My Clinical Experiences with Evolocumab in ACS Patients

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AMGEN Repatha

Key Questions

01 How should we control LDL cholesterol after ACS?

02 How should we communicate the benefits of PCSK9i with a patient?

03 How long should we keep patient on PCSK9i?

04 Recent Update on Fourier Study Subanlysis

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Case

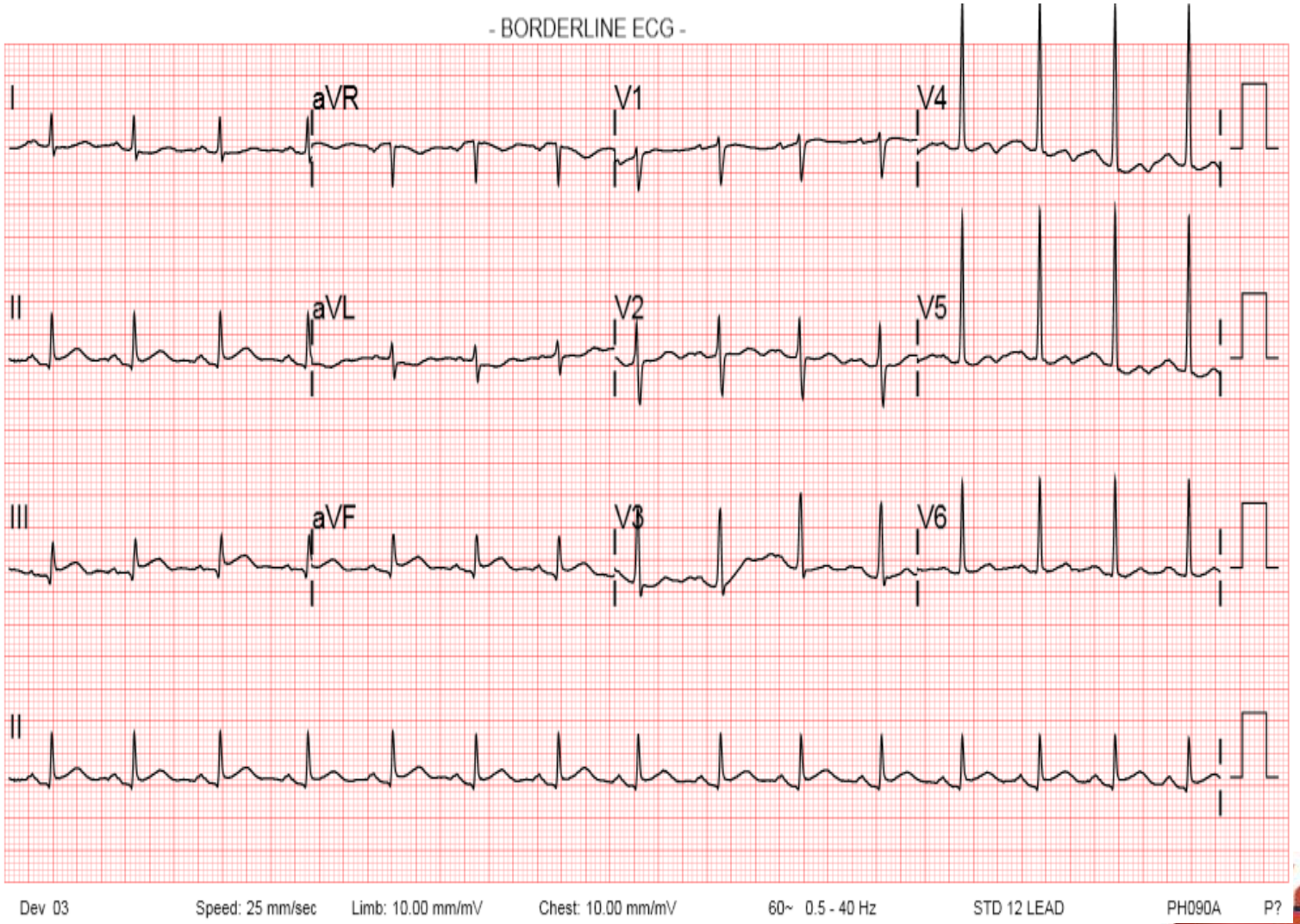
- M/35
- CC> Chest pain
- PI> VF arrest

→ ROSC in 4 min.

