What are the real-world issue to keep LDL-C lower for longer

Gyeongsang National University Hospital
Seok-Jae, Hwang

ORGANON

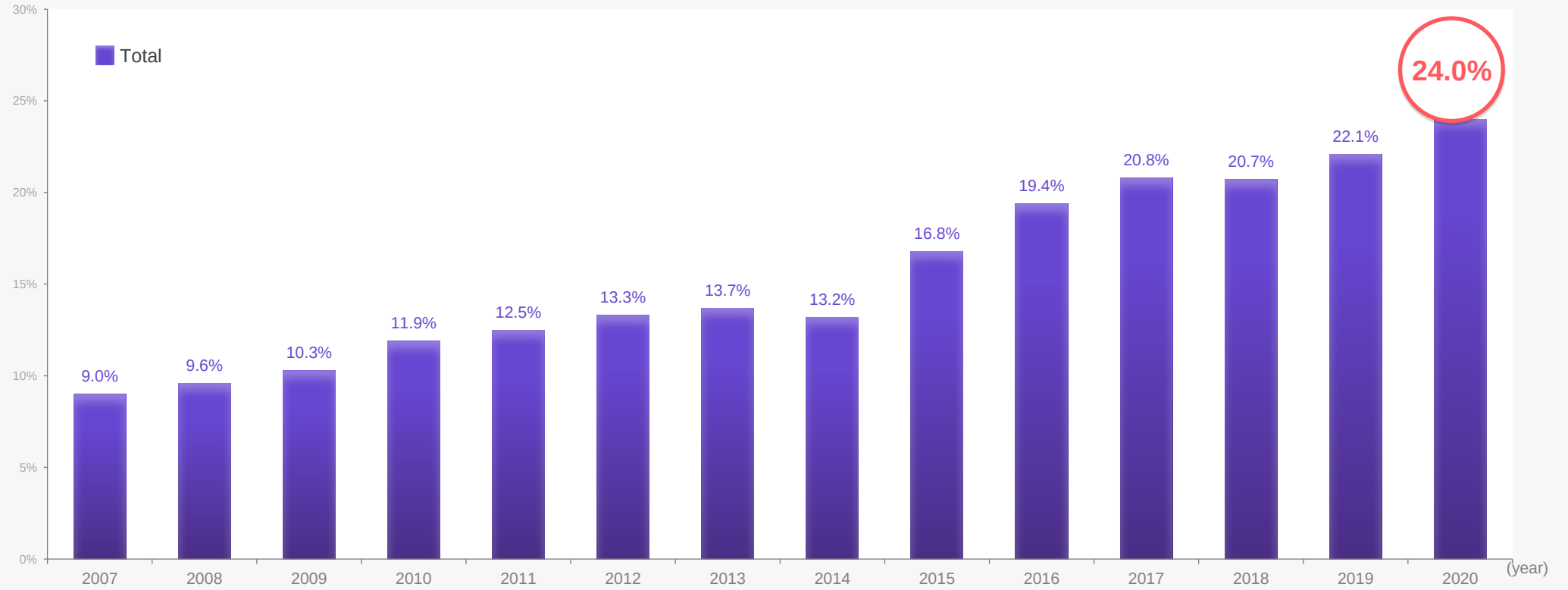
LDL-C : Low-density lipoprotein cholesterol

Contents

Dyslipidemia in Korea

- Hypercholesterolemia is steadily increasing. Nearly 1 out of 4 adults has hypercholesterolemia.

Crude prevalence of hypercholesterolemia



Adapted from KSoLA.[1]

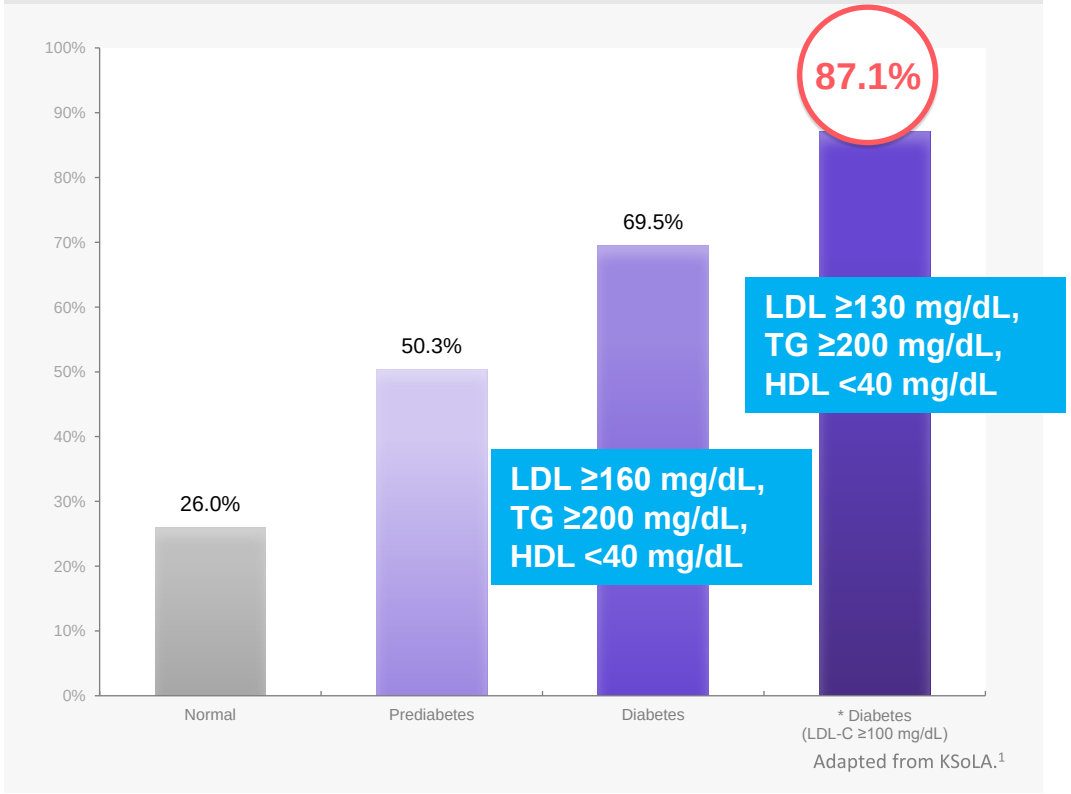
Data: 2007-2020 KNHANES; adults aged 20+ years
Hypercholesterolemia: total cholesterol ≥240 mg/dL or taking a lipid-lowering drug.

Reference 1. The Korean Society of Lipid and Atherosclerosis (KSoLA). *Dyslipidemia fact sheet in Korea*. 2022.

Dyslipidemia according to comorbidity status in Korea

- Almost 90% of people with diabetes have dyslipidemia.

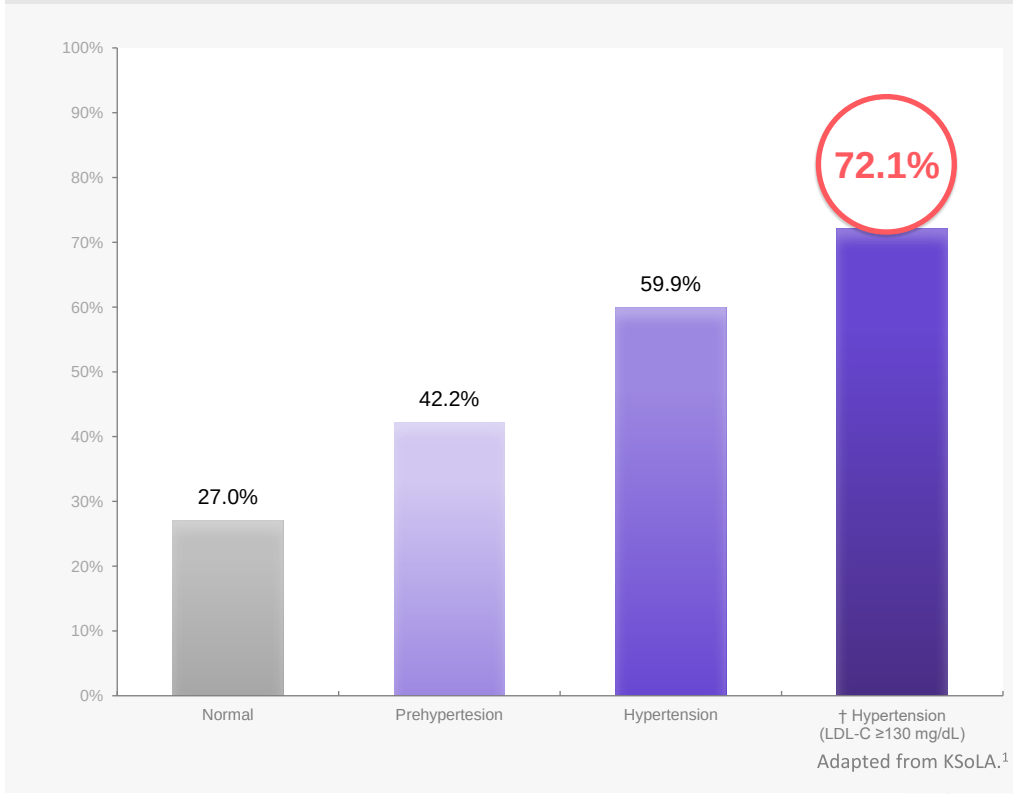
Dyslipidemia in adults with diabetes



Data: 2016-2020 KNHANES; adults aged 20+ years
Prediabetes: fasting glucose 100-125 mg/dL or HbA1c 5.7-6.4%
Diabetes: fasting glucose ≥126 mg/dL, HbA1c ≥6.5%, previously diagnosed, or taking glucose-lowering drugs or insulin
Dyslipidemia: LDL-cholesterol ≥160 mg/dL, triglyceride ≥200 mg/dL, HDL-cholesterol <40 mg/dL, or taking a lipid-lowering drug
* Dyslipidemia: LDL-cholesterol ≥100 mg/dL, triglyceride ≥200 mg/dL, HDL-cholesterol <40 mg/dL, or taking a lipid-lowering drug

- Almost 70% of people with hypertension have dyslipidemia.

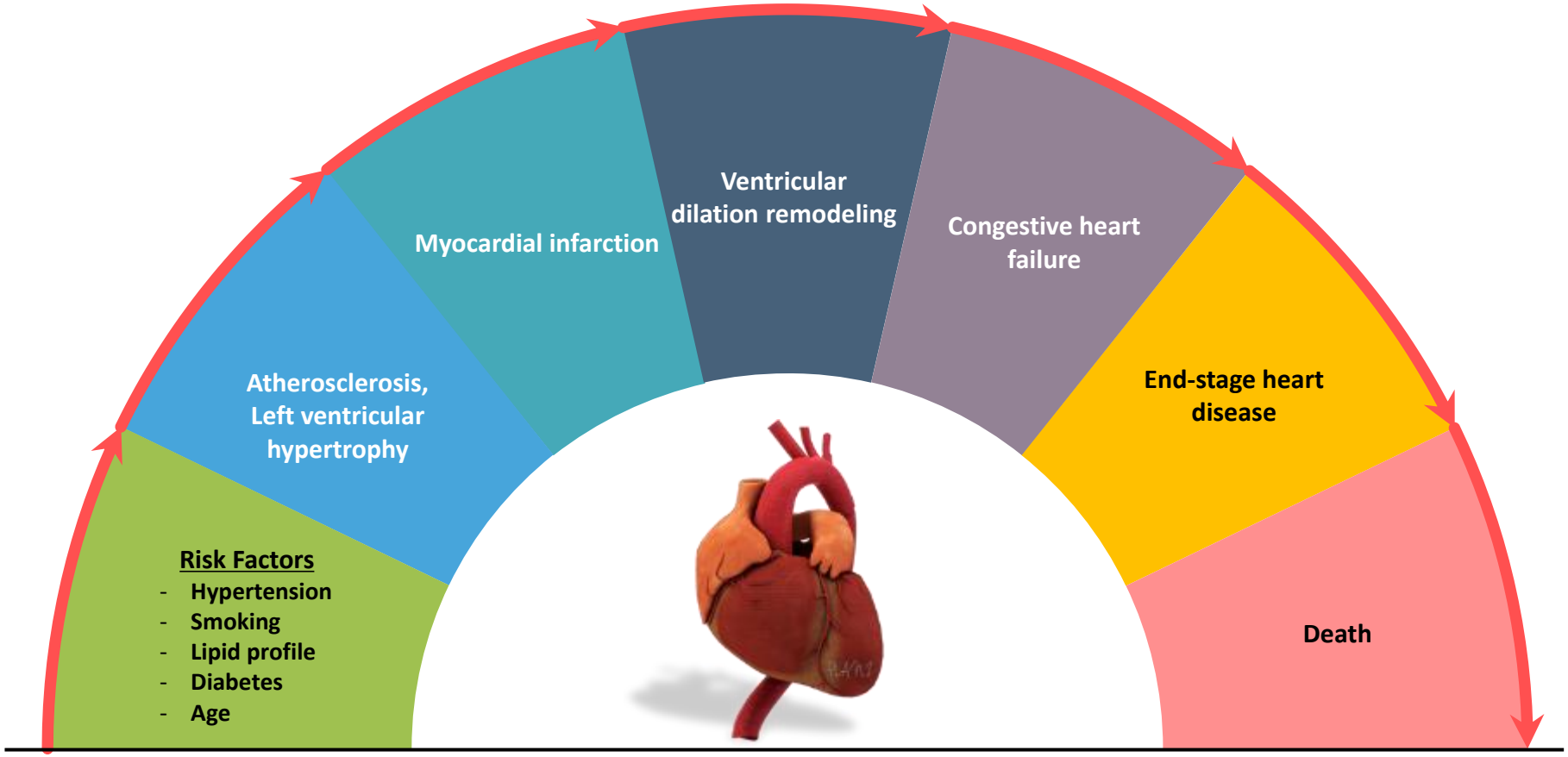
Dyslipidemia in adults with hypertension



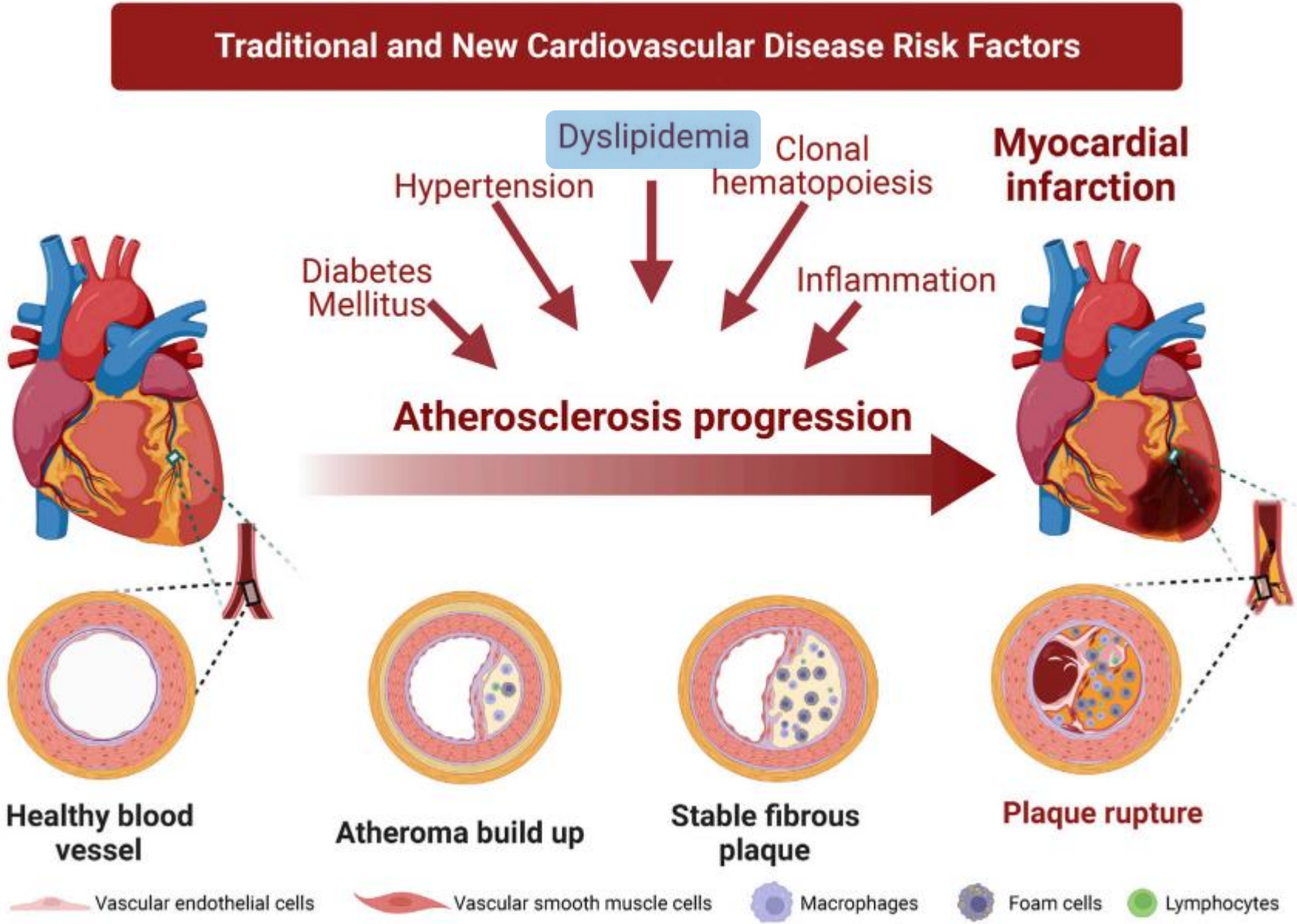
Data: 2016-2020 KNHANES; adults aged 20+ years
Prehypertension: SBP 120-139 mmHg or DBP 80-89 mmHg
Hypertension: SBP ≥140 mmHg, DBP ≥90 mmHg, or taking a BP-lowering drug
Dyslipidemia: LDL-cholesterol ≥160 mg/dL, triglyceride ≥200 mg/dL, HDL-cholesterol <40 mg/dL, or taking a lipid-lowering drug
† Dyslipidemia: LDL-cholesterol ≥130 mg/dL, triglyceride ≥200 mg/dL, HDL-cholesterol <40 mg/dL, or taking a lipid-lowering drug

Reference 1. The Korean Society of Lipid and Atherosclerosis (KSoLA). *Dyslipidemia fact sheet in Korea*. 2022.

