Intensive Lipid-Lowering Therapy for Early Achievement of LDL-C Target in Cardiovascular Disease

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M/60, ER for Aggravating Chest Pain

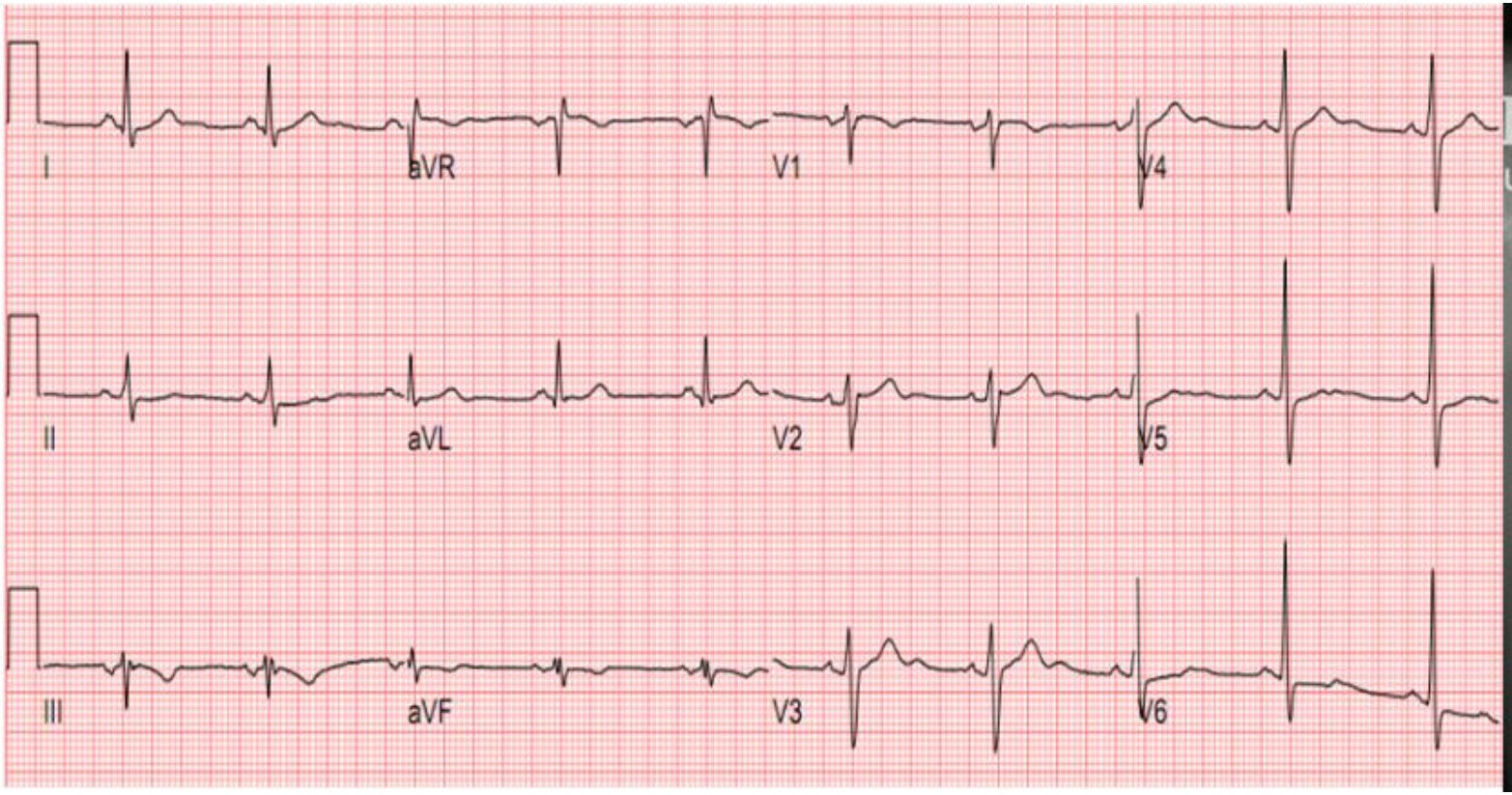
- Visit ER d/t Effort angina (onset: 1 month ago)

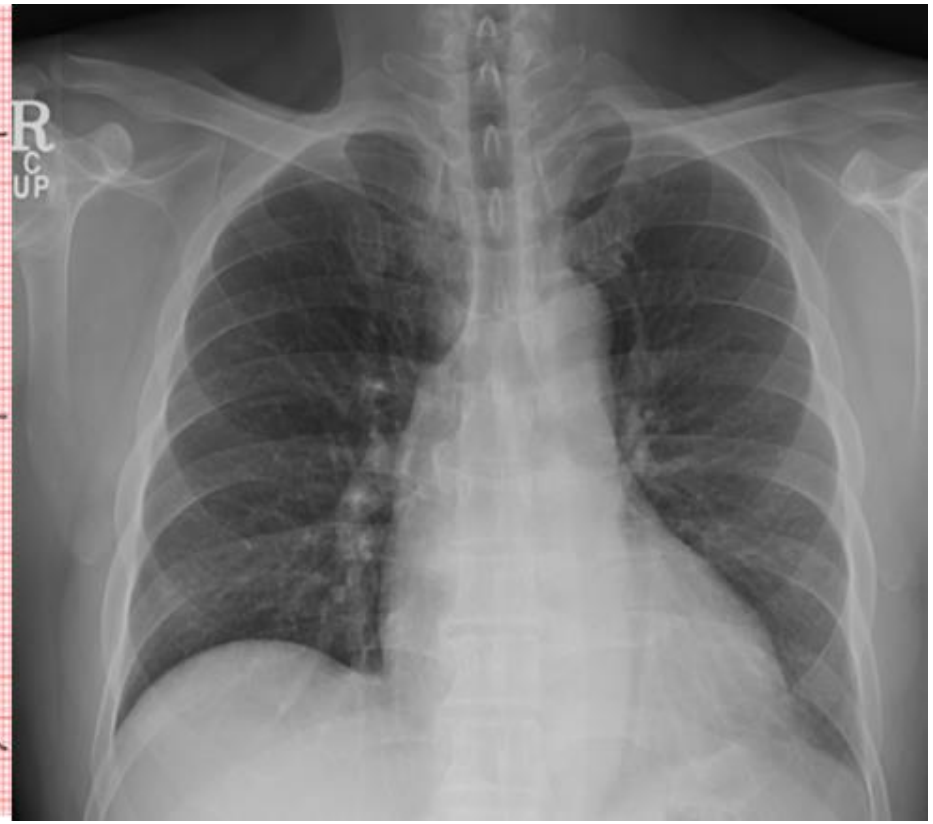
- Hypertension on Amlodipine 5mg qd, Current smoker

- Serum Creatinine 1.0 mg/dl
- Total Cholesterol : 230 mg/dl, LDL-Cholesterol 140 mg/dl
- Cardiac enzyme : normal

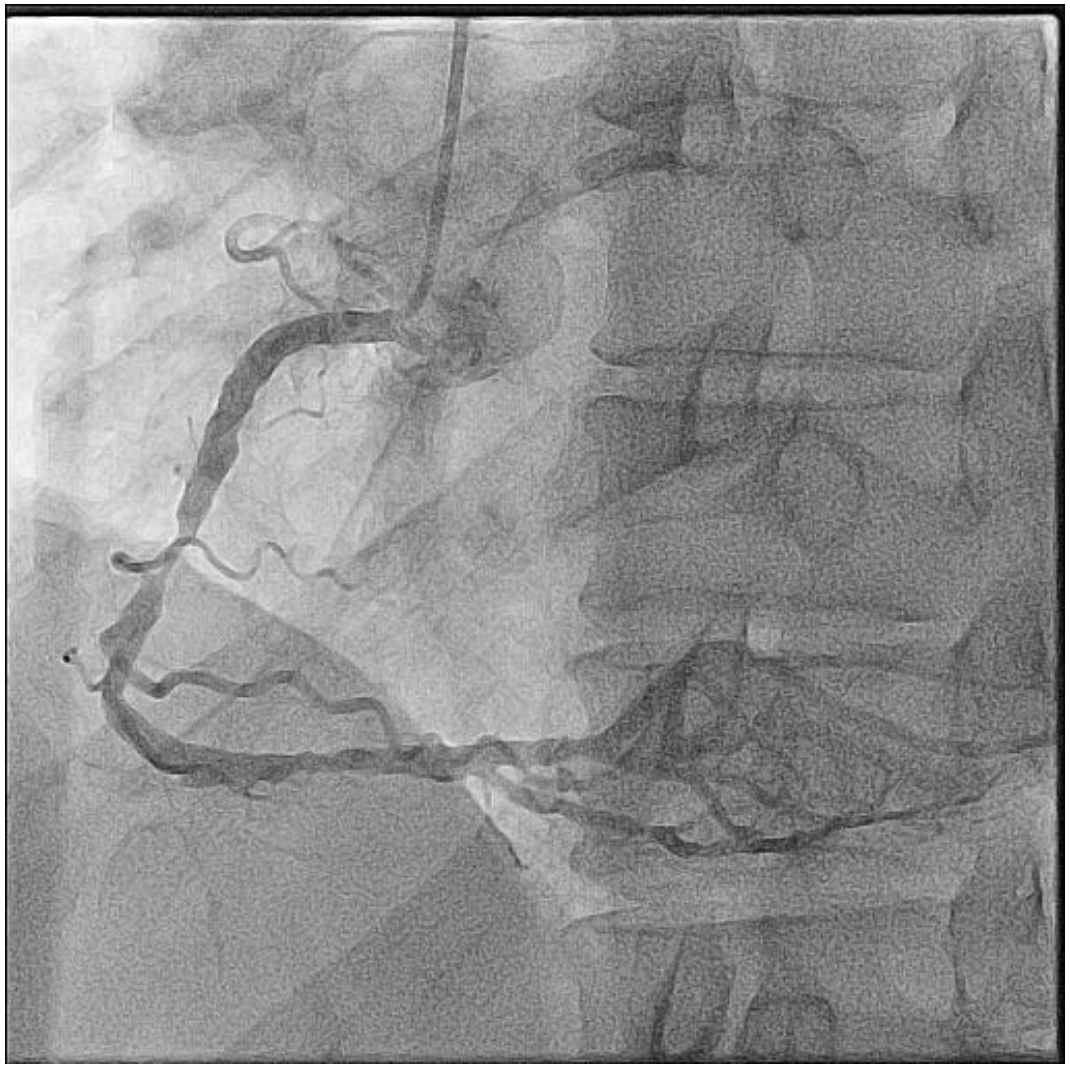
- EKG : Normal sinus rhythm
- CXR : WNL
- TTE : LV EF 60% without RWMA

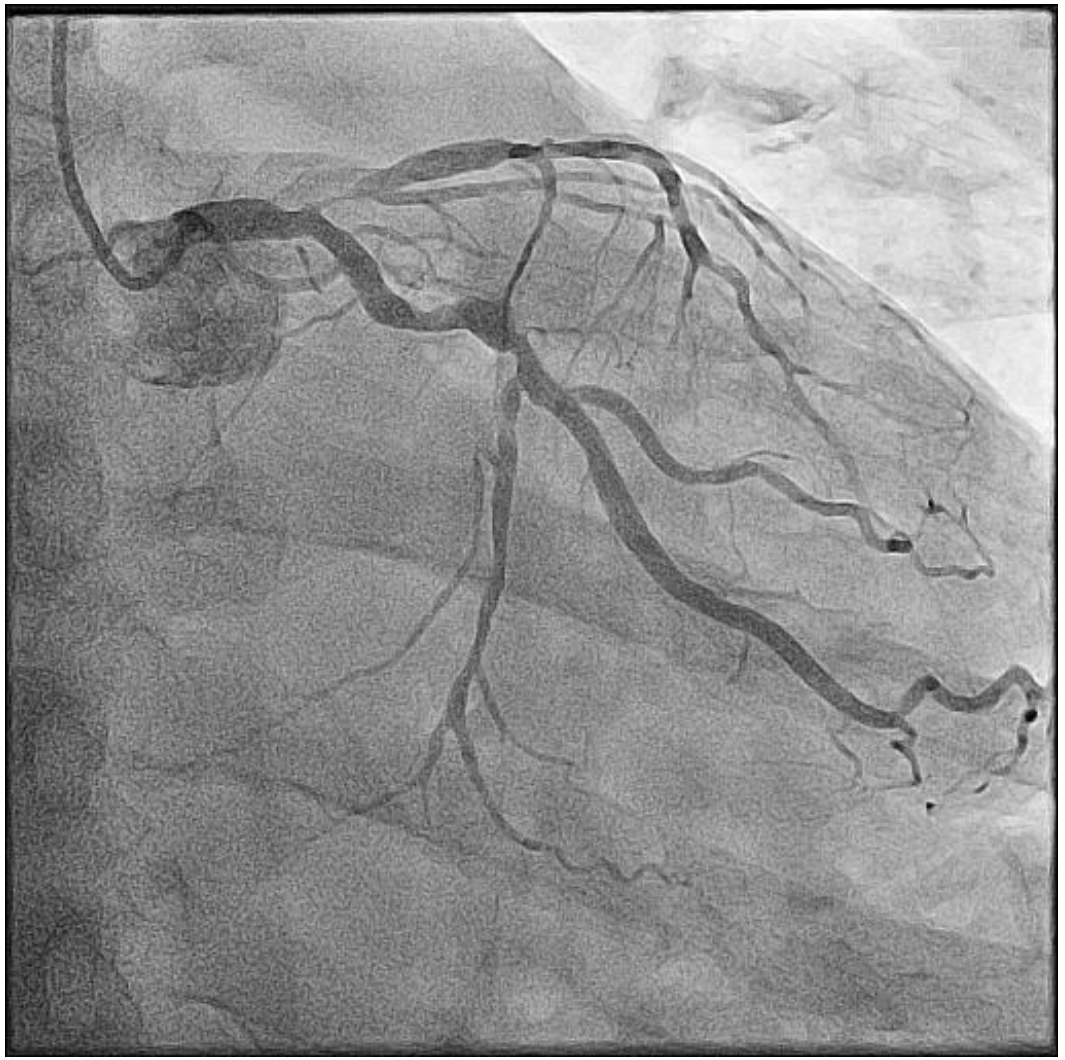
M/60 with Unstable Angina



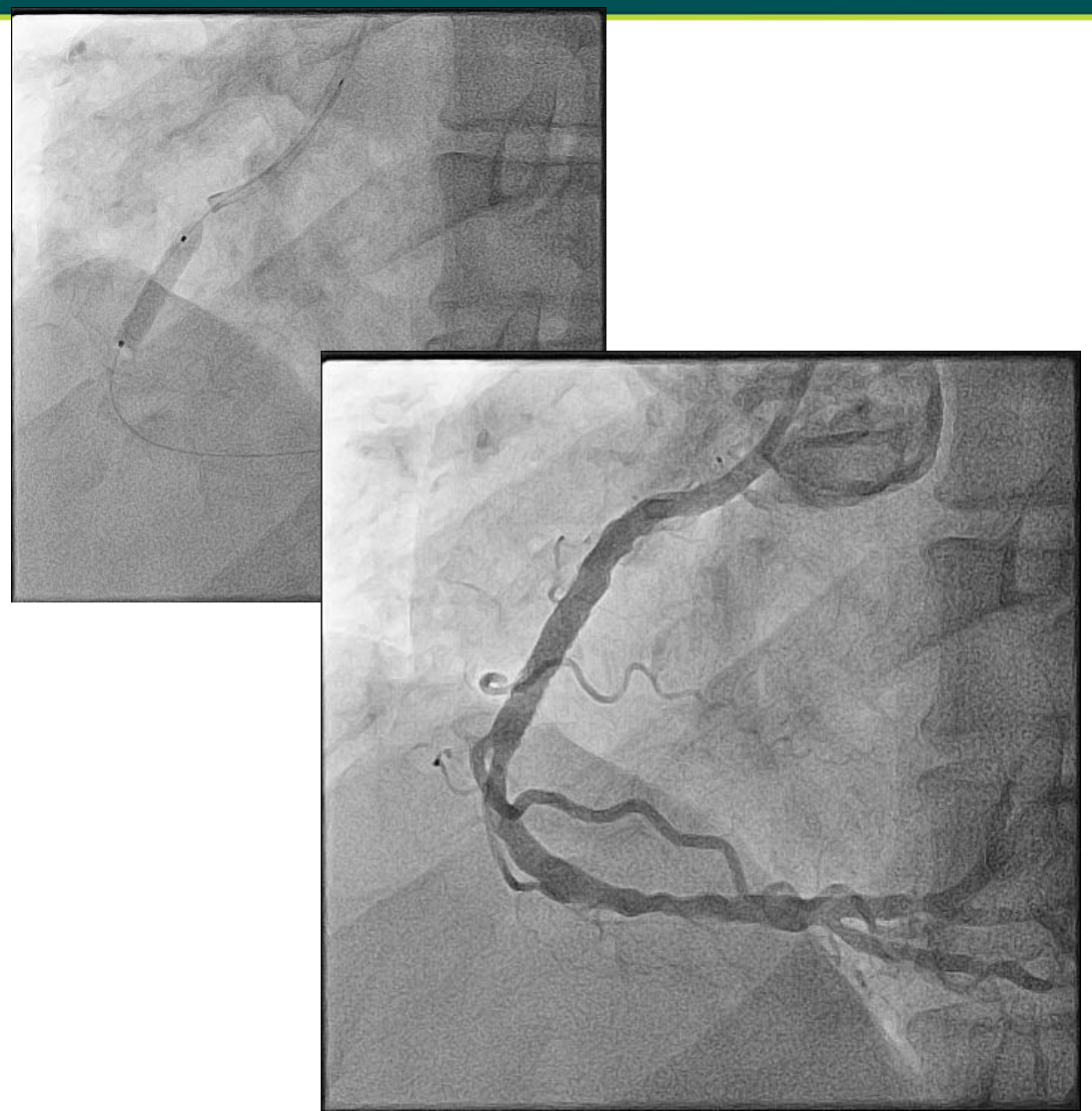


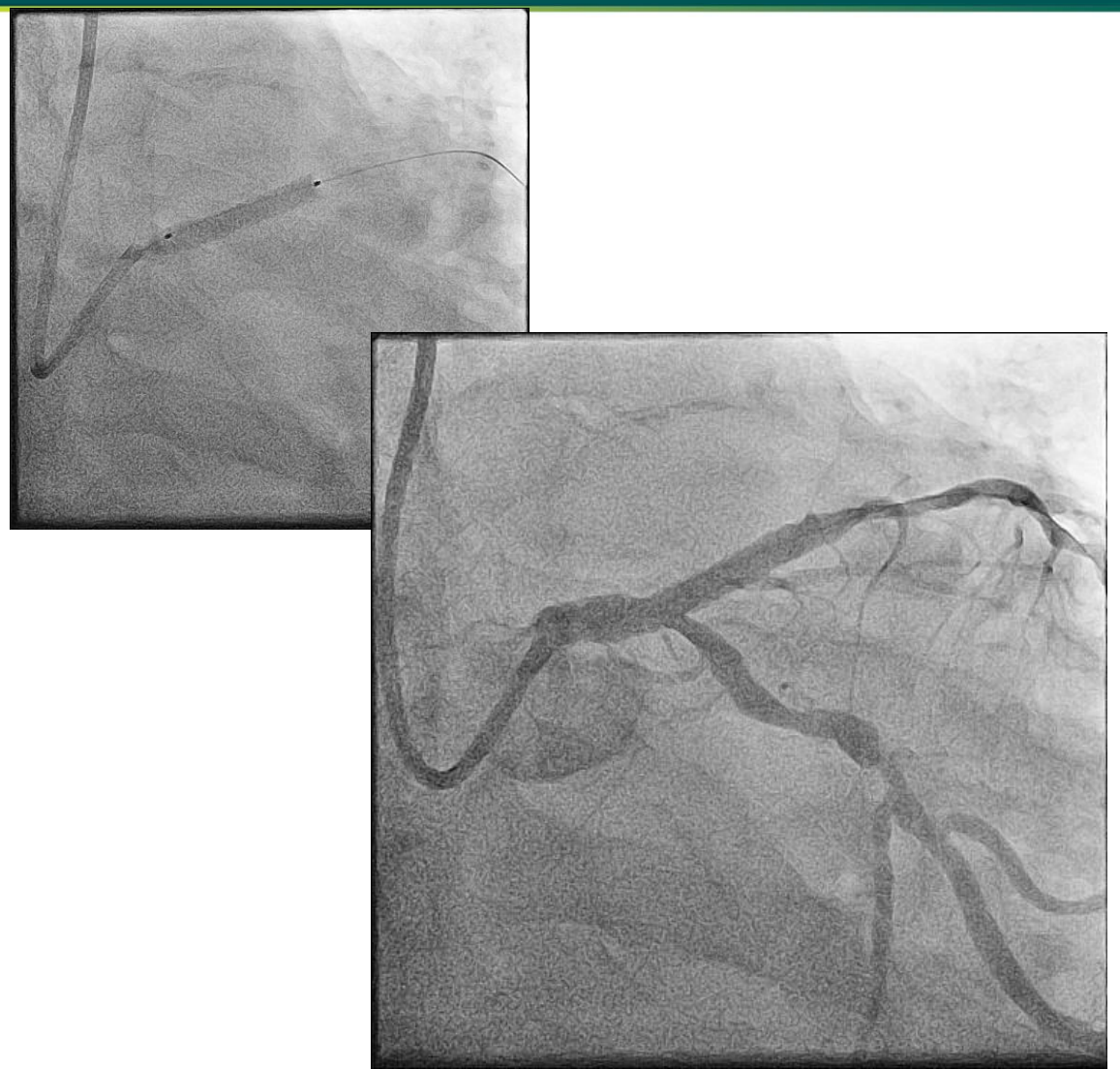
M/60 with Unstable Angina





M/60 with Unstable Angina, PCI at LAD & RCA



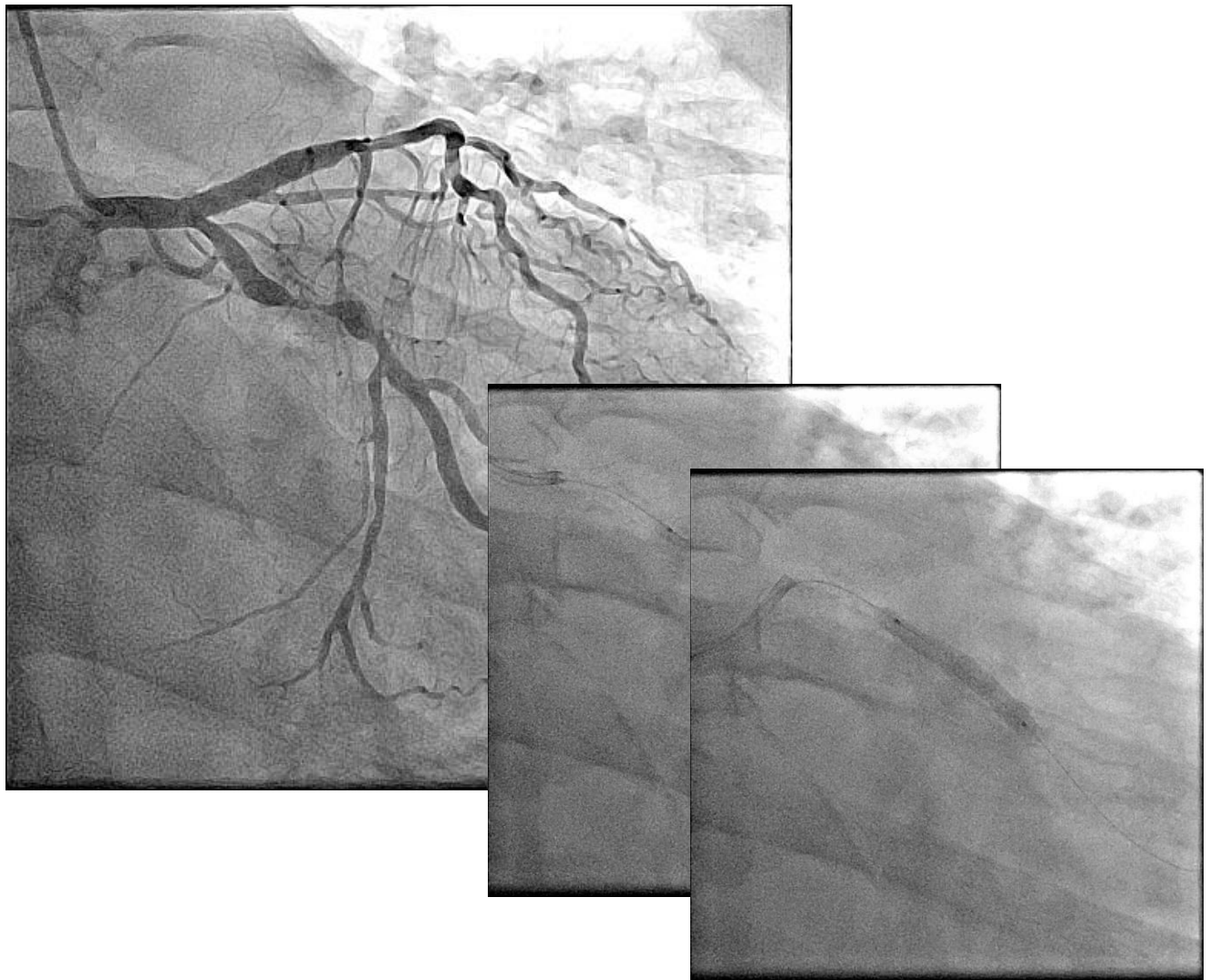


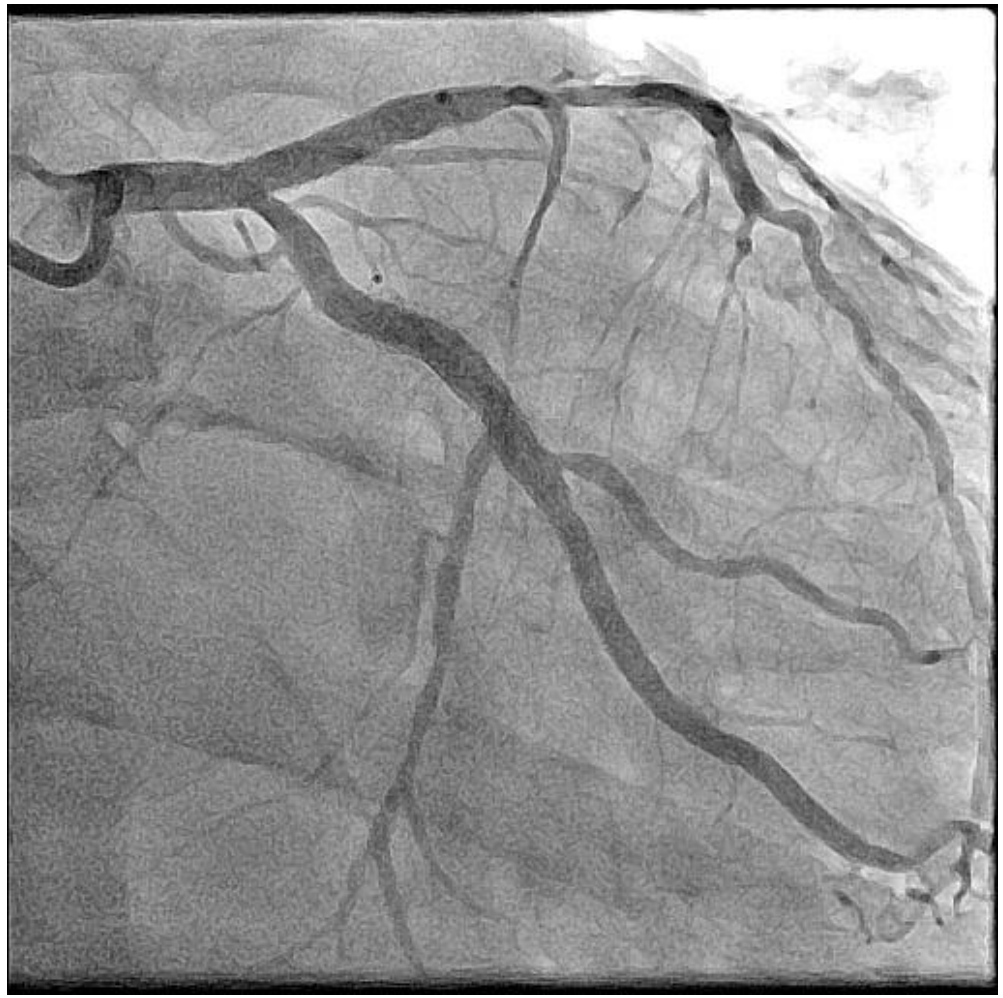
M/60 with Unstable Angina, s/p PCI at LAD & RCA

