Meeting Nazionale ITACARE-P 2025

La Cardiologia Riabilitativa e Preventiva come snodo fondamentale della cura della persona con cardiopatia

CENTRO CONGRESSI FRENTANI
Roma, 21-22 novembre 2025

Simposio ITACAREP- Istituto Superiore di Sanità

La vasculopatia polidistrettuale dalla epidemiologia alla clinica

Interventi farmacologici mirati ed effetti sulla prognosi

Gian Francesco Mureddu

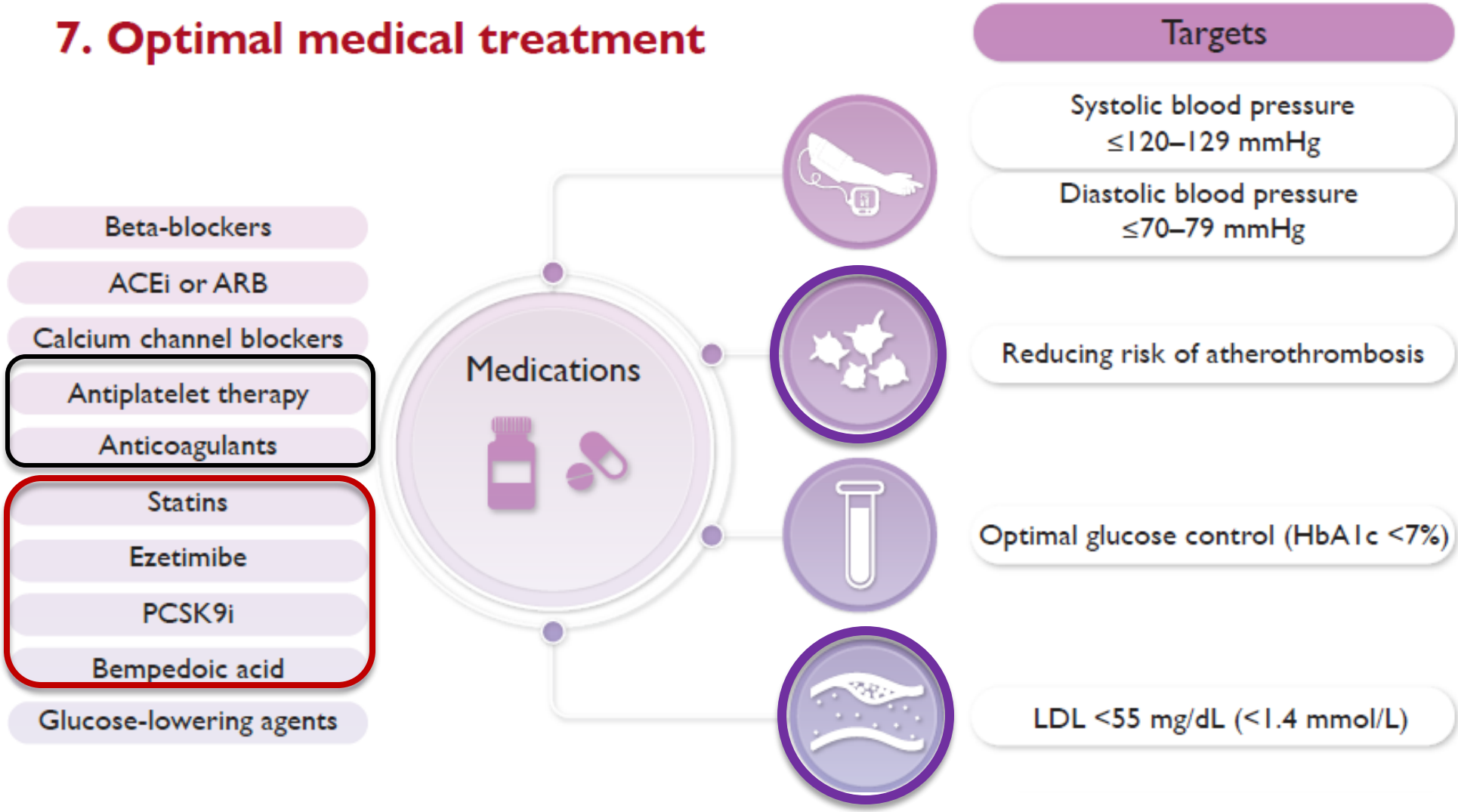
Cardiologia Riabilitativa

AO San Giovanni-Addolorata, Roma

2024 ESC Guidelines for the management of peripheral arterial and aortic diseases

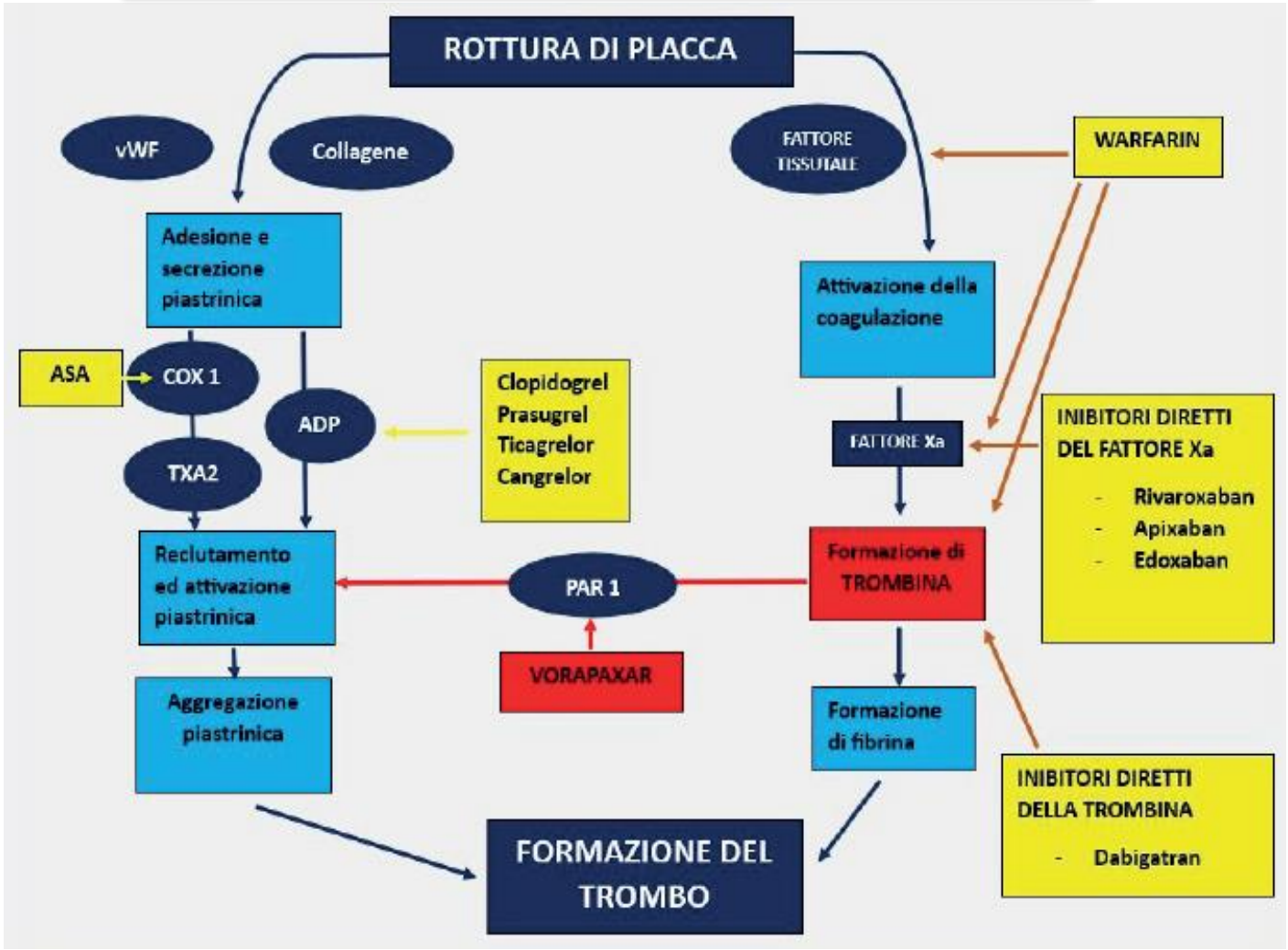
ESC

7. Optimal medical treatment



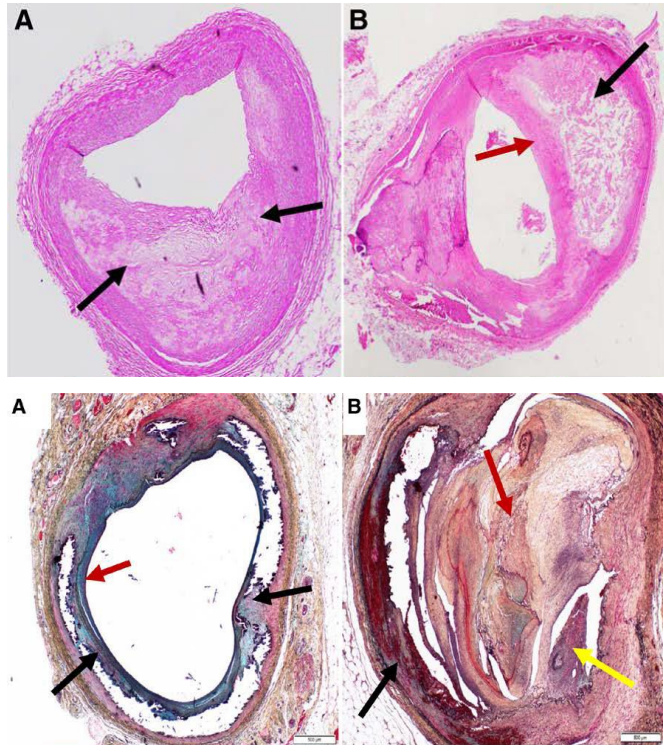
"Dual pathway inhibition" nell'arteriopatia periferica

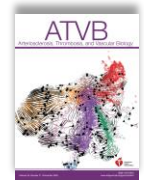
Vito Altamura[1], Gian Francesco Mureddu[2], Roberto Ceravolo[3], Gaetano Marino[1], Alessandro Alonzo[1], Stefano Aquilani[1], Lorenzo Castello[1], Stefania Angela Di Fusco[1], Furio Colivicchi[1]



Altamura V et al. G Ital Cardiol 2024;25

Pathologic Disparities Between Peripheral Artery Disease and Coronary Artery Disease





