

A Summary of the Clinical Practice Guidelines for the Management of Patients with Peripheral Arterial Disease in Myanmar

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Abstract

Peripheral artery disease (PAD) broadly encompasses vascular diseases caused primarily by atherosclerosis and thromboembolic pathophysiologic processes that alter the normal structure and function of the aorta, its visceral arterial branches, and the arteries of the lower extremity. The aims of the Myanmar clinical practice guidelines for the management of patients with PAD are to assist physicians in selecting the best management strategies for an individual patient with peripheral artery disease with main focus on lower extremity artery disease (LEAD) due to atherosclerosis, to help the physician to make decisions in their daily practice, and to aid in appropriate referrals to specialists. Early detection and treatment guidelines for the treatment of PAD are important to reduce the morbidity and mortality of patients with vascular problems in Myanmar.

Key words: peripheral arterial disease, clinical practice guidelines, Myanmar

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of death and disability worldwide. Coronary artery disease (CAD) is the main cause of death, but stroke, renal failure, and severe ischaemia of the lower extremities also contribute to a significant burdens. There are studies which shown evidences of a substantial percentage of patients with chronic CAD have associated with cerebrovascular disease, lower extremity artery disease (LEAD), or both.¹

Therefore, the patients with heart disease are required to be assessed for vascular problems in other territories, both symptomatic and asymptomatic, that may affect their prognosis and treatment strategy. The patients with PAD will also probably die from CAD.²

The term peripheral artery disease (PAD) broadly encompass the vascular diseases caused primarily by atherosclerosis and thromboembolic pathophysiologic processes that alter the normal structure and function of the aorta, its visceral arterial branches, and the arteries of the lower extremity. PAD is the preferred clinical term and should be used to denote stenotic, occlusive and aneurysmal diseases of the aorta and its branch arteries, exclusive of the coronary arteries.³

PAD has a significant impact of on the incidence of major amputations and its consequent poor prognosis as patients

are more at risk for repeated amputations of remaining limbs and even death.⁴

The aims of this guideline is for assisting physicians in selecting the best management strategies for an individual patient with peripheral artery disease with main focus on lower extremity artery disease (LEAD) due to atherosclerosis. It will help the physicians to make decisions in their daily practice and aid in appropriate referrals to specialists. However, the final decisions must be made by the responsible physician(s).

Summary of methodology of guideline development

In the development of this guideline, the following issues are taken into consideration, in that the recommendations must be:

- Evidence-based
- Adapted to the local setting
- Considers patient's values in decision making
- Ensure equity

Members of this Task Force were selected to represent professionals involved with the care of patients with peripheral vascular disease. These included general physicians (internists), endocrinologists (including pediatric endocrinologists), cardiac physicians, cardiovascular surgeons, family physicians.

A review of the literatures and evidences regarding the diagnostic and therapeutic procedures was performed.

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The level of evidence and the strength of recommendation of particular treatment options were weighed and graded according to standard scales as mentioned below. It was published after appropriate revisions and approval by all the experts involved in the Task Force.

Summary of Recommendations

Table 1. Classes of recommendations⁹

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/ is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Table 2. Levels of evidence⁹

Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of Evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of Evidence C	Consensus of opinion of the experts and/ or small studies, retrospective studies, registries.

1. Epidemiology

Prevalence of PAD in the general population of different parts of the world including Asian countries ranges from 4% to 20%.⁶⁻¹⁰ In Myanmar, there is no overall prevalence data covering the whole population. However, data from the cardiac surgery unit of Yangon General Hospital (2010 to 2012) indicated that about 10% of total admissions was due to LEAD, of which approximately 75% had undergone intervention procedures such as embolectomy, bypass graft and sympathectomy. Hospital-based study of general surgical ward in Yangon General Hospital indicated that 7% of total admission was due to PAD and 10 % of PAD cases ended in amputation.

The frequency of LEAD is age related: uncommon before 50 years, rising steeply at older age.¹¹ Although more common in males, there is equilibration between sexes with increasing age.

2. Risk factors

Risk factors for PAD are similar to the typical risk factors for atherosclerotic disease. These include the traditional

risk factors: smoking, dyslipidaemia, diabetes mellitus, and hypertension. Smoking would appear to be a stronger risk factor for LEAD than for CAD.

Diabetes mellitus is an important risk for the development of LEAD.¹² Patients with diabetes have an increased prevalence, reported to be as high as 30% in some studies.¹³ In those with intermittent claudication, the strength of the association with diabetes may be comparable with that for coronary heart disease. It appears that the duration and severity of diabetes affect the level of risk.^{12,14}

Most epidemiological studies show an association between hypertension and the presence of LEAD. Hypertension was associated with an increased relative risk of 2.8 for LEAD¹⁵ and a low ABI (<0.90) was associated with both increased systolic and diastolic blood pressure.¹⁶

Most of the studies have found that high total cholesterol and low high-density lipoprotein (HDL) cholesterol are independently related to an increased risk of LEAD. The ratio of total/HDL cholesterol was the lipid measure most strongly related to disease.¹⁷

3. Diagnostic approach of lower extremity artery disease

3.1 Clinical presentation

The Fontaine classification¹⁸ is recommended for the categorization of LEAD because this classification is simple and more applicable for clinical decision in diagnosis and management of LEAD patients in Myanmar.

