Management of Dyslipidemia among Patients with Diabetes

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Nov 2025 – Tehran

Agenda

1. Control of CVD Risk Factors among Patients with Diabetes: Local and International Data
2. Definition and Pathophysiology of Diabetic Dyslipidemia
3. Diabetes Specific Risk Enhancers, ASCVD Risk Factors, High Risk for ASCV in Different Guidelines
4. Efficacy of Statins in Patients with Diabetes
5. Lipid-Modifying Therapy Use in Primary and Secondary Care in Real World Data
6. Compared Target LDL-C Levels in Trials of LODESTAR
7. High Intensity vs. Moderate Intensity Statin Therapy with Ezetimibe in Patients with ASCVD
8. Bempedoic Acid in Statin Intolerant Patients
9. Summary
10. Return to Case

Case Presentation

A 56-year-old man with a five-year history of T2DM is referred for further management His hypertension was diagnosed 4 years ago. He has history of primary PCI following MI, 3 years earlier. He quit smoking following cardiac surgery. There is no evidence of retinopathy.

✓ **At present on P/E:**

- Weight: 98 Kg,
- Height: 175,
- BMI: 32 kg/m^2, WC: 95 cm
- BP: 140/90 mmHg,

(confirmed by home BP monitoring)

- HR: 94/min,
- Ankle brachial ratio: 0.8

✓ **Lab exam:**

- HbA1c: 7.5%,
- eGFR: 55ml/min per 1.73 m^2,
- Total Chol: 154 mg/dL,
- HDL: 38 mg/dL,
- TG: 250 mg/dL,
- LDL: 66 mg/dL,
- K: 4.0 meq/l,
- ACR: 80 mg/gr,
- CRP:3 mg/L
- Platelet: 350 ×10^3 µl,
- AST:35 units/L,
- ALT: 56 units/L

✓ **Patient medication:**

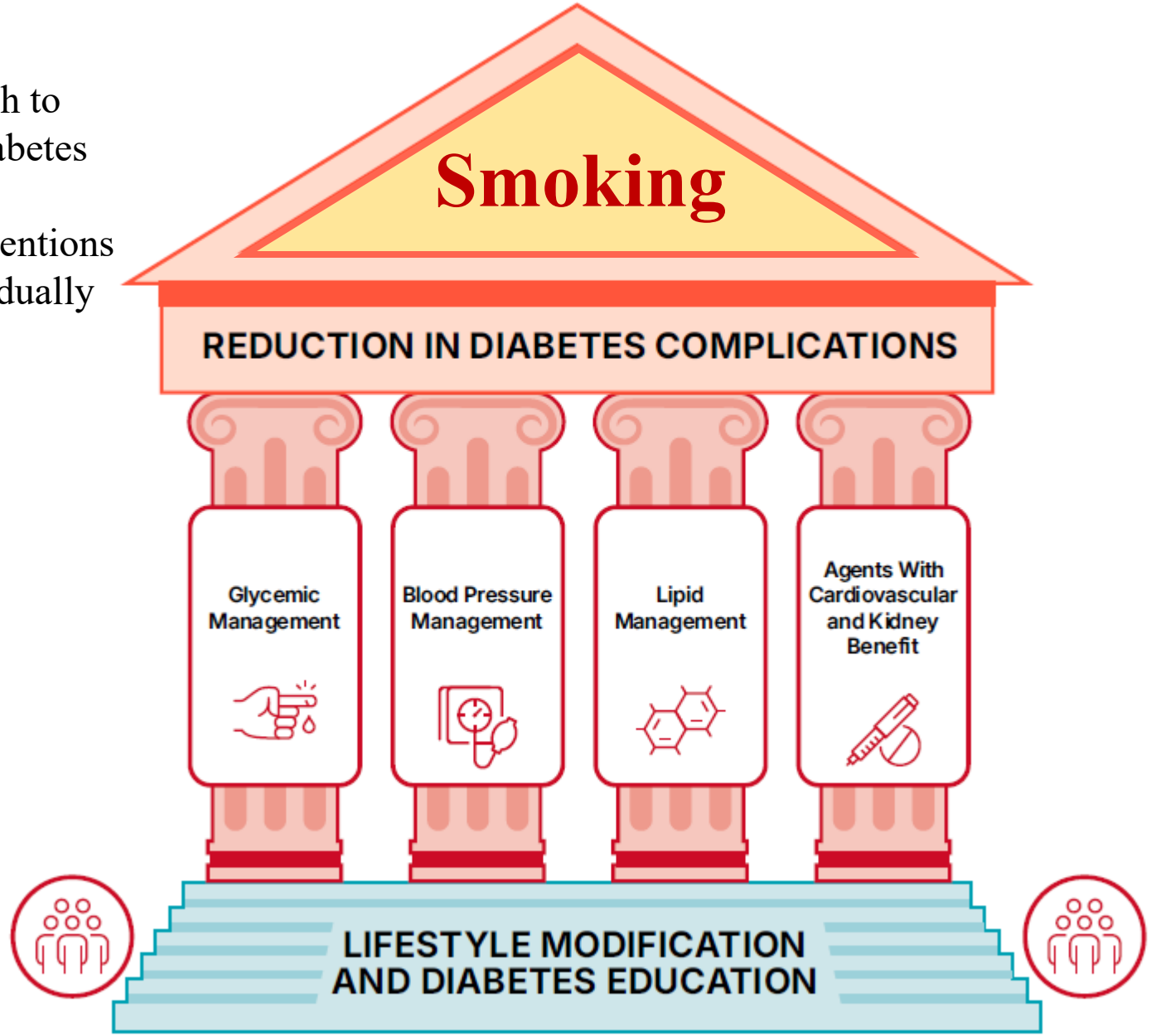
- Metformin: 2000 mg/daily,
- Atorvastatin: 20mg daily,
- Valsartan: 160 mg/daily,
- Carvedilol: 12.5 mg/daily,
- ASA: 80 mg/daily

✓ **Imaging:**

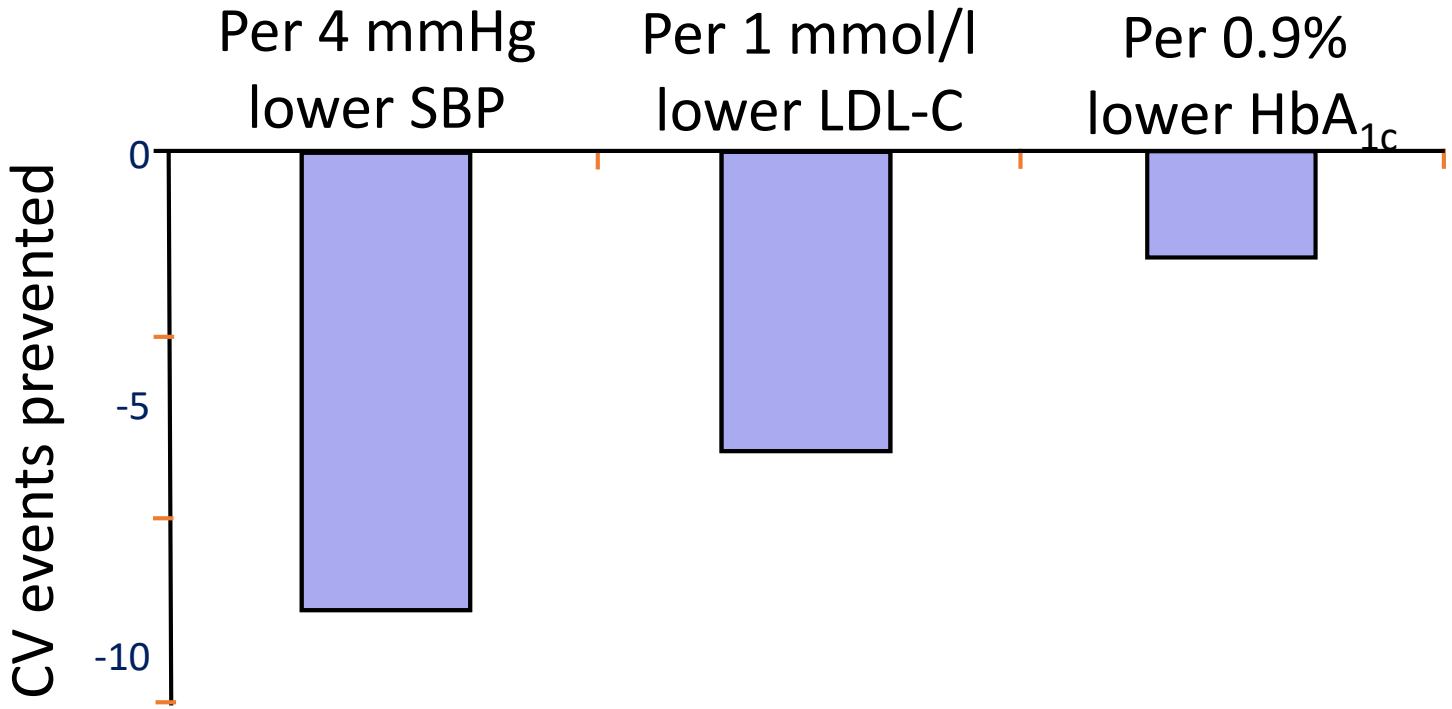
In his recent echocardiography,
LVH and EF=% 50 have been reported

The patient and his primary care physician are concerned about his residual risk of recurrent ASCVD events and his overall prognosis. What is your recommendation for the patient?

Figure 10.1
Multifactorial approach to reduction in risk of diabetes complications.
*Risk reduction interventions to be applied as individually appropriate.



Number of CV events prevented by different interventions



Statin therapy and blood pressure control decrease CHD risk to a greater extent than targeting glucose lowering

Revisiting the links between glycaemia, diabetes and cardiovascular disease. Diabetologia. 2013 Apr;56(4):686-95.

1 Control of CVD Risk Factors among Patients with Diabetes: Local and International Data

The NEW ENGLAND JOURNAL of MEDICINE
2021 Jun 10;384(23):2219-2228.

SPECIAL ARTICLE

Trends in Diabetes Treatment and Control in U.S. Adults, 1999–2018

Michael Fang, Ph.D., Dan Wang, M.S., Josef Coresh, M.D., Ph.D., and Elizabeth Selvin, Ph.D., M.P.H.

BACKGROUND: Documenting current trends in diabetes treatment and risk-factor control may inform public health policy and planning.

METHODS: We conducted a cross-sectional analysis of data from adults with diabetes in the United States participating in the National Health and Nutrition Examination Survey (NHANES) to assess national trends in diabetes treatment and risk-factor control from 1999 through 2018.

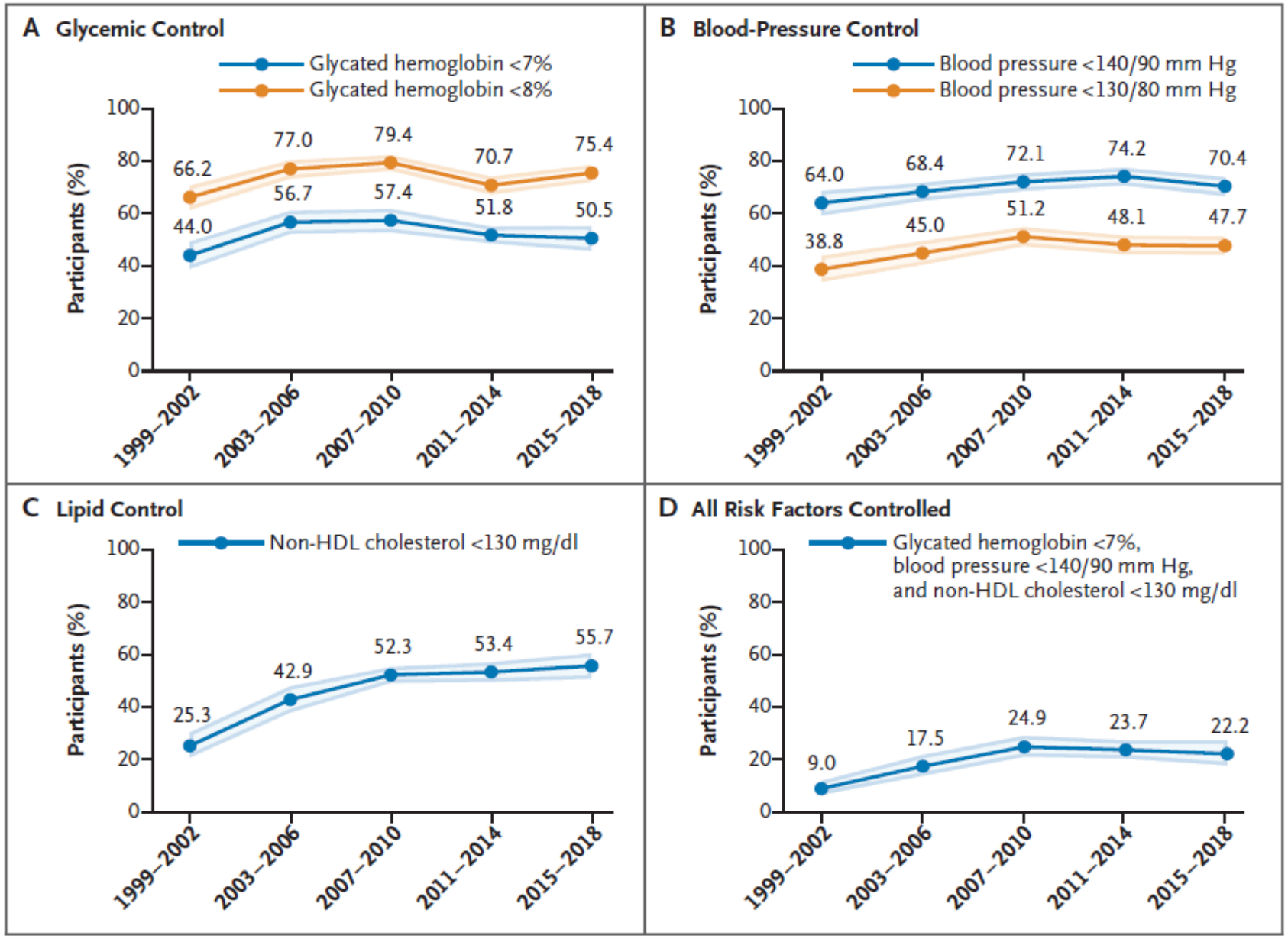
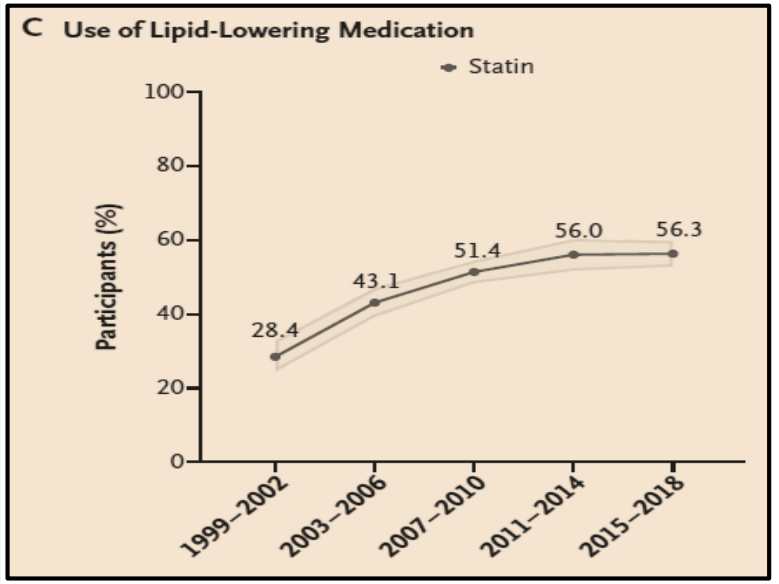


Figure 1
Prevalence of Glycemic, Blood-Pressure, and Lipid Control among Adult NHANES Participants with Diagnosed Diabetes, 1999–2002 to 2015–2018.

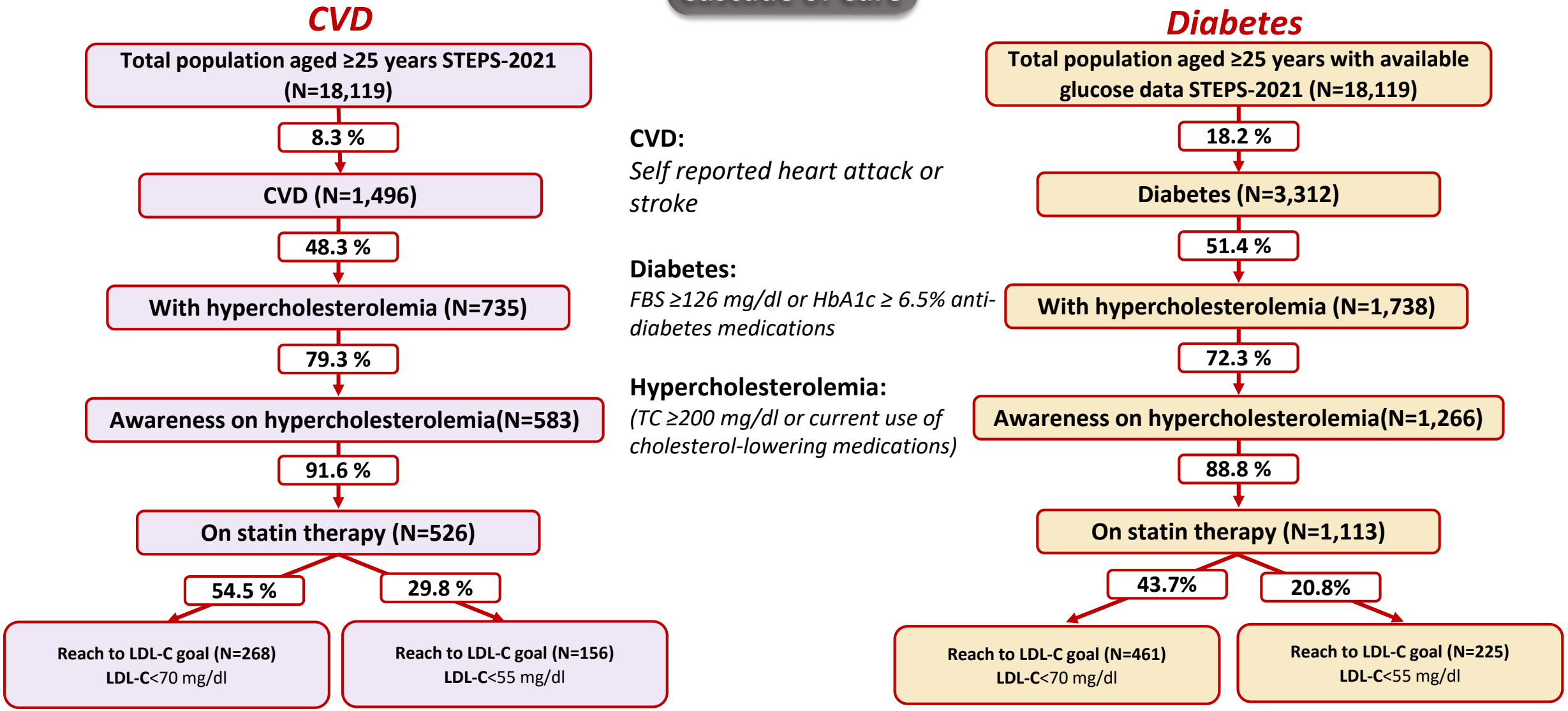


Conclusions

- After more than a decade of progress from 1999 to the early 2010s, glycemic and blood-pressure control declined in adult NHANES participants with diabetes, while lipid control leveled off. (Funded by the National Heart, Lung, and Blood Institute)

STEPS 2021

Cascade of Care



۱. اطلس پیمایش عوامل خطر بیماری های غیرواگیر در ایران (سال ۱۳۹۵) ۲.اطلس پیمایش عوامل خطر بیماری های غیرواگیر در ایران (سال ۱۴۰۰)
3. The prevalence, awareness, and treatment of lipid abnormalities in Iranian adults... Journal of clinical lipidology. 2018 Nov 1;12(6):1471-81.

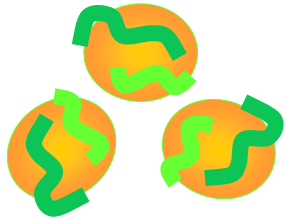
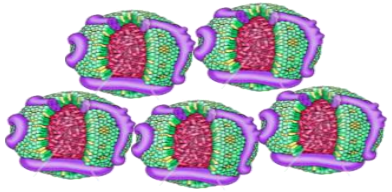
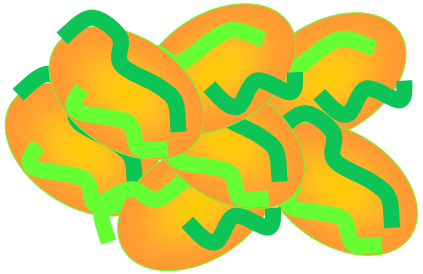
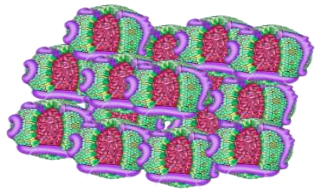
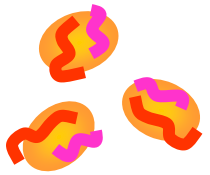
2

Definition and Pathophysiology of Diabetic Dyslipidemia

Diabetic Dyslipidemia

- In patients with type 2 diabetes mellitus, triglycerides are often elevated, HDL-C is often decreased, and LDL-C may be elevated, borderline, or normal.
- LDL particles are small and dense. Thus, the LDL-C concentration may be misleading because there will be more LDL particles for any cholesterol concentration.
- The prevalence of Diabetic Dyslipidemia reported in various studies varied between 35 and 56% and is strongly associated with increased cardiovascular risk.

