Rivaroxaban a bassa dose in associazione ad aspirina dopo rivascolarizzazione acuta nell'arteriopatia periferica

Risultati del trial VOYAGER PAD nei pazienti anziani

Background

- More than 235 million individuals worldwide are afflicted by PAD, and age is one of the most important risk factors.
- Despite an elevated risk for major adverse limb events (MALE) and major adverse cardiovascular events (MACE), patients with PAD are less likely to be treated with antithrombotic therapy compared with their CAD counterparts.
  - Within a nationally representative outpatient population among which 25% of patients with PAD were >80 years of age, just 38% were treated with aspirin.
- One potential reason for undertreatment, despite ACC/AHA PAD secondary prevention guidelines, is concern regarding greater bleeding liability with advanced age.
- Older PAD patients have been underrepresented in earlier antithrombotic trials, and while recent evidence suggests that low-dose rivaroxaban and aspirin is beneficial in stable PAD, the benefit–risk balance in older adults acutely after percutaneous or surgical lower extremity revascularization (LER) has not been previously studied.

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Summary of clinical trials on combined anticoagulant and antiplatelet for PAD

Study	Study design	Participants	Interventions	Main findings
Johnson 2002[9]	Multicentre open label randomized controlled trial Follow-up (mean): 36.6 months (prosthetic bypass group); 39.3 months (vein bypass group)	831 patients who underwent peripheral arterial bypass surgery (including prosthetic and vein bypass). Age (mean): ~64 years Male: 99% Coronary artery disease: 24.4% Stroke: 17.3%	Combined warfarin plus aspirin vs. aspirin alone Time in therapeutic range for warfarin (target INR 1.4–2.8): not stated; however, ~40% of patients in the warfarin arm were off treatment by the end of patency observation.	No significant difference in the patency of graft except in the 6 mm bypass subgroup in which the warfarin arm had a significantly higher patency rate ($P = 0.02$). Higher mortality in the warfarin arm (risk ratio: 1.41, $P = 0.0001$). Major bleeding was higher in the warfarin arm ($P = 0.02$).
WAVE 2007[10]	Multicentre open label randomized controlled trial. Follow-up (mean): 35 months	2161 patients with PAD (81.8% had PAD of lower extremity) Age (mean): 64 years Male: 73.6% Coronary artery disease: 47.3% Stroke: 15.9%	Combined anticoagulation (warfarin/acenocoumarol) plus antiplatelet (aspirin/ticlopidine/clopidogrel) vs. antiplatelet alone Time in therapeutic range for anticoagulation (target INR 2–3): 62.0%	No significant difference between treatment arms in myocardial infarction, stroke, severe ischaemia, or death from cardiovascular causes. Life-threatening bleeding significantly higher in combination arm (relative risk: 3.41, $P < 0.001$),

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Summary of clinical trials on combined anticoagulant and antiplatelet for PAD

Study	Study design	Participants	Interventions	Main findings
Anand 2018 (subanalysis of COMPASS trial)[8]	Multicentre double-blind, double-dummy randomized controlled trial. Follow-up (median): 360 days	6391 patients with lower extremity PAD. Age (mean): 68 years Male: 72.1% Coronary artery disease: 64.9% Stroke: not stated	Rivaroxaban (5 mg twice daily) plus aspirin placebo or rivaroxaban (2.5 mg twice daily) plus aspirin vs. aspirin alone (plus rivaroxaban placebo)	Combination treatment (rivaroxaban 2.5 mg twice daily plus aspirin) reduced incidence of MALE (HR: 0.57, P = 0.01), total vascular amputation (HR: 0.42, P = 0.01), peripheral vascular intervention (HR: 0.76, P = 0.03), and all peripheral vascular outcome (HR: 0.76, P = 0.02) as compared with aspirin treatment arm. No difference in these outcomes observed between the rivaroxaban 5 mg twice daily plus placebo aspirin arm and aspirin arm. Major bleeding significantly increased in both rivaroxaban arms compared with aspirin arm (HR: 1.61, P = 0.01 and HR: 1.60, P = 0.02 for rivaroxaban 2.5 mg twice daily plus aspirin and 5 mg twice daily plus aspirin placebo arm, respectively).
Bonaca 2020 VOYAGER PAD trial[17]	Multicentre double-blind randomized controlled trial. Follow-up (median): 28 months	6564 patients with revascularization for PAD within 10 days of recruitment Age (median): 67 years Male: 74% Coronary artery disease: 31% Stroke: not stated	Rivaroxaban (2.5 mg twice daily) plus aspirin vs. aspirin plus placebo.	Rivaroxaban arm had significantly reduced incidence of primary efficacy outcome (acute limb ischaemia, major vascular amputation, myocardial infarction, ischaemic stroke, or cardiovascular death) compared with aspirin arm (HR: 0.85, P = 0.009). Rivaroxaban arm had significantly increased major bleeding defined by ISTH (HR 1.42, P = 0.007), but not by TIMI classification (HR 1.43, P = 0.07).