Table 3. Clinical staging of LEAD

Fontaine Classification ¹⁸	
Stage	Symptom
I	Asymptomatic
II	Intermittent claudication
III	Ischaemic rest pain
IV	Ulceration or gangrene

They may be asymptomatic or typically present with intermittent claudication, characterized by pain in the calves, increasing with walking; the pain typically disappears quickly at rest.

The Edinburgh Claudication Questionnaire¹⁹ is recommended as a screening method of intermittent claudication.

In physical examination, the feet must be inspected, and the colour, temperature, and integrity of the skin, and the presence of ulcerations recorded. Additionally, calf hair loss and skin changes should also be noted.

Pulse palpation should be done systematically. Palpation of the femoral, popliteal, dorsalis pedis, and posterior tibial sites must be done. Auscultation of bruits over the

femoral artery at the groin and more distally is also suggestive. Examination of other arteries such as radial, carotid, abdominal aorta should also be done.

Table 4. The Edinburgh claudication questionnaire: PAD¹⁹

- (1) Do you get a pain or discomfort in your leg(s) when you walk?
Yes
No
I am unable to walk
If you answered "Yes" to question (1) - please answer the following questions.
Otherwise you need not continue.
- (2) Does this pain ever begin when you are standing still or sitting?
Yes
No
- (3) Do you get it if you walk uphill or hurry?
Yes
No
- (4) Do you get it when you walk at an ordinary pace on the level?
Yes
No
- (5) What happens to it if you stand still?
Usually continues more than 10 minutes
Usually disappears in 10 minutes or less
- (6) Where do you get this pain or discomfort? Mark the place(s) with "x" on the diagram below
Definition of positive classification requires all of the following responses:
'Yes' to (1),
No' to (2),
'Yes' to (3), and
'Usually disappears in 10 minutes or less' to (5);
grade 1 = 'No' to (4) and grade 2 = 'Yes' to (4).



-If these criteria are fulfilled, a definite claudicant is one who indicates pain in the calf, regardless of whether pain is also marked in other sites; a diagnosis of atypical claudication is made if pain is indicated in the thigh or buttock, in the absence of any calf pain.

-Subjects should not be considered to have claudication if pain is indicated in the hamstrings, feet, shins, joints or appears to radiate, in the absence of any pain in the calf.

3.2 Diagnostic tests

3.2.1 Ankle-brachial index

The clinical diagnosis can be strongly improved by measuring the Ankle-Brachial index (ABI). This is the ratio of the ankle to brachial systolic pressure and can be measured easily using a sphygmomanometer and handheld Doppler device. Measurement of ankle brachial pressure index should be taken by properly trained practitioners.

In healthy persons, the ABI is 1.0. ABI of <0.90 had a positive predictive value of $\geq 95\%$; an ABI >1.10 had a negative predictive value of $\geq 99\%$.²⁰ In practice, an ABI of <0.9 is considered to be abnormal. The ABI of patients with intermittent claudication typically lies between 0.5 and 0.9. Critical limb ischaemia (Fontaine stage III or IV) is generally associated with an ABI of <0.5. For values > 1.5, the vessels are likely to be incompressible, and the result can be seen in calcified arteries, in the case of diabetes, ESRD, and in the very elderly.

Although highly sensitive and specific for PAD, a normal ABI at rest, in combination with classic symptoms, will necessitate referral for an ABI measurement after exercise and/or imaging to confirm or refute a possible diagnosis.

Technique of ABI measurement⁵

A 10–12 cm sphygmomanometer cuff placed just above the ankle and a (handheld) Doppler instrument (5–10 MHz) to measure the pressure of the posterior and anterior tibial arteries of each foot are required. Usually the highest ankle systolic pressure is divided by the highest brachial systolic pressure, resulting in an ABI per leg. Recently some papers reported higher sensitivity to detect LEAD if the ABI numerator is the lowest pressure in the arteries of both ankles.²¹

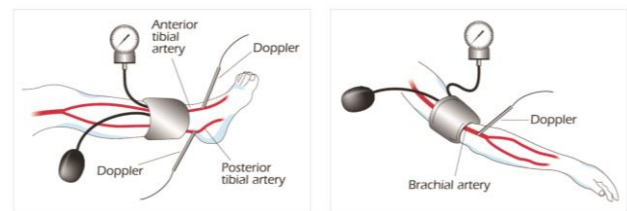


Figure 1. Measurement of the ankle-brachial index (ABI), calculated by dividing the ankle systolic blood pressure by the arm systolic blood pressure⁵

Exercise ankle brachial pressure index

The ABI before and after exercise is helpful in evaluating patients with classic symptoms and a normal or borderline resting ABI.

