ORIGINAL ARTICLE

REAL WORLD APPLICABILITY OF VOYAGER-PAD ACCORDING TO OAC^{3}PAD SCORE

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Abstract

Introduction: *Lower extremity peripheral artery disease (PAD) is associated with a high risk of cardiovascular and limb adverse events. Optimal post intervention antithrombotic strategy may significantly impact medium to long-term outcomes. The VOYAGER PAD trial showed a clinical benefit of combining low dose rivaroxaban plus aspirin by reducing cardiovascular and limb major adverse events. However, safety of this dual pathway inhibition (DPI) may be questionable. Current European Society for Vascular Surgery guidelines on this subject suggest DPI for symptomatic PAD patients undergoing invasive treatment, in the absence of high bleeding risk. However, real-world patients differ from those enrolled in the VOYAGER PAD trial, especially chronic limb threatening ischemia (CLTI) patients. The OAC3PAD score is a novel risk stratification tool to assess bleeding risk in PAD patients that may help balance the benefits and risks of antithrombotic therapy.*

Methods: *Single center retrospective study analyzing data all patients admitted for lower limb revascularization procedures between 2020 and 2023. The primary objective was to evaluate the proportion of patients, as categorized into the different categories of the OAC3PAD score, eligible for DPI, according to the VOYAGER PAD trial criteria.*

Results: *A total of 652 patients were included in this study. Mean age of the patients was 69,6 ±10,3 years, and 76,8% were male. Out of the 652 patients, 12% were classified as high bleeding risk, 23% as intermediate to high bleeding risk, 46% as low to moderate bleeding risk, and 19% as low bleeding risk. Based on the VOYAGER PAD trial criteria, 441 patients (67,6%) were identified as potential candidates for low-dose rivaroxaban therapy. Eligibility for DPI varied significantly ($p<0.001$) across OAC3PAD scores, with the highest proportion of patients observed in the low to intermediate bleeding risk patients, while the lowest was in the high bleeding risk patients.*

Conclusion: *Current evidence points to a higher bleeding risk of PAD patients than previous stated, especially when CLTI patients are being considered. Despite showing promising results, DPI with low dose rivaroxaban plus aspirin may require special caution in almost 50% of CLTI patients due to bleeding risk. This is a more frail and older population were adverse cardiovascular and limb events are more common and would benefit the most from strategies to reduce such events.*

INTRODUCTION

Lower extremity peripheral artery disease (PAD) is associated with a high risk of cardiovascular and limb related events, including amputation.[1,2] Current treatment strategies recommended by guidelines include pharmacological treatment, including high-dose statins and antithrombotic strategies along with other cardiovascular risk factors control.[3-5] For those patients where invasive treatment is performed, optimal pharmacological treatment for PAD may significantly impact medium to long-term outcomes.[6-9]

The VOYAGER PAD trial compares pharmacological treatment with rivaroxaban alone or combined with aspirin for secondary cardiovascular prevention, for patients who underwent lower limb revascularization procedures. It showed a clinical benefit of a reduced composite endpoint of adverse cardiovascular and limb related events.[(10)] Such findings changed clinical practice but also raised several questions, including safety of this dual pathway inhibition due to the increased risk of major bleeding compared with aspirin alone. Current European Society for Vascular Surgery (ESVS) clinical practice guidelines on antithrombotic treatment for vascular diseases suggest the use of dual pathway inhibition for symptomatic patients with PAD undergoing invasive treatment, in the absence of high bleeding risk.[5] However, real-world patients differ from those enrolled in the VOYAGER PAD trial, as they are generally older, with more severe PAD, a higher bleeding risk, and poorer prognosis, as demonstrated in

some observational studies.[2, 11-13] This may unbalance the risk-benefit of a dual pathway inhibition strategy towards a higher bleeding risk. [6]

The OAC³PAD score is a novel risk stratification tool developed to assess bleeding risk in PAD patients. This score was developed to assess the one-year major bleeding risk, based on data from 81,930 patients in the German healthcare system and validated in another independent German cohort of 5,479 patients[14]. The OAC³PAD score may serve as a tool to facilitate decision making about antithrombotic therapy, providing a standardized method to evaluate bleeding risk. It may help clinicians balance the benefits and risks of antithrombotic therapy, thereby potentially improving patient outcomes in PAD management.