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VOYAGER PAD

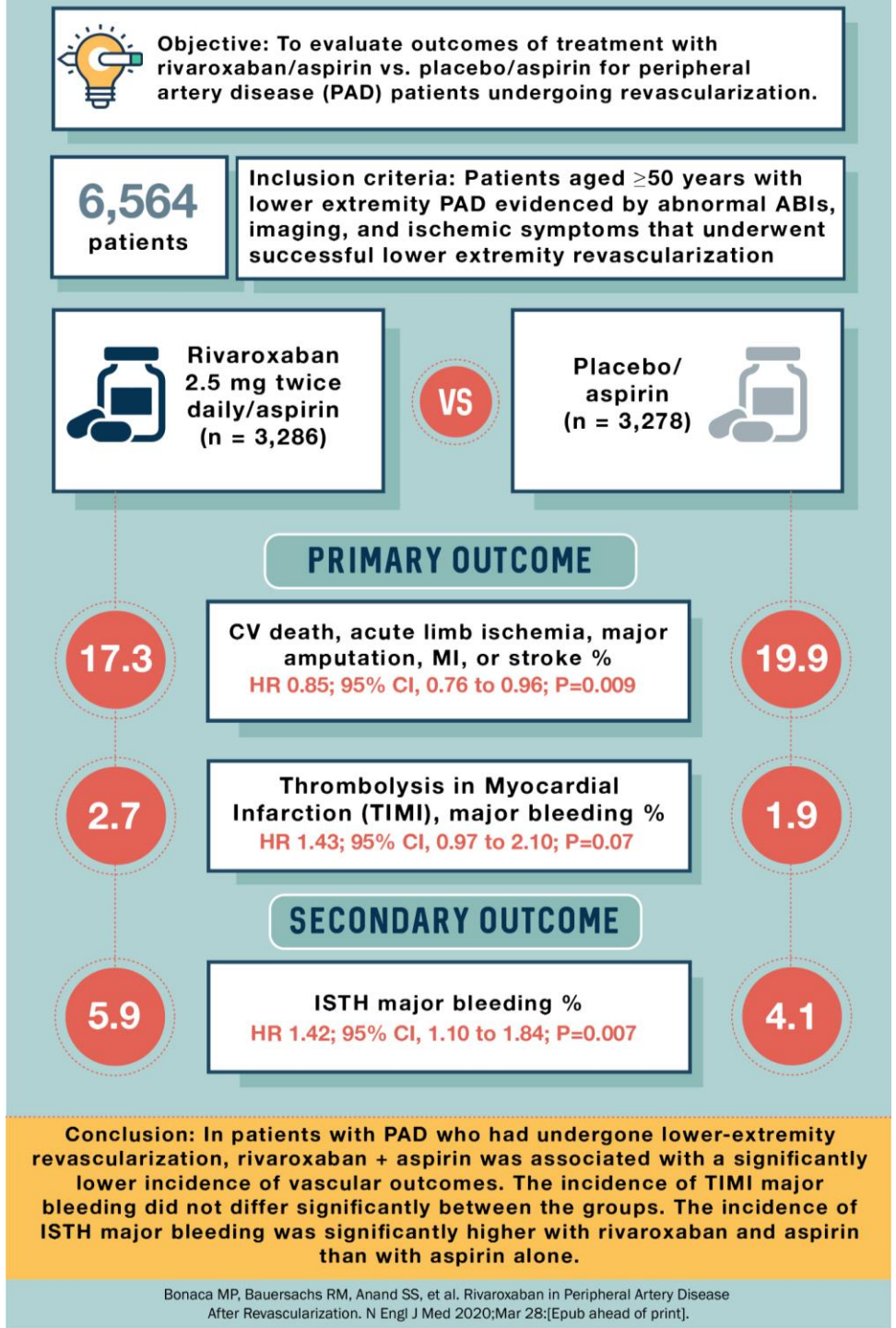
2020

VOYAGER PAD

Rivaroxaban in Peripheral Artery Disease After Revascularization

AMERICAN COLLEGE of CARDIOLOGY

Randomized, parallel, stratified clinical trial



Low-dose rivaroxaban plus aspirin in older patients with peripheral artery disease undergoing acute limb revascularization: insights from the VOYAGER PAD trial

