CLINICAL PRACTICE GUIDELINE DOCUMENT

Editor's Choice — European Society for Vascular Surgery (ESVS) 2023 Clinical Practice Guidelines on Antithrombotic Therapy for Vascular Diseases

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ABBREVIATIONS AND ACRONYMS

AAA	Abdominal Aortic Aneurysm
AF	Atrial Fibrillation
ALI	Acute Limb Ischaemia
APTT	Activated Partial Thromboplastin Time
AVF	Arteriovenous Fistula
AVG	Arteriovenous Graft
CAD	Coronary artery (atherosclerotic) disease
CAS	Carotid Artery Stenting
CEA	Carotid Endarterectomy
CI	Confidence Interval
CKD	Chronic Kidney Disease
CLTI	Chronic Limb Threatening Ischaemia
COVID-19	Coronavirus Disease 2019
COX	Cyclo-oxygenase
CT	Computed Tomography
DAPT	Dual Antiplatelet Therapy
DOAC	Direct Oral Anticoagulant
DVT	Deep Vein Thrombosis
eGFR	Estimated Glomerular Filtration Rate
ESVS	European Society for Vascular Surgery
EVAR	Endovascular Abdominal Aortic Aneurysm Repair
GRADE	Grading of Recommendation Assessment, Development, and Evaluation system[1]
GWC	Guideline Writing Committee
GUSTO	Global Utilisation of Streptokinase and Tissue plasminogen activator for Occluded Arteries
HIT	Heparin Induced Thrombocytopenia
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
INR	International Normalised Ratio
ISTH	International Society on Thrombosis and Haemostasis
IU	International Units
LEAD	Lower Extremity Arterial Disease (atherosclerotic)
LMWH	Low Molecular Weight Heparin
MACE	Major Adverse Cardiovascular Events
MALE	Major Adverse Limb Events
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
OR	Odds Ratio
PAD	Peripheral Artery Disease
PPI	Proton Pump Inhibitor
PE	Pulmonary Embolism
RCT	Randomised Controlled Trial
RR	Risk Ratio
SD	Standard Deviation
SVT	Superficial Vein Thrombosis
TIA	Transient Ischaemic Attack
TIMI	Thrombolysis In Myocardial Infarction
UFH	Unfractionated Heparin
VKA	Vitamin K Antagonist
VTE	Venous Thromboembolism
WG	Working Group
	Randomised trial acronyms
ACE	Aspirin and Carotid Endarterectomy[2]
AMBDAP	AMBulatory Dual AntiPlatelet[3]
AMPLIFY	Oral Apixaban for the Treatment of Acute Venous Thromboembolism[4]
Dutch BOA	Dutch Bypass Oral anticoagulants or Aspirin study[5]
EUCLID	Examining Use of tiCagreLor in PAD[6]
CALISTO	Comparison of Arixtra in lower LImb Superficial vein Thrombosis with placebO[7]
CADISS	Cervical Artery Dissection In Stroke Study[8]
CAPRIE	Clopidogrel versus vs.Aspirin in Patients at Risk of Ischaemic Events[9]
CARESS	Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic carotid Stenosis[10]
CASPAR	Clopidogrel and AcetylSalicylic Acid in bypass Surgery for Peripheral ARterial Disease[11]
CHANCE	Clopidogrel in High risk patients with Acute Non-disabling Cerebrovascular Events[12]
CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilisation, Management, and Avoidance[13]
COMPASS	Cardiovascular OutcoMes for People using Anticoagulation Strategies[14]
CREST	Carotid Revascularisation Endarterectomy versus Stenting Trial[15]
ESPRIT	European-Australasian Stroke Prevention in Reversible Ischaemia Trial[16]
ESPS-2	The European Stroke Prevention Study-2[17]
FASTER	Fast Assessment of Stroke and Transient ischaemic attack to prevent Early Recurrence[18]
MIRROR	Management of perIpheral aRterial interRventions with mono Or dual antiplatelet theRapy trial[19]
POISE-2	Peri-Operative ISchaemic Evaluation 2[20]
POINT	Platelet Oriented Inhibition in New TIA and Minor Ischaemic Stroke[21]
POPADAD	Prevention Of Progression of Arterial Disease And Diabetes[22]
PRoFESS	Prevention Regimen for Effectively Avoiding Second Strokes[23]
STEFLUX	Superficial ThromboEmbolism and FLUXum[24]
STENOX	Superficial Thrombophlebitis treated by ENOXaparin[25]
SURPRISE	Superficial vein thrombosis treated for 45 days with rivaroxaban versus fondaparinux[26]
THALES	Acute STroke or Transient IscHaemic Attack Treated With TicAgreLor and ASA for PrEvention of Stroke and Death[27]
TRA 2P-TIMI 50	Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischaemic Events trial[28]
VOYAGER	Vascular Outcomes Study of ASA (acetylsalicylic acid) Along with Rivaroxaban in Endovascular or surgical limb Revascularisation for Peripheral Arterial Disease[29]
WAVE	Warfarin and Antiplatelet Vascular Evaluation[30]

1. INTRODUCTION

1.1. Purpose

The European Society for Vascular Surgery (ESVS) has developed a series of clinical practice guidelines for clinicians caring for patients with vascular diseases. This is the first guideline specifically examining antithrombotic therapy. The aim of the guideline is to assist clinicians and patients in selecting an optimal antithrombotic strategy.

The antithrombotic field has evolved rapidly over the last few years with the introduction of new classes of agents and a better understanding of the use of established agents. This guideline is all encompassing to cover as many arterial and venous conditions as possible for patients cared for by vascular departments across Europe and the rest of the world. Some arterial territories are beyond the scope of this guidance such as intracerebral and coronary, although occasionally data have been extrapolated from trials in these areas.

The term "patient" as used in the guideline is all encompassing. Where age is important for a specific recommendation, it will be considered in the relevant section. Otherwise, these guidelines apply to adults over the age of 18. The clinician responsible for that person's care will differ by condition and country. They will include angiologists, cardiologists, interventional radiologists, haematologists, neurologists, phlebologists, vascular physicians, and vascular surgeons. The guidelines were therefore developed by a multidisciplinary group of specialists in the field to promote a high standard of care based on the highest quality evidence available. As always, guidelines should not be viewed as a legal standard of care. The document provides guidance and support, and the choice of therapy will depend on the individual patient and treatment setting.

This guidance and support is especially important in the context of antithrombotic therapy as some drugs will not be available in certain countries, or the cost of use may be prohibitive. There may also be more than one antithrombotic option available for a patient. This is where shared decision making is particularly important and will need to balance the risk of bleeding (section 1.3.1) with the reduction in risk of cardiovascular events.

Cost is likely to be the greatest barrier to implementation of these guidelines, especially for newer drugs. These guidelines do not have the scope to go into detail on the health economics of antithrombotic drugs, as both cost and cost thresholds vary by country. Health economic analysis will need to be performed locally, when relevant, using standardised methodology.[31] Bleeding concerns are also likely to be a barrier to implementation. This has been considered in detail in the relevant chapters, as well as section 1.3.

Vascular centres are encouraged to audit any implementations made as a result of this guideline. Audit cycles should be repeated regularly and changes implemented based on results. As well as use of appropriate antithrombotic assessments, major bleeding using a standard definition should also be monitored (see section 1.3). There are many ways to perform clinical audit, and most centres now require that any audit is registered with a local audit committee. Paid and not-for-profit tools are readily available online if necessary.

To enhance the global reach and applicability of this guideline, external international reviewers have reviewed the document. All ESVS guidelines and the app can be downloaded free of charge from the ESVS website (https://www.esvs.org/journal/guidelines/).

The abbreviation "peripheral artery disease" (PAD) is used in the guideline to encompass atherosclerotic lower extremity arterial disease (LEAD) from the aorta to the toes, atherosclerotic upper limb arterial disease, atherosclerotic visceral artery disease, and atherosclerotic cerebrovascular disease. There are many terms and definitions for "chronic" or "stable" atherosclerotic arterial disease. In the guideline the term "chronic" is used to cover all non-acute presentations.

1.2. Methodology

The AGREE reporting standards for clinical practice guidelines were used throughout the guideline process and the checklist is included as Appendix B.[32]

1.2.1. Writing Committee. Members of the Guideline Writing Committee (GWC) were selected by the guideline chairs and ESVS Guideline Steering Committee to represent clinician groups involved in antithrombotic therapy decision making for patients with vascular disease. This included representation from the disciplines of angiology, phlebology, cardiology, clinical pharmacology, interventional radiology, vascular medicine, and vascular surgery (Appendix A). Members of the GWC have provided disclosure statements regarding relationships that might be perceived as conflicts of interest. These are available from ESVS headquarters (info@esvs.org). Members of the GWC received no financial support from any pharmaceutical, device, or industry body to develop these guidelines. Videoconference software support was funded by the ESVS. The ESVS Guideline Steering Committee was responsible for undertaking the review process and reviewed the document at each round. The final version was checked and approved by the GWC and ESVS Guideline Steering Committee.

1.2.2. Definition of clinically relevant issues. The GWC held an introductory meeting on 3 and 4 July 2020 by videoconference where the list of topics and author tasks were determined. The GWC met monthly by videoconference to discuss the writing process and ongoing issues. After the first draft was completed and internally reviewed, the GWC held a further videoconference on 15 and 16 April 2021 to

review and approve the wording of each recommendation. Consensus recommendations were discussed and agreed during these meetings and had to have majority consensus from all members of the GWC to be included. A further videoconference was held on 10 January 2022 to review and approve the wording of each recommendation following changes made after peer review.

1.2.3. Literature search. Detailed search strategies for sections of the guideline are available in Appendix C. Members of the GWC performed literature searches in Medline (through PubMed), Embase, Clinical Trials databases, and the Cochrane Library from inception up to the date specified in the search for peer reviewed publications. Hand searching of included references was also performed. Literature searches were updated for guideline publication in October 2022.

Selection of studies for inclusion was based on the titles and abstracts of retrieved studies. The selection process followed the pyramid of evidence with systematic review and meta-analysis of randomised controlled trials (RCT) at the top, followed by RCTs, meta-analysis of observational studies, and finally observational studies. Case reports, abstracts, and *in vitro* studies were excluded leaving expert opinion at the base of the pyramid.

Expanded information from the studies used for each recommendation is shown in the tables of evidence (ToE, Appendix D).

1.2.4. Studies performed for this guideline. A fundamental part of this guideline is to guide clinicians in assessing the risk of bleeding when recommending antithrombotic therapy (see section 1.3). There was no well validated scoring system to assess the risk of bleeding for a patient with PAD, so a study was performed to create and internally validate a score by the GermanVasc group and members of the GWC.[33] This score (the OAC^3 PAD score) used data from over 80 000 patients hospitalised with PAD in Germany to predict the risk of major bleeding at one year. There is more detail in section 1.3.1.

Section 3.2.2 on antiplatelet function testing following arterial endovascular intervention had a large amount of low quality literature with no RCT to form recommendations. A systematic review and meta-analysis specifically on the impact of antiplatelet function testing to detect high on treatment platelet reactivity following endovascular intervention was therefore performed by members of the GWC.[34] This meta-analysis included eight prospective and two retrospective studies examining platelet resistance (high on treatment platelet reactivity) in 1 444 patients following endovascular intervention for LEAD. The meta-analysis findings were of such low certainty that evidence based recommendations based on them could not be made (see section 3.2.2).

Section 4.8, antithrombotics for aneurysmal disease had no systematic review and meta-analysis available to combine the small number of heterogeneous RCTs and cohort studies available. This was therefore performed by members of the GWC to guide recommendations (sections 4.8.1 — 4.8.2, recommendations 46 — 48).[35]

Finally, an update of the Cochrane review, Medical adjuvant treatment to increase patency of arteriovenous fistulae and grafts,[36] was triggered by the process of writing this guideline to guide recommendations in section 4.10 Vascular access for haemodialysis (section 4.10).

1.2.5. Evidence and recommendations criteria. A modification of the European Society of Cardiology (ESC) system was used for grading the level of evidence and class of recommendations. For each recommendation made in the guideline, the level of evidence was graded from A to C (Table 1) with A being the highest. The strength (class) of each recommendation was graded from I to III, with I being the strongest (Table 2).

1.2.6. Areas covered by other European Society for Vascular Surgery guidelines and overlap. Almost every ESVS guideline has a section on antithrombotic therapy. The purpose of this guideline was to update and add significant detail over the basic recommendations made in pre-existing guidelines. This led to differences in recommendations which are explained in Tables 3 and 4. There are multiple other guidelines from other major bodies with antithrombotic recommendations. Major differences in recommendations are also explored in Table 3 and 4. This guideline often goes into more detail and has more recommendations on various antithrombotic therapies than other guidelines. Unless there is a clear clash these are not highlighted. This includes recommendations on aspirin and rivaroxaban which were not considered by other guidelines (other than the 2023 update to the ESVS carotid guideline[37] and the European Society for Cardiology focused update[38]) as the seminal studies were not published.

1.2.7. The revision process. The guideline document underwent a formal external expert peer review process, and, additionally, was reviewed and approved by the ESVS Guideline Steering Committee and by the editors of the *European Journal of Vascular and Endovascular Surgery*. This document was reviewed over three rounds by 19 reviewers, including 15 members of the ESVS Guideline Steering Committee (with a review coordinator) and four external worldwide reviewers. All reviewers assessed all versions and approved the final version of this document on

Table 1. Levels of evidence from the adapted European Society of Cardiology evidence grading system

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

Table 2. Class of recommendations from the European Society of Cardiology evidence grading system

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

27 February 2023, which was accepted for publication on 28 February 2023.

1.2.8. Guideline implementation, auditing, and update plan. Guideline implementation tools include guideline summary documents, links to flow charts and algorithms, and the ESVS Guidelines App. Monitoring of the application of guideline recommendations and the impact of implementing recommendations will be via surveys of ESVS members and oral feedback by clinicians, experts in the field, and other key stakeholders. Evidence for antithrombotic therapy evolves constantly and current recommendations can become outdated. It is the aim of the ESVS to revise the guidelines when important new evidence is published or in accordance with the ESVS policy to update all guidelines.

1.2.9. Patient and public involvement. Members of the public were not directly involved in the guideline development or literature review. To facilitate patient and public involvement in the guideline, a plain language summary was prepared applying standards set by the MECIR (Methodological Expectations of Cochrane Intervention Reviews) working group.[51] This was reviewed and commented on by two members of the public involved in vascular surgery research from the Centre for Trials Research, Cardiff, UK.

1.3. Benefit vs. harm

The fundamental balance of antithrombotic therapy hinges on providing benefit by preventing cardiovascular and limb events, while causing harm, mainly via major bleeding events. For every indication where antithrombotic therapy is recommended, the harm caused by potential major bleeding must be considered. The events prevented must be important enough to a patient to accept the risks involved. This risk perception will differ for each individual patient and should be discussed as part of shared decision making when antithrombotic therapy is being considered.

As an example, it is worth considering a widely accepted indication for antiplatelet therapy. In a recent meta-analysis, single antiplatelet therapy for secondary cardiovascular prevention in patients with chronic symptomatic LEAD is recommended by this guideline and prescribed widely. However, the only adverse clinical event notably reduced is cardiovascular death, where for every 1 000 patients prescribed antiplatelet therapy, eight events are prevented.[52] Seven major bleeding events will be caused by the antiplatelet single therapy in the same 1 000 patients. Absolute precision in estimating this balance from meta-analysis is made difficult by heterogeneous trials of different antiplatelet agents with different endpoints and definitions, but this example illustrates the occasionally tenuous balance struck when antithrombotic therapy is recommended by the guideline. The same risk balance exists for every indication for antithrombotic therapy; however, the number of events prevented starts to increase when the patient has a higher risk of thrombotic events, such as patients undergoing intervention or with symptomatic arterial disease in more than one territory.[52,53] Some recommendations are therefore tailored to different outcomes depending on this risk balance.

A major problem in defining the risk balance is the lack of standardised definitions in RCTs, especially of major bleeding. Specific systems include GUSTO (Global Utilisation Of Streptokinase and Tissue plasminogen activator for Occluded Arteries), TIMI (Thrombolysis In Myocardial Infarction), and ISTH (International Society on Thrombosis and Haemostasis).[54] These all differ in their definitions, making accurate comparison of bleeding rates between RCTs impossible. They are mentioned in the text, where applicable, for context. The other major problem is that patients entered into RCTs tend to be at lower risk of bleeding than the general population.[55,56] This is due to trial exclusion criteria which do not always reflect real world practice.

1.3.1. Bleeding risk assessment and risk reduction. There are many risk prediction scores for assessing an individual's bleeding risk, although none are well validated or widely used in the patient populations considered by this guideline. The population considered by the guideline at highest risk of bleeding is the symptomatic LEAD group and LEAD groups undergoing intervention.

As part of the development of this guideline, several of the authors collaborated on a new bleeding score generated and internally validated from a population of 81 930 patients undergoing inpatient treatment for LEAD on a range of antithrombotic agents (including antiplatelets and anticoagulants) from a large German health

Table 3. Differences between recommendations from other major guidelines and this guideline for Section 4. Antithrombotics for patients with arterial disease

Guideline, publication year	Recommendation	ESVS antithrombotic guideline recommendation	Reasons for differences
Antithrombotic therapies in aortic and peripheral arterial diseases in 2021: a consensus document from the ESC working group on aorta and peripheral vascular diseases, the ESC working group on thrombosis, and the ESC working group on cardiovascular pharmacotherapy[38] 2021	Long term low dose rivaroxaban plus aspirin may be proposed for inpatients with asymptomatic carotid stenosis or in those with a history of carotid revascularisation, who are considered at very high risk because of associated comorbidities (especially polyvascular patients), provided bleeding risk is not high	No recommendation for aspirin and rivaroxaban for carotid disease	This GWC along with the ESVS carotid guideline GWC notes the major problem with forming recommendations for patients with carotid stenoses from COMPASS was that patients with pre-existing indications for DAPT and a non-aspirin antiplatelet were excluded, which would exclude many patients with asymptomatic carotid disease
2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery[39] 2017	For patients requiring antiplatelet therapy, clopidogrel may be preferred over aspirin (Class IIb, level B)	Patients with chronic symptomatic lower extremity arterial disease should be considered for clopidogrel (75 mg) as the first choice antiplatelet agent when single antiplatelet therapy is indicated for secondary cardiovascular prevention (Class IIa, level B)	The recommendation for stable or chronic symptomatic patients with LEAD was re-considered in the light of the COMPASS trial. The decision for this to be IIa or IIb was debated extensively over the course of developing this guideline, but on balance it was changed to IIa in line with the new recommendation on aspirin plus low dose rivaroxaban
	DAPT with aspirin and clopidogrel for at least one month should be considered after infrainguinal stent implantation (Class I, level B)	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 month to a maximum of six) dual antiplatelet therapy (aspirin 75 mg plus clopidogrel 75 mg) to reduce the risk of secondary cardiovascular and major adverse limb events (Class IIb, level C)	As there is no powered RCT evidence to support DAPT, this was downgraded. The only RCT (leading to a level B in the ESC guidelines) is MIRROR, which is too underpowered to be considered level B
	Combination treatment with ASA and cilostazol may be considered to improve patency and reduce amputation rates following infra-inguinal endovascular treatment	No recommendations on cilostazol	This GWC recognised that cilostazol was contentious. The randomised evidence is weak (underpowered) and confusion over the antiplatelet properties of cilostazol with subsequent reports of major bleeding has led to a notification from the European Medicines Agency. This led the GWC to not form any recommendations
2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease[40] 2017	The effectiveness of dual antiplatelet therapy (aspirin and clopidogrel) to reduce the risk of cardiovascular ischaemic events in patients with symptomatic PAD is not well established (Class IIb, level B)	Patients with chronic symptomatic lower extremity arterial disease are not recommended to have dual antiplatelet therapy for secondary cardiovascular prevention (Class III, level B)	The recommendation from the AHA is more of a statement than guideline recommendation. Meta-analysis of RCTs shows only harm for dual antiplatelet therapy when used for patients with chronic symptomatic lower extremity arterial disease. As a result, its use is not recommended

Continued

Table 3-*continued*

Guideline, publication year	Recommendation	ESVS antithrombotic guideline recommendation	Reasons for differences
Vascular Access: 2018 Clinical Practice Guidelines of the European Society for Vascular Surgery[41] 2018	No recommendation	Patients undergoing arteriovenous fistula or graft formation are not recommended to have systemic unfractionated heparin because of the increased risk of bleeding and lack of benefit for patency (Class III, level A)	The ESVS vascular access guideline does not make a recommendation. It cited the same meta-analysis and concluded there was an increased risk of bleeding but no advantage to systemic heparinisation. It was felt that a recommendation was important because there was level A evidence for harm with no clear evidence of benefit
	Long term antithrombotic therapy should not be used to prolong vascular access patency in haemodialysis patients (Class III, level C)	Patients undergoing formation of arteriovenous fistulas should be considered for clopidogrel (75 mg) for up to six months as the first line antiplatelet agent to improve fistula patency (Class IIa, level B)	The ESVS vascular access guidelines and this guideline are similar except this guideline recommends the specific agents to use rather than blanket recommending stopping in the long term. There is no RCT evidence to support the use of antiplatelet agents over six months following formation of the fistula
		Patients undergoing formation of arteriovenous fistulas may be considered for aspirin (75 − 100 mg) for up to six months to improve fistula patency if clopidogrel is contraindicated (Class IIb, level A)	
		Patients undergoing formation of non-autologous arteriovenous grafts may be considered for single antiplatelet therapy for up to six months to improve fistula patency (Class IIb, level C)	
Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guideline for vascular access: 2019 update[42] 2019	10.5 KDOQI does not suggest the use of adjuvant clopidogrel monotherapy initiation in the peri-operative period to improve AVF maturation and reduce the likelihood of primary failure. (Conditional Recommendation, Low Quality of Evidence)	Patients undergoing formation of arteriovenous fistulas should be considered for clopidogrel (75 mg) for up to six months as the first line antiplatelet agent to improve fistula patency (Class IIa, level B)	The KDOQI guideline does not consider the two meta-analyses of RCTs included here. It bases its recommendation on fewer RCTs. The present AVF recommendations, while different, therefore have a higher level of evidence. The AVG recommendations are similar in in the KDOQI and this guideline. Again, meta-analysis of RCTs where they consider individual RCTs are now available
	14.4 There is inadequate evidence for KDOQI to make a recommendation on the use of clopidogrel or prostacyclin to improve AVF primary failure.	Patients undergoing formation of arteriovenous fistulas may be considered for aspirin (75 − 100 mg) for up to six months to improve fistula patency if clopidogrel is contraindicated (Class IIb, level A)	

Continued

Table 3-*continued*

Guideline, publication year	Recommendation	ESVS antithrombotic guideline recommendation	Reasons for differences
	14.5 KDOQI suggests careful consideration of potential individual patient benefits, risks, and circumstances prior to the use of combination dipyridamole (200 mg) and aspirin (25 mg) twice daily to improve AVG primary unassisted patency. (Conditional Recommendation, High Quality of Evidence)	Patients undergoing formation of non-autologous arteriovenous grafts may be considered for single antiplatelet therapy for up to six months to improve fistula patency (Class IIb, level C)	
European Society for Vascular Surgery 2019 Clinical Practice Guidelines on the Management of Abdominal Aorto-iliac Artery Aneurysms[43] 2018	Blood pressure control, statins, and antiplatelet therapy should be considered in all patients with abdominal aortic aneurysm (Class IIa, level B)	Patients with small abdominal aortic aneurysms may be considered for aspirin (75 − 100 mg) to reduce the risk of cardiovascular events (Class IIb, level C)	These are different recommendations in that the ESVS AAA guideline recommends antihypertensives, statins, and antiplatelet therapy (for which there is better evidence of risk reduction in combination) than antiplatelet agents alone. The combination is not considered to be an antithrombotic guideline
	An established monotherapy with aspirin or thienopyridines (e.g., clopidogrel) is recommended to be continued during the peri-operative period after open and endovascular abdominal aortic aneurysm repair (Class I, level B) In patients surviving AMI, secondary medical prevention including smoking cessation, statin therapy, and antiplatelet or anticoagulation treatment, is recommended (Class I, Ievel C)	Patients undergoing endovascular or open abdominal aortic aneurysm repair should be considered for aspirin (75 − 100 mg) following repair, to reduce the risk of secondary cardiovascular events (Class IIa, level B)	The strongest evidence for risk reduction in this group of patients is for statin and antiplatelet therapy combined which is not considered in this guideline. The AAA guidelines are currently being updated and are considering this evidence
European Society for Vascular Surgery Clinical Practice Guidelines Management of the Diseases of Mesenteric Arteries and Veins[44] 2017		Patients post-revascularisation for atherosclerotic renal or mesenteric artery disease who are not at high risk of bleeding should be considered for short course (a minimum of one to a maximum six months) dual antiplatelet therapy (aspirin 75 mg and clopidogrel 75 mg) to reduce the risk of stent thrombosis (Class IIa, level C)	These are different recommendations in that the antithrombotics to use are specified so are given an appropriate class. The mesenteric guideline makes a blanket secondary prevention recommendation so has a different class and level
ESO guideline for the management of extracranial and intracranial artery dissection[45] 2022	In the acute phase of symptomatic extracranial artery dissection it is recommended that clinicians can prescribe either anticoagulants or antiplatelet therapy. Quality of evidence: Moderate Strength of recommendation: Strong for an intervention	Patients with extracranial carotid or vertebral artery dissection are recommended to have single antiplatelet therapy for at least three months to reduce the risk of subsequent ischaemic stroke (Class I, level B)	The same evidence as the ESO guideline was considered. In addition, they performed their own meta-analysis showing no difference between antiplatelets or anticoagulation for treatment of cervical dissection. This guideline focuses on the risks of anticoagulation, and in this context it was felt anticoagulation could not be recommended when it was non-inferior to antiplatelet therapy

AVF = arteriovenous fistula; AVG = arteriovenous graft; DAPT = dual antiplatelet therapy; DOAC = direct oral anticoagulant; ESC = European Society of Cardiology; ESO = European Stroke Organisation; ESVS = European Society for Vascular Surgery; GL = guideline; GWC = Guideline Writing Committee; KDOQI = Kidney Disease Outcomes Quality Initiative; LMWH = low molecular weight heparin; NICE = National Institute for Health and Care Excellence; RCT = randomised control trial; TIA = transient ischaemic attack; VTE = venous thromboembolism.