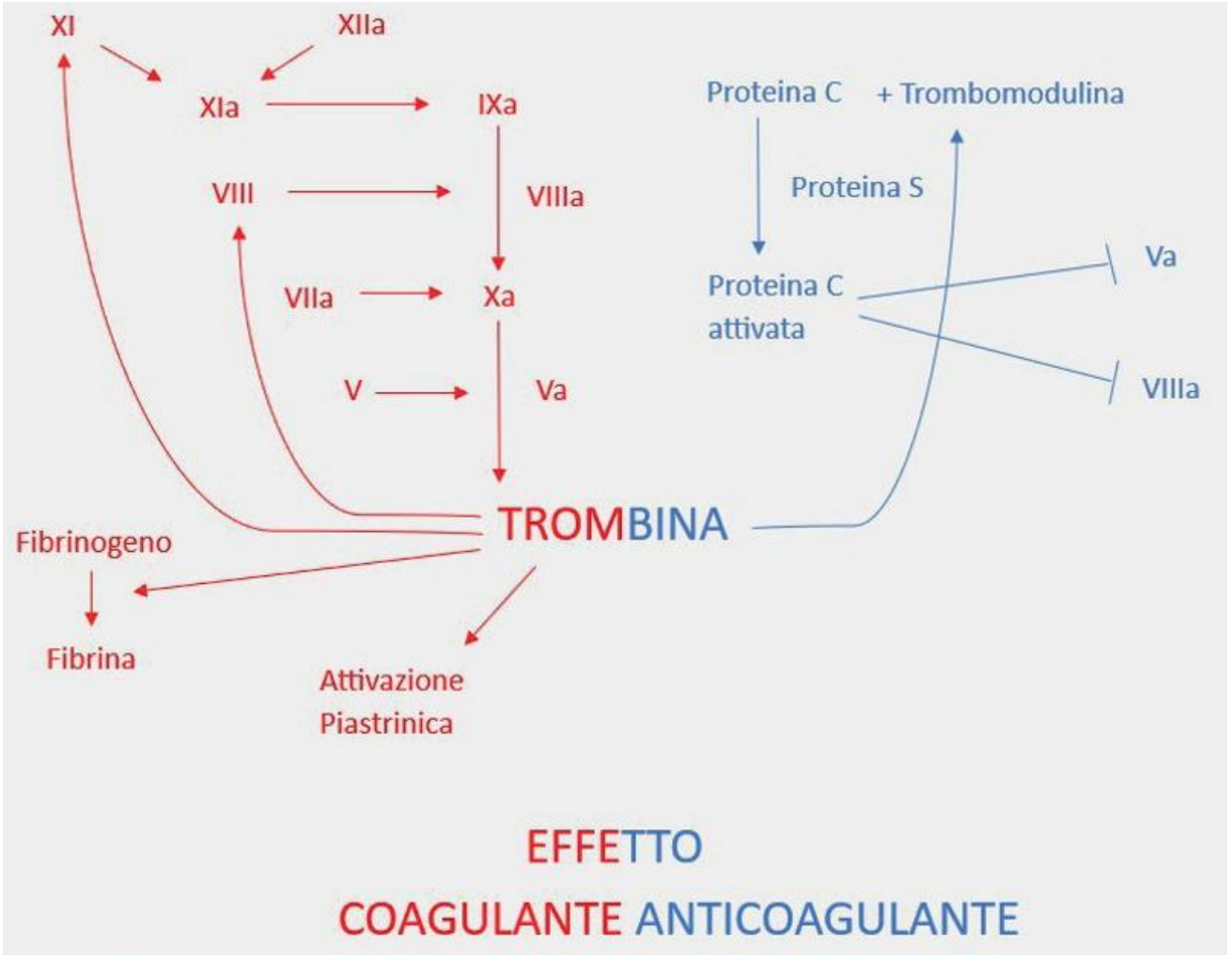
Luminal thrombosis is the pathological basis of acute coronary syndrome and critical limb ischemia.

- Acute coronary syndrome is primarily due to **luminal thrombus associated with atherosclerosis.**
- On the other hand, the majority of the arteries in critical limb ischemia have **luminal thrombi not associated with atherosclerosis**

Narula N et al. *Arterioscler Thromb Vasc Biol.* 2020;40:1982–1989

"Dual pathway inhibition" nell'arteriopatia periferica

Vito Altamura[1], Gian Francesco Mureddu[2], Roberto Ceravolo[3], Gaetano Marino[1], Alessandro Alonzo[1], Stefano Aquilani[1], Lorenzo Castello[1], Stefania Angela Di Fusco[1], Furio Colivicchi[1]



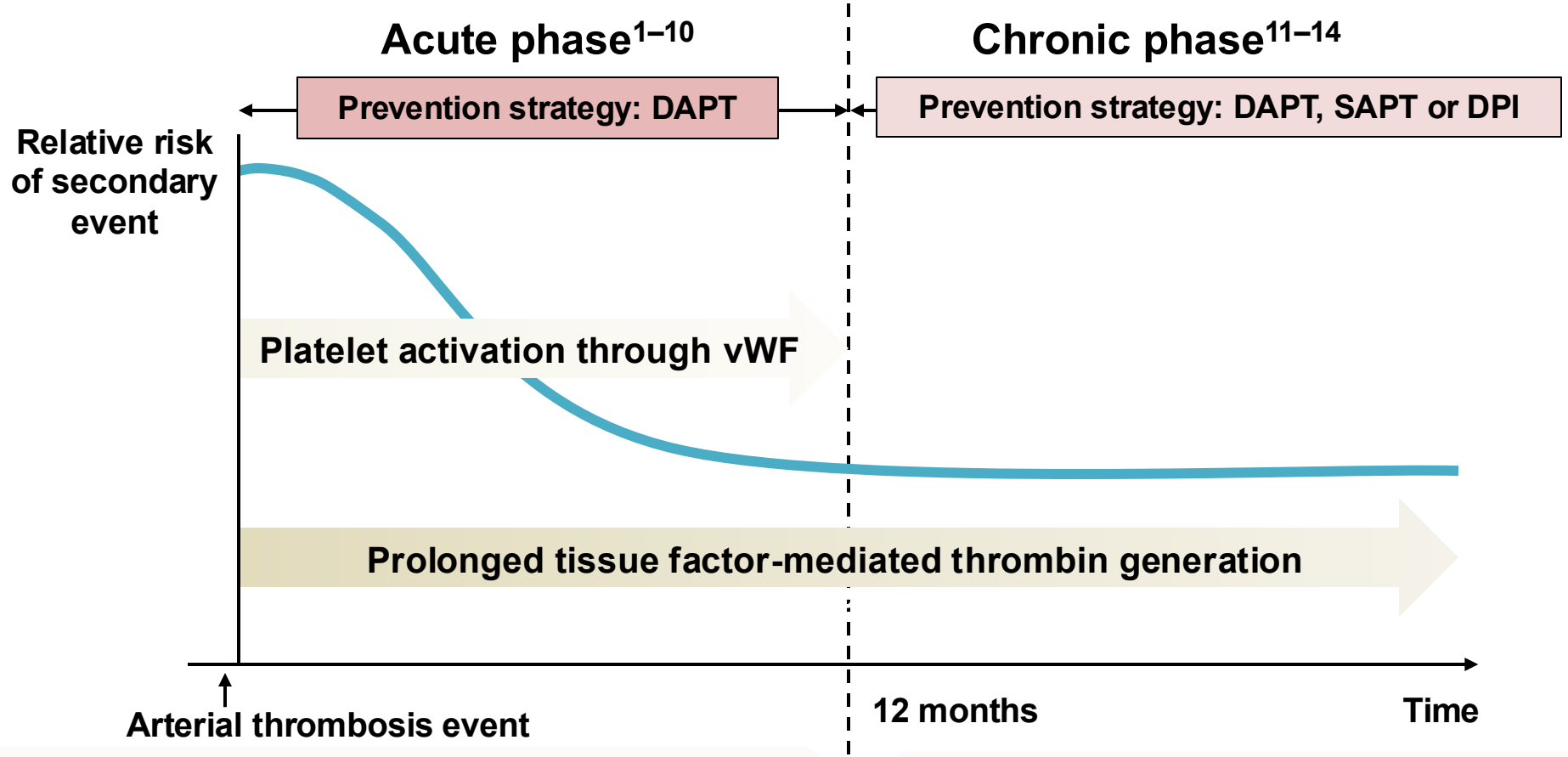
Il paradosso della trombina

La trombina è in grado sia di promuovere che di prevenire la trombosi, in funzione del substrato che incontra e delle proprie concentrazioni.

- L'endotelio danneggiato espone fattore tissutale e la trombina agisce come procoagulante, attivando le piastrine e trasformando il fibrinogeno in fibrina
- Nei territori che hanno endotelio integro, la trombomodulina si lega alla trombina, e attraverso l'attivazione della proteina C ed S, inattiva i fattori della coagulazione V ed VIII contrastando quindi l'evento trombotico.
- L'altro elemento che modifica il ruolo della trombina è la sua concentrazione.
- La persistenza nel tempo di elevati valori di protrombina e trombina correla direttamente con un incremento significativo di eventi cardiovascolari

Griffin JH. Blood coagulation. The thrombin paradox. Nature 1995;378:337-8.

Tailoring secondary prevention strategies to the underlying pathophysiology following an arterial thrombosis event



- Plaque rupture causes platelet activation through two distinct pathways, leading to amplification and aggregation[1–2]
- DAPT is therefore effective in this setting because this is where platelet recruitment, activation and amplification is strongest[3–10]

- Hypercoagulability persists due to ongoing thrombin generation[11–12]
- Adding rivaroxaban vascular dose to aspirin may be effective in this phase[13–14]

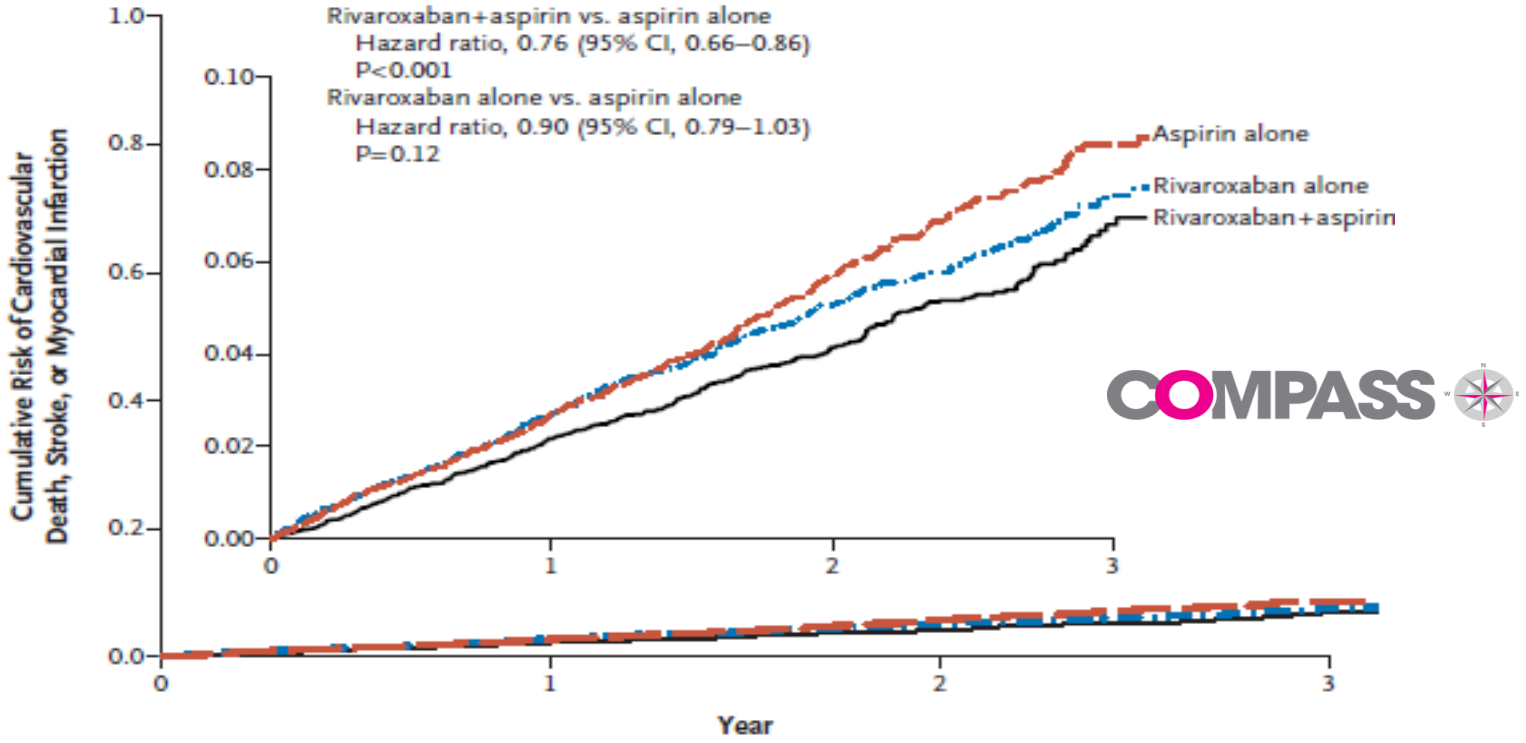
Dual Pathway Inhibition with Rivaroxaban Vascular Dose 2.5 mg bid + Aspirin Reduced CV Death, Stroke and MI

Key inclusion criteria*

PAD

CAD with ≥1 of:

- Age ≥65 years
- Age <65 years plus atherosclerosis in ≥2 vascular beds or ≥2 additional risk factors
- Current smoker
- Diabetes mellitus
- Renal dysfunction (eGFR<60 ml/min)
- Heart failure
- Non-lacunar ischemic stroke ≥1 month ago

