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BEST APPROACHES TO TREAT MI PATIENTS

BEST APPROACHES TO TREAT MI PATIENTS

CONTENT

Topic	Facilitator
STEMI management approaches	Prof. Pepe Zamorano
NSTEMI management approaches	Prof. François Mach
Panel Discussion / Audience Q & A	Prof. Gilles Montalescot

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INTRODUCING THE EXPERT PANEL

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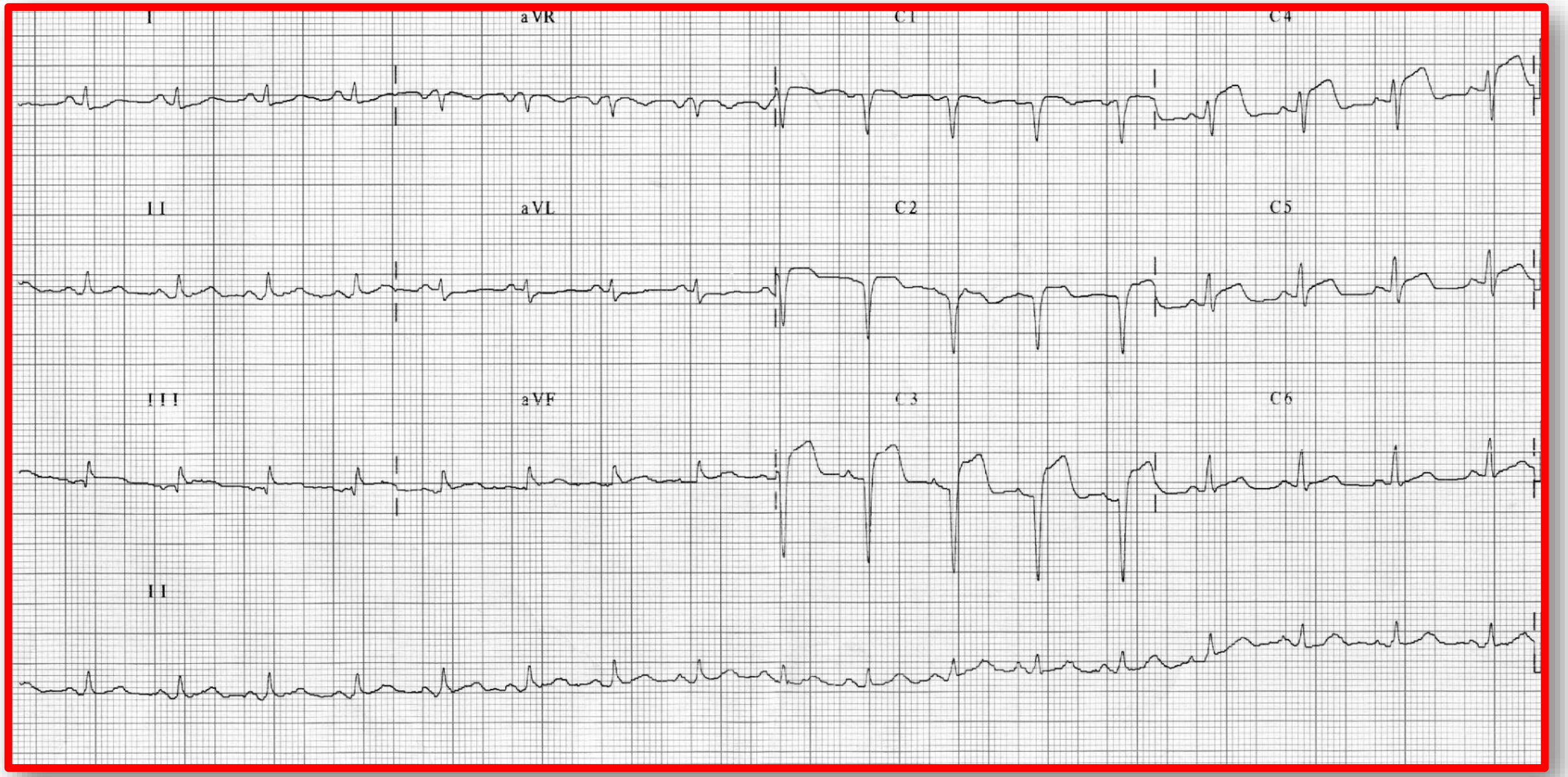
BEST APPROACHES TO TREAT MI PATIENTS. STEMI

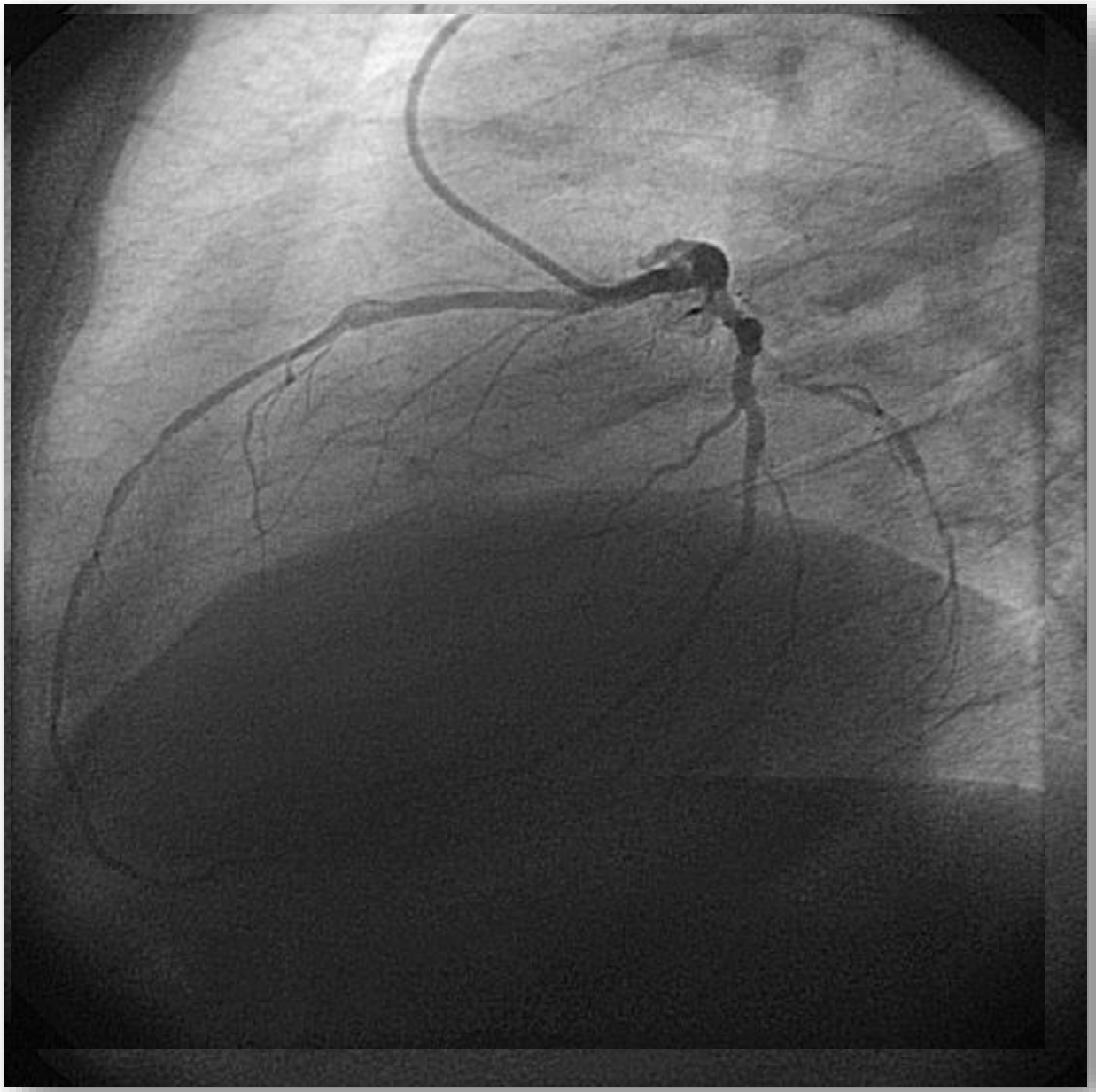
Prof. J Zamorano
Head of Cardiology
University Ramón y Cajal. Madrid

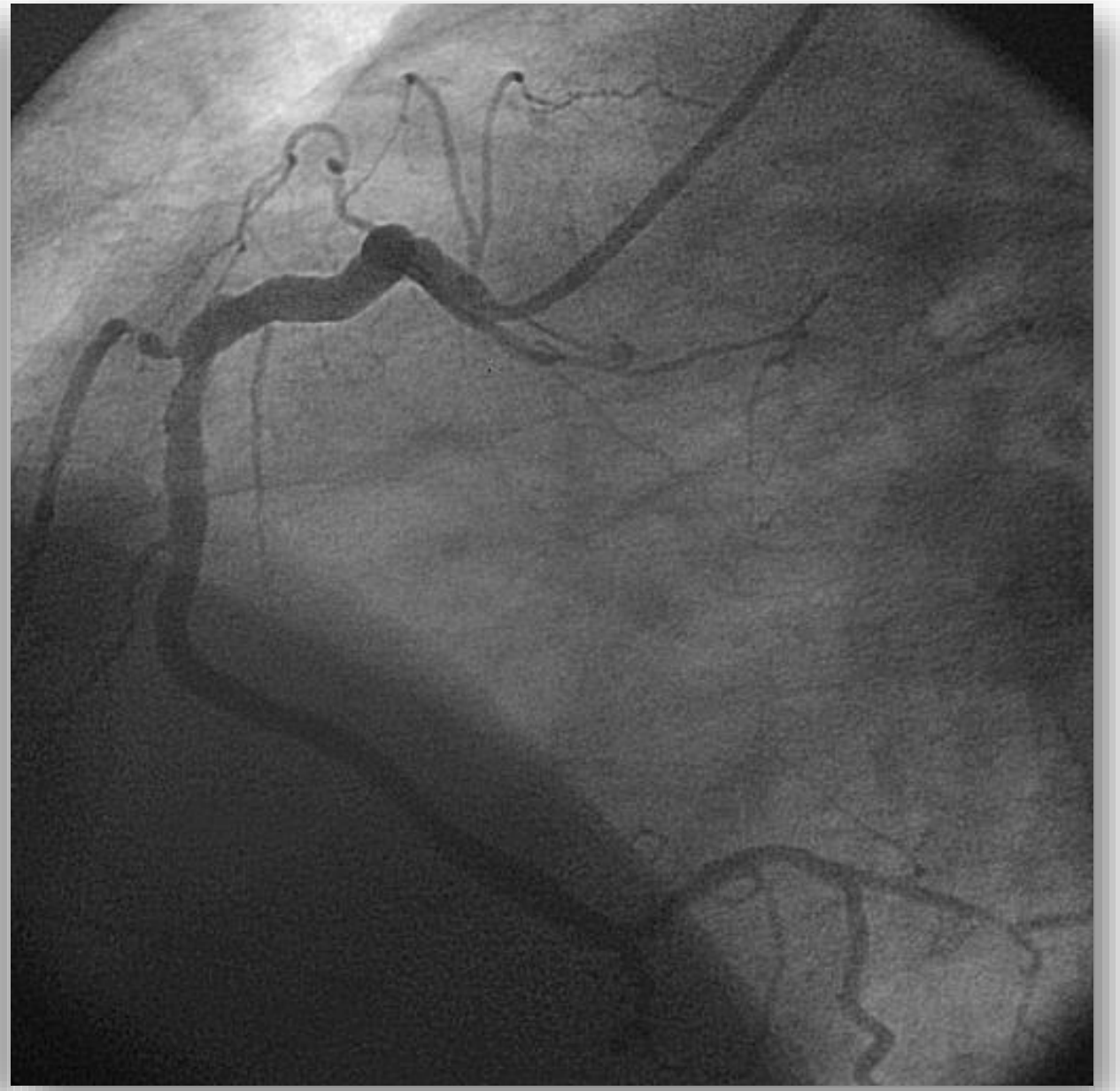
PATIENT RL

Smoker; age 62 years

- **Lawyer:**
  ‘I do not have time to exercise’
- No alcohol
- Hypertension → amlodipine/valsartan/ hydrochlorothiazide 10 mg/160 mg/25 mg
- **Admitted with acute chest pain**


I
aVR
C1
C4
II
aVL
C2
C5
III
aVF
C3
C6
II





Cx, circumflex artery; LAD, left anterior descending

PATIENT RL

Smoker; age 62 years

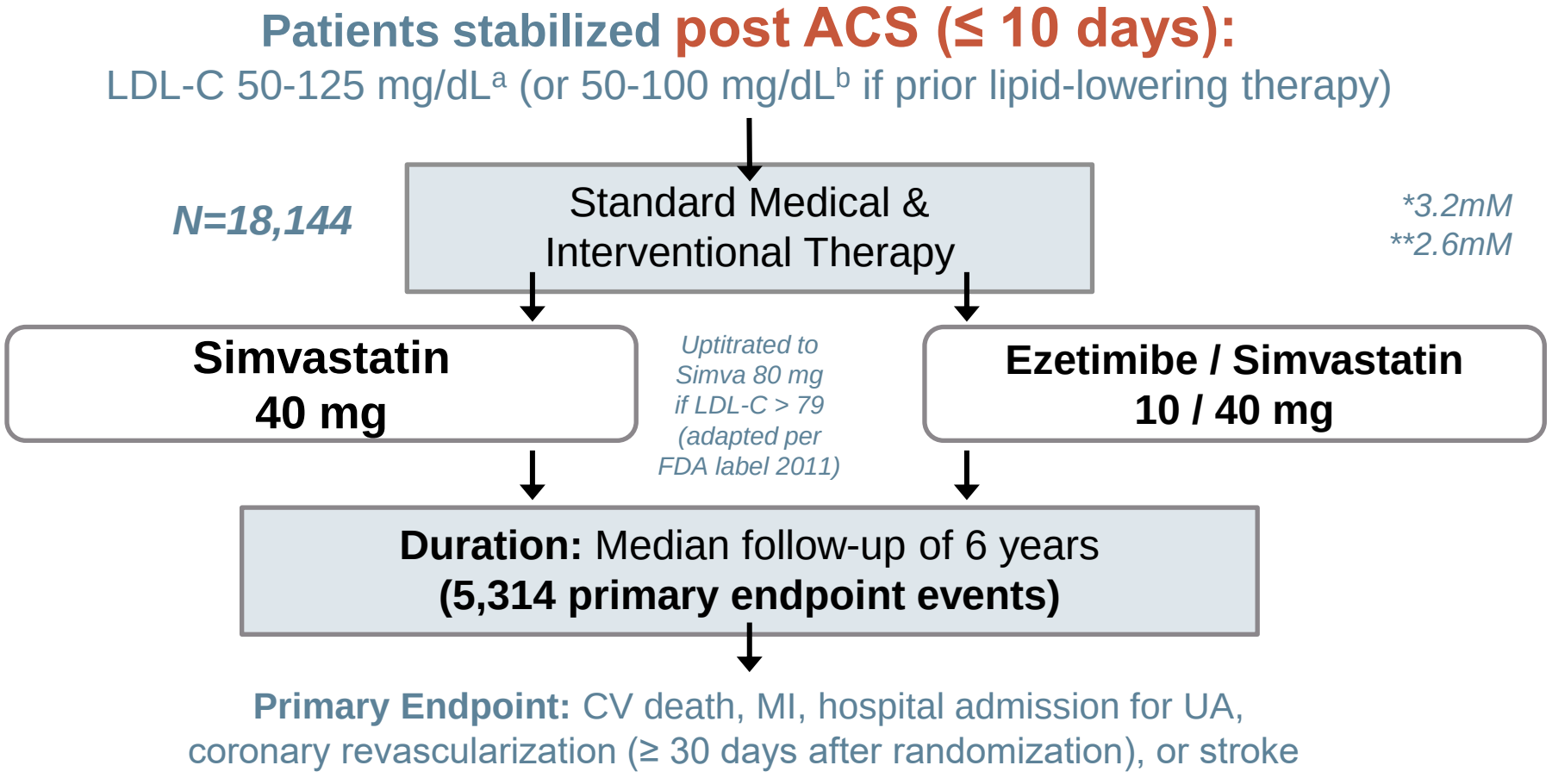
- **Lawyer:**
  'I do not have time to exercise'
- No alcohol
- Hypertension → amlodipine/valsartan/ hydrochlorothiazide 10 mg/160 mg/25 mg
- **Admitted with acute chest pain**

Lab tests normal… except:

- LDL-C: 190 mg/dL
- Lp(a): 120 mg/dL
- Ejection fraction: 40%
- Primary PCI was done →
- ASA 100 mg
- Clopidogrel 75 mg
- Atorvastatin/ezetimibe 80 mg/10 mg
- Bisoprolol 5 mg
- Ramipril 5 mg

ASA, acetylsalicylic acid; LDL-C, low density lipoprotein cholesterol; Lp(a), lipoprotein little a; PCI, percutaneous coronary intervention

STUDY DESIGN



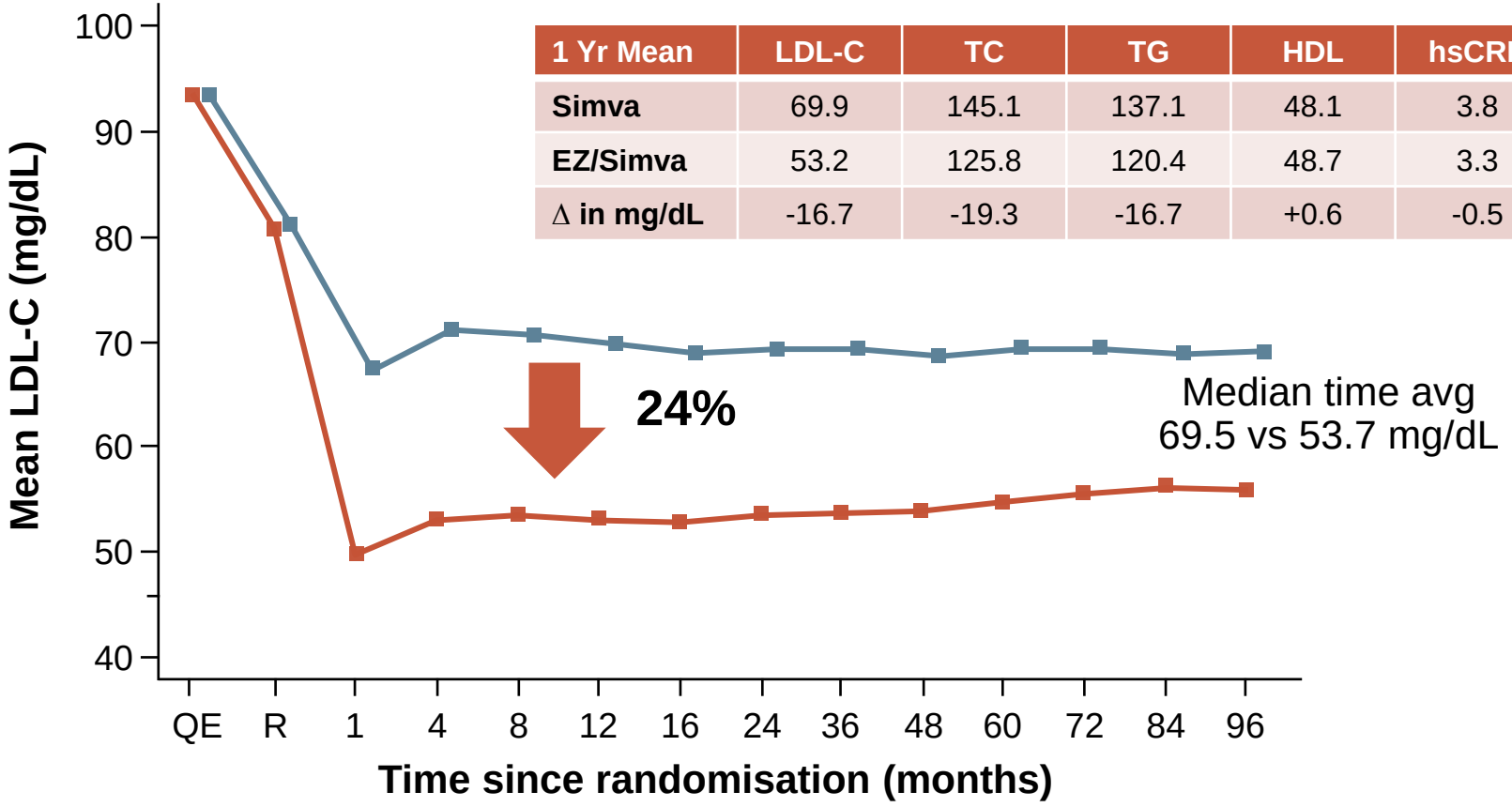
[a] 3.2 mmol/L; [b] 2.6 mmol/L

ACS, acute coronary syndromes; CV, cardiovascular; LDL-C, low density lipoprotein cholesterol; MI, myocardial infarction; UA, unstable angina

Blazing MA, AM Heart J. 2014;168:205-12; Califf RM, et al. N Engl J Med. 2009;361:712-7; Cannon CP, et al. Am Heart J. 2008;156:826-3

LDL-C AND LIPID CHANGES

1 Yr Mean	LDL-C	TC	TG	HDL	hsCRP
Simva	69.9	145.1	137.1	48.1	3.8
EZ/Simva	53.2	125.8	120.4	48.7	3.3
Δ in mg/dL	-16.7	-19.3	-16.7	+0.6	-0.5



Number at risk:

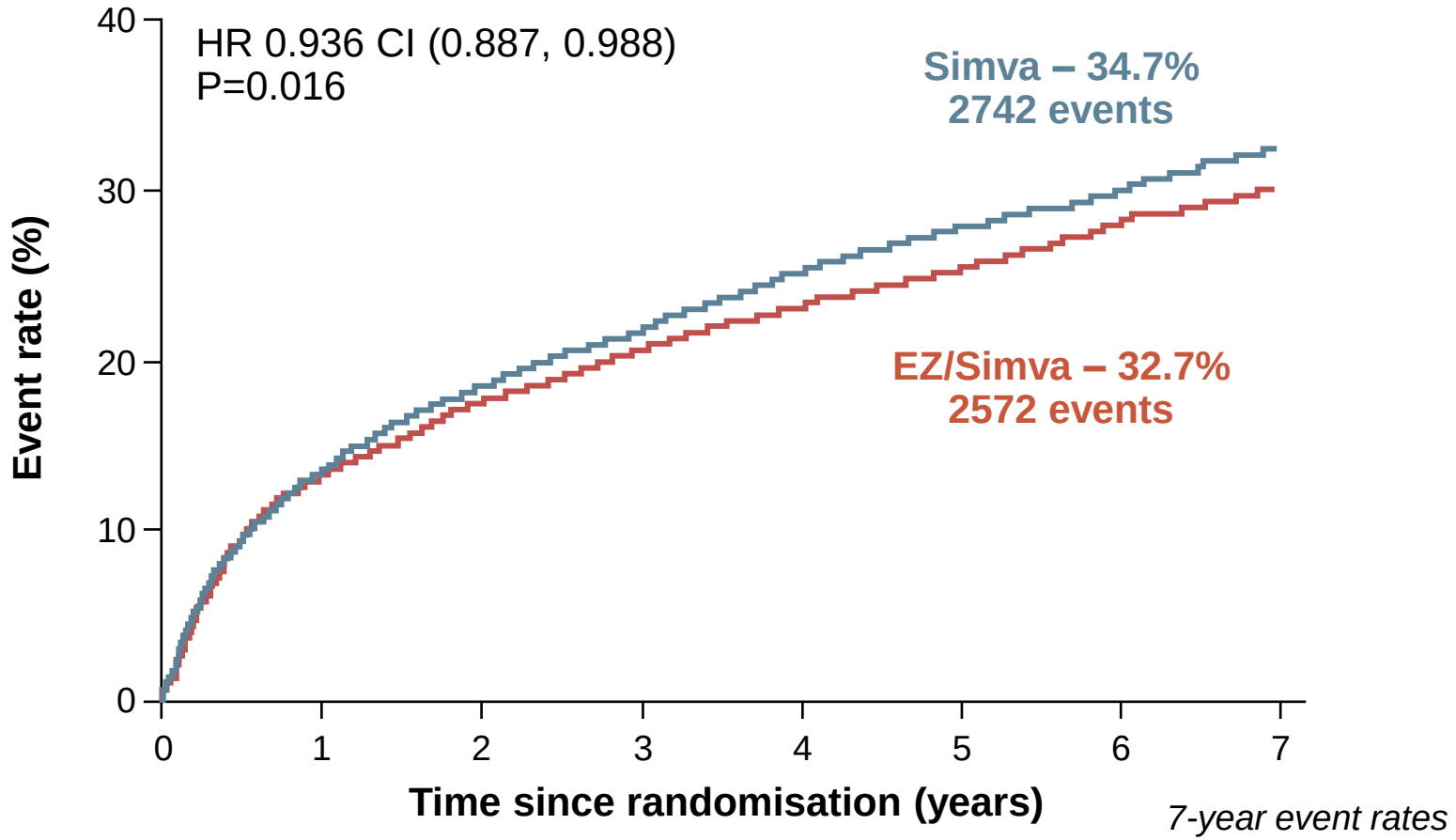
EZ/Simva	8990	8889	8230	7701	7264	6864	6583	6256	5734	5354	4508	3484	2608	1078
Simva	9009	8921	8306	7843	7289	6939	6607	6192	5684	5267	4395	3387	2569	1068

Avg, average; EZ, ezetimibe; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL-C, low density lipoprotein cholesterol; QE, baseline; R, randomisation; Simva, simvastatin; TC, total cholesterol; TG, triglycerides; Yr, year

Adapted from: Cannon CP, et al. N Engl J Med. 2015;372:2387-97

PRIMARY ENDPOINT — ITT

CARDIOVASCULAR DEATH, MI, DOCUMENTED UNSTABLE ANGINA REQUIRING REHOSPITALIZATION, CORONARY REVASCULARIZATION (≥30 DAYS), OR STROKE



7-year event rates

EZ, ezetimibe; HR, hazard ratio; ITT, intention to treat; Simva, simvastatin
Adapted from: Cannon CP, et al. N Engl J Med. 2015;372:2387-97

Very-high-risk

People with any of the following:

Documented ASCVD, either clinical or unequivocal on imaging

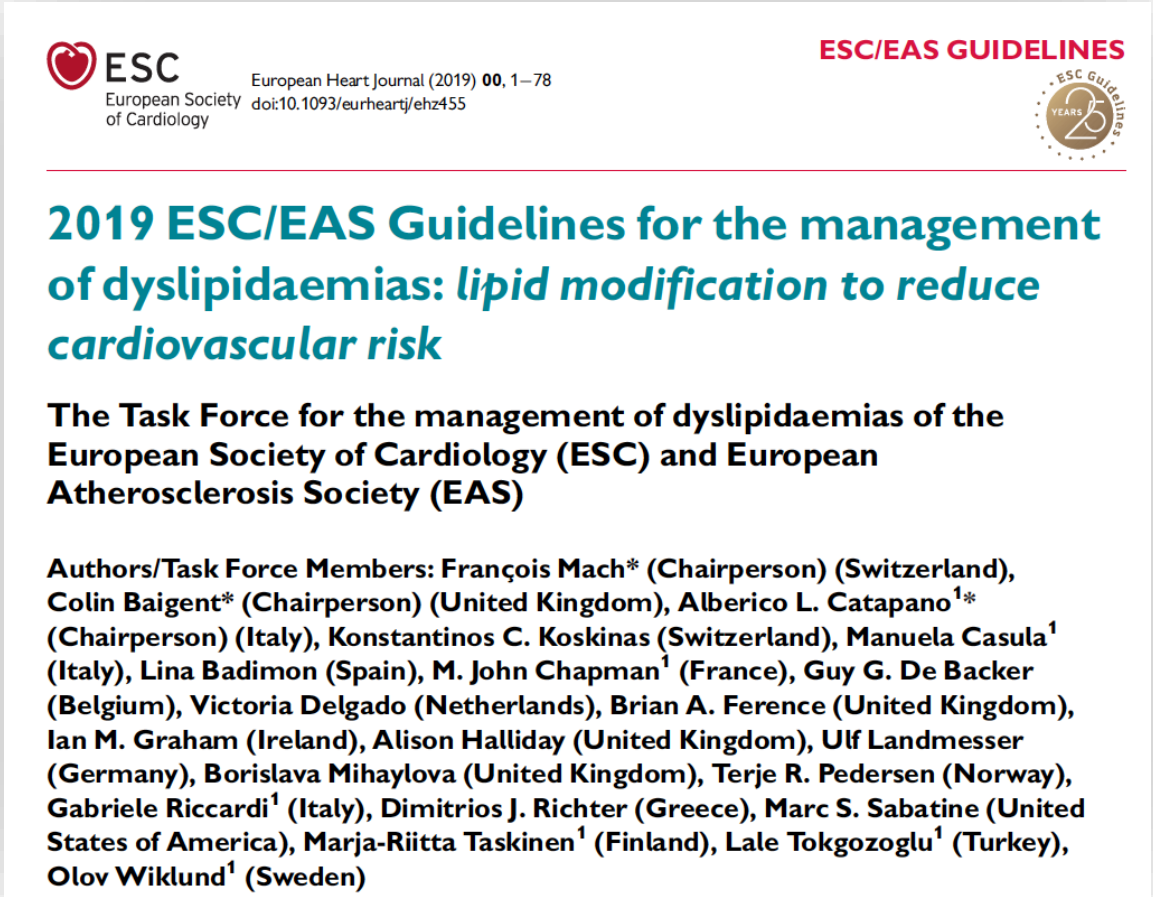
Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound

DM with target organ damage,* or at least three major risk factors, or early onset of T1DM of long duration (>20 years)

Severe CKD (eGFR <30 mL/min/1.73 m^2)

A calculated SCORE ≥10% for 10-year risk of fatal CVD

FH with ASCVD or with another major risk factor



ESC European Society of Cardiology

European Heart Journal (2019) **00**, 1–78
doi:10.1093/eurheartj/ehz455

ESC/EAS GUIDELINES

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Authors/Task Force Members: François Mach* (Chairperson) (Switzerland), Colin Baigent* (Chairperson) (United Kingdom), Alberico L. Catapano[1]* (Chairperson) (Italy), Konstantinos C. Koskinas (Switzerland), Manuela Casula[1] (Italy), Lina Badimon (Spain), M. John Chapman[1] (France), Guy G. De Backer (Belgium), Victoria Delgado (Netherlands), Brian A. Ference (United Kingdom), Ian M. Graham (Ireland), Alison Halliday (United Kingdom), Ulf Landmesser (Germany), Borislava Mihaylova (United Kingdom), Terje R. Pedersen (Norway), Gabriele Riccardi[1] (Italy), Dimitrios J. Richter (Greece), Marc S. Sabatine (United States of America), Marja-Riitta Taskinen[1] (Finland), Lale Tokgozoglu[1] (Turkey), Olov Wiklund[1] (Sweden)