Table 4. Differences between recommendations from other major guidelines and this guideline for section 5. Antithrombotics for patients with venous disease

Management of acute and chronic iliofemoral venous outflow obstruction: a multidisciplinary team consensus[46] 2019	LMWH then warfarin is recommended for at least six months after acute deep vein intervention. LMWH for two to three weeks then anticoagulation or aspirin 75 − 100 mg following chronic venous intervention for non-thrombotic venous intervention	Patients undergoing iliofemoral venous stenting for deep venous disease should be considered for an individualised antithrombotic regimen considering the risk of bleeding for more aggressive strategies (Class IIa, level C)	The consensus statement considered individual reports of stent thrombosis on DOACs following acute intervention as grounds for recommending warfarin, but this GWC did not consider that to be strong enough evidence to outweigh the large volume of RCT evidence for the class effect of DOACs *vs.* warfarin. The absence of high level evidence in this area is recognised. The recommendation after chronic intervention is the same
Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report[47] 2021	In patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy and do not have a contraindication to aspirin, aspirin is suggested over no aspirin to prevent recurrent VTE (weak recommendation, low certainty evidence)	Patients with unprovoked deep vein thrombosis who are eligible for anticoagulants are not recommended to have aspirin for extended antithrombotic therapy to reduce the risk of thromboembolic events (Class III, level A)	These recommendations concern different patient groups but are included as the difference between guidelines may cause confusion. The CHEST guideline expert panel recommendation concerns patients who decide to stop taking anticoagulants, whereas here is a broader recommendation for all patients. The CHEST guideline reviews the same data as here in their text and comes to the same broad conclusions. We think their recommendation may create confusion because the interpretation is that aspirin is indicated in extended treatment for all patients and not just those stopping anticoagulation
	For patients with acute VTE in the setting of cancer (cancer associated thrombosis), an oral Xa inhibitor (apixaban, edoxaban, rivaroxaban) is recommended over LMWH for the initiation and treatment phases of therapy (strong recommendation, moderate certainty evidence)	Patients with cancer associated venous thromboembolism are recommended to have anticoagulation with low molecular weight heparin to reduce the risk of further thromboembolic events (Class I, level A)	Although this recommendation from the CHEST Guideline Expert Panel is strong favouring oral Xa inhibitors over LMWH, the explanation in their manuscript states that either apixaban or LMWH may be the preferred option in patients with GI malignancies. In addition, there is no evidence in this guide to support direct oral anticoagulants over LMWH, except the advisability of oral treatment with DOAC once a day.
		Patients with cancer associated venous thromboembolism and a low risk of gastrointestinal or genitourinary bleeding are recommended to be considered for anticoagulation with a direct oral anticoagulant, preferably apixaban alternatively rivaroxaban or edoxaban, as an alternative to low molecular weight heparin. (Class I, level A)	Instead, the panel recommends the use of LMWH as the first option in cancer patients in general, due to its well known results and extensive experience in its use. In turn, the use of direct oral anticoagulants is suggested as an alternative in selected patients

Continued

Table 4-*continued*

NICE guidance: Venous thromboembolism in adults: summary of updated NICE guidance on diagnosis, management, and thrombophilia testing[48] 2020	Suggests considering aspirin 75 mg or 150 mg daily for those who decline extended anticoagulation treatment	Patients with unprovoked deep vein thrombosis who are eligible for anticoagulants are not recommended to have aspirin for extended antithrombotic therapy to reduce the risk of thromboembolic events (Class III, level A)	This recommendation from the panel of experts of the NICE guidance is based on the fact of some people with VTE who are at risk of recurrence decide against continuing anticoagulation. They stated that ideally, people would take an anticoagulant rather than aspirin but suggested it in that case
European Society for Vascular Surgery (ESVS) 2022 Clinical Practice Guidelines on the Management of Chronic Venous Disease of the Lower Limbs[49] 2022	For patients with superficial venous incompetence undergoing intervention, individualised thromboprophylaxis strategies should be considered. (Class IIa, level B)	Patients with superficial venous incompetence undergoing high ligation and stripping of the great saphenous vein should be considered for thromboprophylaxis with a low molecular weight heparin to prevent post-operative venous thromboembolism (Class IIa, level B) Patients with superficial venous incompetence undergoing endovenous ablation of the great saphenous vein who are thought to be at higher risk of deep vein thrombosis should be considered for thromboprophylaxis with a low molecular weight heparin to prevent post-operative venous thromboembolism (Class IIa, level C)	During the review process there were a lot of questions about being more specific for patients undergoing open and endovascular venous intervention. These recommendations were therefore updated in conjunction with members of the chronic venous disease group
European Society for Vascular Surgery (ESVS) 2021 Clinical Practice Guidelines on the Management of Venous Thrombosis[50] 2021	In selected patients with cancer associated deep vein thrombosis, with the malignancy not located in the gastrointestinal or genitourinary systems, an approved direct oral anticoagulant for initial, principal, and extended treatment should be considered (Class IIa, level A)	Patients with cancer associated venous thromboembolism and a low risk of gastrointestinal or genitourinary bleeding are recommended to be considered for anticoagulation with a direct oral anticoagulant, preferably apixaban alternatively rivaroxaban or edoxaban, as an alternative to low molecular weight heparin (Class I, level A)	Clinical practice has changed rapidly in the past two years with DOACs now used very commonly for cancer associated VTE, especially to reduce the need for injection. Those involved in forming this recommendation for the VTE guidelines felt the change was acceptable

AVF = arteriovenous fistula; AVG = arteriovenous graft; DAPT = dual antiplatelet therapy; DOAC = direct oral anticoagulant; ESC = European Society of Cardiology; ESO = European Stroke Organisation; ESVS = European Society for Vascular Surgery; GL = guideline; GWC = Guideline Writing Committee; KDOQI = Kidney Disease Outcomes Quality Initiative; LMWH = low molecular weight heparin; NICE = National Institute for Health and Care Excellence; RCT = randomised control trial; TIA = transient ischaemic attack; VTE = venous thromboembolism.

insurance registry.[33] The end score comprises eight independent predictors (see Table 5) that can be used to stratify the bleeding risk for an individual patient into one of four groups: low risk; low to moderate; moderate to high; and high. This could potentially help with antithrombotic selection when several choices seem reasonable. It must be stressed that the score has not yet been validated externally in publication, and nor has any other risk score for this patient population.

There is better validation for risk scores for coronary intervention such as the Academic Research Consortium High Bleeding Risk (ARC-HBR)[57] and Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy (PRECISE-DAPT) scores.[57,58] These are not well validated in the PAD populations in this guideline.

For this reason, although some form of bleeding risk assessment should be performed for all patients with LEAD being offered antithrombotic therapy, a specific system cannot yet be recommended.

One value of considering the bleeding risk for a patient is the opportunity to potentially treat reversible causes of bleeding. While there is a lack of clinical evidence that reversing factors such as anaemia or platelet levels or reducing the use of non-steroidal anti-inflammatories will impact the future risk of bleeding for patients with vascular diseases, it would still be prudent to consider such factors. One specific intervention which has now been shown to

Table 5. The OAC[3] PAD score to determine the bleeding risk for a patient with symptomatic lower extremity arterial disease

Condition	Description	Score
Oral anticoagulation before index hospitalisation	Any oral anticoagulant for any indication	5
Age	Over 80 years old	2
Chronic limb threatening ischaemia	Fontaine III and IV	4
Congestive heart failure	*	3
Chronic kidney disease	Estimated glomerular filtration rate < 30 mL/min/1.73m^2	3
Prior bleeding	Transfusion during index hospital admission, prior diagnosis of coagulopathy, or a primary diagnosis of major bleeding requiring hospitalisation in the previous year.	5
Anaemia	*	8
Dementia	*	3
Risk stratification		
Low risk		0
Low to moderate risk		1–4
Moderate to high risk		5–9
High risk		10–33

* Variables defined via the Elixhauser Comorbidity Index which is a method of categorising comorbidities of patients based on the International Classification of Diseases diagnosis codes.

reduce the subsequent bleeding risk for patients taking antithrombotics is the addition of a proton pump inhibitor (PPI) such as pantoprazole. A recent meta-analysis of RCTs of over 200 000 patients taking dual antiplatelet therapy (DAPT) following percutaneous coronary intervention showed that addition of a PPI substantially reduced the risk of gastrointestinal bleeding (RR 0.32; 95% CI 0.20 — 0.52) but did not reduce the risk of all cause mortality (RR 1.35; 95% CI 0.56 — 3.23).[59] The largest RCT contributing to that meta-analysis was the COMPASS study in which pantoprazole 40 mg was randomised within the study arms. This did reduce the risk of bleeding from gastroduodenal lesions (HR 0.52; 95% CI 0.28 — 0.94, $p = .030$) but the number needed to treat was high ($n = 982$; 95% CI 609 — 2 528).[60] Additionally, higher risk patients were already taking PPIs in this study before randomisation making it impossible to generalise that all patients should be offered PPI. The use of risk scores should be considered to help guide PPI prescription.[33,61-63] A history of upper gastrointestinal lesions is the single most predictive factor for further risk of bleeding so should be considered separately. Other potentially modifiable risks to consider include stopping non-steroidal anti-inflammatories; giving clear advice on the risk of bleeding, especially with trauma in active people; giving clear advice on what to do if bleeding happens with antithrombotics; and balancing the risk of stopping or bridging an anticoagulant for an invasive procedure.

There are several risk scores for predicting risk of bleeding from anticoagulation for venous indications, for example the American College of Chest Physicians risk score,[64] the VTE BLEED score,[65] or the REITE score.[66] The American College of Chest Physicians risk score is often advocated but is not well validated.[64] Patients with a venous indication for anticoagulation also appear to be at a lower risk of major bleeding than those with an arterial indication.[52,67]

Recommendation 1

Patients being prescribed antithrombotic therapy are recommended to have a bleeding risk assessment performed to aid shared decision making.

Class	Level	Reference
I	C	Consensus

Recommendation 2

Patients with a modifiable risk of bleeding being prescribed antithrombotic therapy are recommended to have adequate management to limit the corresponding bleeding risk.

Class	Level	Reference
I	C	Consensus

Recommendation 3

Patients taking antithrombotic therapy with a history of upper digestive tract lesions, or who are at higher risk of gastrointestinal bleeding, should be considered for proton pump inhibitor therapy to reduce the risk of gastrointestinal bleeding.

Class	Level	Reference
IIa	C	Consensus

2. ANTITHROMBOTIC AGENTS

2.1. Antiplatelet agents

Platelets are subcellular fragments derived from the cytoplasm of megakaryocytes. They play an instrumental role in thrombosis, haemostasis, and wound healing.[68,69]

Under normal circumstances, platelets circulate in an inactive state.[69] Endothelial damage, for example after trauma, surgery, or vascular intervention, results in platelet activation through a wide array of mediators including platelet surface receptors, signalling molecules, and endothelial products.[70] These mediators can be targeted by antiplatelet agents to reduce platelet aggregation and subsequent thrombotic risk.

Increased platelet activity is encountered in patients with PAD or venous thrombosis and has been associated with an increased risk of thrombotic events leading to Major Adverse Cardiovascular Events (MACE) and Major Adverse Limb Events (MALE).[71,72] The terms antiplatelet resistance or high on treatment platelet reactivity are used to describe patients with higher than expected platelet function despite

taking an antiplatelet agent. It is a blanket term for patients with decreased drug effectiveness due to various genetic or induced differences in metabolism, as well as receptor site variations and competition during action and metabolism.[34] The clinical relevance is discussed in section 3.

The following sections examine the mechanisms of actions of commonly used antiplatelet agents.

2.1.1. Cyclo-oxygenase inhibitors. This class of antiplatelet agents includes aspirin (acetylsalicylic acid) and triflusal. Cyclo-oxygenases (COX) are a family of enzymes, which form prostanoids, such as thromboxane, and prostaglandins. Following platelet activation, arachidonic acid is released from the sn-2 position in membrane phospholipids via cytosolic phospholipase A2. Arachidonic acid is then converted to the unstable intermediates prostaglandin G2/H2. These reactions within platelets are catalysed by prostaglandin H (PGH) synthase-1, which exhibits COX-1 and hydroperoxidase activities; COX-1 converts arachidonic acid to prostaglandin G2, which is then converted to PGH2 by the hydroperoxidase activity of PGH synthase-1. In platelets, PGH2 is metabolised to TxA2 by TxA2 synthase. In endothelial cells, PGH2 is metabolised to prostaglandin I2 (PGI2) by PGI2 synthase. TxA2 is a platelet agonist. Inhibition of COX-1 substantially inhibits TxA2 dependent platelet activation.[69,73] However, other platelet activation pathways are unaffected. Aspirin and triflusal are irreversible inhibitors of COX-1. Low dose aspirin inhibits only COX-1, while high dose ($\geq$ 500 mg) inhibits both COX-1 and COX-2, and therefore decreases the production of prostacyclin by endothelial cells.[74]

2.1.2. Adenosine diphosphate receptor inhibitors. Adenosine diphosphate (ADP) is a primary platelet activator which interacts with two purinergic receptors on the platelet membrane to initiate and promote platelet activation. These receptors are the P2Y1 receptor, which initiates the platelet response, and the P2Y12 receptor, which promotes it. Their blockade inhibits the effect of ADP, leading to a substantial reduction in platelet aggregation.[75]

This class of antiplatelet agents comprises two families of ADP receptor inhibitors. The first family, known as thienopyridines, includes ticlopidine, clopidogrel, and prasugrel. These agents are prodrugs that require enzymatic activation by the hepatic cytochrome P450 into their active metabolites. They cause irreversible inhibition of the P2Y12 receptor. The second comprises the non-thienopyridines: ticagrelor and cangrelor. They do not require enzymatic conversion and reversibly inhibit P2Y12 receptors.[76]

The first thienopyridine licenced for clinical use was ticlopidine, which has gradually been withdrawn from the market in certain regions due to the risk of neutropenia and aplastic anaemia. Clopidogrel is one of the most commonly used antiplatelet agents in patients with PAD; it has been investigated specifically in a subgroup of patients with PAD (not undergoing intervention) who took part in CAPRIE.[9] Clopidogrel usually becomes active within two hours of oral ingestion. It is a prodrug requiring bioactivation, which is performed primarily via the CYP2C9 enzyme. Around 30% of people have genetically decreased CYP2C9 enzyme activity, so have a decreased amount of the clopidogrel active metabolite.[77] Drugs which interact with this enzyme such as proton pump inhibitors potentially reduce the action of clopidogrel, although there is no clear evidence of an association between PPIs and adverse cardiac events.[59] Prasugrel has a faster onset of action and is less affected by variability in enzymatic activity. As a result, it is more effective than clopidogrel in preventing thrombotic complications in patients with coronary artery disease (CAD),[78] but is not well investigated for PAD.

The most widely used agent from the non-thienopyridine family is ticagrelor. As it does not require enzymatic conversion to an active metabolite, it is less prone to resistance due to genetic polymorphisms affecting the P450 enzyme.[79]

Cangrelor has not been designed for oral use, and its short half life makes it unsuitable for use in the setting of cardiovascular prevention.[80]

2.1.3. Phosphodiesterase inhibitors. Phosphodiesterase inhibitors act by suppressing intracellular signalling pathways in platelets. This results in an increase in the activity of endogenous platelet inhibitors or blocks the synthesis of pro-aggregating factors reducing platelet aggregation.[81] Phosphodiesterase inhibitors specifically inhibit the enzyme phosphodiesterase which usually catalyses the hydrolysis of cyclic adenosine monophosphate and cyclic guanosine monophosphate, which are intracellular second messengers involved in platelet aggregation.

The most commonly used phosphodiesterase inhibitors in clinical use are cilostazol and dipyridamole. Cilostazol is rapidly absorbed and reaches peak concentration two and a half hours after oral ingestion. It is limited by a relatively high incidence of side effects which include headaches, tachycardia, palpitations, and diarrhoea.[82]

There is currently a paucity of evidence that dipyridamole alone exerts a clinically significant antiplatelet effect, thus most clinical studies have assessed its efficacy in combination with aspirin.[81]

2.1.4. Other antiplatelet agents. Glycoprotein IIb/IIIa receptor antagonists act on the glycoprotein IIb/IIIa receptors on the platelet surface. Receptor activation by fibrinogen and von Willebrand factor released after endothelial injury or plaque rupture usually promotes platelet aggregation.[83] This class of antiplatelet agents comprises abciximab, tirofiban, and eptifibatide. They are administered intravenously and have been found to result in a reduced risk of death and myocardial infarction (MI) in patients with acute coronary syndromes.[84] Data on their efficacy in PAD is lacking.

2.2. Anticoagulant agents

Drugs that inhibit the coagulation cascade play a major role in the prevention and management of thrombosis for

vascular patients. The mechanism of action of the most frequently used anticoagulants is explained in this section.

2.2.1. Unfractionated heparin. Unfractionated heparin (UFH) is made of a group of sulphated glycosaminoglycans. It inhibits coagulation *in vivo* and *in vitro* by enhancing the catalytic speed of the endogenous anticoagulant antithrombin. Antithrombin inhibits serine proteases, most commonly known as coagulation factors in the blood by attaching to serine residues.[85] By activation of antithrombin, UFH inhibits several coagulation factors of the coagulation system including factors XIIa, XIa, IXa, and Xa, as well as factor VIIa (and its clotting activity)[86] and factor IIa (thrombin). While UFH acts immediately after intravenous infusion, there is a time lag of approximately 60 minutes after subcutaneous injection, which necessitates an intravenous bolus in emergency settings, often maintained by a continuous infusion. The half life of UFH is approximately one hour but increases with increasing doses. The activated partial thromboplastin time (APTT) is usually monitored, and the dose of UFH adjusted so the values fall within the therapeutic range. Notably, the APTT is not an ideal measure of heparinisation due to the potential for other factors interfering with it (see section 3.2). For example, lupus anticoagulant may prolong the APTT while causing both venous and arterial thrombosis. The APTT and the anti-Xa assay measure different aspects of heparinisation and provide complementary information. Intra-operatively UFH is monitored by the activated clotting time. UFH is used in open and endovascular arterial surgery and in acute limb ischaemia scheduled for immediate revascularisation (see section 3.2).

2.2.2. Low molecular weight heparins. Low molecular weight heparins (LMWH; dalteparin, enoxaparin, tinzaparin, nadroparin, bemiparin, and parnaparin), which are fractions of UFH, are now more commonly used than UFH itself.[87] LMWH increases activation of antithrombin and its inhibition of factor Xa to a greater extent than UFH, but affects thrombin less. This is because LMWH molecules are too small to attach to both antithrombin and thrombin. In contrast, structures as small as pentasaccharides (section 2.2.3) are sufficient for factor Xa inhibition. While UFH inhibits both factor IIa and factor Xa equally well, the Xa/IIa inhibition ratio by LMWH varies between 2:1 and 4:1.[88]

LMWHs are typically injected subcutaneously although they may also be given intravenously for acute coronary syndromes, haemodialysis, or during endovascular procedures (part of which is off label use). They have a longer elimination half life (three to four hours)[88] compared with UFH irrespective of the dose, allowing longer intervals between dosing. LMWHs can be administered once or twice daily for prophylactic and therapeutic indications. While LMWH is less likely to prolong the APTT than UFH, the LMWH preparations with lower Xa to IIa ratios have a greater effect on the APTT. For example, tinzaparin and to a lesser extent dalteparin prolong the APTT. Anti-factor Xa monitoring is not necessary, except in obese patients and particularly in those with renal failure.[85] Efficacy of LMWHs is comparable with that of UFH, but they are associated with a major reduction in bleeding side effects and complications.[89]

2.2.3. Pentasaccharides. Pentasaccharides are synthetic molecules that derive from the five saccharide effector site of the heparin molecule. They share the same mechanism of action as LMWH with the difference of no residual anti-IIa action, that is, they have only anti-Xa activity. Fondaparinux is representative of this group.[90] Fondaparinux binds reversibly and specifically to the activation site of antithrombin and enhances its catalytic inactivation of factor Xa 300 fold.[91] Fondaparinux is licensed for the prophylaxis and treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) in high risk patients with major orthopaedic surgery, where it reduced VTE by over 50% compared with LMWH. Unfortunately, a recent meta-analysis indicated that fondaparinux also appears to increase major bleeding risk compared with LMWH in post-operative thromboprophylaxis.[92] It is also effective in patients with lower limb superficial vein thrombosis (SVT).[7] Its long half life of around 17 hours permits once daily injections of 2.5 mg for prophylaxis, but requires anti-factor Xa monitoring in chronic kidney disease (CKD).

2.2.4. Danaparoid. Danaparoid inhibits thrombin generation by enhancing antithrombin mediated inactivation of factor Xa. It is a low molecular weight heparinoid product, which also has a weak but direct role in thrombin inactivation.[93] Danaparoid has a half life of 25 hours and is excreted renally. Although cross reactivity with heparin induced thrombocytopenia (HIT) antibodies has been reported, it has rarely contributed to the worsening of HIT. Thus danaparoid is indicated as an UFH substitute in HIT.[94]

2.2.5. Vitamin K antagonists. Vitamin K is necessary for the formation of factors II, VII, IX, and X. It is a cofactor of the enzyme gamma-glutamyl carboxylase and it is necessary for the γ carboxylation of non-functional forms of factors II, VII, IX, and X into their respective functional forms.

Because of a structural similarity to vitamin K, the vitamin K antagonists (VKAs) competitively inhibit the enzymatic reduction of vitamin K into its active form. Effects of VKAs are seen several days after administration until the already carboxylated coagulation factors are degraded.[95] Prothrombin (factor IIa) has the longest half life of the vitamin K dependent factors (two to three days) and it can take 14 days until trough levels are reached. Therefore, an early change in prothrombin time may be driven by a decrease in Factor VII activity and does not represent therapeutic anticoagulation.

Additionally, there may be an initial phase of hypercoagulability, as a result of a faster inhibition of protein C and S activation.[95] As a consequence, overlapping heparin treatment is mandatory in most cases when initially starting a VKA, except for atrial fibrillation.

Food and drug interactions with VKAs are very common and require frequent monitoring of the International Normalised Ratio (INR). Patients who eat substantial amounts of vegetables rich in Vitamin K, such as dark green vegetables, Brussels sprouts, and cabbage demonstrate a decrease in anticoagulation as measured by the INR.[96] Factors influencing the expression and activity of CYP2C9 influence plasma concentrations of VKAs.[97] Other natural substances and foods, such as garlic, gingko, coenzyme Q, danshen, ginseng, vitamin E, and papaya all increase the effects of VKAs.[97] Green tea and St. John's wort antagonise VKA. Equally important are drug to drug interactions. On the one hand, frequently used drugs including metronidazole, amiodarone, or voriconazole reduce the clearance of warfarin and increase the INR values; on the other hand, compounds like carbamazepine or phenytoin enhance the clearance of warfarin and decrease INR values. Warfarin is almost completely absorbed by the gastrointestinal tract and is eliminated via hepatic clearance; it has a half life of 35 hours.[95] It binds to plasma proteins (mainly albumin) with high affinity and is metabolised via cytochrome P450—2C9. Acenocoumarol is an alternative VKA with a shorter half life.

2.2.6. Direct thrombin inhibitors. Dabigatran is an oral direct thrombin inhibitor. It is a prodrug that is converted into its active form in the intestine, plasma, and liver. The absolute bioavailability after oral intake is around 6.5% but it is rapidly absorbed. It can inhibit both free and bound thrombin, which enables it to inhibit the coagulation cascade as well as platelet activation.[98] The latter has been demonstrated *ex vivo* but this remains to be demonstrated as a useful clinical effect. Additionally, dabigatran is a substrate of the P-glycoprotein drug transporter, therefore its use should be monitored and it should not be used together with medications that inhibit or induce P-glycoprotein such as ketoconazole, amiodarone, and quinidine. Dabigatran has a half life of 12 — 14 hours. It is eliminated renally so its use should be monitored in patients with renal dysfunction (Table 6). Idarucizumab is available as a specific reversal agent. Dabigatran is indicated for stroke prevention in patients with non-valvular atrial fibrillation and for treatment of VTE after the use of LMWH or UFH for five days.

Argatroban is a parenteral direct thrombin inhibitor which binds rapidly and reversibly to both clot bound and soluble thrombin. It is eliminated by hepatic metabolism and has a relatively short half life of approximately 45 minutes.[99] Argatroban is approved for both prophylaxis and treatment of thrombosis in patients with HIT and as an antithrombotic agent during percutaneous coronary interventions in patients with HIT or a history of HIT.[100] Argatroban can be monitored using the APTT for low doses and the activated clotting time for high doses. The specific inhibition of thrombin can be measured with the ecarin clotting time. The intravenous infusion is initiated at 2 μg/kg/min and is adjusted to target an APTT at 1.5—3 times the patient's baseline.

Bivalirudin is a synthetic 20 amino acid peptide that also directly inhibits thrombin. In contrast to dabigatran, it is administered intravenously, and it has a half life of around 30 minutes.[101] Unlike other direct thrombin inhibitors, only a small amount of the drug is excreted renally (20%) with the majority of elimination via proteolytic cleavage. This makes it an attractive option in patients with renal and or hepatic dysfunction because it appears at least as safe and effective as UFH.[102]

2.2.7. Factor Xa inhibitors. Rivaroxaban, apixaban, betrixaban, and edoxaban are all direct inhibitors of Factor Xa. Previously known as NOACs (novel oral anticoagulants), they are now referred to as DOACs (direct oral anticoagulants). Dabigatran (section 2.2.6) is the only thrombin inhibitor among the DOACs. The pharmacological properties of major DOACs are shown in Table 6.

DOACs appear to be generally safer and more effective than warfarin for stroke prevention in atrial fibrillation (AF),[103] and are also safer in the management of VTE, with observational and trial data showing similar outcomes.[104,105] Unlike warfarin, they achieve stable enough plasma levels not to require clinical laboratory monitoring, but should still be tailored to the patient. Andexanet alfa is a reversal agent for both apixaban and rivaroxaban, as are prothrombin complex concentrates.[106] Unfortunately, the high cost of andexanet alfa reversal agent limits its use in clinical practice. While immediate reversal may be necessary in emergency situations before endovascular procedures, stopping a DOAC 48 hours prior to the procedure is usually sufficient for elective procedures.

Table 6. Pharmacological properties of the major direct oral anticoagulant agents

	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Time to maximum effect — h	2—4	3—4	1—3	1—3
Bioavailability — %	80—90 (increased by food)	30—90	62	6.5
Half life — h	5—13	8—15	10—14	8—17
Protein binding — %	92—95	87	54	35
Renal elimination — %	33	30	35	80
Hepatic metabolism — %	66	70	65	20

3. MEASUREMENT OF ANTITHROMBOTIC EFFECT

3.1. Patients not undergoing intervention

Measurement of the INR is the international standard for warfarin dose monitoring, with clear evidence of major bleeding with higher INR values.[107] Specific ranges are defined where vitamin K antagonists are recommended by this guideline.

There are a wide variety of tests for monitoring platelet reactivity. The relationship between high on treatment platelet reactivity (good platelet function despite taking an antiplatelet agent) and clinical events is most commonly examined when assessing the value of antiplatelet function testing. There is no clinical evidence for the usefulness of antiplatelet function testing for a patient with stable non-intervened PAD. Antiplatelet function testing following intervention is examined in subsequent sections.

3.2. Post-intervention

3.2.1. Antiplatelet agents after open arterial surgery. There are three prospective cohort studies examining the relationship between high on treatment platelet reactivity and clinical events for open arterial surgery.[108-110] Bleeding is most commonly examined in the literature for open surgery, whereas other clinical events have been better studied after endovascular intervention.