A sequence of cardiovascular events, Cardiovascular Disease Continuum

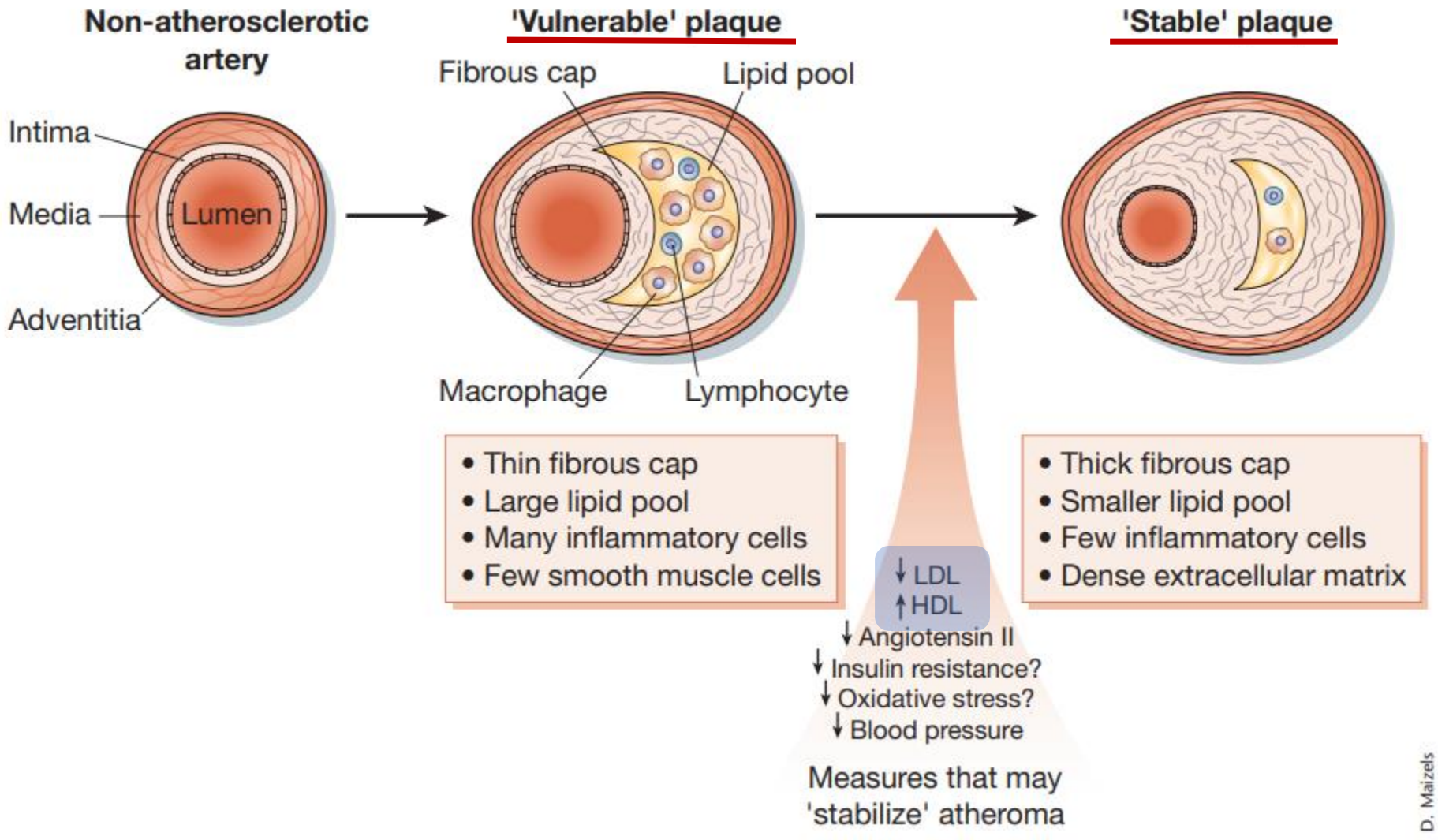


Ref. Dzau V et al. Am Heart J. 1991;121:1244-1263.



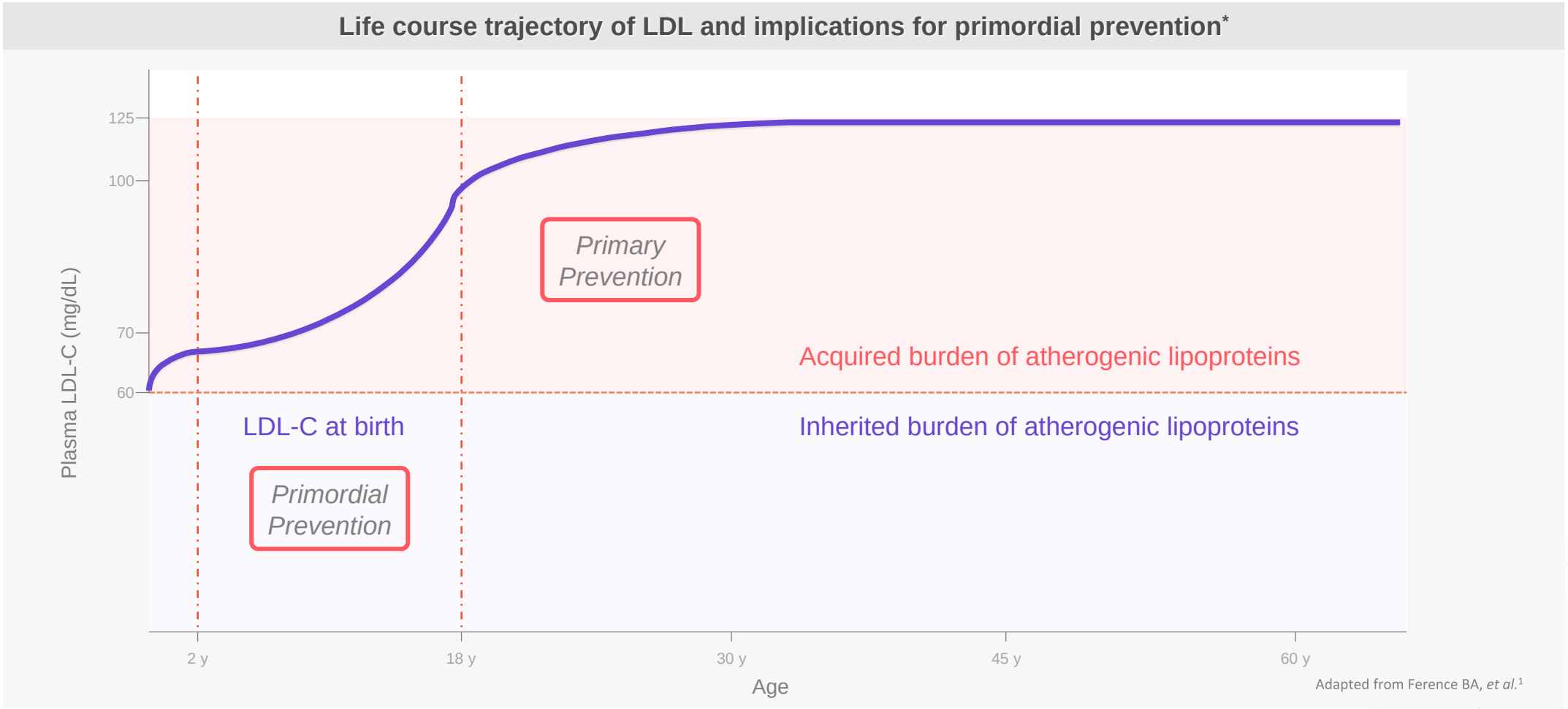
Isabella Hetherington et al. Molecular Therapy. 2022

Plaque stabilization by lipid lowering therapy



PETER LIBBY et al. Nat Med. 2002

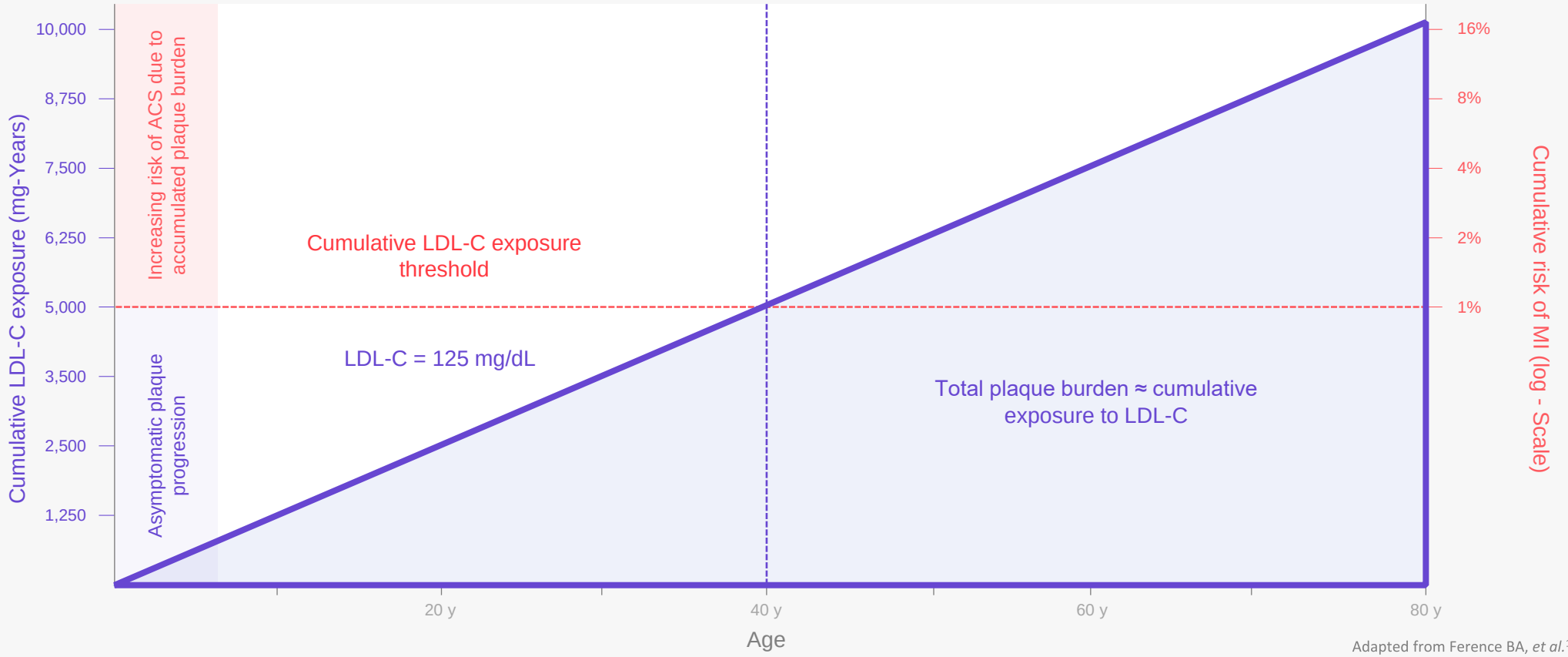
2 strategies to prevent cardiovascular events by keeping low LDL-C and other apo B



Reference 1. Ference BA, *et al.* Impact of Lipids on Cardiovascular Health: JACC Health Promotion Series. *J Am Coll Cardiol.* 2018 Sep 4;72(10):1141-1156.

Effect of cumulative exposure to LDL

Effect of cumulative exposure to LDL on plaque burden and risk of cardiovascular disease*

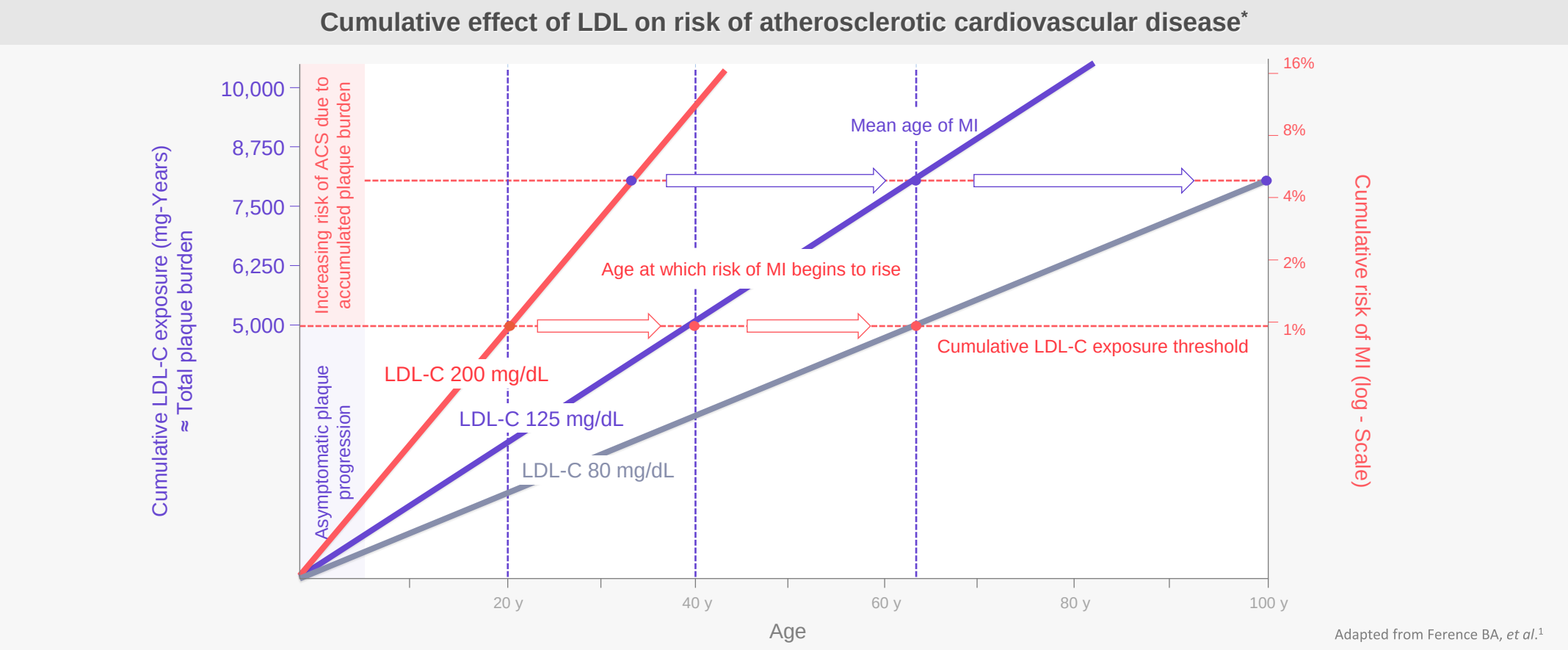


Adapted from Ference BA, *et al.*[1]

Reference 1. Ference BA, *et al.* Impact of Lipids on Cardiovascular Health: *JACC* Health Promotion Series. *J Am Coll Cardiol.* 2018 Sep 4;72(10):1141-1156.

Legacy effect (early and intensive control)

- Total atherosclerotic plaque burden is proportional to person's cumulative exposure to LDL and other apo B.



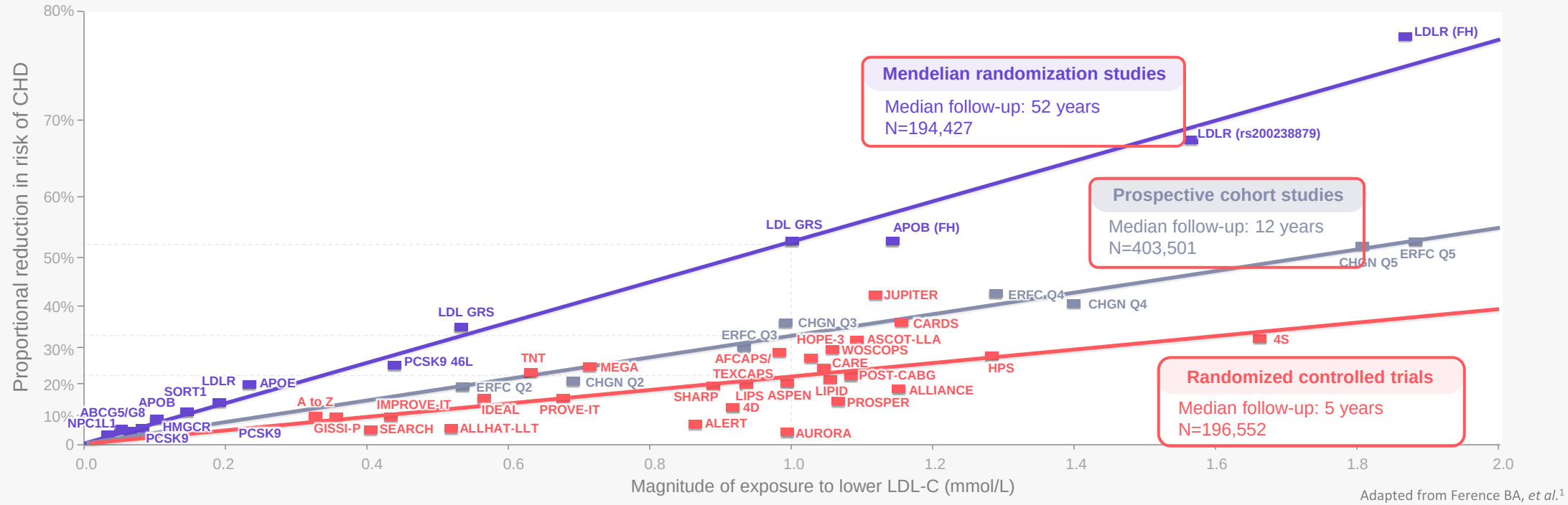
Reference 1. Ference BA, *et al.* Impact of Lipids on Cardiovascular Health: *JACC* Health Promotion Series. *J Am Coll Cardiol.* 2018 Sep 4;72(10):1141-1156.

Mendelian Randomization

Lower is Better ➔ *Early & Lower for Longer*

- The increasingly steeper slope of the log-linear association with increasing length of follow-up time implies that LDL-C has both a causal and a cumulative effect on the risk of cardiovascular disease.

Change in LDL-C and the risk of cardiovascular disease

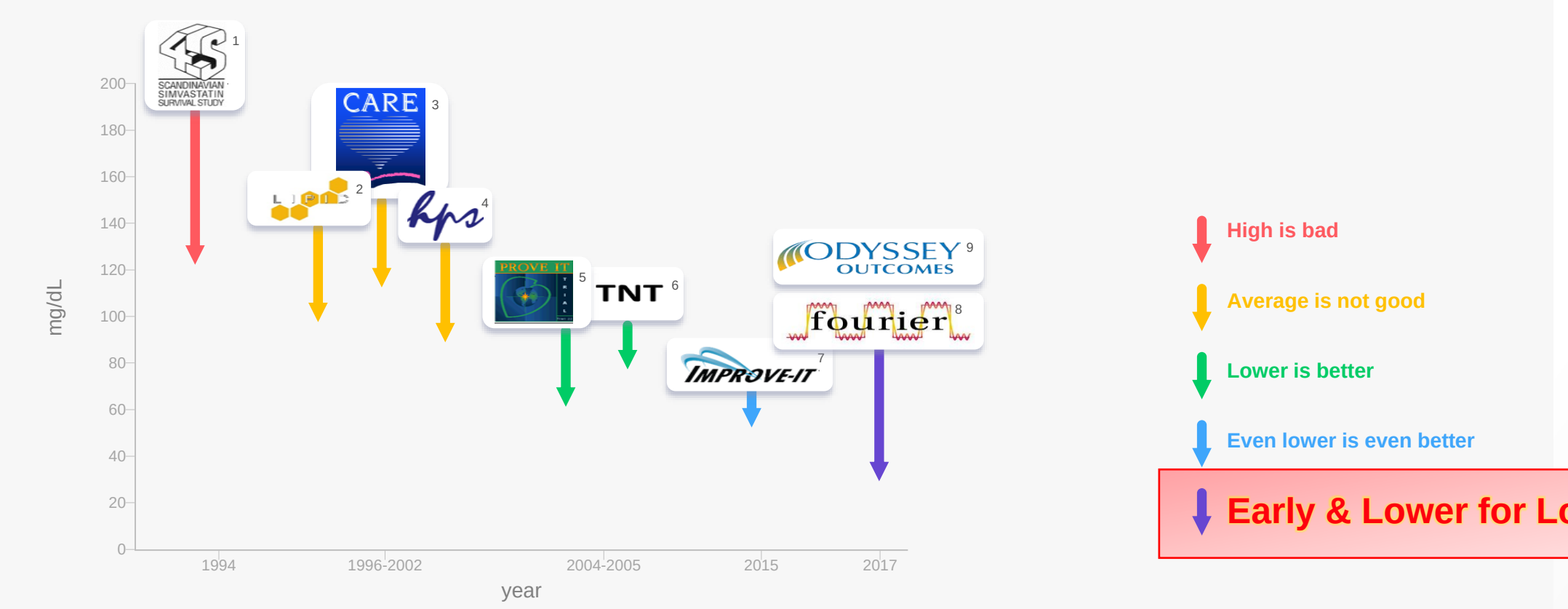


Adapted from Ference BA, *et al.*[1]

Reference 1. Ference BA, *et al.* Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J*. 2017 Aug 21;38(32):2459-2472.

Changes in LDL-C Control Concept

- Further LDL-C reduction below the target gives additional CV benefit.