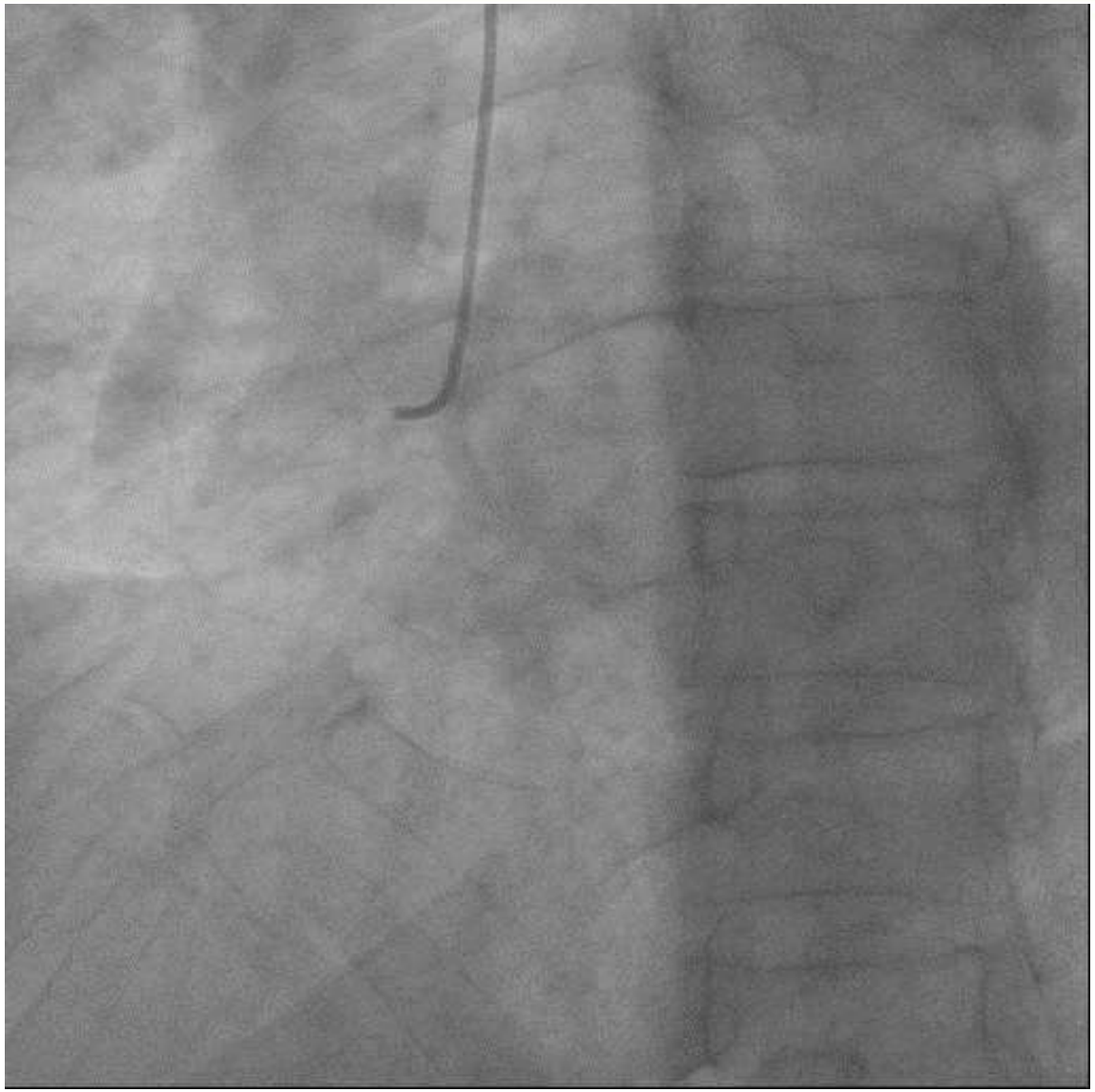
ECG: inf. STEMI

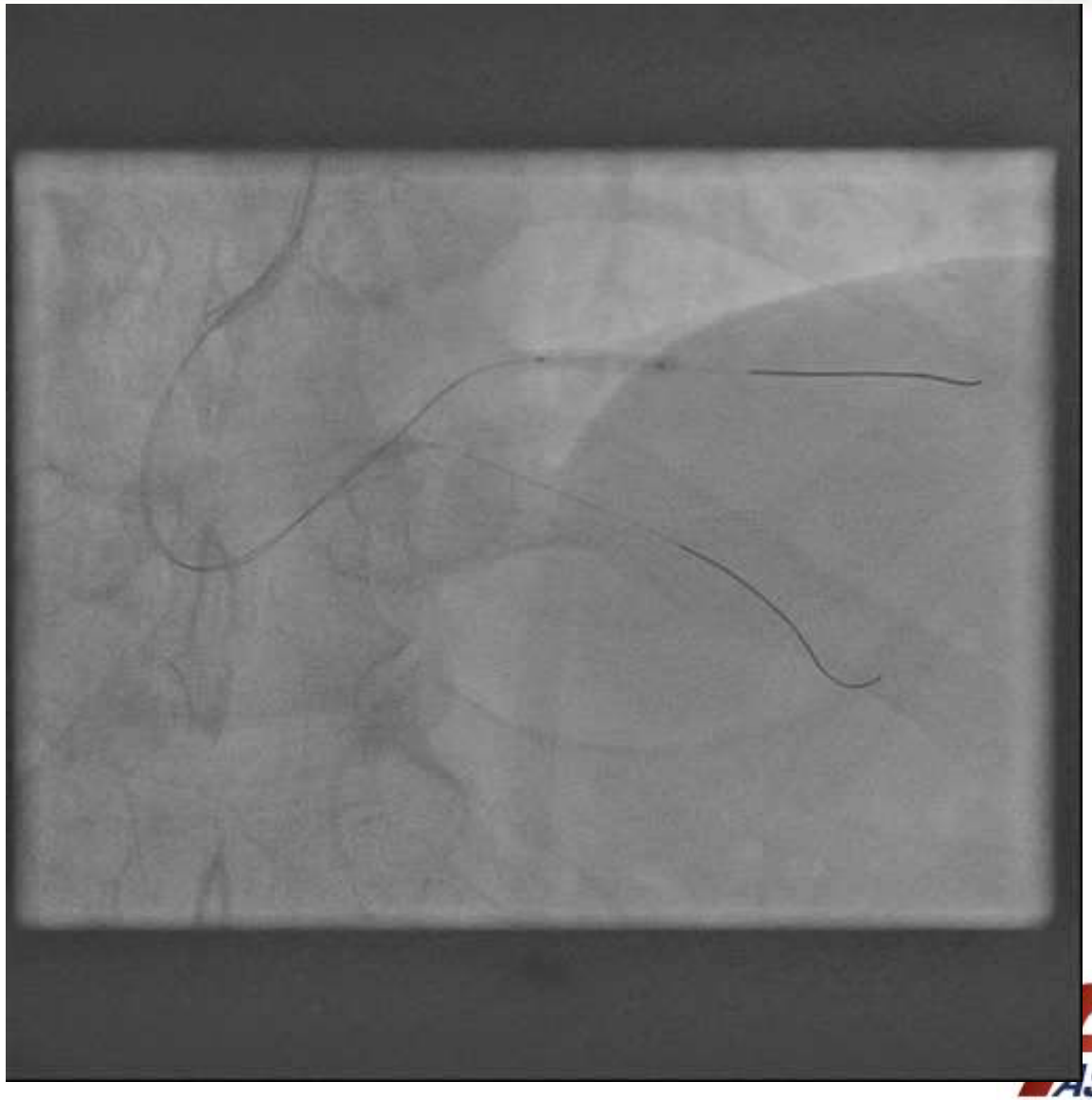
→ Primary PCI

- Risk factors: Dyslipidemia, Smoking

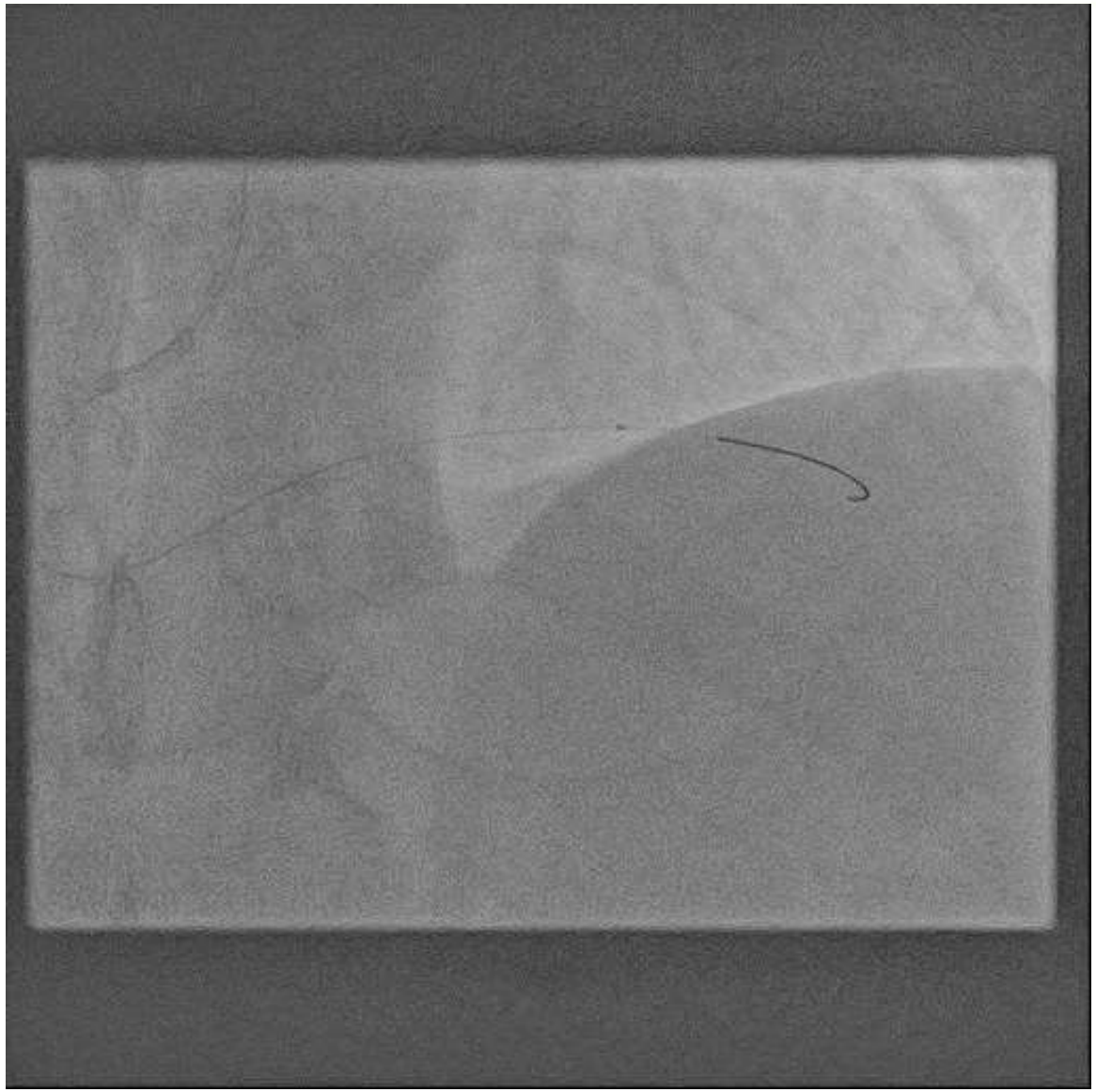


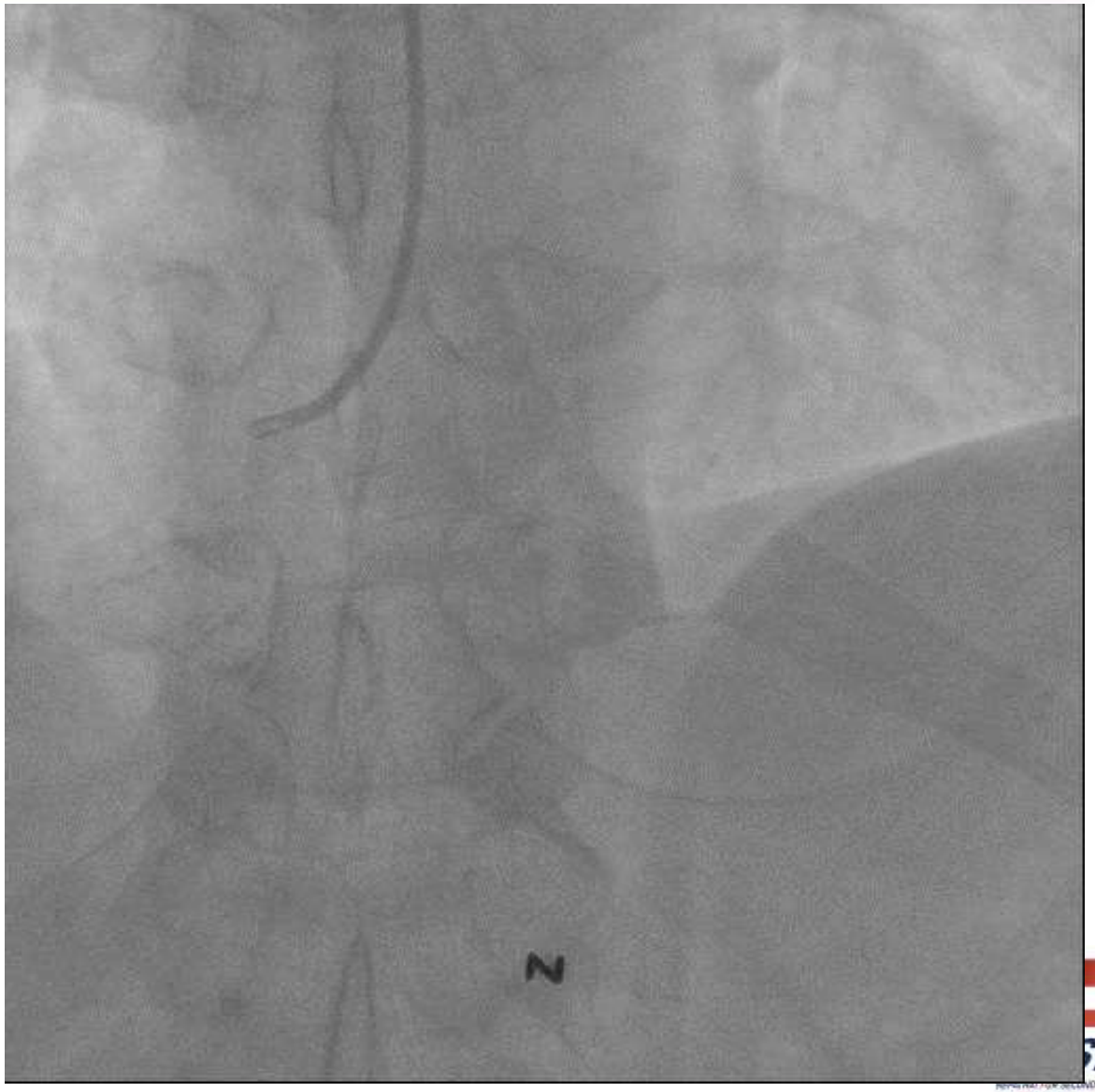
Primary PCI





Primary PCI





Clinical course

- **Residual heavy plaque burden at pRCA**
- **Patient was already on rosuvastatin 10mg and fenofibrate 160mg →**
  - **Initial lab: TG 149 HDL 47 LDL 125 (10/8)**

1. How should we control LDL cholesterol after ACS?

01

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Assess ASCVD risk (ACC/AHA Guidelines 2018)

Secondary ASCVD Prevention

Clinical ASCVD

Healthy lifestyle

Major ASCVD Events

- **Recent ACS (within past 12 months)**
- History of MI (other than recent ACS event listed above)
- History of ischemic stroke
- Symptomatic peripheral arterial disease (history of claudication with ABI < 0.85, or previous revascularization or amputation)

High-Risk Conditions

- Age ≥ 65 years
- Diabetes mellitus
- Hypertension
- HeFH
- Prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
- Currently smoking
- CKD (eGFR 15–59 mL/min/1.73 m^2)
- Persistent LDL-C ≥ 100 mg/dL (≥ 2.6 mmol/L) despite maximally tolerated statin therapy and ezetimibe
- History of congestive HF

Very high-risk ASCVD

Includes history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions

Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CKD, us familial hypercholesterolemia; HF, heart failure; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCSK9, proprotein convertase subtilisin kexin 9; RCT, randomized-controlled trial; SR, systematic review.

1. Grundy SM, et al. *J Am Coll Cardiol*. 2019;73:e285-350.

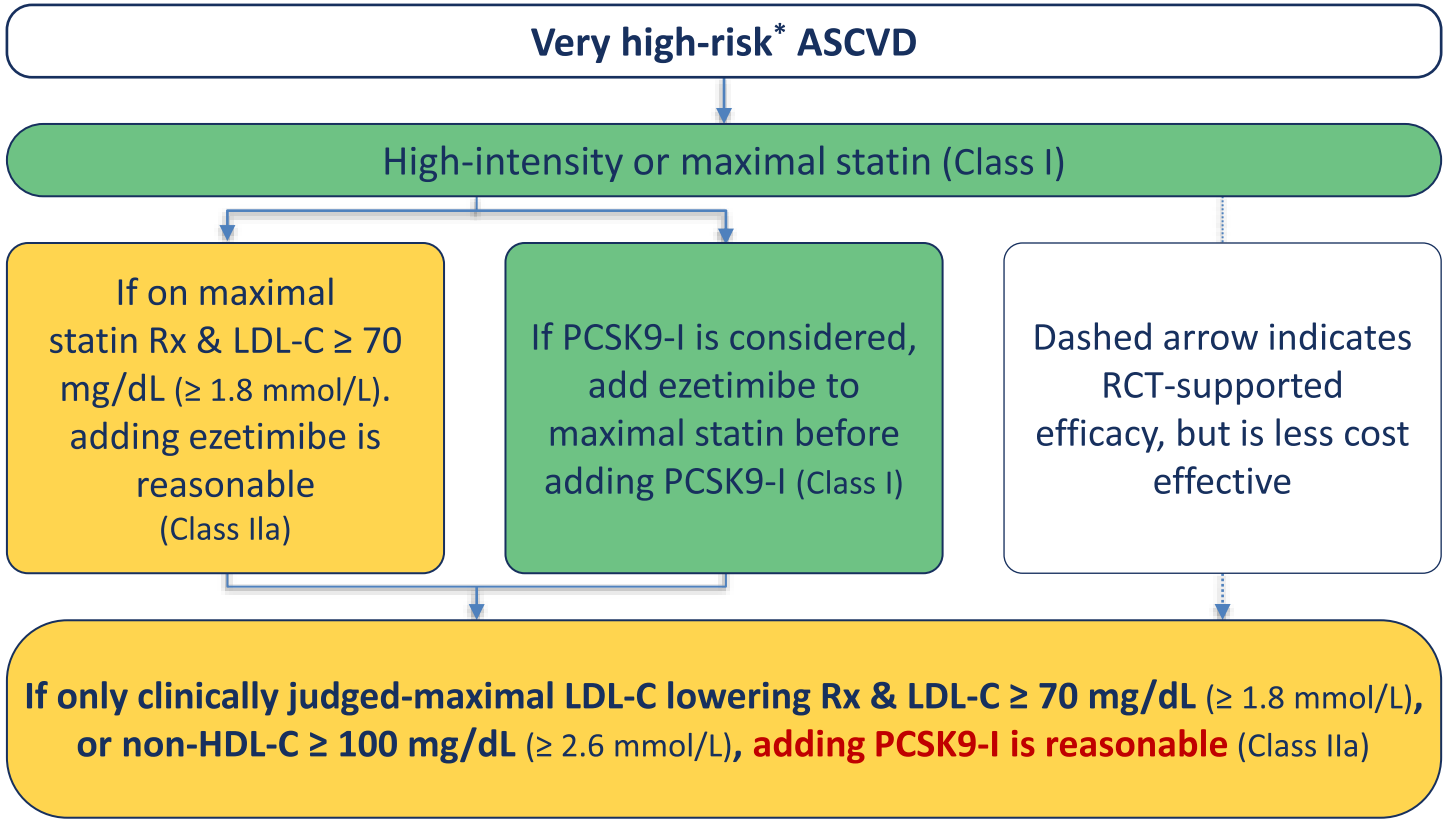
Assess ASCVD risk (ESC/EAS 2019 Guidelines)

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), 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,[a] 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.
High-risk	People with: Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP ≥180/110 mmHg. Patients with FH without other major risk factors. Patients with DM without target organ damage,[a] with DM duration ≥10 years or another additional risk factor. Moderate CKD (eGFR 30–59 mL/min/1.73 m^2). A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1 % and <5% for 10-year risk of fatal CVD.
Low-risk	Calculated SCORE <1% for 10-year risk of fatal CVD.

*Defined as microalbuminuria, retinopathy, or neuropathy. ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CABG, coronary artery bypass graft; CKD, chronic kidney disease; CT, computed tomography; CVD, cardiovascular disease; DM, diabetes mellitus; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; eGFR, estimated glomerular filtration rate; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SCORE, Systematic Coronary Risk Estimation; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TIA, transient ischaemic attack; UA, unstable angina.

1. Mach F, et al. *Eur Heart J*. 2019. doi:10.1093/eurheartj/ehz455. [Epub ahead of print.]

2018 ACC/AHA guideline: Secondary ASCVD prevention



✓ In patients at **very high risk*** whose LDL-C level **remains ≥ 70 mg/dL** (≥ 1.8 mmol/L) on maximally tolerated statin and ezetimibe therapy, adding a **PCSK9 inhibitor is reasonable**.

*Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions. Major ASCVD events: Recent ACS (within the past 12 months); history of MI (other than recent ACS event listed above); history of ischemic stroke; symptomatic PAD (history of claudication with ankle brachial index < 0.85, or previous revascularization or amputation); High-risk conditions: Age ≥ 65 years; heterozygous familial hypercholesterolemia; History of prior CABG or PCI outside of the major ASCVD event(s); DM; hypertension; CKD (eGFR 15-59 mL/min/1.73 m2); current smoking; persistently elevated LDL-C [LDL-C ≥ 100 mg/dL (≥ 2.6 mmol/L)] despite maximally tolerated statin therapy and ezetimibe; History of congestive heart failure.

ACC/AHA = American College of Cardiology/American Heart Association; ASCVD, atherosclerotic cardiovascular disease; LDL-C, low density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; CVD, cardiovascular disease; MI, myocardial infarction; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery; TIA, transient ischaemic attack; PAD, peripheral arterial disease; DM, diabetes mellitus; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SCORE, systematic coronary risk estimation.

1. Grundy SM, et al. Circulation. 2018;0:CIR.0000000000000625.

The Updated 2019 ESC/EAS Guidelines Recommend Aggressive LDL-C Goals for Very High Risk Patients

Very High Risk	High Risk	Moderate Risk	Low Risk
Primary or secondary prevention • **≥50% LDL-C reduction from baseline* and LDL-C <1.4 mmol/L (<55 mg/dL)** • No current statin use likely requires high -intensity LDL-lowering therapy • Current LDL-lowering therapy requires in creased treatment intensity	• ≥50% LDL-C reduction from baseline* and LDL-C <1.8 mmol/L (<70 mg/dL)	• LDL-C <2.6 mmol/L (<100 mg/dL)	• LDL-C <3.0 mmol/L (<116 mg/dL)

No level of LDL-C below which benefit ceases or harm occurs has been defined, and there are no known adverse effects of very low LDL-C levels (< 1.0 mmol/L [< 40 mg/dL])

*Baseline refers to the LDL-C level in a person not taking any lipid-lowering therapy or to the extrapolated baseline value for those who are on current treatment.
CV, cardiovascular; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; LDL-C, low-density lipoprotein cholesterol.
1. Mach F, et al. *Eur Heart J*. 2019. doi:10.1093/eurheartj/ehz455. [Epub ahead of print.]

