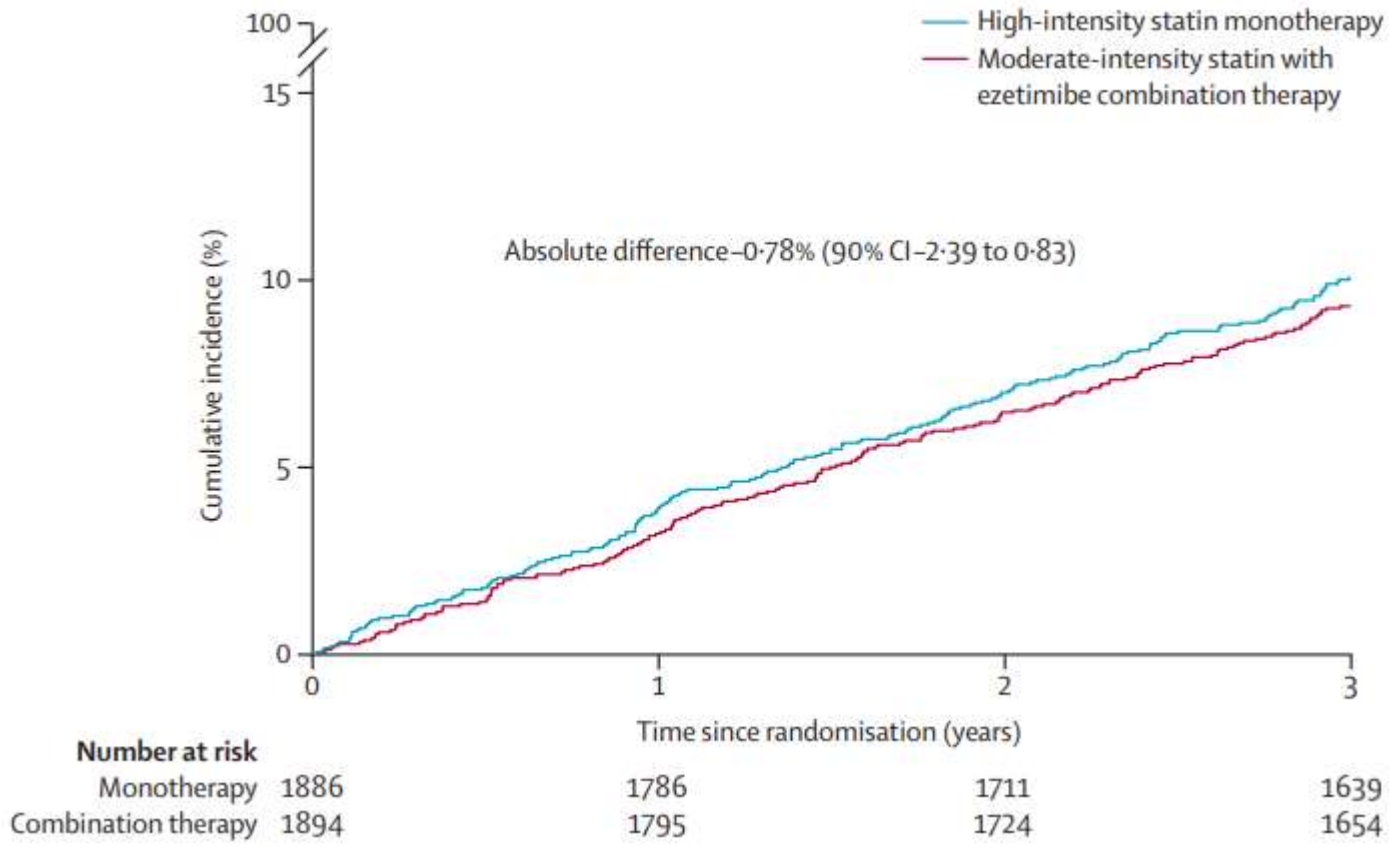
Rosuvastatin 10mg with ezetimibe vs rosuvastatin 20mg
1,894 combination therapy vs 1,886 monotherapy

Primary endpoint: 3-year composite of CV death, major CV events, or non-fatal stroke, in the intention-to-treat population with a non-inferiority margin of 2.0%

Byeong-Keuk Kim et al Lancet 2022

Moderate intensity statin+EZ vs High intensity statin

Moderate-intensity statin with ezetimibe combination therapy was **non-inferior** to high-intensity statin monotherapy for the 3-year composite outcomes



