Effetti del vorapaxar nei pazienti con arteriopatia periferica

ANALISI DAL TRA 2°P-TIMI 50 TRIAL

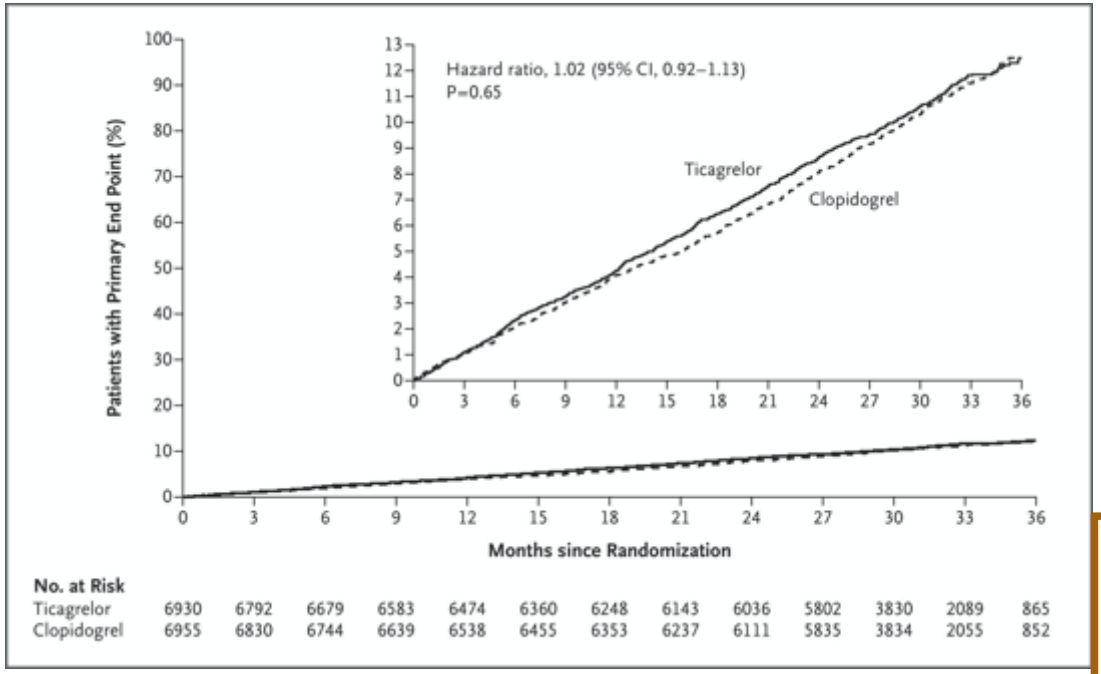
Background

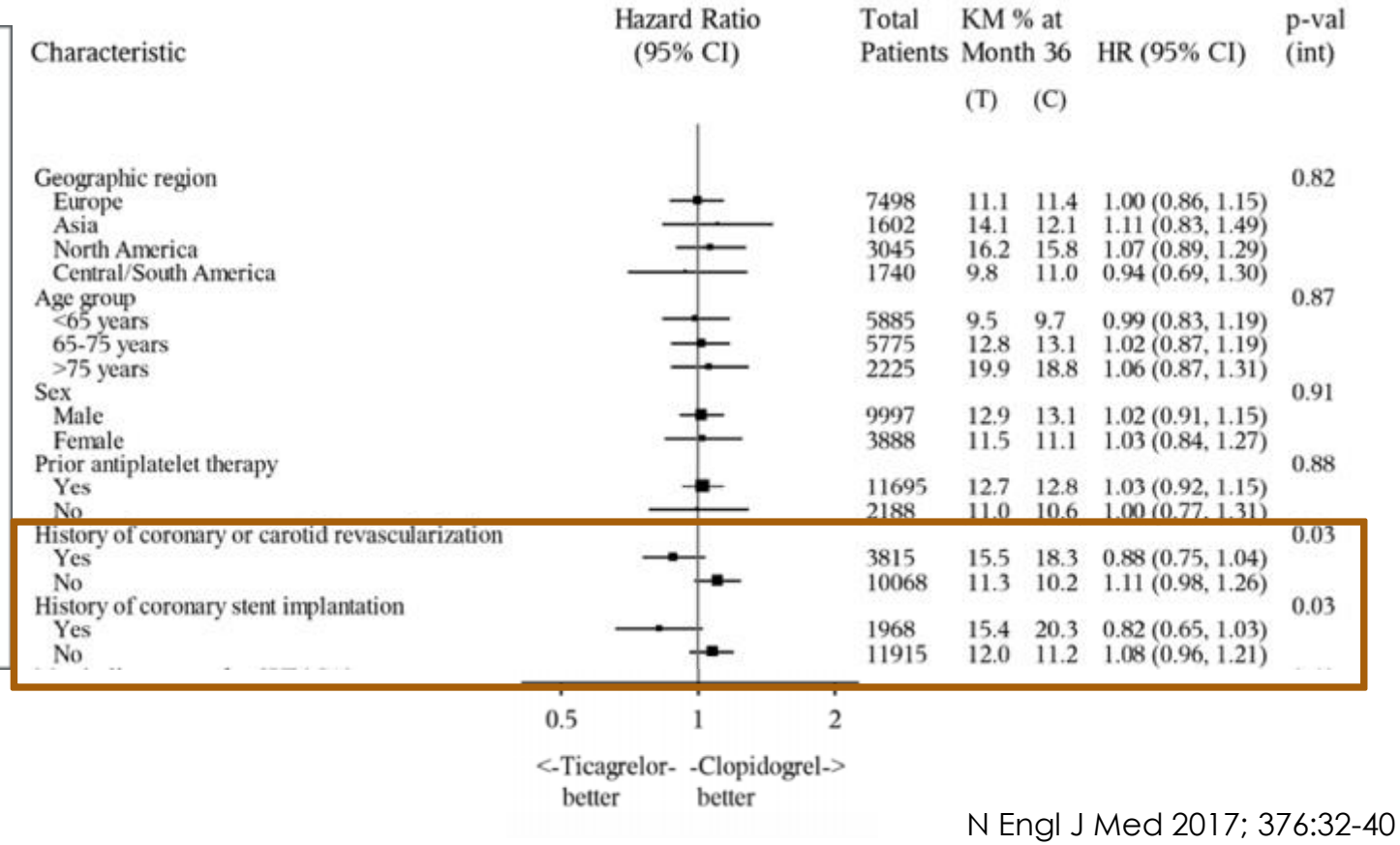
- More than 200 million individuals have peripheral artery disease (PAD) globally

