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Revascularisation for Symptomatic Peripheral Artery Disease: External Applicability of the VOYAGER PAD Trial

Mette Søgaard [a,b,*], **Peter B. Nielsen** [a,b], **Flemming Skjøth** [b,c], **Torben B. Larsen** [a,b], **Nikolaj Eldrup** [d,e]

[a] Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark
[b] Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Faculty of Health, Aalborg University, Aalborg, Denmark
[c] Unit for Clinical Biostatistics, Aalborg University Hospital, Aalborg, Denmark
[d] Rigshospitalet, Copenhagen University, Copenhagen, Denmark
[e] Danish Vascular Registry, Danish Regions, Aarhus, Denmark

WHAT THIS PAPER ADDS

The VOYAGER PAD trial demonstrated that low dose rivaroxaban plus aspirin was superior to aspirin alone in preventing major adverse limb and cardiovascular events. This paper evaluates the external applicability of the VOYAGER PAD data, and shows that 27% of patients that underwent revascularisation in routine practice would have been eligible in the VOYAGER PAD trial. Compared with enrolled trial participants, patients in routine care were older, had more severe PAD, higher bleeding risk, and poorer prognosis. This indicates that caution is required when making inferences about VOYAGER PAD to wider patient populations, but confirms that eligible patients have a high risk of cardiovascular events and are in greater need of an effective prevention therapy.

Objective: In the VOYAGER PAD trial, rivaroxaban 2.5 mg plus aspirin significantly reduced the primary composite efficacy outcome of acute limb ischaemia, major amputation, myocardial infarction, ischaemic stroke, or cardiovascular death compared with aspirin alone. However, patients enrolled in the trial may not reflect patients encountered in daily clinical practice. This study described the proportion of patients eligible for VOYAGER PAD within the nationwide Danish Vascular Registry (DVR), reasons for ineligibility, and outcomes according to eligibility.
Methods: In total, 32 911 patients who underwent lower extremity revascularisation for symptomatic peripheral arterial disease (PAD) in the DVR (2000—2016) were identified. Trial inclusion and exclusion criteria were applied, and the three year cumulative incidence of primary and secondary trial outcomes was estimated.
Results: Altogether, 27.1% of patients with PAD in the DVR were "VOYAGER eligible". Of those not included, 30.7% had at least one exclusion criterion ("VOYAGER excluded"), and an additional 42.3% did not fulfil the inclusion criteria ("VOYAGER not included"). The main reasons for exclusion were atrial fibrillation (32.3%), poorly regulated hypertension (20.6%), requirement for long term dual antiplatelet therapy (10.9%), cytochrome P450 inhibitors or inducers (9.7%), and renal failure (9.3%). The three year rate of the primary efficacy outcome was 10.08 per 100 person years among the "VOYAGER eligible", 16.32 among "VOYAGER excluded", and 6.98 among the "VOYAGER not included". For the primary safety outcome of thrombolysis in myocardial infarction (TIMI) major bleeding, rates were 2.24, 3.76, and 1.17, respectively. Rates of secondary endpoints were also consistently lower for patients who did not meet the inclusion criteria (predominantly due to central aorto-iliac procedures) and highest for "VOYAGER excluded" patients. "VOYAGER eligible" patients experienced a higher cumulative incidence of most endpoints than patients enrolled in the control arm of the VOYAGER PAD trial.
Conclusion: Among patients in routine clinical practice, 27.1% were eligible for the VOYAGER PAD trial. These patients were older, had more severe vascular symptoms, higher bleeding risk, and worse prognosis than trial participants.

Keywords: Aspirin, External applicability, Generalisability, Peripheral arterial disease, Rivaroxaban, VOYAGER PAD trial
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* Corresponding author. Sønder Skovvej 15 Aalborg, 9000, Denmark.
E-mail address: mette.soegaard@rn.dk (Mette Søgaard).

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INTRODUCTION

Peripheral artery disease (PAD) is a clinical manifestation of systemic atherosclerosis, where atherosclerotic plaques cause progressive stenosis and occlusion of cerebral,

coronary, and peripheral arteries, leading to a high risk of cardiovascular (CV) and major adverse limb events (MALE).[1,2]

Guidelines recommend single antiplatelet therapy with either aspirin or clopidogrel to reduce risks of MALE and major CV events in patients with symptomatic PAD, regardless of whether they receive conservative medical treatment or undergo revascularisation (class IA recommendation).[3–5] However, peripheral artery revascularisation is associated with an immediate high risk of post-procedural re-thrombosis of the peripheral arteries, and elevated risk of major CV and limb events, which persists long after the intervention, despite antiplatelet and statin therapy.[1,6,7] As the residual risk remains high, there is a focus on the role of more intense antithrombotic strategies to reduce major CV events without significantly increasing the risk of bleeding.[8] In the VOYAGER PAD trial, dual pathway therapy with low dose rivaroxaban added to aspirin, compared with aspirin alone, reduced the composite endpoint of acute limb ischaemia (ALI), major amputation due to vascular aetiology, myocardial infarction (MI), ischaemic stroke, or CV death in patients after a receent peripheral revascularisation for symptomatic PAD (hazard ratio [HR] 0.85, 95% confidence interval [CI] 0.76–0.96).[9]

The choice of intensified antithrombotic therapy is a tradeoff between a favourable effect on major limb and CV outcomes and increased bleeding risk.[8] Patients with symptomatic PAD who undergo revascularisation represent a vulnerable subgroup of multimorbid patients at high risk of complications.[1,10] These factors are known to influence enrolment in trials and raise questions about the external applicability of trial results to patients in daily clinical practice. Using a nationwide cohort of patients who underwent vascular interventions, whether these routine clinical care patients would have been eligible for the VOYAGER PAD trial was examined. The principal reasons for ineligibility were assessed, and the clinical characteristics and outcomes compared according to eligibility for enrolment.

