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FASTTRACK CLINICAL RESEARCH
Thrombosis and antithrombotic treatment

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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See page 4049 for the editorial comment for this article 'Low-dose rivaroxaban plus aspirin for elderly patients with symptomatic peripheral artery disease: is it worth the bleeding risk?', by J. Zhang, *et al.*, https://doi.org/10.1093/eurheartj/ehab602.

Aims In this secondary analysis of the VOYAGER trial, rivaroxaban 2.5 mg twice/day plus aspirin 100 mg/day was assessed in older adults. Advanced age is associated with elevated bleeding risk and unfavourable net benefit for dual antiplatelet therapy in chronic coronary artery disease. The risk–benefit of low-dose rivaroxaban in patients ≥75 years with peripheral artery disease (PAD) after lower extremity revascularization (LER) has not been described.

Methods and results 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. Absolute 3-year Kaplan–Meier cumulative incidence rates for primary efficacy (23.4% vs. 19.0%) and safety (3.5% vs. 1.5%) endpoints were higher in elderly vs. non-elderly patients. Efficacy of rivaroxaban (*P*-interaction 0.83) and safety (*P*-interaction 0.38) was consistent irrespective of age. The combination of intracranial and fatal bleeding was not increased in patients >75 years (2 rivaroxaban vs. 8 placebo). Overall, benefits (absolute risk reduction 3.8%, number needed to treat 26 for the primary endpoint) exceeded risks (absolute risk increase 0.81%, number needed to harm 123 for TIMI major bleeding).

Conclusion Patients ≥75 years with PAD are at both heightened ischaemic and bleeding risk after LER. No excess harm with respect to major, intracranial or fatal bleeding was seen in older patients yet numerically greater absolute benefits were observed. This suggests that low-dose rivaroxaban combined with aspirin should be considered in PAD after LER regardless of age.

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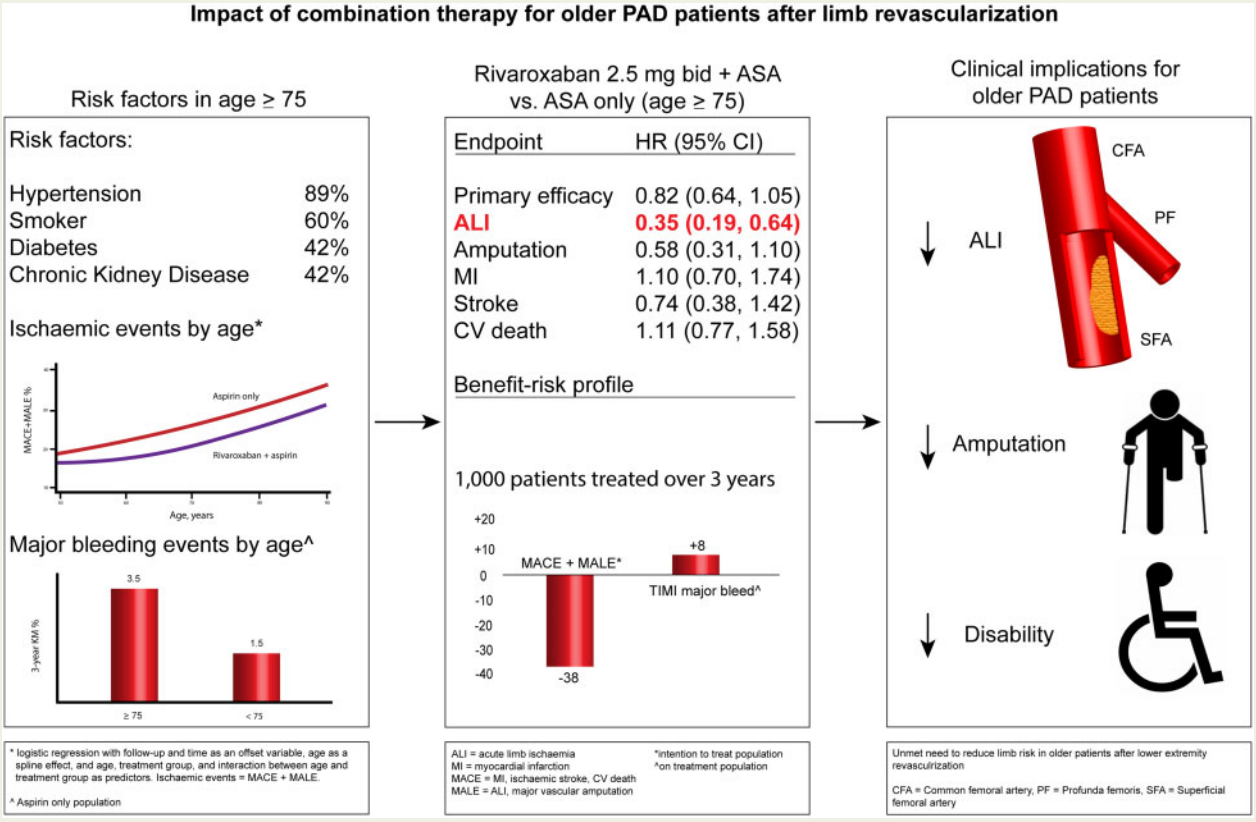
Graphical Abstract



