Table 9. Risk factors associated with an increased risk of subsequent major adverse cardiovascular events (MACE) and or major adverse limb events (MALE) events; only one factor is needed to be classified as high risk. Symptomatic lower extremity atherosclerotic disease presentations thought to be higher risk for subsequent MACE and/or MALE events

Ischaemic risk factor	Reference
Symptomatic arterial disease in more than one territory	Kaplovitch *et al.* (2021),[185] Weissler *et al.* (2020),[53] Sigvant *et al.* (2017)[169]
Chronic kidney disease including dialysis dependent renal failure*	Kaplovitch *et al.* (2021),[185] Baubeta Fridh *et al.* (2018),[189] Kreutzburg *et al.* (2021)[187]
Diabetes mellitus	Kaplovitch *et al.* (2021),[185] Long *et al.* (2020),[190] Baubeta Fridh *et al.* (2018),[189] Kreutzburg et al. (2021)[187]
Heart failure	Kaplovitch *et al.* (2021),[185] Baubeta Fridh *et al.* (2018)[189]
Chronic limb threatening ischaemia	Kaplovitch *et al.* (2021),[185] Long *et al.* (2020),[190] Norgren *et al.* (2018),[191] Kreutzburg *et al.* (2021)[187]
Acute presentations of chronic lower extremity arterial disease	Kaplovitch *et al.* (2021),[185] Weissler *et al.* (2020)[53]
Previous lower limb amputation	Kaplovitch *et al.* (2021),[185] Long *et al.* (2020)[190]
Previous lower limb revascularisation	Kaplovitch *et al.* (2021),[185] Baumgartner *et al.* (2018)[192]

* COMPASS and VOYAGER excluded patients with dialysis dependent renal failure so absolute benefit of aspirin plus rivaroxaban 2.5 mg twice daily is uncertain.

Recommendation 28

Patients with chronic symptomatic lower extremity arterial disease who are not at high risk of bleeding, especially those at higher ischaemic risk, should be considered for aspirin (75 – 100 mg once daily) in combination with rivaroxaban (2.5 mg twice daily) for secondary cardiovascular and major adverse limb event risk reduction.

Class	Level	References	ToE
IIa	B	Eikelboom *et al.* (2017),[184] Kaplovitch *et al.* (2021),[185] Kreutzburg *et al.* (2021)[187]	

higher risk of amputation than ALI with no underlying LEAD.[195] In the EUCLID trial, ALI was associated with subsequent MACE (HR 1.4; 95% CI 1.0 – 2.1), all cause death (HR 3.3; 95% CI 2.4 – 4.6), and major amputation (HR 14.2; 95% CI 9.7 – 20.8).[196] In VOYAGER, ALI was the most commonly reported endpoint for patients with LEAD (373 of 6 564 patients) during a median follow up of 28 months.[29] Although direct evidence on the benefits and harms of specific antithrombotic treatment strategies in this particular patient population is lacking, it is reasonable to consider patients with LEAD complicated by ALI as being at substantially elevated risk of MACE and MALE as part of the treatment pathway in Figure 2.

Initial treatment with intravenous UFH or LMWH in therapeutic doses is an integral part of the initial management of patients with ALI of any cause. Infusions may be non-body weight adjusted, for example, a bolus dose of 5 000 International Units (IU) of unfractionated heparin followed by a maintenance dose of 1 000 – 2 000 IU/h, or body weight adjusted. LMWH may be given once (e.g., enoxaparin 1.5 mg/kg) or twice (e.g., enoxaparin 1 mg/kg twice/day). After the acute event is managed, the recommendations fall into the post-revascularisation recommendations in section 4.5.5, bearing in mind that by definition these patients are at higher ischaemic risk (Table 9).

Recommendation 29

Patients with acute limb ischaemia are recommended to have immediate intravenous unfractionated or low molecular weight heparin to reduce the risk of thrombus propagation.