METHODS

Study Design and Population

This retrospective study analyzed data from a hospital database who were admitted to a single center vascular surgery department for lower limb revascularization procedures between 2020 and 2023. The procedures included both open surgery and endovascular interventions. The primary aim was to evaluate the proportion of patients, as categorized by the OAC³PAD score, who would be candidates for low-dose rivaroxaban therapy according to the VOYAGER PAD trial criteria.

Data Source and Collection

The data was sourced from a hospital database, compiled by independent physicians for hospital funding purposes. These physicians coded each patient's clinical course based on operative and clinical notes as well as discharge reports. However, the research team had access only to the coded data, not the original clinical documents. The coding adhered to the 10th edition of the International Classification of Diseases (ICD-10), including details on comorbidities, diagnoses, and procedural codes. Additionally, the research team had access to patients' birth date and date of procedure.

OAC3PAD Score Calculation

The OAC³PAD score was calculated for each patient based on the available ICD-10 coded data. The score incorporates various clinical parameters, such as oral anticoagulation, age, congestive heart failure, chronic renal disease, chronic limb threatening ischemia, history of bleeding, anemia and dementia. The patients were categorized into four risk groups: high, intermediate to high, low to moderate, and low bleeding risk. Additional information regarding the OAC³PAD score can be found in figure 1.

Eligibility for Low-Dose Rivaroxaban

To determine eligibility for low-dose rivaroxaban, we applied the criteria from the VOYAGER PAD trial. Patients classified into different OAC³PAD risk categories were assessed to see if they met these criteria based on the coded data. Inclusion and exclusion criteria from the VOYAGER PAD trial can be found in table 1.

Statistical Analysis

Descriptive statistics were used to summarize the demographic and clinical characteristics of the study population. The proportion of patients in each OAC³PAD risk category was calculated, and the percentage of patients who would be candidates for low-dose rivaroxaban therapy according to the VOYAGER PAD trial criteria was determined. Chi-square tests were employed to compare the distribution of patients across different risk categories.

All statistical analyses were performed using SPSS software (version 26.0). A p-value of less than 0.05 was considered statistically significant.

Ethical Considerations

The study was approved by the hospital's institutional review board. Since this was a retrospective study using de-identified data, individual patient consent was waived.

RESULTS

A total of 652 patients who underwent at least one procedure for lower limb revascularization between 2020 and 2023 were included in this study. The cohort comprised patients who underwent both open surgical (14,3%), endovascular (56,7%) and hybrid procedures (29,0%), mainly for CLTI (73.3%, versus intermittent claudication 26.7%). The mean age of the patients was 69,6 ±10,3 years, and 76,8% were male. The baseline characteristics of the study population are summarized in Table 2. Specific data regarding antithrombotic therapy before the revascularization procedure could not be assessed. By default, all patients in our department with symptomatic PAD are at least under single antiplatelet therapy, preferable with aspirin. Anticoagulation indication may be given by previous event of acute limb ischemia, venous embolism or cardiac reasons.

The distribution of patients according to the OAC3PAD score is shown in Figure 1. Out of the 652 patients, 12% were classified as high bleeding risk, 23% as intermediate to high bleeding risk, 46% as low to moderate bleeding risk, and 19% as low bleeding risk.

Based on the VOYAGER PAD trial criteria, 441 patients (67,6%) were identified as potential candidates for low-dose rivaroxaban therapy. The eligibility distribution across different OAC³PAD risk categories is presented in Table 2.