Byeong-Keuk Kim et al Lancet 2022

Moderate intensity statin+EZ vs High intensity statin

DC or dose reduction due to adverse events or intolerance **lower** in 88 pts (4·8%) in the combination group & 150 pts (8·2%) in monotherapy group (p<0·0001)

	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**

Byeong-Keuk Kim et al Lancet 2022

Moderate intensity statin+EZ 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)

ng-Keuk Kim et al Lancet 2022

2021 EAS Task force statement

Recently, the EAS TF announced a statement that **Statin/Ezetimibe combination therapy is needed from the beginning to reach target LDL-C in very-high risk groups (ASCVD, FH).**

Atherosclerosis 325 (2021) 99–109

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journal homepage: www.elsevier.com/locate/atherosclerosis

From the EAS

Practical guidance for combination lipid-modifying therapy in high- and very-high-risk patients: A statement from a European Atherosclerosis Society Task Force

A B S T R A C T

Background and aims: This European Atherosclerosis Society (EAS) Task Force provides practical guidance for combination therapy for elevated low-density lipoprotein cholesterol (LDL-C) and/or triglycerides (TG) in high-risk and very-high-risk patients.

Methods: Evidence-based review.

Results: Statin-ezetimibe combination treatment is the first choice for managing elevated LDL-C and should be given upfront in very-high-risk patients with high LDL-C unlikely to reach goal with a statin, and in primary prevention familial hypercholesterolaemia patients. A proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor may be added if LDL-C levels remain high. In high and very-high-risk patients with mild to moderately elevated TG levels (>2.3 and < 5.6 mmol/L [>200 and < 500 mg/dL) on a statin, treatment with either a fibrate or high-dose omega-3 fatty acids (icosapent ethyl) may be considered, weighing the benefit versus risks. Combination with fenofibrate may be considered for both macro- and microvascular benefits in patients with type 2 diabetes mellitus.

Conclusions: This guidance aims to improve real-world use of guideline-recommended combination lipid modifying treatment.

Ref. Practical guidance for combination lipid-modifying therapy in high- and very-high-risk patients: A statement from a European Atherosclerosis Society Task Force (atherosclerosis-journal.com)

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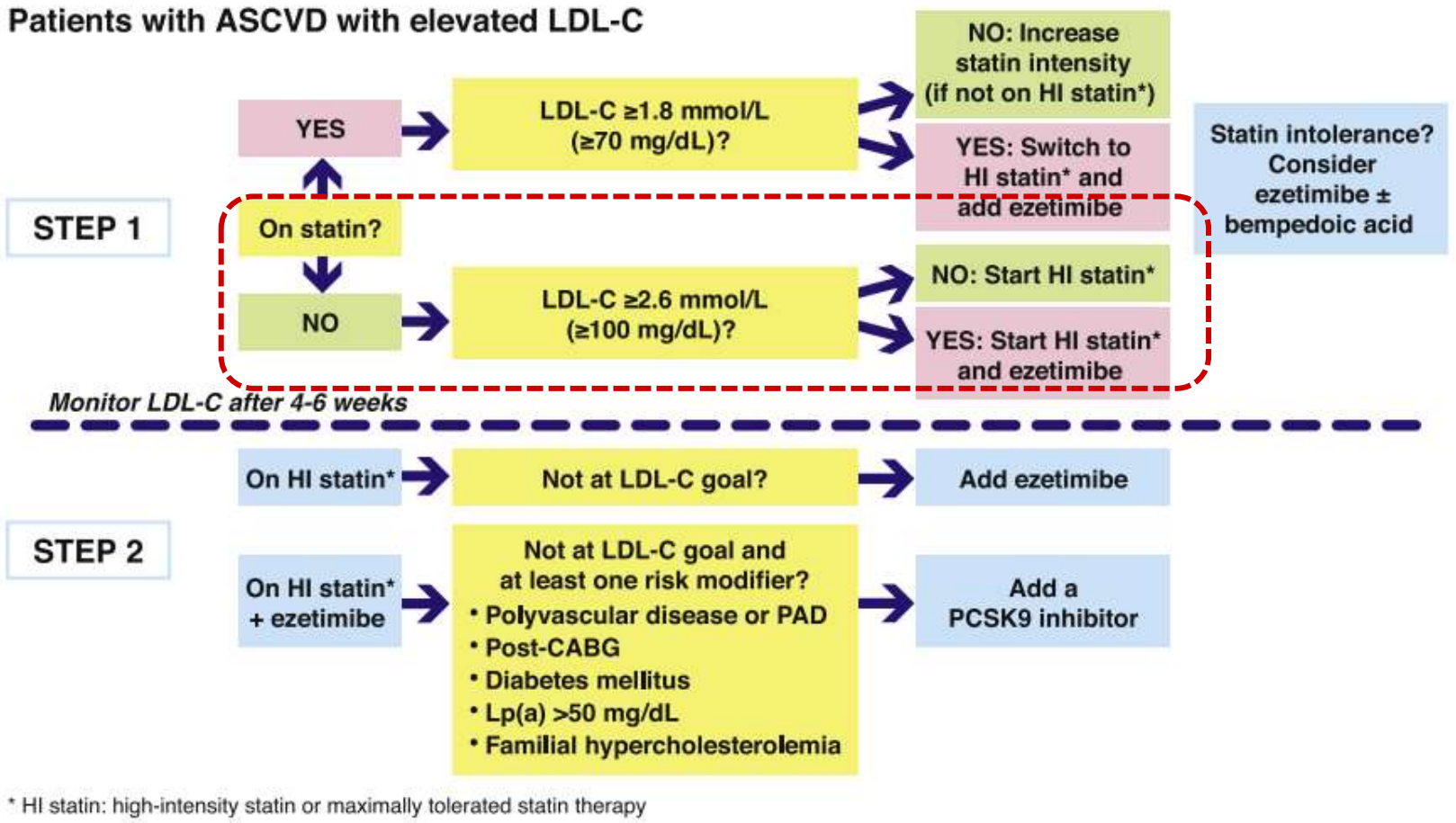
Algorithm for managing high LDL-C levels in ASCVD patients