The dyslipidemia of intra-abdominal obesity and type 2 diabetes

	VLDL	LDL	HDL
Normal			
Insulin resistance			
	↑ VLDL triglycerides ↑ VLDL apo B	↑ LDL apo B ↑ particle number ↓ particle size (small, dense)	↓ HDL cholesterol ↓ particle number ↓ particle size (small, dense)

VLDL: very low-density lipoprotein; LDL: low-density lipoprotein
HDL: high-density lipoprotein; Apo B: apolipoprotein B

Watts G. Diapedia 2014. Available at: http://www.diapedia.org/61040851150/rev/5. Last accessed September 2016

Total Cholesterol
Remnant-C >>> LDL-C

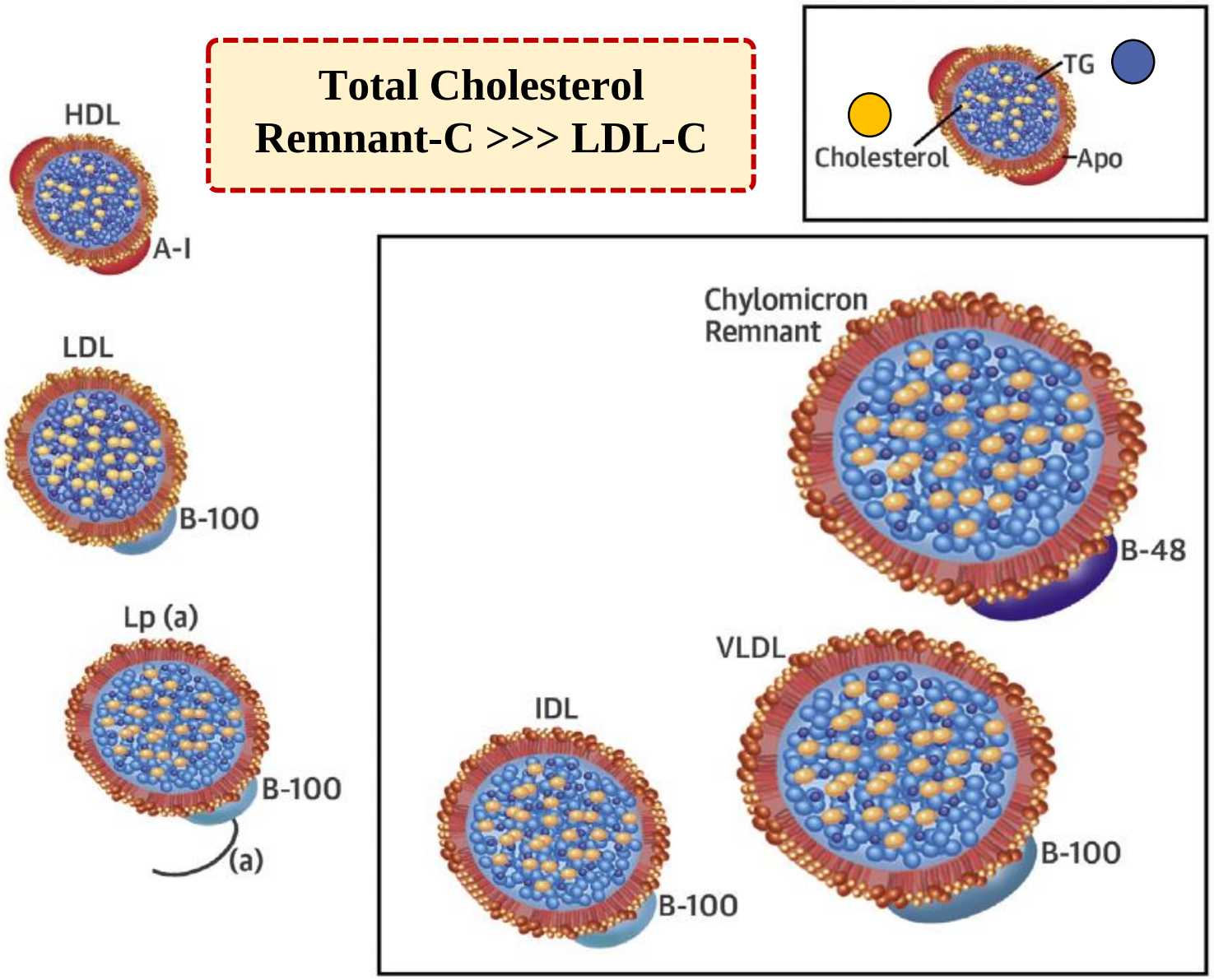
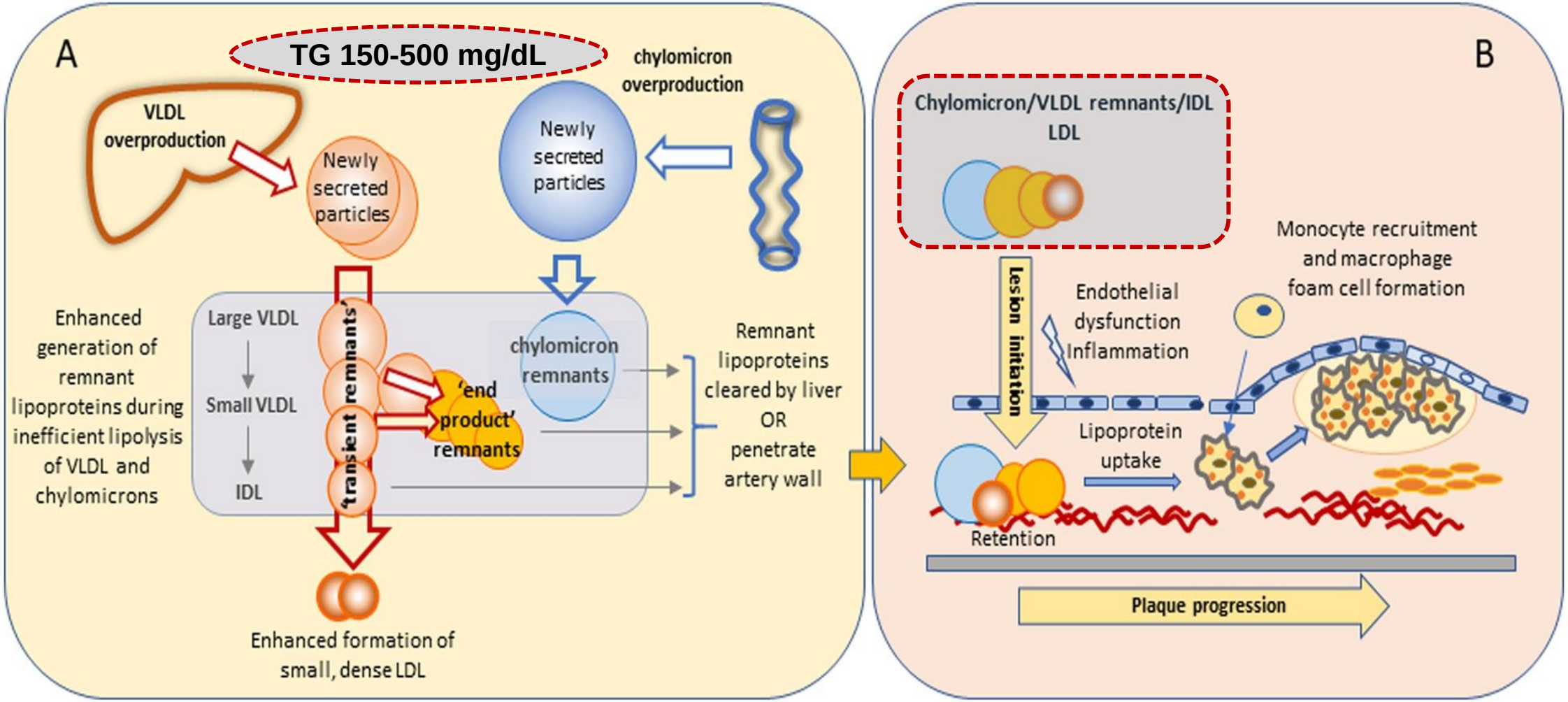


Figure 1
Spectrum of Lipoproteins Indicating the Remnant TG-Rich Lipoproteins

Remnant cholesterol contributes to, but differs from non-HDL cholesterol, which is the sum of cholesterol carried within the atherogenic apo B–containing lipoproteins, including lipoprotein(a).

The effects of high triglyceride levels on atherosclerotic disease are in fact mediated by the cholesterol content of remnant particles.

Formation of triglyceride-rich lipoprotein remnants and their role in atherogenesis. Metabolic scheme for the generation and clearance of triglyceride-rich lipoprotein remnant particles (A). In hypertriglyceridaemia, overproduction and inefficient lipolysis of both VLDL and chylomicrons lead to increased remnant formation. Triglyceride-rich lipoprotein remnants contribute to the initiation and progression of atherosclerotic lesions (B). Particle retention in the subendothelial space is followed by inflammation, cholesterol deposition, and macrophage foam cell formation.



Diabetes Specific Risk Enhancers, ASCVD Risk Factors, High Risk for ASCV in Different Guidelines

Very High Risk	People with any of the following: • Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), chronic coronary syndromes, 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 (>50% stenosis) or CT scan or on carotid or femoral ultrasound or markedly elevated CAC score by CT, CAC>300 • DM with target organ damage, (microalbuminuria, retinopathy, or neuropathy) or at least three major risk factors, or early onset of T1DM of long duration (>20 years) • Severe CKD (eGFR <30 mL/min/1.73 m^2) • A calculated SCORE2 (ACC/AHA/PREVENT) ≥20% for 10 year risk of fatal or non-fatal CVD • FH with ASCVD or with another major risk factor
High Risk	People with any of the following: • Markedly elevated single risk factors, in particular TC >310 mg/dL), LDL-C >190 mg/dL, or BP ≥180/110 mmHg • Patients with FH without other major risk factors • Patients with DM without target organ damage, with DM duration ≥10 years or another additional risk factor • Moderate CKD (eGFR 30–59 mL/min/1.73 m^2) • A calculated SCORE2 (ACC/AHA/PREVENT) ≥10% and <20% for 10 year risk of fatal or non-fatal CVD

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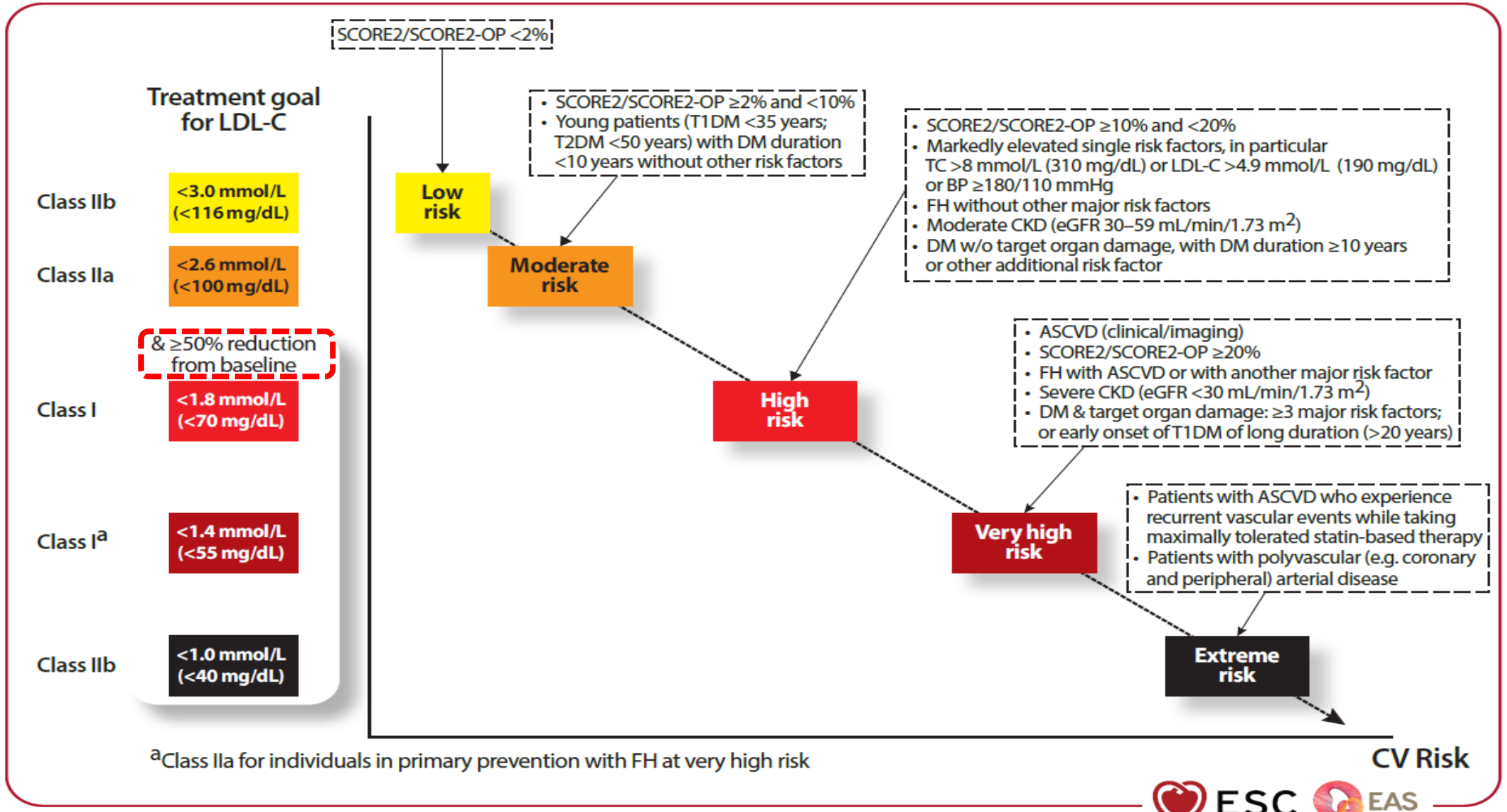
ASCVD

- Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, any revascularization procedure). Variably included: conditions such as transient ischemic attach, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease

Indicators of high risk

- While definitions vary, most comprise ≥ 55 years of age with two or more additional risk factors (including obesity, hypertension, smoking dyslipidemia, or albuminuria)

Treatment goals for low-density lipoprotein cholesterol across categories of total cardiovascular risk.



Efficacy of Statins in Patients with Diabetes

Outcome	No of studies	No of events/total: Statin group	No of events/total: Control group	Odds ratio (95% CI)	Odds ratio (95% CI)	Absolute risk difference (95% CI)	Test of effect (P value)	I^2 (%) (95% CI)	Q test (P value)
Muscle symptoms	21	3459/36 026	2785/29 278	1.06 (1.01 to 1.13)		15 (1 to 29)	0.030	1 (0 to 47)	0.45
Muscle disorders	25	70/46 746	55/38 994	0.88 (0.62 to 1.24)		0 (-1 to 1)	0.461	0 (0 to 0)	0.99
Liver dysfunction	21	406/31 305	217/23 498	1.33 (1.12 to 1.58)		8 (3 to 14)	0.001	0 (0 to 23)	0.84
Renal insufficiency	8	597/16 858	520/15 143	1.14 (1.01 to 1.28)		12 (1 to 24)	0.037	0 (0 to 23)	0.89
Diabetes	9	1190/29 318	1161/29 311	1.01 (0.88 to 1.16)		1 (-10 to 13)	0.882	50 (0 to 77)	0.04
Eye conditions	6	321/15 282	234/10 046	1.23 (1.04 to 1.47)		14 (2 to 29)	0.019	0 (0 to 36)	0.85
Myocardial infarction	22	996/50 093	1316/45 055	0.72 (0.66 to 0.78)		-19 (-23 to -15)	<0.001	33 (0 to 60)	0.07
Stroke	17	634/39 340	786/39 133	0.80 (0.72 to 0.89)		-9 (-12 to -5)	<0.001	20 (0 to 55)	0.22
Death from CVD	22	836/51 005	979/44 954	0.83 (0.76 to 0.91)		-8 (-12 to -4)	<0.001	27 (0 to 57)	0.12

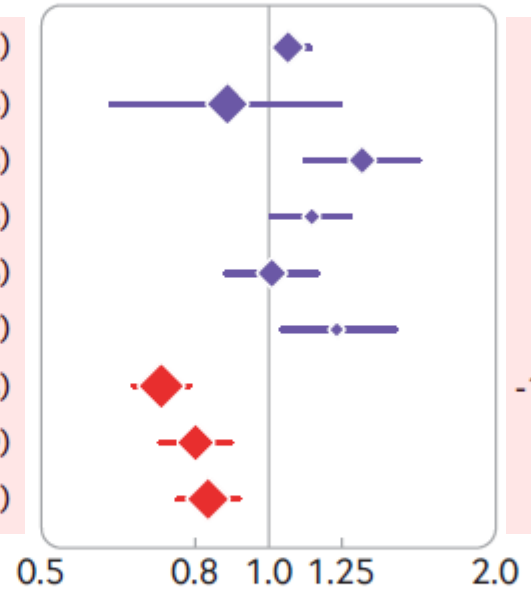


Fig 3 | Associations of statins with safety and efficacy outcomes from pairwise meta-analyses. Symbols and horizontal bars represent pooled odds ratios with 95% confidence intervals calculated by pairwise meta-analyses, comparing statins and non-statin controls. Symbol sizes are proportional to the total numbers of participants included in the analyses of each outcome. Vertical line represents the odds ratio value that indicates no association (odds ratio=1). Blue symbols denote effects on safety outcomes (adverse events) and red symbols denote effects on efficacy outcomes (major cardiovascular events). Absolute risk difference is the number of events per 10 000 people in a year. CVD=cardiovascular disease

Statin safety

Statin-associated muscle symptoms

- Definition. SAMS are the most commonly reported adverse effects of statins (present in 10–29% of patients taking statin therapy according to observational studies). This observation is in sharp contrast with the results of RCTs, which often report minimal differences in the rates of muscle symptoms between statin-treated and placebo-treated groups.
- Of note, SAMS often occur in the absence of an elevation in creatine kinase plasma levels, and the symptoms can vary from myalgia to rhabdomyolysis.

BOX 1 The statin-associated muscle symptom clinical index

Overview

The SAMS-Clinical Index (SAMS CI) was designed to help clinicians determine the likelihood that a patient's muscle symptoms (myalgia or myopathy) were caused by or associated with statin use.

If one regimen of statin involved

Questions regarding this regimen

Location and pattern of muscle symptoms	Score
Symmetric, hip flexors or thighs	3
Symmetric, calves	2
Symmetric, proximal upper extremity	2
Asymmetric, intermittent or not specific to an area	1

Timing of muscle symptom onset	
<4 weeks	3
4–12 weeks	2
>12 weeks	1

Timing of symptom improvement after statin withdrawal	
<2 weeks	2
2–4 weeks	1
No improvements after 4 weeks	0

Rechallenge with a statin regimen

Timing of recurrence of similar muscle symptoms after starting second regimen	
<4 weeks	3
4–12 weeks	1
>12 weeks or symptoms did not reoccur	0

Total: All four scores above must be entered before totalling

If ≥2 regimens of statin involved

Questions regarding the regimen before the most recent regimen

Location and pattern of muscle symptoms	Score
Symmetric, hip flexors or thighs	3
Symmetric, calves	2
Symmetric, proximal upper extremity	2
Asymmetric, intermittent or not specific to an area	1

Timing of muscle symptom onset	
<4 weeks	3
4–12 weeks	2
>12 weeks	1

Timing of symptom improvement after statin withdrawal	
<2 weeks	2
2–4 weeks	1
No improvements after 4 weeks	0

Questions regarding the most recent regimen

Timing of recurrence of similar muscle symptoms after starting second regimen	
<4 weeks	3
4–12 weeks	1
>12 weeks or symptoms did not reoccur	0

Total: All four scores above must be entered before totalling

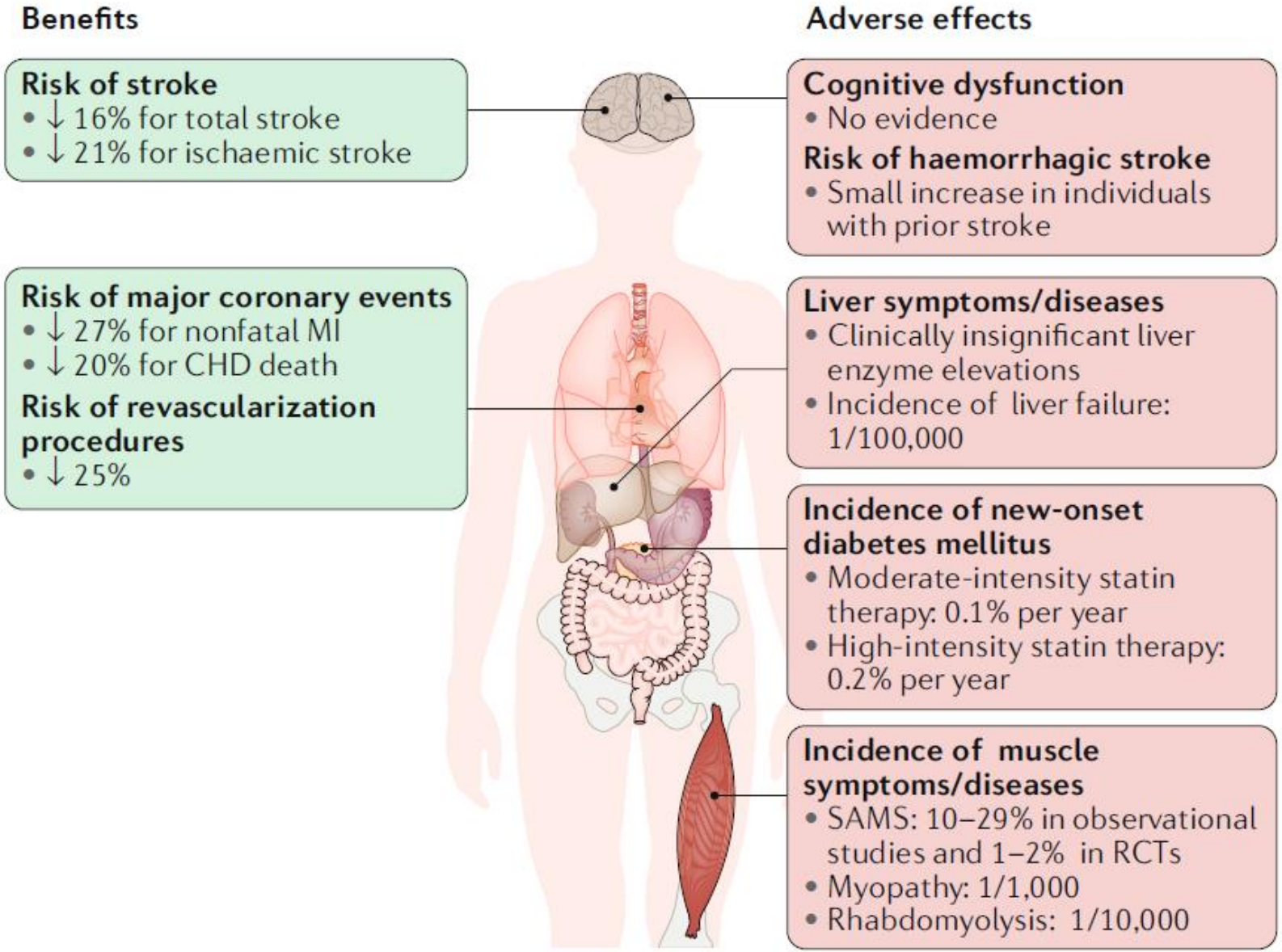
Interpretation (score: likelihood of SAMS)

- 2–6: unlikely
- 7–8: possible
- 9–11: probable

Safety of Statin Therapy

- The next step in evaluating SAMS is statin discontinuation and rechallenge with either a lower dose of the same statin or the use of another statin. A washout period of several weeks might be helpful before rechallenge. Another strategy to consider after failing a third statin at its lowest dose is to consider alternate-day dosing of longer-acting statins, such as rosuvastatin or atorvastatin.
- A meta-analysis of 13 RCT studies showed that alternate-day dosing can be a efficacious as daily dosing in lowering LDL-C levels, but its effect on ASCVD outcomes remains unclear

Clinical benefits and potential adverse effects of statin therapy



ADA 2025

A concern that statins or other lipid-lowering agents might cause cognitive dysfunction or dementia is not currently supported by evidence and should not deter their use in individuals with diabetes at high risk for ASCVD.

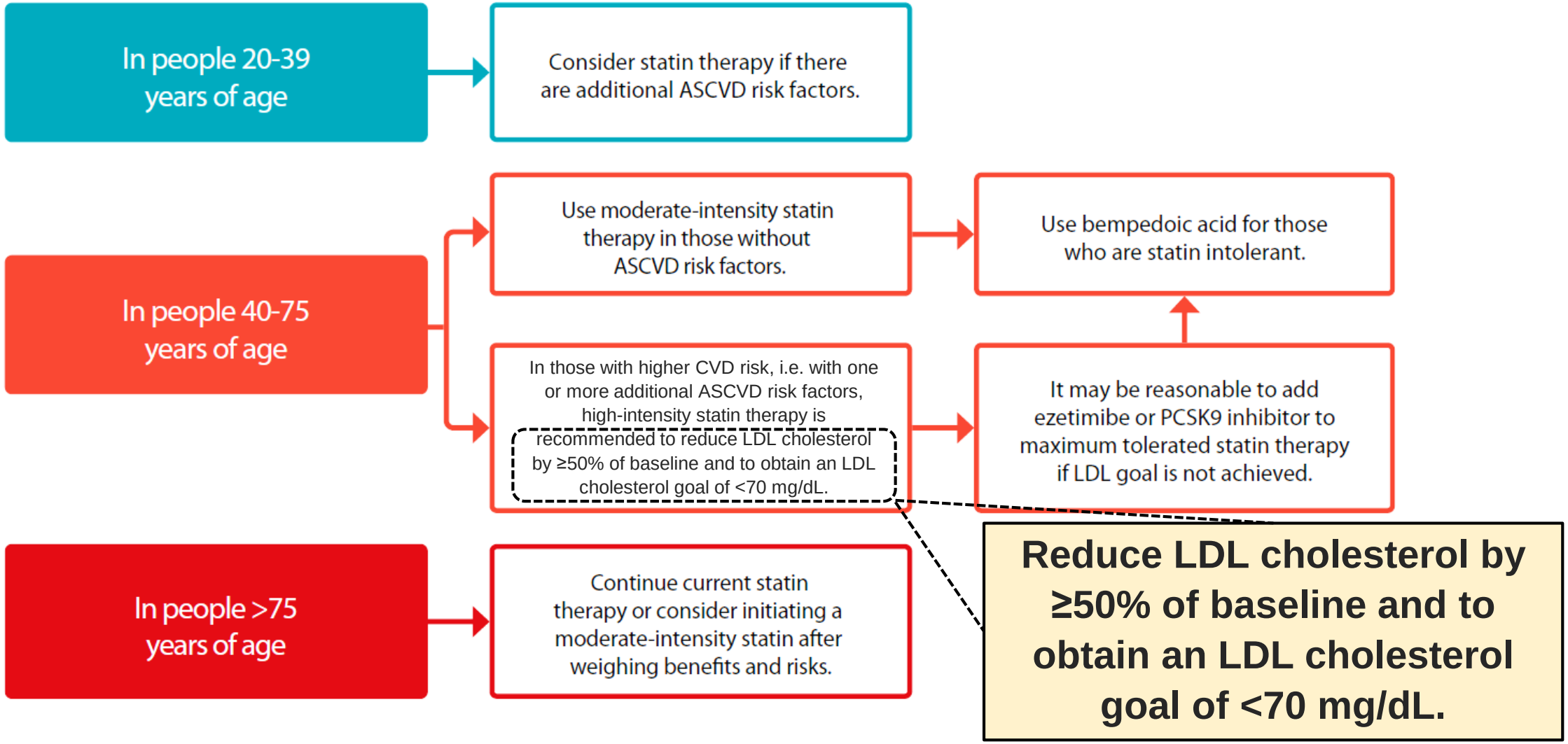
Safety and efficacy of statin therapy. Nat Rev Cardiol. 2018 Dec;15(12):757-769.