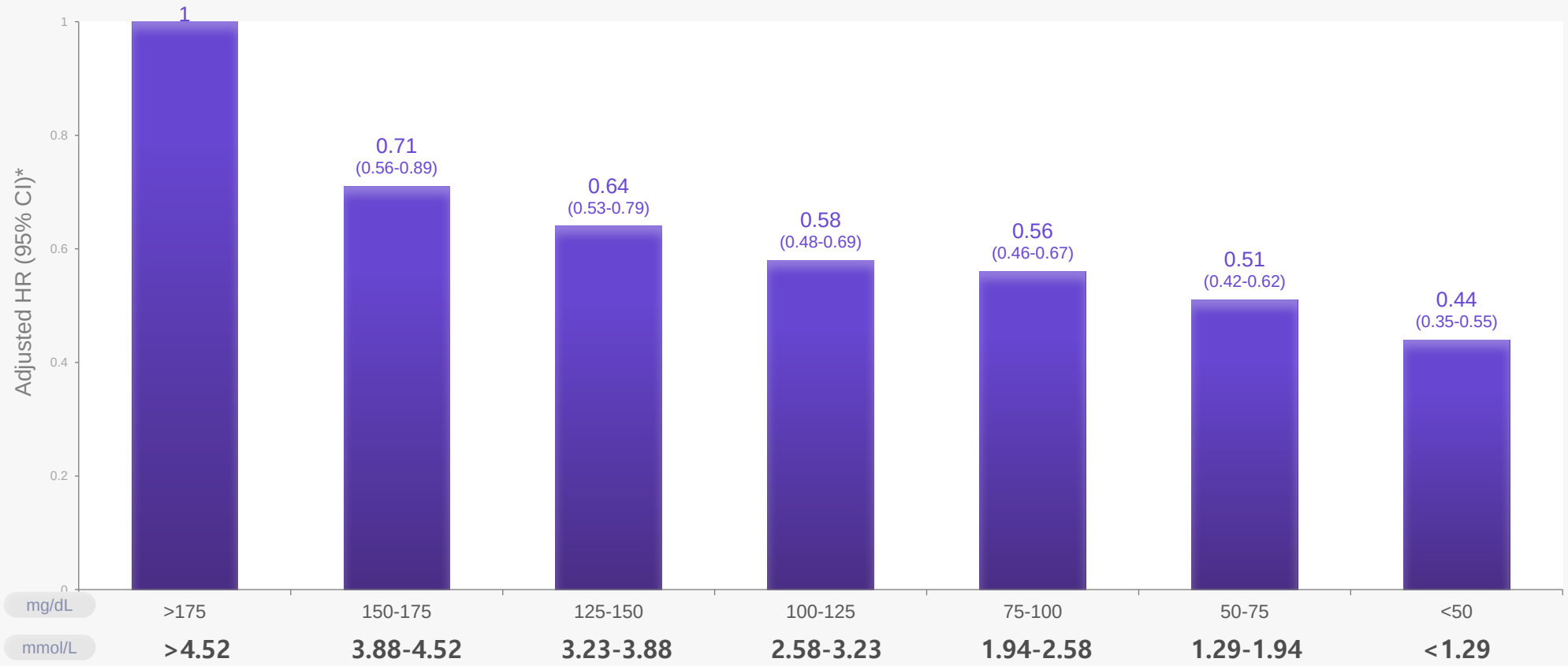


LDL-C : Low-density lipoprotein cholesterol, **CV** : Cardiovascular, **4S** : Scandinavian Simvastatin Survival Study; **LIPID** : Long-term Intervention with Pravastatin in Ischaemic Disease; **CARE** : Cholesterol and Recurrent Events; **HPS** : Heart Protection Study; **PROVE-IT** : PRavastatin or atOrVastatin Evaluation and Infection Therapy; **TNT** : Treating to New Targets; **IMPROVE-IT** : Improved Reduction of Outcomes: Vytorin Efficacy International Trial; **ODYSSEY Outcomes** : Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab; **FOURIER** : Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk

1. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet.* 1994 Nov 19;344(8934):1383-9. **2.** The Lipid Study Group. Design features and baseline characteristics of the LIPID (Long-Term Intervention with Pravastatin in Ischemic Disease) study: a randomized trial in patients with previous myocardial infarction and/or unstable angina pectoris. *Am J Cardiol.* 1995;76:474-479. **3.** Pfeffer MA, *et al*. Cholesterol and Recurrent Events: a secondary prevention trial for normolipidemic patients. CARE Investigators. *Am J Cardiol.* 1995 Sep 28;76(9):98C-106C. **4.** Collins R, *et al*. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet*. 2003 Jun 14;361(9374):2005-16. **5.** Cannon CP, *et al.* Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350:1495-1504. **6.** LaRosa JC, *et al*. Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease. *N Engl J Med.* 2005;352:1425-35. **7.** Cannon CP, *et al.* Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med.* 2015 Jun 18;372(25):2387-97. **8.** Sabatine MC, *et al*. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med*. 2017 May 4;376(18):1713-1722. **9.** Schwartz GG, *et al*. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med.* 2018 Nov 29;379(22):2097-2107.

Even below LDL-C target further LDL-C reduction gives additional CV benefit

Risk for major CV events by achieved on-trial LDL-C levels



Reference 1. Boekholdt SM, *et al*. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. *J Am Coll Cardiol.* 2014;64:485-494.

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

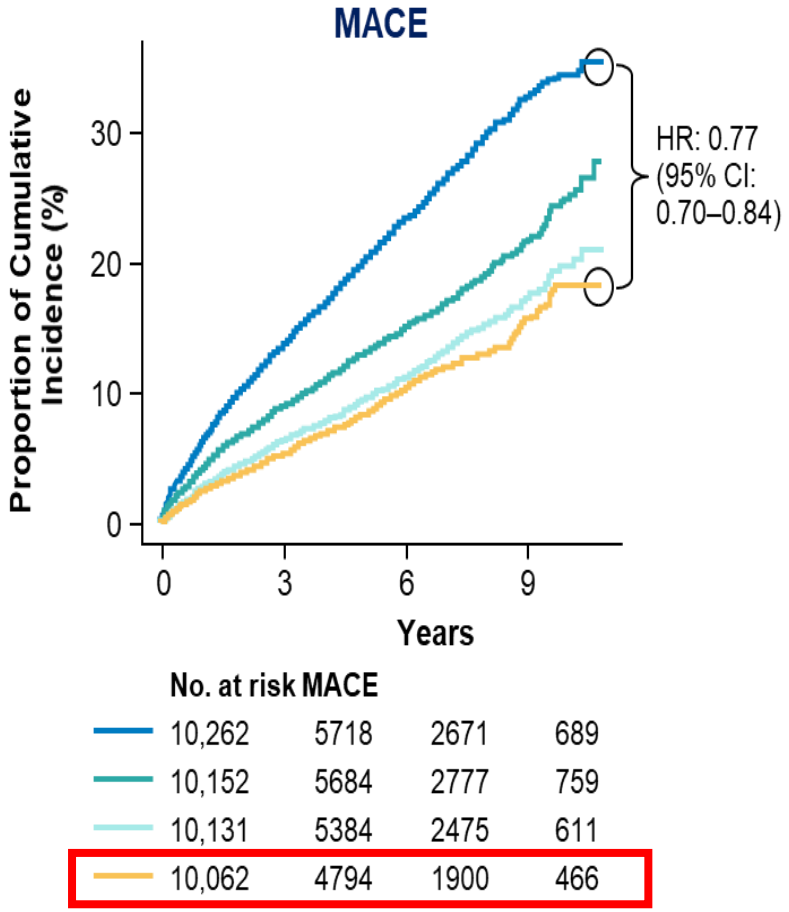
N = 40,607

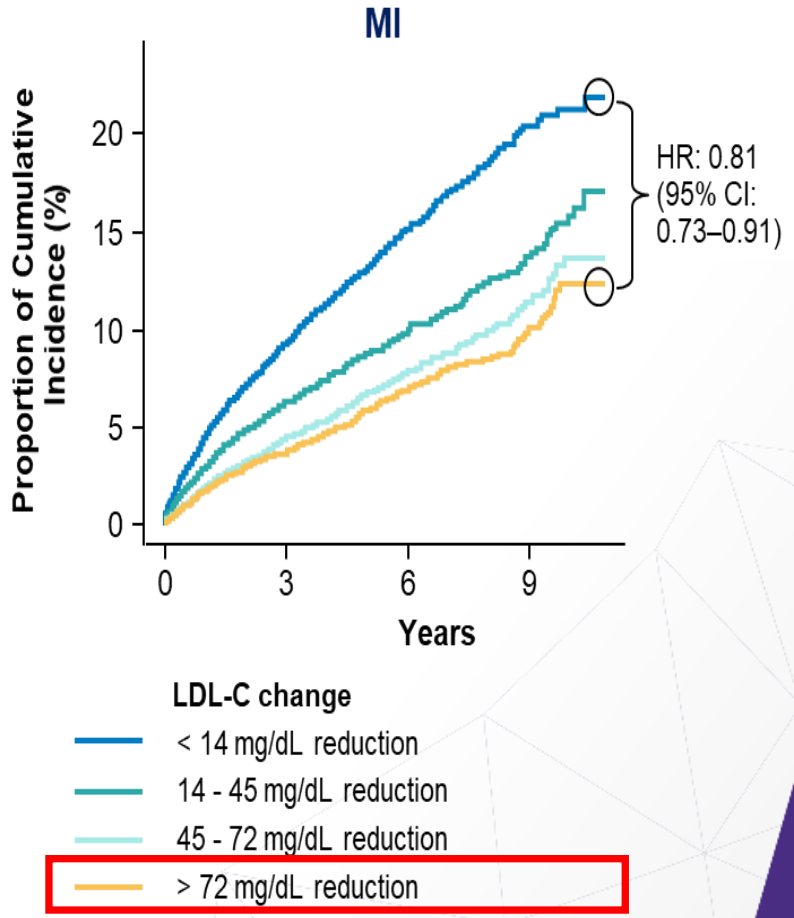
Population: 30–74 years of age admitted for MI in Sweden 2006–2016, alive at follow-up in cardiac rehab 6–10 weeks post-discharge

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



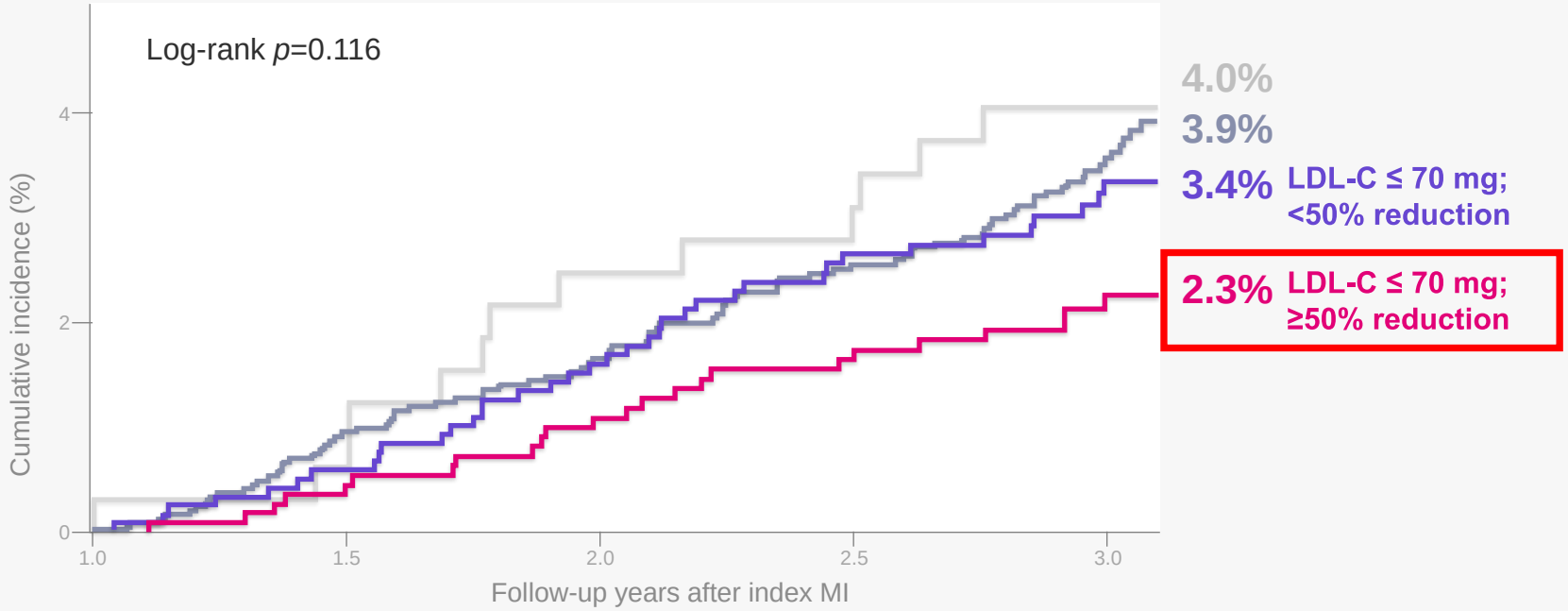


European Heart Journal (2021) 42, 243–252

A Korean Nationwide Cohort Study

Achieving both a ≥50% reduction and an LDL-C level ≤ 70 mg/dL for secondary prevention is crucial for improving clinical outcomes in post-MI patients.

Major adverse cardiac and cerebrovascular events



Number at risk						HR [95% CI]	*p*-value
LDL-C ≤ 70 mg/dL; ≥ 50% reduction	1114	1106	1080	1045	762	**Reference**	
LDL-C ≤ 70 mg/dL; < 50% reduction	1189	1180	1153	1102	805	**1.49 [0.90-2.49]**	**0.123**
LDL-C > 70 mg/dL; ≥ 50% reduction	324	322	316	307	220	**1.86 [0.95-3.65]**	**0.071**
LDL-C > 70 mg/dL; < 50% reduction	2422	2396	2346	2265	1616	**1.70 [1.08-2.66]**	**0.022**

Adapted from Kim JH, *et al.*

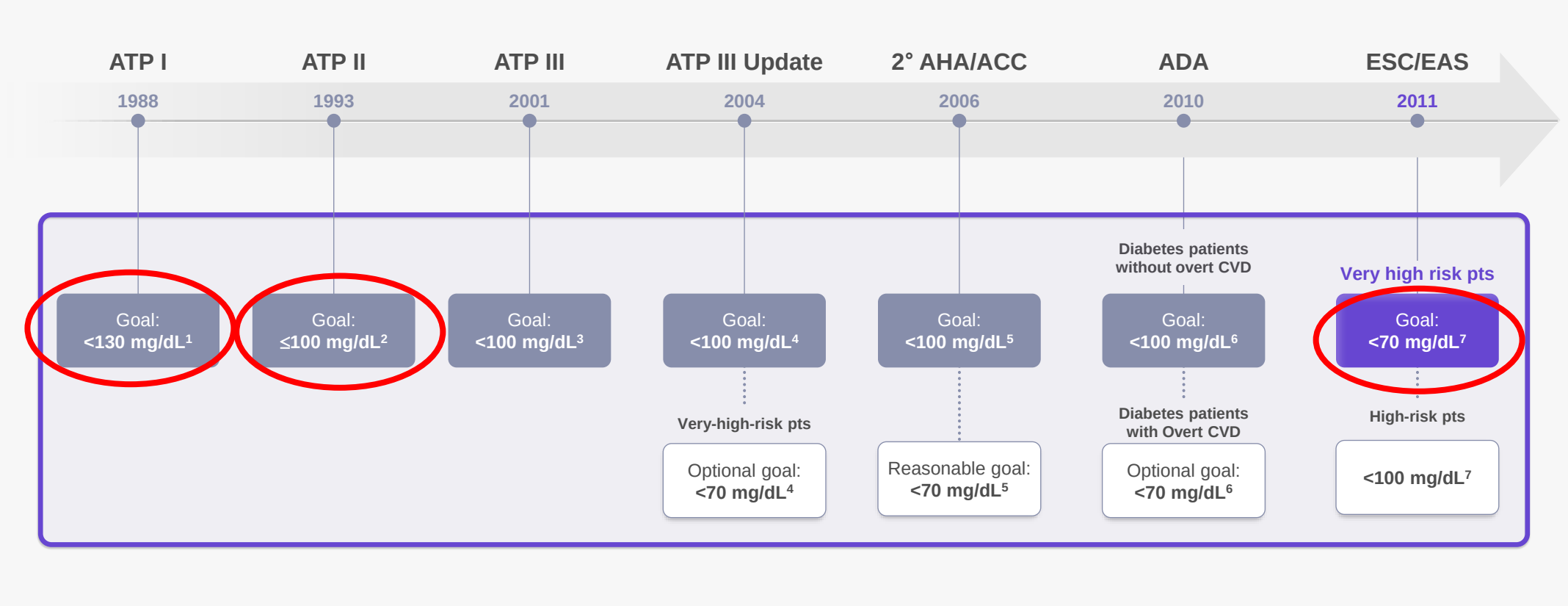
LDL-C : Low-density lipoprotein cholesterol, **MI :** Myocardial infarction, **HR :** Hazard ratio, **CI :** Confidence interval

Study design a. A Korean Nationwide Cohort Study was to investigate recurrent ASCVD events in post-MI patients who did or did not achieve LDL-C target goals and evaluate the relationship between LDL-C changes and clinical outcomes. From the Korea Acute Myocardial Infarction-National Institutes of Health registry, a total of 5,049 patients with both measurements of plasma LDL-C levels at index admission and at the one-year follow-up visit were identified from November 2011 to December 2015. Patients who achieved an LDL-C reduction ≥ 50% from the index MI and an LDL-C level ≤ 70 mg/dL at follow-up were classified as target LDL-C achievers. The primary endpoint was a two-year major adverse cardiac and cerebrovascular event (MACCE), including cardiovascular mortality, recurrent MI, and ischemic stroke.

1. Kim JH, *et al.* Target Low-Density Lipoprotein-Cholesterol and Secondary Prevention for Patients with Acute Myocardial Infarction: A Korean Nationwide Cohort Study. *J Clin Med.* 2022 May 8;11(9):2650.

More Intensive LDL-C Goals for High-Risk Patients

- As part of therapeutic lifestyle changes, including diet, **LDL-C treatment goals for high-risk patients have been lowered over time.**

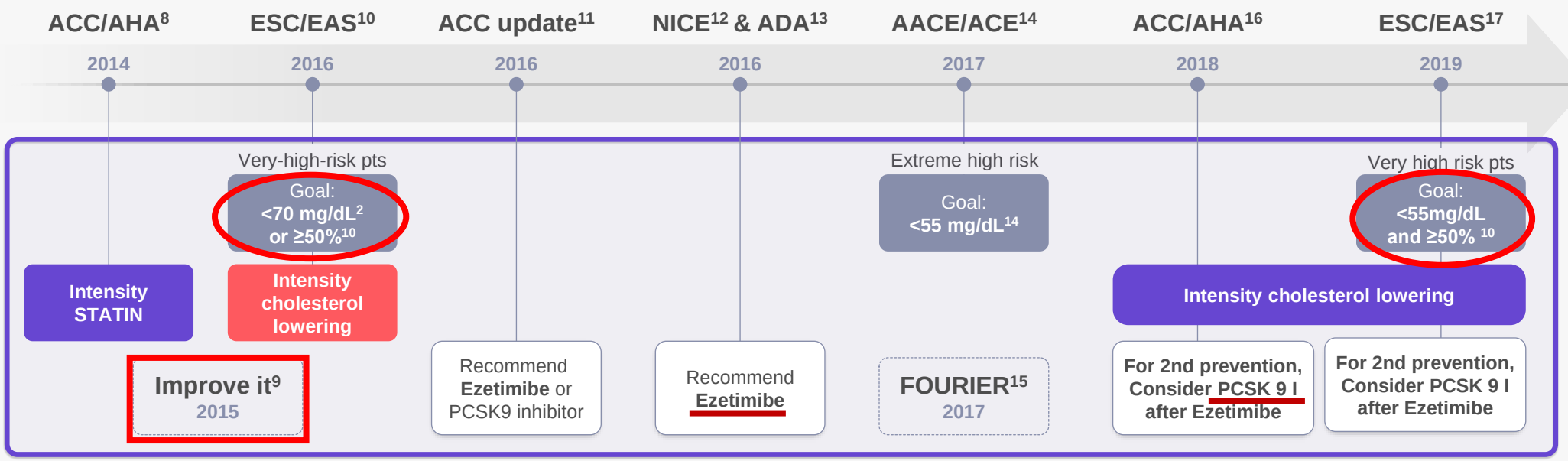


LDL-C : Low-density lipoprotein cholesterol, **ATP** : Adult Treatment Panel, **AHA/ACC** : American Heart Association/American College of Cardiology **ACS** : Acute coronary syndrome, **CVD** : Cardiovascular disease, **ESC :** European Society of Cardiology, **EAS** : European Atherosclerosis Society, **ADA** : American Diabetes Association,

1. Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. The Expert Panel. *Arch Intern Med.* 1988;148:36–69; **2.** Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). JAMA. 1993;269:3015–3023; **3.** Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA.* 2001;285:2486–2497; **4.** Grundy SM *et al.* Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation.* 2004;110:227–239; **5.** Smith SC Jr *et al.* AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. *Circulation*. 2006;113:2363–2372; **6.** ADA. Standards of medical care in diabetes—2010. Diabetes Care. 2010;33(suppl 1):S11–S61. **7.** Reiner Z. *et al.* ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J.* 2011 Jul;32(14):1769-818.

