

# Start Tailored approach on cholesterol management for ASCVD patients

Jung Ho Heo, MD, PhD  
Cardiovascular Center,  
Kosin University Gospel Hospital



UNIVERSITY  
GOSPEL  
HOSPITAL

Care &

고신대학교복음병원  
KOSIN UNIVERSITY GOSPEL HOSPITAL



# Disclaimer

본 심포지엄의 발표는 비아트리스코리아(주) (이하 "비아트리스") 의약품에 대한 과학적 정보 공유를 목적으로 하고 있고 해당 의약품의 허가 범위 내에서 사용과 관련된 정보 공유를 목적으로 하고 있습니다. 발표를 하는 과정에 있어서 비아트리스의 의도와 무관하게 언급될 수 있는 허가 범위 밖 사항에 대해서는 발표자의 견해일 뿐 비아트리스의 견해가 아님을 알려드립니다. 개별 특정 의약품의 허가 범위 내 사용에 있어 고려해야 할 충분한 안전성 및 효능 정보는, 반드시 해당 의약품의 제품설명서 및 참고 문헌을 참조해야 합니다. 의료인은 전문가로서의 의학적 판단과 일반적으로 용인되는 치료 기준에 따라, 의약품이 적절하게 처방되고 사용되도록 할 책임이 있습니다.

The presentation of this symposium aims to share scientific information about Viatris Korea (hereinafter "Viatris") products and information related to the approved use of products. Please note that any information or views about non approved use of products that may be mentioned during the live presentation regardless of Viatris's intent are the views of the speaker and not necessarily those of Viatris. Full prescribing information and primary references should be consulted for complete safety and efficacy information relating to the approved use of such products. Physicians will have the professional responsibility to ensure that pharmaceutical products are prescribed and used appropriately, based on their own medical judgment and accepted standards of care.

# CONTENTS

- Lipid guidelines and management status in high-risk patients
- Tailored approach for LDL-C management in high-risk patients
- Tailored approach for CV prevention with Atorvastatin



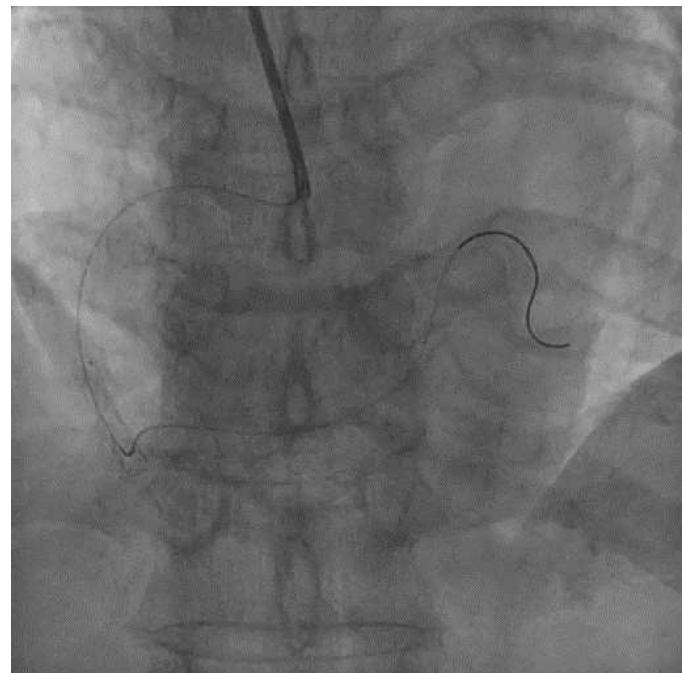
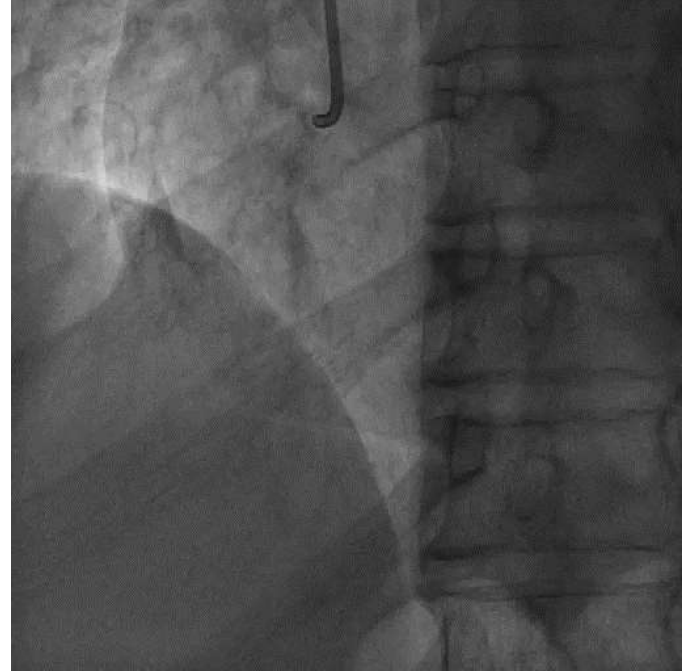
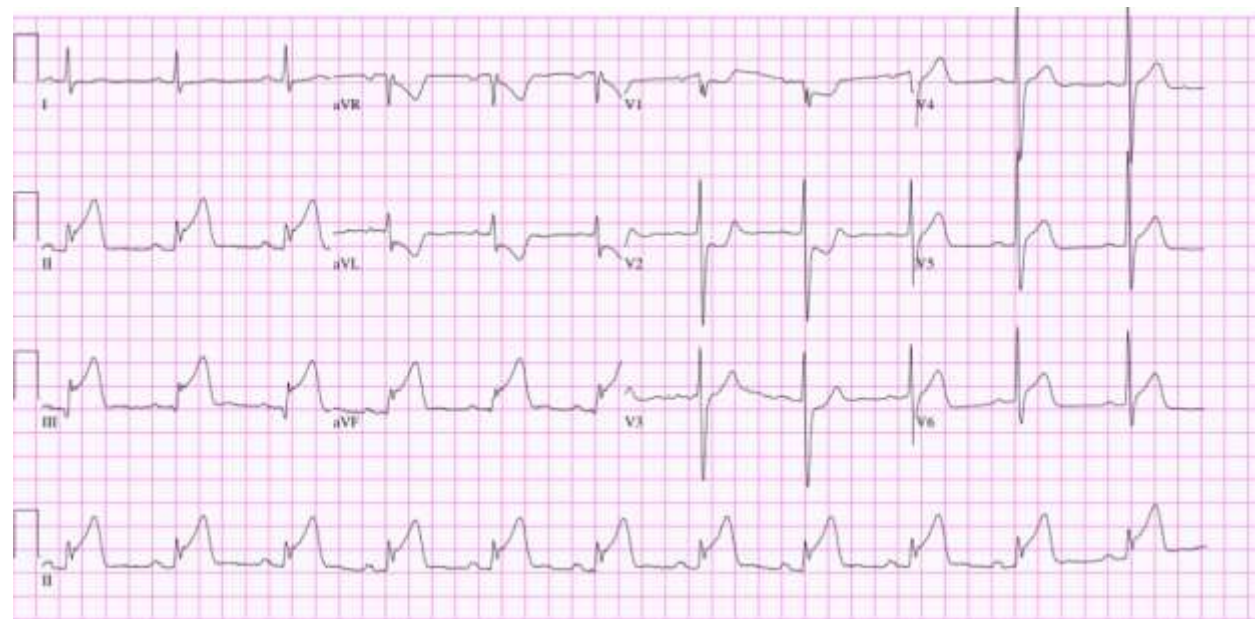
## **Lipid guidelines and management status in high-risk patients**

# Statins are recommended as 1st treatment option

Class of Recommendations for statin therapy in each guideline

	2018 ACC <sup>1</sup>	2019 ESC <sup>2</sup>	2022 KSoLA <sup>3</sup>
<b>Statins up to maximal tolerable dose</b> are recommended to reach the goal.	I	I	I

# 65/M STEMI

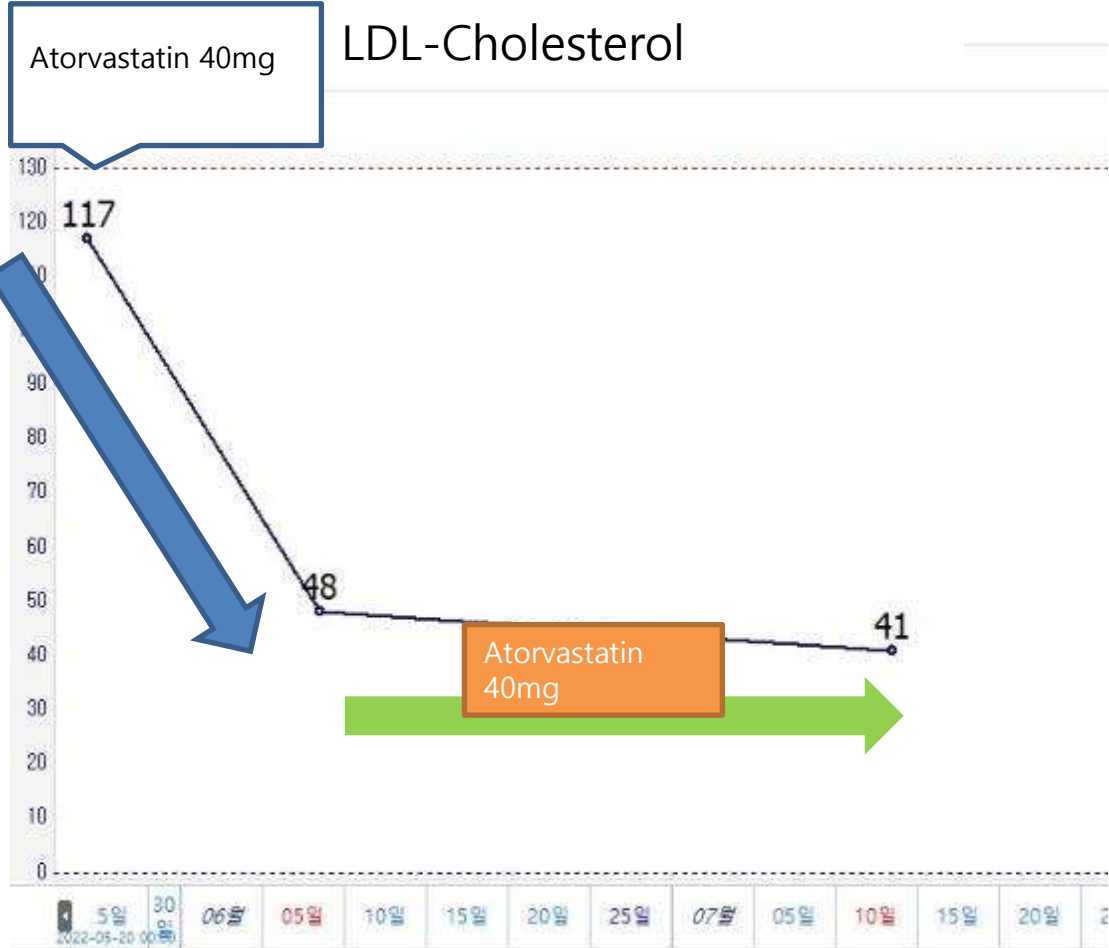


2022.05.26	결과	단위
Cholesterol total	195	Mg/dl
Triglyceride	88	Mg/dl
HDL-Cholesterol	61.7	Mg/dl
LDL-Cholesterol	117	Mg/dl
Calculated LDL-C	115.7	Mg/dl

Atorvastatin 40mg

2022.07.14	결과	단위
Cholesterol total	119	Mg/dl
Triglyceride	137	Mg/dl
HDL-Cholesterol	57.7	Mg/dl
LDL-Cholesterol	41	Mg/dl
Calculated LDL-C	33.9	Mg/dl