- Discharge medication
  : Aspirin 100mg qd, Clopidogrel 75mg qd, Diltiazem 90mg bid
  Atorvastatin 40mg / Ezetimibe 10mg qd

- FU Lab at 1 month
  - Total cholesterol 136 mg/dL
  - LDL cholesterol 78 mg/dL

11 months later… ER with NSTEMI





LDL-C is a main target for CVD patients

Cardiovascular disease is highly associated with dyslipidemia[1-3]

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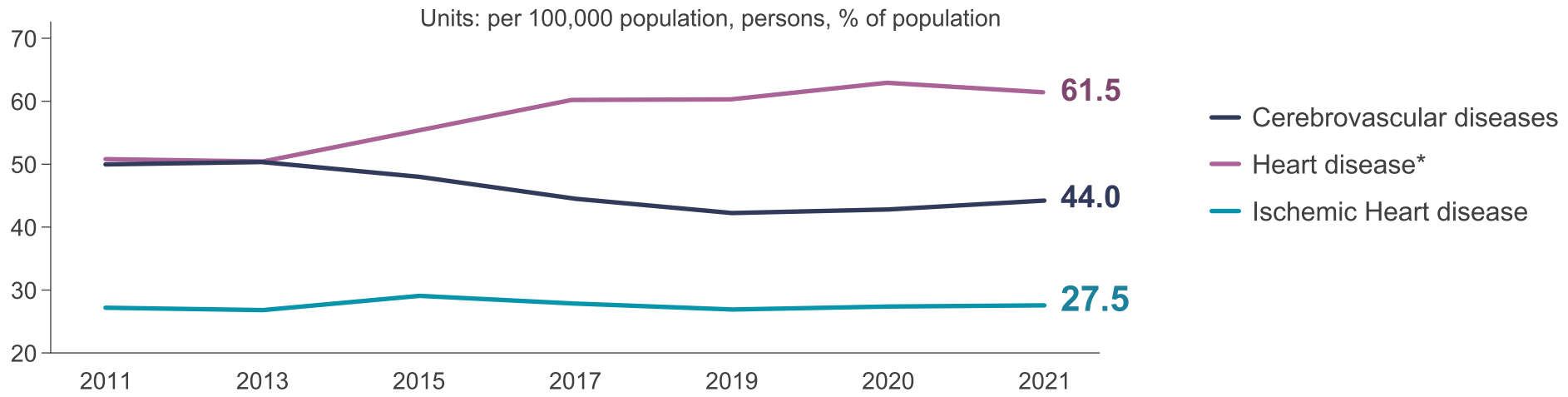
According to domestic mortality statistics, the number of deaths due to cerebrovascular disease has decreased rapidly, but the death rate due to ischemic heart disease is increasing.This is believed to be due to improved levels of hypertension management and increased prevalence of dyslipidemia.[1]

Mortality trends for circulatory diseases in Korea 2011-2021[2]



Dyslipidaemia increases the risk of ischaemic heart disease more than cerebrovascular disease.[3]

* Heart disease includes ischaemic heart disease (myocardial infarction, angina, etc.) and other heart conditions (heart failure, endocarditis, etc.).

Reference. 1. 통계청. 사망원인 통계(2021). 2. 통계청, 사망원인 통계(2020) 3. KSoLA 이상지질 진료지침 제 5판. 한국지질·동맥경화학회 진료지침위원회. 2022;1-281

High LDL-C levels increase cardiovascular risk and contribute to cardiovascular disease[1]

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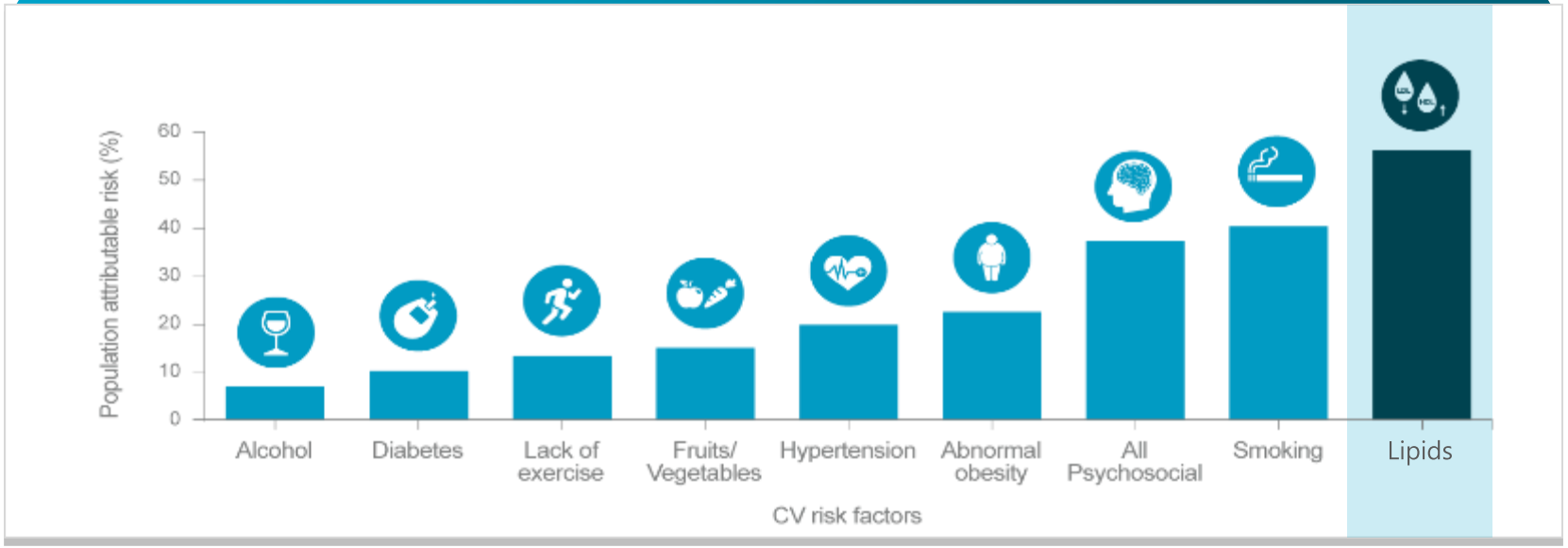
- Cardiovascular risk factors determine cardiovascular disease progression and clinical event presentation.[1]
- Identification of modifiable cardiovascular risk factors such as high LDL-C levels has enabled the design of targeted prevention strategies in order to reduce the impact on disease progression.[2,3]

Population attributable risks for the association of risk factors to myocardial infarction[3]



Study Design

This study sought to assess the effect of potentially modifiable risk factors associated with myocardial infarction. It is a standardised case-control study of acute myocardial infarction in 52 countries, enrolling 15,152 cases and 14,820 controls.[3]

LDL-C, low-density lipoprotein cholesterol.

Reference. 1. Badimon L, *et al*. Int J Cardiol. 2016;217:S7–S9; 2. Mannsverk J, *et al*. Circulation. 2016;133:74–81; 3. Yusuf S, *et al*. Lancet. 2004;364:937–952.

Rate of CV events are related to risk level and LDL-C[1]

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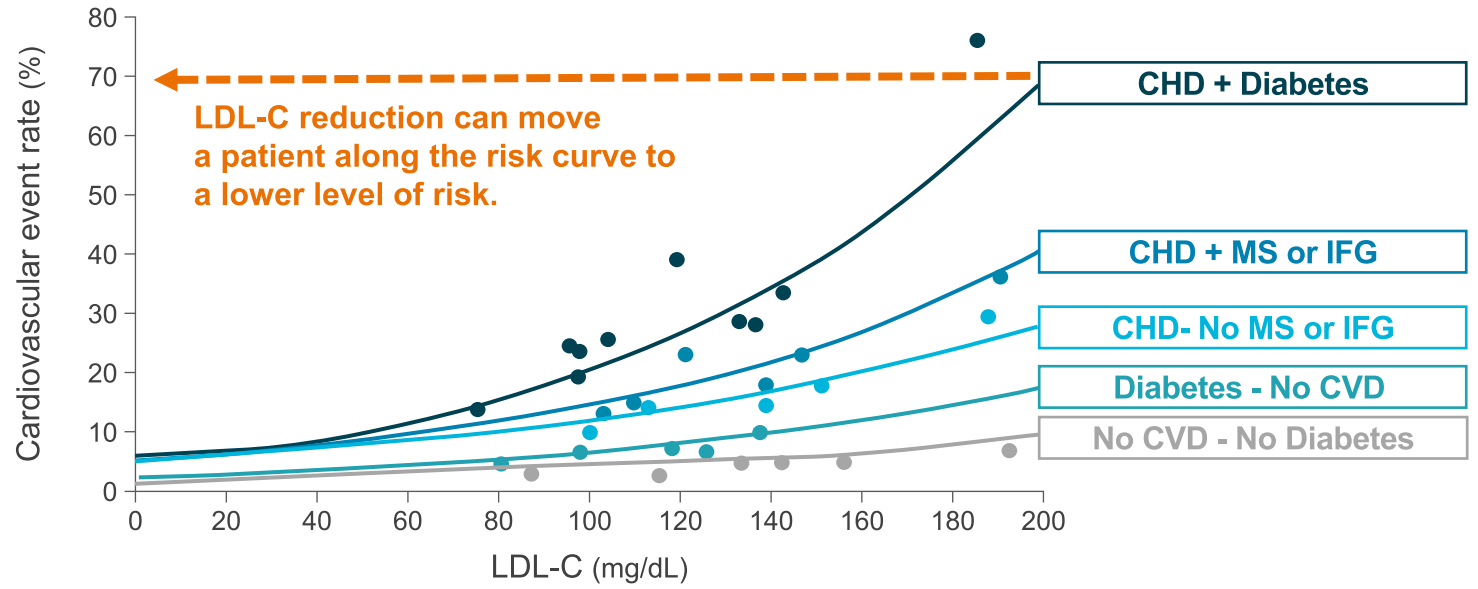
Intent-to-treat LDL cholesterol level and risk for hard cardiovascular events (nonfatal myocardial infarction, CHD death, and stroke) by the presence of coronary heart disease (CHD), metabolic syndrome (MS), impaired fasting glucose (IFG), or diabetes in placebo-controlled statin trials of approximately 5 years in duration[1]



Study Design

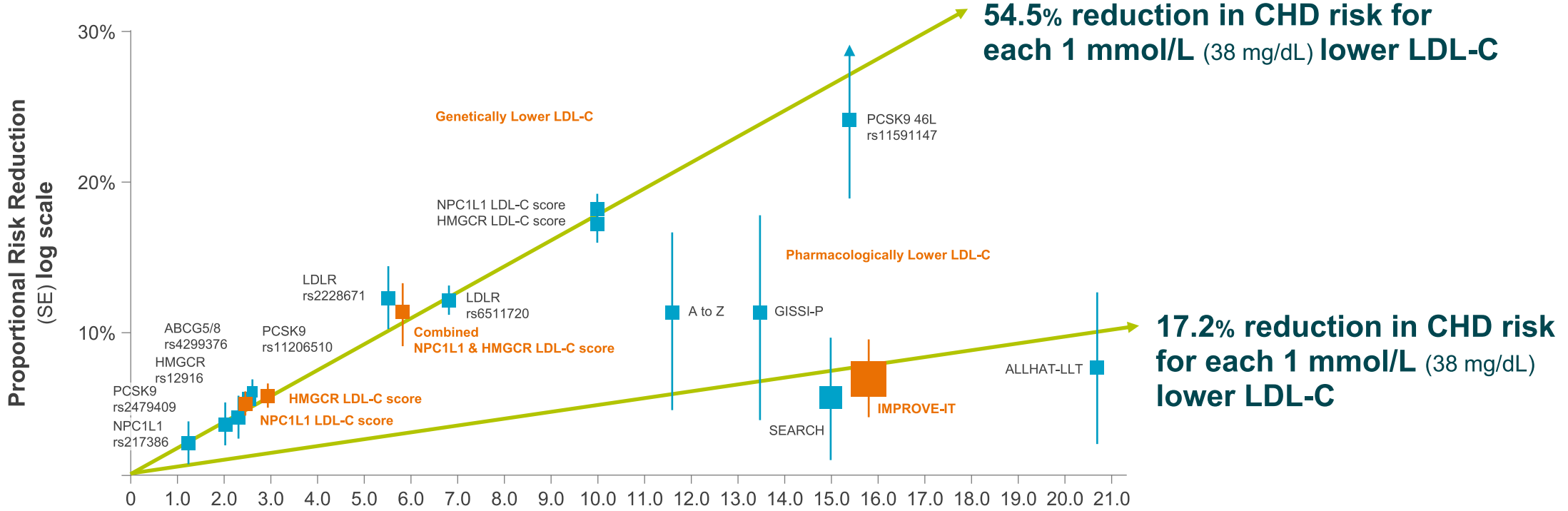
Review article to identify patients for aggressive cholesterol lowering.[1]

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

Reference. 1. Robinson JG, *et al.* Am J Cardiol. 2006 Nov 15;98(10):1405-1408.

The lower the better

Clinical benefit is determined by absolute exposure to lower LDL



Reference. 1. Ference *et al.* J Am Coll Cardiol 2015;65:1552–1561.

Cumulative Effect of LDL on Risk of Atherosclerotic Cardiovascular Disease[1]

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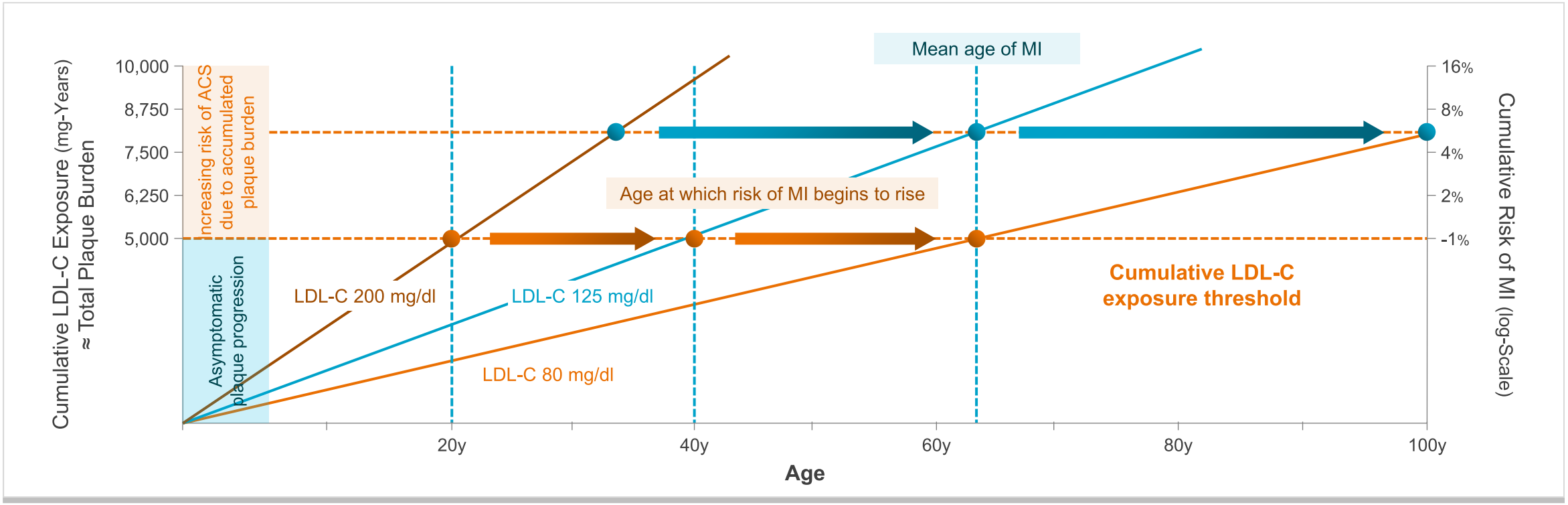
The lower cumulative exposure to LDL-c can slow plaque progression and delay the onset of myocardial infarction and other acute coronary syndromes.



Reference. 1. Frence, Graham, Tokgozoglu, Catapano JACC 2018; 92: 1141-1156

Cholesterol control is fundamental in reducing the risk of ASCVD events[1,2]

Lifetime exposure to elevated LDL-C is a causal and cumulative risk factor for ASCVD[1]

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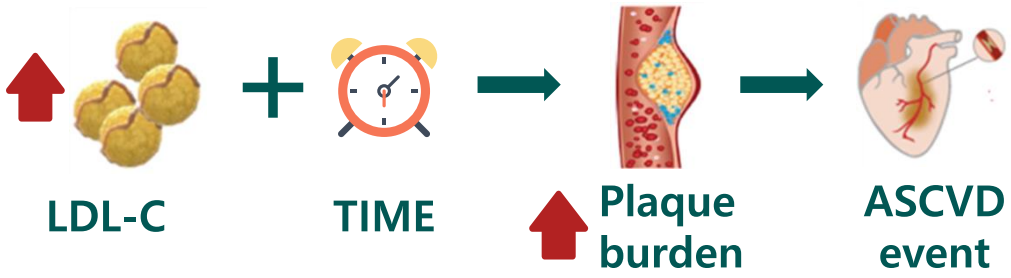
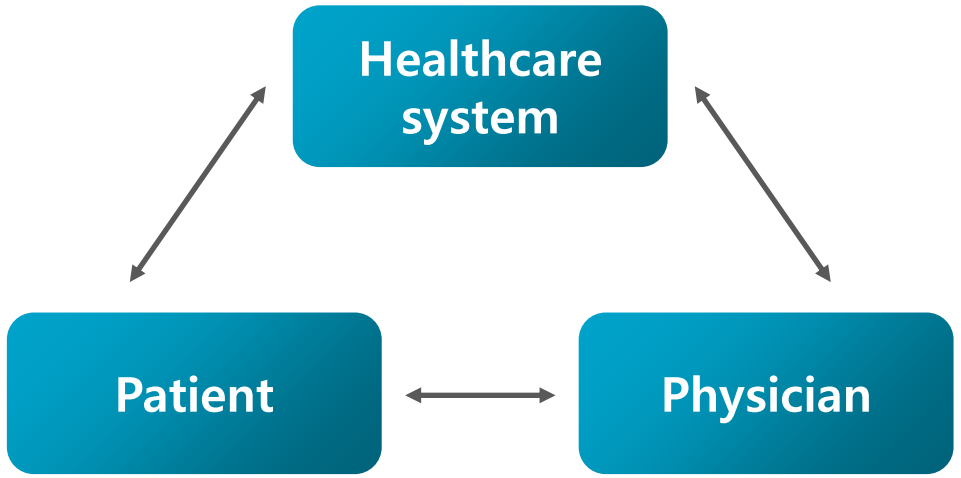


Sustained **lifetime exposure** to **high cholesterol** leads to an increase in the **plaque burden** and eventually to **ASCVD** events[1]



Roll out population-based approaches to prevent ASCVD and reduce population level cholesterol exposure throughout the life-course[2]

ASCVD, atherosclerotic cardiovascular diseases; LDL-C, low-density lipoprotein cholesterol.

[Study design[1]] This review describes the cumulative effect of lipid-carrying lipoproteins on the risk of cardiovascular disease, estimates the magnitude of the clinical benefit that can be achieved by maintaining optimal lipid levels, identifies the most effective timing for implementing strategies designed to achieve optimal lipid levels, and provides a clinical pathway to help people achieve the lipid levels necessary for ideal cardiovascular health.

[Study design[2]] Through a review of published guidelines and research papers since 2017, and consultation with a committee composed of experts in clinical management of dyslipidaemias and health systems research in low-and-middle income countries (LMICs), this Roadmap identifies (1) key principles to effective ASCVD prevention (2) gaps in implementation of these interventions (knowledge-practice gaps); (3) health system roadblocks to treatment of elevated cholesterol in LMICs; and (4) potential strategies for overcoming these.

Reference 1. Ference BA, et al. J Am Coll Cardiol. 2018 Sep 4;72(10):1141-1156. 2. Ray KK, et al. Glob Heart. 2022 Oct 14;17(1):75.