The patient is asked to walk (commonly on a treadmill at 3.2 km/h at a 10–20% slope) until claudication pain occurs and impedes walking. An ABI drop after exercise indicates LEAD.²²

Recommendations for ABI measurement

Measurement of the ABI is indicated as a first-line noninvasive test for screening and diagnosis of LEAD. (Class I, Level B)²³

3.2.2 Ultrasound methods

Duplex Ultrasonography (DUS)

DUS provides extensive information on both arterial anatomy and blood flow. DUS sensitivity to detect >50% diameter angiographic stenosis is 85–90%, with a specificity >95%.^{24–26}

Combined with the ABI, DUS provides all the information necessary for management decisions in the majority of patients with LEAD.

DUS is also highly useful for the follow-up after angioplasty or to monitor bypass grafts.^{27,28}

Recommendations for DUS

Non-invasive assessment method, DUS is indicated as first-line method to confirm and localize LEAD lesions. (Class I, Level B)^{29,30}

3.2.3 Angiography

Computed tomography angiography

The use of computed tomography angiography (CTA) is not recommended for screening purposes.

CTA can detect aortoiliac stenoses > 50% (sensitivity 96% and specificity 98%),³¹ stenoses of femoropopliteal region (sensitivity 97% and specificity 94%) and the below-knee arteries (sensitivity 95%, specificity 91%) respectively.³¹

The great advantage of CTA remains the visualization of calcifications, clips, stents and bypasses.

Magnetic resonance angiography

MRA can non-invasively visualize the lower limb arteries even in the most distal parts. MRA has an excellent sensitivity (93–100%) and specificity (93–100%).^{25,32-36}

Recommendation for angiography

DUS and/or CTA and/or MRA are indicated to localize LEAD lesions and consider revascularization options. (Class I, Level A)^{25,26,27,28,31-36,37,38}

4. Management

The management of peripheral arterial disease should include:

- (1) General management
 - Lifestyle modification
 - Cardiovascular risk reduction
- (2) Specific management of LEAD
 - Conservative treatment
 - Endovascular treatment or surgery

4.1 General management (Treatment of both asymptomatic and symptomatic LEAD)

4.1.1 Lifestyle modification

Recommendation regarding nutrition

A healthy diet is recommended as being the cornerstone of CVD prevention. (Class I, Level B)³⁹⁻⁴⁵

Table 5. A healthy diet has the following characteristics:³⁹⁻⁴⁵

Saturated fatty acids to account for <10% of total energy intake, through replacement by polyunsaturated fatty acids.
Trans-unsaturated fatty acids: as little as possible, preferably no intake from processed food, and <1% of total energy intake from natural origin.
<5 g of salt per day.
30–45 g of fibre per day, from wholegrain products, fruits, and vegetables
200 g of fruit per day (2–3 servings).
200 g of vegetables per day (2–3 servings).
Fish at least twice a week, one of which to be oily fish.
Consumption of alcoholic beverages should be limited to two glasses per day (20 g/day of alcohol) for men and one glass per day (10 g/day of alcohol) for women.

Recommendations regarding physical activity

Patients with previous CVD should undergo moderate to vigorous intensity aerobic exercise training ≥ 3 times a week and 30 min per session. Sedentary patients should be strongly encouraged to start light-intensity exercise programmes after adequate exercise-related risk stratification. (Class I, Level A)^{46,47}

Recommendation regarding body weight

Both overweight and obesity are associated with a risk of death in CVD. There is a positive linear association of BMI with all-cause mortality. All-cause mortality is lowest with a BMI of 20–25 kg/m².⁴⁸⁻⁵⁰

Weight reduction in overweight and obese people is recommended as this is associated with favourable effects on blood pressure and dyslipidaemia, which may lead to less CVD. (Class I, Level A)⁴⁸⁻⁵⁰

4.1.2 Cardiovascular risk reduction

Smoking cessation

Smokers should be advised to quit smoking.

Nicotine replacement therapy and/or bupropion or varenicline can be used to facilitate smoking cessation.⁵¹

Lipid lowering drugs

Statins reduce the risk of mortality, cardiovascular events and stroke in patients with PAD with and without CAD.

It also has preliminary positive effects on PAD and increase in maximal walking distance of 163 m.⁵²

Antihypertensive drugs

Treatment with angiotensin-converting enzyme (ACE) inhibitors or Angiotensin Receptor Blockers has shown a beneficial effect beyond a blood pressure decrease in high-risk groups. Beta-blockers are not contraindicated in patients with LEAD.^{53,54}

Antiplatelet and antithrombotic drugs

Low-dose aspirin (75–150 mg daily) is as effective as higher daily doses.⁵⁵ Clopidogrel is an alternative to aspirin.⁵⁶

Dual antiplatelet therapy should not be recommended in patients with LEAD due to an increased bleeding risk.^{57,58}

Recommendation for general management

All patients with PAD who smoke should be advised to stop smoking. (Class I, Level B)⁵⁹