The impact of combination therapy for older patients with symptomatic peripheral artery disease after lower extremity revascularization. ALI, acute limb ischaemia; CV Death, cardiovascular death; MACE, major adverse cardiovascular events; MALE, major adverse limb events; MI, myocardial infarction; PAD, peripheral artery disease; TIMI, thrombolysis in myocardial infarction.

Keywords Peripheral arterial disease • Antithrombotic • Novel oral anticoagulant • Elderly • Acute limb ischaemia • Major adverse limb events

Introduction

Peripheral artery disease (PAD) is a progressive atherosclerotic disorder; it can be asymptomatic, but often results in profound functional limitation, acute limb-threatening ischaemia, and amputation.[1] More than 235 million individuals worldwide are afflicted, and age is one of the most important risk factors for PAD.[1,2] 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 coronary artery disease (CAD) counterparts.[3] Within a nationally representative outpatient population among which 25% of patients with PAD were ≥80 years of age, just 38% were treated with aspirin.[4] One potential reason for undertreatment, despite American College of Cardiology/American Heart Association (ACC/AHA) PAD secondary prevention guidelines,[5] is concern regarding greater bleeding liability with advanced age. Quantification of bleeding risk by cardiologists, however, is poor and bleeding scores such as ACUITY and CRUSADE add little to enhance risk prediction.[6] Moreover, while 90% of patients overestimate bleeding risk from antithrombotic therapy,[7] physicians also overestimate risk and hesitate to initiate anticoagulation.[8,9] Clinical uncertainty regarding benefit–risk balance is reinforced by bleeding scores such as ACUITY, CRUSADE, DAPT, and PRECISE-DAPT, which emphasize advanced age as a negative consideration for the initiation of antithrombotic agents for secondary prevention in patients with atherosclerosis.[6,10]

Older PAD patients have been under-represented in earlier antithrombotic trials,[11] and while recent evidence suggests that low-dose rivaroxaban and aspirin is beneficial in stable PAD,[12] the benefit–risk balance in older adults acutely after percutaneous or surgical lower extremity revascularization (LER) has not been previously studied. Given this background, the present study sought to address uncertainty regarding the use of combination antithrombotic therapy for patients ≥75 years. We ascertained efficacy and safety within the Vascular

Outcomes Study of Aspirin Along with Rivaroxaban in Endovascular or Surgical Revascularization (VOYAGER) PAD study, which encompasses a large, contemporary population of older individuals.[13]

Methods

Study design and patient population

VOYAGER PAD was a randomized, double-blind, placebo-controlled trial, which tested the hypothesis that low-dose rivaroxaban in addition to an antiplatelet agent would reduce ischaemic limb and cardiovascular events among PAD patients undergoing revascularization. The trial design and primary results have been previously published.[13,14] Specifically, the addition of a selective, direct factor Xa inhibitor (rivaroxaban 2.5 mg twice daily) plus acetylsalicylic acid (aspirin 100 mg daily) was compared with aspirin monotherapy. Computerized randomization was performed centrally, stratified according to index LER procedure (endovascular vs. surgical) and by clopidogrel use/non-use within patients who underwent an endovascular procedure. Study participant randomization was not stratified by age.