Evidence supports LDL as causal[1]

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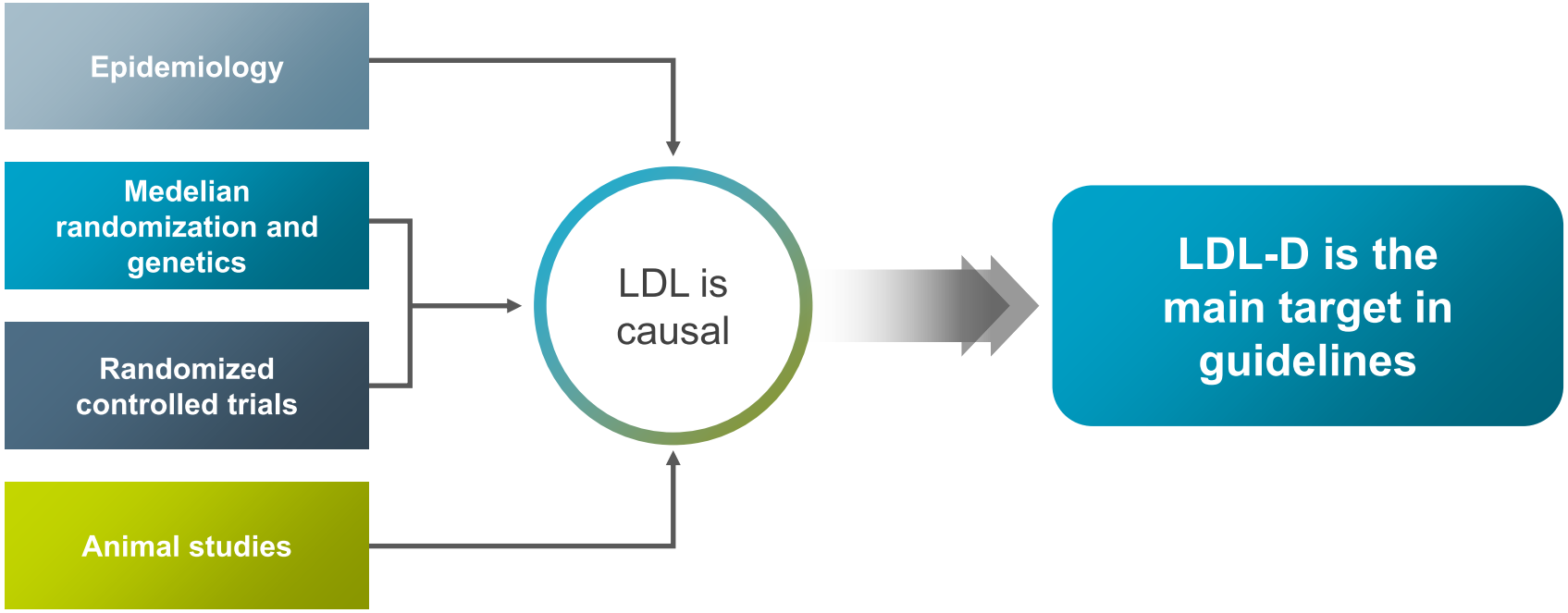
- Reducing LDL-C should have a constant effect on the risk of ASCVD per unit absolute reduction in LDL-C, and because LDL-C has both a causal and a cumulative effect on the risk of ASCVD therefore are most likely to benefit from therapies that lower LDL-C.[1]



ASCVD, atherosclerotic cardiovascular diseases; LDL-C, low-density lipoprotein cholesterol.

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Reference 1. Ference BA, et al. Eur Heart J. 2017 Aug 21;38(32):2459-2472.

2019 ESC/EAS Guideline

Treatment goals for LDL-C across CV risk categories[1]

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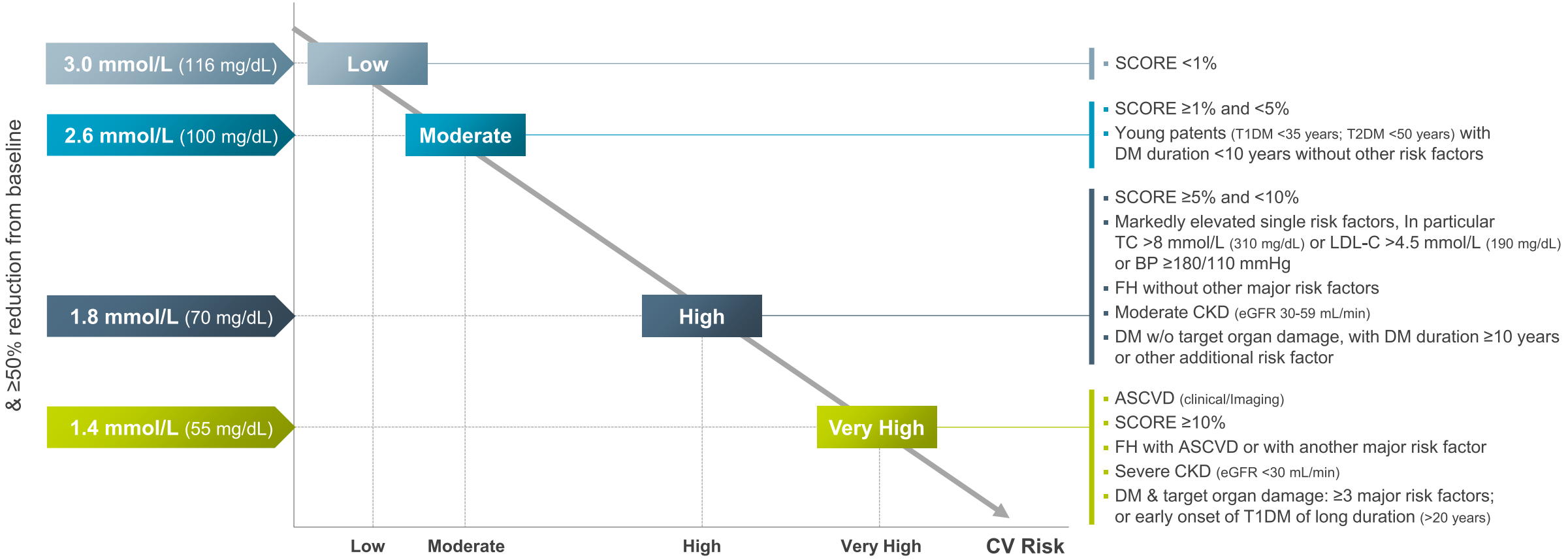

ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; eGFR, estimated glomerular filtration rate; FH, familial hypercholesterolaemia; SCORE, Systematic COronary Risk Evaluation; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TC, total cholesterol.

Reference. 1. Mach F, *et al.* Eur Heart J. 2020 Jan 1;41(1):111-188.

2019 ESC/EAS Guideline

Lower LDL-C goals are recommended for the patients with ACS[1]

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"More intensive LDL-C reduction is recommended across very high and high-risk CV categories[1]"

Class	Level	CV risk category	LDL-C goals		
I	A	In secondary prevention for patients at very high risk	Reduction of ≥50% from baseline	**and**	<55 mg/dL (<1.4 mmol/L)
I	A	In patients at high risk	Reduction of ≥50% from baseline	**and**	<70 mg/dL (<1.8 mmol/L)

Class I: Evidence and/or general agreement that a given treatment or procedure is beneficial, useful and effective; **Level A**: Data derived from multiple randomised clinical trials or meta-analyses.

Very high-risk: People with any of the following: ① 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. ② DM with target organ damage, or at least three major risk factors, or early onset of T1DM of long duration (>20 years). ③ Severe CKD (eGFR <30 mL/min/1.73 m^2). ④ A calculated SCORE ≥10% for 10-year risk of fatal CVD. ⑤ FH with ASCVD or with another major risk factor; **High-risk: People with:** ① 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. ② Patients with FH without other major risk factors. ③ Patients with DM without target organ damage, with DM duration ≥10 years or another additional risk factor. ④ Moderate CKD (eGFR 3059 mL/min/1.73 m^2). ⑤ A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.

ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CKD, chronic kidney disease; DM, diabetes mellitus; EAS, European Atherosclerosis Society; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors; SCORE, Systemic COronary Risk Evaluation; TC, total cholesterol.

Reference. 1. Mach F, *et al*. Eur Heart J. 2020 Jan 1;41(1):111-188.

2022 KSoLA Guideline

Treatment strategies according to risk categories and LDL-C[1]

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Risk category	LDL-C(mg/dL)					
	<55	55-69	70-99	100-129	130-159	≥ 160
Coronary artery disease[1)]*	Lifestyle modification and consider drug	Lifestyle modification and concomitant drug intervention	Lifestyle modification and concomitant drug intervention	Lifestyle modification and concomitant drug intervention	Lifestyle modification and concomitant drug intervention	Lifestyle modification and concomitant drug intervention
Atherosclerotic stroke and transient ischemic attack* Carotid artery disease* Peripheral artery disease* Abdominal arotic aneurysm* Diabetest mellitus (duration ≥ 10 years or major risk factor† or target organ damage)[2)]	Lifestyle modification	Lifestyle modification and consider drug	Lifestyle modification and concomitant drug intervention	Lifestyle modification and concomitant drug intervention	Lifestyle modification and concomitant drug intervention	Lifestyle modification and concomitant drug intervention
Diabetes mellitus (duration < 10 years and no major risk factors†)	Lifestyle modification	Lifestyle modification	Lifestyle modification and consider drug	Lifestyle modification and concomitant drug intervention	Lifestyle modification and concomitant drug intervention	Lifestyle modification and concomitant drug intervention
Moderate risk[3)] (major risk factors† ≥ 2)	Lifestyle modification	Lifestyle modification	Lifestyle modification	Lifestyle modification and consider drug	Lifestyle modification and concomitant drug intervention	Lifestyle modification and concomitant drug intervention
Low risk[3)] (major risk factors† ≤ 1)	Lifestyle modification	Lifestyle modification	Lifestyle modification	Lifestyle modification	Lifestyle modification and consider drug	Lifestyle modification and concomitant drug intervention

* 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 diabetic patients with target organ damage (albuminuria, CKD [eGFR <60 mL/min/1.73m^2], retinopathy, neuropathy, left ventricular hypertrophy) or major risk factors† ≥ 3 (optional).
3) In groups with moderate and low risk, statin is considered when LDL-C is consistently high even after several weeks or months of lifestyle modification.

LDL-C, low-density lipoprotein cholesterol.

Reference. 1. 한국지질동맥경화학회(KSoLA). 2022 이상지질혈증 치료지침 제5판.

“Fast first time right”

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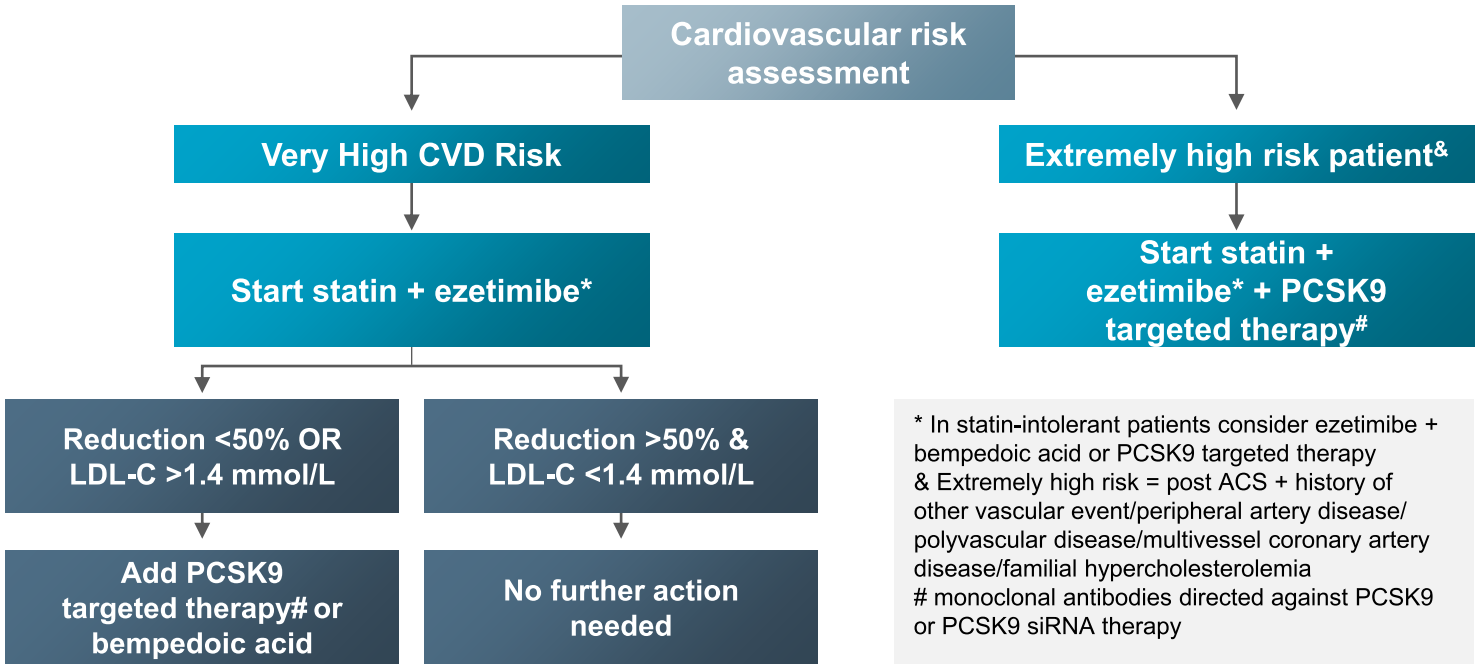
Recommended to shift the paradigm for very high-risk patients from ‘an intensive statin therapy first’ approach to an ‘**intensive lipid-lowering therapy**’ approach.[1]



* In statin-intolerant patients consider ezetimibe + bempedoic acid or PCSK9 targeted therapy
& Extremely high risk = post ACS + history of other vascular event/peripheral artery disease/ polyvascular disease/multivessel coronary artery disease/familial hypercholesterolemia
# monoclonal antibodies directed against PCSK9 or PCSK9 siRNA therapy

Combination lipid-lowering therapy as first line strategy in very high-risk patients

ACS, acute coronary syndrome; CVD, cardiovascular disease; LDL-C, low-density lipoprotein; PCSK9, proprotein convertase subtilisin/kexin type 9; siRNA, small interfering RNA.

Reference. 1. Ray KK, et al. Eur Heart J. 2022 Feb 22;43(8):830-833.

History of LDL-C lowering trials[1]

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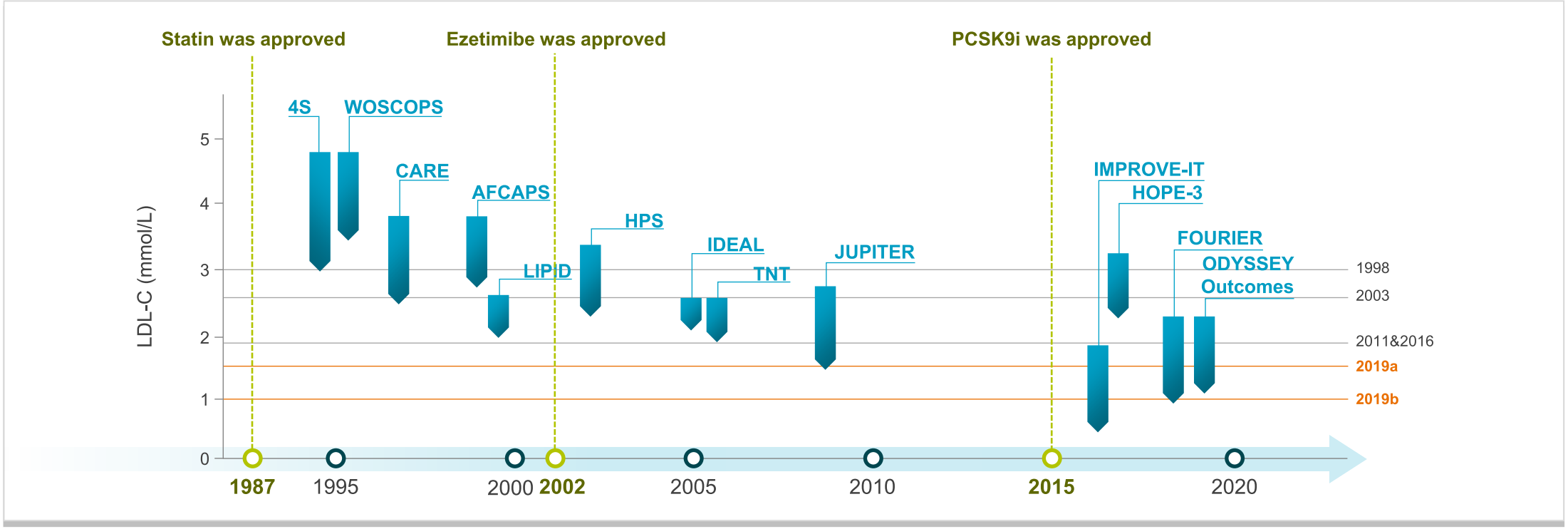
LDL-C lowering with statins alone and in combination with ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors has been remarkably successful as an intervention strategy.[1]



Inhibition of PCSK9 has made it possible to use combination therapy to attain even lower LDL-C levels.

LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.

[Study design[1]] This review summarises key data supporting the ESC/EAS recommendation to reduce markedly LDL-C levels, with aggressive goals for LDL-C in patients at highest risk, and provides expert opinion on its significance for clinical practice.

Reference. 1. Packard C, et al. Heart. 2021 Sep;107(17):1369-1375.

LDL-C lowering and benefits of Statins[1]

Clear relationship of fewer CV events with lower LDL-C levels.[1]

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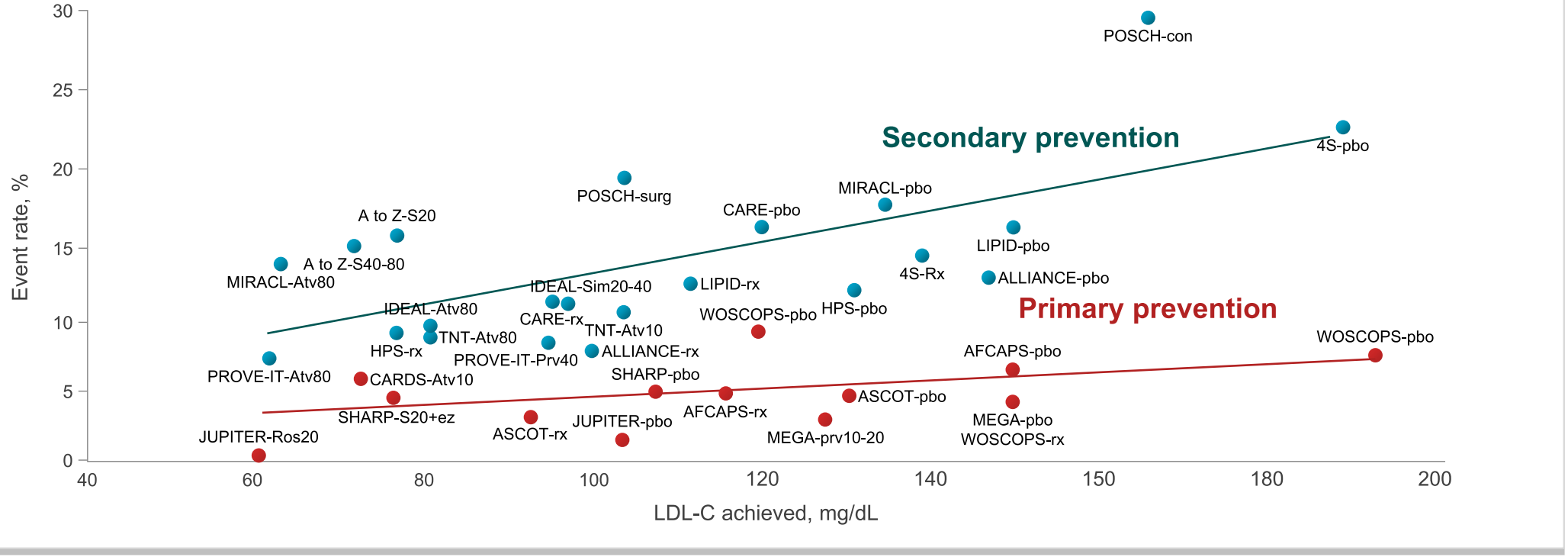
LDL-C levels vs rates of coronary events[1]



4S-pbo, Scandinavian Simvastatin Survival Study placebo group; 4S-rx, 4S simvastatin group; A to Z-S20, A to Z trial simvastatin 20 mg group; A to Z-S40-80, A to Z trial simvastatin 40–80 mg group; AFCAPS-pbo Air Force/Texas Coronary Atherosclerosis Prevention Study placebo group; AFCAPS-rx, AFCAPS lovastatin 20–40 mg group; ALLIANCE-pbo, Aggressive Lipid-Lowering Initiation Abates New Cardiac Events study placebo group; ALLIANCE-rx, ALLIANCE atorvastatin group; ASCOT-pbo, Anglo-Scandinavian Cardiac Outcomes Trial placebo group; ASCOT-rx, ASCOT atorvastatin group; CARDS-pbo, Collaborative Atorvastatin Diabetes Study placebo group; CARDS-Atv10, CARDS atorvastatin 10 mg group; CARE-pbo, Cholesterol and Recurrent Events trial placebo group; CARErx, CARE pravastatin group; HPS-pbo, Heart Protection Study placebo group; HPS-rx, HPS simvastatin 40 mg group; IDEAL-Sim20–40, Incremental Decrease in End Points Through Aggressive Lipid Lowering trial simvastatin 20–40 mg group; IDEAL-Atv80, IDEAL atorvastatin 80 mg group; JUPITER-pbo, Justifi cation for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin placebo group; JUPITER-Ros20, JUPITER rosuvastatin 20 mg group; LIPIDpbo, Long-Term Intervention With Pravastatin in Ischaemic Disease placebo group; LIPID-rx, LIPID pravastatin group; MEGA-pbo, anagement of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese study placebo group; MEGA-Prv10-20, MEGA pravastatin 10–20 mg group; MIRACL-pbo, Myocardial Ischemia Reduction With Acute Cholesterol Lowering trial placebo group; MIRACL-Atv80, MIRACL trial atorvastatin 80 mg group; POSCH-con, Program on the Surgical Control of the Hyperlipidemias control group; POSCH-surg, POSCH ileal bypass group; PROVE-IT-Prv40, Pravastatin or Atorvastatin Evaluation and Infection Therapy pravastatin 40 mg group; PROVE-IT-Atv80, PROVE-IT atorvastatin 80 mg group; SHARP-pbo, Study of Heart and Renal Protection placebo group; SHARP-S20+ez, SHARP simvastatin 20 mg plus ezetimibe group; TNT-Atv10, Treating to New Targets atorvastatin 10 mg group; TNT-Atv80, TNT atorvastatin 80 mg group; WOSCOPS-pbo West of Scotland Coronary Prevention Study placebo group; WOSCOPS-rx, WOSCOPS pravastatin group.

Reference 1. Sabatine MS. Cleve Clin J Med. 2016 Mar;83(3):181-6.

Reduction of LDL-C with statins reduce the risk of major vascular events; CTTC[1]

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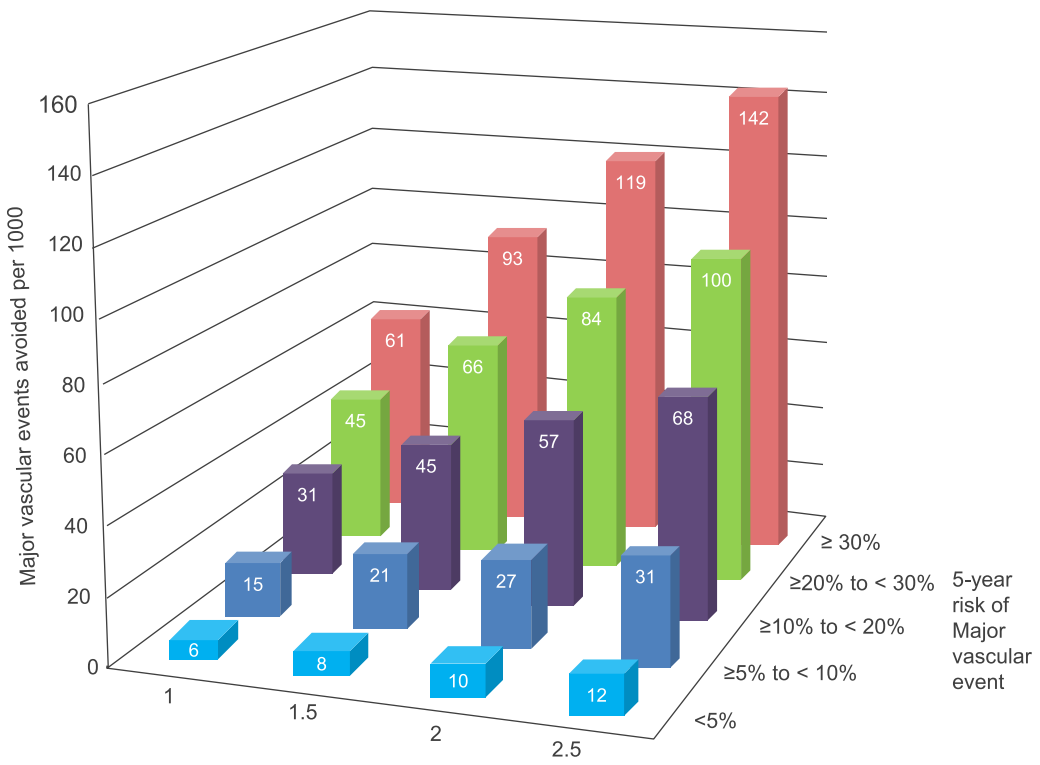

Study Design

A meta-analysis by CTT included individual patient data from 22 trials of statin vs. control (n=134,537; mean LDL-C difference 1.08 mmol/L; median follow up 4.8 years) and five trials more vs. less statin (n=39,612; difference 0.51 mmol/L; 5.1 years)

Results

Reduction of LDL-C with statins reduced the risk of major vascular events (RR, 0.79; 95% CI: 0.77-0.81; per 1.0 mmol/L reduction)

- there was no evidence that a reduction of LDL-C with statins increased cancer incidence, cancer mortality or other non-vascular mortality
- Higher absolute risk = greater absolute reduction = lower NNT

In these individual, each 1 mmol/L reduction in LDL-C produced an absolute reduction in major vascular events of about 11 per 1,000 over 5 years.

Benefit of LDL-C reduction through statin therapy exceed and known hazards

CCTC, cholesterol treatment trialists' collaboration; LDL-C, low-density lipoprotein cholesterol.