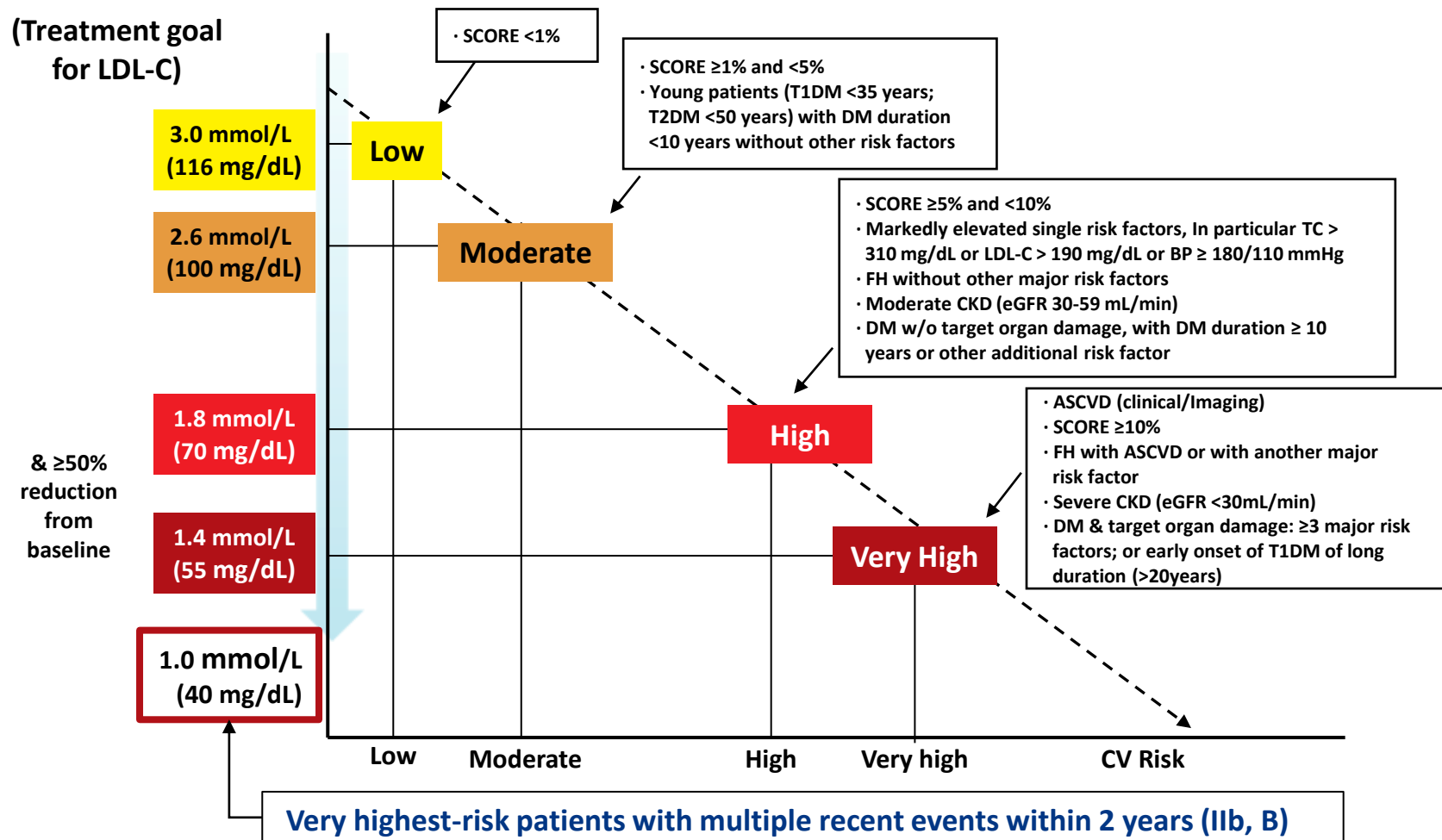
2022/05/26





# 2019 ESC/EAS Lipid management guideline

## The lower treatment goal for LDL-C by cv risk



# 2022 Korean guidelines for the management of dyslipidemia

## Recommendations for treatment goals

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

\*It is also recommended to reduce LDL-C by ≥ 50% from the baseline level.

†Age (men ≥ 45 years, women ≥ 55 years), family history of premature ASCVD, hypertension, smoking, and low HDL cholesterol level.

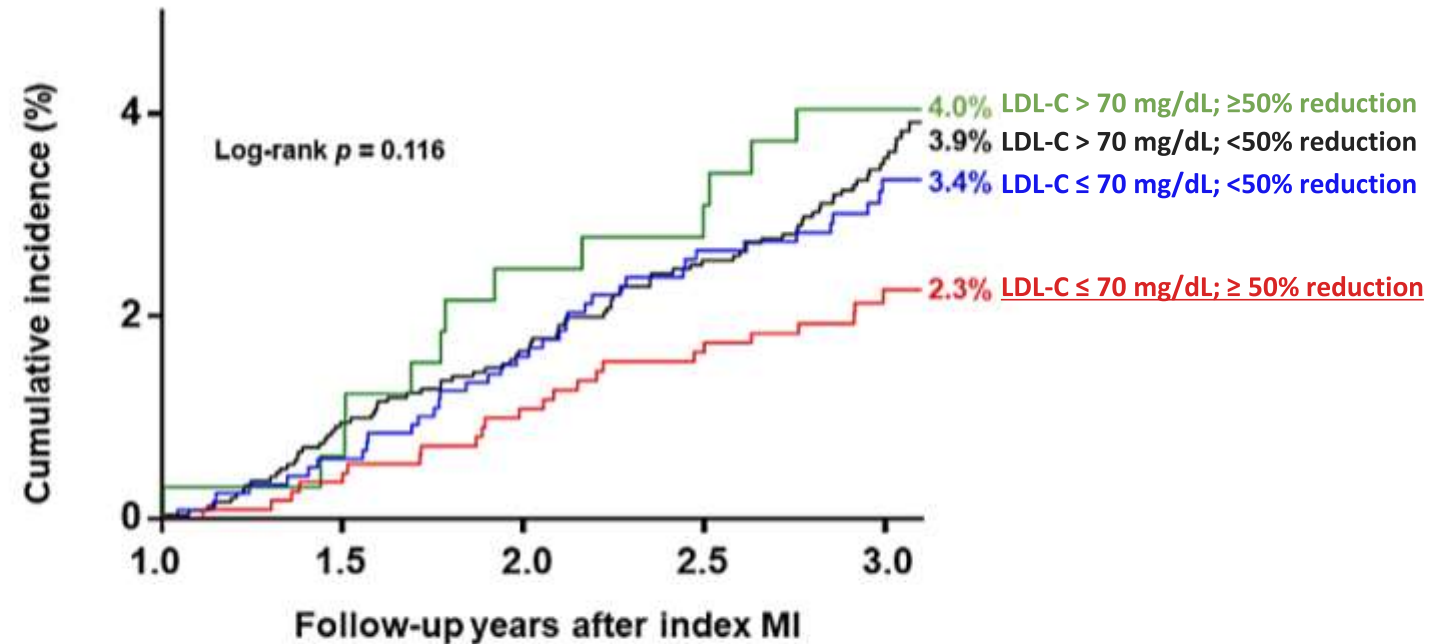
1) In patient with acute myocardial infarction, statin is recommended irrespective of LDL-C level.

2) In diabetes mellitus with target organ damage (albuminuria, nephropathy, retinopathy and neuropathy) or major risk factors<sup>†</sup> ≥ 3: target LDL-C < 55 mg/dL (optional)

# LDL-C goal for secondary prevention in Korean acute MI patients

## LDL-C $\leq 70$ mg/dL & $\geq 50\%$ reduction from baseline

Cumulative incidence of MACCE according to the achievement of either target LDL-C goal.

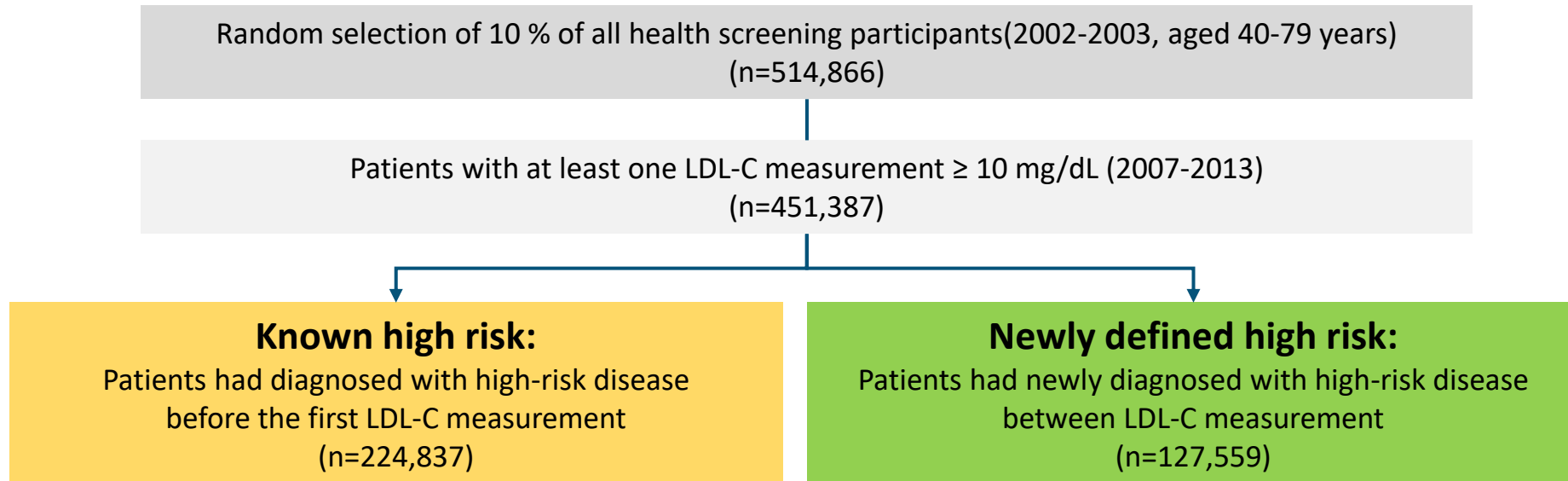


	Number at risk					HR [95% CI]	p-value
LDL-C $\leq 70$ mg/dL; $\geq 50\%$ reduction	1114	1106	1080	1045	762	Reference	
LDL-C $\leq 70$ mg/dL; < 50% reduction	1189	1180	1153	1102	805	1.49 [0.90–2.49]	0.123
LDL-C > 70 mg/dL; $\geq 50\%$ reduction	324	322	316	307	220	1.86 [0.95–3.65]	0.071
LDL-C > 70 mg/dL;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