- Patients with PAD are at heightened risk of
  - MACE: cardiovascular death, myocardial infarction, stroke
  - MALE: acute limb ischemia (ALI), urgent revascularization for ischemia, major amputations

EUCLID trial

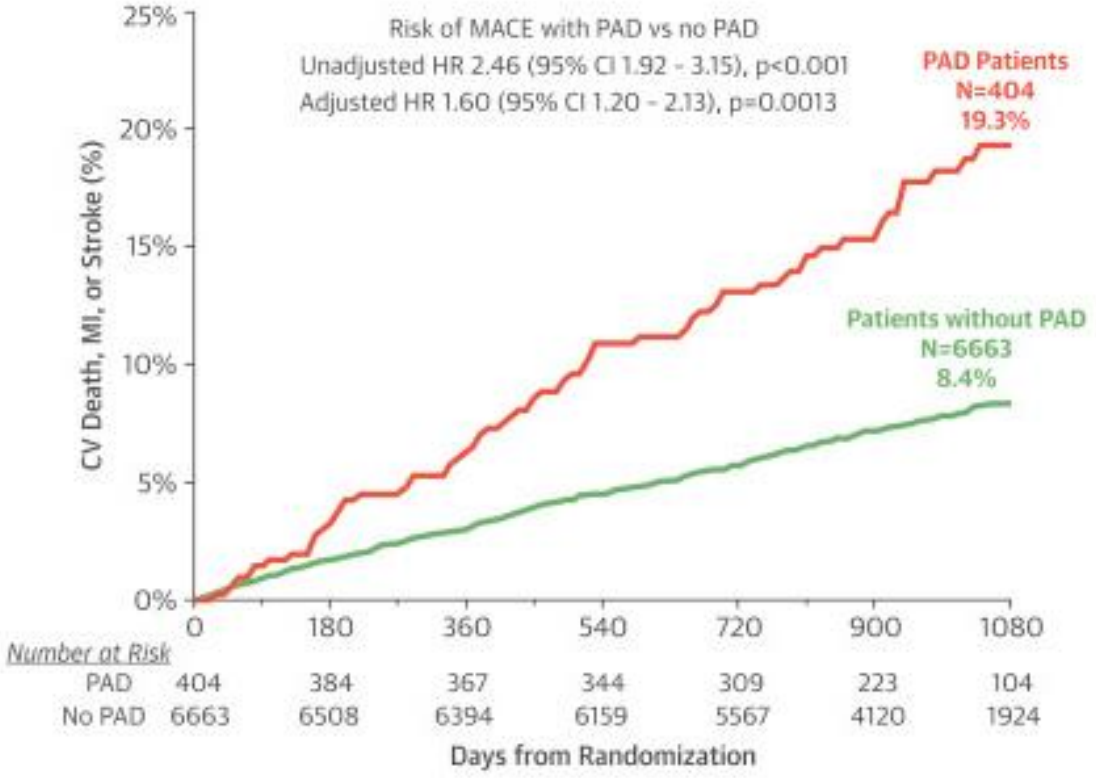
13,885 patients with symptomatic peripheral artery disease

