Effetto dei PCSK9 inibitori nella stabilizzazione e regressione di placca in periferia

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ESC
Working Group
Aorta & Peripheral
Vascular Diseases

European Heart Journal (2014) 35, 2864–2872
doi:10.1093/eurheartj/ehu080

CLINICAL RESEARCH
Vascular medicine

Statin therapy and long-term adverse limb outcomes in patients with peripheral artery disease: insights from the REACH registry

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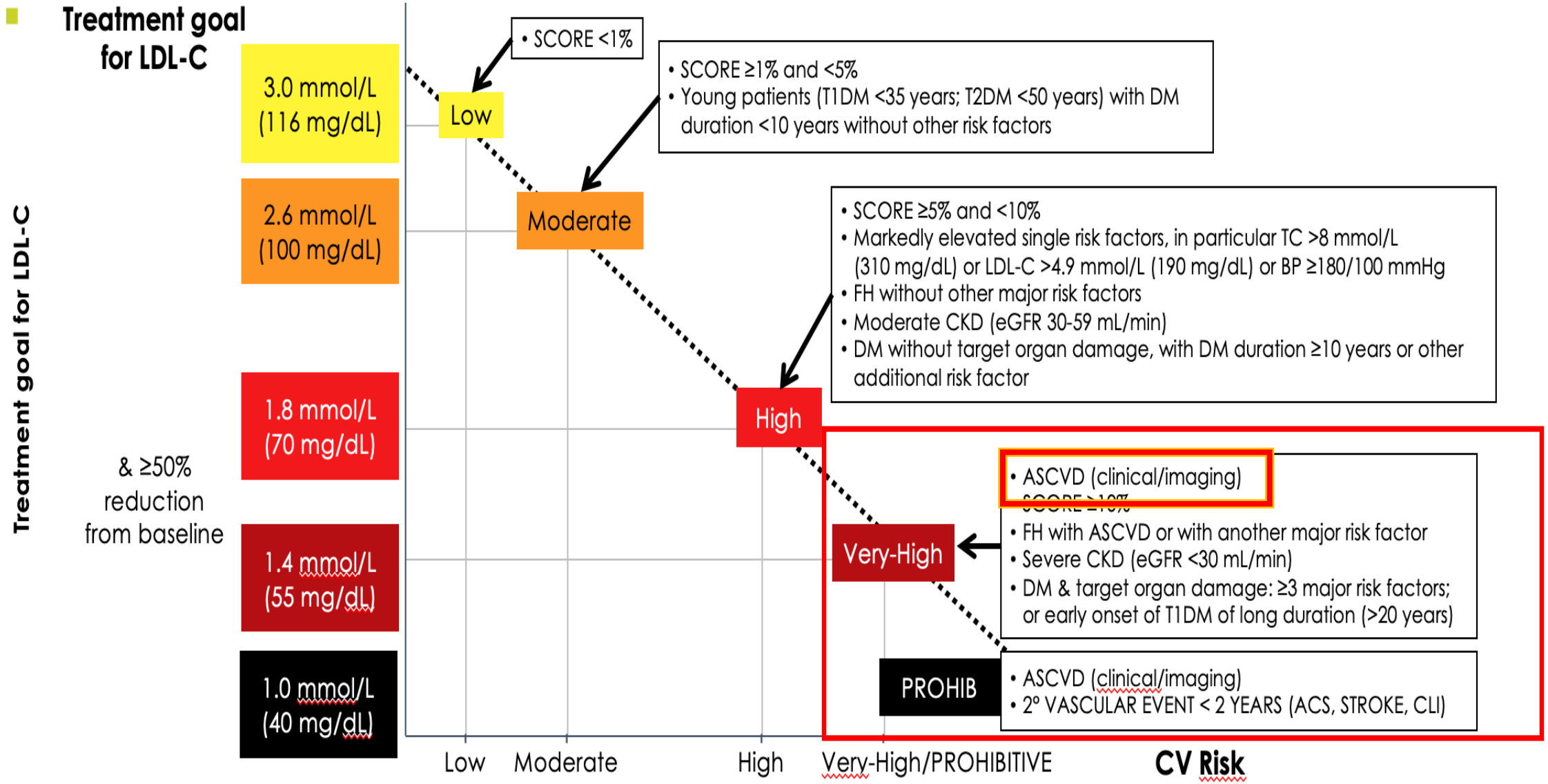
Adjusted multivariate hazard ratios for 4-year systemic and adverse limb outcomes in patients who were on statins vs. those who were not

Endpoint	Multivariate adjusted model for statin non-use at baseline ($n = 5861$), HR (95% CI); *P*-value	Multivariate adjusted model for time-varying statin use ($n = 5006$), HR (95% CI); *P*-value
Adverse limb outcomes		
Worsening PAD[b]	0.82 (0.72–0.92); $P = 0.0013$	0.85 (0.75–0.97); $P = 0.018$
Worsening claudication or new CLI	0.82 (0.70–0.95); $P = 0.0087$	0.84 (0.72–0.99); $P = 0.037$
New revascularization procedure	0.83 (0.72–0.95); $P = 0.0079$	0.90 (0.77–1.04); $P = 0.14$
New amputation	0.64 (0.48–0.86); $P = 0.0027$	0.60 (0.44–0.82); $P = 0.0014$
Systemic outcomes		
CV death/MI/stroke	0.83 (0.73–0.96); $P = 0.01$	0.79 (0.67–0.93); $P = 0.0038$
All-cause mortality	0.83 (0.72–0.96); $P = 0.014$	0.79 (0.65–0.94); $P = 0.0098$
CV mortality	0.84 (0.70–1.00); $P = 0.05$	0.78 (0.61–0.98); $P = 0.034$
Non-fatal MI	0.85 (0.63–1.14); $P = 0.28$	0.80 (0.58–1.11); $P = 0.18$
Non-fatal stroke	0.74 (0.57–0.95); $P = 0.016$	0.75 (0.57–0.97); $P = 0.029$

REACH REGISTRY
REduction of Atherothrombosis for Continued Health

Khumbani et al . *Eur Heart Journal* 2014



Mach F et al. *Eur Heart J* 2019

Cardiovascular and Limb Outcomes Among the Overall PAD Population

MACE: 3.7 100 pts/yr
MACE +MALE: 4.7 100 pts/yr
Elective LLR : 6.6 100 pts/yr

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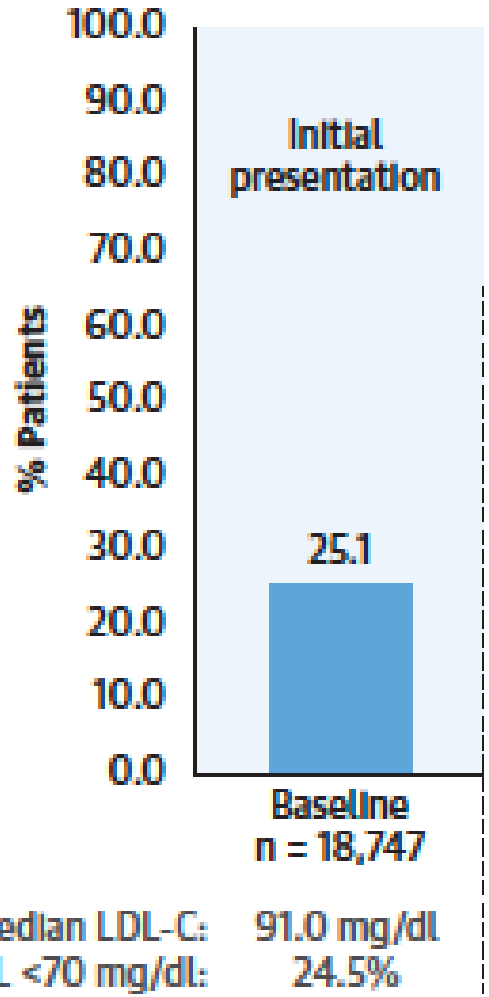
Outcome	No. of Events	Person-Years	Incidence Rate Per 100 Patient-Years (95% CI)
Myocardial infarction or ischemic stroke	12,154	337,906	3.6 (3.5-3.7)
Myocardial infarction	9,356	340,333	2.8 (2.7-2.8)
Ischemic stroke	3,121	345,196	0.9 (0.9-0.9)
Major adverse limb event*	3,023	344,727	0.9 (0.9-0.9)
Major amputation	1,642	346,355	0.5 (0.5-0.5)
Acute limb ischemia	1,524	346,057	0.4 (0.4-0.5)
Critical limb ischemia	4,976	342,301	1.5 (1.4-1.5)
Elective lower extremity revascularization	21,376	322,177	6.6 (6.6-6.7)

Hess, C.N. et al. *J Am Coll Cardiol*. 2021

Use of a High-Intensity Lipid-Lowering Strategy After Ischemic Events

Hess, C.N. et al.
J Am Coll Cardiol. 2021



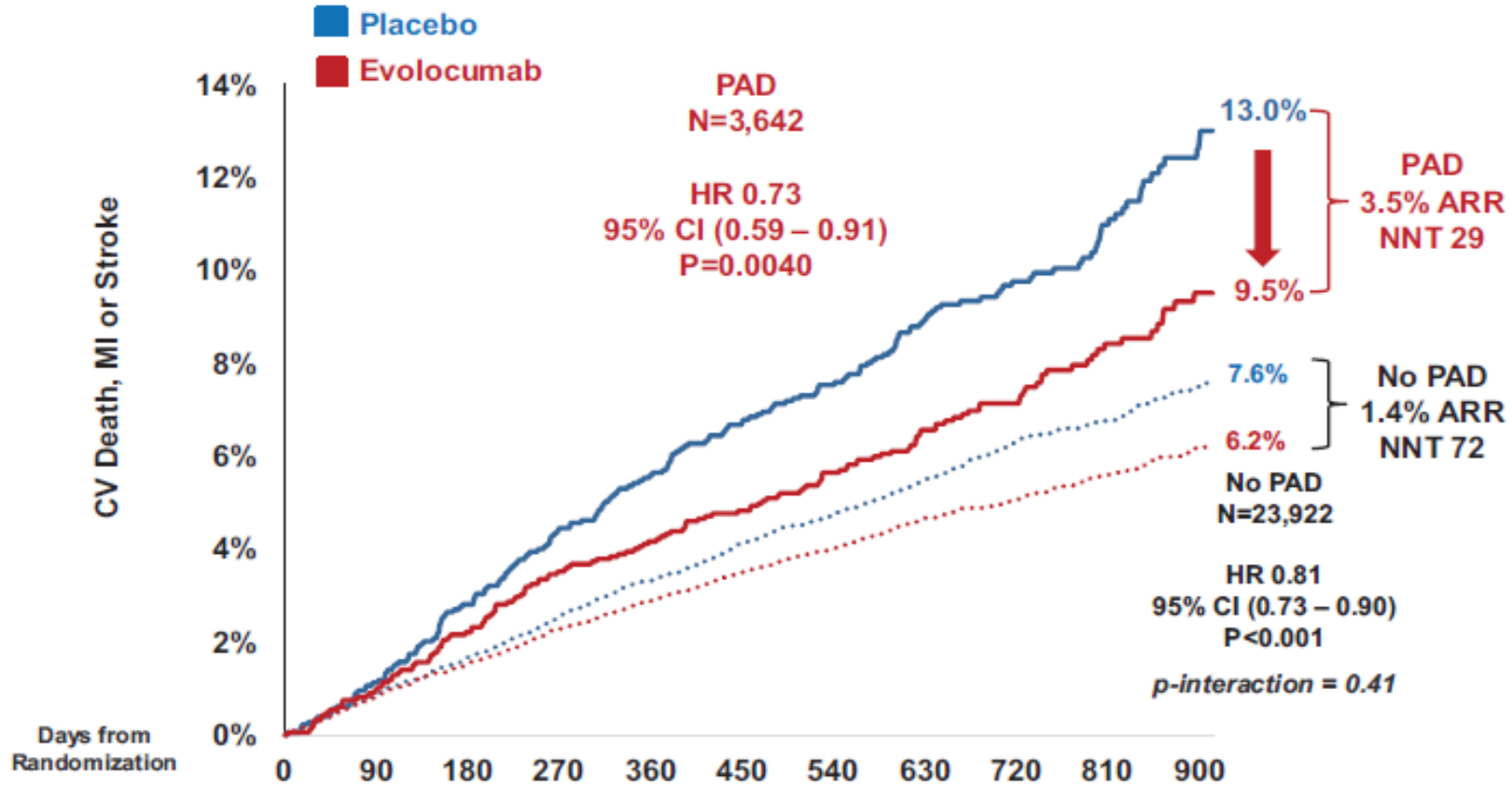
Intensity of lipid-lowering treatment

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%

ESC

2021 ESC Guidelines on cardiovascular disease prevention

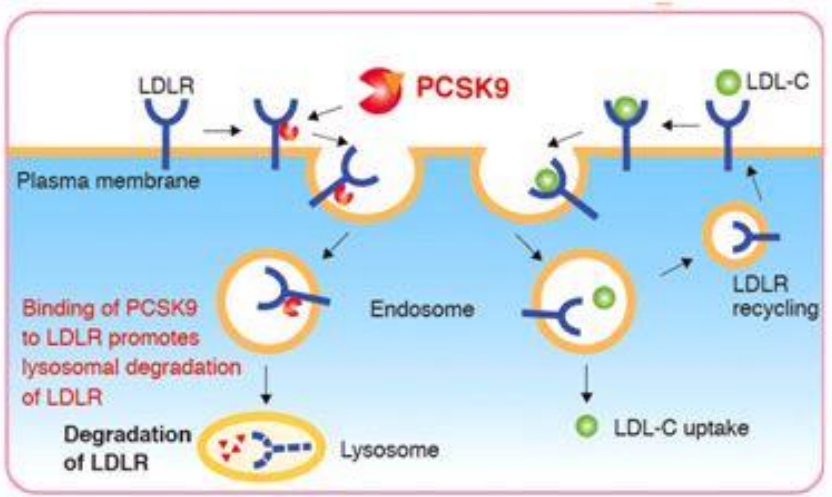
B CV Death, MI or Stroke in Patients with and without PAD



Number at risk

Placebo PAD	1784	1756	1721	1685	1654	1632	1587	1332	1014	729	452
Evolocumab PAD	1858	1834	1806	1774	1758	1740	1692	1427	1091	779	480
Placebo no PAD	11996	11861	11732	11606	11494	11375	10767	9099	7167	5429	3636
Evolocumab no PAD	11926	11802	11699	11583	11490	11397	10828	9138	7258	5474	3649

Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With ASCVD (FOURIER Trial)



Bonaca M at al. *Circulation* 2018

Alirocumab and Cardiovascular Outcomes after ACS: ODYSSEY Outcomes Tral

ESC Working Group Aorta & Peripheral Vascular Diseases

Randomized, Double-blind, Placebo-controlled, Parallel-group Study

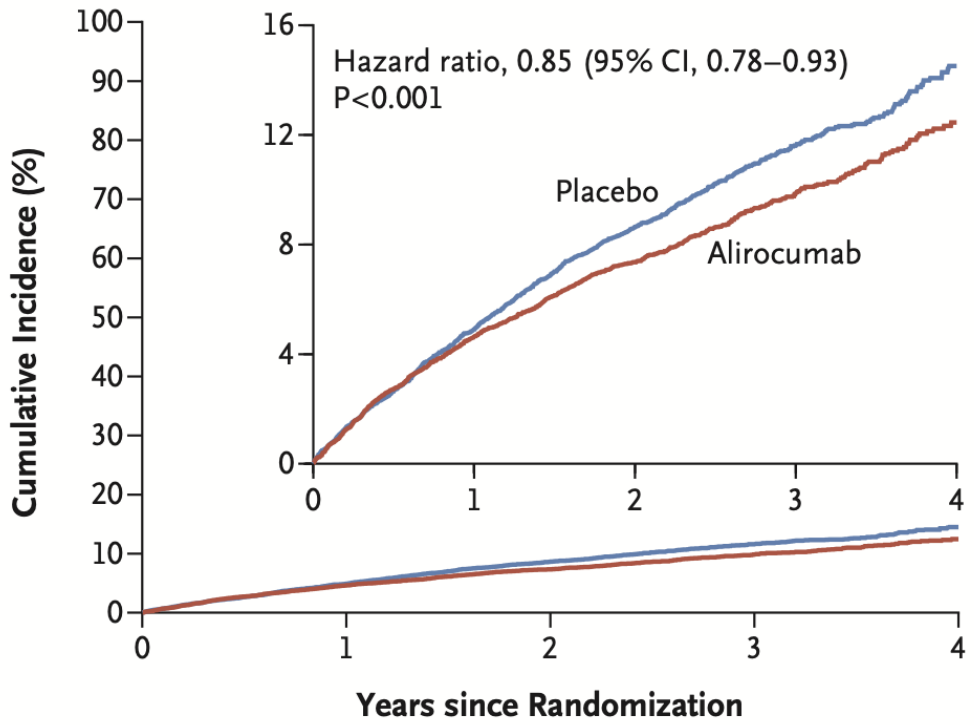
>40 y, ACS history past 1-12 months, on high statin dose and inadeguate lipids control