Table 10.1—High-intensity and moderate-intensity statin therapy

High-intensity statin therapy (lowers LDL cholesterol by ≥50%)	Moderate-intensity statin therapy (lowers LDL cholesterol by 30–49%)
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg
	Simvastatin 20–40 mg
	Pravastatin 40–80 mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg
	Pitavastatin 1–4 mg

Once-daily dosing. XL, extended release.

Lipid Management for Primary Prevention of Atherosclerotic Cardiovascular Disease Events in People with Diabetes in Addition to Healthy Behavior Modification



Statin Treatment as Secondary Prevention in PWD

10.27 For people of all ages with diabetes and ASCVD, high-intensity statin therapy should be added to lifestyle therapy. **A**

10.28 For PWD and ASCVD, treatment with high-intensity statin therapy is recommended to obtain an LDL-C reduction of ≥50% from baseline **and** an LDL-C goal of <55 mg/dL.

- Addition of ezetimibe or a PCSK9 inhibitor with proven benefit in this population is recommended if this goal is not achieved on maximum tolerated statin therapy. **B**

10.29b For PWD and ASCVD intolerant to statin therapy, PCSK9 inhibitor therapy with monoclonal antibody treatment, **A** bempedoic acid therapy, **A** or PCSK9 inhibitor therapy with inclisiran siRNA **E** should be considered as an alternative cholesterol-lowering therapy.

5 Lipid-Modifying Therapy Use in Primary and Secondary Care in Real World Data

ESC European Society of Cardiology
European Journal of Preventive Cardiology (2021) **28**, 1279–1289
doi:10.1093/eurjpc/zwaa047
FULL RESEARCH PAPER

EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care: the DA VINCI study

Kausik K. Ray[1]*, Bart Molemans[2], W. Marieke Schoonen[3], Periklis Giovas[4],

Aims: To provide contemporary data on the implementation of European guideline recommendations for lipid-lowering therapies (LLTs) across different settings and populations and how this impacts LDL-C goal achievement.

Methods and results: 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 ESC/EAS LDL-C goal while receiving stabilized LLT; 2019 goal achievement was also assessed.

Overall, 5888 patients (3000 primary and 2888 secondary prevention patients) were enrolled.

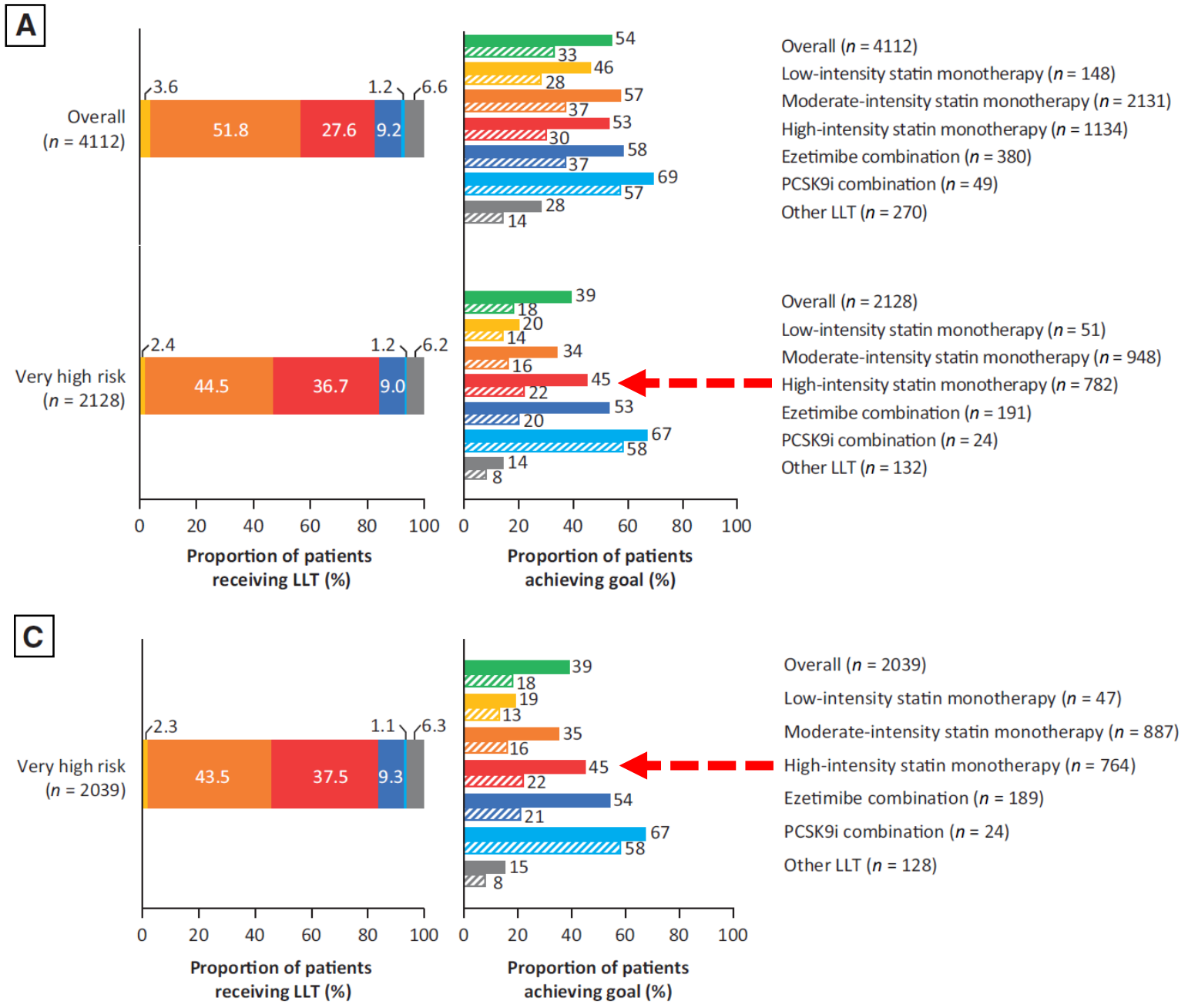


Figure 2
European Society of Cardiology/European Atherosclerosis Society 2016 and 2019 risk-based LDL-C goal attainment among patients stabilized on lipid-lowering regimens summarized by level of risk and statin regimen.

(**A**)The overall group summarized by level of risk and statin regimen,
(**C**) The established ASCVD groups summarized by level of risk and statin regimen.

2016/2019 risk-based LDL-C targets:

Low Risk: 2016/2019, <116 mg/dL

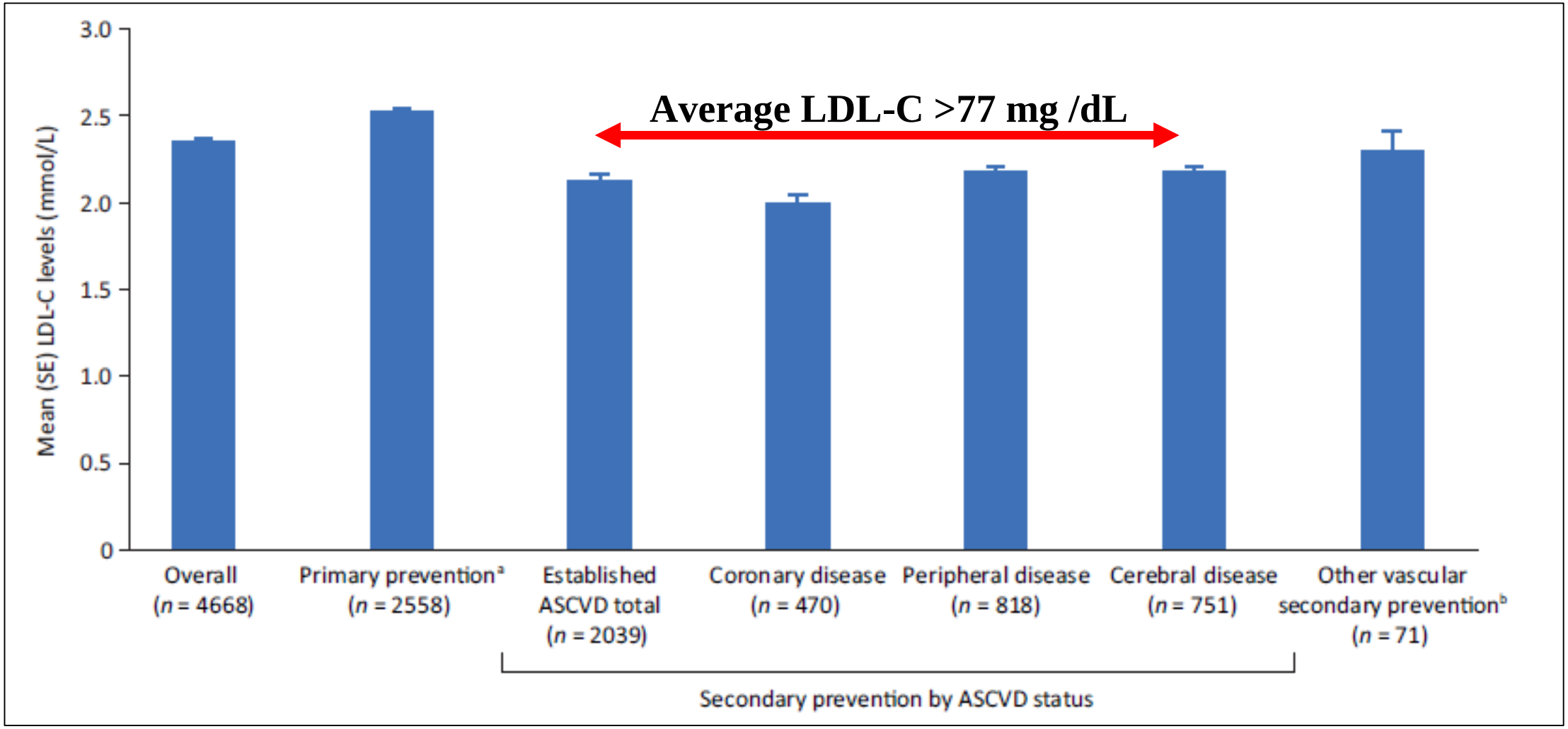
Moderate Risk 2016, <116 mg/dL; 2019, <100 mg/dL

High Risk: 2016, <100 mg/dL; 2019, <70 mg/dL

Very High Risk: 2016, <70 mg/dL; 2019, <54 mg/dL

2016 2019
- Overall
- Low-intensity statin monotherapy
- Moderate-intensity statin monotherapy
- High-intensity statin monotherapy
- Ezetimibe combination
- PCSK9i combination
- Other LLT

Figure 3 Mean low-density lipoprotein cholesterol levels in patients with stabilized lipid-lowering therapy



Attainment of 2019 ESC/EAS guideline low-density lipoprotein cholesterol goals

- Among very high-risk patients receiving statin monotherapy, goal attainment was 14%, 16%, and 22% in those receiving low, moderate-, and high-intensity statins, respectively.
- Only 22% of individuals with ASCVD receiving high intensity statin monotherapy achieved the 2019 LDL-C goal of < 55 mg/dL, compared with 45% achieving the 2016 LDL-C goal of <70 .
- Average LDL-C among patients candidate for secondary prevention was >77 mg/dL. Increasing statin intensity from moderate to high, would only offer a further 6–12% LDL-C reduction. Therefore, for most patients, an LDL-C goal of <55 mg/dL would be unattainable with monotherapy.
- In this regard, our data offer further insights into potential benefits from combination therapy.
- Even with optimized statin usage, the prevalent gap between guideline recommended LDL-C goals and their implementation in clinical care will require greater utilization of non-statin LLT in combination with statins for patients at highest risk.

Compared Target LDL-C Levels in Trials of LODESTAR

JAMA | Original Investigation 2023;329(13):1078-1087.

Treat-to-Target or High-Intensity Statin in Patients With Coronary Artery Disease
A Randomized Clinical Trial

Sung-Jin Hong, MD; Yong-Joon Lee, MD; Seung-Jun Lee, MD; Bum-Kee Hong, MD; Woong Chol Kang, MD;

Importance: In patients with CAD, some guidelines recommend initial statin treatment with high-intensity statins to achieve at least a 50% reduction in LDL-C. An alternative approach is to begin with moderate-intensity statins and titrate to a specific LDL-C goal. These alternatives have not been compared head-to-head in a clinical trial involving patients with known coronary artery disease.

Objective: To assess whether a treat-to-target strategy is no inferior to a strategy of high-intensity statins for long-term clinical outcomes in patients with coronary artery disease.

Design, Setting, and Participants: A randomized, multicenter, noninferiority trial in patients with a CAD including stable ischemic heart disease treated at 12 centers in **South Korea**.

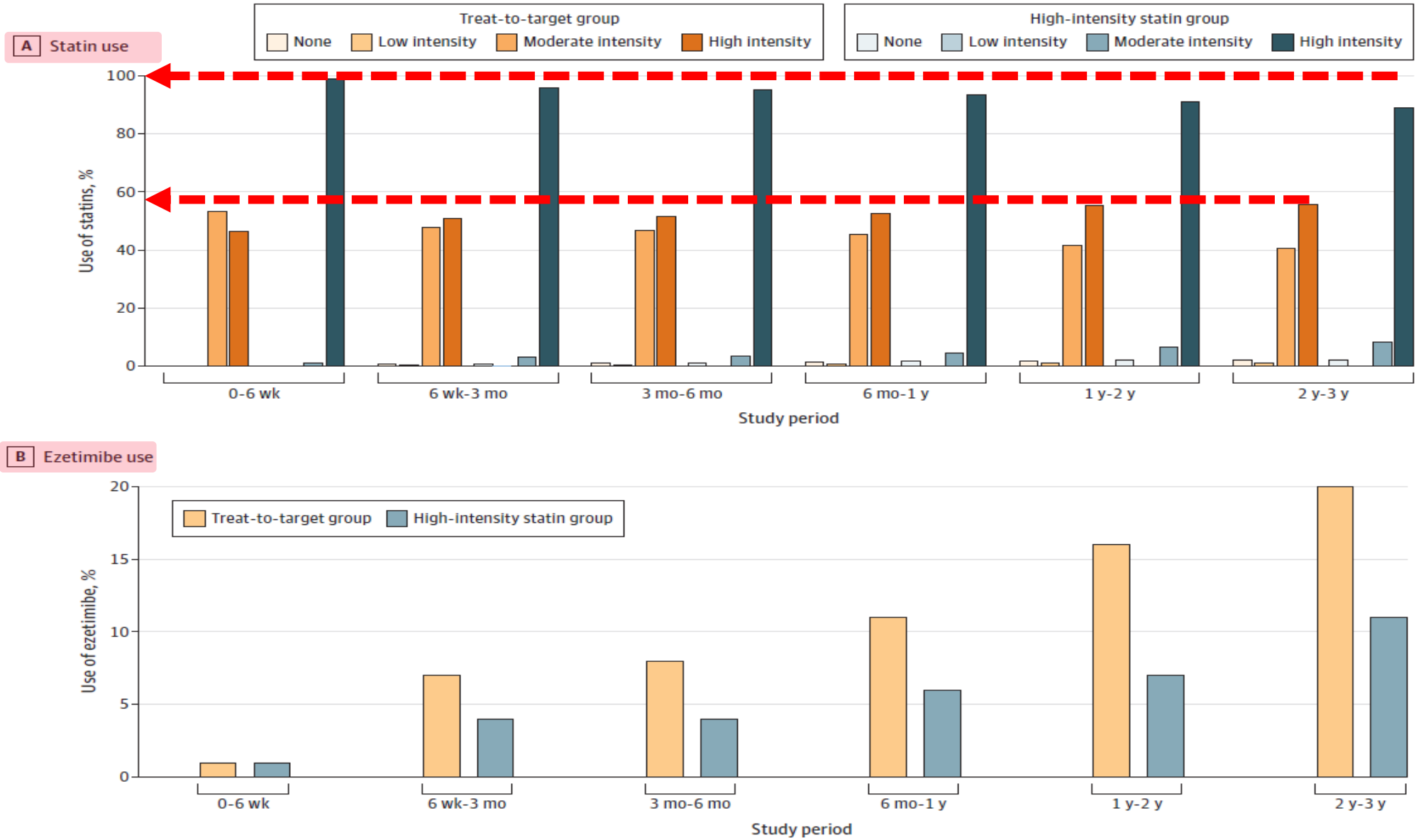
Interventions: Patients were randomly assigned to receive either the LDL-C target strategy, with an LDL-C level between 50 and 70 mg/dL as the target, or high-intensity statin treatment, which consisted of rosuvastatin, 20 mg, or atorvastatin, 40 mg.

Main Outcomes and Measures: Primary end point was a 3-year composite of death, myocardial infarction, stroke, or coronary revascularization with a non-inferiority margin of 3.0 percentage points.

- The use of high-intensity statin might be simple because it reduces the need to adjust statin intensity according to follow-up of LDL-C levels, but it raises concerns about individual variability in drug response and the adverse effects of long-term use of high-intensity statins.
- An alternative approach is to begin with moderate-intensity statins and titrate to a specific LDL-C goal. This treat-to target strategy could allow a tailored approach and facilitate patient-physician communication, which can enhance adherence to therapy.
- It was hypothesized that high-intensity statin therapy would be less needed in a treat-to-target strategy compared with a high-intensity statin strategy. Consequently, it could be advantageous in regard to the safety concerns related to the long-term use of high intensity statin therapy if equally effective.

LODESTAR

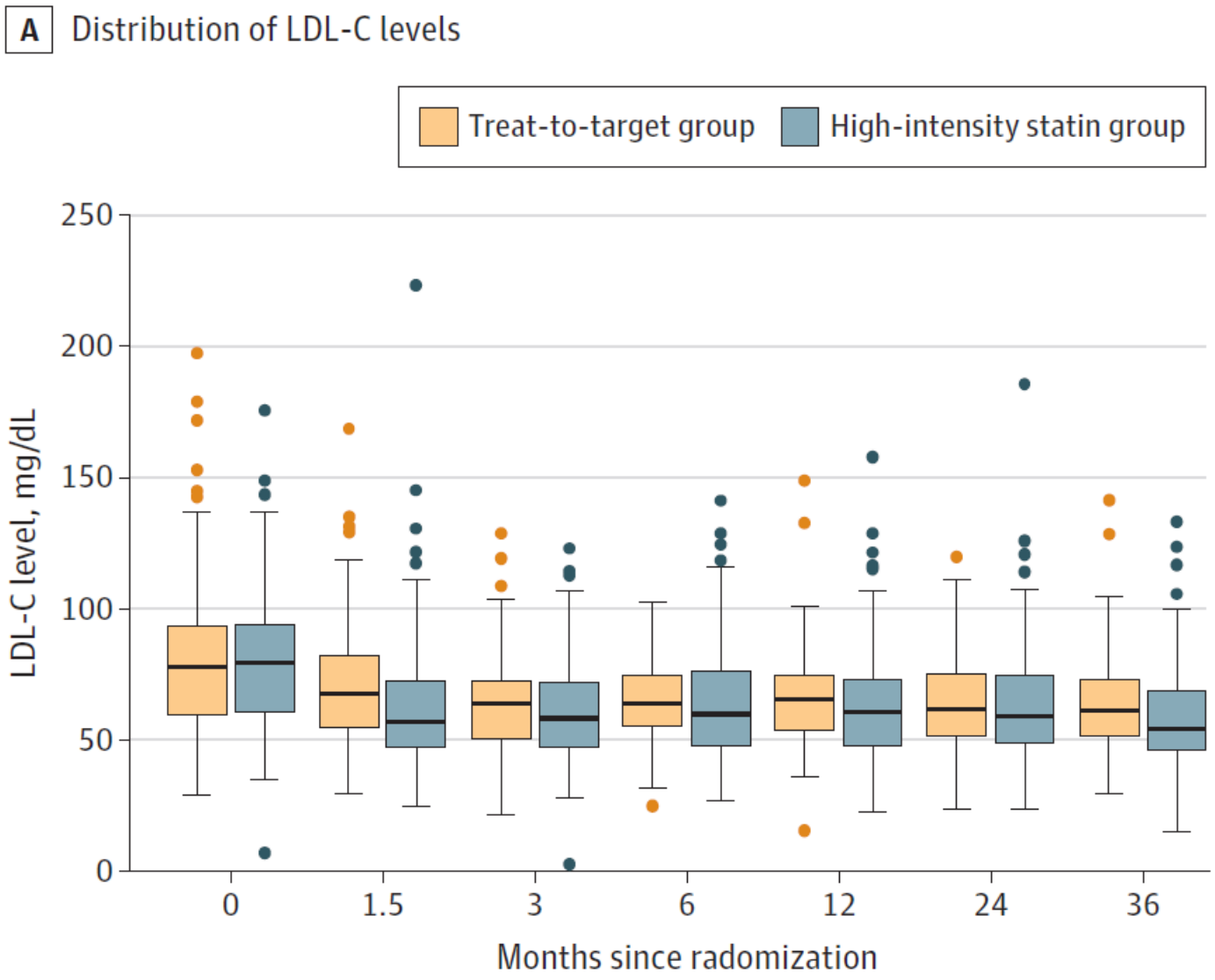
Figure 2. Lipid-Lowering Therapy During the Study Period



Non statin add-on therapy such as ezetimibe, was not recommended strongly in the treat-to-target group, even when the target was not achieved with high intensity statin therapy, to focus on the strategy for choosing statin intensity and avoid confounding by any imbalance in their use.

For the overall study period, in the treat-to-target group, statin intensity was up titrated 17%, down titrated in 9%, and maintained without changes in **73%**.

Figure 3. Changes in LDL-C Levels and Kaplan-Meier Curves for the Primary End Point[a]



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During the overall study period, the mean (SD) LDL-C level was 69.1 (17.8) mg/dL in the treat-to-target group and 68.4 (20.1) mg/dL in the high-intensity statin therapy group, which was not a significant difference (P = 0.21).