All patients with PAD should have their LDL cholesterol lowered to <2.5 mmol/L (100 mg/dL), and optimally to <1.8 mmol/L (70 mg/dL), or $\geq 50\%$ when the target level cannot be reached. (Class I, Level C)

All patients with PAD should have their blood pressure controlled to $\leq 140/90$ mmHg. (Class I, Level A)⁶⁰

β -Blockers are not contraindicated in patients with LEAD, and should be considered in the case of concomitant

coronary artery disease and/or heart failure. (Class IIa, Level B)^{61,62}

Antiplatelet therapy is recommended in patients with symptomatic PAD. (Class I, Level C)⁵⁵

In patients with PAD and diabetes, the HbA1c level should be kept at $\leq 6.5\%$. (Class I, Level C)

In patients with PAD, a multidisciplinary approach is recommended to establish a management strategy. (Class I, Level C)

4.2 Specific management of LEAD (treatment of symptomatic LEAD-Intermittent Claudication)

4.2.1 Conservative treatment

The aim of conservative treatment in patients with intermittent claudication is to improve symptoms, i.e., increase walking distance and comfort. Two strategies are currently used:

- (i) Exercise therapy
- (ii) Pharmacotherapy

4.2.1.1 Exercise Therapy

Training therapy is effective in improving symptoms and increasing exercise capacity. The training programme lasts for 3 months, with three sessions per week. Daily walking, or repeated series of heel raising or knee bending are realistic possibilities.⁶³ Patients with Fontaine class IV should not be submitted to regular exercise training.

4.2.1.2 Pharmacotherapy

Pharmacotherapy can be used to increase walking distance in patients with intermittent claudication.

Cilostazol (100 mg BD)

Cilostazol is a phosphodiesterase-3 inhibitor. The dose of cilostazol 50 mg/day can increase the maximal walking distance 36 m on average and almost twice (70 m) with the 100 mg dose.⁵² Improvement in quality of life is also reported in claudicants.⁶⁴

Pentoxifylline (400 mg tds)

Pentoxifylline is a phosphodiesterase inhibitor and a significant increase in maximal walking distance was found with pentoxifylline (+59 m).⁵²

4.2.2 Revascularization

To select the most appropriate revascularization procedure, the main issues to be considered are the anatomical suitability (Lesion classification according to the Trans Atlantic Inter-Society Consensus TASC), comorbidities, local availability and expertise and the patient's preference.

4.2.2.1 Endovascular treatment of lower extremity artery disease

Endovascular interventions are not indicated as prophylactic therapy in an asymptomatic patient. In Myanmar, endovascular intervention by stent is rarely done.

The major drawback of endovascular interventions—compared with surgery—is the lower long-term patency.

4.2.2.2 Surgery

Bypass surgery presents the most common surgical approach for diffuse occlusive disease. Different graft materials can be applied. Autologous vein or artery grafts are the best options. If it is not always available or applicable, prosthetic grafts are considered.

Primary amputation may best be served for the patients with extensive necrosis or infectious gangrene and those who are non-ambulatory.

Amputation remains the last surgical step to solve irreversible limb ischaemia.

Recommendation for surgical revascularization

When surgery is considered to revascularize infrailiac lesions, the autologous saphenous vein is the bypass graft of choice. (Class I, Level A)^{65,66}

Recommendations for antiplatelet and anticoagulant therapy after revascularization

Antiplatelet therapy with aspirin is recommended in all patients with angioplasty for LEAD to reduce the risk of systemic vascular events. (Class I, Level C)

Dual antiplatelet therapy with aspirin and a thienopyridine for at least one month is recommended after infrainguinal bare-metal-stent implantation. (Class I, Level C)

Antiplatelet treatment with aspirin or a combination of aspirin and dipyridamole is recommended after infrainguinal bypass surgery. (Class I, Level A)⁶⁷

Antithrombotic treatment with vitamin K antagonists may be considered after autogenous vein infrainguinal bypass. (Class IIb, Level B)⁶⁸

Dual antiplatelet therapy combining aspirin and clopidogrel may be considered in the case of below-knee bypass with a prosthetic graft. (Class IIb, Level B)⁶⁹