The peri-operative use of clopidogrel, including DAPT with clopidogrel and aspirin, has been associated with increased bleeding events in both cardiac and non-cardiac surgery.[109,111] One prospective case control study examined the value of thromboelastogram values in predicting the peri- and post-operative bleeding risk of clopidogrel for non-cardiac surgery.[108] This study found that thromboelastogram values in the accepted range for good platelet inhibition (low on treatment platelet reactivity) were predictive of higher bleeding risk, and a cutoff of 34% for platelet receptor inhibition was associated with a substantially lower risk of bleeding. Low on treatment platelet reactivity when using ADP receptor inhibitors in non-cardiac surgery was also associated with a higher risk of major bleeding and subsequent transfusion in another prospective study.[109] However, there was not enough evidence to stratify bleeding risk by platelet reactivity testing results, and no data to show that changing agents or stopping them would change clinical outcomes. More recently, 194 patients undergoing open or endovascular intervention were examined for aspirin resistance peri-operatively. While they found that almost 30% of patients showed peri-operative aspirin resistance, it was not associated with myocardial injury.[110] They did not examine the effect of changing the antiplatelet agent. There are not enough data in the literature to make a clear recommendation.

3.2.2. Antiplatelet agents after endovascular intervention. There are more data on clinical events other than bleeding for high on treatment platelet reactivity after endovascular intervention. A systematic review performed for this guideline found 10 low quality studies.[34] Meta-analysis showed that patients taking ADP receptor inhibitors displaying high on treatment platelet reactivity had a higher risk of death, MALE, and arterial re-stenosis following endovascular intervention for PAD than those without. There was insufficient evidence to stratify bleeding risk by the individual platelet reactivity test result, and no data to show that changing agents or stopping them would change clinical outcomes. Detecting high on treatment platelet reactivity does, however, allow the clinician to identify a patient at higher risk of death and MALE, which may affect subsequent risk factor decision making.

Similar effects were shown by meta-analysis following percutaneous intervention for CAD.[112] There have subsequently been randomised trials examining the value of adjusting antiplatelet therapy after platelet function testing for percutaneous coronary intervention, which have demonstrated heterogeneous results. However, meta-analysis of all of these trials did show a clinical benefit with a reduction in MACE (RR 0.78; 95% CI 0.63 − 0.95, $p = .015$), cardiovascular death (RR 0.77; 95% CI 0.59 − 1.00, $p = .049$), MI (RR 0.76; 0.60 − 0.96, $p = .021$), stent thrombosis (RR 0.64; 0.46 − 0.89, $p = .011$), stroke (RR 0.66; 0.48 − 0.91, $p = .010$), and minor bleeding (RR 0.78; 0.67 − 0.92, $p = .003$).[113]

3.2.3. Heparins. The use of intravenous UFH has established monitoring protocols using the internationally standardised APTT or APTT ratio.[114] The rate of heparin infusion is changed based on the APTT result, which is usually based on local protocols by patient weight and renal function as there is no agreed optimal dosing strategy.[114] Higher APTT values are associated with increased rates of major bleeding. Therefore, intravenous heparin infusions should be monitored by APTT, or by anti-Xa level monitoring depending on local set up.

Recommendation 4

Patients receiving unfractionated heparin infusions are recommended to have the activated partial thromboplastin time or activated partial thromboplastin time ratio monitored to reduce the risk of bleeding.

Class	Level	Reference	ToE
I	C	Smythe *et al.* (2016)[114]	

Repeated, intermittent doses of heparin (also given as a bolus injection) are commonly used in open and endovascular arterial surgery. The activated clotting time may be used as a bedside test to guide heparin bolus dosing. It does not correlate as strongly as a laboratory tested APTT with heparin concentration, but is used commonly during open and endovascular intervention as it can be measured quickly in an operating theatre environment.[115] A recent meta-analysis has shown that there is both a lack of data in the literature as well as no consensus on the optimal activated clotting time for use in non-cardiac arterial procedures.[116] The activated clotting time appeared to correlate with thromboembolic and bleeding surrogates in the included trials.

Recommendation 5			
Patients undergoing open or endovascular arterial intervention being administered a bolus of unfractionated heparin may be considered for activated partial thromboplastin time, activated partial thromboplastin time ratio or activated clotting time monitoring as a measure of anticoagulation.			
Class	**Level**	**References**	**ToE**
IIb	C	Doganer *et al.* (2020),[116] Smythe *et al.* (2002)[115]	

LMWH may also be monitored using Factor Xa levels. Trough (lowest between doses) Xa levels appear to be the most appropriate time to monitor LMWH function.[117] There is not enough data in the literature to make clear recommendations for patients with PAD.

3.2.4. Oral anticoagulants. Measurement of the INR is the international standard for warfarin dose monitoring, with clear evidence of major bleeding with higher INR values.[107] Specific ranges are defined where warfarin is recommended by this guideline so no recommendation is made here.

The use of DOACs for PAD is new, with a low dose of rivaroxaban (2.5 mg twice a day) as used in COMPASS and VOYAGER, forming recommendations. Observational data have confirmed that DOAC levels do not need routine monitoring in clinical practice.[118] The doses used for PAD are lower than full doses, and were chosen as phase II studies showed a similar efficacy with fewer bleeding events.[119] COMPASS and VOYAGER did not routinely measure levels and found acceptable safety compared with previous RCTs of full dose rivaroxaban.[14,29]

4. ANTITHROMBOTICS FOR PATIENTS WITH ARTERIAL DISEASE

This section covers recommendations for patients with atherosclerotic arterial disease unless specifically indicated. There are a number of RCTs which are mentioned and form the basis of recommendations in several parts of section 4. These are shown in Table 7 to reduce detail in the text.

Table 7. Randomised controlled trials including patients with peripheral arterial diseases used in more than one section of the guideline

Patient population and setting	Intervention *vs.* control	Outcome measures	Relevant findings	Notes
*Asymptomatic Atherosclerosis trial**[120], 2010				
28 980 patients with screened ABI < 0.95 and no known cardiovascular disease.	Aspirin 100 mg (n = 1 675) vs. placebo (n = 1 675).	Primary endpoint: composite of initial fatal or non-fatal coronary event or stroke or revascularisation. Secondary endpoints: all initial vascular events, defined as a composite of a primary endpoint event or angina, intermittent claudication or transient ischaemic attack; and all cause mortality.	After a mean (SD) follow up of 8.2 (1.6) years, no statistically significant difference was found between groups for the primary endpoint (HR 1.03, 95% CI 0.84−1.2) or the secondary endpoints (HR 1.00, 95% CI 0.85−1.17, and HR 0.95, 95% CI 0.77−1.16, respectively). There was also no difference in major bleeding between the groups (HR 1.71, 95% CI 0.99 −2.97).	
*Dutch Bypass Oral anticoagulants or Aspirin study**,[5], *2000*				
2 690 patients undergoing infrainguinal bypass.	Oral anticoagulants (target INR 3.0−4.5, n = 1 339) *vs.* aspirin (80 mg daily, n = 1 351).	Primary outcome was graft occlusion.	No difference between oral anticoagulants and aspirin overall (HR 0.95, 95% CI 0.82−1.11). Oral anticoagulants were beneficial in patients with vein grafts (HR 0.69, 95% CI 0.54−0.88), whereas aspirin had better results for non-vein grafts (HR 1.26, 95% CI 1.03−1.55). The composite outcome of vascular death, myocardial infarction, stroke, or amputation occurred 248 times in the oral anticoagulants group and 275 times in the aspirin group (0.89, 0.75−1.06). Patients treated with oral anticoagulants had more major bleeding episodes than those treated with aspirin (HR 1.96, 95% CI 1.42−2.71).	The INR range was set high (3.0−4.5) in the trial. Type of bypass was co-randomised; vein bypass grafts benefitted more from anticoagulation.

Continued

Table 7-*continued*

Patient population and setting	Intervention *vs.* control	Outcome measures	Relevant findings	Notes
EUCLID (Examining Use of tiCagreLor In paD)[*,6]*, 2017*				
13 885 patients with established symptomatic PAD, either as defined by ABI criteria or previous revascularisation.	Ticagrelor monotherapy, $n = 6\ 930$ *vs.* clopidogrel monotherapy, $n = 6\ 955$.	The primary efficacy endpoint was a composite of adjudicated cardiovascular death, myocardial infarction, or ischaemic stroke. The primary safety endpoint was major bleeding.	The primary efficacy endpoint occurred in 10.8% receiving ticagrelor and in 10.6% receiving clopidogrel (HR 1.02, 95% CI 0.92−1.13). In each group, major bleeding occurred in 1.6% (HR 1.10, 95% CI 0.84−1.43).	The EUCLID trial excluded patients who were poor clopidogrel metabolisers, (considering the cytochrome P-450 2C19 allele, defined as a genotype with two loss of function alleles) which may not make findings generalisable.
CAPRIE (Clopidogrel vs. Aspirin in Patients at Risk of Ischaemic Events)[†,9]*, 1996*				
19 185 patients with atherosclerotic vascular disease, manifested as either recent ischaemic stroke, recent myocardial infarction, or symptomatic peripheral arterial disease.	Clopidogrel monotherapy $n = 9\ 599$, of which $n = 3\ 223$ had symptomatic PAD *vs.* aspirin monotherapy $n = 9\ 586$, of which $n = 3\ 229$ had symptomatic PAD.	The primary endpoint was the composite outcome of ischaemic stroke, myocardial infarction, or vascular death (3-P MACE); safety endpoints included major bleeding events.	In the overall study population, a relative risk reduction of 8.7% (95% Cl 0.3−16.5) regarding 3-P MACE (in favour of clopidogrel) was observed. Overall, major bleeding events were less common in the clopidogrel study arm, with substantially fewer gastrointestinal bleeding events.	In the PAD subgroup, the corresponding risk reduction ratio was 23.8% (95% CI 8.9−36.2 in favour of clopidogrel).
CASPAR (Clopidogrel and AcetylSalicylic Acid in bypass Surgery for Peripheral Arterial Disease)[*,11]*, 2010*				
851 patients undergoing unilateral, below knee bypass grafting for atherosclerotic peripheral arterial disease (PAD).	Aspirin plus clopidogrel ($n = 425$) *vs.* aspirin plus placebo ($n = 426$).	The primary endpoint was defined as the first occurrence, over the duration of: occlusion of the index bypass graft documented by any imaging procedure or any surgical or endovascular revascularisation procedure on the index bypass graft or para-anastomotic region; or amputation above the ankle of the index limb; or death.	There was no difference in the primary endpoint between the two groups (HR 0.98, 95% CI 0.78−1.23) in the overall population. The primary endpoint was reduced by DAPT for prosthetic grafts (HR 0.65, 95% CI 0.45−0.95, $p = .025$) but not for vein grafts (HR 1.25, 95% CI 0.94−1.67). No notable difference in GUSTO bleeding between groups.	The majority of patients had CLTI (around 66%) who had venous grafts (around 70%).
CHARISMA (Clopidogrel and Aspirin vs. Aspirin Alone for the Prevention of Atherothrombotic Events)[†,13]*, 2006*				
15 603 patients with either clinically evident cardiovascular disease or multiple CV risk factors.	DAPT with clopidogrel plus aspirin ($n = 1\ 659$ with CV risk factors and $n = 6\ 062$ patients with established CV disease) *vs.* placebo plus aspirin ($n = 1\ 625$ with CV risk factors and $n = 6\ 091$ with established CV disease).	The primary efficacy endpoint was a composite of myocardial infarction, stroke, or death from cardiovascular causes.	The relative risk was similar between treatment arms (RR 0.93, 95% CI 0.83−1.0). In the subgroup with established CV disease the RR was 0.88, 95% CI 0.77−0.998 in favour of DAPT. Overall, moderate bleeding events were more common in the DAPT arm (HR 1.62, 95% CI 1.27−2.08).	Among patients with established CV disease, 2 838 had PAD as study entry criteria. A *post hoc* subgroup analysis in this subgroup demonstrated a non-significant reduction in MACE in the DAPT arm (HR 0.87, 95% CI 0.67−1.13) The rates of severe, fatal, or moderate bleeding did not differ between the groups in this *post hoc* analysis, whereas minor bleeding was increased with DAPT.

Continued

Table 7-*continued*

Patient population and setting	Intervention *vs.* control	Outcome measures	Relevant findings	Notes
COMPASS (Cardiovascular OutcoMes for People using Anticoagulation Strategies)[†,14]*, 2017*				
7 470 patients with stable atherosclerotic vascular disease.	Rivaroxaban 2.5 mg twice a day plus aspirin 100 mg once a day $n = 9\ 152$ *vs.* rivaroxaban 5 mg twice a day plus placebo $n = 9\ 117$ *vs.* aspirin 100 mg plus placebo $n = 9\ 126$.	The primary efficacy endpoint was a composite of myocardial infarction, stroke, or death from cardiovascular causes.	Compared with aspirin monotherapy, the hazard ratio for the primary efficacy outcome was 0.76, (95% CI 0.66−0.86) in favour of rivaroxaban plus aspirin. Major bleeding events were more common in the rivaroxaban plus aspirin group (HR 1.70, 95% CI 1.40−2.05). Rivaroxaban monotherapy was not superior to aspirin monotherapy but resulted in more major bleeding events.	In a symptomatic LEAD subgroup analysis (n =4 129), the estimated net clinical benefit of the combination treatment (defined as the combined risk of MACE and MALE events including major amputation) balanced against fatal or critical organ bleeding was 22% (HR 0.78, 95% CI 0.63−0.95).
				Pantoprazole 40g was also randomised within the study arms. Pantoprazole reduced the risk of bleeding from gastroduodenal lesions (HR 0.52, 95% CI 0.28−0.94, $p = .03$) but the number needed to treat was high ($n = 982$, 95% CI 609−2 528).
POPADAD (Prevention Of Progression of Arterial Disease And Diabetes)[*,22]*, 2008*				
1 276 adults aged >40 with type 1 or type 2 diabetes and an ankle brachial pressure index of ≥ .99 but no symptomatic cardiovascular disease.	Aspirin plus placebo ($n = 318$) or aspirin plus antioxidant ($n = 320$) *vs.* placebo plus placebo ($n = 318$)	Two hierarchical composite primary endpoints of death from coronary heart disease or stroke, non-fatal myocardial infarction or stroke, or amputation above the ankle for critical limb ischaemia; and death from coronary heart disease or stroke.	No statistically significant difference between any endpoint for any group.	
VOYAGER PAD (Vascular Outcomes Study of ASA (acetylsalicylic acid) Along with Rivaroxaban in Endovascular or surgical limb Revascularisation for Peripheral Arterial Disease)[†,29]*, 2020*				
6 564 patients with chronic lower limb atherosclerotic disease undergoing revascularisation (open or endovascular).	Aspirin 100 mg once a day plus rivaroxaban 2.5 mg twice a day (n =3 286) *vs.* aspirin 100 mg plus placebo ($n = 3\ 278$)	Primary efficacy outcome: a composite of acute limb ischaemia, major amputation for vascular causes, myocardial infarction, ischaemic stroke, or death from cardiovascular causes. Principal safety outcome: major bleeding, defined according to the Thrombolysis in Myocardial Infarction (TIMI) classification. ISTH major bleeding was a secondary outcome.	After three year follow up there was a statistically significantly lower incidence of the primary efficacy outcome in the aspirin plus rivaroxaban group (HR 0.85, 95% CI 0.76−0.96), with no statistically significant increase in TIMI major bleeding, but a significant incidence of ISTH major bleeding (HR 1.42, 95% CI 1.10−1.84) when compared with aspirin alone.	Multiple subgroup analyses have been published. A reduction in ALI was the main outcome in the composite, driving the significant result (HR 0.67, 95% CI 0.55−0.82). There was concomitant, non-randomised use of clopidogrel in approximately 51% of trial patients. Additionally, the surgical subgroup (HR 0.79 95% CI 0.66−0.95) showed a significant difference for the primary efficacy outcome while the endovascular subgroup difference did not reach significance (HR 0.90 95% CI 0.77−1.05).

Continued

Table 7-continued

Patient population and setting	Intervention *vs.* control	Outcome measures	Relevant findings	Notes
WAVE (Warfarin and Antiplatelet Vascular Evaluation)[†,30], *2007*				
2 161 patients with PAD and established atherosclerosis of lower limb, carotid, or subclavian arteries. 82% of randomised patients had lower limb atherosclerosis; all these patients were, or had previously been, symptomatic.	VKA plus antiplatelet therapy (n = 1 080) *vs.* antiplatelet therapy (n = 1 081).	The first co-primary outcome was myocardial infarction, stroke, or death from cardiovascular causes (3-P MACE). The second co-primary outcome was myocardial infarction, stroke, severe ischaemia of the peripheral or coronary arteries leading to urgent intervention, or death from cardiovascular causes (4-P MACE).	Both 3-P and 4-P MACE rates were similar between treatment arms (RR 0.92, 95% CI 0.73−1.16 and RR 0.91, 95% CI 0.74−1.12, respectively). Life threatening bleeding was more common in patients treated with VKA + aspirin (RR 3.41, 95% CI 1.84 −6.35).	The INR was set at 2.0 −3.0. Patients with a pre-existing indication for antithrombotics were excluded. Most patients had LEAD (82%).

ABI = ankle brachial index; ALI = acute limb ischaemia; CI = confidence interval; CLTI = chronic limb threatening ischaemia; CV = cardiovascular; DAPT = dual antiplatelet therapy; GFR = glomerular filtration rate; INR = International Normalised Ratio; ISTH = International Society on Thrombosis and Haemostasis; HR = hazard ratio; LEAD = lower extremity arterial disease; MACE = major adverse cardiovascular events; MALE = major adverse limb events; OR = odds ratio; TIMI = Thrombolysis In Myocardial Infarction; PAD = peripheral arterial diseases; RR = risk ratio; SD = standard deviation, VKA = vitamin K antagonist.
* Dedicated LEAD trial.
† Subgroup analysis of broader arterial disease trial.

In the whole of section 4, primary (cardiovascular) prevention refers to the prevention of cardiovascular events in patients with no history of prior events. Secondary (cardiovascular) prevention refers to the prevention of cardiovascular events for a patient who has already experienced a cardiovascular event (Table 7).

4.1. Atherosclerotic carotid artery disease

Antithrombotic treatment for patients with atherosclerotic carotid disease depends on asymptomatic or symptomatic presentation and whether the patient is undergoing surgical or endovascular treatment or medical management alone. The aim of antithrombotic medication in this setting is to reduce the risk of ischaemic cerebral events, as well as reducing the risk of future non-cerebral secondary cardiovascular events.

This section covers antithrombotic recommendations for patients with established atherosclerotic carotid artery stenosis. It was developed at the same time as the 2023 update of the ESVS Management of Atherosclerotic Carotid and Vertebral Artery Disease guidelines.[37]

4.1.1. Asymptomatic atherosclerotic carotid disease not undergoing intervention. This section considers patients presenting with asymptomatic atherosclerotic carotid disease with no symptomatic atherosclerosis in any other territory. In a systematic review of 11 391 patients with > 50% asymptomatic carotid artery stenosis, two thirds of deaths were cardiac.[121] In the Asymptomatic Cervical Bruit RCT, 372 patients with > 50% asymptomatic carotid stenoses were randomised to 325 mg aspirin *vs.* placebo. There was no difference in all cause ischaemic events or all cause death at two years, although the study may have been underpowered.[122] In the prospective cohort Asymptomatic Carotid Emboli Study (ACES), aspirin therapy was associated with lower rates of ipsilateral stroke and cardiac death in asymptomatic patients with atherosclerotic carotid disease.[123] One hundred and one patients with asymptomatic carotid disease in the prospective Oxford vascular study who took aspirin and eventually experienced a cerebral event were less likely to present with a major stroke; however, this was based on one minor stroke event.[124]

CAPRIE did not specifically report for patients with asymptomatic carotid stenoses; however, it showed that clopidogrel was associated with a reduction in future cardiovascular events in patients with established PAD.[9] A combination of aspirin and clopidogrel was assessed in the CHARISMA trial, where 7% of recruits had an asymptomatic 50 − 99% carotid stenosis; there was no evidence that aspirin with clopidogrel conferred a benefit over aspirin alone.[13]

These data were examined in a systematic review and expert consensus process for the ESVS carotid guideline.[125] The conclusion was that patients with > 50% asymptomatic carotid stenoses are recommended to have aspirin monotherapy, with clopidogrel or dipyridamole considered if intolerant.

Recommendation 6

Patients with asymptomatic > 50% carotid artery stenoses are recommended to be offered aspirin (75 − 325 mg) to reduce the risk of secondary cardiovascular events.

Class	Level	References	ToE
I	B	King *et al.* (2013),[123] Murphy *et al.* (2019)[125]	

Recommendation 7			
Patients with asymptomatic > 50% carotid artery stenoses who are intolerant or allergic to aspirin should be offered clopidogrel (75 mg) to reduce the risk of secondary cardiovascular events. If allergic to both aspirin and clopidogrel, dipyridamole (200 mg twice daily) should be considered.			
Class	**Level**	**References**	**ToE**
IIa	C	CAPRIE (1996),[9] Murphy *et al.* (2019)[125]	

4.1.2. Symptomatic atherosclerotic carotid disease. The majority of the included RCTs examining antiplatelet therapy after transient ischaemic attack (TIA) or ischaemic stroke only included patients with high risk TIA defined as an ABCD^2 score[126] of $\geq$ 4, or minor ischaemic stroke defined as National Institutes of Health Sciences Score[127] $<$ 3 and no persistent disabling neurological deficit. These trials also measured the degree of carotid stenoses variably and excluded patients undergoing intervention. These inclusion and exclusion criteria are different from the studies used to determine benefit from carotid intervention and recommendations reflect these facts wherever possible in the class and level chosen.

4.1.2.1. Early initiation of antiplatelet therapy following symptoms. Starting antiplatelet therapy as early as possible following cerebral ischaemic events is important; a meta-analysis of 12 randomised trials including 15 778 patients reported that aspirin monotherapy started immediately after ischaemic stroke or TIA reduced the risk of recurrent stroke by 60% and disabling or fatal recurrent stroke by 70% when compared with placebo or nothing.[128]

4.1.2.2. Dual antiplatelet therapy for patients not undergoing intervention. Three randomised trials compared aspirin plus dipyridamole with aspirin alone.[16,17,129] These trials randomised patients within 24 hours of symptoms to six months after TIA or ischaemic stroke symptoms to aspirin plus dipyridamole, aspirin monotherapy, or placebo. Aspirin plus dipyridamole was more effective than aspirin monotherapy in preventing recurrent stroke[17] or recurrent ischaemic vascular events in patients with TIA or ischaemic stroke[16] and can be safely started within 24 hours of symptom onset.[129] Long term aspirin plus dipyridamole has not been shown to be superior to clopidogrel monotherapy in reducing recurrent stroke for patients with ischaemic stroke in a well powered (20 332 patient) RCT.[130]

Two RCTs, POINT[21] and CHANCE[12] have shown that DAPT (dose ranges were clopidogrel 300 — 600 mg with aspirin 50 — 325 mg to load, followed by 75 mg of clopidogrel and 75 mg of aspirin during the first 21 or 90 days after the index event) reduced the risk of stroke, MI, and cardiovascular death by 30%, compared with aspirin alone for patients with TIA or minor stroke. This benefit was seen most within the first 21 days after the index event; however, these trials excluded patients waiting for a carotid endarterectomy (CEA). A pooled meta-analysis of both trials also showed a reduction in disabling stroke or death, mainly up to 21 days after the index event.[131] A further meta-analysis that also included the FASTER trial[18] (which was stopped early due to a failure to recruit patients at the pre-specified minimum enrolment rate), showed that, at 90 days, the combination of aspirin and clopidogrel substantially reduced non-fatal ischaemic or haemorrhagic stroke, non-fatal ischaemic stroke, and functional disability compared with aspirin alone.

Three smaller RCTs and one observational study have also evaluated the effect of aspirin plus clopidogrel *vs.* aspirin alone on rates of spontaneous micro-embolic signals in patients with symptomatic carotid stenosis, which is an important predictor of increased stroke risk.[132] The CARESS RCT reported significant reductions in ongoing micro-embolisation in patients randomised to aspirin plus clopidogrel with a $>$ 50% symptomatic carotid stenosis who were micro-embolic signal positive at baseline compared with aspirin alone.[10] However, it was not powered to show differences in clinical outcome. The AMBDAP RCT revealed a similar reduction in embolisation of the two study groups, that is, aspirin plus dipyridamole and aspirin plus clopidogrel for patients with $>$ 50% symptomatic carotid stenosis.[3] In a prospective audit, starting aspirin plus clopidogrel in the TIA clinic (after intracranial haemorrhage was excluded on computed tomography [CT] or magnetic resonance imaging [MRI]) was associated with reductions in recurrent TIA or stroke before expedited CEA, plus reductions in micro-embolic signals.[133] Sustained embolisation in the early period after CEA is a predictor of post-operative thromboembolic stroke.[134] One study randomised 100 CEA patients established on 150 mg aspirin daily (84% SCS) to a single dose of 75 mg clopidogrel ($n = 46$) or placebo ($n = 54$) 12 hours before CEA.[135] Compared with placebo, clopidogrel statistically significantly reduced the odds of having $>$ 20 emboli on transcranial doppler in the first three post-operative hours ($p = .010$).

In the THALES trial (which also excluded patients undergoing CEA), aspirin (300 — 325 mg followed by 75 — 100 mg) with ticagrelor (180 mg loading dose followed by 90 mg twice/day) *vs.* aspirin monotherapy resulted in a 17% relative risk reduction of stroke or death at 30 days for patients with TIA or minor stroke.[27] In a subgroup analysis, ticagrelor with aspirin also prevented disabling stroke or death defined in patients with a recurrent stroke at day 30.[136] However, ticagrelor with aspirin was not directly compared with clopidogrel with aspirin and these patients were not awaiting CEA.

The ESPS-2 study randomised aspirin (50 mg twice/day) *vs.* dipyridamole (200 mg twice/day) *vs.* aspirin and dipyridamole. There was benefit to the aspirin and dipyridamole in combination with a 25% reduction in stroke compared with aspirin

alone.[17] Aspirin and dipyridamole therefore remains a valid choice if the patient is intolerant or allergic to clopidogrel.

Recommendation 8

Patients with transient ischaemic attack or minor ischaemic stroke with any degree of carotid artery stenosis not undergoing carotid endarterectomy or stenting are recommended to have dual antiplatelet therapy with aspirin (75 – 325 mg) and clopidogrel (75 mg) for 21 days followed by clopidogrel 75 mg, or long term aspirin (75 – 100 mg) plus dipyridamole (200 mg twice daily) to reduce the risk of stroke.

Class	Level	References	ToE
I	A	Johnston *et al.* (2018),[21] Wang *et al.* (2013),[12] Kennedy *et al.* (2007)[18]	

Recommendation 9

Patients intolerant or allergic to clopidogrel with transient ischaemic attack or minor ischaemic stroke with any degree of carotid artery stenosis not undergoing carotid endarterectomy or stenting should be considered for dual antiplatelet therapy with aspirin and ticagrelor (30 days) or aspirin and dipyridamole (14 days) as an alternative to aspirin and clopidogrel to reduce the risk of stroke.