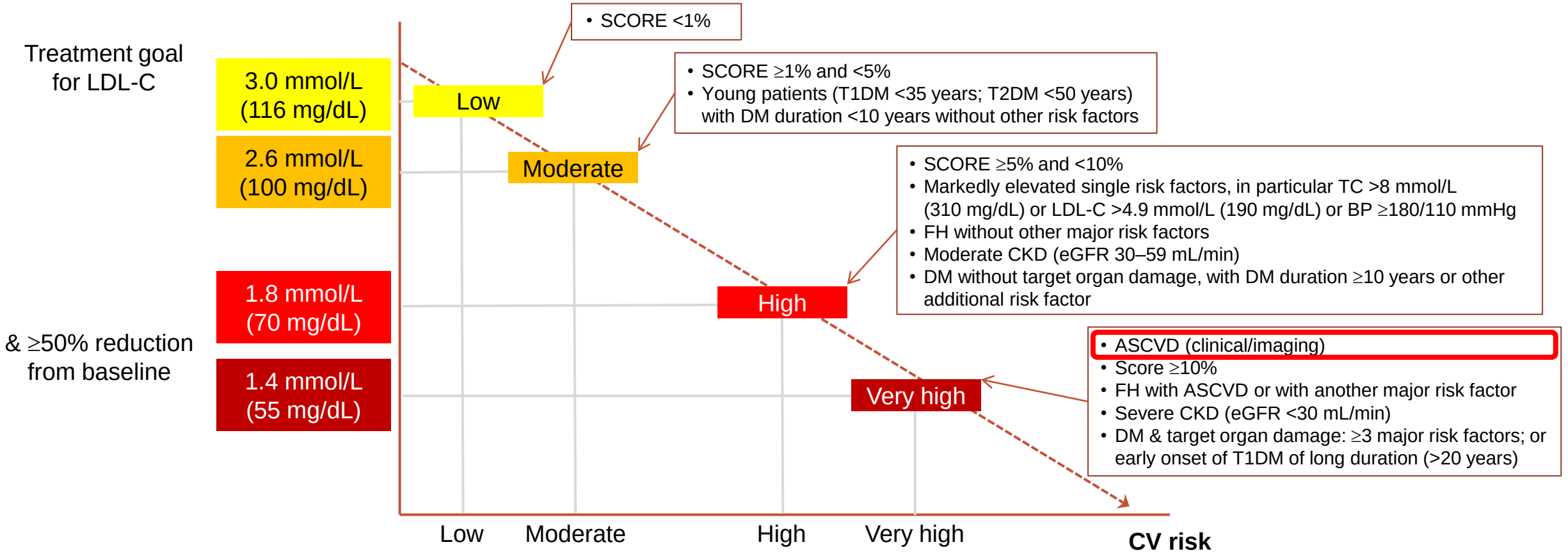
[a] Target organ damage is defined as microalbuminuria, retinopathy, or neuropathy

ACS, acute coronary syndromes; ASCVD, atherosclerotic cardiovascular disease; CABG, coronary artery bypass graft; CKD, chronic kidney disease; CT, computed tomography; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; FH, familial hypercholesterolaemia; MI, myocardial infarction; PCI, percutaneous coronary intervention; SCORE, Systematic Coronary Risk Estimation; T1DM, type 1 diabetes mellitus; TIA, transient ischaemic attack; UA, unstable angina

Mach F, et al. Eur Heart J. 2020;41:111-88

2019 ESC/EAS DYSLIPIDEMIA GUIDELINES: TARGET LIPID LEVELS IN VERY HIGH RISK PEOPLE WITH DIABETES AND ACS/ASCVD

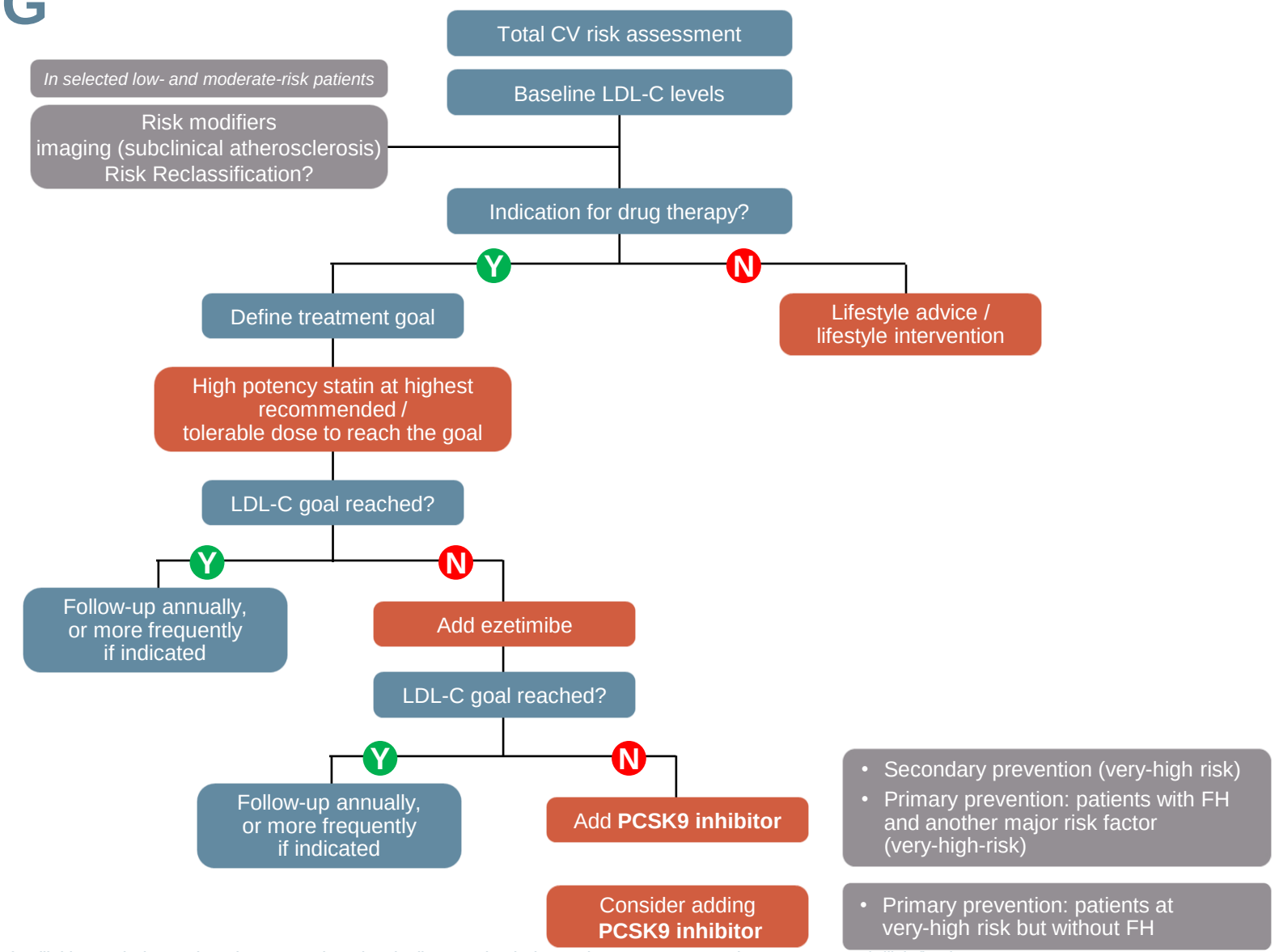
TREATMENT GOALS FOR LDL-C ACROSS CATEGORIES OF TOTAL CV RISK



ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CKD, chronic kidney disease; CV, cardiovascular; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; SCORE, Systematic COronary Risk Estimation; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TC, total cholesterol

Mach F, et al. Eur Heart J. 2020;41:111-88

TREATMENT ALGORITHM FOR PHARMACOLOGICAL LDL-C LOWERING



CV, cardiovascular; DM, diabetes mellitus; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9

Mach F, et al. Eur Heart J. 2020;41:111-88

TREATMENT TARGETS

LDL-C

Very high-risk in primary or secondary prevention

A therapeutic regimen that achieves at least a 50% LDL-C reduction from baseline[a] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL).

No current statin use: this is likely to require high-intensity LDL-lowering therapy.

Current LDL-lowering treatment: an increased treatment intensity is required.

High risk: A therapeutic regimen that achieves at least a 50% LDL-C reduction from baseline[a] and an LDL-C goal of <1.8 mmol/L (<70 mg/dL).

E[a] The term 'baseline' refers to the LDL-C level in a person not taking any lipid lowering medication, or to the extrapolated baseline value for those who are on current treatment

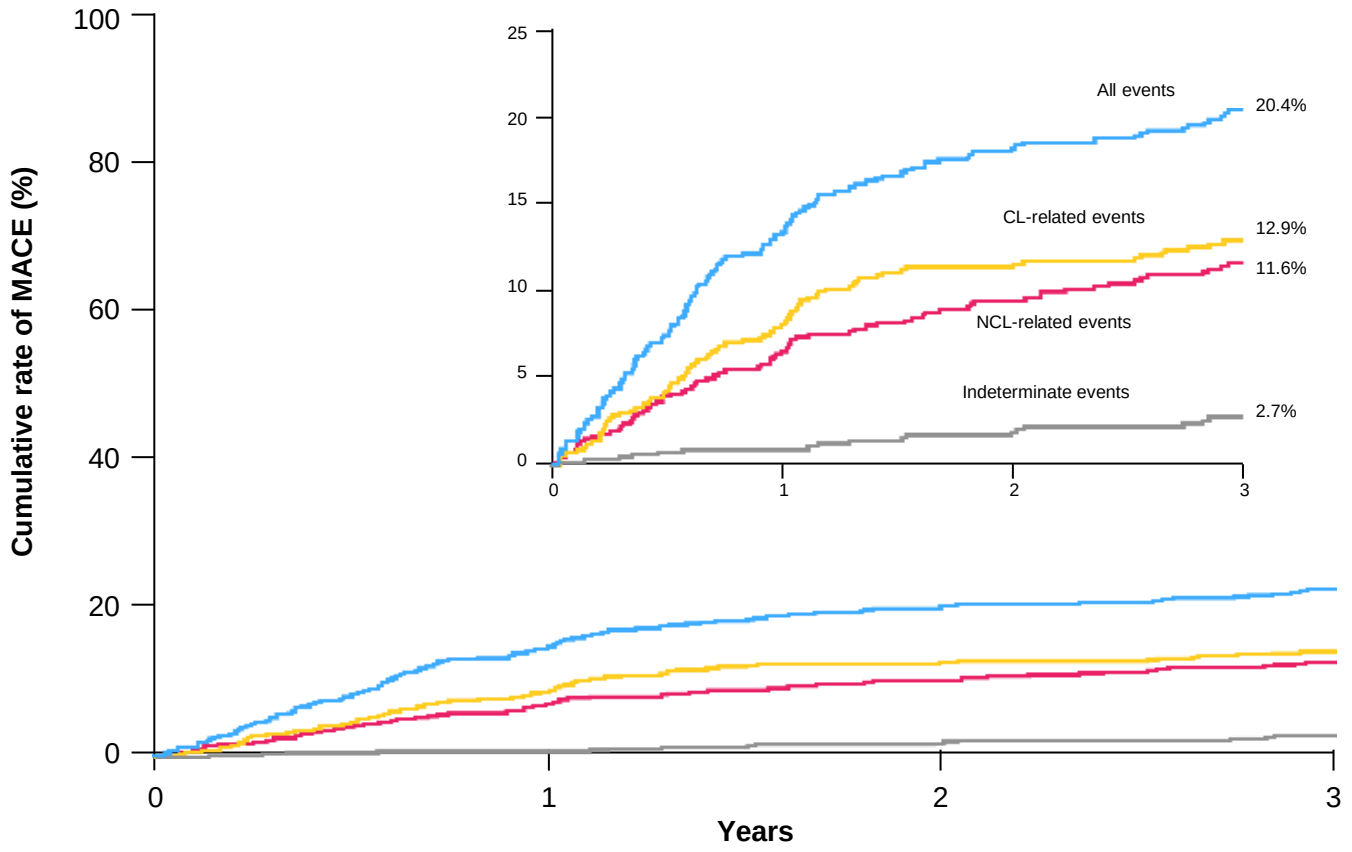
LDL-C, low-density lipoprotein cholesterol

Mach F, et al. Eur Heart J. 2020;41:111-88

CAN WE DO IT BETTER?

ACS CONSIDERATIONS

- ACS and recurrence of events are frequent
- Therapies prevent event recurrence
  - Culprit and non-culprit vessels
- Intensive LDL-C lowering changes plaque biology

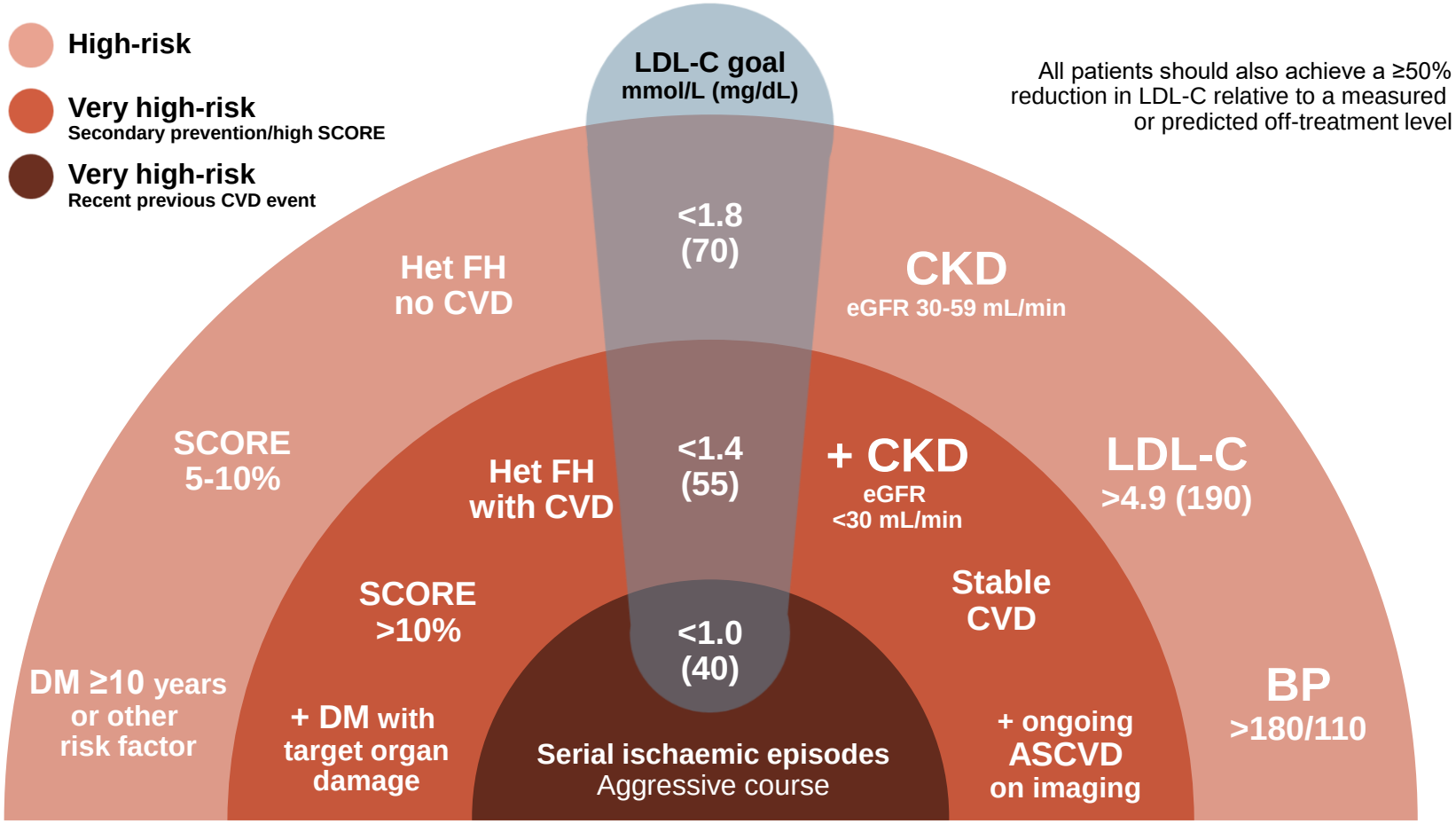


No. at risk				
All patients	697	557	506	480
Patients with CL-related events	697	590	543	518
Patients with NCL-related events	697	595	553	521
Patients with indeterminate events	697	634	604	583

ACS, acute coronary syndromes; CL, culprit lesion; MACE, major adverse cardiovascular events; NCL, non-culprit lesion

Adapted from: Stone GW, et al. N Engl J Med. 2011;364:226-35

INTENSIVE LOW-DENSITY LIPOPROTEIN CHOLESTEROL LOWERING IN CVD PREVENTION

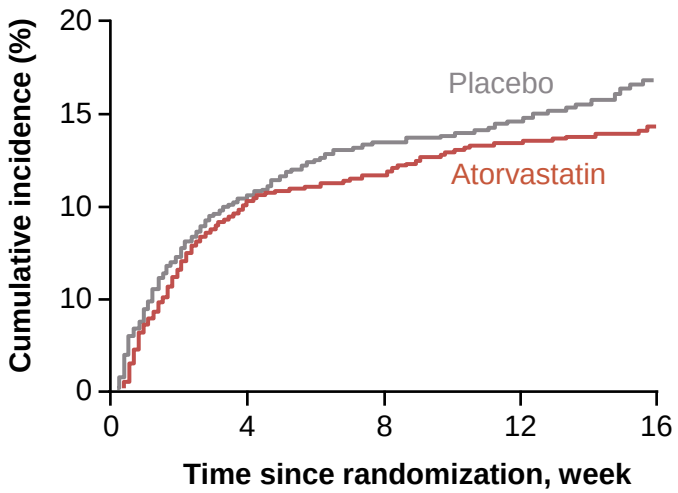


ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; Het FH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; SCORE, Systematic Coronary Risk Estimation; T1DM, type 1 diabetes mellitus

Packard C, et al. Heart. 2021;107:1369-75

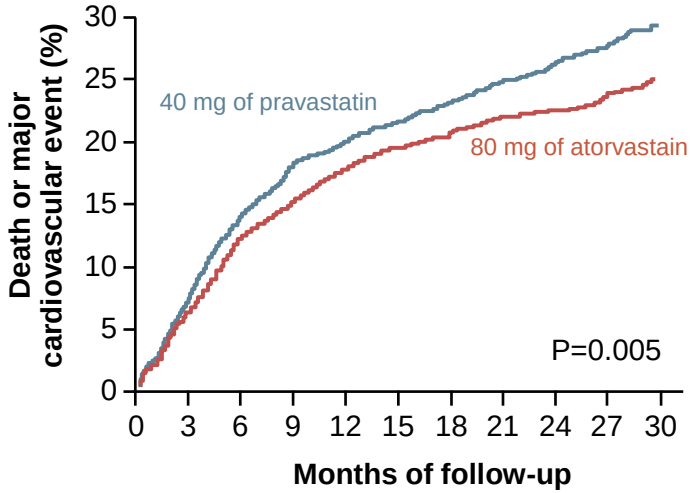
ACS → EARLY AND INTENSIVE STATIN THERAPY

MIRACL: High-intensity statins vs pl° (1-4 days post ACS)
LDL-C during study: 72 vs 135 mg/dL



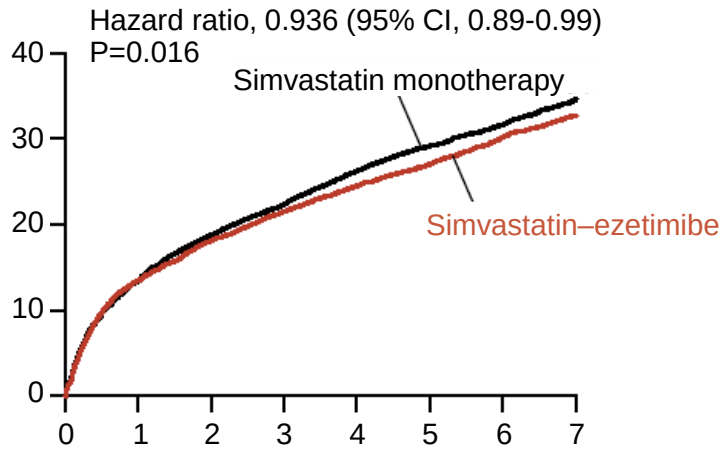
Schwartz JAMA
2001;285:1711-18

PROVE-IT: High vs low-intensity statins (10 days post ACS)
LDL-C during study: 62 vs 95 mg/dL RR=16%



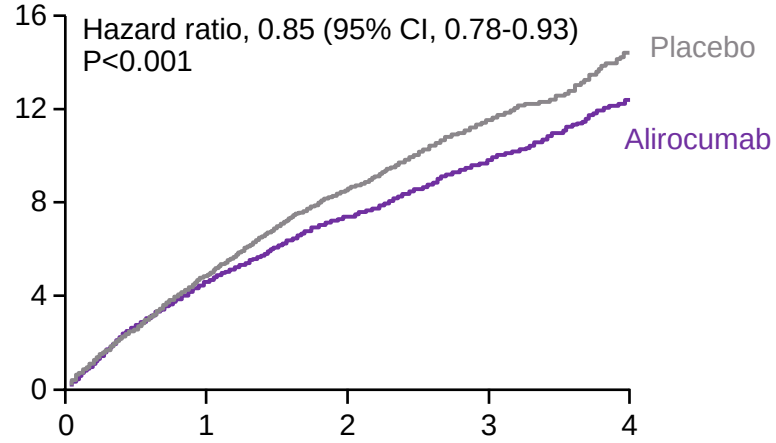
Cannon NEJM.
2004;350(15):1495-504

IMPROVE-IT: Simvastatin mod-intensity vs +ezetimibe (10 days post ACS)
LDL-C during study: 54 vs 69 mg/dL RRR=6%



Cannon NEJM.
2015;372:2387-97

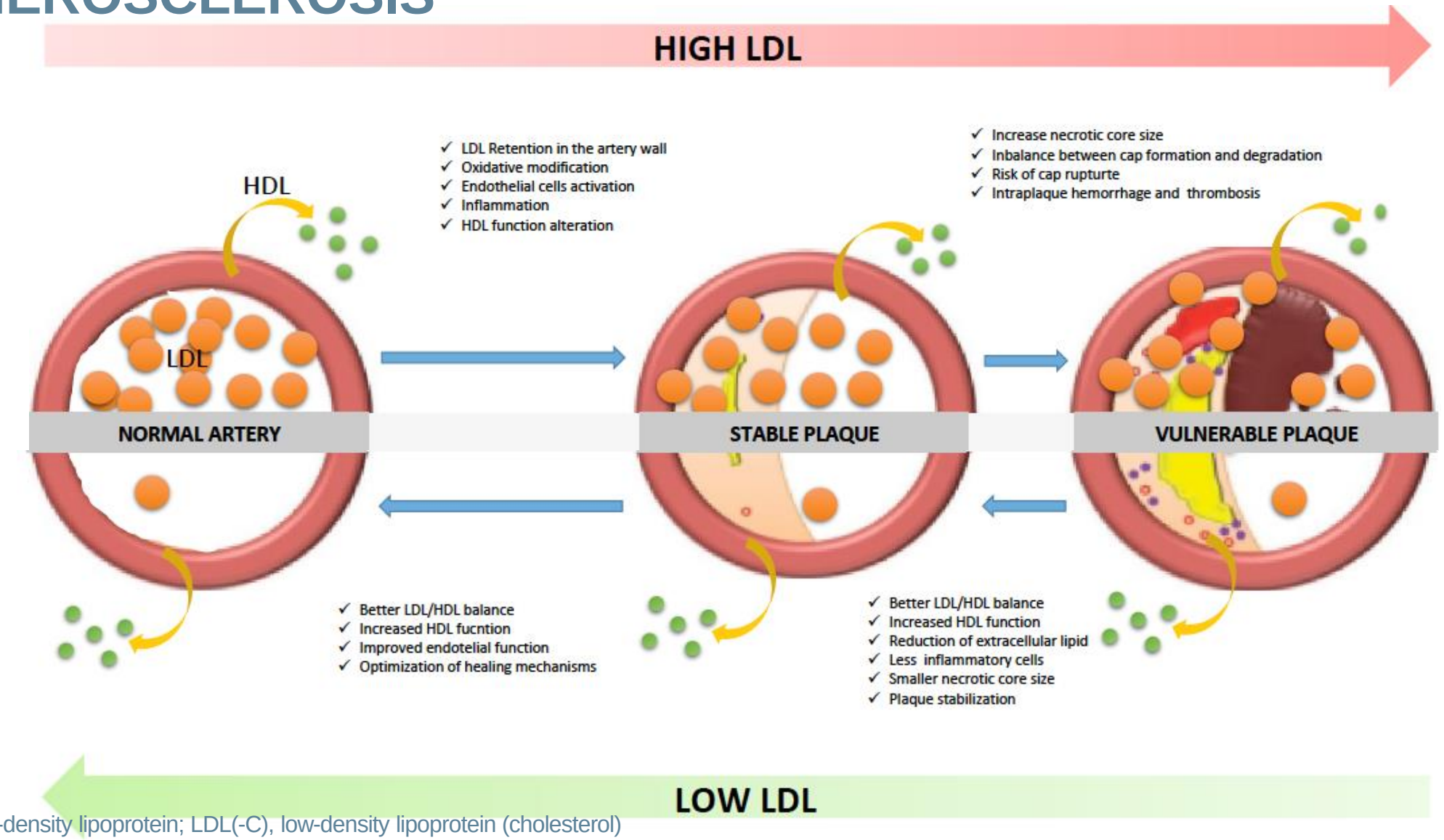
ODYSSEY: High-intensity statin vs +alirocumab (1-12 mths post ACS)
LDL-C during study: 48 vs 96 mg/dL RR=15%



Schwartz NEJM.
2018;379:2097-107

ACS, acute coronary syndromes, CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; mths, months; plº, placebo; RRR, relative risk reduction; wk, weeks

LDL-CHOLESTEROL IS A CAUSAL FACTOR FOR ATHEROSCLEROSIS

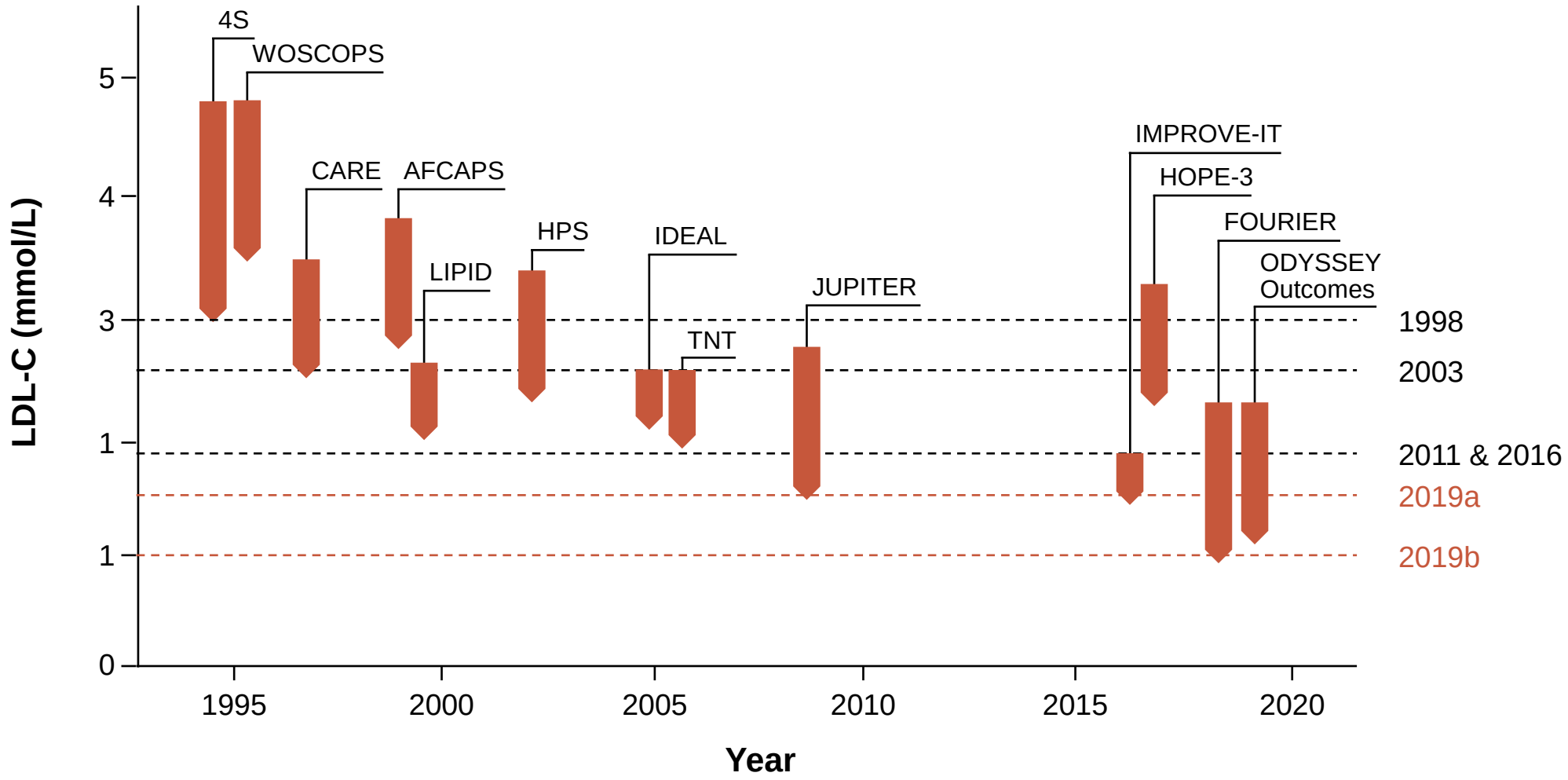


HDL, high-density lipoprotein; LDL(-C), low-density lipoprotein (cholesterol)

Masana L, et al. 2019.