History of Guidelines on Dyslipidemia since 2004

- Therapy is changing from high-intensity statin to a high-intensity cholesterol-lowering therapy.



Key Changes after IMPROVE-IT Study

- More aggressive lipid-lowering therapy is warranted for both high and very-high risk patients
- Ezetimibe add-on therapy is in the spotlight with an evidence from IMPROVE-IT study

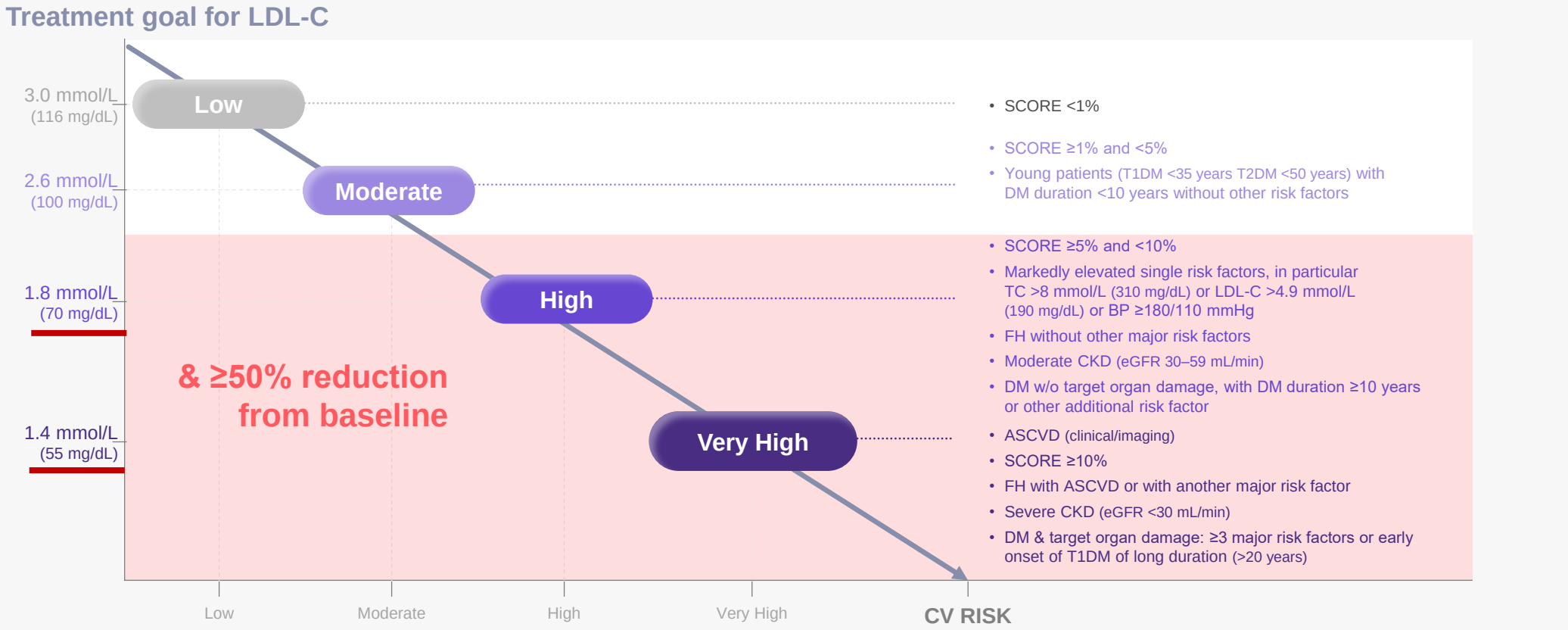
- Patients may be eligible for the second-line lipid lowering therapy with ezetimibe being the first-line of choice if,
  1. patient's therapeutic goal is not achieved at the maximal tolerated statin dose*
  2. patients are intolerant to statins
  3. patients who have contraindications to statins

8. 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. *J Am Coll Cardiol.* 2014 Jul 1;63(25 Pt B):2889-934. **9.** Cannon CP, *et al.* Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med*. 2015 Jun 18;372(25):2387-97. **10**. Catapano AL, *et al*. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. *Eur Heart J*. 2016 Oct 14;37(39):2999-3058. **11.** Lloyd-Jones DM, *et al.* 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol.* 2016 Jul 5;68(1):92-125. **12**. NICE guidance: Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia. 2016 (Accessed at https://www.nice.org.uk/guidance/ta385) **13.** American diabetes association, Standards of Medical Care in Diabetes 2016. **14.** Jellinger PS, *et al*. American association of clinical endocrinologists and american college of endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. *Endocr Pract*. 2017 Apr;23(Suppl 2):1-87.**15.** Sabatine MC, *et al.* Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med.* 2017 May 4;376(18):1713-1722. **16.** Grundy SM, *et al*. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation.* 2019 Jun 18;139(25):e1046-e1081. **17.**Mach F, *et al*. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J.* 2020 Jan 1;41(1):111-188.

2019 ESC/EAS Dyslipidemia Guidelines

Treatment goals for LDL-C across categories of total cardiovascular disease risk

- 2019 ESC/EAS guidelines recommend both a **≥50% LDL-C reduction from baseline** and **an absolute LDL-C treatment goal** of <55 mg/dL (<1.4 mmol/L) for very high-risk patients, and <70 mg/dL (<1.8 mmol/L) for high-risk patients.

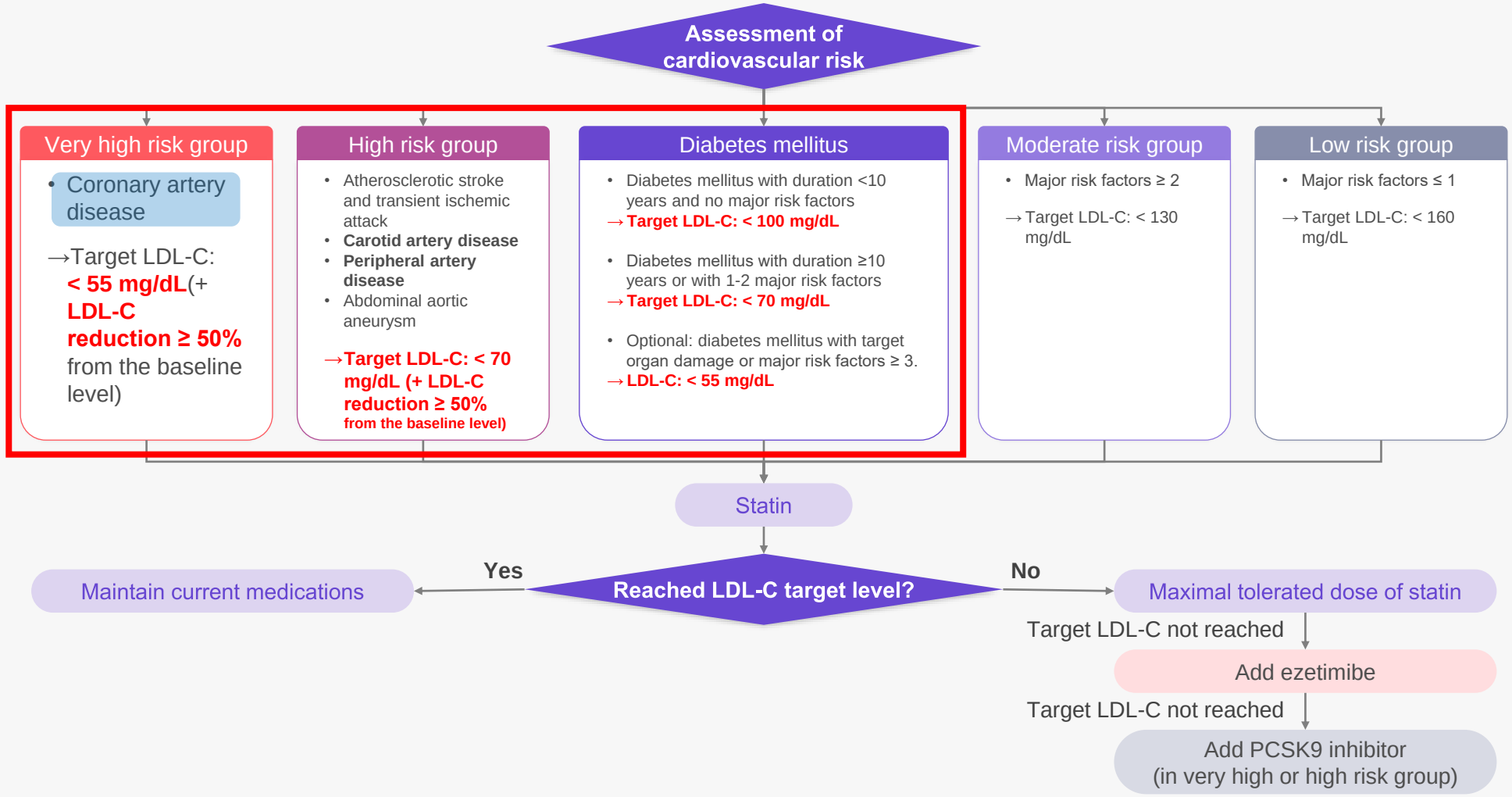


Adapted from Mach F, *et al.*[1]

Reference 1. Mach F, *et al*. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J.* 2020 Jan 1;41(1):111-188.

2022 KSoLA Guideline

Guidelines for dyslipidemia



Adapted from KSoLA.[1]

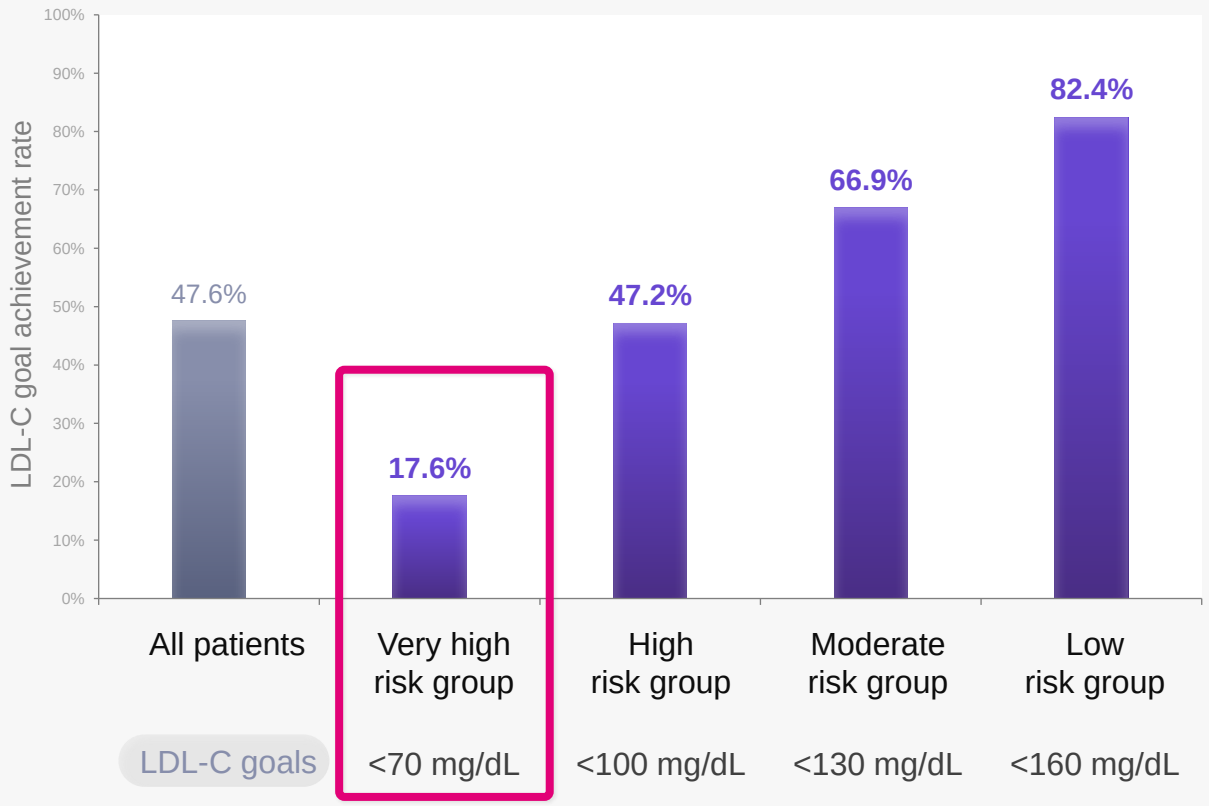
Reference 1. The Korean Society of Lipid and Atherosclerosis (KSoLA). *Guidelines for management of dyslipidemia 5th edition*. 2022.

Contents

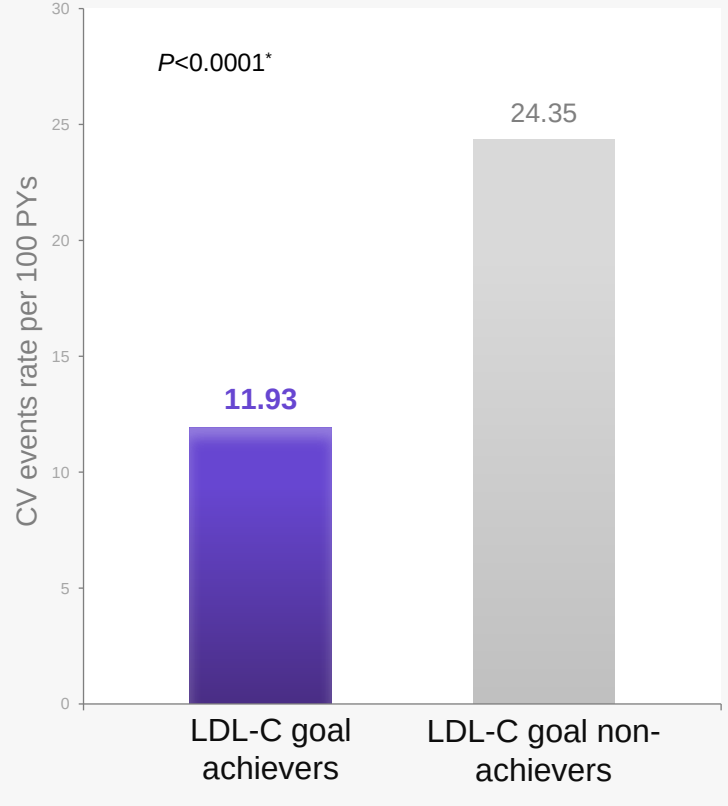
Retrospective cohort study in Korea

LDL-C goal achievement among patients with very high or high CV risk was suboptimal in Korea

LDL-C goal achievement rates among patients with dyslipidemia (based on the 2015 Korean guidelines)



Total cardiovascular events† rates based on LDL-C goal achievement



* *P*-values for differences between rates of LDL-C goal achievers and non-achievers. † Total CV events included all-cause death, acute coronary syndrome, ischemic stroke, and peripheral artery disease.

CV : Cardiovascular, **LDL-C :** Low-density lipoprotein cholesterol, **PY :** Person-year

Study design a. This retrospective cohort study was to examine the low-density lipoprotein cholesterol (LDL-C) goal achievement among patients with dyslipidemia in Korea, the rates of CV events based on LDL-C goal achievement, and the factors associated with LDL-C goal achievement by using that utilizes nationwide health screening data from January 1, 2006 to December 31, 2013. This data was provided information on laboratory results, health behaviors, medical treatment, death, and demographics over an 8-year period. The LDL-C goal achievement was assessed by comparing the LDL-C value on the index date with the LDL-C goal defined based on the 2015 Korean guidelines. 69,942 patients were eligible for the study and 33,270 of these patients achieved LDL-C. The main outcome was to examine the LDL-C goal achievement among patients with dyslipidemia in South Korea against the 2015 Korean guidelines, the crude rates of CV events based on LDL-C goal achievement, and the factors associated with LDL-C goal achievement.

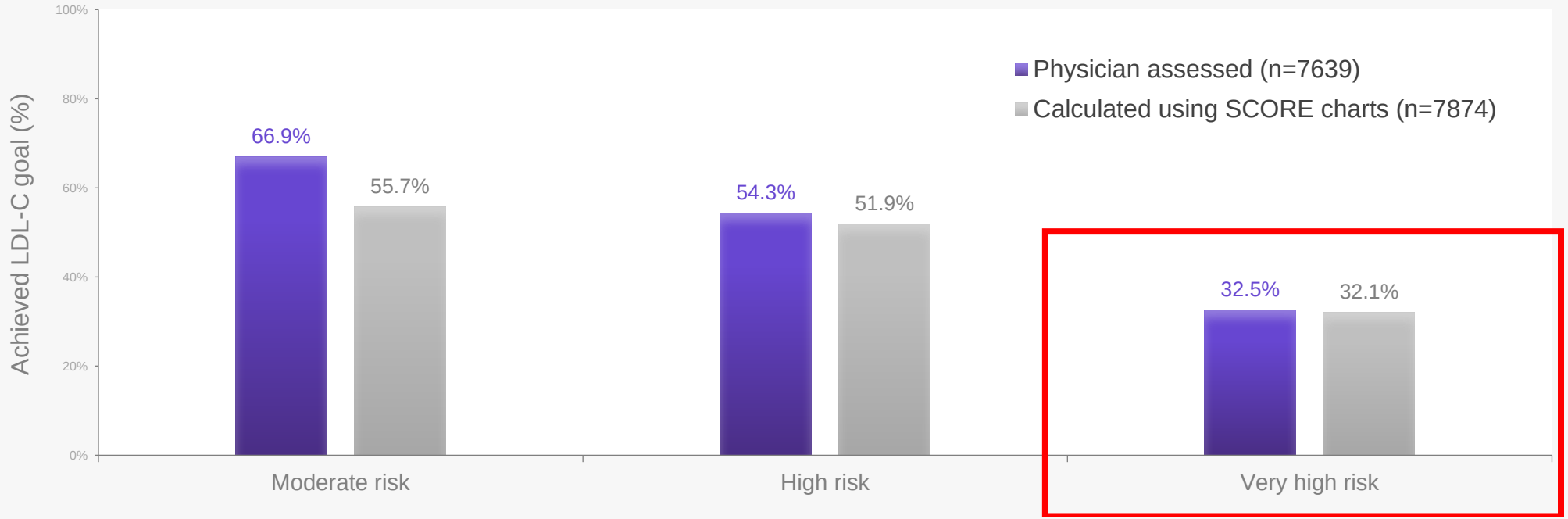
1. Kim S, *et al*. Achievement of the low-density lipoprotein cholesterol goal among patients with dyslipidemia in South Korea. *PLoS One*. 2020 Jan 30;15(1):e0228472.