The proportion of participants with an LDL-C level below 70mg/dL, which was the goal for the treat-to-target group, was
55.7% at 6 weeks,
59.2% at 3 months,
57.7% at 6 months,
55.7% at 1 year,
60.8% at 2 years,
58.2% at 3 years.
This proportion was significantly lower in the treat-to target group than the high-intensity statin therapy group at 6 weeks and 3 months

LODESTAR

Table 2. Primary and Secondary End Points at 3 Years After Randomization[a]

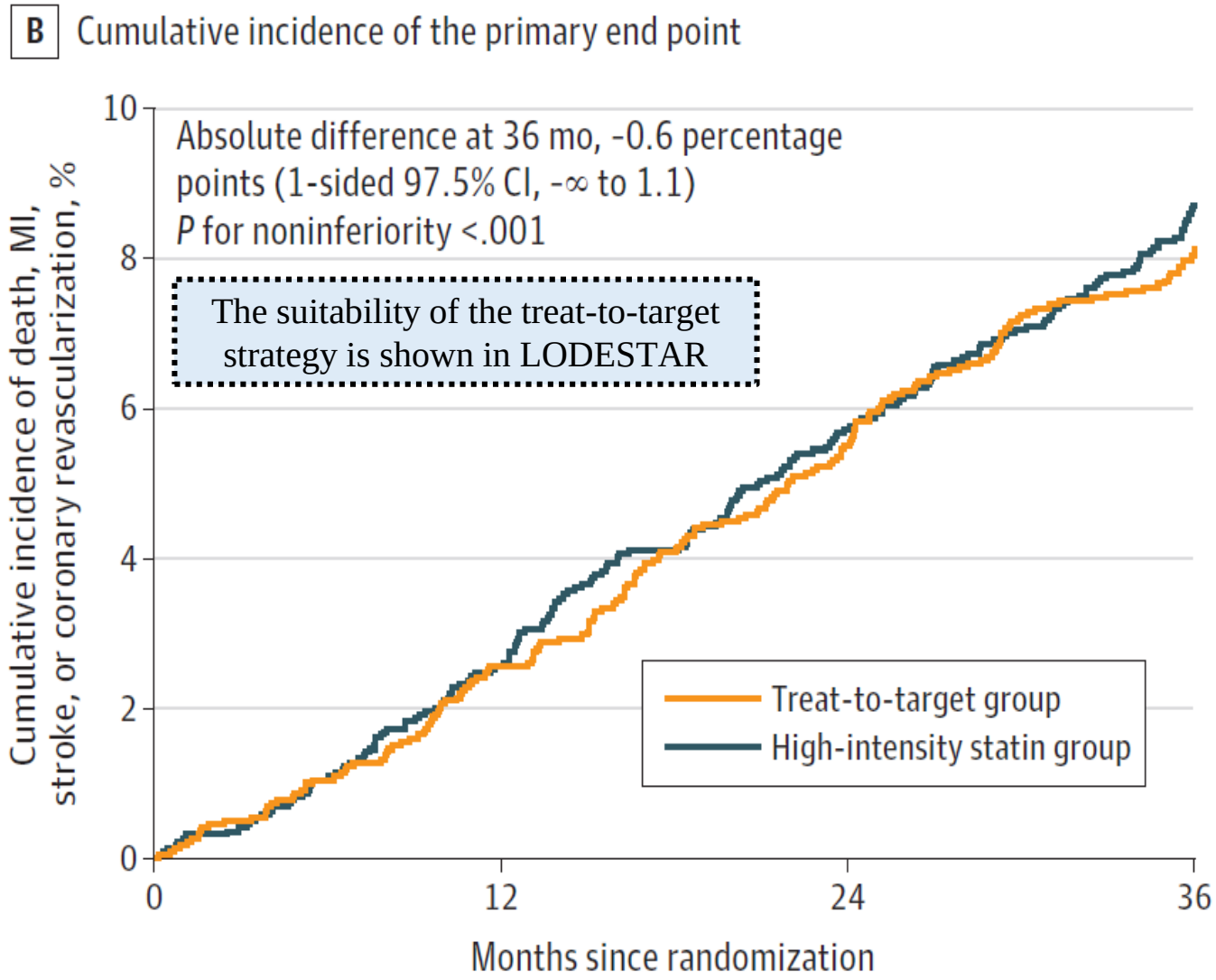
Outcome	Patients, No. (%)		Absolute difference, % (95% CI)[b]	*P* value
	Treat-to-target group (n = 2200)	High-intensity statin group (n = 2200)		
Primary end point				
Death, myocardial infarction, stroke, or coronary revascularization	177 (8.1)	190 (8.7)	−0.6 (−∞ to 1.1)[c]	<.001[d]
Secondary end points				
New-onset diabetes	121 (5.6)	150 (7.0)	−1.3 (−2.8 to 0.1)	.07
Initiation of antidiabetic medication	73	105		
Cataract operation	43 (2.0)	42 (1.9)	0.1 (−0.8 to 0.9)	.90
Discontinuation of statin therapy	31 (1.5)	46 (2.2)	−0.7 (−1.5 to 0.1)	.09
Composite of laboratory abnormalities[f]	18 (0.8)	30 (1.3)	−0.5 (−1.1 to 0.1)	.11
Aminotransferase elevation	8	12		
Creatine kinase elevation	3	8		
Creatinine elevation	7	11		
Peripheral artery revascularization	12 (0.6)	17 (0.8)	−0.2 (−0.8 to 0.3)	.35
Hospitalization due to heart failure	13 (0.6)	7 (0.3)	0.3 (−0.1 to 0.7)	.17
End-stage kidney disease	3 (0.1)	10 (0.5)	−0.3 (−0.7 to 0.0)	.05
Deep vein thrombosis or pulmonary embolism	4 (0.2)	5 (0.2)	<0.1 (−0.3 to 0.2)	.74
Deep vein thrombosis	2	5		
Pulmonary embolism	3	0		
Aortic intervention or surgery	2 (0.1)	3 (0.1)	NR	
Endovascular therapy	1	2		
Surgical therapy	1	1		
Composite of new-onset diabetes, aminotransferase or creatine kinase elevation, or end-stage kidney disease (post hoc)	132 (6.1)	177 (8.2)	−2.1 (−3.6 to −0.5)	.009

Non-inferiority margin of 3.0 percentage points

NNH=47

LODESTAR

Figure 3. Changes in LDL-C Levels and Kaplan-Meier Curves for the Primary End Point[a]



A lower use of high-intensity statin in those in the treat to target group compared with the high intensity statin therapy group (54% vs 92%) indicated that the treat-to-target strategy was a tailored approach that accounted for individual variability in therapeutic response to statin therapy.

The current findings of a numerically lower rate of secondary end points (new-onset diabetes, end-stage kidney disease, or composite of laboratory abnormalities) (number needed to harm = 48 patients during 3-year) may favor the treat-to-target strategy in regard to the safety issues.

7

High Intensity vs. Moderate Intensity Statin Therapy with Ezetimibe in Patients with ASCVD

RACING

Lancet. 2022 Jul 30;400(10349):380-390.

Long-term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease (RACING): a randomised, open-label, non-inferiority trial

Byeong-Keuk Kim, Sung-Jin Hong*, Yong-Joon Lee, Soon Jun Hong, Kyeong Ho Yun, Bum-Kee Hong, Jung Ho Heo, Seung-Woon Rha,*

Background: Drug combinations rather than increasing doses of one drug can achieve greater efficacy and lower risks. Thus, as an alternative to high-intensity statin monotherapy, moderate-intensity statin with ezetimibe combination therapy can lower LDL cholesterol concentrations effectively while reducing adverse effects. However, evidence from randomised trials to compare long-term clinical outcomes is needed.

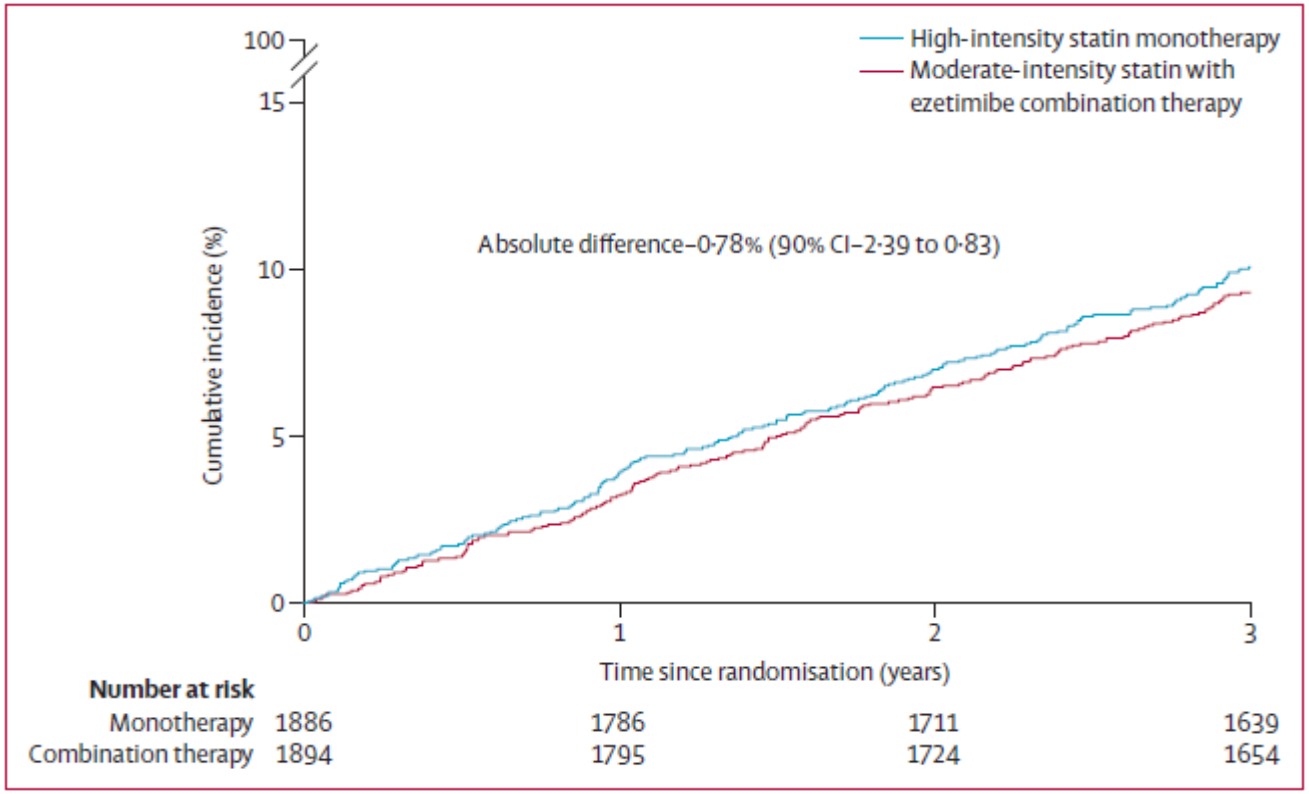
Methods: In this randomised, open-label, non-inferiority trial, patients ASCVD at 26 clinical centers in **South Korea** were randomly assigned (1:1) to receive either moderate-intensity statin with ezetimibe combination therapy (Rosuvastatin 10 mg with Ezetimibe 10 mg) or high-intensity statin monotherapy (Rosuvastatin 20 mg).

The primary endpoint was the 3-year composite of MACE, in the intention-to-treat population with a non-inferiority margin of 2·0%.

Findings: Between Feb 14, 2017, and Dec 18, 2018, 3780 patients were enrolled: 1894 patients to the combination therapy group and 1886 to the high-intensity statin monotherapy group.

RACING

Kaplan-Meier curves of the primary endpoint of the intention-to-treat population



Non-inferiority margin of 2·0%

	Moderate-intensity statin with ezetimibe combination therapy (n=1894)	High-intensity statin monotherapy (n=1886)	Absolute difference (90% CI)	Hazard ratio (95% CI)	p value
Primary endpoint					
Composite of cardiovascular death, major cardiovascular event, or non-fatal stroke	172 (9·1%)	186 (9·9%)	−0·78% (−2·39 to 0·83)	0·92 (0·75 to 1·13)	0·43
Secondary efficacy endpoint					
Composite of all-cause death, major cardiovascular event, or non-fatal stroke	186 (9·8%)	197 (10·4%)	−0·62% (−2·28 to 1·03)	0·94 (0·77 to 1·15)	0·94

Data are the number of events (%).

Table 2: 3-year clinical endpoint in the intention-to-treat population

RACING

	Moderate-intensity statin with ezetimibe combination therapy	High-intensity statin monotherapy	Absolute differences in proportions, % (95% CI)	
1 year				
Number of patients	1675	1673	..	
Number of patients with LDL cholesterol concentrations <70 mg/dL	1217 (73%)	923 (55%)	17·5 (14·2 to 20·7)	NNT= 5.7
LDL cholesterol concentration (mg/dL)	58 (47–71)	67 (55–80)	..	
2 years				
Number of patients	1558	1539	..	
Number of patients with LDL cholesterol concentrations <70 mg/dL	1168 (75%)	924 (60%)	14·9 (11·6 to 18·2)	NNT= 6.7
LDL cholesterol concentration (mg/dL)	57 (45–70)	65 (53–79)	..	
3 years				
Number of patients	1349	1315	..	
Number of patients with LDL cholesterol concentrations <70 mg/dL	978 (72%)	759 (58%)	14·8 (11·1 to 18·4)	NNT= 6.7
LDL cholesterol concentration (mg/dL)	58 (47–71)	66 (54–80)	..	

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

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

RACING

	Moderate-intensity statin with ezetimibe combination therapy (n=1846)	High-intensity statin monotherapy (n=1832)	Absolute difference (95% CI)
Serious adverse events			
Death	26 (1·4%)	22 (1·2%)	0·21 (−5·88 to 1·01)
Adverse events			
Discontinuation or dose reduction of study drug due to intolerance	88 (4·8%)	150 (8·2%)	−3·42 (−5·07 to −1·80)
New-onset diabetes	145 (7·9%)	159 (8·7%)	−0·82 (−2·65 to 1·00)
New-onset diabetes with anti-diabetic medication initiation	95 (5·1%)	107 (5·8%)	..
Muscle-related adverse events	21 (1·1%)	34 (1·9%)	0·69 (−2·22 to 0·82)
Myalgia	17 (0·9%)	29 (1·6%)	0·66 (−1·46 to 1·06)
Myopathy	2 (0·1%)	4 (0·2%)	−0·11 (−0·50 to 0·25)
Myonecrosis*	11 (0·6%)	13 (0·7%)	0·11 (−0·72 to 0·48)
Gallbladder-related adverse events	13 (0·7%)	7 (0·4%)	0·32 (−0·22 to 0·89)
Major bleeding	17 (0·9%)	13 (0·7%)	0·21 (−0·44 to 0·87)
Cancer diagnosis	37 (2·0%)	28 (1·5%)	0·48 (−0·43 to 0·14)
New-onset neurocognitive disorder	4 (0·2%)	2 (0·1%)	0·11 (−0·25 to 0·50)
Cataract surgery	19 (1·0%)	21 (1·1%)	−0·12 (−0·86 to 0·62)

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

Table 4: Secondary safety endpoint of the safety population

NNH=30

Conclusions

- Among patients with documented ASCVD, moderate-intensity statin with ezetimibe combination therapy was non-inferior to high-intensity statin monotherapy in terms of a 3-year composite of MACE with a higher proportion of patients who achieved LDL-C <70 mg/dL and lower drug discontinuation or dose reduction owing to intolerance.

Implications of all the available evidence

- Our results support recommending the addition of ezetimibe for patients who are taking moderate-intensity statins at a maximal tolerance.
- These findings suggest that ezetimibe combination therapy might be considered earlier in the use of moderate-intensity statin therapy rather than doubling the statin dose for patients at high risk of adverse effects or statin intolerance with high-intensity statin therapy.

Lancet Editorial

Is it time for a paradigm shift in the management of lipids toward an approach with combination therapy as an initial treatment option that is more similar to the treatment of hypertension?

This therapeutic inertia might be overcome through early initiation of combination LLT, leading to a greater proportion of patients with ASCVD meeting the LDL cholesterol goal.

A pre-specified subgroup analysis of the randomized RACING trial

Moderate-intensity statin+ezetimibe combination therapy — 701

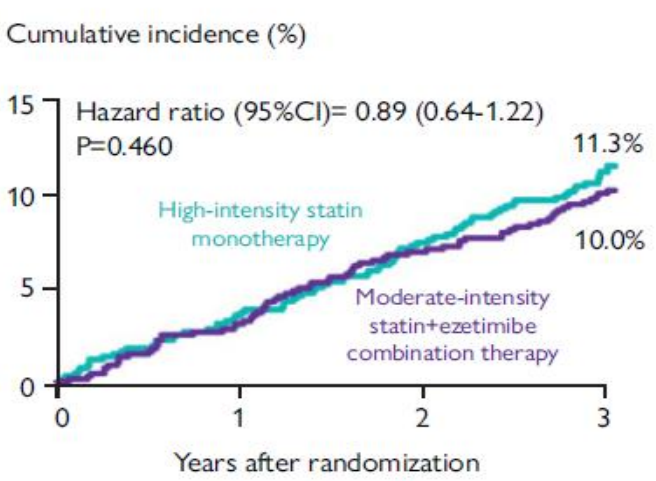
High-intensity statin monotherapy — 697

Composite of cardiovascular death, major cardiovascular events, or nonfatal stroke at 3 years

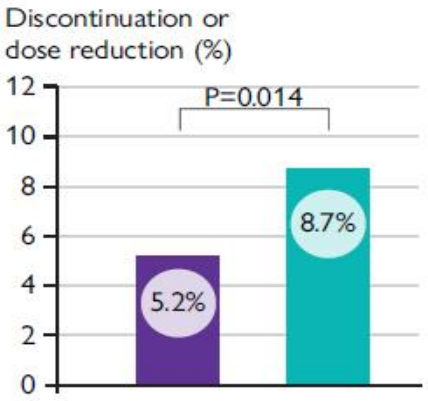
Intolerance-related drug discontinuation or dose reduction

Proportion of patients with LDL cholesterol levels <70 mg/dL

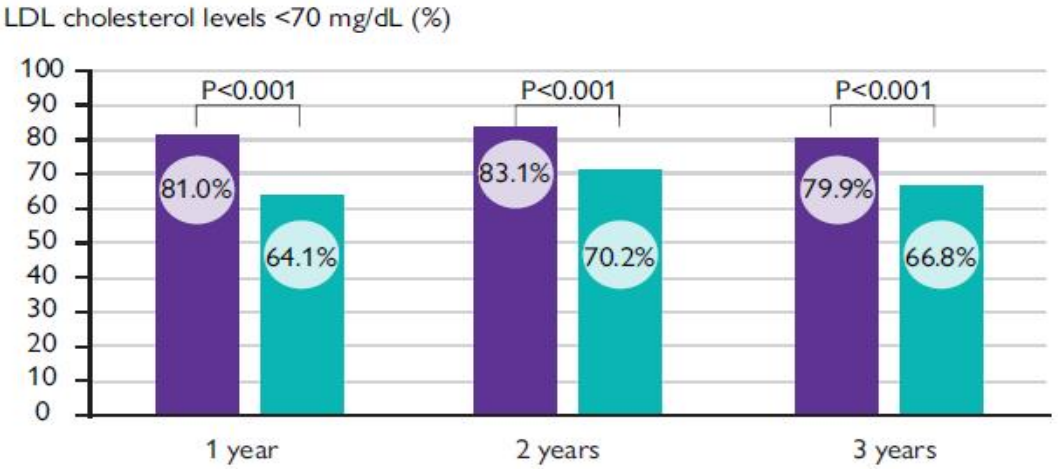
Composite cardiovascular outcomes



Intolerance



LDL cholesterol reduction



Take Home Message

The use of moderate-intensity statin with ezetimibe combination therapy is a reasonable alternative to high-intensity statin monotherapy, as recommended by the current guidelines for secondary prevention among patients with DM and ASCVD.

Combination Therapy of Statins with Proportion Convertase Subtilisin-Kexin9 (PCSK9) Inhibitors

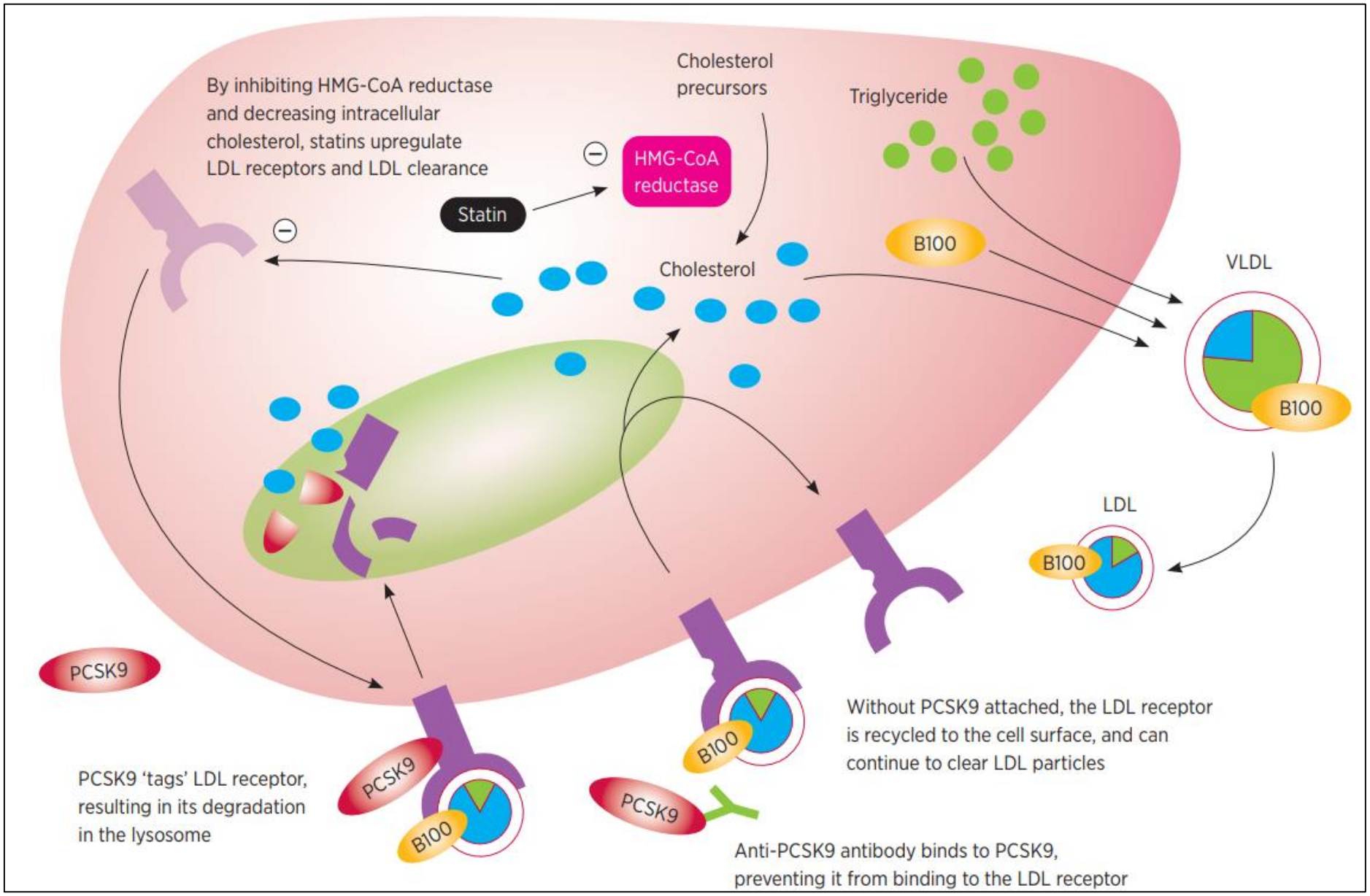


Fig. 1 Mechanism of action of statins and anti-PCSK9 monoclonal antibodies

VLDL is secreted by the liver and converted to LDL, which delivers cholesterol to peripheral tissues and is atherogenic.

LDL particles are taken up via LDL receptors, primarily on hepatocytes, and degraded.

The production of LDL receptors is decreased by intracellular cholesterol, so lowering intracellular cholesterol with statins results in increased LDL receptors and LDL uptake.

LDL-receptor degradation is enhanced by PCSK9, so inhibiting PCSK9 with antibodies increases LDL-receptor recycling and LDL uptake.

FOURIER

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 4, 2017 VOL. 376 NO. 18

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Clinical Question

Among patients with **clinical atherosclerotic disease** and LDL >70 despite **high- or moderate-intensity statin therapy**, does the addition of PCSK9 inhibitor evolocumab reduce major cardiovascular events compared to placebo?