Class	Level	References	ToE
IIa	B	Diener (1996),[17] Amarenco *et al.* (2020)[136]	

4.1.2.3. Antiplatelet therapy before and after carotid endarterectomy. The Aspirin and Carotid Endarterectomy (ACE) randomised trial examined varying doses of aspirin prior to CEA for TIA or stroke.[2] The combined rate of stroke, MI, and death was lower in the low dose groups than in the high dose groups at 30 days (5.4 *vs.* 7.0%; $p = .070$) and at three months (6.2 *vs.* 8.4%; $p = .030$).

While the RCTs outlined in section 4.1.2.2 have been shown to benefit from DAPT after minor stroke or high risk TIA for patients not undergoing intervention, there is no high quality randomised clinical evidence for dual antiplatelets for patients undergoing CEA. A prospective audit has shown that during a 48 — 72 hour delay between patients being seen in a TIA clinic and undergoing endarterectomy, 13% experienced recurrent stroke or TIA.[133] Starting aspirin and clopidogrel immediately in the TIA clinic reduced recurrent clinical cerebrovascular events prior to CEA from 13% to 3% and was not associated with a notable increase in bleeding complications.[133] A further study reported that the incidence of re-exploration for neck haematoma was 1.5% on no antiplatelet therapy, 1.2% on aspirin monotherapy, 0.7% on clopidogrel monotherapy, and 1.4% on aspirin with clopidogrel therapy.[137] Two prospective studies have shown that long term aspirin therapy after CEA was associated with a substantial improvement in long term survival.[138,139] There is currently no high quality evidence regarding the safety of ticagrelor or combination of aspirin with ticagrelor in patients awaiting urgent CEA.

Because of a lack of evidence on following the new DAPT regimens prior to CEA,[140] a definitive recommendation on antiplatelet therapy cannot be made. However, the magnitude of benefit for DAPT has recently been shown to be so great that it must be considered by local teams. As part of local protocols, several recommendations can be made around the timing and dose of therapy. The term recently symptomatic includes patients with symptoms in the past six months, which was the inclusion criterion in the European Carotid Surgery Trial/North American Carotid Endarterectomy Trial.[141,142]

Recommendation 10

Protocols for antiplatelet therapy for symptomatic patients prior to carotid endarterectomy or stenting should be made by local teams. Doses should follow the major randomised trial regimens.

Class	Level	References
I	C	Consensus

Recommendation 11

Patients who are to undergo carotid endarterectomy are recommended to have antiplatelet therapy before the procedure, in the peri-operative period, and over the long term.

Class	Level	References	ToE
I	A	Kretschmer (1990),[138] Lindblad (1993),[139] Murphy (2019)[125]	

Recommendation 12

Patients with a > 50% carotid stenosis experiencing transient ischaemic attack or minor stroke awaiting carotid endarterectomy are recommended for early institution of antiplatelet therapy to reduce recurrent stroke risk.

Class	Level	References	ToE
I	B	Pan *et al.* (2019),[131] Batchelder *et al.* (2015),[133] Stone *et al.* (2011),[137] Payne *et al.* (2004)[135]	

Recommendation 13

Recently symptomatic patients who are to undergo carotid endarterectomy should be considered for dual antiplatelet therapy with aspirin (75 – 325 mg) and clopidogrel (75 mg) peri-operatively to reduce recurrent stroke risk.

Class	Level	References	ToE
IIa	C	Payne *et al.* (2004),[135] Markus *et al.* (2005),[10] Batchelder *et al.* (2015),[133] Pan *et al.* (2019)[131]	

Recommendation 14			
Recently symptomatic patients who are to undergo carotid endarterectomy for whom antiplatelet monotherapy is preferred should be considered for aspirin (300 – 325 mg daily) for 14 days followed by lower doses (75 – 162 mg daily) to reduce the recurrent stroke risk.			
Class	**Level**	**References**	**ToE**
IIa	B	Taylor *et al.* (1999)[2]	

Recommendation 15			
Patients who are to undergo carotid endarterectomy are recommended to preferentially have low dose aspirin (75 – 325 mg daily) rather than higher doses to reduce recurrent stroke risk.			
Class	**Level**	**References**	**ToE**
I	B	Taylor *et al.* (1999)[2]	

4.1.2.4. Antiplatelet therapy before and after carotid artery stenting. The same principles for cardiovascular prevention apply for patients undergoing carotid artery stenting (CAS) as for those undergoing CEA. Additionally, there are four principal mechanisms involved in stroke occurrence in CAS: distal embolisation due to ruptured plaque, mural thrombus formation mediated by platelet activation secondary to intimal injury due to stent placement, stent thrombosis, and haemodynamic compromise around the procedure.[143,144] There is again a paucity of large volume randomised data regarding antithrombotic therapy both in the peri-operative period and in the long term after CAS. There are two small RCTs examining peri-operative antithrombotic treatment for CAS. One compared low dose aspirin plus clopidogrel with aspirin plus anticoagulation in the form of heparin. This RCT showed a lower incidence of both ischaemic (0 *vs.* 25%, respectively) and haemorrhagic complications (9 *vs.* 17%, respectively) in the dual antiplatelet arm.[145] The trial was stopped early because of complications in the aspirin plus heparin arm. The second compared aspirin plus ticlopidine with aspirin plus heparin in 100 patients, 50 in each arm. Aspirin plus heparin was associated with a statistically significant increase in ipsilateral ischaemic stroke or TIA (16% *vs.* 2%; $p < .050$) and no difference was found in bleeding complications (4% *vs.* 2%; $p > .050$).[146] These trials set a standard for DAPT for CAS, and was carried through into the protocols of some of the larger trials comparing carotid stenting with CEA. In CREST, aspirin 325 mg twice a day and clopidogrel 75 mg twice a day was recommended for $\geq$ 48 hours before CAS, followed by aspirin 325 mg daily for 30 days, combined with either clopidogrel 75 mg daily or ticlopidine 250 mg twice daily for at least four weeks.[15]

Most investigators, supported by a consensus document on CAS by five societies, advise at least four weeks of treatment with aspirin and clopidogrel post-procedure.[147]

Recommendation 16			
Patients scheduled for carotid artery stenting for carotid stenosis are recommended to have dual antiplatelet therapy consisting of aspirin (75 – 325 mg) plus clopidogrel (75 mg) to reduce recurrent stroke risk. Clopidogrel should be started at least three days before stenting or as a single 300 mg loading dose in urgent cases.			
Class	**Level**	**References**	**ToE**
I	C	McKevitt *et al.* (2005),[145] Murphy *et al.* (2019)[125]	

Recommendation 17			
Patients undergoing carotid artery stenting are recommended to have dual antiplatelet therapy with aspirin and clopidogrel continued for at least four weeks after carotid stenting, then clopidogrel 75 mg continued indefinitely to reduce stroke risk.			
Class	**Level**	**References**	**ToE**
I	C	McKevitt *et al.* (2005),[145] Murphy *et al.* (2019)[125]	

4.1.2.5. Antiplatelet therapy for prevention of future cerebral and cardiovascular events following symptoms or intervention. Several randomised trials have assessed single or DAPT in patients with ischaemic cerebral events: ESPS-2,[17] CAPRIE,[9] ESPRIT,[16] PRoFESS,[23] CHANCE,[12] POINT,[21] and THALES.[27] In terms of longer term outcomes when considering de-escalation of DAPT, ESPS-2[17] and ESPIRIT[16] did not de-escalate DAPT (aspirin plus dipyridamole which was long term) in the treatment arm during the trial design. CHANCE[12] and POINT[21] both examined DAPT (aspirin plus clopidogrel *vs.* aspirin for 90 days) after stroke and did not de-escalate the DAPT arm. THALES[27] examined DAPT with aspirin plus ticagrelor *vs.* aspirin for 30 days after stroke and did not examine antiplatelet de-escalation.

PRoFESS[23] randomised 20 332 patients with ischaemic stroke to aspirin plus dipyridamole *vs.* clopidogrel. There was no difference in recurrent stroke rates between aspirin plus dipyridamole *vs.* clopidogrel at three months. CAPRIE[9] examined aspirin *vs.* clopidogrel in patients with arterial disease, including a subgroup of patients with ischaemic stroke and a subgroup with carotid atherosclerosis, and found in favour of clopidogrel (Table 7). The (non-powered) stroke subgroup showed no clear difference for the primary outcome between aspirin and clopidogrel.[9] Based on these RCTs, clopidogrel single therapy following DAPT with aspirin plus clopidogrel or aspirin plus ticagrelor, or long term aspirin and dipyridamole is the recommended first line medium and long term antithrombotic therapy for patients with ischaemic stroke. This is worked into the post-intervention recommendations above.

There is evidence both following coronary stenting[148] and stroke or TIA not undergoing intervention,[149] that long term

DAPT with aspirin and clopidogrel increases the risk of major bleeding more than it improves the risk of cardiovascular events.

Recommendation 18			
Patients with ischaemic cerebral events both undergoing and not undergoing carotid intervention are not recommended to have dual antiplatelet therapy with aspirin and clopidogrel long term as it confers no benefit over single antiplatelet therapy but increases the bleeding risk.			
Class	**Level**	**References**	**ToE**
III	A	Navarese (2015),[148] Diener (2004)[149]	

4.1.2.6. Anticoagulation for atherosclerotic carotid disease. The WAVE trial, which randomised the combination of VKA at full dose plus aspirin *vs.* aspirin alone, included some patients with carotid artery atherosclerosis. The exact number was not stated, but 394 of the 2 161 patients in the trial had "other arterial disease" as defined by subclavian artery stenosis, prior CEA, TIA or stroke, or asymptomatic carotid stenosis of $>$ 50%.[30] There was no difference in major cardiac or limb events; however, there was a three-fold increased risk of life threatening bleeding with full dose warfarin in addition to antiplatelet therapy.[30]

The COMPASS trial randomised patients to aspirin and low dose rivaroxaban, aspirin alone, and low dose rivaroxaban alone, and included 1 919 patients with carotid disease which was defined as prior carotid revascularisation or asymptomatic carotid artery stenosis of at least 50% diagnosed by duplex ultrasound or angiography.[14] The whole trial results favoured the combination of aspirin and low dose rivaroxaban. There was no statistically significant benefit for combination therapy with aspirin and low dose rivaroxaban, *vs.* aspirin alone in the carotid subgroup for preventing stroke, MI, or cardiovascular death.[150] However, non-powered subgroups would not be expected to reach statistical significance. The major problem with forming recommendations for patients with carotid stenoses from COMPASS was that patients with pre-existing indications for DAPT and a non-aspirin antiplatelet were excluded, which would exclude many patients in this section. Figure 1 summarises antithrombotic recommendations for patients with atherosclerotic carotid and vertebral artery disease.

4.2. Atherosclerotic vertebral artery disease

There is considerably less literature reporting antithrombotics for patients with atherosclerotic vertebral disease (asymptomatic or symptomatic). There have been no specific trials evaluating the effect of antiplatelet therapy in patients with asymptomatic or symptomatic vertebral stenosis; however, given their risk profile, it is reasonable to adopt the same recommendation strategy as for carotid disease. There are no data regarding anticoagulation for patients with atherosclerotic vertebral disease. There are also no long term data regarding long term DAPT in this population and the safety of dual antiplatelet regimens has not been assessed in patients with vertebral artery disease.

4.3. Atherosclerotic upper limb arterial disease

Asymptomatic upper limb atherosclerotic arterial disease may be seen by vascular specialists. There is no specific evidence on the risks and benefits of antithrombotics for this patient group. Patients with asymptomatic upper limb arterial disease will have been included in both the Asymptomatic Atherosclerosis trial[120] and the POPADAD trial[22] because of their selection criteria; however, subgroup analyses are not presented and there is no evidence in the literature on antithrombotics for isolated asymptomatic upper limb arterial disease. The cardiovascular risk of isolated asymptomatic upper limb disease is also not well described in the literature.

Symptomatic upper limb arterial disease represents an independent cardiovascular risk factor.[151] It is strongly associated with arterial disease in other territories such as the coronary arteries, lower extremities, or carotids.[152,153] The most frequent lesions in this vascular bed affect the subclavian arteries and the innominate trunk.[151]

No RCTs have studied the influence of antithrombotic treatment on the symptoms of patients with upper limb atherosclerotic disease, nor on their cardiovascular risk. A retrospective study of 274 patients compared the haemodynamic and clinical evolution of atherosclerotic upper limb arterial disease with antiplatelet therapy *vs.* endovascular repair.[154] After a mean follow up of 42 months, patients treated endovascularly had long term haemodynamic improvement but, at the same time, many of those treated conservatively improved clinically until they became asymptomatic.

This lower quality evidence combined with the evidence for trials of PAD in sections 4.5.2 and 4.5.5 leads to a recommendation of single antiplatelet therapy for chronic symptomatic disease and an individualised strategy post-intervention for the innominate and subclavian arteries. Specific agents cannot be recommended based on the literature because patients with subclavian disease were not formally included in the major trials, and while some may have been captured by the inclusion criteria, no separate data have been published.[9,14,29]

Recommendation 19			
Patients with chronic symptomatic upper limb arterial disease should be considered for single antiplatelet therapy for secondary prevention of cardiovascular events.			
Class	**Level**	**References**	**ToE**
IIa	C	Aboyans (2007),[151] Schillinger (2002)[154]	

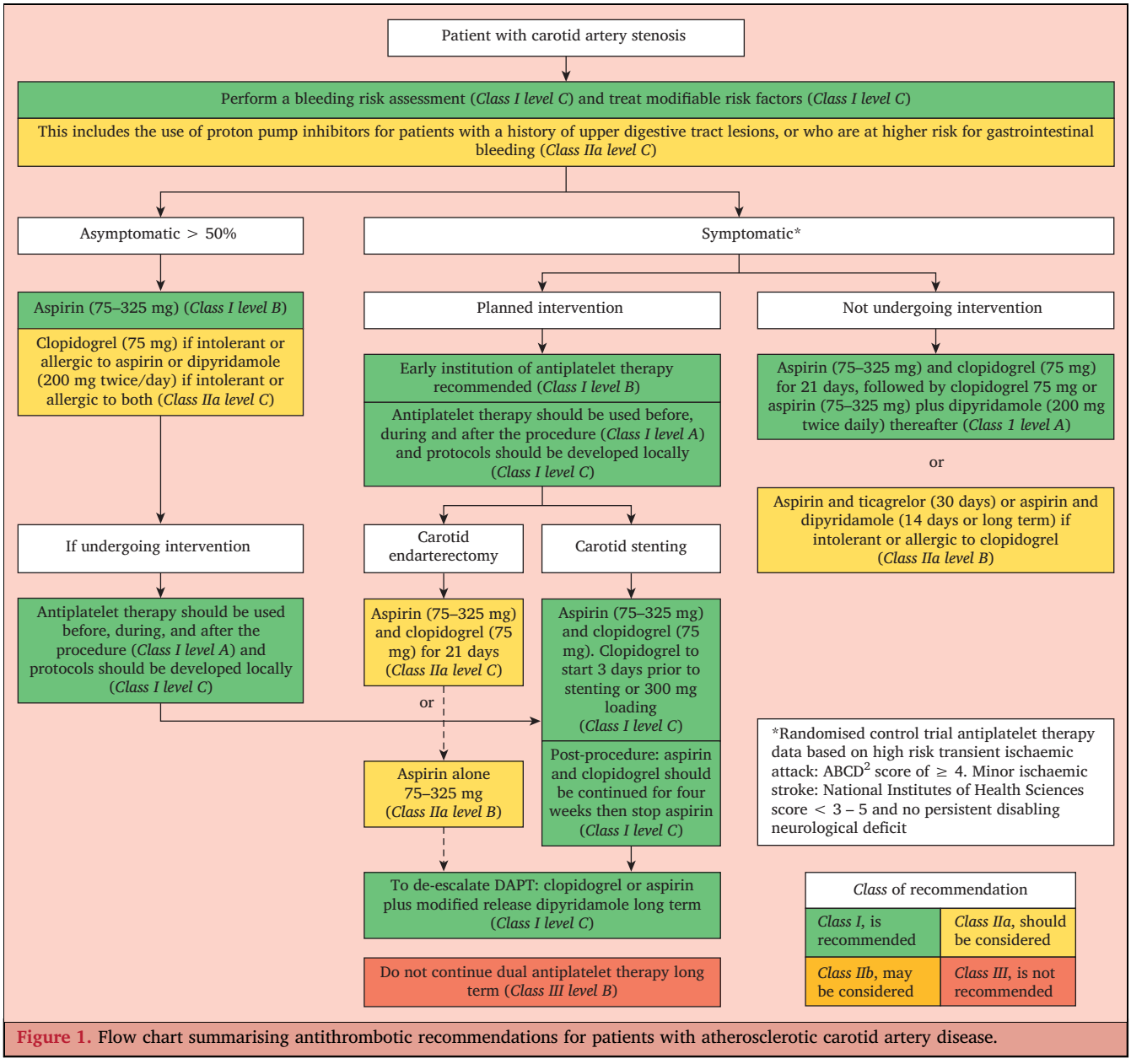

Figure 1. Flow chart summarising antithrombotic recommendations for patients with atherosclerotic carotid artery disease.

Recommendation 20		
Patients post-revascularisation for upper limb atherosclerotic arterial disease are recommended to have an individualised antithrombotic strategy balancing risks and benefits to reduce the risk of secondary cardiovascular and limb events.		
Class	**Level**	**References**
I	C	Consensus

4.4. Atherosclerotic renal and mesenteric arterial disease

Renal and mesenteric artery atherosclerotic lesions are associated with an increased cardiovascular risk.[155] In addition, the involvement of the renal artery can cause hypertension, which may be difficult to manage, and worsen kidney function.

There are minimal data in the literature on antithrombotic therapy specifically for atherosclerotic renal arterial disease. There are no RCTs examining the effect of antithrombotic treatment on the cardiovascular prognosis, renal function, or control of arterial hypertension of patients with renal artery stenosis. However, renal artery stenosis is strongly associated with poor cardiovascular outcomes and is often asymptomatic from a patient point of view, even if there is decreased renal function or hypertension.[156] A retrospective case series of 226 patients with renal arterial disease showed a reduced risk of death from (unspecified) antiplatelet therapy compared with no antiplatelet therapy started after the diagnosis of symptomatic or asymptomatic renal artery ste-

nosis.[157] There are several large RCTs on the effect of endovascular intervention on renal artery stenosis. Only three of the seven of these published up to 2016 specified the use of antiplatelet therapy in their protocol, but it is reasonable to assume that the medical therapy arm of these trials included single antiplatelet therapy.[156]

Patients with mesenteric arterial disease are also known to have a high risk of cardiovascular events including cardiac death.[155] There are no RCTs examining the use of antithrombotics for mesenteric arterial disease. Two low quality retrospective case series show a reduced incidence of complications during endovascular intervention for patients taking unspecified antiplatelet therapy,[158] as well as a reduction in the mortality rate.[159] Taking these factors into account it is reasonable to recommend single antiplatelet therapy for patients with chronic mesenteric ischaemia. Acute embolic mesenteric ischaemia should be treated as per recommendations in section 4.7.

There is no evidence for antithrombotic therapy following endovascular revascularisation for renal or mesenteric arterial disease. Based on coronary and lower limb endovascular practice (see section 4.5.5.2), a limited course of DAPT should be considered.

Recommendation 21

Patients with asymptomatic or symptomatic > 50% atherosclerotic renal or mesenteric artery stenotic disease should be considered for single antiplatelet therapy for secondary prevention of cardiovascular events.

Class	Level	References	ToE
IIa	C	Ritchie *et al.* (2016),[157] Oderich *et al.* (2012)[158]	

Recommendation 22

Patients post-revascularisation for atherosclerotic renal or mesenteric artery disease who are not at high risk of bleeding should be considered for a short course (minimum of one to maximum six months) dual antiplatelet therapy (aspirin 75 mg and clopidogrel 75 mg) to reduce the risk of stent thrombosis.

Class	Level	References
IIa	C	Consensus

4.5. Atherosclerotic lower extremity arterial disease

Lower extremity arterial disease is common worldwide, increasing in prevalence, and certain presentations are associated with a notable risk of death, cardiovascular and limb events.[160,161]

4.5.1. Asymptomatic lower extremity arterial disease. There are a number of ways LEAD without symptoms can be diagnosed. An ankle brachial index may be performed as part of a clinical examination. Diagnostic imaging for other purposes such as CT, duplex ultrasound, and MRI may all show LEAD incidentally. Due to the known cardiovascular risks involved, patients with asymptomatic LEAD are often referred to the vascular specialist and risk factor management will be the mainstay of treatment.[39] For the purpose of this section, this patient group does not have symptomatic arterial disease in any territory, or a pre-existing indication for antithrombotic therapy.

There have been a number of RCTs examining antiplatelet therapy for asymptomatic PAD (which included a large proportion of patients with asymptomatic LEAD), the largest of which were the Aspirin for Asymptomatic Atherosclerosis trial[120] and the POPADAD trial.[22] Neither of these trials showed benefit for aspirin over placebo, the latter (POPADAD) included only diabetics (Table 7). These trials, in addition to several smaller randomised trials examining single and DAPT for asymptomatic LEAD were combined in meta-analyses showing no substantial benefit for any antiplatelet therapy combination over placebo for any outcome, although the bleeding risk was also not substantially higher.[52]

Recommendation 23

Patients with isolated asymptomatic lower extremity artery disease are not recommended to have aspirin for cardiovascular prevention.

Class	Level	References	ToE
III	A	Ambler *et al.* (2020)[52]	

4.5.2. Chronic symptomatic lower extremity arterial disease. The benefit to risk ratio for antiplatelet therapy for symptomatic LEAD is more favourable than for asymptomatic LEAD, because symptomatic patients experience more ischaemic events than those who are asymptomatic.[52] In this context antiplatelet therapy serves two primary purposes. The first is to reduce the risk of serious secondary cardiovascular events such as MI, stroke, and cardiovascular death.[162] The second is to reduce the risk of acute limb ischaemia (ALI), the development of chronic limb threatening ischaemia (CLTI), and the subsequent risk of unplanned revascularisation.[163,164]

Patients with chronic symptomatic LEAD represent a population at substantial risk of MACE, where the benefits of antithrombotic treatment compared with placebo or no treatment have been clearly demonstrated in large RCTs and meta-analyses.[165,166] Numerous studies have also demonstrated that secondary preventive pharmacotherapy, including antithrombotic therapies are generally underused in patients with LEAD.[167] This especially holds true for patients who are not offered lower limb revascularisation[168-170] Vascular specialists therefore need to attach a high priority to the implementation or optimisation of secondary preventive pharmacotherapies whenever encountering a patient with chronic symptomatic LEAD.

4.5.2.1. Single antiplatelet therapy. While the optimal choice of antiplatelet agent has been extensively debated, low dose aspirin or clopidogrel single therapy have remained the most widely used antiplatelet agents in

patients with chronic symptomatic LEAD.[35] Large meta-analyses lend support to this therapeutic choice by demonstrating a relative risk reduction in excess of 20% for the prevention of secondary cardiovascular events by antiplatelet agents.[52,165] However, these analyses are based on older data that do not reflect complementary medical risk reduction therapy, and a substantial proportion of RCTs included in these evaluations studied an antiplatelet agent other than aspirin or studied aspirin in combination with dipyridamole. This may have distorted the results and renders conclusions about the efficacy of low dose aspirin single therapy uncertain.[165] A growing body of evidence has questioned the efficacy of low dose aspirin when used as a standalone therapy in LEAD.[70,171-173]

In a subgroup analysis of CAPRIE, single antiplatelet therapy with clopidogrel 75 mg was superior in terms of MACE reduction compared with aspirin 325 mg, and the overall safety profile of clopidogrel was at least as good as that of aspirin (Table 7).[9] CAPRIE is now historical, and modern patient populations will have different comorbidities and medical therapies co-prescribed. Clopidogrel single therapy was compared with ticagrelor single therapy among patients with chronic LEAD in the EUCLID trial.[6] Although the safety profiles for the two treatments were comparable, treatment with ticagrelor did not reduce the primary MACE endpoint compared with clopidogrel.[6] It should be noted that the EUCLID trial actively excluded patients who were poor metabolisers of clopidogrel, which may not make results generalisable to a non-tested population.

Recommendation 24

Patients with chronic symptomatic lower extremity arterial disease are recommended to have single antiplatelet therapy for secondary cardiovascular prevention.

Class	Level	References	ToE
I	A	Antithrombotic Trialists (2009),[165] Nastasi *et al.* (2018),[170] Ambler *et al.* (2020)[52]	

Recommendation 25

Patients with chronic symptomatic lower extremity arterial disease should be considered for clopidogrel (75 mg) as the first choice antiplatelet agent when single antiplatelet therapy is indicated for secondary cardiovascular prevention.

Class	Level	References	ToE
IIa	B	CAPRIE (1996),[9] Hiatt *et al.* (2017)[6]	

The antiplatelet agent cilostazol appears to confer a walking distance benefit in patients with intermittent claudication.[174] However, there is currently no high quality evidence that it reduces MACE and or MALE events for chronic LEAD patients not eligible for revascularisation.[174] The benefit to risk ratio of cilostazol is also not completely clear and has been questioned previously by the European Medicines Agency leading to a restriction in its use.[175] Clinicians often view cilostazol as a drug to improve walking distance for claudication rather than as an antiplatelet drug. As a result of these factors there is insufficient evidence to make a useful guideline recommendation.