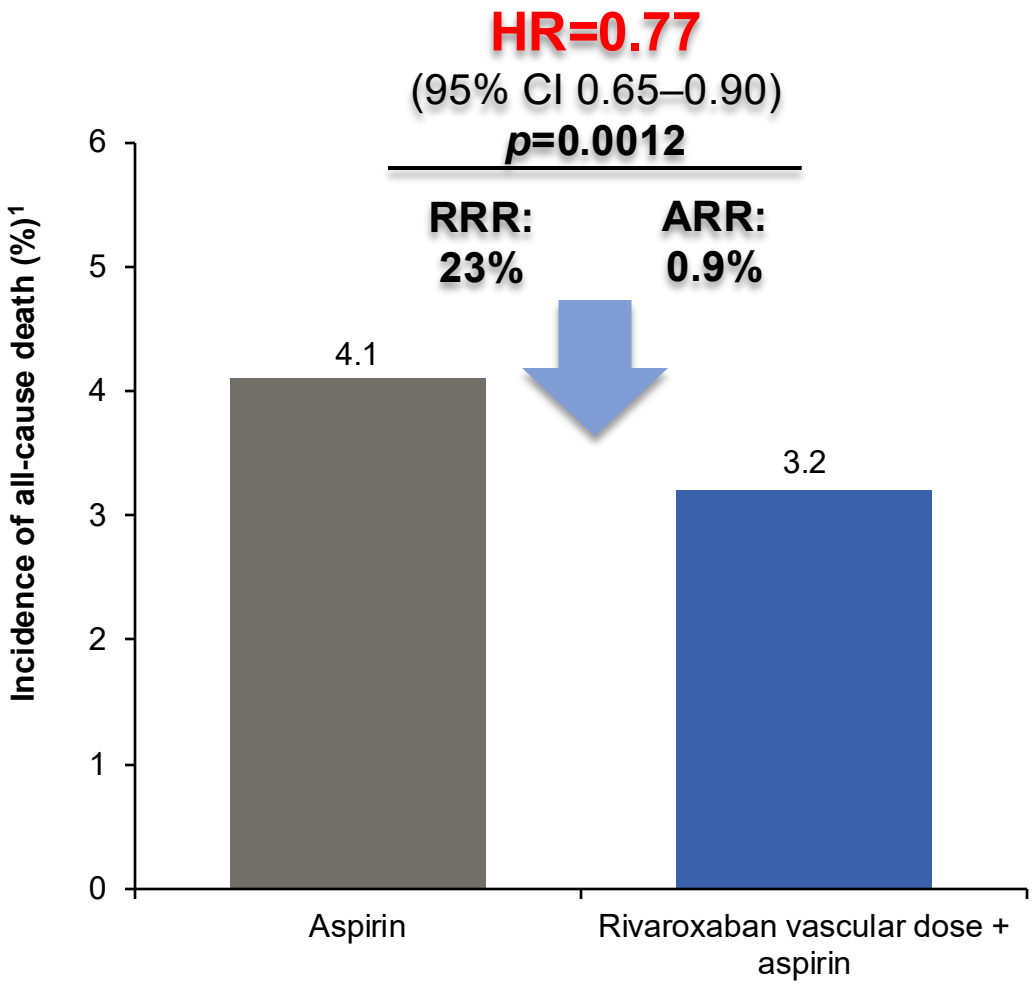


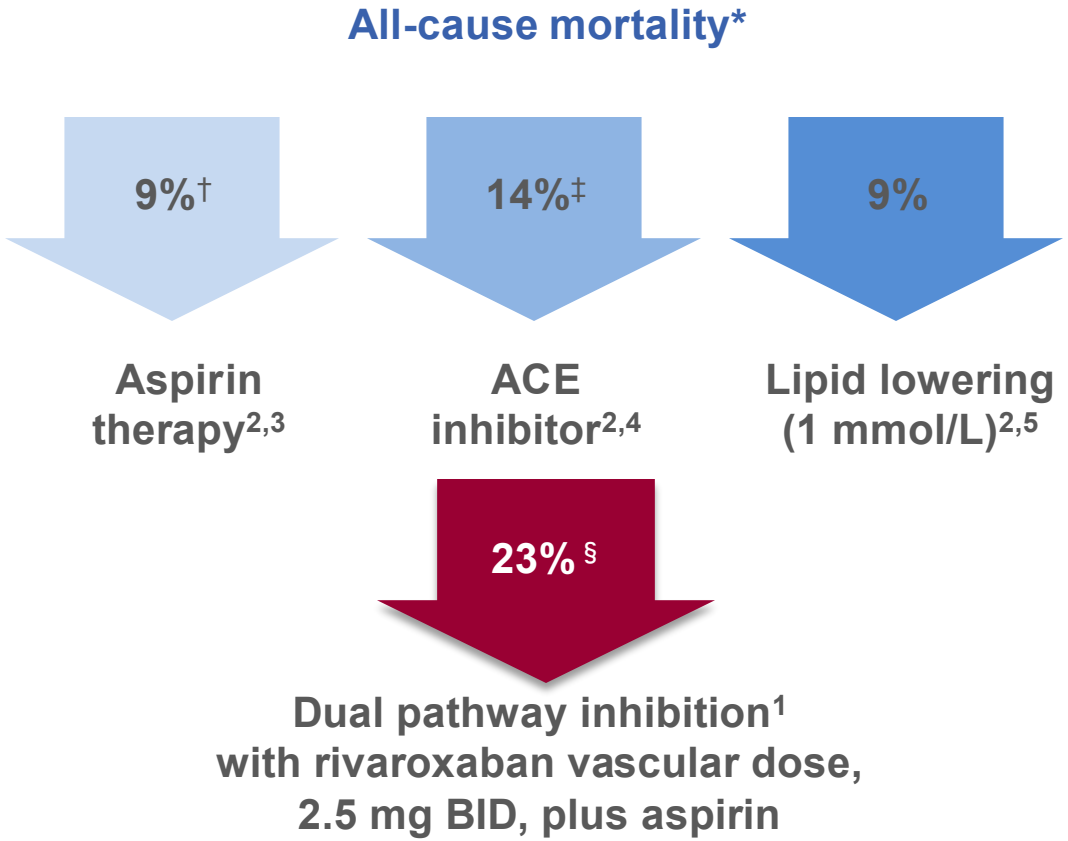
COMPASS

No. at Risk				
Aspirin alone	9126	7808	3860	669
Rivaroxaban alone	9117	7824	3862	670
Rivaroxaban+aspirin	9152	7904	3912	658

The NEW ENGLAND JOURNAL of MEDICINE

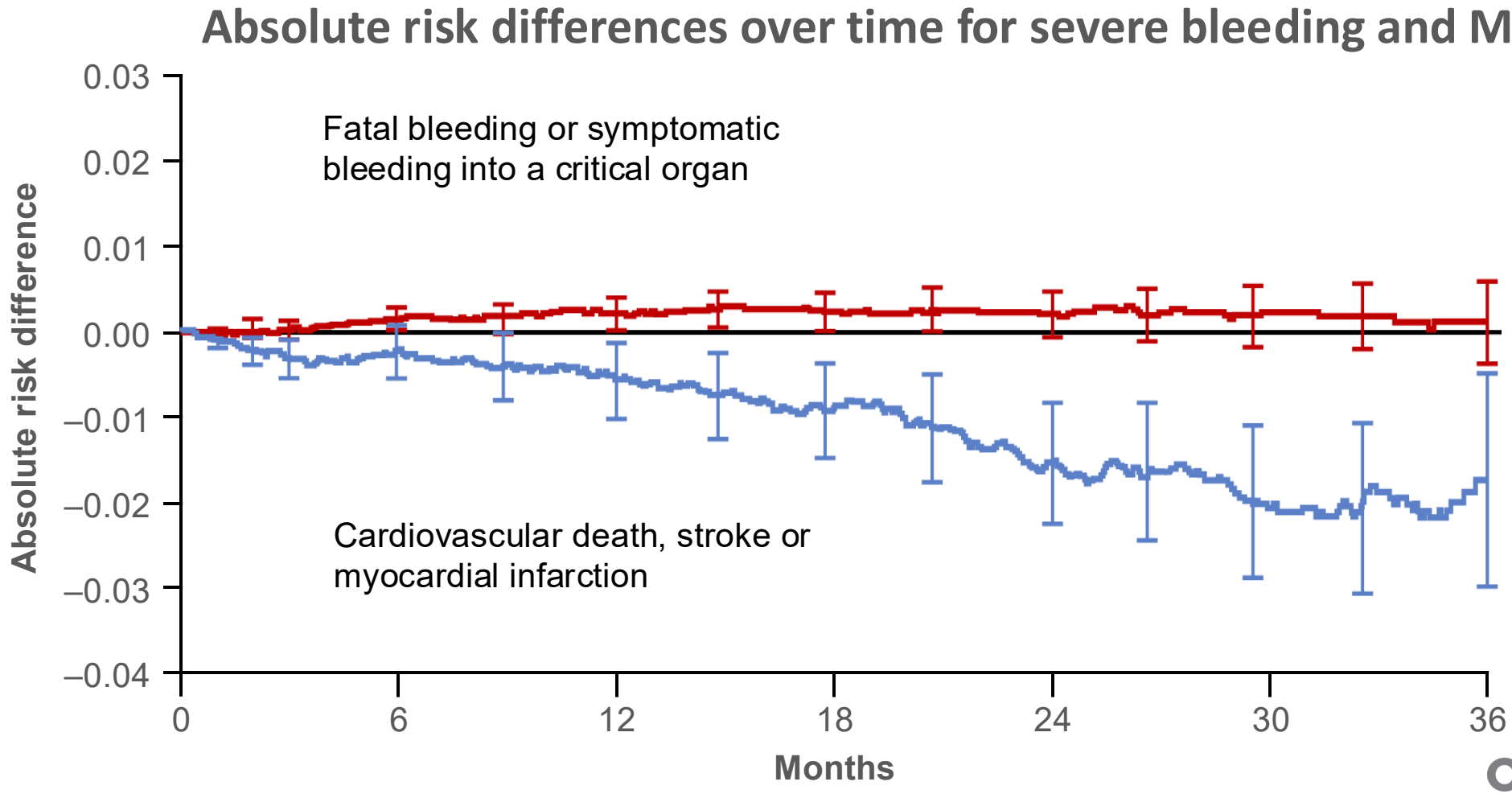
COMPASS Is the First Antithrombotic in a Chronic CAD Population to Show a Mortality Benefit





*1. Connolly SJ et al. *Lancet* 2018;391:205–218; 2. Fox KAA et al. *Eur Heart J* 2018; doi:10.1093/eurheartj/ehy347; 3. ATT Collaboration. *Lancet* 2009; 373:1849–1860; 4. Dagenais GR et al. *Lancet* 2006;368:581–588; 5. CTT Collaboration. *Lancet* 2015;385:1397–1405.