Design

N= 27,564 : Evolocumab (n=13,784), Placebo (n=13,780)

Enrollment: February 2013 - June 2015

Median follow-up: 26 months

Analysis: Intention-to-treat

Primary outcome: Major CV events (CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization)

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February 2013 through June 2015

27,564

Patients : Age ≥ 40 and ≤ 85, ASCVD with LDL-C ≥ 70 mg/dL or Non–HDL cholesterol ≥ 100 mg/dL

1 : 1
Randomization

13,780

Atorvastatin 20 mg + Placebo

13,784

Atorvastatin 20 mg + Evolocumab

Diabetic population :37%

CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization

follow-up: 26 months

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Table 1. Characteristics of the Patients at Baseline.*

Characteristics	Evolocumab (N = 13,784)	Placebo (N = 13,780)
Statin use — no. (%)§		
High intensity	9,585 (69.5)	9,518 (69.1)
Moderate intensity	4,161 (30.2)	4,231 (30.7)
Low intensity, unknown intensity, or no data	38 (0.3)	31 (0.2)
Ezetimibe — no. (%)	726 (5.3)	714 (5.2)
Other cardiovascular medications — no./total no. (%)		
Aspirin, $P2Y_{12}$ inhibitor, or both	12,766/13,772 (92.7)	12,666/13,767 (92.0)
Beta-blocker	10,441/13,772 (75.8)	10,374/13,767 (75.4)
ACE inhibitor or ARB, aldosterone antagonist, or both	10,803/13,772 (78.4)	10,730/13,767 (77.9)
Median lipid measures (IQR)		
LDL cholesterol — mg/dl	92 (80–109)	92 (80–109)
Total cholesterol — mg/dl	168 (151–188)	168 (151–189)
HDL cholesterol — mg/dl	44 (37–53)	44 (37–53)
Triglycerides — mg/dl	134 (101–183)	133 (99–181)
Lipoprotein(a) — nmol/liter	37 (13–166)	37 (13–164)

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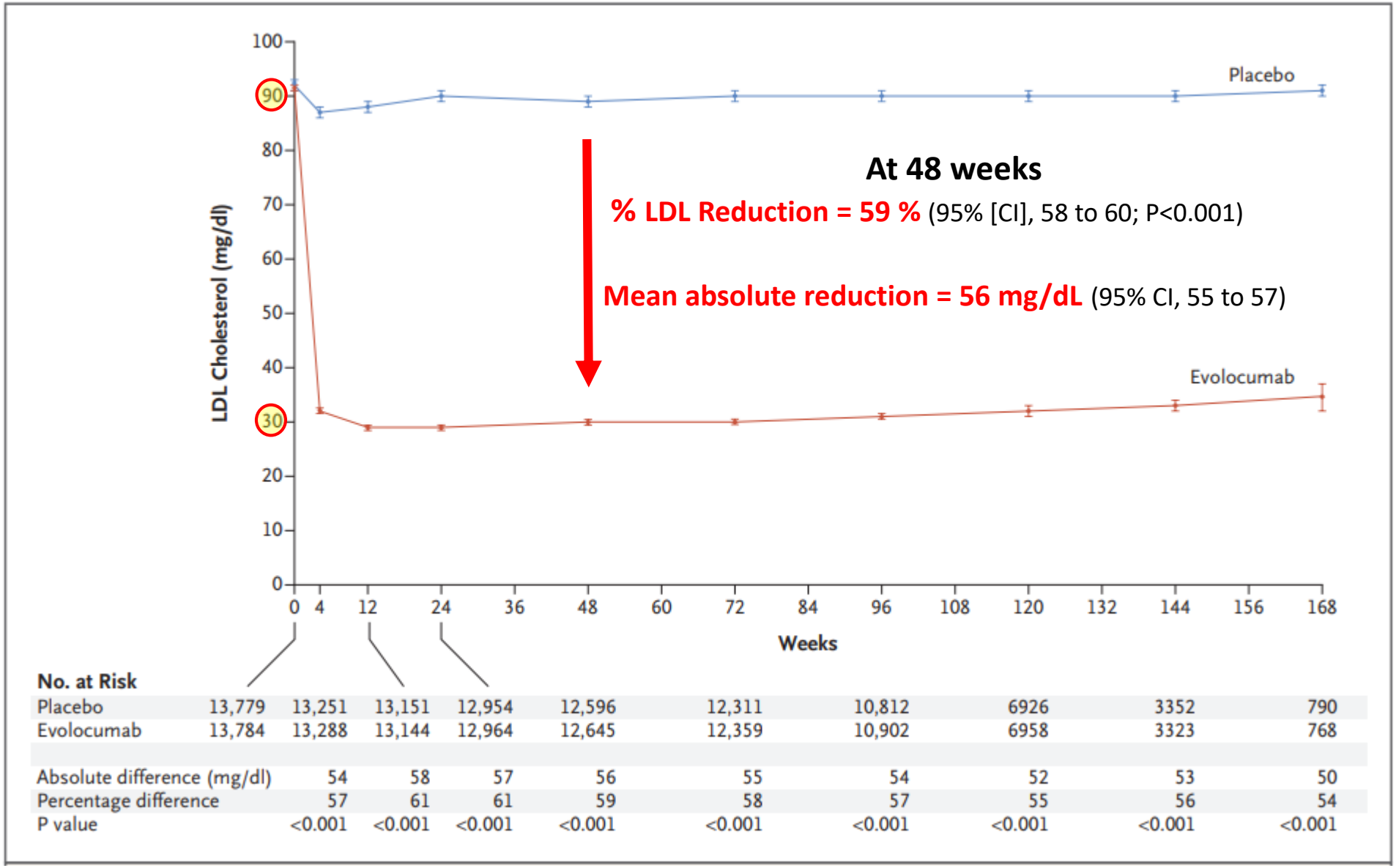

No. at Risk									
Placebo	13,779	13,251	13,151	12,954	12,596	12,311	10,812	6926	3352	790
Evolocumab	13,784	13,288	13,144	12,964	12,645	12,359	10,902	6958	3323	768
Absolute difference (mg/dl)		54	58	57	56	55	54	52	53	50
Percentage difference		57	61	61	59	58	57	55	56	54
P value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Figure 1
Low-Density Lipoprotein (LDL) Cholesterol Levels over Time. Shown are median values in the two study groups; I bars indicate 95% confidence intervals. Below the graph, the absolute and percentage reductions in LDL cholesterol level in the evolocumab group are compared with those in the placebo group and are presented as least-squares means or means.

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Results

NNT=67

Primary Outcome

Cardiovascular death, MI, stroke, hospitalization for unstable angina, coronary revascularization — **15 % ⬇**

1344 (9.8%) vs. 1563 (11.3%) [HR 0.85, 95% CI 0.79-0.92, p<0.001]

Secondary Outcomes

Cardiovascular death, MI, stroke : 816 (5.9%) vs. 1013 (7.4%) [HR 0.80, 95% CI 0.73-0.88, p<0.001] — **20 % ⬇**

Cardiovascular death : 251 (1.8%) vs. 240 (1.7%) [HR 1.05, 95% CI 0.88-1.25, p=0.62] — **NS**

All-cause death : 444 (3.2%) vs. 426 (3.1%) [HR 1.04, 95% CI 0.91-1.19, p=0.54] — **NS**

Myocardial infarction : 468 (3.4%) vs. 639 (4.6%) [HR 0.73, 95% CI 0.65-0.82, p<0.001] — **27 % ⬇**

Stroke : 207 (1.5%) vs. 262 (1.9%) [HR 0.79, 95% CI 0.66-0.95, p=0.01] — **21 % ⬇**

Coronary revascularization : 759 (5.5%) vs. 965 (7.0%) [HR 0.78, 95% CI 0.71-0.86, p<0.001] — **22 % ⬇**

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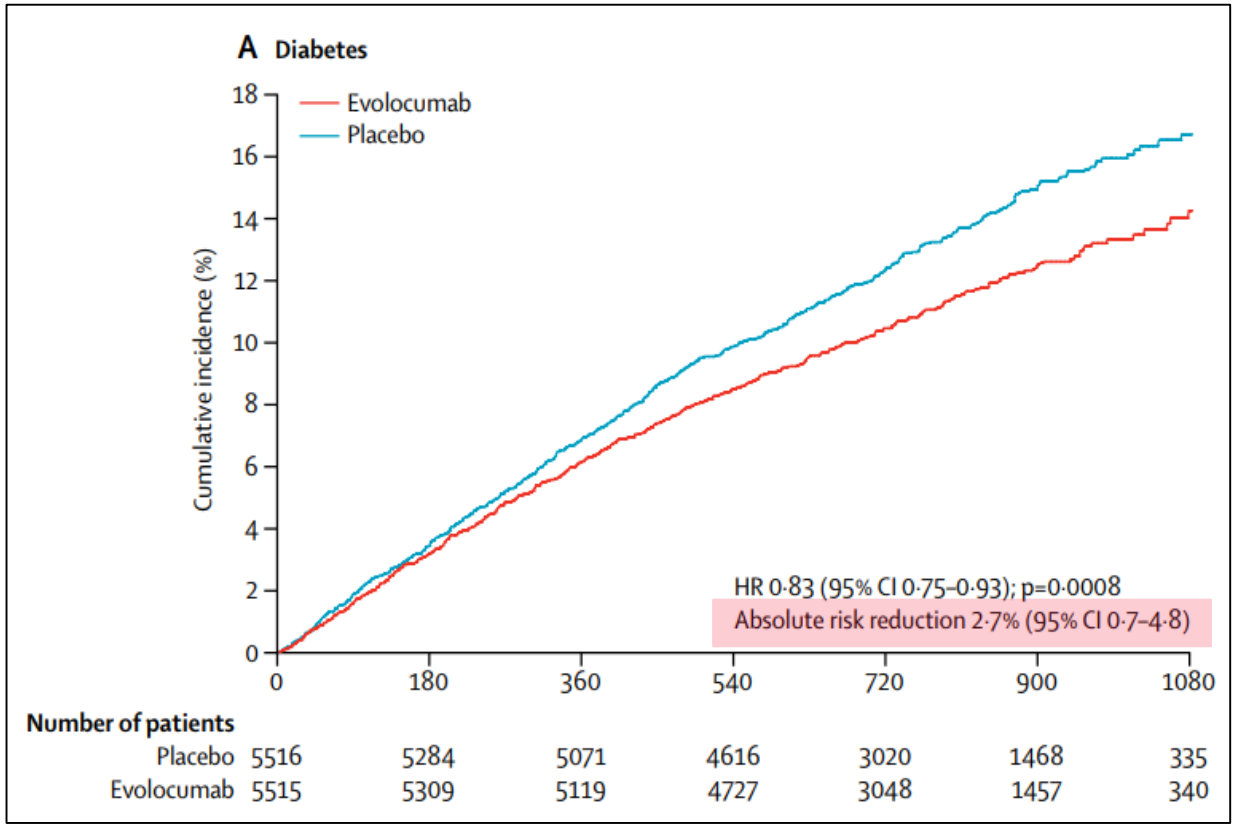
Key messages

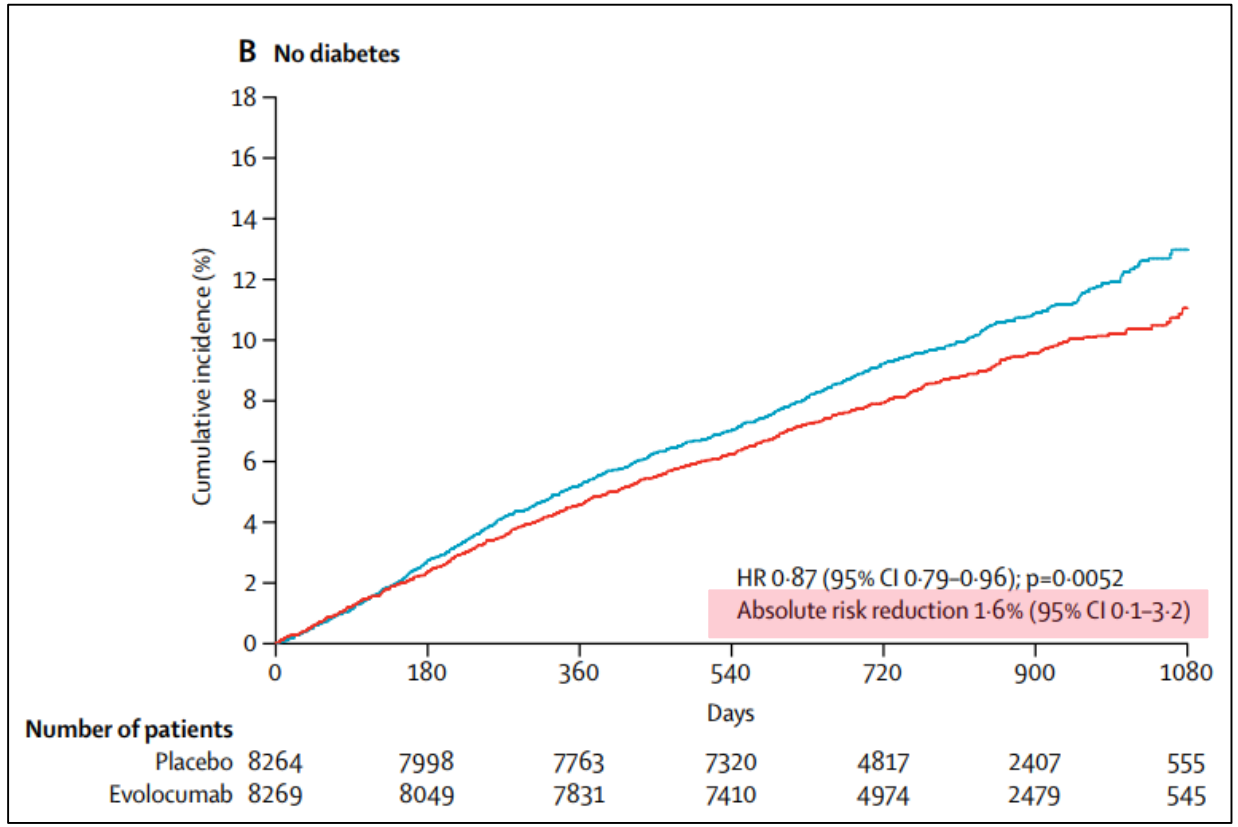
- Inhibition of PCSK9 with evolocumab on a background of statin therapy lowered LDL cholesterol levels to a median of 30 mg /dL and reduced the risk of cardiovascular events, with no accompanying safety issue after a median follow-up of 2.2 years for this low level of LDL-C
- These findings show that patients with atherosclerotic cardiovascular disease benefit from the lowering of LDL cholesterol levels below current targets

Evolocumab significantly reduced cardiovascular risk in patients with and without diabetes

NNT = 37



NNT = 62



$(p_{interaction}=0\cdot60)$

ODYSSEY OUTCOME

Lancet Diabetes Endocrinol. 2019 Aug;7(8):618-628.

Effects of alirocumab on cardiovascular and metabolic outcomes after acute coronary syndrome in patients with or without diabetes: a prespecified analysis of the ODYSSEY OUTCOMES randomised controlled trial

Kausik K Ray*, Helen M Colhoun*, Michael Szarek*, Marie Baccara-Dinet, Deepak L Bhatt, Vera A Bittner, Andrzej J Budaj, Rafael Diaz,

Background: After acute coronary syndrome, diabetes conveys an excess risk of ischaemic cardiovascular events. A reduction in mean LDL cholesterol to 54-70 mg/dL with ezetimibe or statins reduces CVD in patients with an ACS and diabetes. However, the efficacy and safety of further reduction in LDL cholesterol with an inhibitor of PCSK9 after ACS is unknown.

Methods: ODYSSEY OUTCOMES was a randomised, double-blind, placebo-controlled trial, done at 1315 sites in 57 countries, that compared alirocumab with placebo in patients who had been admitted to hospital with an ACS (myocardial infarction or unstable angina) 1-12 months before randomisation and who had raised concentrations of atherogenic lipoproteins despite use of high-intensity statins. Patients were randomly assigned (1:1) to receive alirocumab or placebo every 2 weeks; randomisation was stratified by country and was done centrally with an interactive voice-response or web-response system. Alirocumab was titrated to target LDL cholesterol concentrations of 25-50 mg/dL.

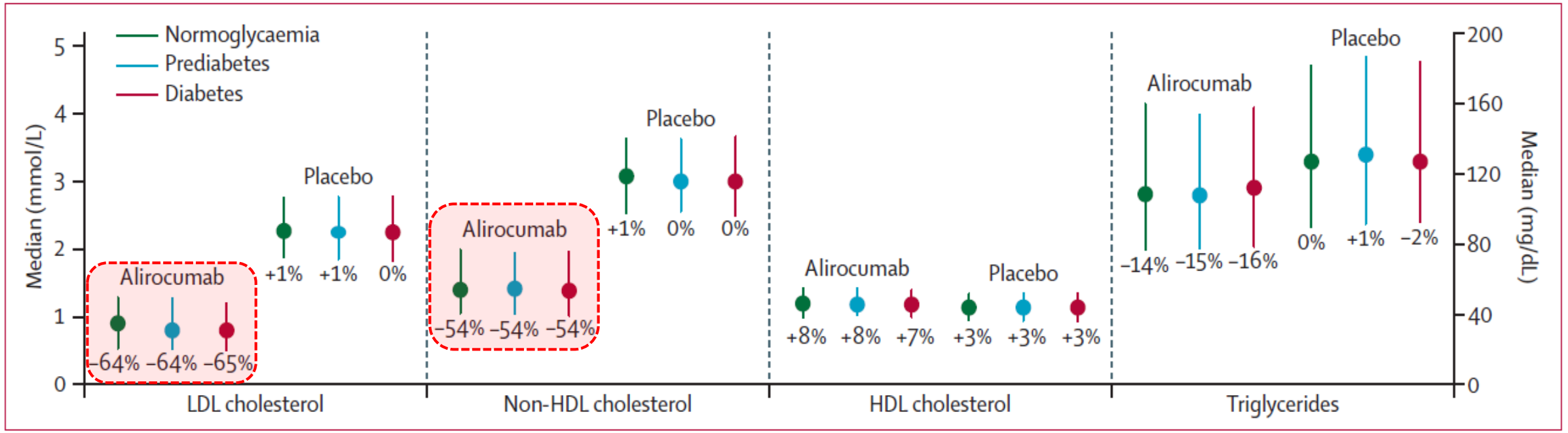


Figure 2: **Lipid concentrations at 4 months after randomisation, by baseline glycaemic status (intention-to-treat analysis)**
Error bars are IQRs. Median within-patient percentage changes from baseline are shown below each data point.

ODYSSEY OUTCOME

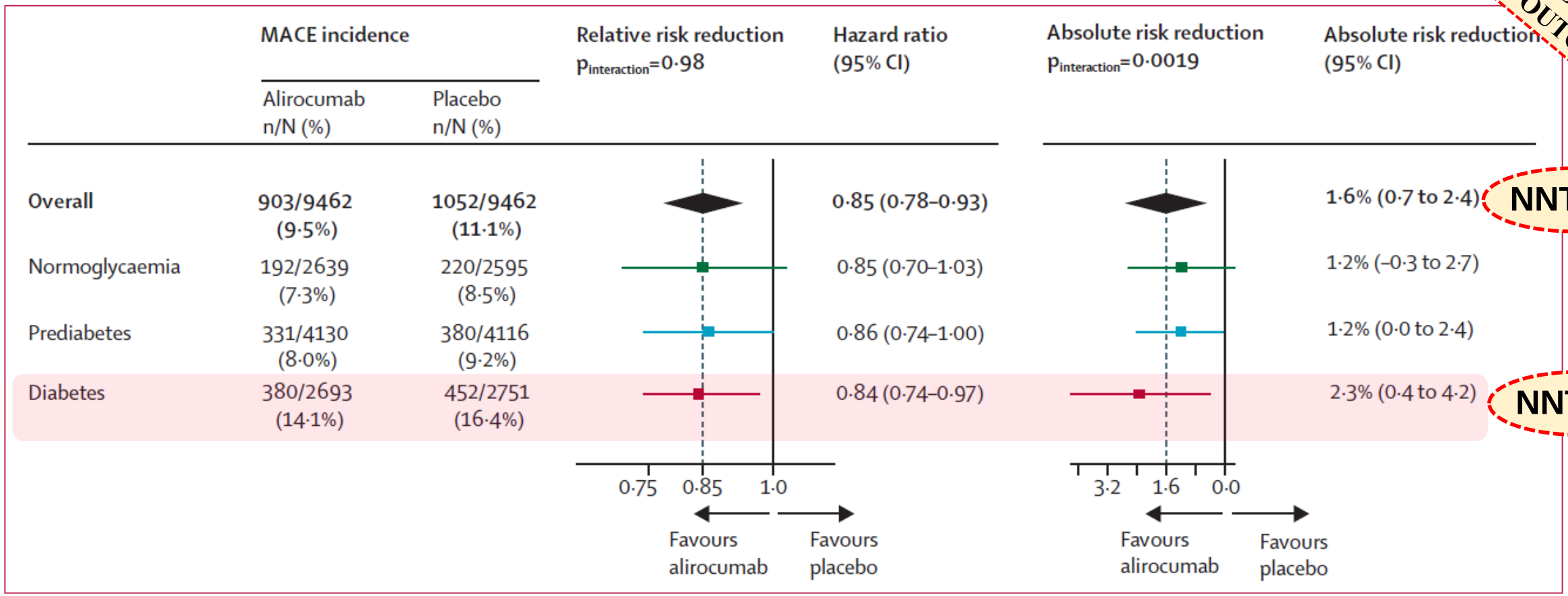


Figure 4: **Relative and absolute risk reduction with alirocumab, by baseline glycaemic status**
Median follow-up was 2·8 years (IQR 2·3–3·4). MACE=major adverse cardiovascular events.

After a recent acute coronary syndrome, alirocumab treatment targeting an LDL cholesterol concentration of 25-50 mg/dL produced about twice the absolute reduction in cardiovascular events among patients with diabetes as in those without diabetes. Alirocumab treatment did not increase the risk of new-onset diabetes.

ADA 2025

10.29b For people with diabetes and ASCVD intolerant to statin therapy, PCSK9 inhibitor therapy with monoclonal antibody treatment, should be considered as an alternative cholesterol-lowering therapy. A

The NEW ENGLAND JOURNAL of MEDICINE

November 8, 2025

ORIGINAL ARTICLE

Evolocumab in Patients without a Previous Myocardial Infarction or Stroke

Erin A. Bohula, M.D., D.Phil.,[1] Nicholas A. Marston, M.D., M.P.H.,[1]

Background: The effect of evolocumab on the risk of MACE among patients without a previous MI/Stroke is unknown.

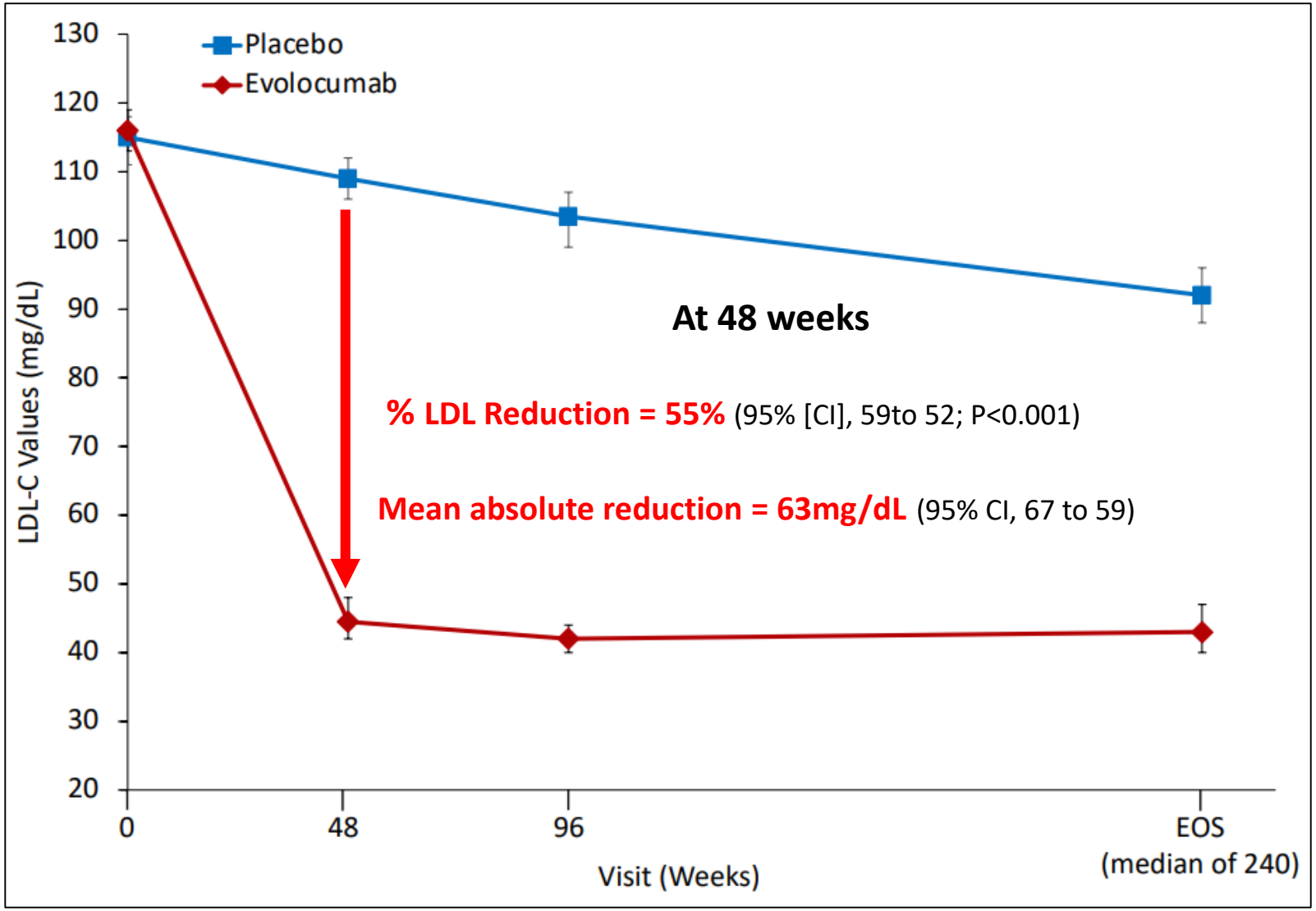
Methods: We conducted an international, double-blind, randomized, placebo-controlled trial of evolocumab in patients with atherosclerosis or diabetes and without a previous MI/Stroke who had a LDL-C of at least 90 mg per deciliter. Patients were randomly assigned in a 1:1 ratio to receive evolocumab at a dose of 140 mg every 2 weeks or placebo.
The two primary end points were a composite of death from CHD, MI, or ischemic stroke (3-point MACE) and a composite of 3-point MACE or ischemia-driven arterial revascularization (4-point MACE).