Another antiplatelet agent that has been studied in patients with LEAD is vorapaxar which is no longer available in the European Union but is included for completeness. The TRA 2P-TIMI 50 trial enrolled 26 449 patients with different atherosclerotic manifestations and compared the efficacy and safety of vorapaxar with placebo in addition to standard of care.[28] Among them 3 787 patients had LEAD. The overall MACE rate was comparable between vorapaxar and placebo (11.3% *vs.* 11.9%; HR 0.94, 95% CI 0.78 — 1.14) in the LEAD group; however, in a pre-specified secondary analysis vorapaxar reduced the risk of ALI (2.3% *vs.* 3.9%; HR 0.58, 95% CI 0.39 — 0.86) and also the rates of lower limb revascularisation (18.4% *vs.* 22.2%; HR 0.84, 95% CI 0.73 — 0.97). Bleeding, including GUSTO moderate and severe bleeding, occurred more frequently with vorapaxar compared with placebo (7.4% *vs.* 4.5%; HR 1.62, 95% CI 1.21 — 2.18).[176]

4.5.2.2. Dual antiplatelet therapy. The CHARISMA trial enrolled 15 603 patients with established atherosclerotic disease or multiple cardiovascular risk factors and studied the efficacy of DAPT with clopidogrel plus aspirin *vs.* placebo plus aspirin for the prevention of MACE. Although there was no overall difference, a *post hoc* subgroup analysis of 2 838 patients with symptomatic LEAD demonstrated a non-significant reduction in MACE in the DAPT arm (Table 7).[13,177,178] The rates of severe, fatal, or moderate bleeding did not differ between the groups in this *post hoc* analysis, whereas minor bleeding was increased with DAPT. Further meta-analysis of all available evidence was reported more recently in a systematic review.[179] In this analysis, DAPT did not reduce the risk of the composite endpoint (all cause death, MI, and stroke) in the subgroup with LEAD (n = 4 320; OR 0.84, 95% CI 0.65 — 1.08). When analysing the overall population (n = 55 563), which included a majority of patients with CAD, the long term use of DAPT was also associated with a substantial increase in major bleeding risk (OR 1.65; 95% CI 1.23 — 2.21).[179] In a more recent umbrella review including mixed LEAD populations, DAPT treatment did not reduce the risk of MACE (n = 19 517; RR 1.12, 95% CI 0.99 — 1.28) but had a higher rate of major bleeding than single therapy (RR was 0.74; 95% CI 0.57 — 0.95 for SAPT *vs.* DAPT).[52]

Dipyridamole in combination with aspirin has also been studied historically. A comprehensive systematic review examined the effect of dipyridamole in combination with aspirin and as a standalone treatment in a wide range of arterial vascular diseases (CAD, MI, angina pectoris, retinopathy, nephropathy, peripheral arterial disease, and TIA or stroke).[180] Dipyridamole had no effect on vascular death (RR 0.99; 95% CI 0.87 — 1.12) compared with the control treatment. Dipyridamole substantially reduced MACE events in patients with cerebral ischaemia (RR 0.88;95% CI 0.81 — 0.95). However, there were not enough data for patients with LEAD from which to draw firm conclusions. Further network meta-analysis confirmed that DAPT with

aspirin plus clopidogrel was no more effective in reducing MACE than single therapy alone.[181]

Recommendation 26			
Patients with chronic symptomatic lower extremity arterial disease are not recommended to have dual antiplatelet therapy for secondary cardiovascular prevention.			
Class	**Level**	**References**	**ToE**
III	B	Ambler *et al.* (2020),[52] De Carlo *et al.* (2021)[181]	

Triple antiplatelet therapy (mainly based on short term treatment with glycoprotein IIb/IIIa receptor antagonists but also on the addition of cilostazol to DAPT) has been studied for the early management of acute coronary syndromes. In a large systematic review of triple antiplatelet therapy strategies, no trial that compared triple *vs.* DAPT in patients with LEAD was identified.[182]

4.5.2.3. Anticoagulant and combination therapy. Full dose anticoagulation (anticoagulation with a clinical effect based on the range of a therapeutic INR) has been examined as an alternative to antiplatelet therapy for chronic symptomatic LEAD (also see section 4.11.3). There is no evidence of superiority, but a clear risk of harm in terms of major bleeding.[183] The WAVE trial randomised patients with LEAD to receive either a full dose VKA in combination with antiplatelet therapy or antiplatelet therapy alone (Table 7).[30] The combination of VKA plus antiplatelet therapy was no more effective than antiplatelet therapy alone in terms of MACE prevention but was associated with a substantial increase in life threatening bleeding.

Recommendation 27			
Patients with chronic lower extremity arterial disease with no other indication for anticoagulation are not recommended to have full dose anticoagulation for secondary cardiovascular prevention.			
Class	**Level**	**References**	**ToE**
III	A	Cosmi *et al.* (2014),[183] Anand *et al.* (2007)[30]	

The COMPASS trial was designed to assess the clinical benefit of dual pathway inhibition with an antiplatelet agent (aspirin) and anticoagulation (rivaroxaban). COMPASS enrolled 27 395 participants with chronic atherosclerotic arterial disease. In the overall trial, the combination therapy with aspirin and rivaroxaban was more efficient in terms of MACE reduction while the incidence of major bleeding was higher both in the overall trial and among patients with LEAD.[14,184] In a symptomatic LEAD subgroup analysis, the estimated net clinical benefit of the combination treatment (defined as the combined risk of MACE and MALE events including major amputation) balanced against fatal or critical organ bleeding was 22% (HR 0.78; 95% CI 0.63 — 0.95, Table 8).[185] Importantly, patients randomised in COMPASS (and VOYAGER, see section 4.5.5) were at a lower risk of bleeding than the general population.[55] This problem with bleeding risk is inherent to almost all RCTs of antithrombotics and only the COMPASS and VOYAGER risk of bleeding criteria have been included as the most up to date RCT definitions. When considering patients for the trial aspirin and rivaroxaban combination, particular attention needs to be paid to the individual risk of bleeding.

Table 8. Patients referred to in recommendations as high risk of bleeding as defined by the COMPASS and VOYAGER exclusion criteria

The definition of high risk of bleeding used in COMPASS[119]
High risk of bleeding as defined by the randomising clinician
Stroke within one month
Any history of haemorrhagic or lacunar stroke or hepatic disease associated with coagulopathy
The definition of high risk of bleeding used in VOYAGER[29]
Medical history or active clinically significant bleeding, lesions, or conditions within the last six months prior to randomisation, considered to be a significant risk of major bleeding
Any known hepatic disease associated with coagulopathy or bleeding risk

The obvious problem for guideline recommendations is a lack of data comparing aspirin plus rivaroxaban with clopidogrel. A network meta-analysis showed no superiority for aspirin plus rivaroxaban over clopidogrel alone for the primary composite endpoint in the chronic LEAD subgroups of CAPRIE and COMPASS.[186] Therefore in the absence of a RCT directly comparing the two, both clopidogrel alone and aspirin with rivaroxaban are reasonable choices for secondary cardiovascular prevention for patients with chronic symptomatic LEAD. A recent cohort series applying these criteria to real world data show that only around 30% of patients hospitalised for PAD were eligible for the COMPASS (or VOYAGER) aspirin and rivaroxaban combination.[55]

4.5.2.4. High risk chronic lower extremity arterial disease populations. Patients with certain diseases and clinical stages of LEAD have been found to be at higher risk of MACE, MALE, and death (Table 9).[53,187,188] Depending on the individual risk profile, the five year incidence of amputation or death varied from 9% to 48% in patients suffering from intermittent claudication and from 25% to 88% in patients with CLTI.[187]

The main risk factors that have been consistently found to increase the risk of MACE, MALE, and death from subgroup analyses of RCTs and large registries are listed in Table 9. In such high risk populations, the choice of antithrombotic treatment, as well as the intensity of the treatment offered, may be important to mitigate this increased risk. A higher risk of bleeding complications may be acceptable to such patients given the added absolute benefit of the treatment.[53,185]

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

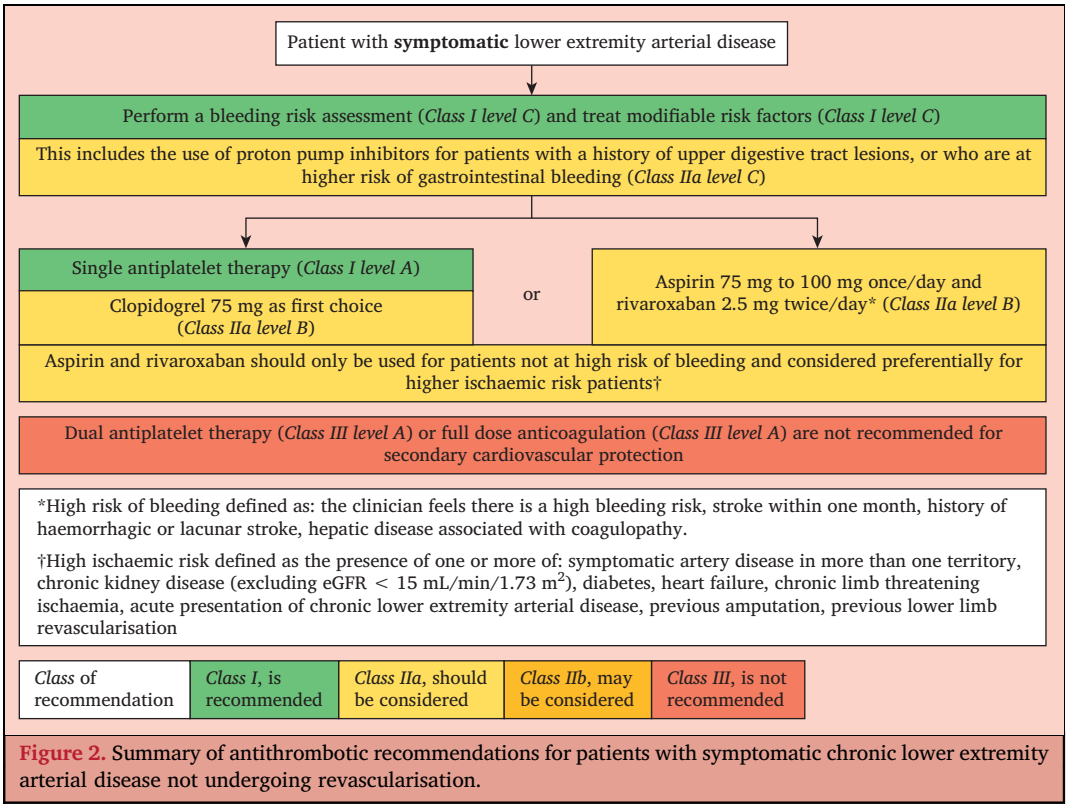

Figure 2. Summary of antithrombotic recommendations for patients with symptomatic chronic lower extremity arterial disease not undergoing revascularisation.

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.

4.5.5.3. Endovascular arterial intervention post-procedure anticoagulants and combination therapy. The combination of aspirin 100 mg once per day and rivaroxaban 2.5 mg twice per day was examined in VOYAGER.[29] The definitions for high risk of bleeding were slightly different between VOYAGER and COMPASS (Table 8 and Fig. 2). The risk of bleeding in the RCT was low overall, and lower than real world populations.[55,56] The main finding was that treatment with aspirin and rivaroxaban improved the primary composite efficacy outcome compared with aspirin single therapy during a median follow up of 28 months.[29] The majority of patients in the trial underwent endovascular revascularisation (66%) for claudication (77% of endovascular group). Although VOYAGER was not powered to detect a difference in particular subgroups, treatment strategy subanalysis showed that the positive primary efficacy outcome was statistically significant in the surgical subgroup (HR 0.79; 95% CI 0.66 — 0.95) but not the endovascular subgroup (HR 0.90; 95% CI 0.77 — 1.05), although there was no statistically significant difference between these subgroups when tested.[29] There was also a concomitant use of clopidogrel in VOYAGER, which was given to 51% of patients in addition to the primary treatment strategy, and was used more in the post-endovascular intervention group.[206] In a non-powered subgroup analysis, clopidogrel did not affect the effectiveness of aspirin and rivaroxaban over aspirin alone for the primary composite endpoint when added to the primary treatment strategy; however, it did increase ISTH criteria major bleeding when used for more than 30 days.[206]

One additional small multicentre double blind RCT (n = 203) compared aspirin plus edoxaban with aspirin plus clopidogrel for three months following endovascular intervention.[207] After six months there was no difference in the re-stenosis and re-occlusion rate (RR 0.89; 95% CI 0.59 — 1.34). There was no statistically significant difference in major bleeding rates between the groups.

A network meta-analysis comparing all of the available combinations after intervention including the VOYAGER result concluded that while aspirin plus low dose rivaroxaban enjoyed a reduced risk of repeat revascularisation compared with aspirin alone, “the evidence for other comparators, in particular antiplatelet regimens, was insufficient to guide treatment decisions and highlights the challenge in establishing the magnitude of comparative efficacy using existing RCTs”.[208] Figure 3 summarises antithrombotic recommendations for patients undergoing endovascular intervention for lower extremity arterial disease.

Recommendation 36

Patients undergoing endovascular intervention for lower extremity arterial disease who are not at high risk of bleeding should be considered for aspirin (75 — 100 mg once daily) combined with rivaroxaban (2.5 mg twice daily) to reduce the risk of secondary cardiovascular and major adverse limb events.

Class	Level	References	ToE
IIa	B	Bonaca *et al.* (2020)[29]	

Recommendation 37

If clopidogrel (75 mg) is added in exceptional circumstances to aspirin (75 — 100 mg once daily) in combination with rivaroxaban (2.5 mg twice daily) for patients undergoing endovascular intervention for lower extremity arterial disease who are not at high risk of bleeding, it is not recommended for longer than 30 days as the bleeding risk is likely to outweigh the benefit.

Class	Level	References	ToE
III	C	Hiatt *et al.* (2020)[206]	

4.5.5.4. Open arterial surgery antiplatelet therapy. Between 1985 and 2020 twenty one RCTs have compared different antithrombotic strategies in patients undergoing open surgical revascularisation for LEAD (Appendix E). Most RCTs before the year 2000 enrolled less than 300 patients and are outdated in terms of sample size and a lack of concurrent background medical therapy.

A Cochrane review has examined the effects of antiplatelet therapy for patients who underwent femoropopliteal or femorodistal bypass grafting.[209] This showed that antiplatelet therapy with aspirin or with aspirin plus dipyridamole had a beneficial effect on primary patency compared with placebo or no treatment after 12 months (OR 0.42; 95% CI 0.22 — 0.83). However, this effect was not evident when evaluating venous grafts alone (OR 0.76; 95% CI 0.26 — 2.25) but was strong for prosthetic grafts (OR 0.14; 95% CI 0.04 — 0.51).[209] It must be emphasised that none of the included trials were stratified by graft type before randomisation, and results should therefore be considered subgroup analyses. Furthermore, the authors highlighted that the small number of participants probably limited the conclusions concerning side effects, and that further high quality RCTs with adequate sample sizes are required to evaluate the efficacy of antiplatelet medications following bypass surgery.[209]

In the CASPAR trial, 851 patients who underwent below knee bypass grafting were randomised to either receive clopidogrel plus aspirin or placebo plus aspirin.[11] The primary efficacy composite endpoint showed that no statistically significant differences were found in the overall population. However, a secondary subgroup analysis revealed that clopidogrel plus aspirin improved the primary endpoint for patients with prosthetic grafts but not for patients with venous grafts (Table 7). No statistically significant differences in bleeding rates were observed between the groups.[11]

4.5.5.5. Open arterial surgery anticoagulants and combination therapy. Nine RCTs comprising 7 817 patients have examined oral anticoagulants in patients undergoing peripheral bypass surgery. In the Dutch Bypass Oral anticoagulants or Aspirin (BOA) RCT, 2 690 patients who had undergone infrainguinal bypass were randomly assigned to oral anticoagulation with a VKA (international normalised ratio 3.0 — 4.5) or aspirin 80 mg.[5] The primary outcome event was graft occlusion. While anticoagulants were beneficial for bypass patency for patients with vein grafts (HR 0.69; 95% CI 0.54 — 0.88), aspirin had better bypass patency results in patients with prosthetic grafts after a mean follow up of 21 months (HR

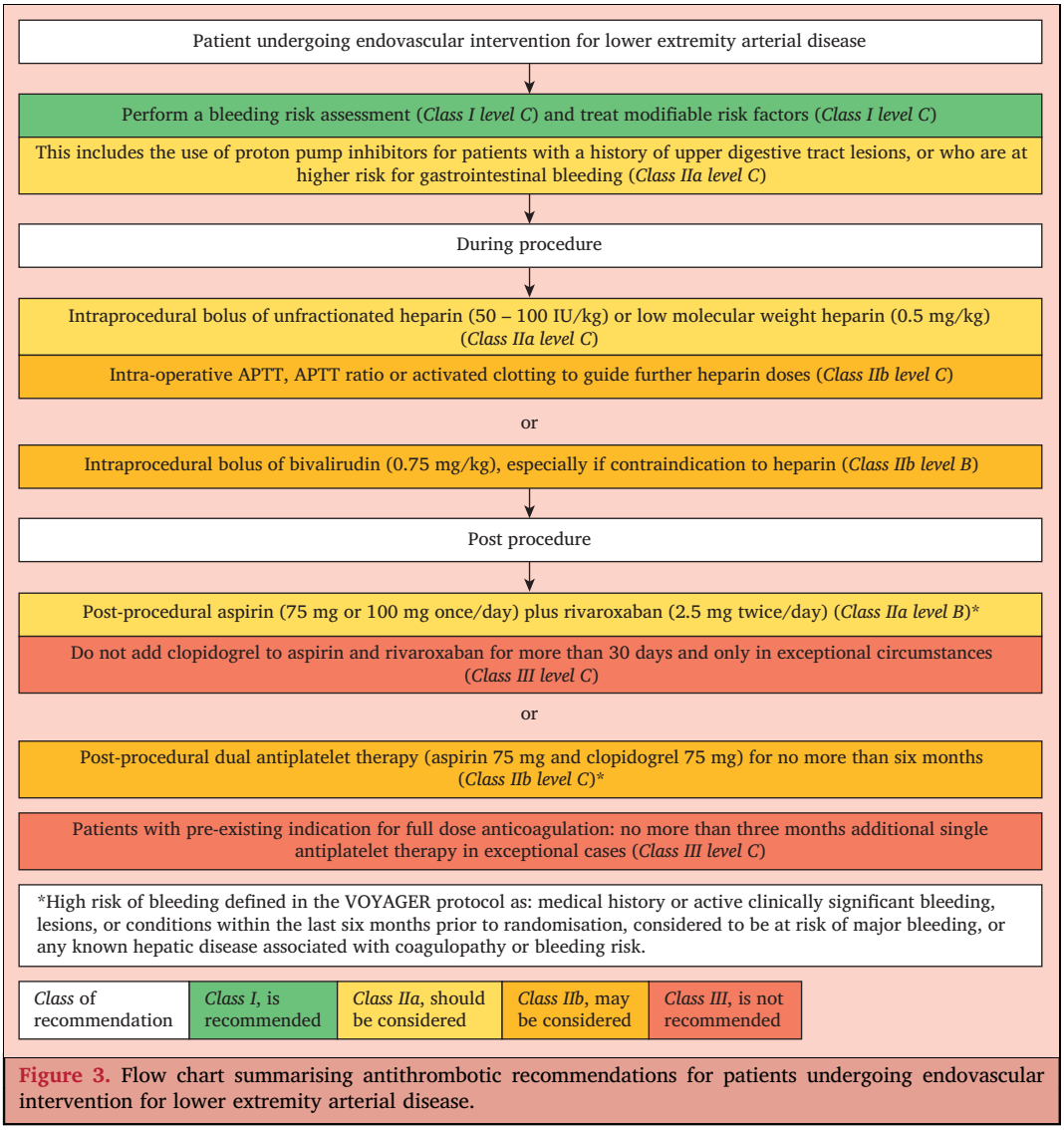

Figure 3. Flow chart summarising antithrombotic recommendations for patients undergoing endovascular intervention for lower extremity arterial disease.

1.26; 95% CI 1.03 — 1.55). The target INR for VKA therapy in the BOA trial was set high (3.0 — 4.5) and the patients receiving VKAs were within this treatment range in only about 50% of the study time. The major bleeding rate was twice as common in the VKA group as in the aspirin group (9.5% *vs.* 4.1%; HR 1.96, 1.42 — 2.71). In a further subgroup analysis of the BOA trial including 2 650 patients, major bleeding (n = 101) was independently associated with major ischaemic complications, further emphasising the relevance of this adverse event.[210] The majority of INR values outside this range were lower, from 2.0 to 2.5. Despite this, the risk of bleeding was still high. The WG felt that the INR range should not be specified as high as the Dutch BOA trial, so a pragmatic consensus recommendation has been made recommending a level of 2.0 — 3.0 with a target of 2.5.

A RCT enrolled 831 patients undergoing bypass for LEAD in a multicentre trial to compare the efficacy and safety of warfarin (INR 1.4 — 2.8) in addition to aspirin 325 mg *vs.* aspirin alone.[211] A higher overall mortality rate (32% *vs.* 23%, RR 1.41; 95% CI 1.09 — 1.84, p = .0001) and more haemorrhagic events (35 *vs.* 15, p = .020) in the warfarin group were accompanied by better patency rates (71% *vs.* 58%, p = .020) in the subgroup receiving 6 mm prosthetic conduits (not apparent in 8 mm synthetic conduits or vein bypasses). Hence, the authors concluded that long term administration of warfarin plus aspirin had only a few and highly selected indications.[211,212]

Another study enrolled 341 patients who underwent femoropopliteal bypass to compare warfarin (INR 2.0 — 2.5) plus clopidogrel 75 mg with DAPT (aspirin 100 mg plus clopidogrel 75 mg).[213] Primary study endpoints were graft patency and the absence of severe peripheral arterial ischaemia. DAPT was less effective than warfarin plus clopidogrel in increasing graft patency for patients with poor arterial runoff (OR 3.0; 95% CI 1.07 — 9.63) and for reducing severe ischaemia requiring amputation for all patients (96.7% *vs.* 92.2%; p = .040), while the incidence of minor bleeding complications was higher in the warfarin plus clopidogrel group (2.9% per patient year *vs.* 1.4% per patient year; p = .030).[213] A prospective cohort study of 300 patients undergoing bypass surgery or conservative treatment for claudication taking vitamin K antagonists (Fenprocoumon or

Marcoumar) or placebo again showed a reduction in disease progression for those taking vitamin K antagonists over 5 years (9% *vs.* 29%, $p<.001$).[214]

Most recently, VOYAGER also included patients undergoing open bypass (see previous chapters and Table 7).[29] As discussed in section 4.5.5.3 on anticoagulant and combination therapy, subgroup analysis by treatment strategy actually showed that the positive primary efficacy outcome was driven by the surgical subgroup (HR 0.79; 95% CI 0.66 — 0.95)[215] while the endovascular subgroup difference did not reach significance (HR 0.90; 95% CI 0.77 — 1.05). Moreover, the incidence of major bleeding was higher in the aspirin plus rivaroxaban group after endovascular treatment (HR 1.60; 95% CI 1.02 — 2.51) but not after surgical treatment (HR 1.02; 95% CI 0.47 — 2.19).[29] The overall bleeding rate in VOYAGER (2.7% aspirin plus rivaroxaban *vs.* 1.9% aspirin; HR 1.43, 95% CI 0.97 — 2.10) was much lower overall than in the Dutch BOA RCT (9.5% VKA *vs.* 4.1% aspirin; HR 1.96, 1.42 — 2.71) despite different bleeding definitions. This, in combination with the efficacy results has led to a higher class of recommendation for aspirin plus rivaroxaban than VKA. Results were not stratified by graft type and again, unpowered subgroup analysis of RCTs should be interpreted with caution.

In a non-powered subgroup analysis, clopidogrel did not affect the effectiveness of aspirin and rivaroxaban compared with aspirin alone for the primary composite endpoint when added to the primary treatment strategy; however, it did increase ISTH criteria major bleeding when used for more than 30 days.[206] A recent network meta-analysis comparing these trials concluded that there was insufficient evidence to provide a single best treatment recommendation.[208] Figure 4 shows a flow chart summarising antithrombotic recommendations for patients undergoing lower limb bypass for lower extremity arterial disease.

Recommendation 38

Patients undergoing infrainguinal endarterectomy or bypass using autologous vein or prosthetic conduit for lower extremity arterial disease who are not at high risk of bleeding should be considered for aspirin (75 — 100 mg once daily) in combination with rivaroxaban (2.5 mg twice daily) to reduce the risk of secondary cardiovascular and major adverse limb events.

Class	Level	References	ToE
IIa	B	Bonaca *et al.* (2020),[29] Debus *et al.* (2021)[215]	

Recommendation 39

If clopidogrel (75 mg) is added in exceptional circumstances to aspirin (75 — 100 mg once daily) in combination with rivaroxaban (2.5 mg twice daily) for patients undergoing infrainguinal bypass surgery using autologous vein or prosthetic conduit for lower extremity arterial disease who are not at high risk of bleeding, it is not recommended for longer than 30 days as the bleeding risk is likely to outweigh the benefit.

Class	Level	References	ToE
III	C	Hiatt *et al.* (2020)[206]	

Recommendation 40

Patients undergoing infrainguinal bypass with autologous vein for lower extremity arterial disease who are not at high risk of bleeding may be considered for vitamin K antagonists to improve graft patency.

Class	Level	References	ToE
IIb	A	Monaco *et al.* (2012),[213] Dutch Bypass Oral anticoagulants or Aspirin Study Group (2000),[5] van Hattum *et al.* (2009),[210] de Smit *et al.* (1992)[214]	

Recommendation 41

Patients taking a vitamin K antagonist to improve patency of an infrainguinal vein bypass graft should have an international normalised ratio of 2.0 — 3.0 with a target of 2.5.

Class	Level	References
IIa	C	Consensus

Recommendation 42

Patients undergoing infrainguinal bypass surgery with a prosthetic conduit for lower extremity arterial disease may be considered for single antiplatelet therapy to improve graft patency.

Class	Level	References	ToE
IIb	B	Bedenis *et al.* (2015)[209]	

Recommendation 43

Patients at high risk of bleeding undergoing infrainguinal bypass using an autologous vein or prosthetic conduit for lower extremity arterial disease may be considered for single antiplatelet therapy to improve graft patency.