Statistical Analysis revealed a significant difference in the distribution of low-dose rivaroxaban eligibility across the OAC³PAD risk categories ($p < 0.001$). The highest proportion of eligible patients was observed in the low to intermediate bleeding risk patients, while the lowest was in

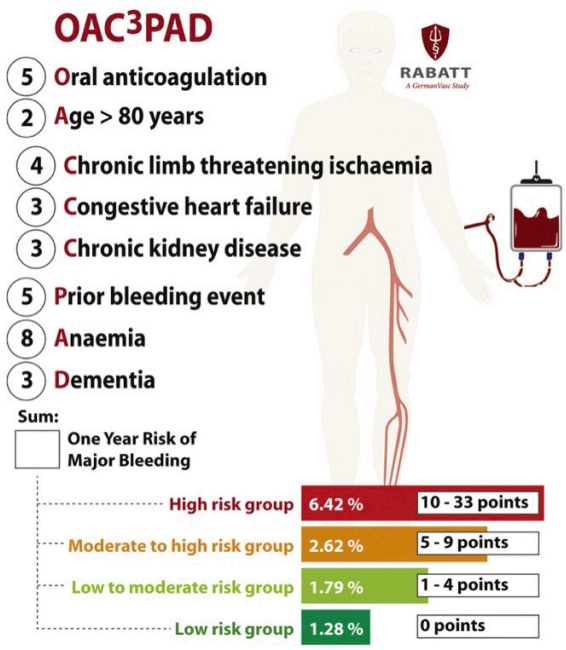

Figure 1 *OAC³PAD risk score, according to Behrendt et. al*

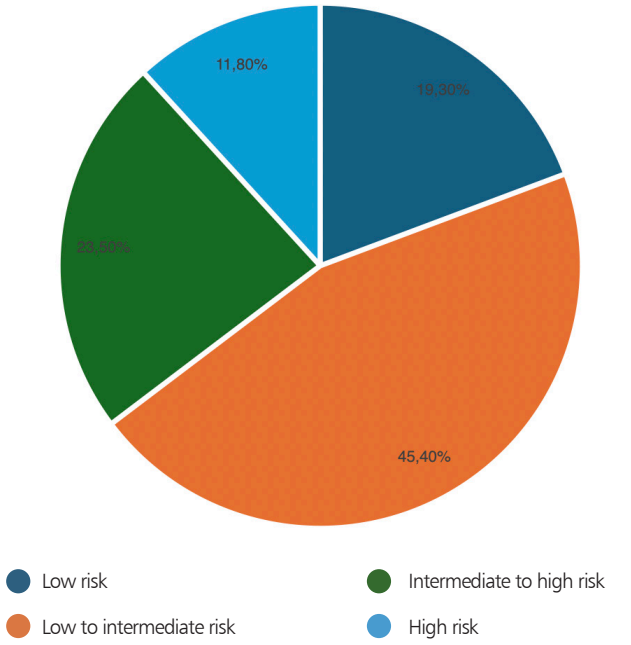

Figure 2 *Distribution of OAC³PAD score*

the high bleeding risk patients. More detailed information can be found on table 3.

DISCUSSION

Current evidence suggests that patients with PAD have a higher bleeding risk.[2, 12, 13, 15] Since more than one-third of real-world patients have at least an intermediate to high bleeding risk, and existing studies often do not reflect this reality, careful consideration must be given to the safety of antithrombotic therapy in this population.

This is especially true when CLTI patients are being considered, which is our department's PAD main population. The OAC³PAD score is a helpful tool for every vascular surgeon to assess each patient's bleeding risk. Current ESVS guidelines on antithrombotic therapy after lower limb revascularization bases their recommendations mostly on the VOYAGER PAD trial. The subgroup population of CLTI patients is considerably different (older, more frequently diabetic and with chronic renal insufficiency) making conclusions regarding safety difficult to assess.

Patients with intermediate to high or high bleeding risk, as given by the OAC³PAD score, are underrepresented in the VOYAGER PAD trial. Therefore, the bleeding risk in these patients could be significantly higher than what was reported in VOYAGER PAD. Given an older, frailer and more propense to complications, including hemorrhagic complications, it is in our opinion that it is more safely to restrict dual pathway inhibition to low or low to intermediate bleeding risk patients when CLTI is being considered.