Adapted from: Borén J, et al. Eur Heart J. 2020;41:2313-30

HISTORY OF LDL-C LOWERING TRIALS

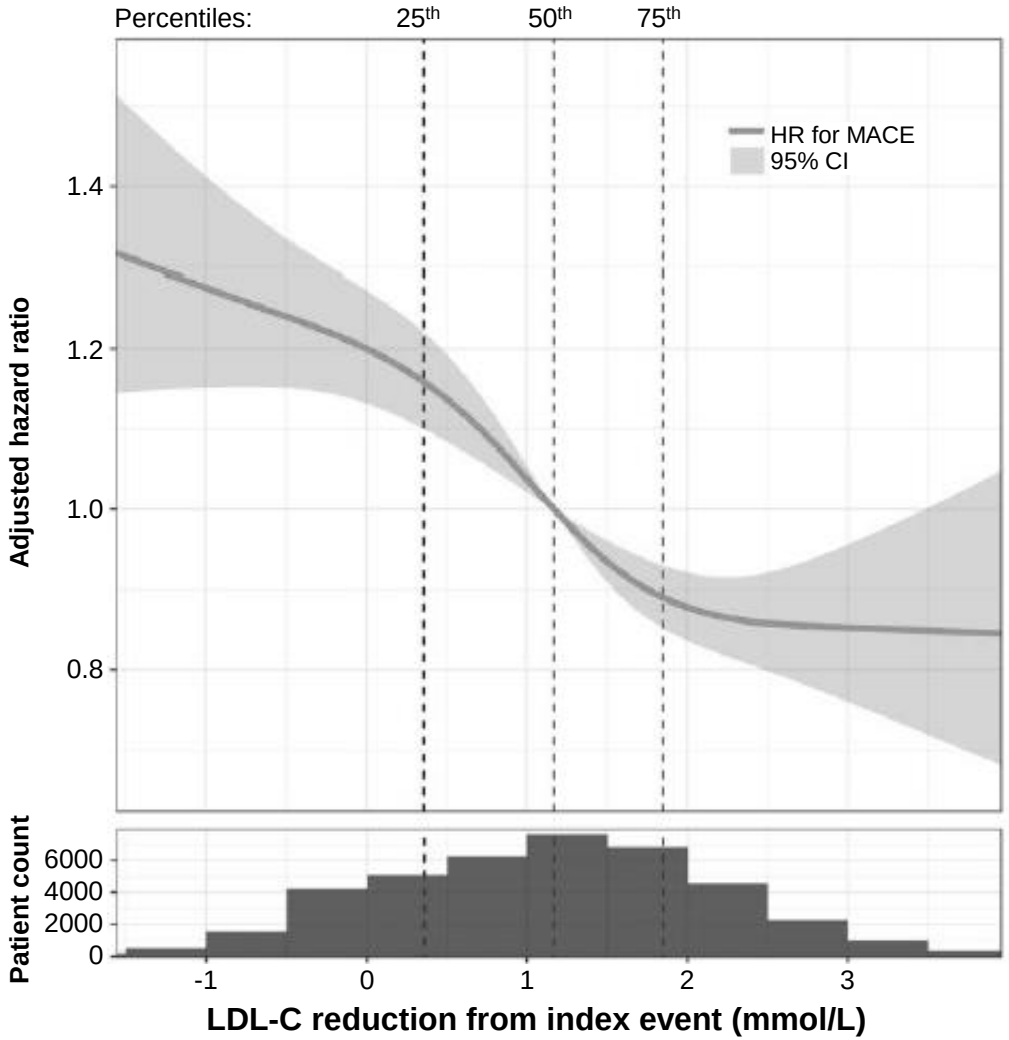


Grey dotted lines represent previous recommended LDL-C ESC/EAS goals for intervention and the red dotted lines (2019a,2019b) represent the current LDL-C ESC/EAS goals

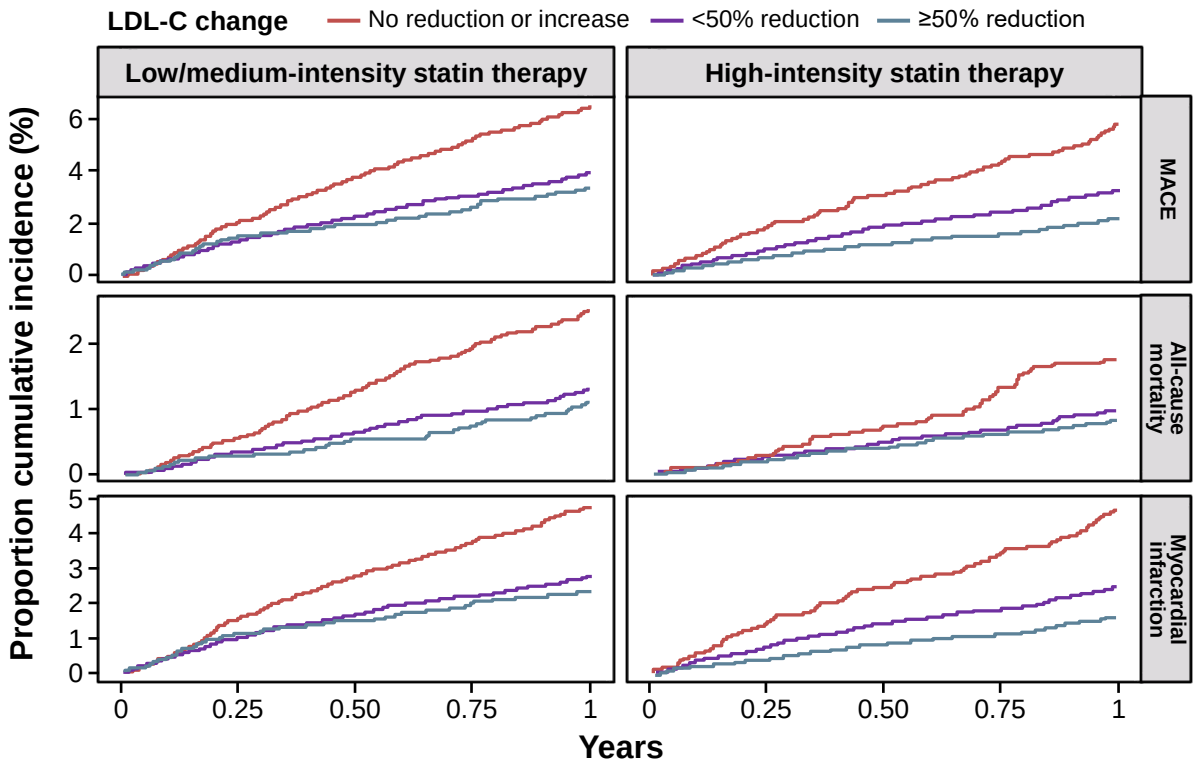
ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; LDL-C, low-density lipoprotein cholesterol

Packard C, et al. Heart. 2021;107:1369-75

THE ABSOLUTE LDL-C REDUCTION DETERMINES CARDIOVASCULAR EVENT RISK: SWEDEHEART



The incidence rates by LDL-cholesterol change were identical regardless of statin intensity therapy used



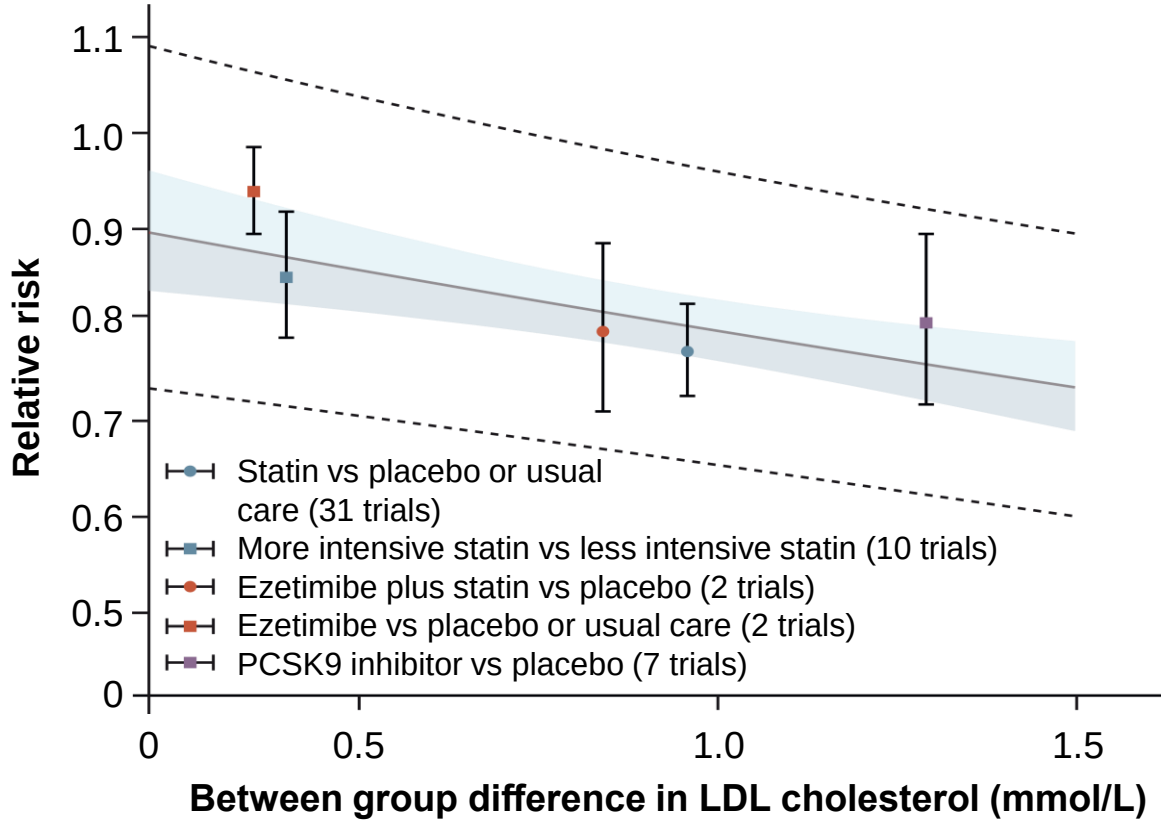
40,607 MI patients 3.78 years follow-up

CI, confidence interval; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; MI, myocardial infarction

Schubert J, et al. Eur Heart J. 2021;42:243-52

INTENSIVE LDL CHOLESTEROL-LOWERING TREATMENT BEYOND CURRENT RECOMMENDATIONS STILL IMPROVES THE PREVENTION OF MAJOR VASCULAR EVENTS

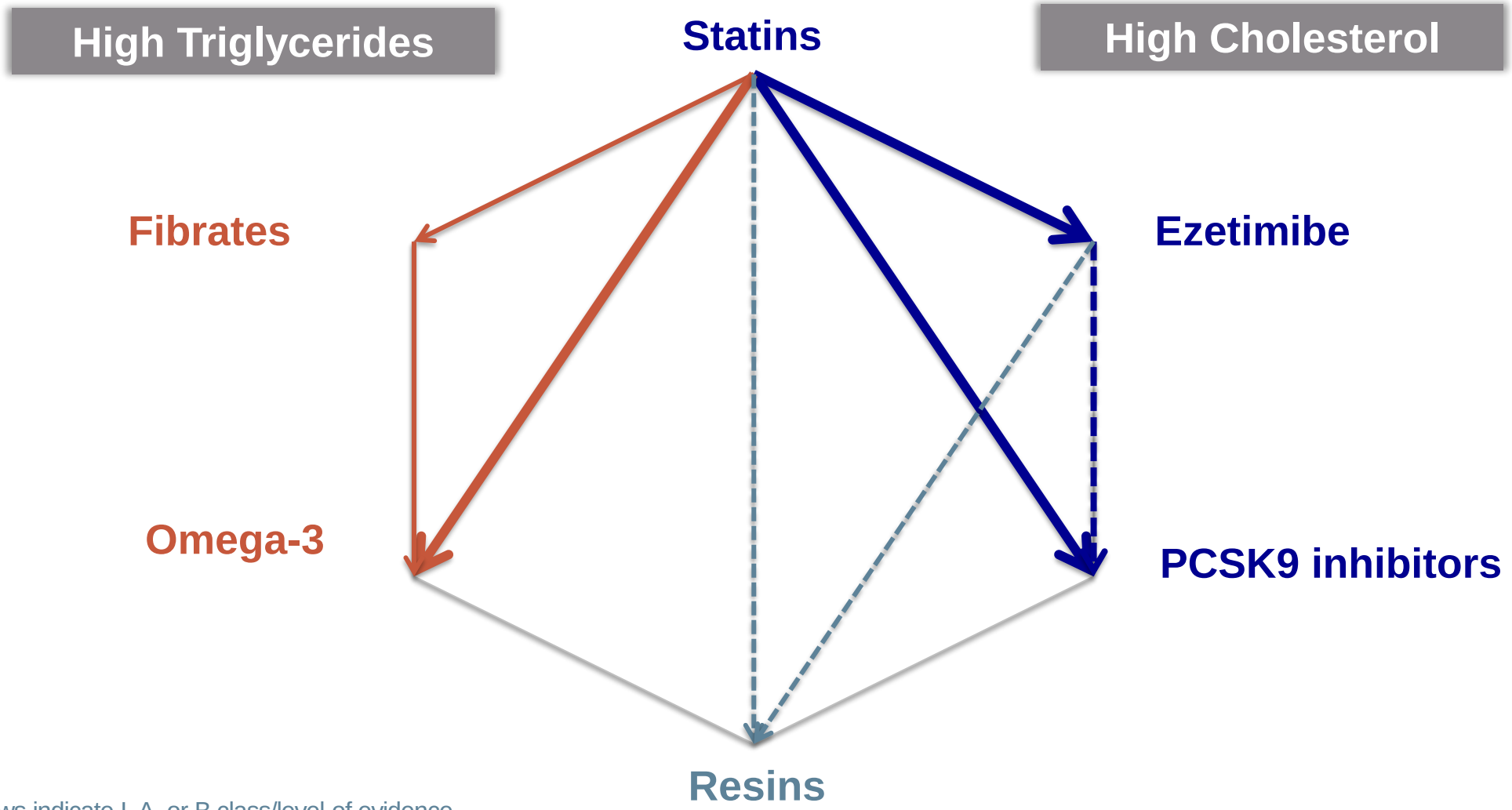
A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMISED TRIALS INCLUDING 327 037 PARTICIPANTS



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

Wang N, et al. Lancet Diabetes Endocrinol. 2020;8:36-49

EVIDENCE-BASED COMBINED LIPID LOWERING THERAPIES

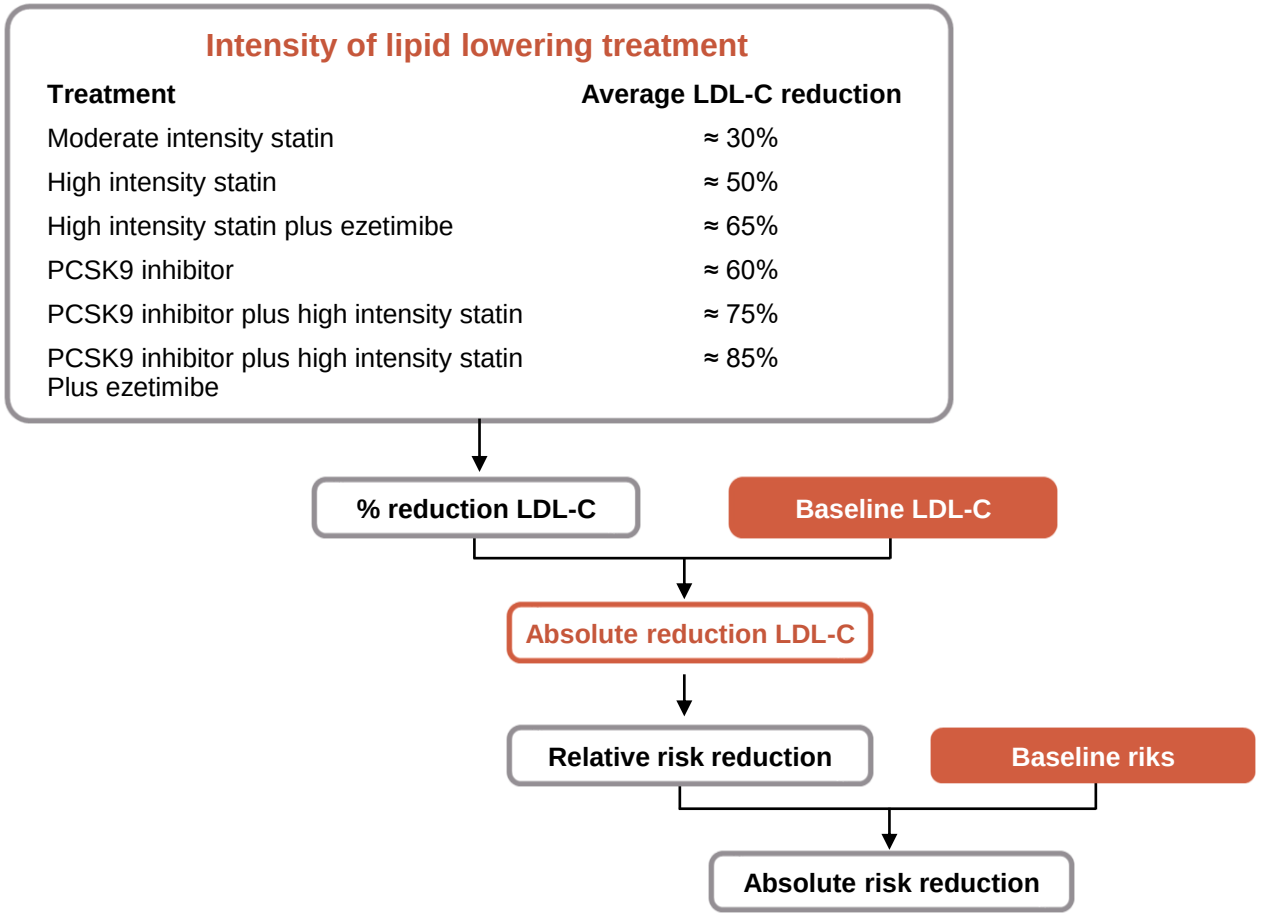


Thick arrows indicate I. A, or B class/level of evidence

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

Adapted from: Masana L, et al. Curr Cardiol Rep. 2020;22:66

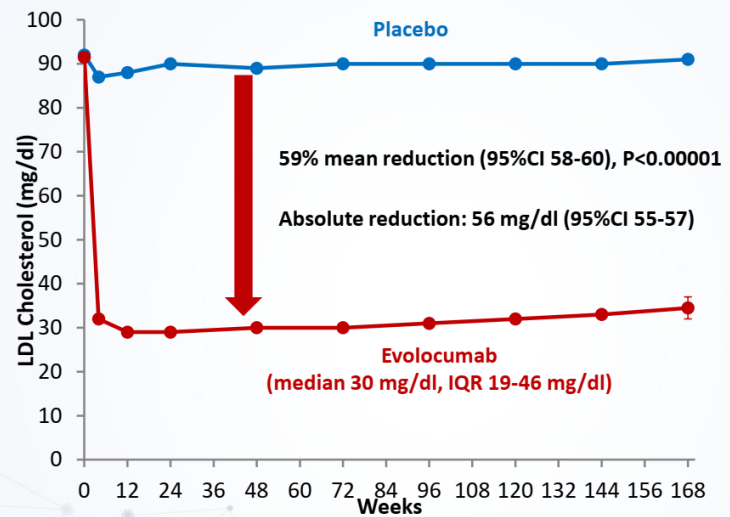
2019 ESC/EAS DYSLIPIDEMIA GUIDELINES: PLANNING THERAPY STRATEGY

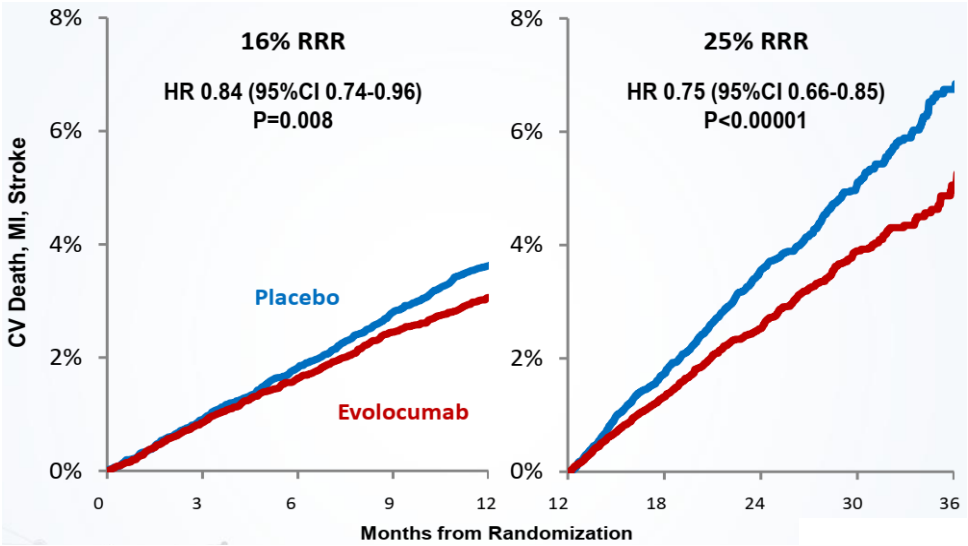


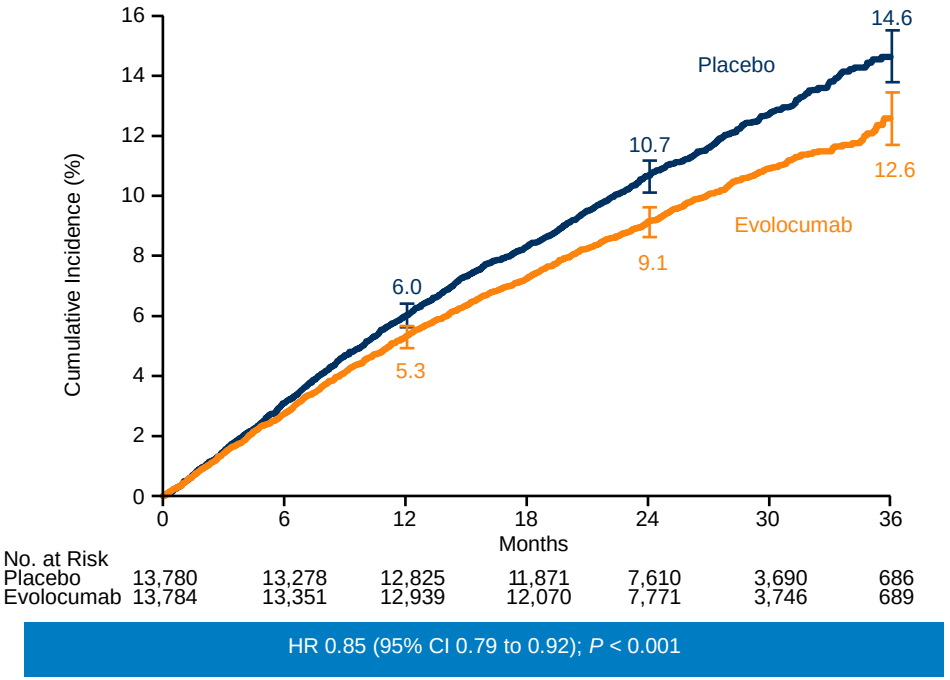
ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9

Mach F, et al. Eur Heart J. 2020;41:111-88

FOURIER: CHANGE IN PARADIGM







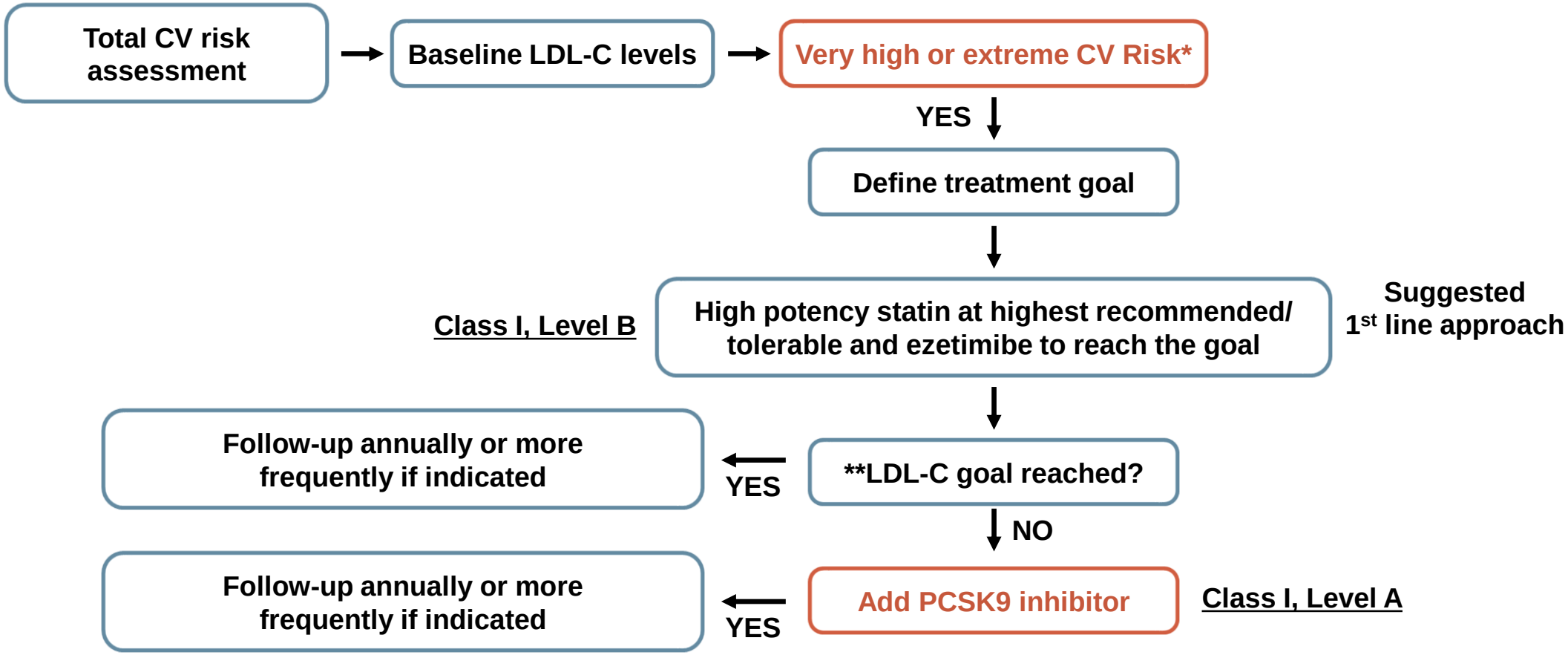
HR 0.85 (95% CI 0.79 to 0.92); *P* < 0.001

LDL:
Pathogenic factor
The lower the better
LDL lowering:
The earlier the better
The longer time on targets the better

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; IQR, interquartile range; MI, myocardial infarction; RRR, relative risk reduction

Adapted from: Sabatine MS, et al. N Engl J Med. 2017;376:1713-22

INTENSIVE LDL-CHOLESTEROL LOWERING IN ONE STEP



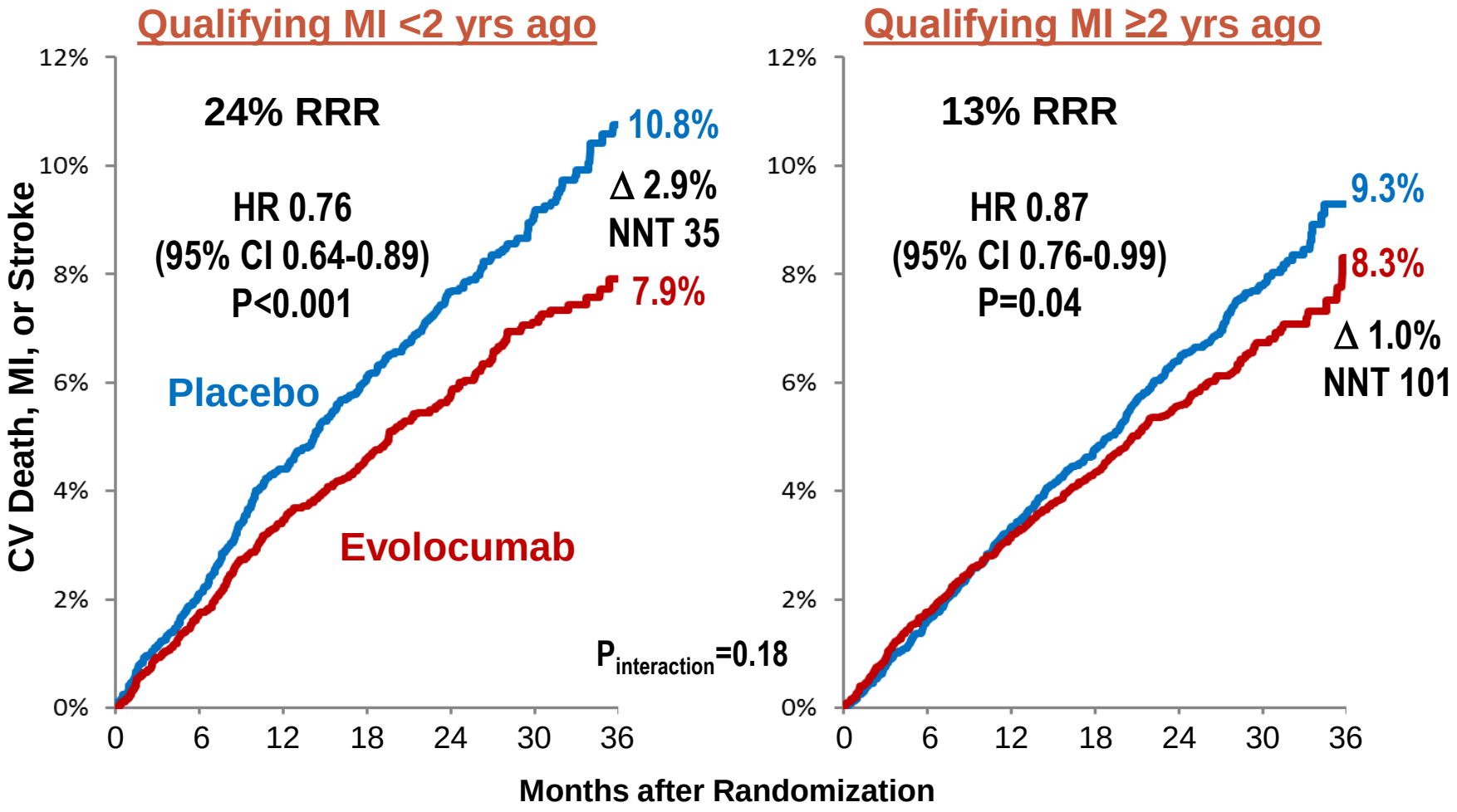
* Extreme CV Risk: diabetes and coronary heart disease, multivessel CV disease, peripheral arterial disease recurrent MI, Het FH and coronary heart disease, Het FH with other CVD risk factors;

** LDL-C assessed after 4-6 weeks

CV, cardiovascular; CVD, cardiovascular disease; Het FH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type 9

Watts GF, et al. Atheroscler Suppl. 2020;42:e30-3

CLINICAL BENEFIT OF EVOLOCUMAB IN PATIENTS WITH A HISTORY OF MI: AN ANALYSIS FROM FOURIER

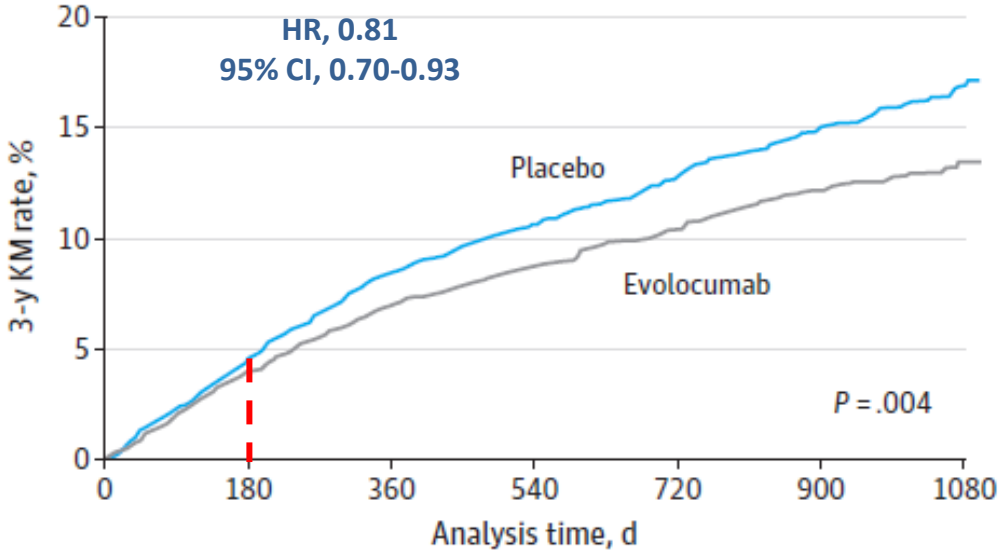


CV, cardiovascular; HR, hazard ratio; MI. myocardial infarction; NNT, number needed to treat; RRR, relative risk reduction

Adapted from: Sabatine MS, et al. Circulation. 2018;138:756-66

TREATMENT WITH EVOLOCUMAB IN PATIENTS WITH RECENT MI

Recent MI (1-12 months). N=5711 p=26

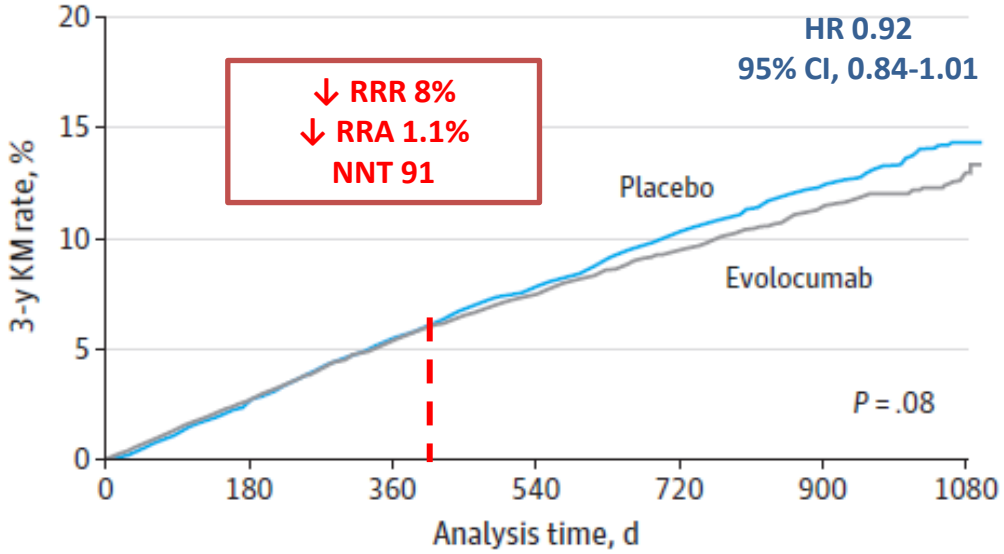


No. at risk

Placebo	2890	2748	2628	2462	1716	999	309
Evolocumab	2821	2696	2602	2470	1705	988	299