Three Key Concepts of Lipid-lowering Strategies to Reduce Cardiovascular Diseases in 2019 ESC/EAS Guidelines

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*

- **Concept Change I: Start Early**
  - *Less "lipid-exposure" leads to prevention of lesion formation*
- **Concept Change II: Treat (Much More) Aggressively**
  - *From desirable target to "LDL-C elimination in the blood"*
- **Concept Change III: Use Combination Therapy**
  - *Statin + Ezetimibe (+/- PCSK9 Inhibitor) induced LDL-C lowering reduces CV risk*

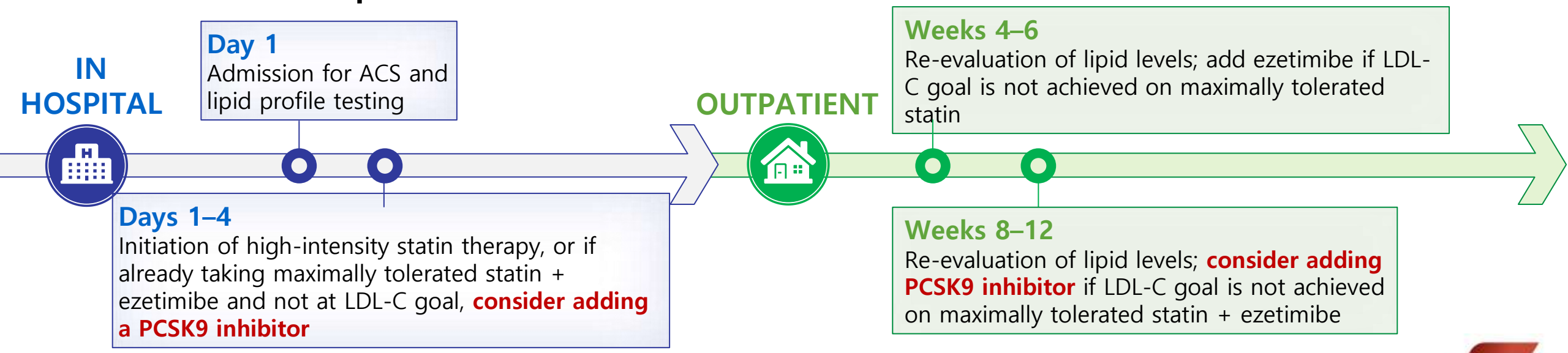
1. Mach F, *et al.* European Heart Journal (2019) 00, 1-78

Early Intervention Is Important to Reduce Risk of Another ACS Event (ESC/EAS Guideline 2019)

General Guidance

- Lipid profile should be obtained as soon as possible after admission for ACS
- **Lipid-lowering therapy should be initiated as soon as possible to increase patient adherence after discharge**
- Lipid levels should be re-evaluated 4–6 weeks after an ACS event to:
  - Determine if treatment goals have been achieved
  - Check for safety issues
  - Adapt the treatment regimen, as needed

Recommended Lipid Intervention Timeline for Patients With ACS



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

1. Mach F, et al. *Eur Heart J*. 2019. doi:10.1093/eurheartj/ehz455. [Epub ahead of print.].

Clinical course

- **Evolocumab 140mg right after PCI (+ atorvastatin 40mg, ezetimibe 10mg)**
- **Discharged with Evolocumab 140mg for 2 weeks later**

- **One month f/u lab: TG 56 HDL 39 LDL 32 (11/8)**

125 x 0.94 = 117.5
X 0.80 = 94
x 0.6 = 37.6

2. How should we communicate the benefits of PCSK9i with a patient?

03

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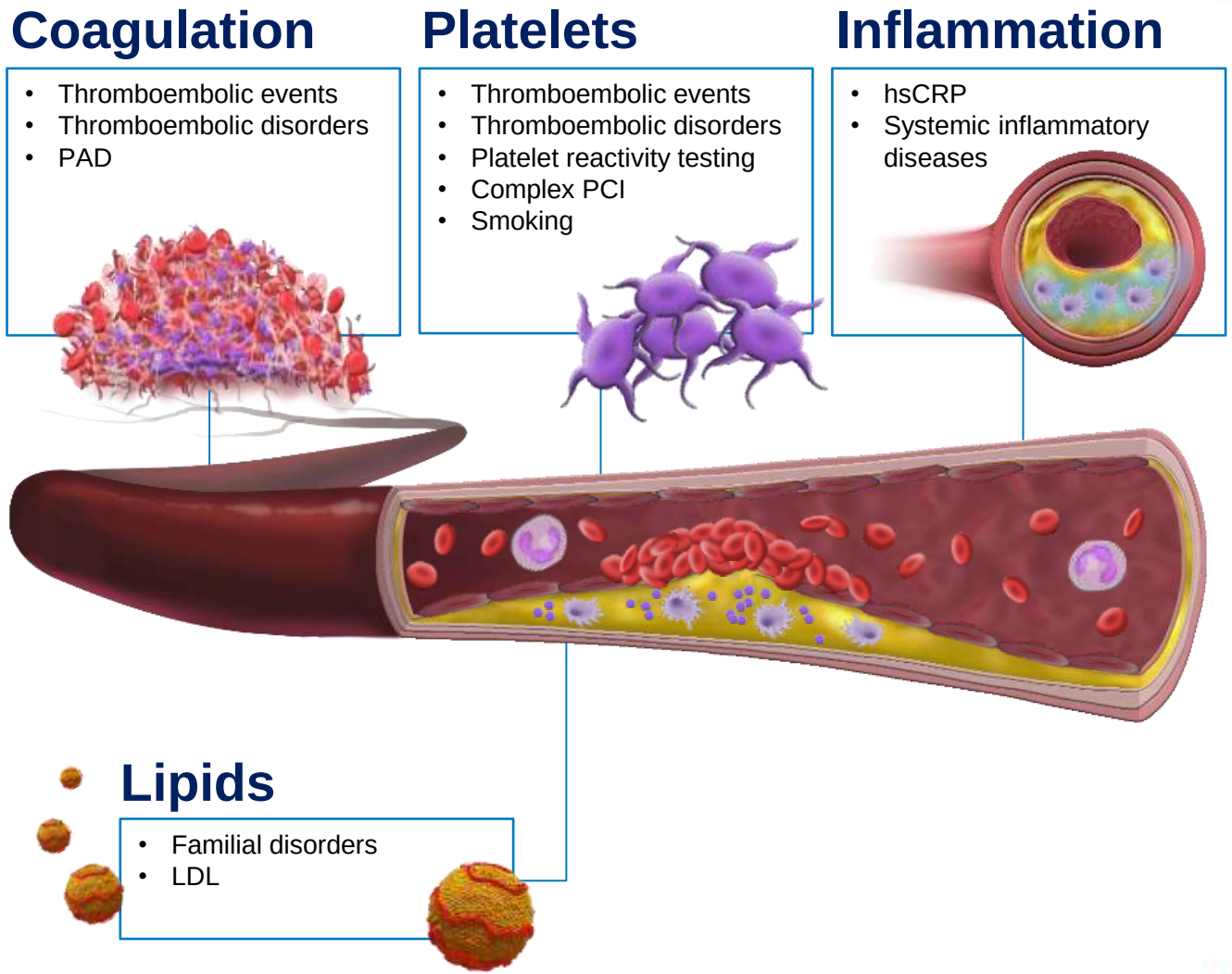
LDL cholesterol is building block of atherosclerosis

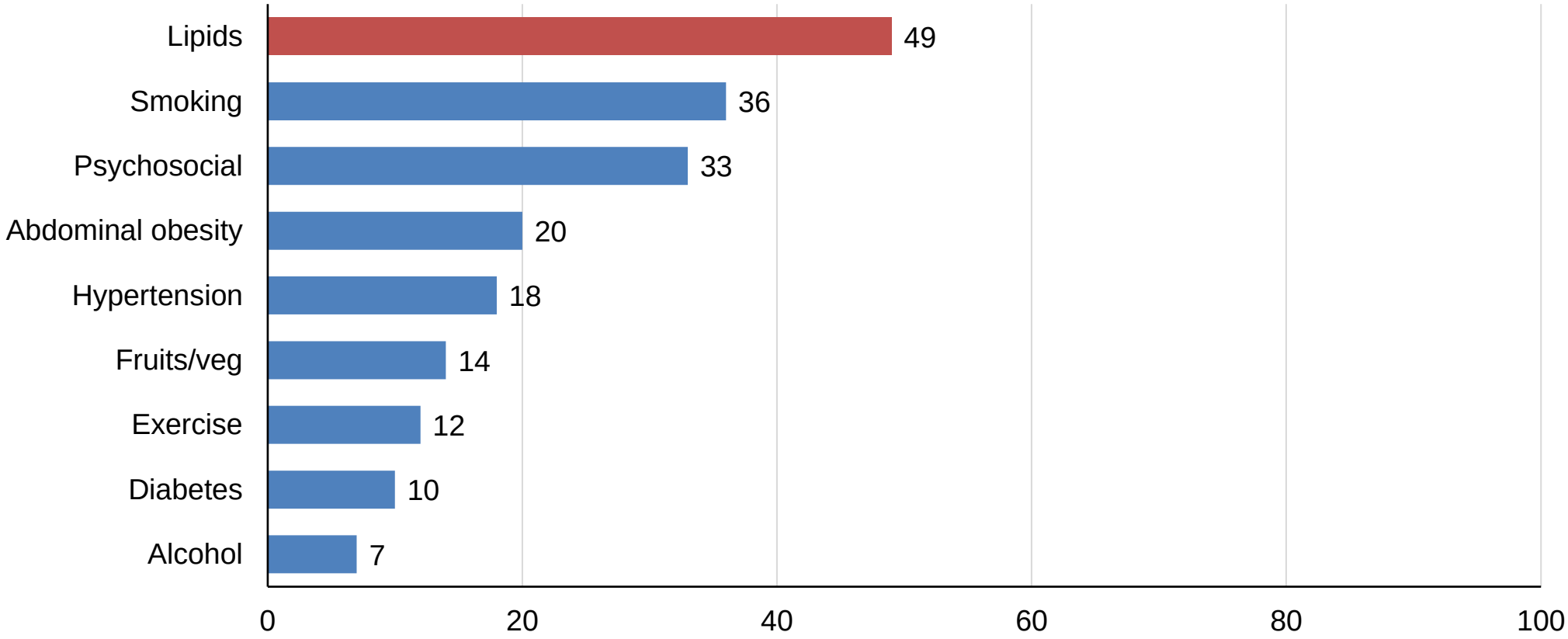
- Following ACS, patients have a high risk of subsequent ischemic events
- Each recurrent episode associates with increased mortality
- Heightened predisposition to atherothrombotic events may persist for years, suggesting pathobiology of recurrent events post-ACS differs from that of stable CAD with no prior ischemic events
- The goal is for optimal medical management and risk factor control that targets atherosclerotic burden as a whole



CAD = coronary artery disease; CHIP = clonal hematopoiesis of indeterminate potential; PAD = peripheral artery disease.

Gallone G, et al. *J Am Coll Cardiol.* 2018;72:2886-2903.

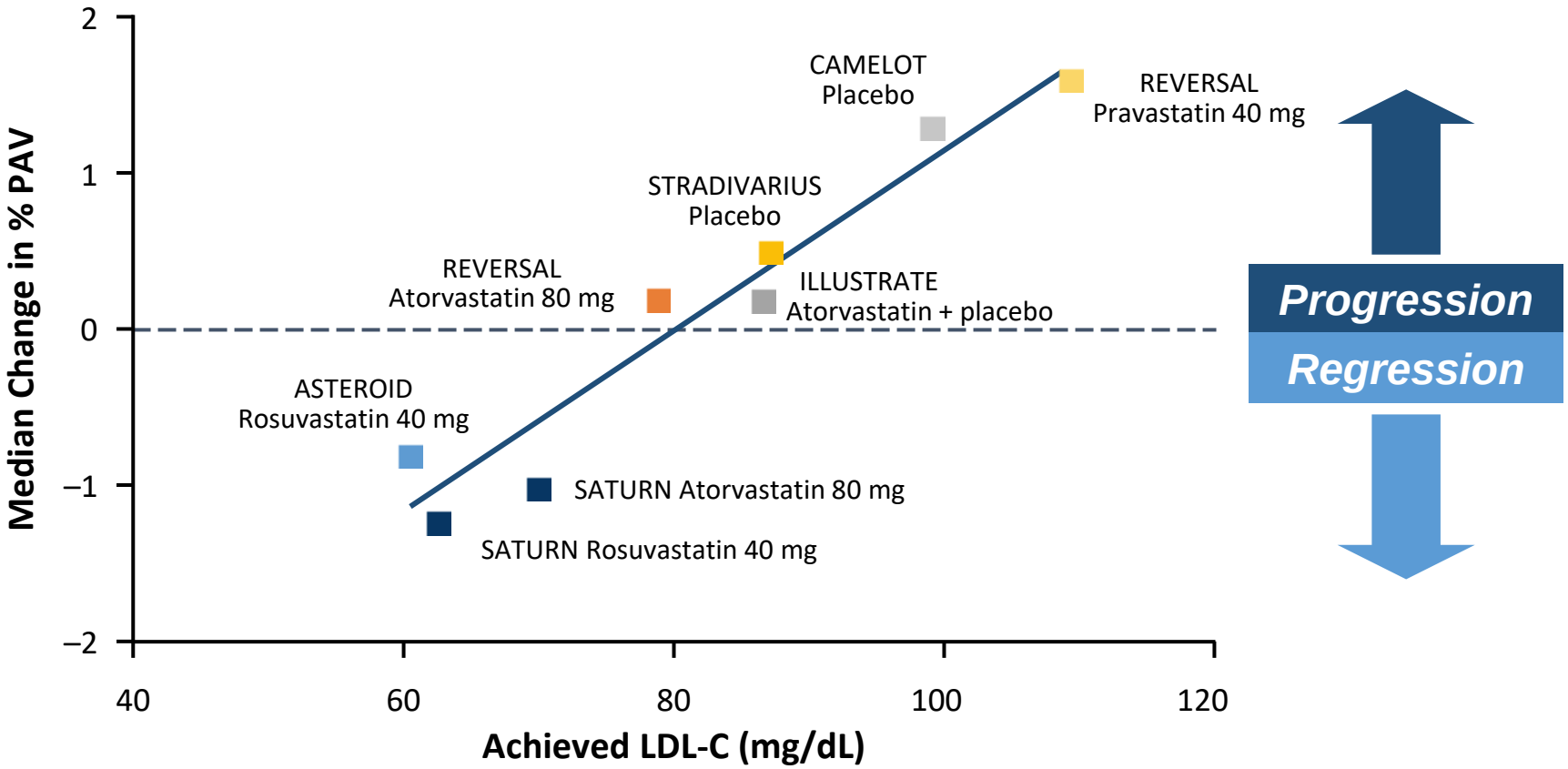
Lipids: One of the Most Critical Modifiable CV Risk Factor for Acute MI[1]



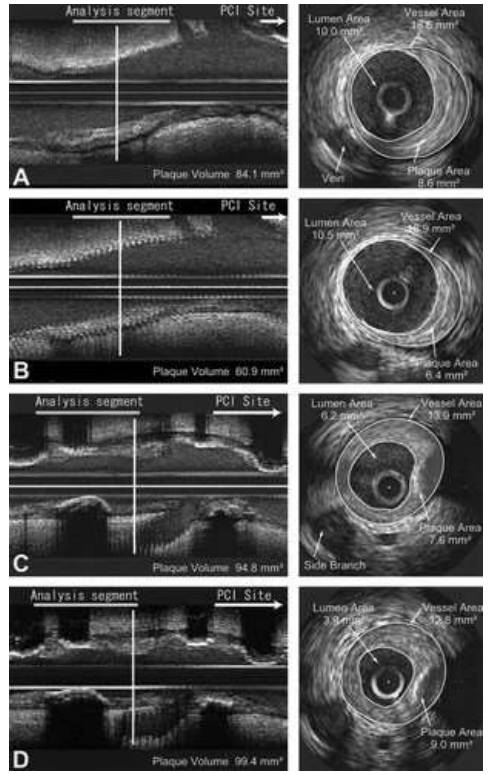
INTERHEART: 9 modifiable factors account for 90% of first-MI risk worldwide, N = 15,152 patients and 14,820 controls in 52 countries.[1] *Proportional reduction in population disease that would occur if exposure to a risk factor were reduced to an alternative ideal exposure scenario (eg. no tobacco use).[2] PAR = population attributable risk, adjusted for all risk factors.