1. Reduction of F/U period
2. Able to reach target in the shortest time
3. Positive impact of CV outcome

From the EAS. Maurizio Averna et al. Atherosclerosis. 2021

Today’s Contents

1. Current status of heart disease and the need for active LDL-C management

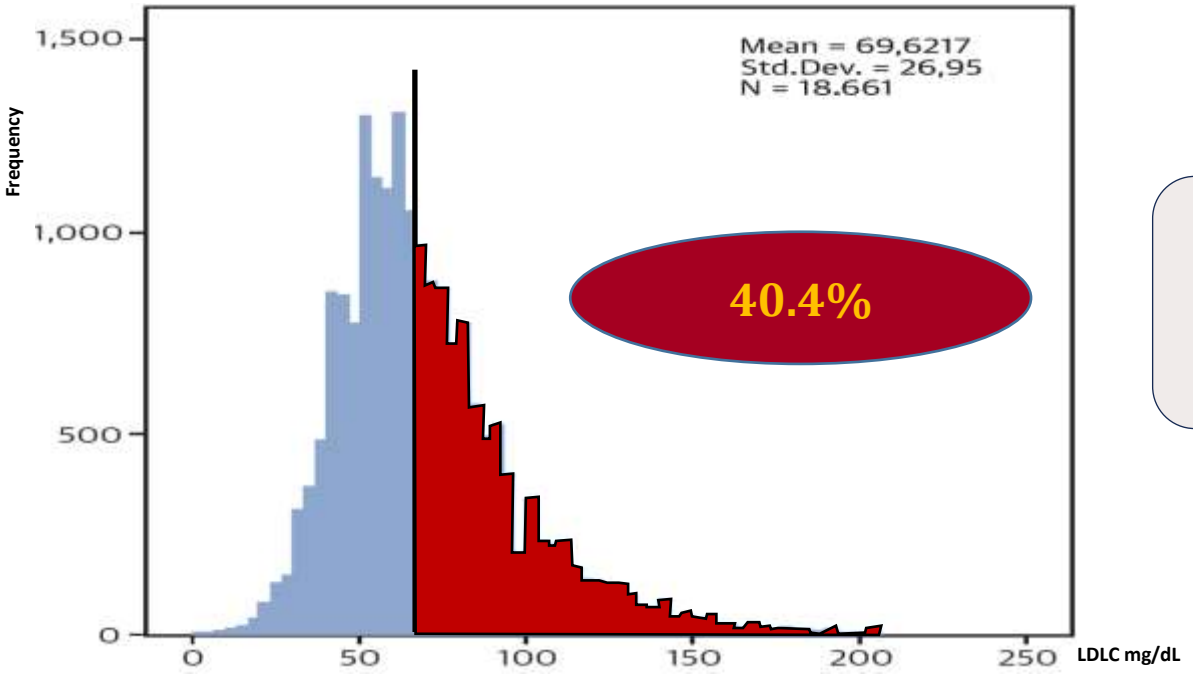
2. Latest guideline trend and Korean dyslipidemia guidelines