Results: A total of 12,257 patients were randomly assigned to receive evolocumab (6129 patients) or placebo (6128) and were included in the efficacy analyses. The median age of the patients was 66 years, 43% were women. The median follow-up was 4.6 years.

Eligible patients must have been without a history of MI/Stroke and had to meet trial criteria for at least one of the following four disease categories:

- ✓ CAD, atherosclerotic CVD, PAD, high-risk diabetes:
- ✓ Patients with diabetes that is long-standing (≥10 years' duration), is treated with daily insulin, or is complicated by microvascular disease.
- ✓ Eligible patients were also required to have at least one additional criterion that placed them at higher risk for CVD, such as an age of 65 years or older, active smoking, very elevated lipid levels, or concomitant atherosclerosis and diabetes.

Low-Density Lipoprotein (LDL) cholesterol levels over time.



Median LDL at baseline =122

and

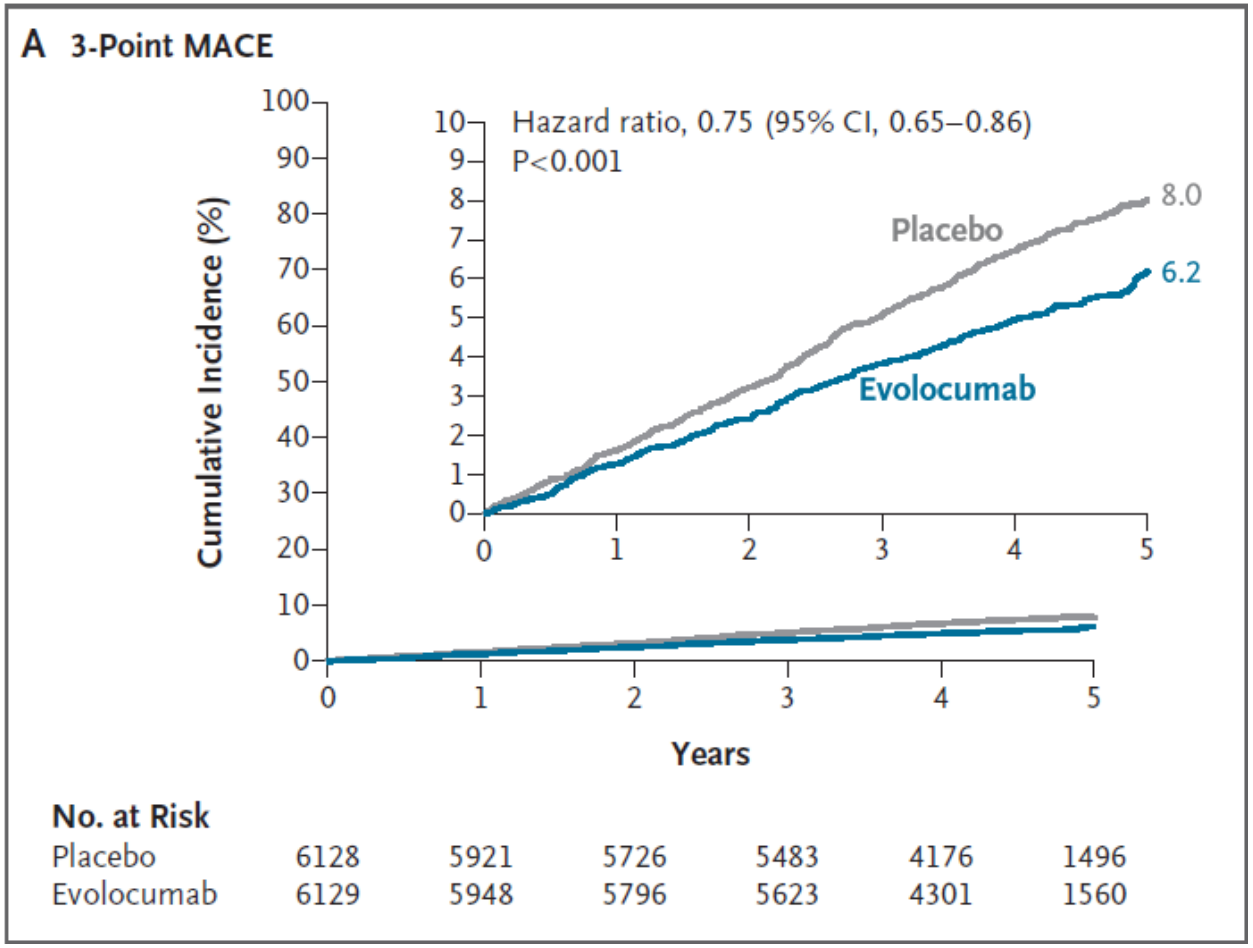
at 48 Weeks =45 mg/dL

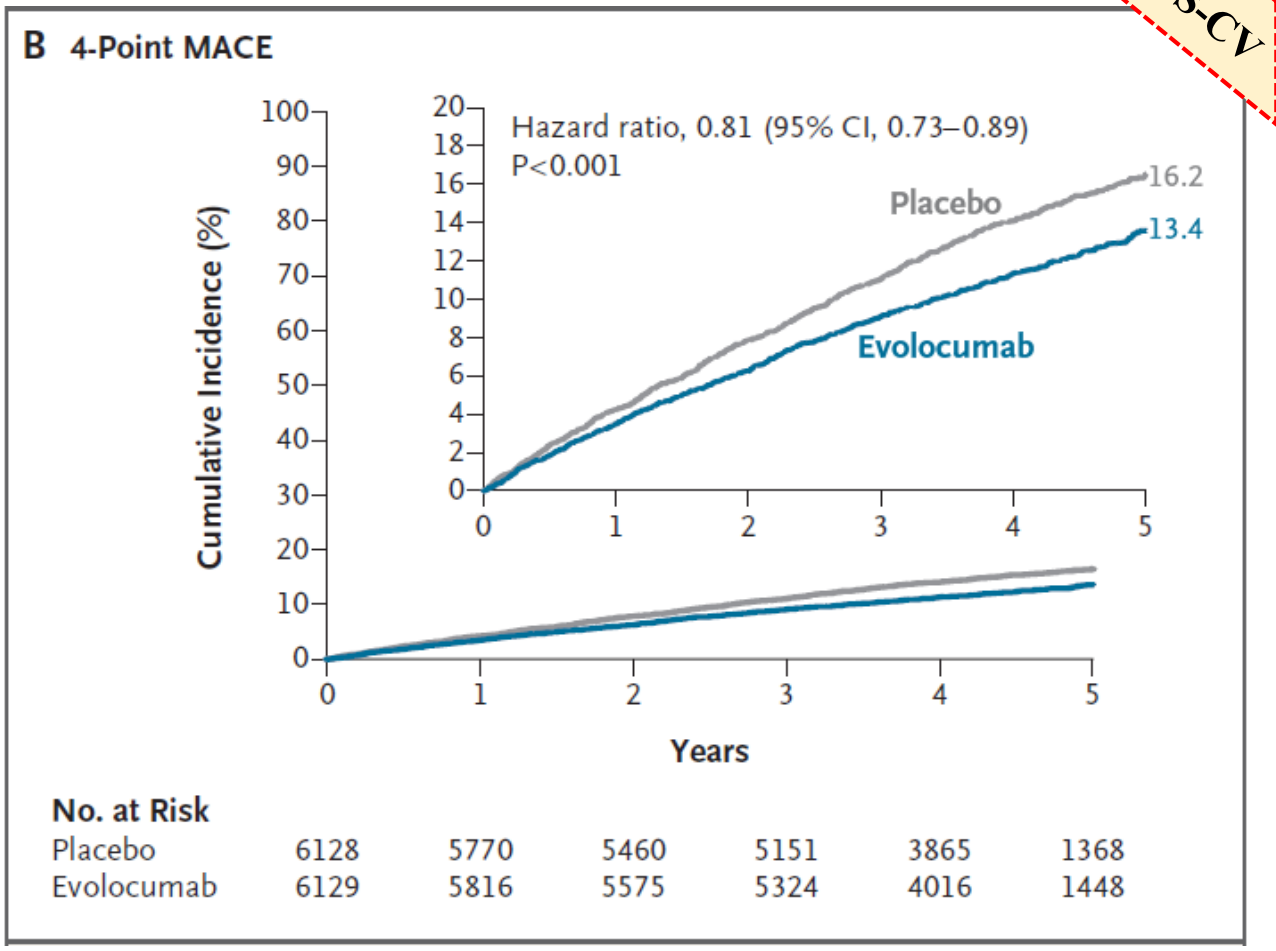
- 92% on LLT
- 72% on high intensity LLT
- 68% on high intensity Statin
- 20% on Ezetimibe
- 13 % not received Statin

Median with nonparametric rank-based 95% confidence intervals for LDL-C values.

Primary Efficacy End Points over Time

VESALIUS-CV





Shown is the cumulative incidence of the two primary end points: the composites of death from coronary heart disease, myocardial infarction, or ischemic stroke (3-point major adverse cardiac events [MACE]) (Panel A)
and of 3-point MACE or ischemia-driven arterial revascularization (4-point MACE) (Panel B).

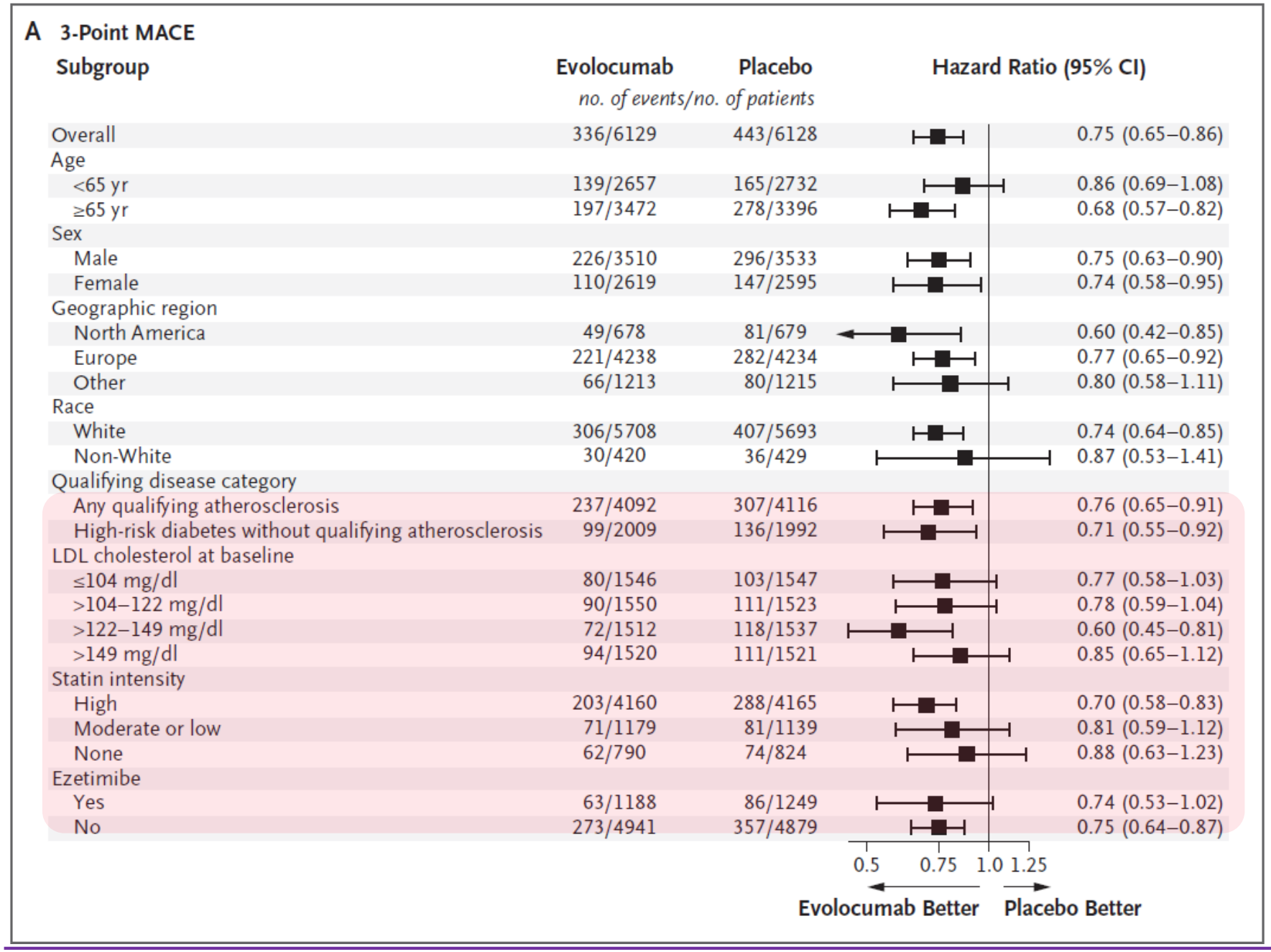
VESALIUS-CV

Table 2. Primary and Secondary End Points.*

End Point	Evolocumab (N = 6129)	Placebo (N = 6128)	Hazard Ratio (95% CI)	P Value
	no. (5-yr Kaplan–Meier estimate, %)			
Primary end points†				
3-Point MACE	336 (6.2)	443 (8.0)	0.75 (0.65–0.86)	<0.001
4-Point MACE	747 (13.4)	907 (16.2)	0.81 (0.73–0.89)	<0.001
Secondary end points‡				
Myocardial infarction, ischemic stroke, or ischemia-driven arterial revascularization	674 (12.2)	834 (15.0)	0.79 (0.72–0.88)	<0.001
Death from coronary heart disease, myocardial infarction, or ischemia-driven arterial revascularization	664 (11.9)	819 (14.6)	0.79 (0.72–0.88)	<0.001
Death from cardiovascular causes, myocardial infarction, or ischemic stroke	374 (6.8)	503 (9.1)	0.73 (0.64–0.84)	<0.001
Death from coronary heart disease or myocardial infarction	232 (4.2)	313 (5.6)	0.73 (0.62–0.87)	<0.001
Myocardial infarction	149 (2.7)	229 (4.1)	0.64 (0.52–0.79)	<0.001
Ischemia-driven arterial revascularization	561 (10.1)	699 (12.5)	0.79 (0.70–0.88)	<0.001
Death from coronary heart disease	105 (1.9)	117 (2.1)	0.89 (0.68–1.16)	0.39
Death from cardiovascular causes	156 (2.8)	195 (3.6)	0.79 (0.64–0.98)	NA
Death from any cause	434 (7.9)	539 (9.7)	0.80 (0.70–0.91)	NA
Ischemic stroke	115 (2.3)	144 (2.7)	0.79 (0.62–1.01)	NA

VESALIUS-CV

Key Subgroup Analyses for the Primary Efficacy End Points.



PCSK9 inhibition with evolocumab led to a lower risk of first cardiovascular events than placebo among patients with atherosclerosis or diabetes and without a previous myocardial infarction or stroke.

Bempedoic Acid in Statin Intolerant Patients

CLEAR Outcomes

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 13, 2023 VOL. 388 NO. 15

Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients

S.E. Nissen, A.M. Lincoff, D. Brennan, K.K. Ray, D. Mason, J.J.P. Kastelein, P.D. Thompson, P. Libby, L. Cho,

Background: Bempedoic acid, an ATP citrate lyase inhibitor, reduces low-density lipoprotein (LDL) cholesterol levels and is associated with a low incidence of muscle-related adverse events; its effects on cardiovascular outcomes remain uncertain.

Methods: We conducted 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 median duration of follow-up was 40.6 months

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.

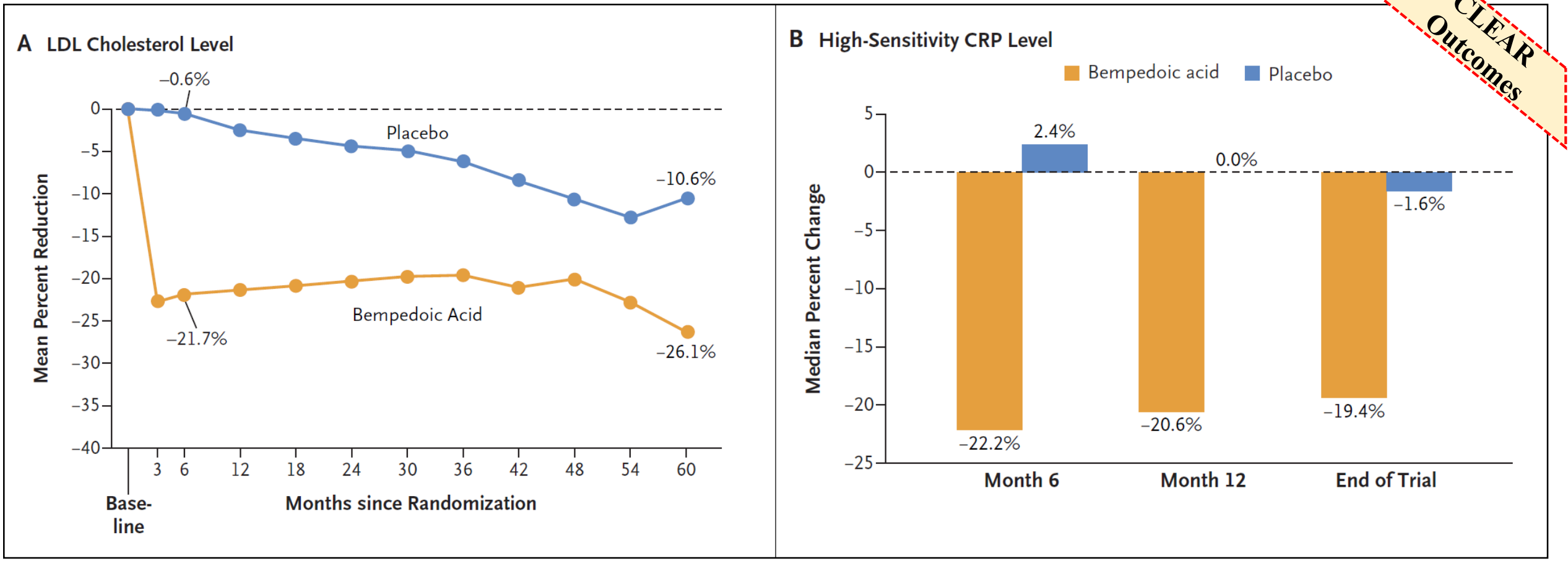
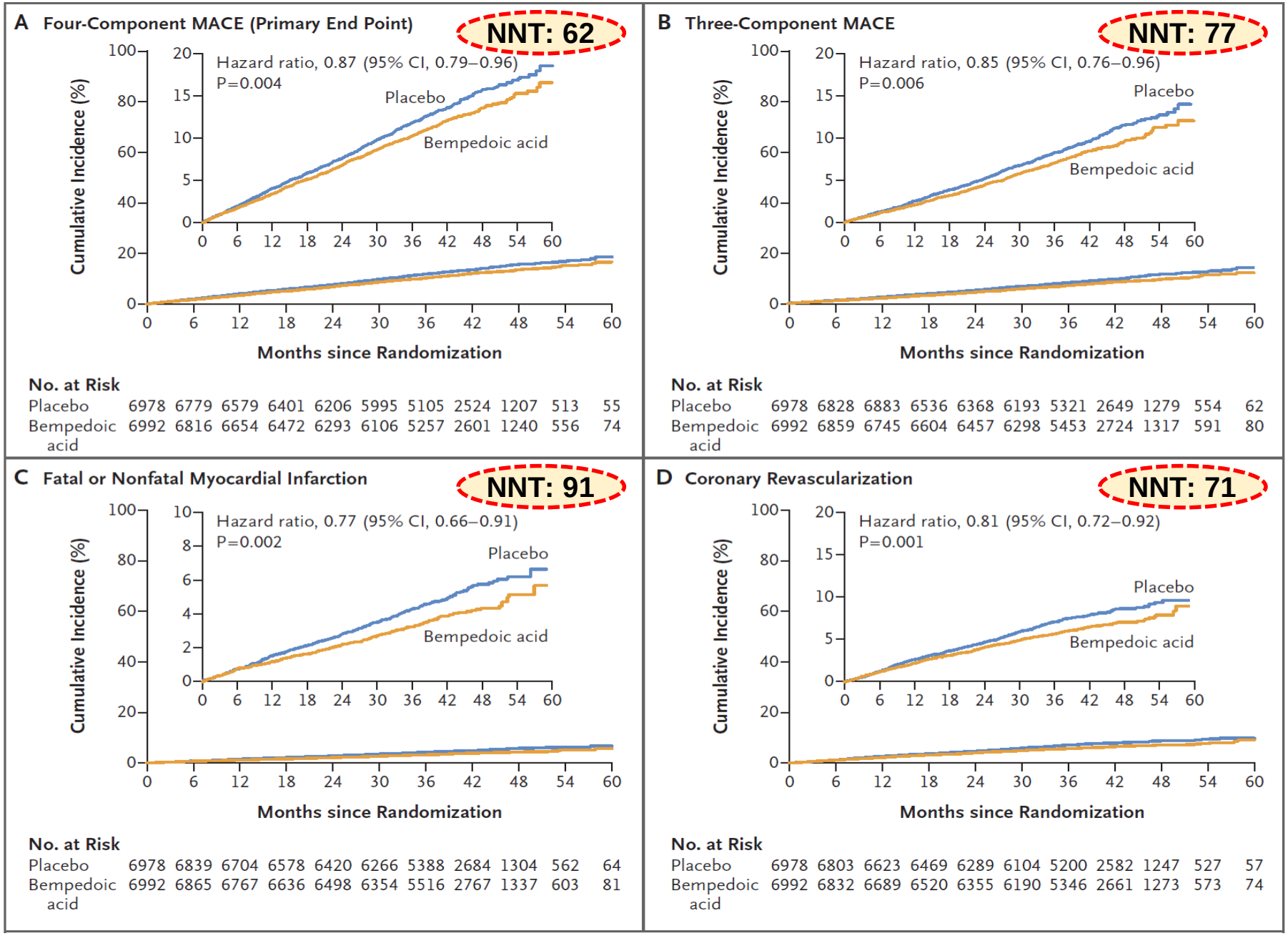


Figure 1. Changes in LDL Cholesterol and High-Sensitivity CRP Levels over Time.