METHODS

This registry based cohort study was performed in compliance with the General Data Protection Regulation, and the North Denmark Region's record of processing activities (project no. 2017-40). No further ethics approval or informed consent were needed according to Danish law. Data for the study were provided by the Danish Vascular Registry (DVR) and Statistics Denmark.

VOYAGER PAD trial design

The VOYAGER PAD trial (ClinicalTrials.gov identifier: NCT02504216) was an international, multicentre phase III randomised controlled trial (RCT) designed to assess the efficacy and safety of 2.5 mg rivaroxaban twice daily added to background therapy of 100 mg aspirin once daily for the prevention of major atherothrombotic vascular events in patients with symptomatic PAD after a recent revascularisation. The trial enrolled 6 564 symptomatic patients with PAD who had undergone a technically successful surgical or endovascular revascularisation procedure to treat symptomatic infra-inguinal PAD (occlusive disease distal to the external iliac artery).[9,11] Major trial inclusion and exclusion criteria are provided in Table 1, and described in detail in Supplementary Table S1. The primary efficacy outcome was a composite of ALI, major amputation due to vascular aetiology, MI, ischaemic stroke, or CV death. The primary safety outcome was thrombolysis in myocardial infarction (TIMI) major bleeding. Event probabilities were estimated as the cumulative incidence at three years after randomisation.

The Danish Vascular Registry

The DVR[12–14] has recorded data on all patients undergoing vascular interventions (surgical and endovascular) at all seven vascular departments in Denmark since 1994. Information includes data on lifestyle risk factors (e.g., height, weight, and smoking), laboratory values, comorbidities, symptoms, procedures, complications, and follow up data. Reporting is mandatory and annual audits ensure high data completeness and external validity (>90% since 2001) of all procedures.[12–14] In this registry, all patients who underwent a first open surgical or endovascular revascularisation procedure in the lower extremities or abdomen from 2000 to 2016 were identified. All patients with ischaemia, either acute (thrombosis or embolisation) or chronic (claudication, rest pain, ulcer, or gangrene) in the foot or leg were included. Acute events were included because it is difficult to distinguish embolic from atherosclerotic events clinically, and 97% of included patients with acute events were also diagnosed with PAD (e.g., acute on chronic exacerbations). Patients for whom detailed data regarding eligibility in VOYAGER PAD were missing or incomplete, and those aged <40 years (as ischaemia in younger individuals is usually unrelated to PAD) were excluded. This way, a VOYAGER PAD evaluable cohort was simulated, which formed the study population for the present analyses (Fig. 1).

Classification according to trial inclusion and exclusion criteria

To determine eligibility in the VOYAGER PAD trial, data on baseline clinical characteristics, comorbidities within five years prior to revascularisation (index date), and comedications within the year prior (for code definitions, see Supplementary Table S3) were extracted. Next, the trial inclusion and exclusion criteria were applied to the VOYAGER PAD evaluable cohort in the DVR.

Key exclusion criteria included long term dual antiplatelet therapy (DAPT) beyond six months after the qualifying revascularisation, clinical requirement for systemic anticoagulation, recent ALI or acute coronary syndrome (ACS), medical conditions that could increase the risk of major bleeding, impaired renal function, and any documented

Table 1. Overview of the main VOYAGER PAD randomised controlled trial inclusion and exclusion criteria and the adaptions used for the Danish nationwide registries. Detailed information on inclusion and exclusion criteria are provided in Supplementary Table S1

VOYAGER PAD criteria	Adapted criteria based on the Danish registries
Inclusion criteria	
Age ≥50 y	Age ≥50 y
Documented moderate to severe symptomatic lower extremity occlusive PAD	All patients who underwent a first open surgical or endovascular revascularisation for symptomatic PAD
Technically successful peripheral revascularisation distal to the external iliac artery within the last 10 days prior to randomisation	Technically successful peripheral revascularisation distal to the external iliac artery defined as absence of records of occlusion and/or amputation at the time of discharge
Exclusion criteria as labelled in trial design	
Revascularisation for asymptomatic PAD or mild claudication without functional limitation.	All patients were required to have function limiting symptoms; patients with an ABI >0.80 were excluded
Recurrent revascularisation (<10 d)	Restriction to incident revascularisation
ALI (<2 w) or major tissue loss in either leg	Information on ALI without revascularisation was not available in the Danish registries
Clinical requirement for aspirin dose >100 mg daily	Prescription claim for aspirin ≥500 mg per dose
Need for long term dual antiplatelet therapy (>6 mo)	ACS or PCI (<6 mo), considering that no current guideline recommend systematic continuation of dual antiplatelet therapy for more than 12 mo following ACS/PCI
Need for antiplatelet or anticoagulation therapy other than aspirin and/or clopidogrel	Prescription claim for antiplatelet agents other than clopidogrel and aspirin within 30 days after the index date, and patients with AF, mechanical heart valves, or prior VTE
Systemic treatment with strong inhibitors or inducers of cytochrome P450 isoenzyme 3A4 (CYP3A4) and p-glycoprotein inhibitors	Prescription claim for inhibitors or inducers of CYP3A4 or p-glycoprotein inhibitors within 30 d after the index date.
High risk of bleeding	Major bleeding requiring hospital contact (<6 mo) or severe liver disease (<365 d)
Requirement for dialysis or renal replacement therapy, or renal impairment (eGFR <15 mL/min/1.73 m^2)	Dialysis or eGFR <15 mL/min/1.73 m^2
ACS (<30 d), major trauma or accidents (<30 d), or history of intracranial haemorrhage, stroke, or transient ischaemic attack	Diagnoses of ACS (<30 d), trauma or accidents (<30 d), or intracranial haemorrhage, stroke, or transient ischaemic (<365 d)
Active malignancy	Cancer diagnosis, systemic anticancer treatment, recurrent or metastatic cancer (<6 mo)
Poorly controlled diabetes or severe uncontrolled hypertension	Poorly regulated hypertension (blood pressure at admission >140/90 mmHg). Information on glycaemic control is not available in the Danish registry data
Life expectancy <1 y	Not available in the Danish registry data

