Improving medical adherence and antithrombotic management for patients with chronic limb threatening ischaemia in Singapore

Dear Editor,

Chronic limb threatening ischaemia (CLTI) represents the most advanced stage of peripheral artery disease (PAD), which, if left untreated, can progress to ulceration, gangrene, sepsis, major lower extremity amputation (LEA) and premature death. The prevalence of PAD ranges from 3% to 10% in the general population, increasing to 15–20% in people aged ≥ 70 years. According to the 2015 report by the Organization for Economic Co-operation and Development,¹ major LEA rates in Singapore are 2–3 times higher than those in Western countries, and are in fact the highest in the world. In Singapore, PAD patients are predominantly diabetic compared to PAD patients in Western populations (diabetes mellitus type 2, 90% versus 50%), younger at onset (50 vs 60 years), present with minimal claudication symptoms, and largely below-knee atherosclerotic occlusions (vs aorto-iliac-femoral disease), and more likely to have chronic renal failure (50% vs 27%).²

The 1-year risk of major LEA in patients with CLTI exceeds 15–20% and the 5-year all-cause mortality rate is approximately 50%.³ As they have significant systemic atherosclerosis, patients with CLTI are at increased risk of premature death and have a higher incidence of cardiovascular (CV) events.⁴ Therefore, with a heightened risk of global atherothrombosis, systemic vascular prevention strategies are essential for the best holistic treatment. Current guidelines recommend antiplatelet monotherapy for prevention of CV events with a class IA recommendation for aspirin or clopidogrel, based on results of large CV outcome trials. In contrast, dual antiplatelet therapy combining aspirin and clopidogrel is used after intervention—regardless of surgical or endovascular revascularisation for the reduction of post-procedural complications. It was given a class IIa, level C recommendation in the absence of any randomised data to support this indication.⁵ A recent rapid review in the *Annals* by our group suggested adherence to evidence-based medical treatment is extremely variable and that undertreatment is common in the PAD setting.⁶ Furthermore, data from Asian countries on this front are lacking.

Our institution, the Singapore General Hospital, a tertiary vascular centre that performs over 900

lower limb endovascular revascularisation procedures annually, currently sends its lower limb angioplasty data to the US Vascular Quality Initiative (VQI)⁷ database and is the only participating centre from the Asia-Pacific region. Our aim is to improve the quality of our lower limb angioplasty outcomes by collating our data to allow valid comparison and benchmarking to other global centres of excellence. VQI is a network of vascular specialists seeking to improve the quality and safety of vascular care by sharing data. Consent to collect, analyse and publish anonymised patient data was waived. Since subscribing in July 2019, we have logged 1,361 procedures (1,016 limbs, 873 patients and 2,749 lesions) as of May 2021. Table 1 shows the baseline demographics, which is notably significant.

Only 73% of patients were on an antiplatelet agent (APA) and 84% on lipid lowering therapy at presentation. Furthermore, considering that approximately 40% of patients had prior peripheral vascular intervention, only 51/345 (15%) were on dual APA therapy. Potentially adjunct medical therapy plays an important role in minimising further limb and CV adverse events in what is a relentlessly progressive disease. In spite of this, best medical therapy is either being stopped or discontinued by the physician or patient at the primary and secondary level of outpatient specialist care. Valid reasons for non-adherence or discontinuation of these medications include symptoms such as muscle cramps or liver function derangement with statins, or bleeding complications and gastrointestinal upset with APA. Also, polypharmacy and altered physiological reserve increase the risk of adverse drug events in these frail and challenging patients. These latest Singapore data suggest we could do more to maximise adherence to existing PAD guidelines by trying to understand initially why a significant portion of our patients discontinue or are not put on best medical therapy.

It is also important to highlight that there may be a significant benefit for patients with PAD—both primarily and after revascularisation—in taking a combination of aspirin and low-dose rivaroxaban (rivaroxaban, a factor Xa inhibitor) to reduce first and subsequent adverse CV outcomes. There is emerging evidence that there is a fourfold risk of acute limb ischaemia and approximately 30% increased risk of

Table 1. Patient demographics

	Number of patients (n=873)	Percentage (%)
Mean age $\pm$ SD, years	69.0 $\pm$ 10.8	
Mean BMI $\pm$ SD, kg/m ²	24.6 $\pm$ 4.6	
Sex		
Male	566	64.8
Female	307	35.2
Ethnic group		
Asian	865	99.1
Caucasian	4	0.5
Other	4	0.5
Smoking status		
Non-smoker	496	56.8
Ex-smoker	198	22.7
Smoker	179	20.5
Comorbidities		
Hypertension	811	92.9
Diabetes	732	83.8
Coronary artery disease	512	58.6
Chronic kidney disease	303	34.7
Cerebrovascular disease	227	26.0
Dysrhythmia	160	18.3
Congestive heart failure	161	18.4
Chronic obstructive pulmonary disease	27	3.1
Medication history		
Statin	736	84.3
Antiplatelets	636	72.9
ARB	396	45.4
Anticoagulants ^a	53	6.1
Insulin	344	39.4
Non-insulin medication	388	44.4
Ambulation		
Ambulatory	406	46.5
Ambulatory with assistance	301	34.5
Wheelchair-bound	157	18.0
Bedridden	9	1.0

Table 1. Patient demographics (Cont'd)

	Number of patients (n=873)	Percentage (%)
Prior interventions		
Leg arterial bypass/ endarterectomy/PVI	345	39.5
Percutaneous coronary intervention	221	25.3
Coronary artery bypass graft	169	19.4
	Number of limbs (n=1016)	Percentage (%)
Urgency		
Emergency	598	58.9
Elective	418	41.1

ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; BMI: body mass index; PVI: peripheral vascular intervention; SD: standard deviation

^a Comprising all types of anticoagulants including rivaroxaban

myocardial infarction in patients who have previously undergone a lower extremity revascularisation procedure.⁸ Therefore, the need for peripheral revascularisation identifies a PAD subpopulation to be at a heightened risk of future vascular ischaemic events. The Vascular Outcomes study of ASA (acetylsalicylic acid) along with rivaroxaban in Endovascular or surgical limb Revascularisation for Peripheral Artery Disease (VOYAGER PAD) study was initiated to evaluate the efficacy and safety of low dose rivaroxaban (2.5mg PO BD) used together with aspirin in high-risk PAD patients undergoing lower extremity revascularisation.⁹

This landmark study enrolled 6,564 patients in 34 countries who had PAD and had undergone lower extremity revascularisation. Patients were randomly assigned to receive either rivaroxaban or a placebo, in addition to daily aspirin. There was a 15% significant relative risk reduction of developing a first major adverse limb or CV event in patients who received rivaroxaban compared to those who received placebo, seen as early as at 3 months, with a continued effect through to 3 years follow-up. Rates of the principal safety outcome of major bleeding increased but were not significantly different between the 2 groups (2.7% vs 1.9%; $P=0.07$). During 3 years of follow-up, approximately a third of patients had a CV event, in spite of high utilisation of background medical therapy.¹⁰

However, there was an absolute risk reduction of 12.5% in those receiving low dose rivaroxaban, which

is a big advantage in avoiding the need for patients to be admitted for treatment of vascular complication. From our VQI database to date, only 17/873 (1.9%) were placed on the low dose rivaroxaban regimen following revascularisation. Cost and access to the low dose formulation may be limiting factors currently, but snapshots from the current data suggest we could do more to improve not only medical adherence to traditional APA therapy, but also start a low dose thrombin inhibitor to prevent future CV events and reduce the number of major LEAs.

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