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Methods

- The primary endpoint was a composite of acute limb ischaemia, major amputation, myocardial infarction, ischaemic stroke, or cardiovascular death.
- The principal safety outcome was thrombolysis in myocardial infarction (TIMI) major bleeding analysed by the pre-specified age cut-off of 75 years.
- Of 6564 patients randomized, 1330 (20%) were >75 years.

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Baseline characteristics	Age ≤75 years (*n* = 5234)	Age ≥75 years (*n* = 1330)	*P*-value
Age, median (IQR), years	64.0 (10.0)	78.0 (5)	<0.0001
Female sex, *n* (%)	1180 (22.54)	524 (39.40)	<0.0001
Race, no. (%)			<0.0001
White	4399 (84.05)	904 (67.97)	
Black	121 (2.31)	34 (2.56)	
Asian	601 (11.48)	365 (27.44)	
Other	56 (2.14)	27 (2.06)	
Comorbidities, *n* (%)			
Hypertension	4160 (79.48)	1182 (88.87)	<0.0001
Hyperlipidaemia	3153 (60.24)	786 (59.10)	0.4519
Current/former smoker	4413 (84.31)	797 (59.92)	<0.0001
Diabetes mellitus	2073 (39.61)	556 (41.80)	0.1496
Chronic kidney disease[a]	774 (14.79)	553 (41.58)	<0.0001
Coronary artery disease	1579 (30.17)	488 (36.69)	<0.0001
Previous myocardial infarction	569 (10.87)	145 (10.90)	0.9607
Carotid artery disease	433 (8.27)	142 (10.68)	0.0066
Body mass index, median (IQR) kg/m^2	26.22 (5.85)	24.98 (5.72)	<0.0001
eGFR, median (IQR) mL/min/1.73m^2	82.0 (30.0)	62.0 (26.6)	<0.0001
Baseline medications, no. (%)			
Statin	4248 (81.16)	1001 (75.26)	<0.0001
ACE inhibitor or ARB	3268 (62.44)	891 (66.99)	0.0022
Clopidogrel	3093 (59.09)	826 (62.11)	0.7299
Beta-receptor antagonists	2201 (42.05)	592 (44.51)	0.1065
Ankle Brachial Index, median (IQR)	0.550 (0.250)	0.560 (0.230)	0.1173
Previous amputation, *n* (%)	316 (6.04)	74 (5.56)	0.5589
Index revascularization, no. (%)			<0.0001
Endovascular	3162 (60.41)	929 (69.85)	
Hybrid	233 (4.45)	55 (4.14)	
Surgical	1839 (35.14)	346 (26.02)	
Critical limb ischaemia, *n* (%)	1162 (22.20)	371 (27.89)	<0.0001
Prior limb revascularization, *n* (%)	2049 (39.15)	512 (38.50)	0.6824