Class	Level	References
IIb	C	Consensus

4.6. Non-atherosclerotic peripheral artery diseases

Non-atherosclerotic peripheral arterial disease is a heterogeneous group of uncommon conditions. One common observation is that decreased responsiveness to aspirin and clopidogrel may be observed in inflammatory vascular disease, due to antiplatelet resistance caused by systemic inflammation.[216]

4.6.1. Adamantiades-Behçet's disease. Adamantiades-Behçet's disease is a rare, recurrent inflammatory multisystemic disorder characterised by skin and mucosal lesions and systemic involvement including the gastrointestinal, musculoskeletal, and neurological systems, and major vessels. Up to 40% of patients have vascular manifestations.[217] The most frequent manifestations are superficial venous thrombosis and lower extremity vein thrombosis, followed by vena cava thrombosis, pulmonary artery aneurysms, thrombosis of hepatic veins (Budd-Chiari syndrome), peripheral artery

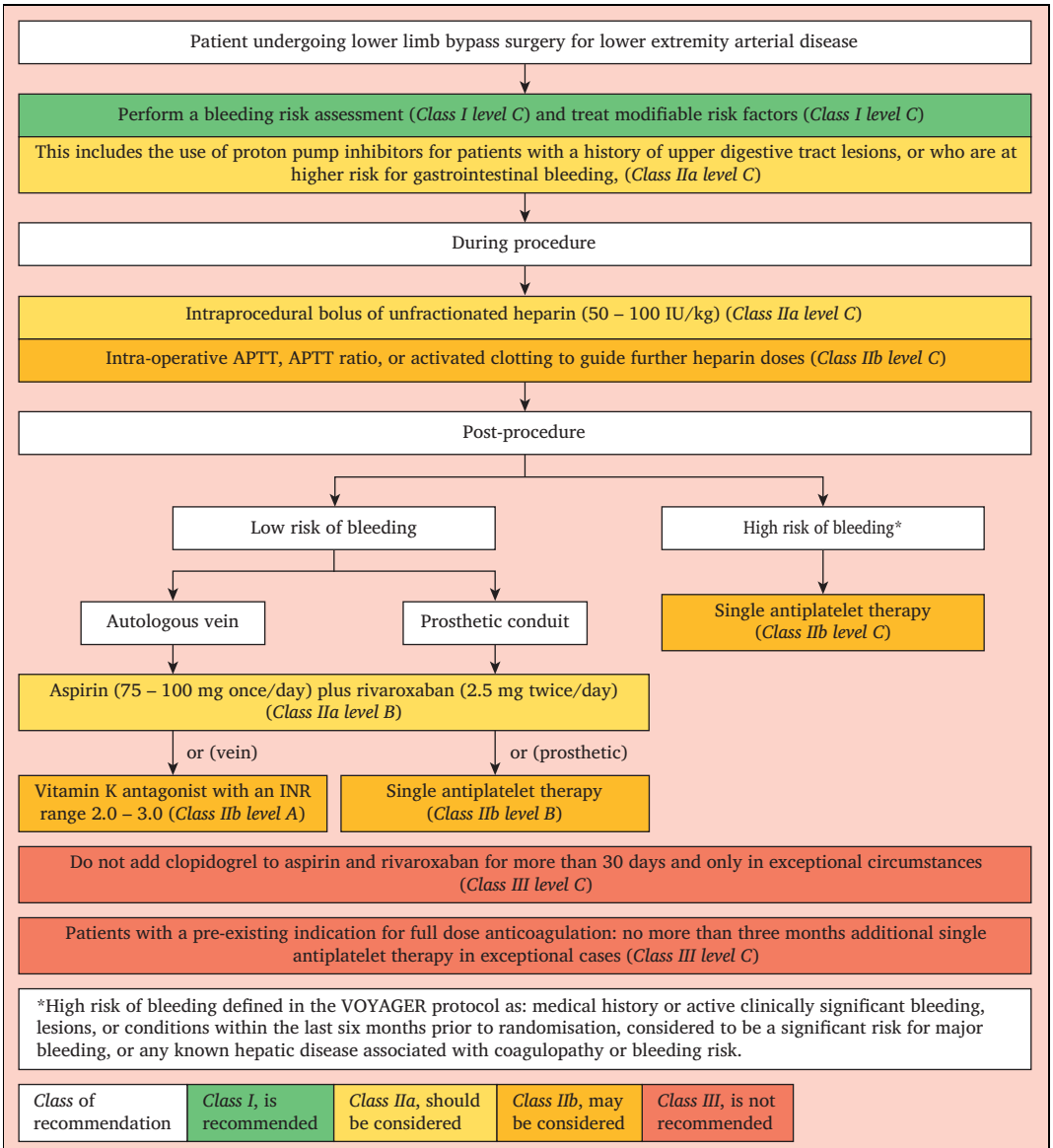

Figure 4. Flow chart summarising antithrombotic recommendations for patients undergoing lower limb bypass for lower extremity arterial disease.

aneurysms, dural sinus vein thrombosis, and abdominal aortic aneurysms. Anticoagulation has a predominant role in the management of dural sinus vein or lower limb thrombosis as per recommendations in section 5. Immunosuppressive treatment is the cornerstone for the management of peripheral vascular manifestations, while long term anticoagulant therapy has been an issue of debate as it does not appear to reduce the risk of DVT recurrence or to increase the risk of rupture of related aneurysms.[217]

4.6.2. Buerger's disease (thromboangiitis obliterans). Buerger's disease (thromboangiitis obliterans) is a non-atherosclerotic, segmental inflammatory pathology that most commonly affects small and medium sized arteries and veins in the upper and lower extremities. A recent Cochrane analysis gave moderate quality evidence that intravenous iloprost (a prostacyclin analogue with antiplatelet effect) is more effective than aspirin for treating rest pain and healing ischaemic ulcers.[218] However, iloprost comes with side effects including headache (the dose is often titrated to a tolerable headache) and a risk of MI. There is no specific evidence on antithrombotics for symptomatic Buerger's disease, so recommendations in section 4.5 are still relevant.

4.6.3. Large vessel vasculitis. Large vessel vasculitis is another inflammatory non-atherosclerotic vasculitis. Based on the 2018 update of the European League against Rheumatism consensus, antiplatelet or anticoagulant therapy should not be routinely used for treatment of large vessel vasculitis unless it is indicated for other reasons. In special situations such as vascular ischaemic complications or high risk of cardiovascular disease, these might be considered on an individual basis.[219]

4.6.4. Virus related vascular disease. Vasculitis is rare in patients with human immunodeficiency virus (HIV). The spectrum of vasculitis ranges from life threatening conditions to relatively mild skin conditions. Reliable studies on the prevalence of HIV associated vasculitis are scarce. In line with recommendations in section 4, antiplatelet or anticoagulant therapy is generally not recommended for asymptomatic disease.[220,221] Following intervention it is reasonable to follow the recommendations in section 4.5.5.

SARS-CoV-2 coronavirus (COVID-19) infection also has a related inflammatory vasculitis. This potentially affects prophylactic anticoagulation and treatment of arterial and venous thrombosis both medically and pre- and post-procedure. Multiple RCTs are running internationally to determine the optimal prophylactic anticoagulation strategy with no clear evidence in the literature currently. One RCT from Iran showed no benefit to intermediate dose prophylactic anticoagulation compared with standard dose in patients admitted to the intensive care unit with COVID-19.[222] However, other, larger trials are still to report. While heparin resistance has been observed in patients with COVID-19,[223-225] the incidence is uncertain and heparinisation should be performed as per the relevant recommendation in this guideline. Indeed, in terms of PAD and venous disease, there are no data to support changes to the recommendations in this guideline for any COVID related indication at present. The relevant recommendation from the relevant section should be followed. It should be noted that evidence is rapidly evolving as RCTs report.

4.7. Arterial embolism

Anticoagulation is an integral part of the initial management of acute embolic ischaemia and is rapidly achieved with intravenous UFH (recommendations in section 4.5.4). The purpose is to prevent further arterial thrombosis extension and to reduce the risk of recurrent events, often in a different vascular bed. Established nomograms for dose adjustment in relation to the measured APTT[90] are recommended to monitor anticoagulation and ensure therapeutic anticoagulant levels; particularly during patient transfer from an outside institution, an initial period of non-interventional treatment, or after an intervention. Alternatively, anti-Xa level monitoring, depending on local set up, may be used to monitor and adjust UFH dose. Post-intervention, LMWHs or fondaparinux are frequently used as a bridge to warfarin or DOACs, depending on the cause of embolism. A single centre case series showed long term oral anticoagulation reduced the risk of recurrent ALI and amputation.[226] A very small single centre case series showed that patients experiencing arterial embolic events needing thromboembolectomy without atrial fibrillation ($n = 32$) seemed to have fewer thromboembolic events during follow up than those with atrial fibrillation ($n = 19$).[227]

However, large RCTs examining embolic stroke of unknown aetiology have shown no benefit to long term DOAC therapy (one used dabigatran[228] and one rivaroxaban[229]) when compared with aspirin. Some subgroups (age > 75 years, renal disease, or enlarged left atrium) may benefit from DOACs, but this needs prospective confirmation. The results of two ongoing trials with apixaban, ATTICUS (Apixaban for treatment of embolic stroke of undetermined source)[230] and ARCADIA (AtRial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke, NCT03192215), are awaited. Of note, cryptogenic events other than stroke (e.g., acute limb ischaemia) have not been specifically studied in a RCT and the conclusions here are extrapolated from studies on cryptogenic stroke.

Recommendation 44

Patients experiencing arterial embolus of unknown origin who are not at high risk of bleeding may be considered for long term therapeutic anticoagulation to reduce the risk of recurrent embolic events.

Class	Level	References	ToE
IIb	C	Campbell *et al.* (2000),[226] Forbes *et al.* (2002),[227] Healey *et al.* (2019),[229] Diener *et al.* (2019)[228]	

4.8. Aneurysmal disease

4.8.1. Abdominal aortic aneurysm. Patients with small AAA are known to be at a higher risk of cardiovascular death than people without, with a recent meta-analysis estimating the incidence to be 3% per annum.[231] There are, however, no specific randomised trials examining antithrombotics for cardiovascular risk reduction for patients with AAA. The large RCTs examining antithrombotics for LEAD do not specifically include patients with AAA, unless they were detected with arterial disease in another territory, and do not report separate outcomes.

Meta-analysed data show no difference in all cause mortality when antiplatelet agents are compared with placebo or nothing for patients with small AAA, and a lack of evidence to assess cardiovascular outcomes alone.[35] The included studies are likely to be underpowered to detect differences in cardiovascular events based on earlier aggregated data so cannot be seen as definitive.[231] A large prospective cohort of 12 485 patients with AAA showed an adjusted improvement in five year survival for patients on antiplatelet agents compared with those who were not.[232] There is stronger evidence for cardiovascular risk reduction in patients taking the combination of antiplatelet, statin, and antihypertensive therapy.[43,232] For the purposes of this guideline, we have considered antiplatelet therapy in isolation.

Several non-randomised studies have examined the effect of antiplatelet agents compared with no antiplatelet agents on the growth of small AAA. Because of the large number of patients needed to detect a substantial change in growth, these studies were all relatively underpowered with mixed results. A cohort study within an RCT showed a lower sac expansion rate in AAAs 40 — 49 mm in diameter for patients taking aspirin, but could not rule out residual confounding and found no effect on AAAs of any other size.[233] One RCT has examined the effect of ticagrelor

compared with aspirin on AAA growth.[234] This study randomised 139 patients with small AAA to ticagrelor or aspirin and found no difference in sac expansion or intraluminal thrombus between the groups, although follow up was only 12 months.

A meta-analysis performed for this guideline combined the studies above with other cohort studies.[35] No effect on growth of small AAA was seen for antiplatelets in general (standardised mean difference −0.36 mm/year; 95% CI −0.75 — −0.02, $p = .060$, certainty of evidence: very low); however, low quality evidence from observational data suggest a potential association between aspirin and reduced aneurysm growth rates (standardised mean difference −0.61 mm/year; 95% CI −0.94 — −0.28, $p < .001$, certainty of evidence: low).[35] This is not strong enough to suggest an effect of aspirin on growth to form a recommendation. The effect of antiplatelet therapy on subsequent unrepaired small AAA rupture or need for repair has been evaluated in retrospective cohort studies. No clear benefit to any antiplatelet agent was confirmed by meta-analysis.[35] There is therefore enough evidence to recommend aspirin for a cardiovascular event risk reduction for patients with small AAA, but not for a reduction in growth.

Recommendation 45

Patients with a small abdominal aortic aneurysm may be considered for aspirin (75 – 100 mg) to reduce the risk of cardiovascular events.

Class	Level	References	ToE
IIb	C	Bahia *et al.* (2016),[232] Bath *et al.* (2015)[231]	

Antiplatelet agents have been shown to increase the 30 day post-operative mortality rate following AAA repair in meta-analysis (OR 2.33; 95% CI 1.52 — 3.59, $p < .001$, GRADE certainty high),[35] which included the vascular subgroup of the POISE-2 RCT[235] and large cohort study.[236] POISE-2 randomised 10 010 patients undergoing non-cardiac surgery who were either already taking aspirin or not, to receive aspirin or placebo during the peri-operative phase.[20] The vascular subgroup of 603 patients (265 undergoing AAA surgery) showed no benefit for the primary outcome of death and non-fatal MI (in keeping with the whole trial result), but there were more death and MI events in the aspirin arm for the AAA patients (HR 1.48; 95% CI 0.71 — 3.09).[235] There was no increase in major bleeding, and no difference in occlusive complications during the operations (HR 0.82; 95% CI 0.46 — 1.43). A large cohort of 2 765 patients undergoing elective open and endovascular AAA repair showed antiplatelet medication at the time of surgery to be an independent predictor of worse 30 day mortality (OR 2.39; 95% CI 1.54 — 3.73).[236] Major bleeding was not shown to be increased peri-operatively for patients taking antiplatelet agents in the same meta-analysis (OR 0.95; 95% CI 0.47 — 1.95, $p = .97$). It is impossible to attribute causation of the increased mortality rate to antiplatelet agents as the observed effect may be due to the medical condition for which the patients were taking the medication. Until the effect is clear, a recommendation for or against the use of antiplatelet therapy peri-operatively cannot be made.

Post-operatively, patients with repaired AAAs also have a high risk of cardiovascular events. This was 2.5% higher than the general population for MI and 2.9% higher for stroke in a cohort study of 11 094 Danish patients.[237] Meta-analysis of retrospective studies has shown low dose aspirin use to independently improve long term survival after AAA repair, mainly by reducing cardiovascular events.[35] Again, there is stronger evidence for cardiovascular risk reduction for patients taking the combination of antiplatelet, statin, and antihypertensive therapy.[43,232] For the purposes of this guideline, we have considered antiplatelet therapy in isolation.

There is currently no evidence to suggest superiority or inferiority of any other antithrombotic therapy following repair of an aortic aneurysm, including complex aneurysm procedures.

Recommendation 46

Patients undergoing endovascular or open abdominal aortic aneurysm repair should be considered for aspirin (75 – 100 mg) following repair to reduce the risk of secondary cardiovascular events.

Class	Level	References	ToE
IIa	B	Wong *et al.* (2022)[35]	

4.8.2. Popliteal aneurysm. Five observational studies contain results comparing antithrombotic use for patients with popliteal aneurysms.[238-242] Meta-analysis was not possible due to heterogeneous reporting.[35] Three studies included popliteal aneurysms under surveillance or being managed conservatively. One retrospective cohort study compared warfarin use with antiplatelet use in 36 patients (54 limbs).[240] This prospective cohort study found no statistically significant differences in a composite of complication rate, defined as any increase in popliteal aneurysm size and mural thrombosis formation (14.3% aspirin *vs.* 0% warfarin, $p > .050$). Another small retrospective cohort study compared anticoagulants with no anticoagulants in 65 patients (87 limbs) and found no statistically significant differences in thrombus burden between the two groups ($p = .96$).[242]

Two studies reported primary patency following popliteal aneurysm repair. One study compared clopidogrel use with no clopidogrel in 57 popliteal aneurysms undergoing endovascular repair.[239] Uni- and multivariable analysis found that clopidogrel was associated with a statistically significantly higher primary patency rate at 24 months ($p < .010$). A retrospective cohort study included 64 patients (73 limbs) with PAA undergoing open or endovascular repair.[241] Overall, there was no statistically significant difference in primary patency rates when comparing aspirin with no aspirin, and clopidogrel with no clopidogrel, across either open or endovascular repair groups.

It is logical to assume that these patients might benefit from similar cardiovascular prevention strategies as those with AAA; however, there is currently no high quality data, either epidemiological or randomised, testing this assumption. Post-procedurally, patients with popliteal aneurysm repair are not the same as those undergoing bypass grafting for LEAD as they theoretically have a lower risk of MALE with graft loss so may not benefit from the more aggressive antithrombotic regimens. As there is no literature, the WG have made a consensus recommendation to continue the single antiplatelet to reduce the risk of limb events.

Recommendation 47

Patients with popliteal aneurysms should be considered for single antiplatelet therapy to reduce the risk of major adverse limb events.

Class	Level	References
IIa	C	Consensus

Recommendation 48

Patients undergoing open popliteal aneurysm repair may be considered for single antiplatelet therapy post-operatively to reduce the risk of major adverse limb events.

Class	Level	References
IIb	C	Consensus

4.9. Arterial dissection

4.9.1. Aortic dissection. There is minimal evidence examining antithrombotic therapy for acute aortic dissection. Two retrospective case series of type A aortic dissection repair showed DAPT had no benefit on the 30 day mortality rate but increased intra-operative bleeding.[243,244] A retrospective analysis of 288 patients undergoing endovascular type B aortic dissection repair (both acute and chronic) showed that aspirin monotherapy did not increase bleeding, nor did it reduce any secondary cardiovascular endpoint.[245] No clear recommendations can be made from this literature.

4.9.2. Extracranial carotid and vertebral artery dissection. A systematic review and meta-analysis summarised the antithrombotic literature for extracranial artery dissection up to 2015.[246] Thirty eight retrospective studies were included with 1 398 patients. There was no difference between anticoagulation with heparin (usually with subsequent warfarin) and antiplatelet therapy, in terms of death, ischaemic stroke, symptomatic intracranial haemorrhage or other bleeding. No studies examined antithrombotics *vs.* no antithrombotics.

Subsequent to this meta-analysis the Cervical Artery Dissection in Stroke Study (CADISS) randomised 250 patients (118 carotid and 132 vertebral): 126 to antiplatelet treatment and 124 to anticoagulants.[8] One limitation was the heterogeneous antiplatelet therapy; aspirin, clopidogrel and DAPT with aspirin and clopidogrel were all used. Anticoagulation was consistent with UFH then warfarin. The study reported no major differences for stroke or death but was limited by a small number of events.[8] Of the 181 patients with complete imaging at baseline and three months, no differences in residual narrowing or occlusion were detected between groups. There were also no differences between groups in the proportion of bleeds, with only one major bleed in the whole study in the group that received anticoagulation. The combined endpoint of stroke, death, or major bleeding presented four events in the antiplatelet arm and three in the anticoagulation arm.[8]

TREAT CAD randomised 194 patients to aspirin or vitamin K antagonists (with or without bridging with LMWH or UFH) following cervical artery dissection. Aspirin was found to be non-inferior to vitamin K antagonists for the primary composite endpoint which was a composite of clinical outcomes (stroke, major haemorrhage, or death) and MRI outcomes (new ischaemic or haemorrhagic brain lesions).[247] The only major bleeding event happened in the VKA arm. However, anticoagulation in general is known to cause more major bleeding events than antiplatelet therapy, which limits its use for dissection where there is no clear advantage.[52]

Recommendation 49

Patients with extracranial carotid or vertebral artery dissection are recommended to have single antiplatelet therapy for at least three months to reduce the risk of subsequent ischaemic stroke.

Class	Level	References	ToE
I	B	Chowdhury *et al.* (2015),[246] Markus *et al.* (2019),[8] Engelter *et al.* (2021)[247]	

4.9.3. Other arterial dissection. A meta-analysis has examined antithrombotic therapy for isolated dissection of the superior mesenteric artery.[248] Data from 35 studies involving 725 patients showed no benefit for antithrombotic therapy over no antithrombotic therapy in terms of dissection resolution or progression. There were no adverse events reported from the antithrombotic therapy. The included studies were of low quality and the subgroup of dissection with thrombotic events could not be examined separately. No other arterial dissection has clear evidence in the literature.

Recommendation 50

Patients with isolated superior mesenteric artery dissection should be considered for single antiplatelet therapy to reduce the risk of ischaemic small bowel events.

Class	Level	References
IIa	C	Consensus

4.10. Vascular access for haemodialysis

Arteriovenous access for haemodialysis can be categorised into arteriovenous fistulas (AVF) using native vein and arteriovenous grafts (AVG) using a prosthetic conduit. Arteriovenous access research separates outcomes into AVF

maturation and patency (AVF and AVG). For antithrombotic therapy for patients with chronic kidney disease (CKD), see section 4.11.1.

The effect of intra-operative UFH on immediate fistula patency has been studied in four RCTs which have been meta-analysed.[249] Although there is an increase in initial patency for AVF (RR 0.57), there was a much larger increase in bleeding events (RR 2.41). There was no effect for AVG. Late patency was not affected. Intra-operative anticoagulation should therefore not be used during AVF or AVG formation.

Recommendation 51

Patients undergoing arteriovenous fistula or graft formation are not recommended to have systemic unfractionated heparin because of the increased risk of bleeding and lack of benefit for patency.

Class	Level	References	ToE
III	A	Smith *et al.* (2016)[249]	

Two meta-analyses examine the literature for antithrombotic therapy following AVF and AVG formation.[36,250] The RCTs in this area are all generally small and underpowered. These meta-analyses pooled data differently so have different conclusions using the same trials. For the Cochrane review,[36] 13 RCTs were included in the meta-analyses with nine different comparisons of combinations of antiplatelet agents, warfarin and placebo. The main problem with the Cochrane review was that all antiplatelet agents *vs.* placebo were not pooled leaving fewer trials and multiple small meta-analyses. The comparison clopidogrel *vs.* placebo had the most patients available, with one very large RCT[251] showing a statistically significant reduction in early thrombosis for AVF patients taking clopidogrel (RR 0.63; 95% CI 0.46 — 0.97) but no improvement in the number of fistulas available for dialysis. In meta-analysis in combination with another lower quality trial, this effect became statistically non-significant (OR 0.40; 95% CI 0.13 — 1.19).[36] However, the larger, higher quality RCT randomised 877 patients to either clopidogrel 75 mg or placebo and was at lower risk of bias so is considered the dominant evidence. This showed a benefit for clopidogrel.[251]

A more extensive meta-analysis than the Cochrane review pooled 21 antiplatelet monotherapy RCTs.[250] This showed a clear benefit in favour of antiplatelet agents reducing AVF failure (RR 0.49; 95% CI 0.30 — 0.81). The converse argument to the Cochrane review is that including all antiplatelet agents increased heterogeneity, but there were clear group effects to antiplatelet agents used for recommendations in this guideline and the WG felt that this was reasonable. The majority of the RCTs included in the more extensive meta-analysis only had up to six months follow up data. Meta-analysis for AVF maturation was impossible because of a lack of data, and the endpoint definition was heterogeneous. There was no evidence of harm with similar bleeding events between the antiplatelet monotherapy and placebo groups in meta-analysis (RR 0.93; 95% CI 0.58 — 1.49).[250]

There is therefore evidence to support the use of antiplatelet monotherapy for AVFs after formation in the short (up to six months) term.[250] Clopidogrel should be used as the first line antiplatelet agent as it has the largest, highest quality trial to support a recommendation.[251] While this trial only has outcomes up to six weeks, the more extensive meta-analysis has outcomes for antiplatelet monotherapy up to six months in favour of antiplatelet monotherapy with no increase in bleeding risk.[250]

Recommendation 52

Patients undergoing formation of an arteriovenous fistula should be considered for clopidogrel (75 mg) for up to six months as the first line antiplatelet agent to improve fistula patency.

Class	Level	References	ToE
IIa	B	Dember *et al.* (2008)[251]	

Recommendation 53

Patients undergoing formation of an arteriovenous fistula may be considered for aspirin (75 — 100 mg) for up to six months to improve fistula patency if clopidogrel is contraindicated.

Class	Level	References	ToE
IIb	A	Palmer *et al.* (2013)[250]	

Patients with an AVF will often undergo angioplasty of stenotic lesions to maintain patency for dialysis. This can be prophylactic to prevent occlusion and is also frequently used to restore a thrombosed fistula. While there is no specific evidence, a single dose of UFH is often used during these procedures, and antiplatelet therapy is maintained throughout.

There is less evidence to support the use of antiplatelet monotherapy for use for AVGs for haemodialysis access. Meta-analysis including three low quality RCTs showed no benefit in terms of early primary patency over placebo.[250] Long term outcomes have never been studied in randomised trials. However, as the most recent meta-analysis, a large national database case series has shown an early thrombosis benefit to antiplatelet monotherapy for prosthetic grafts used for dialysis.[252]

Recommendation 54

Patients undergoing formation of a non-autologous arteriovenous graft may be considered for single antiplatelet therapy for up to six months to improve graft patency.

Class	Level	References	ToE
IIb	C	Hsu *et al.* (2018),[252] Palmer *et al.* (2013)[250]	

4.11. Specific patient populations

4.11.1. Chronic kidney disease. Several high quality studies have documented that patients with CKD (eGFR < 60 mL/min/1.73m^2 for at least three months) experience a higher

prevalence of both atherosclerotic and thrombotic diseases than the general population.[253-255] Antithrombotic therapy is therefore of great importance in this population, with or without PAD. However, patients with CKD also have an increased risk of major bleeding complications, because of the potential for platelet dysfunction and abnormalities in the coagulation cascade as a result of CKD.[256-260]

Unfortunately, patients with CKD have been excluded or are under represented in cardiovascular clinical trials, rendering clear evidence based decision making impossible. Patients with end stage renal disease (eGFR $<$ 15 mL/min/1.73m^2) have historically been excluded completely. Primary cardiovascular prevention trials for aspirin monotherapy show no benefit for patients with CKD but an increased risk of bleeding.[261] Data from the Clopidogrel for Reduction of Events During Observation (CREDO) trial suggest that people with CKD may not derive the same degree of benefit from clopidogrel therapy as those with normal renal function for cardiovascular prevention.[262]

When patients with PAD have CKD there is evidence of an increased risk of ischaemic events as discussed in section 4.5.2. In the COMPASS trial, 6 276 patients had a CKD stage of 3 or 4 at baseline.[263] Both the primary outcome (cardiovascular death, MI, or stroke) and major bleeding were more frequent in those with CKD, and the frequency of these outcome events was inversely related to eGFR. These results suggest that the COMPASS rivaroxaban plus aspirin strategy may be effective at reducing major vascular and cardiac events. While COMPASS excluded patients with an eGFR $<$ 15 mL/min/1.73m^2 (CKD stage 5), it is important to stress that it is one of the few studies in this area to include patients with an eGFR between 15 and 30 mL/min/1.73m^2.[263] The choice of antithrombotic therapy for patients with CKD and both stable and intervened PAD therefore still follows recommendations in section 4, bearing in mind that the presence of CKD puts these patients at higher risk of ischaemic events as outlined in Table 9.

For anticoagulation for patients with AF, a systematic review found that there was no difference in stroke outcomes between dabigatran or edoxaban *vs.* warfarin for patients with moderate CKD (stages 1 — 3).[264] Dabigatran (150 mg twice daily) and apixaban both reduced the risk of stroke and systemic embolism compared with warfarin.[264] Both edoxaban and apixaban were associated with reduced major bleeding events compared with warfarin. Rivaroxaban and dabigatran 110 mg and 150 mg showed no substantial difference in major bleeding *vs.* warfarin. In patients with severe CKD on haemodialysis, there was no difference in stroke outcomes between apixaban, dabigatran, or rivaroxaban *vs.* warfarin. In these patients, rivaroxaban and dabigatran were associated with an increased major bleeding risk, whereas there was no major bleeding difference with apixaban compared with warfarin.[264] Several oral antithrombotic agents require dosage adjustments in patients with CKD, including tirofiban, bivalirudin, enoxaparin, and fondaparinux. Long term oral anticoagulation with warfarin also requires careful dosing and more frequent monitoring.

Recommendation 55

Patients with chronic kidney disease (estimated glomerular filtration rates ≥ 30 mL/min/1.73m^2) requiring anticoagulation for a peripheral arterial disease indication may be considered for direct oral anticoagulants, and patients with a glomerular filtration rate < 30 mL/min/1.73m^2, may be considered for vitamin K antagonists; however, the risk balance is complex and must be strictly individualised.

Class	Level	References	ToE
IIb	C	Feldberg *et al.* (2019)[264]	

With regards to anticoagulation for the prevention of recurrent VTE for patients with CKD, a meta-analysis of ten phase 3 RCTs with 10 840 patients was published in 2021.[265] Patients were stratified into four categories based on severity of renal impairment using serum creatinine clearance (SCr) as the marker, for example, mild ($>$ 50 — $<$ 80 mL/min), moderate ($>$ 30 — $\leq$ 50 mL/min), severe ($<$ 30 mL/min), and any level (from $<$ 30 — $<$ 80 mL/min). There was no difference between DOACs and VKAs in decreasing the risk of recurrent VTE among patients with any level of renal impairment. There was also no difference in efficacy between LMWH and VKAs among patients with moderate and any level of renal impairment. DOACs compared with VKAs had a lower risk of combined major and non-major bleeding (RR 0.74; 95% CI 0.65 — 0.84), major bleeding (RR 0.51; 95% CI 0.38 — 0.69), and non-major clinically relevant bleeding (RR 0.73; 95% CI 0.57 — 0.94), respectively. The risk of intracranial bleeding was comparable (RR 0.68; 95% CI 0.19 — 2.44). There was no difference in the risk of major bleeding between LMWH and any oral anticoagulant (RR 0.83; 95% CI 0.46 — 1.51).[265]

Recommendation 56

Patients with chronic kidney disease (estimated glomerular filtration rates ≥ 30 mL/min/1.73m^2) requiring anticoagulation for the prevention of recurrent venous thromboembolism should be considered for direct oral anticoagulants.