In VOYAGER, enrolled subjects had moderate to severe symptomatic lower extremity atherosclerotic PAD as evidenced by functional limitations, ischaemic rest pain, or ischaemic ulceration with corresponding imaging evidence of disease distal to the external iliac artery. Patients were required to have undergone an infra-inguinal, peripheral revascularization procedure within 10 days prior to randomization. Patients ≥50 years of age were included, without an upper age limit cut-off. Key exclusion criteria included recent acute limb ischaemia (ALI) or acute coronary syndrome, any medical condition that could increase the risk of major bleeding, documented history of intracranial haemorrhage, stroke, or transient ischaemic attack or severely impaired renal function at baseline screening defined as an estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2 or the receipt of chronic renal replacement therapy. We sought to assess differences in both ischaemic and bleeding outcomes with combined antithrombotic therapy according to categorical age thresholds. Older age was prespecified as ≥75 years prior to closure of the database, analogous to the highest age strata specified in the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial.[12]

Efficacy and safety outcomes

The primary efficacy outcome was the composite of ALI, major amputation of a vascular aetiology, myocardial infarction (MI), ischaemic stroke, or cardiovascular death including unknown and sudden death. The individual components of the efficacy composite were also assessed. Secondary efficacy endpoints included unplanned hospitalization for a coronary or peripheral vascular event of a thrombotic nature and unplanned revascularization for ischaemia in the index limb. The principal safety outcome was thrombolysis in myocardial infarction (TIMI) classification major bleeding. Secondary safety endpoints included TIMI minor bleeding, International Society on Thrombosis and Haemostasis (ISTH) major bleeding and Bleeding Academic Research Consortium (BARC) 3b or higher bleeding events. All efficacy and safety events were adjudicated centrally.[14]

Statistical analysis

Efficacy analyses were conducted on all randomized patients using the principle of intention-to-treat (ITT). Safety analyses were conducted as on-treatment, which included all individuals who received at least one dose of study drug and followed for 2 days after the last receipt of active treatment to approximate 5 half-lives of oral rivaroxaban. Event probabilities were expressed as Kaplan–Meier (KM) estimates of the cumulative incidence of each pre-specified outcome at 3 years. Hazard ratios with 95% confidence interval (CI) were then generated by stratified Cox proportional hazards modelling and all reported *P*-values were two-sided, with a *P*-value of <0.05 considered statistically significant. Interaction *P*-values were generated for efficacy and safety results, evaluating differences between the subgroups of age <75 years vs. ≥75 years. All *P*-values were based on the Monte Carlo Estimate for the Wilcoxon exact test for continuous variables and on either Fisher's exact test or the Monte Carlo estimate for the Freeman–Halton exact test for categorical variables.

The probability of the primary outcome of MALE plus MACE as a function of age as a spline effect of degree 3 (piecewise cubic curve) was estimated for each treatment group by logistic regression, with a logit link function and the logarithm of follow-up time utilized as an offset variable in the models. Absolute risk reduction (ARR), absolute risk increase (ARI) and number needed to treat (NNT) and number needed to harm (NNH) were calculated to assess the benefit–risk balance of low-dose rivaroxaban. Events prevented vs. caused were calculated using ITT analyses for efficacy and on-treatment for evaluating safety. All analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC, USA).