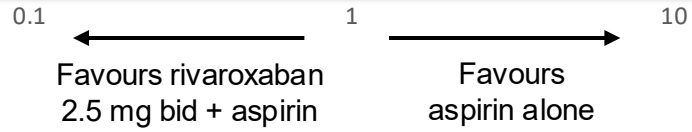
The Balance Between The Increase in Bleeding Events and Reduction in MACE Suggests a Net Clinical Benefit Over Time



Efficacy of Rivaroxaban Vascular Dose 2.5 mg bid + Aspirin Was Consistent Across Subgroups

COMPASS

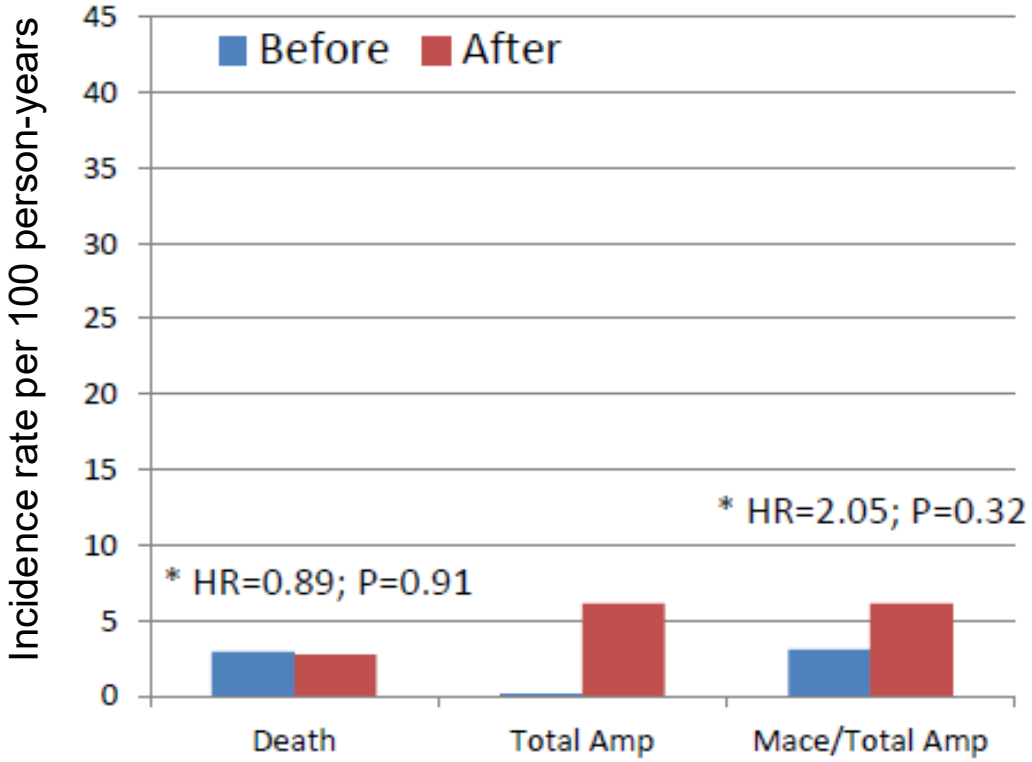
Subgroup	Rivaroxaban 2.5 mg bid + aspirin n/N (%)		Aspirin alone n/N (%)		HR (95% CI)	HR (95% CI)	*p*-value
All participants	347/8313	(4)	460/8261	(6)		0.74 (0.65–0.86)	
History of MI							0.93
<2 years prior	49/1218	(4)	67/1205	(6)		0.70 (0.48–1.01)	
2–5 years prior	71/1612	(4)	91/1665	(5)		0.81 (0.59–1.10)	
≥5 years prior	127/2824	(4)	174/2849	(6)		0.72 (0.57–0.91)	
No MI prior	100/2661	(3.8)	128/2540	(5)		0.76 (0.58–0.98)	
History of PCI/PTCA							0.85
Yes	201/4971	(4)	270/4905	(6)		0.74 (0.61–0.88)	
No	146/3342	(4)	190/3356	(6)		0.76 (0.61–0.94)	
History of CABG							0.01
Yes	121/2232	(5)	117/2143	(5)		0.99 (0.77–1.28)	
No	226/6081	(4)	343/6119	(6)		0.66 (0.56–0.78)	
MI or PCI or CABG >2 years							0.71
Yes	78/2269	(3)	102/2141	(5)		0.71 (0.53–0.95)	
No	269/6044	(4)	358/6120	(6)		0.76 (0.65–0.89)	



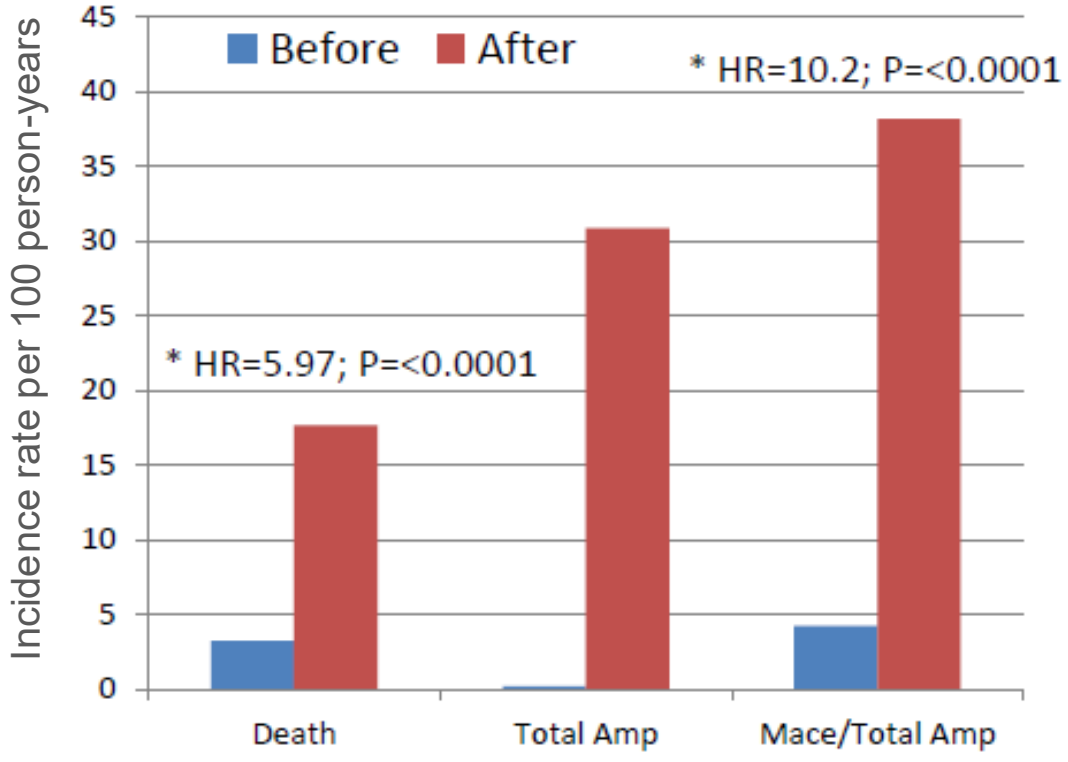
Prognosis of MALE by randomized treatment group (incidence rates/100 person-year)

COMPASS

Prognosis of MALE in patients randomized to receive rivaroxaban 2.5 mg bid + aspirin 100 mg



Prognosis of MALE in patients randomized to receive aspirin 100 mg alone



*Anand SS *et al*, *J Am Coll Cardiol* 2018; doi: 10.1016/j.jacc.2018.03.008; Anand S *et al*, ACC 2018:Oral presentation 407-16

Long-Term Treatment with the Combination of Rivaroxaban and Aspirin in Patients with Chronic Coronary or Peripheral Artery Disease: Outcomes During the Open Label Extension of the COMPASS trial

Open Label Long-term Extension:

Rivaroxaban 2.5 mg bid + Aspirin od

Participate in LTOLE: N = 12,965

ESC European Society of Cardiology

Aims To describe outcomes of patients with chronic coronary artery disease (CAD) and/or peripheral artery disease (PAD) enrolled in the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) randomized trial who were treated with the combination of rivaroxaban 2.5 mg twice daily and aspirin 100 mg once daily during long-term open-label extension (LTOLE).

Table 6 Incidence rates for cardiovascular death, stroke, or myocardial infarction and modified International Society on Thrombosis and Haemostasis major bleeding during randomized treatment and during long-term open-label extension according to original treatment assignment

Event	Rivaroxaban 2.5 mg twice daily + aspirin 100 mg once daily ($n = 4\,399$)	Rivaroxaban 5 mg twice daily ($n = 4292$)	Aspirin 100 mg once daily ($n = 4273$)
CV death, stroke, or MI			
During randomized treatment	2.27 (2.12, 2.42)	2.71 (2.55, 2.88)	2.98 (2.81, 3.16)
During LTOLE	2.47 (2.06, 2.94)	2.46 (2.04, 2.93)	2.12 (1.73, 2.57)
ISTH modified major bleeding			
During randomized treatment	1.62 (1.45, 1.82)	1.45 (1.28, 1.63)	0.98 (0.84, 1.13)
During LTOLE	0.79 (0.56, 1.07)	1.12 (0.85, 1.45)	1.13 (0.85, 1.47)

Conclusion In patients with chronic CAD and/or PAD, extended combination treatment for a median of 1 year and a maximum of 3 years was associated with incidence rates for efficacy and bleeding that were similar to or lower than those seen during the randomized treatment phase, without any new safety signals.

2024 ESC Guidelines for the management of peripheral arterial and aortic diseases

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Recommendation Table 14 — Recommendations for antithrombotic therapy in patients with peripheral arterial disease

Recommendations	Class[a]	Level[b]
Use of antiplatelet therapy with aspirin alone (range 75–160 mg o.d.) or clopidogrel alone (75 mg o.d.) is recommended for the reduction of MACE in patients with symptomatic PAD.[488–490]	I	A
Treatment with combination rivaroxaban (2.5 mg b.i.d.) and aspirin (100 mg o.d.) should be considered for patients with PAD, high ischaemic risk,[c] and non-high bleeding risk.[d,429,498,499]	IIa	A
Treatment with combination rivaroxaban (2.5 mg b.i.d.) and aspirin (100 mg o.d.) should be considered for patients with PAD and non-high bleeding risk following lower-limb revascularization.[490,505]	IIa	B

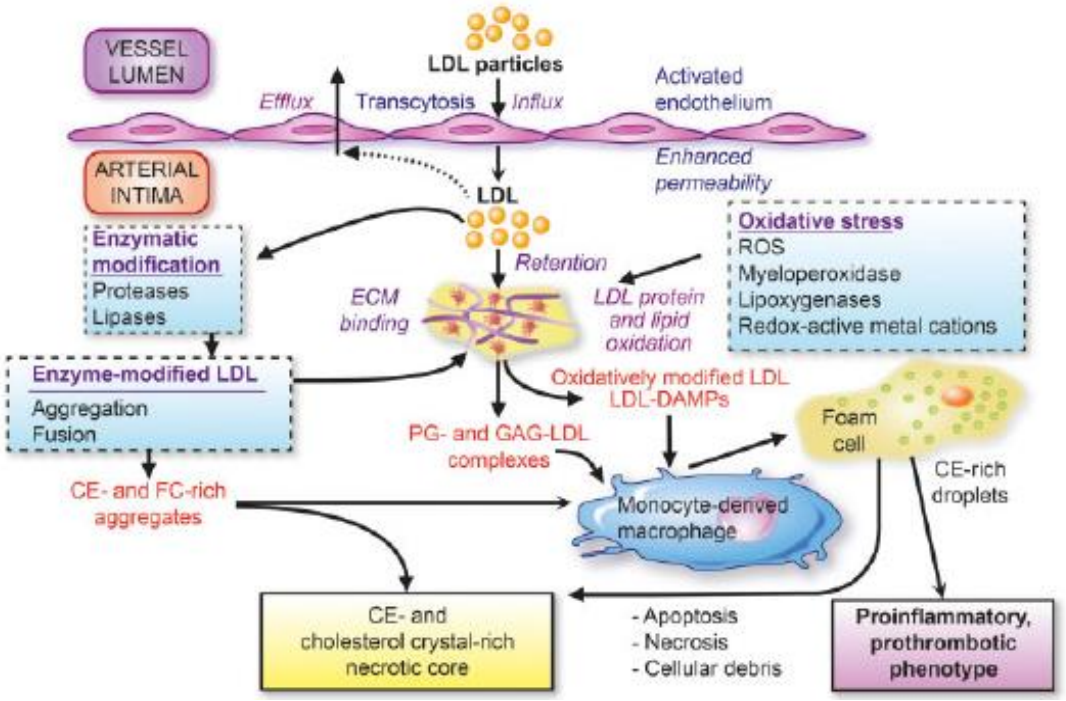
8. Peripheral arterial disease

c **High ischaemic risk**: previous amputation, critical limb threatening ischaemia, previous revascularization, high-risk comorbidities (heart failure, diabetes, vascular disease in two or more vascular beds), eGFR <60 mL/min/1.73 m2.498

High bleeding risk: dialysis or renal impairment GFR <15 mL/min/1.73 m2, acute coronary syndrome <30 days, history of intracranial haemorrhage, stroke or TIA, active or clinically significant bleeding.

Long-term DAPT in patients with PAD is not recommended.[489]	III	A

Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel



Low-density lipoprotein (LDL) as the primary driver of atherogenesis.