PAD = peripheral arterial disease; ABI = ankle brachial index; ALI = acute limb ischaemia; ACS = acute coronary syndrome; PCI = percutaneous coronary intervention; AF = atrial fibrillation; VTE = venous thromboembolism; eGFR = estimated glomerular filtration rate.

history of intracranial haemorrhage, stroke, or transient ischaemic attack. An overview of the inclusion and exclusion criteria, and the definitions used for the classification of patients in the DVR, is provided in Table 1 (see Supplementary Table S1 for a detailed specification). Criteria that could not be applied to the Danish registries included diagnoses of ALI and major tissue loss, contraindications to aspirin, poorly controlled diabetes, life expectancy of less than one year, and close affiliation with the investigational site (Supplementary Table S2). Based on this, the following three subpopulations were defined (Fig. 1): (1) "VOYAGER PAD eligible", i.e., patients fulfilling the inclusion and without exclusion criteria; (2) "VOYAGER PAD excluded", i.e., patients with at least one exclusion criterion; and (3) "VOYAGER PAD not included", i.e., patients undergoing lower extremity revascularisation for symptomatic PAD without exclusion criteria but not fulfilling inclusion criteria.

The "VOYAGER PAD excluded" group combined all patients with at least one exclusion criterion, regardless of whether they fulfilled inclusion criteria. Detailed data on characteristics and outcomes for patients with exclusion criteria stratified by fulfilment of inclusion criteria are provided in the Supplementary Material.

Outcomes

The cohort was followed for three year after revascularisation, or until administrative censoring at 31 December 2016, for the occurrence of outcomes, similar to the follow up in Voyager PAD. Data on revascularisations due to ALI were available but data on ALI diagnoses without revascularisation were lacking in the Danish registries (Supplementary Table S2). Consequently, the primary efficacy outcome differed from VOYAGER PAD because it was a composite of revascularisation for ALI, major amputation,

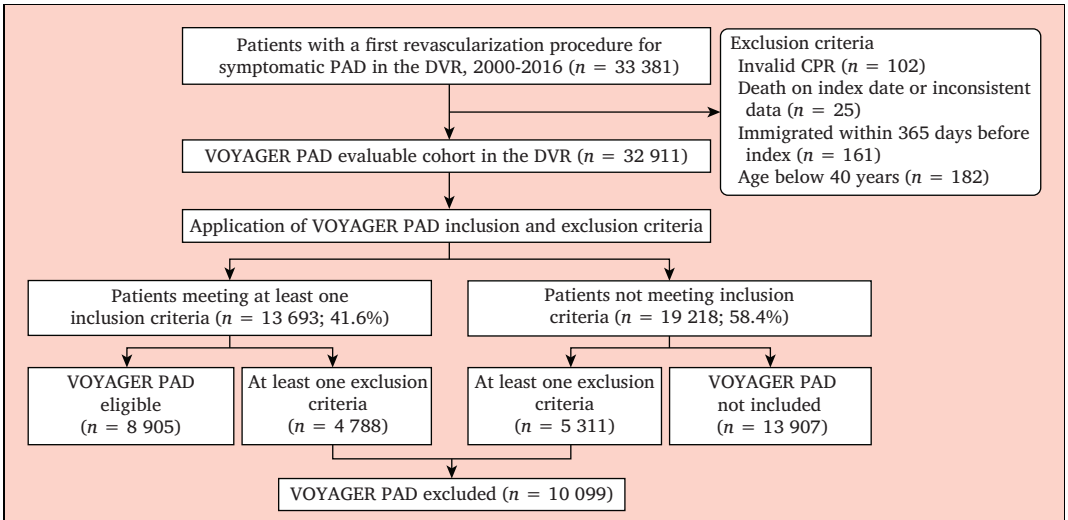

Figure 1. Flowchart for the identification of patients with symptomatic peripheral arterial disease (PAD) in the Danish Vascular Registry (DVR) according to VOYAGER PAD trial inclusion and exclusion criteria. CPR = Central Person Register (Danish civil registration number).

MI, ischaemic stroke, or CV death. Secondary outcomes for which data were available in the registries were also analysed: MI; ischaemic stroke; all cause major amputation; venous thromboembolic events (VTE); CV death; and all cause death, as well as the primary safety outcome of major bleeding. All outcomes, except three, were based on primary diagnoses recorded in the Danish National Patient Registry. The exceptions were major bleeding, which were based on primary and secondary inpatient diagnoses, and amputations and revascularisation, which were based on surgical procedure codes. Major bleeding was defined as a composite of intracranial bleeding, gastrointestinal bleeding, and major bleeding in other critical anatomical sites. CV deaths were defined as deaths within 30 days after a primary diagnosis of CV disease, as done previously (see Supplementary Table S3 for details).[15]

Statistical analysis

Descriptive characteristics at the time of index revascularisation are provided for the three subpopulations as proportions for discrete variables, and means ± standard deviations (SD) for continuous variables. Assuming that data were missing at random, multivariable imputation by chained equations was performed to impute missing data in the Danish Vascular Registry (Supplementary Table S4 displays the number and percentage of records with missing data).[16] Time to event analysis was performed to estimate the three year risk of study outcomes. The time to event interval was measured from the date of revascularisation to each outcome of interest, death (if not the outcome of interest), emigration, or study end, whichever came first. Event rates were calculated as the number of events divided by person, time stratified by eligibility. Development of primary outcome risk over time was depicted using cumulative incidence curves, based on the Aalen—Johansen estimator considering death a competing risk.