Reference. 1. Cholesterol Treatment Trialists' (CTT) Collaborators; Mihaylova B, et al. Lancet. 2012 Aug 11;380(9841):581-90.

DA VINCI study: combination therapy required[1]

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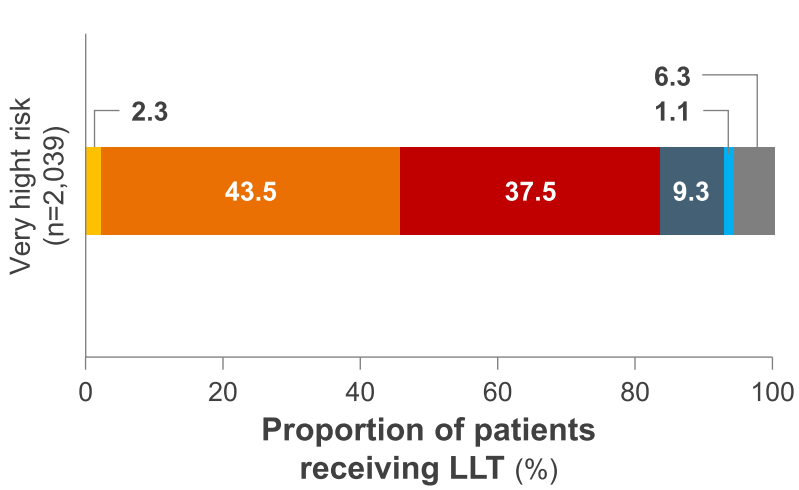

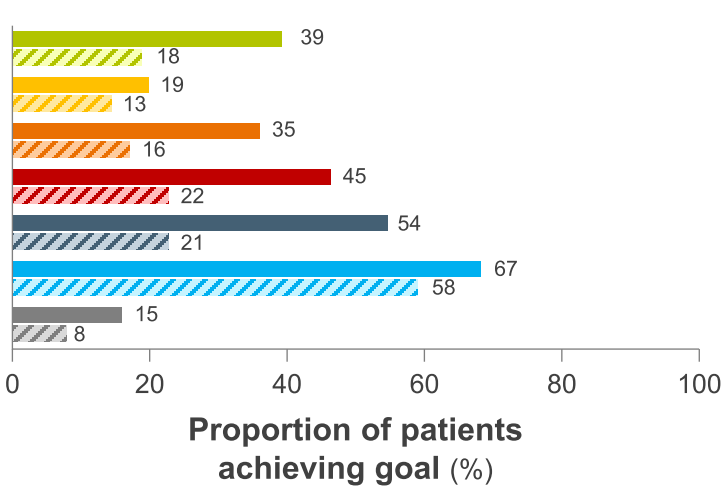

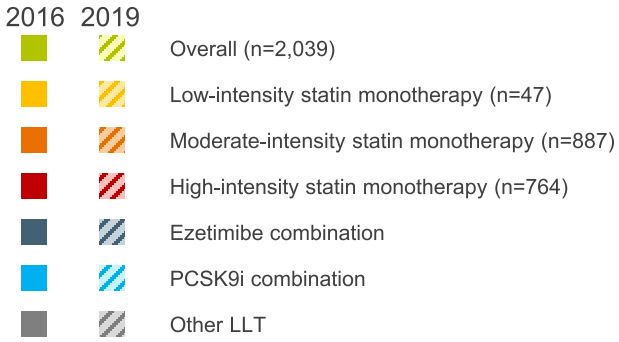

2016-2019 riak-based LDL-C targets:
Low risk: 2016/2019, < 3.0 mmol/L
Moderate risk: 2016, < 3.0 mmol/L; 2019 < 2.6 mmol/L
High risk: 2016, < 2.6 mmol/L; 2019, < 1.8 mmol/L
Very high risk: 2016, < 1.8 mmol/L; 2019, < 1.4 mmol/L

- With more stringent LDL-C goals by 2019 ESC/EAS guidelines, goal attainment is even lower.[1]
- It is clear that the 2019 ESC/EAS LDL-C goal for high and very high-risk patients is largely unattainable on high-intensity statin monotherapy;[1]
- Patients also require combination therapy[1]

EAS, european atherosclerosis society; ESC, eropean society of cardiology; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapies.

[Study design[1]] Investigators aimed an 18 country, cross-sectional, observational study of patients prescribed LLT for primary or secondary prevention in primary or secondary care across Europe. Between June 2017 and November 2018, data were collected at a single visit, including LLT in the preceding 12 months and most recent LDL-C. Primary outcome was the achievement of risk-based 2016 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) LDL-C goal while receiving stabilized LLT; 2019 goal achievement was also assessed.

Reference. 1. Ray KK, et al. Eur J Prev Cardiol. 2021 Sep 20;28(11):1279-1289.

How to Overcome the clinical inertia in the management of ACS

2016-2019 ESC/EAS LDL-C goals and lipid management in clinical practice[1-4]

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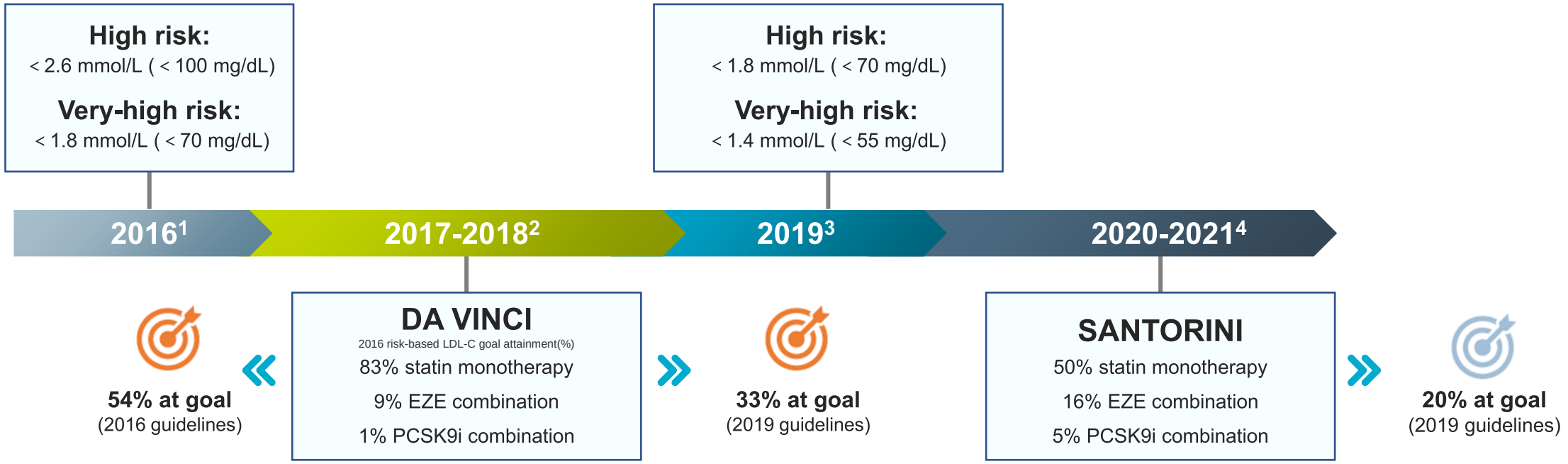

EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; EZE, ezetimibe; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9 inhibitors.

[Study design[2]] Investigators aim was to comprehensively describe how LLT is used in Europe for primary and secondary prevention of ASCVD, in different healthcare settings and populations, in order to assess how current practice impacts LDL-C goal attainment. An 18 country, cross-sectional, observational study of patients prescribed LLT for primary or secondary prevention in primary or secondary care across Europe. Between June 2017 and November 2018, data were collected at a single visit, including LLT in the preceding 12 months and most recent LDL-C. The primary outcome was the proportion of patients achieving the risk-based LDL-C goals recommended by the 2016 ESC/EAS guidelines while receiving stabilized LLT.

[Study design[4]] Investigators conducted the Treatment of high and very high riSk dyslipidemic pAtients for the preveNTion of cardiOvasculaR events in Europe–a multInatioNal observatIonal (SANTORINI) study to describe the approaches to lipid management in patients with higher CV risk (high and very high risk) across 14 European countries. The primary objective of this manuscript is to report baseline patient characteristics from the SANTORINI study and document approaches to lipid management used in clinical practice and to what extent at the time of study enrolment these might result in achievement of the 2019 guidelines, or whether changes in our approach are needed.

Reference. 1. Catapano AL, et al. Eur Heart J. 2016 Oct 14;37(39):2999-3058. **2.** Ray KK, et al. Eur J Prev Cardiol. 2021 Sep 20;28(11):1279-1289. **3.** Mach F, et al. Eur Heart J. 2020 Jan 1;41(1):111-188. **4.** Ray KK, et al. Lancet Reg Health Eur. 2023 Apr 5;29:100624.

The ACS EuroPath story: Overcoming barriers & Implementing solutions

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ESC/EAS 2019 Guidelines[2]

ACS EuroPath I (2018)

Cardiologist survey evaluated adherence to current guidelines[1]

ACS EuroPath II (2019)

Self-assessment tool developed to support clinicians in evaluation of individual day-to-day practice[3]

ACS EuroPath III (2020–2021)

GP and ACS patient survey brought together all key stakeholders to understand **main areas of improvement** needed[4]

ACS EuroPath IV (2022)

Cardiologist Survey 2022 – to reassess clinical practice[5]

- **18** European countries
- A few **non-European countries**

ACS, acute coronary syndrome; GP, general practitioner.

Reference. 1. Landmesser U, et al. Atherosclerosis Suppl. 2020;42:e49–e58. 2. Mach F, et al. Eur Heart J. 2020;41(1):111–188. 3. Sionis A, et al. Atherosclerosis Suppl. 2020;42:e65–e71. 4. Catapano AL, et al. Clin Cardiol. 2023 Apr;46(4):407-415. 5. Laufs et al. Vascul Pharmacol 2023;148:107141.

EuroPath I :
The survey was performed in 7 European countries

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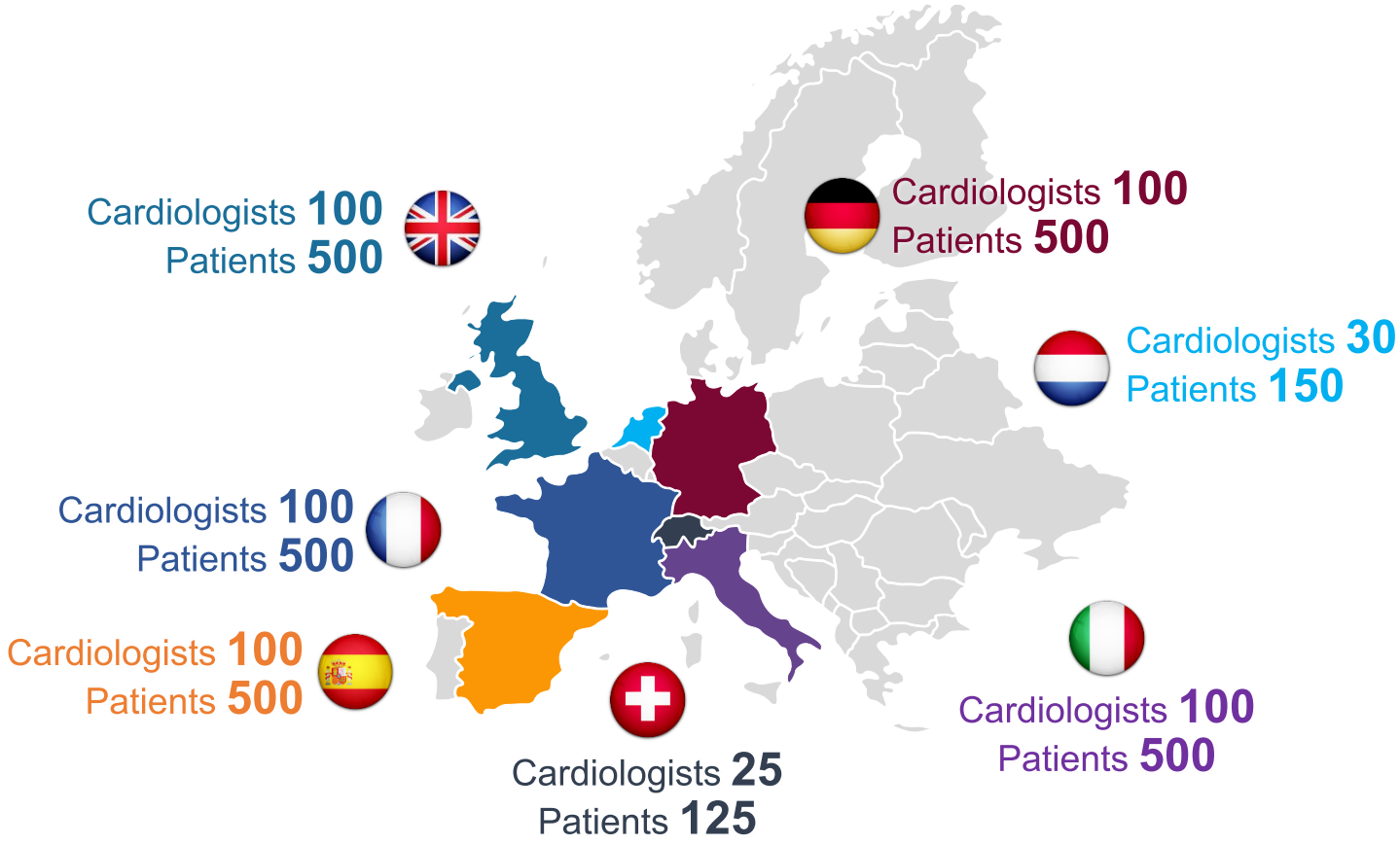
Aim of this survey was to review the current clinical practice regarding the lipid management.



Reference. 1. Landmesser U, et al. Atherosclerosis Suppl. 2020;42:e49–e58.

EuroPath I : ACS Pathway Practices in EU

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60% of patients had a first follow up more than 6 weeks after the event *

75% of uncontrolled patient had no add-on treatment at 1st FU*

68% of patients had LDL-C > 70 mg/dL at 2nd FU*

*ACS European Pathway Survey – average 2018 data in Europe.
ACS, acute coronary syndrome.
Reference. 1. Landmesser U, et al. Atherosclerosis Suppl. 2020;42:e49–e58.

Most GPs responded they believe managing lipid levels is very important however, fewer said they were confident in their ability to manage lipid levels

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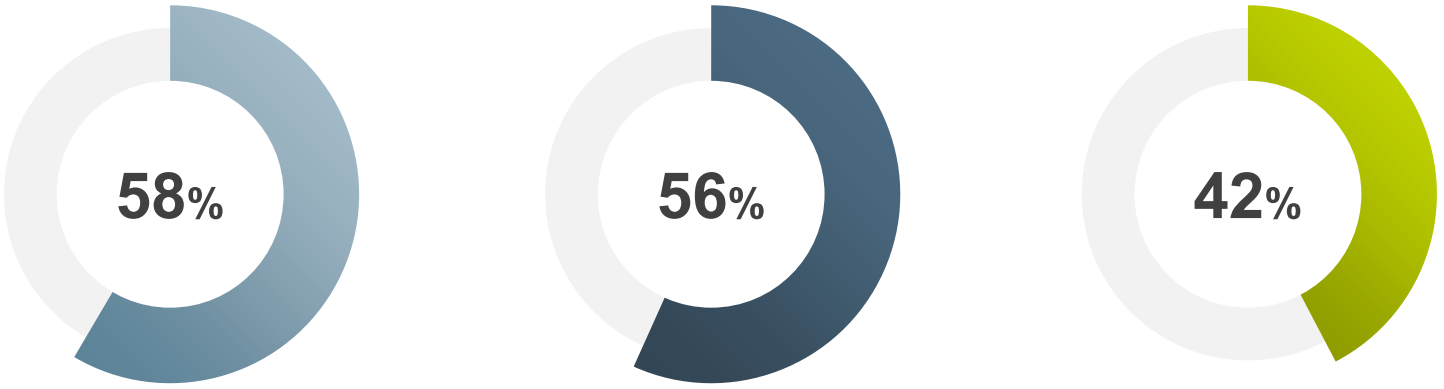
The main barriers to optimal lipid management for patients with ACS (from a GP perspective)



ACS, acute coronary syndrome; GP, general practitioner; PCSK9, proprotein convertase subtilisin/kexin type 9.

Reference. 1. Catapano AL et al. Clin Cardiol.2023;1-9.

ACS EuroPath III: 5 key areas identified for improvement

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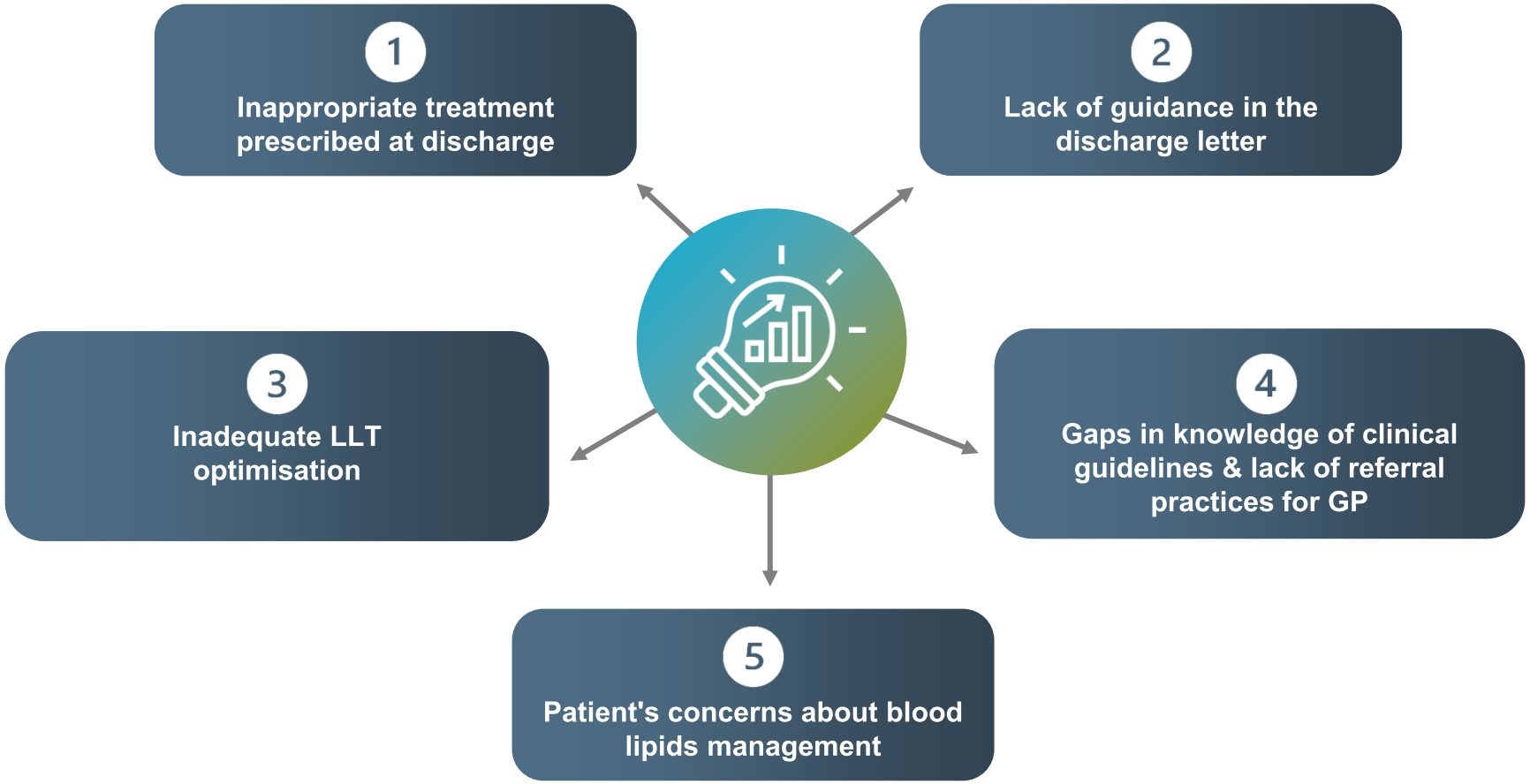

GP, general practitioner; LLT, lipid-lowering therapies.

Reference. 1. Catapano AL et al. Clin Cardiol.2023;1-9.

Key areas for improvement & Proposed solutions (1/5)

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1 Inappropriate treatment prescription at discharge

Survey findings

- **The lack of lipid blood test** within 1 day of admission and **high number of patients who received statin therapy** on day 2 or later.
- Approximately one-third of patients were **not receiving HIS at discharge** or had **LDL-C > 70 mg/dL** at the first follow-up.

Proposed solutions

- Development of an algorithm for hospital cardiologists during the acute phase to provide guidance on the **LDL-C goal and recommended LLT treatment approach, based on the "Fire early according to risk and follow to goal/target" strategy”**

ACS, acute coronary syndrome; EAS, European atherosclerosis society; ESC, European society of cardiology; GP, general practitioner; HIS, high-intensity statin; LDL-C, low-density lipoprotein cholesterol; LLT, lipid lowering therapy; PCSK9i, Proprotein convertase subtilisin/kexin type 9 inhibitor.

Reference. 1. Catapano AL et al.Clin Cardiol.2023;1-9, 2. Mach F et al.Eur Heart J. 2020;41:111-188, 3. Barrios V et al.Rev Esp Cardiol. 2020;7311:910-918.

Key areas for improvement & Proposed solutions (2/5)

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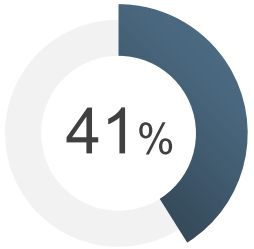
2 Lack of lipid management guidance in the discharge letter

Survey findings



- The lack of lipid management information in the discharge letter was a barrier to optimal lipid management.
- Approximately one-third of patients were **not receiving HIS at discharge** or had **LDL-C > 70 mg/dL** at the first follow-up.

Proposed solutions

- Need for **clear guidelines** on how to draft a comprehensive discharge letter using a standardized template for GPs.

ACS, acute coronary syndrome; EAS, European atherosclerosis society; ESC, European society of cardiology; GP, general practitioner; HIS, high-intensity statin; LDL-C, low-density lipoprotein cholesterol; LLT, lipid lowering therapy; PCSK9i, Proprotein convertase subtilisin/kexin type 9 inhibitor.

Reference. 1. Catapano AL et al.Clin Cardiol.2023;1-9, 2. Mach F et al.Eur Heart J. 2020;41:111-188, 3. Barrios V et al.Rev Esp Cardiol. 2020;7311:910-918.

Key areas for improvement & Proposed solutions (3/5)

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3 Inadequate LLT optimization

Survey findings

- The almost half of patients who had not achieved LDL-C target at first follow-up had no subsequent change made to their LLT treatment regimen.

Proposed solutions

- A standardized approach should be implemented to evaluate the effectiveness of LLT during the 4-6 weeks follow-up.[1]

ACS, acute coronary syndrome; EAS, European atherosclerosis society; ESC, European society of cardiology; GP, general practitioner; HIS, high-intensity statin; LDL-C, low-density lipoprotein cholesterol; LLT, lipid lowering therapy; PCSK9i, Proprotein convertase subtilisin/kexin type 9 inhibitor.

Reference. 1. Catapano AL et al.Clin Cardiol.2023;1-9, 2. Mach F et al.Eur Heart J. 2020;41:111-188, 3. Barrios V et al.Rev Esp Cardiol. 2020;7311:910-918.

Key areas for improvement & Proposed solutions (4/5)

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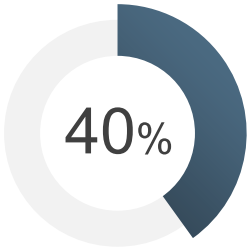
4 Gaps in knowledge of clinical guidelines & lack of referral practices for GP

Survey findings



- Respondents are not familiar with the 2019 ESC/EAS clinical guidelines.

Proposed solutions

- Emphasizing on the substantial benefit of LLT and safety in achieving guidelines goals and engaging patients and GPs as key pillars for the evidence-based lipid goals

ACS, acute coronary syndrome; EAS, European atherosclerosis society; ESC, European society of cardiology; GP, general practitioner; HIS, high-intensity statin; LDL-C, low-density lipoprotein cholesterol; LLT, lipid lowering therapy; PCSK9i, Proprotein convertase subtilisin/kexin type 9 inhibitor.

Reference. 1. Catapano AL et al.Clin Cardiol.2023;1-9, 2. Mach F et al.Eur Heart J. 2020;41:111-188, 3. Barrios V et al.Rev Esp Cardiol. 2020;7311:910-918.

Key areas for improvement & Proposed solutions (5/5)

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5 Patient's concerns about blood lipids management

Survey findings

- Many patients may be less able to absorb necessary information and key messages about their ongoing treatment on their own at the point of discharge.

Proposed solutions

- Developing a **"patient engagement discharge kit"** designed to be offered to patients during their discharge briefing.