Panel A shows the percent changes from baseline in the low-density lipoprotein (LDL) cholesterol level in the bempedoic acid group and placebo group throughout the trial. The mean baseline LDL cholesterol level in both groups was 139.0 mg per deciliter.

The time-averaged difference in the reduction in LDL cholesterol level between the bempedoic acid group and the placebo group over the duration of the trial was −22.0 mg per deciliter; the difference in percent reduction was 15.9 percentage points in favor of bempedoic acid.

Panel B shows the changes from baseline in the high-sensitivity C-reactive protein (CRP) level in the bempedoic acid group and placebo group at several time points during the trial. The median baseline high-sensitivity CRP was 2.3 mg per liter.



CLEAR Outcomes

Figure 2. Cumulative Incidence of Cardiovascular Events.

Panel A shows the cumulative incidence of a primary end-point event, a four-component composite of major adverse cardiovascular events (MACE), defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization.

Panel B shows the cumulative incidence of a three-component MACE, defined as death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (the first key secondary end point).

The results for the other key secondary end points (fatal or nonfatal stroke, death from cardiovascular causes, and death from any cause) did not differ significantly between the bempedoic acid group and the placebo group.

Adverse Events

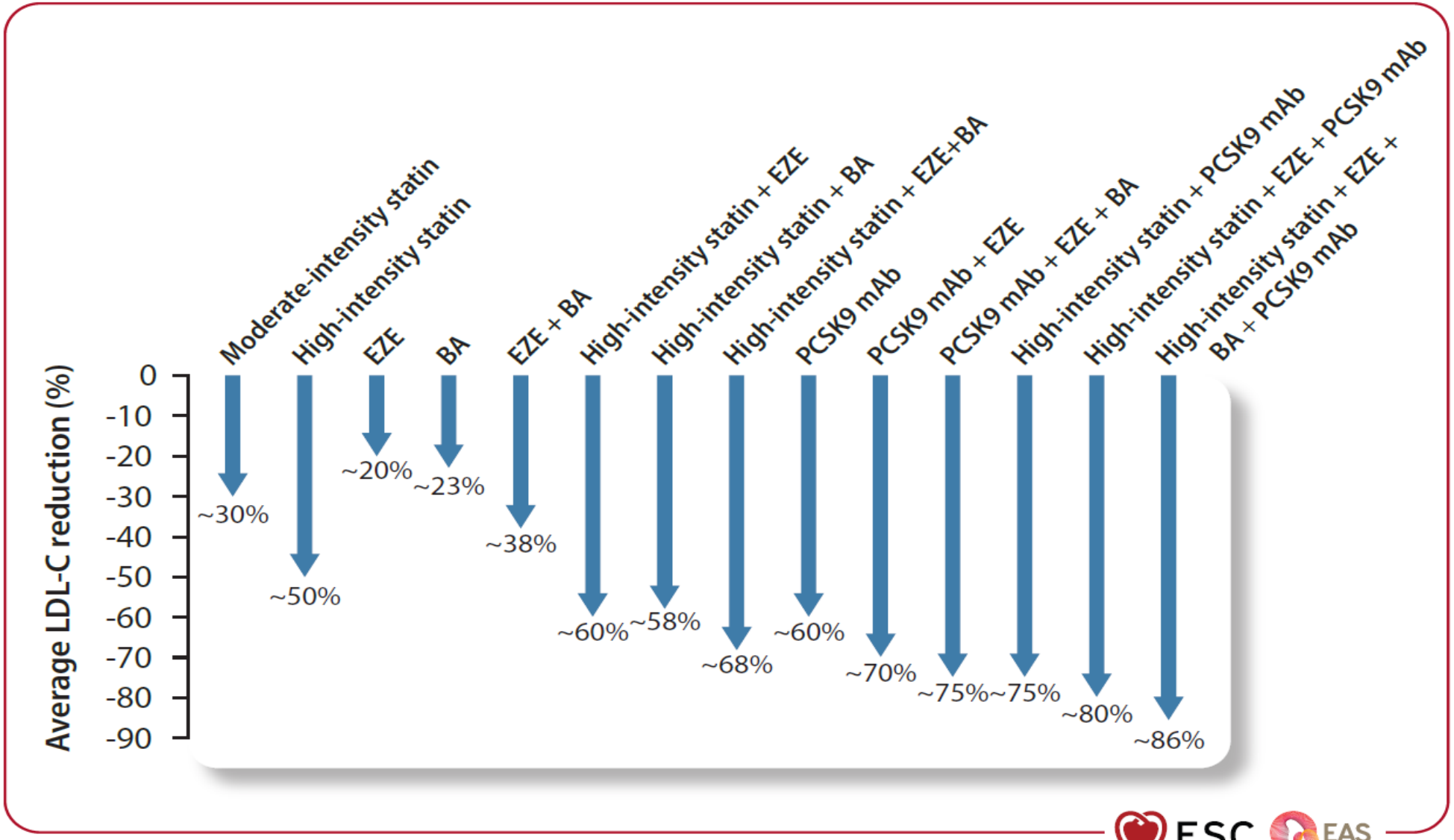
CLEAR Outcomes

- The overall incidences of adverse events, serious adverse events, and adverse events leading to discontinuation of the trial regimen did not differ meaningfully between the bempedoic acid group and the placebo group.
- Elevations in the hepatic enzyme level (4.5% in the bempedoic acid group vs. 3.0% in the placebo group), renal events (11.5% in the bempedoic acid group vs. 8.6% in the placebo group). Myalgias were reported in 5.6% of the patients in the bempedoic acid group and in 6.8% of those in the placebo group.
- Elevations in liver aminotransferase levels of more than three times the upper limit of the normal range occurred more frequently in the bempedoic acid group than in the placebo group, and the mean changes from baseline in the creatinine and uric acid levels were greater in the bempedoic acid group.
- The incidence of hyperuricemia was higher in the bempedoic acid group than in the placebo group (10.9% vs. 5.6%), as were the incidences of gout (3.1% vs. 2.1%) and cholelithiasis (2.2% vs. 1.2%).

ADA 2025

10.25 In people with diabetes with or without ASCVD intolerant to statin therapy, treatment with bempedoic acid is recommended to reduce cardiovascular event rates as an alternative cholesterol-lowering plan. A

Average reduction in low-density lipoprotein cholesterol levels with different pharmacological therapies with proven cardiovascular benefits.



Recommendations for pharmacological low-density lipoprotein cholesterol lowering

Recommendations	Class	Level
Non-statin therapies with proven cardiovascular benefit,[c] ([c]Ezetimibe, PCSK9 monoclonal antibodies, bempedoic acid) taken alone or in combination, are recommended for patients who are unable to take statin therapy to lower LDL-C levels and reduce the risk of CV events. The choice should be based on the magnitude of additional LDL-C lowering needed	I	A
Bempedoic acid is recommended in patients who are unable to take statin therapy to achieve the LDL-C goal.	I	B

Recommendations	Class	Level
The addition of bempedoic acid to the maximally tolerated dose of statin with or without ezetimibe should be considered in patients at high or very high risk in order to achieve the LDL-C goal.	IIa	C
Evinacumab should be considered in patients with homozygous familial hypercholesterolaemia aged 5 years or older who are not at LDL-C goal despite receiving maximum doses of lipid-lowering therapy to lower LDL-C levels	IIa	B

Combination Therapy of Statins with Fibrate

ADA 2025

10.30 For individuals with fasting triglyceride levels ≥ 500mg/dL, evaluate for secondary causes of hypertriglyceridemia and consider medical therapy to reduce the risk of pancreatitis. C

10.31 In adults with hypertriglyceridemia (fasting triglycerides >150 mg/ dL or non fasting triglycerides >175 mg/dL), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes, chronic liver or kidney disease and/or nephrotic syndrome, and hypothyroidism), and medications that raise triglycerides. C

Published in final edited form as:
N Engl J Med. 2010 April 29; 362(17): 1563–1574. doi:10.1056/NEJMoa1001282.

Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus

The ACCORD Study Group*

- Randomized, placebo-controlled, double-blind clinical trial conducted in 77 clinical sites in the U.S. and Canada
- Sample size: 5518 patients with type 2 diabetes
- Mean follow-up : 4.7 years.

Primary outcome

Primary Outcome:	Fenofibrate (N=2765)		Placebo (N=2753)			
	N of Events	Rate (%/yr)	N of Events	Rate (%/yr)	HR (95% CI)	P Value
Major Fatal or Nonfatal Cardiovascular Event	291	2.24	310	2.41	0.92 (0.79 - 1.08)	0.32

ACCORD Lipid trial does not support use of the combination of fenofibrate and simvastatin, compared to simvastatin alone, to reduce CVD events in the majority of patients with T2DM who are at high risk for CVD.

Post – hoc analysis

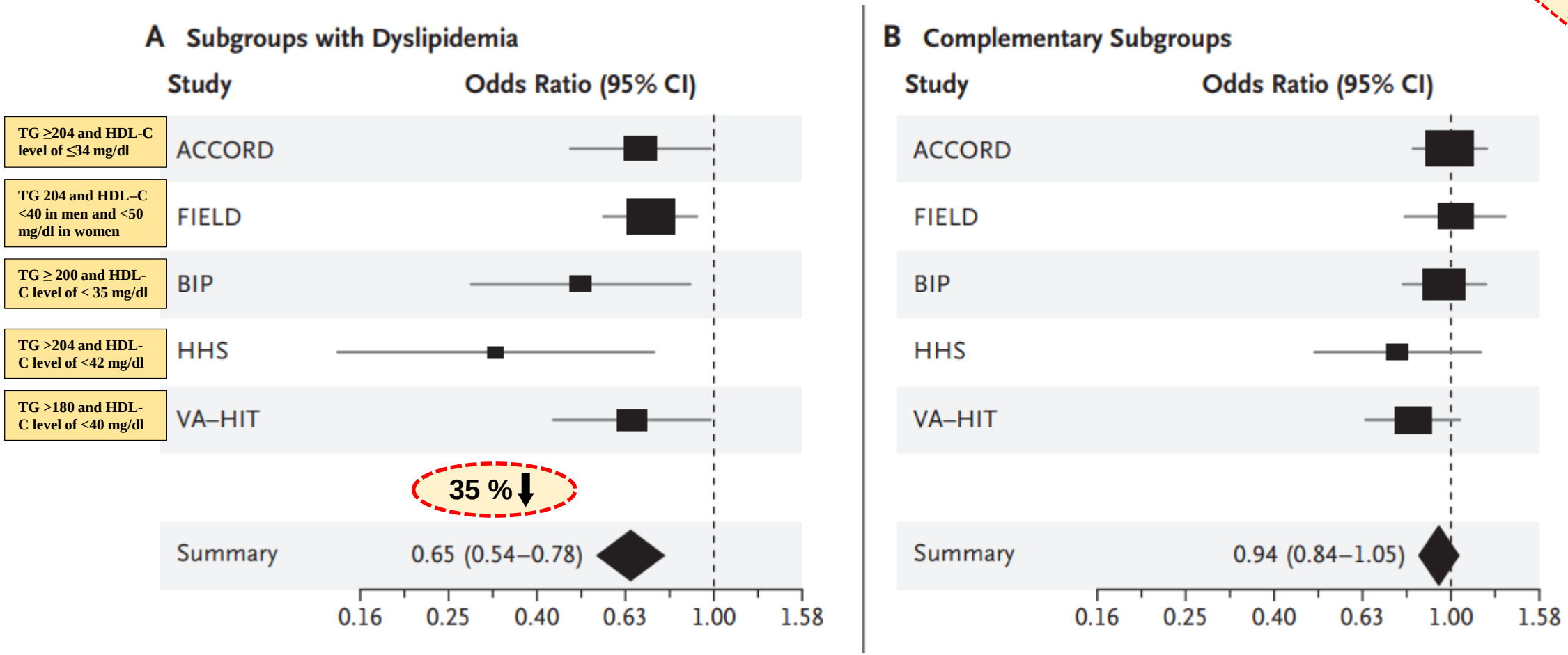


Figure 1. Forest Plot of the Treatment Effect in Subgroups. Data from a meta-analysis of randomized trials of fibrate drugs are shown; an odds ratio of less than unity indicates a beneficial therapeutic effect. Panel A shows data from subgroups of patients with dyslipidemia (i.e., high levels of triglycerides and low levels of high-density lipoprotein [HDL] cholesterol), and Panel B shows data from the complementary subgroups without this type of dyslipidemia. The subgroup with dyslipidemia defined according to criteria prespecified in the ACCORD Lipid trial (a triglyceride level of ≥204 mg per deciliter and an HDL cholesterol level of ≤34 mg per deciliter) and the subgroup with levels closest to these lipid criteria in each of the other trials were used. Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. Bezafibrate Infarction Prevention (BIP) study, Helsinki Heart Study (HHS). Veterans Affairs HDL Intervention Trial (VA-HIT).

The outcome defined for the subgroup analysis in each trial was used. The subgroups with dyslipidemia in all five studies included a total of 2428 study participants and 302 events among the patients who received fibrate therapy and 2298 study participants and 408 events among those who received placebo. A random-effects meta-analysis5 was used. The area of the rectangles is proportional to the precision of the study-specific estimated effect. The horizontal lines indicate the 95% confidence intervals for study-specific odds ratios. The diamonds represent the summary odds ratios, with the width indicating the 95% confidence interval.

ADA 2025

Treatment of Other Lipoprotein Fractions or Goals

- **10.30** secondary causes of hypertriglyceridemia and consider medical therapy to reduce the risk of pancreatitis. C
- **10.31** In adults with hypertriglyceridemia (fasting triglycerides >150 mg/dL [>1.7 mmol/L] or nonfasting triglycerides >175 mg/dL [>2.0 mmol/L]), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes, chronic liver or kidney disease and/or nephrotic syndrome, and hypothyroidism), and medications that raise triglycerides. C

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 24, 2022 VOL. 387 NO. 21

PROMINENT

Triglyceride Lowering with Pemafibrate to Reduce Cardiovascular Risk

A. Das Pradhan, R.J. Glynn, J.-C. Fruchart, J.G. MacFadyen, E.S. Zaharris, B.M. Everett, S.E. Campbell, R. Oshima,

ABSTRACT

BACKGROUND

High triglyceride levels are associated with increased cardiovascular risk, but whether reductions in these levels would lower the incidence of cardiovascular events is uncertain. Pemafibrate, a selective peroxisome proliferator–activated receptor α modulator, reduces triglyceride levels and improves other lipid levels.

METHODS

In a multinational, double-blind, randomized, controlled trial, we assigned patients with type 2 diabetes, mild-to-moderate hypertriglyceridemia (triglyceride level, 200 to 499 mg per deciliter), and high-density lipoprotein (HDL) cholesterol levels of 40 mg per deciliter or lower to receive pemafibrate (0.2-mg tablets twice daily) or matching placebo. Eligible patients were receiving guideline-directed lipid-lowering therapy or could not receive statin therapy without adverse effects and had low-density lipoprotein (LDL) cholesterol levels of 100 mg per deciliter or lower. The primary efficacy end point was a composite of nonfatal myocardial infarction, ischemic stroke, coronary revascularization, or death from cardiovascular causes.

RESULTS

Among 10,497 patients (66.9% with previous cardiovascular disease), the median baseline fasting triglyceride level was 271 mg per deciliter, HDL cholesterol level 33 mg per deciliter, and LDL cholesterol level 78 mg per deciliter. The median follow-up was 3.4 years. As compared with placebo, the effects of pemafibrate on lipid levels at 4 months were –26.2% for triglycerides, –25.8% for very-low-density lipoprotein (VLDL) cholesterol, –25.6% for remnant cholesterol (cholesterol transported in triglyceride-rich lipoproteins after lipolysis and lipoprotein remodeling), –27.6% for apolipoprotein C-III, and 4.8% for apolipoprotein B. A primary endpoint event occurred in 572 patients in the pemafibrate group and in 560 of those in the placebo group (hazard ratio, 1.03; 95% confidence interval, 0.91 to 1.15), with no apparent effect modification in any prespecified subgroup. The overall incidence of serious adverse events did not differ significantly between the groups, but pemafibrate was associated with a higher incidence of adverse renal events and venous thromboembolism and a lower incidence of nonalcoholic fatty liver disease.

CONCLUSIONS

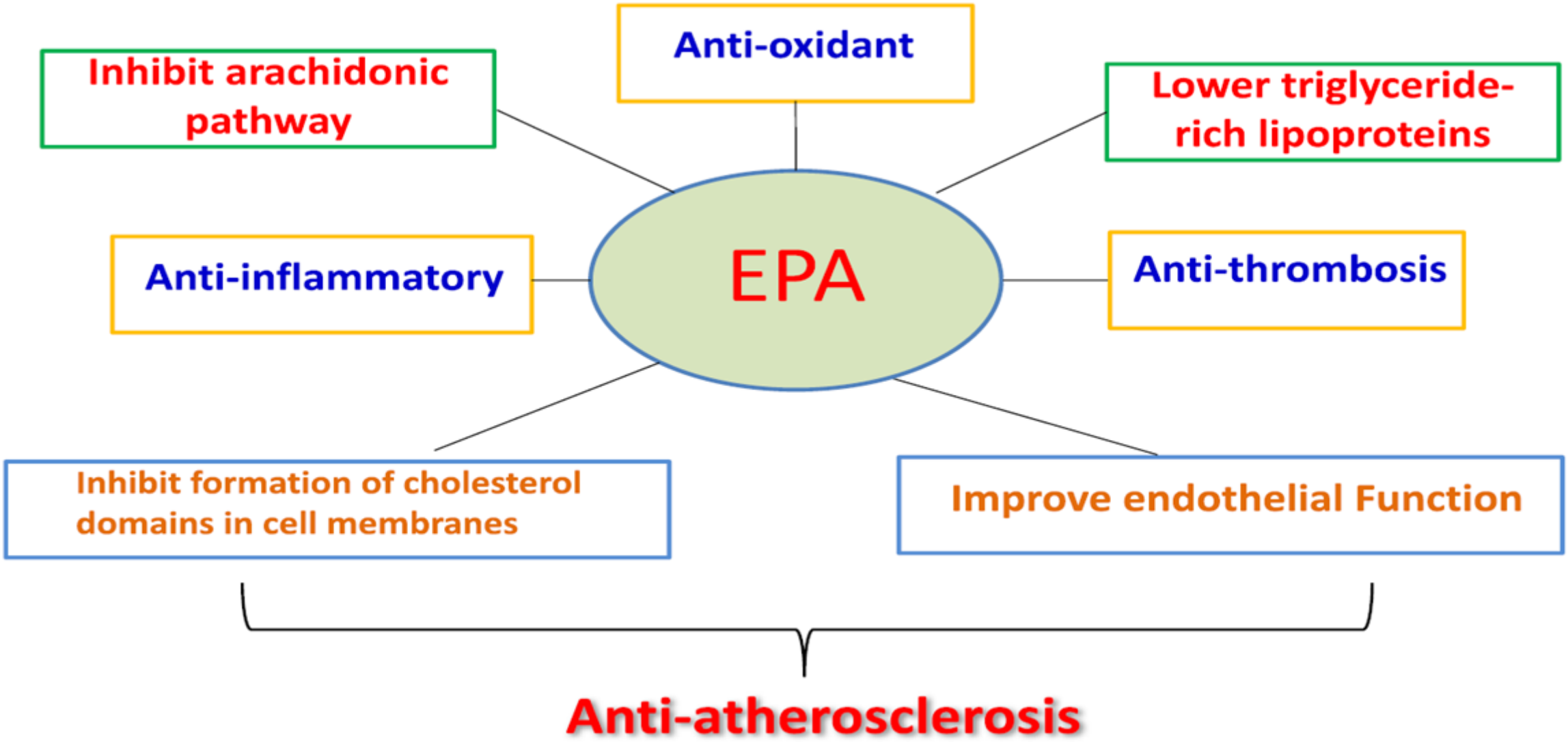
Among patients with type 2 diabetes, mild-to-moderate hypertriglyceridemia, and low HDL and LDL cholesterol levels, the incidence of cardiovascular events was not lower among those who received pemafibrate than among those who received placebo, although pemafibrate lowered triglyceride, VLDL cholesterol, remnant cholesterol, and apolipoprotein C-III levels. (Funded by the Kowa Research Institute; PROMINENT ClinicalTrials.gov number, NCT03071692.)

ADA 2025

10.33 Statin plus fibrate combination therapy has not been shown to improve ASCVD outcomes and is generally not recommended. A

Combination Therapy of Statins with OM3FA

Figure 3 Multipotential actions of Eicosapentaenoic Acid (EPA)



REDUCE-IT

The NEW ENGLAND JOURNAL of MEDICINE
2019 Jan 3;380(1):11-22

ORIGINAL ARTICLE

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D.,

BACKGROUND

Patients with elevated triglyceride levels are at increased risk for ischemic events. Icosapent ethyl, a highly purified eicosapentaenoic acid ethyl ester, lowers triglyceride levels, but data are needed to determine its effects on ischemic events.

METHODS

We performed a multicenter, randomized, double-blind, placebo-controlled trial involving patients with established CVD or with diabetes (aged ≥50 y) and other risk factors, who had been receiving statin therapy and who had a fasting triglyceride level of 135 to 499 mg per deciliter and a LDL-C level of 41 to 100 mg per deciliter .The patients were randomly assigned to receive 2 g of icosapent ethyl twice daily (total daily dose, 4 g) or placebo (contains mineral oil). The primary end point was a composite of CV-death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina. The key secondary end point was a composite of CV- death, nonfatal MI, or nonfatal stroke.