Results

Patient population

Overall, 1330 (20%) of the 6564 patients included in VOYAGER PAD were ≥75 years old at randomization. The age range in those ≥75 was 75–95 years old. Patients ≥75 years had a significantly greater prevalence of cardiovascular disease risk factors including hypertension and chronic kidney disease (*Table 1*). Notably, the median eGFR was much lower in the elderly population (62.0 vs. 82.0 mL/min/1.73 m^2). Cardiovascular medication use was relatively balanced regarding clopidogrel, beta-receptor antagonists, and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, but the proportion receiving 3-hydroxy-3-methylglutaryl-CoA reductase (statins) was lower among older vs. younger patients (75% vs. 81%).

Ischaemic and bleeding risk by age

There was a roughly linear relationship between age and the risk of the primary efficacy outcome in both treatment arms (*Figure 1*). Patients ≥75 years vs. <75 years who were randomized to placebo (aspirin ± clopidogrel) had a significantly higher risk of the primary efficacy outcome (3-year KM rate 23.44% vs. 19.02%) with almost 1 in 4 patients having a first event over that time period. In the older vs. younger group, the KM estimates for ALI (7.01% vs. 6.24%), major amputation (4.43% vs. 3.74%), MI (5.95% vs. 5.04%), and ischaemic stroke (3.84% vs. 2.81%) were significantly higher; and the risk of cardiovascular death (10.32% vs. 5.48%) was nearly doubled compared with the younger patient population in the aspirin treatment arm. In addition, rates of bleeding were significantly higher and more than doubled in placebo patients ≥75 vs. <75 years. This included TIMI major bleeding (3.50% vs. 1.50%), intracranial bleeding (2.26% vs. 0.61%), BARC 3b and above bleeding (4.95% vs. 2.45%), and ISTH major bleeding (6.83% vs. 3.42%).

Efficacy and safety of rivaroxaban

Composite and individual efficacy outcomes by age strata are illustrated in *Table 2*. The primary efficacy outcome of ALI, major

Table 1 Baseline demographic and clinical characteristics by age strata

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

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate.
[a]Defined as GFR <60 mL/min/1.73 m^2.

amputation of a vascular aetiology, MI, ischaemic stroke, or CV death was reduced by rivaroxaban consistently among patients ≥75 years [hazard ratio (HR) 0.82, 95% CI 0.64, 1.05, *P* = 0.058], and those aged <75 years (HR 0.86, 95% CI 0.75, 0.98, *P* for interaction 0.83) (*Figures 1 and 2*). The benefit of rivaroxaban in patients ≥75 was primarily driven by reductions in limb vascular events including ALI (HR 0.35, 95% CI 0.19–0.64, *P* = 0.0004) and the occurrence of major amputation of vascular aetiology (HR 0.58, 95% CI 0.31–1.10, *P* = 0.09, *Table 2*). Overall, there was consistency for the effect of rivaroxaban amongst the components of the primary efficacy outcome with the exception of ALI, where the benefit appeared to be even greater in those ≥75 years relative to those <75 years (HR 0.74, 95% CI 0.60–0.93, *P*-interaction 0.0193). Overall, rivaroxaban reduced the first five of the pre-specified secondary outcomes and there was no statistical heterogeneity in treatment effect in those ≥75 vs. <75 years (*Table 2*). Among these outcomes, the composite of ALI, major amputation of a vascular aetiology, MI, ischaemic stroke, or coronary heart disease death (HR 0.74, 95% CI 0.57–0.97) and hospitalization for a coronary or peripheral event of a thrombotic nature (HR 0.64, 95% CI 0.44–0.94, *P* = 0.0211) were significantly reduced in those ≥75 years old.