↓ RRR 19%
↓ RRA 3.7%
NNT 27

Remote MI (>12 months). N=17516 p=26



↓ RRR 8%
↓ RRA 1.1%
NNT 91

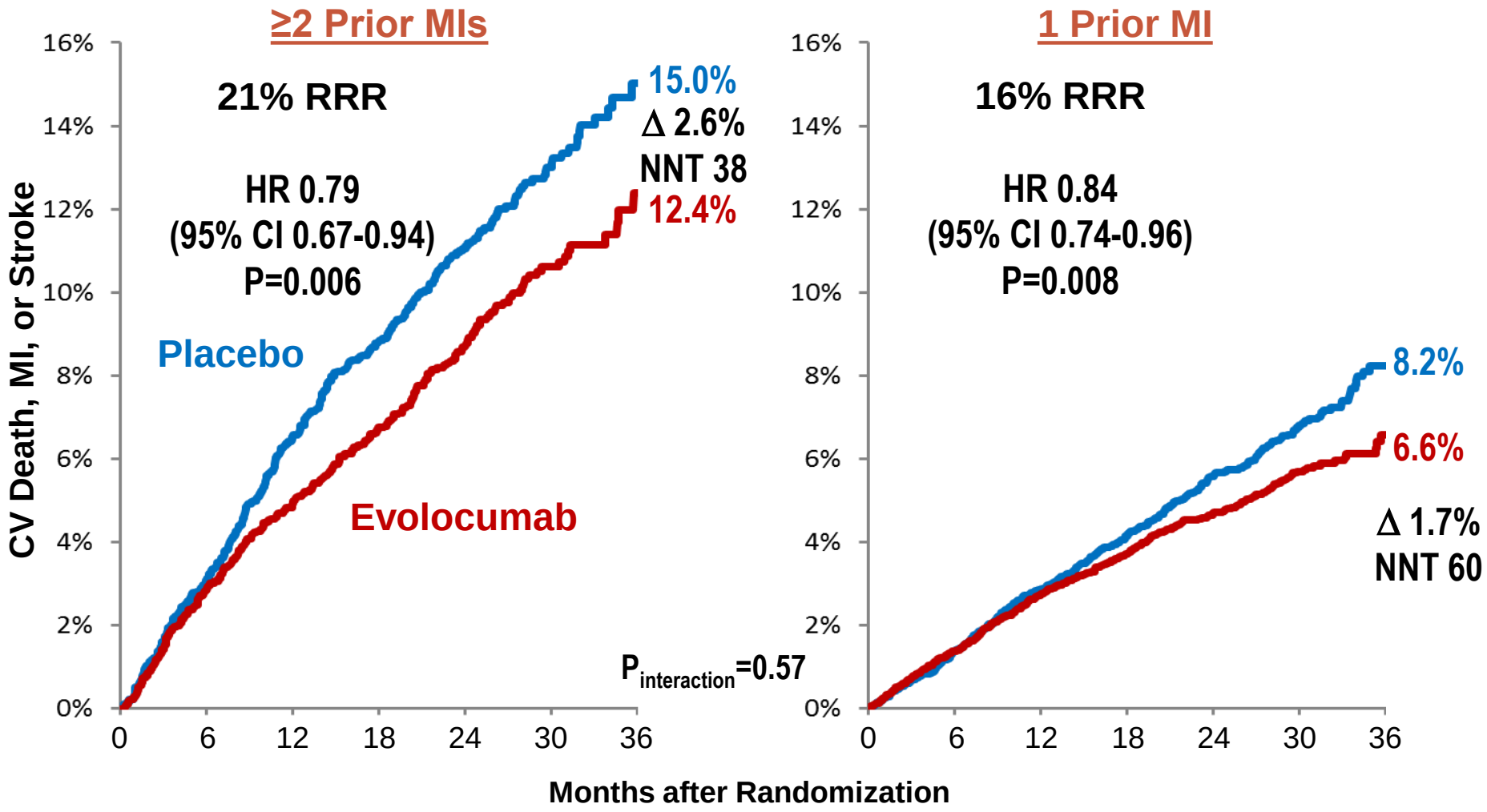
No. at risk

Placebo	8301	8034	7770	7204	4695	2298	468
Evolocumab	8308	8058	7796	7286	4791	2332	480

ARR, absolute risk reduction; CI, confidence interval d, day; HR, hazard ratio; KM, Kaplan-Meier; MI, myocardial infarction; NNT, number needed to treat; RRR, relative risk reduction; y, year

Gencer B, et al. JAMA Cardiol. 2020;5:952-7

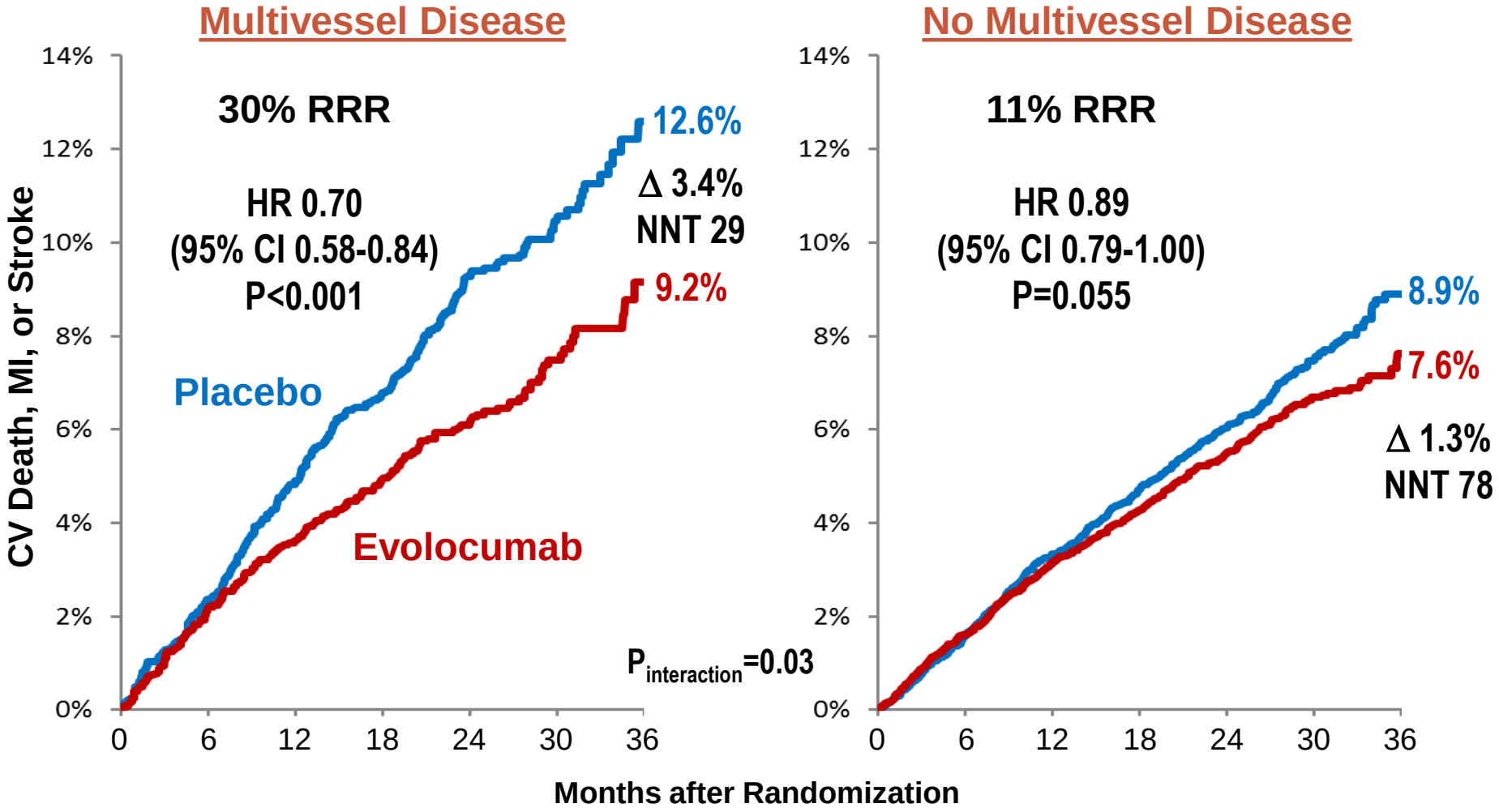
CLINICAL BENEFIT OF EVOLOCUMAB IN PATIENTS WITH A HISTORY OF MI: AN ANALYSIS FROM FOURIER



CV, cardiovascular; HR, hazard ratio; MI. myocardial infarction; NNT, number needed to treat; RRR, relative risk reduction

Adapted from: Sabatine MS, et al. Circulation. 2018;138:756-66

CLINICAL BENEFIT OF EVOLOCUMAB IN PATIENTS WITH A HISTORY OF MI: AN ANALYSIS FROM FOURIER



CV, cardiovascular; HR, hazard ratio; MI. myocardial infarction; NNT, number needed to treat; RRR, relative risk reduction

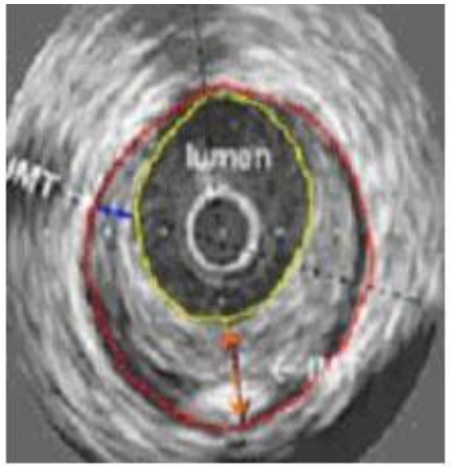
Adapted from: Sabatine MS, et al. Circulation. 2018;138:756-66

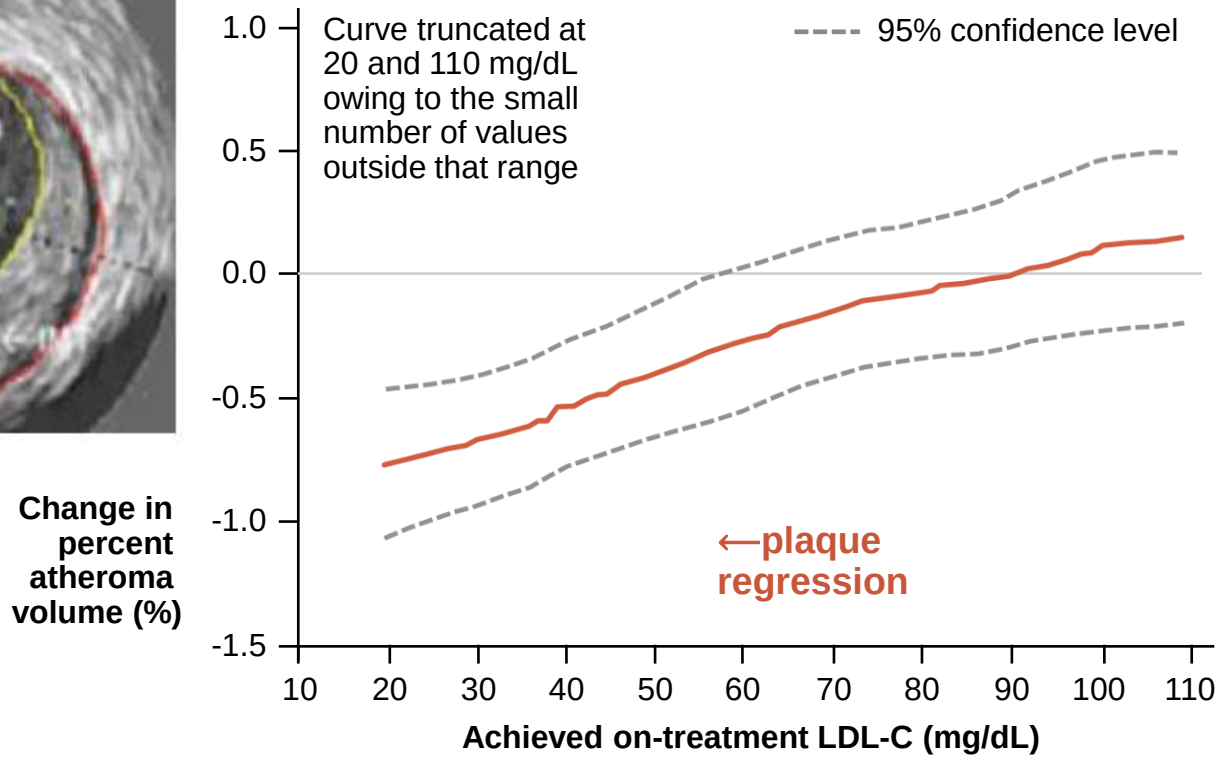
GLAGOV: MEAN LDL AND CHANGE IN PERCENT ATHEROMA VOLUME

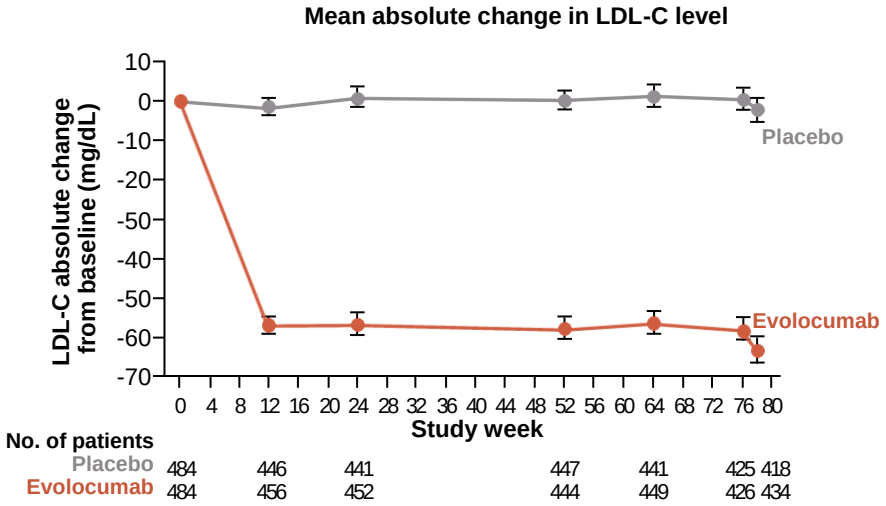
JAMA | Original Investigation

Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients

The GLAGOV Randomized Clinical Trial







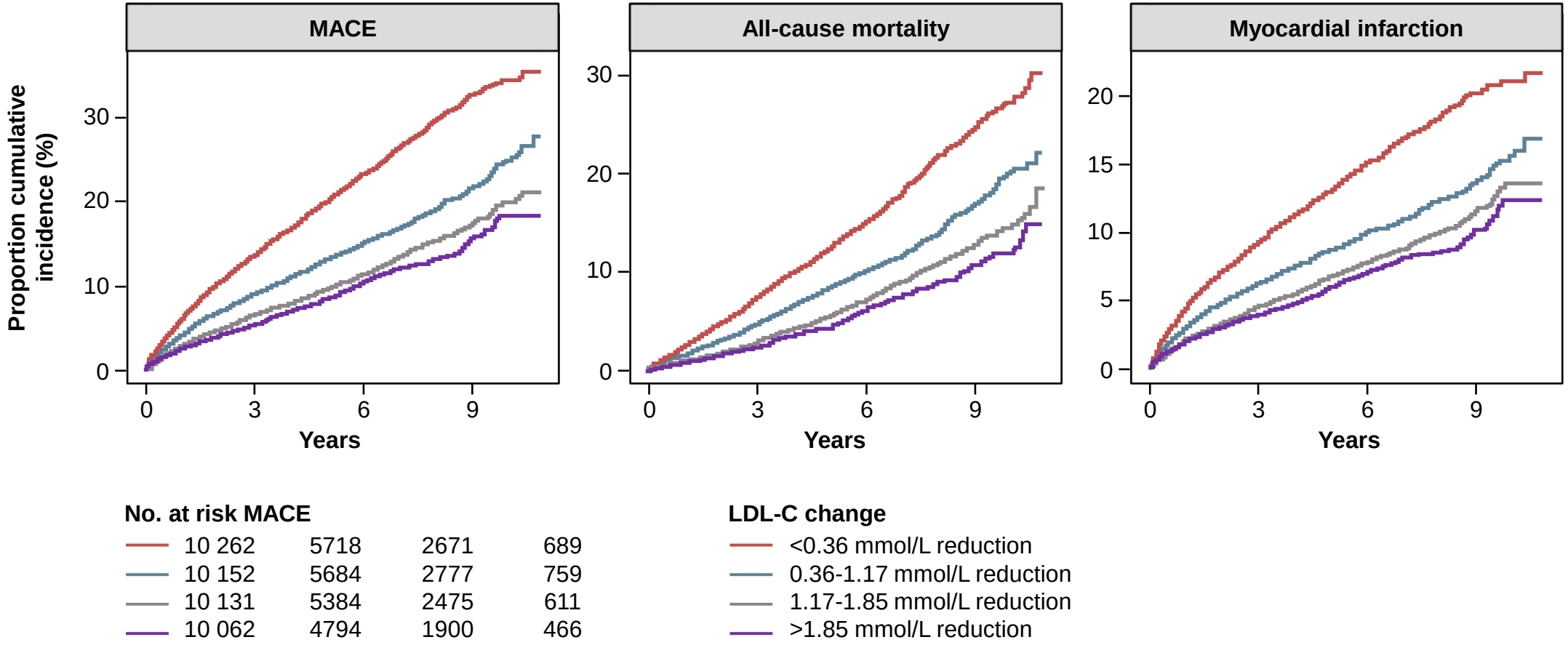
Parameter	On-treatment		P value[a]
	Placebo (N=484)	Evolocumab (N=484)	
Cholesterol, mean (95% CI), mg/dL			
TC	169.1 (166.3-172.0)	108.6 (106.0-111.3)	<.001
LDL-C[b]	93.0 (90.5-95.4)	36.6 (34.5-38.8)	<.001
HDL-C	47.1 (46.0-48.2)	51.0 (49.8-52.1)	<.001
Triglycerides, median (IQR), mg/dL[c]	130.5 (100.3-177.2)	105.1 (82.5-141.6)	<.001

[a] p value for between–treatment group comparison; [b] When the calculated LDL-C level is less than 40 mg/dL or triglyceride level is greater than 400 mg/dL, ultracentrifugation LDL-C was determined from the same blood sample; [c] Tested using Wilcoxon rank-sum test

HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides

Nicholls SJ, et al. JAMA. 2016;316:2373-84

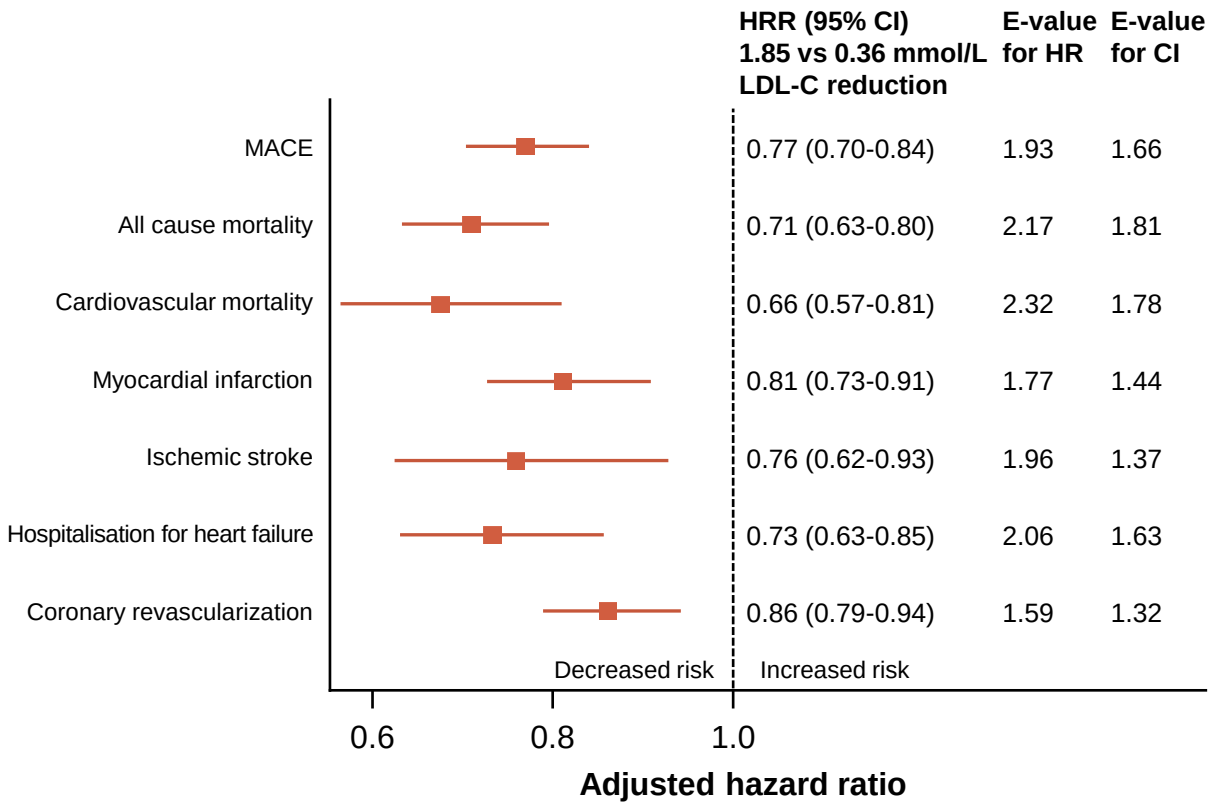
NOT ONLY THE LOWER THE BETTER.
ALSO THE FASTEST THE BETTER

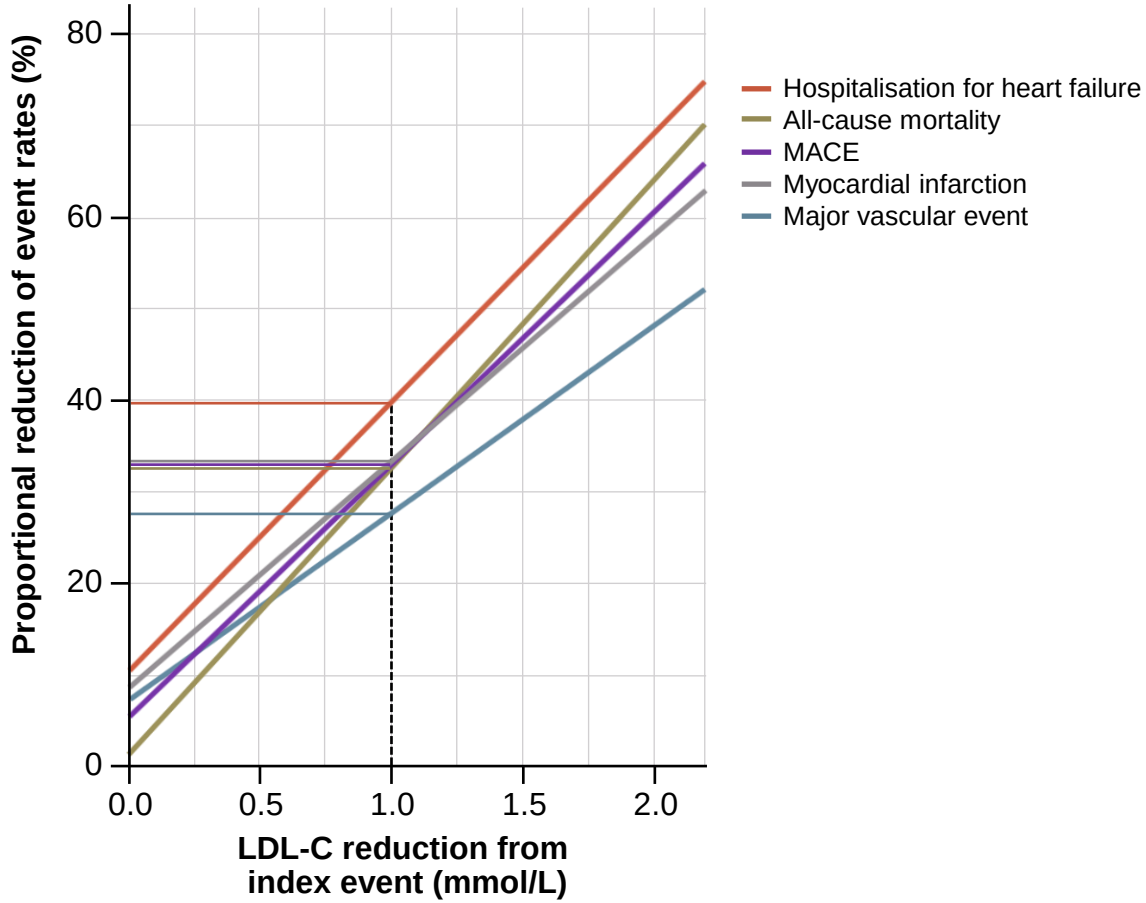


LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events

Schubert J, et al. Eur Heart J. 2021;42:243-52

AFTER AN ACS, EARLY AND INTENSE LDL REDUCTION (6 WEEKS) IMPROVES PROGNOSIS

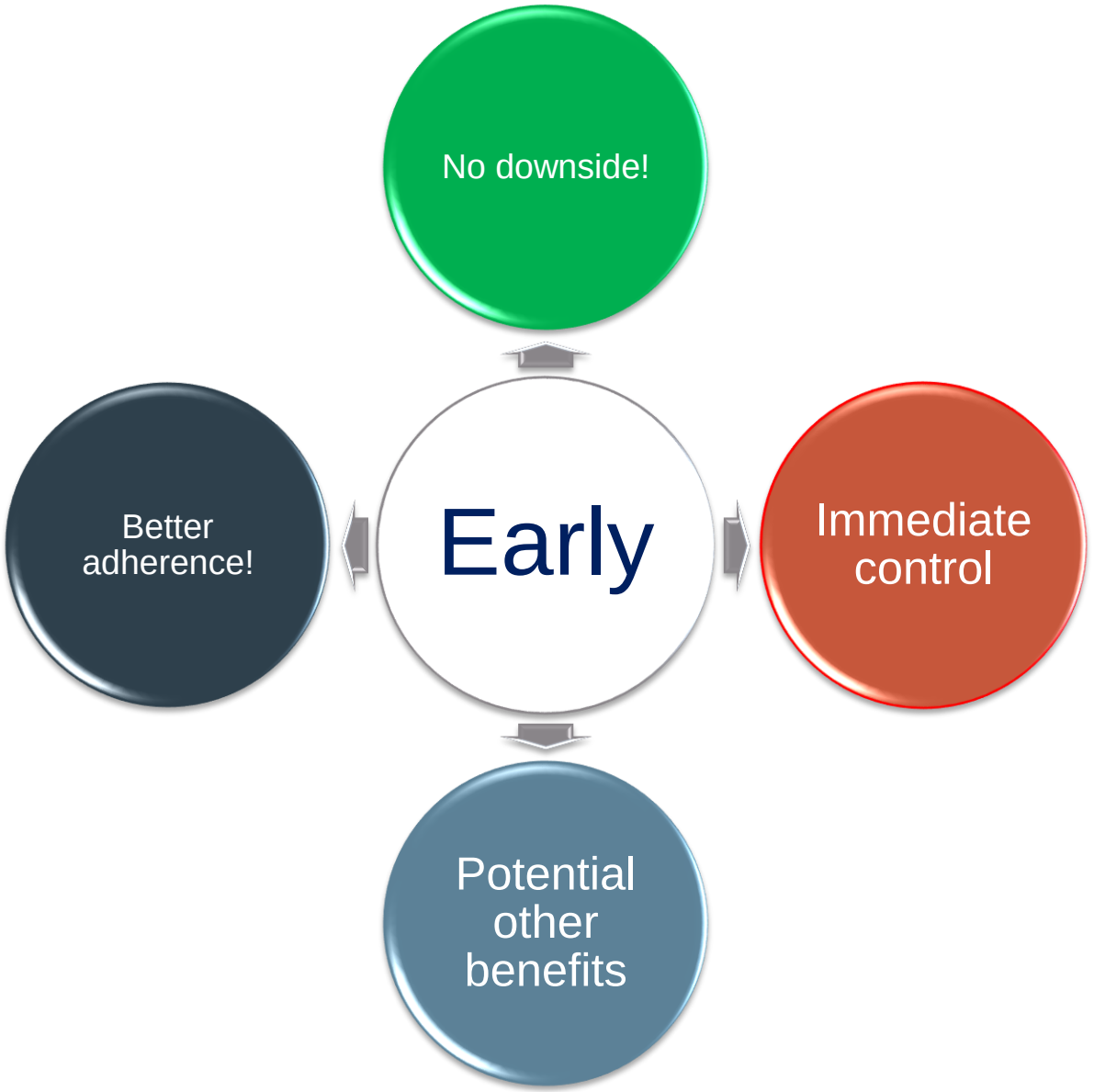




ACS, acute coronary syndromes; CI, confidence interval; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events

Schubert J, et al. Eur Heart J. 2021;42:243-52

NO REASON TO DELAY !

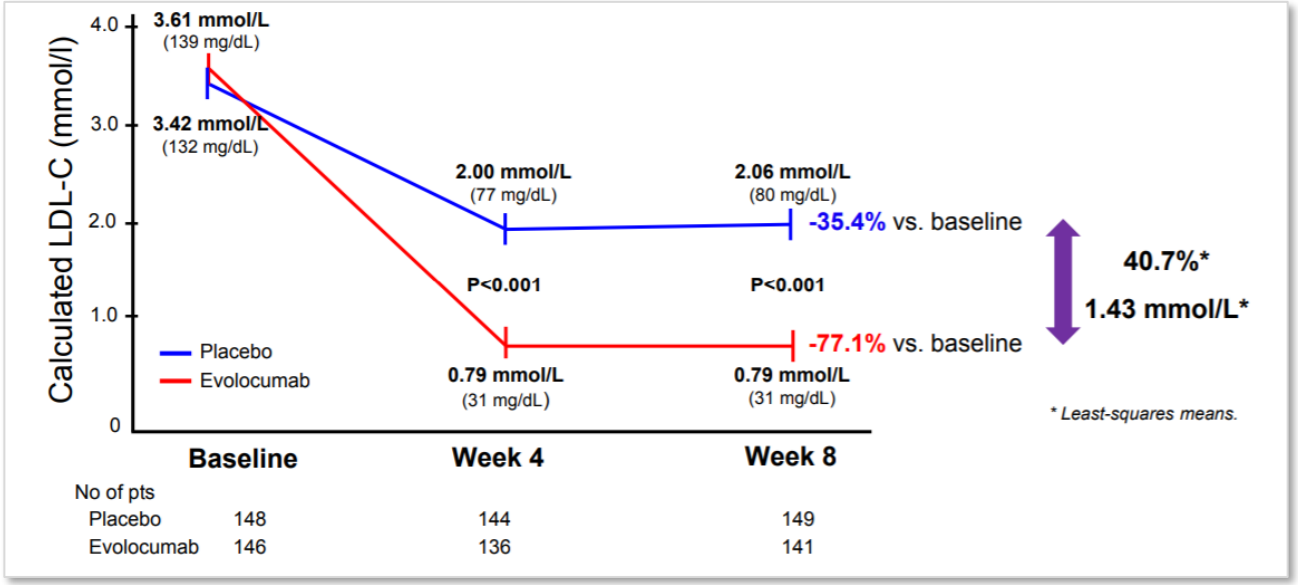


Courtesy Professor Montalescot

PCSK9I AT ACUTE PHASE: EARLY AND WELL-TOLERATED LDL-C REDUCTION

EVOPACS

- **Primary endpoint:** % change LDL-C from baseline to 8 weeks with evolocumab in ACS patients
  - 308 patients hospitalised for ACS with elevated LDL-C levels
  - Randomised 1:1 to receive SC evolocumab 420 mg or matching placebo, administered in-hospital and after 4 weeks, on top of atorvastatin 40 mg



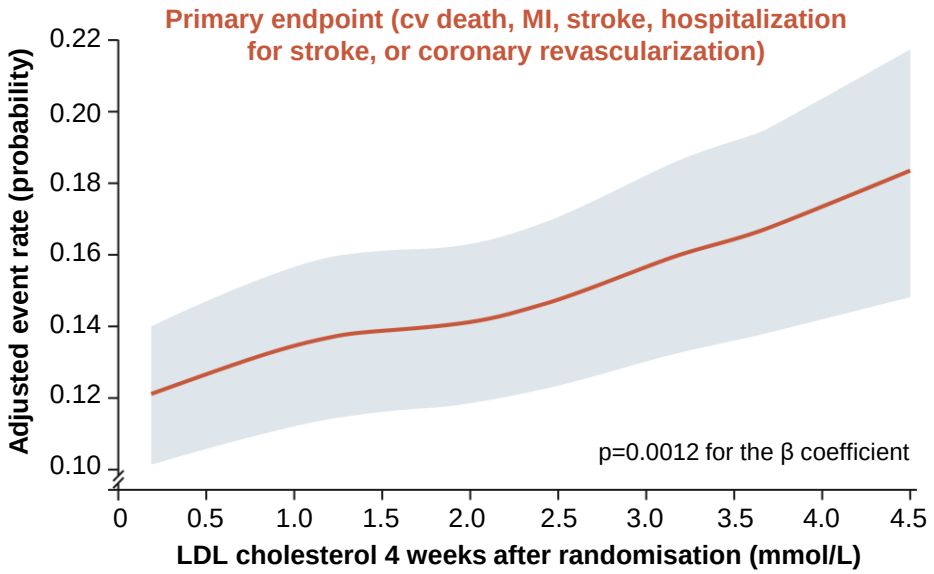
Evolocumab added to high-intensity statin therapy was well tolerated and resulted in substantial reduction in LDL-C levels

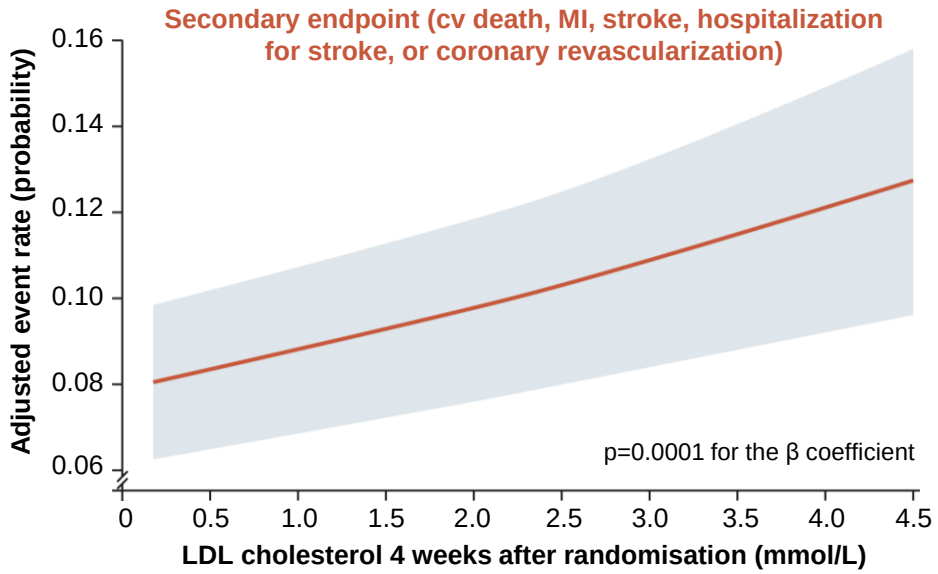
LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; pts, patients; SC, subcutaneous

Adapted from: Koskinas KC, et al. J Am Coll Cardiol. 2019;74:2452-62

IS IT SAFE?