3. The ways to reach the goal

4. Treatment gaps

Residual CV risk in high-intensity statin therapy

- **Achieved on-statin LDL-C in meta-analysis of 4 RCTs of high-dose* therapy.**



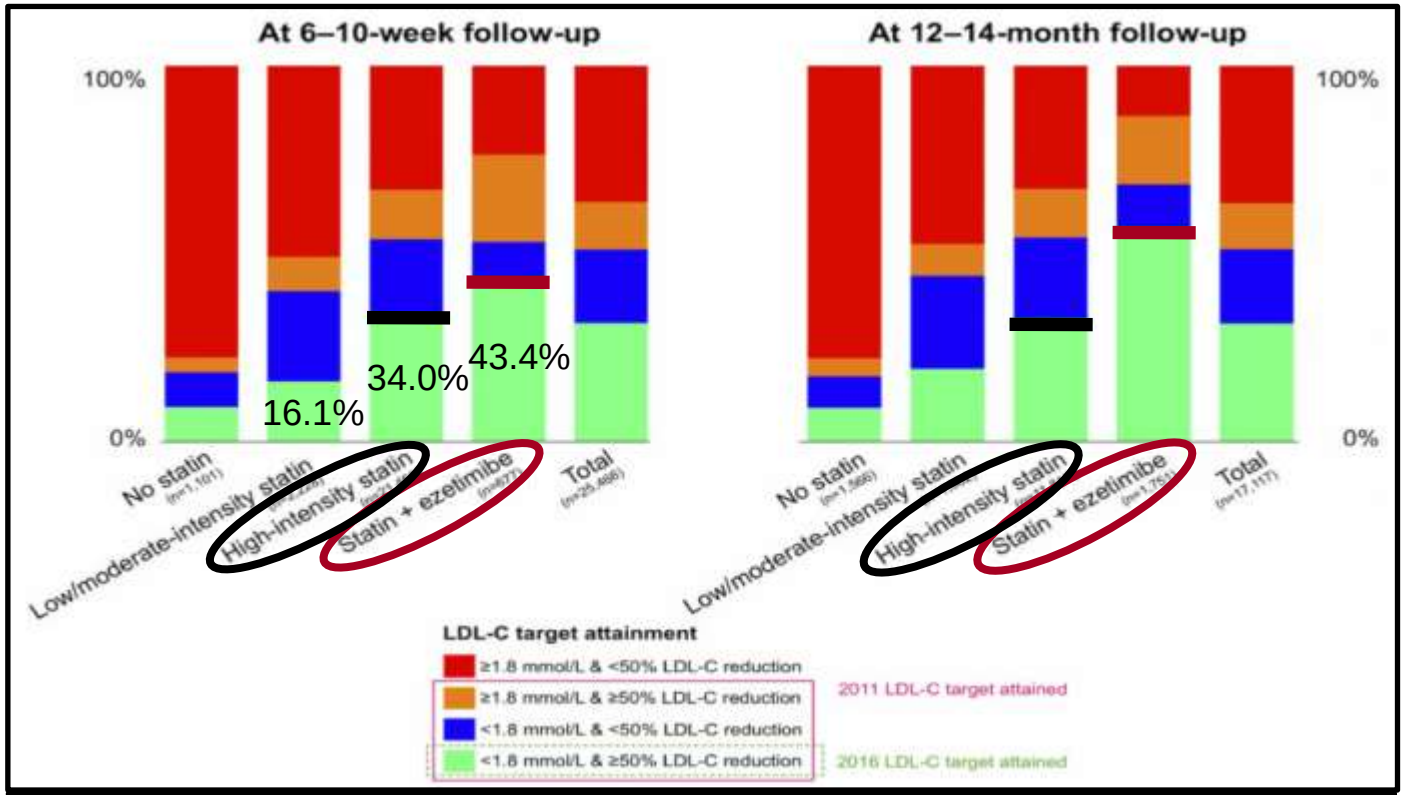
40.4% of statin trial participants assigned to high-dose therapy did not reach an LDL-C concentration below 70 mg/dL.