MACCE, major adverse cardiac and cerebrovascular event

# LDL-C goal attainment rates in Korean high-risk\* patients

## Retrospective cohort study (NHIS-HEALS database, 2002-2015)



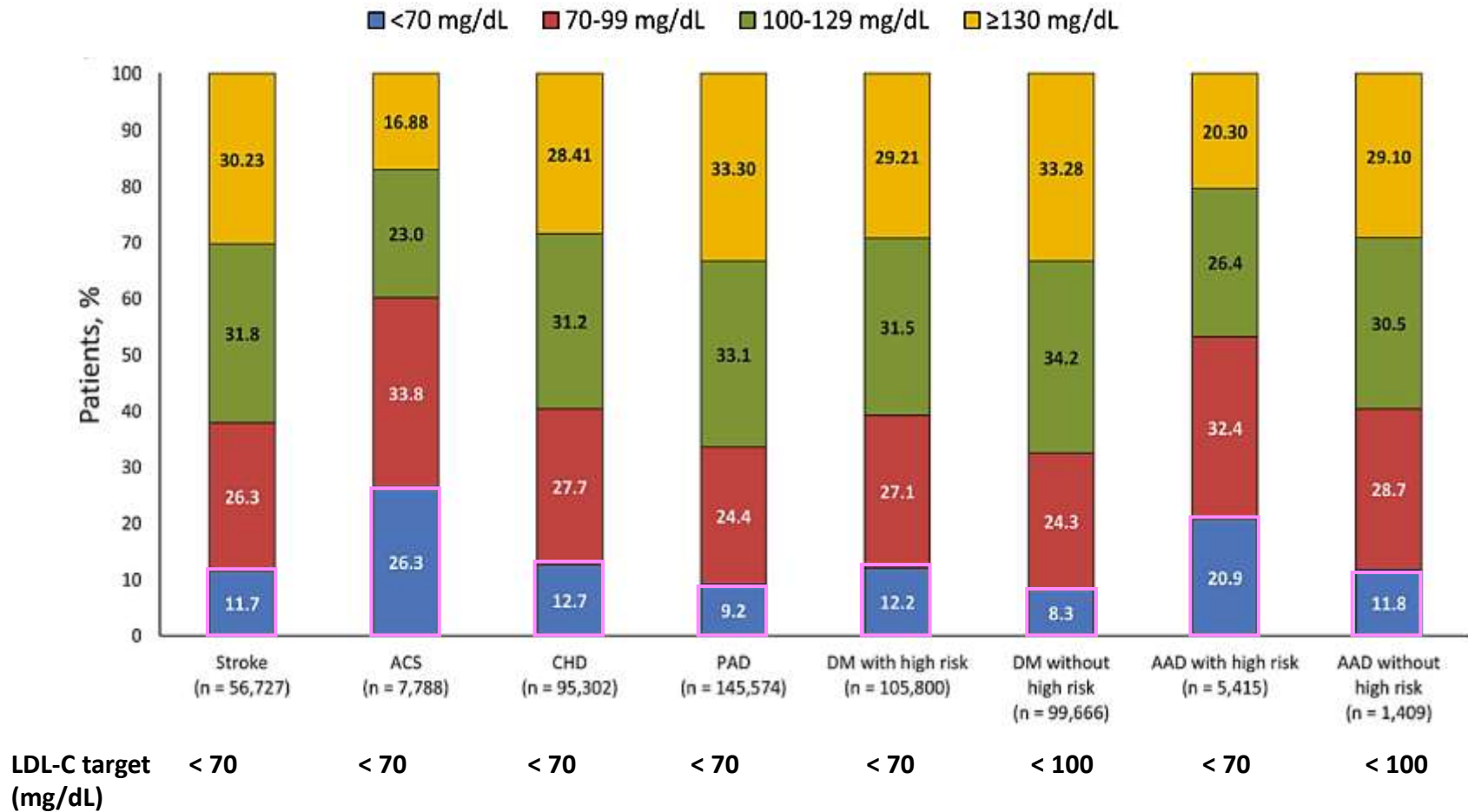
### \*Definition of high-risk disease & LDL-C goal attainment

	Disease	LDL-C goal attainment	
		2018 Korean national guidelines	2013 ACC/AHA guideline
<b>Very high risk</b>	Stroke & TIA, ACS, CHD, PAD	<70 mg/dL	> 50% reduction in baseline LDL-C for high-intensity statin
<b>High risk</b>	DM, AAD	<100 mg/dL	

NHIS-HEALS, National Health Insurance Service-National Health Screening; ACS, acute coronary syndrome, CHD, coronary heart disease; PAD, peripheral artery disease; DM, diabetes mellitus; AAD, atherosclerotic artery disease

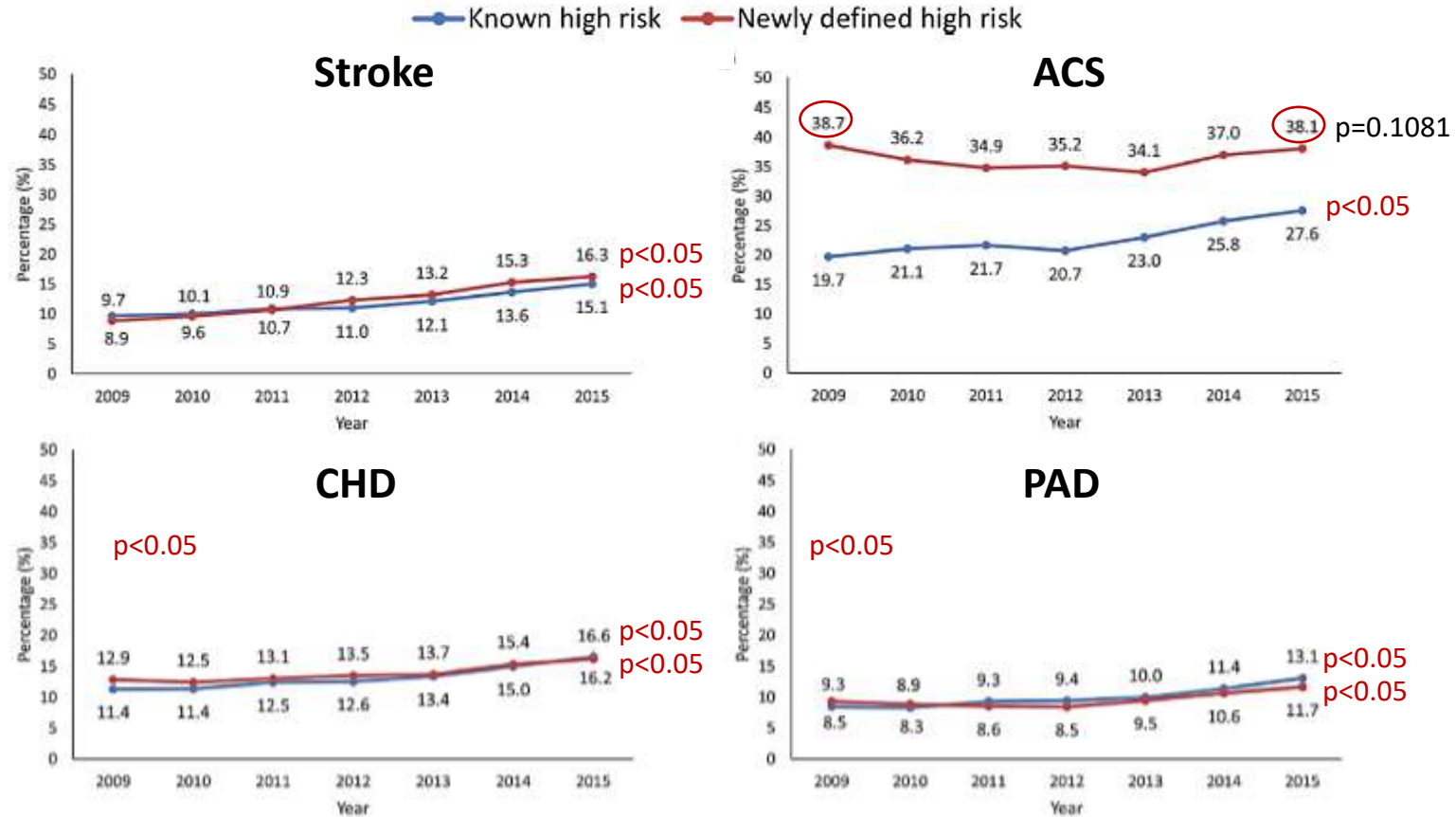
# Less than 50% of Korean high-risk patients achieved LDL-C goal

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



# LDL-C goal attainment increased in patients with ACS but the goal-achiever proportion remained about 38%

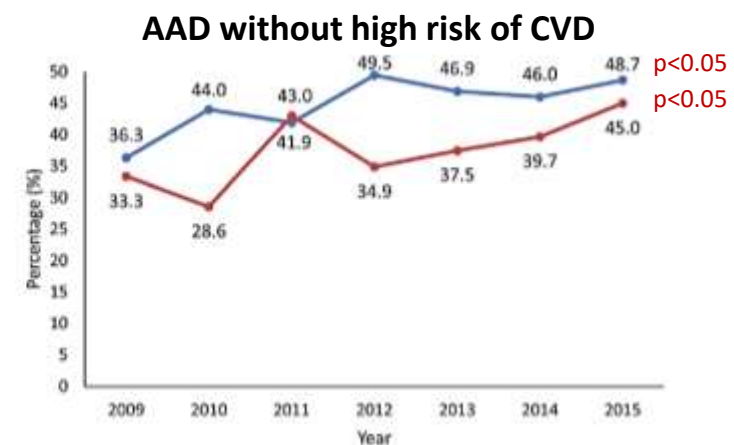
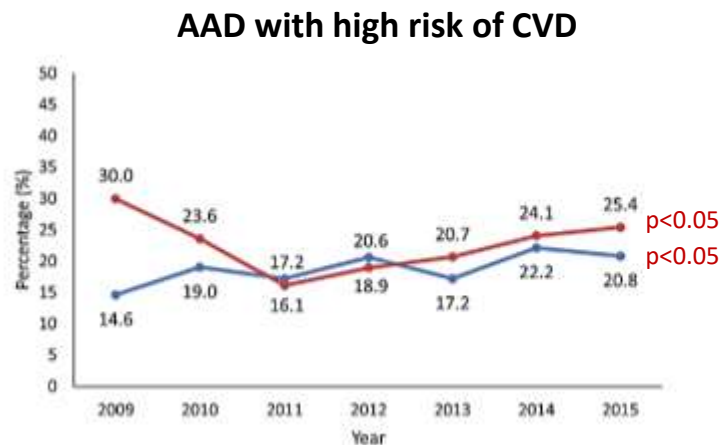
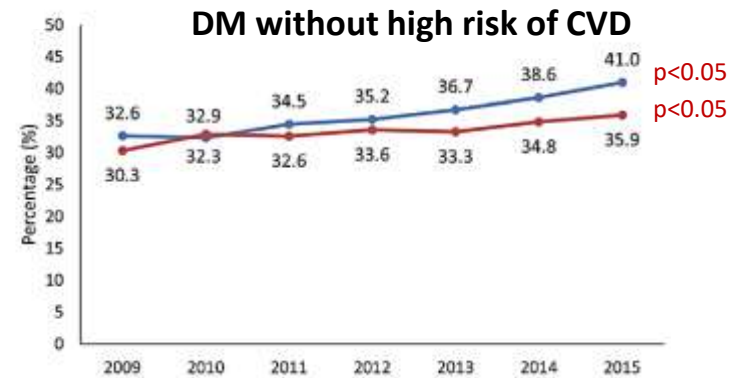
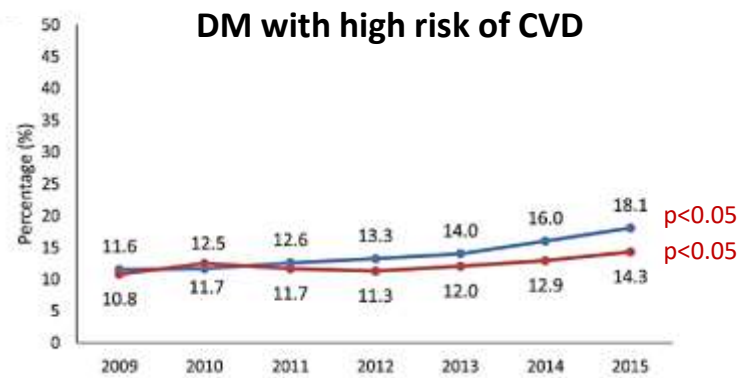
Time trends of goal attainment in known and newly defined high-risk patients