Supplementary and sensitivity analyses

As the thresholds for revascularisation, secondary prevention, and prognosis have changed over time,[10] a supplementary analysis was conducted restricted to patients who underwent revascularisation during the period 2010—2016. Also, because data were lacking on diagnoses of acute ischaemia and major tissue loss, which were exclusion criteria in VOYAGER PAD, a sensitivity analysis was performed in which patients who underwent revascularisation owing to acute ischaemia or gangrene were categorised as "excluded", to assess how this influenced eligibility and outcomes.

Analyses were performed with STATA/MP (version 15.1; StataCorp, College Station, TX, USA).

RESULTS

After exclusions, owing to invalid data ($n = 102$), inconsistent data on death or death on the index date ($n = 25$), immigration ($n = 161$), or age <40 years ($n = 182$), the study population included 32 911 patients with symptomatic PAD among whom eligibility for the VOYAGER PAD trial was evaluable (Fig. 1). After applying trial eligibility criteria, 27.1% would have been eligible, 30.7% had at least one exclusion criterion, and 42.3% had no exclusion criteria but did not meet the inclusion criteria (Fig. 2). Of the "VOYAGER PAD excluded" patients, 47.2% met at least one inclusion criterion (Supplementary Fig. S1). The main reasons for exclusion varied little according to whether patients met inclusion criteria (Supplementary Fig. S2). The main reasons for non-inclusion were central aorto-iliac procedures

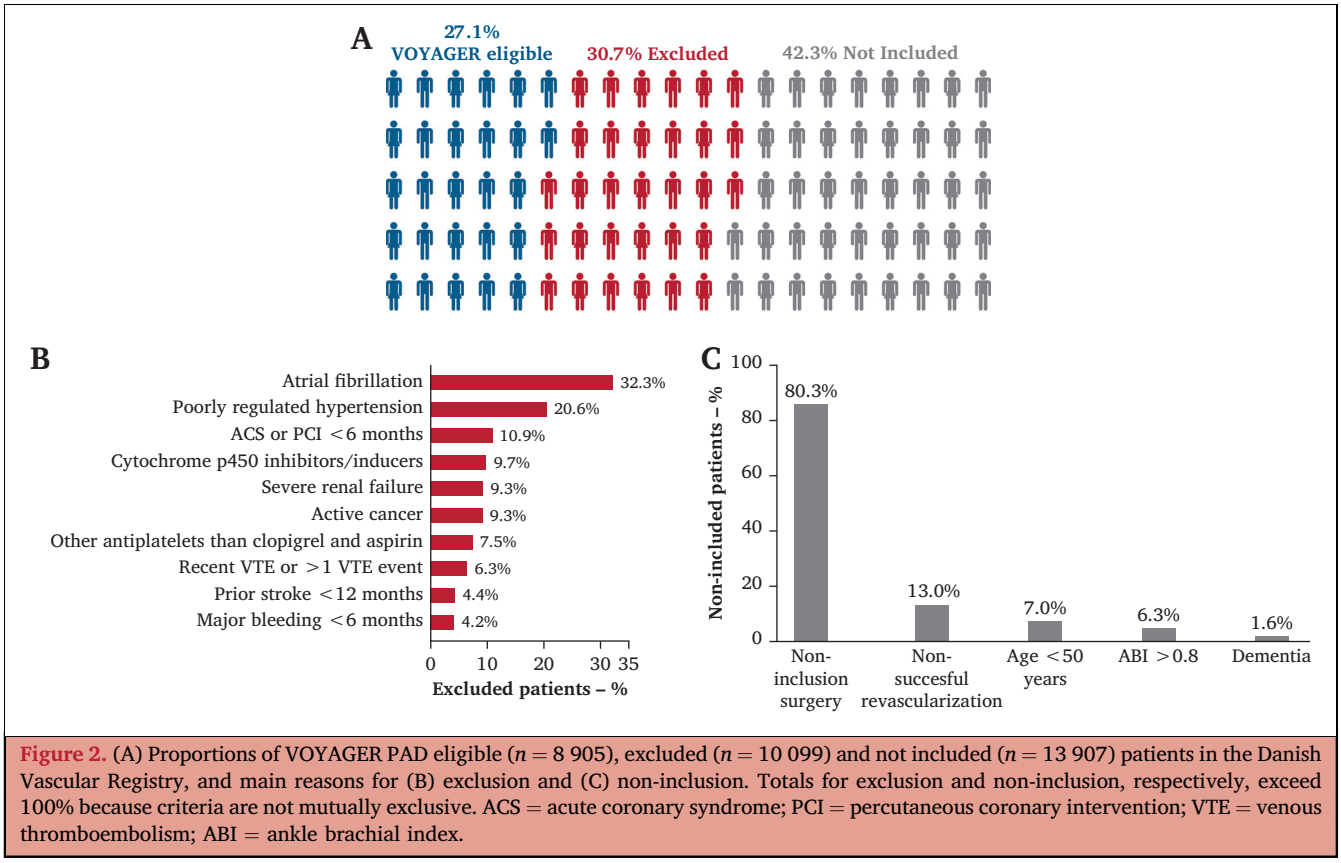

Figure 2. (A) Proportions of VOYAGER PAD eligible ($n = 8\,905$), excluded ($n = 10\,099$) and not included ($n = 13\,907$) patients in the Danish Vascular Registry, and main reasons for (B) exclusion and (C) non-inclusion. Totals for exclusion and non-inclusion, respectively, exceed 100% because criteria are not mutually exclusive. ACS = acute coronary syndrome; PCI = percutaneous coronary intervention; VTE = venous thromboembolism; ABI = ankle brachial index.

(80.3%), non-successful revascularisation (13.0%), and age <50 years (7.0%) (Fig. 2).