RESULTS

A total of 8179 patients were enrolled (70.7% for secondary prevention of CVD) and were followed for a median of 4.9 years. A primary end-point event occurred in 17.2% of the patients in the icosapent ethyl group, as compared with 22.0% of the patients in the placebo group

NNT = 20 for median of 4.9 years

NNT = 28 for median of 4.9 years

REDUCE-IT

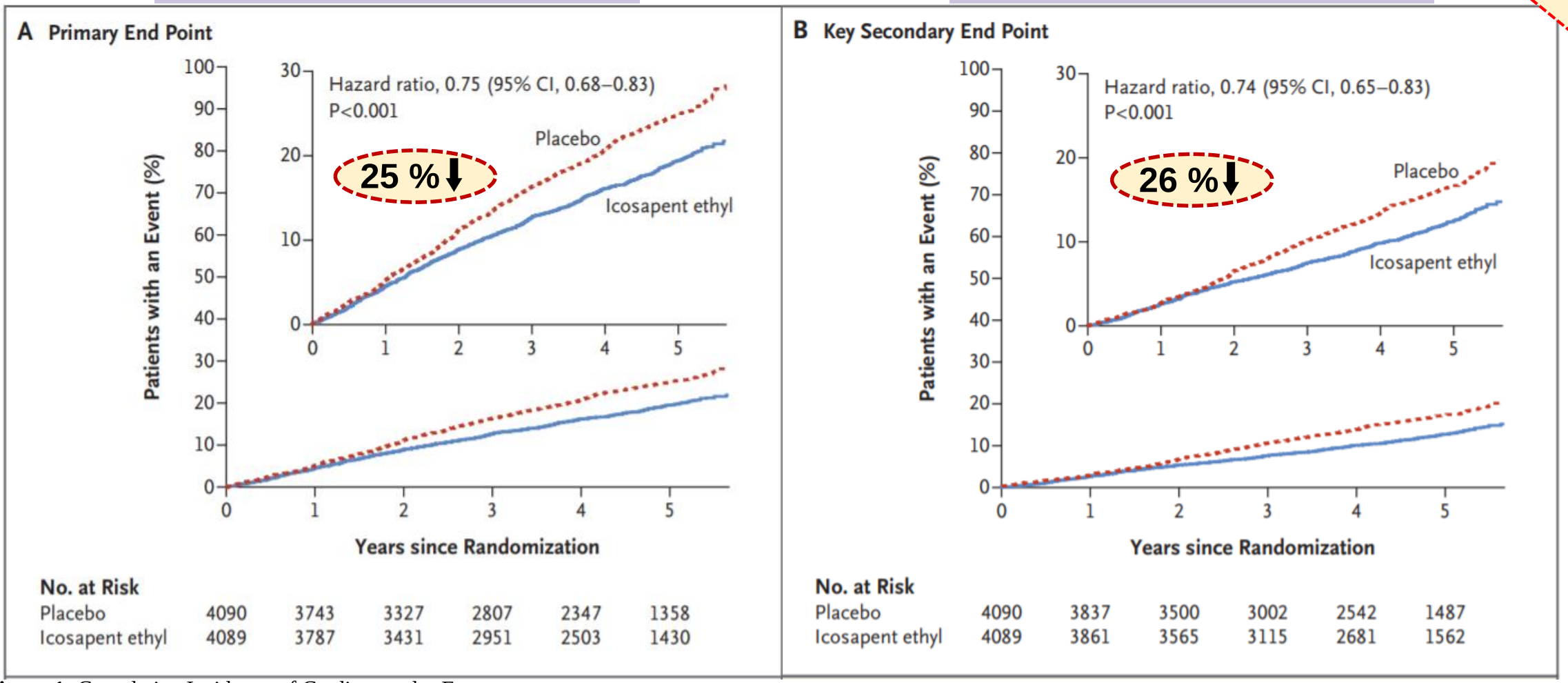
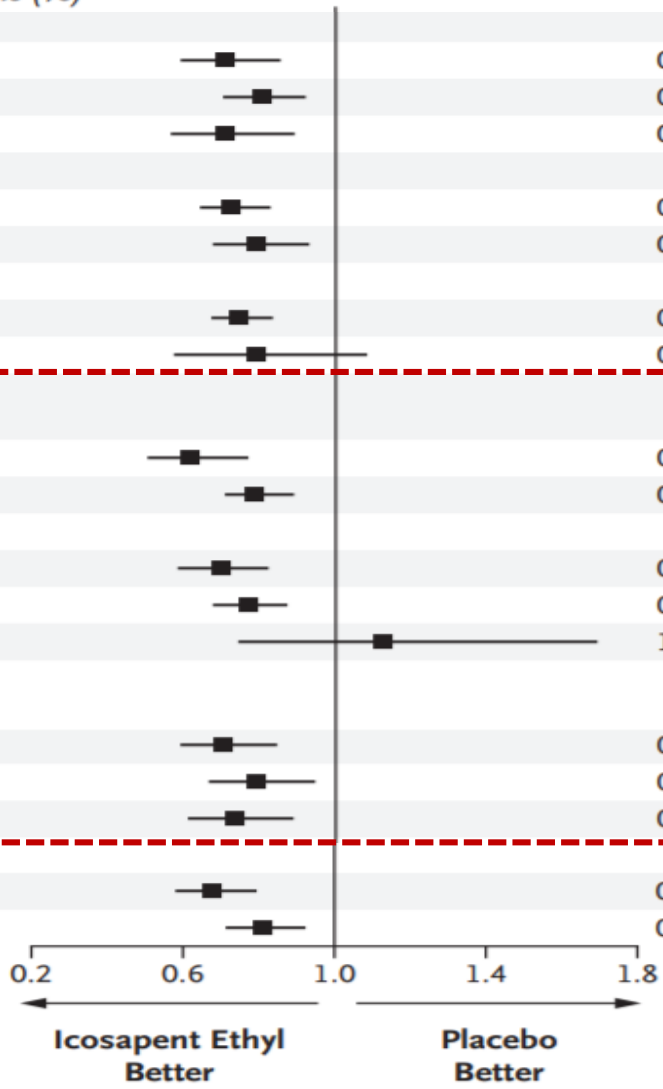


Figure 1: Cumulative Incidence of Cardiovascular Events.

Panel A shows the Kaplan–Meier event curves for the primary efficacy composite end point of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina in the icosapent ethyl group and the placebo group, in a time-to-event analysis. Panel B shows the Kaplan Meier event curves for the key secondary efficacy composite end point of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in the two trial groups, in a time-to-event analysis. In each panel, the inset shows the same data on an expanded y axis. The curves were visually truncated at 5.7 years because a limited number of events occurred beyond that time point; all patient data were included in the analyses.

REDUCE-IT

Subgroup	Icosapent Ethyl	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients with event/total no. of patients (%)			
Baseline estimated GFR				0.41
<60 ml/min/1.73 m²	197/905 (21.8)	263/911 (28.9)	0.71 (0.59–0.85)	
≥60 to <90 ml/min/1.73 m²	380/2217 (17.1)	468/2238 (20.9)	0.80 (0.70–0.92)	
≥90 ml/min/1.73 m²	128/963 (13.3)	170/939 (18.1)	0.70 (0.56–0.89)	
Baseline triglycerides				0.45
≥200 mg/dl	430/2481 (17.3)	559/2469 (22.6)	0.73 (0.64–0.83)	
<200 mg/dl	275/1605 (17.1)	342/1620 (21.1)	0.79 (0.67–0.93)	
Baseline triglycerides				0.83
≥150 mg/dl	640/3674 (17.4)	811/3660 (22.2)	0.75 (0.68–0.83)	
<150 mg/dl	65/412 (15.8)	90/429 (21.0)	0.79 (0.57–1.09)	
Baseline triglycerides ≥200 mg/dl and HDL cholesterol ≤35 mg/dl				0.04
Yes	149/823 (18.1)	214/794 (27.0)	0.62 (0.51–0.77)	
No	554/3258 (17.0)	687/3293 (20.9)	0.79 (0.71–0.88)	
Baseline statin intensity				0.12
High	232/1290 (18.0)	310/1226 (25.3)	0.69 (0.58–0.82)	
Moderate	424/2533 (16.7)	543/2575 (21.1)	0.76 (0.67–0.86)	
Low	48/254 (18.9)	45/267 (16.9)	1.12 (0.74–1.69)	
Baseline LDL cholesterol (derived) in thirds				0.62
≤67 mg/dl	244/1481 (16.5)	302/1386 (21.8)	0.72 (0.61–0.85)	
>67 to ≤84 mg/dl	248/1347 (18.4)	307/1364 (22.5)	0.81 (0.68–0.96)	
>84 mg/dl	213/1258 (16.9)	292/1339 (21.8)	0.74 (0.62–0.89)	
Baseline high-sensitivity CRP				0.07
≤2 mg/liter	288/1919 (15.0)	407/1942 (21.0)	0.68 (0.58–0.79)	
>2 mg/liter	417/2167 (19.2)	494/2147 (23.0)	0.81 (0.71–0.93)	



The primary efficacy composite end point of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina, as assessed in a time-to-event analysis.

- ✓ Among patients with elevated triglyceride levels despite the use of statins, the risk of ischemic events, including CV-death, was significantly lower among those who received 2 g of icosapent ethyl twice daily than among those who received placebo. (Funded by Amarin Pharma; REDUCE-IT ClinicalTrials.gov number, NCT01492361)

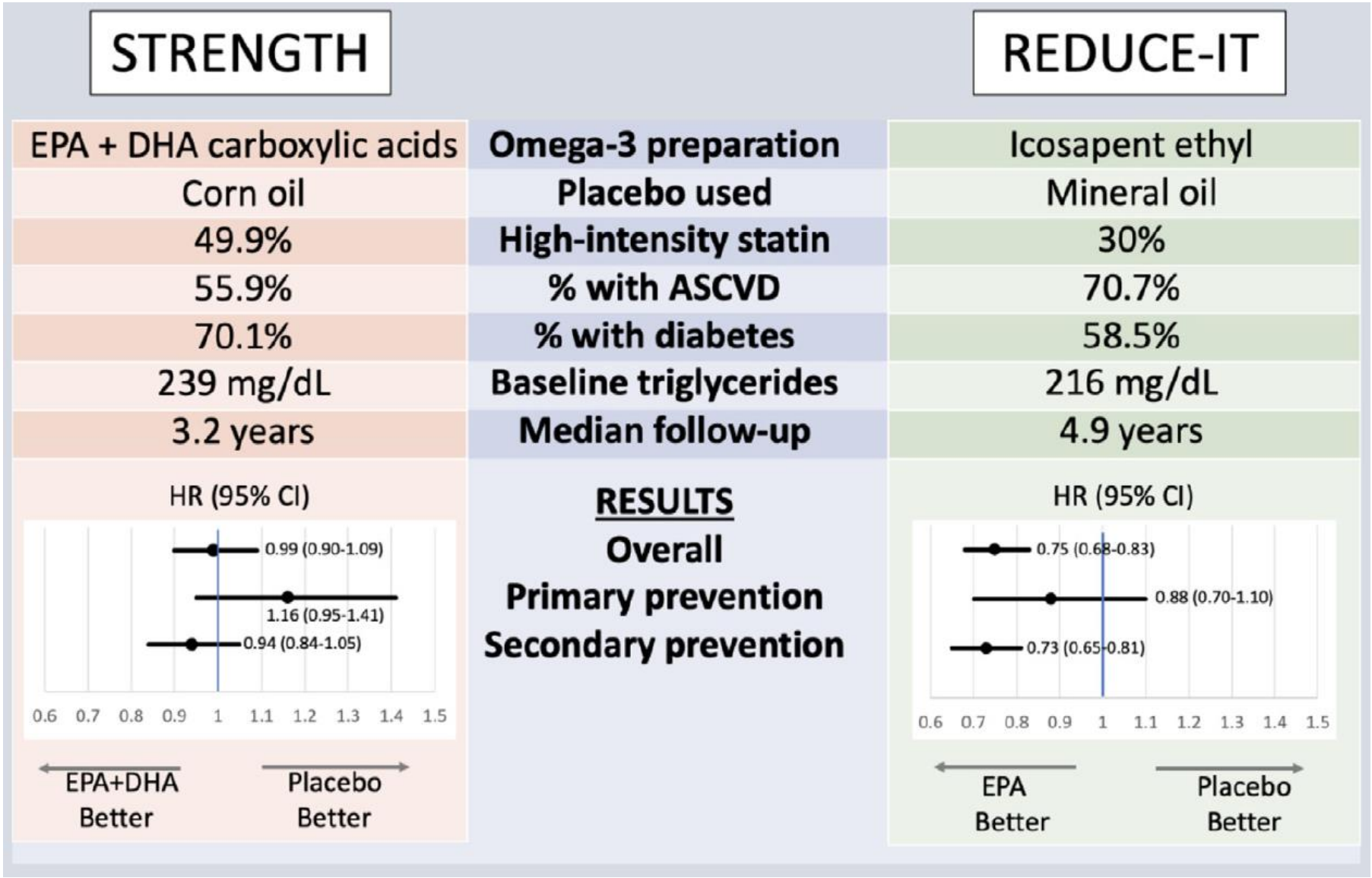


Fig. 1
Differences between the STRENGTH and REDUCE-IT trial in terms of design, patient characteristics and key results. Hazard ratios and 95% confidence intervals shown refer to the primary composite endpoint for each trial, comprising the composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and coronary revascularization or unstable angina requiring hospitalization. Results of subgroup analyses by primary and secondary prevention strata are also shown.

Recommendation Table 5

Recommendations for drug treatment of patients with hypertriglyceridaemia

ESC 2025

Recommendations	Class	Level
High-dose icosapent ethyl (2 × 2 g/day) should be considered in combination with a statin in high-risk or very high-risk patients with elevated triglyceride levels (fasting triglyceride level 135–499 mg/dL) to reduce the risk of cardiovascular events.	**IIa**	**B**

ADA 2025

10.32 In individuals with ASCVD or other cardiovascular risk factors on a statin with managed LDL cholesterol but elevated triglycerides (150–499 mg/dL [1.7–5.6 mmol/L]), the addition of icosapent ethyl can be considered to reduce cardiovascular risk. B

Summary

ADA 2025

Lipid Management Lifestyle Intervention Recommandation

- **10.15** Lifestyle modification focusing on weight loss (if indicated); application of a Mediterranean or Dietary Approaches to Stop Hypertension (DASH) eating pattern; reduction of saturated fat and trans fat; increase of dietary n-3 fatty acids, viscous fiber, and plant stanols/sterols intake; and increased physical activity should be recommended to improve the lipid profile and reduce the risk of developing atherosclerotic cardiovascular disease in people with diabetes. A

- **10.16** Intensify lifestyle therapy and optimize glycemic control for patients with elevated triglyceride levels (≥150 mg/dL) and/or low HDL cholesterol (<40 mg/dL for men, <50 mg/dL for women). C

- **10.17** Obtain a lipid profile at initiation of statins or other lipid-lowering therapy, 4–12 weeks after initiation or a change in dose, and annually thereafter, as it facilitates monitoring the response to therapy and informs medication-taking behavior. A

2.2. Measurements of LDL-C and Non–HDL-C

Recommendations for Measurements of LDL-C and Non–HDL-C Referenced studies that support recommendations are summarized in Online Data Supplement 1.		
COR	**LOE**	**Recommendations**
I	B-NR	1. In adults who are 20 years of age or older and not on lipid-lowering therapy, measurement of either a fasting or a nonfasting plasma lipid profile is effective in estimating ASCVD risk and documenting baseline LDL-C (S2.2-1–S2.2-6).
I	B-NR	2. In adults who are 20 years of age or older and in whom an initial nonfasting lipid profile reveals a triglycerides level of 400 mg/dL (≥4.5 mmol/L) or higher, a repeat lipid profile in the fasting state should be performed for assessment of fasting triglyceride levels and baseline LDL-C (S2.2-1–S2.2-4).
IIa	C-LD	3. For patients with an LDL-C level less than 70 mg/dL (<1.8 mmol/L), measurement of direct LDL-C or modified LDL-C estimate is reasonable to improve accuracy over the Friedewald formula (S2.2-7–S2.2-9).
IIa	C-LD	4. In adults who are 20 years of age or older and without a personal history of ASCVD but with a family history of premature ASCVD or genetic hyperlipidemia, measurement of a fasting plasma lipid profile is reasonable as part of an initial evaluation to aid in the understanding and identification of familial lipid disorders.

Table 13 Summary of recommendations for monitoring lipids and enzymes in patients, before and on lipid-lowering therapy

Testing lipids
How often should lipids be tested?
• Before starting lipid-lowering drug treatment, at least two measurements should be made, with an interval of 1–12 weeks, with the exception of conditions where prompt drug treatment is suggested, such as ACS and very high-risk patients.
How often should a patient's lipids be tested after starting lipid-lowering treatment?
• After starting treatment: 8 (±4) weeks. • After adjustment of treatment: 8 (±4) weeks until the goal is achieved.
How often should lipids be tested once a patient has achieved the target or optimal lipid level?
• Annually (unless there are adherence problems or other specific reasons for more frequent reviews).
Monitoring liver and muscle enzymes
How often should liver enzymes (ALT) be routinely measured in patients on lipid-lowering drugs?
• Before treatment. • Once, 8–12 weeks after starting a drug treatment or after dose increase. • Routine control of ALT thereafter is not recommended during statin treatment, unless symptoms suggesting liver disease evolve. During treatment with fibrates, control of ALT is still recommended.

Return to Case

Case Presentation

A 56-year-old man with a five-year history of T2DM is referred for further management His hypertension was diagnosed 4 years ago. He has history of primary PCI following MI, 3 years earlier. He quit smoking following cardiac surgery. There is no evidence of retinopathy.

✓ **At present on P/E:**

- Weight: 98 Kg,
- Height: 175,
- BMI: 32 kg/m^2, WC: 95 cm
- BP: 140/90 mmHg,

(confirmed by home BP monitoring)

- HR: 94/min,
- Ankle brachial ratio: 0.8

✓ **Lab exam:**

- HbA1c: 7.5%,
- eGFR: 55ml/min per 1.73 m^2,
- Total Chol: 154 mg/dL,
- HDL: 38 mg/dL,
- TG: 250 mg/dL,
- LDL: 66 mg/dL,
- K: 4.0 meq/l,
- ACR: 80 mg/gr,
- CRP:3 mg/L
- Platelet: 350 ×10^3 µl,
- AST:35 units/L,
- ALT: 56 units/L

✓ **Patient medication:**

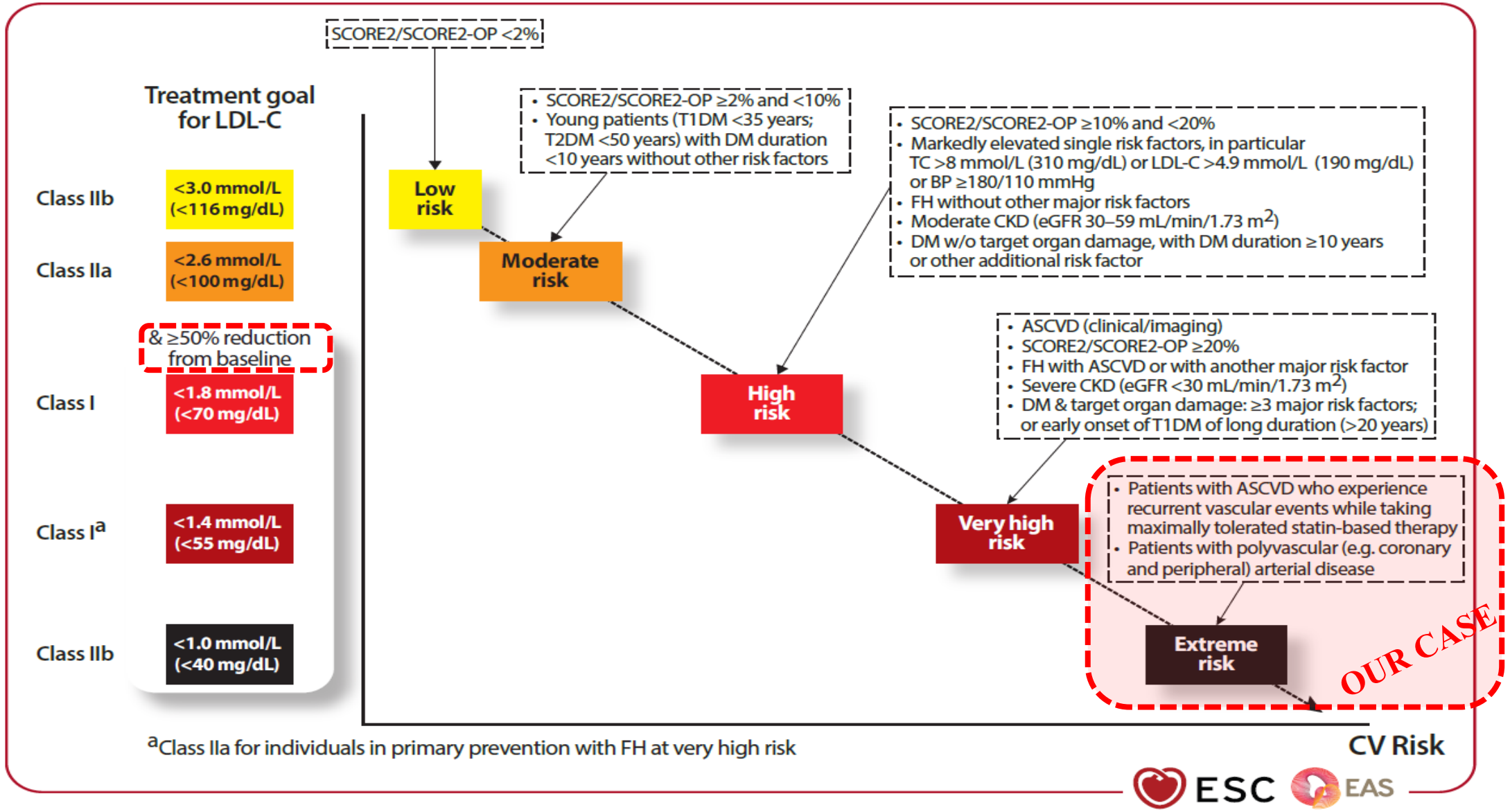
- Metformin: 2000 mg/daily,
- Atorvastatin: 20mg daily,
- Valsartan: 160 mg/daily,
- Carvedilol: 12.5 mg/daily,
- ASA: 80 mg/daily

✓ **Imaging:**

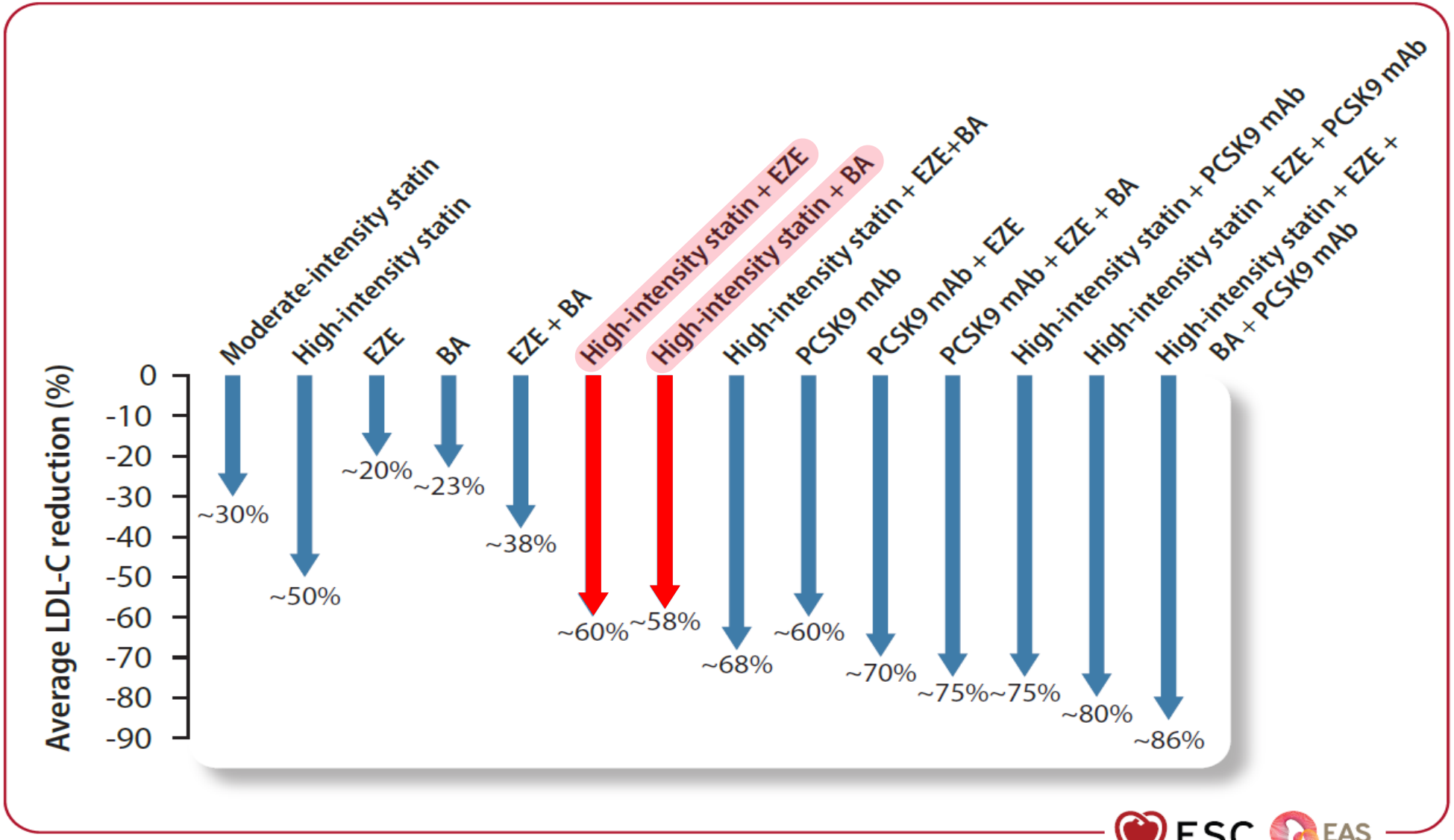
In his recent echocardiography,
LVH and EF=% 50 have been reported

The patient and his primary care physician are concerned about his residual risk of recurrent ASCVD events and his overall prognosis. What is your recommendation for the patient?

Treatment goals for low-density lipoprotein cholesterol across categories of total cardiovascular risk.



Average reduction in low-density lipoprotein cholesterol levels with different pharmacological therapies with proven cardiovascular benefits.



Lipid Approach:

1) Add Fenofibrate 100 mg/Day
2) Continue Atorvastatin 20 mg/Day
3) Lower LDL-C<55 mg/dL (and even < 40 mg/dL) with increasing dose of Atorvastatin to 40 mg/Day
4) Add Ezetimibe 10 mg/Day (combo high dose statin + Ezetimibe)
5) Add SGL2 inhibitor

Thanks for
your patience,
dear colleagues!