# DM and AAD patients without high risk had higher LDL-C attainment rates than those with high risk

Time trends of goal attainment in known and newly defined high-risk patients

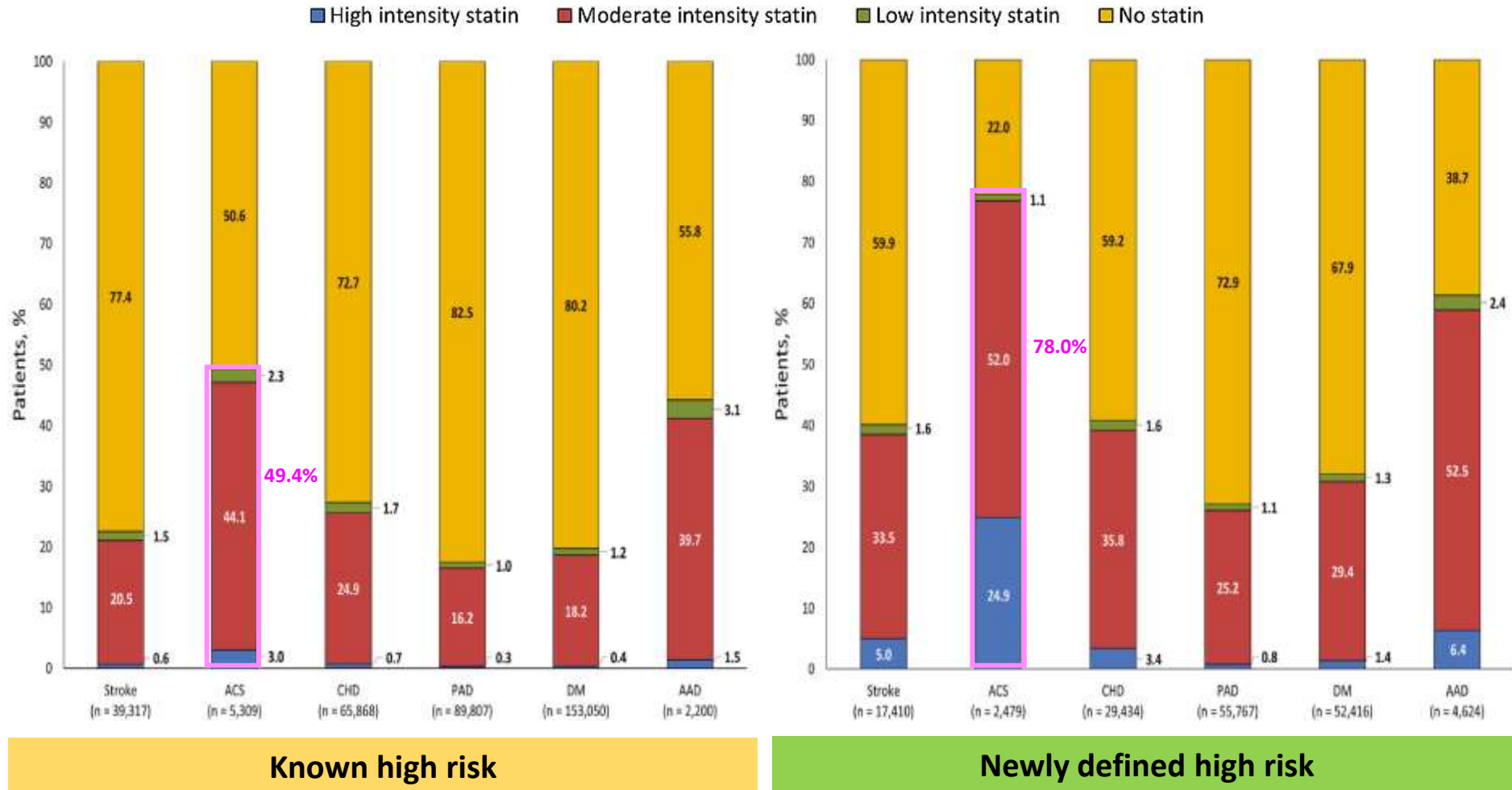
— Known high risk\* — Newly defined high risk\*



\*Subjects with a high-risk of CVD prior to LDL-C measurement and subjects who were newly-diagnosed for high-risk of CVD following LDL-C measurement were defined as known high-risk patients (n = 224,837) and newly defined high-risk patients (n = 127,559), respectively.

# Relatively low proportions of subjects were under statin use (known high-risk: 21.5%, newly defined high-risk: 34.4%)

Statin use in cardiovascular high-risk groups









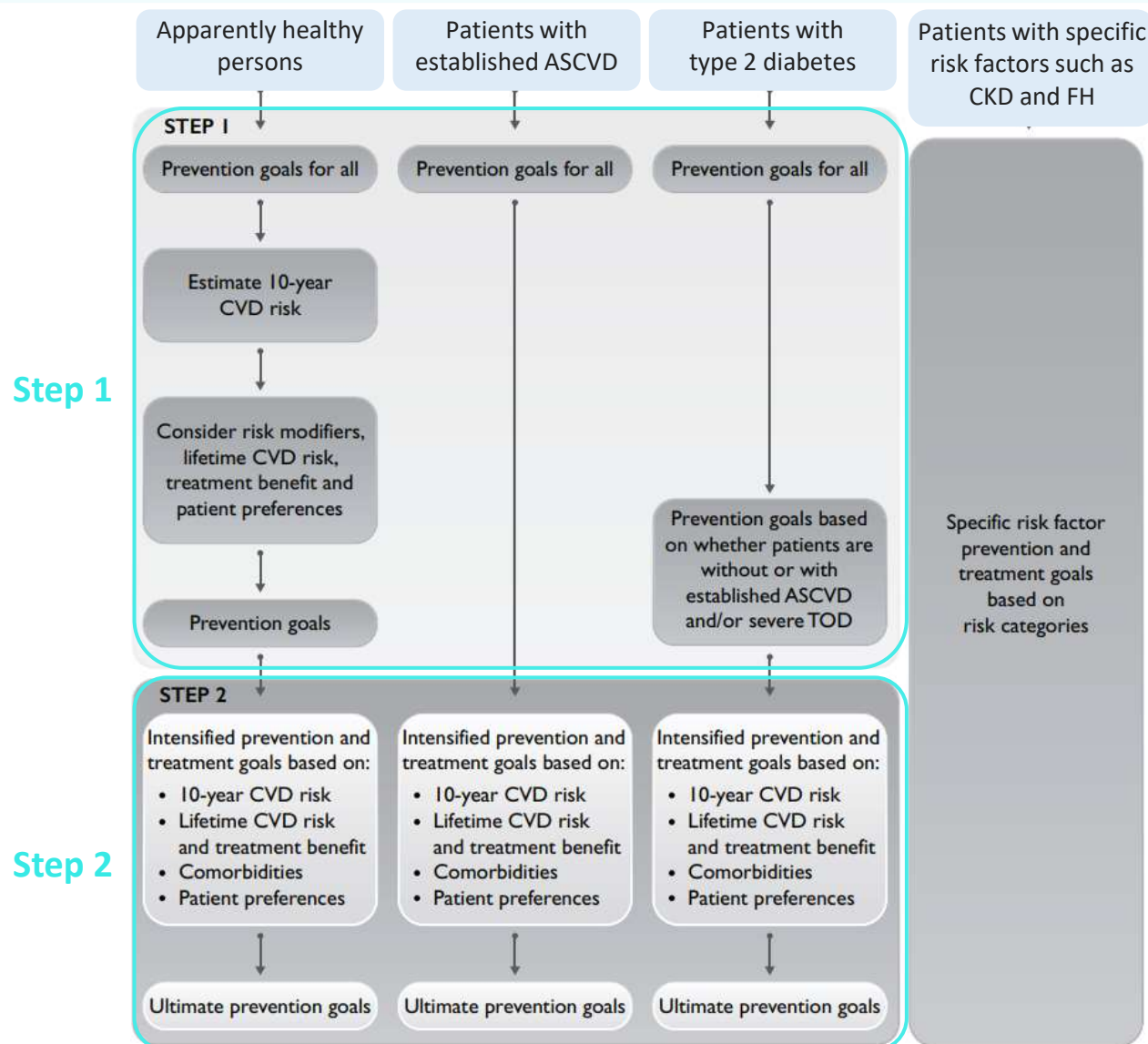
**Tailored approach for LDL-C management in high-risk patients**

# 2021 ESC Guidelines on CVD prevention

- **More personalized CVD prevention guideline, instead of a one-size-fits-all**
- **More attention to CVD prevention in older persons.**
- **Introduce a new stepwise treatment-intensification approach.**
- **Embrace the recently published Systemic Coronary Risk Estimation 2 (SCORE2) and Systemic Coronary Risk Estimation 2-Older Persons (SCORE2-OP) algorithms.**
- **Introduce age-specific risk thresholds for risk factor treatments in apparently healthy people and provide estimation of lifetime CVD risk and treatment benefit.**
- **The ultimate lipid goals are the same as in the 2019 ESC/EAS dyslipidemia guideline**

# 2021 ESC Guidelines on CVD prevention

## New stepwise treatment-intensification approach



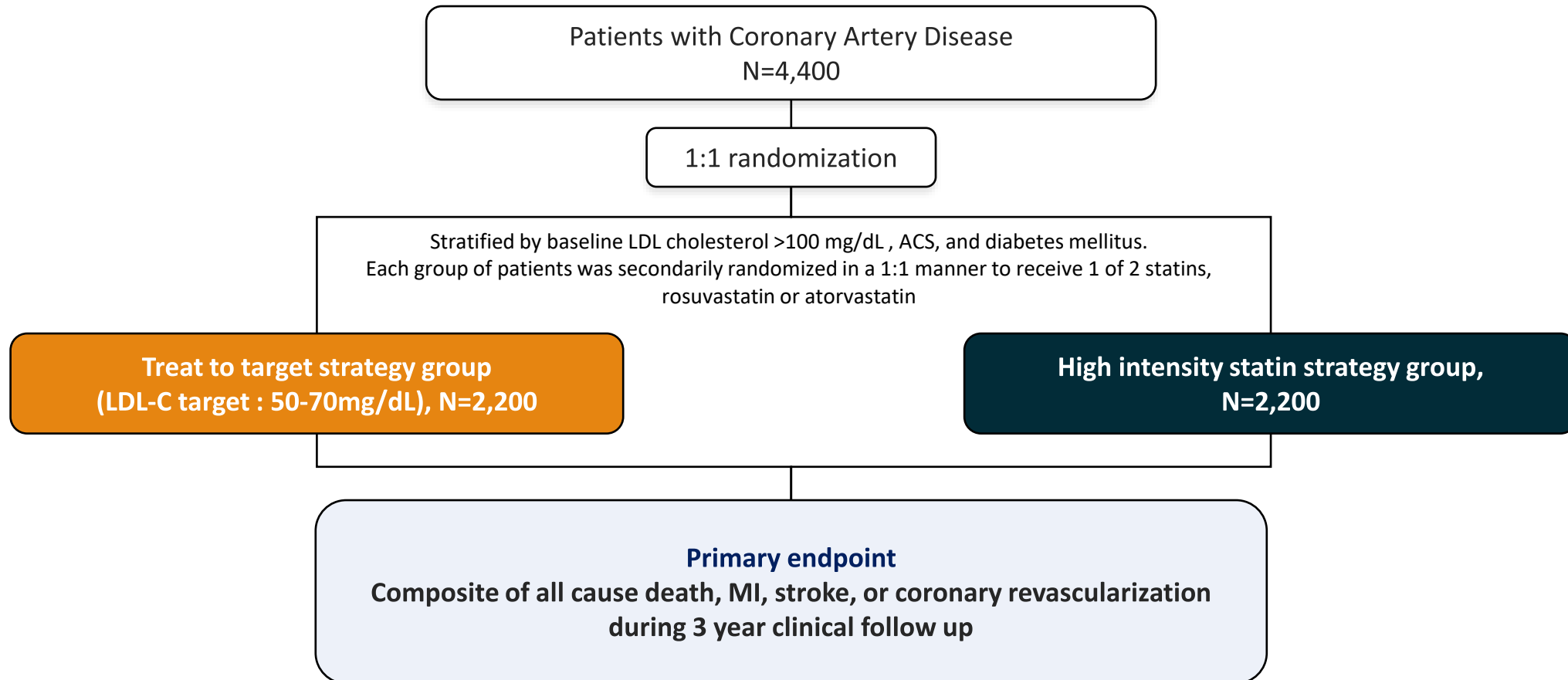
**A stepwise treatment intensification approach is recommended** for apparently healthy people at high or very high CVD risk, as well as patients with established ASCVD and/or DM, with consideration of **CVD risk, treatment benefit of risk factors, risk modifiers, comorbidities, and patient preferences.**  
*(Class I, Level C)*