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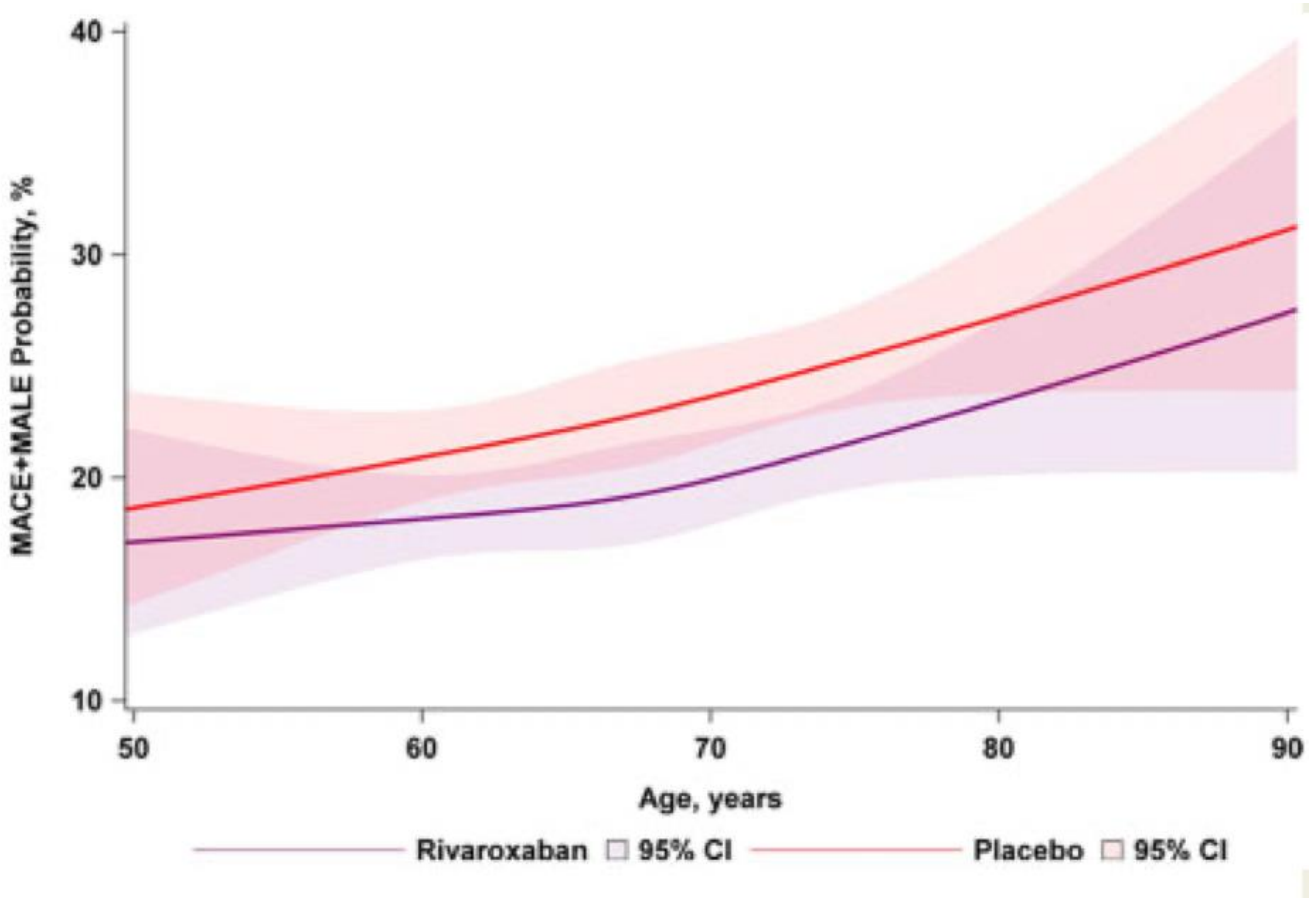
Primary efficacy event rate by age and treatment assignment

- Estimated probability of MACE or MALE through 3years, shown as a function of baseline age for each treatment group. Data are derived from a logistic regression model with a logit link function.
- P-interaction=0.92.
- Red line represents the risk probability for placebo and purple rivaroxaban.
- Shaded areas represent the 95% CI of the estimates.



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Efficacy outcomes by age strata

No interaction for the primary endpoint

Superior benefit in reduction of acute limb ischemia in >75 yrs group

	Rivaroxaban		Placebo		HR (95% CI)	*P*-value	*P*-int.
	n (%)	KM 3 years	*n* (%)	KM 3 years			
Primary efficacy outcome							0.8314
<75 *N* = 5234	391 (14.96)	16.73	446 (17.02)	19.02	0.86 (0.75–0.98)	0.0265	
≥75 *N* = 1330	117 (17.38)	19.64	138 (21.00)	23.44	0.82 (0.64–1.05)	0.058	
Acute limb ischaemia							0.0193[a]
<75	141 (5.40)	5.94	186 (7.10)	7.93	0.74 (0.60–0.93)	0.0076	
≥75	14 (2.08)	2.43	41 (6.24)	7.01	0.35 (0.19–0.64)	0.0004	
Major amputation							0.1724
<75	88 (3.37)	3.61	89 (3.40)	3.74	0.97 (0.73–1.31)	0.8625	
≥75	15 (2.23)	2.67	26 (3.96)	4.43	0.58 (0.31–1.10)	0.0907	
Myocardial infarction							0.2131
<75	91 (3.48)	4.05	113 (4.31)	5.04	0.80 (0.61–1.06)	0.1203	
≥75	40 (5.94)	6.49	35 (5.33)	5.95	1.10 (0.70–1.74)	0.6767	
Ischaemic stroke							0.6142
<75	55 (2.10)	2.52	61 (2.33)	2.81	0.91 (0.63–1.31)	0.5991	
≥75	16 (2.38)	3.44	21 (3.20)	3.84	0.74 (0.38–1.42)	0.3605	
Cardiovascular death							0.8656
<75	134 (5.13)	6.09	116 (4.43)	5.48	1.15 (0.90–1.48)	0.2548	
≥75	65 (9.66)	10.92	58 (8.83)	10.32	1.11 (0.77–1.58)	0.5798	