Alirocumab	Placebo
75-150 mg LDL-C goal 25-50 mg/dl **N= 9462**	Dosed accordingly to study drug **N= 9462**

9.5%	**Major Adverse Cardiac Events (MACE)** HR 0.85 (0.78-0.93), p=0.0003	11.1%
6.6%	**Myocardial Infarction** HR 0.86 (0.77-0.96), p=0.006	7.6%
1.2%	**Ischemic Stroke** HR 0.73 (0.57-0.93), p=0.01	1.6%
3.5%	**All-Cause Mortality** HR 0.85 (0.73-0.98), p=0.026	4.1%
7.7%	**Coronary revascularization** HR 0.98 (0.79-0.97), p<0.001	8.8%

Primary Efficacy Endpoint

Composite of death from coronary heart disease, nonfatal MI, ischemic stroke, or unstable angina



Schwartz GG, et al. N Engl J Med. 2018

Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With ASCVD (FOURIER Trial)

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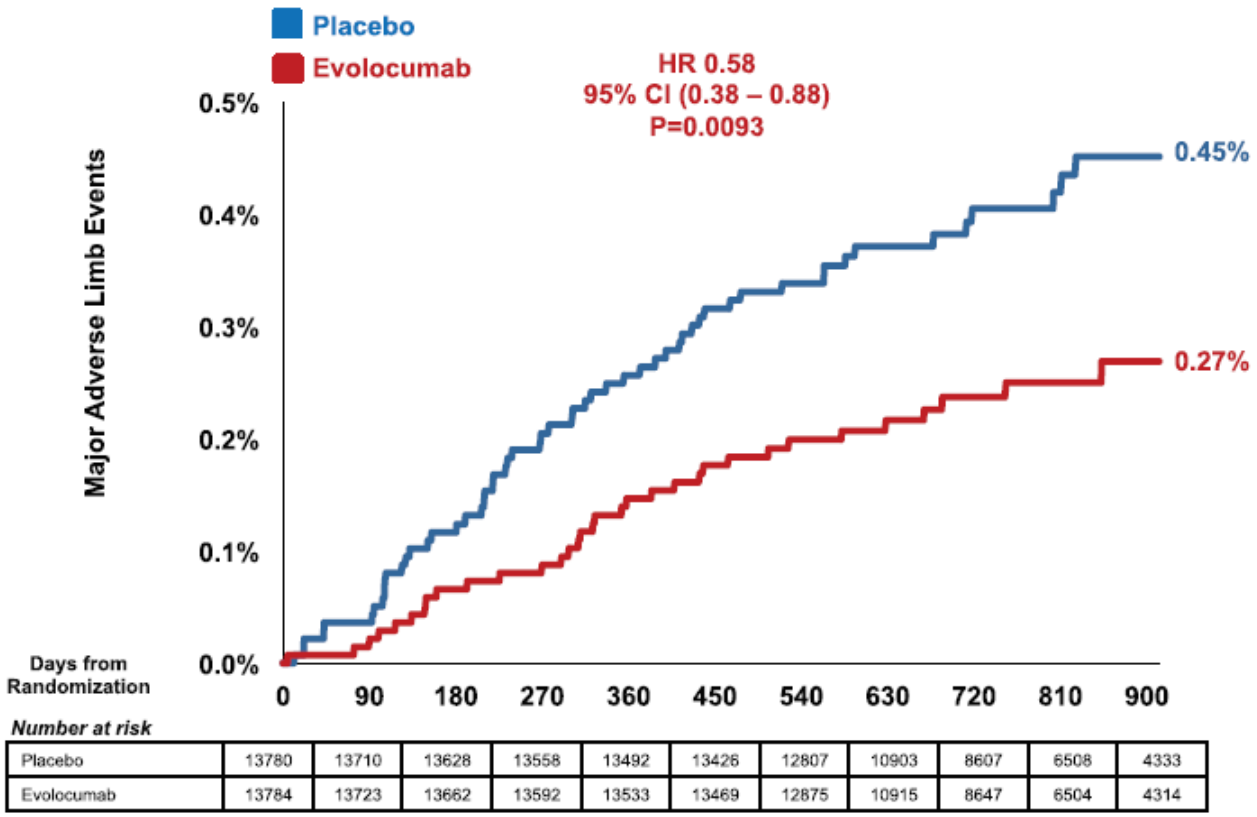
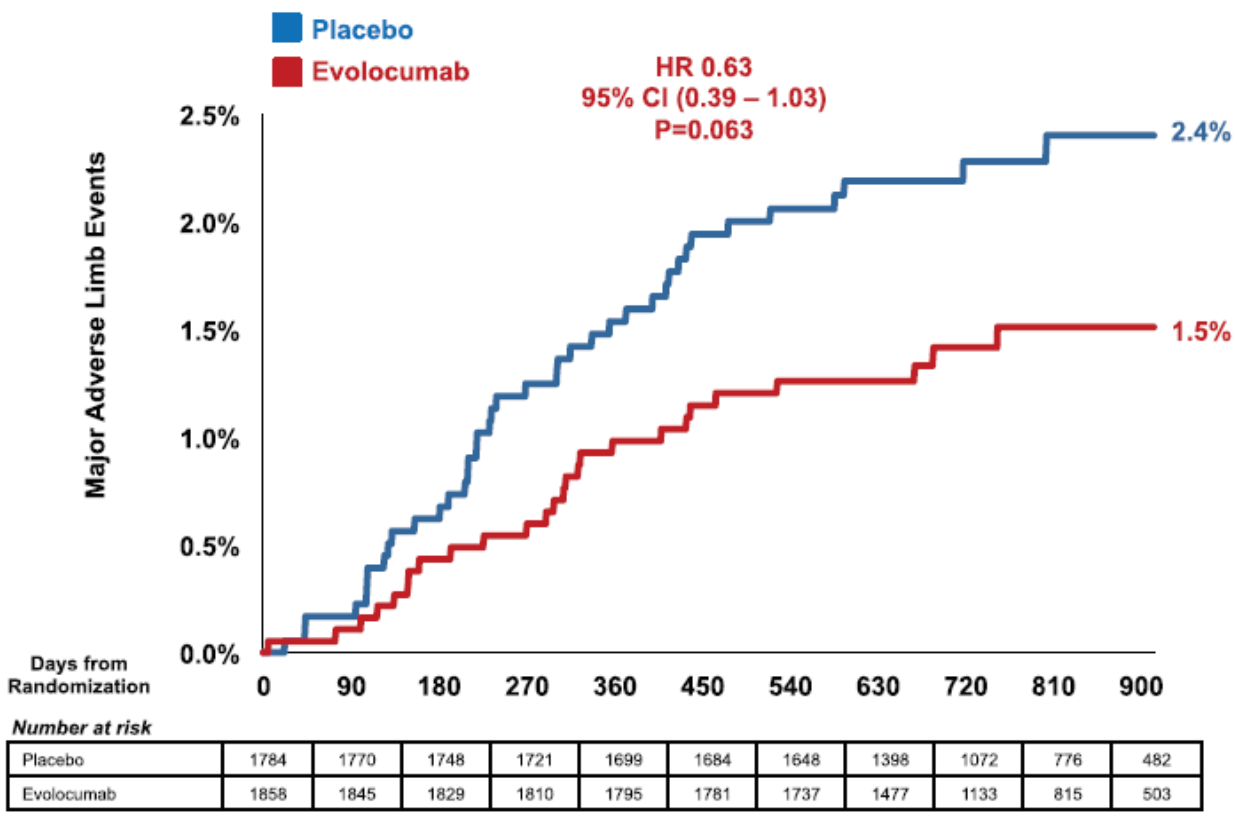
A



Number at risk

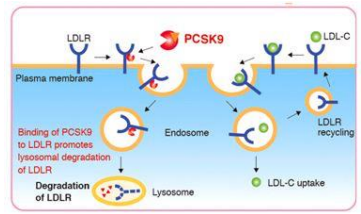
Placebo	13780	13710	13628	13558	13492	13426	12807	10903	8607	6508	4333
Evolocumab	13784	13723	13662	13592	13533	13469	12875	10915	8647	6504	4314

B



Number at risk

Placebo	1784	1770	1748	1721	1699	1684	1648	1398	1072	776	482
Evolocumab	1858	1845	1829	1810	1795	1781	1737	1477	1133	815	503



Bonaca M at al. *Circulation* 2018

Patients with MSAD Have High Risk of Morbidity and Mortality

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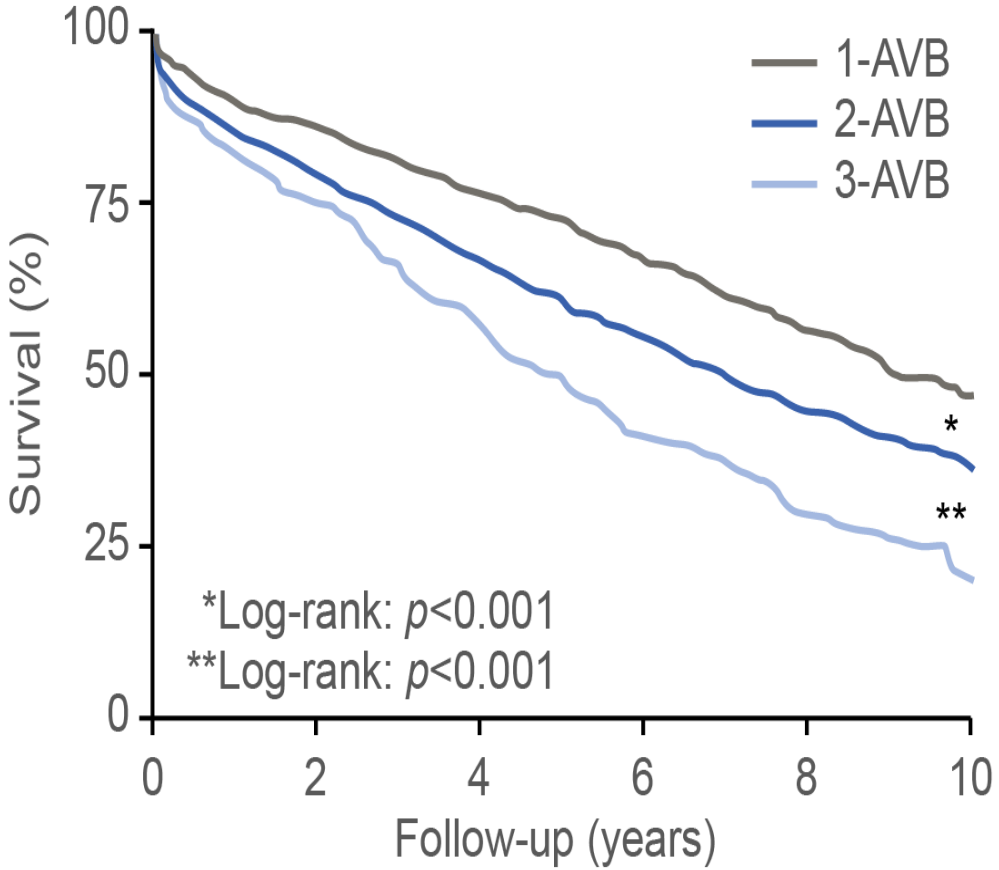
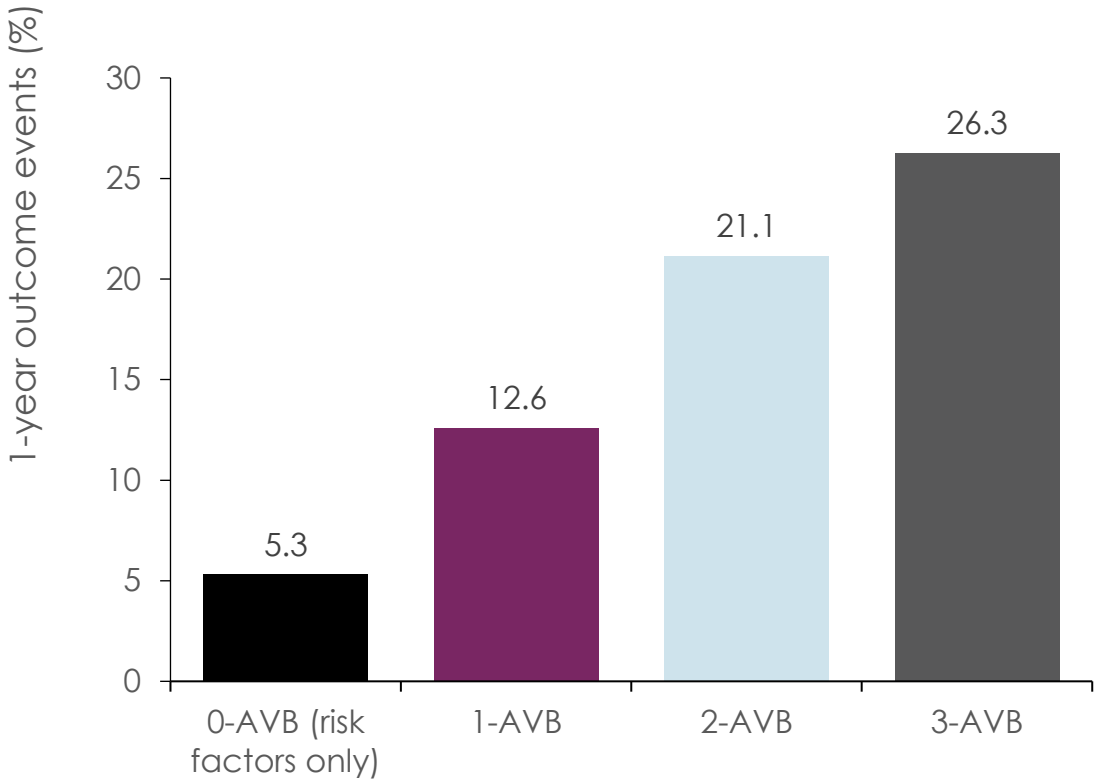


Long-term all cause mortality in patients with PAD stratified according to number of affected vascular beds (AVB)[1]



MACCE or hospitalization for atherothrombotic events according to number of AVB [2]