Baseline characteristics of Danish Vascular Registry evaluable patients according to eligibility

Baseline characteristics differed according to eligibility (Table 2). As per definition, the "excluded" patients had a higher prevalence of baseline comorbidities and medications than "eligible" and "not included" patients. This pattern remained unchanged, regardless of whether patients fulfilled the inclusion criteria (Supplementary Table S5). "Eligible" patients were older (median age 72 *vs.* 67 years), less likely to be female (41.7% *vs.* 48.2%), less likely to undergo endovascular procedures (32.1% *vs.* 67.3%), or to have intermittent claudication (35.2% *vs.* 63.9%) than the "not included" patients. Conversely, baseline comorbidities and medications differed little (Table 2).

Outcomes among Danish Vascular Registry evaluable patients according to eligibility

Supplementary Figures S3 and S4 show the cumulative incidence curves of the primary efficacy outcome and the primary safety outcome. The three year rate of the primary efficacy outcome was 10.08 per 100 person years among "eligible", 16.32 among "excluded", and 6.98 among "not included" patients (Table 3). For the primary safety outcome, rates were 2.24, 3.76, and 1.17, respectively. At three years, event rates and cumulative incidence of all outcomes were consistently higher in patients with exclusion criteria, and lowest in patients categorised as "not included" (Table 3, Fig. 3).

Danish Vascular Registry "eligible" vs. VOYAGER PAD participants

A total of 3 278 patients were included in the VOYAGER PAD aspirin alone (placebo) treatment arm.[9] Informal comparison with the "eligible" group identified in the DVR showed that trial participants were younger (mean age 67 years *vs.* 72 years), less likely to be female (26.1% *vs.* 41.7%), smokers (34.5% *vs.* 47.0%), and had less extensive limb morbidity (mean ankle brachial index 0.56 *vs.* 0.41) (Table 2). Conversely, the prevalence of co-existing conditions and medications were higher in VOYAGER PAD participants. As shown in Fig. 4, the incidence of the primary efficacy outcome was higher in "eligible in the DVR" than in VOYAGER PAD enrolled trial participants (24.1% *vs.* 19.9% at three years). The same applied to risks of major amputation (12.0% *vs.* 3.9%), ischaemic stroke (4.5% *vs.* 3.0%), all cause mortality (23.3% *vs.* 10.9%), VTE (2.6% *vs.* 1.7%), and major bleeding (6.4% *vs.* 1.9%). In contrast, the cumulative incidence of ALI was higher in VOYAGER PAD participants (7.8% *vs.* 2.3%).

Supplementary and sensitivity analyses

A total of 13 944 patients underwent revascularisation between 2010 and 2016; 25.7% were categorised as "eligible"; 32.9% as "excluded"; and 41.4% as "not included". The baseline characteristics of the 3 588 "eligible" patients in 2010—2016 differed little from the main

Table 2. Baseline characteristics of patients enrolled in the aspirin alone treatment arm of the VOYAGER PAD trial *vs.* patients in the Danish Vascular Registry according to VOYAGER PAD trial inclusion and exclusion criteria

Characteristic	VOYAGER PAD trial (aspirin alone arm) (n = 3 278)	Danish Vascular Registry		
		VOYAGER PAD eligible (n = 8 905)	VOYAGER PAD excluded (n = 10 099)	VOYAGER PAD not included (n = 13 907)
Demographics				
Age − y	67.0 (61.0–73.0)	72.0 (65.0–79.0)	72.0 (64.0–79.0)	67.0 (59.0–74.0)
Female sex	857 (26.1)	3 714 (41.7)	4 333 (42.9)	6 698 (48.2)
Living independently	–	7 178 (82.4)	7 401 (75.4)	12 059 (89.1)
Current smoker	1 132 (34.5)	4 039 (47.0)	4 092 (42.3)	7 384 (55.0)
BMI − kg/m^2	26.0 (23.2–29.1)	24.8 (22.1–27.8)	24.7 (22.0–27.8)	24.5 (21.9–27.5)
eGFR<60 mL/min/1.73 m^2	666 (20.3)	2 373 (29.8)	3 610 (41.6)	2 431 (21.0)
Surgical procedure				
Endovascular treatment	2 140 (65.3)	2 858 (32.1)	5 132 (50.8)	9 362 (67.3)
Acute surgery	–	1 436 (16.1)	2 043 (20.2)	1 280 (9.2)
Elective surgery	–	7 469 (83.9)	8 056 (79.8)	12 627 (90.8)
Vascular morbidity				
Time since first PAD diagnosis − y	–	2.1 ± 4.4	2.3 ± 4.7	1.9 ± 4.2
ABI	0.56 (0.42–0.67)	0.41 (0.28–0.53)	0.40 (0.27–0.55)	0.47 (0.33–0.60)
ABI < 0.8	–	8 854 (100)	5 985 (95.2)	12 985 (93.7)
Index revascularisation performed for:				
Acute peripheral ischaemia	–	512 (5.7)	805 (8.0)	482 (3.5)
Claudication	2 521 (76.7)*	3 134 (35.2)	3 555 (35.2)	8 887 (63.9)
Rest pain	–	1 962 (22.0)	1 818 (18.0)	1 913 (13.8)
Ulcer	–	2 345 (26.3)	2 595 (25.7)	1 733 (12.5)
Gangrene	–	952 (10.7)	1 326 (13.1)	892 (6.4)
Co-existing conditions				
Hypertension	2 658 (81.1)	4 983 (56.0)	7 206 (71.4)	7 102 (51.1)
Hyperlipidaemia	1 316 (40.1)	690 (7.7)	1 670 (16.5)	1 124 (8.1)
Diabetes	–	2 152 (24.2)	2 786 (27.6)	2 470 (17.8)
Atrial fibrillation	–	0.0 (0)	3 259 (32.3)	0.0 (0)
Congestive heart failure	–	553 (6.2)	1 884 (18.7)	698 (5.0)
Ischaemic stroke	1 015 (31.0)	352 (4.0)	1 233 (12.2)	438 (3.2)
Previous bleeding	349 (10.6)	1 175 (13.2)	2 248 (22.3)	1 633 (11.7)
Coronary artery disease	–	1 282 (14.4)	3 140 (31.1)	1 644 (11.8)
Myocardial infarction	–	435 (4.9)	1 206 (11.9)	604 (4.3)
Prior CABG	–	461 (5.2)	1 007 (10.0)	593 (4.3)
Prior PCI	–	508 (5.7)	1 332 (13.2)	787 (5.7)
Cancer	–	437 (4.9)	1 179 (11.7)	636 (4.6)
Chronic pulmonary disease	–	894 (10.0)	1 599 (15.8)	1 292 (9.3)
Alcohol related disease	–	782 (8.8)	1 113 (11.0)	1 370 (9.9)
Medications				
Aspirin	3 248 (99.1)	5 256 (59.0)	6 290 (62.3)	8 496 (61.1)
Clopidogrel	1 655 (50.5)	535 (6.0)	1 324 (13.1)	776 (5.6)
Oral anticoagulants	–	219 (2.5)	2 157 (21.4)	244 (1.8)
Statins	2 641 (80.6)	4 903 (55.1)	6 091 (60.3)	8 696 (62.5)
ACE inhibitor	2 063 (62.9)	4 282 (48.1)	5 769 (57.1)	6 113 (44.0)

