

Safety and efficacy of combined antiplatelet and low-dose rivaroxaban in patients with chronic limb threatening ischaemia in Singapore

Dear Editor,

Peripheral artery disease (PAD) is characterised by the debilitating atherosclerotic occlusion of arteries in the lower extremities, with chronic limb threatening ischaemia (CLTI) representing the most advanced stage of this disease process. Left untreated, these sequelae will invariably progress to major lower extremity amputation (LEA) and premature death. In Singapore, the rate of major LEA from vascular causes is 2- to 3-fold higher than in Western countries, ranking it one of the highest in the world.¹

The high prevalence of diabetes mellitus among PAD patients in Singapore probably accounts for the exceptionally high rate of major LEA. A recent large prospective cohort study revealed that diabetes is associated with the highest estimated risk for developing severe CLTI, conferring more than a 10-fold increase in CLTI-associated major LEA.² The tissue ulceration and wound infections that commonly plague diabetic patients likely contribute to this elevated risk. Peripheral arterial occlusive disease in diabetics preferentially affects the distal small vessels, with a high proportion of patients harbouring multilevel or long-segment femoropopliteal-tibial lesions.³ Open or endovascular revascularisation is offered to these patients with the aim of preventing or limiting tissue loss. Unfortunately, their disease morphology often poses a significant technical challenge, thus limiting the therapeutic benefit achieved by surgical intervention.³ Even with successful revascularisation, these patients remain at a higher risk for subsequent vascular complications, such as an increased risk of acute limb ischaemia, and consequently, prolonged hospitalisation with a higher incidence of limb loss and death. There is therefore an urgent need for strategies to reduce the risk of major LEA and PAD-associated mortality in patients with severe CLTI.

Successful risk modification of acute limb ischaemia in patients with PAD was first demonstrated by the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial.⁴ Through the addition of low-dose rivaroxaban (2.5mg twice daily) to aspirin, ischaemic risk—including the risk of major adverse limb events—was lowered in a population with chronic stable PAD. Thereafter, the Vascular Outcomes Study of Acetylsalicylic Acid (ASA) Along

with Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD (VOYAGER PAD) trial tested the effect of combined antiplatelet and antithrombotic drug treatment on cardiovascular risk modification in patients with symptomatic PAD post-revascularisation.⁵ The study demonstrated that low-dose rivaroxaban plus aspirin significantly lowered the incidence of the composite primary endpoint of myocardial ischaemia, ischaemic stroke, major amputation and cardiovascular mortality when compared to aspirin alone. This significant reduction of 15% was heavily influenced by the reduction of acute limb ischaemia. Crucially, the primary safety outcome of major bleeding was not significantly different between the 2 study arms.

The landmark study showed medical therapy improved the outcomes of post-revascularisation PAD patients. However, in contrast to our Singapore population of PAD patients, the trial recruited mostly instead of claudicants, which is not a common term, in which there was also a lower prevalence of diabetes (40% versus 80%) and chronic renal failure (27% vs 50%).⁶ Given these marked differences, we sought to validate the applicability of the VOYAGER PAD dual-drug regimen in our Asian population with different disease-related histories and pharmaco-genomic profiles.

In a joint collaborative effort, 37 patients with PAD were recruited post-revascularisation from 2 tertiary vascular centres in Singapore (Singapore General Hospital and National University Hospital) and followed up for a median of 11.7±4.1 months until November 2021. The patients' baseline demographics are shown in Table 1. Of note, nearly 90% of patients were diabetic, of whom nearly half were insulin-dependent. The average wound, ischaemia, and foot infection (WIFI) score in our cohort was 3.41±2.13, with a median score of 3 (interquartile range 2–5). Twenty patients (54.1%) underwent revascularisation for multilevel disease, where the average lesion length was 175.9±142.1mm. The overall mortality rate over the study period was 8.1%. Amputation-free survival (AFS) was 86.5% with an average time interval of 6.1 months to major amputation in 5 patients. Of note, this was much lower than the estimated 3-year AFS of 97.9% of the intervention arm of the VOYAGER cohort. Freedom from target lesion recurrence was 70.2% with an

Table 1. Baseline demographics

Characteristics	No. of patients (%) N=37
Age, mean±SD, years	67±8.3
BMI, mean±SD, kg/m ²	23.8±4.2
Male sex	30 (81.1)
Ethnic group	
Chinese	25 (67.8)
Malay	1 (2.7)
Indian	11 (29.7)
Smoking status	
Smoker	10 (27.0)
Non-smoker	11 (29.7)
Ex-smoker	16 (43.2)
Comorbidities	
Diabetes	33 (89.2)
Hypercholesterolaemia	31 (83.8)
Hypertension	32 (86.5)
Cerebrovascular accident	5 (13.5)
Myocardial infarction	13 (35.1)
End-stage renal failure	2 (5.4)
Medication history	
Insulin	14 (37.8)
Oral diabetes mellitus medications	23 (62.2)
Angiotensin receptor blockers	10 (27.0)
Angiotensin-converting enzyme inhibitors	11 (29.7)
Statins	31 (83.8)
Beta-blockers	19 (51.4)
Calcium channel blockers	15 (40.5)
Diuretics	9 (24.3)
Nitrates	10 (27.0)
Aspirin	27 (73.0)
Clopidogrel	18 (48.6)
Rutherford classification	
2 (moderate claudication)	4 (10.8)
3 (severe claudication)	10 (27.0)
4 (ischaemic rest pain)	6 (16.2)
5 (minor tissue loss)	12 (32.4)
6 (major tissue loss)	5 (13.5)

average time interval of 5.4 months to revascularisation in 11 patients. There was a substantial improvement in the mean Rutherford score from 4.11 to 2.81, with 56.3% of patients showing an improvement of ≥ 1 Rutherford class.

Serial evidence has suggested an increased risk of bleeding with novel oral anticoagulants (NOACs) in Asians compared to non-Asians.⁷ However, there were no major bleeding events reported in this study. Anaemia was noted in 2 patients who were initiated on the VOYAGER regimen; however, no definite sources of bleeding were identified. Despite the lack of bleeding events reported, rivaroxaban was stopped in favour of a single antiplatelet regimen of aspirin in 5 patients, and switched to clopidogrel in 3 patients. The treatment amendments probably reflect the perceived increase in bleeding risk associated with this dual-drug regimen.

Recently published data from the Singapore chapter of the Society for Vascular Surgery Vascular Quality Initiative database found that only 1.9% of patients were placed on the low-dose rivaroxaban regimen following revascularisation.⁸ Lack of awareness of the VOYAGER regimen, coupled with apprehension regarding its side effects are likely contributing factors to the limited uptake by local physicians thus far. In the small population of patients in which rivaroxaban is initiated, accessibility and affordability remain key issues in patients' adherence to treatment.^{8,9}

We report the early data from the first Asian series of 37 patients, demonstrating the application of the VOYAGER regimen in post-revascularisation PAD patients. Our Singapore data suggest that the addition of low-dose rivaroxaban to aspirin is safe, with a minimal bleeding risk and provides an acceptable improvement in disease severity and AFS despite the prevalence of more severe comorbidities and complex pathology. Moving forward, we aim to undertake a propensity-matched analysis comparing CLTI patients who do not receive anticoagulation (i.e. aspirin alone) after revascularisation with those who do, in order to interrogate the true benefit of low-dose NOACs in this challenging population of patients.

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