1. van Kuijk P *et al*, *Eur Heart J* 2010 ; 2. Steg P *et al*, *JAMA* 2007

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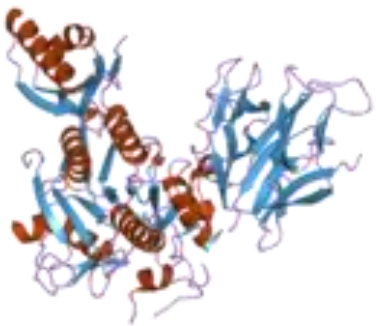
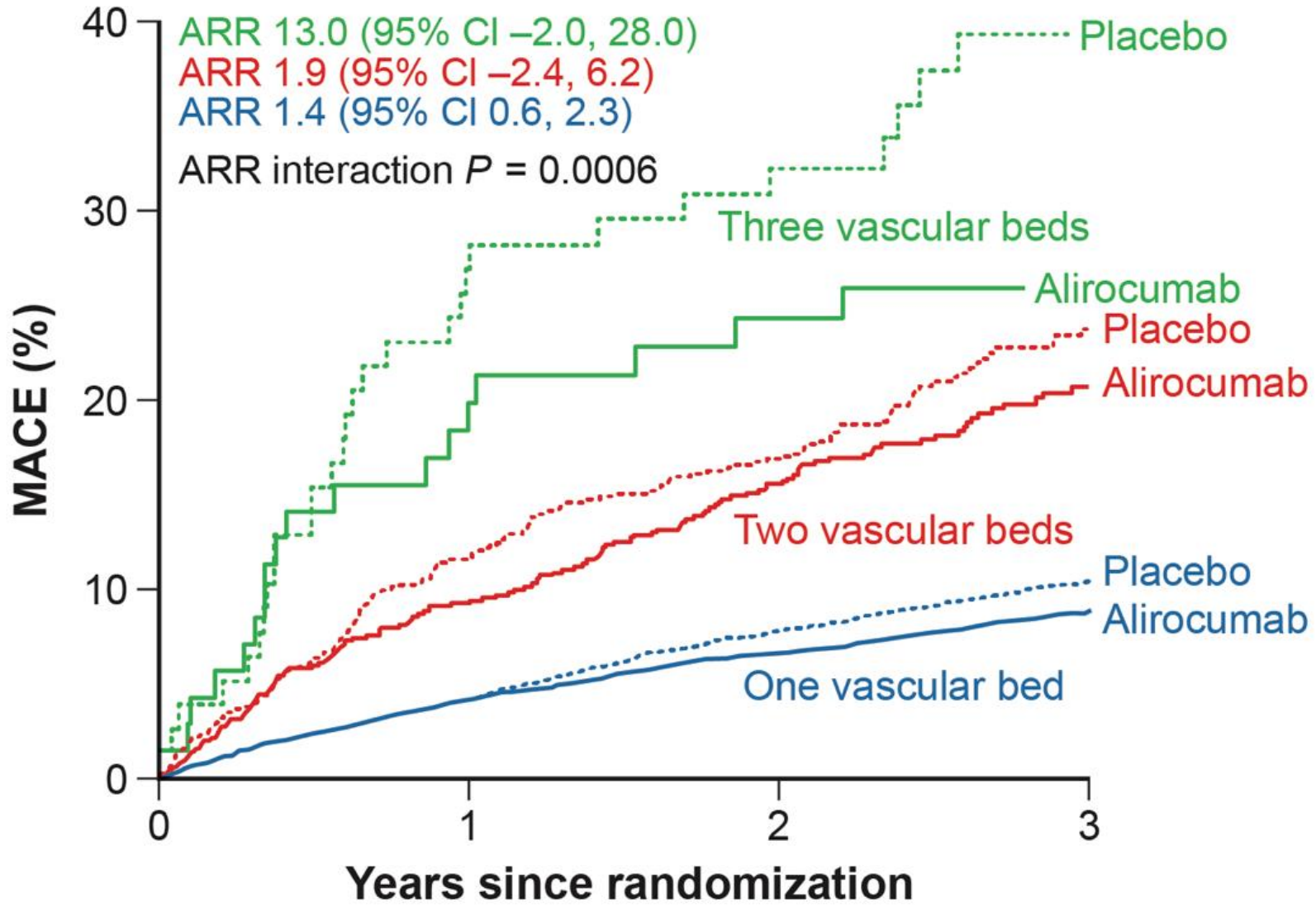
ORIGINAL INVESTIGATIONS

Alirocumab in Patients With Polyvascular Disease and Recent Acute Coronary Syndrome

ODYSSEY OUTCOMES Trial

CAD
PAD
CVD





Ray KK et al. *J Am coll Cardiol* 2019

Effect of Evolocumab on acute arterial events across all vascular territories: A Panvascular effect

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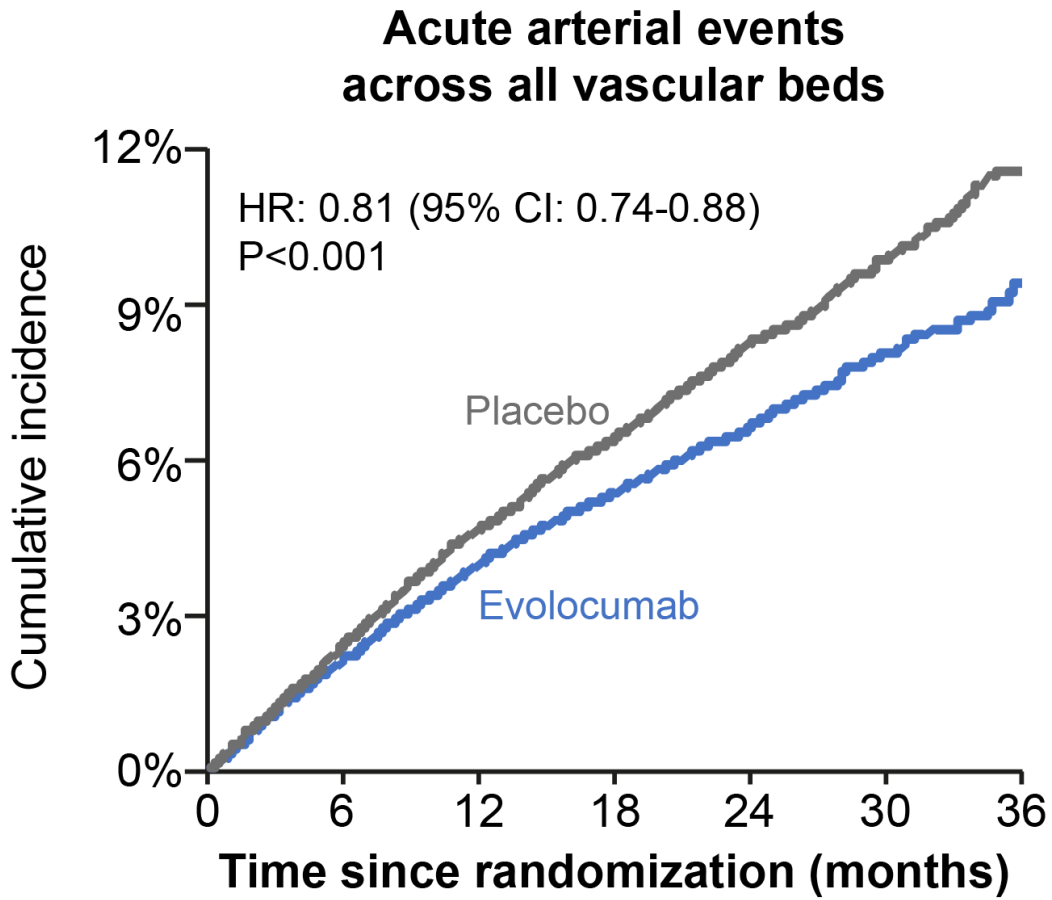
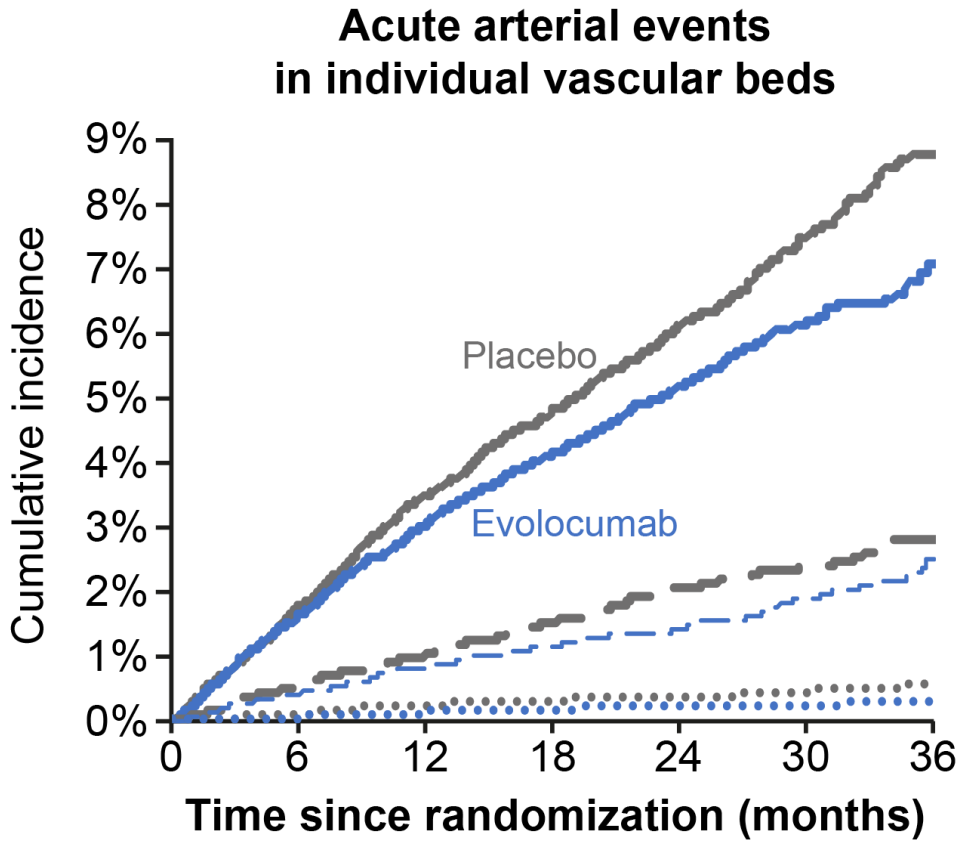




Coronary events
HR 0.83 (95% CI 0.75-0.91)
P<0.001

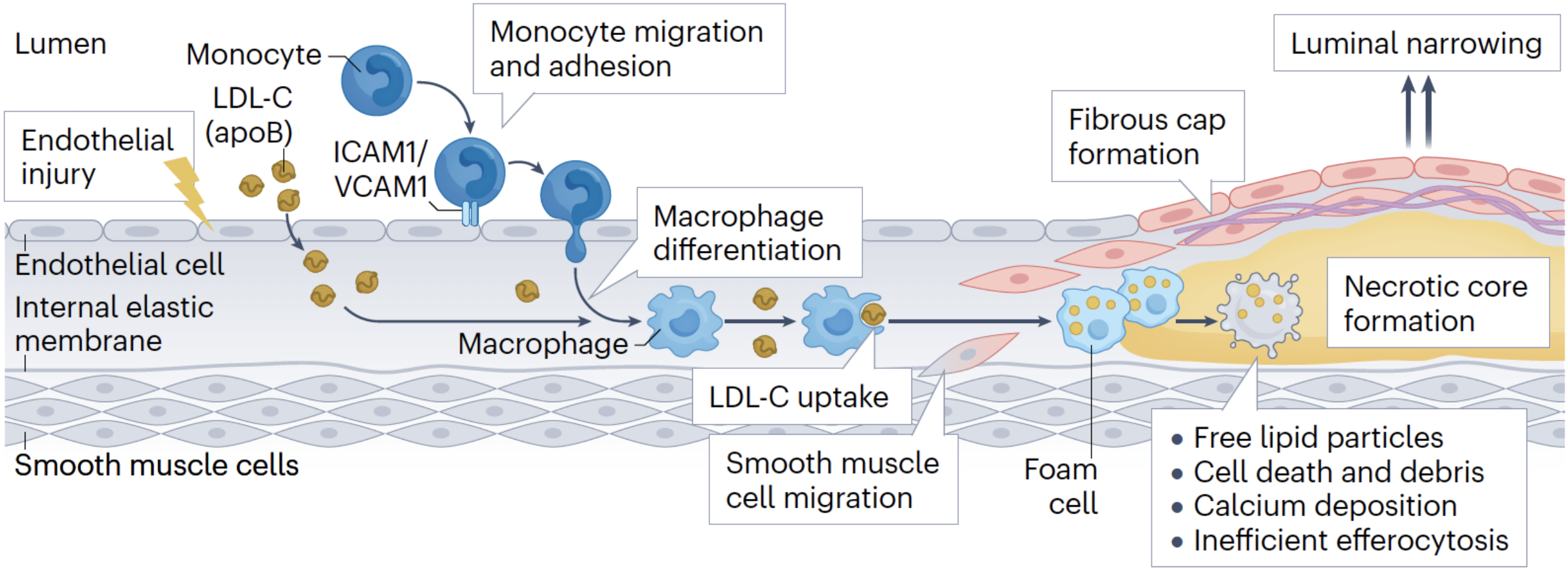
Cerebrovascular events
HR 0.77 (95% CI 0.65-0.92)
P=0.004

Peripheral vascular events
HR 0.58 (95% CI 0.38-0.88)
P=0.01

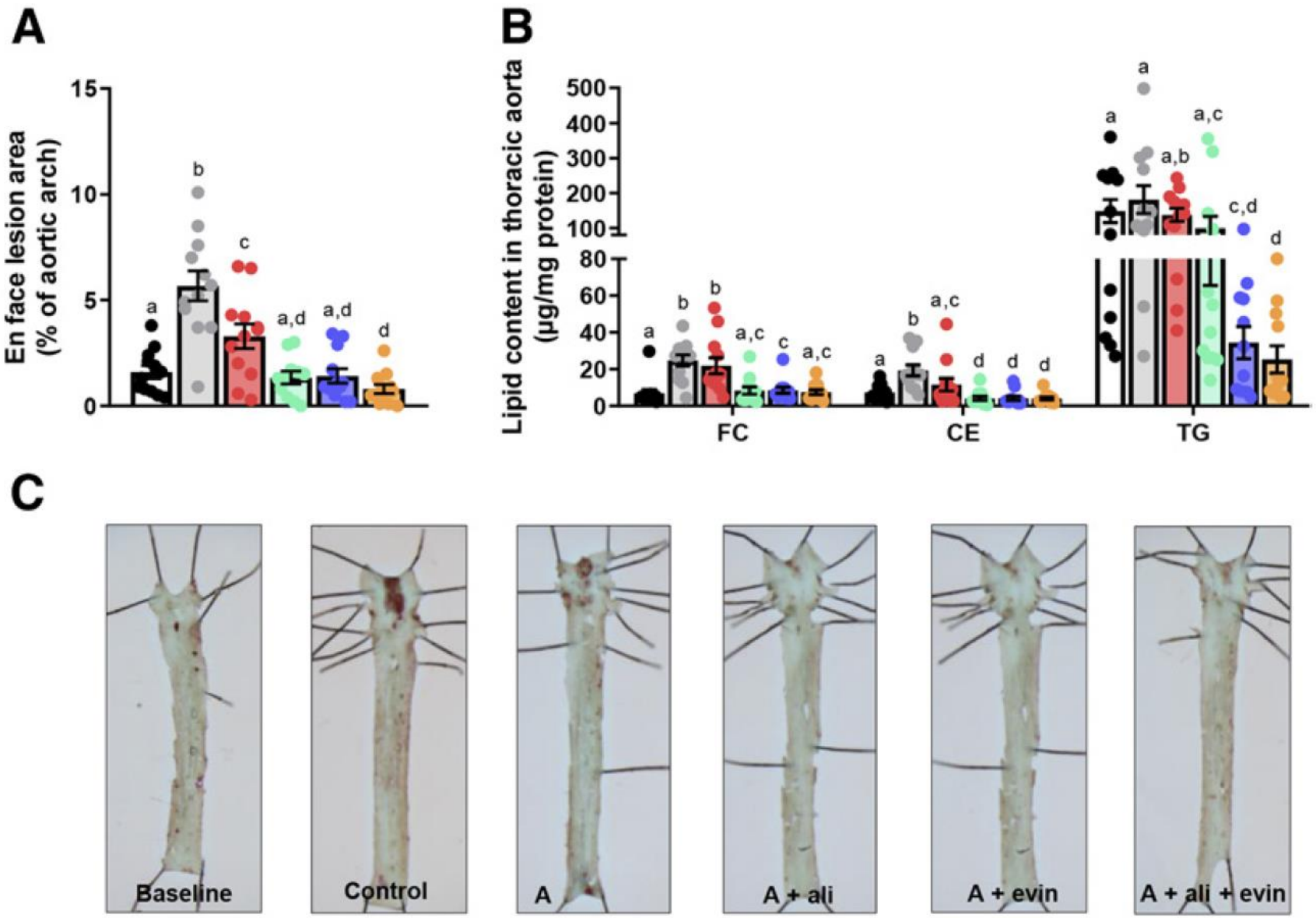
Oyama K et al. *European Heart Journal* 2021