Achievement of LDL-C goals is suboptimal in outside Western Europe

From a cross-sectional observational study which was conducted in 452 centres in 18 countries in Eastern Europe

- Only **32.1%** of **very high risk patients** (according to SCORE) achieved their LDL-C goals.

Patients who achieved the 2011 ESC/EAS LDL-C goals, according to physician-estimated or calculated cardiovascular risk level (calculated using SCORE)



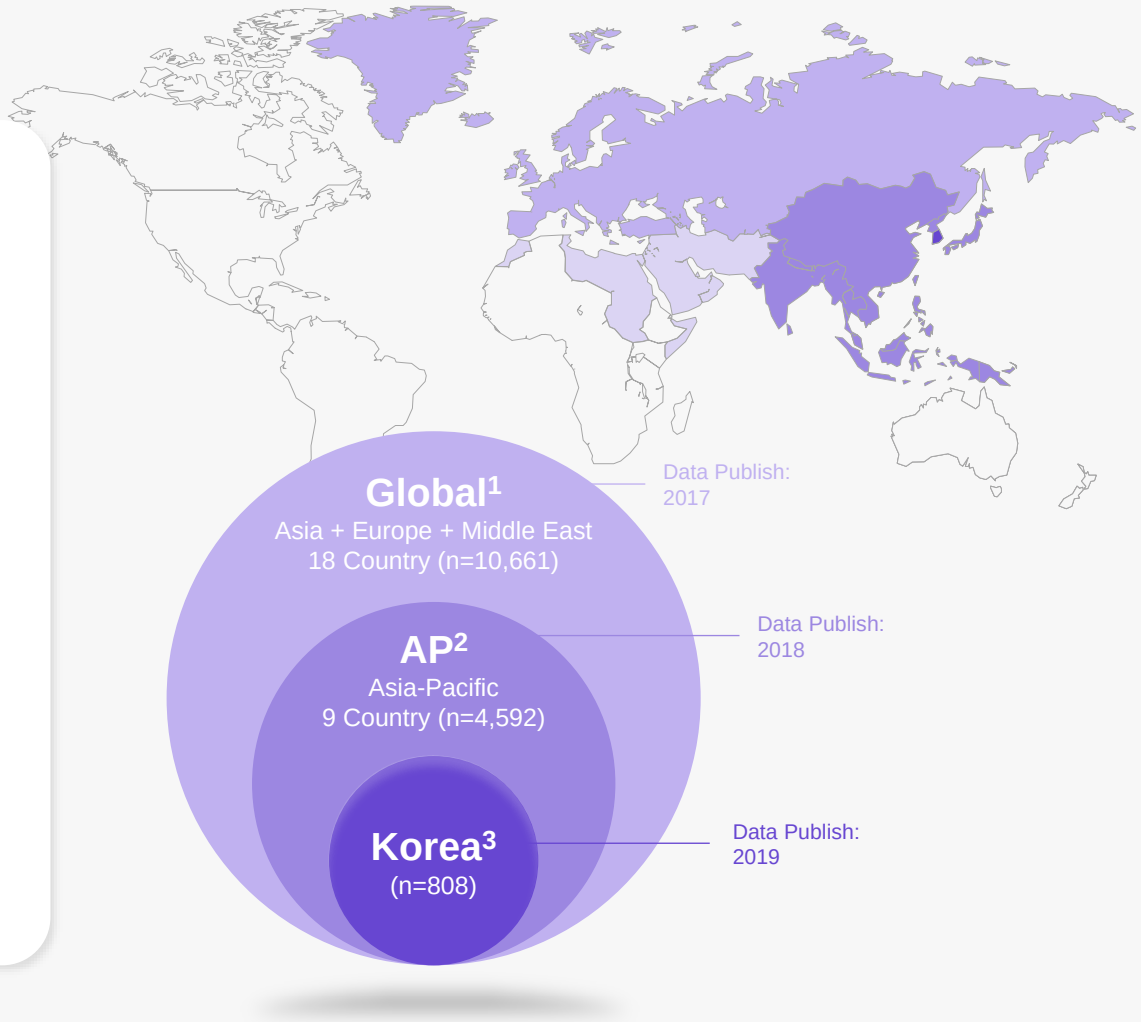
Adapted from Danchin N, *et al.*[1]

Reference 1. Danchin N, *et al.* Achievement of low-density lipoprotein cholesterol goals in 18 countries outside Western Europe: The International ChoLesterol management Practice Study (ICLPS). *Eur J Prev Cardiol.* 2018 Jul;25(10):1087-1094.

DYSIS II: Enrollment by region (18 country)

Global 18 country[1] (n=10,661)

Asia	**South Korea** Hong Kong India The Philippines Singapore Thailand Taiwan Vietnam
Europe	France Greece Germany Ireland Italy
The Middle East	Egypt Jordan Lebanon Saudi Arabia The United Arab Emirates



DYSIS : Dyslipidemia International Study, **AP** : Asia-Pacific

References 1. Gitt AK, *et al.* Cholesterol target value attainment and lipid-lowering therapy in patients with stable or acute coronary heart disease: Results from the Dyslipidemia International Study II. *Atherosclerosis.* 2017;266:158-166. **2.** Poh KK, *et al.* Low-density lipoprotein cholesterol target attainment in patients with stable or acute coronary heart disease in the Asia-Pacific region: results from the Dyslipidemia International Study II. *Eur J Prev Cardiol*. 2018;25(18):1950-1963. **3.** SH Lee, *et al.* Dyslipidemia and Rate of Under-Target Low-Density Lipoprotein-Cholesterol in Patients with Coronary Artery Disease in Korea. *J Lipid Atheroscler.* 2019;8(2):242-251.

DYSIS II : Global

DYSIS II: Study design

Dyslipidemia International Study II (DYSIS II)

Multinational, multicenter, prospective observational study

Subjects

10,661 patients(≥18 y) with stable **CHD**(n=6,794) and **ACS**(n=3,867) from **18** countries

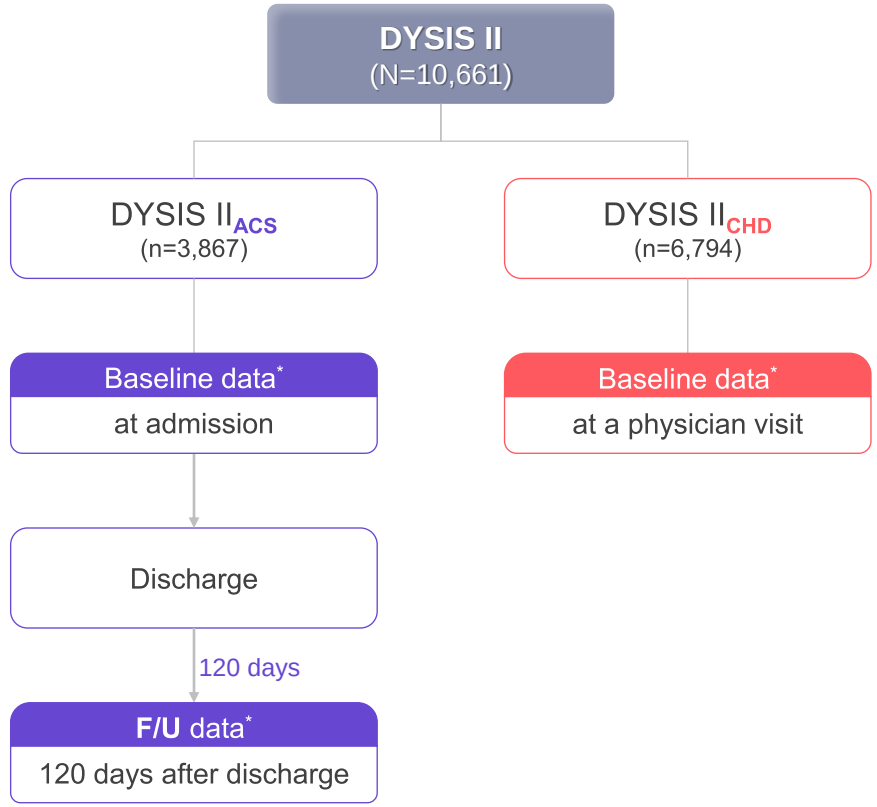
Objective

Determining of lipid profiles, **lipid target value attainment, use of lipid lowering therapy, cardiovascular outcomes**

Data collection

[ACS group] **Admission** (baseline) → Discharge → 120 days later **(F/U)**

[CHD group] Physician visit (baseline)



DYSIS : Dyslipidemia International Study, **CHD** : Coronary heart disease, **ACS** : Acute coronary syndrome, **F/U** : Follow-up

Reference 1. Gitt AK, *et al*. Cholesterol target value attainment and lipid-lowering therapy in patients with stable or acute coronary heart disease: Results from the Dyslipidemia International Study II. *Atherosclerosis.* 2017;266:158-166.

DYSIS II : Global

DYSIS II: LDL-C goal attainment rate

- LDL-C target attainment was poor in very high-risk patients (CHD/ACS).
- Although use of LLT was widespread, potency of LLT was insufficient for reducing the CV risk of these patients.

ACS CHD

LDL-C goal (<70 mg/dL) attainment rate

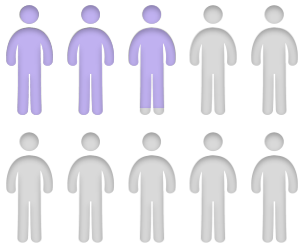
CHD patients

Baseline
(Total N=6,792)

LDL-C at goal

29.4%

(N=1,994)



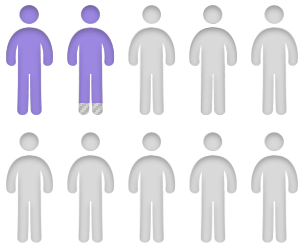
ACS patients

Baseline*
(N=3,867)

LDL-C at goal

18.9%

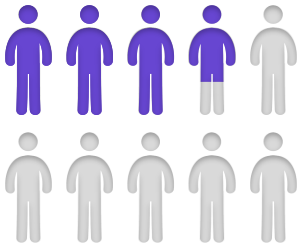
(N=731)



Follow-Up*
(N=1,071)

LDL-C at goal

37.0%



* Includes only patients with lipid levels available from both baseline and 4-month follow-up.

DYSIS : Dyslipidemia International Study, **CHD** : Coronary heart disease, **ACS** : Acute coronary syndrome, **LLT** : Lipid-lowering therapy, **LDL-C** : Low-density lipoprotein cholesterol, **CV** : Cardiovascular

Reference 1. Gitt AK, *et al.* Cholesterol target value attainment and lipid-lowering therapy in patients with stable or acute coronary heart disease: Results from the Dyslipidemia International Study II. *Atherosclerosis.* 2017;266:158-166.

LDL-C goal attainment rate

- Only a minority of patients were under target LDL-C level (<70 mg/dL) at enrollment.[1-3]

ACS | CHD

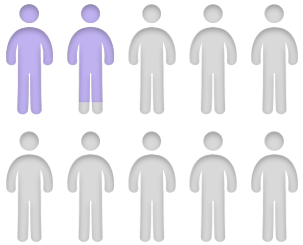
LDL-C goal (<70 mg/dL) attainment rate (Baseline) Global, AP and South Korea

Global[1,a]
(Total N=3,867)

LDL-C at goal

18.9%

(N=731)

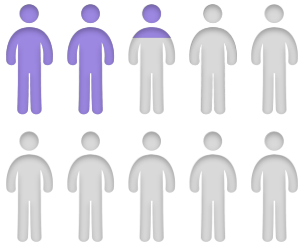


AP[2,b]
(Total N=1,798)

LDL-C at goal

23.0%

(N=414)

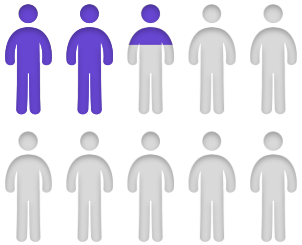


Korea[3,c]
(Total N=308)

LDL-C at goal

23.7%

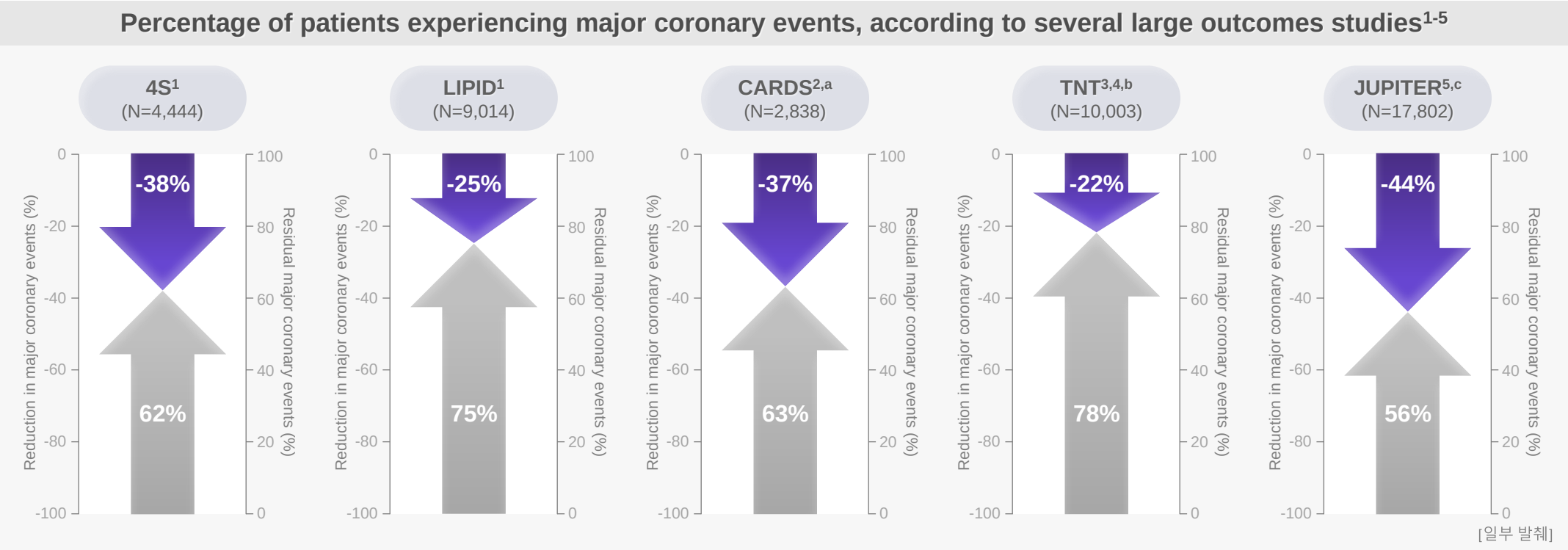
(N=73)



DYSIS : Dyslipidemia International Study, **ACS** : Acute coronary syndrome, **CHD** : Coronary heart disease, **LDL-C** : Low-density lipoprotein cholesterol, **AP** : Asia-Pacific

References 1. Gitt AK, *et al.* Cholesterol target value attainment and lipid-lowering therapy in patients with stable or acute coronary heart disease: Results from the Dyslipidemia International Study II. *Atherosclerosis.* 2017;266:158-166. **2.** Poh KK, *et al.* Low-density lipoprotein cholesterol target attainment in patients with stable or acute coronary heart disease in the Asia-Pacific region: results from the Dyslipidemia International Study II. *Eur J Prev Cardiol.* 2018;25(18):1950-1963. **3.** Lee SH, *et al.* Dyslipidemia and Rate of Under-Target Low-Density Lipoprotein-Cholesterol in Patients with Coronary Artery Disease in Korea. *J Lipid Atheroscler.* 2019;8(2):242-251.

Majority of residual risk for CV events remains despite LDL lowering Therapy



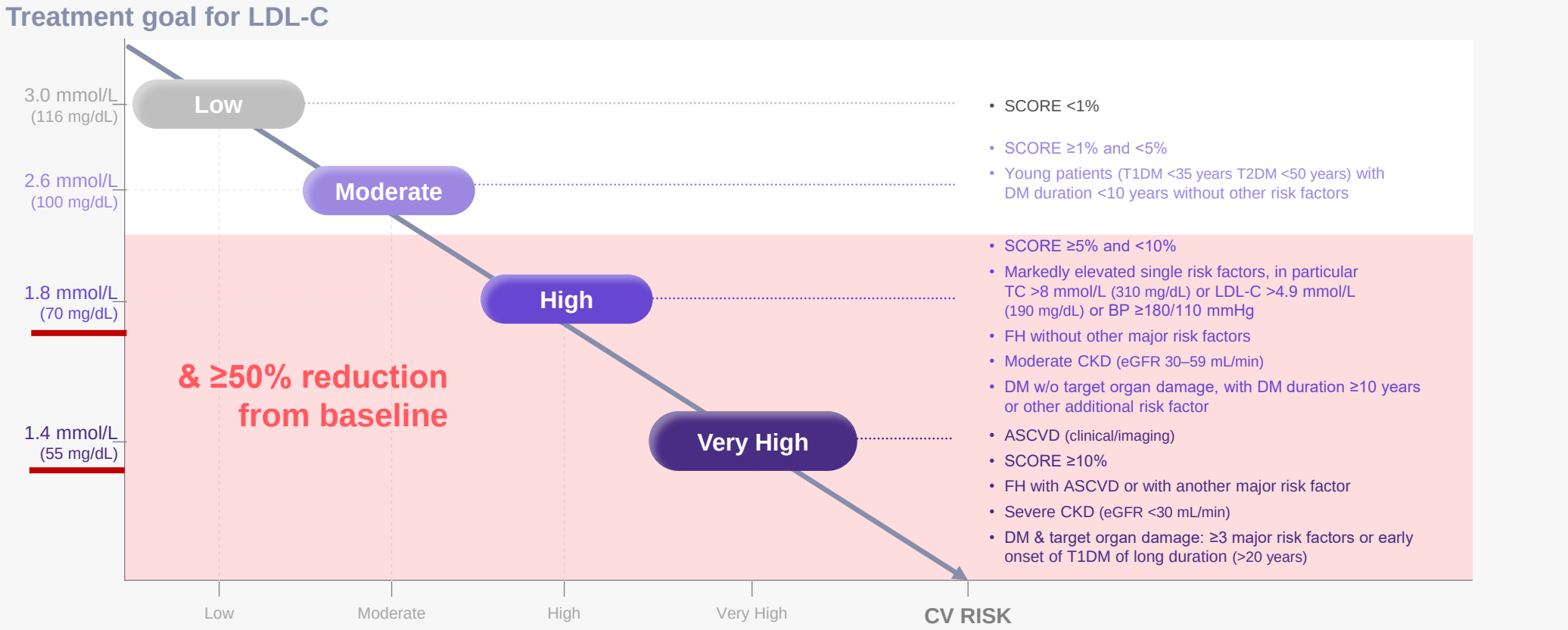
References 1. Libby P. The forgotten majority: unfinished business in cardiovascular risk reduction. *J Am Coll Cardiol.* 2005;46:1225-28. **2.** Colhoun HM, *et al.* Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet.* 2004;364:685-96. **3.** Waters DD, *et al.* Treating to New Targets (TNT) Study: does lowering low-density lipoprotein cholesterol levels below currently recommended guidelines yield incremental clinical benefit? *Am J Cardiol.* 2004;93:154-8. **4.** LaRosa JC, *et al*. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med.* 2005 Apr 7;352(14):1425-35. **5.** Ridker PM, *et al.* Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med.* 2008 Nov 20;359(21):2195-207.