SAFETY AND EFFICACY OF VERY LOW LEVELS OF LDL-C





The risk of primary and secondary composite variables was progressively lower as the LDL-C achieved at week 4 decreased

	Ultra-low LDL cholesterol reached in week 4							
	<10 (N=504)			<15 (N=1,335)			≥100 (N=4,395)	
	N (%)	Adjusted HR (95% CI)	P	N (%)	Adjusted HR (95% CI)	P	N (%)	ARR
Efficacy variables								
Primary efficacy endpoint	37 (7.3)	0.69 (0.49-0.97)	0.0354	105 (7.9)	0.71 (0.56-0.89)	0.0031	521 (11.9)	**4.6**
CV death, MI, stroke	22 (4.4)	0.59 (0.37-0.92)	0.0203	66 (4.9)	0.66 (0.50-0.88)	0.0049	345 (7.8)	**3.4**

RRR 15%
ARR 1.5%

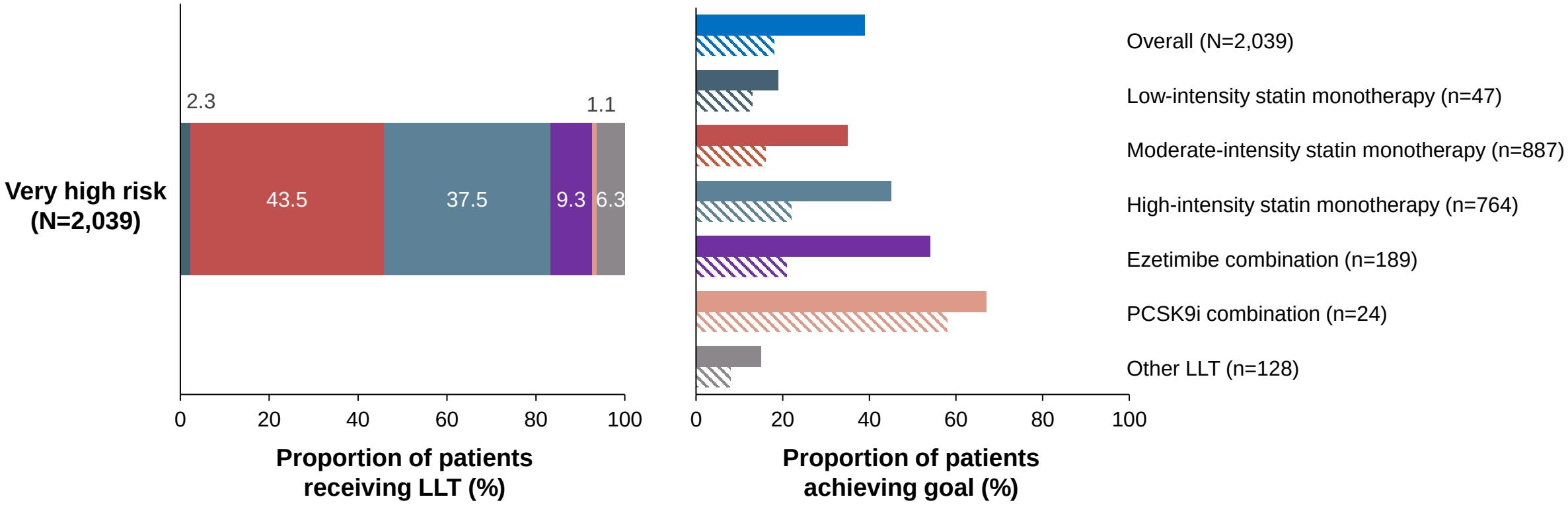
ARR, absolute risk reduction; CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; RRR; relative risk reduction

Giugliano RP, et al. Lancet. 2017;390:1962-71

TO KNOW IS NOT TO DO

THE PROPORTION OF HIGH CV RISK PATIENTS ACHIEVING THE LDL-C TARGETS IS VERY LOW.

THE DA VINCI STUDY



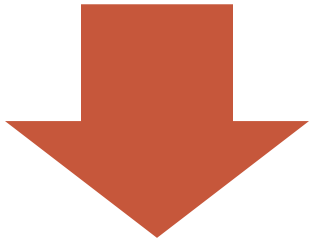
CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; PCSK9, proprotein convertase subtilisin/kexin type 9

Ray KK, et al. Eur J Prev Cardiol. 2021;28:1279-89

CONCLUSIONS TO REMEMBER

1. **All patients with an ACS are at very high risk and frequent recurrent events**
2. **Intense, rapid and long lasting LDL reduction is followed by better prognosis and less events**

"even lower even better"



"even earlier, even better"

COR2ED
THE HEART OF MEDICAL EDUCATION

Expert Knowledge Share
Best Approaches to Treat MI Patients
January 31st, 2023

Best approaches to treat patients with MI (NSTEMI)

Prof. François Mach, MD, FESC
Cardiology Department
Geneva University Hospital
francois.mach@hcuge.ch

Service de Cardiologie

HUG Hôpitaux Universitaires Genève

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

MI, myocardial infarction; NSTEMI, non ST-elevation myocardial infarction

ESC European Society of Cardiology
European Heart Journal (2021) 42, 1289–1367
doi:10.1093/eurheartj/ehaa575

ESC GUIDELINES

2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC)

Authors/Task Force Members: Jean-Philippe Collet * (Chairperson) (France), Holger Thiele * (Chairperson) (Germany), Emanuele Barbato (Italy), Olivier Barthélémy (France), Johann Bauersachs (Germany), Deepak L. Bhatt (United States of America), Paul Dendale (Belgium), Maria Dorobantu (Romania), Thor Edvardsen (Norway), Thierry Folliguet (France), Chris P. Gale (United Kingdom), Martine Gilard (France), Alexander Jobs (Germany), Peter Jüni (Canada), Ekaterini Lambrinou (Cyprus), Basil S. Lewis (Israel), Julinda Mehilli (Germany), Emanuele Meliga (Italy), Béla Merkely (Hungary), Christian Mueller (Switzerland), Marco Roffi (Switzerland), Frans H. Rutten (Netherlands), Dirk Sibbing (Germany), George C.M. Siontis (Switzerland)

2.3 What is new?

New key recommendations

Diagnosis

As an alternative to the ESC 0 h/1 h algorithm, it is recommended to use the ESC 0 h/2 h algorithm with blood sampling at 0 h and 2 h, if an hs-cTn test with a validated 0 h/2 h algorithm is available.

For diagnostic purposes, it is not recommended to routinely measure additional biomarkers such as CK, CK-MB, h-FABP, or copeptin, in addition to hs-cTn.

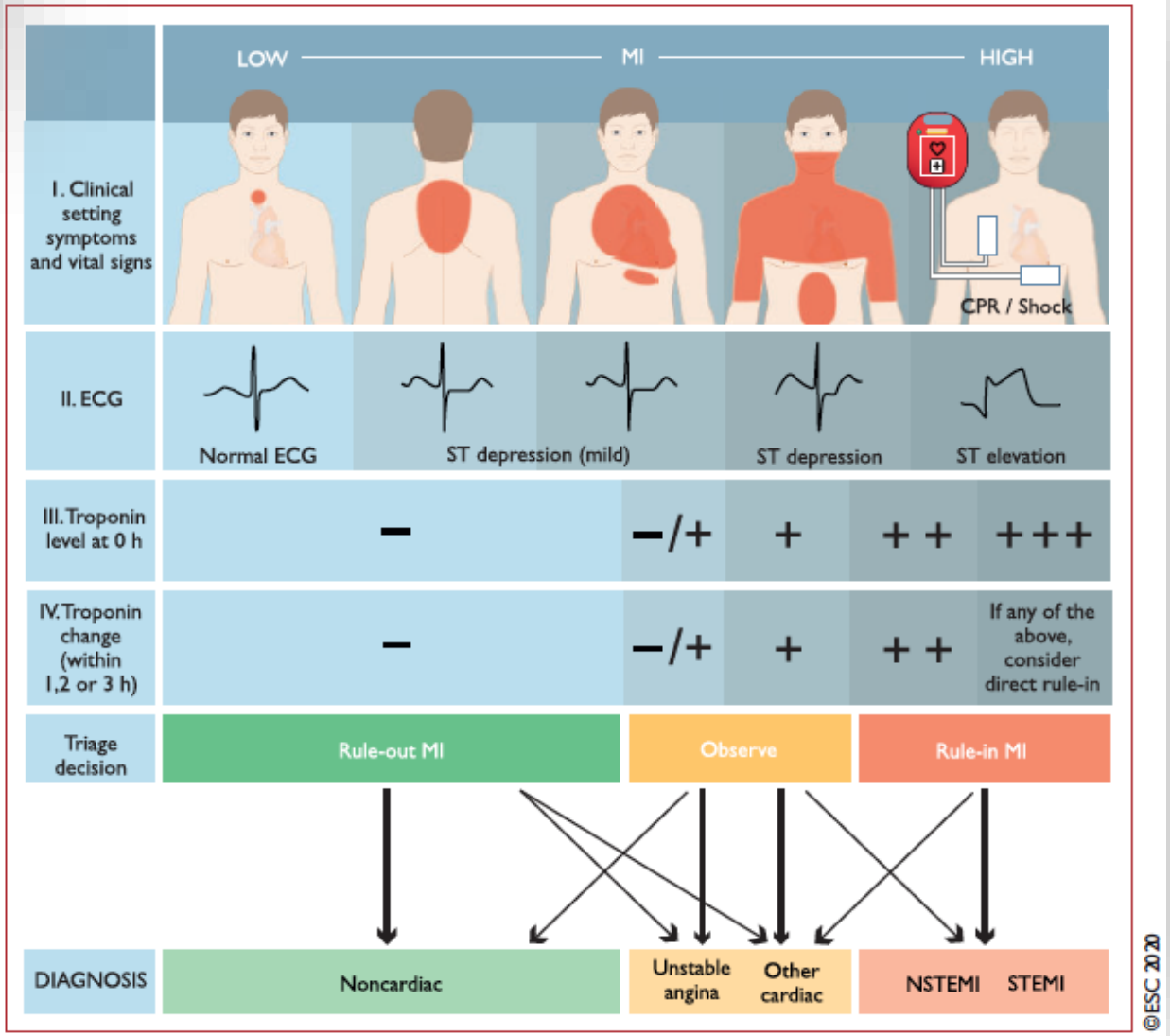
Risk stratification

Measuring BNP or NT-proBNP plasma concentrations should be considered to gain prognostic information.

ACS, acute coronary syndromes; BNP, B-type natriuretic peptide; CK, creatine kinase; CK-MB, creatine kinase myocardial band; ESC, European Society of Cardiology; h, hour; h-FABP, heart-type fatty acid-binding protein; hs-cTn, high-sensitivity cardiac troponin; NT-proBNP, N-terminal pro-B-type natriuretic peptide; STEMI, ST-elevation myocardial infarction
Collet JP, et al. Eur Heart J. 2021;42:1289-367

ESC European Society of Cardiology
European Heart Journal (2021) 42, 1289–1367
doi:10.1093/eurheartj/ehaa575
ESC GUIDELINES

2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation



CPR, cardiopulmonary resuscitation; ECG, electrocardiogram/electrocardiography; MI, myocardial infarction; NSTEMI, non ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction
Collet JP, et al. Eur Heart J. 2021;42:1289-367

ESC European Society of Cardiology
European Heart Journal (2021) 42, 1289–1367
doi:10.1093/eurheartj/ehaa575

2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

Antithrombotic treatment

Prasugrel should be considered in preference to ticagrelor for NSTE-ACS patients who proceed to PCI.

It is not recommended to administer routine pre-treatment with a $P2Y_{12}$ receptor inhibitor to patients in whom the coronary anatomy is not known and early invasive management is planned.

In patients with NSTE-ACS who cannot undergo an early invasive strategy, pre-treatment with a $P2Y_{12}$ receptor inhibitor may be considered depending on bleeding risk.

De-escalation of $P2Y_{12}$ inhibitor treatment (e.g. with a switch from prasugrel or ticagrelor to clopidogrel) may be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for potent platelet inhibition. De-escalation may be done unguided based on clinical judgment, or guided by platelet function testing, or CYP2C19 genotyping depending on the patient's risk profile and availability of respective assays.

In patients with AF (CHA_2DS_2-VASc score ≥1 in men and ≥2 in women), after a short period of TAT (up to 1 week from the acute event), DAT is recommended as the default strategy using a NOAC at the recommended dose for stroke prevention and single oral antiplatelet agent (preferably clopidogrel).

Discontinuation of antiplatelet treatment in patients treated with OACs is recommended after 12 months.

DAT with an OAC and either ticagrelor or prasugrel may be considered as an alternative to TAT with an OAC, aspirin, and clopidogrel in patients with a moderate or high risk of stent thrombosis, irrespective of the type of stent used.

Invasive treatment

An early invasive strategy within 24 h is recommended in patients with any of the following high-risk criteria:

- Diagnosis of NSTEMI.
- Dynamic or presumably new contiguous ST/T-segment changes suggesting ongoing ischaemia.
- Transient ST-segment elevation.
- GRACE risk score >140.

A selective invasive strategy after appropriate ischaemia testing or detection of obstructive CAD by CCTA is recommended in patients considered at low risk.

Delayed, as opposed to immediate, angiography should be considered in haemodynamically stable patients without ST-segment elevation successfully resuscitated after an out-of-hospital cardiac arrest.

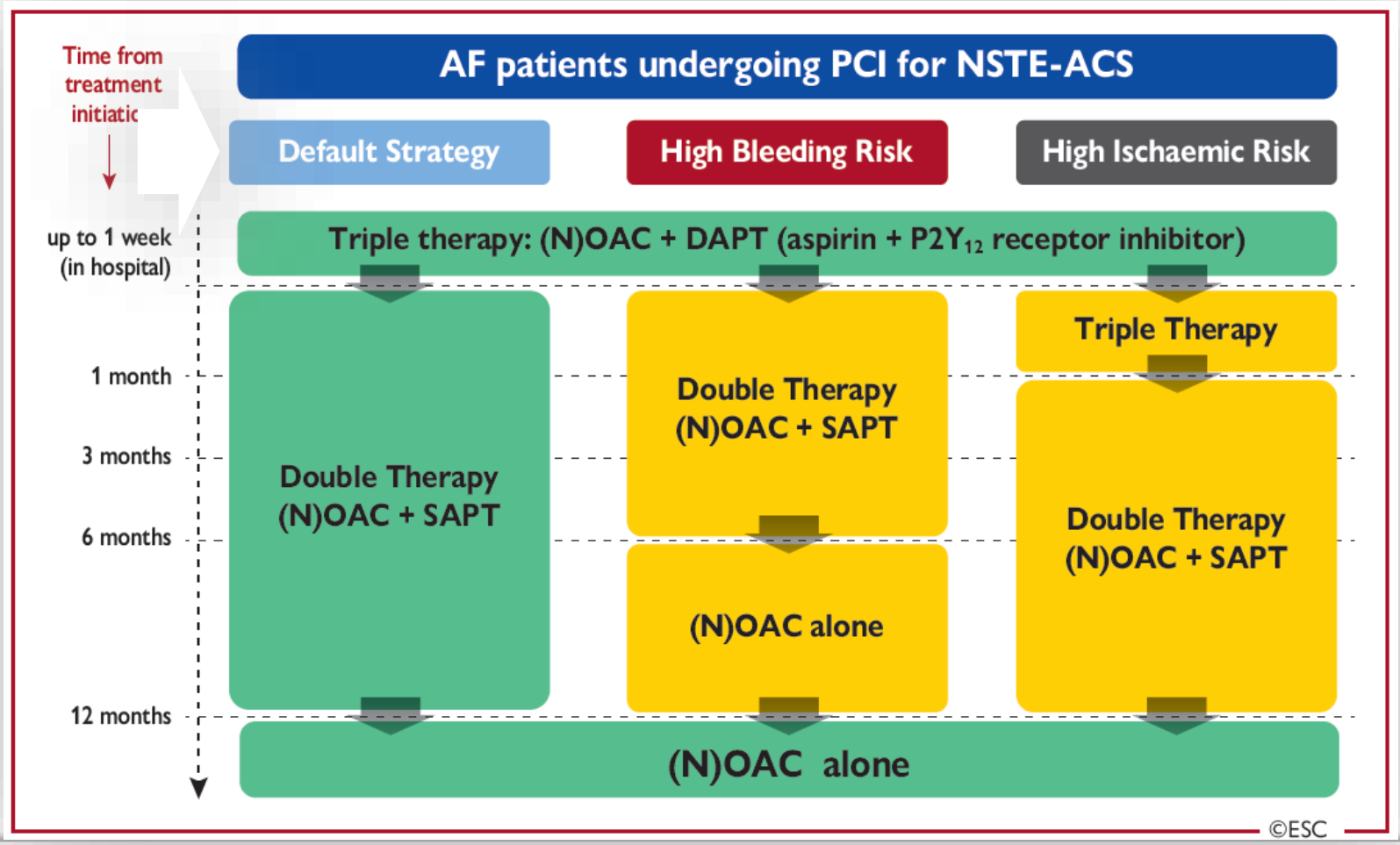
Complete revascularization should be considered in NSTE-ACS patients without cardiogenic shock and with multivessel CAD.

Complete revascularization during index PCI may be considered in NSTE-ACS patients with multivessel disease.

FFR-guided revascularization of non-culprit NSTE-ACS lesions may be used during index PCI.

ACS, acute coronary syndromes; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CHA2DS2-VASc, Congestive heart failure, Hypertension, Age >_75 years (2 points), Diabetes, Stroke (2 points) Vascular disease, Age 65-74, Sex category (female); DAPT, dual antiplatelet therapy; DAT, dual antithrombotic therapy; FFR, fractional flow reserve; GRACE, Global Registry of Acute Coronary Events; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; NOAC, oral anticoagulation/anticoagulant; NSTEMI, non-ST-segment elevation myocardial infarction; OAC, oral anticoagulation/anticoagulant; PCI, percutaneous coronary intervention; TAT, triple antithrombotic therapy
Collet JP, et al. Eur Heart J. 2021;42:1289-367

Antithrombotic therapy in patients with AF with NSTE-ACS undergoing PCI or medical management



Green (Class I)
Yellow (Class IIa)

ACS, acute coronary syndromes; AF, atrial fibrillation; DAPT, dual antiplatelet therapy; (N)OAC, oral anticoagulation/anticoagulant; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; SAPT, single antiplatelet therapy

Collet JP, et al. Eur Heart J. 2021;42:1289-367

Risk stratification for an early invasive approach

Very high risk

- Haemodynamic instability
- Cardiogenic shock
- Recurrent/refractory chest pain despite medical treatment
- Life-threatening arrhythmias
- Mechanical complications of MI
- Acute heart failure clearly related to NSTE-ACS
- ST-segment depression >1 mm/6 leads plus ST-segment elevation aVr and/or V1

Immediate (<2 hours) angiography

High risk

Established NSTEMI diagnosis

Dynamic new or presumably new contiguous ST/S-segment changes (symptomatic or silent)

Resuscitated cardiac arrest without ST-segment elevation or cardiogenic shock*

GRACE risk score >140

Angiography within 24 hours

Low risk

Lack of any of the very high or high risk characteristics

Angiography vs noninvasive testing

No more intermediate risk (2015 guidelines)

Intermediate-risk criteria
• Diabetes mellitus
• Renal insufficiency (eGFR <60 mL/min/1.73 m²)
• LVEF <40% or congestive heart failure
• Early post-infarction angina
• Prior PCI
• Prior CABG
• GRACE risk score >109 and <140

* Delayed angiography

aVr, augmented vector right; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; GRACE, Global Registry of Acute Coronary Events; LVEF, left-ventricular ejection fraction; MI, myocardial infarction; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; NSTEMI, non ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention

Collet JP, et al. Eur Heart J. 2021;42:1289-367
Roffi M, et al. Eur Heart J. 2016;37:267-315

Timing of coronary angiography in transient ST-elevation

Recommendations	Class	Level
Timing of invasive strategy		
An early invasive strategy **within 24 h** is recommended in patients with any of the following high-risk criteria: • Diagnosis of NSTEMI suggested by the diagnostic algorithm recommended in Section 3 • Dynamic or presumably new contiguous ST/T-segment changes suggesting ongoing ischaemia • Transient ST-segment elevation • GRACE risk score >140	I	A

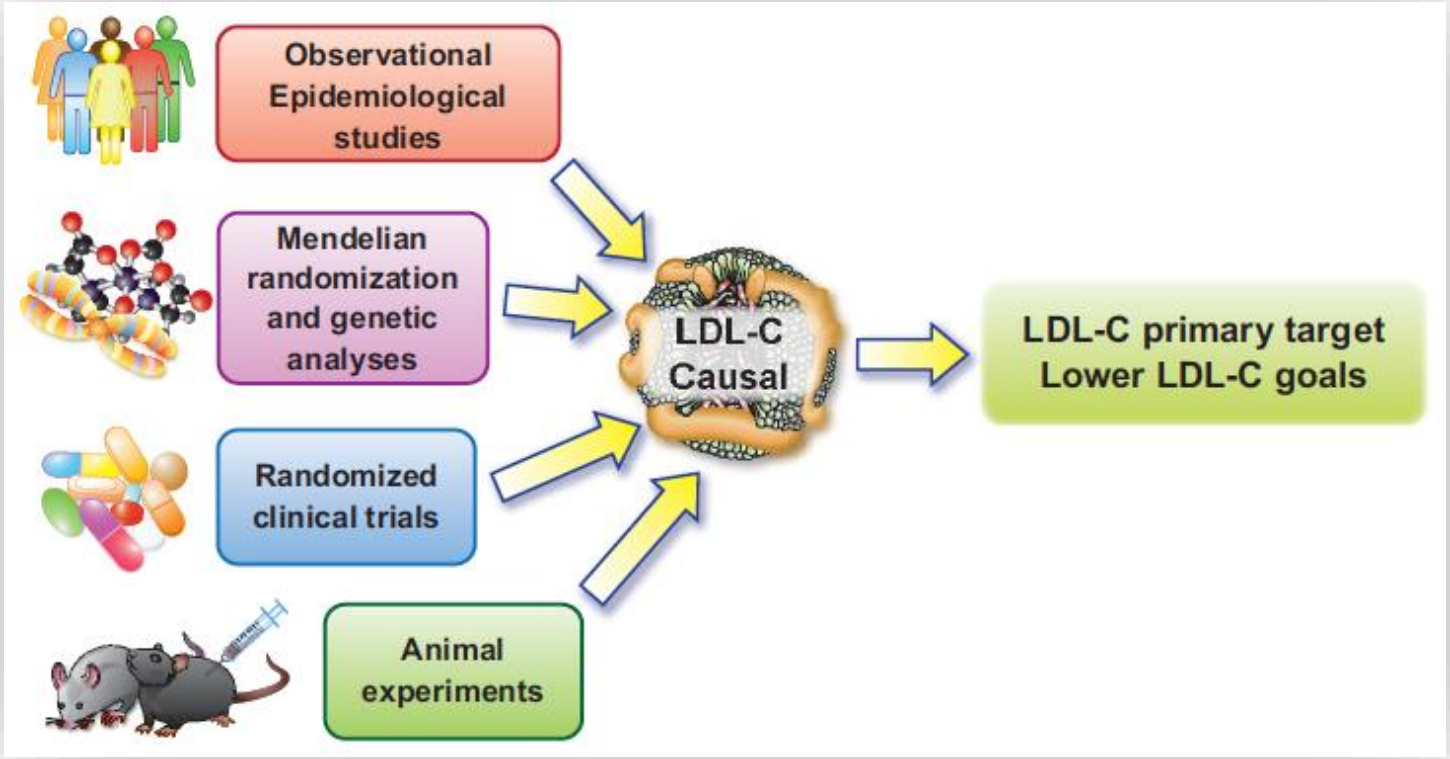
ESC 2015 NSTE-ACS Guide Lines →
immediate angiography for transient ST-elevation

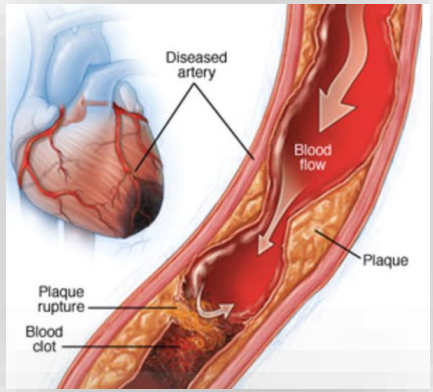
ESC, European Society of Cardiology; GRACE, Global Registry of Acute Coronary Events; h, hours; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; NSTEMI, non ST-segment elevation myocardial infarction

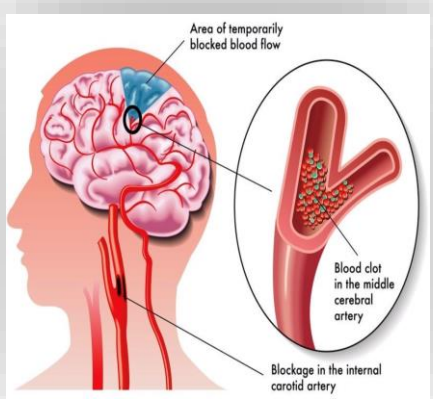
Collet JP, et al. Eur Heart J. 2021;42:1289-367
Roffi M, et al. Eur Heart J. 2016;37:267-315

Clear relationship between LDL-C and risk of CV events

LDL-C is the main driver for atherosclerosis: four compelling lines of evidence

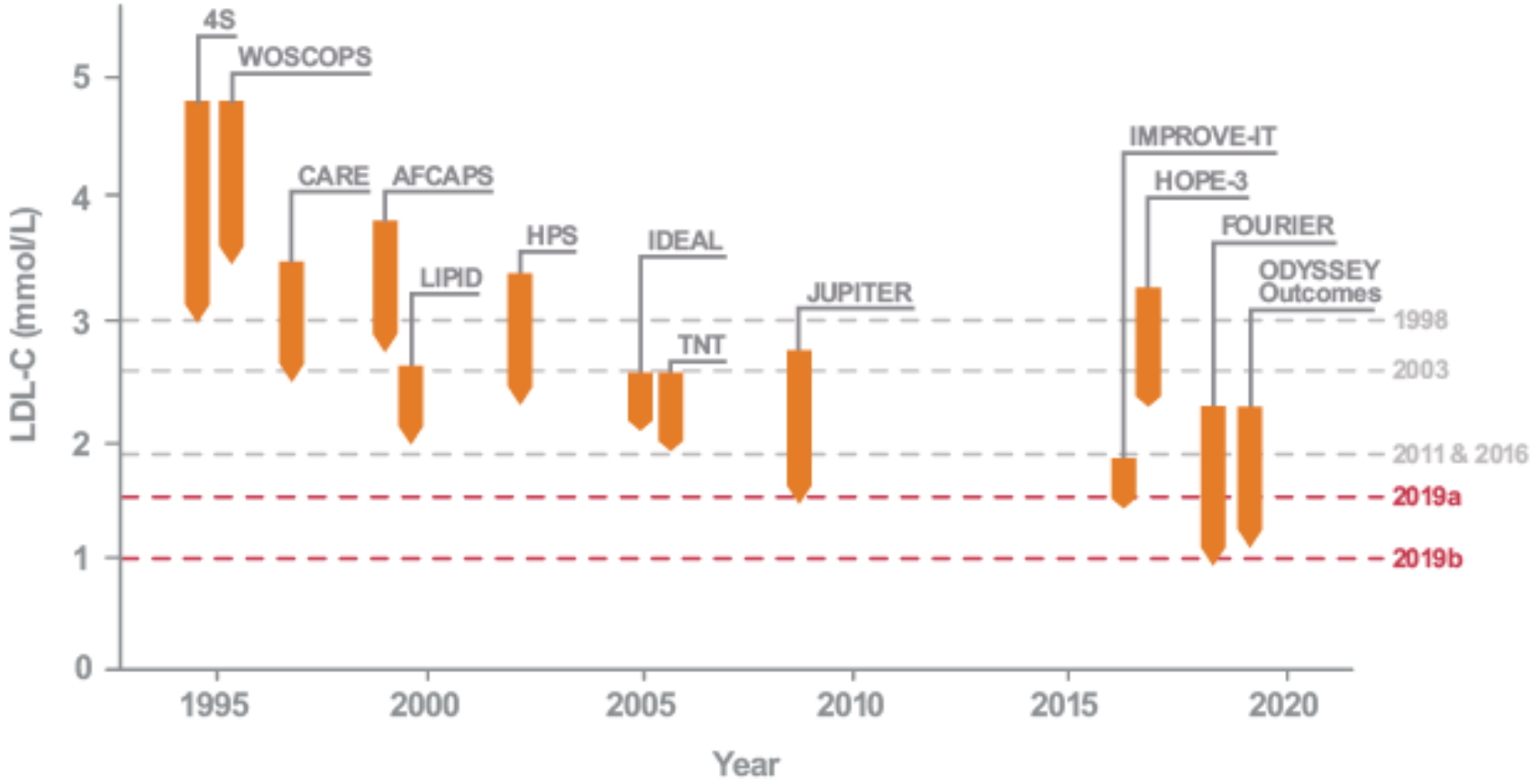






CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol
Tokgözoğlu L, Libby P. Eur Heart J. 2022;43:3198-208