Development of an atherosclerotic plaque

ESC Working Group Aorta & Peripheral Vascular Diseases



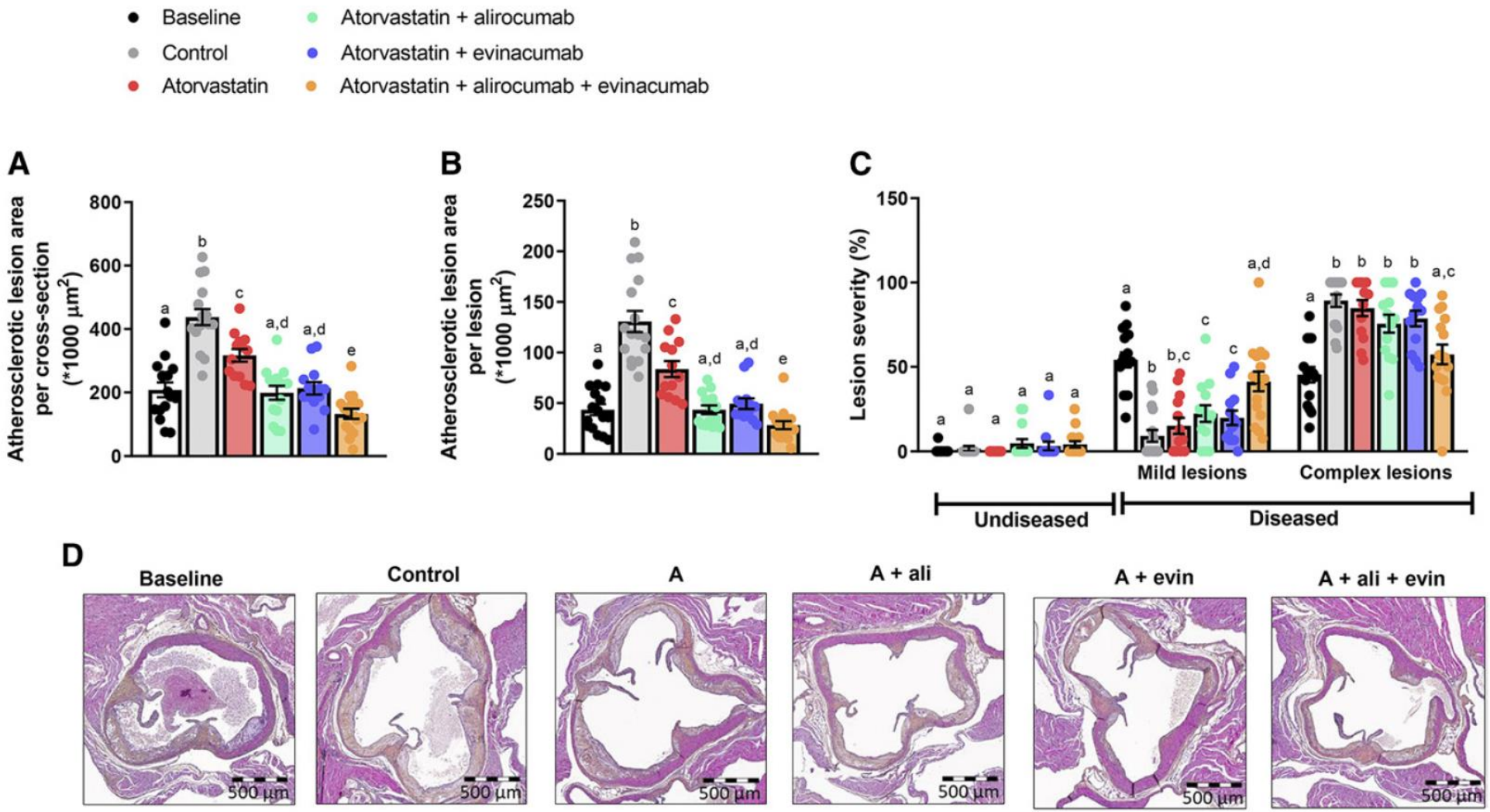
Serraju and Nisssen. *Nat Rev Cardiol 2024*



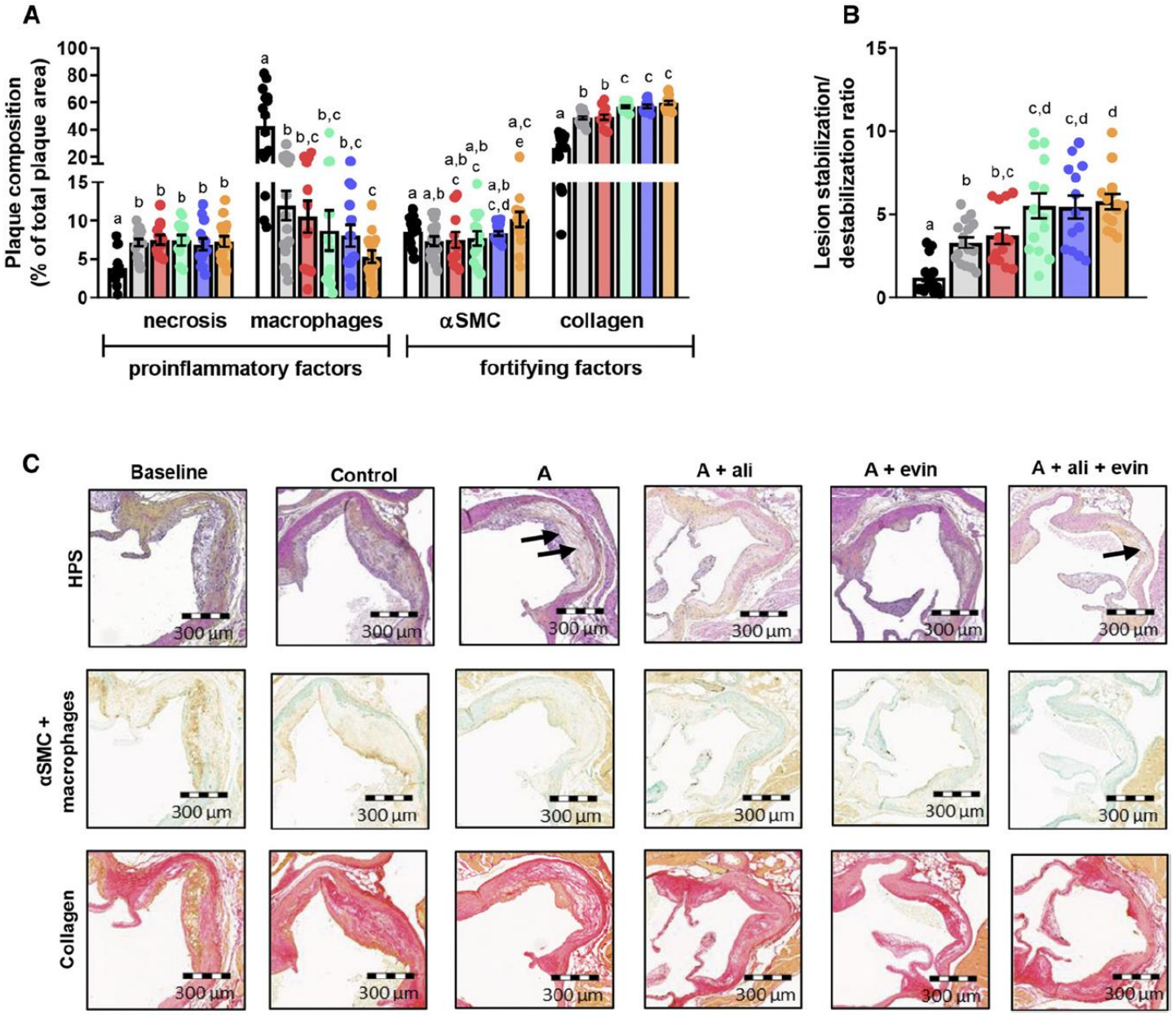
Alirocumab, evinacumab, and atorvastatin triple therapy regresses plaque lesions and improves lesion composition in mice

Pouwer MG et al.
Journal of Lipid Research 2020

Alirocumab, evinacumab, and atorvastatin triple therapy regresses plaque lesions and improves lesion composition in mice



Pouwer MG et al. *Journal of Lipid Research* 2020



Alirocumab, evinacumab, and atorvastatin triple therapy regresses plaque lesions and improves lesion composition in mice

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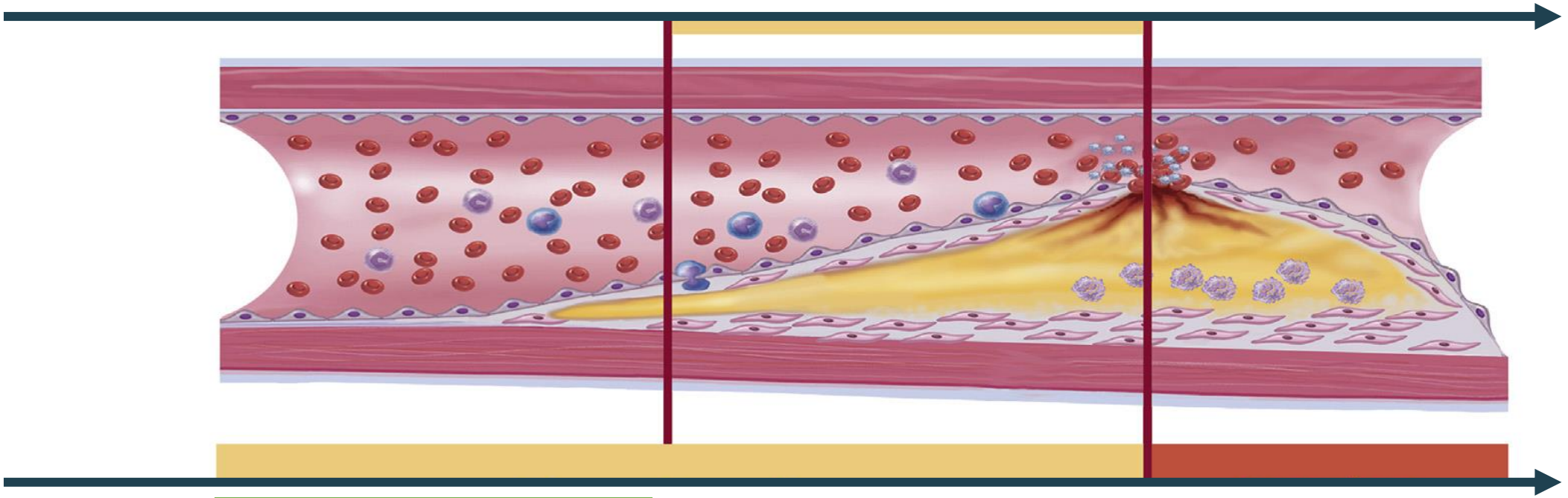
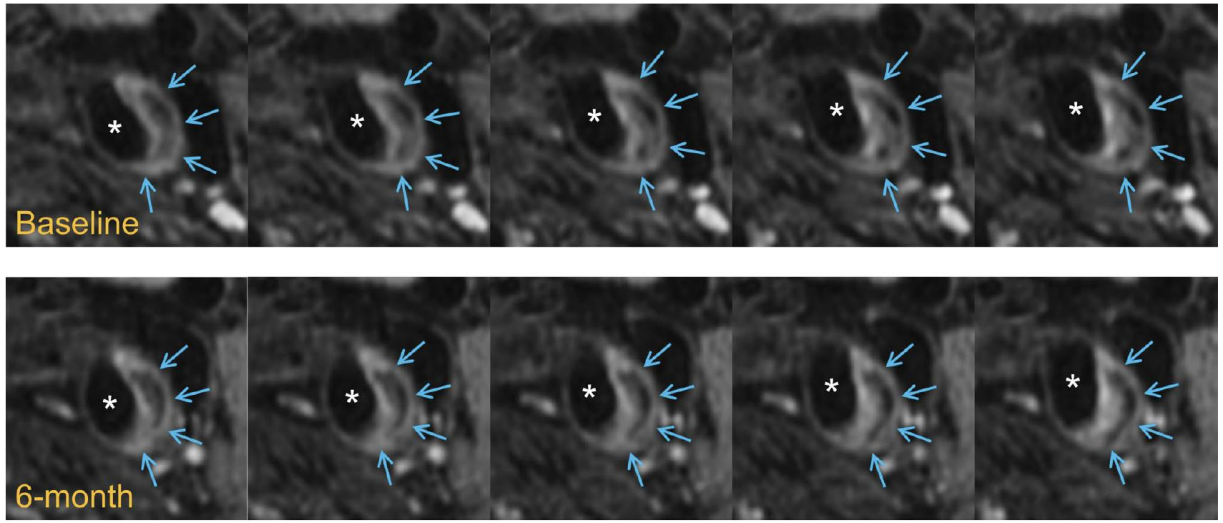


PRIMORDIAL PREVENTION
(AVOID RISK FACTOR DEVELOPMENT)

PRIMARY PREVENTION
(RISK FACTOR ASSESSMENT AND TREATMENT)

SECONDARY PREVENTION

Ahmadi et al. *J Am Coll Cardiol* 2019



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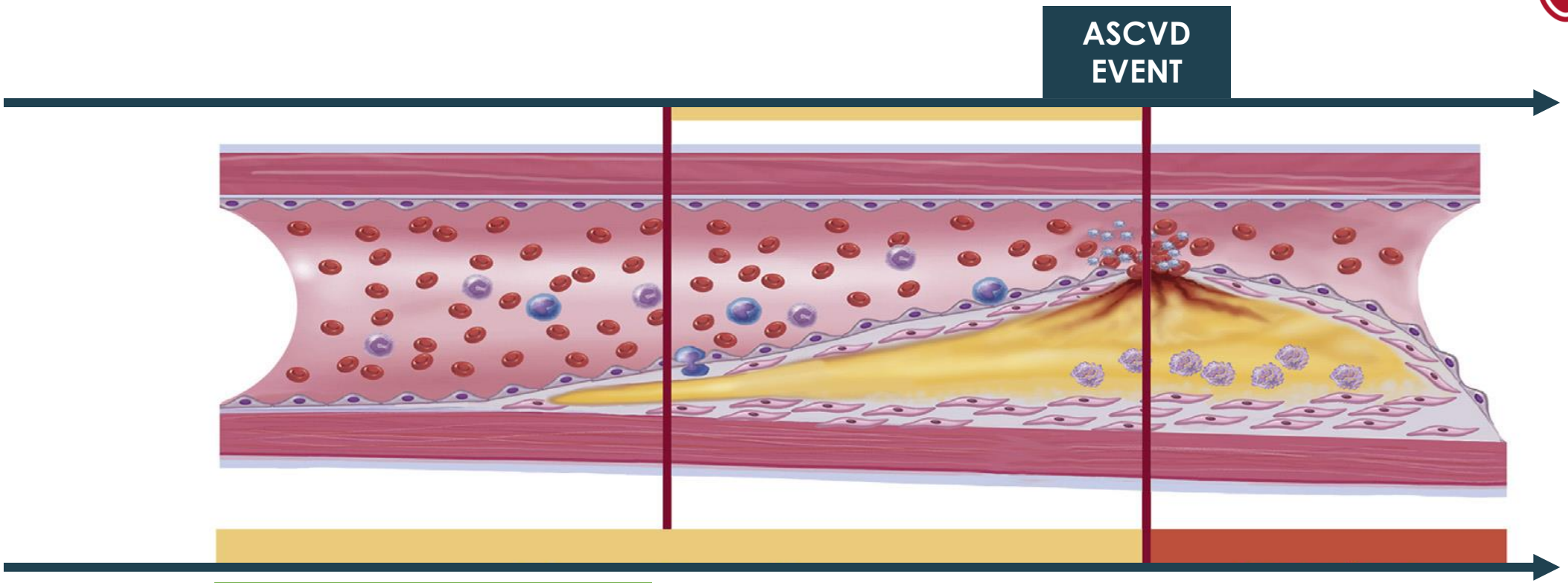
Serial magnetic resonance imaging letects a rapid reduction in plaque lipid content under PCSK9 inhibition with alirocumab

	Baseline[a]	6-Month[a]	Absolute change	
			Mean (95% CI)	*p* value[b]
Plaque burden				
Mean lumen area, mm^2	36.1 ± 15.9	36.8 ± 16.8	0.7 (− 0.6, 2.1)	0.88
Mean wall area, mm^2	38.5 ± 9.8	37.9 ± 9.4	− 0.6 (− 1.7, 0.5)	0.57
Mean total vessel area, mm^2	74.6 ± 21.8	74.7 ± 22.3	0.1 (− 1.3, 1.5)	0.71
Plaque composition				
Percent lipid-core, %	9.9 (5.9, 14.3)	8.2 (4.6, 13.6)	− 2.1 (− 3.5, − 0.7)	0.005
Percent calcification, %	2.2 (0.4, 4.5)	2.3 (0.0, 5.3)	0.2 (− 0.6, 1.0)	0.81
Percent fibrous tissue, %	87.2 (80.1, 91.5)	88.1 (83.4, 92.5)	1.9 (0.6, 3.2)	0.003