In this real-world population cohort, only about two thirds of patients were eligible for dual pathway inhibition with aspirin 100mg once per day plus rivaroxaban 2.5mg twice a day according to the VOYAGER PAD trial criteria, which is slightly above the remaining literature.[11, 13] This higher eligibility may be due to selection bias. Of those, more than 30% were classified as intermediate to high or high bleeding risk according to the OAC³PAD score, leaving a remaining 303 patients out of the initial 652 patients (51%) as potential candidates for safely initiation of the dual pathway inhibition strategy. This means that nearly half of the patients require careful safety considerations before initiating DPI, as they are likely the ones who could benefit the most from it, being the most severely ill. Alternative treatment strategies are still needed to optimize outcomes in patients for whom dual pathway inhibition is not a safe option.

Our study has several limitations. First, there is a real chance of selection bias introduced by the ICD-10 coding data due to probable underreporting, namely on comorbidities included in the OAC³PAD score and criteria for exclusion in the VOYAGER PAD, like diabetes, smoking habits, prevalence of anemia, anticoagulation history, chronic kidney disease or carotid artery stenosis, compared to similar studies.[2] Also, there is an overlap between VOYAGER PAD exclusion criteria and OAC³PAD score components, which makes it expected that patients with higher bleeding risk are more frequently excluded.

While the authors believe this bias does not

Table 1 **Exclusion criteria for the VOYAGER PAD trial; DAPT = dual antiplatelet therapy**

Exclusion criteria related to PAD:
1. Patients undergoing revascularization for asymptomatic PAD and mild claudication
2. Patients undergoing revascularization of the index leg to treat an asymptomatic or minimally symptomatic restenosis of a bypass graft or target lesion restenosis
3. Prior revascularization on the index leg within 8 weeks of the qualifying revascularization
4. Acute limb ischemia (ALI) within 2 weeks prior to the qualifying revascularization
Exclusion criteria related to concomitant and study treatment:
5. Patients requiring treatment with ASA at doses >100 mg
6. Planned DAPT use for the qualifying revascularization procedure of clopidogrel in addition to ASA for >30 days* after the qualifying revascularization procedure
7. Planned DAPT use for any other indication(s) with any P2Y12 antagonists
8. Any active clinical condition requiring systemic anticoagulation
9. Hypersensitivity or any other contraindication listed in the local labeling for ASA or rivaroxaban
10. Systemic treatment with strong inhibitors of both CYP3A4 and p-glycoprotein inhibitors
Exclusion criteria related to bleeding risks or systemic conditions:
11. Medical history or active clinically significant bleeding
12. Any known hepatic disease associated with coagulopathy or bleeding risk
13. Medical history of chronic renal failure
14. Confirmed acute coronary syndrome within 30 days prior to randomization
15. Major trauma or accidents within 30 days prior to randomization
16. History of intracranial hemorrhage, stroke, or transient ischemic attack
17. Known active malignancy
18. Poorly controlled diabetes
19. Severe uncontrolled hypertension
20. Overall life expectancy < 1 year

Table 2

Baseline characteristics of patients who underwent lower limb revascularization procedures for symptomatic lower limb peripheral artery disease stratified by OAC³PAD risk score level; Data are presented as n (%) or mean ± standard deviation. CLTI = chronic limb threatening ischemia; TIA = transient ischemic attack; COPD = chronic obstructive pulmonary disease