1. Yusuf S, et al. *Lancet*. 2004:364;937-952. 2. 2. World Health Organization. https://www.who.int/healthinfo/global_burden_disease/metrics_paf/en/. Accessed February 1, 2019

Changes in Atherosclerotic Burden Have Been Demonstrated With LDL-C Lowering



The ESTABLISH Study

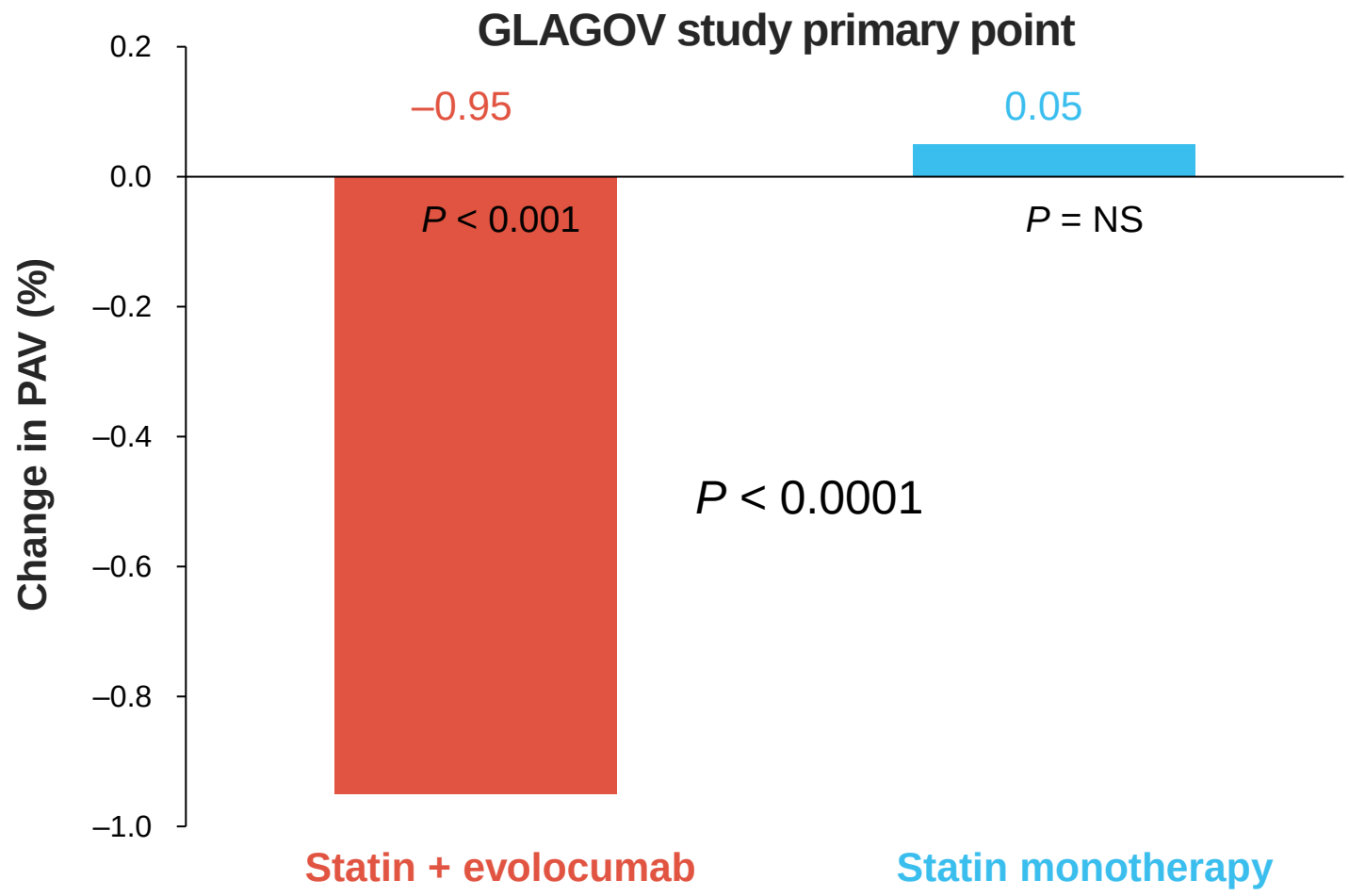


1. LDL-C = low-density lipoprotein cholesterol; PAV = percent atheroma volume.
Puri R, et al. Am Heart J. 2016;176:83-92.

2. Circulation. 2004;110:1061-1068.

Early Intensive Lipid Lowering in the Case of ACS

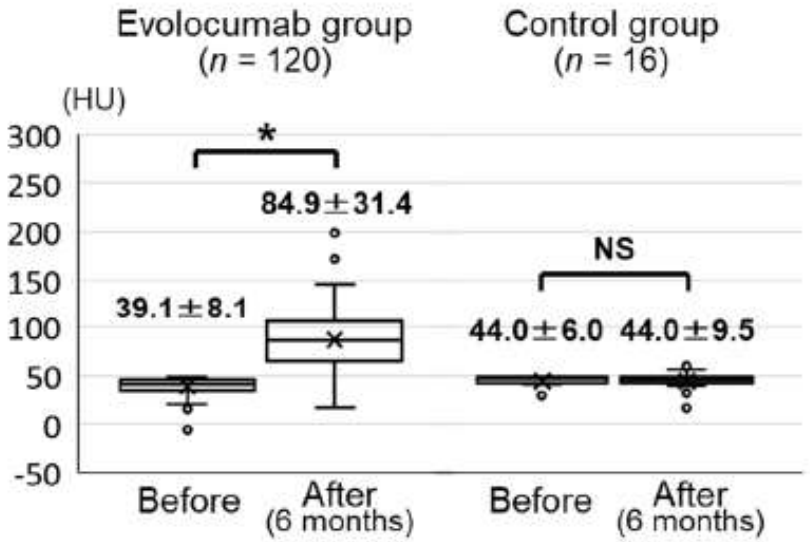
Lipid Lowering Therapy Using PCSK9I Stabilizes LRP Through the Reduction of Plaque Volume



NS, not significant; PAV, percentage atheroma volume
Nicholls SJ, et al. *JAMA*. 2016;316:2373-84.

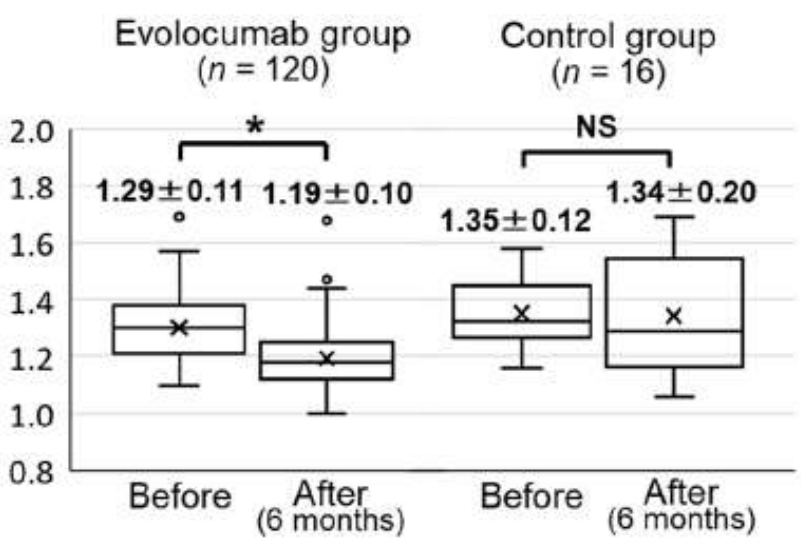
Evolocumab Stabilized Vulnerable Coronary Plaques and Reduced Their Size

Stability (evaluated by minimum CT density) of vulnerable coronary plaque



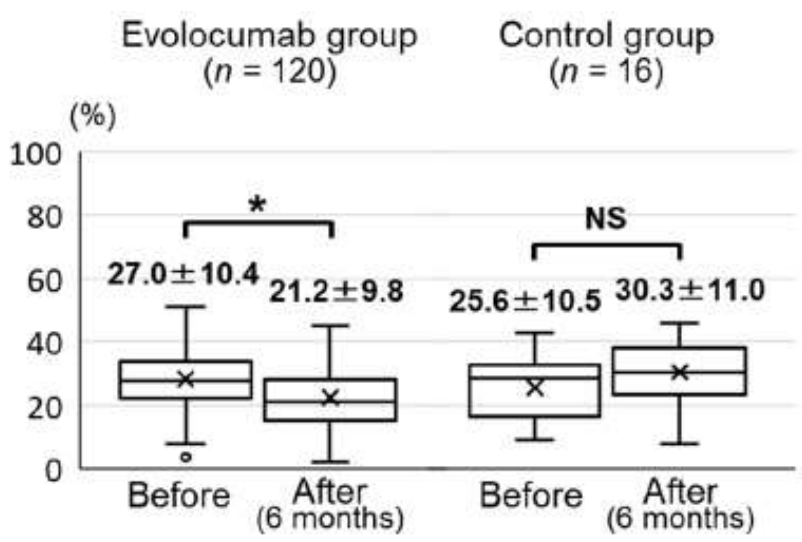
P < 0.001

Size (evaluated by remodeling index) of vulnerable coronary plaque



P < 0.001

Percent stenosis at vulnerable coronary plaque site



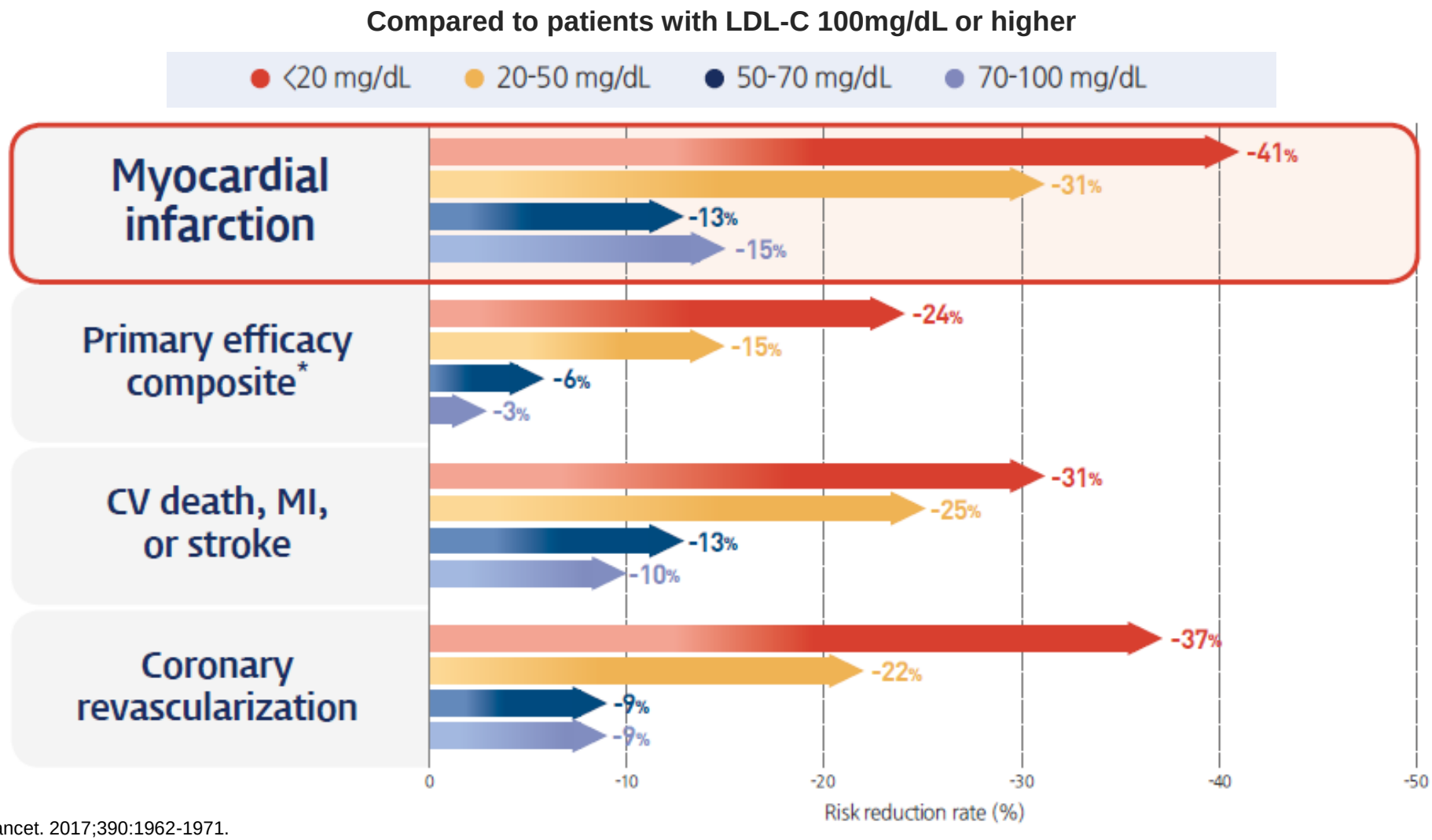
P < 0.001

Evolocumab significantly increased the minimum CT density, reduced the remodeling index, and decreased the percent stenosis

J. Clin. Med. 2020, 9, 3338; doi:10.3390/jcm9103338

Evolocumab Showed a Greater Risk Reduction When Patients Achieving Below LDL-C 50mg/dL (or 20mg/dL)

Event rates and adjusted risk of efficacy endpoints by achieved LDL-C group at 4 weeks from FOURIER



1. Giugliano RP, et al. Lancet. 2017;390:1962-1971.

Clinical course

Patient asks "Do I really have to use this expensive drug?"