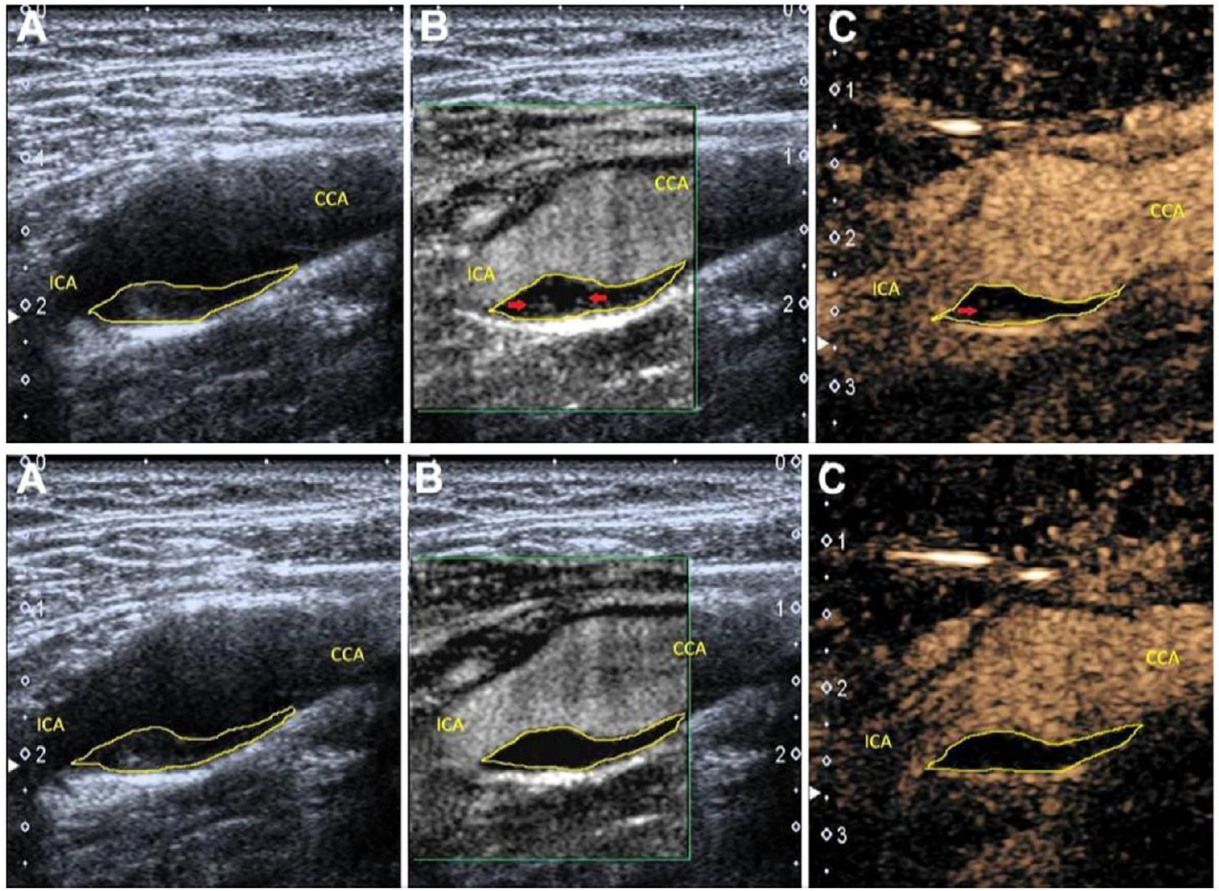
Sun et al. *The International Journal of Cardiovascular Imaging* 2021



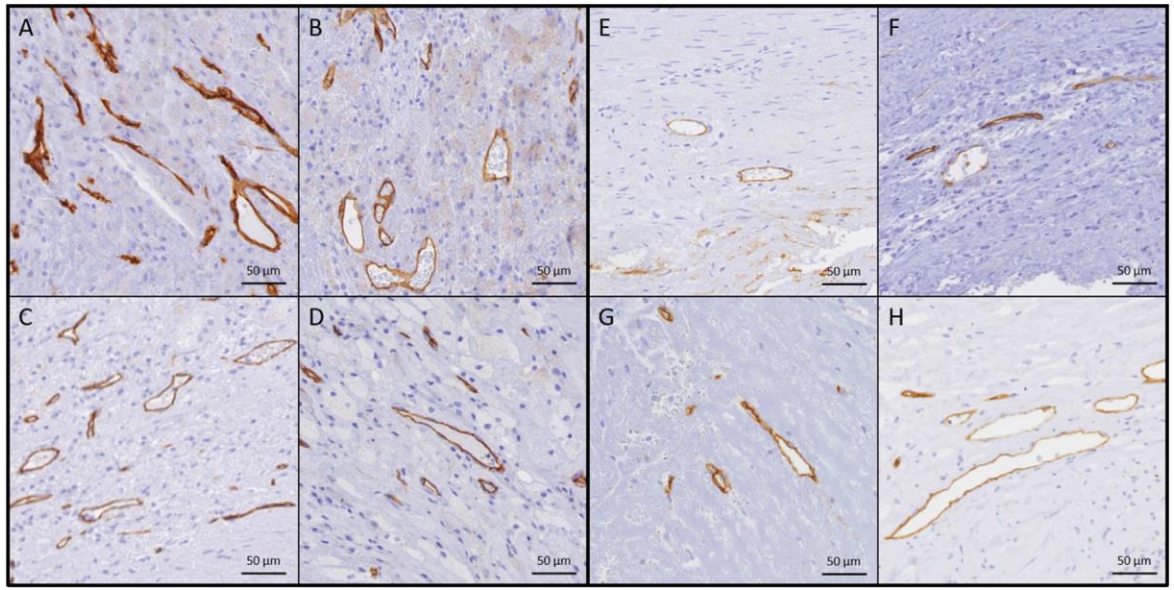
Ahmadi et al. *J Am Coll Cardiol* 2019

Effect of pharmacologic anti-atherosclerotic therapy on carotid intraplaque neovascularization

ESC Working Group Aorta & Peripheral Vascular Diseases



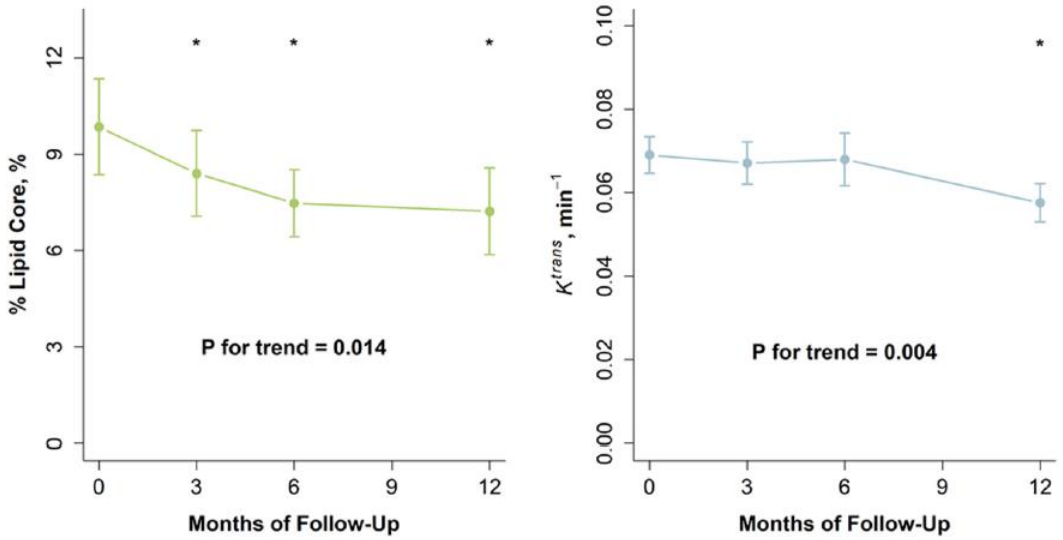
Zhu YC et al. Evaluating the Efficacy of Atorvastatin on Patients with Carotid Plaque by an Innovative Ultrasonography. *J Stroke Cerebrovasc Dis Off J Natl Stroke Assoc* 2019

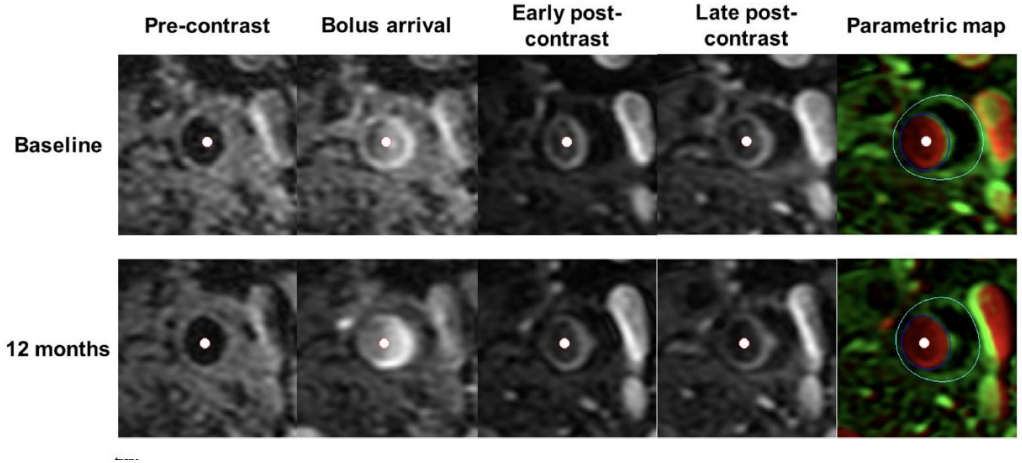


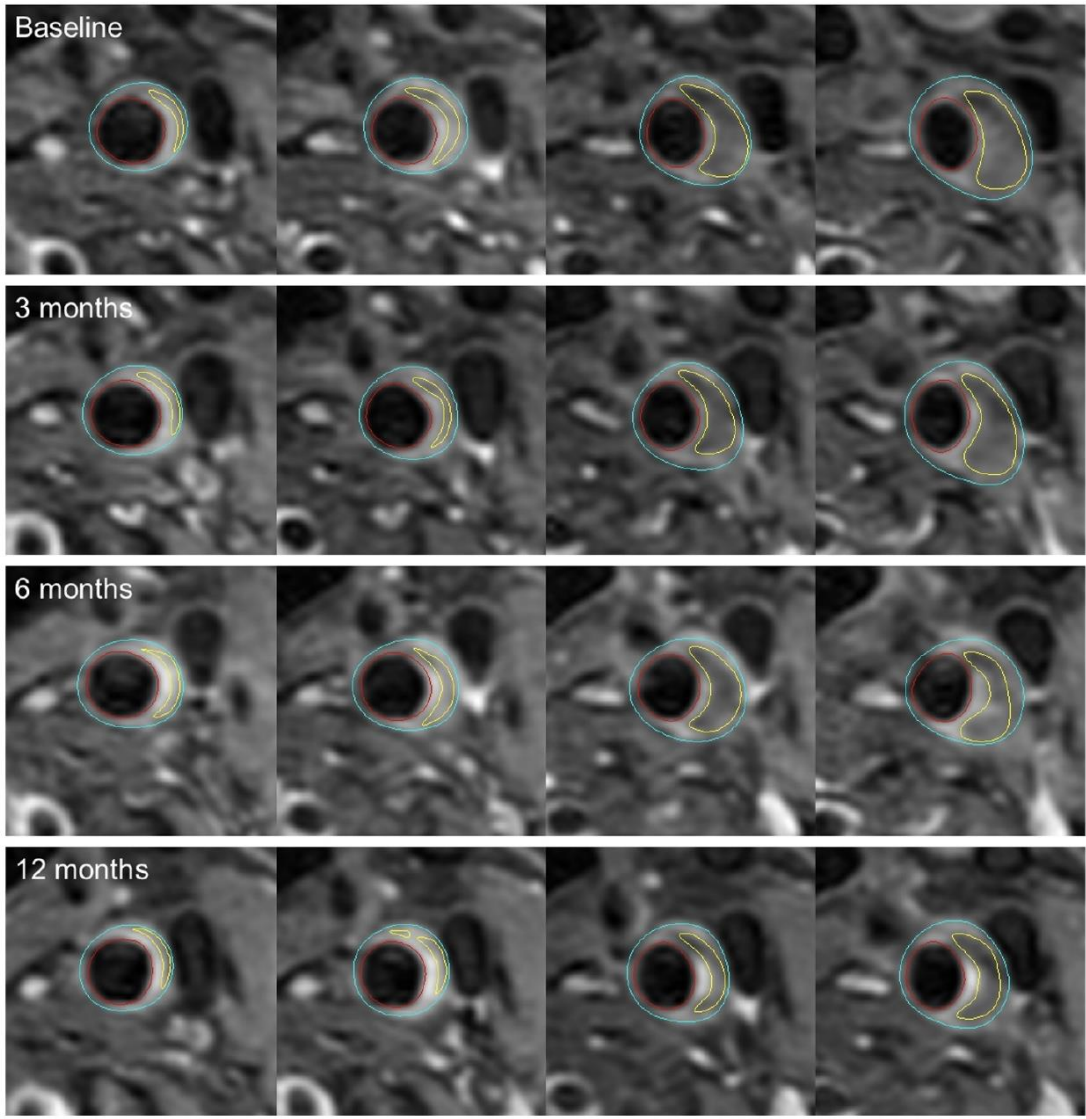
Konishi T et al. Stabilization of symptomatic carotid atherosclerotic plaques by statins: a clinico-pathological analysis. *Heart Vessels* 2018

Regression in carotid plaque lipid content and neovasculature with PCSK9 inhibition: A time course study