Characteristic	Total	Low risk n=126; 19.3%		Low to intermediate risk n=296; 45.4%		Intermediate to high risk n=153; 23.5%		High risk n=77; 11.8%	
Male sex	501 (76.8%)	97	(77.0%)	243	(82.1%)	98	(64.1%)	63	(81.8%)
Age	70±10	66±8		68±9		76±10		70±11	
CLTI	478 (73.3%)	0	(0.0%)	269	(90.9%)	138	(90.2%)	71	(92.2%)
Diabetes	49 (7.5%)	6	(4.8%)	21	(7.1%)	11	(7.2%)	11	(14.3%)
Anemia	63 (9.7%)	0	(0.0%)	0	(0.0%)	3	(2.0%)	60	(77.9%)
Previous major hemorrhagic event	26 (4.0%)	0	(0.0%)	0	(0.0%)	14	(9.2%)	12	(15.6%)
Anticoagulation	23 (3.5%)	0	(0.0%)	0	(0.0%)	10	(6.5%)	13	(16.9%)
Stroke or TIA	3 (0.5%)	2	(1.6%)	1	(0.3%)	0	(0.0%)	0	(0.0%)
Cardiac arrythmia	35 (5.4%)	6	(4.8%)	10	(3.4%)	7	(4.6%)	12	(15.6%)
Myocardial infarction	72 (11.0%)	12	(9.5%)	30	(10.1%)	14	(9.2%)	16	(20.8%)
Congestive heart failure	106 (16.3%)	0	(0.0%)	11	(3.7%)	62	(40.5%)	33	(42.9%)
Hypertension	5 (0.8%)	1	(0.8%)	0	(0.0%)	2	(1.3%)	2	(2.6%)
Chronic kidney disease	23 (3.5%)	0	(0.0%)	1	(0.3%)	9	(5.9%)	13	(16.9%)
COPD	8 (1.2%)	1	(0.8%)	3	(1.0%)	4	(2.6%)	0	(0.0%)
Erosive gastric disease	17 (2.6%)	2	(1.6%)	5	(1.7%)	4	(2.6%)	6	(7.8%)
Carotid stenosis	7 (1.1%)	1	(0.8%)	3	(1.0%)	2	(1.3%)	1	(1.3%)
Aneurysmal disease	22 (3.4%)	9	(7.1%)	4	(1.4%)	7	(4.6%)	2	(2.6%)
Acute limb ischemia event	75 (11.5%)	20	(15.9%)	32	(10.8%)	10	(6.5%)	13	(16.9%)
Cancer	44 (6.7%)	8	(6.3%)	23	(7.8%)	8	(5.2%)	5	(6.5%)
Dementia	9 (1.4%)	0	(0.0%)	1	(0.3%)	5	(3.3%)	3	(3.9%)
Active smoking	4 (0.6%)	0	(0.0%)	3	(1.0%)	1	(0.7%)	0	(0.0%)
Alcohol abuse	4 (0.6%)	0	(0.0%)	3	(1.0%)	1	(0.7%)	0	(0.0%)

Table 3 **OAC³PAD score distribution according to eligibility to VOYAGER PAD trial**

OAC³PAD SCORE	Eligible for VOYAGER PAD		
	Yes	No	*p*-value
Low risk	80 (63.5%)	46 (36.5%)	
Low to intermediate risk	223 (75.3%)	73 (24.7%)	
Intermediate to high risk	103 (67.3%)	50 (32.7%)	<.001
High risk	35 (45.5%)	42 (52.5%)	
Total	441 (67.6%)	211 (32.4%)	

invalidate the conclusions, it is important to acknowledge that the actual bleeding risk is likely higher than reported, potentially further limiting the applicability of DPI in this population.

CONCLUSION

According to the OAC³PAD score, some high bleeding risk patients were included in the VOYAGER PAD trial despite its exclusion criteria. Even though it showed promising results in reducing adverse cardiovascular and limb related events, DPI with low dose rivaroxaban plus aspirin warrants special safety considerations in almost 50% of CLTI patients due to bleeding risk. Nevertheless, a high bleeding risk per OAC³PAD is not an absolute contraindication for DPI. On the contrary, these patients often face an even greater thrombotic burden and may derive the most benefit from DPI, if safety is carefully managed. This is particularly relevant in CLTI patients, who tend to be older and frailer, with a heightened risk of both thrombotic and bleeding complications. There is still a need to optimize outcomes in this population.

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