Safety outcomes by age category are shown in *Table 3*. Rivaroxaban increased TIMI major bleeding overall with consistent results regardless of age group (≥75 years: HR 1.11, 95% CI 0.55–2.26; <75 years: HR 1.60, 95% CI 1.01–2.55, *P*-interaction 0.38). There was no heterogeneity for rates of intracranial haemorrhage or fatal bleeding; however, the incidence was low and in those ≥75, there were numerically fewer in the rivaroxaban group (two with rivaroxaban, eight with placebo). Secondary bleeding outcomes including ISTH major and BARC 3b or greater events showed the same relationship with a consistent pattern of excess risk with rivaroxaban regardless of age (*Table 3*). Among those ≥75 years of age on

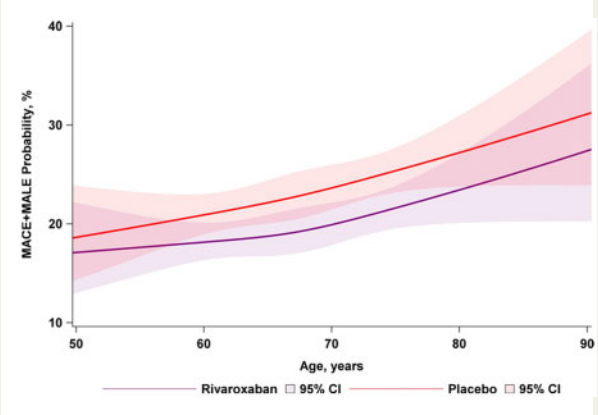


Figure 1 Primary efficacy event rate by age and treatment assignment. Estimated probability of major adverse cardiac events (MACE) or major adverse limb events (MALE) through 3 years, shown as a function of baseline age for each treatment group. Data are derived from a logistic regression model with a logit link function. Interaction *P*-value of treatment and spline for age (*P*-interaction) was 0.92. The red line represents the risk probability for placebo and purple rivaroxaban. Shaded areas represent the 95% confidence intervals (CI) of the estimates.

clopidogrel at baseline, there were 10 TIMI major bleeding events out of 349 patients in the rivaroxaban group balanced with 10 out of 343 patients in the placebo group.

Benefit–risk balance

Overall, in VOYAGER PAD, there was a favourable benefit–risk profile when considering the number of primary efficacy outcomes prevented vs. the number of principal safety outcomes caused. In the current analysis, due to their higher overall risk of the primary outcome, patients ≥75 had a greater ARR in the ITT analysis (3.8% ARR in those ≥75 vs. 2.5% ARR <75 years) resulting in a more favourable NNT of 26 vs. 41 in those age categories, respectively. The cost of this, when considering the on-treatment safety analysis, was an ARI in those ≥75 for TIMI major bleeding of 0.81% translating to an NNH of 123 individuals. In addition, there was no pattern for increased intracranial haemorrhage or fatal bleeding in those ≥75 and numerically fewer with rivaroxaban vs. placebo in the on-treatment analysis. When considering 1000 PAD patients after LER followed for 3 years with rivaroxaban add-on therapy, 38 events (predominantly ALI and major amputation) would be prevented at the cost of 8 TIMI major bleeds but no intracranial haemorrhage or fatal bleeding events (*Figure 3*).

Discussion

The current study demonstrates several noteworthy observations. First, the risk of the composite outcome of ALI, major amputation of a vascular aetiology, MI, ischaemic stroke, or cardiovascular death in PAD patients after LER is higher in those ≥75 vs. <75 years old. Second, although the risk of cardiovascular and limb outcomes was globally higher in those ≥75 years, ALI remained significantly more frequent than MI or stroke, where the benefit of rivaroxaban was primarily driven by reductions in ALI and amputation. Third, the benefit of rivaroxaban in this population was consistent regardless of age; however, due to the higher risk profile of patients ≥75, this population had a larger absolute benefit and lower NNT driven by an even greater benefit for ALI. In fact, there was a significant interaction indicating the possibility for an even greater benefit in those ≥75 vs. <75 years. Finally, although patients ≥75 are generally at higher bleeding risk, there was no pattern for excess bleeding with rivaroxaban in those ≥75 and numerically fewer severe bleeding events such as intracranial or fatal haemorrhage (*Graphical abstract*). In addition, female sex was more prevalent in PAD patients who were ≥75 at randomization, which is a population of special interest where hesitancy prescribing antithrombotic therapy may also exist and where sex-based differences in outcomes have been described.[15] Moreover, the elderly subgroup included a higher proportion of Asian patients, which supports the generalizability of our findings. Taken together, these data underscore the high limb risk among patients ≥75 with PAD undergoing LER and that the net benefit of rivaroxaban remains favourable in this diverse, elderly population.