ESC Working Group Aorta & Peripheral Vascular Diseases

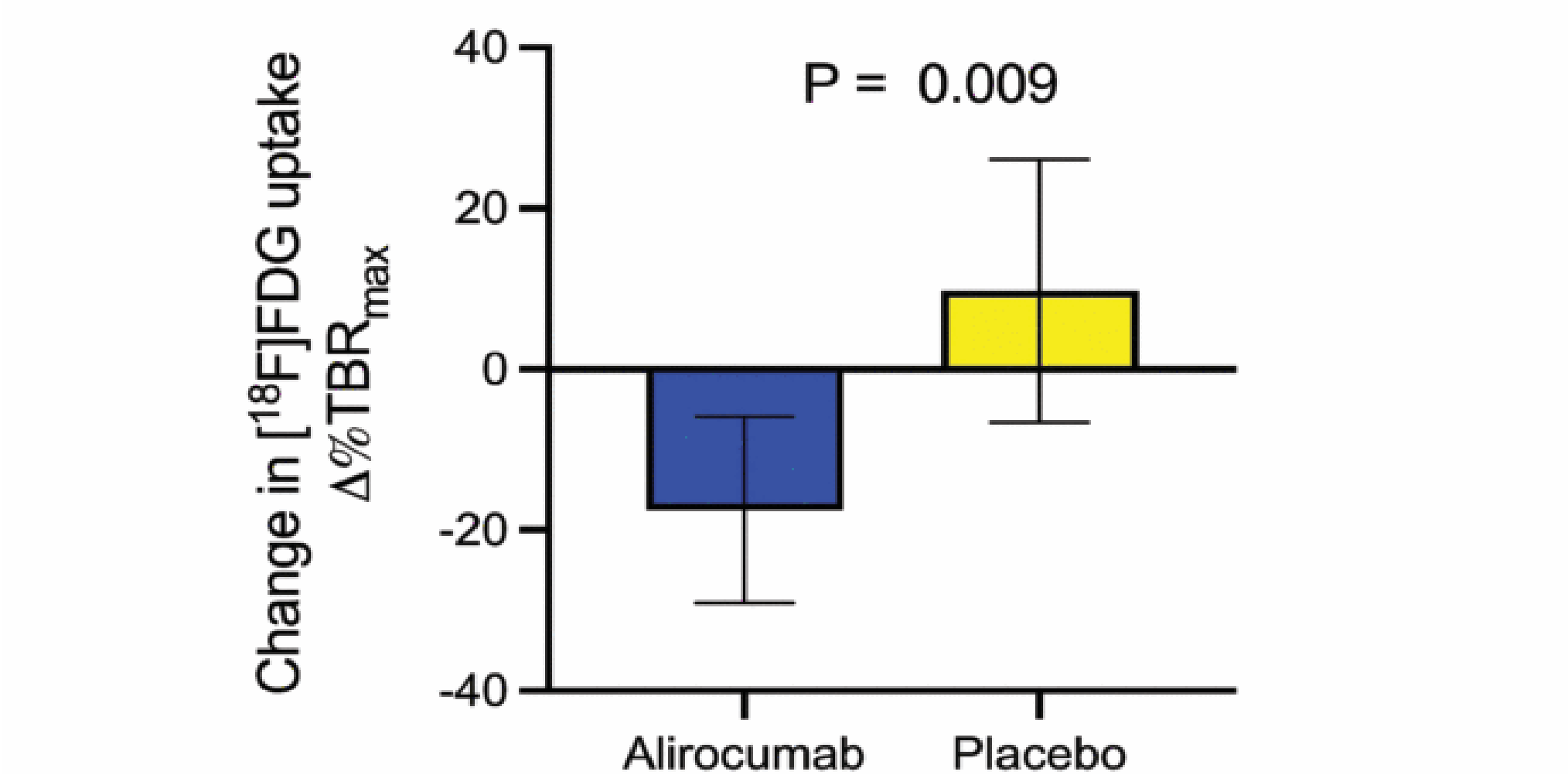




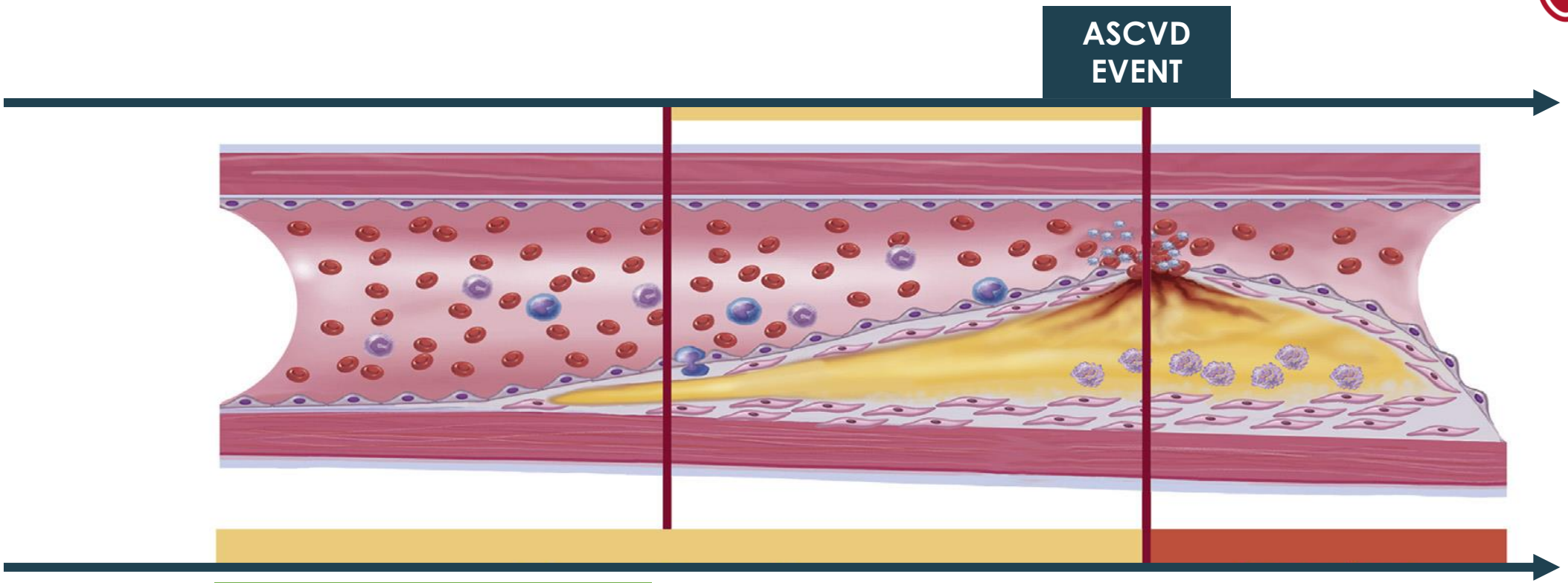


Lepor NE et al. Atherosclerosis 2020

alirocumab treatment was associated with decreased carotid inflammation by FDG-PET in patients with AMI



Bang et al. Abstract ACC2024



Ahmadi et al. *J Am Coll Cardiol* 2019

Alirocumab and plaque volume, calf muscle blood flow, and walking performance in peripheral artery disease: A randomized clinical trial

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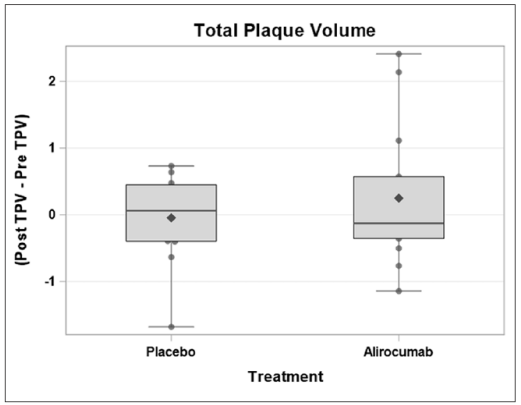
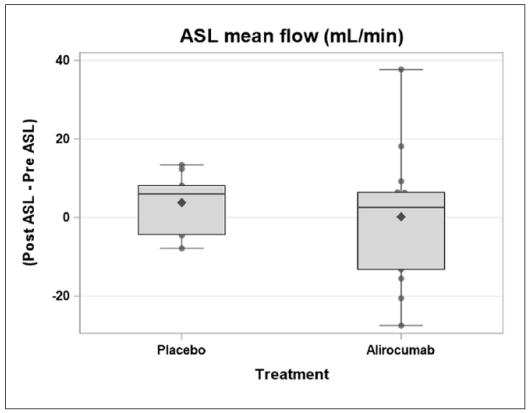
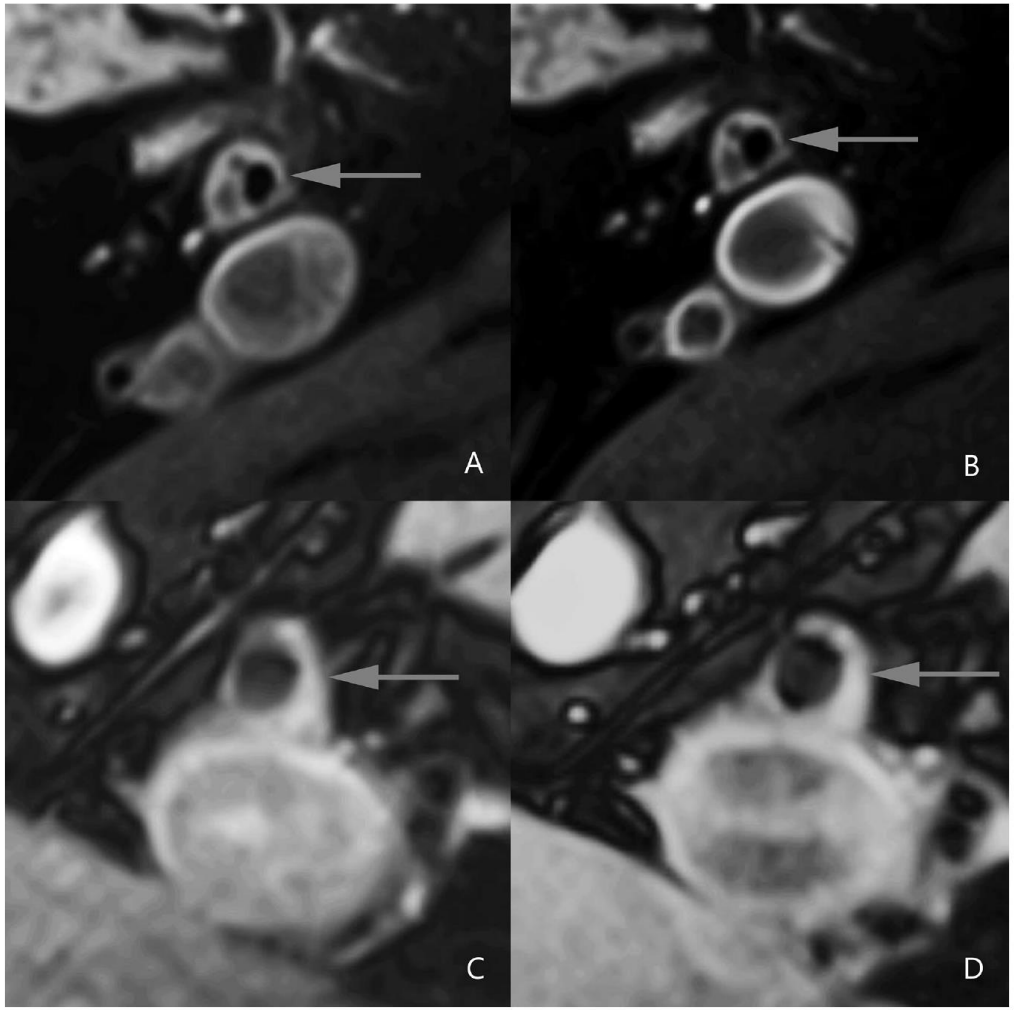




End point	Alirocumab			Placebo			Drug – placebo	95% CI of difference
	Baseline	Final	Change	Baseline	Final	Change		
TPV	2.61	2.86	0.25	3.07	3.03	−0.04	−0.29	(−0.98, 0.40)
ASL	17.84	18.05	0.22	12.61	16.43	3.81	3.59	(−7.67, 14.86)
6MWD	1188.53	1180.82	−7.71	924.88	890.44	−34.44	−26.73	(−130.40, 76.89)
TC	176.61	125.50	−51.11	180.82	166.47	−14.35	36.76	(13.39, 60.12)
LDL	107.56	57.72	−49.83	106.35	98.65	−7.71	42.13	(22.50, 61.76)
TG	131.17	117.22	−13.94	148.76	117.12	−31.64	−17.70	(−57.48, 22.08)
hsCRP	6.16	5.84	−0.32	6.44	7.63	1.18	1.50	(−5.02, 8.03)
Lp(a)	79.35	75.18	−4.18	84.35	88.71	4.35	8.53	(−0.41, 17.47)
Fibrinogen	380.61	389.89	9.28	389.53	408.18	18.65	9.37	(−59.38, 78.12)



Rrapo-Kaso E et al. Vasc Med 2023

Evolocumab addition to maximal tolerated statin therapy improves walking performance in patients with PAD and intermittent claudication (EVOL-PAD)

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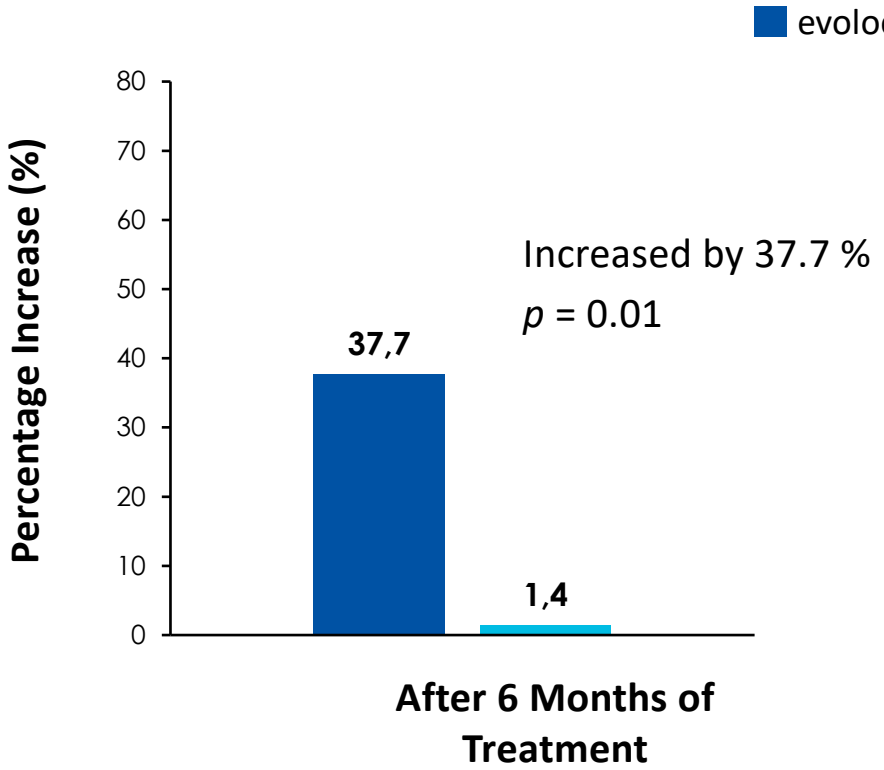
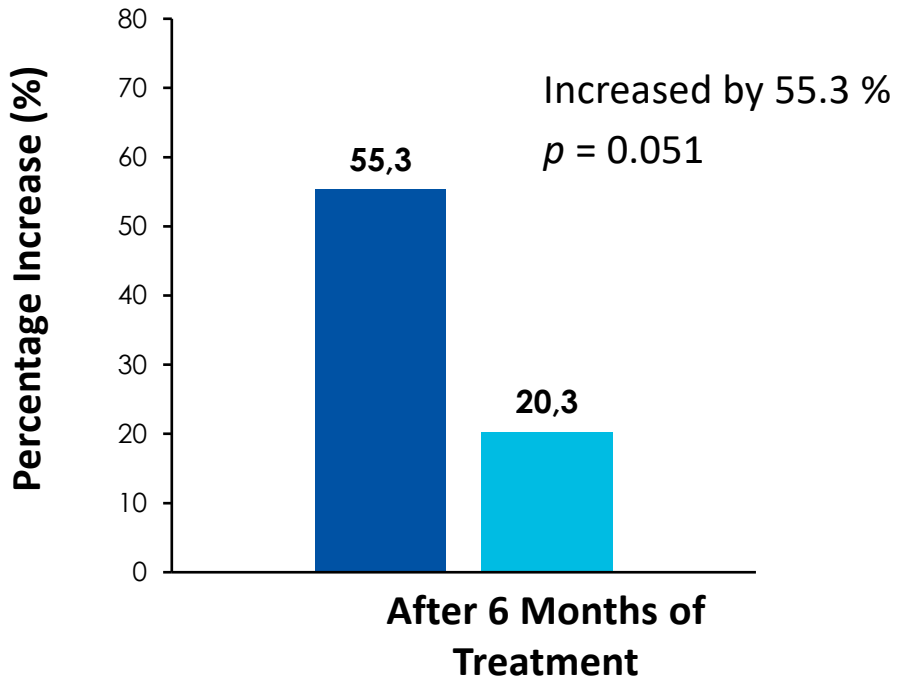
Maximal walking time (MWT)

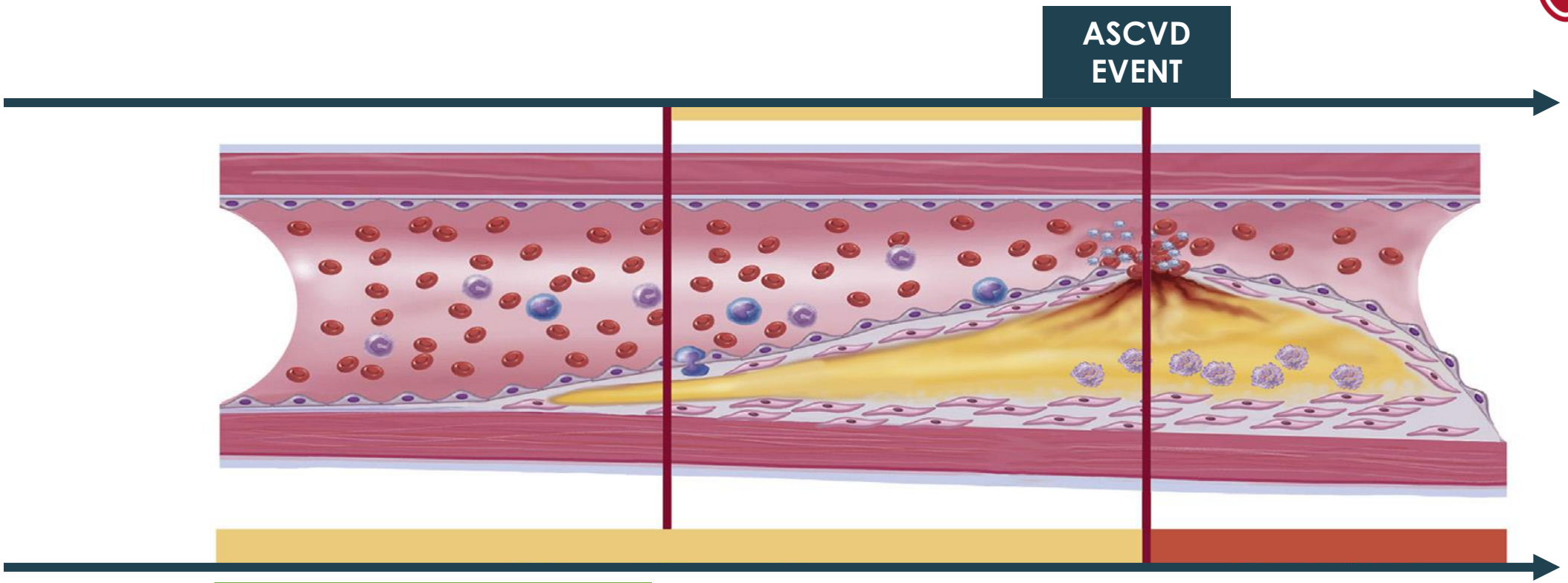


Pain free walking time (PFWT)



A double-blind, randomized, placebo-controlled study to compare maximal walking time (MWT) and pain free walking time (PFWT) in patients with PAD and claudication treated with monthly evolocumab 420 mg (n=35) or placebo (n=35).