History of LDL-C lowering trials



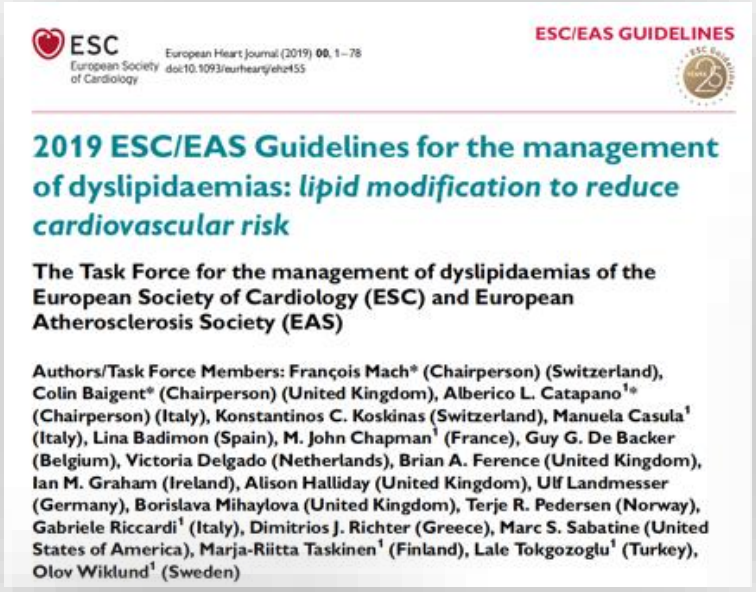
This schematic depicts average baseline (top of orange arrow) and on-treatment LDL-C levels (bottom of orange arrow)
Grey dotted lines represent previous recommended LDL-C ESC/EAS goals for intervention and the red dotted lines (2019a,b) represent the current LDL-C ESC/EAS goals
ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; LDL-C, low-density lipoprotein cholesterol
Packard C, et al. Heart. 2021;107:1369-75

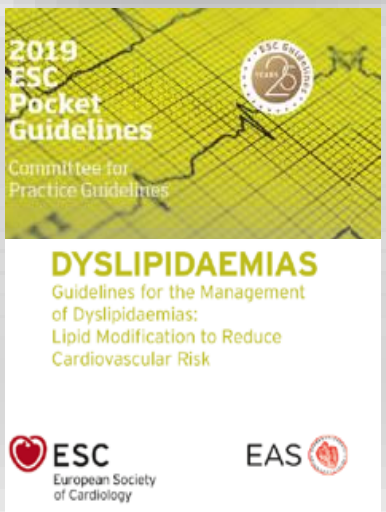
Evidence for efficacy of LDL-lowering therapies down to below 1.4 mmol/L (55 mg/dL)

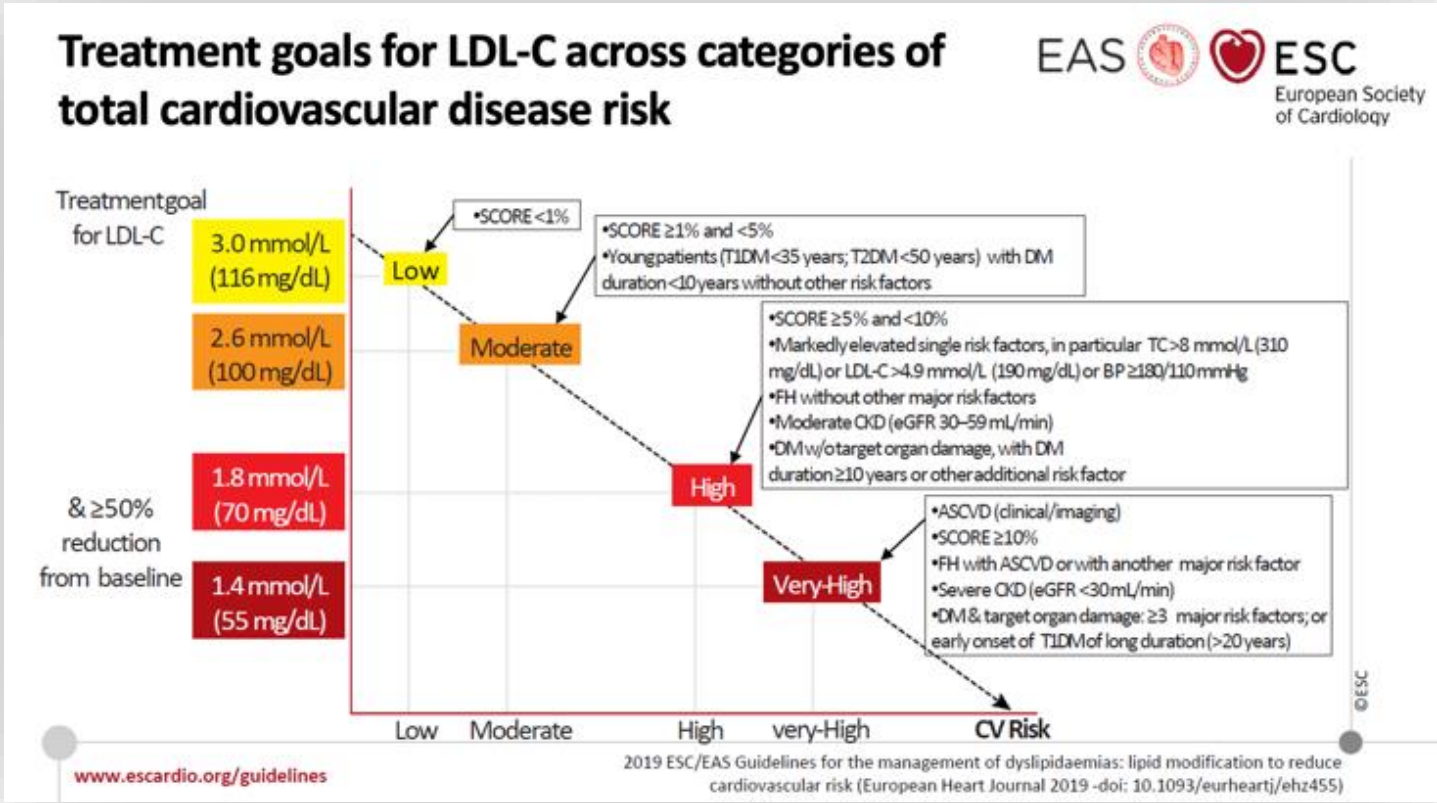
Source of evidence	Mean reduction in LDL cholesterol; mmol/L [mg/dL]	Outcome	RR (95% CI)
CTT meta-analysis[1] (high-intensity vs standard statin; subgroup <2.0 mmol/L)	1.71 [66] vs 1.32 [50]	MI, CHD death, stroke, coronary revascularisation	0.71 (0.56-0.91) [per mmol/L]
IMPROVE-IT[2] (ezetimibe plus statin vs statin)	1.80 [70] vs 1.40 [54]	CV death, MI, stroke, UA, coronary revascularisation	0.94 (0.89-0.99)
FOURIER[3] (evolocumab plus high-dose statin ± ezetimibe vs high-dose statin ± ezetimibe)	2.37 [92] vs 0.78 [30]	CV death, MI, stroke, UA, coronary revascularisation	0.85 (0.79-0.92)
ODYSSEY OUTCOMES[4] (alirocumab plus high-dose statin ± ezetimibe vs high-dose statin ± ezetimibe)	2.37 [92] vs 1.37 [53]	MI, CHD death, stroke, UA	0.85 (0.78-0.93)

CI, confidence interval; CHD, coronary heart disease; CTT, Cholesterol Treatment Trialists; CV, cardiovascular; ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; LDL, low-density lipoprotein; MI, myocardial infarction; RR, relative risk; UA, unstable angina

Adapted from: 1. CTT Collaboration, et al. Lancet. 2010;376:1670-81. 2. Cannon CP, et al. N Engl J Med. 2015;372:2387-97. 3. Sabatine MS, et al. N Engl J Med. 2017;376:1713-22. 4. Schwartz GG, et al. N Engl J Med. 2018;379:2097-107 5. Mach F, et al. Eur Heart J. 2020;41:111-88







ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CKD, chronic kidney disease; DM, diabetes mellitus; ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; eGFR, estimated glomerular filtration rate; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; SCORE, Systematic Coronary Risk Estimation; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TC, total cholesterol

Mach F, et al. Eur Heart J. 2020;41:111-88

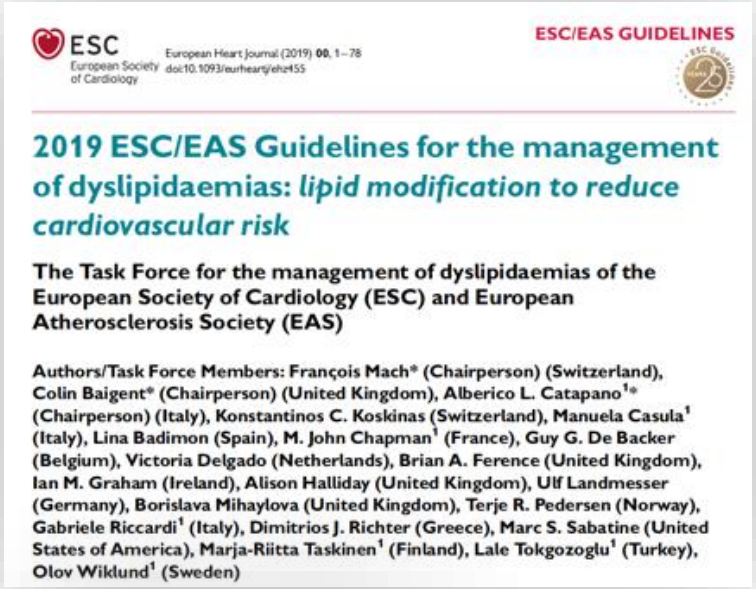
www.escardio.org/guidelines

Recommendations for LDL-C lowering

Recommendations	Class	Level
For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered.	IIb	B

ASCVD, atherosclerotic cardiovascular disease; ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; LDL-C, low-density lipoprotein cholesterol

Mach F, et al. Eur Heart J. 2020;41:111-88



ESC European Society of Cardiology

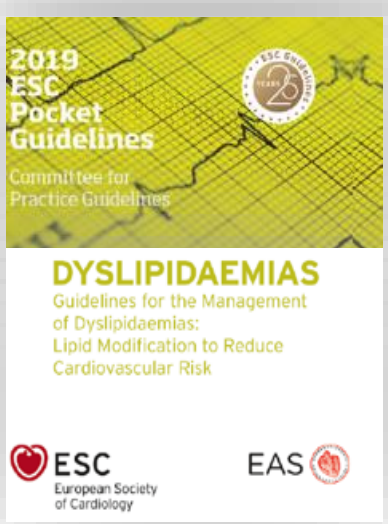
European Heart Journal (2019) 00, 1–78
doi:10.1093/eurheartj/ehz455

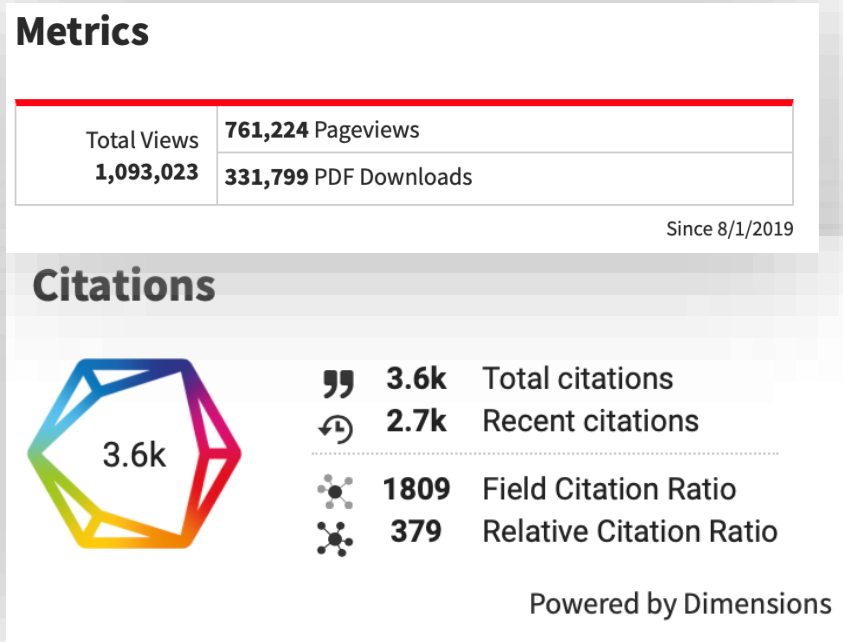
ESC/EAS GUIDELINES

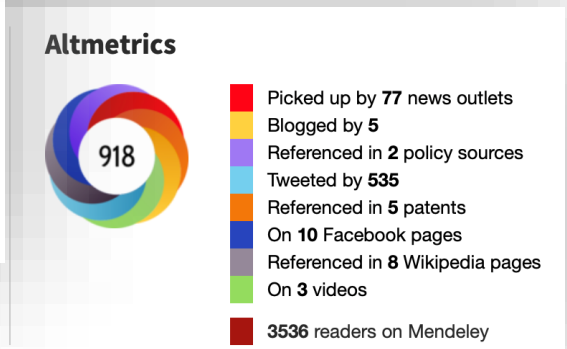
2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Authors/Task Force Members: François Mach* (Chairperson) (Switzerland), Colin Baigent* (Chairperson) (United Kingdom), Alberico L. Catapano[1]* (Chairperson) (Italy), Konstantinos C. Koskinas (Switzerland), Manuela Casula[1] (Italy), Lina Badimon (Spain), M. John Chapman[1] (France), Guy G. De Backer (Belgium), Victoria Delgado (Netherlands), Brian A. Ference (United Kingdom), Ian M. Graham (Ireland), Alison Halliday (United Kingdom), Ulf Landmesser (Germany), Borislava Mihaylova (United Kingdom), Terje R. Pedersen (Norway), Gabriele Riccardi[1] (Italy), Dimitrios J. Richter (Greece), Marc S. Sabatine (United States of America), Marja-Riitta Taskinen[1] (Finland), Lale Tokgozoglu[1] (Turkey), Olov Wiklund[1] (Sweden)







ESC/EAS, European Society of Cardiology/European Atherosclerosis Society
Mach F, et al. Eur Heart J. 2020;41:111-88

Intensity of pharmacological LDL-C lowering

Intensity of lipid lowering treatment

Treatment	Average LDL-C reduction
Moderate intensity statin	≈ 30%
High intensity statin	≈ 50%
High intensity statin plus ezetimibe	≈ 65%
PCSK9 inhibitor	≈ 60%
PCSK9 inhibitor plus high intensity statin	≈ 75%
PCSK9 inhibitor plus high intensity statin plus ezetimibe	≈ 85%

LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9
Mach F, et al. Eur Heart J. 2020;41:111-88

Recommendations for pharmacological LDL-C lowering

Recommendations	Class	Level
It is recommended to prescribe a high-intensity statin up to the highest tolerated dose to reach the goals[c] set for the specific level of risk.	I	A
If the goals[c] are not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended.	I	B

LDL-C, low-density lipoprotein cholesterol
Mach F, et al. Eur Heart J. 2020;41:111-88

Recommendations for pharmacological LDL-C lowering

Recommendations	Class	Level
For secondary prevention, patients at very-high risk not achieving their goal[c] on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.	I	A
For primary prevention patients at very-high risk, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor may be considered.	IIb	C

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

Mach F, et al. Eur Heart J. 2020;41:111-88

Recommendations for lipid-lowering therapy in very-high-risk patients with ACS

Recommendations	Class[a]	Level[b]
If the LDL-C goal is not achieved after 4–6 weeks despite maximal tolerated statin therapy and ezetimibe, adding a PCSK9 inhibitor is recommended.	I	B
In patients with confirmed statin intolerance or in patients in whom a statin is contra-indicated, ezetimibe should be considered.	IIa	C
For patients who present with an ACS and whose LDL-C levels are not at goal despite already taking a maximally tolerated statin dose and ezetimibe, adding a PCSK9 inhibitor early after the event (if possible, during hospitalization for the ACS event) should be considered.	IIa	C

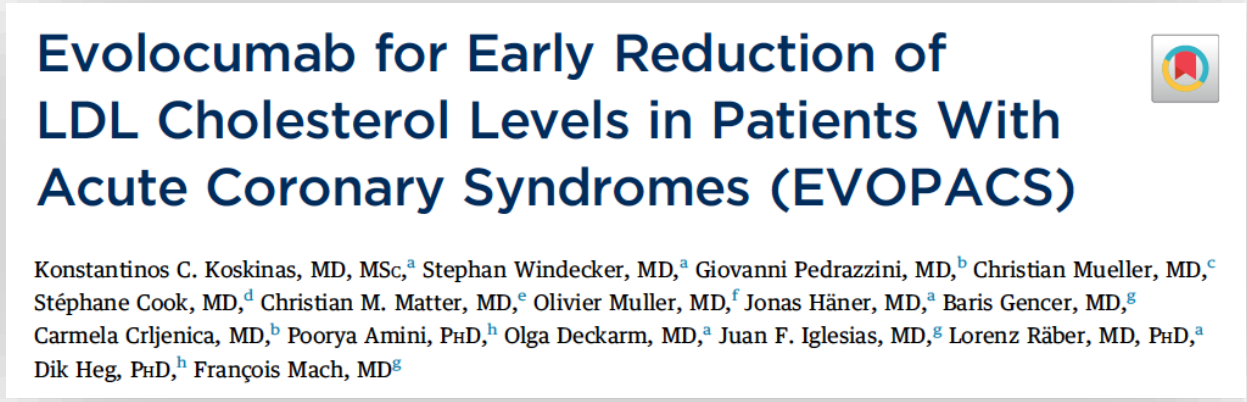
ACS, acute coronary syndromes; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9

Mach F, et al. Eur Heart J. 2020;41:111-88

Summary

In patients presenting with ACS and elevated LDL-C levels, in-hospital initiation of evolocumab on top of high-intensity statin therapy for 8 weeks:

- Achieved average LDL-C levels of **0.79 mmol/L** vs **2.06 mmol/L** with statin alone
- Led **>90%** of patients (vs **11%** of placebo-treated patients) to be within currently recommended target levels of LDL-C
- Was **well tolerated** during the short duration of the study
- Did not result in measurable differences in surrogate outcomes:
  - Inflammatory biomarkers
  - Platelet reactivity
  - Acute kidney injury
  - Myocardial injury



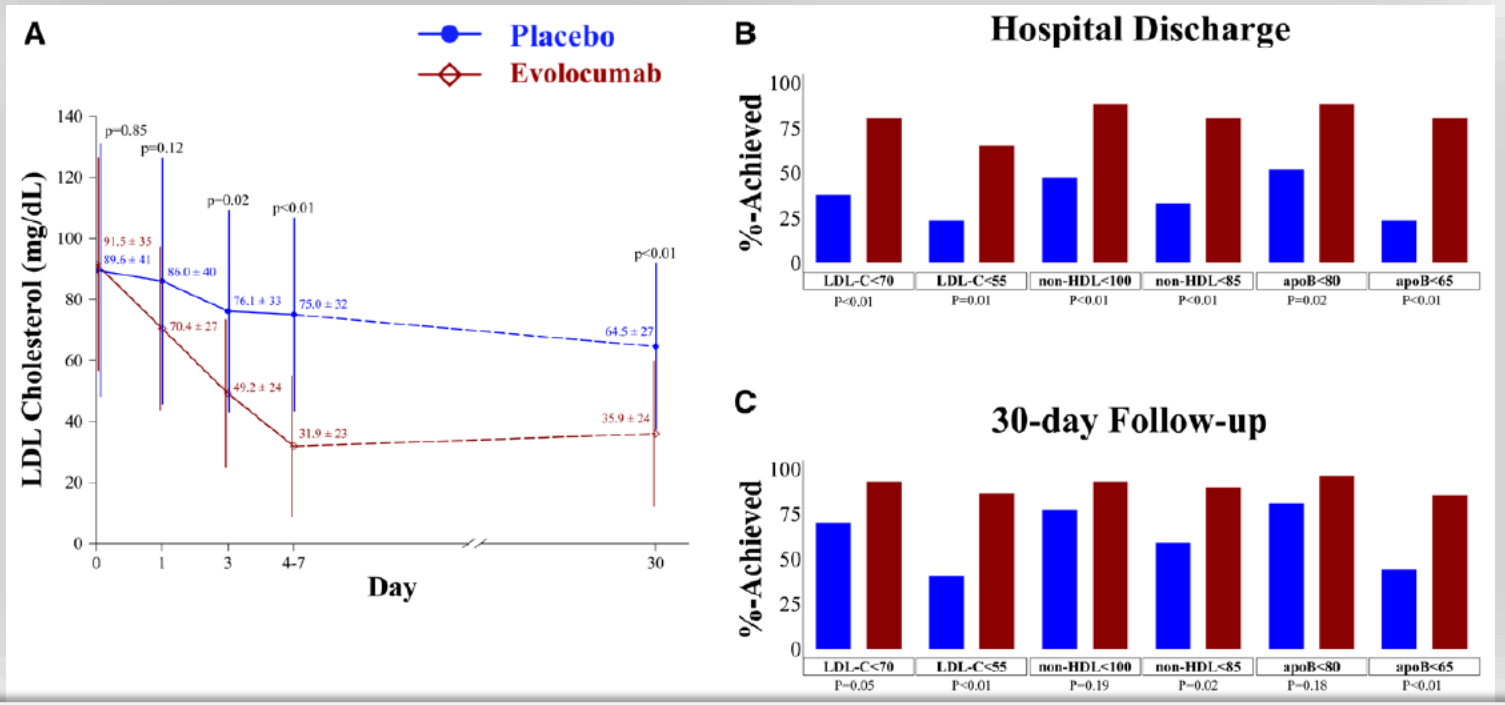
ACS, acute coronary syndromes; LDL-C, low-density lipoprotein cholesterol
Koskinas KC, et al. J Am Coll Cardiol. 2019;74:2452-62

LDL-C: should we go lower after ACS ?

RESEARCH LETTER

Effect of Evolocumab on Atherogenic Lipoproteins During the Peri- and Early Postinfarction Period

A Placebo-Controlled, Randomized Trial



ACS, acute coronary syndromes; LDL-C, low-density lipoprotein cholesterol

Leucker TM, et al. Circulation. 2020;142:419-21

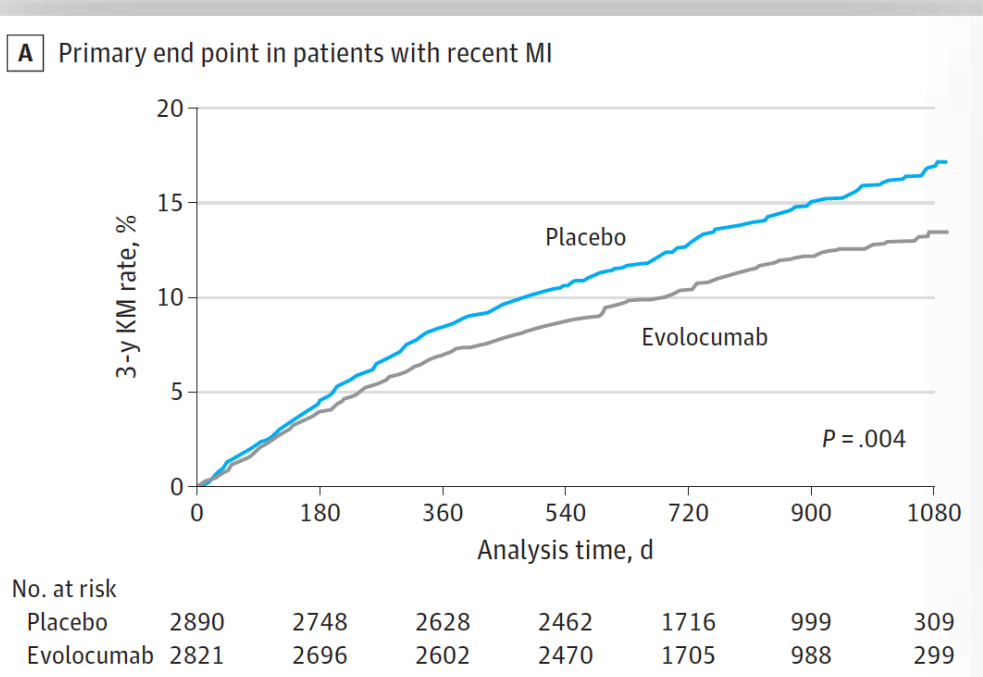
PCSK9 mAbs: efficacy after recent MI

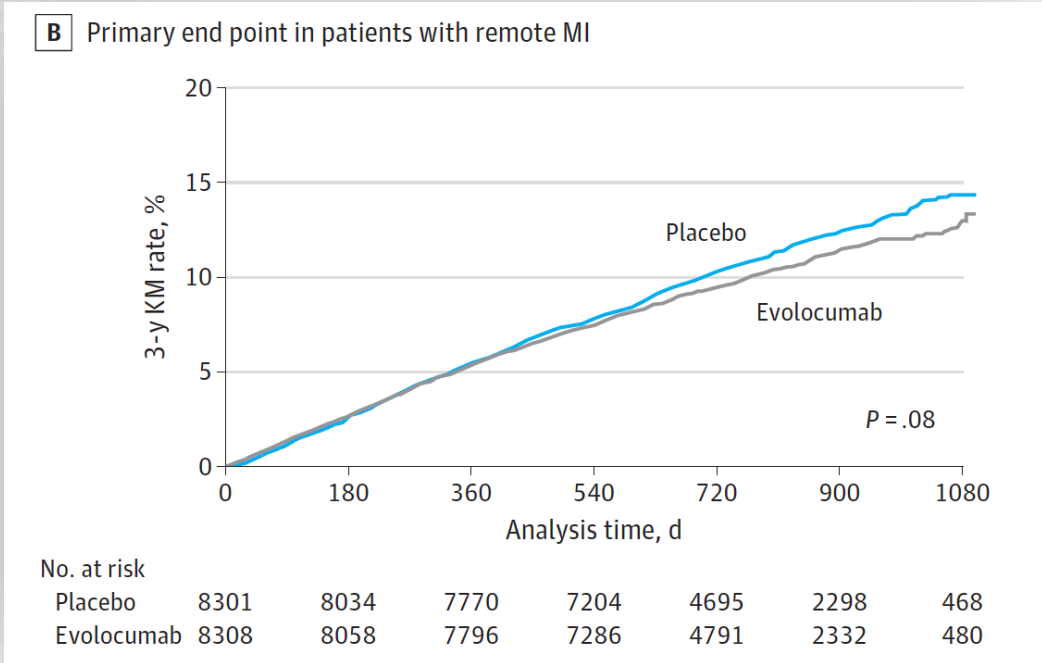
JAMA Cardiology | Brief Report

Efficacy of Evolocumab on Cardiovascular Outcomes in Patients With Recent Myocardial Infarction

A Prespecified Secondary Analysis From the FOURIER Trial

Baris Gencer, MD; François Mach, MD; Sabina A. Murphy, MPH; Gaetano M. De Ferrari, MD; Kurt Huber, MD; Basil S. Lewis, MD; Jorge Ferreira, MD; Christopher E. Kurtz, MD; Huei Wang, PhD; Narimon Honarpour, MD; Anthony C. Keech, MD; Peter S. Sever, MD; Terje R. Pedersen, MD; Marc S. Sabatine, MD, MPH; Robert P. Giugliano, MD, SM





D, day; KM, Kaplan–Meier; MI, myocardial infarction; PCSK9 mAb, proprotein convertase subtilisin/kexin type 9 monoclonal antibody; y, year

Gencer B, et al. JAMA Cardiol. 2020:952-7

PCSK9 mAbs: efficacy after recent MI

JAMA Cardiology | Brief Report

Efficacy of Evolocumab on Cardiovascular Outcomes in Patients With Recent Myocardial Infarction

A Prespecified Secondary Analysis From the FOURIER Trial

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- Patients with recent MI were at higher risk of major adverse CV events compared with those with a remote MI
- In patients with recent MI:
  - Evolocumab reduced the risk of the primary endpoint by 19%, with an NNT of 27 over 3 years
  - The risk of CV death, MI, or stroke was reduced by 25%, with an NNT of 32 over 3 years

CV, cardiovascular; MI, myocardial infarction; NNT, number needed to treat; PCSK9 mAb, proprotein convertase subtilisin/kexin type 9 monoclonal antibody

Gencer B, et al. JAMA Cardiol. 2020:952-7

Long-Term Evolocumab in Patients with Established Atherosclerotic Cardiovascular Disease:

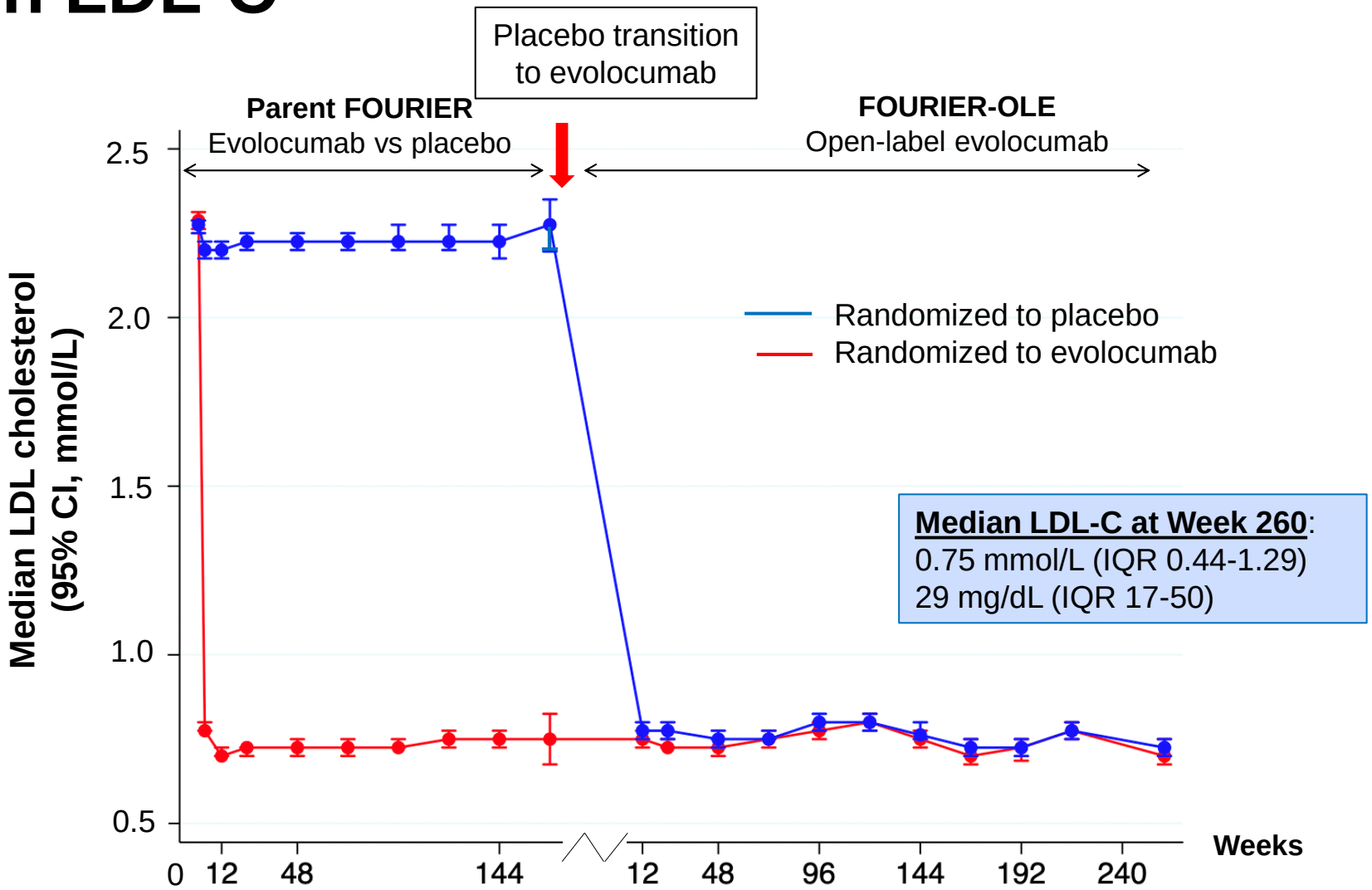
Primary Results of the FOURIER-OLE (Open-Label Extension) Studies

Michelle L. O'Donoghue, Robert P. Giugliano, Sarina Trindade, Dan Atar, Anthony Keech, Julia Kuder, KyungAh Im, Sabina Murphy, Jose H. Flores-Arredondo, J. Antonio G. López, Mary Elliott-Davey, Bei Wang, Maria Laura Monsalvo, Siddique Abbasi, Marc S. Sabatine

- *On Behalf of the FOURIER-OLE Investigators*

O'Donoghue ML, et al. Circulation. 2022;146:1109-19 (Primary results presented at ESC 2022)