Our findings that advanced age is associated with a higher risk for MALE and MACE events, which can be reduced by rivaroxaban on top of aspirin, has also been demonstrated in the COMPASS trial.[12] This study evaluated patients with stable atherosclerotic vascular disease that had not required a recent LER procedure. In contrast to VOYAGER PAD, 90.6% of the participants in COMPASS had CAD, while just 27.3% had PAD. Nonetheless, in COMPASS, combination therapy was effective in reducing major limb complications across all age strata including those ≥75 years, consistent with the current study. From a public health perspective, the higher observed rates of MALE and MACE in older adults is particularly important since hospitalization and the inherent activity restriction is associated with substantial disability among older patients in the USA.[16]

The benefit–risk profile of a low-dose anticoagulation-aspirin strategy in older adults with PAD after LER appears very favourable. The efficacy of this combination of an antiplatelet drug and an agent targeting thrombin is further supported by the findings with vorapaxar, a novel antagonist of platelet receptor for thrombin, which showed reductions in MALE and MACE across age strata including those ≥75 years.[17] However, comparative efficacy relative to the often-prescribed dual antiplatelet therapy (DAPT) regimen has not been characterized in head-to-head clinical trials. Dual antiplatelet therapy is commonly utilized after percutaneous peripheral arterial revascularization analogous to its use after percutaneous coronary intervention, though it currently is not an AHA/ACC class Ia guideline recommendation in PAD patients.[5] Moreover, DAPT possesses a distinct bleeding liability, particularly in the elderly. For example, in patients with stable CAD, the combination of the $P2Y_{12}$ inhibitor ticagrelor plus aspirin minimally reduced the incidence of cardiovascular events, yet TIMI major bleeding was significantly increased.[18] In contrast, in VOYAGER, rivaroxaban was efficacious in those ≥75, but without a disproportionate major bleeding signal and no increase in fatal or intracranial haemorrhage. Taken together, these data support a dual pathway approach in high-risk patients regardless of age. A paradigm of low-dose anticoagulation combined with a low dose/low potency antiplatelet drug may provide an optimal benefit–risk balance in older PAD patients after LER. Accordingly, an index limb

Table 2 Efficacy outcomes by age strata

	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	
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

CHD, coronary heart disease; HR, hazard ratio; KM, Kaplan–Meier; MI, myocardial infarction; *P*-int, *P*-interaction.
[a]Significant *P*-interaction.

revascularization procedure could serve as a clinical trigger to initiate rivaroxaban. This strategy is foundational to the AHA Get With The Guidelines (GWTG) programme, where inpatient initiation of guideline-directed medical therapies is the strongest predictor of long-term adherence and improved outcomes.[19]

Notable and novel in the current analysis is the marked reduction in ischaemic limb events and major amputations. This is a potentially critical finding since the occurrence of major limb events has substantial downstream implications for event-free survival. In support of this, a recent analysis from COMPASS found that the development of MALE is associated with a dire prognosis.[20] The index limb event in COMPASS, modelled as a time-dependent covariate in a Cox proportional hazards model, resulted in a staggering risk of total vascular amputation (HR 197.5, 95% CI, 97.33–400.8), cardiovascular hospitalization (HR 11.72, 95% CI 9.04–15.21), and all-cause mortality (HR 3.23, 95% CI 1.87–5.56). Similar findings were observed within a national, hospital database where among 393,017 revascularized patients, 12.9% experienced MALE after just 2.7 years of follow-up.[21] This underscores the substantial unmet need for safe and effective secondary prevention therapies in patients with PAD be it stable disease as studied in COMPASS or unstable, symptomatic PAD requiring revascularization in VOYAGER. The observed benefits also