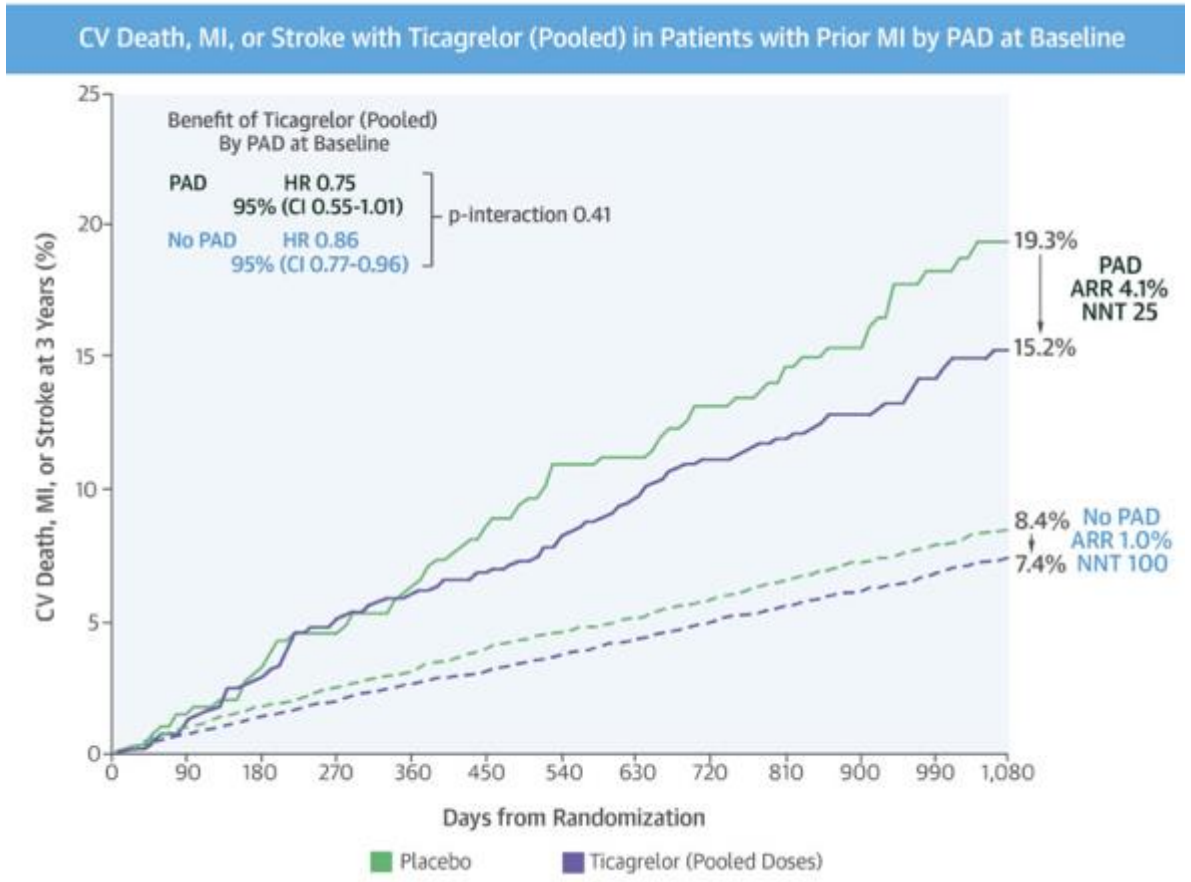




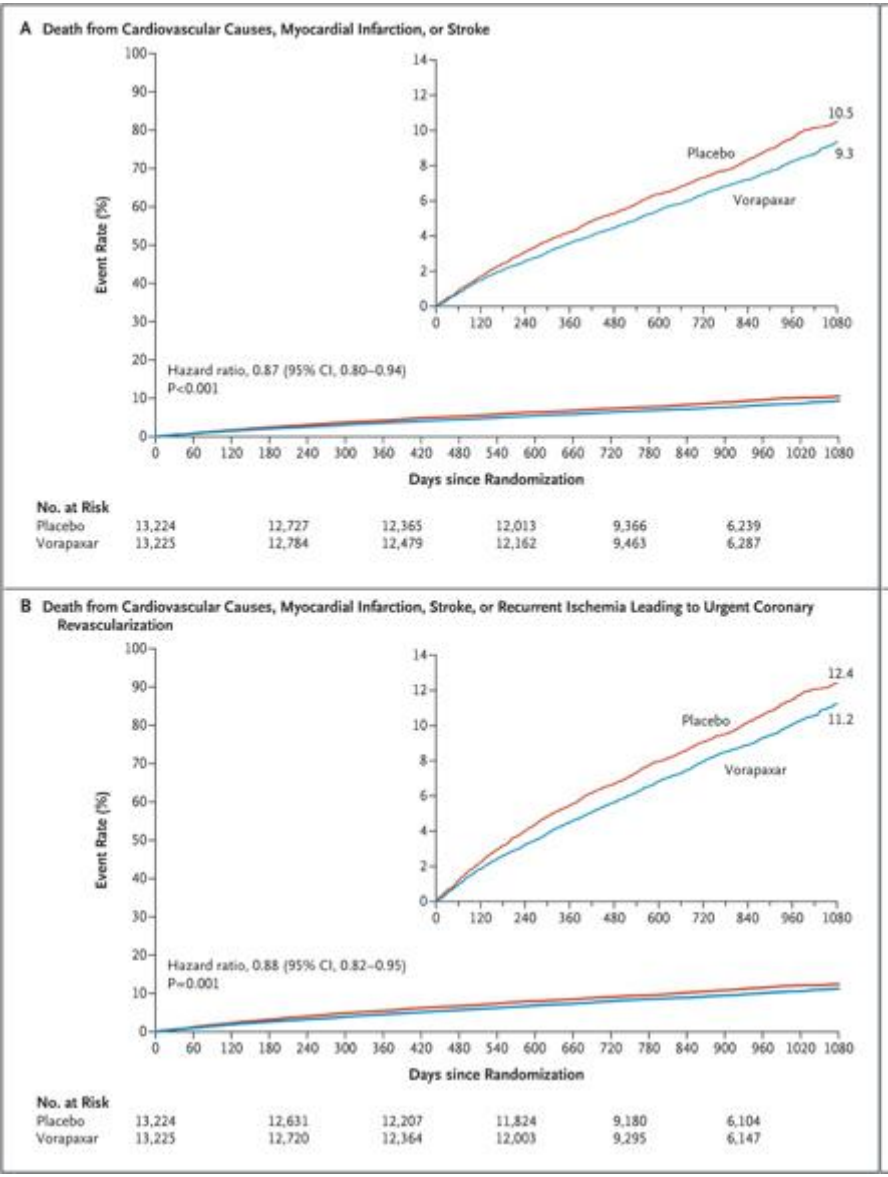
N Engl J Med 2017; 376:32-40

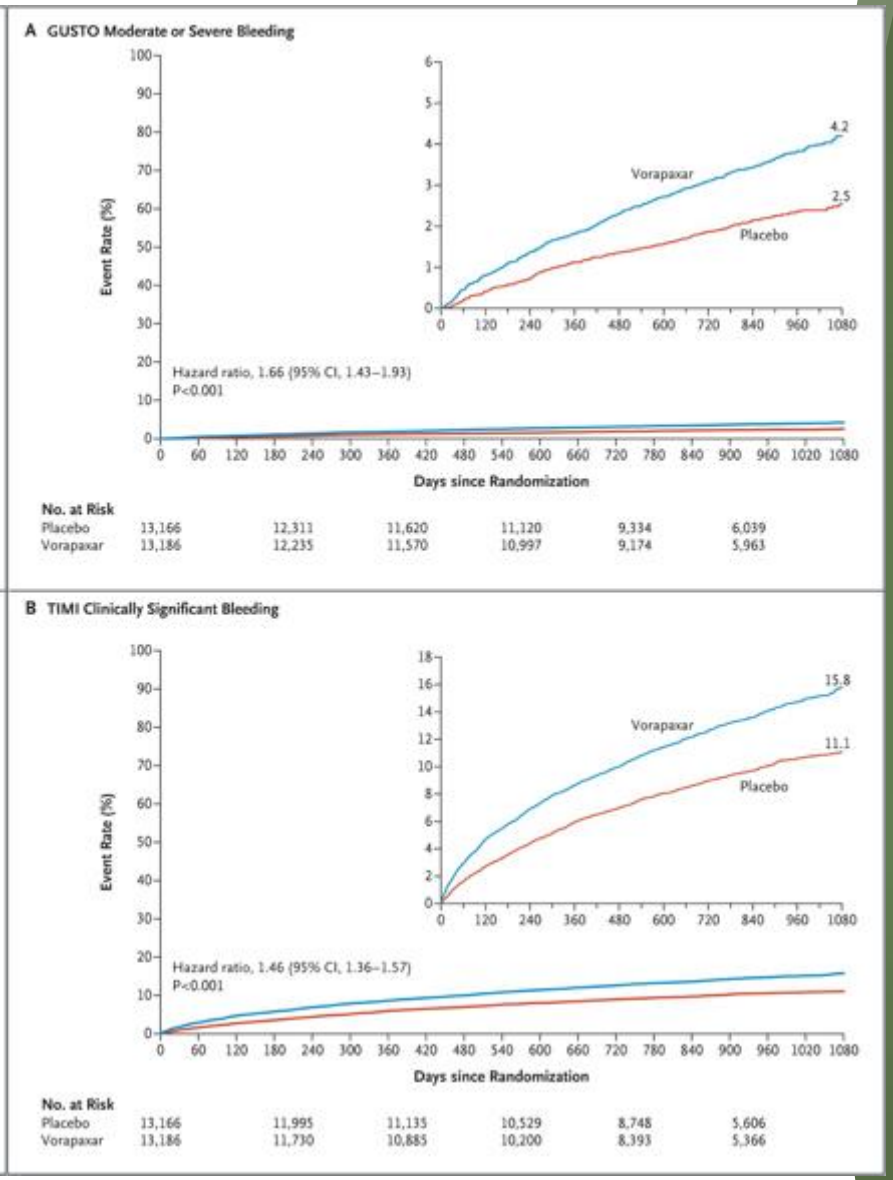
PEGASUS-TIMI 54 subanalysis





Bonaca, M.P. et al. J Am Coll Cardiol. 2016;67(23):2719-28.





TRA 2°P-TIMI 50 trial

26,449 patients with history of myocardial infarction, ischemic stroke, or peripheral arterial disease

N Engl J Med 2012; 366:1404-1413

Effect of vorapaxar on cardiovascular and limb outcomes in patients with peripheral artery disease with and without coronary artery disease: Analysis from the TRA 2°P-TIMI 50 trial

Arman Qamar[1], David A Morrow[1], Mark A Creager[2], Benjamin M Scirica[1], Jeffrey W Olin[3], Joshua A Beckman[4], Sabina A Murphy[1] and Marc P Bonaca[1,5]

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Aim

- The authors evaluated whether risk of MACE and MALE in 6136 patients with PAD enrolled in the TRA 2°P-TIMI 50 trial differed on the basis of concomitant CAD and prior peripheral revascularization, and whether the absolute benefits of more intensive antiplatelet therapy with vorapaxar differed by these criteria.

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Variable	PAD (n = 6136)	No history of PAD (n = 14,034)	p-value
Demographics			
Age, median (IQR), years	64 (57–71)	58 (51–65)	< 0.001