# Patients with coronary artery disease

## Treat-to-Target strategy vs. High-Intensity statin therapy

### LODESTAR trial

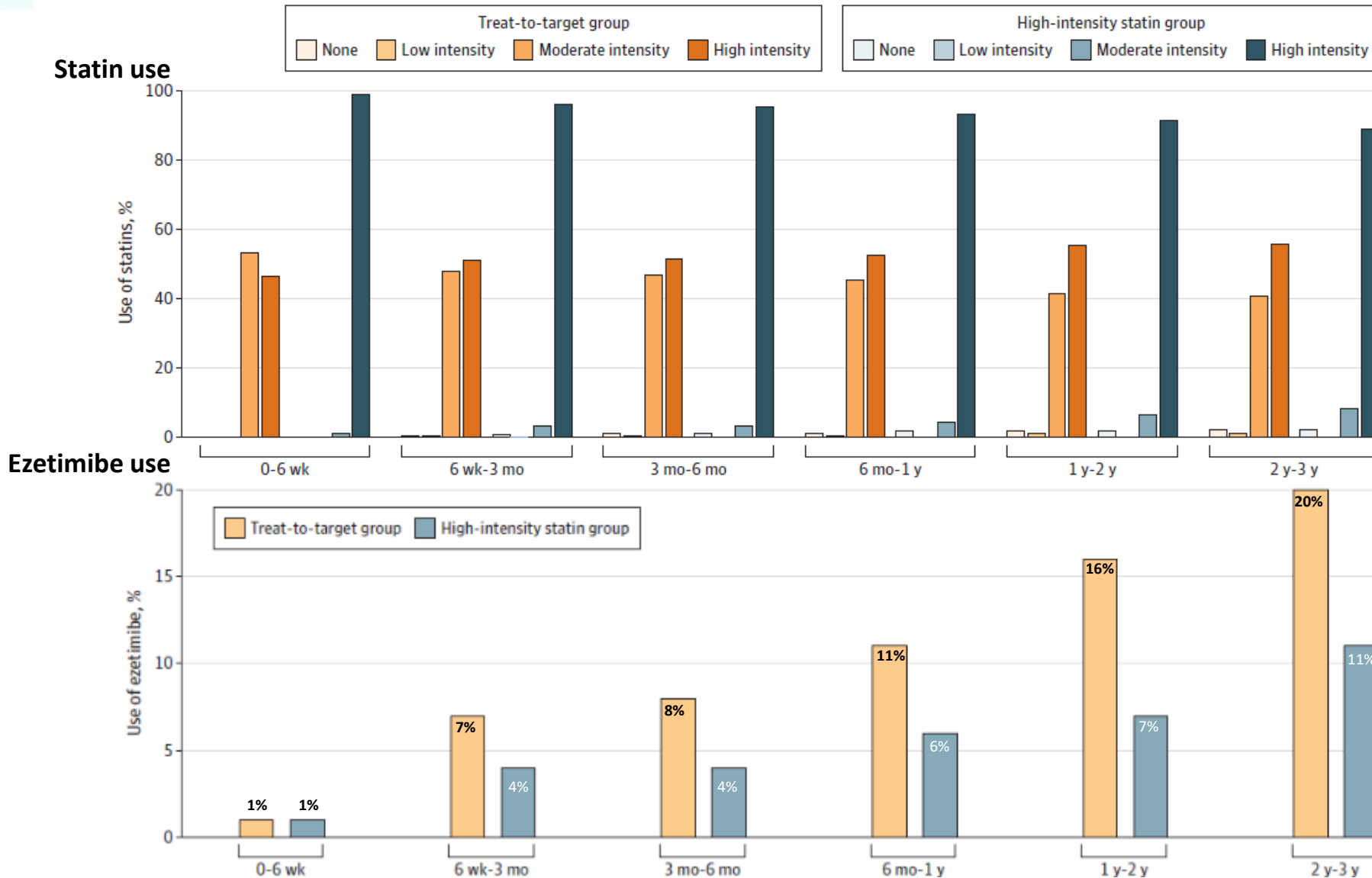
(Low-Density Lipoprotein Cholesterol- Targeting Statin Therapy Versus Intensity-Based Statin Therapy in Patients With Coronary Artery Disease)



ACS, acute coronary syndrome; MI, myocardial infarction

# LODESTAR trial

## Lipid-lowering therapy during the study period



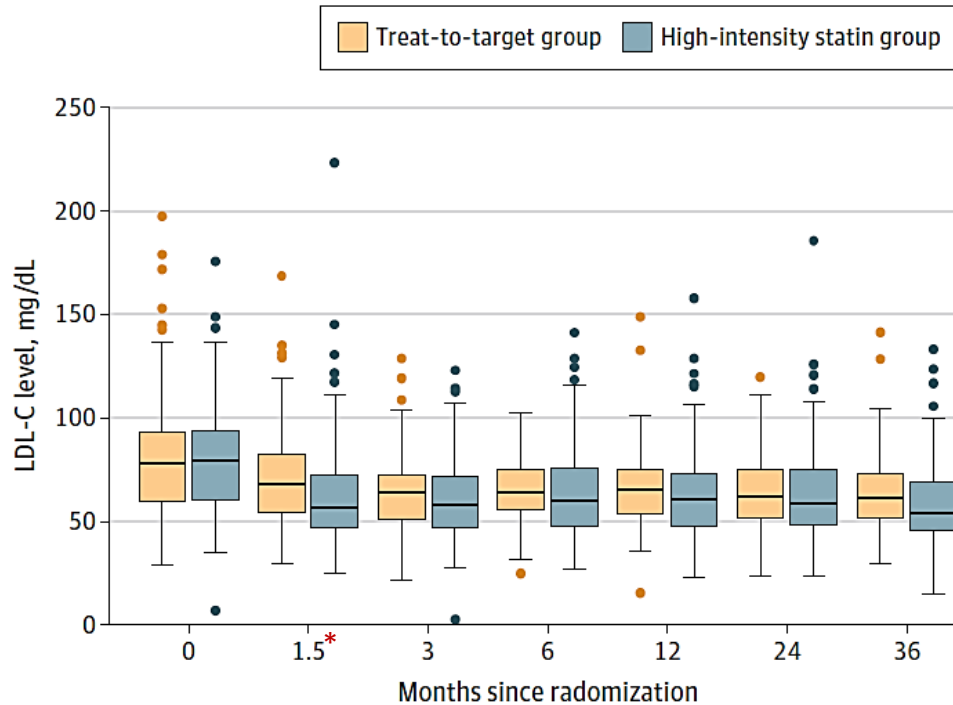
Overall period	Treat to Target group	High intensity group
Moderate intensity statin	43%	6%
High intensity statin	54%	92%

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

# LODESTAR trial

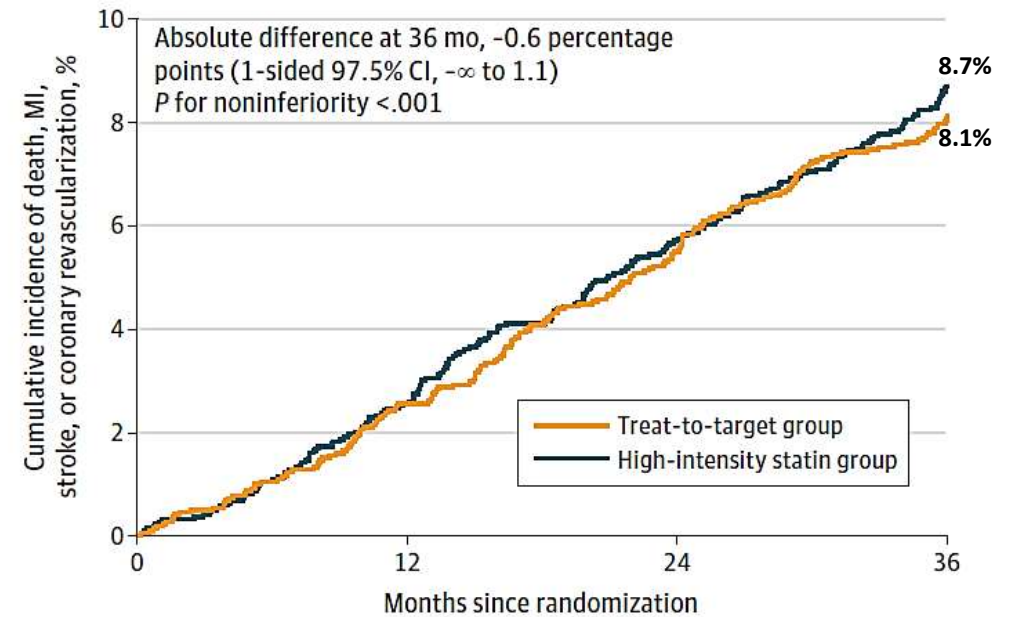
## LDL-C levels and Cumulative incidence of primary end point

Distribution of LDL-C levels



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

Cumulative incidence of the primary end point



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

\* $P < 0.001$  at 1.5 months (6 weeks)