[a]Post-hoc, meta-analysis evaluated 38,153 patients (155,573 PY) from eight, controlled statin studies (4S, AFCAPS-TexCAPS, LIPID, CARDS, TNT, IDEAL, SPARCL, JUPITER) to determine the proportion of patients who achieved LDL goals and the association with cardiovascular risk. [b]Major CV events defined as fatal or nonfatal MI, fatal "other CHD," hospitalization for unstable angina, or fatal or nonfatal stroke. [c]Adjusted for sex, age, smoking status, presence of diabetes, systolic blood pressure, high-density lipoprotein cholesterol concentration, and trial. HR = hazard ratio; PY = person-years; CV = cardiovascular; LDL-C = low-density lipopro teins cholesterol; RCT = randomized controlled trial. **1**.Boekholdt et al. *J Am Coll Cardiol.* 2014;64:485-94. **2.** Agabiti Rosei E et al. *High Blood Press Cardiovasc Prev*. 2016;23:217-230.

In LDL-C management for MI patients, the rate of reaching the target goal of statin ezetimibe combination therapy is relatively high, and the number of prescription patients tends to increase over time.

nationwide registers, n=44,890, aged 21–74 admitted for MI, 2013–17

2016년:
LDLC
<70mg/dL **and**
≥50% reduction

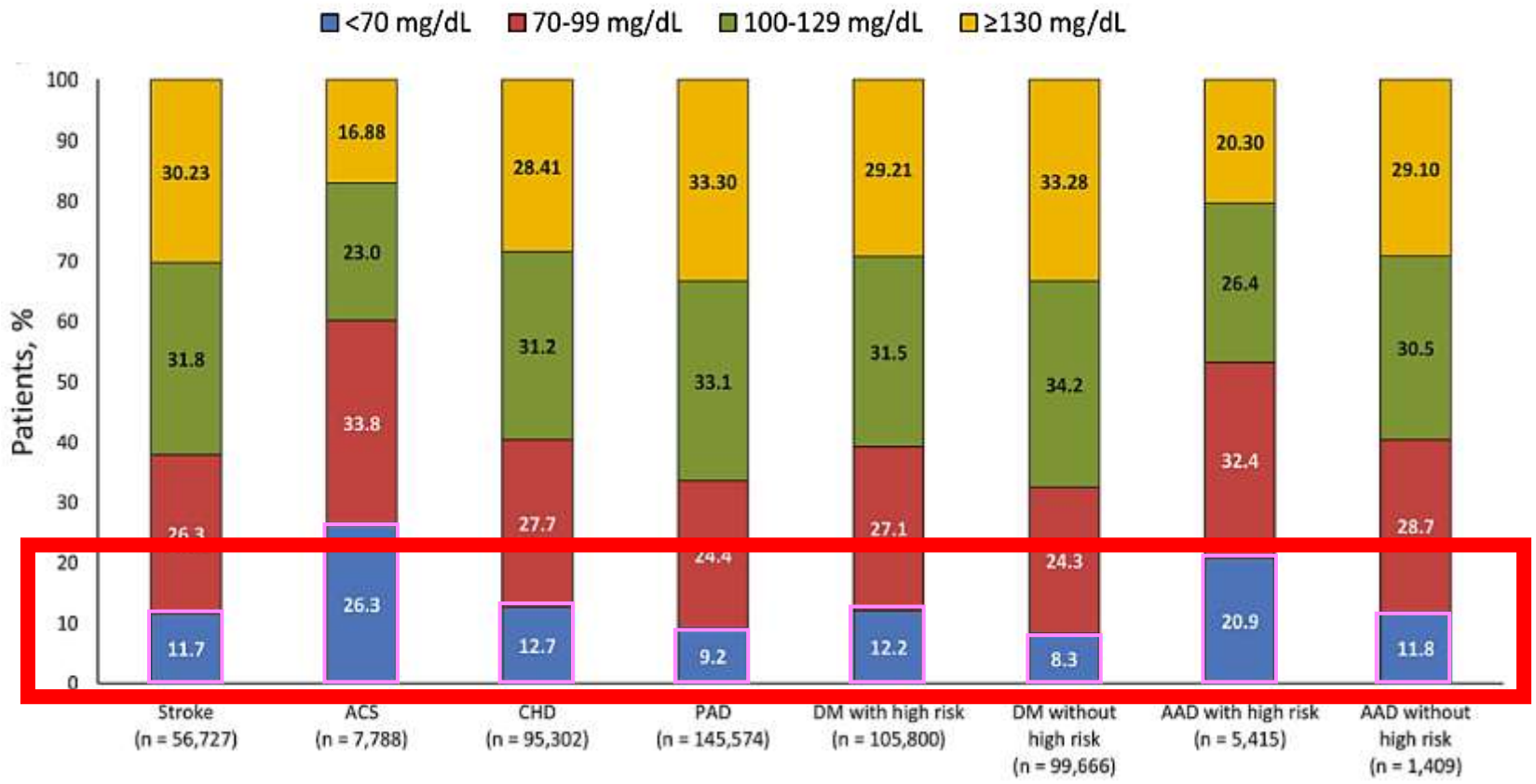


Achievement of an LDL-C level of <1.8 mmol/L and a >_50% reduction in LDL-C level by category of lipid-lowering therapy at 6–10 weeks and 12–14 months after myocardial infarction. LDL-C, low-density lipoprotein cholesterol.

Eur Heart J Qual Care Clin Out 2021;7:59-67

Less than 50% of Korean high-risk patients achieved LDL-C goal

LDL-C goal attainment rates All patients (known + newly defined high-risk patients)