Female sex, n (%)	1756 (29)	2613 (19)	< 0.001
White, n (%)	5446 (89)	12,417 (89)	0.54
BMI, median (IQR), kg/m^2	27.5 (24.7–30.7)	27.9 (25.3–31)	< 0.001
Clinical characteristics, n (%)			
Diabetes mellitus	2051 (33)	2711 (19)	< 0.001
Hypertension	4691 (76)	8393 (60)	< 0.001
Hyperlipidemia	5324 (87)	11,803 (84)	< 0.001
Current smoker	1760 (29)	2597 (19)	< 0.001
Prior myocardial infarction	3743 (61)	14,017 (99.9)	< 0.001
Any coronary artery disease	4684 (76)	14,034 (100)	< 0.001
Prior coronary revascularization	3788 (62)	12,119 (86)	< 0.001
History of atrial fibrillation or flutter	302 (4.9)	509 (3.6)	< 0.001
eGFR < 60 mL·min^{-1}·1.73 m^{-2}	1432 (24)	1427 (10)	< 0.001
PAD details, n (%)			
Peripheral artery revascularization	2431 (40)	–	
Prior amputation for limb ischemia	176 (2.9)	–	
Prior carotid intervention	316 (5.1)	–	
Any carotid stenosis (⩾ 50%)	729 (12)	–	
ABI ⩽ 0.9	4431 (75)	–	
ABI > 1.3	92 (1.5)	–	
Claudication (Fontaine class > 1)	3288 (54)	–	
Baseline medical therapy, n (%)			
Antiplatelet therapy			
No aspirin or thienopyridine	129 (2.1)	50 (0.4)	< 0.001
Aspirin	5691 (93)	13,811 (98)	< 0.001
Thienopyridine	3314 (54)	11,078 (79)	< 0.001
Aspirin and thienopyridine	2998 (49)	10,905 (78)	< 0.001
Cilostazol	395 (6.4)	17 (0.1)	< 0.001
ACE inhibitor or ARB	4471 (73)	10,826 (77)	< 0.001
Statin therapy	5377 (88)	13,410 (96)	< 0.001