# LODESTAR trial

## Patients with LDL-C below 70 mg/dL

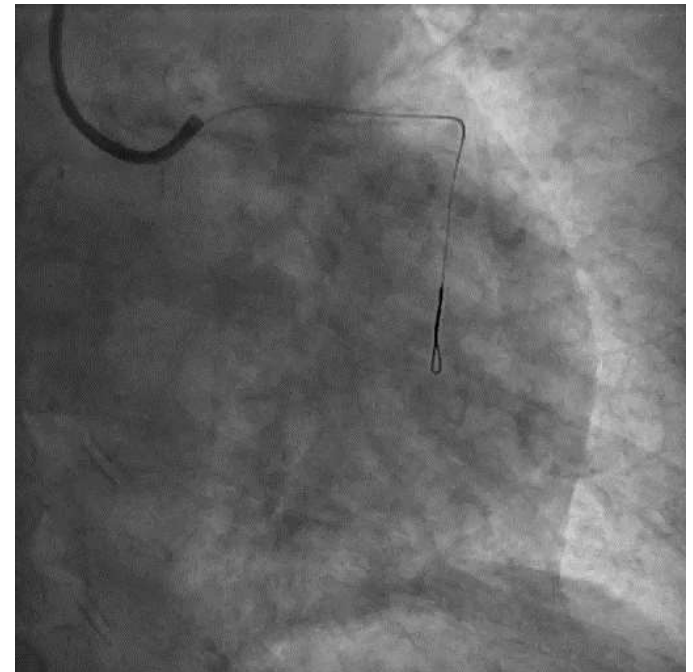
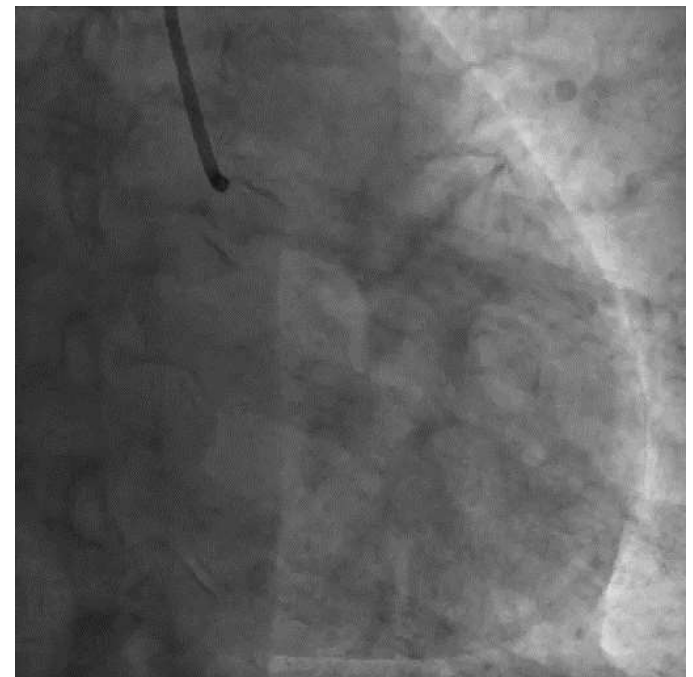
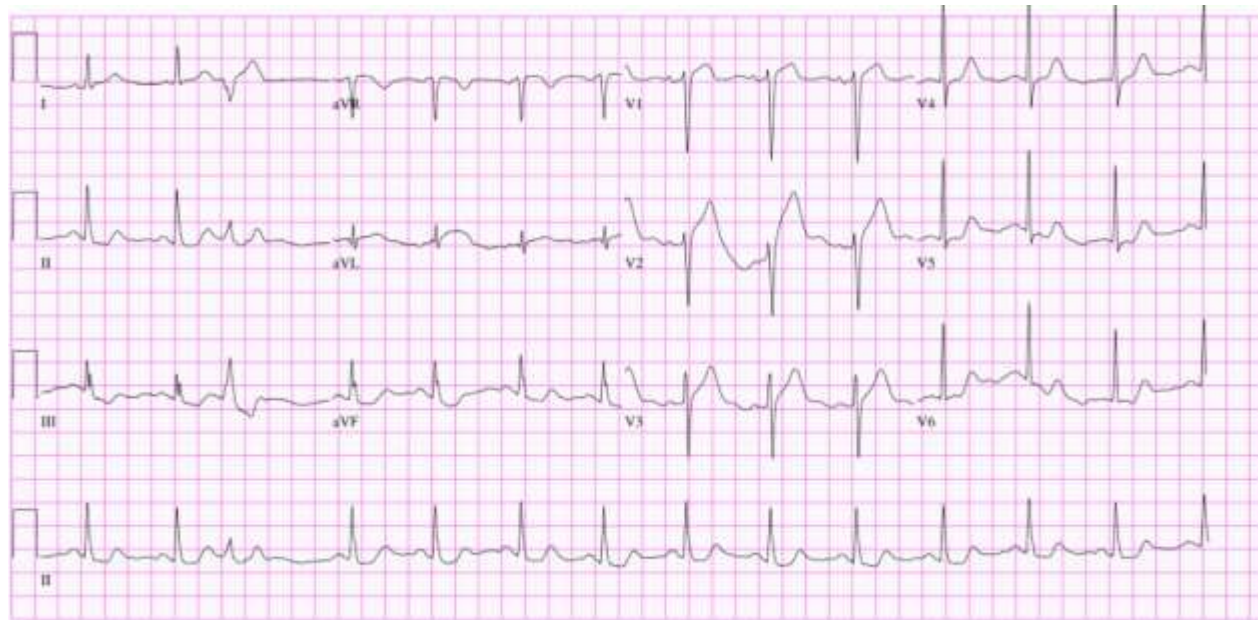
	Treat-to-target	High-intensity statin	Absolute Difference (95% confidence interval)	P Value
At randomization	712/2200 (32.4)	655/2200 (29.8)	2.6 (-0.1 to 5.3)	.06
At 6 weeks	890/1598 (55.7)	987/1601 (61.6)	-6.0 (-9.4 to -2.5)	<.001
At 3 months	261/441 (59.2)	267/397 (67.3)	-8.1 (-15.6 to -5.3)	.02
At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



## If the LDL-C goal is not reached with statins, recommendation of statin/ezetimibe combination

	2018 ACC <sup>1</sup>	2019 ESC <sup>2</sup>	2022 KSoLA <sup>3</sup>
<b>Statins up to maximal tolerable dose</b> are recommended to reach the goal.	I	I	I
<b>If the goal is not reached, a statin combined with ezetimibe</b> should be considered or is recommended.	I, IIa, IIb	I	I

# 77/F STEMI with atorvastatin 20mg



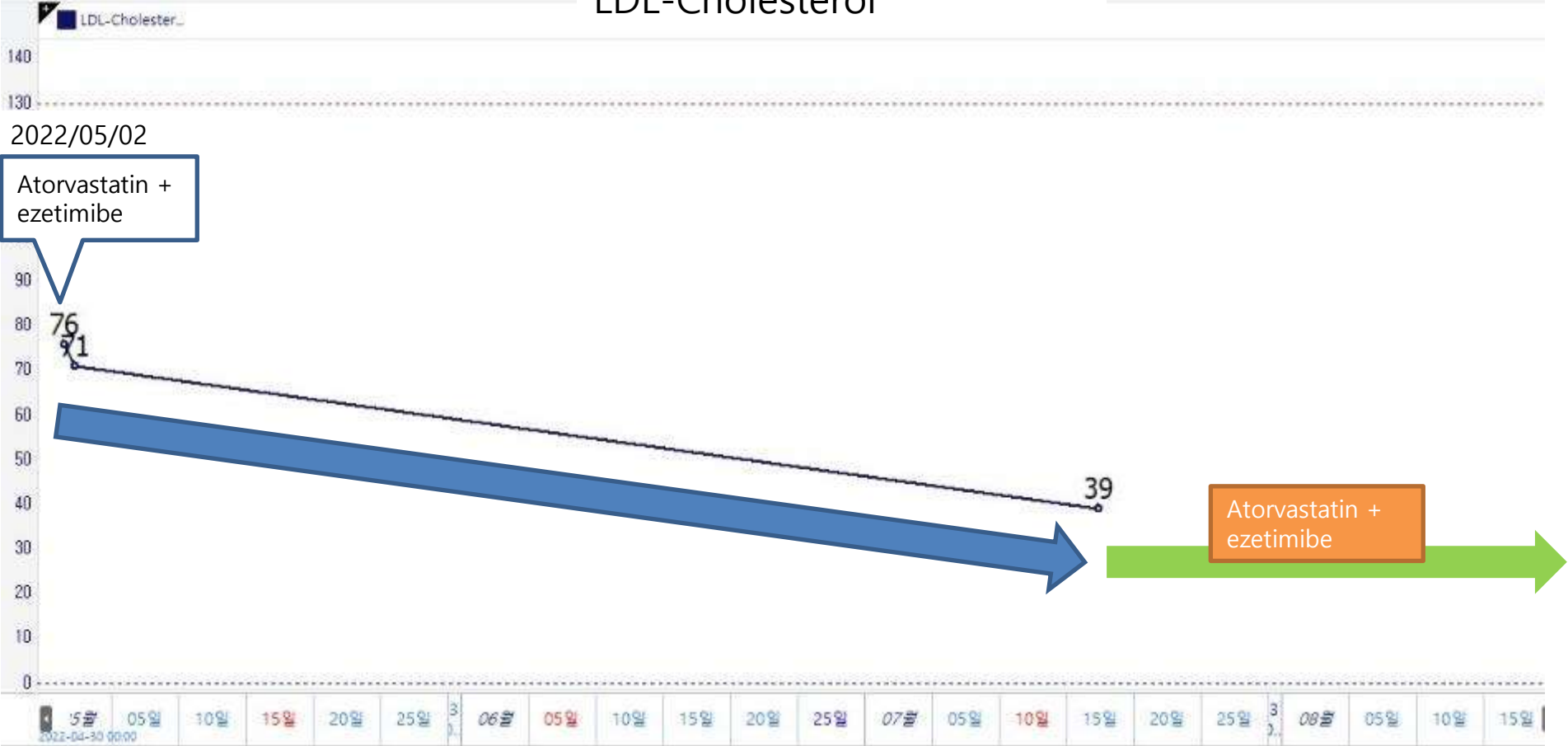
2022.05.02	결과	단위
Cholesterol total	152	Mg/dl
Triglyceride	111	Mg/dl
HDL-Cholesterol	53.8	Mg/dl
LDL-Cholesterol	76	Mg/dl
Calculated LDL-C	76	Mg/dl

Atorvastatin 40mg + Ezetimibe 10mg



2022.07.18	결과	단위
Cholesterol total	90	Mg/dl
Triglyceride	57	Mg/dl
HDL-Cholesterol	38.7	Mg/dl
LDL-Cholesterol	39	Mg/dl
Calculated LDL-C	39.9	Mg/dl

# LDL-Cholesterol



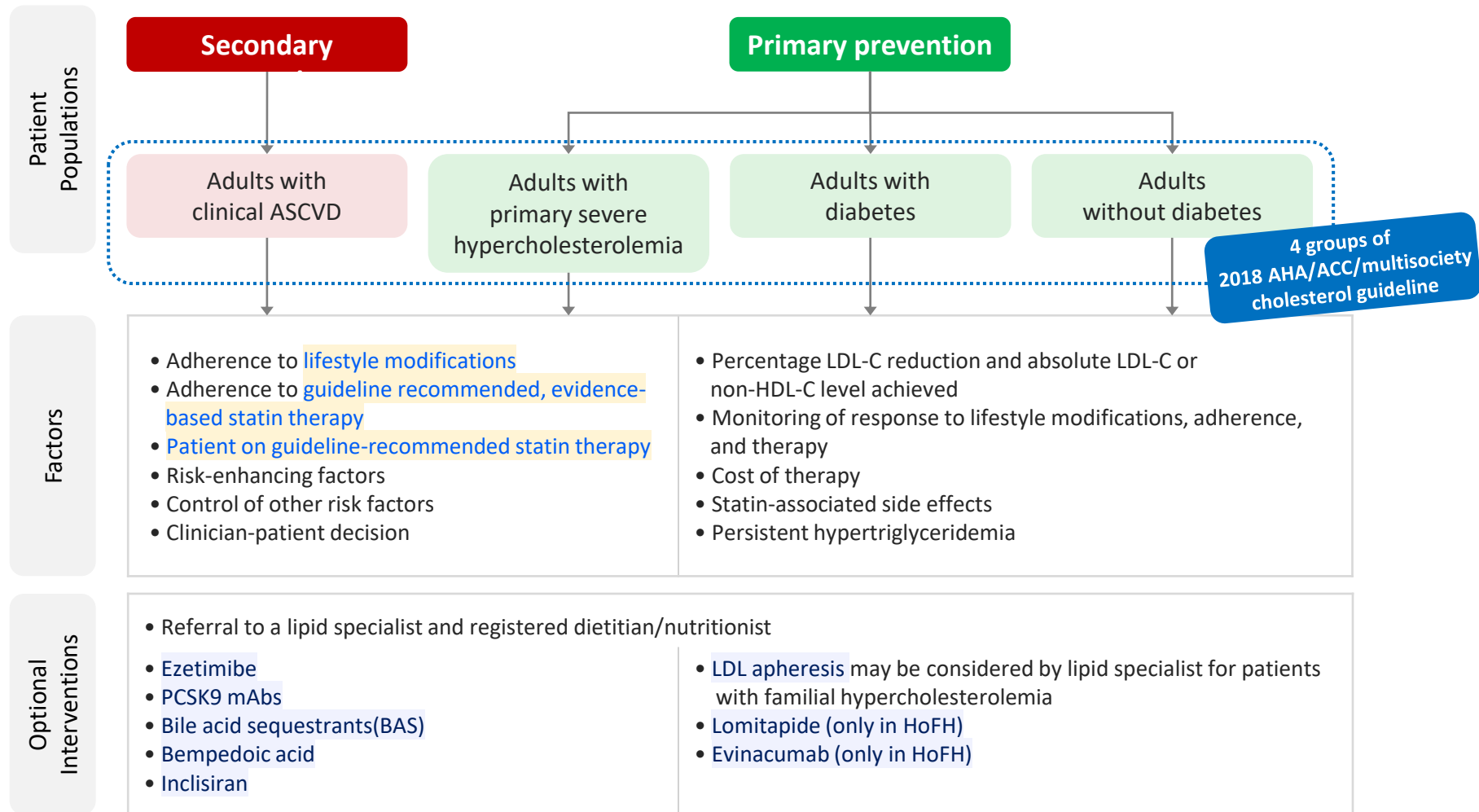
# 2022 ACC Expert Consensus Decision Pathway

## Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of ASCVD Risk

3 Questions regarding the use of nonstatin therapies

1. In **what patient populations** should newer nonstatin therapies be considered?
2. In **what situations** should newer nonstatin therapies be considered?
3. **Which newer nonstatin therapies** should be considered and in **what order** to maximize patient benefit and preference?