Boren J et al. European Heart Journal (2020) 41, 2313–2330

2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias

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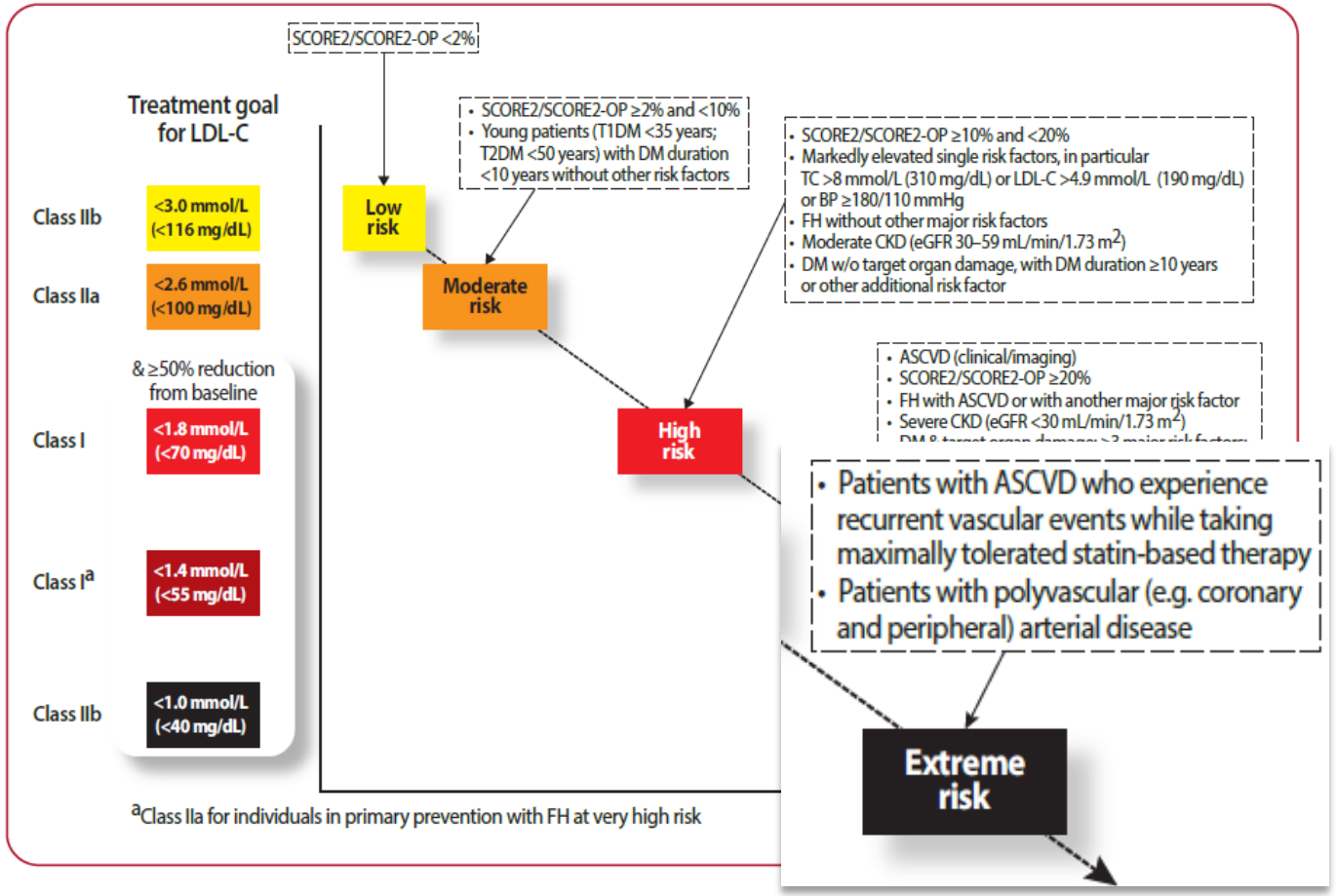


Mach F et al. European Heart Journal (2025) 00, 1–20

Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease

Circulation

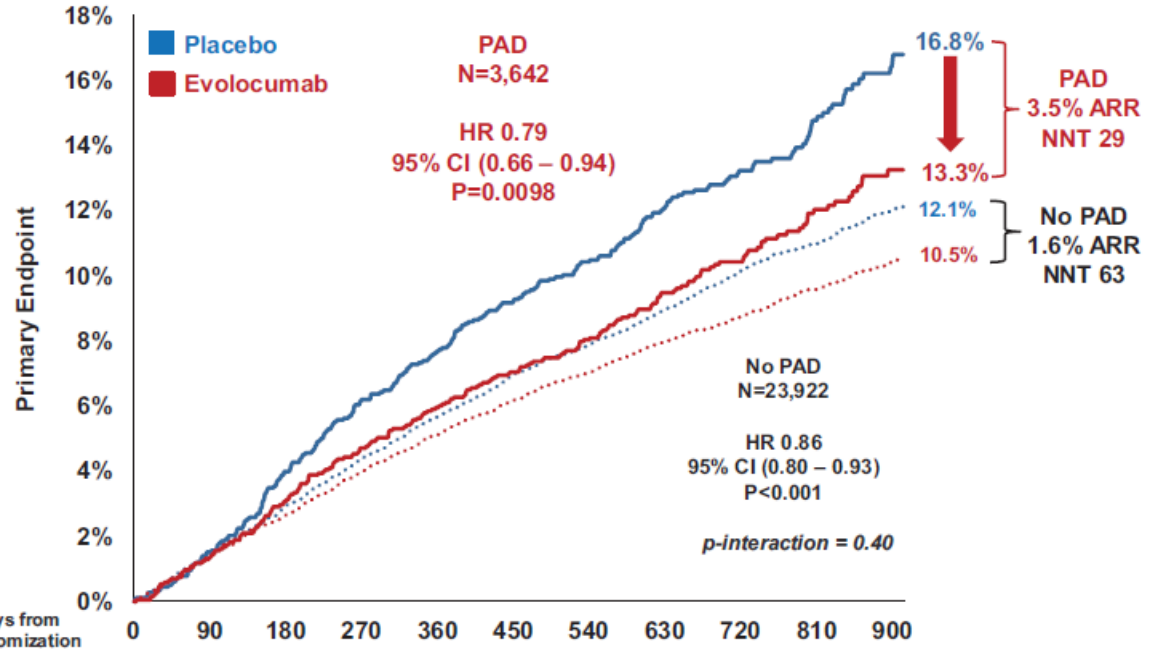
fourier

27 564 patients with atherosclerotic disease on statin therapy followed for a median of 2.2 years. Patients were identified as having PAD at baseline if they had intermittent claudication and an ankle brachial index of <0.85, or if they had a prior peripheral vascular procedure

The primary end point was a composite of cardiovascular death, myocardial infarction, stroke, hospital admission for unstable angina, or coronary revascularization.

A

Primary Endpoint in Patients with and without PAD

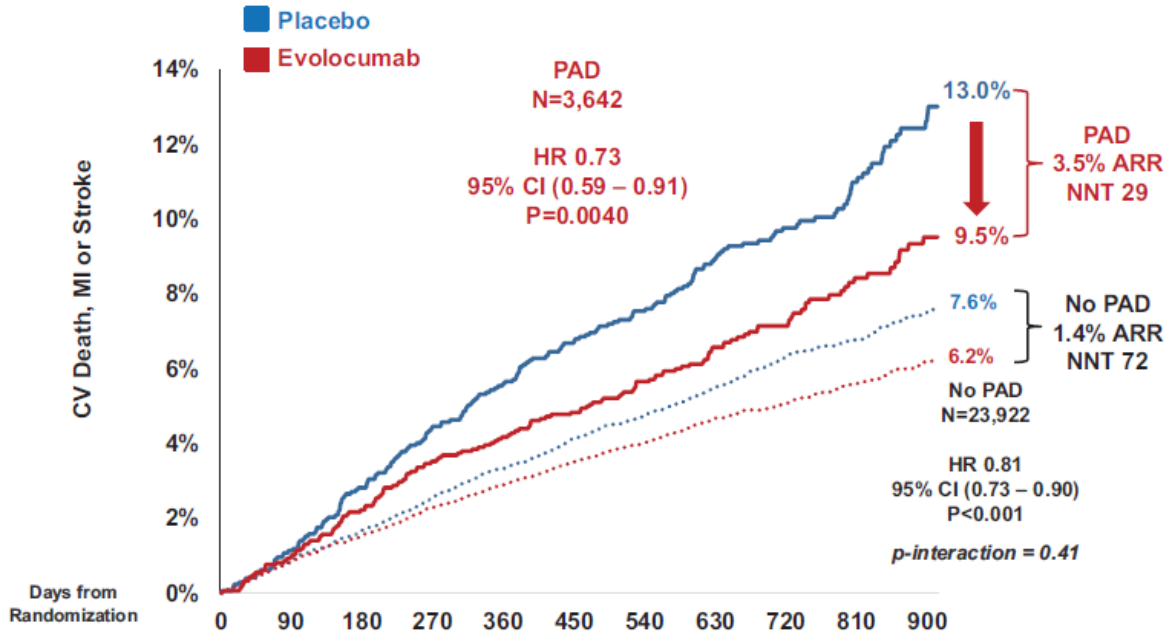


Number at risk

Placebo PAD	1784	1749	1700	1654	1617	1588	1536	1281	973	695	432
Evolocumab PAD	1858	1827	1790	1753	1726	1701	1651	1378	1050	749	460
Placebo no PAD	11996	11793	11582	11390	11217	11039	10400	8759	6864	5173	3443
Evolocumab no PAD	11926	11736	11568	11384	11224	11081	10486	8807	6972	5242	3476

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

Effect of evolocumab on acute arterial events across all vascular territories : results from the FOURIER trial

ESC European Society of Cardiology

fourier

In the **FOURIER** trial, **27,564 patients** with prior MI, non-hemorrhagic stroke, or symptomatic PAD were randomized to **evolocumab** (PCSK9 inhibitor) vs **placebo** with a median follow-up of 2.2 years.

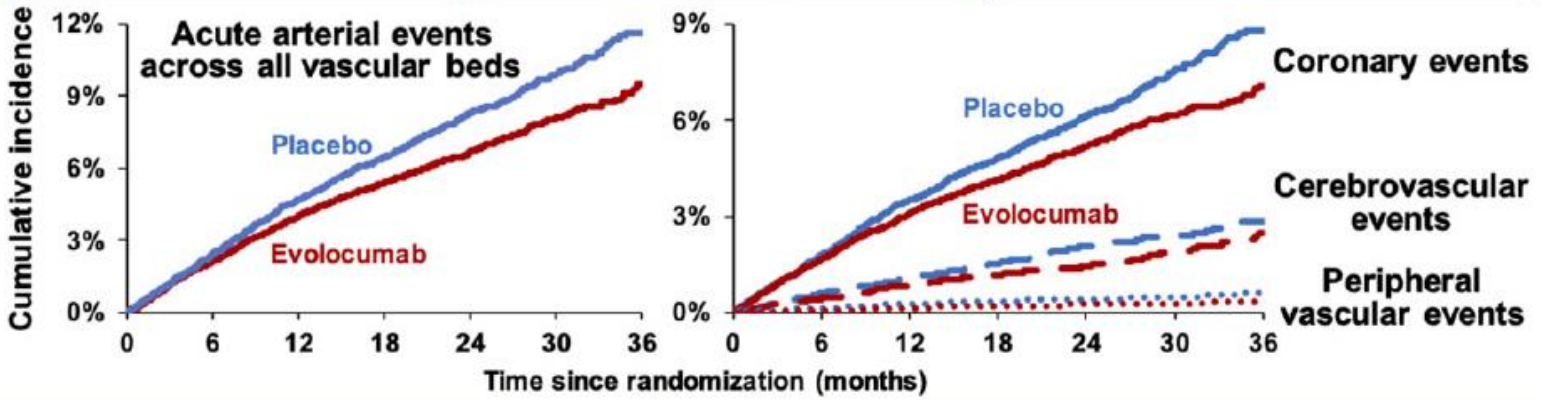
Effect of evolocumab on acute arterial events across all vascular territories