Baseline characteristics

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Efficacy and safety outcomes in patients with PAD + CAD and in those with PAD alone

Endpoint	Subgroup	Vorapaxar *n* (%)[a]	Placebo *n* (%)[a]	NNT / NNH	ARD (95% CI) (%)	Gail–Simon *p*-value for interaction
MACE	PAD with CAD	247 (10.6)	301 (12.8)	45	–2.2 (–4.0, –0.4)	0.03
	PAD alone	57 (7.7)	54 (7.6)	1000	0.1 (–2.6, 2.9)	
MALE	PAD with CAD	61 (2.6)	72 (3.1)	250	–0.4 (–1.4, 0.5)	0.003
	PAD alone	27 (3.7)	51 (7.2)	29	–3.5 (–5.9, –1.2)	
MACE or MALE	PAD with CAD	298 (12.8)	359 (15.3)	40	–2.5 (–4.5, –0.5)	0.004
	PAD alone	81 (11.0)	99 (13.9)	33	–3.0 (–6.4, 0.4)	
ISTH major bleeding	PAD with CAD	158 (6.8)	122 (5.2)	62	1.6 (0.2, 2.9)	0.004
	PAD alone	43 (5.9)	26 (3.7)	45	2.2 (0.0, 4.4)	
Net outcome	PAD with CAD	313 (13.4)	374 (15.9)	40	–2.5 (–4.5, –0.5)	0.006
	PAD alone	85 (11.5)	102 (14.3)	36	–2.8 (–6.3, 0.6)	

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Efficacy endpoints in the overall population of patients with PAD

Endpoint	Vorapaxar (n = 3071) n (%)[a]	Placebo (n = 3065) n (%)[a]	HR (95% CI)	p-value
Cardiovascular outcomes				
MACE: CV death/MI/stroke	304 (9.9)	355 (11.6)	0.85 (0.73, 0.99)	0.034
CV death	131 (4.3)	152 (5.0)	0.85 (0.68, 1.08)	0.18
MI	181 (5.9)	200 (6.5)	0.90 (0.73, 1.10)	0.30
Stroke	51 (1.7)	65 (2.1)	0.77 (0.53, 1.11)	0.17
All-cause death	234 (7.6)	258 (8.4)	0.90 (0.75, 1.07)	0.23
Limb outcomes				
MALE: hospitalization for ALI/urgent peripheral revascularization/ major amputation	88 (2.9)	123 (4.0)	0.70 (0.53, 0.92)	0.011
Hospitalization for ALI	41 (1.3)	70 (2.3)	0.57 (0.39, 0.84)	0.005
Urgent peripheral revascularization	60 (2.0)	87 (2.8)	0.68 (0.49, 0.94)	0.02
Major amputation	40 (1.3)	44 (1.4)	0.90 (0.59, 1.38)	0.62
Any peripheral revascularization	348 (11.3)	432 (14.1)	0.79 (0.68, 0.91)	< 0.001
Elective peripheral revascularization	312 (10.2)	381 (12.4)	0.80 (0.69, 0.93)	0.004
Hospitalization for ALI or major amputation	67 (2.2)	99 (3.2)	0.66 (0.49, 0.91)	0.01
MACE or MALE	379 (12.3)	458 (14.9)	0.81 (0.71, 0.93)	0.003