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Efficacy outcomes by age strata

No interaction for the secondary endpoint

	Rivaroxaban		Placebo		HR (95% CI)	*P*-value	*P*-int.
	n (%)	KM 3 years	*n* (%)	KM 3 years			
Secondary outcomes							
Acute limb ischaemia, major amputation, MI, ischaemic stroke, or CHD death							
<75	339 (12.97)	14.43	405 (15.45)	17.44	0.82 (0.71–0.95)	0.0068	
≥75	94 (13.97)	15.63	123 (18.72)	21.24	0.74 (0.57–0.97)	0.0310	0.5825
Unplanned index limb revascularization for recurrent limb ischaemia							
<75	479 (18.33)	20.58	544 (20.76)	23.30	0.87 (0.77–0.99)	0.0301	
≥75	105 (15.60)	17.73	111 (16.89)	19.31	0.93 (0.71–1.22)	0.6007	0.6736
Hospitalization for a thrombotic coronary or peripheral event							
<75	218 (8.34)	9.10	288 (10.99)	12.21	0.74 (0.62–0.88)	0.0008	
≥75	44 (6.54)	7.01	68 (10.35)	11.48	0.64 (0.44–0.94)	0.0211	0.5089
Acute limb ischaemia, major amputation, MI, ischaemic stroke, or all-cause mortality							
<75	465 (17.80)	19.55	512 (19.53)	21.74	0.89 (0.78–1.01)	0.0624	
≥75	149 (22.14)	24.85	167 (25.42)	29.06	0.86 (0.69–1.08)	0.1892	0.8953
All-cause mortality							
<75	221 (8.46)	9.64	198 (7.55)	9.18	1.12 (0.92–1.35)	0.2652	
≥75	100 (14.86)	16.66	99 (15.07)	17.88	0.99 (0.75–1.31)	0.9617	0.5379
Venous thrombo-embolism							
<75	18 (0.69)	0.75	29 (1.11)	1.52	0.63 (0.35–1.13)	0.1163	
≥75	7 (1.04)	0.88	12 (1.83)	2.26	0.63 (0.25–1.59)	0.3214	0.8910