Clavijio L et al. *Cardiovascular Revascularization Medicine* 2023



Ahmadi et al. *J Am Coll Cardiol* 2019

Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With ASCV (FOURIER Trial)

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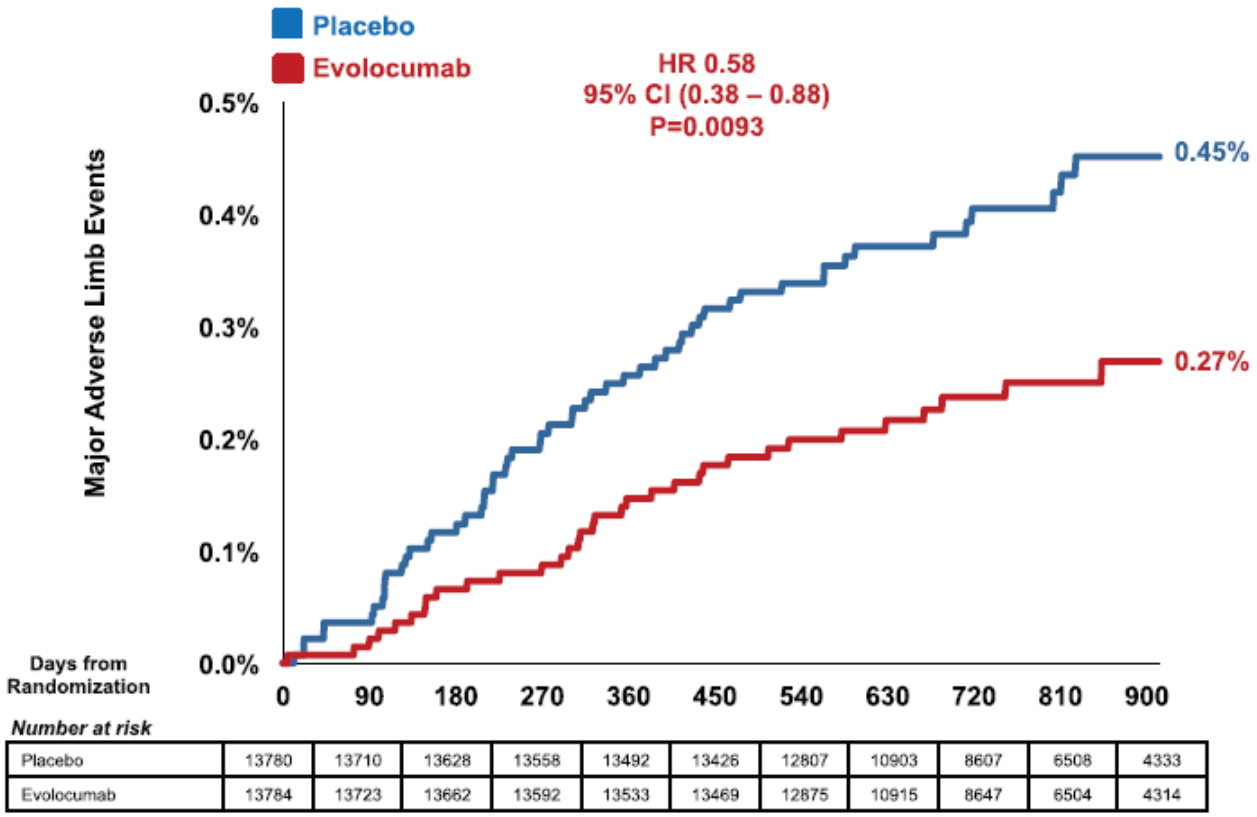
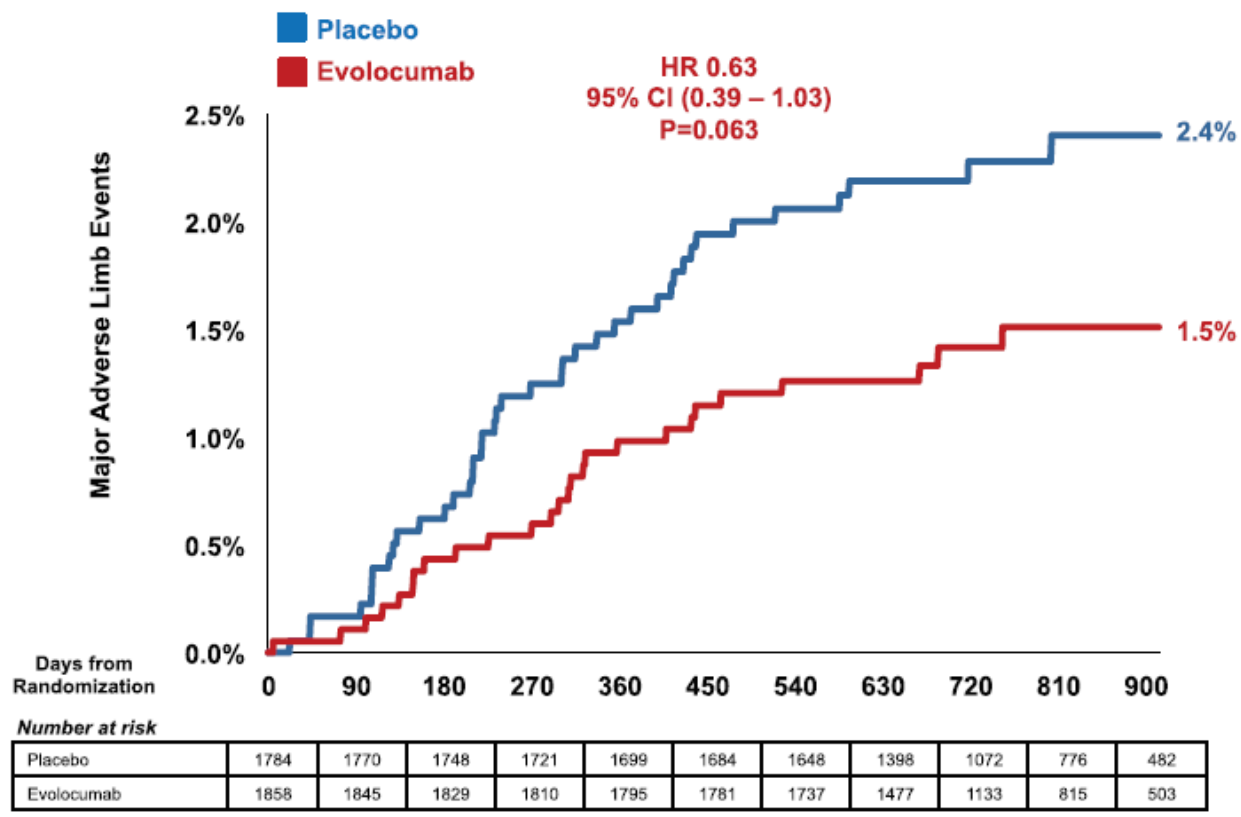
A



Number at risk

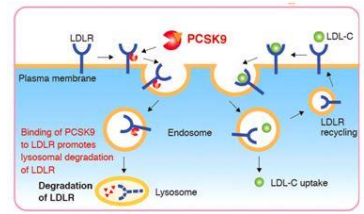
Placebo	13780	13710	13628	13558	13492	13426	12807	10903	8607	6508	4333
Evolocumab	13784	13723	13662	13592	13533	13469	12875	10915	8647	6504	4314

B



Number at risk

Placebo	1784	1770	1748	1721	1699	1684	1648	1398	1072	776	482
Evolocumab	1858	1845	1829	1810	1795	1781	1737	1477	1133	815	503



Bonaca M at al. *Circulation* 2018

Evolocumab Was Associated With an Improved AFS in Patients With Severe PAD at 1 Year

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Single-center prospective observational analysis of patients with chronic limb-threatening ischemia in Japan

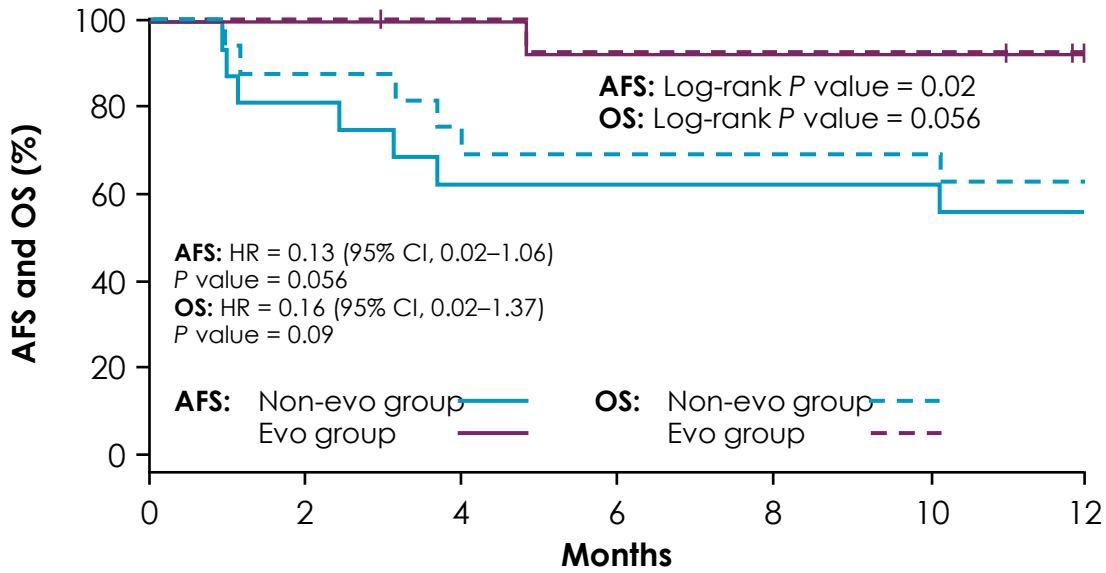
Patients: N = 30

Mean follow-up: 18 months

Primary outcome: 1 year free from major amputation

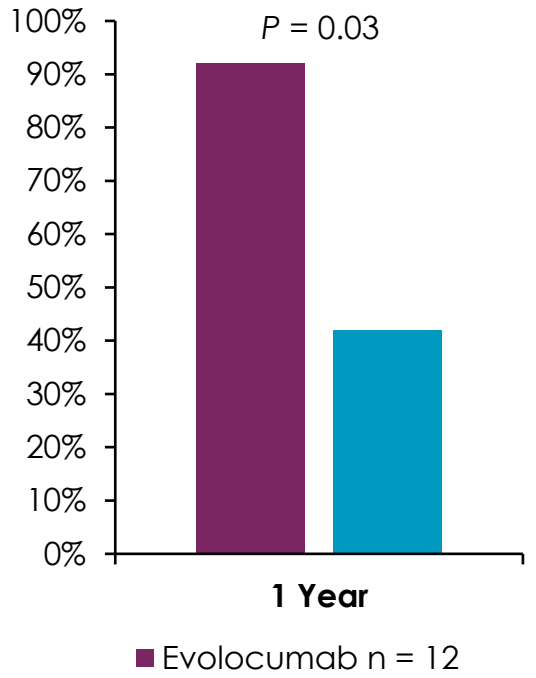
Secondary outcomes:
1 year AFS, OS, and wound-free limb salvage

1 Year AFS and OS in Evolocumab vs Non-Evolocumab Groups



No. at risk							
AFS non-evo group	16	13	10	10	10	10	9
AFS evo group	14	14	13	12	12	12	9
OS non-evo group	16	14	12	11	11	11	10
OS evo group	14	14	13	12	12	12	9

Wound-Free Limb Salvage*

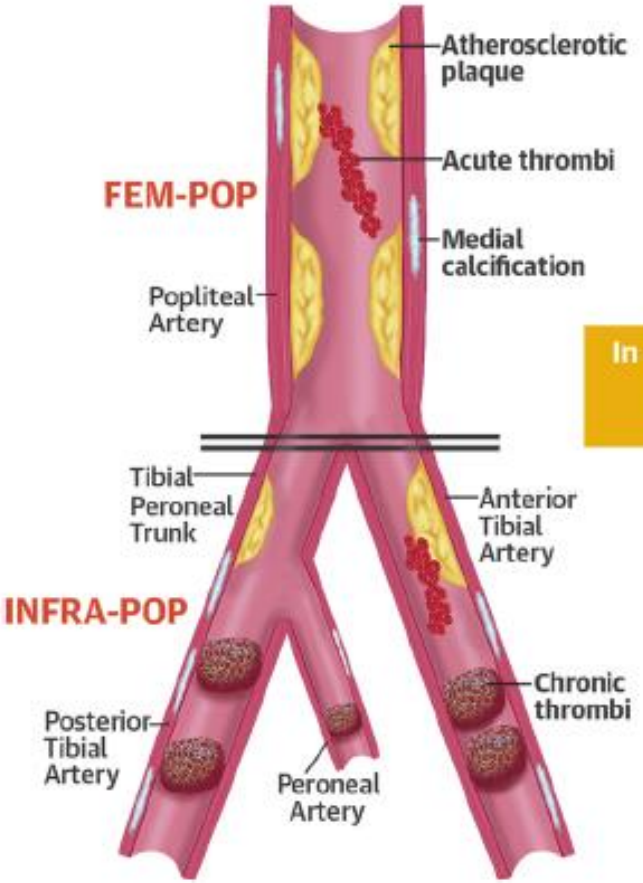


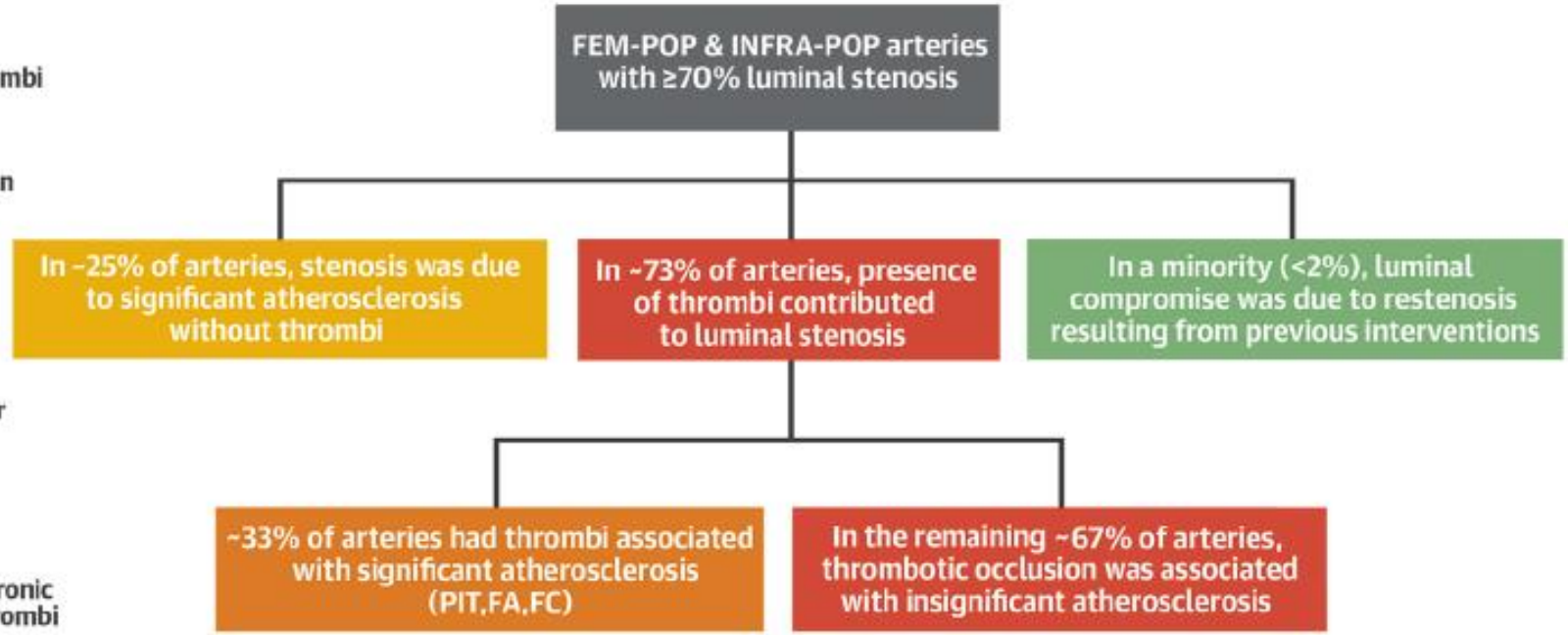
Administration of evolocumab for 1 year contributed to an improvement in the proportion of patients with AFS, wound-free limb salvage, and a tendency toward improving OS

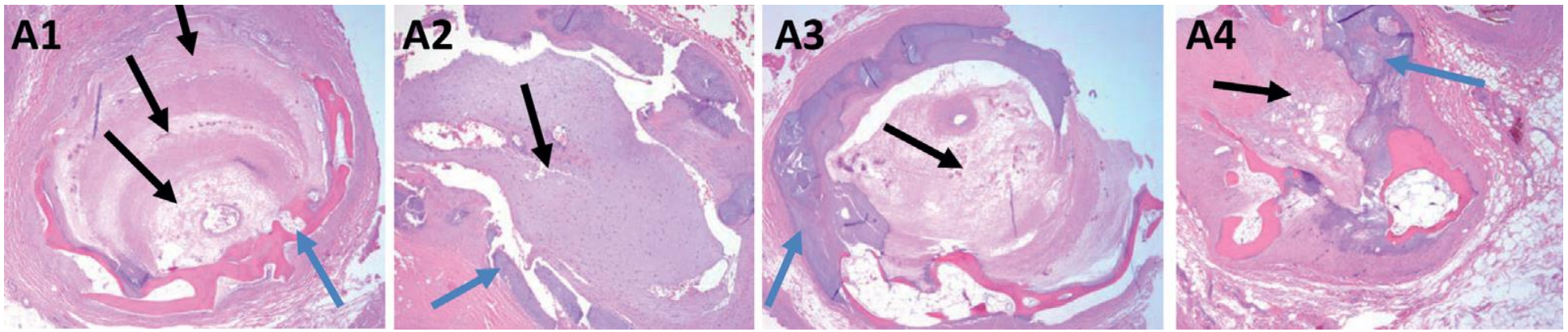
*Rutherford classifications of 5 and 6.