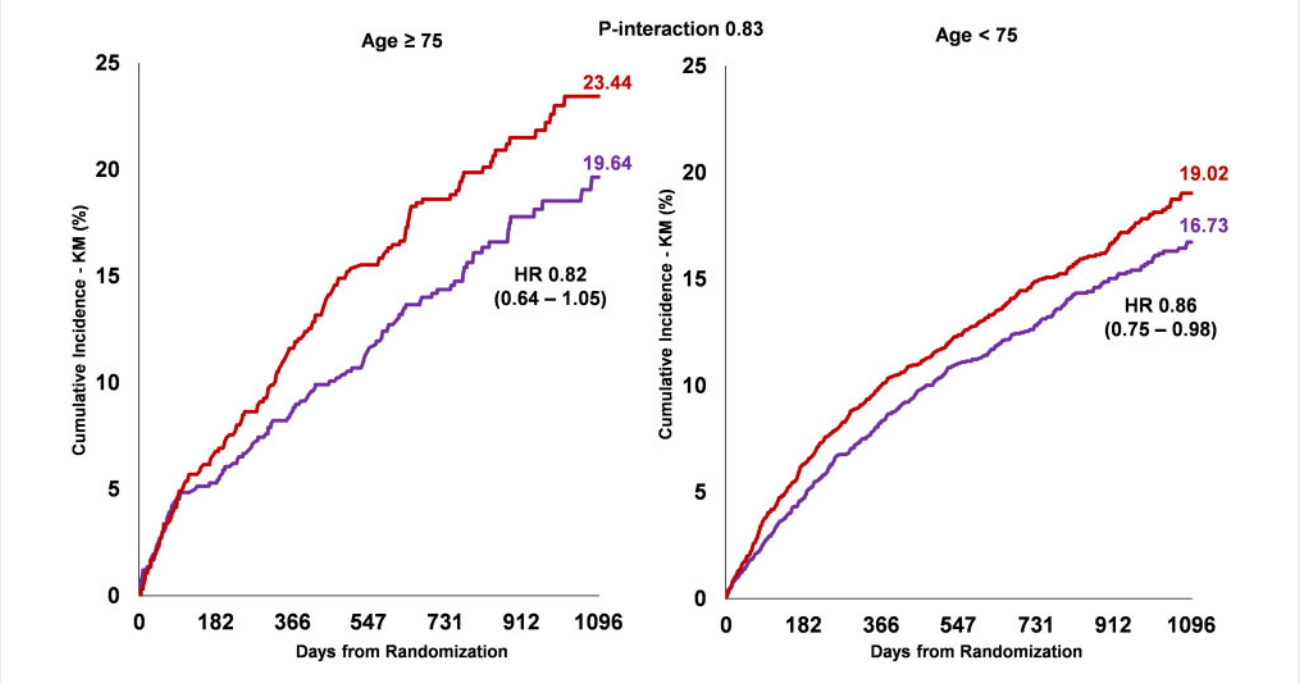


Figure 2 Primary efficacy outcome by age and treatment. The Kaplan–Meier (KM) cumulative incidence rates over 3 years in patients ≥75 years (left panel) and in those <75 years (right panel) stratified by treatment allocation (red = placebo, purple = rivaroxaban) were consistent (*P*-value for interaction = 0.83).

Table 3 Safety outcomes by age strata

	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	

BARC, Bleeding Academic Research Consortium; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis; KM, Kaplan–Meier; *P*-int, *P*-interaction.