I say "YEEEEEESSSS"

- ***Lipid is the building block!***
- ***Luckily, it is modifiable, and we have very good drugs!***
- ***You cannot take another hit! Controlling LDL cholesterol prevents recur!***
- ***The lower the LDL, the bigger benefit you get, and it should at least under 70mg/dL! (and it is covered by National healthcare insurance)***

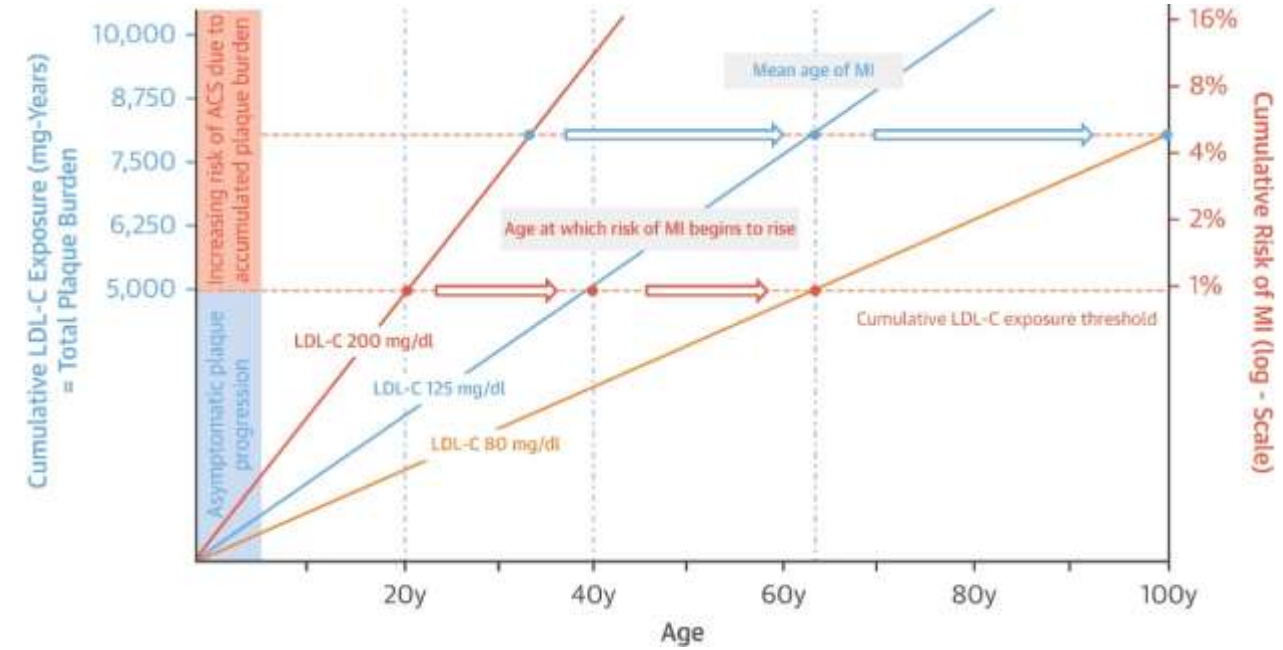
→ I communicate this messages before discharge after ACS event, set the stage in advance, and it is much easier to initiate PCSK9i at outpatient clinic.

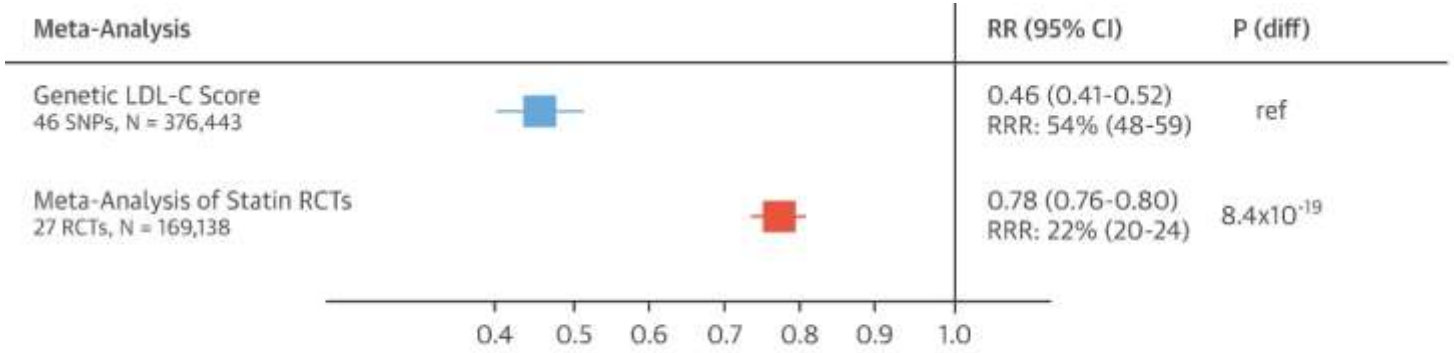
3. How long should we keep patient on PCSK9i?

04

Life-time cumulative burden of LDL-Cholesterol

Impact of Lipids on Cardiovascular Health: *JACC* Health Promotion Series



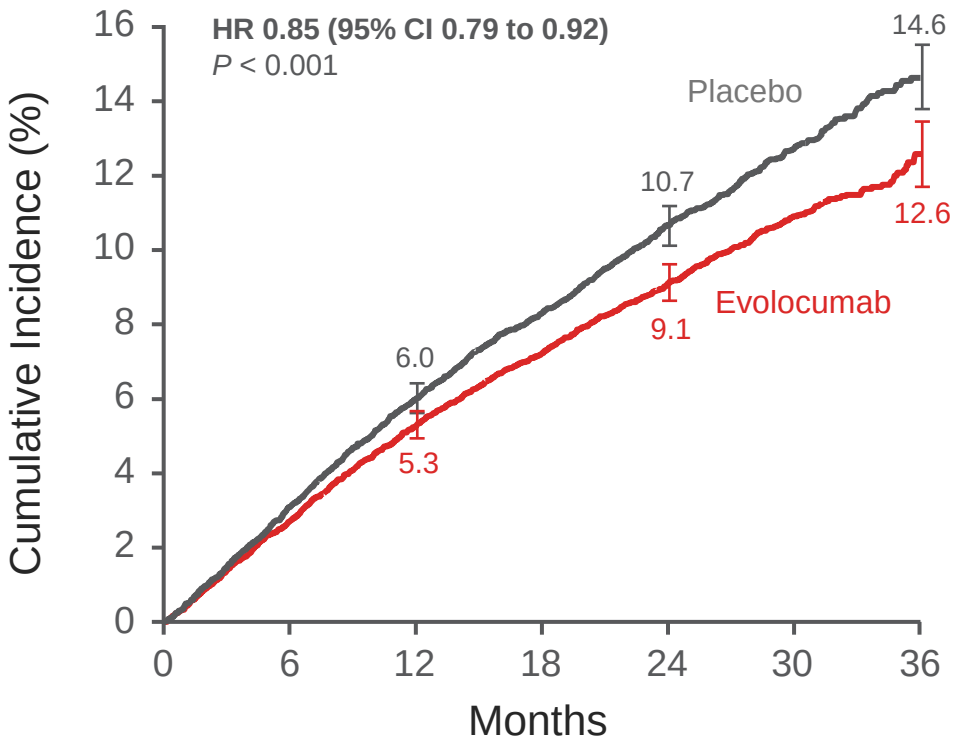


Long-term exposure to lower LDL-C associated with much greater reduction in CHD risk per unit lower LDL-C ($p_{(difference)} = 8.4x10^{-19}$)

BA Ferrence et al. JACC, Volume 72, Issue 10, 4 September 2018, Pages 1141-1156.

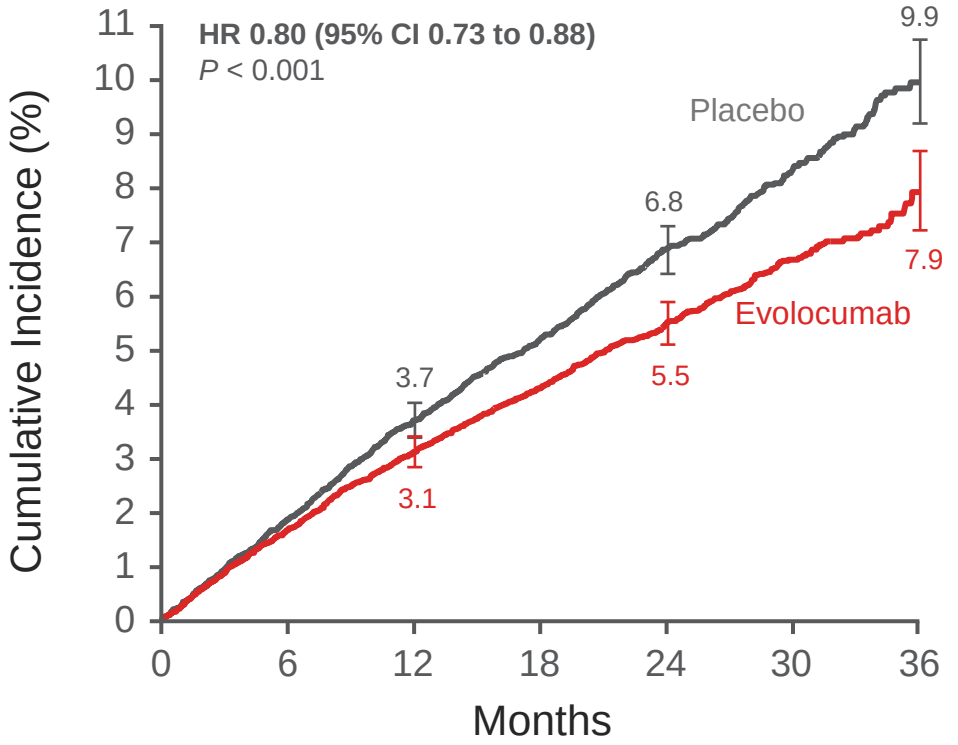
FOURIER: Two lines continue to diverge – the longer the better

Primary Composite Endpoint*



No. at Risk							
Placebo	13780	13278	12825	11871	7610	3690	686
Evolocumab	13784	13351	12939	12070	7771	3746	689

Key Secondary Composite Endpoint†



No. at Risk							
Placebo	13780	13449	13142	12288	7944	3893	731
Evolocumab	13784	13501	13241	12456	8094	3935	724

*Primary composite endpoint: CV death, MI, stroke, hospitalization for UA, or coronary revascularization
†Secondary composite endpoint: CV death, MI or stroke
CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; UA, unstable angina.

1. Sabatine MS, et al. N *Engl J Med*. 2017;376:1713-1722.

FOURIER: Adverse events and laboratory test results (followed up for a median of 2.2 years)

Outcome	Evolocumab (n=13,769)	Placebo (n=13,756)
Adverse events - no. of patients (%)		
Any	***10,664 (77.4)***	***10,644 (77.4)***
Serious	***3,410 (24.8)***	***3,404 (24.7)***
Thought to be related to the study agent and leading to discontinuation of study regimen	226 (1.6)	201 (1.5)
Injection-site reaction*	296 (2.1)	219 (1.6)
Allergic reaction	420 (3.1)	393 (2.9)
Muscle-related event	682 (5.0)	656 (4.8)
Rhabdomyolysis	8 (0.1)	11 (0.1)
Cataract	228 (1.7)	242 (1.8)
Adjudicated case of new-onset diabetes†	677 (8.1)	644 (7.7)
Neurocognitive event	217 (1.6)	202 (1.5)
Laboratory results - no. of patients/total no. (%)		
Aminotransferase level > 3 times the upper limit of the normal range	240/13,543 (1.8)	242/13,523 (1.8)
Creatine kinase level > 5 times the upper limit of the normal range	95/13,543 (0.7)	99/13,523 (0.7)

No significant between-group differences were seen in the overall **rates of adverse events**

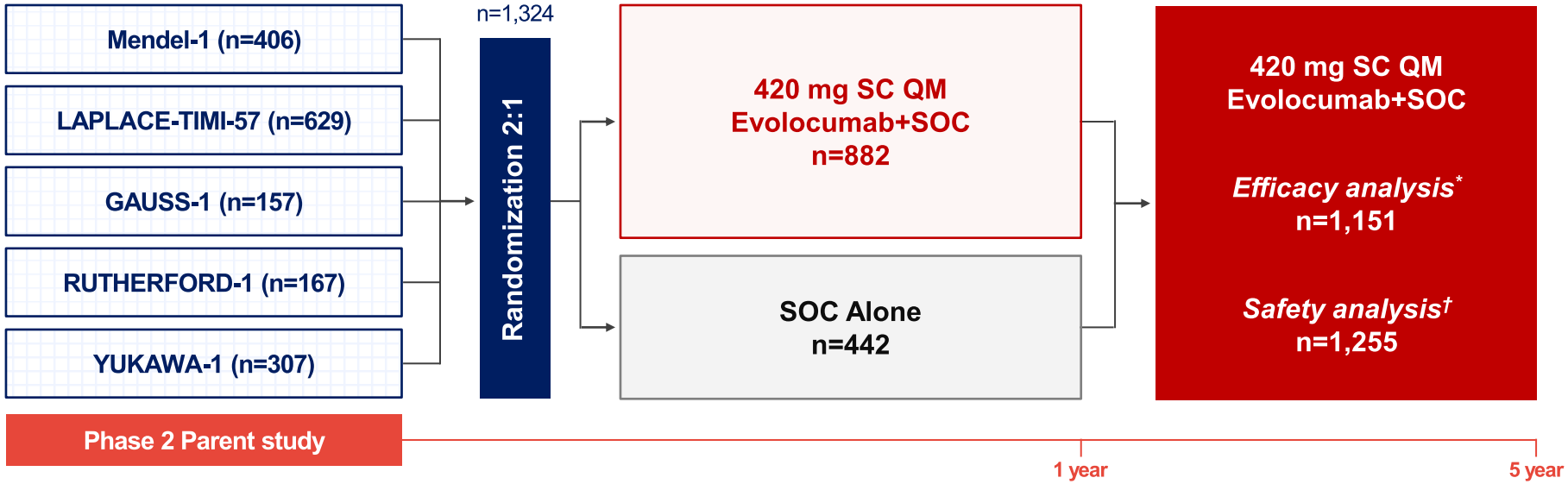
*The between-group difference was nominally significant($P<0.001$); †The total numbers of patients were 8,337 in the evolocumab group and 8,339 in the placebo group, because patients with prevalent diabetes at the start of the trial were excluded.