# Patient Populations, Factors and Interventions to Consider



\*2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk, \*\* LDL-C  $\geq 190$  mg/dL

PCSK9 mAb includes alirocumab and evolocumab. ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; PCSK9 mAb, proprotein convertase subtilisin/kexin type 9 monoclonal antibodies

# Nonstatin Options to Consider for ASCVD Secondary Prevention

	Adults with clinical ASCVD	Adults with clinical ASCVD, and LDL-C ≥190	Adults with clinical ASCVD, at very high risk	Adults with clinical ASCVD, at very high risk and LDL-C ≥190
<b>Statin therapy</b>	<b>Maximally-tolerated statin therapy</b>			
LDL-C target	≥50% LDL-C reduction and LDL < 70 mg/dL		≥50% LDL-C reduction and LDL < 55 mg/dL	
Factor to consider	1. Evaluate and optimize lifestyle modifications, statin adherence, risk factor control, and SASEs 2. Increase to high-intensity statin therapy, if not already taking 3. Consider referral to lipid specialist and RD/RDN for all patients, especially for HoFH (if LDL-C ≥ 190 mg/dL)			
<b>Situation to consider nonstatin agents</b>	<b>If not achieved LDL target, consider the following as the initial nonstatin agent</b>			
Option 1	Ezetimibe	Ezetimibe and/or PCSK9 mAb	Ezetimibe and/or PCSK9 mAb	Ezetimibe and/or PCSK9 mAb
Option 2	Adding or replacing with PCSK9 mAb	Bempedoic acid or inclisiran	Bempedoic acid or inclisiran	Bempedoic acid or inclisiran
Option 3	Bempedoic acid or inclisiran	LDL apheresis	-	Evinacumab, Lomitapide, and/or LDL apheresis for HoFH

ASCVD, atherosclerotic cardiovascular disease; RD/RDN, registered dietitian/registered dietitian nutritionist; SASE, statin-associated side effect; HoFH, homozygous familial hypercholesterolemia; PCSK9 mAb, proprotein convertase subtilisin/kexin type 9 monoclonal antibody

# Nonstatin Options to Consider for ASCVD Primary Prevention

	Adults aged 40-75 years			Adults aged 40-75 years with diabetes		Adults with LDL-C ≥190
	10-y risk 5-20% and CAC score >100 AU <sup>†</sup>		10-y risk ≥20%	Not high risk	High risk*	
<b>Statin therapy</b>	<b>Moderate to high-intensity statin</b>		<b>High-intensity statin</b>	<b>Moderate-intensity statin</b>	<b>High-intensity statin</b>	<b>Maximally-tolerated statin therapy</b>
<b>LDL-C target</b>	≥50% LDL-C reduction and LDL < 70 mg/dL			≥50% LDL-C reduction and LDL < 100 mg/dL	≥50% LDL-C reduction and LDL < 70 mg/dL if 10-y risk ≥ 20 %	≥50% LDL-C reduction and LDL < 100 mg/dL
<b>Factor to consider</b>	CAC score ≥ 100 AU <sup>†</sup> → Consider moderate to high intensity statin	CAC score ≥ 1000 AU → Consider high intensity statin	-	1. Calculate 10-y risk and consider diabetes risk enhancers** 2. Evaluate and optimize lifestyle modifications, statin adherence, risk factor control, and SASEs 3. Referral to RD/RDN		1. Evaluate and optimize lifestyle modifications, statin adherence, risk factor control, and SASEs 2. Increase to high-intensity statin therapy 3. Consider referral to lipid specialist and RD/RDN for all patients, especially for HoFH
<b>Situation to consider nonstatin agents</b>	<b>If not achieved LDL target, on high-intensity statin, may be reasonable to consider the following</b>		<b>If not achieved LDL target, may be reasonable to consider ezetimibe</b>	<b>If not achieved LDL target, high-intensity statin therapy</b>	<b>If not achieved LDL target on maximally-tolerated statin, consider ezetimibe</b>	<b>If not achieved LDL target, consider the following as the initial nonstatin agent</b>
<b>Option 1</b>	Ezetimibe	Ezetimibe	Ezetimibe	-	Ezetimibe	Ezetimibe and/or PCSK9 mAb
<b>Option 2</b>		PCSK9 mAb	-	-	-	Bempedoic acid or inclisiran
<b>Option 3</b>			-	-	-	Evinacumab, Lomitapide, and/or LDL apheresis for HoFH

<sup>†</sup>CAC score >100 AU or ≥75th percentile for the patient's age, sex, and race

\*10-year risk ≥7.5%, diabetes-specific risk enhancers, or subclinical atherosclerosis; \*\*Long duration (≥10 years for type 2 diabetes or ≥ 20 years for type 1 diabetes, albuminuria ≥ 30 mcg of albumin/ mg creatinine, eGFR <60 mL/min/1.73 m<sup>2</sup>, retinopathy, neuropathy, ankle-brachial index <0.9



# 2022 ACC Expert Consensus Decision Pathway

## Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of ASCVD Risk

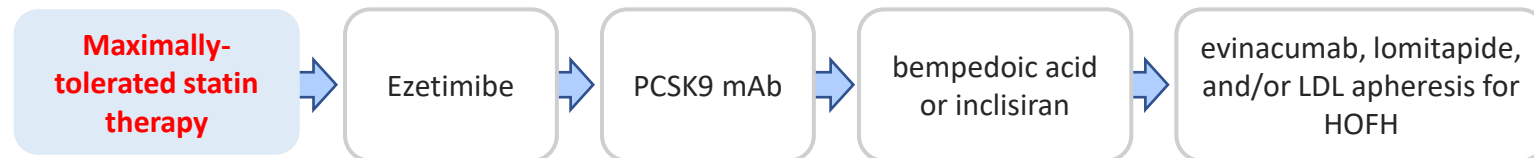
### 1. In what patient populations should newer nonstatin therapies be considered?

The algorithms endorse the **4 evidence-based patient management groups (Adults with clinical ASCVD, primary severe hypercholesterolemia, diabetes and without diabetes)** and assume that the **patient is currently taking or has attempted to take a statin, given that this is the most effective initial therapy.**

### 2. In what situations should newer nonstatin therapies be considered?

- ✓ When statins do not fully achieve the LDL-C goals for reducing ASCVD risk
- ✓ When statins are not tolerated at effective doses

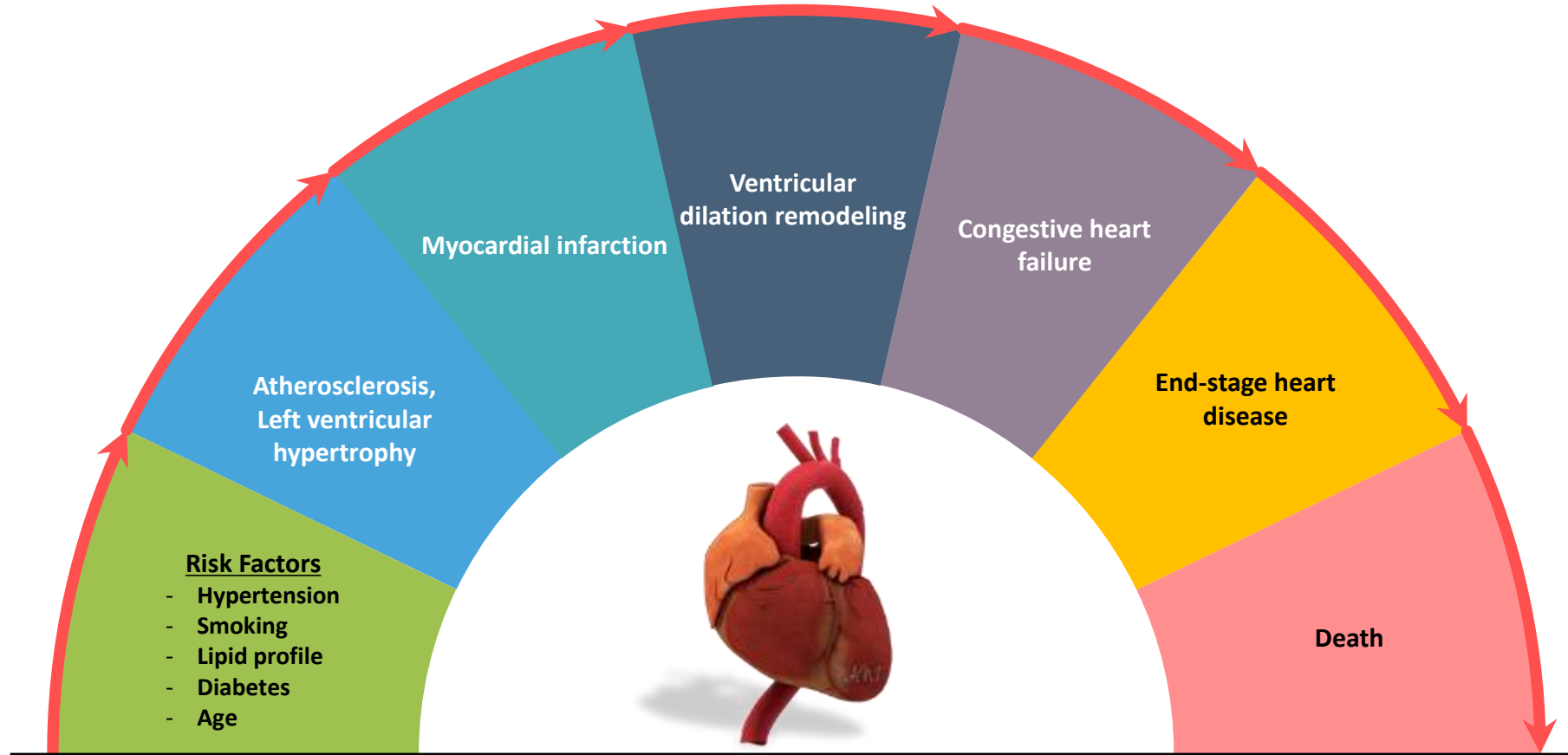
### 3. Which newer nonstatin therapies should be considered and in what order to maximize patient benefit and preference?