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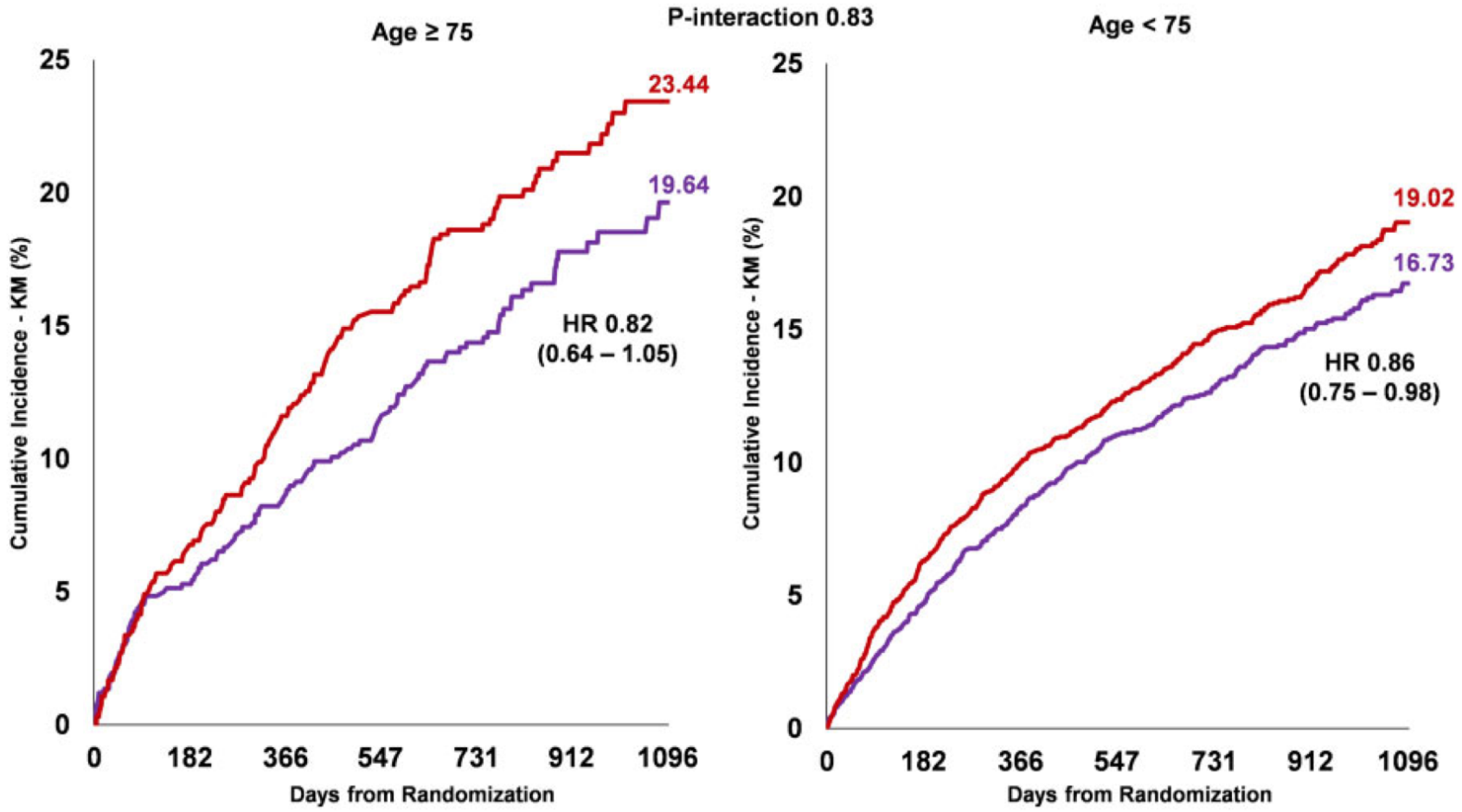
Primary efficacy outcome by age and treatment

The Kaplan–Meier cumulative incidence rates over 3 years in patients >75 years (left panel) and in those <75 years (right panel) stratified by treatment allocation (red = placebo, purple = rivaroxaban) were consistent (P-value for interaction = 0.83).