ACS, acute coronary syndrome; EAS, European atherosclerosis society; ESC, European society of cardiology; GP, general practitioner; HIS, high-intensity statin; LDL-C, low-density lipoprotein cholesterol; LLT, lipid lowering therapy; PCSK9i, Proprotein convertase subtilisin/kexin type 9 inhibitor.

Reference. 1. Catapano AL et al.Clin Cardiol.2023;1-9, 2. Mach F et al.Eur Heart J. 2020;41:111-188, 3. Barrios V et al.Rev Esp Cardiol. 2020;7311:910-918.

EuroPath IV : METHODS

Switzerland was included in the 2018 scope.
Data comparison between 2022 & 2018 in this report are based on comparable country scopes i.e., only the countries included in both surveys

Methodology

- Online questionnaires including questions on lipid profile and medications were used to compare data from acute or follow-up ACS patients treated in 2022 in 6 European countries with data from patients from the ACS EuroPath I survey (2018).

General Results

- A total of 530 cardiologists participated in the survey.
- The survey included a total of 2,650 ACS patients; 35% in acute phase and 65% follow-up phase.

(*) Interventional cardiologists (IV CARDs) and general cardiologists (general CARDs) self defined by respondent.
(^) Data collected from Patient Record Forms (PRFs).

Reference. 1. Laufs, et al. Vascul Pharmacol 2023;148:107141.

Lipid testing was similar in 2022 and 2018, but occurred sooner after admission in 2022

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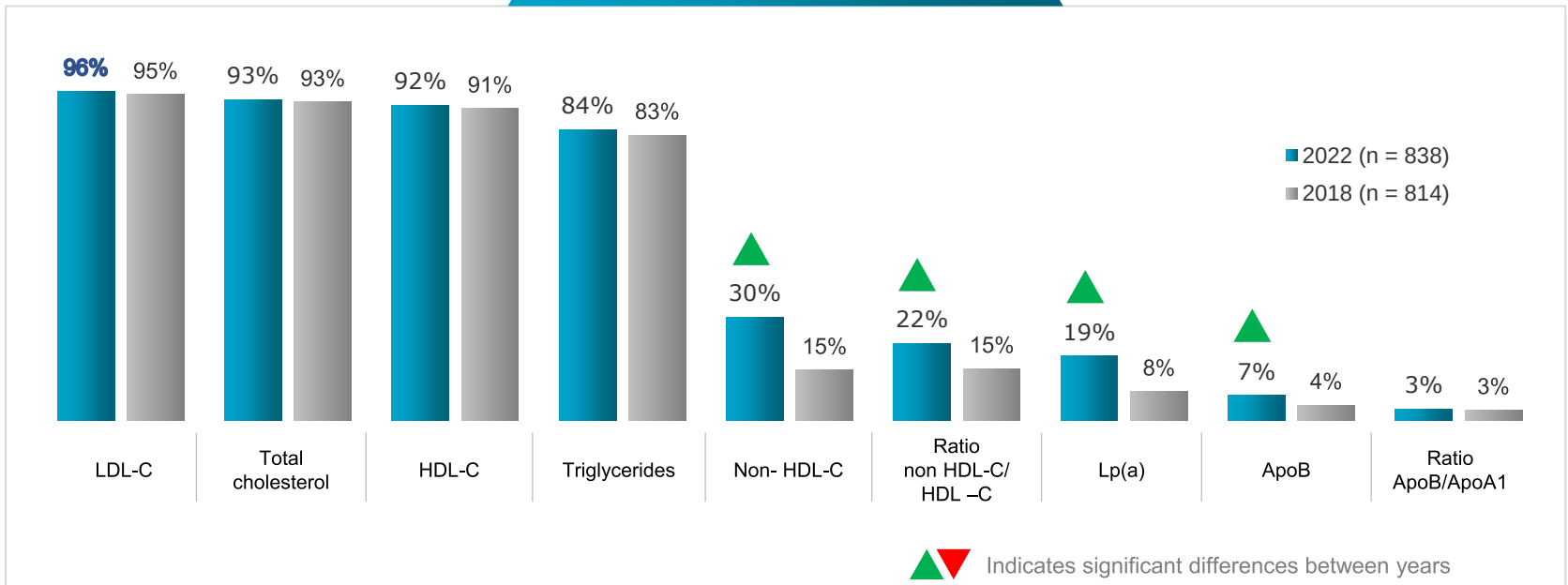
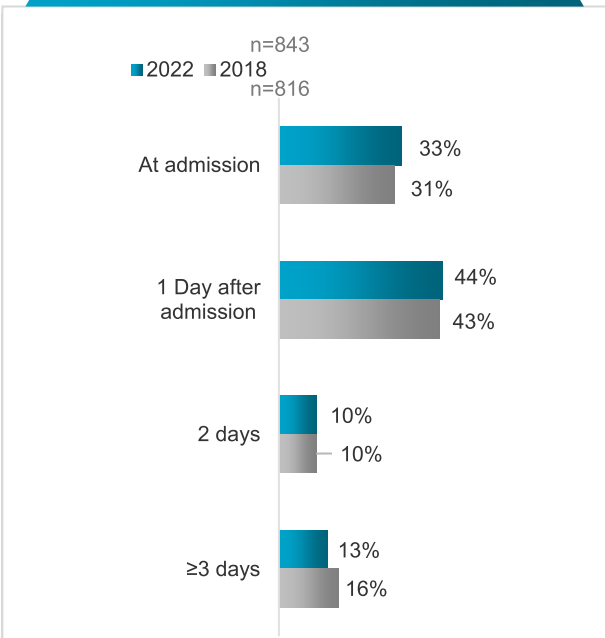
- The % of patients receiving **lipid testing was similar in 2018 (90%; n=900) and 2020 (90%; n=929)**
- The average time for **lipid testing decreased from 1.7 to 1.4 days** in 2022 vs. 2018

Lipid analyses tested



Time of lipid testing



Data derived from answers to questionnaire sections: P12a, P12b and P13
ApoB, Apolipoprotein B; ACS, acute coronary syndrome; CAD, coronary artery disease; CV, cardiovascular; HDL, high-density lipoprotein; Lpa(a); Lipoprotein a; LDL-C, low density lipoprotein; SD, standard deviation.

Reference. 1. Laufs, et al. Vascul Pharmacol 2023;148:107141.

A higher proportion of patients receiving statin + ezetimibe combination at discharge in 2022 vs. 2018

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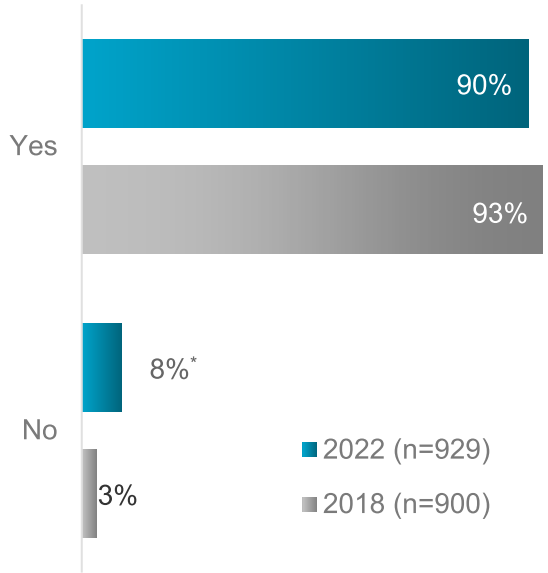
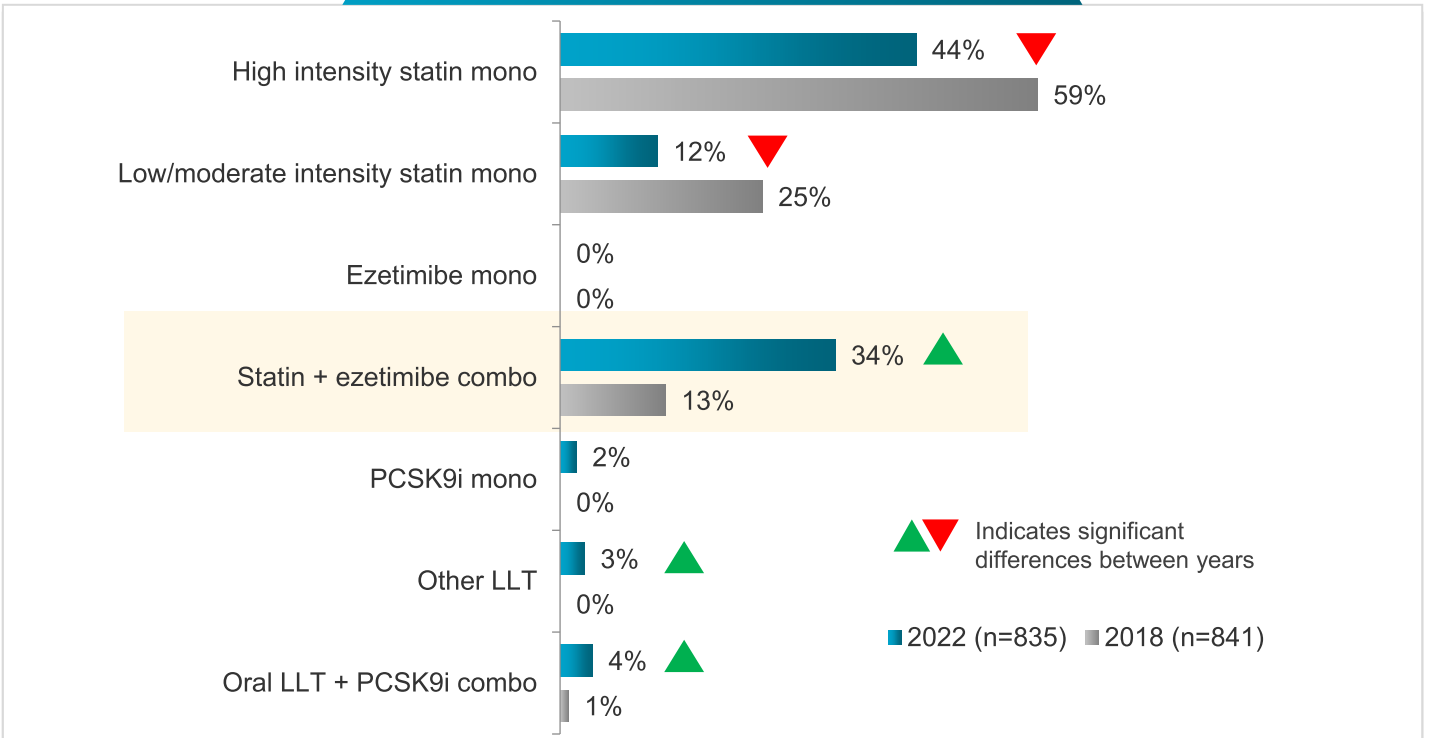
Patients receiving LLT at discharge



Treatments prescribed at discharge



* Significant difference between 2022 and 2018.

Combo, combination; LLT, lipid lowering therapies; mono, monotherapy; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors.

Reference. 1. Laufs, et al. Vascul Pharmacol 2023;148:107141.

More patients achieved guideline recommended LDL-C goals at each follow-up in 2022 vs. 2018 survey

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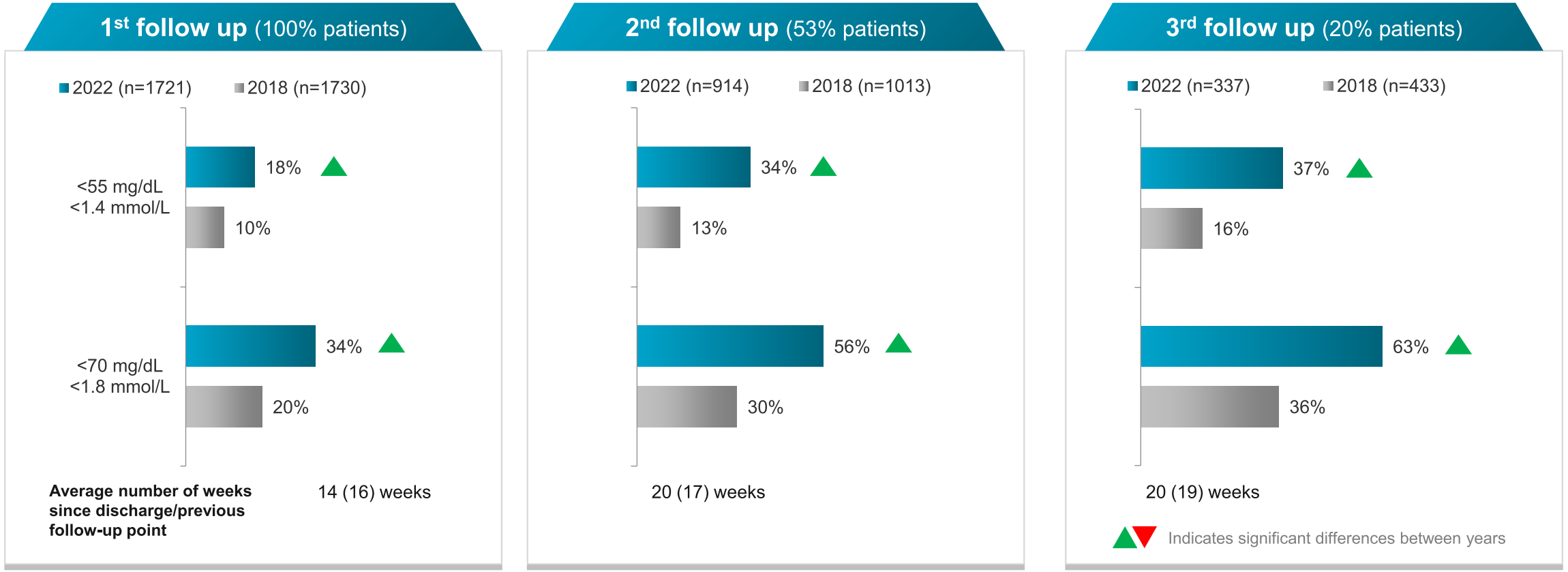
Proportion of patients achieving targets (%)



LDL-C, low-density lipoprotein cholesterol.

Reference. 1. Laufs, et al. Vascul Pharmacol 2023;148:107141.

In 2022, physicians ranked high LDL-C levels in the priority risk factors when managing post-ACS patients

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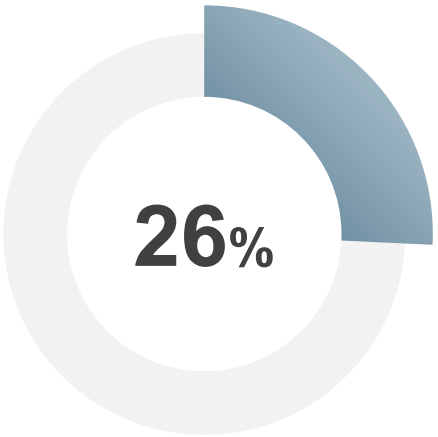
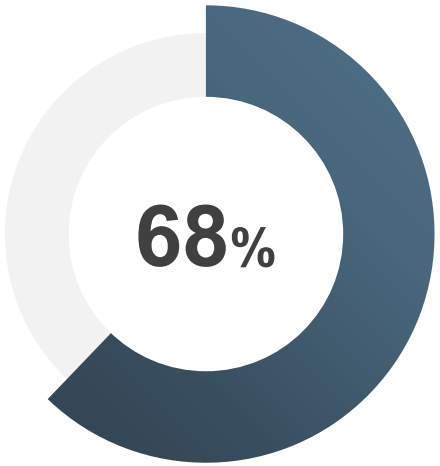
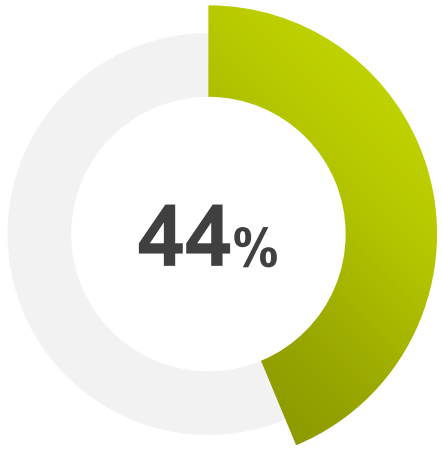


26% of cardiologists set an **LDL-C goal of < 55 mg/dL**



68% expected a **50% reduction** from baseline



44% expected to achieve the target within **2-3 Months**

No HCPs recommended a timeframe >12 months or stated that they did not know what timeframe to select
HCP, healthcare professional; LDL-C, low-density lipoprotein cholesterol.

Reference. 1. Laufs, et al. Vascul Pharmacol 2023;148:107141.

Only 55% of patients treated in Australia for ACS were undergoing intensive lipid-lowering therapy for 6 or 12 months after their hospitalization[1]

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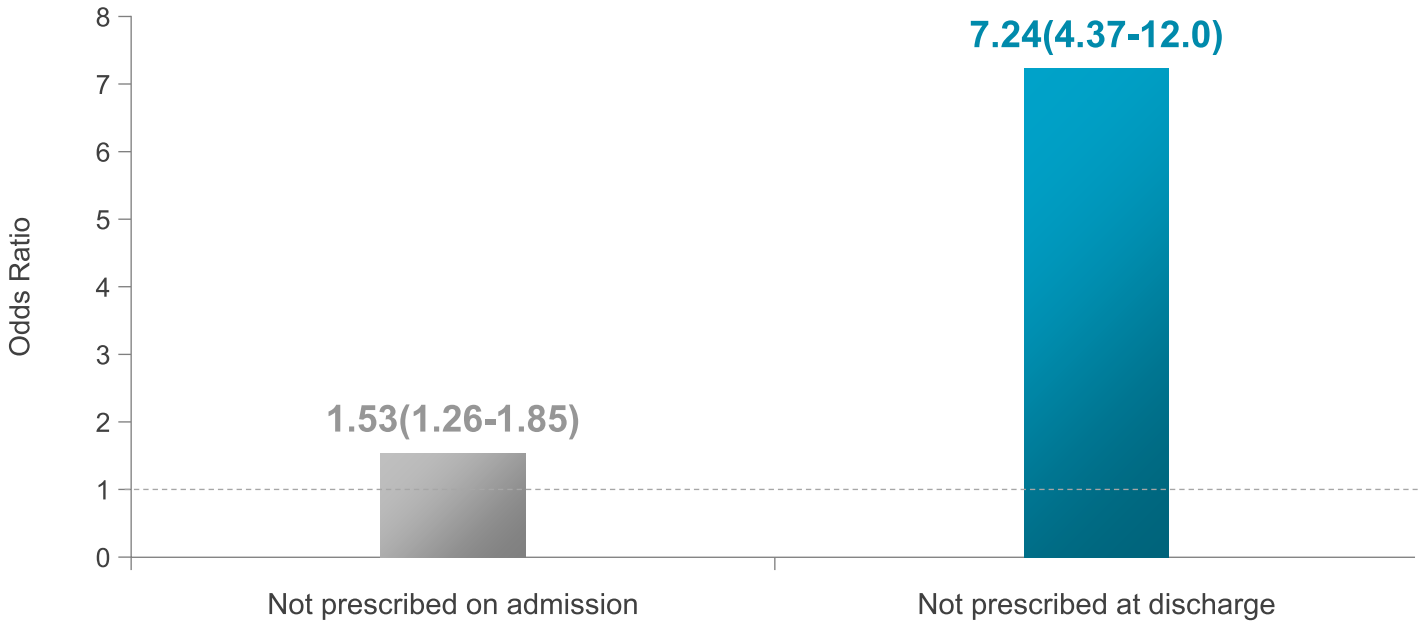
Predictors of intensive lipid lowering use 12 months Post ACS[1]



ACS, acute coronary syndrome.

[Study design[1]] Investigators conducted the prevalence and identify predictors of people hospitalised with acute coronary syndrome (ACS) receiving intensive lipid-lowering therapy during the 12 months after their discharge from hospital to retrospective observational analysis.Data were extracted from CONCORDANCE, a prospective, Australian investigator-initiated ACS registry.The endpoint of interest was whether a patient received intensive lipid-lowering therapy, defined as treatment with atorvastatin (≥ 40 mg/day), rosuvastatin (≥ 20 mg/day), or simvastatin (≥ 80 mg/day), with or without ezetimibe; lower intensity statin therapy with ezetimibe; or ezetimibe alone.

Reference. 1. Brieger D, et al. Med J Aust. 2019 Feb;210(2):80-85.

We don’t follow up with Lipid tests

Only 21% of MI patients were discharged on a high-intensity statin

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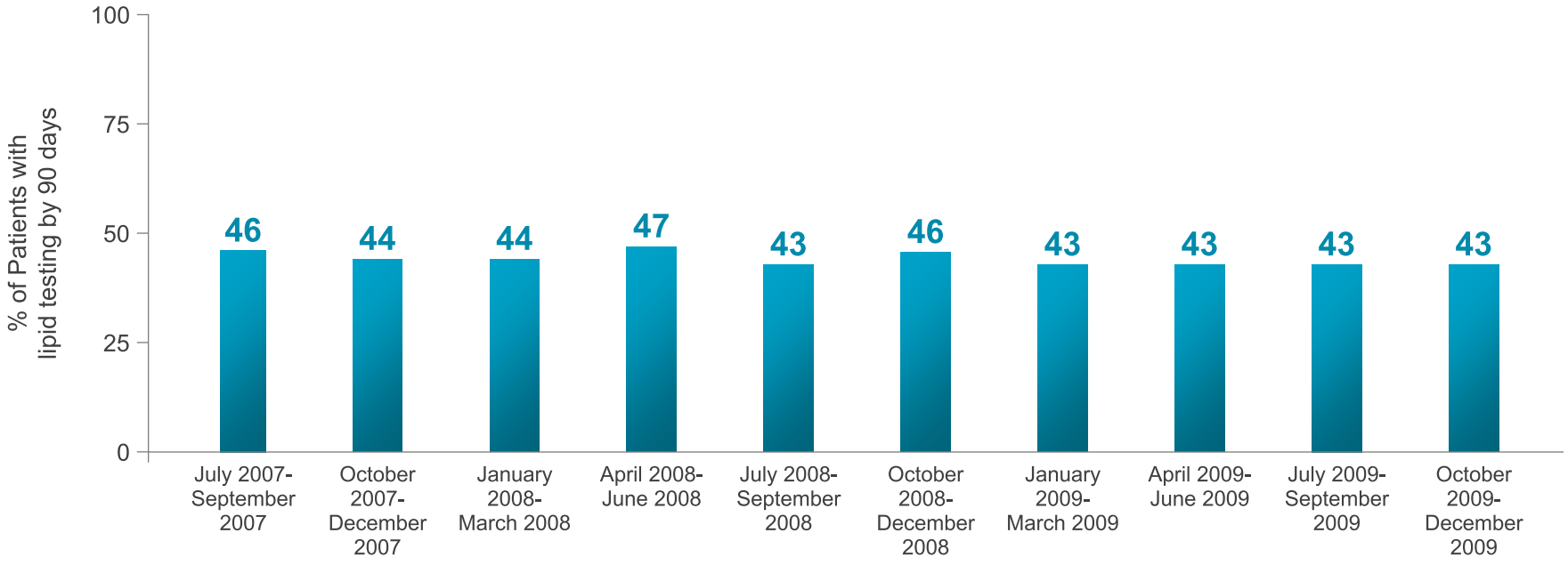
Post discharge lipid testing is a predicor of high-intensity statn use 12-month



MI, myocardial infaction; OR, odds ratio.

[Study design[1]] Investigators evaluated the frequency of postdischarge lipid testing and high-intensity statin use among MI patients discharged on a statin during the ATP III guidelines era, we linked ACTION (Acute Coronary Treatment and Intervention Outcomes Network) Registry data to Medicare claims for 11 046 MI patients aged ≥65 years who were discharged alive on a statin from 347 hospitals (2007–2009). Based on patients' in-hospital LDL-C levels and the intensity of statin therapy that they were prescribed at discharge, we estimated the proportion of patients who would reach the guideline-recommended target of <70 mg/dL by 1 year after discharge.

Reference. 1. Wang WT, et al. J Am Heart Assoc. 2018 Jan 25;7(3):e006460.

Dyslipidemia, Mortality and evidence; Can PCSK9i address the challenges?

Cardiovascular disease is the second leading cause of death in KOREA[1,2]

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Major causes of death in 2021[2]

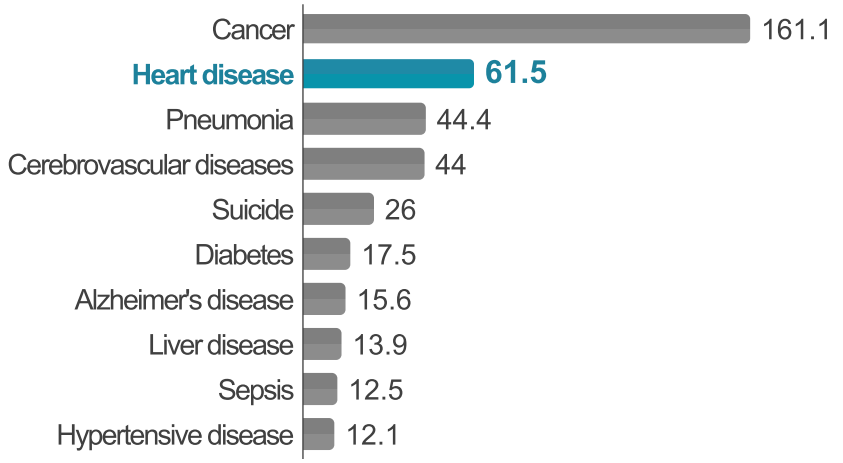
Units: per 100,000 population, persons, % of population

Heart disease

61.5%

Cerebrovascular diseases

44%



It is estimated that 56% of ischaemic heart disease and 18% of stroke are associated with dyslipidemia[1]

Reference. 1. KSoLA 이상지질 진료지침 제 5판. 한국지질·동맥경화학회 진료지침위원회. 2022;1-281. 2. 통계청. 사망원인 통계(2021).