Data are presented as n (%), median (interquartile range), or mean ± standard deviation. BMI = body mass index; eGFR = estimated glomerular filtration rate; PAD = peripheral artery disease; ABI = ankle brachial index; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; ACE = angiotensin converting enzyme.

* History of claudication may not equal that claudication was the indication for the index revascularisation.

population of DVR "eligible" patients (Supplementary Table S6), except for more frequent endovascular treatment and more optimal secondary medical prevention. Outcome event also remained virtually unchanged (Supplementary Fig. S5). Eligibility was 21.3% when patients with revascularisation for ALI or gangrene in 2010–2016 were categorised as "excluded". The three year cumulative incidence of outcomes of DVR "eligible", excluding these patients, were lower, but, in particular, major amputation (9.6% *vs.* 3.9%), major bleeding (6.4% *vs.* 1.9%), and all cause mortality (19.6% *vs.* 10.9%) remained higher than in VOYAGER PAD participants (Supplementary Fig. S5).

Table 3. Number of events and event rates per 100 person years among patients in the Danish Vascular Registry according to VOYAGER PAD trial eligibility at the three year follow up

Outcome	VOYAGER PAD eligible (n = 8 905)		VOYAGER PAD excluded (n = 10 099)		VOYAGER PAD not included (n = 13 907)	
	Events	Rate	Events	Rate	Events	Rate
Primary efficacy outcome*	1902	10.08	2976	16.32	2233	6.98
Revascularisation for acute limb ischaemia	174	0.83	154	0.72	203	0.59
Major amputation	953	4.81	1541	7.89	1129	3.41
Myocardial infarction	423	2.04	589	2.82	504	1.47
Ischaemic stroke	324	1.55	536	1.54	402	1.17
Death from vascular causes	494	2.33	1034	4.80	557	1.59
Death from any cause	1914	9.01	3385	15.70	2177	6.23
Venous thromboembolism	194	0.93	238	1.12	230	0.66
Principal safety outcome†	464	2.24	778	3.76	586	1.71
Intracranial haemorrhage	56	0.26	71	0.33	49	0.14

* Composite endpoint of revascularisation for acute limb ischaemia, major amputation, myocardial infarction, ischaemic stroke, and death from vascular causes.
† Composite endpoint of intracranial bleeding, gastrointestinal bleeding, and major bleeding in other anatomical sites.

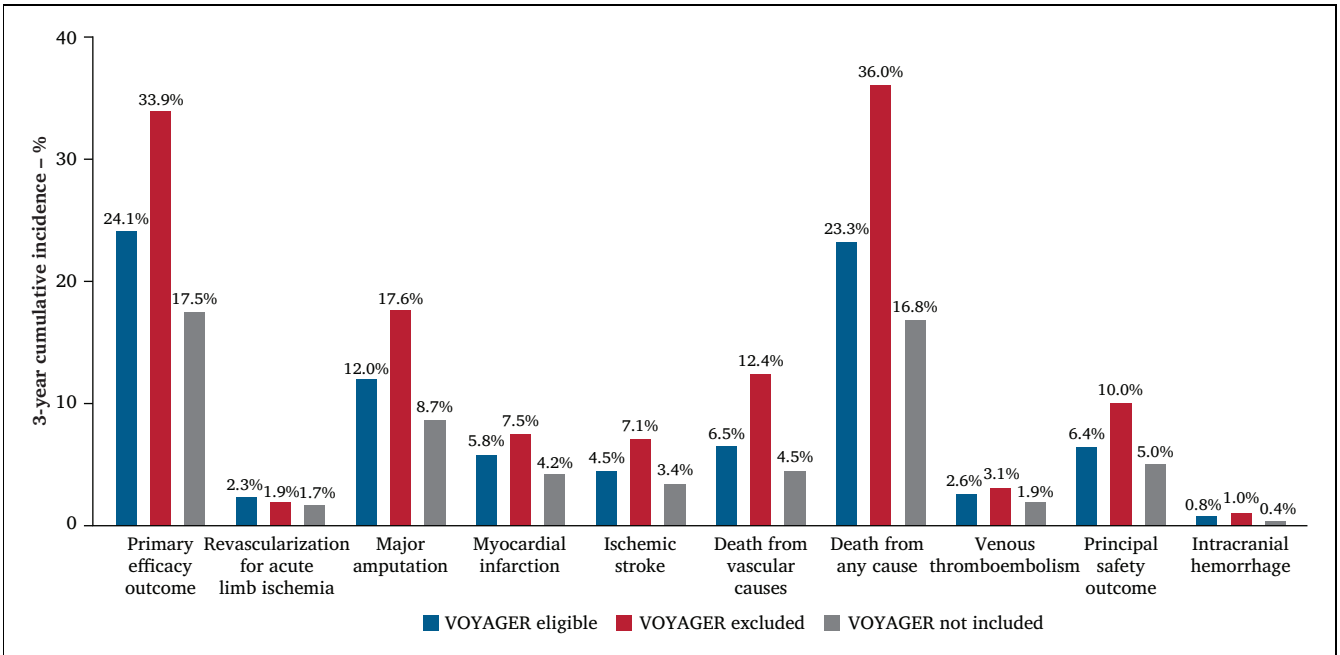

Figure 3. Cumulative incidence at the three year follow up according to VOYAGER PAD trial eligibility among 32 911 patients with symptomatic peripheral arterial disease in the Danish Vascular Registry.