AFS, amputation-free survival; CI, confidence interval; evo, evolocumab; HR, hazard ratio; OS, overall survival.

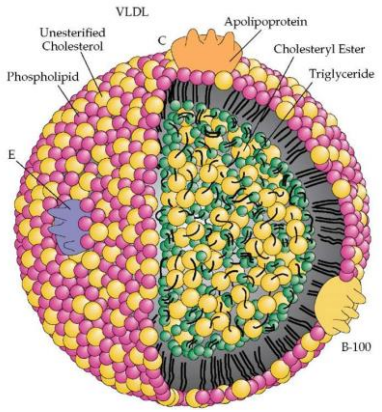
Sato Y, et al. *J Atheroscler Thromb*. 2020.







Narula N et al. *J Am Coll Cardiol* 2018



"it is vital that we rid the system of its most potent toxin: LDL-C, a metabolite responsible for the death and disability of more people than any other known product of human physiology"

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"…No reasonable clinician would wait for kidney damage or a cerebrovascular event before treating hypertension, delay managing hyperglycaemia until kidney failure or retinal haemorrhage, hold off on an antibiotic for pneumonia or cellulitis or let joints deteriorate before treating rheumatoid arthritis. In contrast, addressing hypercholesterolemia is frequently delayed until after a cardiovascular event occurs…"

ASPC
The American Society for Preventive Cardiology

ESC
Working Group
Aorta & Peripheral
Vascular Diseases

UNIVERSITÀ DEGLI STUDI DELLA BASILICATA
1982

European Heart Journal (2014) 35, 2864–2872
doi:10.1093/eurheartj/ehu080

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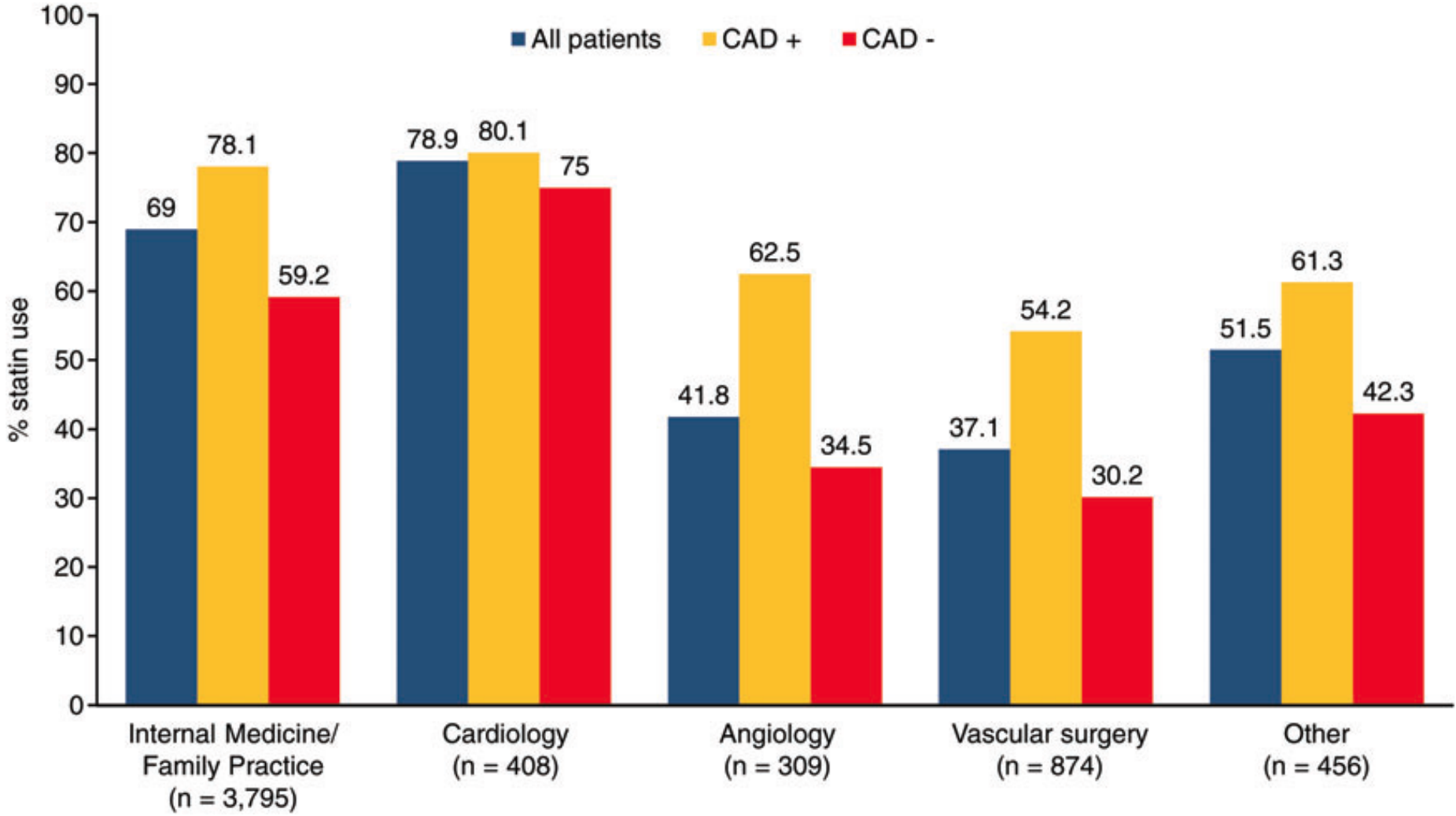
Aorta & Peripheral Vascular Diseases

Statin therapy and long-term adverse limb outcomes in patients with peripheral artery disease: insights from the REACH registry

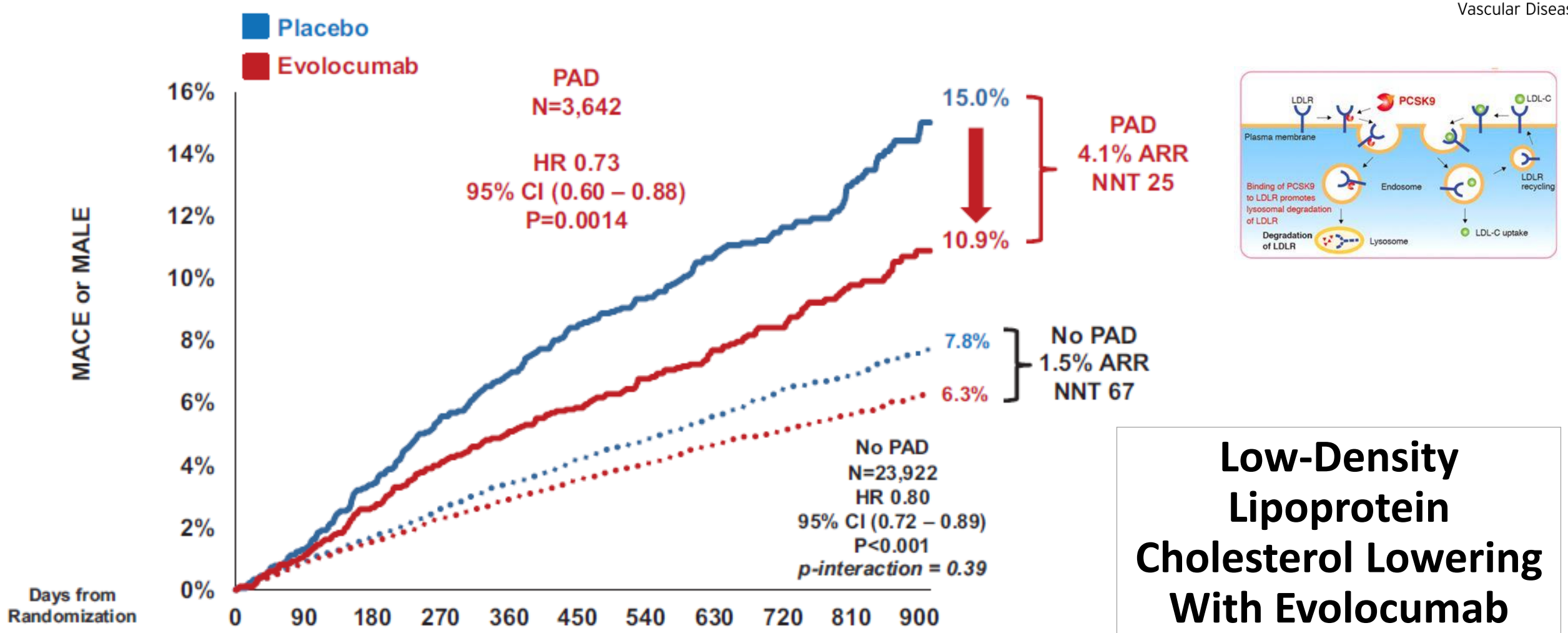
Proportion of patients on statins at enrolment based on enrolling investigator's subspecialty

REACH REGISTRY
REduction of Atherothrombosis for Continued Health



Khumbani et al .
Eur Heart Journal 2014

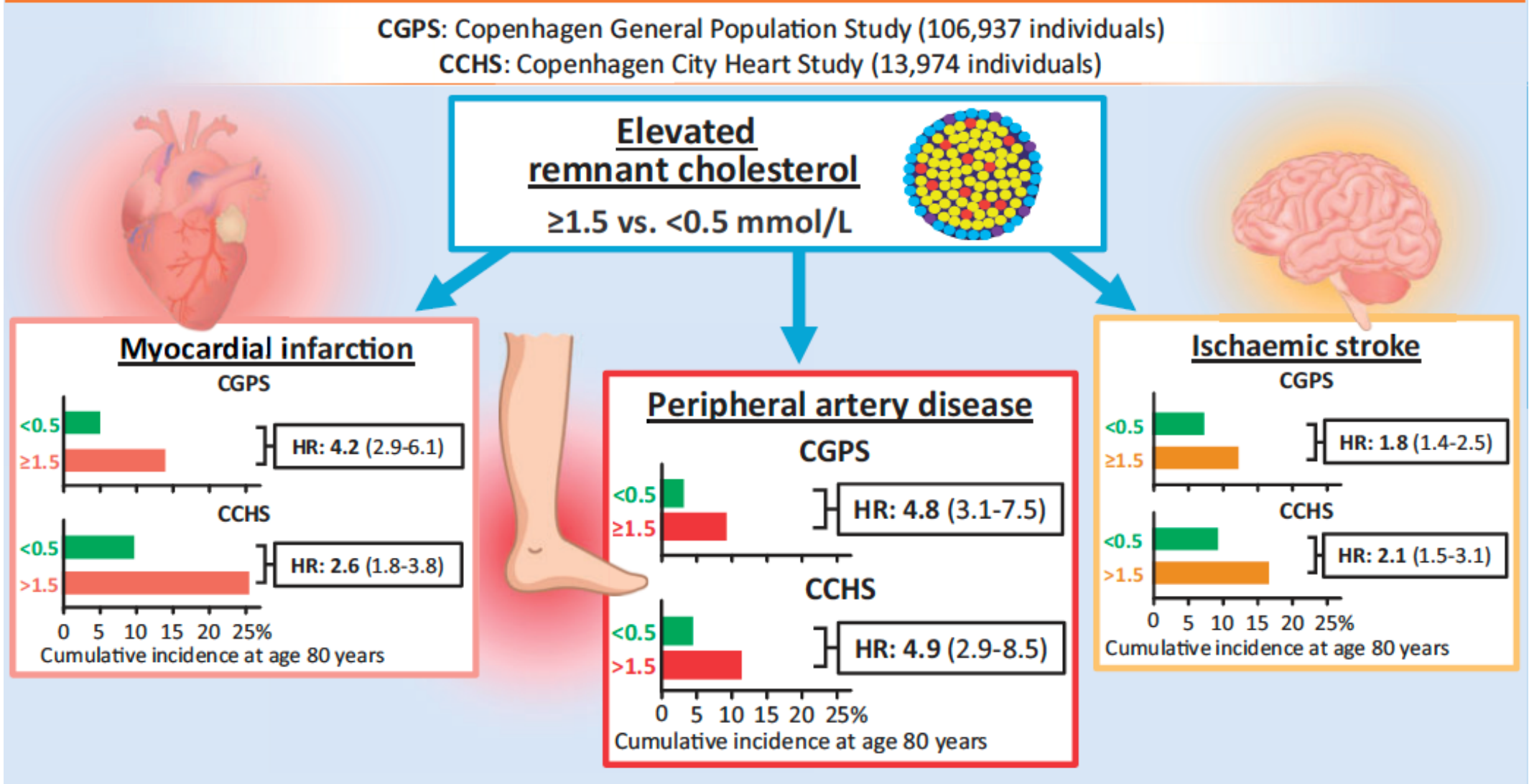
MACE or MALE in Patients with and without PAD



Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With ASCVD (FOURIER Trial)

Bonaca M at al. *Circulation* 2018

Elevated remnant cholesterol increases the risk of peripheral artery disease, myocardial infarction and ischaemic stroke: a cohort-based study



Wadstrom BN et al. *European Heart Journal* 2022

Background

ApoB → Peripheral artery disease

ApoB = Remnants + LDL

Methods

- **ApoB and remnant + LDL cholesterol** levels measured with standard clinical assays **in 93,461 individuals**

- **Remnant + LDL particle numbers** measured with nuclear magnetic resonance spectroscopy **in 25,347 of the indivíduals**

ApoB
- **Remnant** cholesterol
- **Remnant** particles
- **LDL** cholesterol
- **LDL** particles

? → **Peripheral artery disease**

Follow-up up to 15 years

Results

Fraction of peripheral artery disease risk conferred by apoB explained by:

Remnant cholesterol **73%** (95%CI: 32-100%)

ApoB

LDL cholesterol **8%** (95%CI: 0-46%)

No. of events: 1,207

Fraction of myocardial infarction risk conferred by apoB explained by:

Remnant cholesterol **41%** (95%CI: 27-55%)

ApoB

LDL cholesterol **69%** (95%CI: 38-70%)

No. of events: 2,022

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uk biobank

PAD risk conferred by elevated apoB-containing lipoproteins was explained mainly by elevated remnants, while myocardial infarction risk was explained by both elevated remnants and LDL.

Wadstrom BN et al.
Arterioscler Thromb Vasc Biol 2024