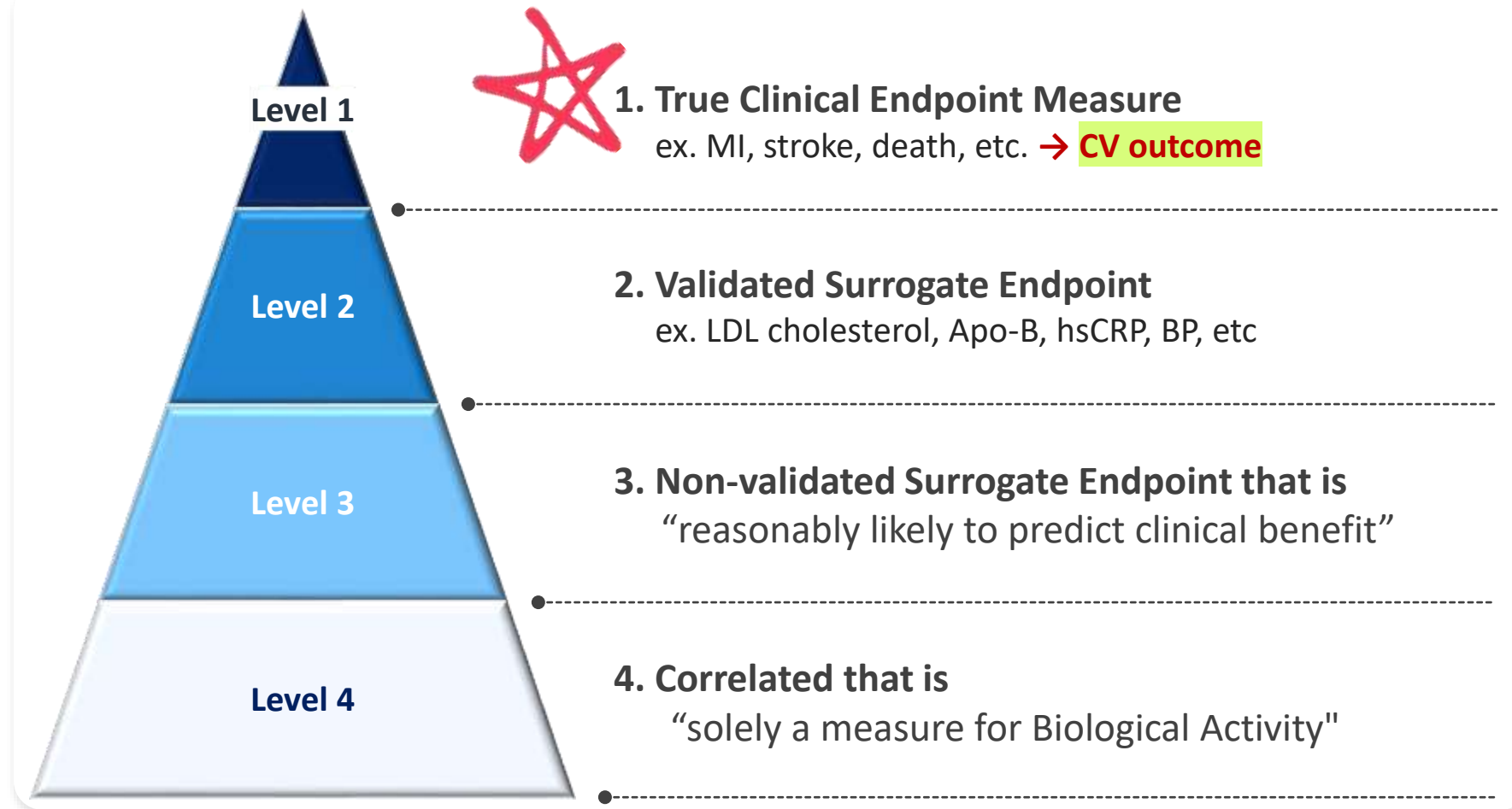
ACC: American College of Cardiology, ASCVD: Atherosclerotic Cardiovascular Disease

**Tailored approach for CV prevention with *Atorvastatin***

# A sequence of cardiovascular events, Cardiovascular Disease Continuum



# Hierarchy for outcome measures



# Lipitor's CV outcome trials



Number of clinical trials proved CV outcome<sup>1-11</sup>

11



Number of clinical trials reached on primary endpoint<sup>1-7</sup>

8

## Lipitor's landmark trials reached on primary endpoint<sup>1-7</sup>

- ✓ **ASCOT-LLA** Proven CVD prevention in patients **with Hypertension**<sup>3</sup>
- ✓ **CARDS** Proven CVD prevention in patients **with T2DM**<sup>1</sup>
- ✓ **TNT** Proven CVD prevention in patients **with CAD**<sup>2</sup>
- ✓ **ALLIANCE** Proven CVD prevention in patients **with CAD**<sup>4</sup>
- ✓ **GREACE** Proven CVD prevention in patients **with CAD**<sup>6</sup>
- ✓ **MIRACL** Proven CVD prevention in patients **with ACS**<sup>5</sup>
- ✓ **PROVE-IT** Proven CVD prevention in patients **with ACS**<sup>7</sup>
- ✓ **SPARCL** Proven CVD prevention in patients **with Stroke**<sup>8</sup>

# Lipitor's CV outcome trials is cited as evidence for major clinical guidelines

## 2018 ACC/AHA Cholesterol Guideline

Cited 9 trials

- ASCOT-LLA
- CARDS
- TNT
- ALLIANCE
- GREACE
- PROVE-IT
- IDEAL
- ASPEN
- Wanner C, et al.

## 2019 ACC/AHA Primary Prevention of CVD Guideline

Cited 3 trials

- ASCOT-LLA
- CARDS
- ASPEN

## 2019 ESC/EAS Cholesterol Guideline

Cited 4 trials

- MIRACL
- PROVE-IT
- Wanner C, et al.
- SPARCL

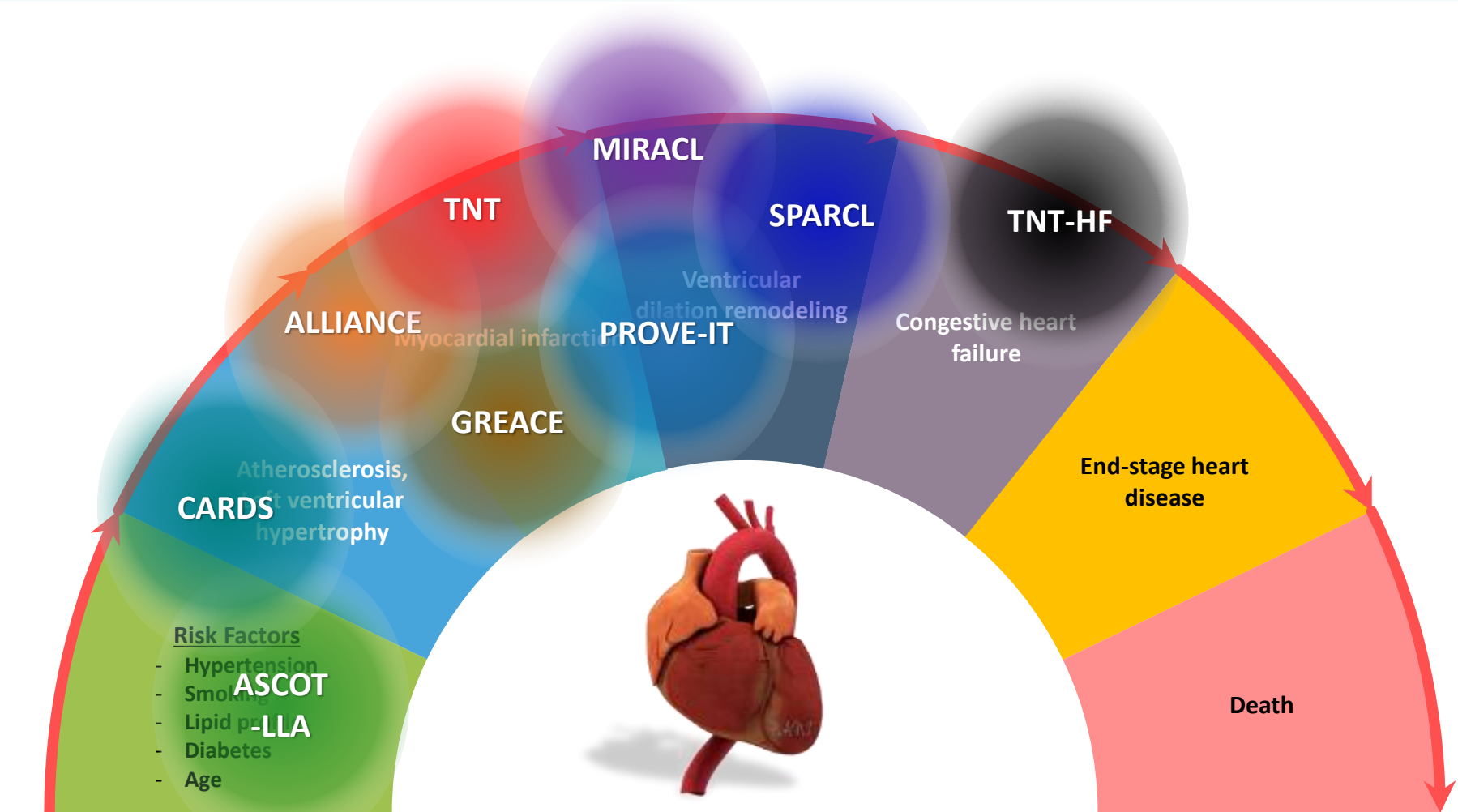
## 2022 KSoLA Dyslipidemia Guideline

Cited 6 trials





- CARDS
- TNT
- PROVE-IT
- IDEAL
- Wanner C, et al.
- SPARCL

ACC/AHA, American College of Cardiology/American Heart Association; ESC/EAS, European Society of Cardiology and European Atherosclerosis Society; KSoLA, Korean Society of Lipid and Atherosclerosis


# A sequence of cardiovascular events, Cardiovascular Disease Continuum



# Tailored Approach with Lipitor portfolio

	Lipitor 10mg	Lipitor 20mg	Lipitor 40mg	Lipitor 80mg
<b>Image<sup>2</sup></b>				
<b>Price<sup>2</sup></b> (2023.01)	<b>642won</b>	<b>690won</b>	<b>1,338won</b>	<b>1,523won</b>
<b>LDL-C reduction (%)</b> <b>from baseline<sup>*,3</sup></b> (Adjusted mean %)	<b>-39%</b>	<b>-43%</b>	<b>-50%</b>	<b>-60%</b>

\*Adjusted mean % change from baseline. Results are pooled from 2 multicenter, placebo-controlled, dose-response studies in patients with primary hyperlipidemia. LIPITOR was given as a single dose over 6 weeks

	Lipitor Plus 10/10mg	Lipitor Plus 10/20mg	Lipitor Plus 10/40mg
<b>Image<sup>4</sup></b>			
<b>Price<sup>4</sup></b> (2023.01)	<b>637won</b>	<b>808won</b>	<b>1,415won</b>
<b>LDL-C reduction (%)</b> <b>from baseline<sup>*,5</sup></b> (Mean change %)	<b>-53%</b>	<b>-54%</b>	<b>-56%</b>

\*Results are from a multicenter, double-blind, placebo-controlled, clinical study in patients with primary hyperlipidemia.



# Take Home Messages

1. **Statins up to maximal tolerable dose are recommended to reach the goal**
2. **If the goal is not reached, a statin combined with ezetimibe should be considered or is recommended**
3. **Atorvastatin family has full lineup treatment option for Cardiovascular Disease Continuum**