CONCLUSION

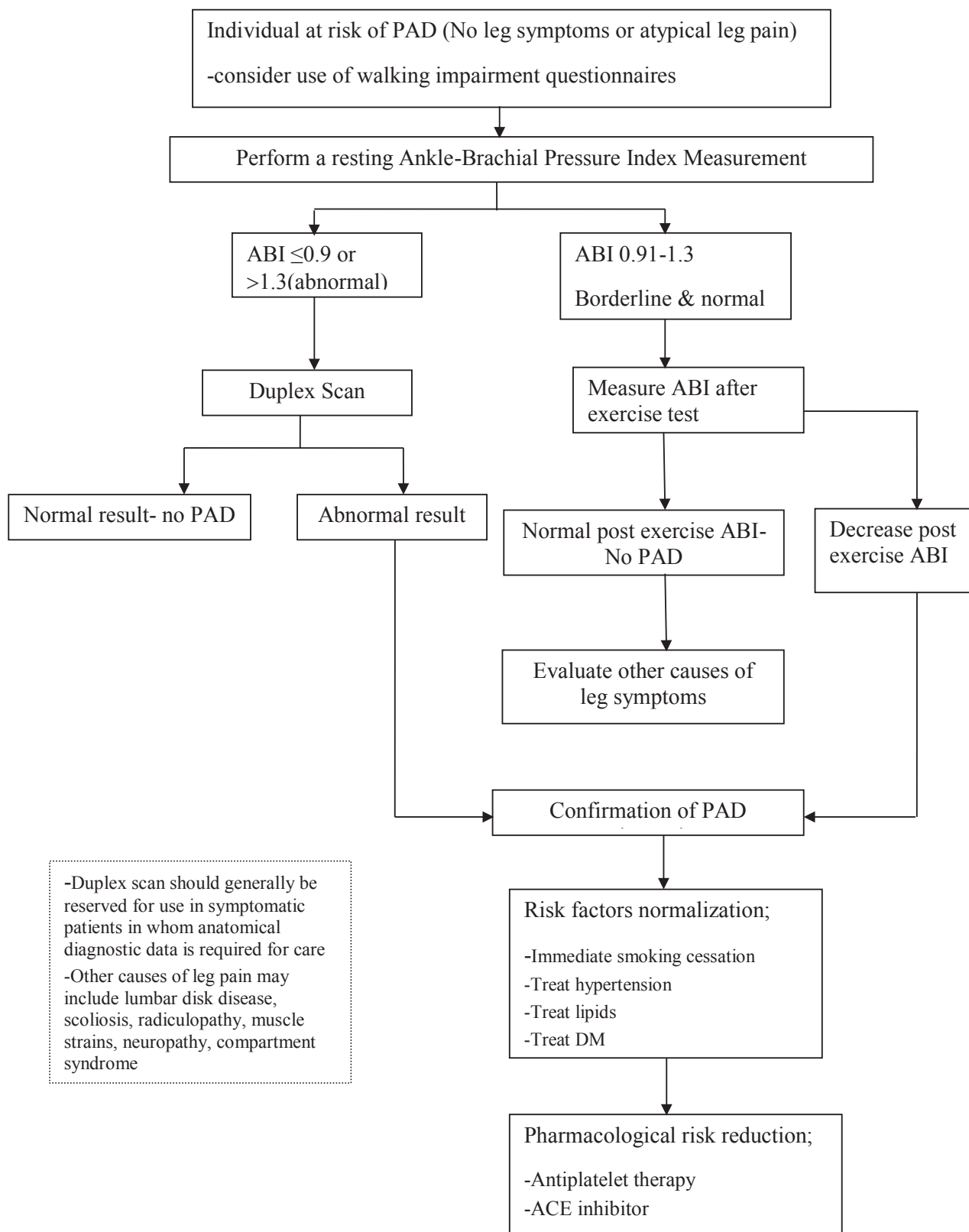
Since the patients with PAD will also probably die from CAD, screening and evaluation of comorbidities may affect their treatment outcome.

On the other hand, all the patients with CAD should be assessed for vascular problems in other territories.

The combination of early detection and clear guideline for the treatment of PAD will definitely help to reduce the morbidity and mortality of patients with vascular problems.