1. Sabatine MS, et al. *N Engl J Med.* 2017;376:1713-1722.

Repatha® OSLER-1 Study Design:

Open-label extension of 5 phase 2 studies with **up to 5 years exposure**

- **1 of 5 eligible phase 2 parent studies of evolocumab** from 192 sites in 18 countries.
- At randomization, and for 12 weeks thereafter, central labs lipid results were blinded to investigators. After 12 weeks, investigators received unblinded lab results and could adjust SOC therapies in either arm at their discretion. Local investigators determined SOC therapy.
- Patients randomized to **SOC or evolocumab 420 mg QM (evolocumab+SOC) for year 1.**
  After year 1, patients could enter the all-evolocumab period and receive **evolocumab+SOC for an additional 4 years.**



Efficacy endpoint: Assess annual changes in LDL-C, non-HDL-C, ApoB, total cholesterol/HDL-C ratios, ApoB/apoliprotein A-1 ratios

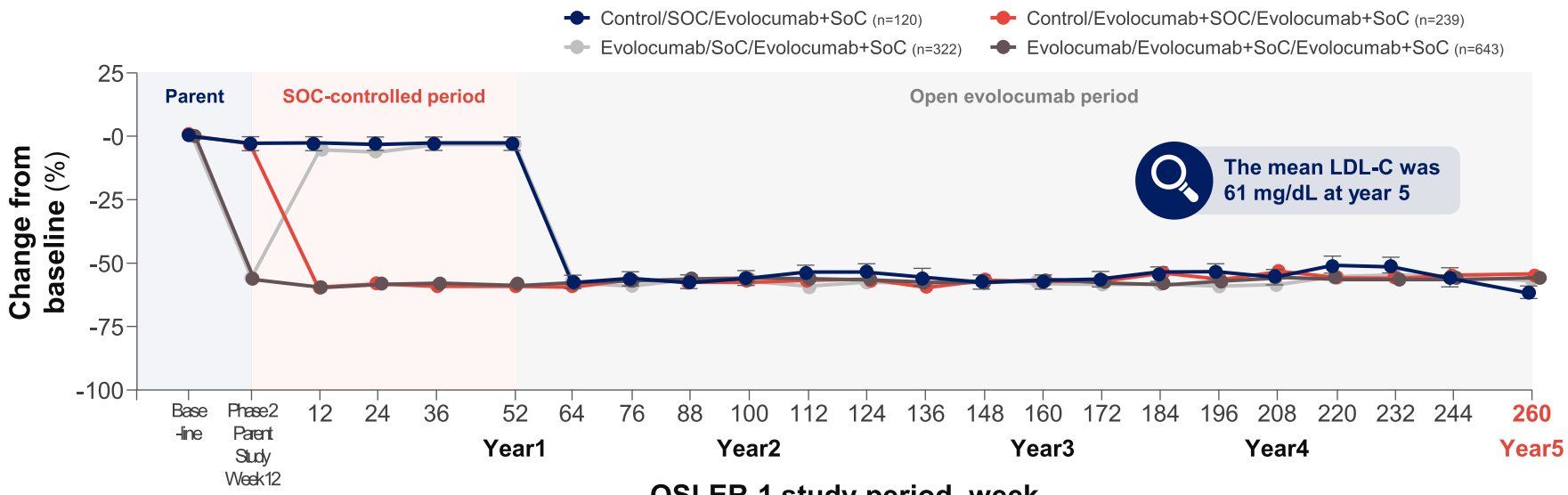
Safety endpoint: Incidence of AEs, SAEs, and AEs leading to discontinuation
Incidence of patients developing anti-evolocumab antibodies (binding or neutralizing)
Incidence of new-onset diabetes, injection-site reactions, neurocognitive events, and adjudicated CV events

*A total of 1,151 patients (efficacy analysis population) progressed to the all-evolocumab period (year 2 and beyond); †A total of 1,255 patients (safety analysis population) randomized into the year 1 SOC-controlled period and received≥1 evolocumab dose. **SC**=subcutaneous; **QM**=once monthly; **SOC**=standard of care; **n**=number; **LDL-C**=low density lipoprotein cholesterol; **HDL-C**=high density lipoproteins cholesterol; **ApoB**=apolipoprotein B; **AE**=adverse events; **SAE**=serious adverse event; **CV**=cardiovascular.

1. Koren MJ, *et al. J Am Coll Cardiol*. 2019;74:2132-2146.

Patients* Maintained Their ~60% Reduction in LDL-C Throughout 5 Years With Repatha®

OSLER-1: LDL-C % change from baseline up to 5 years



Number of subjects:																								
1	120	117	116	111	110	112	99	103	99	101	97	97	93	95	94	93	94	89	89	90	87	81	72
2	239	235	231	228	226	213	200	206	198	196	192	192	239	186	183	182	184	178	172	170	168	164	150
3	322	315	306	301	292	285	258	254	254	253	250	249	243	242	234	236	232	231	223	225	217	215	179
4	643	630	619	597	592	572	534	532	530	521	515	507	509	505	490	481	476	469	459	460	445	452	402

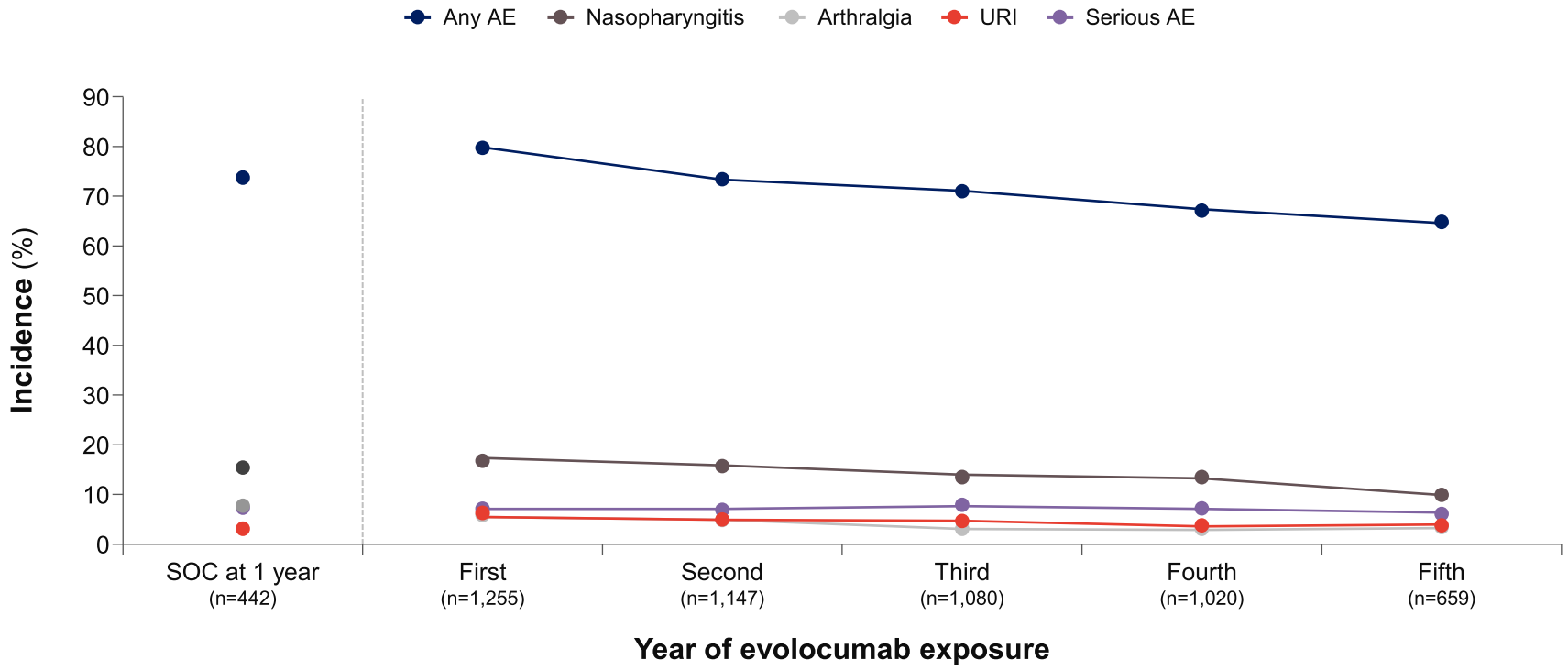
- **Mean baseline LDL-C decreased from 140 to 61 mg/dL on treatment.**
- **Repatha®+SOC persistently lowered mean±SE LDL-C by 56%±0.6%** (n=1,071)**, 57%±0.8%** (n=1,001)**, 56%±0.8%** (n=943)**, and 56%±0.8%** (n=803) **after approximately 2, 3, 4, and 5 years, respectively, from randomization.**

*A total of 1,151 patients (efficacy analysis population) progressed to the all-evolocumab period (year 2 and beyond).
LDL-C=low-density lipoprotein cholesterol; **SOC**=standard of care.

1. Koren MJ, *et al. J Am Coll Cardiol*. 2019;74:2132-2146.

Rates of AE Over 5 Years in OSLER-1 Did Not Change Over Time

Adverse events over time



- **Over 5 years of Repatha® exposure, AEs occurred in 65% of patients; similar to previous years** (67%-80%) **and to year 1 SOC control group** (74%)**.**

AE=adverse event; **SOC**=standard of care; **URI**=upper respiratory infection.