Contents

2019 ESC/EAS Dyslipidemia Guidelines

Treatment goals for LDL-C across categories of total cardiovascular disease risk

- 2019 ESC/EAS guidelines recommend both a **≥50% LDL-C reduction from baseline** and **an absolute LDL-C treatment goal** of <55 mg/dL (<1.4 mmol/L) for very high-risk patients, and <70 mg/dL (<1.8 mmol/L) for high-risk patients.



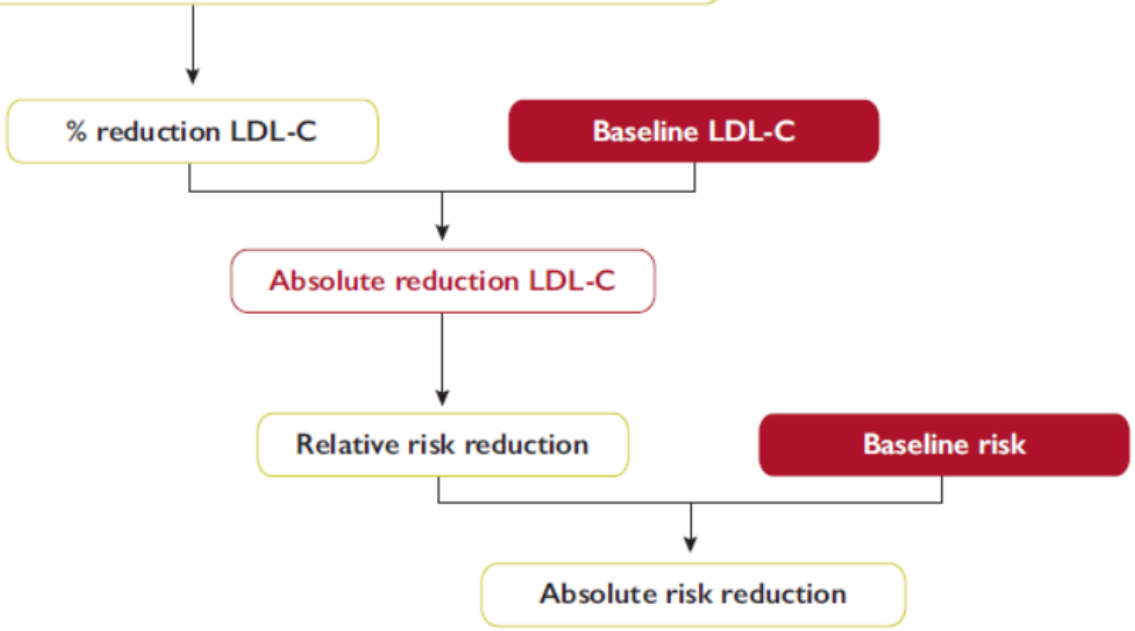
Adapted from Mach F, *et al.*[1]

Reference 1. Mach F, *et al*. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J.* 2020 Jan 1;41(1):111-188.

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]

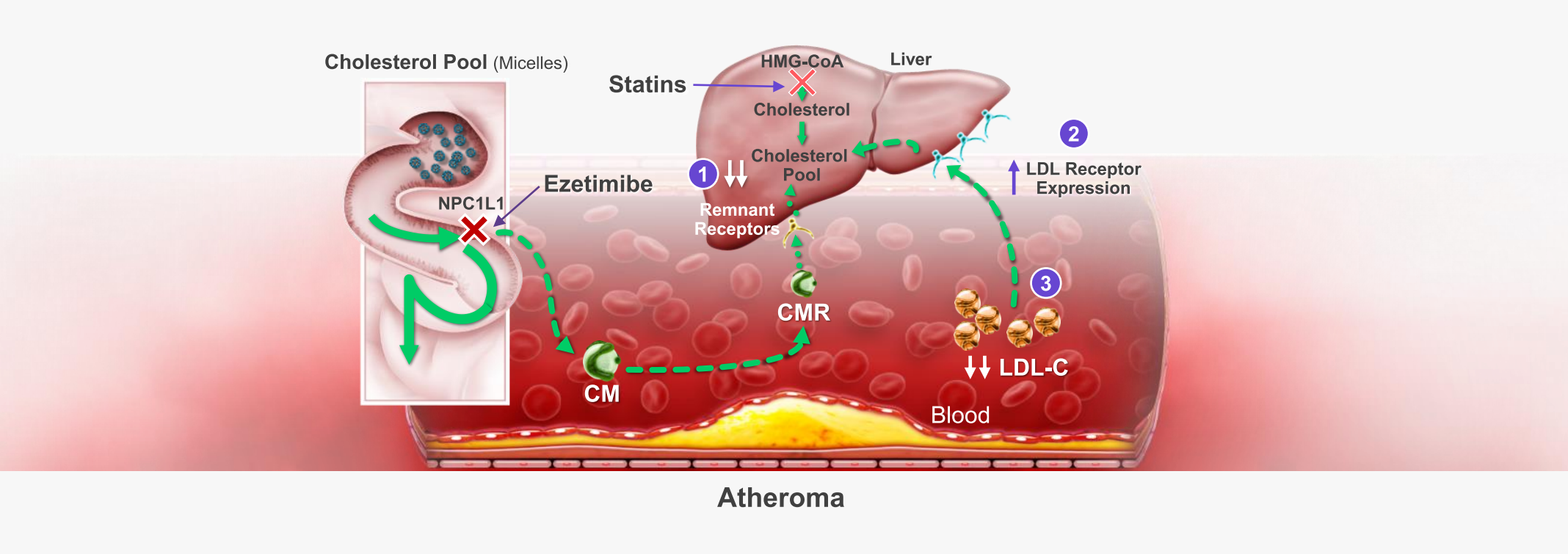
* Specific statins and doses are noted in bold that were evaluated in RCTs demonstrated a reduction in major cardiovascular events.
Statins and doses that are approved by the U.S. FDA but were not tested in the RCTs reviewed are listed in italics.
ACC : American College of Cardiology, AHA : American 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.

Ezetimibe and statins have complementary mechanisms of action.[1]

- 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



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

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

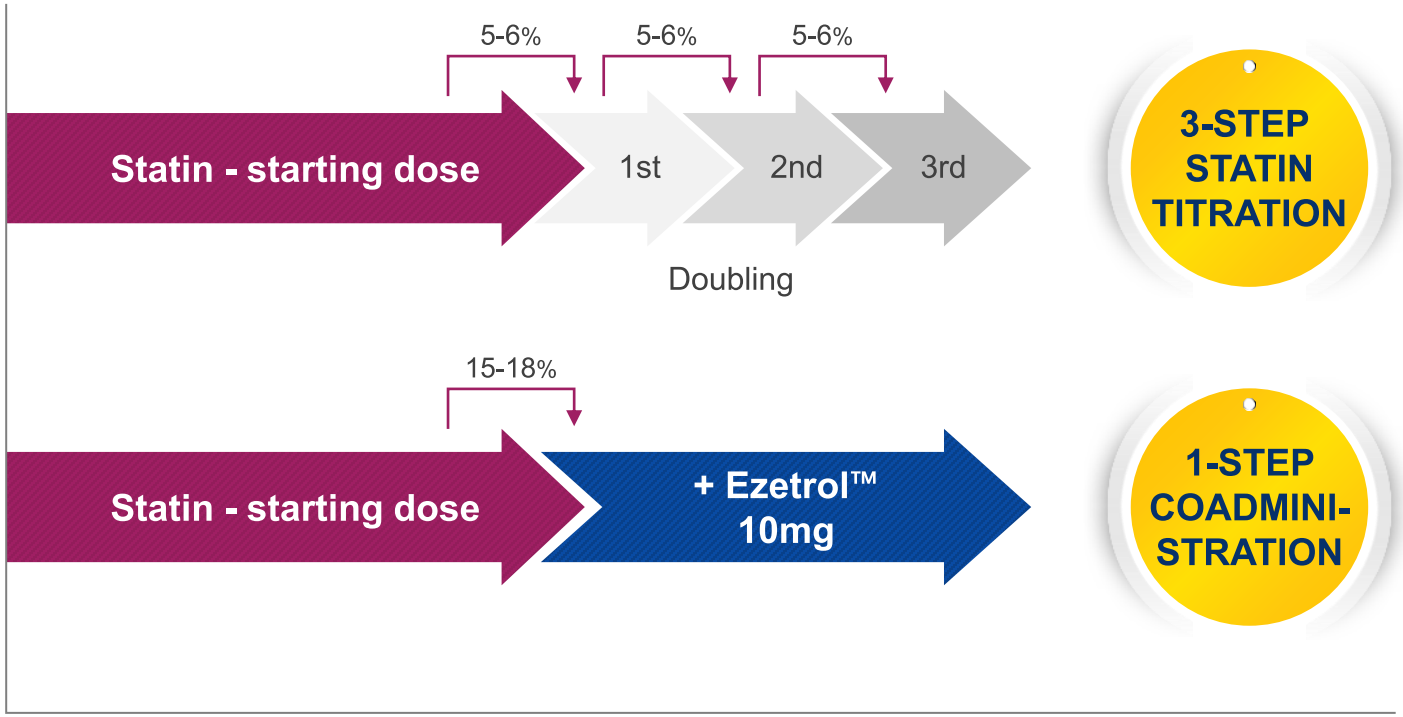
Cholesterol absorption is increased during statin treatment

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

Ezetrol™ add-on therapy was comparable to 3-step statin up-titration in % LDL-C reduction



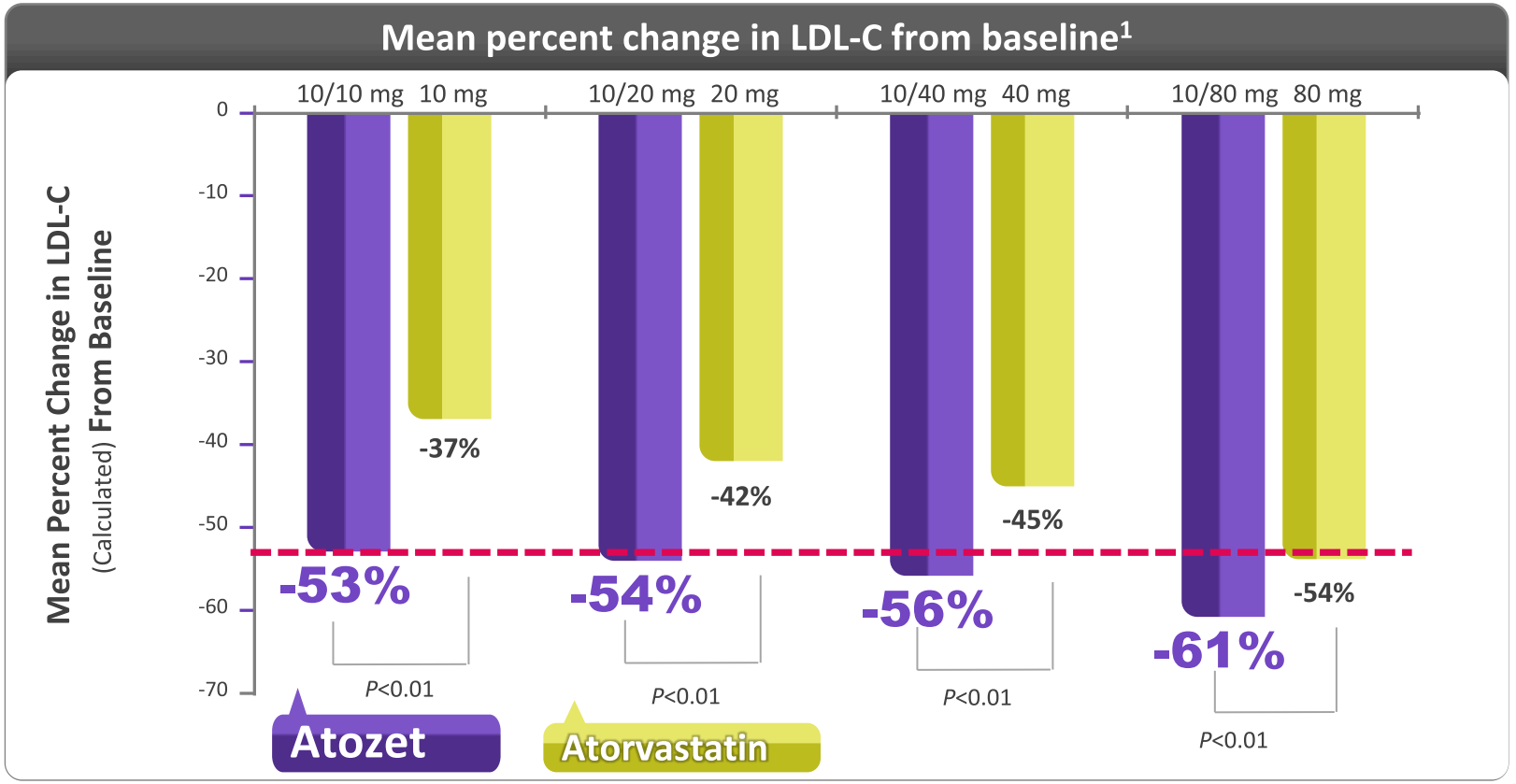
LDL-C : Low-density liopoprotein cholesterol

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.

Ballantyne

Starting Atozet provided significantly greater LDL-C reduction compared with corresponding Atorvastatin doses

- This 12 weeks double-blind study was conducted with 628 primary hypercholesterolemia patients without diabetes mellitus.[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).

LDL-C : Low density lipoprotein cholesterol, **EZE/ATV :** Ezetimibe/atorvastatin

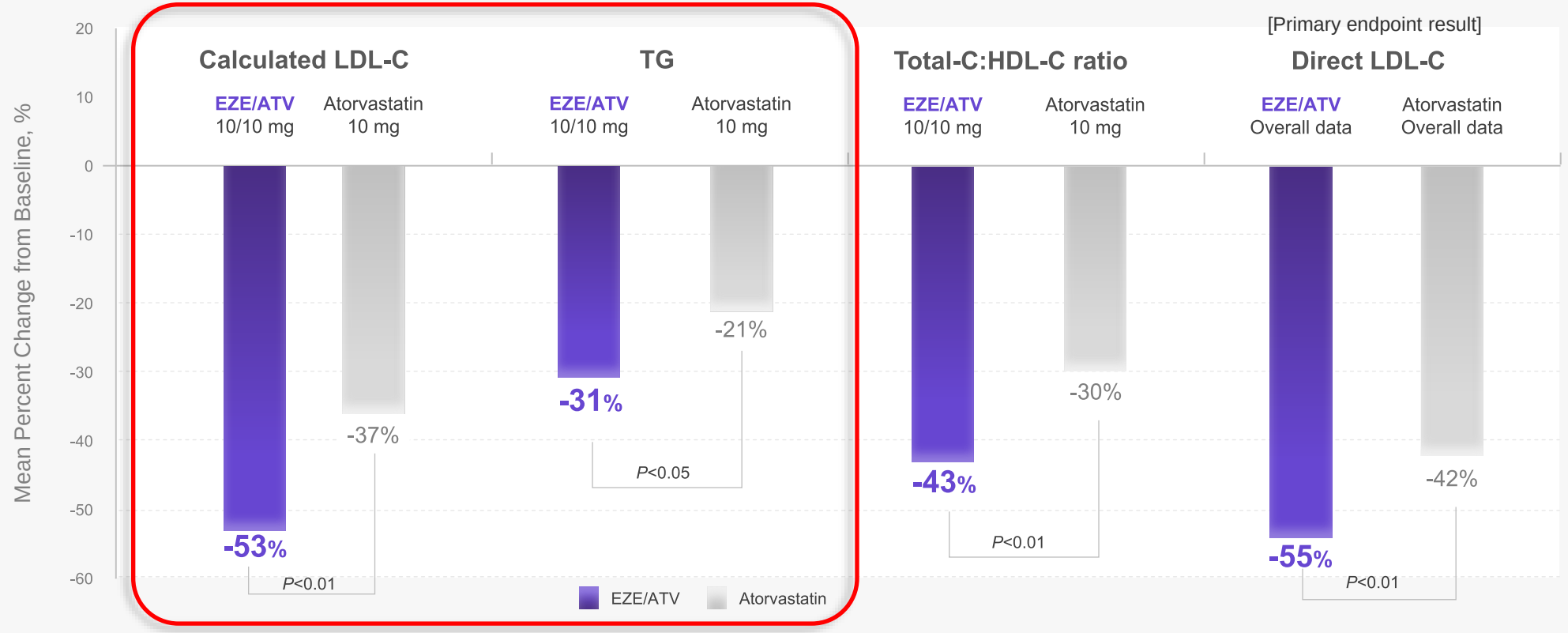
Study design This multicenter study evaluated primary hypothesis that the ezetimibe /atorvastatin combination would result in a significantly greater reduction in LDL-C than atorvastatin alone. Also evaluated were the change from baseline for other lipid variables and for C-reactive protein and the proportions of patients reaching ATP III LDL-C goals at final assessment. In a double-blind study, 628 patients with baseline LDL-C 145 to 250 mg/dL and triglycerides 350 mg/dL were randomly assigned to receive 1 of the following for 12 weeks: ezetimibe (10 mg/d); atorvastatin (10, 20, 40, or 80 mg/d); ezetimibe (10 mg) plus atorvastatin (10, 20, 40, or 80 mg/d); or placebo. The primary efficacy end point was the percentage reduction in direct LDL-C from baseline to final assessment (last available postbaseline direct LDL-C value for each patient) for the intent-to-treat population.

1. Ballantyne CM, *et al*. The effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia. *Circulation*. 2003;107:2409–2415.

Ballantyne

Starting Atozet (Atorvastatin+ezetimibe) provided significantly greater LDL-C and TG reduction compared with corresponding Atorvastatin dose

Change in LDL-C and TG from baseline to final assessment[1,*]



Baseline LDL-C 145 to 250 mg/dL (~3.7 to 6.5 mmol/L) **and triglycerides ≤350 mg/dL** (~4.0 mmol/L).

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

[#] This study was conducted to evaluate the efficacy and safety profile of ezetimibe 10 mg added to atorvastatin 40 mg compared with doubling atorvastatin to 80 mg/day in patients with hypercholesterolemia. This study was not conducted with the fixed dose combination of ezetimibe with atorvastatin.[1] * Mean baseline : Calculated LDL-C was 182 mg/dL (~4.7 mmol/L), total cholesterol was ~6.91 mmol/L, TG was 1.9 mmol/L, direct LDL-C was ~4.65 mmol/L, and HDL-C was ~1.31 mmol/L for Ezetimibe/Atorvastatin arms (n=255) and 181 mg/dL (~4.7 mmol/L), 6.95 mmol/L, 1.7 mmol/L, ~4.65 mmol/L, and ~1.39 mmol/L for atorvastatin arms (n=248).[1]

LDL-C : Low-density lipoprotein cholesterol, **HDL-C :** High-density lipoprotein cholesterol, **TG :** Triglycerides, **Total-C :** Total cholesterol, **EZE/ATV :** Ezetimibe/Atorvastatin

1. Ballantyne CM, *et al*. Effect of Ezetimibe Coadministered With Atorvastatin in 628 Patients With Primary Hypercholesterolemia. *Circulation*. 2003;107:2409-2415.

IMProved Reduction of Outcomes: Vytorin Efficacy International Trial

Compared to Simvastatin alone, **Ezetimibe** add-on therapy reduced LDL-C in **24%** with **NNT of 50**

This study was conducted with ezetimibe and simvastatin.