Class	Level	References
I	C	Consensus

Recommendation 30

Patients with acute limb ischaemia planned for expedited revascularisation are recommended to have immediate intravenous unfractionated heparin to reduce the risk of thrombus propagation.

Class	Level	References
I	C	Consensus

4.5.4. Acute presentations of previously chronic lower extremity arterial disease. This section deals with patients with established LEAD complicated by ALI. More extensive guidance on the overall management of ALI is available from the ESVS acute limb ischaemia guidelines.[193,194] Acute embolic disease is covered in sections 4.7 and 4.11.2. Patients with LEAD complicated by ALI are at particularly high risk of MACE and MALE.[53,185] ALI in this group is also associated with a

4.5.5. Peri-procedural antithrombotics for lower extremity intervention

4.5.5.1. Intraprocedural. Heparin is commonly used during endovascular and open arterial surgery as anticoagulation for the duration of the procedure. While the practice is common, high quality evidence for its use in LEAD patients is sparse. A RCT in the 1990s randomised 284 patients undergoing open abdominal aortic aneurysm (AAA) repair to either receive intravenous UFH or no UFH. Thromboembolic and bleeding

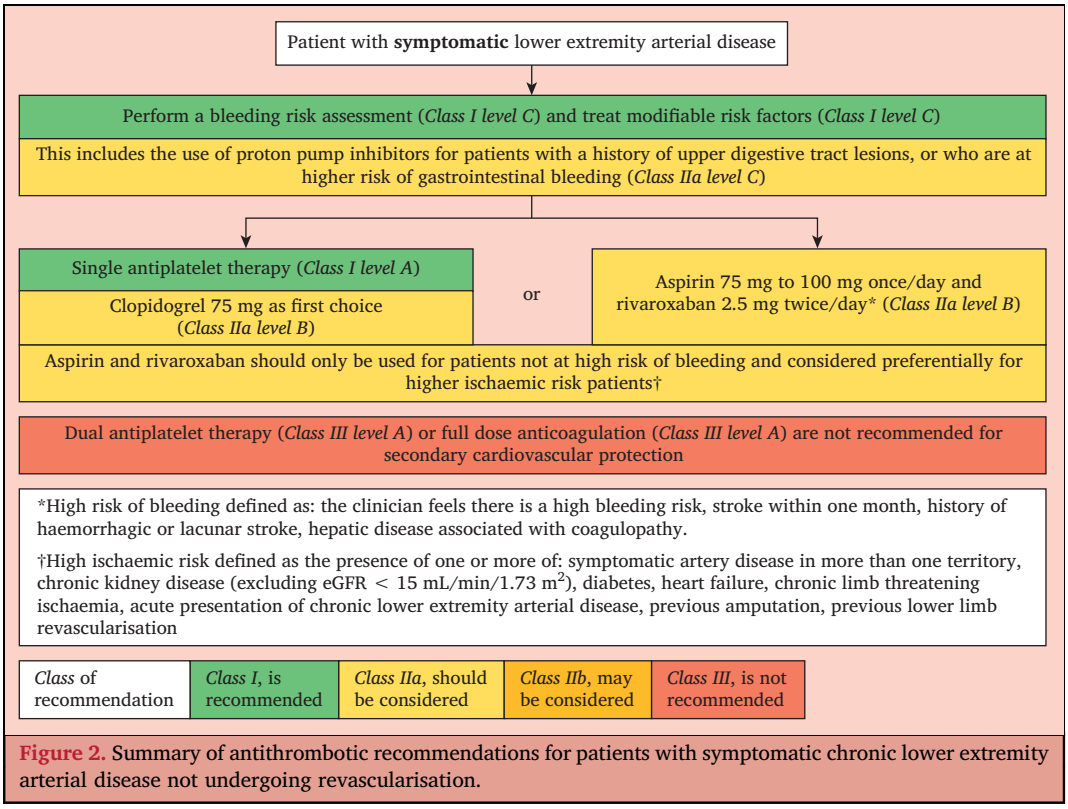

Figure 2. Summary of antithrombotic recommendations for patients with symptomatic chronic lower extremity arterial disease not undergoing revascularisation.