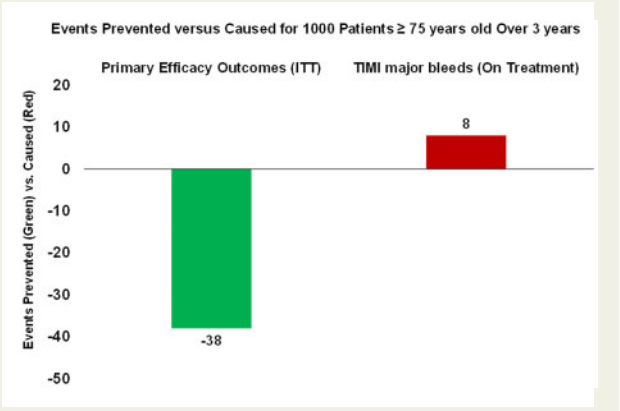


Figure 3 Ischaemic events prevented vs. bleeding caused by rivaroxaban in patients ≥75 years. Primary efficacy outcomes prevented with rivaroxaban vs. placebo (green bar) using the intention-to-treat (ITT) absolute risk difference at 3 years vs. the principal safety outcomes caused with rivaroxaban (red)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

highlight the role of both the coagulation cascade and platelet activation, and the complex interplay between the two, that underlies the pathogenesis of arterial thrombotic events. The robust benefits particularly for ALI suggest that such severe arterial events are highly modifiable using a strategy that combines inhibition of platelets with low-dose anticoagulation and with a tolerable bleeding profile.

The treatment gap in PAD regarding antithrombotic therapy[22] mirrors the gap in other guideline-directed medical therapies such as statins, as observed in the current study. This creates a therapeutic paradox: those at greatest risk are often deemed ineligible despite potentially greater treatment benefits. While recent TASC (Inter-Society Consensus for the Management of Peripheral Artery Disease) guidelines emphasize secondary prevention beyond revascularization,[23] there is often a delay adopting newer therapeutic strategies such as rivaroxaban in clinical practice. Several explanations for this gap are worth considering. Meta-analyses of antiplatelet agents in PAD suggest diminished efficacy relative to CAD patients,[24] which may lead to medical uncertainty. In addition, the landscape for combination antithrombotic therapy is complex. Vorapaxar appears efficacious when combined with both aspirin and clopidogrel but is associated with increased major bleeding and intracranial haemorrhage.[25] However, with the availability of more potent platelet $P2Y_{12}$ inhibitors, such as prasugrel and ticagrelor, triple therapy may be considered unnecessary.[26] Regardless, the totality of efficacy evidence for low-dose rivaroxaban plus aspirin in CAD, PAD, and acute coronary syndrome appears favourable.[12,13,27] Recent European data from Søgaard and colleagues[28] suggest modest temporal improvements in guideline-directed secondary prevention therapy in PAD after LER, with corresponding reductions in MALE. However, utilization patterns for a low-dose anticoagulant-antiplatelet regimen have not been studied and no reduction in major amputation was observed in Søgaard's study. This highlights the urgent need for novel strategies to prevent major vascular amputations as supported by the current VOYAGER PAD trial.

We acknowledge several limitations regarding the interpretation and generalizability of our findings. The current analysis did not demonstrate a statistically significant reduction in all-cause or cardiovascular mortality, given limited patient numbers and a median follow-up of 28 months. Nonetheless, the downstream implications of reduced major amputation and ALI are a study strength, as these events portend high healthcare costs and substantial morbidity including profound disability after amputation. In addition, 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. Finally, 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).

In conclusion, patients with PAD undergoing LER are at high risk of ischaemic events and, particularly, severe limb complications such as ALI and major amputation of a vascular aetiology. Rivaroxaban 2.5 mg twice daily added to low-dose aspirin reduces this risk with consistent benefit across the spectrum of age and potentially with even greater benefit for reducing ALI in those ≥75 years of age. Rivaroxaban numerically increases TIMI major bleeding, but not intracranial haemorrhage or fatal bleeding with no signal of increased bleeding risk. Overall, rivaroxaban therapy is associated with a favourable benefit–risk profile regardless of age and should be considered even in PAD patients ≥75 years of age.

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Data availability

Data are not publicly available at this time. Requests for collaboration and data sharing are governed by a publication committee. Inquiries may be directed to CPC Clinical Research through the senior author.

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