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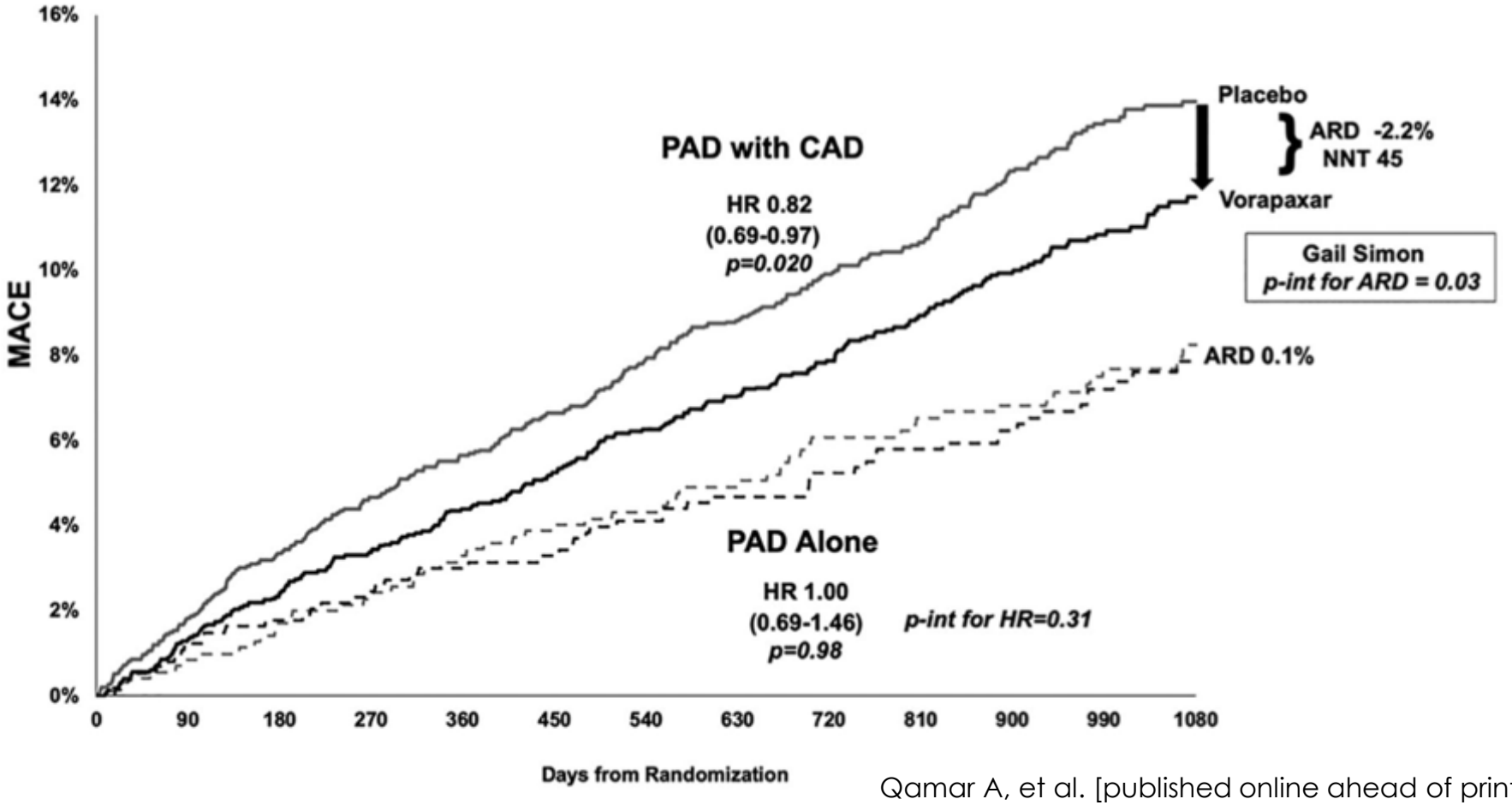
MACE reduction with vorapaxar over 3 years



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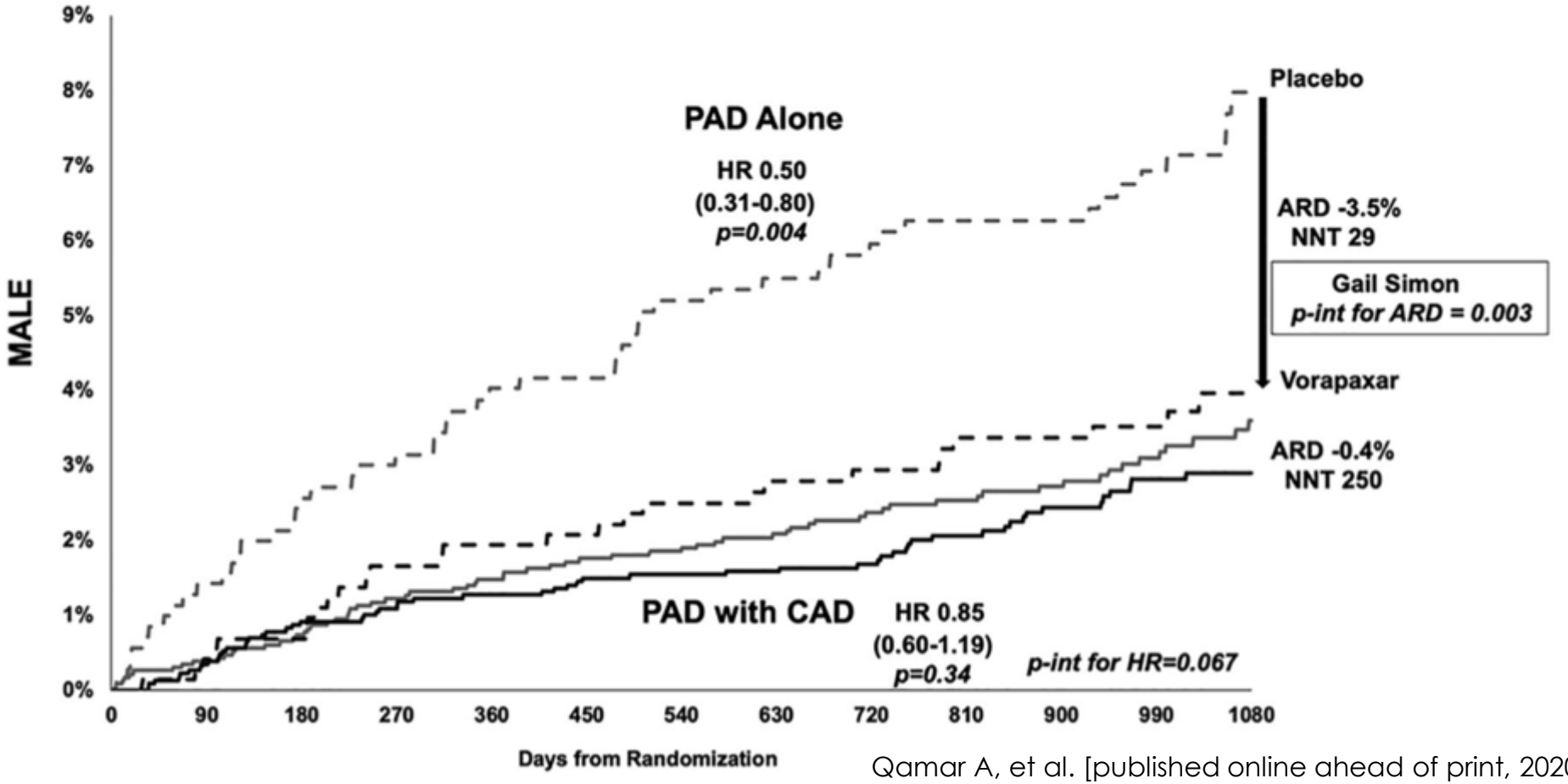
MALE reduction with vorapaxar over 3 years in patients with PAD with CAD and in those with PAD alone