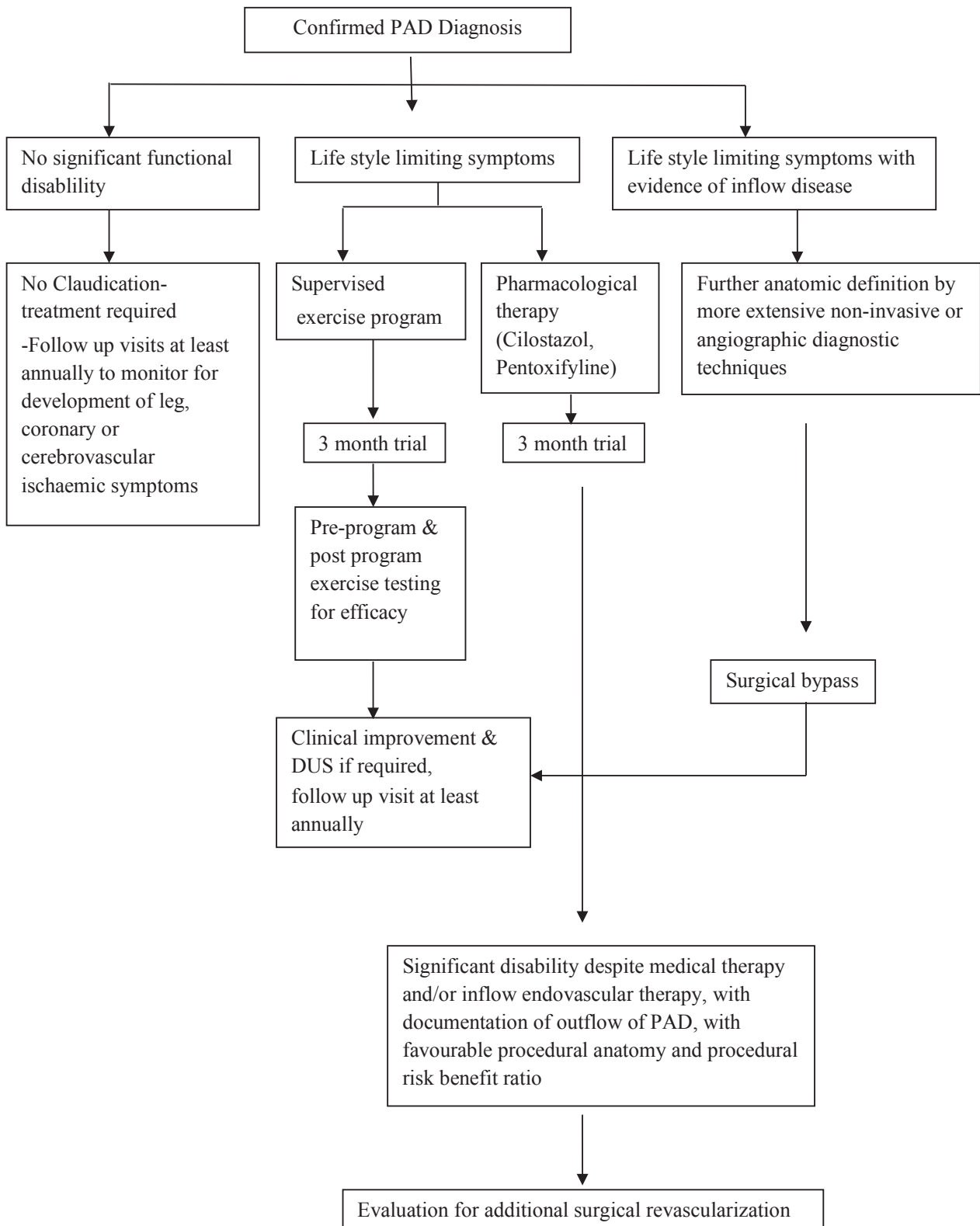
Algorithm (1)

Diagnosis and Treatment of Asymptomatic Peripheral Arterial Disease and Atypical Leg Pain (Adapted from the 2011 ACCF/AHA PAD guideline and modified according to local situation)³



Algorithm (2)

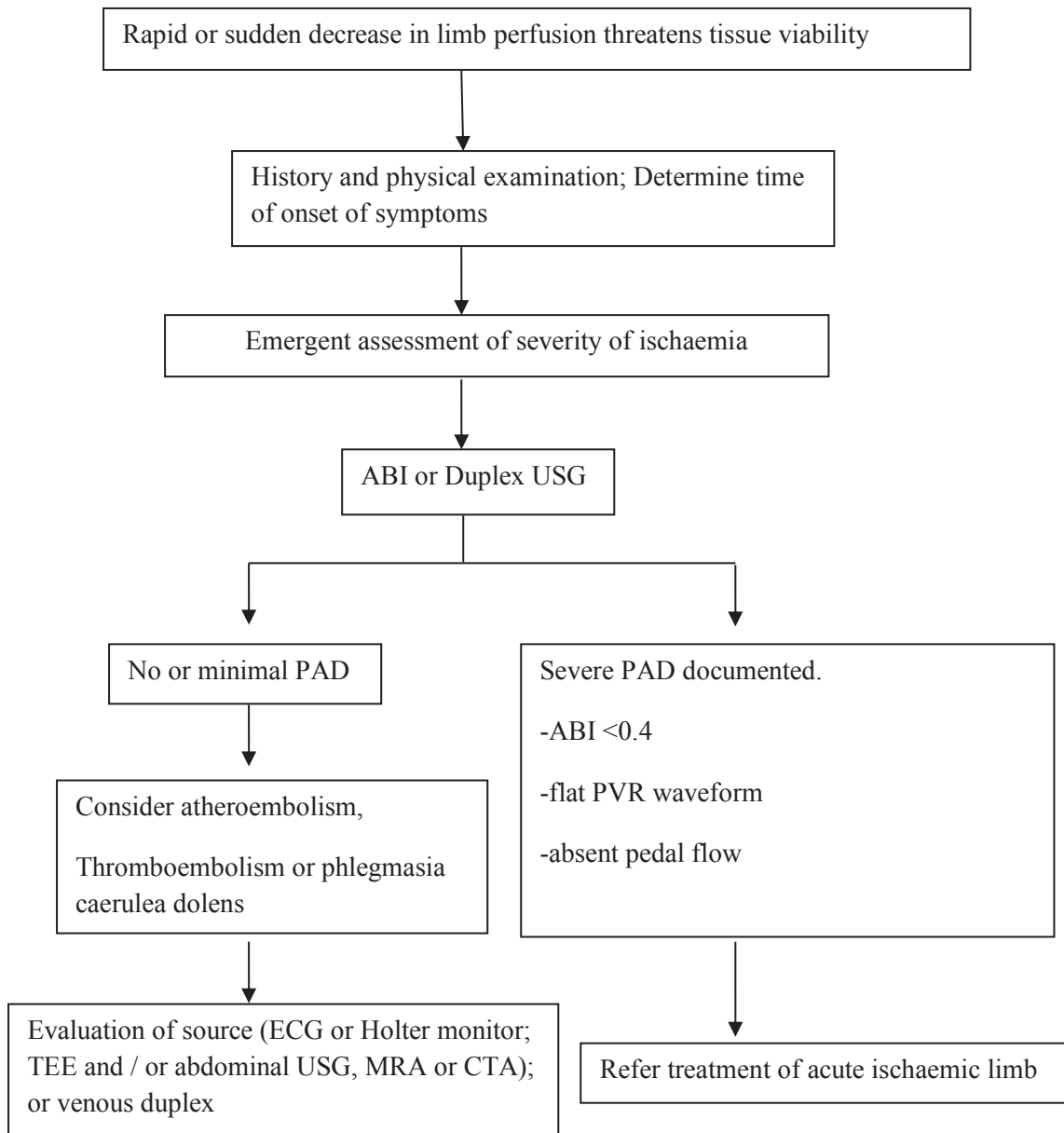
General Management of Intermittent Claudication (Adapted from the 2011 ACCF/AHA PAD guideline and modified according to local situation)³