Each 39 mg/dL reduction in LDL-cholesterol, there is a 20% reduction in the risk of death from cardiovascular disease and a 23% reduction in cardiovascular events.[1]

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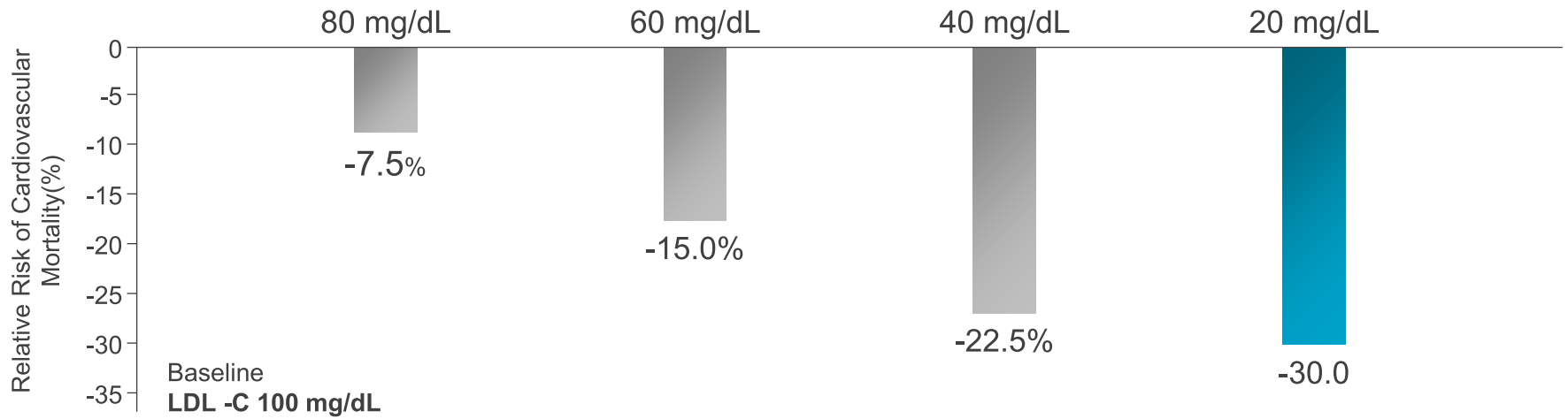
Estimated reduction in cardiovascular disease mortality risk with LDL cholesterol reduction [2,*]



In very high risk patients, lowering LDL cholesterol can lead to a greater reduction in the risk of cardiovascular disease death.[2]

Comparison based on a 15% reduction in the risk of cardiovascular disease death when reducing LDL cholesterol by 38.7 mg/dL (1 mmol/L) in patients with LDL cholesterol of 100 mg/dL.
LDL, Low Density Lipoprotein.

Reference. 1. KSoLA 이상지질 진료지침 제 5판. 한국지질·동맥경화학회 진료지침위원회. 2022;1-281. 2. Khan SU, Michos ED. AJPC. 2020;1:100013.

Long-term exposure to lower LDL-C reduces risk of CVD[1]

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Evidence indicates remarkably consistent dose-dependent log-linear association between the absolute magnitude of exposure to LDL-C and risk of ASCVD[1]

This effect appears to increase with increasing duration of exposure to LDL-C[1]

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

[Study design[1]] This review describes the cumulative effect of lipid-carrying lipoproteins on the risk of cardiovascular disease, estimates the magnitude of the clinical benefit that can be achieved by maintaining optimal lipid levels, identifies the most effective timing for implementing strategies designed to achieve optimal lipid levels, and provides a clinical pathway to help people achieve the lipid levels necessary for ideal cardiovascular health.

Reference. 1. Ference BA, et al. Eur Heart J. 2017;38:2459-2472.

“The lower LDL-C for longer(the earlier you start) the better it is” for CV-risk reduction[1]

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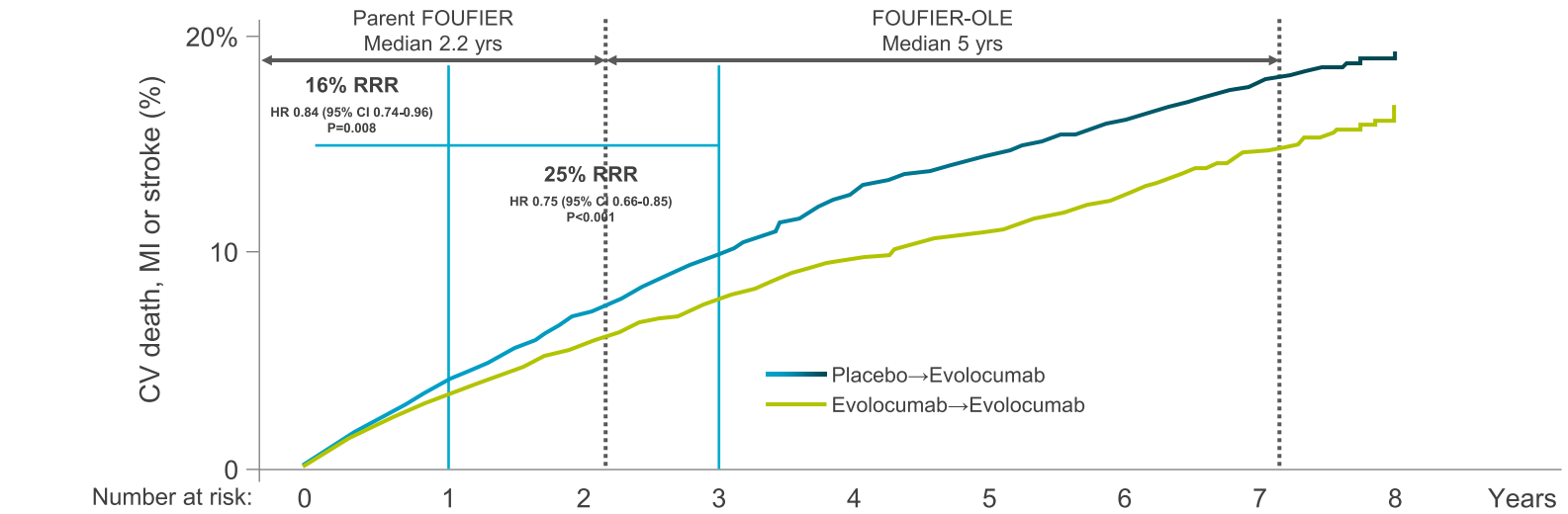
Clinical benefit of earlier initiation of evolocumab was more apparent in the first 3 years[1]

Major cardiovascular events during FOURIER-OLE[1]



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

[Study design[1]] Investigators conducted the long-term reduced low-density lipoprotein cholesterol (LDL-C) and risk of cardiovascular events of PCSK9i in patients at high risk of CV. The parent FOURIER trial randomized 27 564 patients with atherosclerotic cardiovascular disease and LDL-C ≥70 mg/dL on statin to evolocumab vs. placebo. Patients completing FOURIER at participating sites were eligible to receive evolocumab in 2 open-label extension studies (FOURIER-OLE [FOURIER Open-Label Extension]) in the United States and Europe; primary analyses were pooled across studies. The primary end point was the incidence of adverse events. Lipid values and major adverse cardiovascular events were prospectively collected. The primary cardiovascular composite outcome was cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina or coronary revascularization.

Reference. 1. O'Donoghue ML, et al. Circulation. 2022 Oct 11;146(15):1109-1119.

Patients experiencing major CVD events[1-3]

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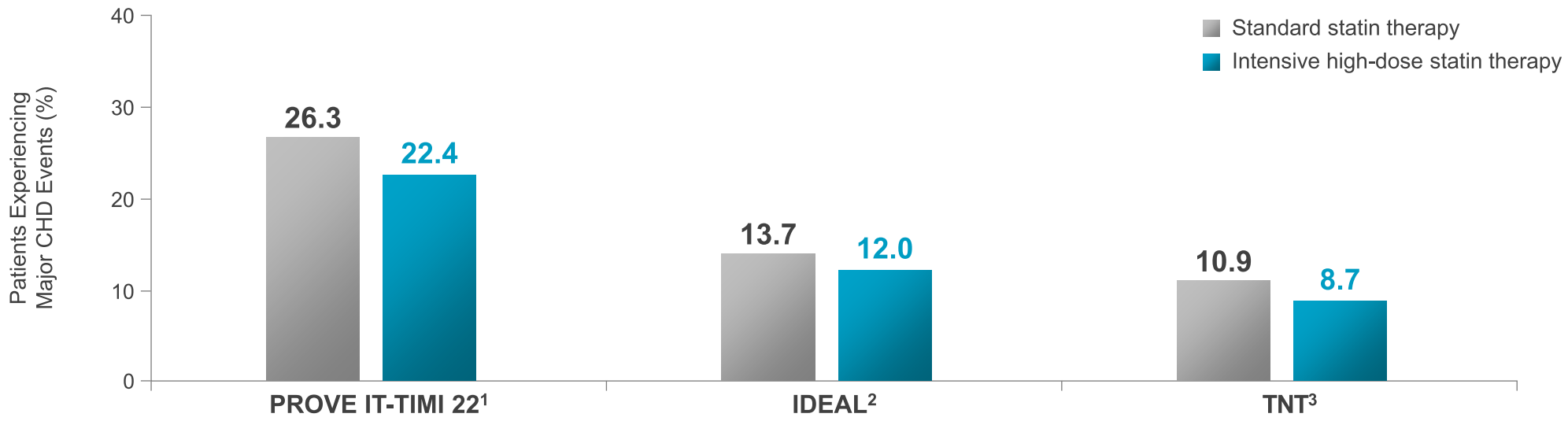

n	4,162		8,888		10,001	
LDL-C* mg/dL	95	62	104	81	101	77

Although intensive high-dose statin therapy reduced LDL-C concentration and the risk of any CHD events, but there were in cardiovascular or all-cause mortality†,2

* Mean or median LDL-C after treatment. † (1) major cardiovascular events (any primary event plus stroke; the diagnosis of stroke required evidence of a neurological deficit, usually localized, lasting ≥24 hours or until death, usually confirmed by diagnostic imaging); (2) any CHD event (any primary event, any coronary revascularization procedure, or hospitalization for unstable angina); (3) any cardiovascular events (any of the former plus hospitalization with a primary diagnosis of congestive heart failure and peripheral arterial disease, defined as new clinical diagnosis or hospitalization for such disease).
CHD, coronary heart disease; **LDL-C,** low-density lipoprotein cholester.
[Stdudy design[1]] The study was designed to establish the noninferiority of pravastatin as compared with atorvastatin with respect to the time to an end-point event. Enrolled 4162 patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days and compared 40 mg of pravastatin daily (standard therapy) with 80 mg of atorvastatin daily (intensive therapy). The primary end point was a composite of death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 days after randomization), and stroke. Follow-up lasted 18 to 36 months (mean, 24).
[Stdudy design[2]] Investigators conducted compare the effects of 2 strategies of lipid lowering on the risk of cardiovascular disease among patients with a previous myocardial infarction (MI).The IDEAL study, a prospective, randomized, open-label, blinded end-point evaluation trial conducted at 190 ambulatory cardiology care and specialist practices in northern Europe between March 1999 and March 2005 with a median follow-up of 4.8 years, which enrolled 8888 patients aged 80 years or younger with a history of acute MI. Patients were randomly assigned to receive a high dose of atorvastatin (80 mg/d; n = 4439), or usual-dose simvastatin (20 mg/d; n = 4449). The primary clinical outcome was time to first occurrence of a major coronary event, defined as coronary death, hospitalization for nonfatal acute myocardial infarction, or cardiac arrest with resuscitation.
[Stdudy design[3]] Investigators conducted the efficacy and safety of lowering LDL cholesterol levels below 100 mg per deciliter (2.6 mmol per liter) in patients with stable coronary heart disease (CHD). A total of 10,001 patients with clinically evident CHD and LDL cholesterol levels of less than 130 mg per deciliter (3.4 mmol per liter) were randomly assigned to double-blind therapy and received either 10 mg or 80 mg of atorvastatin per day. Patients were followed for a median of 4.9 years. The primary end point was the occurrence of a first major cardiovascular event, defined as death from CHD, nonfatal non-procedure-related myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke.
Reference. 1. Cannon CP, et al. New England Journal of Medicine. 2004;350(15):1495-1504. **2.** Pedersen TR, *et al.* Journal of the American Medical Association. 2005;294(19):2437-2445. **3**. LaRosa JC, *et al.* New England Journal of Medicne. 2005;352(14):1425-1435.

Post-ACS, 1:5 patients achieve LDL-C 70 mg/dL despite statin prescription and good adherence[1]

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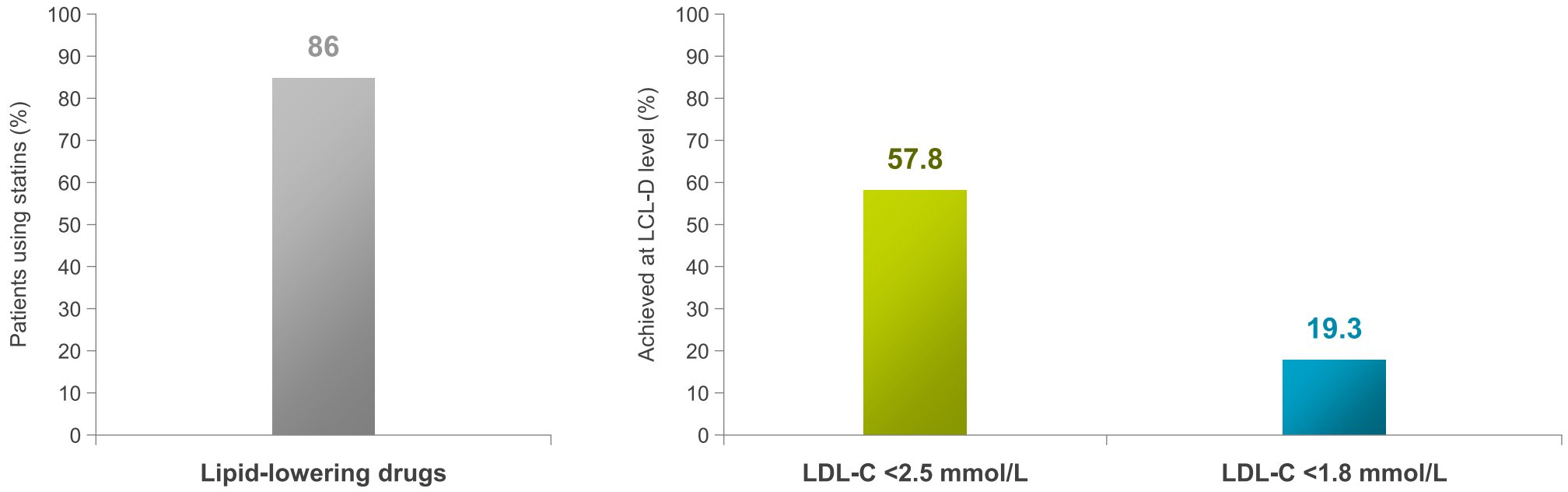
EUROASPIRE IV[1]



ACS, acute coronary syndrome; EUROASPIRE IV, A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries; LDL-C, low-density lipoprotein cholesterol.

[Study design[1]] The aim of this survey was to assess how statins were prescribed in CHD patients at discharge after a coronary event from hospitals throughout Europe and how the intake of these drugs was reported by the patients when they were seen more than one year later in relationship with their achieved LDL-C levels. 6648 CHD patients' data from centres in 24 European countries were gathered using standardized methods. Patients were divided in three groups: high-intensity statin therapy, moderate or low intensity statin therapy and no statin therapy at all.

Reference. 1. Reiner EA, *et al*. Atherosclerosis. 2016 Mar;246:243-250.

DYSIS II for Global vs South Korea[1,2]

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Mean Daily Statin Dosage[1,2,*]

	Goal Attainment			
	Admission		4-Month F/U	>4-Month
	Pre ACS (LDL-C <70 or 100 mg/dL)†	Post ACS (LDL-C <70mg/dL)†		
Global[1]	30% (n=3,866) »	19%	37% (n=1,071)	30% (n=6,792)
South KOREA[2]	40% (n=308) »	24%	62% (n=79)	40% (n=500)

※ ACS on admission - global 22±17/ korea 17±12; at discharge - global 36±24/ Korea 22±14; at 4 month - global 32±21/Korea 21±14; sCHD/stable CAD - global 25±18/korea 17±10.

* Atorvastatin-equivalent daily statin dosage.
† Achievement of LDL-C target levels, as defined in the 2011 ESC/EAS guidelines, was determined for both cohorts. For the CHD cohort, all patients were classed as being at very high risk, and therefore had an LDL-C target of <70 mg/dl. For the ACS cohort, pre-ACS cardiovascular risk status was determined according to the 2011 ESC/EAS guidelines , and targets for LDL-C for very high-risk, high-risk, moderate-risk, and low-risk patients were defined as <70 mg/dl, <100 mg/dl, <115 mg/dl, and <130 mg/dl, respectively.
ACS, acute coronary syndrome; **CHD,** coronary heart disease; **DYSIS,** Dyslipidemia International Study; **F/u,** follow-up; **LDL-C,** low-density lipoprotein cholesterol.
[Study design[1]]This cohort study is determined LDL-C target value attainment, use of lipid-lowering therapy (LLT), and cardiovascular outcomes in patients with stable coronary heart disease (CHD) and those suffering from an acute coronary syndrome (ACS). A a multinational, multicenter, prospective observational study of lipid profiles, lipid target value attainment, and LLT in patients with stable CHD and in patients being hospitalized for an ACS event. From 2012 to 2013, patients were enrolled from eighteen countries in Asia (Hong Kong, India, South Korea, the Philippines, Singapore, Thailand, Taiwan, and Vietnam), Europe (France, Greece, Germany, Ireland, and Italy), and the Middle East (Egypt, Jordan, Lebanon, Saudi Arabia, and the United Arab Emirates). Data were collected by clinical examination and from medical charts. **[Study desig[2]]** The aim of this study was to evaluate under target rates of low-density lipoprotein-cholesterol (LDL-C) in Korean patients with stable coronary artery disease (CAD) or an acute coronary syndrome (ACS) in real world practice. DYSIS II was a multinational, observational, cross-sectional study that enrolled patients over 18 years of age with stable CAD or ACS. Data were collected from 21 countries across the Asia-Pacific region, Europe, and the Middle East and Africa.7,8 The present article involves the patients enrolled in Korea between July 2013 and July 2014. Endpoint was rates of under target LDL-C as per European guidelines, were evaluated, and multivariate regression was performed to identify predictive factors of patients presenting under the target.
Reference. 1. Gitt AK, et al. Atherosclerosis. 2017 Nov;266:158-166. **2.** Lee SH, et al. J Lipid Atheroscler. 2019 Sep;8(2):242-251.

DYSIS II South Korea summary[1]

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ACS

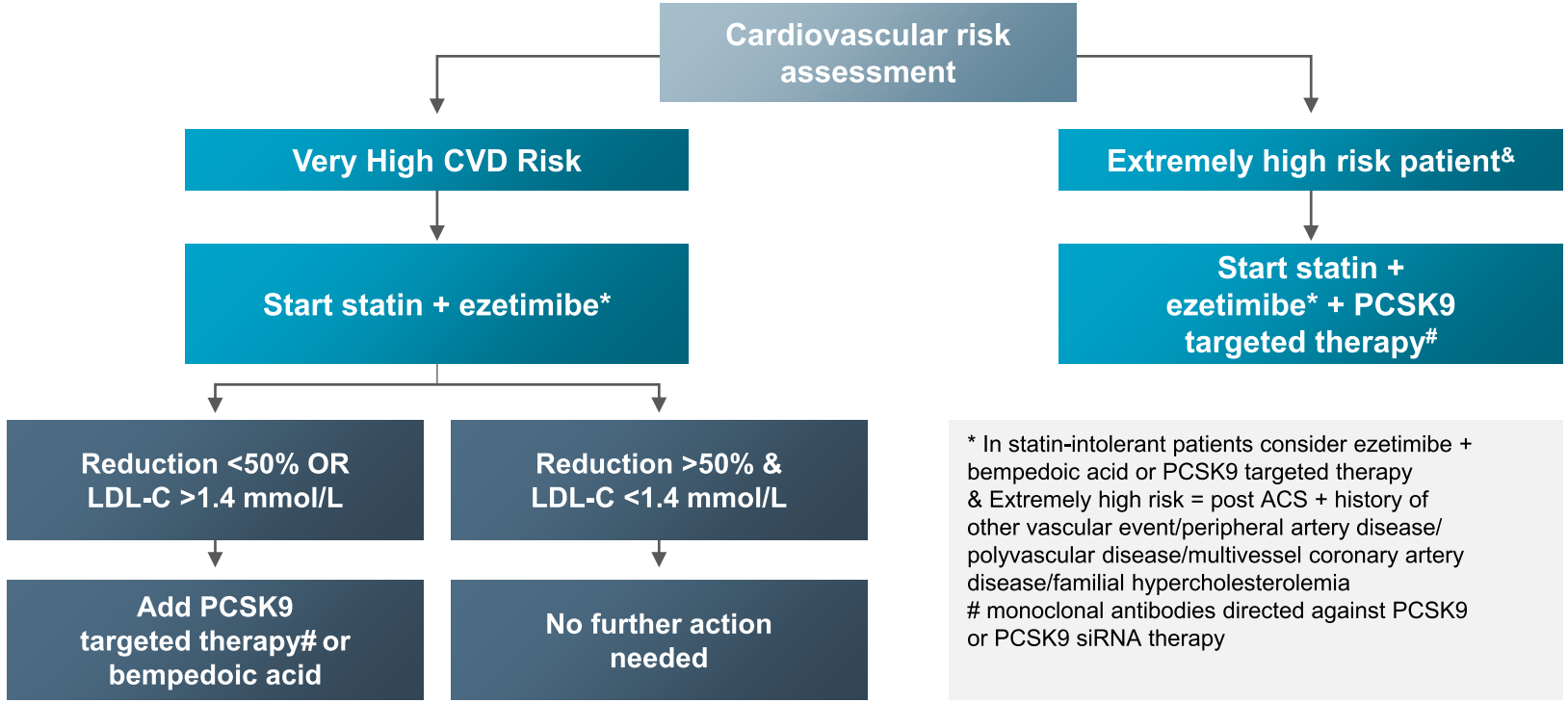
- LDL-C goal attainment rate for ACS patients in South Korea was low.
  - **Almost 75% patients in the ACS group did not attain the LDL-C target** at the hospital admission.
- Statin monotherapy was the most commonly prescribed for management of dyslipidemia and atorvastatin equivalent dose in the ACS group at hospital admission was 17±12 mg/day.
- Only 25% of ACS patients had LDL-C values reported at 4-month follow-up.
- Predictors for LDL-C at goal for patients treated with LLT included sedentary lifestyle and statin dose.

sCHD

- LDL-C goal attainment rate for sCHD patients in South Korea was 40%; 60% of patients still did not attain the goal.
- 90% of sCHD patients were treated with statins and atorvastatin was the most frequently used statin therapy.
- Atorvastatin equivalent dose in the sCHD group was 17±10 mg/day.

ACS, acute coronary syndrome; **CHD,** coronary heart disease; **DYSIS,** Dyslipidemia International Study; **F/u,** follow-up; **LDL-C,** low-density lipoprotein cholesterol; ; **LLT,** Lipid-lowering therapies.
[Study desig²] The aim of this study was to evaluate under target rates of low-density lipoprotein-cholesterol (LDL-C) in Korean patients with stable coronary artery disease (CAD) or an acute coronary syndrome (ACS) in real world practice.
DYSIS II was a multinational, observational, cross-sectional study that enrolled patients over 18 years of age with stable CAD or ACS. Data were collected from 21 countries across the Asia-Pacific region, Europe, and the Middle East and Africa.7,8 The present article involves the patients enrolled in Korea between July 2013 and July 2014. Endpoint was rates of under target LDL-C as per European guidelines, were evaluated, and multivariate regression was performed to identify predictive factors of patients presenting under the target.
Reference. 1. Lee SH, et al. J Lipid Atheroscler. 2019 Sep;8(2):242-251.