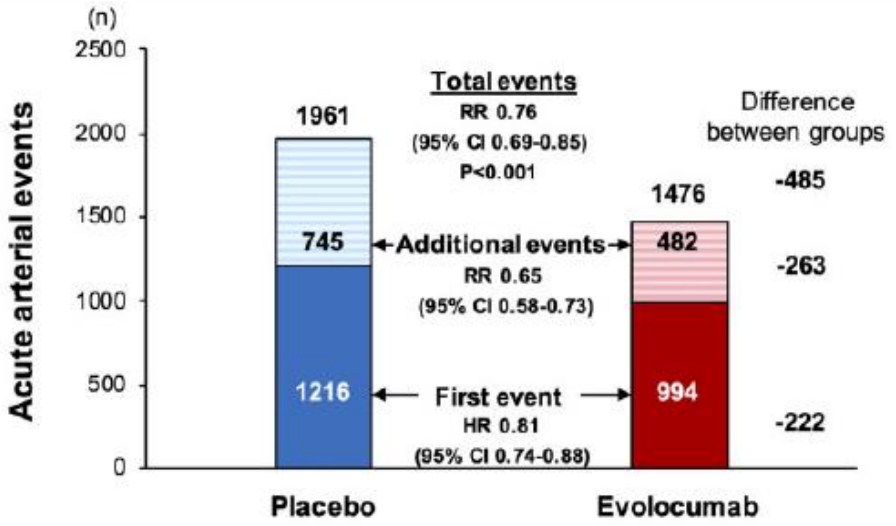
(Acute coronary, cerebrovascular, or peripheral vascular events)

First event: ↓ 19% HR 0.81 (95% CI 0.74-0.88) P<0.001

Total events: ↓ 24% RR 0.76 (95% CI 0.69-0.85) P<0.001

Acute coronary events	Acute cerebrovascular events	Acute peripheral vascular events
(CHD death, MI, or urgent coronary revascularization)	(Ischemic stroke, TIA, or urgent cerebral revascularization)	(ALI, major amputation, or urgent peripheral revascularization)
↓ 17% (First event)	↓ 23% (First event)	↓ 42% (First event)
HR 0.83 (95% CI 0.75-0.91)	HR 0.77 (95% CI 0.65-0.92)	HR 0.58 (95% CI 0.38-0.88)

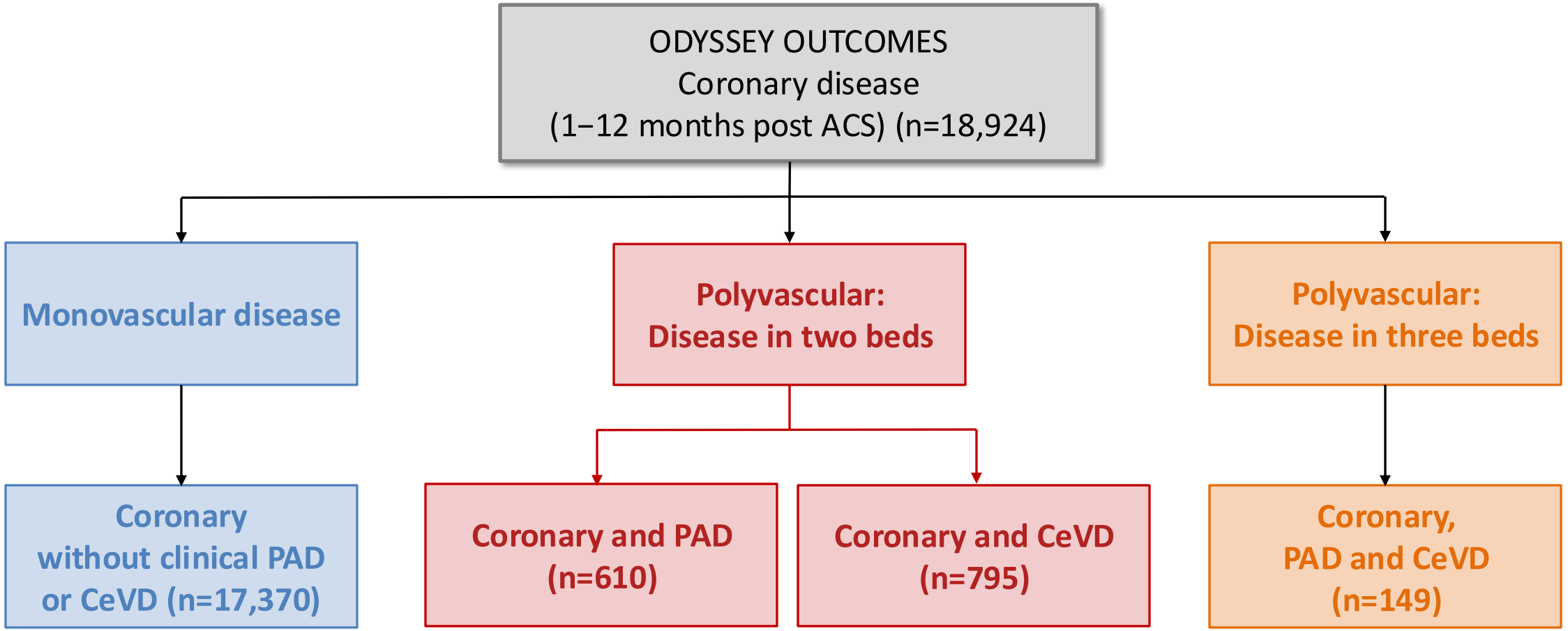




Conclusion The addition of the PCSK9 inhibitor evolocumab to statin therapy reduced acute arterial events across all vascular territories with a robust effect over time, indicating a pan-vascular impact of aggressive lipid-lowering therapy on these acute and clinically meaningful events.

Alirocumab in Patients With Polyvascular Disease and Recent Acute Coronary Syndrome

ODYSSEY OUTCOMES Trial



CeVD, cerebrovascular disease; PAD, peripheral artery disease

Baseline characteristics by history of PAD or CeVD

	Monovascular disease	Disease in two vascular beds		Disease in three vascular beds	P*
	Coronary without PAD or CeVD (n=17,370)	Coronary and PAD (n=610)	Coronary and CeVD (n=795)	Coronary, PAD, and CeVD (n=149)	
Age, years	58 (51,65)	62 (56, 68)	62 (56, 69)	66 (60, 71)	<0.0001
Women	24.7	26.7	33.2	24.8	<0.0001
Index event					<0.0001
NSTEMI	47.9	56.3	55.4	63.1	
STEMI	35.1	31.1	28.6	22.8	
Unstable angina	17.1	11.7	16.0	14.1	
LLT at randomization					<0.0001
High-dose atorvastatin or rosuvastatin	89.2	86.1	85.4	81.2	
Other LLT	10.0	12.3	12.8	16.1	
No LLT	0.9	1.6	1.8	2.7	

Values are median (quartile 1, quartile 3) or %; LLT, lipid-lowering therapy. *Across disease subgroups.

Alirocumab in Patients With Polyvascular Disease and Recent Acute Coronary Syndrome

ODYSSEY OUTCOMES Trial

ODYSSEY OUTCOMES vasculopatia periferica

ODYSSEY OUTCOMES

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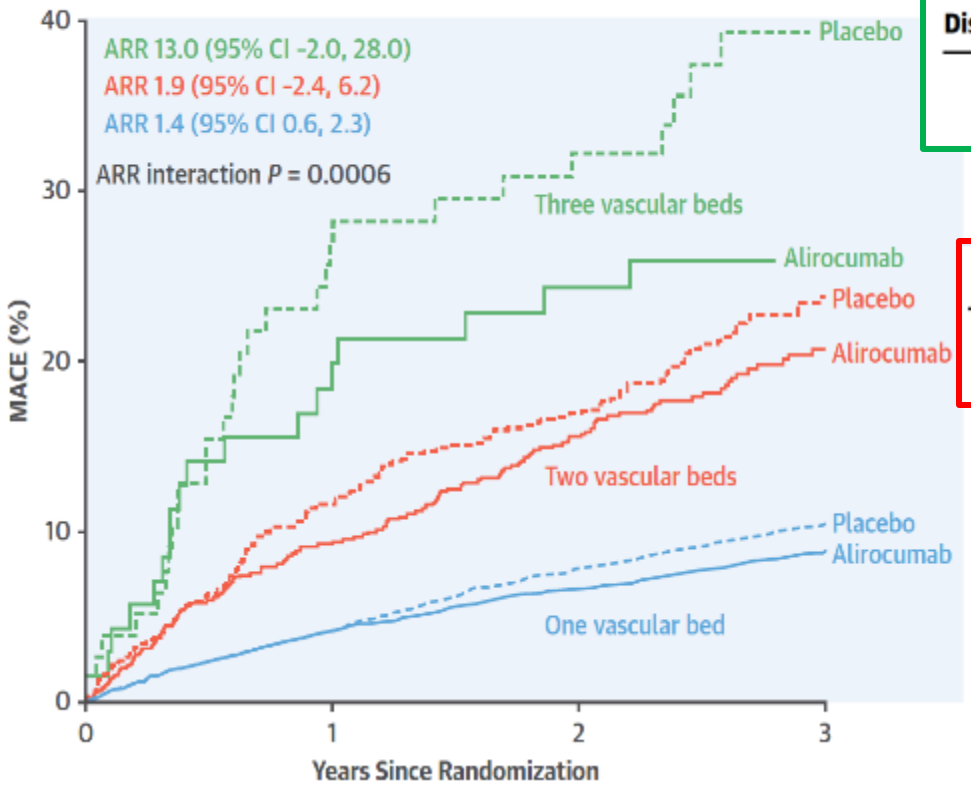
The primary end point was a composite of cardiovascular death, myocardial infarction, stroke, hospital admission for unstable angina, or coronary revascularization.

The key secondary end point was a composite of cardiovascular death, myocardial infarction

CENTRAL ILLUSTRATION Alirocumab and Vascular Disease: Primary Major Adverse Cardiovascular Event Endpoint



Disease in 3 Vascular Beds

CAD, PAD, and CeVD (n = 149)

Disease in 2 Vascular Beds

CAD and PAD (n = 610)	CAD and CeVD (n = 795)

Monovascular Disease

CAD Without PAD or CeVD (n = 17,370)

- **la presenza di polivasculopatia post ACS rappresenta un rischio estremo**
- **la riduzione degli eventi avversi e' maggiore nei pazienti a rischio progressivamente più alto**

Alirocumab in Patients With Polyvascular Disease and Recent Acute Coronary Syndrome

ODYSSEY OUTCOMES Trial

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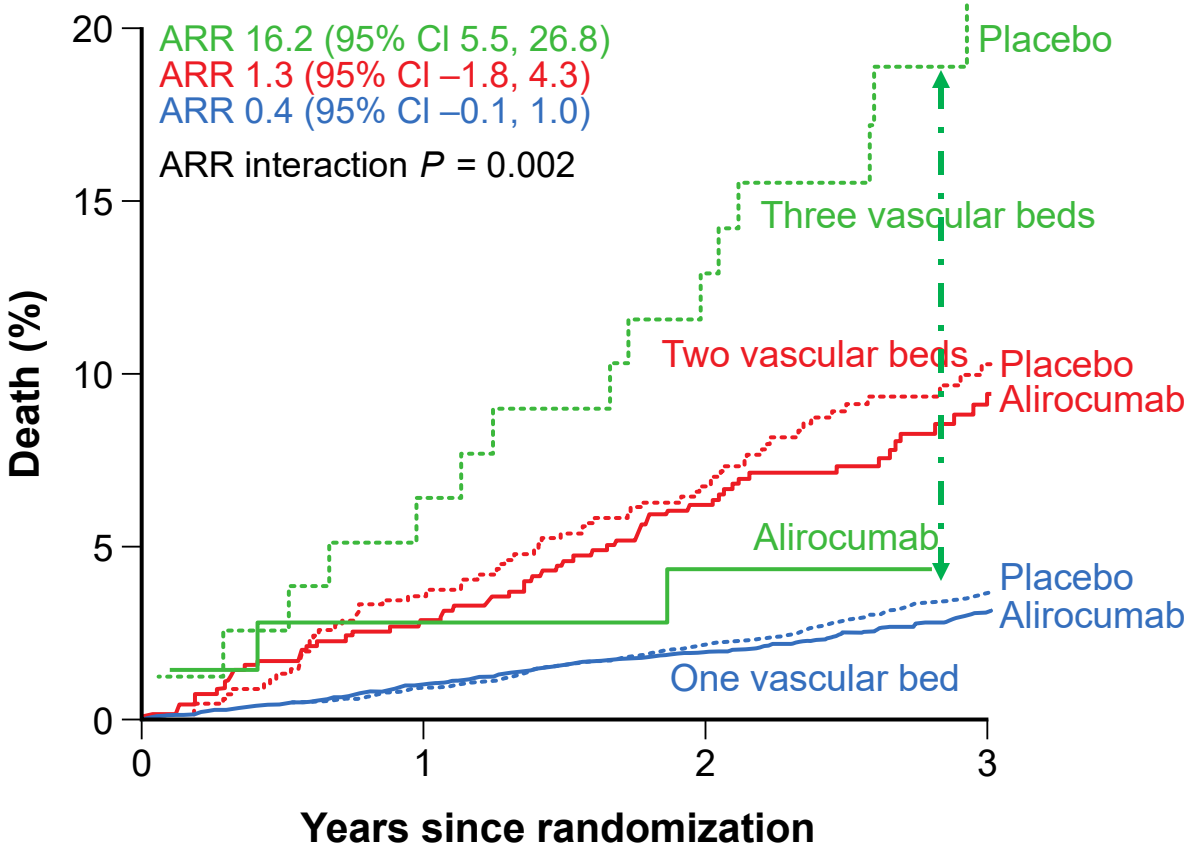
ODYSSEY OUTCOMES vasculopatia periferica