Class	Level	References	ToE
IIa	B	Alhousani *et al.* (2021)[265]	

Finally, when heparin is used for patients with CKD, dose adjustment must be performed as per local protocol as there is no randomised evidence for dose adjustment. UFH in the acute setting is preferred because it has a short half life, even in patients with CKD at high bleeding risk. In addition to this, protamine can be used to rapidly reverse its effects. Therefore, expert opinion practice recommends decreasing the initial standard dose by 33%, and subsequent dose adjustment should be based on APTT levels.[266]

Low molecular weight heparins may be used for patients with CKD.[266] Dosing indications are the result of either small

scale open label studies, or analysis of CKD subgroups in trials. There are two meta-analyses pooling these studies. The first, in 2006, meta-analysed outcomes for patients with severe CKD (eGFR $<$ 30 mL/min/1.73m^2).[267] They found an increased risk of bleeding for LMWH for patients with severe CKD over mild or moderate CKD (OR 2.25; 95% CI 1.19 — 4.27). The most used LMWH was enoxaparin, which showed increased major bleeding in patients with severe CKD when a standard therapeutic dose was used (OR 3.88; 95% CI 1.78 — 8.45) but fewer major bleeding events when an adjusted dose was used (OR 0.58; 95% CI 0.09 — 3.78). The second meta-analysis from 2011 missed some studies included in the earlier analysis. It found that there was more major bleeding for enoxaparin using an eGFR cutoff of 60 mL/min/1.73m^2 (RR 1.67; 95% CI 1.12 — 2.50), but did not stratify by dose.[268] Special attention should be given when prescribing LMWH to patients with CKD, due to a potential cumulative effect resulting from reduced clearance of the LMWH.

Recommendation 57

Patients with chronic kidney disease stage 3 or 4 (estimated glomerular filtration rates from 15 to 59 mL/min/1.73m^2) requiring anticoagulation with low molecular weight heparin should be considered for regular monitoring of renal function and dose adjustment to reduce the risk of bleeding.

Class	Level	References	ToE
IIa	C	Lim *et al.* (2006),[267] Hoffman and Keller (2012)[268]	

4.11.2. Cancer associated arterial thromboembolic events. The risk of arterial thromboembolic events in patients with cancer is highest from five months before diagnosis and peaks 30 days before, with a cumulative incidence of 0.62% compared with 0.11% in controls (OR 5.63; $p < .001$).[269] The risk of cancer associated arterial thromboembolic events is associated with the type and stage of the cancer, with lung (29%), colorectal (24%), prostate (11%), and breast (10%) being the most common.[270] The risk of MI and ischaemic stroke is more than two times higher in patients with cancer (within six months of diagnosis) compared with patients without (4.7% *vs.* 2.2%; HR 2.2, 95% CI 2.1 — 2.3).[269] Prognosis is poor, with a threefold increase in mortality from the cancer once a thromboembolic event has occurred.

There is paucity of randomised controlled data for cancer associated arterial thromboembolic events. The optimal antithrombotic strategy is uncertain, and anticoagulation practice is often extrapolated from trials of cancer associated VTE (section 5.4). No specific recommendations can be made in this guideline.

4.11.3. Patients with pre-existing indications for antithrombotics. Some patients have potential indications for both anticoagulation and antiplatelet therapy. This is common in cardiology where patients with pre-existing indications for anticoagulation such as AF may undergo percutaneous coronary intervention for MI. It may also happen for vascular patients, for example when a patient anticoagulated for AF undergoes peripheral angioplasty.

The international REduction of Atherothrombosis for Continued Health Registry (REACH) registry of 67 888 outpatients with atherosclerosis showed that patients with PAD were at higher risk of subsequent cardiovascular events than patients with CAD.[271] Patients with a pre-existing indication for anticoagulation were at particularly high risk.[272] A major RCT subgroup analysis showed patients with arterial disease in more than one territory to be at the highest risk of subsequent cardiovascular events.[53] Patients undergoing percutaneous coronary intervention for acute coronary syndromes would theoretically be at a higher risk of subsequent events than patients with PAD, although there are no good comparisons between higher risk CAD and higher risk PAD populations from major registries or trials, and there is significant overlap between the groups.[53,273]

There are no RCTs examining anticoagulation alone with anticoagulation plus antiplatelet agent(s) for patients with a pre-existing indication for anticoagulation and PAD. There are also no comparative cohort series as anticoagulation has historically been used so rarely as a primary indication for PAD.

There have been RCTs comparing aspirin plus warfarin with aspirin alone in patients with PAD but no indication for anticoagulation. The major trial was WAVE, which randomised patients with PAD to single antiplatelet therapy plus warfarin or single antiplatelet alone.[30] It is important to stress that WAVE excluded patients with a pre-existing indication for anticoagulation so results are not directly applicable to this population. There were no notable differences between the treatment arms for the primary outcomes; however, major bleeding was increased in the aspirin and warfarin group.[30]

Before WAVE there were two smaller RCTs evaluating oral anticoagulation plus single antiplatelet therapy *vs.* single antiplatelet therapy for patients undergoing bypass for LEAD.[211,274] These were underpowered with conflicting results but included patients with LEAD undergoing intervention and therefore at higher risk of subsequent cardiovascular events. When combined in meta-analysis these two trials showed a statistically significant increase in all cause mortality ($p = .004$) and major bleeding ($p = .004$) in the aspirin plus warfarin group, but no difference in graft occlusion rates ($p = .20$).[275]

The ePAD trial compared aspirin plus edoxaban against DAPT (aspirin plus clopidogrel) after peripheral endovascular therapy.[207] Two hundred and three patients were randomised, with no statistically significant reduction in re-stenosis or major bleeding between the groups. The authors acknowledged the trial was underpowered.

To summarise, patients with PAD and a pre-existing indication for anticoagulation are at a higher risk of subsequent cardiovascular events than those without, but

current evidence does not allow this to be easily considered in forming recommendations. There is only evidence of harm for aspirin plus warfarin over aspirin for patients with PAD and no pre-existing indication for anticoagulation. Therefore, antiplatelet therapy should not routinely be added to full dose anticoagulation for patients with a PAD indication for antiplatelet therapy and a pre-existing indication for anticoagulation. Anticoagulation alone should be used preferentially. Stopping antiplatelet therapy prescribed for any other reason should be performed in liaison with the relevant specialty. This is especially true in cardiology where there are much clearer evidence based algorithms.

It is common practice in cardiology to use a short course of antiplatelet therapy with full dose anticoagulation supported by RCT evidence.[276] This is not supported by any evidence for use in routine practice for any indication for patients with PAD. Pragmatically, where this is felt to be useful post-intervention for PAD in selected cases, acknowledging there is no specific evidence to support the practice but evidence showing an increased bleeding risk during shared decision making, the course of single antiplatelet therapy should be kept as short as possible. Recommendations here do not apply to the aspirin plus low dose rivaroxaban combination from COMPASS and VOYAGER.

Recommendation 58

Patients with chronic peripheral artery disease and a cardiac or vascular indication for full dose anticoagulation are not recommended to have antiplatelet therapy routinely added to anticoagulation.

Class	Level	References	ToE
III	B	WAVE investigators (2007)[30] WAVE investigators (2006)[275]	

Recommendation 59

Patients taking antiplatelet therapy for any peripheral arterial disease indication should have the antiplatelet therapy stopped if full dose anticoagulation becomes indicated for another reason.

Class	Level	References	ToE
III	B	WAVE investigators (2007)[30] WAVE investigators (2006)[275]	

Recommendation 60

Patients with a pre-existing indication for full dose anticoagulation undergoing endovascular intervention may be exceptionally considered for the addition of single antiplatelet therapy for a maximum of three months to reduce the risk of subsequent ischaemic events.

Class	Level	References
IIb	C	Consensus

Patients taking anticoagulants who are subsequently diagnosed with TIA or stroke and who will require carotid surgery should follow the recommendations in section 4.1.

4.11.4. Thrombophilia. The term thrombophilia encompasses a range of conditions both inherited and acquired. As a result, they affect a range of people of different ages and can present with emboli in different arterial territories. Some thrombophilias are associated with both arterial and venous events, and some with venous events only. They are a rare cause of arterial thromboembolic events overall (Table 10). While the acquired thrombophilia antiphospholipid syndrome has a documented increased risk of arterial thromboembolism, other thrombophilia types are not as well associated (Table 10).[277] As a result, evidence or consensus for treatment of thrombophilias presenting with arterial events is lacking. Decisions for both investigating potential thrombophilia, and subsequent antithrombotic therapy, should therefore only be made with a specialist haematologist.

The initial treatment for any embolus with acute ischaemia will be anticoagulation with UFH as per recommendations in section 4.7. If there is no clear precipitating event for an embolus, consideration for thrombophilia testing should only be performed after three months of anticoagulation, if at all.[289] Thrombophilia investigation consensus documents have conflicting recommendations, suggesting not to test for thrombophilia[289] or to test after three months of anticoagulation.[290] There is clear consensus that testing should be highly selective to avoid misdiagnosis and potential overtreatment, so should only be performed by a specialist in this area.

Once thrombophilia is diagnosed, the choice of long term antithrombotic therapy is again controversial because of a lack of data on risk and benefit for individual conditions. The best understood is the antiphospholipid syndrome even though there is a paucity of data specifically for arterial thromboembolic events. A Cochrane review included eight studies comprising 811 patients and compared different anticoagulant and antiplatelet strategies to prevent stroke and thromboembolic events in patients with antiphospholipid syndrome.[291] The whole group results were predominantly based on venous events. This showed DOACs may increase the risk of stroke over VKAs with no improvement in thromboembolic events. There are not enough data for a recommendation on whether to use antithrombotic therapy for any other thrombophilia.[277]

Recommendation 61

Patients with antiphospholipid syndrome presenting with an arterial embolic event are recommended to have anticoagulation with vitamin K antagonists with a target INR of 2 − 3 to reduce the risk of future thromboembolic events.

Class	Level	References	ToE
I	C	Bala *et al.* (2020)[291]	

5. ANTITHROMBOTICS FOR PATIENTS WITH VENOUS DISEASE

5.1. Prophylaxis for venous thromboembolism

Surgical intervention is a well known risk factor for venous VTE due to the inflammatory response to surgical injury and

Table 10. Seminal publications of the association between commonly tested thrombophilias and arterial thrombotic events

Disorder	Reference	Outcome	Age or other characteristic	Genotype or diagnostic category	Result (95% CI)
Factor V Leiden	Kim *et al.*[278]	MI, stroke, PAD	All ages	Heterozygous*	OR 1.21 (0.99–1.49)
			<55y		OR 1.37 (0.96–1.97)
	Ye *et al.*[279]	MI, CAD	NS		Per-allele RR 1.17 (1.08–1.28)
	Mannucci *et al.*[280]	MI	<45y		OR 1.66 (1.15–2.38)
	Chiasakul *et al.*[281]	Stroke	All ages		OR 1.23 (1.05–1.45)
				Homozygous	OR 2.24 (1.26–4.71)
Prothrombin 20210A	Kim *et al.*[278]	MI, stroke	All ages	Heterozygous*	OR 1.32 (1.03–1.69)
			<55 y		OR 1.66 (1.13–2.46)
	Ye *et al.*[279]	MI, CAD	NS		Per-allele RR 1.31 (1.12–1.52)
	Mannucci *et al.*[280]	MI	<45 y		OR 1.28 (0.91–1.79)
	Vazquez *et al.*[282]	PVD	NS		OR 1.68 (0.8–3.2)
		CLI			OR 3.2 (1.6–6.1)
	Chiasakul *et al.*[281]	Stroke	All ages		OR 1.41 (1.13–1.76)
				Homozygous	OR 7.19 (2.47–20.94)
Protein C deficiency	Mahmoodi *et al.*[283]	MI, stroke, TIA, PVD	>15 y	NS	OR 6.9 (2.1–22.2)
	Chiasakul *et al.*[281]	Stroke	All ages		OR 2.13 (1.16–3.90)
Protein S deficiency	Mahmoodi *et al.*[283]	MI, stroke, TIA, PVD	>15 y	NS	OR 4.6 (1.1–18.3)
	Chiasakul *et al.*[281]	Stroke	All ages		OR 2.26 (1.34–3.80)
Antithrombin deficiency	Mahmoodi *et al.*[283]	MI, stroke, TIA, PVD	>15 y	NS	OR 1.1 (0.1–10.9)
	Chiasakul *et al.*[281]	Stroke	All ages		OR 1.25 (0.58–2.67)
Antiphospholipid syndrome	Neville *et al.*[284]	MI, angina, stroke, TIA, other	>18 y	Number ab present (per 1-ab difference)	OR 1.46 (0.93–2.27)
				Anti-cardiolipin antibody; + Lupus anticoagulant + anti-beta2-glycoprotein-I antibody	OR 3.20 (0.60–17.18)
Factor VIII elevation	Zakai *et al.*[285]	Stroke	≥45 y	Per SD increase	HR 1.26 (1.08–1.46)
		CAD		Per SD increase	HR 1.52 (1.29–1.79)
	Folsom *et al.*[286]	CAD	45–84 y	Highest quartile elevation	HR 1.13 (0.80–1.75)
Homocystinuria	Homocysteine Studies Collaboration[287]	CAD	NS	Highest quintile elevation	OR 1.16 (1.02–1.32)
Methylenetetrahydrofolate reductase polymorphism	Kim *et al.*[278]	MI, stroke	All ages	Homozygous C677T	OR 1.20 (1.02–1.41)
			<55 y		OR 1.41 (1.13–1.76)
	Klerk *et al.*[288]	CAD	European	Homozygous C677T	OR 1.14 (1.01–1.28)
			North American		OR 0.87 (0.73–1.05)

Ab = antibody; CAD = coronary artery disease; CI = confidence interval; CLI = critical limb ischaemia; HR = hazard ratio; MI = myocardial infarction; OR = odds ratio; PAD = peripheral arterial disease; PVD = peripheral vascular disease; NS = not stated; RR = risk ratio; SD = standard deviation; TIA = transient ischaemic attack. Studies devoted to paediatric populations (<18 y) not included. Adapted with author and publisher permission from May JE, Moll S. How I treat unexplained arterial thrombosis. *Blood* 2020;**136**:1487–98.[277]

* Most cases are heterozygous but presumably there are a few homozygous included, with exact numbers not reported.

post-operative immobilisation. Patient demographics and the diagnosis requiring surgery (especially malignancy) also play a large role in the risk of post-operative VTE. In venous and arterial vascular intervention, there are a wide variety of interventions and a large proportion of minimally invasive techniques of variable VTE risk.

A meta-analysis has examined prophylaxis to prevent VTE in patients undergoing vascular surgery procedures, including 20 753 patients from 42 publications.[292] The authors also performed subgroup analysis by procedures: all vascular surgery procedures, open aortic surgery, EVAR, open aortic surgery and EVAR, abdominal and peripheral vascular interventions, peripheral bypass grafting, amputations, surgery for venous trauma, and surgical treatment of superficial venous disease. The study included 12 retrospective cohort studies, 17 prospective studies and 13 RCTs, although only five studies had sufficient data to be meta-analysed. In total, 197 of the 13 241 patients receiving prophylaxis developed VTE (1.5%). On the other hand, 72 of 7 512 not receiving prophylaxis developed VTE (0.96%; RR

0.70, 95% CI 0.26 — 1.87). There was also no difference in VTE risk by type of procedure.[292]

There is no validated risk score for VTE risk assessment for vascular surgery procedures. However, another study identified high risk patients, including factors such as age, sex, type of surgery, or malignancy into low, moderate, and high risk patients:[293]

- Low risk patients: patients without risk factors undergoing minor surgery.
- Moderate risk patients: patients over the age of 40 years undergoing major surgery for benign disease in the absence of additional risk factors.
- High risk patients: patients over the age of 60 years undergoing major surgery for benign disease or any patient with additional risk factors.

Most individual institutions have VTE risk assessments which are completed for all patients based on the type of surgery. These will be based on national or institutional guidelines and are equally as valid for vascular patients. If a vascular patient is on a more aggressive antithrombotic regimen such as aspirin and rivaroxaban or DAPT, there is reduced need for prophylactic LMWH and this should be reflected in the individual risk assessment. Likewise, patients who are at very high risk of VTE not on aggressive regimens should be considered for longer courses (up to six weeks post-operatively) of prophylactic LMWH.

Recommendation 62

Patients undergoing any vascular procedure are recommended to have an individually personalised venous thromboembolism risk assessment.

Class	Level	References	ToE
I	C	Toth *et al.* (2020)[292]	

5.2. Deep vein thrombosis

5.2.1. Anticoagulation for the principal treatment phase of deep vein thrombosis. Treatment of DVT can be divided into three phases: acute (up to 10 days after diagnosis), principal (first three months), and extended phase (more than three months). The exact definition of the extended phase varies between RCTs from more than three months to six or even 12 months. For the purposes of this guideline three to six months is used, that is, a further three months after the principal treatment phase. The term proximal is used to describe any DVT proximal (cephalad) to the calf veins.

Intravenous UFH or subcutaneous LMWH have traditionally been used for the initial acute phase, followed by a VKA (acenocoumarol, phenprocoumon or warfarin). On the other hand, the role of LMWH in the principal phase of provoked DVT not related to cancer has not been well defined. One recent Cochrane Review concluded that there were no differences between LMWH and VKA in terms of efficacy and safety.[294]

DOACs have a similar efficacy to VKAs in the treatment of acute symptomatic VTE with a better safety profile (Table 11).[104] One meta-analysis reported an equivalent effect for DOACs in preventing recurrent symptomatic VTE compared with VKAs (RR 0.89; 95% CI 0.75 — 1.05), with a reduction in major bleeding (RR 0.63; 95% CI 0.51 — 0.77). The net clinical benefit favoured DOACs with a RR of 0.79 (95% CI 0.70 — 0.90).[104]

Due to an absence of RCTs that directly compare different DOACs, one meta-analysis compared indirectly their efficacy and safety for treatment to three to six months.[298] All DOACs presented similar efficacy, but different risk profiles were detected. Apixaban presented a lower risk of bleeding compared with the other DOACs and dabigatran was also safer than rivaroxaban and edoxaban (Table 11). The limitations of the study were the methodology and the length of the principal phase of treatment considered, which was up to 12 months in some studies. Therefore, one DOAC cannot be recommended over another. Because there are no studies focused only on provoked or unprovoked DVT, recommendations apply to both.

Finally, patients with deep vein thrombosis and antiphospholipid syndrome who are triple positive or have a history of arterial or small vessel thrombosis, are not recommended to be treated with direct oral anticoagulants; a VKA should be used instead. DOACs and particularly apixaban or dabigatran may be an appropriate option for low risk APS patients (single or double antibody positive),[299,300] pending further evidence.

Recommendation 63

Patients with proximal deep vein thrombosis are recommended to have a three month course of a full dose direct oral anticoagulant rather than a vitamin K antagonist to reduce the risk of recurrent thromboembolic events.

Class	Level	References	ToE
I	A	Kakkos *et al.* (2014)[104]	

5.2.2. Extended phase anticoagulation after deep vein thrombosis. After the principal treatment phase, extended anticoagulation can be beneficial for patients with a high risk of recurrence associated with a tolerable risk of bleeding.

A meta-analysis of 6 778 patients examined extended treatment with aspirin, VKAs, DOACs, and placebo between six and 37 months after VTE.[301] Recurrent VTE events were observed in 9.7% of the placebo group compared with 2.8% of the treatment group (OR 0.21; 95% CI 0.11 — 0.42). VKAs and DOACs presented the best efficacy compared with placebo (OR 0.09; 95% CI 0.03 — 0.25 and OR 0.16; 95% CI 0.11 — 0.24, respectively) and, with the smallest effect, aspirin (OR 0.62; 95% CI 0.44 — 0.87).[301] Another meta-analysis on the use of DOACs for extended anticoagulation additionally reported a reduction of all cause mortality with DOACs compared with placebo.[104]

Table 11. Relative recurrence rates and bleeding events of direct oral anticoagulants compared with vitamin K antagonists used for venous thromboembolic treatment in pivotal trials

Drug	Trial	Number of patients included	Treatment group	Control group	Efficacy	Safety
Apixaban	AMPLIFY[4]	$n = 5\ 395$	Recurrence: 59/2 609 (2.3) Bleeding: 115/2 676 (4.3)	Recurrence: 71/2 635 (2.7) Bleeding: 261/2 689 (9.7)	RR 0.84; 95 CI 0.60–1.18 DR -0.4; 95 CI -1.3–0.4*	RR 0.44; 95 CI 0.36–0.55†
Rivaroxaban	EINSTEIN[295]	$n = 3\ 449$	Recurrence: 36/1 731 (2.1) Bleeding: 139/1 718 (8.1)	Recurrence: 51/1 718 (3.0) Bleeding: 138/1 711 (8.1)	HR 0.68; 95 CI 0.44–1.04‡	HR 0.97; 95 CI 0.76–1.22†
Edoxaban	HOKUSAI[296]	$n = 8\ 240$	Recurrence: 130/4 118 (3.2) Bleeding: 34/4 189 (8.5)	Recurrence: 146/4 122 (3.5) Bleeding: 423/4 122 (10.3)	HR 0.89; 95 CI 0.70–1.13§	HR 0.81; 95 CI 0.71–0.94†
Dabigatran	RE-COVER and RE-COVER II[297]	$n = 5\ 107$	Recurrence: 60/2 553 (2.4) Bleeding: 136/2 553 (5.3)	Recurrence: 55/2 554 (2.1) Bleeding: 217/2 554 (8.5)	HR 1.09 95 CI 0.76–1.57‖	HR 0.62 95 CI 0.50–0.76†

Data are presented as *n* (%) unless stated otherwise. CI = confidence interval; RR = relative risk; DR = difference in risk population; HR = hazard ratio.
* In percentage points. Apixaban was non-inferior to conventional therapy ($p < .001$).
† Safety defined as major bleeding and clinically relevant non-major bleeding.
‡ Rivaroxaban was non-inferior to conventional therapy ($p < .001$).
§ Edoxaban was non-inferior to conventional therapy ($p < .001$).
‖ Dabigatran was non-inferior to conventional therapy ($p < .001$) in both trials.

Recommendation 64

Patients with a proximal deep vein thrombosis requiring extended anticoagulation following the principal three month treatment phase should be considered for full dose direct oral anticoagulants rather than vitamin K antagonists to reduce the risk of further thromboembolic events.

Class	Level	References	ToE
IIa	B	Kakkos *et al.* (2014)[104]	

Recommendation 65

Patients with unprovoked deep vein thrombosis who are eligible for anticoagulants are not recommended to have aspirin for extended antithrombotic therapy to reduce the risk of thromboembolic events.

Class	Level	References	ToE
III	A	Vasanthamohan *et al.* (2018),[302] Marik *et al.* (2015)[301]	

5.2.3. Reduced dose direct oral anticoagulants for extended anticoagulation. Reduced dose DOACs for extended anticoagulation have been tested in a meta-analysis, which found that reduced dose apixaban or rivaroxaban were as effective as full dose in preventing recurrent VTE at one year (RR 1.12; 95% CI 0.67 — 1.87), and more effective than aspirin or than placebo (RR 0.26; 95% CI 0.14 — 0.46).[302] This study was based on more than 5 000 patients and rates of major or clinically relevant non-major bleeding events were similar between DOACs, aspirin, and placebo (RR 1.19; 95% CI 0.81 — 1.77).

There was a non-significant trend towards fewer bleeding episodes when reduced dose and full dose DOACs were compared (RR 0.74; 95% CI 0.52 — 1.05). It is important to highlight that most of patients included in these studies did not have a high risk of recurrence or bleeding. Therefore, reduced dose of DOACs should only be offered to those patients who are not at high risk of recurrence.

Recommendation 66

Patients with a first episode of unprovoked proximal deep vein thrombosis not deemed to be at high risk of recurrence should be considered for reduced dose apixaban (2.5 mg twice daily) or rivaroxaban (10 mg once daily) after the principal three month treatment phase to reduce the risk of further thromboembolic events.