Integrating of combination of ‘Intensive lipid lowering in treatment’ strategy[1]



* In statin-intolerant patients consider ezetimibe + bempedoic acid or PCSK9 targeted therapy
& Extremely high risk = post ACS + history of other vascular event/peripheral artery disease/ polyvascular disease/multivessel coronary artery disease/familial hypercholesterolemia
# monoclonal antibodies directed against PCSK9 or PCSK9 siRNA therapy

Combination lipid-lowering therapy as first line strategy in very high-risk patients[1]

ACS, acute coronary syndrome; CVD, cardiovascular disease; LDL-C, low-density lipoprotein; PCSK9, proprotein convertase subtilisin/kexin type 9; siRNA, small interfering RNA.

Reference. 1. Ray KK, et al. Eur Heart J. 2022 Feb 22;43(8):830-833.

2022 KSoLA Guidelines

Evidence-guided approach algorithm of dyslipidemia treatment[1]

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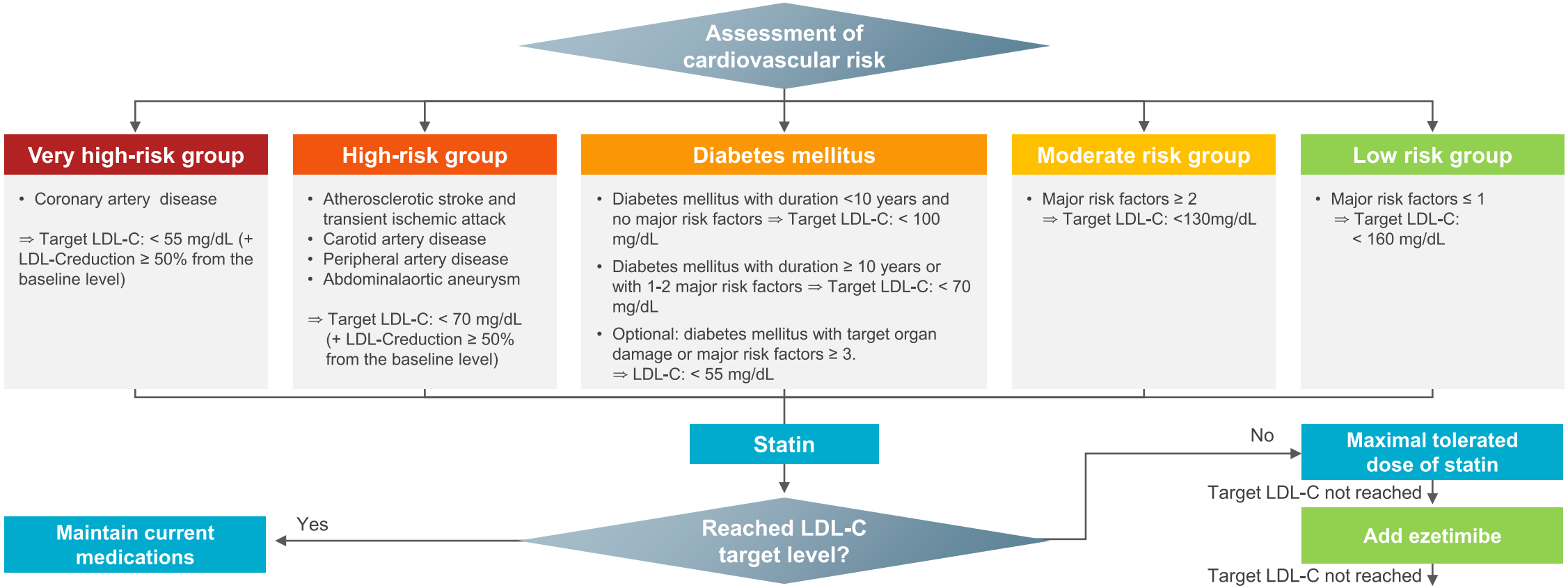

LDL-C, low-density lipoprotein; PCSK9, proprotein convertase subtilisin/kexin type 9.

Reference. 1. 한국지질동맥경화학회(KSoLA). 2022 이상지질혈증 치료지침 제5판.

A greater reduction in LDL-C can be estimated with intensive lipid-lowering treatment.[1-3]

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Intensity of lipid lowering treatment[1-3]

Treatment	Average LDL-C Reduction
Moderate intensity statin	~30%
Ezetimibe + bempedoic acid[2]	~45%
High intensity statin	~50%
High intensity statin + ezetimibe	~65%
Moderate statin + ezetimibe + bempedoic acid[3]	~65%
PCSK9 inhibitor	~60%
PCSK9 inhibitor + high intensity statin	~75%
PCSK9 inhibitor + high intensity statin + ezetimibe	~85%

LDL-C, low-density lipoprotein; PCSK9, proprotein convertase subtilisin/kexin type 9.

[Study design[2]] Investigators conducted to compare 2 doses of ETC-1002, alone or combined with ezetimibe 10 mg (EZE), vs EZE monotherapy for lowering low-density lipoprotein cholesterol (LDL-C).This phase 2b, multicenter, double-blind trial-evaluated hypercholesterolemic patients (LDL-C, 130 to 220 mg/dL) with (n = 177) or without (n = 171) muscle-related intolerance to ≥2 statins; 1 at lowest approved dose. Subjects were randomized to 12-week treatment with ETC-1002 120 mg or ETC-1002 180 mg alone, EZE alone, ETC-1002 120 mg plus EZE, or ETC-1002 180 mg plus EZE.The primary objective was to assess the LDL-C–lowering effect of ETC-1002 monotherapy (120 mg or 180 mg daily) vs EZE monotherapy in hypercholesterolemic patients with or without statin intolerance.

[Study design[3]] Investigators evaluated LDL-C lowering with the combination of bempedoic acid, ezetimibe, and atorvastatin.This was a phase 2, randomized, double-blind, placebo-controlled study (NCT03051100). After washout of lipid-lowering drugs, patients were randomized 2:1 to triple therapy (bempedoic acid 180 mg, ezetimibe 10 mg, and atorvastatin 20 mg; n = 43) or placebo (n = 20) once daily for 6 weeks. The primary endpoint was percent change from baseline in LDL-C at week 6.

Reference. 1. Mach F, et al. Eur Heart J. 2020 Nov 21;41(44):4255. 2. Thompson PD, et al . J Clin Lipidol. 2016 May-Jun;10(3):556-567. 3. Rubino J, et al. Atherosclerosis. 2021 Mar;320:122-128

Statin combination therapy resulted in incremental lowering of LDL-C levels and improved cardiovascular outcome[1-4]

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Outcomes: Non or combination Statin LDL-C lowering therapies

	3-Component MACE	Nonfatal MI
IMPROVE-IT Simvastatin vs. Simvastatin–Ezetimibe [1]	**0.90**(p=0.002)	**0.87**(p=0.003)
FOURIER Evolucumab vs. Placebo[2]	**0.80**	**0.73†**
ODYSSEY Outcomes Alirocumab vs. Placebo[3]	**0.86***	**0.86**
CLEAR Outcomes Bempedoic Acid vs. Placebo[4]	**0.85**	**0.77‡**

*Trial used all-cause mortality rather than CV death; † Fatal and nonfatal MI; ‡ Fatal or nonfatal MI.
MACE, major adverse cardiovascular event; MI, myocardial infarction.
[Stdudy design[1]] Investigators conducted to determine whether adding ezetimibe to statin therapy could further reduce the rate of cardiovascular events. A double-blind, randomized trial involving 18,144 patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days and had LDL cholesterol levels of 50 to 100 mg per deciliter (1.3 to 2.6 mmol per liter). The combination of simvastatin (40 mg) and ezetimibe (10 mg) (simvastatin-ezetimibe) was compared with simvastatin (40 mg) and placebo (simvastatin monotherapy). The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, unstable angina requiring rehospitalization, coronary revascularization (≥30 days after randomization), or nonfatal stroke. The median follow-up was 6 years.
[Stdudy design[2]] Investigators conducted to determine whether PCSK9 therapy could prevent of cardiovascular events. A randomized, double-blind, placebo-controlled trial involving 27,564 patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of 70 mg per deciliter (1.8 mmol per liter) or higher who were receiving statin therapy. Patients were randomly assigned to receive evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or matching placebo as subcutaneous injections. The primary efficacy end point was the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary efficacy end point was the composite of cardiovascular death, myocardial infarction, or stroke. The median duration of follow-up was 2.2 year.
[Stdudy design[3]] Investigators conducted the effects of alirocumab on cardiovascular outcomes after an acute coronary syndrome with patients. ODYSSEY OUTCOMES was a randomised, double-blind, placebo-controlled phase 3 study. 18,924 Patients with a recent MI or unstable angina, and on high-intensity statin (40 or 80 mg atorvastatin or 20 or 40 mg rosuvastatin, or maximally tolerated dose of one of these agents) +/- other lipid-lowering therapy but not at predefined target LDL-C were enrolled. The primary end point was a composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization.
[Stdudy design[4]] Investigators conducted to determine whether bempedoic acid to reduce the rate of cardiovascular events. A double-blind, randomized, placebo-controlled trial involving patients who were unable or unwilling to take statins owing to unacceptable adverse effects ("statin-intolerant" patients) and had, or were at high risk for, cardiovascular disease. The patients were assigned to receive oral bempedoic acid, 180 mg daily, or placebo. The primary end point was a four-component composite of major adverse cardiovascular events, defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization.
Reference. 1. Cannon CP, et al. N Engl J Med. 2015 Jun 18;372(25):2387-2397. **2.** Sabatine MS, et al. N Engl J Med. 2017 May 4;376(18):1713-1722. **3.** Schwartz GG, et al. N Engl J Med. 2018;379(22):2097-2107. **4.** Nissen SE, et al. N Engl J Med. 2023 Apr 13;388(15):1353-1364.

What have we learned?

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Intensive LLT had significantly increased clinical benefit in patients with ACS.[1,2]

Patient at higher risk post-ACS showed greater benefits in mortality

PROVE-IT trial[1]	A to Z trial[2]
Death from any cause (28%, P=0.07)	All-cause mortality Aggressive simvastatin 5.5% vs Placebo 6.7%† (HR, 0.79; 95% CI, 0.61-1.02; P =0.08)

* Although the study was not powered to assess effects on cardiovascular events, exploratory analysis revealed numerically fewer adverse cardiovascular outcomes (12.2% vs 15.3%), nonfatal myocardial infarctions (2.1% vs 2.9%), and coronary revascularization procedures (10.3% vs 13.6%) in the evolocumab vs placebo groups.
† Simvastatin (40/80 mg/d) vs. Placebo + 20 mg/d of Simvastatin
ACS, acute coronary syndrome; **CI,** confidence interval, **HR,** hazard ratio; **LLT,** lipid-lowering therapies.
[Stdudy design[1]] The study was designed to establish the noninferiority of pravastatin as compared with atorvastatin with respect to the time to an end-point event. Enrolled 4162 patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days and compared 40 mg of pravastatin daily (standard therapy) with 80 mg of atorvastatin daily (intensive therapy). The primary end point was a composite of death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 days after randomization), and stroke. Follow-up lasted 18 to 36 months (mean, 24).
[Stdudy design[2]] The study was conducted compare early initiation of an intensive statin regimen with delayed initiation of a less intensive regimen in patients with ACS. International, randomized, double-blind trial of patients with ACS receiving 40 mg/d of simvastatin for 1 month followed by 80 mg/d thereafter (n = 2265) compared with ACS patients receiving placebo for 4 months followed by 20 mg/d of simvastatin (n = 2232), who were enrolled in phase Z of the A to Z trial between December 29, 1999, and January 6, 2003. The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, readmission for ACS, and stroke. Follow-up was for at least 6 months and up to 24 months.
Reference 1. Cannon CP, et al. N Engl J Med. 2004 Apr 8;350(15):1495-1504. **2.** de Lemos JA, et al. JAMA. 2004 Sep 15;292(11):1307-1316.

“The higher the CV-risk, the more benefit”

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PCSK9i(evolocumab) significantly reduces relative risk of CV risk.[1]

Risk of Cardiovascular Outcomes by Risk Group[1] — Analysis From FOURIER[1]

	N	Cumulative incidence of CV death, MI or stroke	RRR	ARR	NNT
Overall patients with prior MI	N=22,351	--	18%	--	--
Time from Qualifying MI	**< 2 y ago** N=8,402	10.8%	24%	2.9%	**35**
	≥ 2 y ago N=13,918	9.3%	13%	1.0%	101
Number of Prior MIs	**≥ 2** N=5,285	15.0%	21%	2.6%	**38**
	1 N=17,047	8.2%	16%	1.7%	60
Residual Multivessel CAD	**MVD** N=5,618	12.6%	30%	3.4%	**29**
	No MVD N=16,715	8.9%	11%	1.3%	78

CAD, coronary artery disease; MI, myocardial infarction; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors.
[Study design[1]] Analysis From FOURIER the 22 351 patients with a prior MI were characterized on the basis of time from most recent MI, number of prior MIs, and presence of residual multivessel coronary artery disease (≥40% stenosis in ≥2 large vessels). The relative and absolute risk reductions in major vascular events, including the primary end point (cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization) and the key secondary end point (cardiovascular death, MI, or stroke), with evolocumab in these subgroups were compared.
Reference 1. Sabatine MS, et al. Circulation. 2018 Aug 21;138(8):756-766.

The benefit of PCSK9i(alirocumab) on tendency to reduce risk of all-cause mortality*, the secondary composite endpoint

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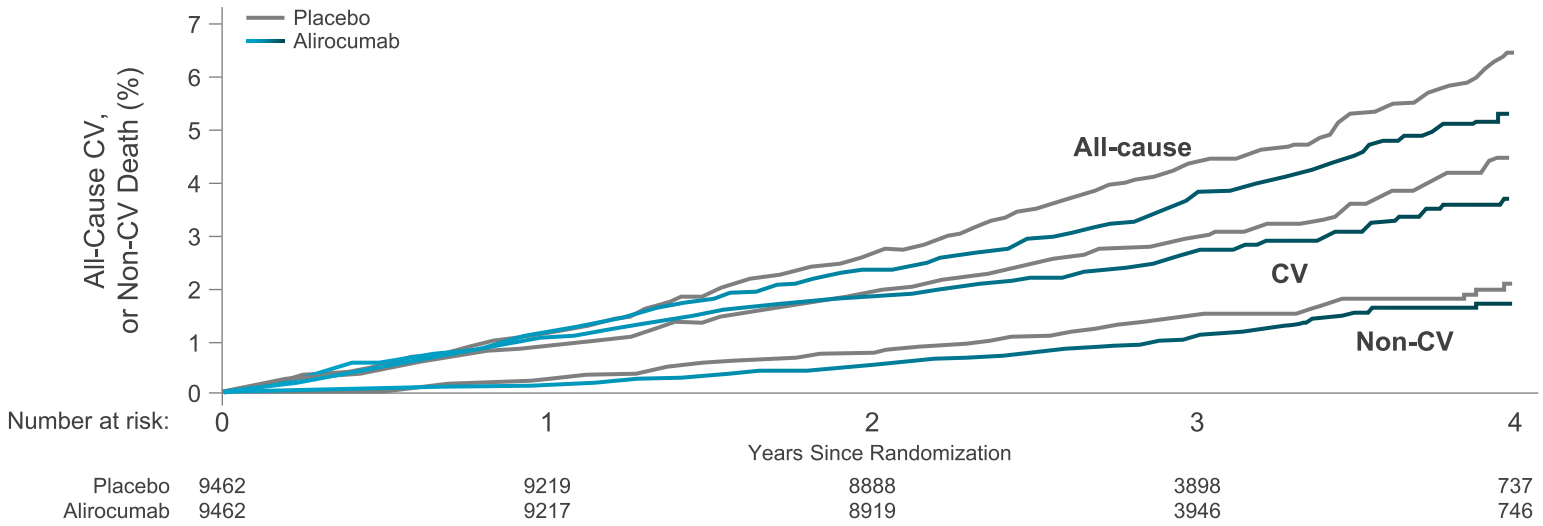
Fewer all-cause deaths occurred in the alirocumab.[1]

ODYSSEY OUTCOMES[1]



All-cause, cardiovascular, and noncardiovascular death (intention-to-treat population)[1]

※ There are some limitations to this study analysis. First, the classification of deaths as cardiovascular or noncardiovascular is unavoidably imperfect. Second, the ODYSSEY OUTCOMES trial was designed to test a treat-to-target approach to lowering LDL-C levels after ACS. Third, the mortality reduction with alirocumab is considered nominal given the position of all-cause death after end points that were not significantly reduced in the prespecified hierarchy of efficacy end points. Fourth, there are no head-to-head comparisons of the effects of PCSK9 inhibitors on clinical outcomes, and thus there are no data to prove that one agent is more effective than another on any specific clinical outcome or in any specific type of patient.

*With only nominal statistical significance by hierarchical testing (HR 0.87, 95% CI 0.72, 1.05; P=0.81, nominal P value); The P value for all-cause death was considered nominal because all-cause death followed CHD death and cardiovascular death in the prespecified hierarchy of main secondary end points

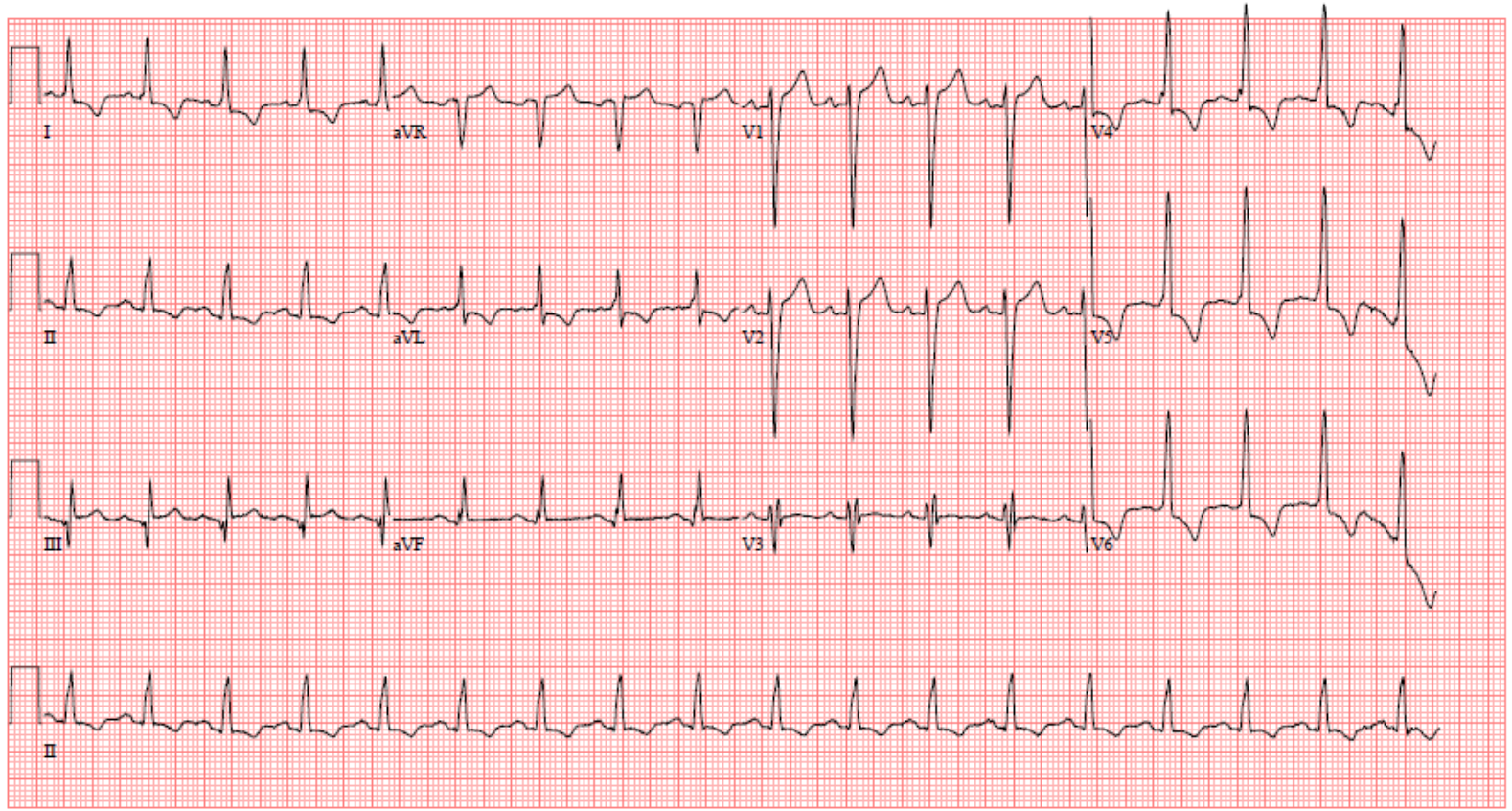
CV, cardiovascular; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors.

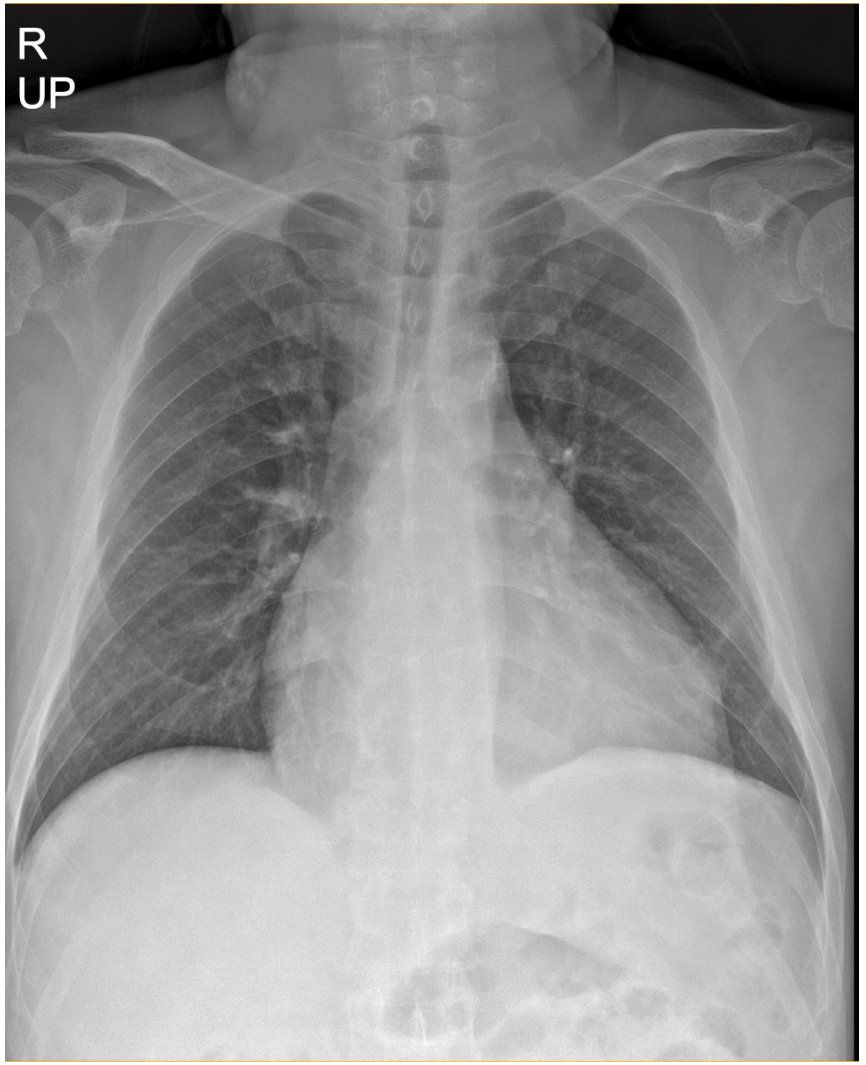
[Study Design[1]] Investigators conducted the effects of alirocumab on death after index acute coronary syndrome. ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) was a double-blind, randomized comparison of alirocumab oanlysis of the ODYSSEY OUTCOMES examined the effects of treatment on all-cause death and its components, cardiovascular and noncardiovascular death, with log-rank testing. Joint semiparametric models tested associations between nonfatal cardiovascular events and cardiovascular or noncardiovascular death.

Reference 1. Steg PG, et al. Circulation. 2019;140:103-112.