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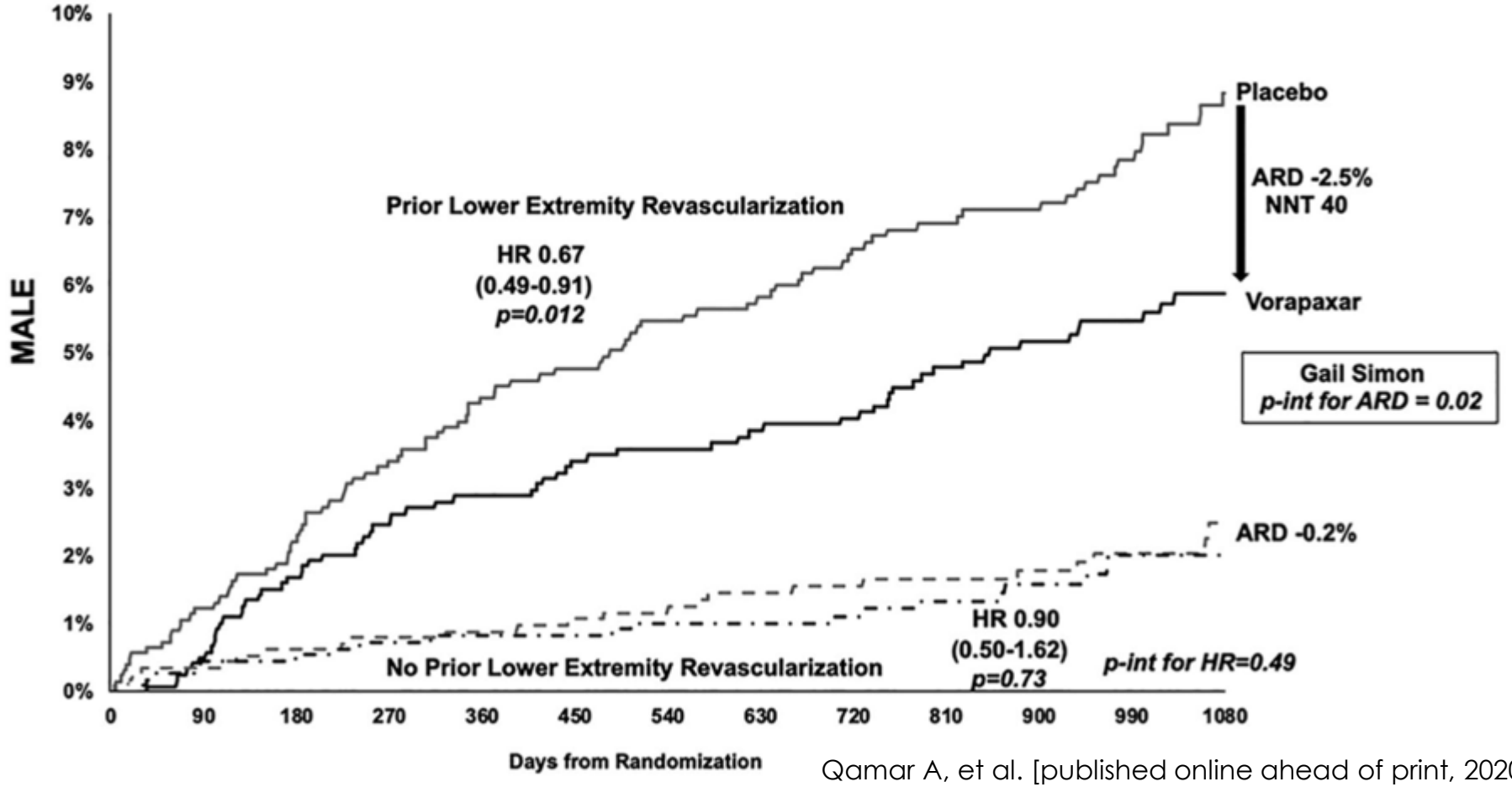
MALE reduction with vorapaxar over 3 years in overall patients with PAD with and without prior lower extremity revascularization