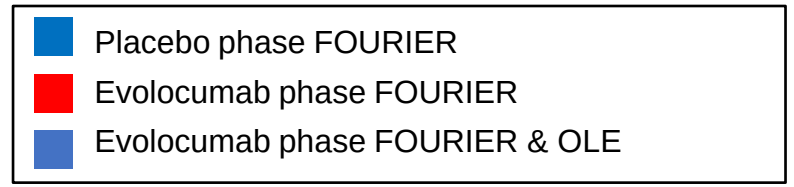
Effect on LDL-C

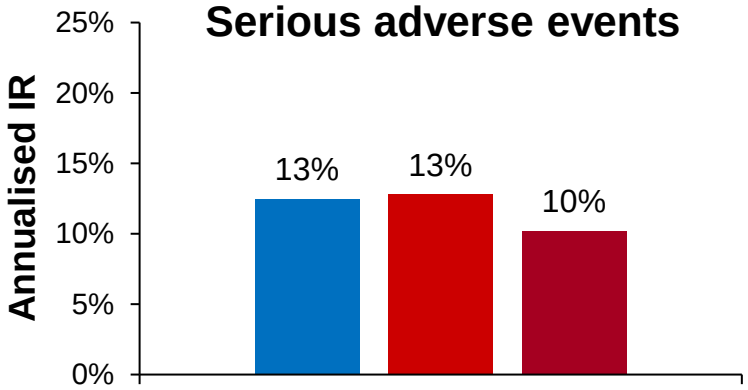


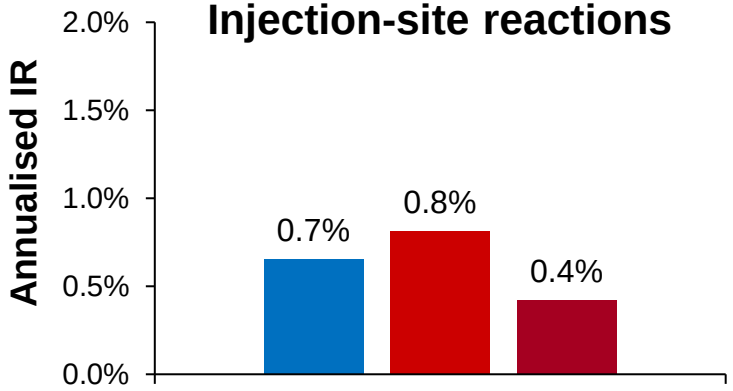
CI, confidence interval; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol

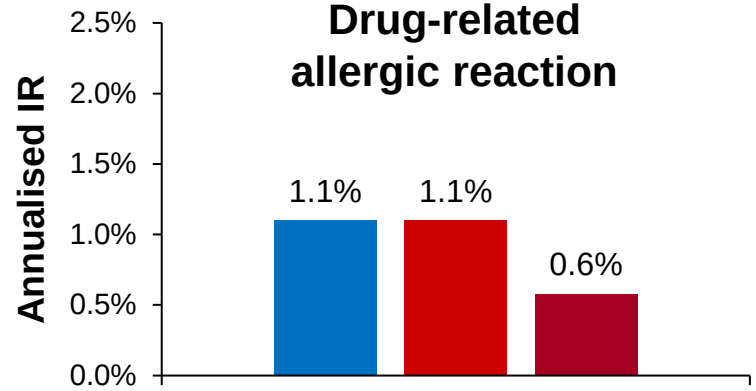
O'Donoghue ML, et al. Circulation. 2022;146:1109-19 (Primary results presented at ESC 2022)

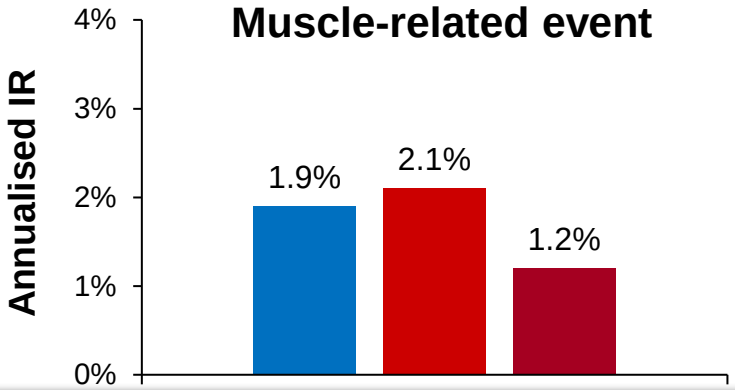
Long-term safety

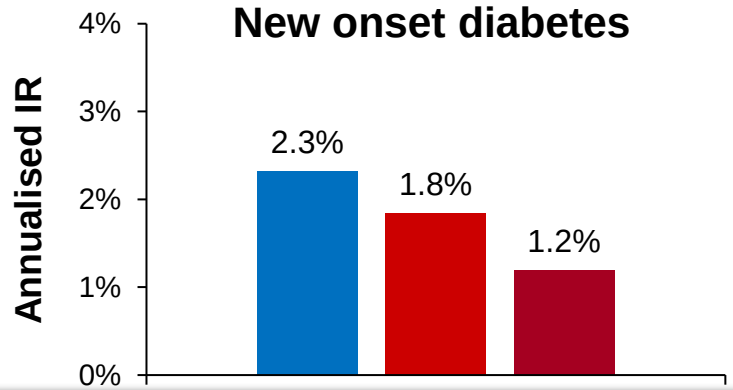


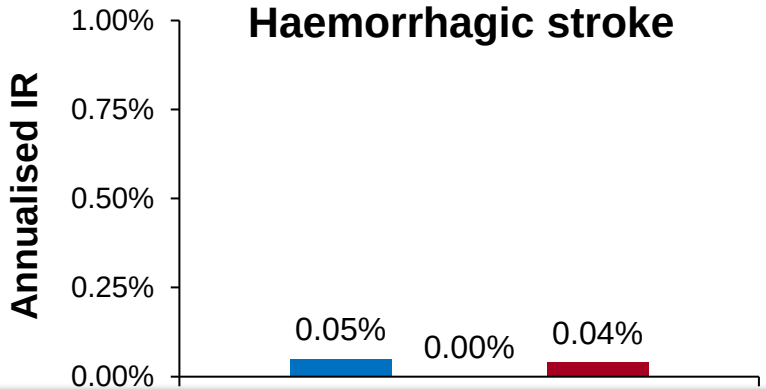








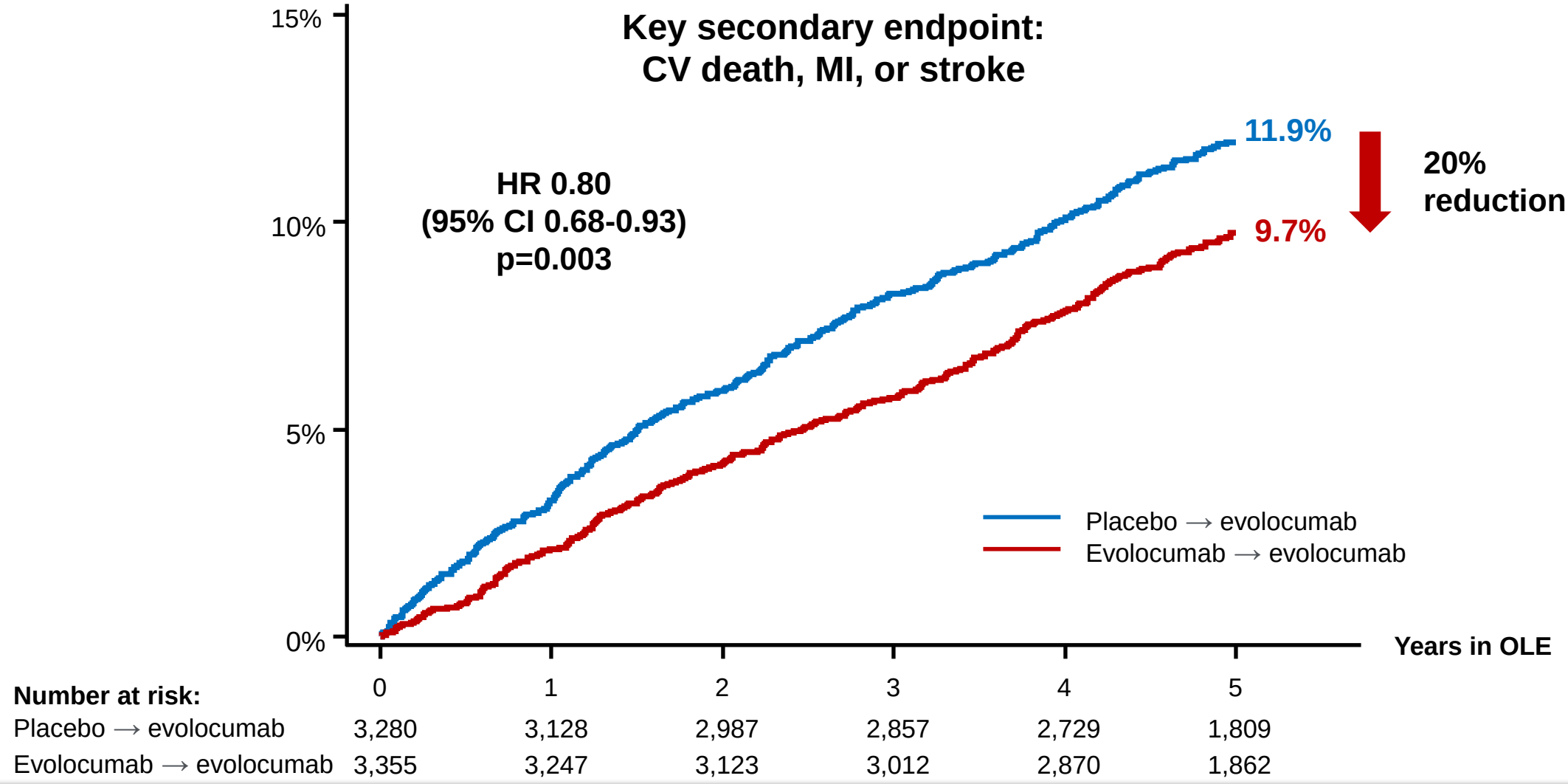




IR, incidence rate

O'Donoghue ML, et al. Circulation. 2022;146:1109-19 (Primary results presented at ESC 2022)

Efficacy during FOURIER-OLE



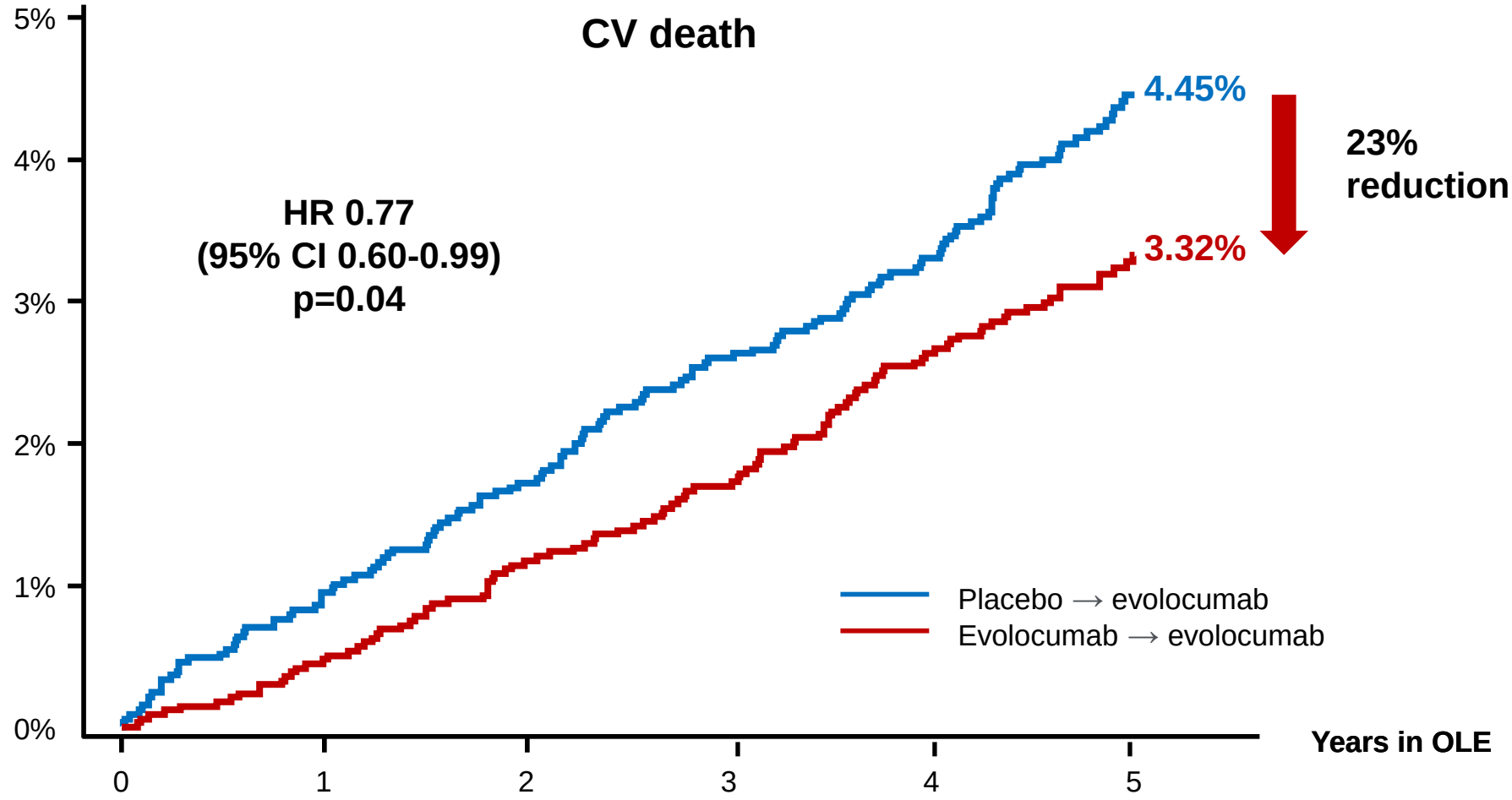
Number at risk:

Placebo → evolocumab	3,280	3,128	2,987	2,857	2,729	1,809
Evolocumab → evolocumab	3,355	3,247	3,123	3,012	2,870	1,862

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; OLE open-label extension

O'Donoghue ML, et al. Circulation. 2022;146:1109-19 (Primary results presented at ESC 2022)

Efficacy during FOURIER-OLE



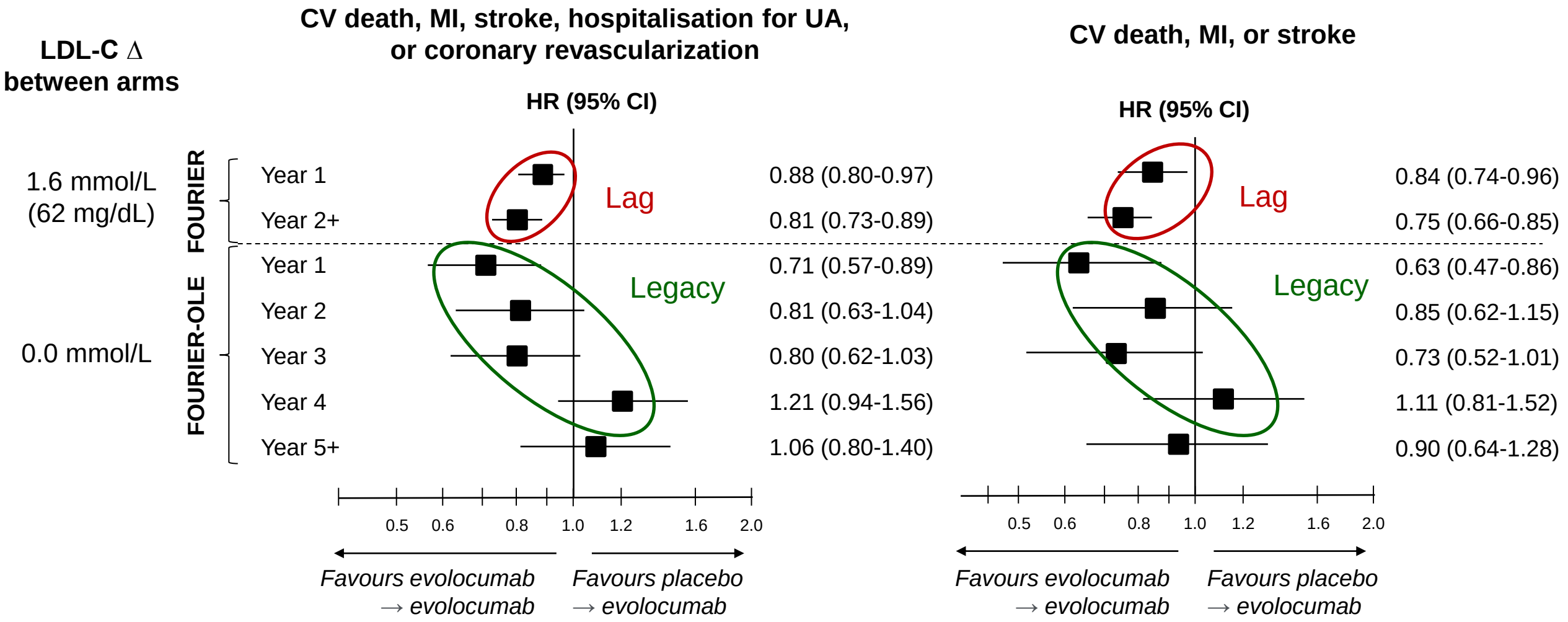
Number at risk:

Placebo → evolocumab	3,280	3,223	3,155	3,081	2,991	2,049
Evolocumab → evolocumab	3,355	3,314	3,244	3,173	3,080	2,069

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; OLE open-label extension

O'Donoghue ML, et al. Circulation. 2022;146:1109-19 (Primary results presented at ESC 2022)

MACE by Year of Study



CI, confidence interval; CV, cardiovascular; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; OLE open-label extension; UA, unstable angina

O'Donoghue ML, et al. Circulation. 2022;146:1109-19 (Primary results presented at ESC 2022)

Safety during FOURIER-OLE

Association Between Achieved LDL-Cholesterol Levels and Long-term Cardiovascular and Safety Outcomes: An Analysis of FOURIER-OLE

Short Title: Long-term Outcomes with Very Low LDL-C

Prakriti Gaba MD[1], Michelle L. O'Donoghue MD MPH[1], Jeong-Gun Park PhD[1], Stephen D. Wiviott MD[1], Dan Atar MD[2], Julia F. Kuder MA[1], KyungAh Im PhD[1], Sabina A. Murphy MPH[1], Gaetano M De Ferrari MD[3], Zbigniew A. Gaciong MD[4], Kalman Toth MD PhD[5], Ioanna Gouni-Berthold MD[6], Jose Lopez-Miranda MD[7], François Schiele MD[8], François Mach MD[9], Jose H. Flores-Arredondo MD[10], J. Antonio G. López MD[10], Mary Elliott-Davey MSc[10], Bei Wang PhD[10], Maria Laura Monsalvo MD[10], Siddique Abbasi MD[10], Robert P. Giugliano, MD SM[1], Marc S. Sabatine, MD MPH[1]

LDL-C, low-density lipoprotein cholesterol

Gaba P, et al. Circulation. Accepted for publication January 20, 2023

Coronary imaging study

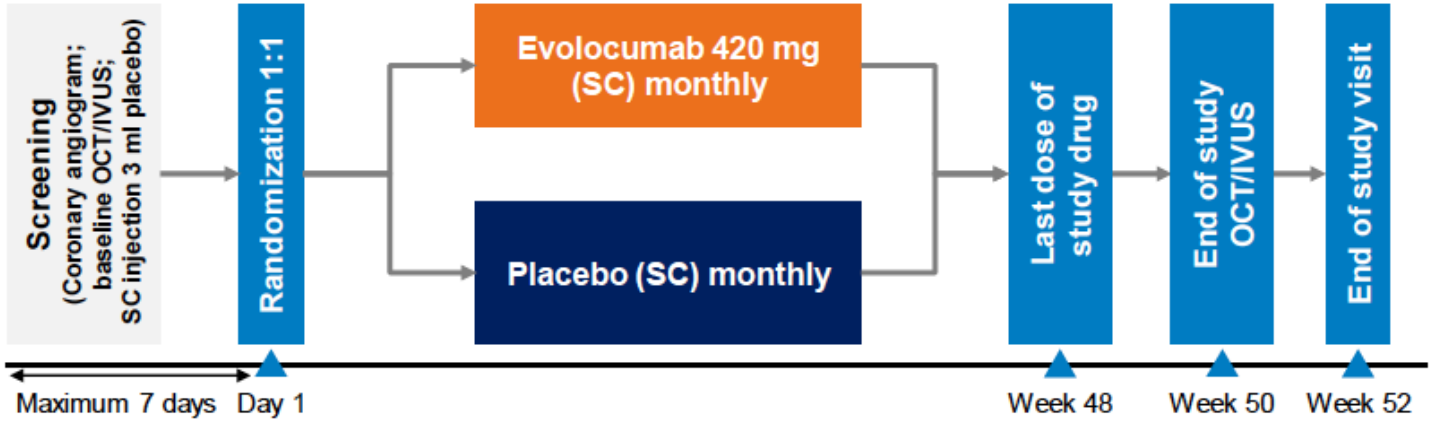
Effect of Evolocumab on Changes in Coronary Plaque Phenotype and Burden in Statin-Treated Patients Following Myocardial Infarction: The HUYGENS Randomized Clinical Trial

Aim: To evaluate the impact of PCSK9 inhibition with evolocumab on coronary atheroma phenotype post-ACS[1,2]

Inclusion Criteria[1,2]

- NSTEMI
- Angiographic CAD
- LDL-C ≥ 1.6 mmol/L on high-intensity statin, ≥ 2.1 mmol/L on low-/moderate-intensity statin, or ≥ 3.4 mmol/L on no statin at screening
- Subsequently treated with maximally tolerated statin
- At least one OCT image with an FCT ≤ 120 µm and one image with lipid arc > 90° in a segment ≥ 40 mm in length[a]

Study Design[2]



Primary Endpoint[1]

Nominal change in minimum FCT in a matched arterial segment from baseline to week 50

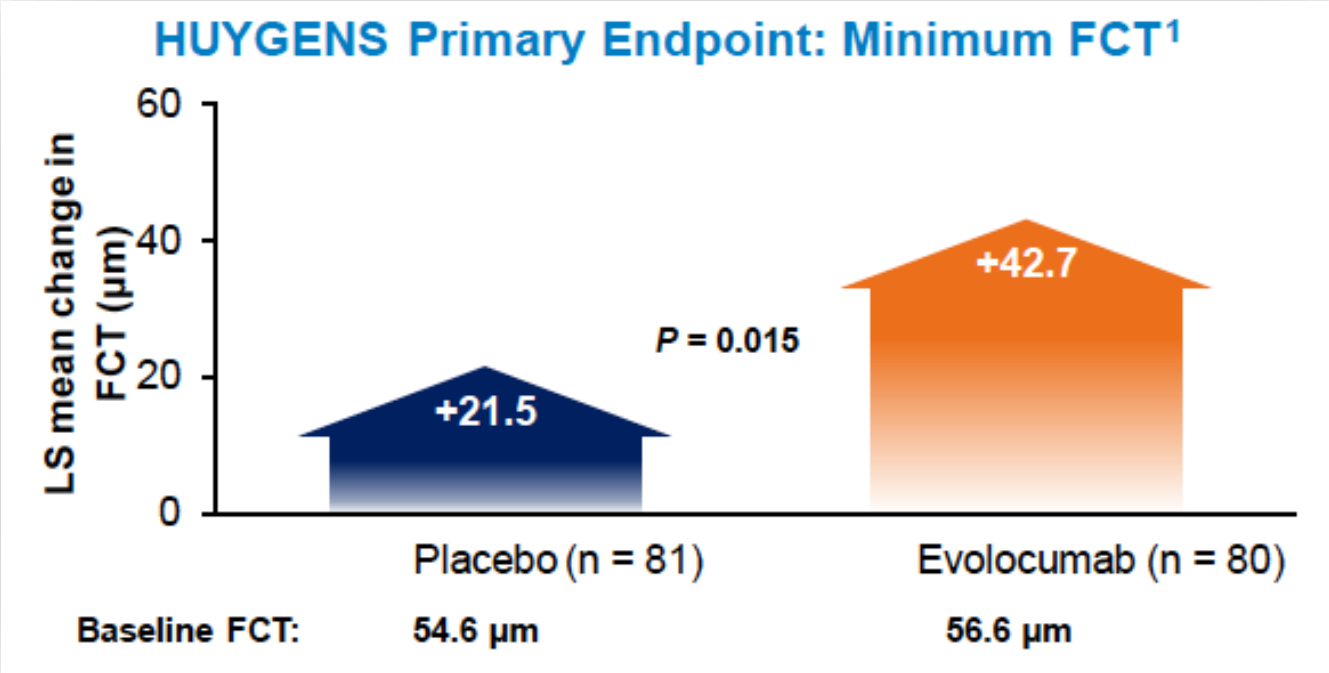
Secondary Endpoints[1]

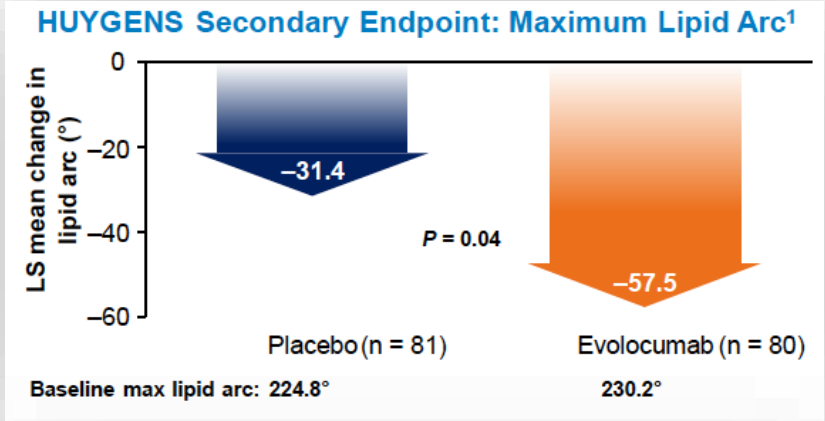
- Percent change in minimum FCT
- Absolute change in the average of the minimum FCT for all images
- Absolute change in the maximum lipid arc

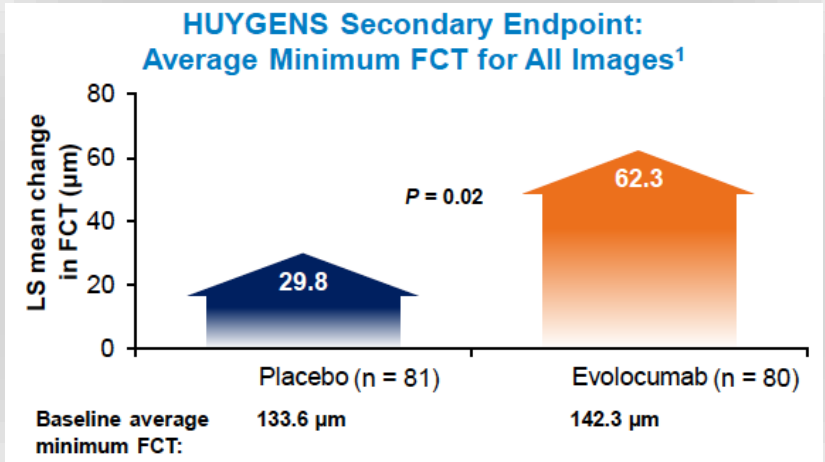
ACS, acute coronary syndromes; CAD, coronary artery disease; FCT, fibrous cap thickness; NSTEMI, non ST-elevation myocardial infarction; OCT/IVUS, optical coherence tomography/intravascular ultrasound; PCSK9, proprotein convertase subtilisin/kexin type 9; SC, subcutaneous

Nicholls SJ, et al. JACC Cardiovasc Imaging. 2022;15:1308-21

Primary endpoint







FCT, fibrous cap thickness; LS mean, least squares mean

Nicholls SJ, et al. JACC Cardiovasc Imaging. 2022;15:1308-21

ORIGINAL RESEARCH

Effect of Evolocumab on Coronary Plaque Phenotype and Burden in Statin-Treated Patients Following Myocardial Infarction

Stephen J. Nicholls, MBBS, PhD,[a,*] Yu Kataoka, MD, PhD,[b,*] Steven E. Nissen, MD,[c] Francesco Prati, MD,[d] Stephan Windecker, MD,[e] Rishi Puri, MBBS, PhD,[c] Thomas Hucko, MD,[f] Daniel Aradi, MD, PhD,[g,h,i] Jean-Paul R. Herrman, MD, PhD,[j] Renicus S. Hermanides, MD, PhD,[k] Bei Wang, PhD,[f] Huei Wang, PhD,[f] Julie Butters, BHSc, MBA,[a] Giuseppe Di Giovanni, BSc (Hons),[l] Stephen Jones, BAppSc, BHSc (Hons),[l] Gianluca Pompili, BSc, BA,[l] Peter J. Psaltis, MBBS, PhD[l,m]

ABSTRACT

OBJECTIVES The purpose of this study was to determine the effect of evolocumab on optical coherence tomography (OCT) measures of plaque composition.

BACKGROUND The proprotein convertase subtilisin kexin type-9 inhibitor evolocumab produced coronary atheroma regression in statin-treated patients.

METHODS Patients with a non-ST-segment elevation myocardial infarction were treated with monthly evolocumab 420 mg (n = 80) or placebo (n = 81) for 52 weeks. Patients underwent serial OCT and intravascular ultrasound imaging within a matched arterial segment of a nonculprit vessel. The primary analysis determined the change in the minimum fibrous cap thickness and maximum lipid arc throughout the imaged arterial segment. Additional analyses determined changes in OCT features in lipid-rich plaque regions and plaque burden. Safety and tolerability were evaluated.

RESULTS Among treated patients, (age 60.5 ± 9.6 years; 28.6% women; low-density lipoprotein cholesterol [LDL-C], 141.3 ± 33.1 mg/dL), 135 had evaluable imaging at follow-up. The evolocumab group achieved lower LDL-C levels (28.1 vs 87.2 mg/dL; $P < 0.001$). The evolocumab group demonstrated a greater increase in minimum fibrous cap thickness (+42.7 vs +21.5 μm; $P = 0.015$) and decrease in maximum lipid arc (−57.5° vs. −31.4°; $P = 0.04$) and macrophage index (−3.17 vs −1.45 mm; $P = 0.04$) throughout the arterial segment. Similar benefits of evolocumab were observed in lipid-rich plaque regions. Greater regression of percent atheroma volume was observed with evolocumab compared with placebo (−2.29% ± 0.47% vs −0.61% ± 0.46%; $P = 0.009$). The groups did not differ regarding changes in microchannels or calcium.