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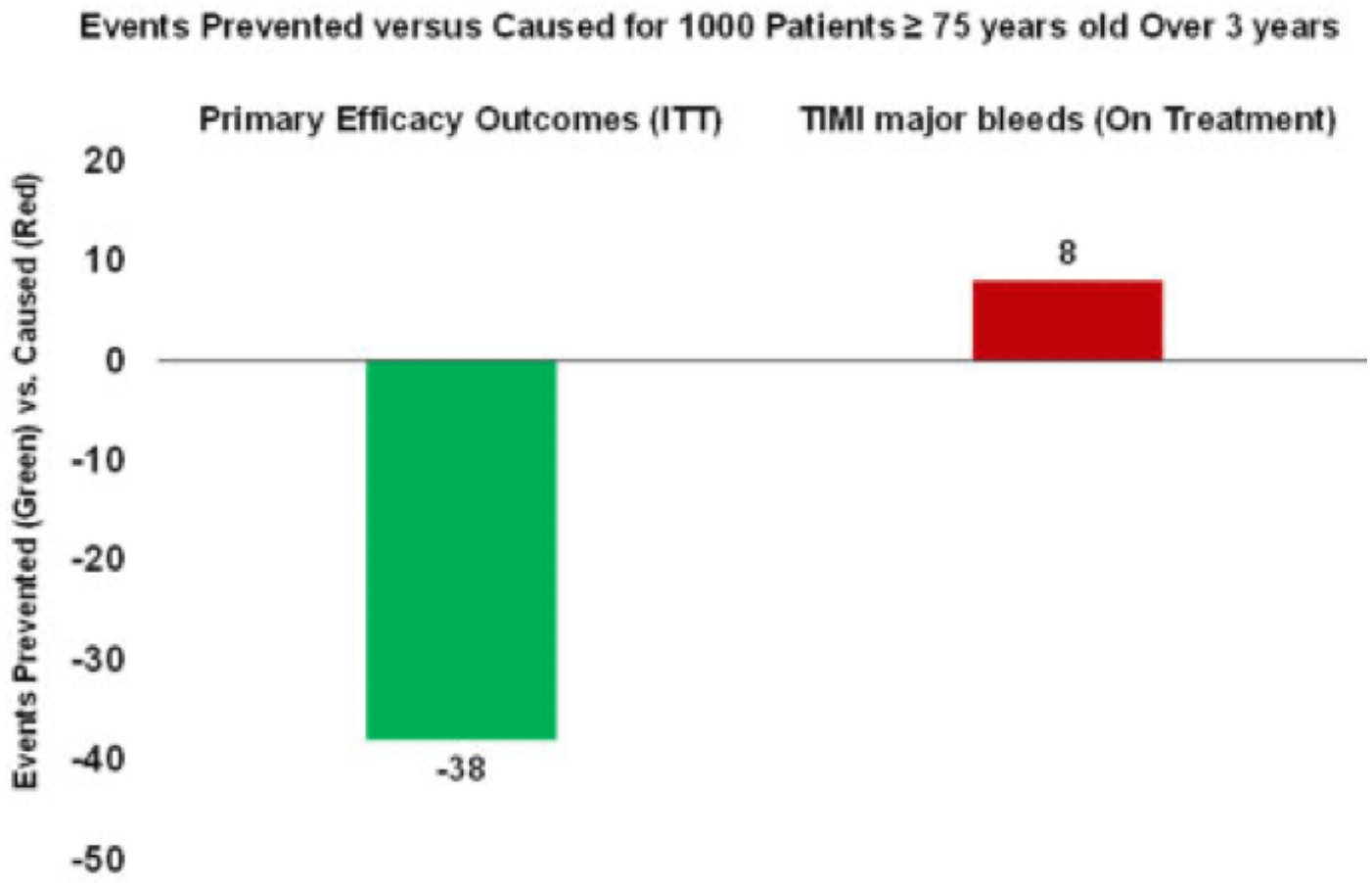
Safety outcomes by age strata

No interaction for the safety endpoint

	Rivaroxaban		Placebo		HR (95% CI)	*P*-value	*P*-int.
	n (%)	KM 3 years	*n* (%)	KM 3 years			
TIMI major bleeding							0.3807
<75 *N* = 5193	46 (1.77)	2.31	29 (1.12)	1.50	1.60 (1.01, 2.55)	0.0444	
≥75 *N* = 1311	16 (2.42)	4.31	15 (2.31)	3.50	1.11 (0.55, 2.26)	0.7632	
Fatal bleeding							
<75	6 (0.23)	0.26	5 (0.19)	0.23	1.21 (0.37, 3.98)	—	
≥75	0 (0.00)	0.00	1 (0.15)	0.16	—	—	
Intracranial haemorrhage							—
<75	11 (0.42)	0.62	10 (0.38)	0.61	1.13 (0.48, 2.67)	—	
≥75	2 (0.30)	0.54	7 (1.08)	2.26	0.29 (0.06, 1.38)	—	
Fatal bleeding or intracranial haemorrhage							0.0536
<75	15 (0.58)	0.79	11 (0.42)	0.65	1.40 (0.64, 3.04)	0.3994	
≥75	2 (0.30)	0.54	8 (1.23)	2.41	0.25 (0.05, 1.20)	0.0616	
Secondary bleeding outcomes							
TIMI minor							0.1632
<75	34 (1.31)	1.54	18 (0.69)	0.91	1.90 (1.07, 3.36)	0.0252	
≥75	12 (1.82)	3.82	13 (2.00)	2.25	0.93 (0.43, 2.05)	0.8653	
BARC 3b and above							0.1614
<75	72 (2.77)	3.56	49 (1.89)	2.45	1.49 (1.04, 2.14)	0.0299	
≥75	21 (3.18)	5.35	24 (3.69)	4.95	0.92 (0.51, 1.65)	0.7773	
ISTH major							0.4387
<75	102 (3.93)	5.10	68 (2.62)	3.42	1.52 (1.12, 2.07)	0.0068	
≥75	38 (5.75)	9.94	32 (4.92)	6.83	1.22 (0.76, 1.96)	0.4016	

Ischaemic events prevented vs. bleeding caused by rivaroxaban in patients >75 years

Primary efficacy outcomes prevented with rivaroxaban vs. placebo (green bar) using the intention-to-treat (ITT) absolute risk difference at 3 years vs. the principal safety outcomes caused with rivaroxaban (red) bar using on-treatment absolute risk difference at 3 years in patients >75 years.