1. Koren MJ, *et al. J Am Coll Cardiol*. 2019;74:2132-2146.

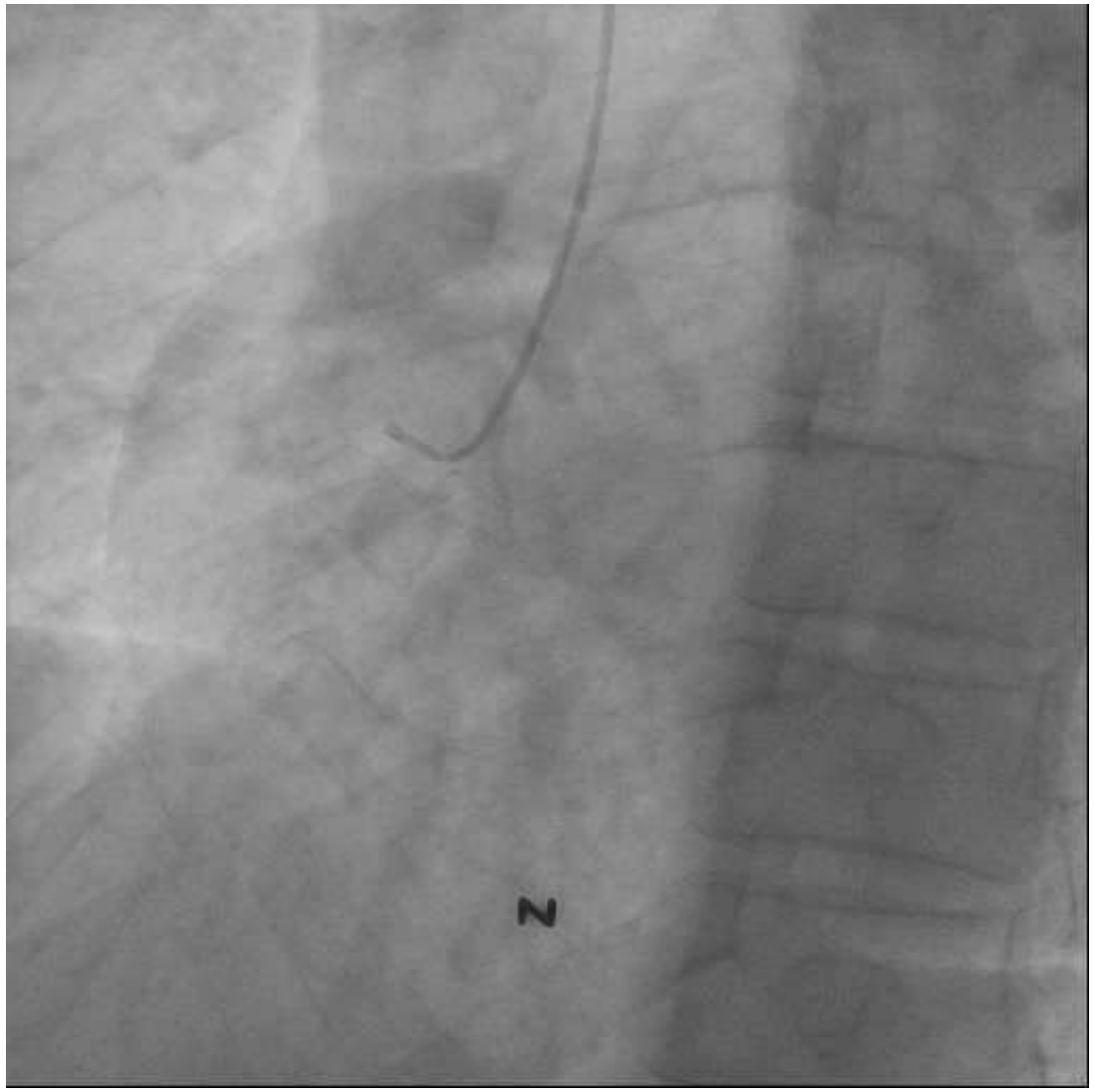
Clinical course

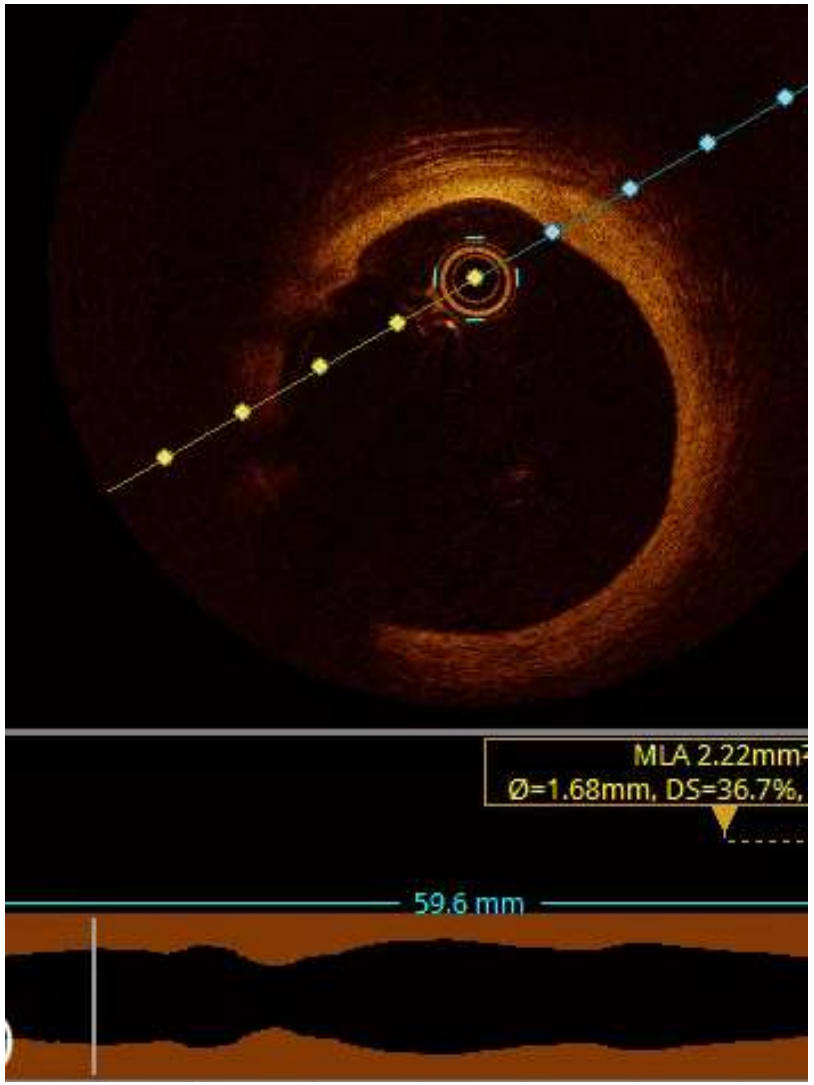
Patient asks "It has been a year already since I had AMI. I have no syptom, and doing well. How long do I have to use this drug?"

I say "Forever!!!"

- ***Share the LDL cholesterol results and encourage patient!***
- ***Very low LDL cholesterol level maintained by PCSK9i has prevented and will prevent recur, and the benefit is greater for longer term!***
- ***If stopped and LDL cholesterol level goes up, then atherosclerosis will progress again!***

F/U CAG





4. Recent Update on Fourier Study Subanalysis

04

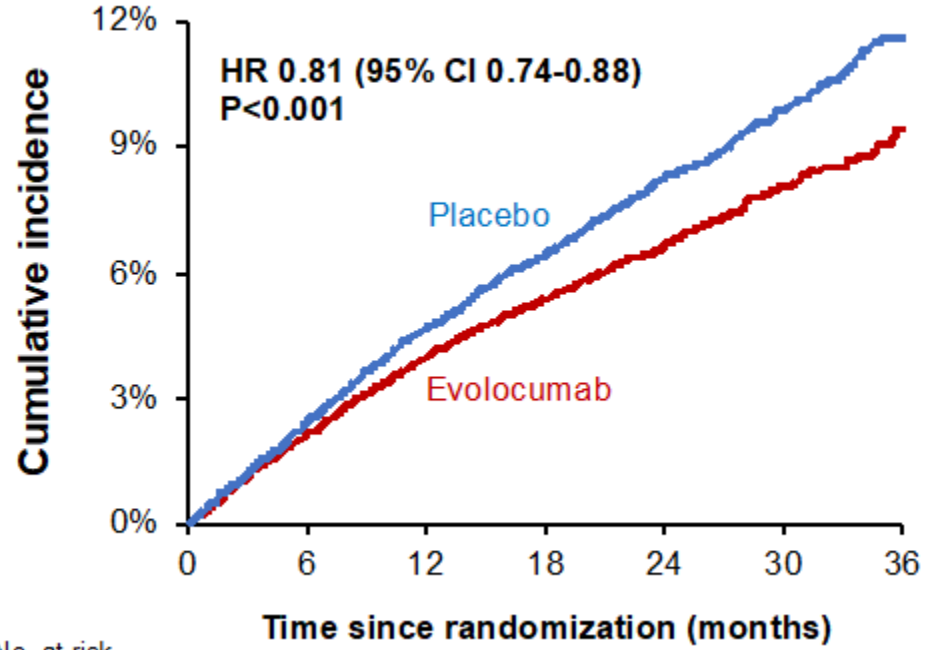
AMGEN Repatha

Effect of Evolocumab on Acute Arterial Events Across All Vascular Territories : Results From the FOURIER Trial

To assess the impact of PCSK9 inhibitor, evolocumab on acute arterial events* across all vascular territories in patients with established ASCVD.

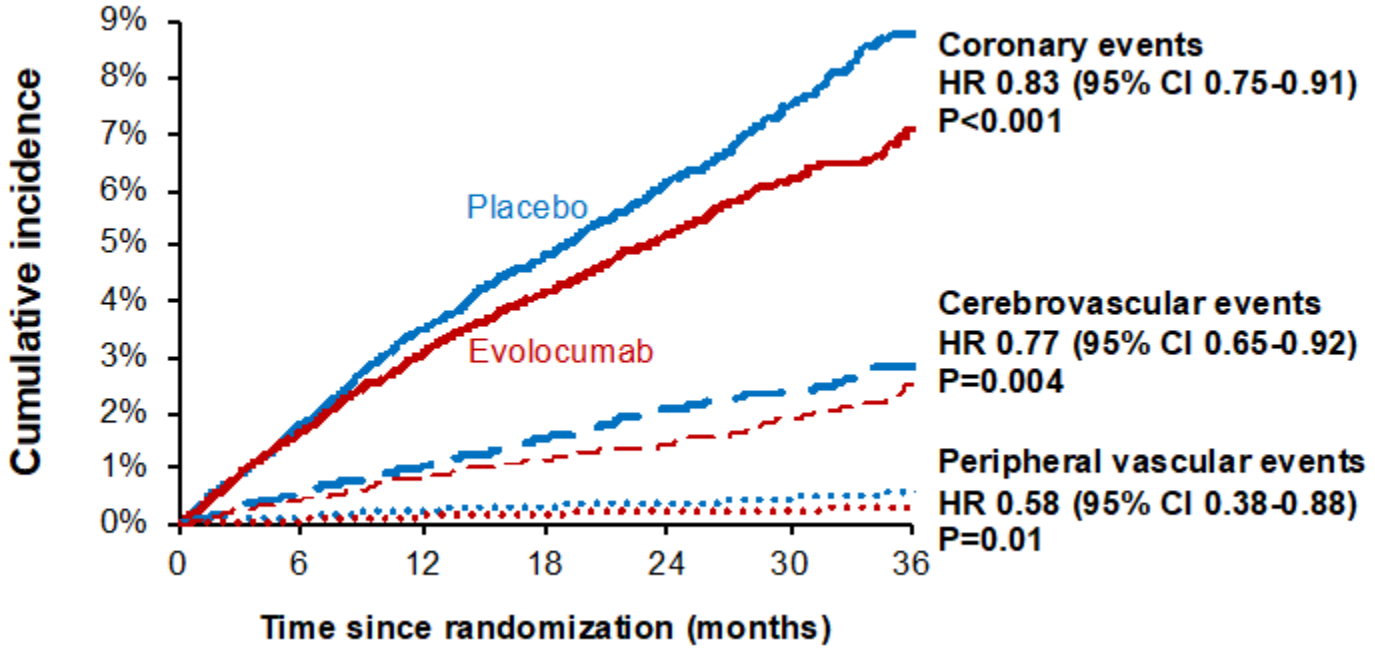
Event curves for acute arterial events* by treatment groups

Acute arterial events across all vascular beds



No. at risk

Acute arterial events in individual vascular beds



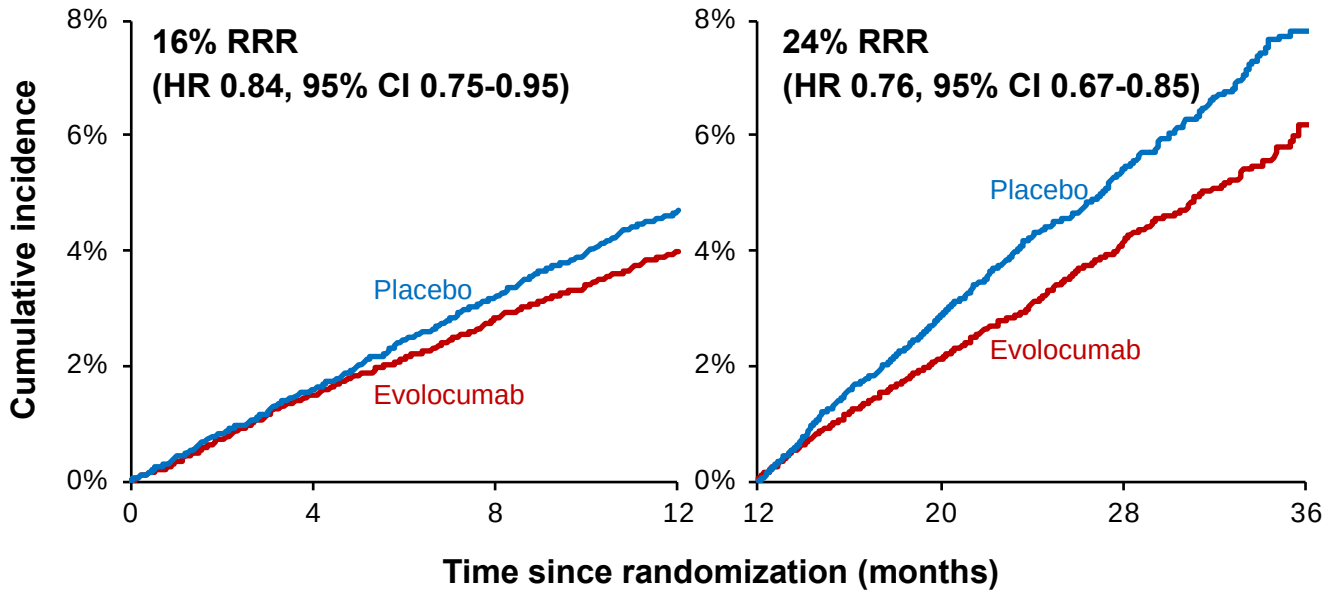
* Acute arterial events were a composite of acute coronary (coronary heart disease death, myocardial infarction, or urgent coronary revascularization), cerebrovascular (ischaemic stroke, transient ischaemic attack, or urgent cerebral revascularization), or peripheral vascular (acute limb ischaemia, major amputation, or urgent peripheral revascularization) events

European Heart Journal (2021) 00, 1–9 doi:10.1093/eurheartj/ehab604

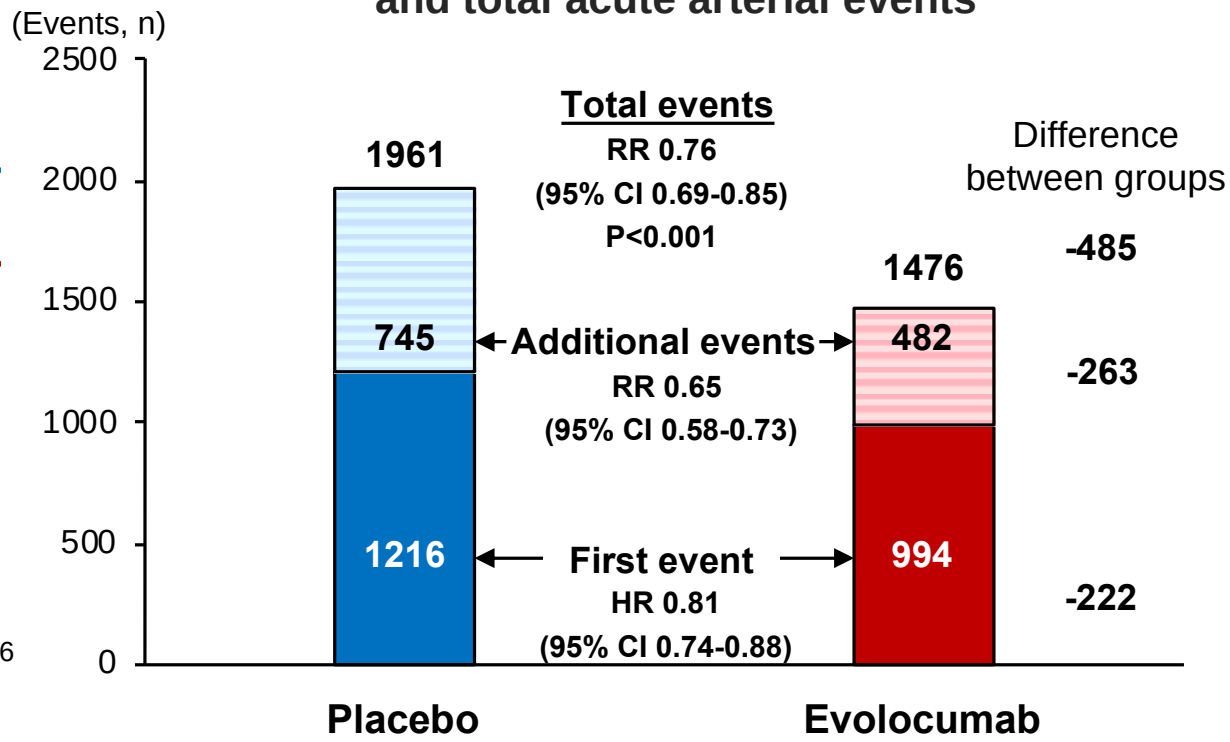
Effect of Evolocumab on Acute Arterial Events Across All Vascular Territories : Results From the FOURIER Trial

Adding evolocumab to statin therapy reduced the risk of acute arterial events across all vascular territories with a robust effect over time on both first events and recurrent events.