complications were not different between the groups; however, peri-operative MI was 1.4% in the group who received UFH and 5.7% in those who did not ($p < .050$).[197] UFH has subsequently been compared with the LMWH (enoxaparin) during endovascular intervention for LEAD.[198] The investigators randomly assigned 210 patients to intravenous UFH (60 IU/kg body weight) or intravenous enoxaparin (0.5 mg/kg). Enoxaparin was safer (GUSTO bleeding composite endpoint in 2.4% *vs.* 10.5%, $p = .035$) with minimal thromboembolic events (one event in UFH group *vs.* none in the LMWH group).[198]

Heparin monitoring is sometimes performed inter-procedurally to guide anticoagulation levels. There is no good evidence to guide this practice. The WG have therefore made a consensus (IIb) recommendation to guide intra-operative monitoring, acknowledging that it is a frequent, if non-evidence based intervention with the potential for harm in the form of bleeding if APTT levels are run in higher ranges.

Recommendation 31

Patients undergoing endovascular arterial intervention are recommended to have a single bolus of intravenous or intra-arterial unfractionated (50 – 100 IU/kg) or low molecular weight (0.5 mg/kg) heparin to reduce the risk of peri-operative acute limb events.

Class	Level	References	ToE
I	B	Duschek *et al.* (2011)[198]	

Recommendation 32

Patients undergoing open arterial surgery should be considered for a single bolus of intravenous or intra-arterial unfractionated heparin (50 – 100 IU/kg) to reduce the risk of peri-operative acute limb events.

Class	Level	References
IIa	C	Consensus

Recommendation 33

Patients undergoing endovascular or open arterial surgery may be considered for intra-operative activated partial thromboplastin time, activated partial thromboplastin time ratio, or activated clotting time measurement to guide further doses or reversal of unfractionated heparin.

Class	Level	References
IIb	C	Consensus

Bivalirudin was shown to be superior to UFH in patients undergoing percutaneous coronary intervention for reducing procedural blood loss in an individual patient meta-analysis of several large RCTs.[199] In a recent meta-analysis of lower quality data on peripheral endovascular re-intervention, bivalirudin lowered peri-operative mortality (OR 0.58; 95% CI 0.40 – 0.86), MACE (OR 0.65; 95% CI 0.51 – 0.83), peri-operative MI (OR 0.73; 95% CI 0.55 – 0.98), as well as major (OR 0.59; 95% CI 0.39 – 0.91) and minor vascular complications (OR 0.58; 95% CI 0.40 – 0.84)

compared with UFH.[200] However, the majority of included studies were retrospective cohorts, with only two of 12 studies being RCTs. There was also notable study heterogeneity for UFH dose and target ACT, and patients were not limited to LEAD.[200]

Recommendation 34			
Patients undergoing endovascular arterial intervention may be considered for a single dose of bivalirudin (0.75 mg/kg) as an alternative to heparin to reduce the risk of peri-operative acute limb events.			
Class	**Level**	**References**	**ToE**
IIb	B	Hu *et al.* (2019)[200]	

4.5.5.2. Endovascular arterial intervention post-procedure antiplatelet therapy. In contrast to patients undergoing percutaneous coronary intervention, evidence for antithrombotic therapy after peripheral endovascular lower limb treatment is sparse and heterogeneous. Current practice has mainly been based on extrapolation of results from studies undertaken in cardiology.[201,202]