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Limitations

- No statistically significant reduction in all-cause or cardiovascular mortality, given limited patient numbers and a median follow-up of 28 months.
- Comparative results with the COMPASS trial although remarkably consistent are limited by an incomplete understanding of the anatomic and physiologic differences in elderly vascular disease patients that are stable vs. those more acutely requiring revascularization.
- Although power to demonstrate statistical significance with a P-value <0.05 is generally limited in any subgroup analysis of a trial, the current analysis included over 250 primary outcome events in over 1300 patients in the subgroup of interest (>75) and showed no evidence of heterogeneity for treatment by age (P-interaction 0.83).

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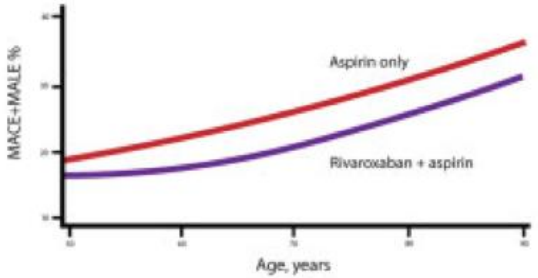
Impact of combination therapy for older PAD patients after limb revascularization

Risk factors in age ≥ 75

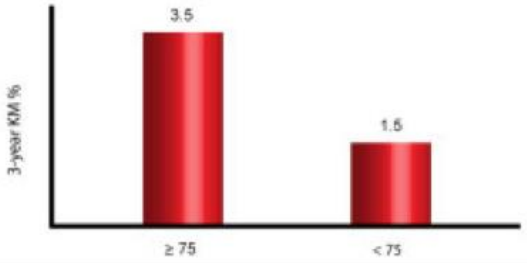
Risk factors:

Hypertension	89%
Smoker	60%
Diabetes	42%
Chronic Kidney Disease	42%

Ischaemic events by age*



Major bleeding events by age^



* logistic regression with follow-up and time as an offset variable, age as a spline effect, and age, treatment group, and interaction between age and treatment group as predictors. Ischaemic events = MACE + MALE.

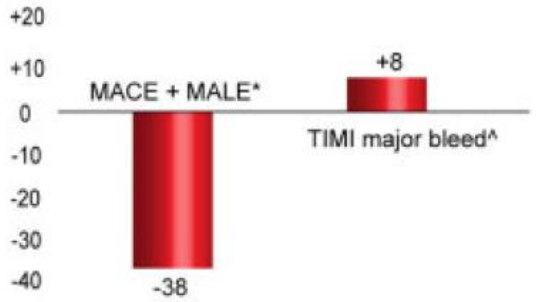
^ Aspirin only population

Rivaroxaban 2.5 mg bid + ASA vs. ASA only (age ≥ 75)

Endpoint	HR (95% CI)
Primary efficacy	0.82 (0.64, 1.05)
ALI	**0.35 (0.19, 0.64)**
Amputation	0.58 (0.31, 1.10)
MI	1.10 (0.70, 1.74)
Stroke	0.74 (0.38, 1.42)
CV death	1.11 (0.77, 1.58)

Benefit-risk profile

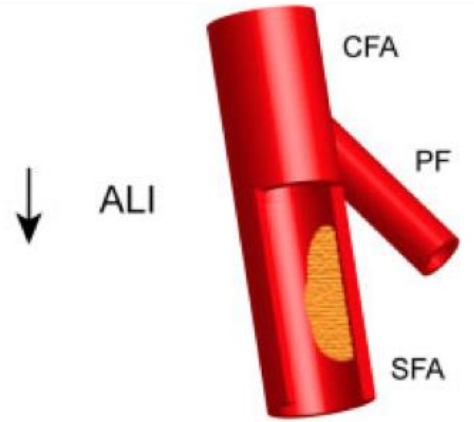
1,000 patients treated over 3 years



ALI = acute limb ischaemia
MI = myocardial infarction
MACE = MI, ischaemic stroke, CV death
MALE = ALI, major vascular amputation

*intention to treat population
^on treatment population

Clinical implications for older PAD patients



↓ ALI

↓ Amputation

↓ Disability

Unmet need to reduce limb risk in older patients after lower extremity revascularization

CFA = Common femoral artery, PF = Profunda femoris, SFA = Superficial femoral artery