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

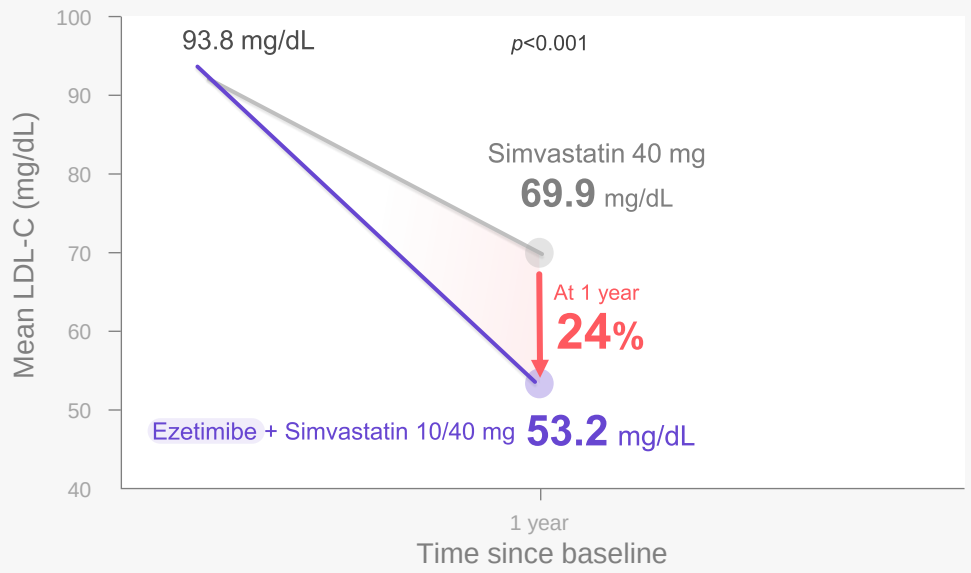
- **Simvastatin 40 mg** (n=9,077)
- **Ezetimibe/simvastatin 10/40 mg** (n=9,067)

Primary endpoint:

CV death, Nonfatal MI, Hospital admission for UA, Coronary revascularization (≥ 30 days after randomization)**, or Nonfatal stroke**

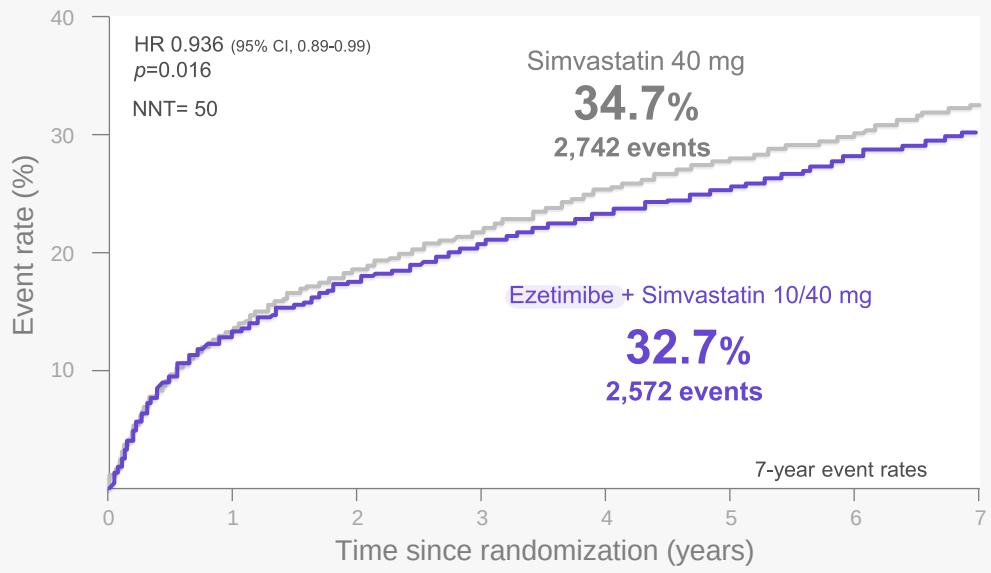
Duration: Minimum 2½-year follow-up (at least 5,250 events)
The median follow-up was 6 years.

Change of LDL-C



Adapted from Cannon CP, *et al.*[1]

Primary endpoint



Adapted from Cannon CP, *et al.*[1]

Reference 1. Cannon CP, *et al.* Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372(25):2387-2397.

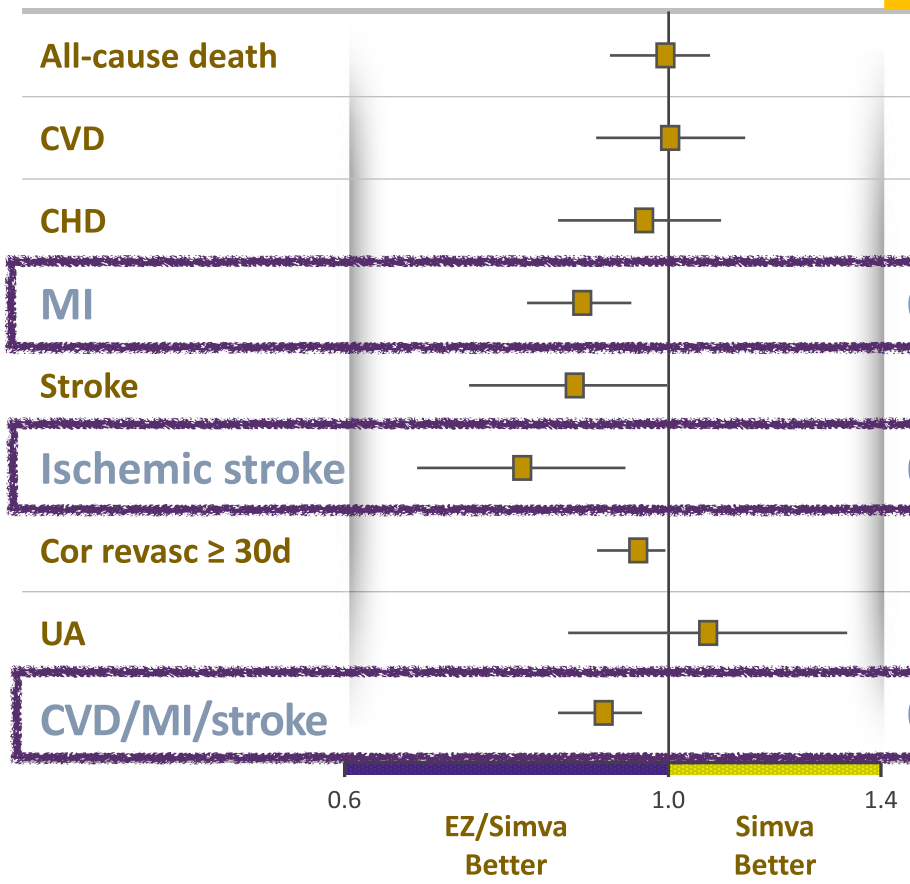
IMPROVE-IT Study

IMProved Reduction of Outcomes: Vytorin Efficacy International Trial

Compared to Simvastatin alone, Ezetimibe add-on therapy reduced LDL-C in 24% with NNT of 50

본 연구는 Ezetimibe/Simvastatin의 임상 연구입니다.

	HR	Simva*	EZ/Simva*	*p*-value
All-cause death	0.99	15.3	15.4	0.782
CVD	1.00	6.8	6.9	0.997
CHD	0.96	5.8	5.7	0.499
MI	**0.87**	**14.8**	**13.1**	**0.002**
Stroke	0.86	4.8	4.2	0.052
Ischemic stroke	**0.79**	**4.1**	**3.4**	**0.008**
Cor revasc ≥ 30d	0.95	23.4	21.8	0.107
UA	1.06	1.9	2.1	0.618
CVD/MI/stroke	**0.90**	**22.2**	**20.4**	**0.003**



Adapted from Cannon CP, *et al.*[1]

* 3.2mM, ** 2.6mM

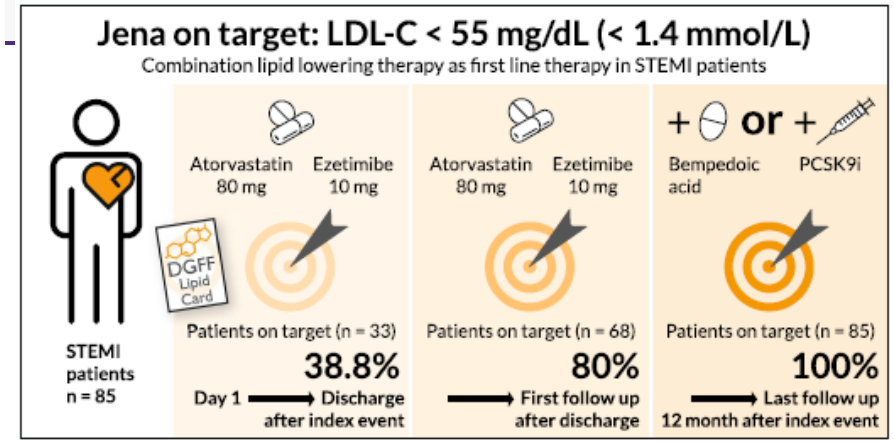
IMPROVE-IT : IMProved Reduction of Outcomes: Vytorin Efficacy International Trial, **ACS :** Acute coronary syndrome, **MI :** Myocardial infarction, **HR :** Hazard Ratio, **UA :** Unstable angina, **LDL-C :** Low density lipoprotein-cholesterol, **CI :** Confidence interval, **NNT :** Number needed to be treated, **CV :** Cardiovascular, **LDL :** Low density lipoprotein

1. Cannon CP, *et al.* Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372(25):2387–2397.

Clinical Research in Cardiology
https://doi.org/10.1007/s00392-022-02147-3

ORIGINAL PAPER

Intensive lipid-lowering therapy for early achievement of guideline-recommended LDL-cholesterol levels in patients with ST-elevation myocardial infarction ("Jena auf Ziel")



Background and aims

Currently, less than 20% of patients at very high-risk achieve ESC/EAS dyslipidemia guideline recommended LDL-C target levels in Europe. "Jena auf Ziel—JaZ" is a prospective cohort study in which **early combination therapy with atorvastatin 80 mg and ezetimibe 10 mg** was initiated on admission in patients with ST-elevation myocardial infarction (STEMI)

Results

A total of 85 consecutive patients were enrolled in the study. On discharge, 32.9% achieved LDL-C targets on **atorvastatin 80 mg and ezetimibe 10 mg.** After 4–6 weeks, **80% of all patients on atorvastatin 80 mg and ezetimibe** started at the index event were **on ESC/EAS LDL-C targets**. In 20%, combined lipid-lowering therapy was escalated with either bempedoic acid or PCSK9 inhibitors. All patients achieved LDL-C levels of or **below 55 mg/dL** during follow-up on triple lipid-lowering therapy. Combined lipid-lowering therapy was **well-tolerated** with rare side effects.

Conclusions

Early combination therapy with a high-intensity statin and ezetimibe and escalation of lipid-lowering therapy with either bempedoic acid or PCSK9 inhibitors gets potentially all patients with STEMI on recommended ESC/EAS LDL-C targets without significant side effects.

1. Makhmudova U, *et al*. Intensive lipid-lowering therapy for early achievement of guideline-recommended LDL-cholesterol levels in patients with ST-elevation myocardial infarction ("Jena auf Ziel"). *Clin Res Cardiol*. 2023 Jan 5. doi: 10.1007/s00392-022-02147-3. Epub ahead of print.

Prospective cohort study

Early initiation of combined lipid-lowering therapy to achieve LDL-C goals as early as possible

Combination lipid lowering therapy as first line therapy in STEMI patients

Jena on target: LDL-C < 55 mg/dL (< 1.4 mmol/L)

STEMI patients
n=85

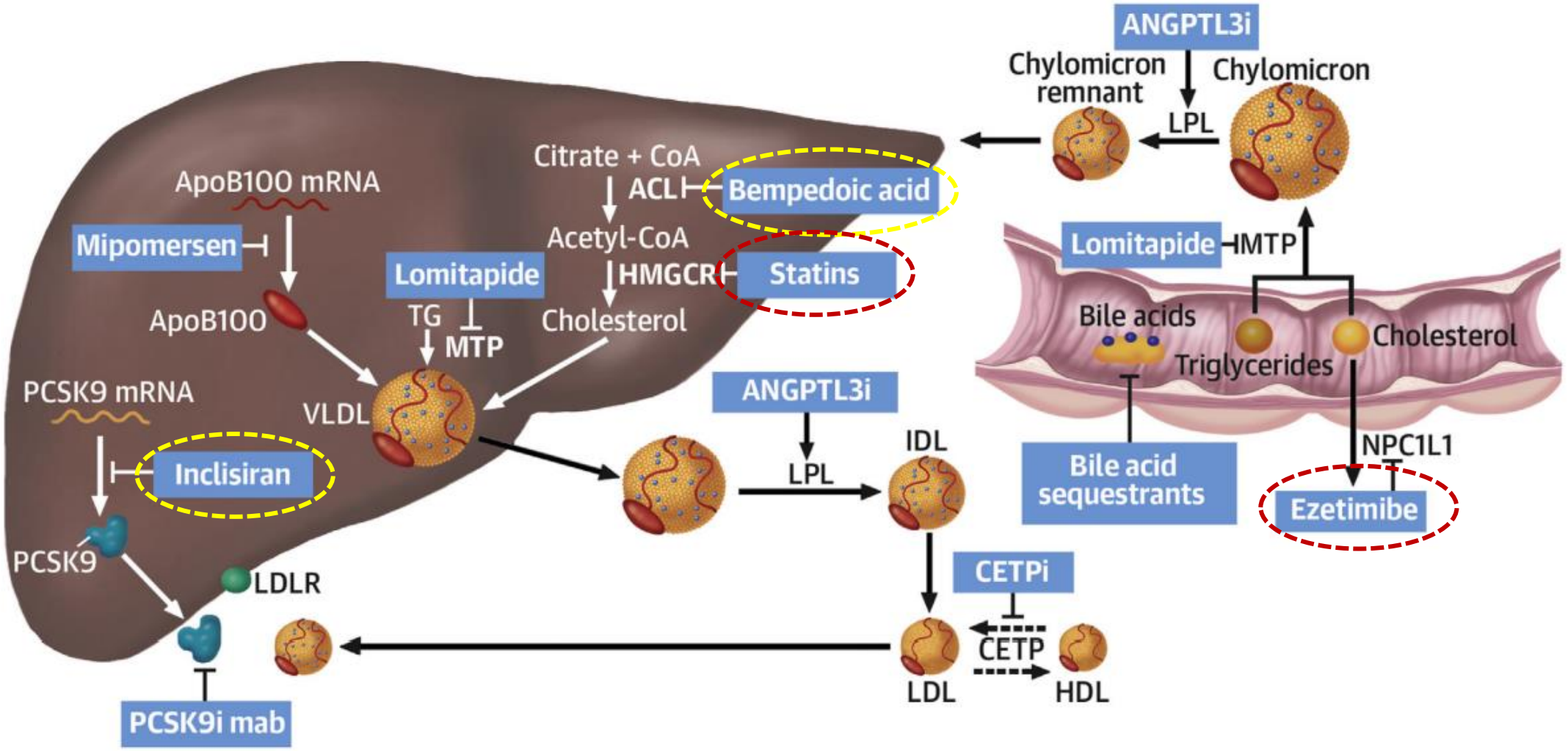
Atorvastatin 80 mg + Ezetimibe 10 mg	**Atorvastatin 80 mg + Ezetimibe 10 mg**	+ Bempedoic acid OR + PCSK9i
Patients on target (n=33)	Patients on target (n=68)	Patients on target (n=85)
38.8%	**80%**	**100%**
Day 1 → Discharge after index event	**→ First follow up after discharge**	**→ Last follow up 12 month after index event**

STEMI : ST-elevation myocardial infarction, **LDL-C :** Low-density lipoprotein cholesterol, **PCSK9i :** Proprotein convertase subtilisin/kexin type 9 inhibitor

Study design a. This prospective cohort study (Jena auf Ziel) was conducted at Jena University Hospital from January 1st to December 31st, 2021 to evaluate the effectiveness of early combination therapy with a high-intensity statin and ezetimibe and escalation of lipid-lowering therapy with either bempedoic acid or PCSK9 inhibitors to achieve recommended low-density lipoprotein (LDL-C) targets in patients with ST-elevation myocardial infarction (STEMI). The study was enrolled 85 consecutive patients with STEMI who were started on atorvastatin 80 mg and ezetimibe 10 mg on admission. LDL-C levels were assessed upon admission, during the hospital stay, and discharge. The primary endpoint was LDL-C target achievement (LDL-C < 1.4 mmol/L, or < 55 mg/dL).

1. Makhmudova U, *et al*. Intensive lipid-lowering therapy for early achievement of guideline-recommended LDL-cholesterol levels in patients with ST-elevation myocardial infarction ("Jena auf Ziel"). *Clin Res Cardiol*. 2023 Jan 5. doi: 10.1007/s00392-022-02147-3. Epub a head of print.

Mechanisms of LDL Lowering Therapies

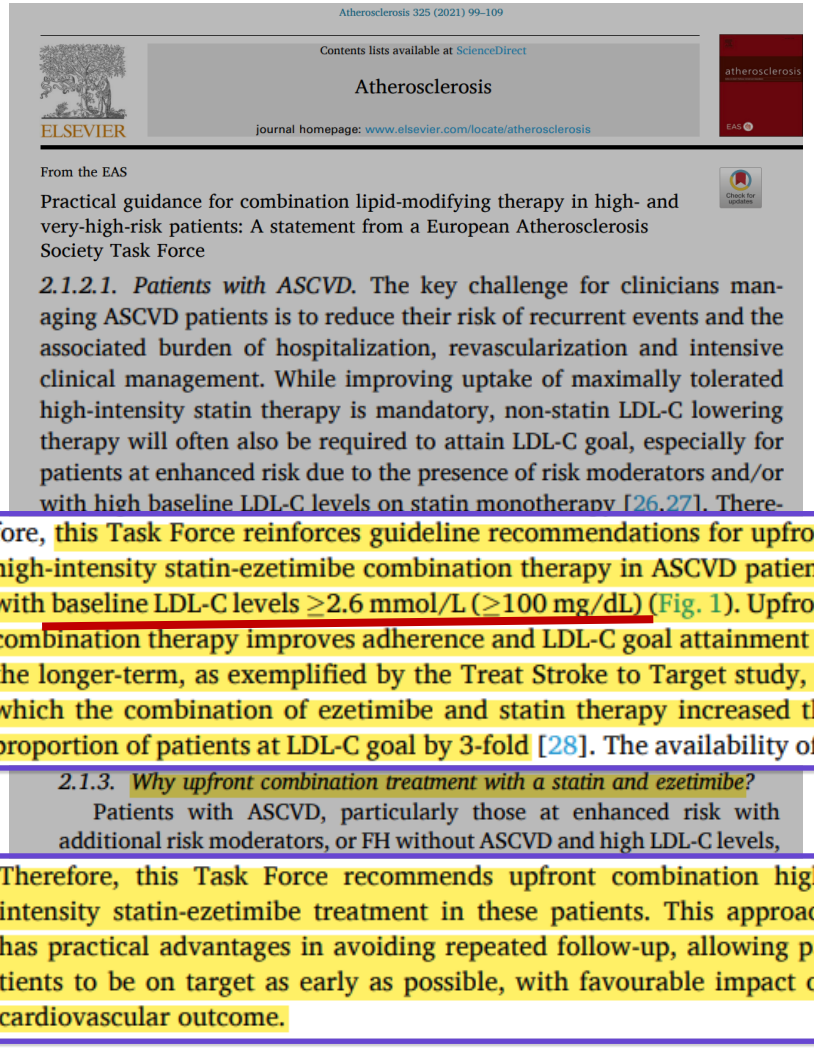


Nurmohamed, N.S. et al. J Am Coll Cardiol. 2021;77(12):1564-75.

2021 EAS Task Force Statement

Practical guidance for combination lipid-modifying therapy in high- and very-high-risk patients

- Statin/Ezetimibe combination therapy is the first choice for the very-high risk group(ASCVD, FH) to reach the target LDL-C.