DISCUSSION

This study showed that 27% of patients in the DVR who underwent revascularisation for symptomatic PAD in routine practice would have been eligible for VOYAGER PAD. Compared with participants enrolled in the trial, these patients were older, more likely to have critical limb ischaemia, and a poorer prognosis with higher incidences of most outcomes. About one third met at least one exclusion criterion. A substantial proportion of the patients would not have been eligible, even though they had no exclusion criteria. This non-inclusion was predominantly related to central aorto-iliac procedures, and these patients had lower event rates.

It is acknowledged that patients with trial exclusion criteria often represent patients with higher baseline risk and worse prognosis. Previously, a cohort study including 2 259 patients with lower extremity revascularisation in a French multicentre registry demonstrated that 30.1% would have been elegible for COMPASS and and only 9.4% for VOYAGER PAD.[17] The present findings confirm and extend this observation. Firstly, important differences were observed in baseline characteristics and outcomes between

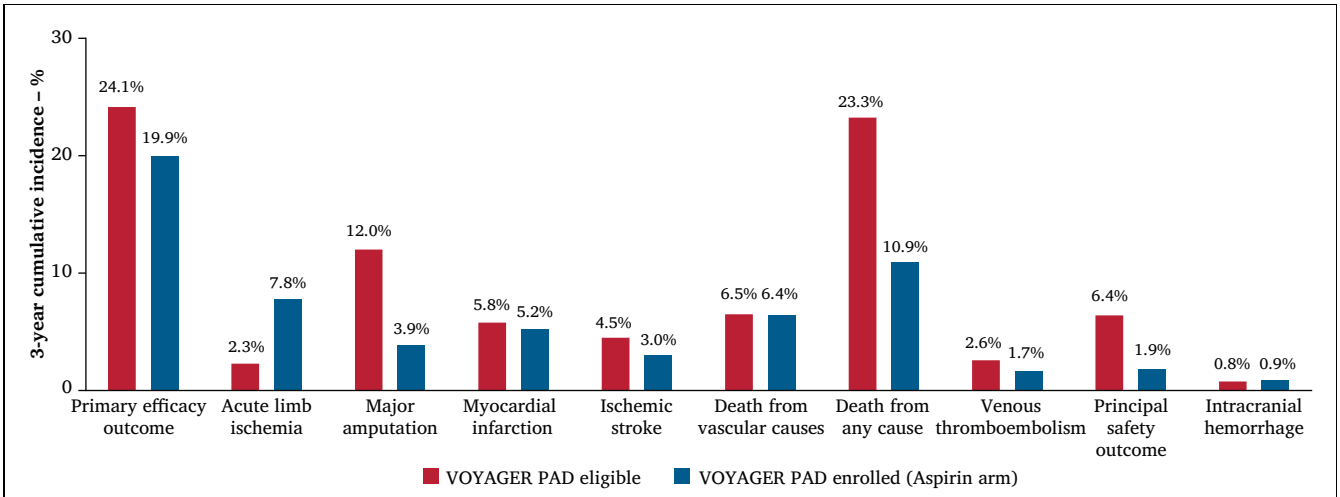

Figure 4. Cumulative incidence at the three year follow up among 8 905 VOYAGER PAD eligible patients with symptomatic peripheral arterial disease in the Danish Vascular Registry and 3 278 VOYAGER PAD enrolled trial participants in the aspirin alone (placebo) treatment arm.

eligible patients in the DVR and Voyager PAD trial participants; VOYAGER PAD participants were younger, more likely to be male, and had less severe vascular symptoms at baseline. For instance, women represented only 26% in VOYAGER PAD *vs.* 42% in the Danish national routine care cohort, which corroborate previous reports on the under representation of women in vascular surgery and PAD trials.[18,19] This may have implications for the interpretation and generalisability of trial results to patients seen in routine clinical care. Secondly, the prevalence of CV comorbidities and evidence based medications was substantially higher in trial participants. This probably reflects better surveillance and treatment in the clinical trial than that provided in everyday clinical care. Thirdly, the incidence of most outcomes assessed were higher in "eligible" patients from the DVR than in VOYAGER PAD trial participants. In particular, all cause mortality was more than twice as high (23.3% *vs.* 10.9%). The markedly lower risk of ALI in DVR patients probably reflects that this estimate pertains to revascularisations needed for ALI and not all diagnoses of ALI. Therefore, it was probable that ALI events were underestimated in the DVR, which also affected the primary composite efficacy endpoint. It is also important to note that the definition of major bleeding used in the DVR (which includes hospitalisation for bleeding) cannot be directly compared with the TIMI definition of major bleeding used in the VOYAGER PAD trial. Finally, there were other major differences in study design (RCT *vs.* observational study), geographical region (recruitment from 542 sites in 34 countries *vs.* nationwide cohort), data capture and monitoring, and event adjudication. In the VOYAGER PAD trial, patients needing anticoagulation and long term DAPT and at high bleeding risk were excluded, and the revascularisation procedure required for trial inclusion had to be successful. This induced a selection bias towards more healthy and stable patients, which may challenge the generalisability of the trial data to routine patients, especially with regard to bleeding risk and net clinical benefit.