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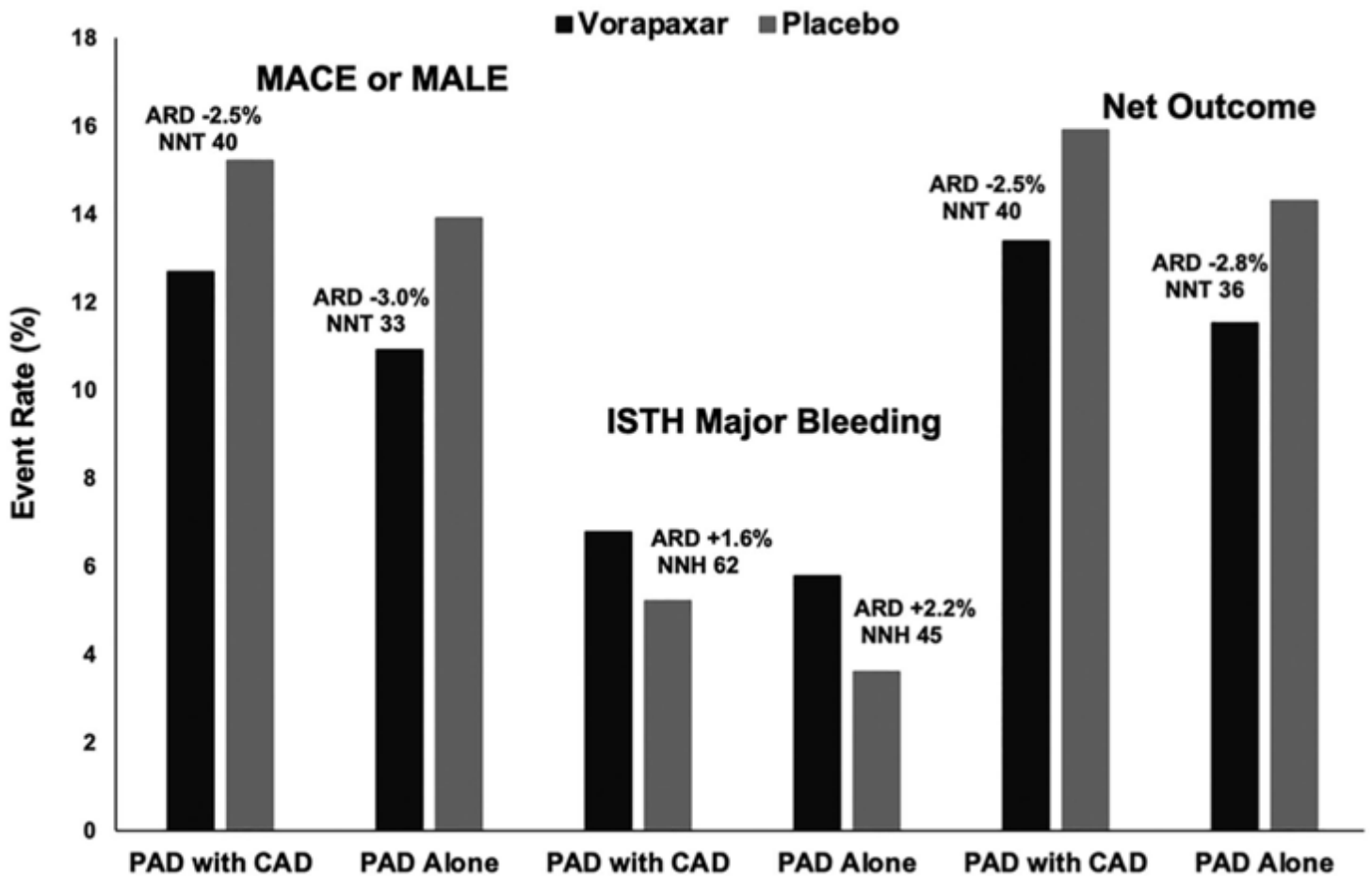

MACE or MALE, ISTH major bleeding, and net clinical outcomes in patients with PAD with CAD and in those with PAD alone

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Bleeding endpoints and net clinical outcomes in a broad population of patients with PAD

Endpoint	Vorapaxar ($n = 3062$) n (%)[a]	Placebo ($n = 3044$) n (%)[a]	HR (95% CI)	p-value
ISTH major bleeding	201 (6.6)	148 (4.9)	1.39 (1.12, 1.71)	0.003
GUSTO moderate/severe bleeding	149 (4.9)	103 (3.4)	1.47 (1.14, 1.89)	0.003
GUSTO severe bleeding	45 (1.5)	41 (1.3)	1.10 (0.72, 1.69)	0.64
Fatal bleeding/intracranial hemorrhage	20 (0.7)	18 (0.6)	1.11 (0.59, 2.11)	0.74
Fatal bleeding	6 (0.2)	8 (0.3)	0.75 (0.26, 2.16)	0.59
Intracranial hemorrhage	16 (0.5)	14 (0.5)	1.15 (0.56, 2.35)	0.71
Symptomatic bleeding into a critical organ	27 (0.9)	23 (0.8)	1.19 (0.68, 2.07)	0.55
Net clinical outcomes	**Vorapaxar ($n = 3071$) n (%)[a]**	**Placebo ($n = 3065$) n (%)[a]**	**HR (95% CI)**	**p-value**
CV death/MI/stroke/MALE/fatal bleeding/symptomatic bleeding into a critical organ	398 (13.0)	476 (15.5)	0.82 (0.72, 0.94)	0.004
All-cause death/MI/stroke/MALE/fatal bleeding/symptomatic bleeding into a critical organ	487 (15.9)	557 (18.2)	0.86 (0.76, 0.97)	0.013

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Limitations

- Exploratory analysis within a randomized trial.
- Vorapaxar is not approved for use in patients with a history of stroke due to an increased risk → findings are not generalizable to those patients
- Very few patients received potent P2Y12 inhibitors, ticagrelor, and prasugrel; thus, the efficacy and safety of vorapaxar in combination with these agents cannot be determined.

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Conclusions

- In patients with PAD, vorapaxar added to aspirin and/or clopidogrel significantly reduces the rate of MACE or MALE and increases ISTH bleeding but not fatal bleeding or intracranial hemorrhage, resulting in **overall positive net outcomes**.
- The risk of MACE and MALE in patients with PAD was **greater in patients with concomitant CAD and peripheral revascularization**, respectively.
- Patients with either of these characteristics appeared to derive a net benefit from the addition of vorapaxar, while those with neither did not appear to benefit.
- These clinical characteristics may be useful in a selection of patients who will benefit from more potent antithrombotic therapies.

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