Algorithm (3)

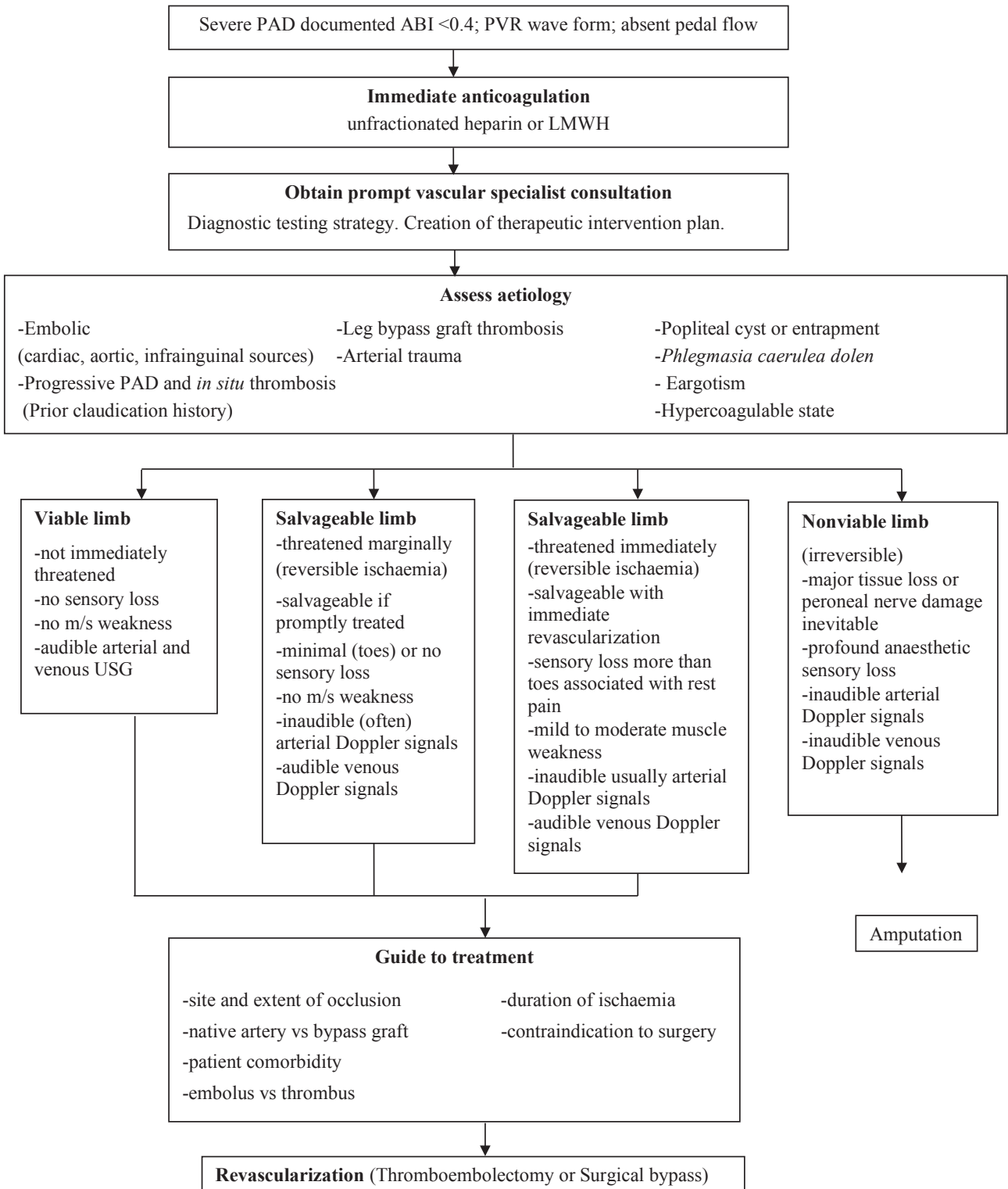
Management of acute limb ischaemia (Adapted from the 2011 ACCF/AHA PAD guideline and modified according to local situation)³