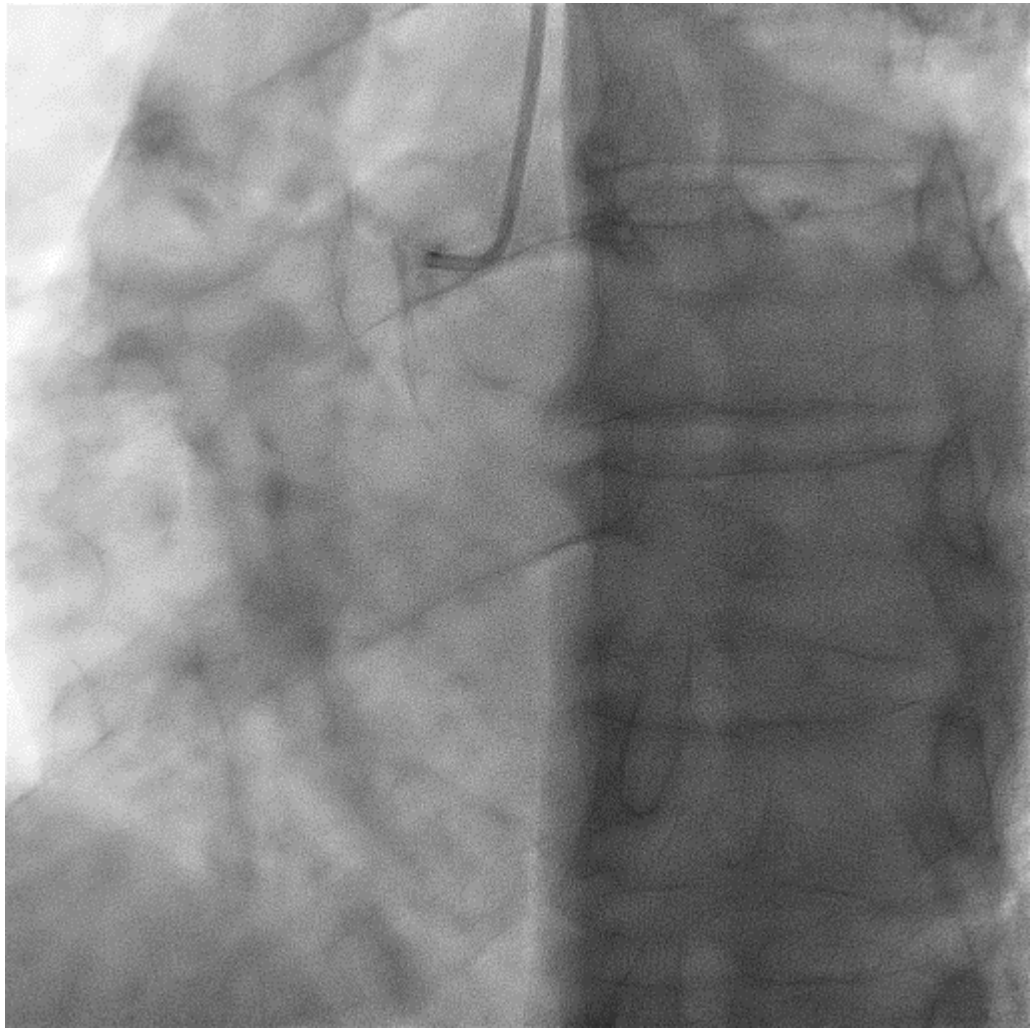
M/62 with Unstable Angina

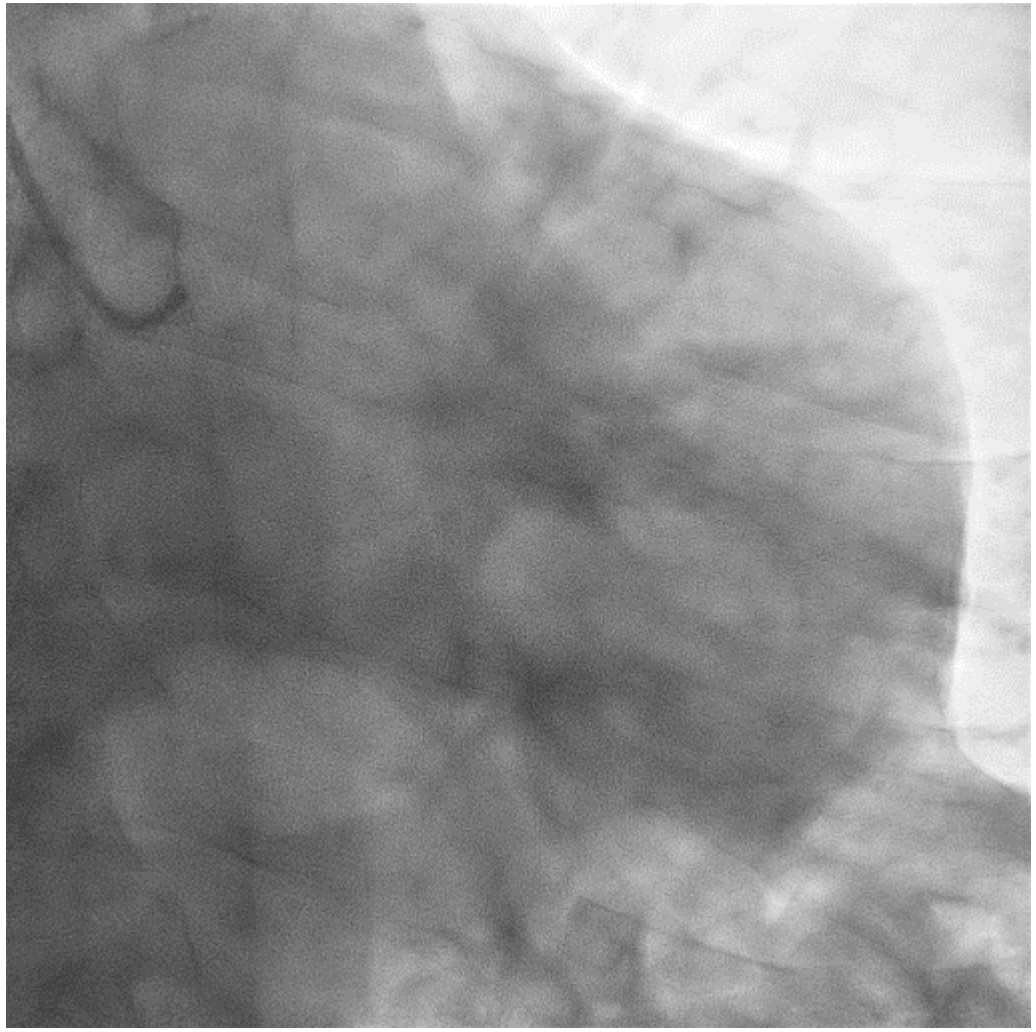
Echo : Severe LV dysfunction with multiple RWMA
(LV EF 33%)



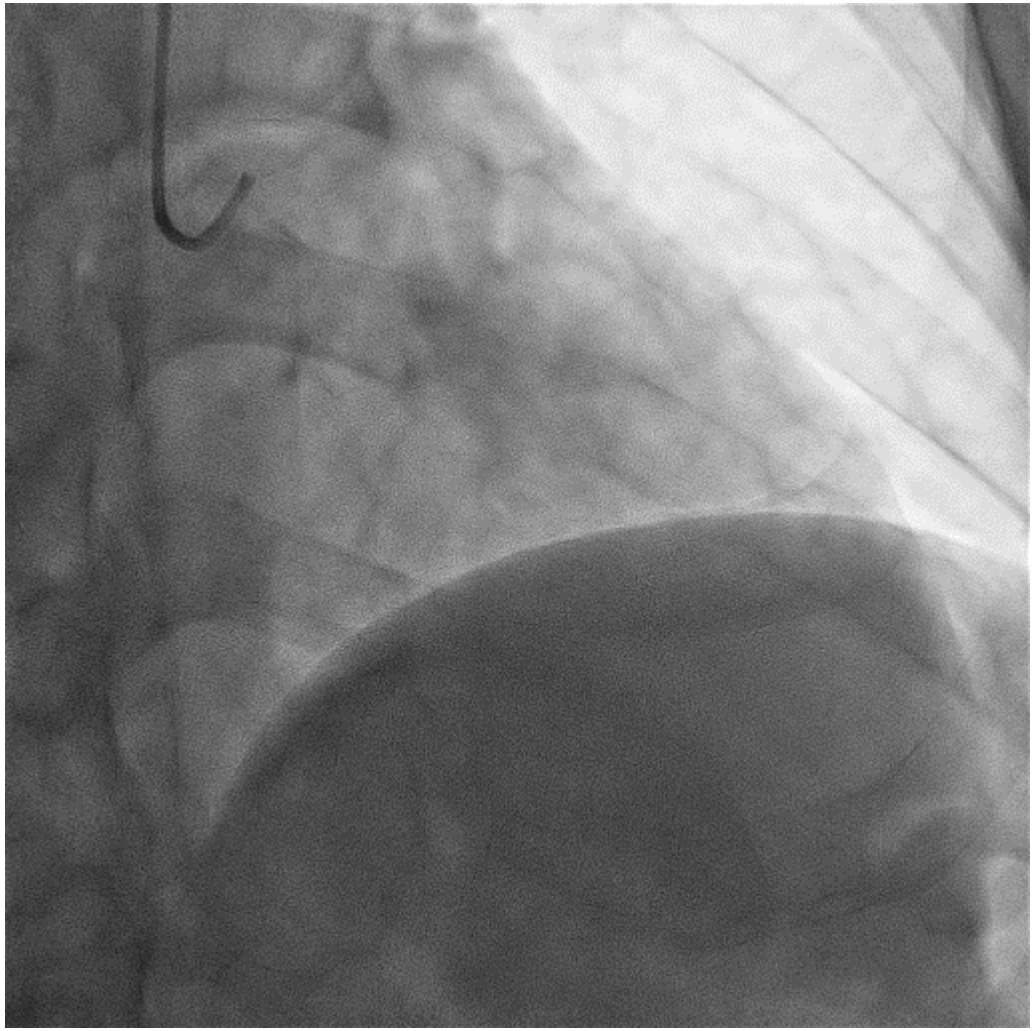


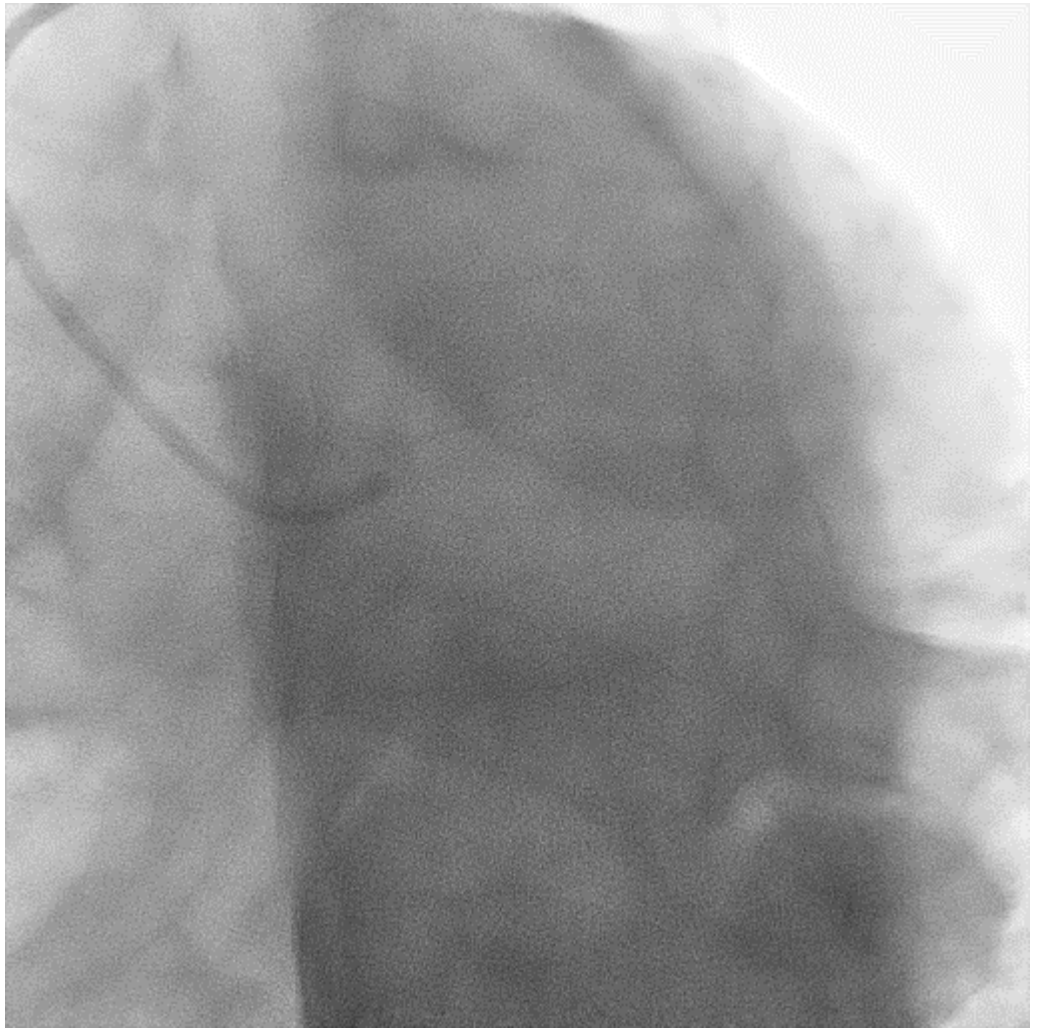
M/62 with Unstable Angina





M/62 with Unstable Angina





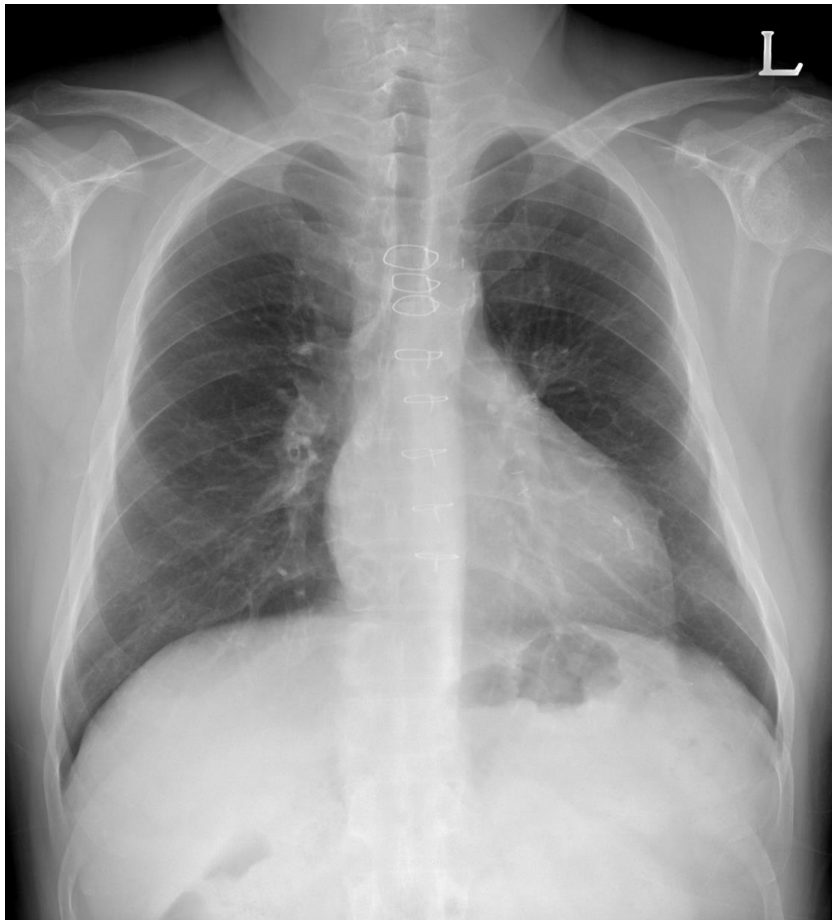
M/62 with Unstable Angina

- 2020.7 CABG surgery was done (LIMA-LAD, SVG-OM, PDA)

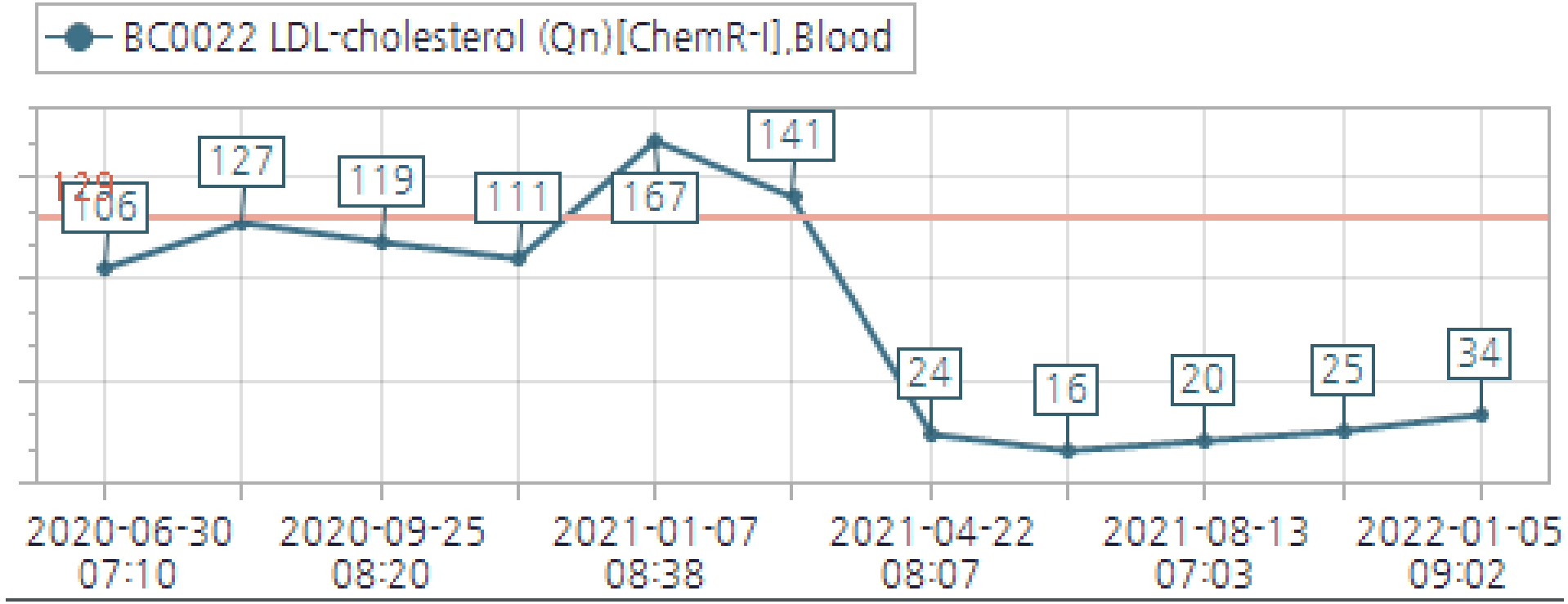
- Discharge Medication
  - Aspirin 100mg qd, olmetec 20mg qd, bisoprolol 2.5mg, lasix 20mg qd, Insulin rosuvastatin 20mg / ezetimibe 10mg

- Sacubitril/Valsartan 100mg bid aldactone 25mg bid, Empagliflozin 10mg was added during OPD FU.

- Praluent 75 mg bid was initiated.



LDL Cholesterol Before and After PCSK9 inhibitor



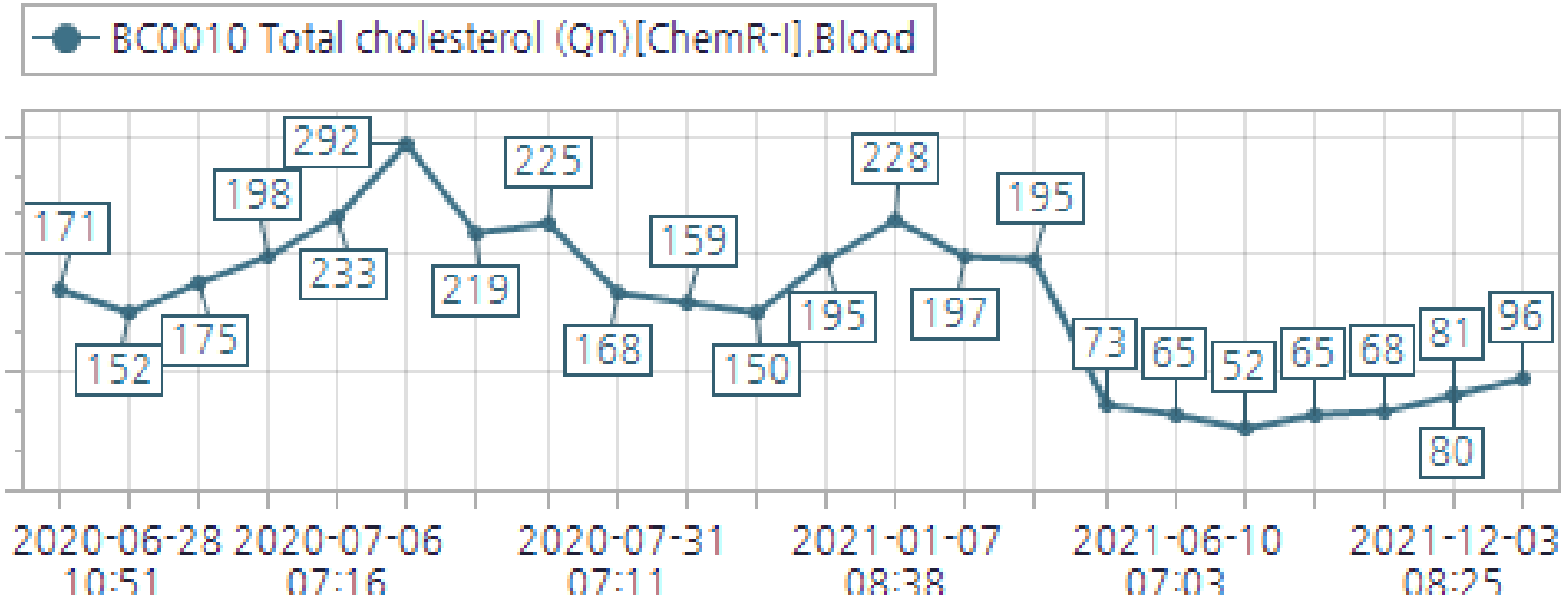
Rosuvastatin 20 mg / Ezetimibe 10 mg

ER

CABG

Praluent 75mg bid

Total Cholesterol Before and After PCSK9 inhibitor



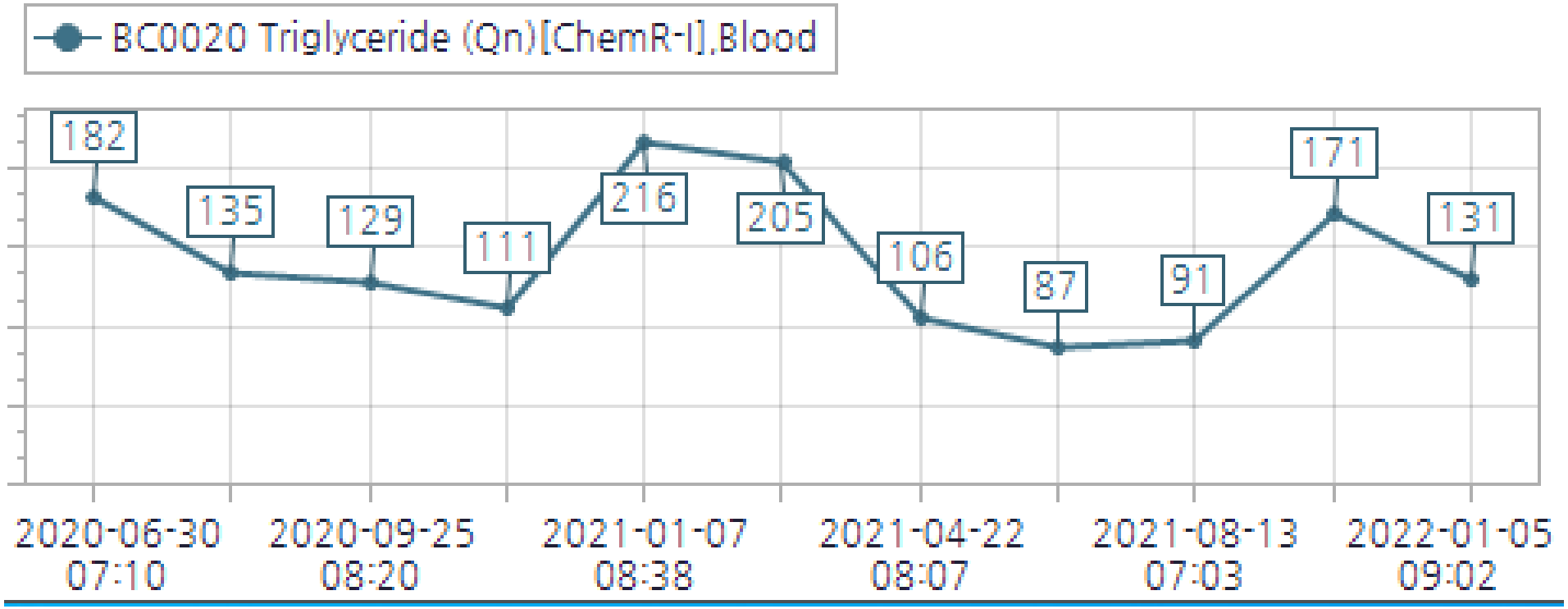
Rosuvastatin 20 mg / Ezetimibe 10 mg

ER

Praluent 75mg bid

CABG

TG Before and After PCSK9 inhibitor



Rosuvastatin 20 mg / Ezetimibe 10 mg

ER

CABG

Praluent 75mg bid

Take Home Message

- Recent LDL-C guidelines, including 2022 Korean guidelines, strongly support "lower and earlier is better" in LDL-C management in high-risk patients.

- Although the current dyslipidemia guidelines recommend lower LDL-C goals among CAD patients, many patients still do not reach recommended LDL-C levels below 55 mg/dL.

- Initiation of Alirocumab in ACS patients can significantly reduce the risk of recurrent major adverse cardiovascular events.