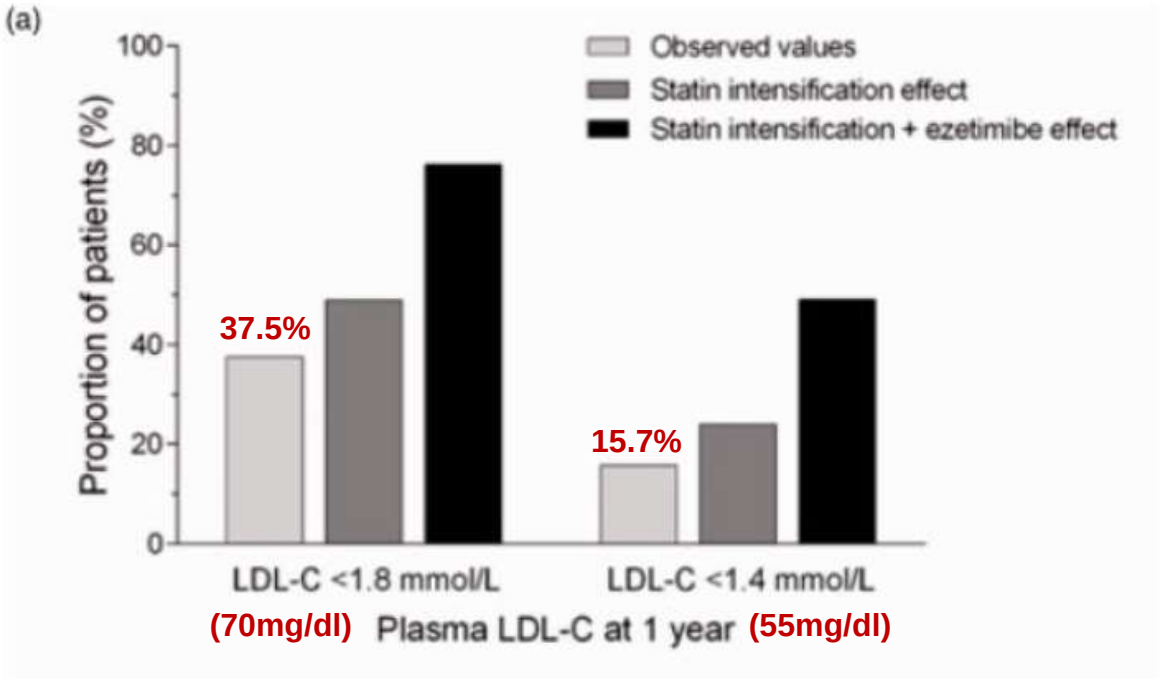


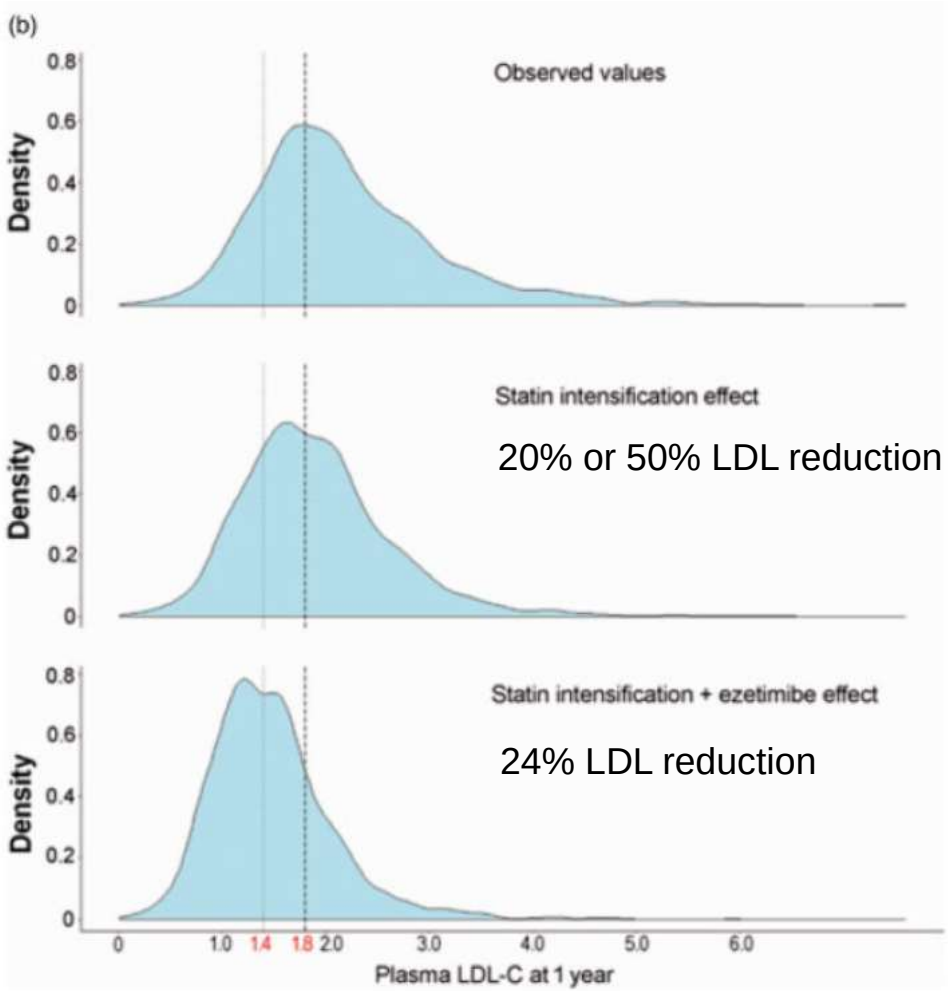
LDL-C target (mg/dL)	**< 70**	**< 70**	**< 70**	**< 70**	**< 70**	**< 100**	**< 70**	**< 100**

Ref. Yang YS, et al. Lipids in Health and Disease (2020) 19:5

Patients eligible for PCSK9i

ACS patients, n=2,521





Patients eligible for **PCSK9i** :

51% according to ESC/EAS criteria(LDL > 55mg)

14% according to ACC/AHA criteria(LDL > 70mg)

Konstantinos C Koskinas. et al. Eur J Prev Cardiol. 2021

Take home message

1 Active management of LDL-C continues to be emphasized to prevent heart disease

Heart disease is the second leading cause of death in Korea, and the number of patients with hyperlipidemia, the main cause, is continuously increasing.
In the fact sheet newly announced at KSoLA in 2022, the prevalence rate continues to increase, and 1 in 4 adults
Is a patient with dyslipidemia.

2 Domestic treatment guidelines have also been updated to recommend more aggressive LDL-C control.

Domestic dyslipidemia treatment guidelines have also been changed to recommend active control.
For patients with coronary artery disease, it is 55 mg/dl or less, and 70 mg/dl for other high-risk patients
50% reduction in LDL-C is recommended. In addition, it is recommended that patients with diabetes be controlled to 70 mg/dl or less if the duration of illness is more than 10 years.

3 The usefulness of EZETIMIBE combination to reach the target exists

In clinical practice, it is showing the usefulness of long-term control through the use of Ezetimibe.
Ezetimibe is a means to reduce the risk of side effects and to achieve the LDL-C target more strongly.

4 Considerable portion of very high risk patients did not achieve target LDL level

Treatment gap still exists in reality. In the 2021 ESC Statement, mentioned that the use of ezetimibe should be considered in order to quickly reach the target goal.

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