Landmark analyses for efficacy of evolocumab



Effect of evolocumab on first, recurrent, and total acute arterial events



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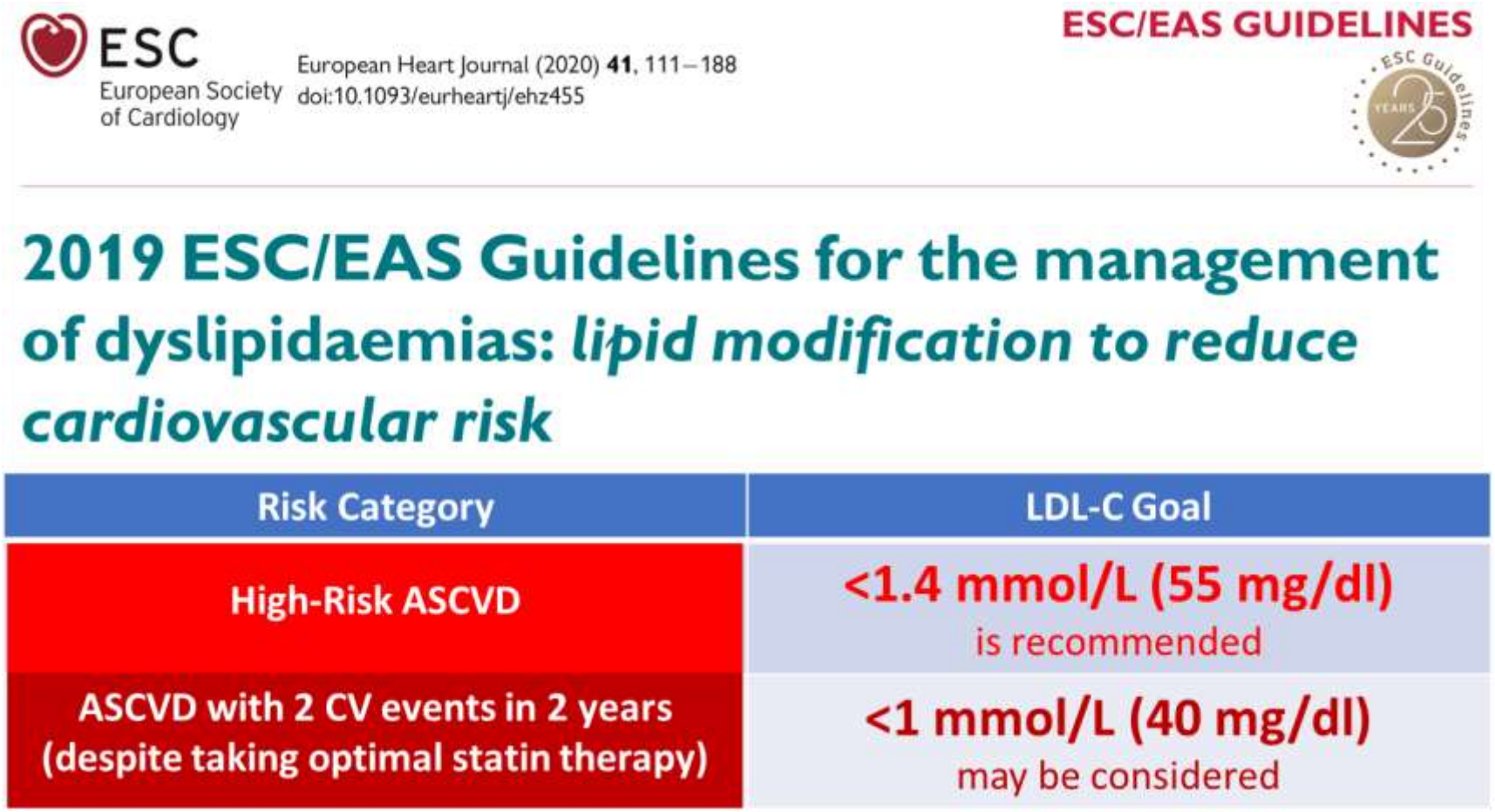
European Heart Journal (2021) 00, 1–9 doi:10.1093/eurheartj/ehab604

2019 ESC/EAS Dyslipidemia Guidelines

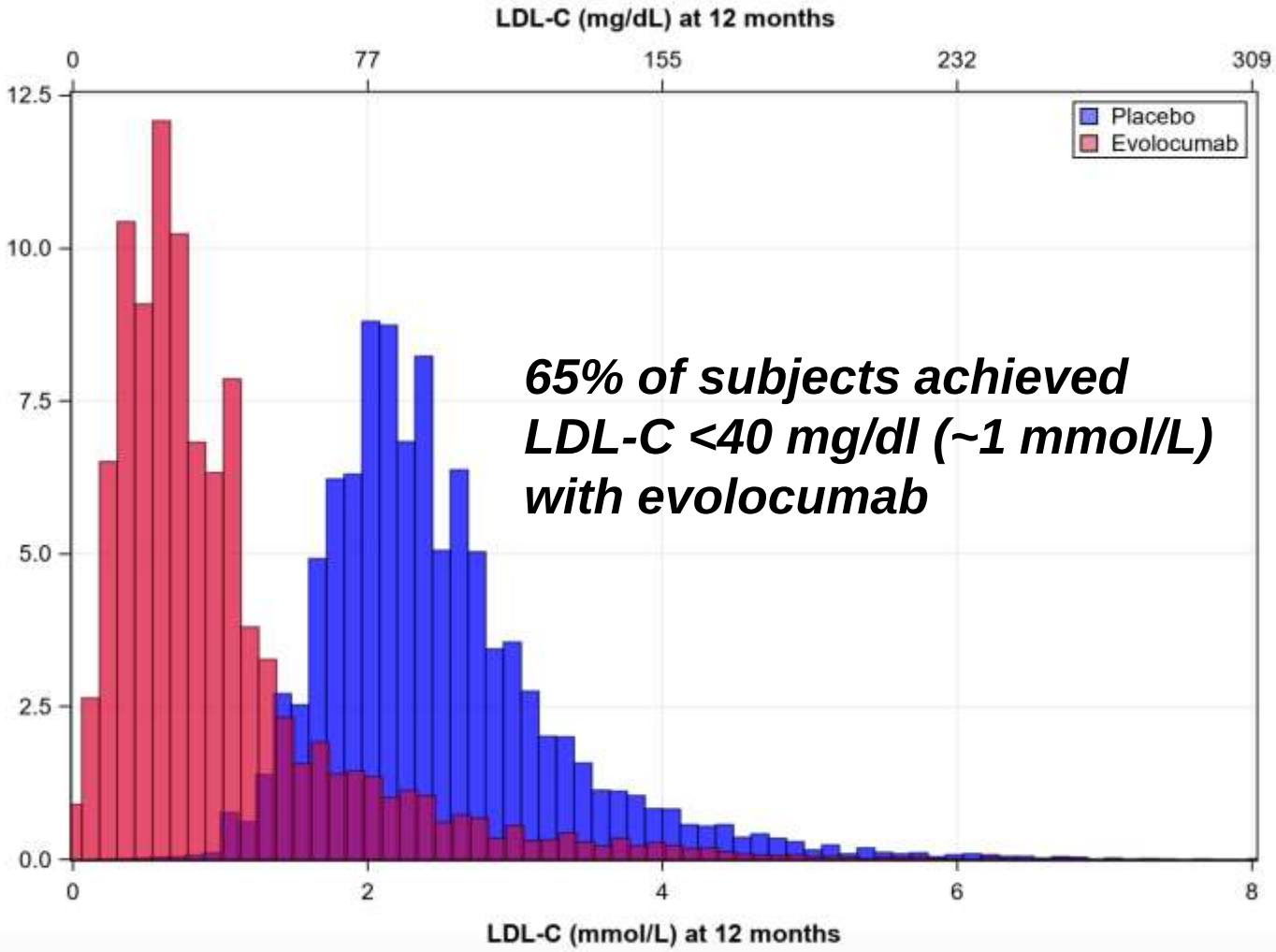
A key question is whether there is evidence of continued clinical benefit with lowering LDL-C below 40 mg/dL.



Mach F, et al. Eur Heart J 2020;41:111-188.

Cardiovascular Benefit of Lowering LDL-C Below ~1 mmol/L (40 mg/dL) : An Exploratory Analysis in the FOURIER Trial

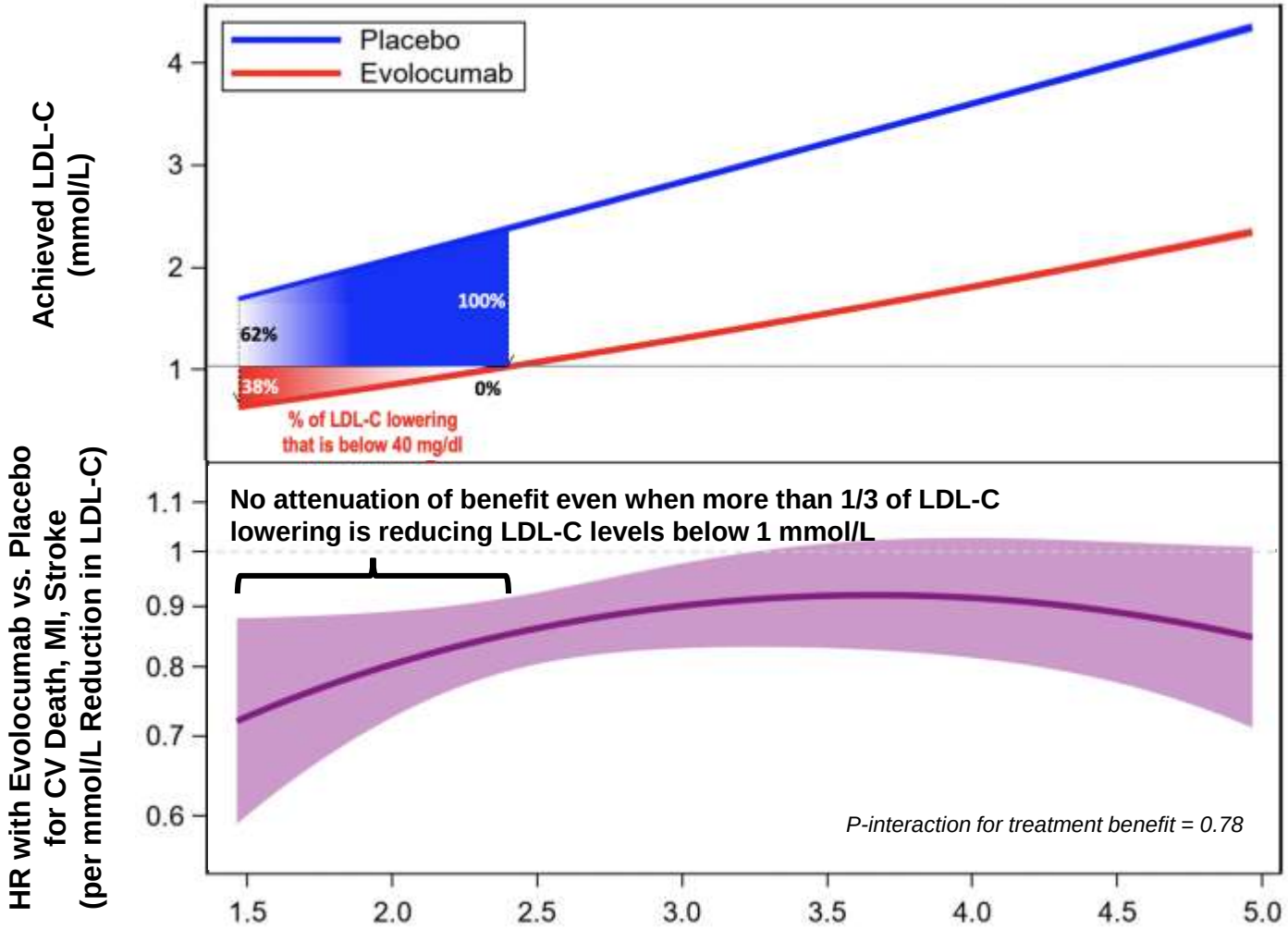
To determine whether there is continued cardiovascular benefit from lowering LDL-C below ~1 mmol/L (40 mg/dl) while maintaining randomization.



10.1161/CIRCULATIONAHA.121.056536

There Is No Evidence for Attenuation of the Clinical Benefit of Lowering LDL-C Below 1 mmol/L (40 mg/dL)

These data support the ESC/EAS Dyslipidemia Guideline recommendations and suggest lowering LDL-C below 1 mmol/L in a wider range of patients with ASCVD would further lower CV risk.



Upper Panel: Achieved LDL-C at 48 weeks and the percentage of LDL-C difference between treatment arms due to lowering LDL-C below 1 mmol/L (<40 mg/dl) as a function of baseline LDL-C.

Lower Panel: Hazard ratio for evolocumab vs. placebo for CV Death, MI, or Stroke per 1 mmol/L reduction in LDL-C as a function of baseline LDL-C.

10.1161/CIRCULATIONAHA.121.056536

Take-Home Messages

- Let's do "**Guideline Directed Therapy**" – earlier and lower!
    - LDL 70mg/dL is not a goal, but a trigger point to mandate more intensive lipid lowering treatment
- **Start communication in the early phase** after ACS event with patients
- To maximize benefit and prevent recurrence of ischemic event, **keep the PCSK9i as long as possible**
- If patient has low LDL at presentation, then **we need to go lower** with PCSK9i!