ODYSSEY OUTCOMES

Death: one, two or three vascular beds

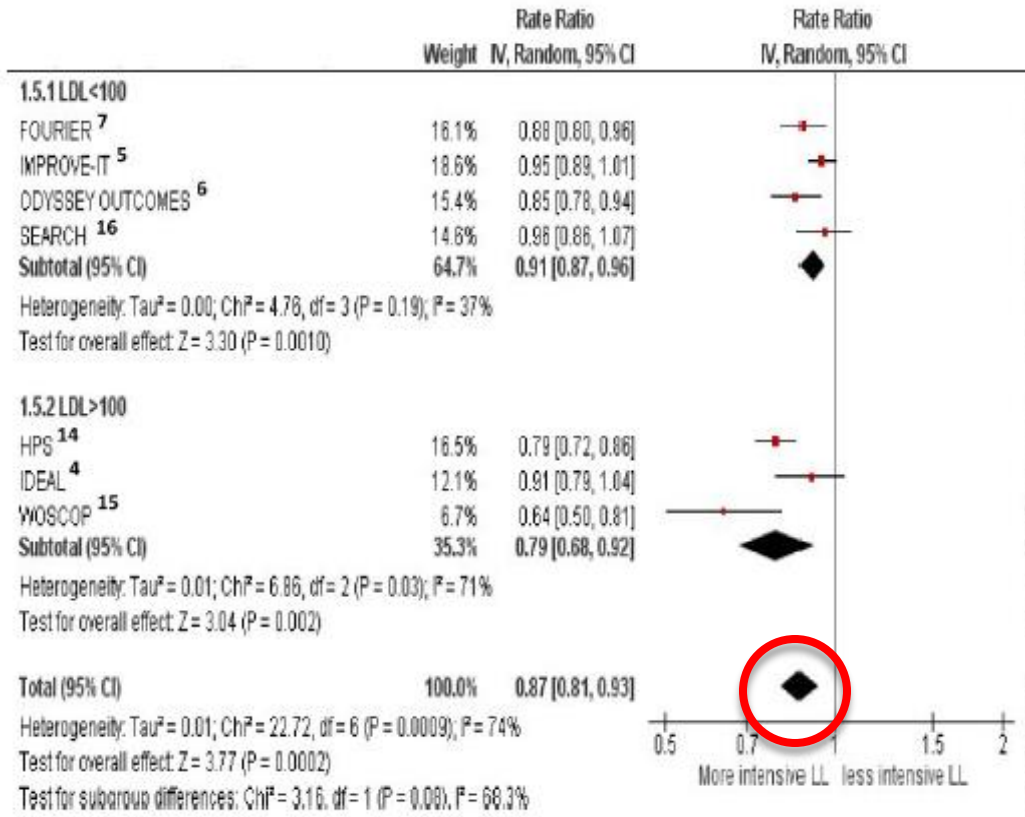


Meta-Analysis of Intensive Lipid-Lowering Therapy in Patients With Polyvascular Disease

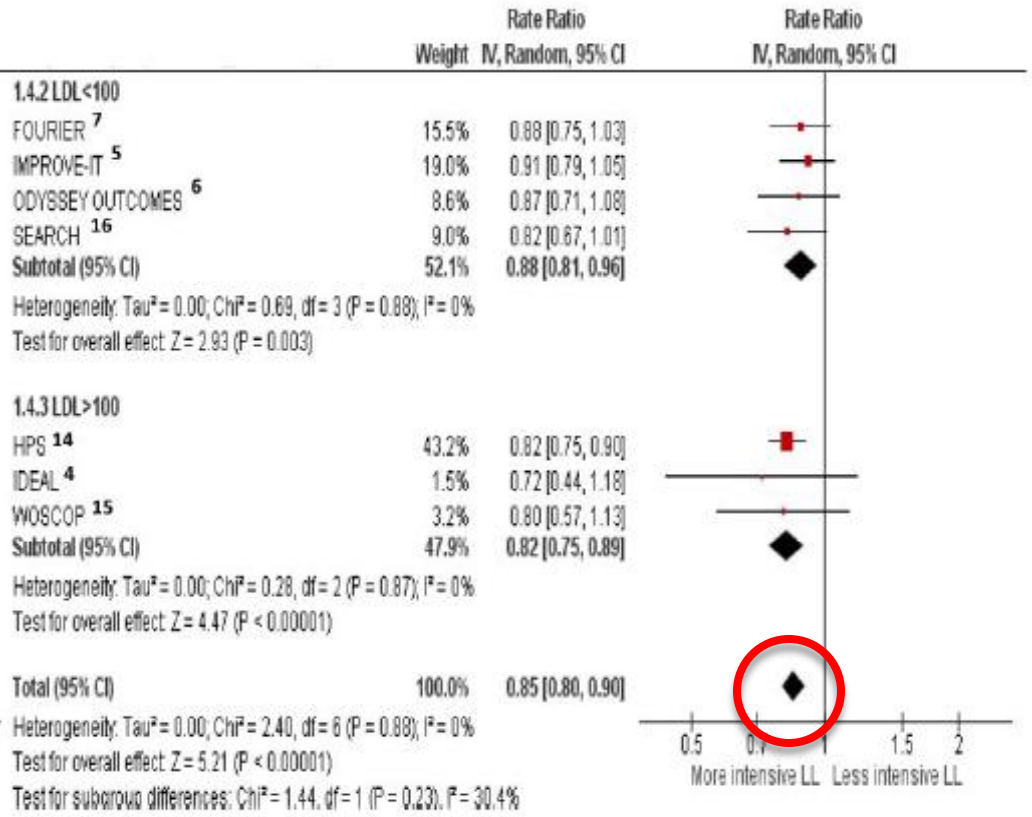
JAHA
Journal of the American Heart Association

SYSTEMATIC REVIEW AND META-ANALYSIS

Monovascular disease



Polyvascular disease



CONCLUSIONS: **Patients with polyvascular disease experienced comparable benefits to those with monovascular disease in response to ILT. The benefits of ILT in patients with polyvascular disease were not dependent on baseline LDL-C**

2024 ESC Guidelines for the management of peripheral arterial and aortic diseases

ESC

7. Optimal medical treatment

7.2.3. Lipid-lowering therapy

Recommendation Table 9 — Recommendations for lipid-lowering therapy in patients with peripheral arterial and aortic diseases

Recommendations	Class[a]	Level[b]
In patients with atherosclerotic PAAD, lipid-lowering therapy is recommended.[242,334–336]	I	A
Statins are recommended in all patients with PAD.[328,329,337,371]	I	A
If the target LDL-C level is not achieved on maximally tolerated statins and ezetimibe, treatment with a PCSK9 inhibitor is recommended in patients with atherosclerotic PAAD, to achieve target values.[372,373]	I	A
If the target LDL-C level is not achieved, a combination of statins and ezetimibe is indicated in patients with atherosclerotic PAAD, to achieve the given target values.[247]	I	B
For statin-intolerant patients with atherosclerotic PAAD, at high CV risk, who do not achieve their LDL-C goal on ezetimibe, it is recommended to add bempedoic acid either alone or in combination with a PCSK9 inhibitor.[361]	I	B
Statins for the reduction of growth and rupture of AAA should be considered.[347–349,352,354]	IIa	B
Statins for the reduction of growth and rupture of TAA may be considered.[350,351,355]	IIb	B
In high-risk patients with PAAD and triglycerides >1.5 mmol/L despite lifestyle measures and statin therapy, icosapent ethyl 2 g b.i.d. may be considered in addition to a statin.[368]	IIb	B

Conclusioni

Interventi farmacologici mirati ed effetti sulla prognosi

- I pazienti con polivasculopatia sono considerati a rischio «estremo»
- Le terapie prognosticamente rilevanti comprendono l'antiaggregazione piastrinica e in alcuni sottogruppi l'associazione aspirina/rivaroxaban a bassa dose
- La stabilizzazione di placca attraverso il raggiungimento del target lipidico. inibitori della PCSK9 ontop della terapia con statine ehanno un ruolo prognostico rilevante nei pazienti polivasculopatici.

Meeting Nazionale ITACARE-P 2025

La Cardiologia Riabilitativa e Preventiva come snodo fondamentale della cura della persona con cardiopatia

La vasculopatia polidistrettuale dalla epidemiologia alla clinica (con la collaborazione scientifica dell'Istituto Superiore di Sanità)

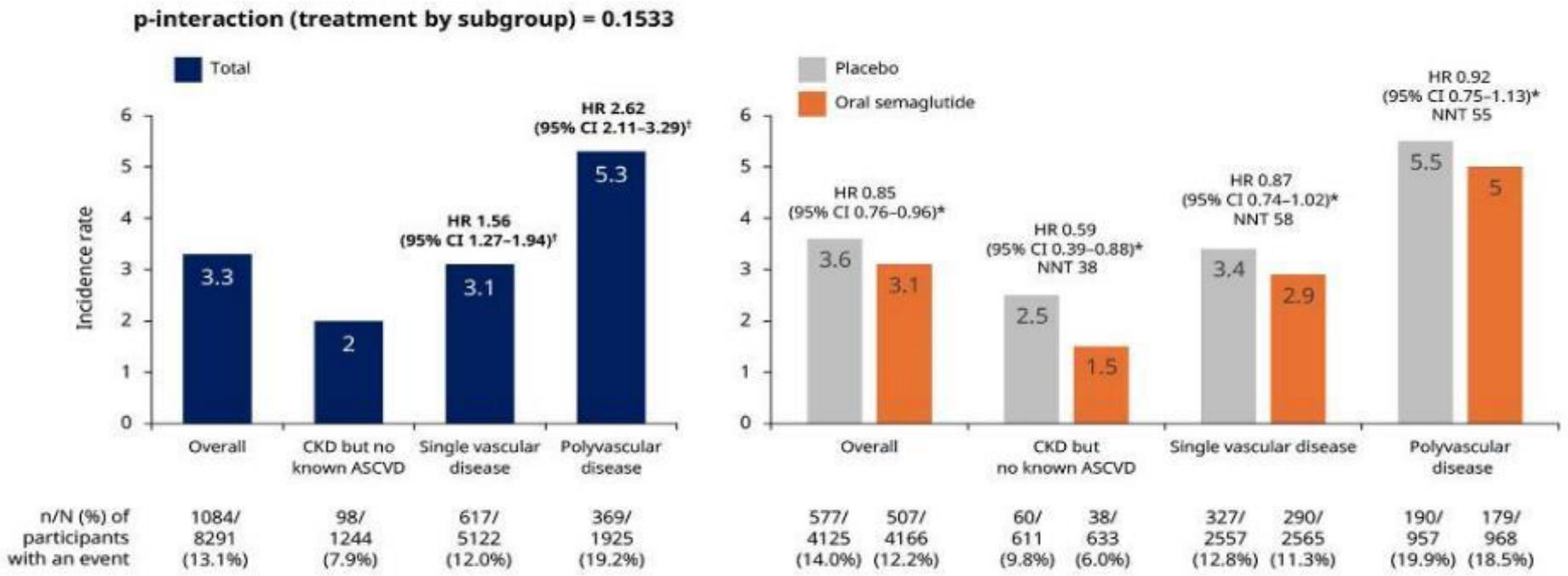
Grazie per l'attenzione

GFMure_2025

Effect of oral semaglutide on CV outcomes across the vascular disease spectrum, from no vascular disease to polyvascular disease, in high-risk type 2 diabetes

Introduction: In the SOUL trial, oral semaglutide, a glucagon-like peptide-1 receptor agonist, reduced major adverse cardiovascular events (MACE) when compared with placebo in people with type 2 diabetes (T2D) and atherosclerotic cardiovascular disease (ASCVD) and/or chronic kidney disease (CKD).