(A) Diagnosis



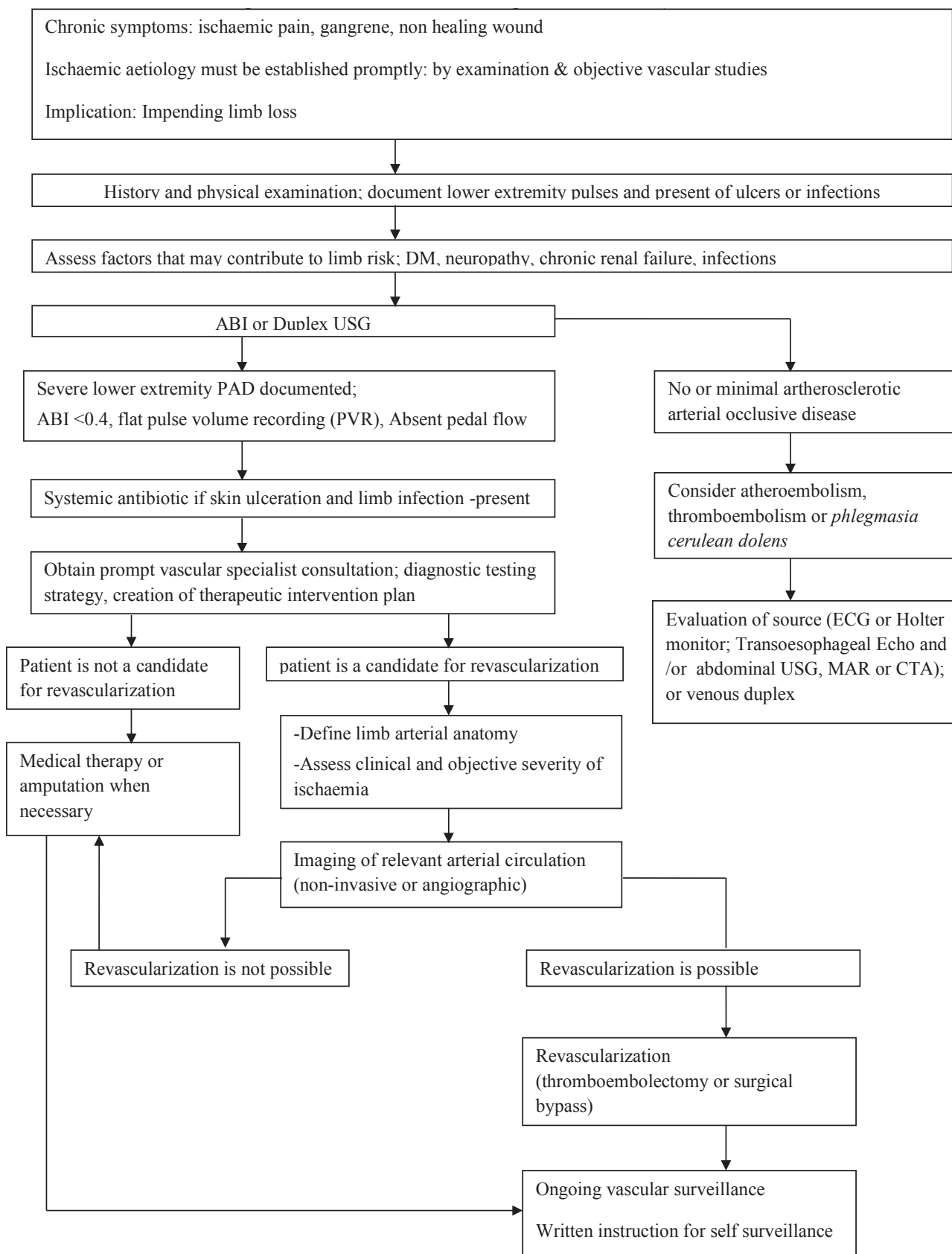
- TEE = Transoesophageal echocardiography
- MRA = Magnetic resonance angiography
- CTA = CT angiography

(B) Treatment of Acute Limb Ischaemia (Adapted from the 2011 ACCF/AHA PAD guideline and modified according to local situation)³



Algorithm (4)

Diagnosis and Treatment of Critical Limb Ischaemia (Adapted from the 2011 ACCF/AHA PAD guideline and modified according to local situation)³



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