CONCLUSIONS The combination of statin and evolocumab after a non-ST-segment elevation myocardial infarction produces favorable changes in coronary atherosclerosis consistent with stabilization and regression. This demonstrates a potential mechanism for the improved clinical outcomes observed achieving very low LDL-C levels following an acute coronary syndrome. (Imaging of Coronary Plaques in Participants Treated With Evolocumab; NCT03570697)
(J Am Coll Cardiol Img 2022;■:■-■)

huygens

Conclusions

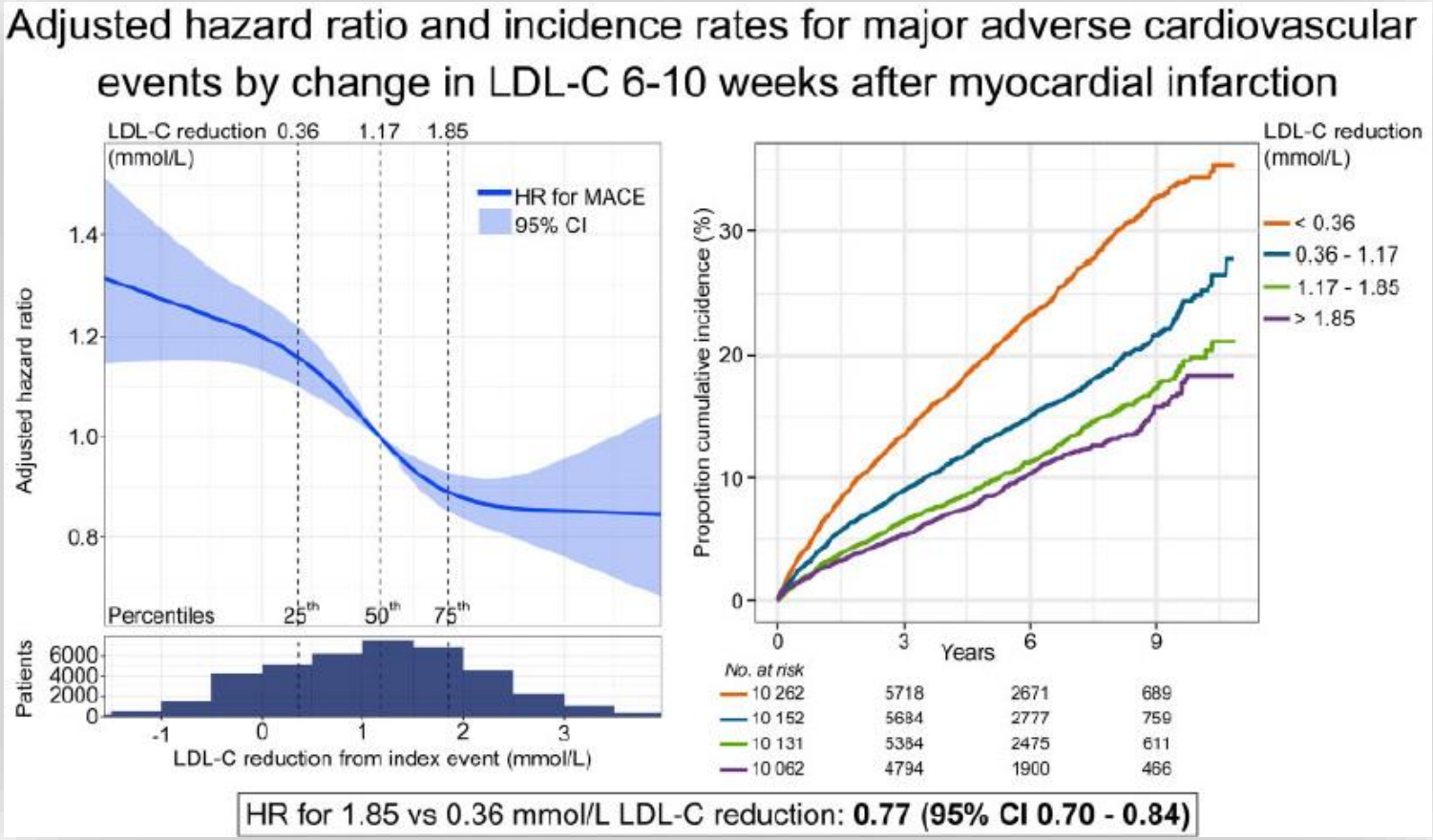
- HUYGENS demonstrated that the combination of evolocumab and statin therapy after an NSTEMI produces favorable changes in coronary atherosclerosis, consistent with stabilization and regression
- Role of intensive lipid lowering is supported by observations of a direct relationship between the degree of LDL-C lowering or achieved LDL-C levels and increasing FCT
- Early administration of a PCSK9 inhibitor was well tolerated and demonstrated a potential mechanism for the improved clinical outcomes in patients who achieve very low LDL-C levels following an ACS

ACS, acute coronary syndromes; FCT, fibrous cap thickness; LDL-C, low-density lipoprotein cholesterol; NSTEMI, non ST-elevation myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type 9
Nicholls SJ, et al. JACC Cardiovasc Imaging. 2022;15:1308-21

LDL-C: should we go lower after ACS?

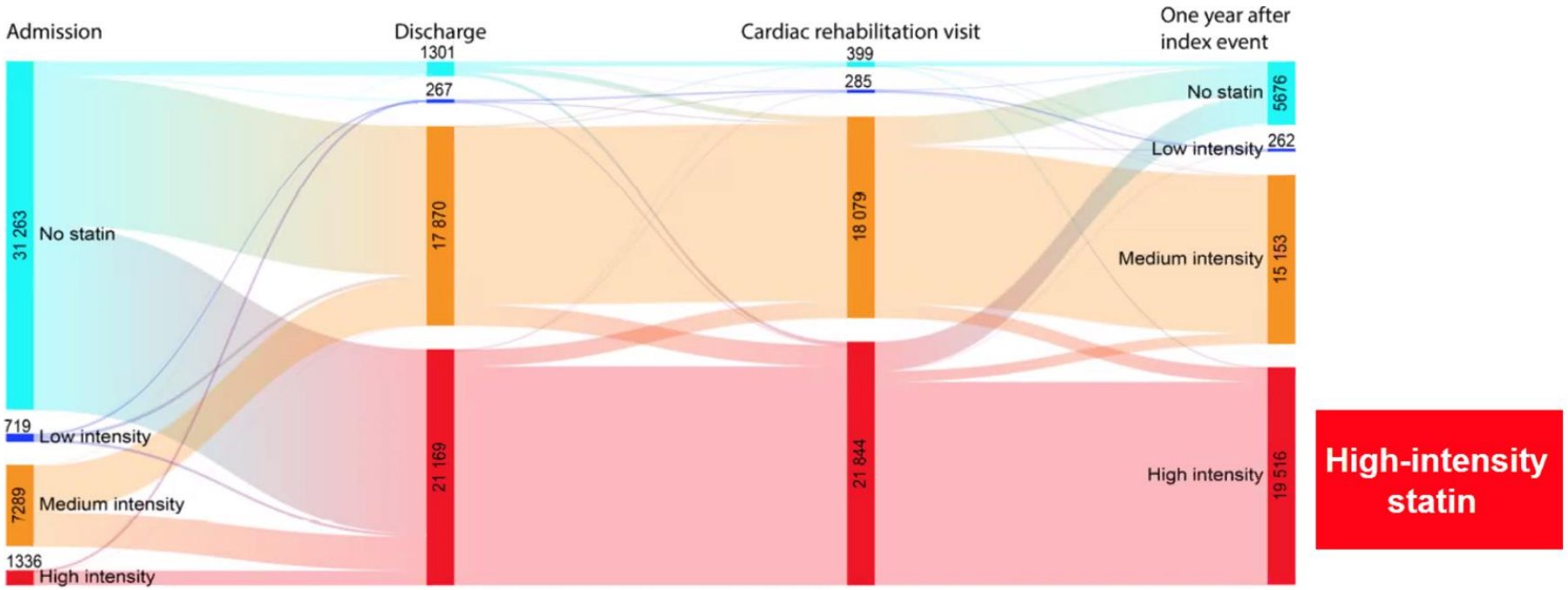
Low-density lipoprotein cholesterol reduction and statin intensity in myocardial infarction patients and major adverse outcomes: a Swedish nationwide cohort study

Jessica Schubert [1]*, Bertil Lindahl [1,2], Håkan Melhus [1], Henrik Renlund [2], Margrét Leosdottir [3,4], Ali Yari [5], Peter Ueda [6], Stefan James [1,2], Stephanie R. Reading [7], Paul J. Dluzniewski[7], Andrew W. Hamer[7], Tomas Jernberg [5], and Emil Hagström[1,2]



ACS, acute coronary syndromes; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events
Schubert J, et al. Eur Heart J. 2021;42:243-52

Statin intensity on admission, at discharge, cardiac rehabilitation, and one year after index event among 40,607 patients post MI



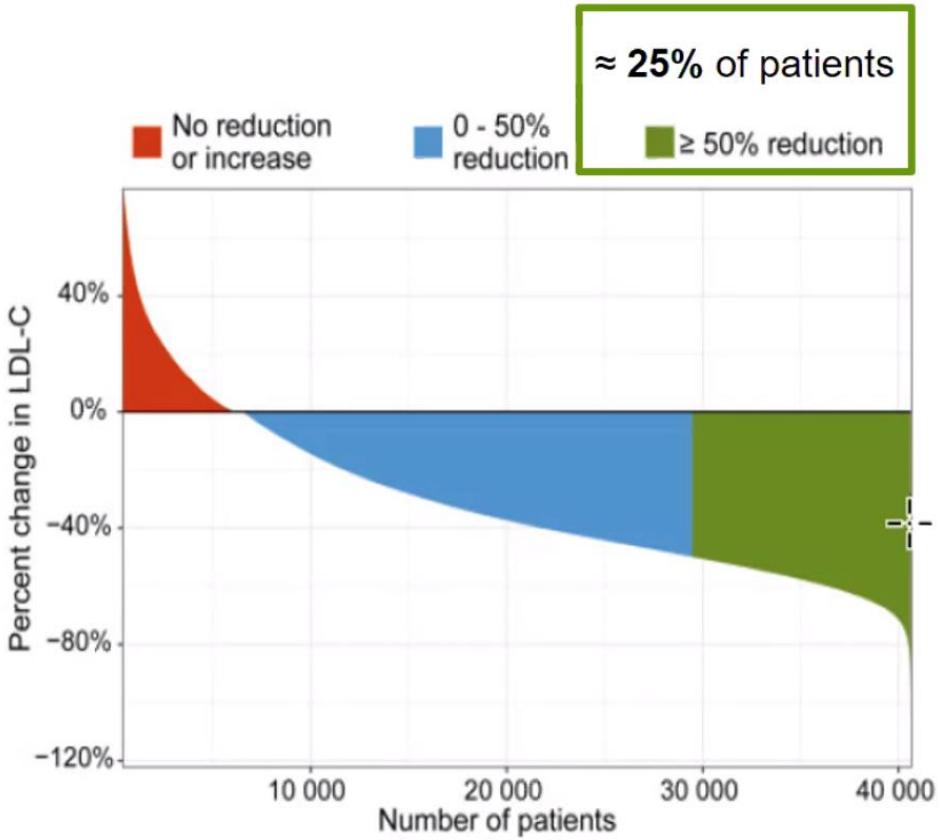
Only ≈ 50% of patients receive high-intensity therapy at discharge and after 1 year

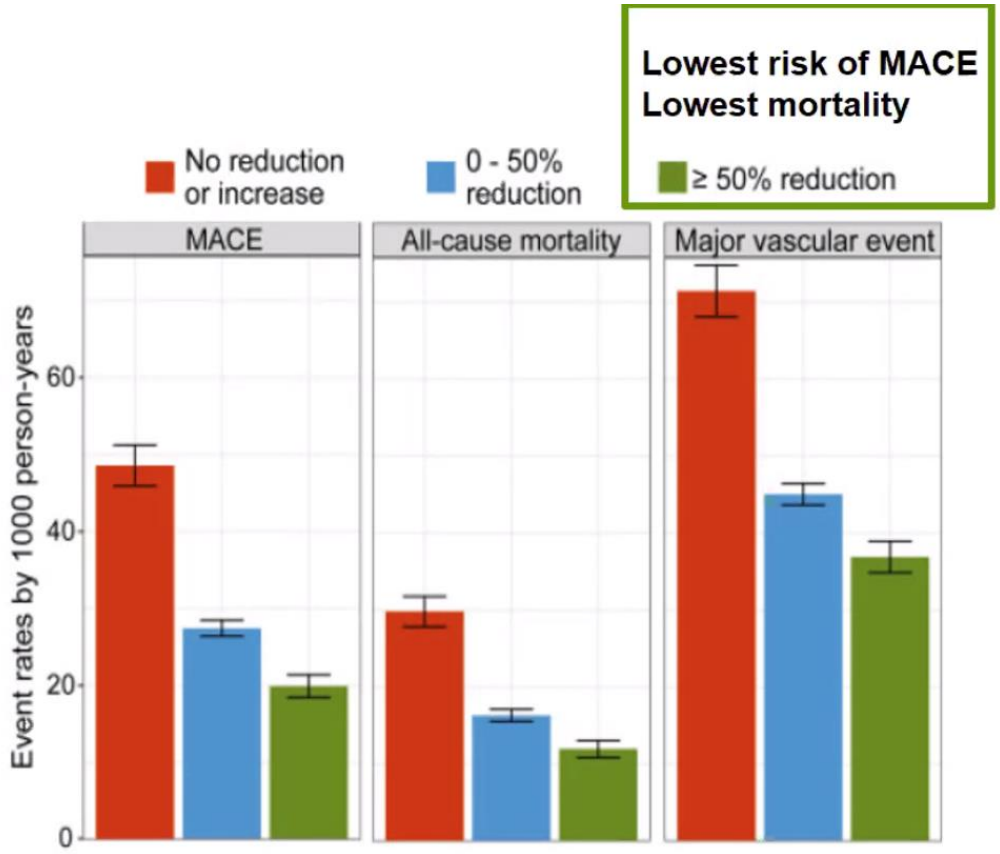
ACS, acute coronary syndromes; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; MI, myocardial infarction

Schubert J, et al. Eur Heart J. 2021;42:243-52

What are the unmet needs in LDL-C lowering?

40,607 patients post MI

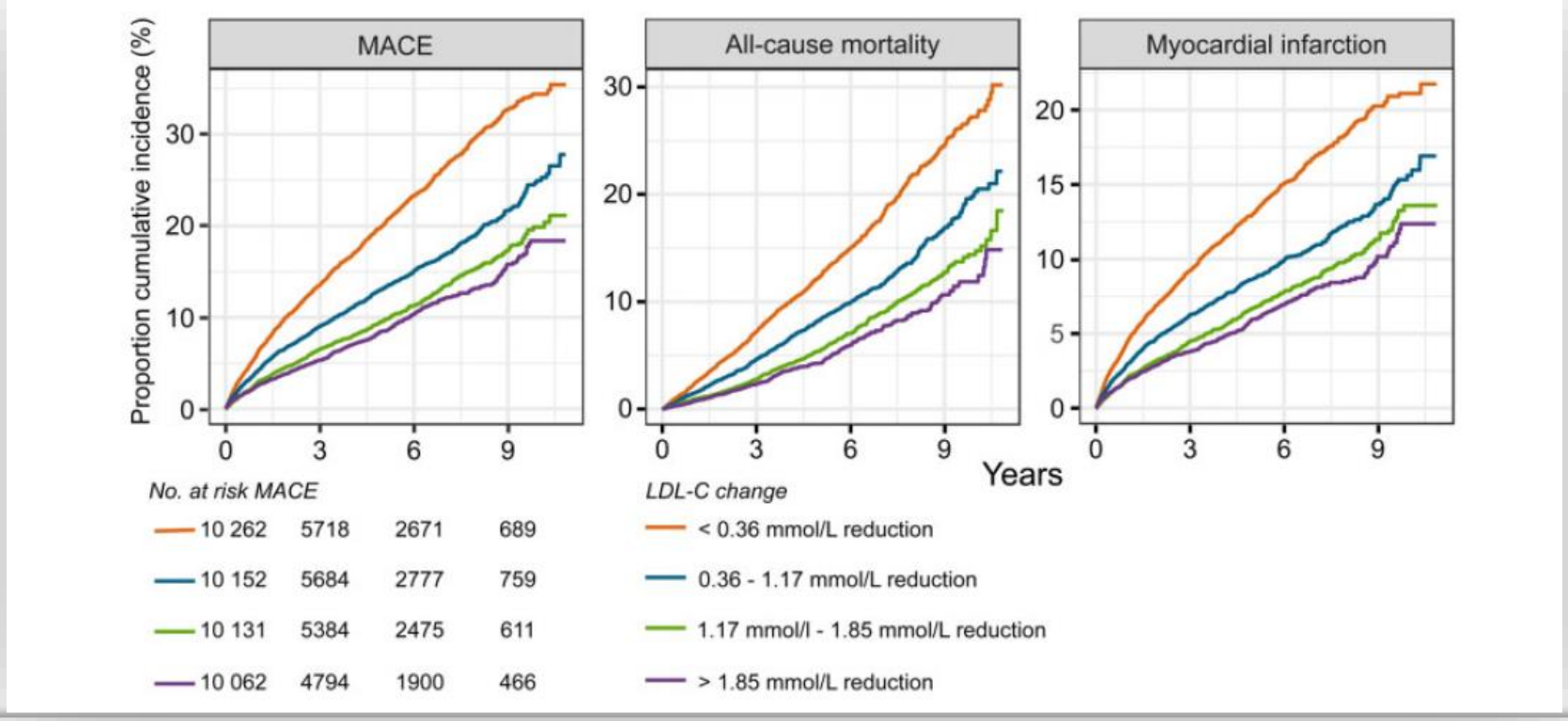




LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; MI, myocardial infarction
Schubert J, et al. Eur Heart J. 2021;42:243-52

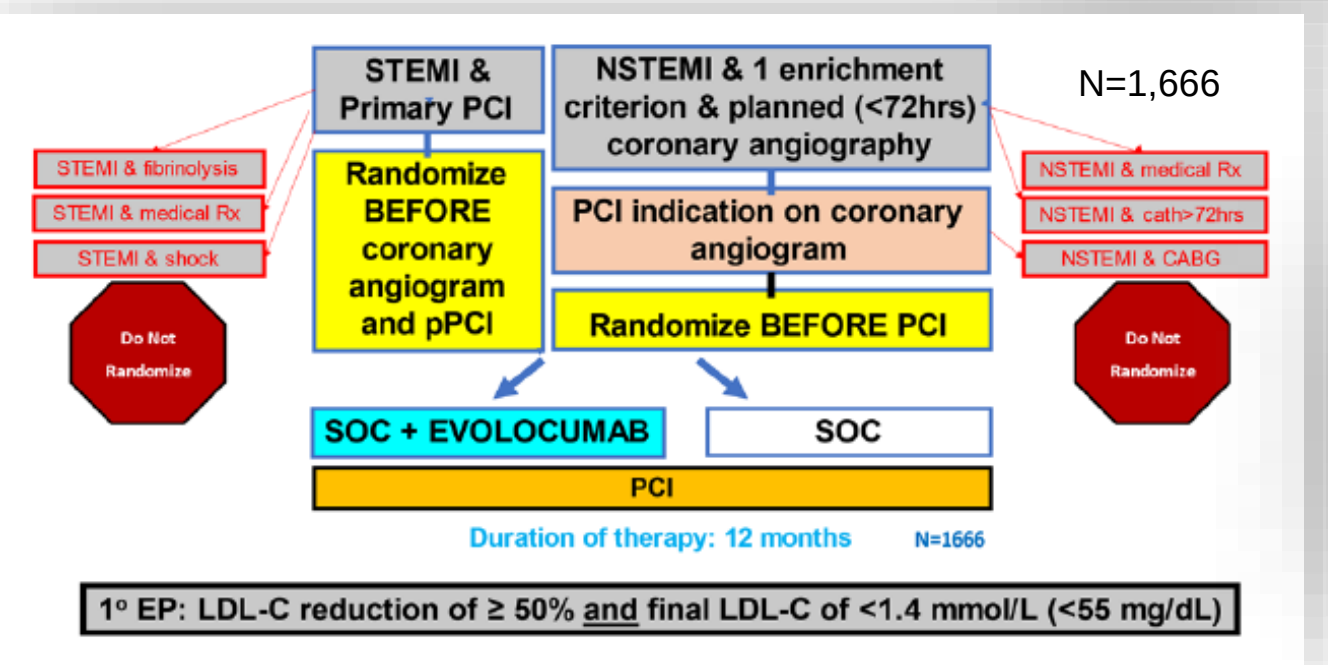
LDL-C: should we go lower after ACS?

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



Outcomes are assessed after the cardiac rehabilitation visit. Numbers at risk shown for MACE (composite outcome of CV mortality, MI, and ischaemic stroke)
ACS, acute coronary syndromes; CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; MI, myocardial infarction
Schubert J, et al. Eur Heart J. 2021;42:243-52

LDL-C: should we go lower after ACS?

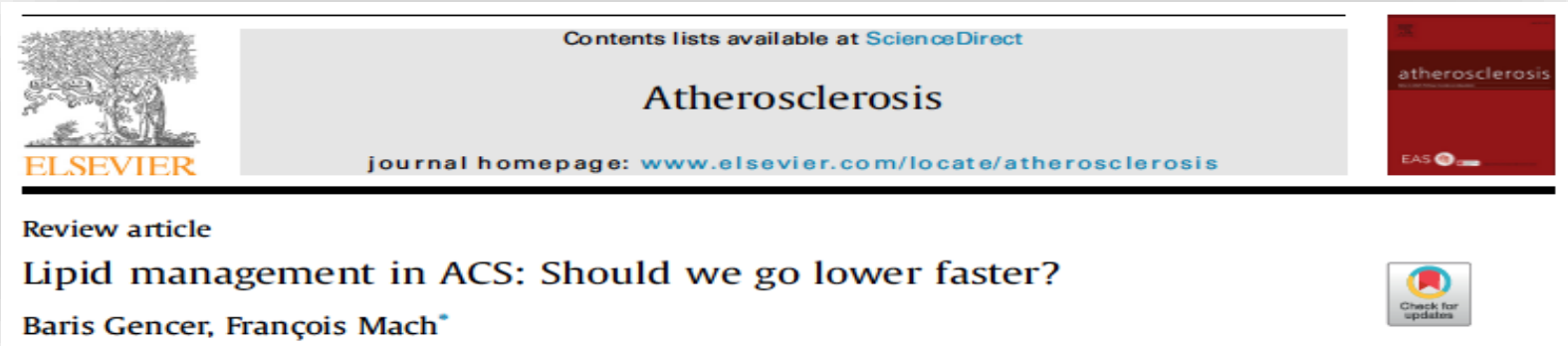


Secondary objectives	The secondary objective is to demonstrate the superiority of evolocumab versus standard of care in reaching a LDL-C reduction of ≥ 50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) at 12 months follow-up, country per country **Exploratory objectives:** To evaluate the effect of evolocumab versus standard of care on clinical outcomes from randomization to 12 months follow-up: - Death or any hospitalization for a CV reason, - Death, MI, stroke, unplanned revascularization, - Individual ischemic endpoints, - Pooled analysis of relationship between time to achieve LDL-C goal and death or any hospitalization for a CV reason.

1o EP, primary endpoint; ACS, acute coronary syndromes; CABG, coronary artery bypass graft; cath, catheterisation; CV, cardiovascular; hrs, hours; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; (N)STEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; Rx, treatment; SOC, standard of care

www.clinicaltrials.gov NCT04951856

LDL-C: should we go lower after ACS?



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Review article

Lipid management in ACS: Should we go lower faster?

Baris Gencer, François Mach*

Yes, for an earlier and lower LDL-C reduction after ACS!

ACS, acute coronary syndromes; LDL-C, low-density lipoprotein cholesterol

Gencer B, Mach F. Atherosclerosis. 2018;275:368-75

The modern concept of lipid-lowering strategies to reduce CV diseases

I: **Start as early as possible**

Screening for FH

II: **Treat (much more) aggressively**

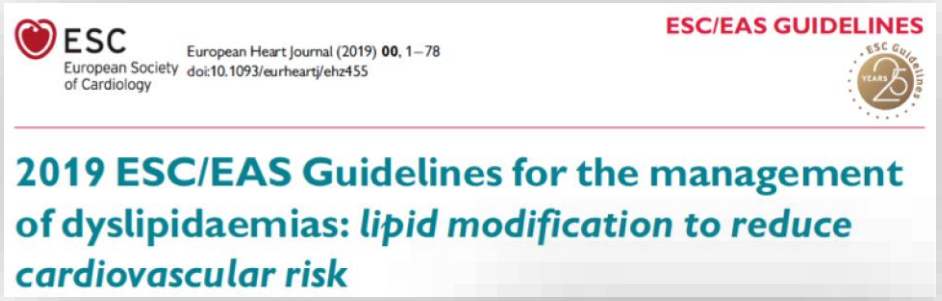
From desirable target to 'LDL elimination in the blood'

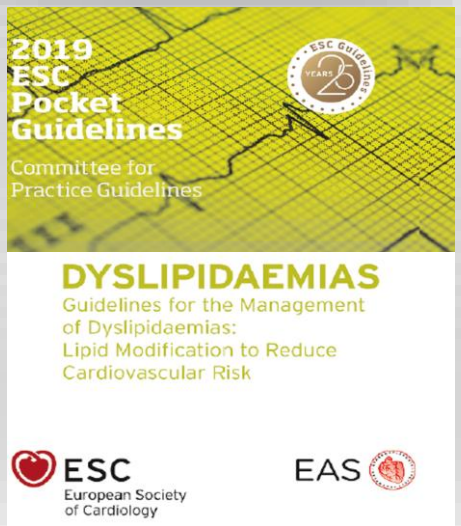
III: **New LDL-C targets for very high risk**

50% reduction from baseline **and** *<1.4 mmol/L (55 mg/dL)*

IV: **Use more lipid-lowering combination therapies**

Statins ± ezetimibe ± PCSK9 inhibitors (mAbs)





CV, cardiovascular; FH, familial hypercholesterolemia; LDL(-C), low-density lipoprotein (cholesterol); mAb, monoclonal antibody; PCSK9, proprotein convertase subtilisin/kexin type 9

Mach F, et al. Eur Heart J. 2020;41:111-88

Combination therapy to better control blood lipid levels

ESC European Society of Cardiology
European Heart Journal (2021) **00**, 1–4
doi:10.1093/eurheartj/ehab718

VIEWPOINT
Epidemiology and prevention

Combi
strate

Kausik K
François
Erik S. G

Combination lipid-lowering therapy as first line strategy

In conclusion, advances in the armamentarium of LDL cholesterol-lowering therapies enable physicians to achieve LDL cholesterol goals in very high-risk patients without restriction to a specific drug class. Indeed, LDL cholesterol lowering *per se*, and not the drug target resulting in LDL cholesterol lowering, is the main driver of cardiovascular risk reduction. Therefore, we should move away from 'high-intensity statin treatment' and 'the wait and watch paradigm' and instead start treating all very high- and extremely high-risk patients with combination therapy as the basic standard of care. This may afford significant improvements in population health across Europe.

ACS, acute coronary syndromes; CVD, cardiovascular disease; FH, familial hypercholesterolemia; LDL(-C), low-density lipoprotein (cholesterol); mAb, monoclonal antibody; PCSK9, proprotein convertase subtilisin/kexin type 9; siRNA, small interfering RNA
Ray KK, et al. Eur Heart J. 2022;43:830-3

The modern concept of lipid-lowering strategies to reduce CV diseases

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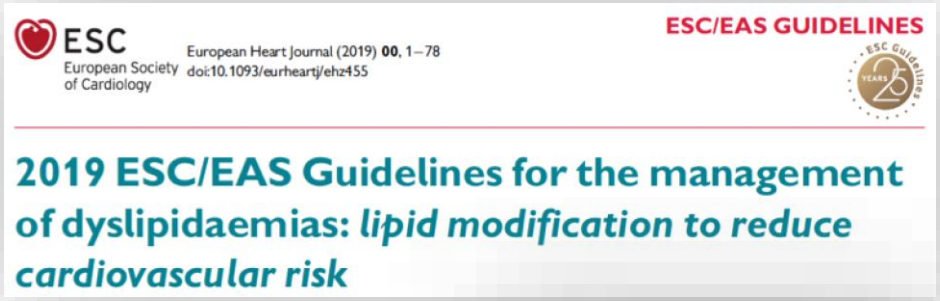
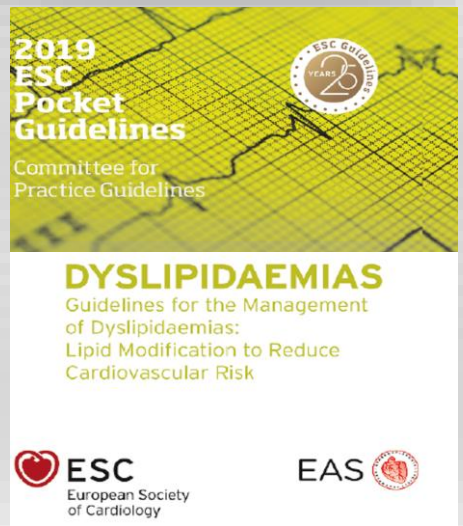
IV: **Use more lipid-lowering combination therapies**

Statins ± ezetimibe ± PCSK9 inhibitors (mAbs)

V: **The lower, the better and the lower for life**

LDL-C lowering with great efficacy, safety, and full adherence will reduce the risk of CV events

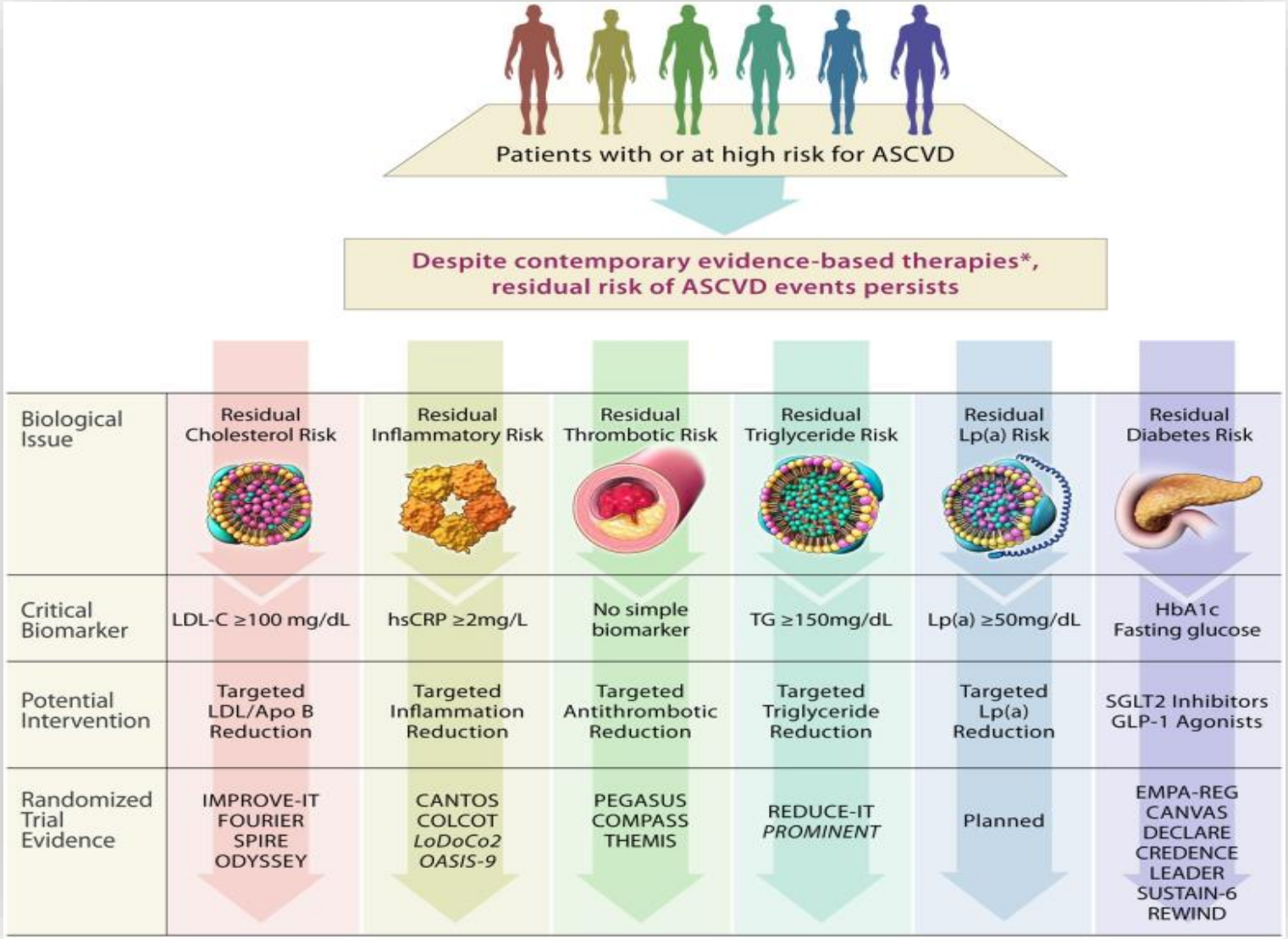




CV, cardiovascular; FH, familial hypercholesterolemia; LDL(-C), low-density lipoprotein (cholesterol); mAb, monoclonal antibody; PCSK9, proprotein convertase subtilisin/kexin type 9

Mach F, et al. Eur Heart J. 2020;41:111-88

Residual risk



* In addition to standard evidence-based therapies, more aggressive blood pressure targets may be considered

ASCVD, atherosclerotic cardiovascular disease; GLP-1, glucagon-like peptide 1; HbA1c, glycated haemoglobin A1C; hsCRP, high-sensitivity C-reactive protein; Lp(a), lipoprotein little a; SGLT2, sodium-glucose cotransporter-2; TG, triglycerides

Lawler PR, et al. Eur Heart J. 2021;42:113-31

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