Relevance to clinical practice and future research

This study should not be viewed as detracting from the value of RCTs. When RCTs are internally valid, they remain a gold standard for estimating treatment efficacy. To do so, trials are directed toward the assessment of treatment effects in an ideal setting with specifically selected populations, and not towards whether the treatment is beneficial to all patients in routine care.[20] This inevitably raises the question of "How do trial results apply to patients for whom the treatment is contemplated?" This study illustrates the proportion, characteristics, and outcomes of patients in everyday clinical care who would have been eligible for enrolment *vs.* patients who were considered ineligible. The proportion of eligible patients may serve as an indicator for selectivity in enrolment. However, it also reflects that many patients in the population were not suitable for dual pathway therapy and were excluded on the basis of the need for oral anticoagulant therapy (e.g., 32.2% of the excluded patients had atrial fibrillation and 6.3% had recent VTE). The eligible subset in the DVR were older and had more severe vascular symptoms than patients actually enrolled, which was reflected in higher outcome rates. In clinical practice, clinicians must balance benefit and risk due to advanced age, multimorbidity, and polypharmacy with their treatment decisions. It is often assumed that patients at higher baseline risk will have greater net benefit with an efficacious treatment. However, the higher bleeding risk in DVR patients furthers the suggestion that this assumption may not always be defensible. The majority of excluded patients had severe comorbidity either contraindicating anticoagulation therapy, necessitating a full therapeutic anticoagulant dose, or demanding long term DAPT. Approximately 30% were excluded owing to uncontrolled

hypertension, recent acute coronary syndrome, and other medication causing interaction with rivaroxaban. These patients should be re-evaluated later for potential rivaroxaban treatment.

These findings should draw attention to the large number of patients with no exclusion criteria, who were not eligible for the trial regimen. This was primarily owing to revascularisation of central iliac and aortic vessels. These patients were at lower risk of adverse events. The net clinical benefit of dual therapy with vascular dose rivaroxaban 2.5 mg twice daily is therefore uncertain because of the observed increased risk of bleeding. Further studies are needed to examine whether rivaroxaban 2.5 mg twice daily on top of aspirin is beneficial in patients with these characteristics. This study confirms that the VOYAGER PAD trial population was a special patient subgroup at considerably lower risk than that seen in a national unselected cohort, and why extrapolation from trial results may be difficult. A recent study assessed the eligibility and preventive potential of new pharmacological therapies using information from 12 RCTs and applied this information to a prospective cohort of Danish patients with prevalent ischaemic heart disease or MI.[15] The authors estimated that new therapies, if applied appropriately, could prevent 1%—20% of major CV events. However, it is emphasised that translation of RCT results to clinical practice is a multifaceted phenomenon.[21,22] Ultimately, the choice of treatment is an individualised process, taking into account the estimated thromboembolic event risk alongside the risk of major bleeding and the prevailing best evidence from both randomised and non-randomised studies. For now, these results serve as a reminder that caution is required when making inferences about the applicability of VOYAGER PAD to a wider patient population, but at the same time confirm that eligible patients have high risk and a potential high benefit of dual pathway treatment.

Strengths and limitations

The strengths of this study stem from the analysis of a large unselected nationwide cohort of patients who underwent revascularisation in every day clinical care. Data were retrieved from a dedicated vascular registry with mandatory reporting.[13,14] All Danish citizens have access to universal public healthcare free of charge, and insurance does not restrict who can attend hospitals. It is therefore assumed that the DVR is a representative population, to evaluate external applicability.

Limitations relate to the use of health administrative data, which are reliant on complete and accurate coding. Each inclusion and exclusion criterion was mirrored as closely as possible, but modifications were needed to accommodate the use of observational data. Some RCT criteria were not available for evaluation (e.g., diagnoses of ALI, major tissue loss, and life expectancy $>$ 6 months). Therefore, the proportion of patients who would have been excluded from the VOYAGER PAD trial and primary outcome events due to lack of diagnoses of ALI may have been underestimated. This study was restricted to patients with a first revascularisation, and the risk of adverse events may have been underestimated if the risk is even higher (especially for major adverse limb events) in patients with redo interventions. Furthermore, outcomes in the present study were not adjudicated and some events identified in the registries may have been missed or misclassified. Validation studies have confirmed high positive predictive values for first time MI (approximately 95%), ischaemic stroke (approximately 97%), atrial fibrillation (approximately 95%), and other CV diagnoses and comorbidities in registries.[23,24]

Conclusion

In this nationwide cohort of routine clinical care patients, 27% were eligible for dual therapy with vascular dose rivaroxaban 2.5 mg twice daily according to VOYAGER PAD criteria following revascularisation for symptomatic PAD. Patients who underwent revascularisation in routine clinical care were older, had more severe vascular symptoms, higher bleeding risk, and worse prognosis than VOYAGER PAD participants. This may potentially affect generalisability, and serves as a reminder that caution is required when making inferences about the applicability of VOYAGER PAD to a wider patient population.

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CONFLICTS OF INTEREST

M. Søgaard has received consulting fees from Bayer. P.B. Nielsen has received fees for speaking engagements from Boehringer Ingelheim and BMS/Pfizer; fees for consulting from Bayer and Daiichi-Sankyo; and grant support from BMS/Pfizer and Daiichi-Sankyo Europe. F. Skjøth has received consulting fees from Bayer. N. Eldrup has served as an investigator for Bayer, and has received fees for speaking engagements from Bayer, Amgen, and AstraZeneca. T.B. Larsen has served as an investigator for Janssen Scientific Affairs and Boehringer Ingelheim; has participated in speaker panels for Bayer, Bristol-Myers Squibb, Pfizer, Roche Diagnostics, and Boehringer Ingelheim; and has received honoraria for consulting activities from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, and Pfizer. T.B. Larsen's institution has received unrestricted funds for investigator-initiated research activities from Bayer, Pfizer, and Daiichi Sankyo.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2021.10.026.

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