In a systematic review and network meta-analysis, a reduction of major amputation rates following lower limb revascularisation was observed for patients treated with clopidogrel and aspirin compared with aspirin alone after endovascular intervention (HR 0.68; 95% CI 0.46 — 0.99).[203] However, this conclusion was based on the results of the CHARISMA,[13,178] CASPAR,[11] and MIRROR[19] trials. CHARISMA included a heterogeneous group of patients (both symptomatic and asymptomatic, and from the symptomatic group, 54.7% underwent peripheral bypass or angioplasty), while CASPAR included only patients undergoing bypass surgery. The only trial to specifically examine patients undergoing endovascular intervention was the MIRROR trial, which only recruited 80 patients in total so was underpowered for clinical outcomes.[19] In the same network meta-analysis, a higher risk of severe bleeding was also observed with DAPT (HR 1.48; 95% CI 1.05 — 2.10).[203] In another meta-analysis, DAPT compared with single antiplatelet therapy resulted in substantially more major bleeding events (37 more major bleeding events per 1 000 studied patients, 95% CI 8 — 102) with no statistically significant clinical benefit.[52]

The MIRROR trial remains the only dedicated RCT of DAPT with clopidogrel plus aspirin *vs.* placebo plus aspirin. MIRROR had a very small study population ($n = 80$) and no sample size calculation. They investigated a primary endpoint of platelet activation markers while surrogate markers of clinical success (mainly binary re-stenosis and target lesion revascularisation) were secondary endpoints. The definition of target lesion revascularisation included angiographic evidence of re-stenosis and as such was not clinically driven. The six month secondary endpoint data demonstrated target lesion revascularisation rates of 5% in the DAPT arm and 20% in the placebo plus aspirin arm; these early benefits were not sustained at 12 months. The quality of evidence from MIRROR is too low for meaningful recommendations. Furthermore, there are currently no dedicated RCTs showing the effect of prolonged DAPT (more than six months) in patients undergoing endovascular lower limb revascularisation.

A Swedish nationwide population based registry study of 1 941 patients with diabetes and CLTI, showed that DAPT lowered the major amputation rate compared with aspirin alone (HR 0.56; 95% CI 0.36 — 0.86), especially in those receiving a stent (HR 0.26; 95% CI 0.13 — 0.52), without notably increasing the bleeding risk (HR 1.4; 95% CI 0.86 — 2.29).[204]

There has been an increasing tendency to use DAPT following endovascular intervention in clinical practice over time.[201,202] This coincided with the introduction of newer technologies such as drug coated balloons and drug eluting stents where RCTs assessing the new technology mandated DAPT following the intervention without justification in their protocols. This, combined with a large volume of data following percutaneous coronary intervention, means that it is reasonable to recommend DAPT following endovascular intervention. However, its use should be limited because of a lack of both safety and efficacy data for patients with LEAD. Following a period of DAPT, patients should be considered as having chronic symptomatic LEAD with recommendations in section 4.5.2.

Recommendation 35		
Patients undergoing endovascular intervention for lower extremity arterial disease who are not at high risk of bleeding may be considered for a short course (a minimum of one to maximum six months) dual antiplatelet therapy (aspirin 75 mg plus clopidogrel 75 mg) to reduce the risk of secondary cardiovascular and major adverse limb events.		
Class	**Level**	**References**
IIb	C	Consensus

The effect of cilostazol following lower limb endovascular intervention has been studied in a recent meta-analysis.[205] Within the context of three heterogeneous RCTs (including 448 patients from Japan) and five observational studies, the addition of 200 mg cilostazol to standard antithrombotic strategies compared with standard antithrombotic strategies alone improved the primary patency (OR 2.28; 95% CI 1.77 — 2.94) while lowering the risk of target lesion revascularisation (OR 0.37; 95% CI 0.26 — 0.52) and major amputation (OR 0.15; 95% CI 0.040 — 0.62) after revascularisation in the femoropopliteal segment (seven of the eight studies). This association remained statistically significant regardless of antithrombotic regimen. Bleeding was not reported consistently in the included studies and could not be analysed. However, as discussed in section 4.5.2.1, cilostazol's use has been limited in Europe, and it has never been compared with other strategies such as DAPT with aspirin and clopidogrel following endovascular intervention. There is insufficient evidence to recommend it following endovascular intervention.