Figure 2. Incidence of MACE in participants with CKD but without known ASCVD, single vascular disease or polyvascular disease in the SOUL trial

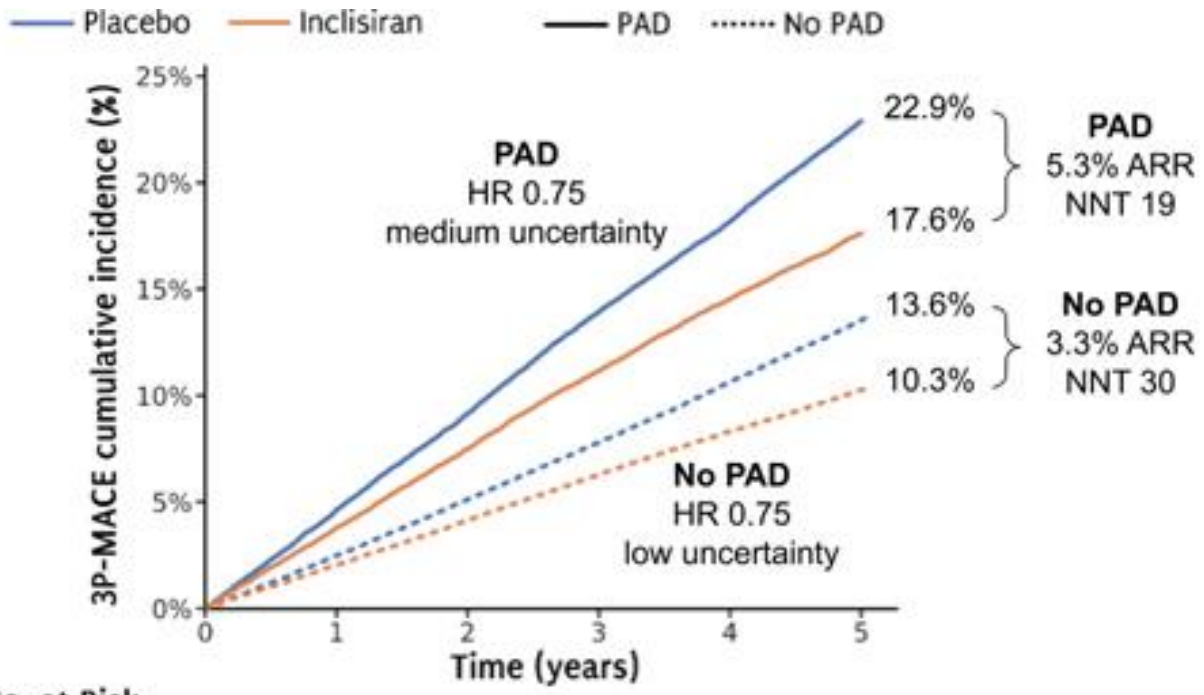


Conclusion: In the SOUL trial, more extensive vascular disease was associated with higher risk of MACE. Oral semaglutide reduced the risk of MACE, irrespective of number of affected vascular beds, which supports the initiation of semaglutide in T2D with CKD, even in the absence of known ASCVD.

Predicted efficacy of inclisiran on cardiovascular outcomes in lower extremity peripheral artery disease: results of the In Silico Sirius study

Research question/Hypothesis: SIRIUS in silico study aims to predict the efficacy of inclisiran on CV outcomes in subgroups of patients with or without PAD.

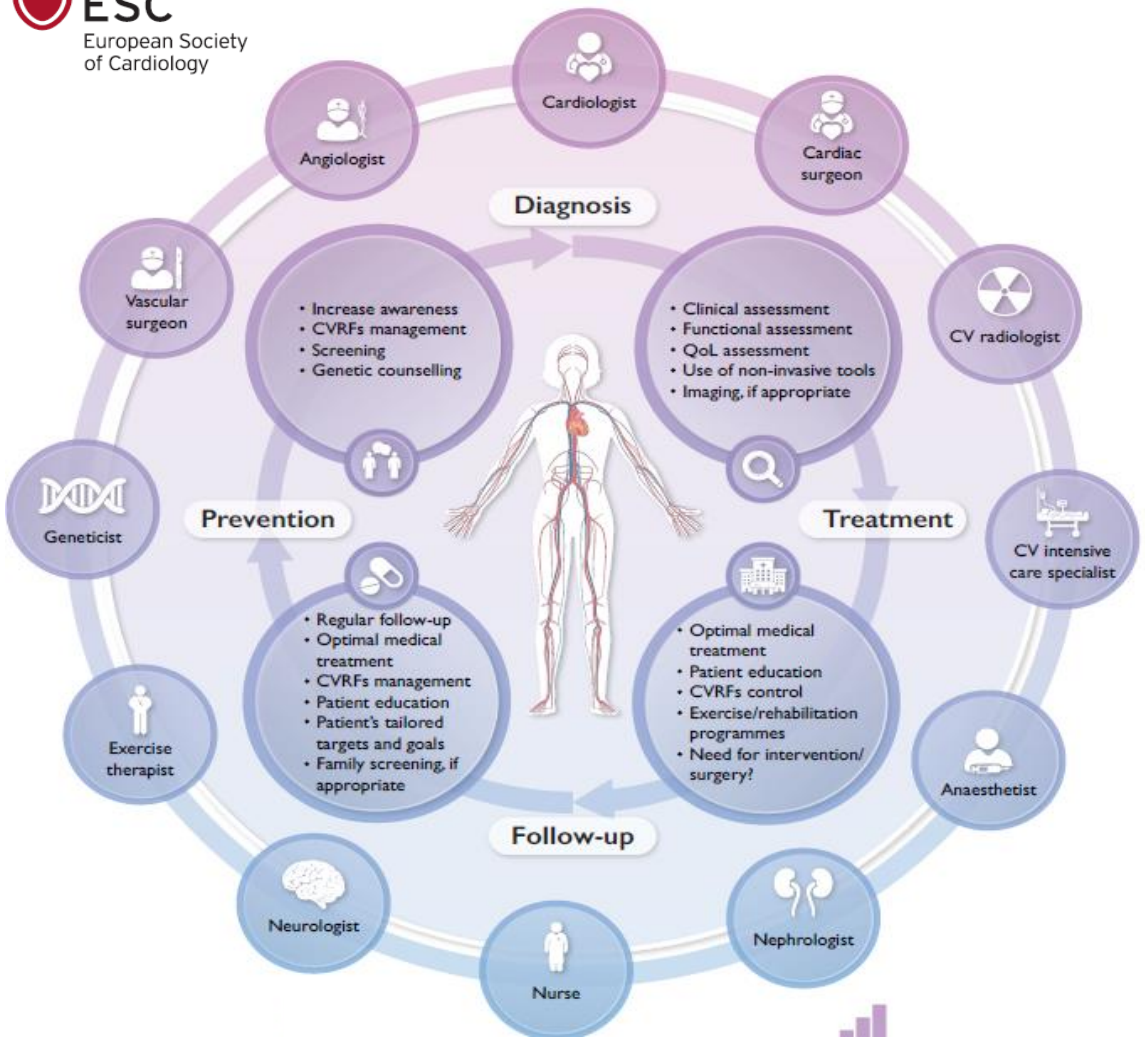
Methods: The SIRIUS in silico trial was conducted using a **knowledge-based mechanistic computational model** of ASCVD applied to a virtual ASCVD population with LDL-C ≥ 70 mg/dL. Each virtual patient is its own control.



No. at Risk						
PAD						
Placebo	28072	26774	25503	24164	22974	21650
Inclisiran	28072	27011	25968	24941	23993	23125
No PAD						
Placebo	176619	172205	167528	162761	157705	152523
Inclisiran	176619	172975	169247	165451	161861	158366

2024 ESC Guidelines for the management of peripheral arterial and aortic diseases

ESC
European Society of Cardiology

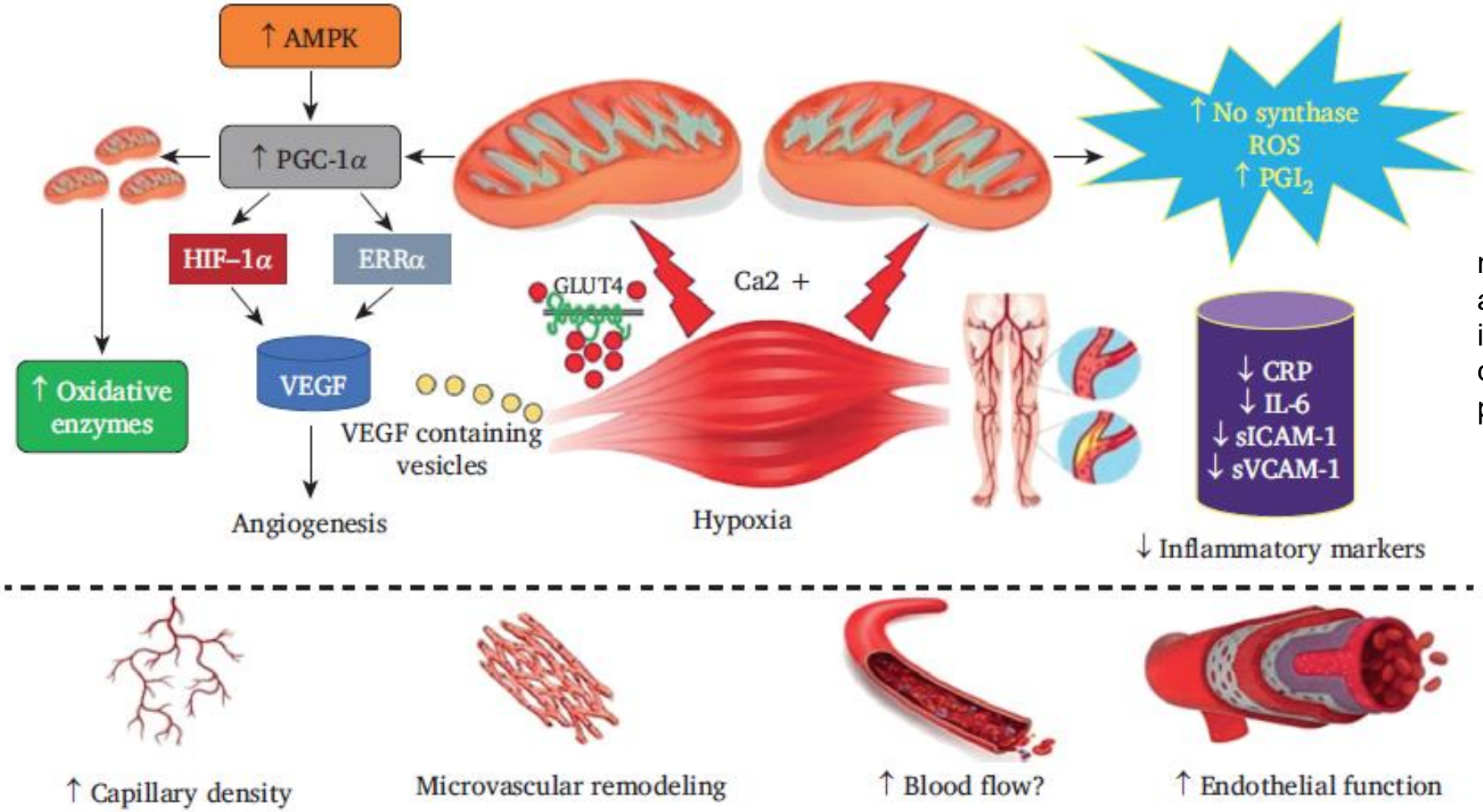


Targets

- Healthy diet
- BMI 20–25 kg/m^2
- Waist: <94 cm men; <80 cm women
- Low-to-moderate exercise training

Dynamic exercise training induces extensive remodelling of the vascular system

Clinical Practice Guidelines



mitochondrial biogenesis, angiogenesis, and increases in the functional capacity of individuals with peripheral arterial disease