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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

2.1.2.1. Patients with ASCVD. The key challenge for clinicians managing ASCVD patients is to reduce their risk of recurrent events and the associated burden of hospitalization, revascularization and intensive clinical management. While improving uptake of maximally tolerated high-intensity statin therapy is mandatory, non-statin LDL-C lowering therapy will often also be required to attain LDL-C goal, especially for patients at enhanced risk due to the presence of risk moderators and/or with high baseline LDL-C levels on statin monotherapy [26,27]. Therefore, this 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) (Fig. 1). Upfront combination therapy improves adherence and LDL-C goal attainment in the longer-term, as exemplified by the Treat Stroke to Target study, in which the combination of ezetimibe and statin therapy increased the proportion of patients at LDL-C goal by 3-fold [28]. The availability of a

2.1.3. Why upfront combination treatment with a statin and ezetimibe?

Patients with ASCVD, particularly those at enhanced risk with additional risk moderators, or FH without ASCVD and high LDL-C levels,

Therefore, this Task Force recommends upfront combination high-intensity statin-ezetimibe treatment in these patients. This approach has practical advantages in avoiding repeated follow-up, allowing patients to be on target as early as possible, with favourable impact on cardiovascular outcome.

Recommendations for upfront Statin+Ezetimibe combination therapy in baseline LDL-C ≥ 100 mg/dL

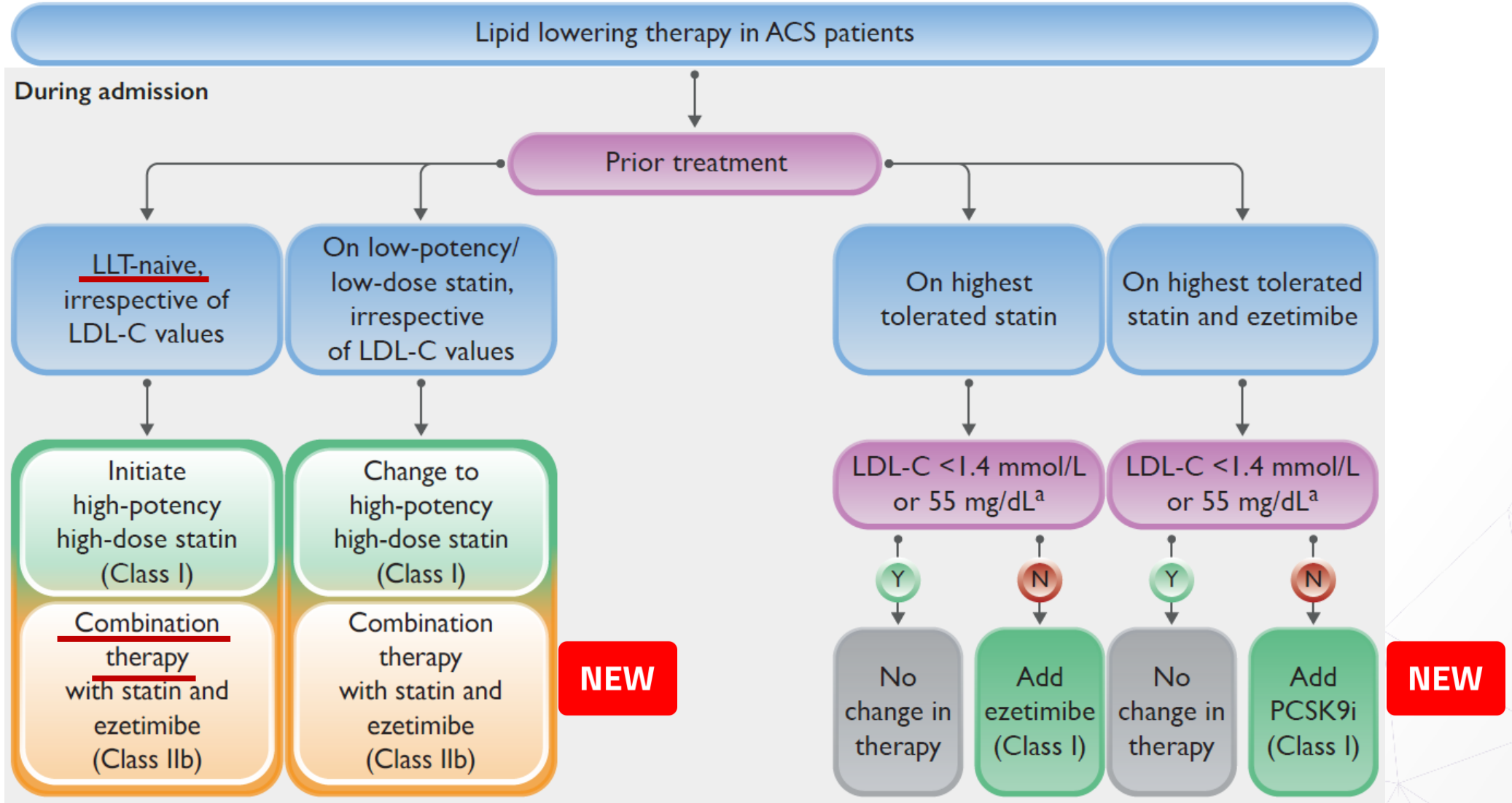
(evidence) From the Treat Stroke to Target study, LDL-C goal achievement was 3 times higher in Statin/Ezetimibe combination therapy group.

The need for upfront Statin+Ezetimibe combination

1. Avoiding repeated follow-up
2. Able to reach target as early as possible
3. Favorable impact on CV outcomes

Reference 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;325:99-109.

2023 ESC Guidelines for the Management of ACS - Lipid-lowering therapy in ACS patients (During Admission)



Statin, ezetimibe combination therapy in chronic phase

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†*

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

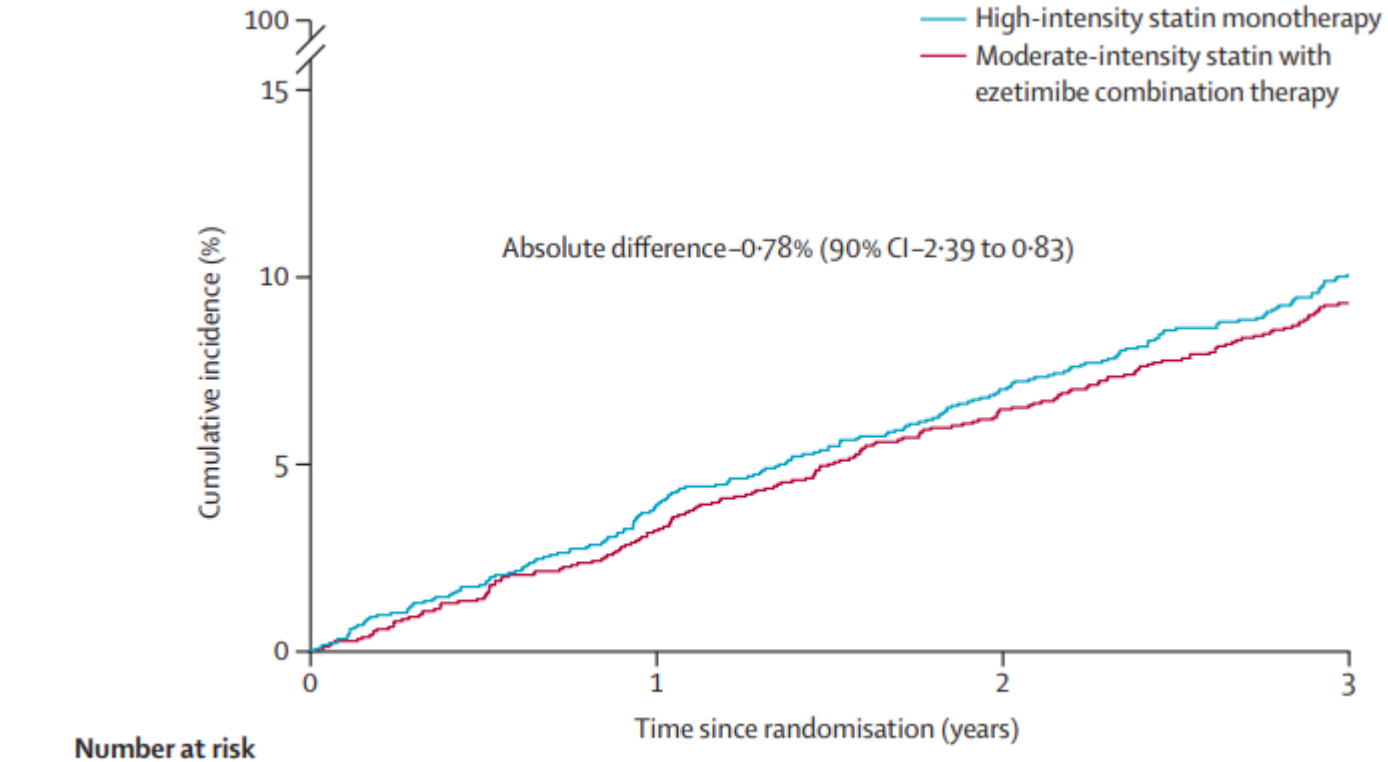
Rosuvastatin 10mg with ezetimibe vs rosuvastatin 20mg
1,894 combination therapy vs 1,886 monotherapy

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

Higher target LDL goal achievement & higher adherence rate

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**

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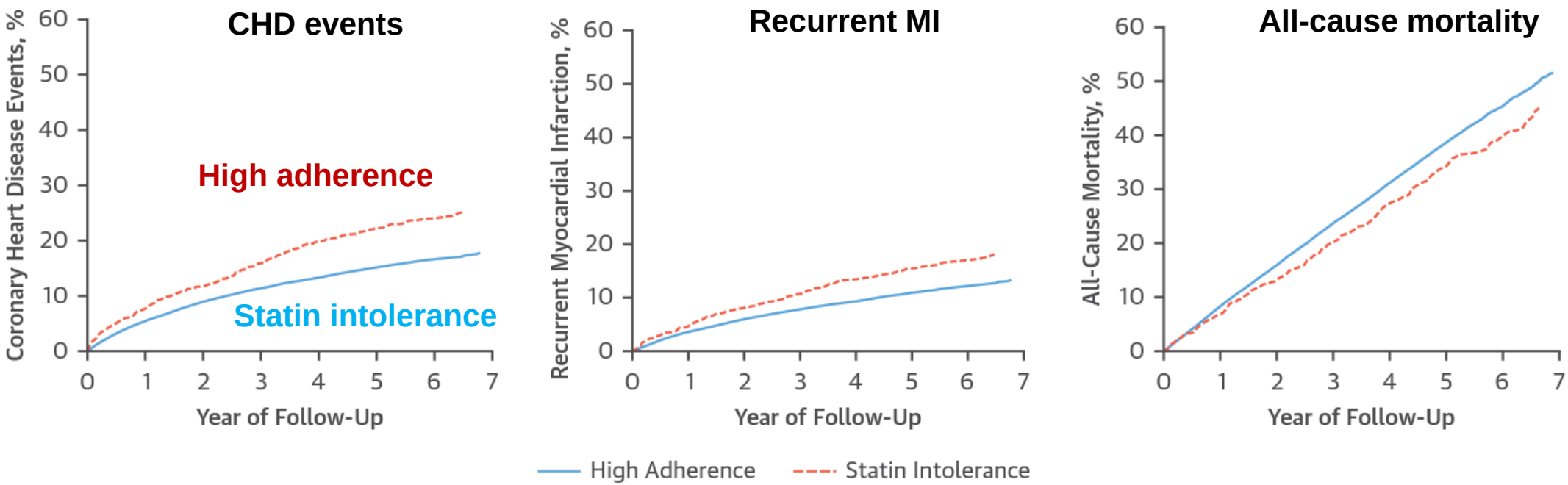
Statin Intolerance and Risk of Coronary Heart Events



Statin intolerance

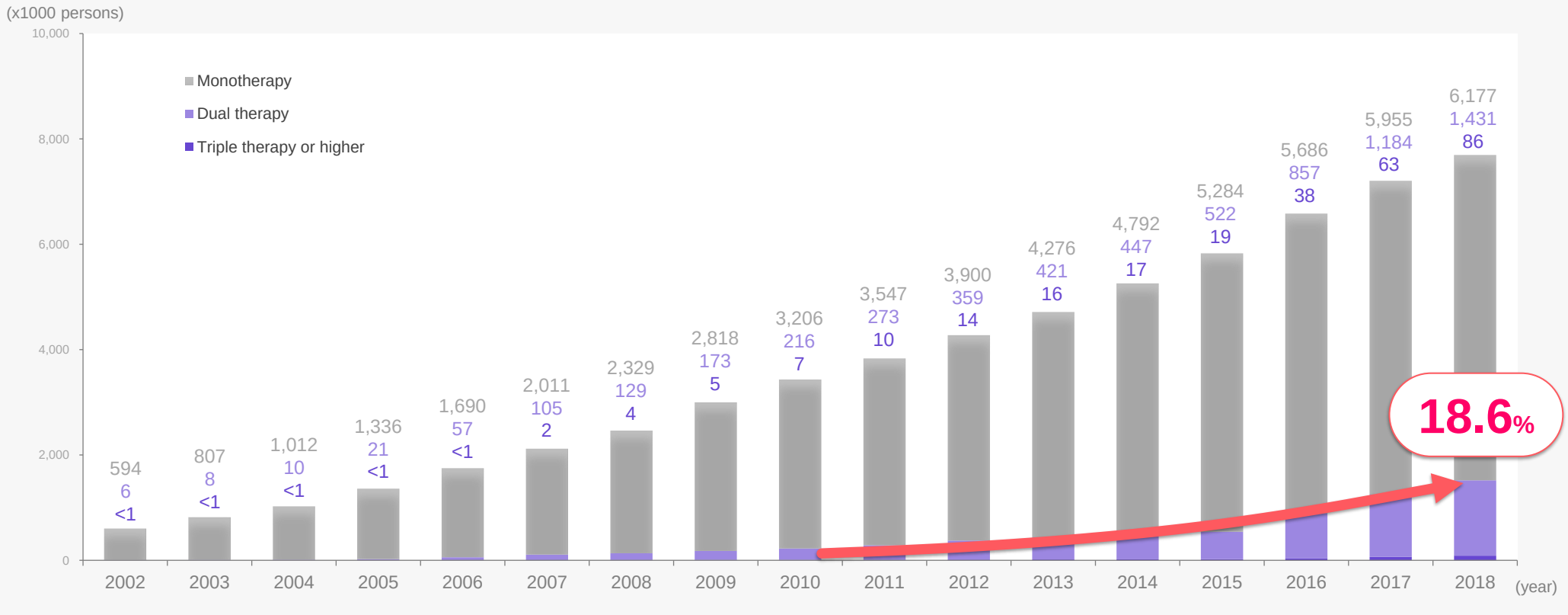
1. Statin **discontinuation** with the initiation of ezetimibe therapy;
2. Initiation of **ezetimibe therapy within 7 days** before or any time after downtitrating statin dose;
3. An inpatient or outpatient claim for **rhabdomyolysis** (defined by ICD-9-CM code 728.88 in any position), followed by statin 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

Changes in dual therapy regimen for dyslipidemia in Korea

- Statins are included in 99% of dual therapy regimen.
- Use of dual therapy for dyslipidemia steadily increased up to 18.6% in 2018.

Estimated number of people with dyslipidemia by treatment strategy

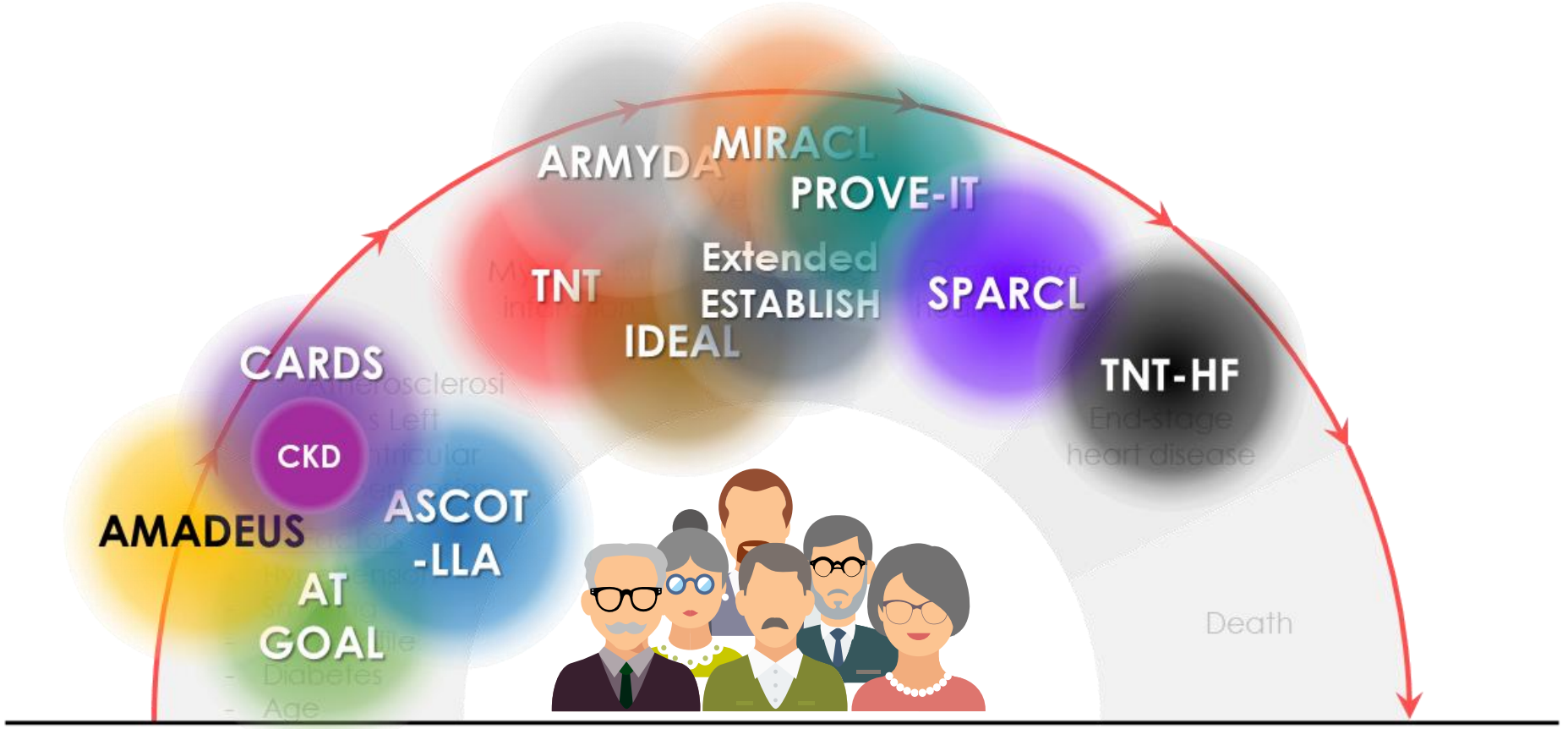


Adapted from KSoLA.[1]

Data source: National Health Insurance Big Data 2002-2018

Reference 1. The Korean Society of Lipid and Atherosclerosis (KSoLA). *Dyslipidemia fact sheet in Korea.* 2020.

Cardiovascular Disease Continuum in Lipitor



Conclusion

1 Continuous increase in dyslipidemia and latest LDL-C management trend(Early & Lower for Longer)

Many epidemiological studies have shown that LDL-C is the biggest risk factor for coronary artery disease and that there is a linear correlation with it. It has been proven that actively lowering LDL-C early and maintaining it for a long time is an effective strategy to prevent cardiovascular disease

2 There is a treatment gap regarding LDL-C management in reality

In particular, although strong LDL-C control is recommended through guidelines to prevent cardiovascular disease in high-risk patients, a treatment gap exists due to the limitations of high-dose single statin therapy.

3 Solutions in closing residual risk of major CV events

To reduce residual risk, combined use of ezetimibe may be helpful in reaching the LDL-C goal. Additionally, research continues to show that it can be positive for reducing CV events