Class	Level	References	ToE
IIa	B	Vasanthamohan *et al.* (2018)[302]	

5.3. Superficial vein thrombosis

Superficial vein thrombosis usually occurs in patients with varicose veins, although cancer, thrombophilia, and Buerger's disease may cause SVT in normal veins. Frequently misdiagnosed as an infection because of localised pain, tenderness, and redness, SVT has a relatively high risk of short and long term thromboembolic complications. In a large prospective observational study, thromboembolic complications including DVT, PE, progression of DVT, or recurrent SVT occurred in 10.2% of patients with SVT during the first three months of follow up.[7] The risk of thromboembolic events

Table 12. Randomised controlled trials examining superficial venous thrombosis treatment published during the last two decades

Study	Design	Patients – *n*	Treatment regimens	Main results
Marchiori, 2002,[310]	Open label	60	Intermediate *vs.* prophylactic SC doses of UFH for four weeks	Intermediate doses more effective in preventing VTE during a six month follow up.
Lozano, 2003,[306]	Open label	80	Saphenofemoral disconnection *vs.* outpatient LMWH SC enoxaparin (full dose for one week and intermediate dose for another three weeks)	LMWH treatment was less expensive, avoiding hospitalisation
STENOX, 2003,[25]	Double blind	427	LMWH enoxaparin in prophylactic or full SC doses, oral tenoxicam or placebo, for 8–12 days	The incidence of VTE and SVT recurrence combined by day 12 was significantly reduced from 30.6% in the placebo group to 8.3%, 6.9%, and 14.9% in the prophylactic dose, full dose, and tenoxicam groups, respectively
Vesalio, 2005,[311]	Double blind	164	LMWH nadroparin in prophylactic or body weight adjusted full SC doses for one month	SVT progression or VTE complications combined during the three month follow up period in the prophylactic and full dose groups occurred in 8.6% and 7.2%, respectively ($p = .74$)
CALISTO, 2010,[7]	Double blind	3 002	Fondaparinux in prophylactic doses or placebo, SC for 45 days	The primary efficacy outcome (composite of death from any cause or symptomatic pulmonary embolism, symptomatic deep vein thrombosis, or symptomatic extension to the saphenofemoral junction or symptomatic recurrence of superficial vein thrombosis) at day 47 was 0.9% in the fondaparinux group and 5.9% in the placebo group (relative risk reduction with fondaparinux, 85%). Except for the outcome of death, each component of the primary efficacy outcome was significantly reduced in the fondaparinux group
STEFLUX, 2012,[313].	Double blind	664	LMWH parnaparin either intermediate dose for 10 days followed by placebo for 20 days or intermediate dose for 30 days or prophylactic dose for 30 days	The composite of symptomatic and asymptomatic DVT, recurrence and or symptomatic or asymptomatic local extension of SVT and symptomatic PE at 33 days and 93 days was significantly reduced with intermediate dose for 30 days
SURPRISE, 2017,[26]	Open label	472	Oral rivaroxaban or SC fondaparinux in prophylactic doses for 45 days	Composite of symptomatic DVT or PE, progression or recurrence of SVT, and all cause mortality at 45 days occurred equally frequently in the two groups

SC = subcutaneous; UFH = unfractionated heparin; LMWH = low molecular weight heparin; VTE = venous thromboembolism; SVT = superficial vein thrombosis; DVT = deep vein thrombosis; PE = pulmonary embolism.

persists for three months after SVT is diagnosed.[24] This risk may be higher during the first month or in subgroups such as those with cancer or extensive thrombosis.[24,303-305]

RCTs comparing anticoagulation with placebo have proved the effectiveness of anticoagulation in reducing thromboembolic events for SVT.[7] Anticoagulation has largely replaced open ligation because of a reduction in hospital stay and complications from surgery.[306] RCTs are shown in Table 12. These have mostly included patients with SVT exceeding 4 – 5 cm in length, ≥ 3 cm away from the junction with the deep veins. It is evident that there is heterogeneity in treatment type, intensity, and duration of anticoagulation, which precludes a formal meta-analysis.[307] Most studies were underpowered for the relatively rare outcomes of DVT and PE. Nevertheless, a shorter duration of anticoagulation was associated with a higher risk of recurrent events,[24] while intermediate LMWH doses (between full anticoagulation and prophylactic, e.g., two thirds of the therapeutic dose) were better than prophylactic LMWH doses in preventing recurrent event. A more recent systematic review demonstrated that fondaparinux achieved the lowest rate of recurrent VTE at 1.4 events per 100 patient years of follow up.[308] The CALISTO randomised trial showed that the rate of DVT or PE was 85% lower in patients treated with fondaparinux 2.5 mg once daily than in patients receiving placebo (0.2% *vs.* 1.3%; $p < .001$).[7] The superiority of fondaparinux over LMWHs was recently shown in the INSIGHTS-SVT observational study where the composite primary outcome of symptomatic DVT, PE, and extension or recurrence of SVT at three months, adjusted by propensity score and for treatment duration was lower with fondaparinux compared with LMWH (4.4% *vs.* 9.6%; HR 0.51, 95% CI 0.3 – 0.9, $p = .017$).[309]

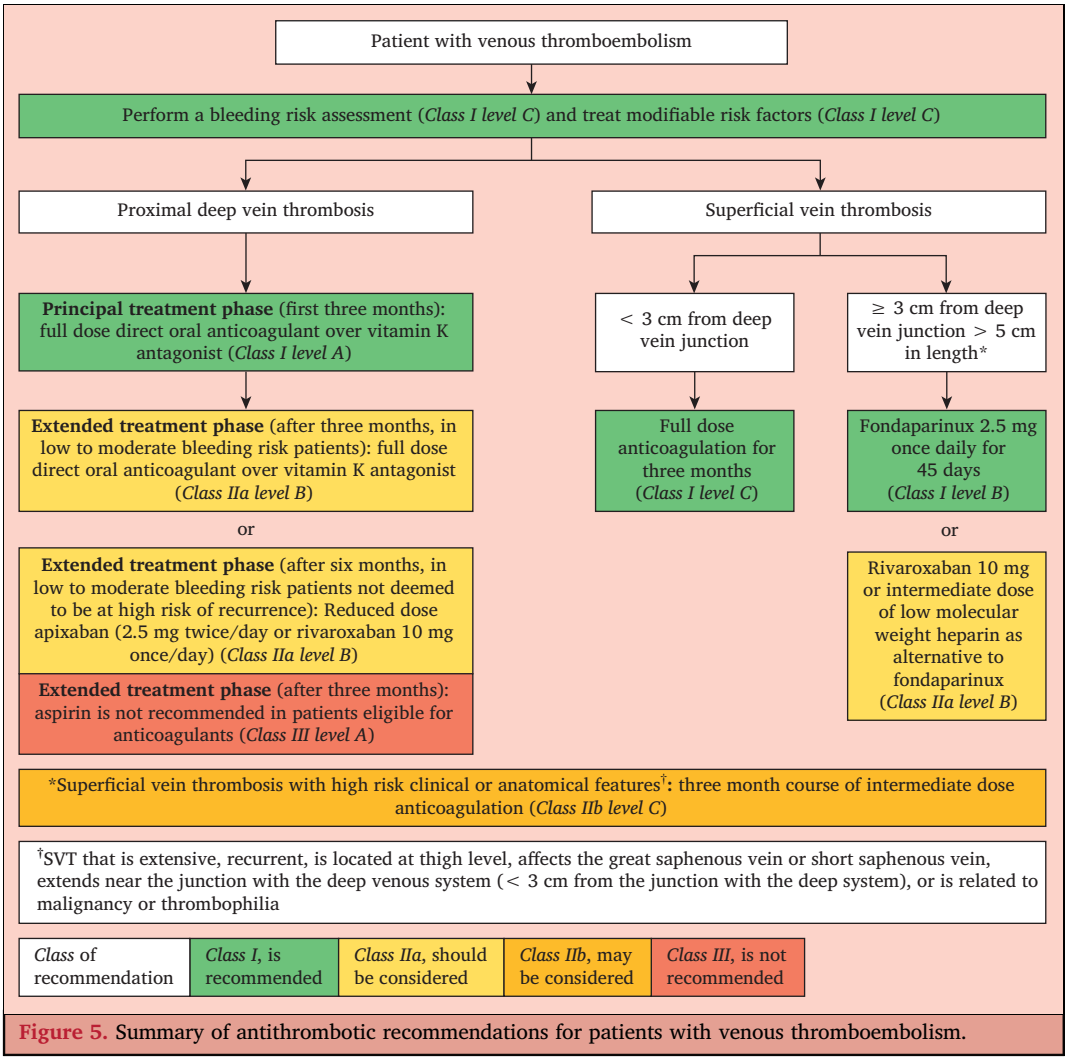

Figure 5. Summary of antithrombotic recommendations for patients with venous thromboembolism.

Recommendation 67

Patients with lower limb superficial vein thrombosis ≥ 3 cm away from the junction with the deep veins and extending ≥ 5 cm in length are recommended to have fondaparinux 2.5 mg once daily for 45 days to reduce the risk of further thromboembolic events.

Class	Level	References	ToE
I	B	Decousus *et al.* 2010[7]	

Recommendation 68

Patients with lower limb superficial vein thrombosis ≥ 3 cm away from the junction with the deep veins and extending ≥ 5 cm in length should be considered for rivaroxaban 10 mg or an intermediate dose of a low molecular weight heparin once daily as an alternative to fondaparinux to reduce the risk of further thromboembolic events.

Class	Level	References	ToE
IIa	B	Cosmi *et al.* (2012),[24] Decousus *et al.* (2010),[7] Beyer-Westendorf *et al.* (2017),[26] Di Nisio *et al.* (2018)[307]	

In patients with lower limb SVT ≤ 3 cm from the junction with the deep veins, full dose anticoagulation is recommended. There is a lack of evidence for short (< 5 cm) SVT, although some patients with a higher than usual thromboembolic risk may receive anticoagulant treatment instead of expectant management. Patients with SVT ≥ 5 cm with a higher than usual thromboembolic risk may receive anticoagulation for a total of three months.[305]

Certain patients with SVT have high risk clinical or anatomical features which make them fall into a higher risk group for complications. These are patients with clinically extensive SVT involving both the calf and the thigh, absence of local pain, superficial axial vein thrombosis, or multiple thrombosed venous sites.[305] These patients may receive a therapeutic or intermediate anticoagulant dose for a longer period, or, alternatively, be switched to prophylactic anticoagulation after 30 — 45 days of initial treatment, for a total of three months of anticoagulant treatment. However, there is little evidence to suggest the routine use of this approach. A similar lack of evidence applies to SVT of short length (< 5 cm), where patients with a higher than usual thromboembolic risk may receive anticoagulant treatment instead of expectant management. Figure 5 summarises antithrombotic recommendations for patients with venous thromboembolism.

Recommendation 69

Patients with lower limb superficial vein thrombosis ≤ 3 cm from the junction with the deep veins are recommended to have three months of full dose anticoagulation to reduce the risk of further thromboembolic events.

Class	Level	References
I	C	Consensus

Recommendation 70

Patients with superficial vein thrombosis of the leg who exhibit high risk clinical and or anatomical features (such as clinically extensive superficial vein thrombosis involving both the calf and the thigh, absence of local pain, superficial axial vein thrombosis or multiple thrombosed venous sites) may be considered for a three month (rather than 45 day) course of intermediate dose anticoagulation to reduce the risk of further thromboembolic events.

Class	Level	References	ToE
IIb	C	Nikolakopoulos *et al.* (2018)[305]	

5.4. Cancer associated venous thromboembolic events

Historically, this association was first described as Trousseau's syndrome; cancer and migrating thrombophlebitis.[312] Cancer is associated with 17 — 29% of all cases of VTE, and the risk of VTE is increased seven fold in patients with cancer compared with patients without (OR 6.7; 95% CI 5.2 — 6.8).[313,314] Haematological malignancies bear the highest VTE risk, with lung and gastrointestinal cancers second (adjusted ORs 28.0, 22.2, and 20.3, respectively).[315] The risk of venous thrombosis is highest in the first few months after the diagnosis of malignancy (adjusted OR 53.5; 95% CI 8.6 — 334.3).[315] Patients with cancer associated VTE had a statistically significantly lower survival rate after one year compared with cancer patients without VTE (12% *vs.* 36%; $p < .001$).[316]

A meta-analysis of 23 RCTs showed that LMWHs are more effective than VKAs in preventing recurrent VTE (RR 0.58; 95% CI 0.45 — 0.75) and DVT (RR 0.44; 95% CI 0.29 — 0.69).[317] Furthermore, five RCTs have reported clinical outcomes of treatment with DOACs (apixaban,[318,319] edoxaban,[296] and rivaroxaban[320,321]) *vs.* the LMWH dalteparin in patients with cancer with acute VTE. A meta-analysis of four of these trials showed that DOACs were non-inferior to LMWH for preventing overall VTE recurrence in patients with active cancer, although there was an increased risk of clinically relevant non-major bleeding (but not major bleeding) with DOACs.[322] Bleeding was mainly attributable to gastrointestinal luminal malignancies.

Recommendation 71

Patients with cancer associated venous thromboembolism are recommended to have anticoagulation with low molecular weight heparin to reduce the risk of further thromboembolic events.

Class	Level	References	ToE
I	A	Sabatino *et al.* (2020)[322]	

Recommendation 72

Patients with cancer associated venous thromboembolism and a low risk of gastrointestinal or genitourinary bleeding are recommended to be considered for anticoagulation with a direct oral anticoagulant preferably apixaban, alternatively rivaroxaban or edoxaban.

Class	Level	References	ToE
I	A	Sabatino *et al.* (2020),[322] Kirkilesis *et al.* (2019)[317]	

5.5. After venous intervention

5.5.1. Superficial and deep venous surgery. A large RCT including 2 196 patients undergoing high ligation and stripping of the great saphenous vein showed that subcutaneous enoxaparin or UFH given for three days postoperatively significantly reduced the incidence of DVT and PE compared with placebo.[323] Bleeding was substantially higher in the UFH group compared with the LMWH group. Because of the low frequency of serious VTE events, and an incidence of leg discomfort associated with bleeding in the treatment group, it has been suggested that thromboprophylaxis should be given only to certain high risk patients, such as those with a previous VTE, obesity, thrombophilia, or a high score on VTE risk assessment.

Unlike ablative superficial venous surgery, deep vein open surgery is performed under systemic heparisation. Antithrombotic therapy is continued post-operatively, with indefinite anticoagulation recommended for most post-thrombotic patients.[50]

Recommendation 73

Patients with superficial venous incompetence undergoing high ligation and stripping of the great saphenous vein who are thought to be at higher risk of deep vein thrombosis should be considered for thromboprophylaxis with a low molecular weight heparin to prevent post-operative venous thromboembolism.

Class	Level	References	ToE
IIa	B	Wang *et al.* (2015)[323]	

5.5.2. Superficial vein ablation. The effect of thromboprophylaxis on VTE and endovenous heat induced thrombosis is largely undetermined. A consensus statement has suggested that patients with a perceived risk factor for DVT should be given thromboprophylaxis with a LMWH (at a lower prophylactic dose rather than treatment dose) following superficial endovenous treatment.[324] The consensus panel felt that BMI > 30 kg/m^2, reduced mobility or calf muscle function, use of hormone replacement therapy or oral contraceptive pill, personal or family history of VTE, flight more than three hours in length within four weeks of the procedure, a past history of malignancy, inherited thrombophilia, or surgery within the last 12 weeks were all risk factors that would make them more likely to prescribe prophylactic LMWH. Fondaparinux and DOACs are frequently prescribed, with no differences seen in case series between a

three and seven day course in a propensity scored analysis of 864 patients.[325] The doses used in the only case series in the literature were rivaroxaban 10 mg and 2.5 mg of fondaparinux. In the absence of well powered data, this single case series makes it difficult to recommend either of these over a lower prophylactic dose of LMWH. The low incidence of VTE or endovenous heat induced thrombosis following superficial venous ablation makes adequately powered studies difficult to achieve.

Recommendation 74

Patients with superficial venous incompetence undergoing endovenous ablation of the great saphenous vein who are thought to be at higher risk of deep vein thrombosis should be considered for thromboprophylaxis with a low molecular weight heparin to prevent post-operative venous thromboembolism.

Class	Level	References
IIa	C	Consensus

5.5.3. Interventions for deep vein thrombosis and chronic obstructive lesions. Standard anticoagulation is indicated following mechanical thrombectomy or thrombolysis for acute DVT as described in detail elsewhere.[50] In the case of provoked DVT, post-intervention anticoagulation may be transitioned to an antiplatelet after three months. However, the ideal antithrombotic strategy and duration of use after venous stenting, both in the acute and chronic setting, is not supported by trial evidence. A recent consensus statement recommended LMWH followed by warfarin following acute deep venous intervention.[46] There have been anecdotal reports of stent thrombosis on DOACs in this setting. However, DOACs have clear class benefits over warfarin for the treatment of DVT so would be expected to perform in the same way after intervention. The same consensus statement recommends warfarin or DOAC following intervention for chronic deep venous disease.[46] Antiplatelets and or anticoagulants are continued post-operatively, with indefinite anticoagulation recommended for most post-thrombotic patients.[50,326,327]

Recommendation 75

Patients undergoing iliofemoral venous stenting for deep venous disease should be considered for an individualised antithrombotic regimen considering the risk of bleeding associated with more aggressive antithrombotic strategies.

Class	Level	References	ToE
IIa	C	Notten *et al.* (2021)[327]	

Recommendation 76

Patients undergoing intervention for deep vein thrombosis (with or without stenting) are recommended to have a duration of anticoagulation at least as long as standard treatment following deep vein thrombosis to prevent recurrent thromboembolic events.

Class	Level	References
I	C	Consensus

6. CONGENITAL VASCULAR MALFORMATION

Venous thromboembolism is a frequent complication among patients with venous malformation,[328,329] as patients often have localised intravascular coagulopathy.[330,331] Laboratory assessments show low levels of fibrinogen and elevated D dimers, while the platelet count usually remains normal or slightly decreased. Localised intravascular coagulopathy rarely results in serious complications but may be aggravated by different stimuli such as surgery, endovascular therapy, or trauma, resulting in disseminated intravascular coagulopathy.[329,332,333] Localised intravascular coagulopathy is responsible for painful thrombotic events within the venous malformation.[331]

Because of a lack of high quality published literature, a consensus on investigations and treatment of venous malformation has been considered by an expert panel of the International Union of Angiology.[332] They noted that the quality of the literature was very low. They felt that prophylactic dose LMWH may be used to treat thrombotic pain associated with localised intravascular coagulopathy, to normalise the coagulation profile, and to prevent progression of severe localised intravascular coagulopathy to disseminated intravascular coagulation before any interventional procedure especially in patients with a low fibrinogen level.[331,334] Prophylactic treatment may be started 10 days before and continued 10 — 20 days after any surgical procedure (including minimally invasive procedures) in patients with an extensive venous malformation, evidence of localised intravascular coagulopathy, and in patients with Klippel Trenaunay syndrome.[335] Antiplatelet agents were not recommended in patients with venous malformation associated coagulopathy and or pain.[336]

Given the strong propensity toward thrombosis, the panel recommended prophylactic anticoagulation in Klippel Trenaunay syndrome patients with an extensive venous malformation, marginal vein, or presence of a marginal vein with co-existing aplastic deep venous system when the risk of VTE is substantial.[332]

There is emerging data for DOACs in improving the D dimer and fibrinogen levels in patients with localised intravascular coagulopathy in the setting of venous malformation.[337-339] There is little evidence on clinical outcomes and the use of these agents is off label.

Recommendation 77

Patients with extensive venous malformation or Klippel Trenaunay syndrome with evidence of localised intravascular coagulopathy confirmed by low fibrinogen and high D dimer levels may be considered for prophylactic anticoagulation (low molecular weight heparin or direct oral anticoagulant) for 10 days before, and 20 days after, any invasive procedure to prevent progression to disseminated intravascular coagulation.

Class	Level	References
IIb	C	Consensus

Recommendation 78		
Patients with venous malformation associated coagulopathy are not recommended to have antiplatelet agents to prevent progression to disseminated intravascular coagulation.		
Class	**Level**	**References**
III	C	Consensus

7. UNRESOLVED ISSUES AND FUTURE RESEARCH

The GWC identified the following unresolved issues where the available evidence is currently insufficient to guide recommendations.

As a general comment, patients and the public have been minimally involved during trial design for antithrombotics. As a result, many endpoints are physician centred and complicated as they are designed to show *any* effect, usually via a complicated non-standard composite, rather than an effect that patients will value. There is a general lack of quality of life, health economic analysis, and patient reported outcomes in trials. As treatments are becoming broadly similar in their preventive and bleeding effects, this will become increasingly important in future trial design. Composite outcomes such as MACE and MALE are poorly defined and vary between trials, limiting their comparison. There is also a problem with heterogeneity in antithrombotic protocols for RCTs examining other factors for vascular intervention such as new technologies.[201] This may introduce bias and needs standardising.

There are now large prospective vascular registries in several countries. These could be used for prospective studies (especially for rarer diseases) and for RCTs as per the SWEDEPAD (SWEdish Drug Elution trials in Peripheral Arterial Disease) model.[340]

Research recommendations:

1. Patient centred trial design for future trials of antithrombotic therapy.
2. Work to define and standardise composite endpoints for RCTs of antithrombotic therapy.
3. Work to standardise antithrombotics protocols in RCTs for other areas of vascular intervention such as new endovascular technology. Core outcome and measurement sets would achieve this aim.
4. Work to facilitate RCT research in more vascular registries internationally.

Section 1.3.1 *Bleeding risk assessment and risk reduction*

There is a lack of validated bleeding risk scores for patients with PAD and for patients requiring anticoagulation for a venous indication. This is increasingly important for shared decision making.

Research recommendations:

5. Development and validation of bleeding risk assessment tools for patients with PAD and venous disease.
6. Better definitions and quantification of major bleeding considering the patient perspective.
7. Definitions of net benefit — the difference between risks and benefits, again taking multiple stakeholder opinions into account.

Section 3. *Antiplatelet function testing*

There is a lack of clinical information on the outcome of high on treatment platelet reactivity for patients with PAD. This includes symptomatic stable patients as well as those undergoing endovascular and open intervention.

Research recommendations:

8. Further clinical studies on the impact of testing for, and then treating high on treatment platelet reactivity for patients with PAD, focussing on patients with a higher risk of thrombotic events (post-intervention and factors listed in Table 9).

Section 4.1 *Atherosclerotic carotid artery disease*

There is a clear lack of RCTs for antiplatelet therapy for patients with symptomatic carotid artery disease undergoing both open and endovascular intervention making clear recommendations impossible. There is also a lack of evidence around antithrombotics for crescendo TIA (as well as a lack of standard definition).

Research recommendations:

9. RCTs examining antiplatelet regimens, especially dual antiplatelets, before, during and after carotid intervention for symptomatic stenoses. Crescendo TIA should be included.

Section 4.3 *Atherosclerotic upper limb arterial disease*

There is a general lack of evidence to understand the role of antithrombotic therapy for atherosclerotic upper limb arterial disease. Prospective or even retrospective studies would be useful to further understand risk for these patients.

Section 4.4 *Atherosclerotic renal and mesenteric arterial disease*

There is a lack of evidence to understand the role of antithrombotics for asymptomatic and intervened visceral artery disease. As a relatively rare condition, cohort studies would be more viable than RCTs.

Section 4.5 *Atherosclerotic lower extremity arterial disease*

The value of antiplatelet agents other than aspirin is poorly investigated for patients with asymptomatic LEAD.

Research recommendations:

10. Further RCTs on high ischaemic risk asymptomatic PAD groups to understand any potential magnitude of the effects of antithrombotics other than aspirin.

There is no randomised comparative evidence for clopidogrel *vs.* aspirin plus low dose rivaroxaban for patients with chronic symptomatic LEAD, meaning recommendations cannot be specific as to which is best. Network meta-

analysis shows that the magnitude of benefit of both regimens over aspirin is similar.[186]

Multiple RCT subgroup analyses have shown certain groups are at higher risk of ischaemic thrombotic events (see Table 9). Further work needs to be performed to understand the impact of different antithrombotic regimens in these higher risk groups, including different arterial territories.

The comparative effects of DAPT, single therapy, and aspirin and rivaroxaban following intervention is currently not understood from RCT evidence, which makes recommendations difficult.

The role of antithrombotic therapy for non-atherosclerotic PAD is poorly understood and could be explored further in prospective registries.

Research recommendations:

11. Further clinical studies on high ischaemic risk chronic symptomatic LEAD groups to understand any comparative magnitude of antithrombotics, especially clopidogrel *vs.* aspirin plus low dose rivaroxaban.
12. RCTs comparing single antiplatelet, dual antiplatelets, and antiplatelet plus low dose anticoagulants after endovascular intervention for LEAD. Focus on high risk groups.
13. RCTs comparing combinations of antiplatelet and anticoagulant following lower limb bypass for LEAD. Focus on high risk groups as well as stratification by arterial territory such as below the knee.

Section 4.8 Aneurysmal disease

There is surprisingly little data for antiplatelet therapy for patients with aneurysms, especially AAA. As a high volume disease, RCTs are feasible.

Isolated thrombus in the aorta or within a stent graft is also an area with no high quality evidence to guide practice.

Research recommendations:

14. RCTs examining the role of antithrombotic therapy for patients with AAA. The most urgent need is for secondary cardiovascular prevention and expansion for patients with small AAA.
15. Cohort or randomised studies on isolated thrombus within the aorta or aortic stent grafts.

Section 5. Antithrombotics for patients with venous disease

There is a lack of evidence for antithrombotic regimens after venous stenting. As this becomes increasingly common it is important to understand both short and long term implications.

For patients with SVT, there is no evidence that intermediate doses of LMWHs reduce VTE (DVT and or PE) *vs.* placebo. There is a paucity of information available for patients with SVT near a junction with the deep veins regarding length of therapeutic anticoagulation. The suggestion on extending anticoagulation beyond 45 days in selected patients with SVT is based on observational data and not an RCT.

Research recommendations:

16. Clinical studies on the effect of antithrombotic therapy before, during, and after venous stenting. Research collaborations may be the best way to achieve this between high volume practitioners.
17. For patients with SVT, further research should investigate the effectiveness of intermediate doses of LMWHs in reducing VTE (DVT and or PE) *vs.* placebo.
18. RCTs should be performed to inform clinical practice regarding the optimum treatment duration for patients with SVT near a junction with the deep veins.
19. Further RCTs are required to provide a higher level of evidence for duration of extended anticoagulation following SVT.

8. PLAIN LANGUAGE SUMMARY AND INFORMATION FOR PATIENTS

This section explains information about this guideline for patients and members of the public.

8.1. What is this guideline about and how was it developed?

This guideline is to help both healthcare professionals and people with diseases of their arteries and veins to make the best decisions about their blood thinning (antithrombotic) tablets. Most people with diseases of their arteries (narrowing or widening), or clots in their veins will be offered blood thinning tablets. There are a lot of different types of blood thinning tablets available, and they have different risks and benefits. This guideline makes recommendations as to which are the best tablets for people with various arterial and venous diseases. Sometimes we cannot make a recommendation, or sometimes we make more than one recommendation for one disease. In the text before each recommendation we explain the reasons behind the recommendation to try and help people understand how we came to that conclusion.

The guidelines were developed by the European Society for Vascular Surgery (ESVS). The ESVS has produced several guidelines to help medical professionals and people with arterial and venous diseases which can be found at: https://esvs.org/guidelines. This guideline does not consider blood thinning tablets for the arteries of the heart or veins in the chest because they are treated by healthcare professionals outside the scope of the ESVS.

8.2. What are antithrombotics?

Antithrombotics are blood thinning tablets that reduce the risk of clots forming. There are two main ways they can prevent clots forming, so two main groups of tablets. One way antithrombotics prevent clots forming is to stop platelets working. Platelets are found in the blood and are the first step in the process of forming a clot. Tablets that

stop platelets working are called antiplatelet tablets, and an example is aspirin. By stopping platelets working, a person is less likely to form clots which can block arteries and then cause problems like a heart attack or stroke.

The other way antithrombotic tablets work is by slowing down coagulation. This is the second step the blood takes in forming a clot after platelets have worked. These tablets are called anticoagulants and an example is warfarin. Anticoagulants make it less likely the body can form clots, which could lead to clots on the leg or lung (deep vein thrombosis or pulmonary embolism). These tablets are stronger than antiplatelet tablets in their effect when stopping clots forming. This means that while they are more likely to stop clots forming, they are also more likely to cause bleeding.

8.3. Why do you need to take antithrombotics?

People need to take antithrombotics or blood thinning tablets to reduce the risk of clots forming. If a person has disease in their arteries, these clots can cause heart attack, stroke, or amputation. If a person has certain diseases of the veins, these clots can lead to deep vein thrombosis or pulmonary embolism. Both arterial and venous clots can lead to someone dying. Blood thinning tablets reduce the risk of these clots forming or stop them getting worse.

Blood thinning tablets can also cause bleeding. Because anticoagulants are stronger than antiplatelets they are more likely to cause bleeding. This bleeding may lead to things like bruising, bleeding from an irritated stomach, or even life threatening bleeding. Life threatening bleeding is much rarer than other types of bleeding, which may be more of an inconvenience than anything else.

When deciding to take a blood thinning tablet, it is important that the balance between preventing clots and causing bleeding is considered and discussed. Steps must be taken to reduce the risk of bleeding where possible. Patients should feel involved in this process, which is called shared decision making. The risks and benefits that a healthcare professional thinks are important might not be the same as those a patient thinks are important. This is especially true for blood thinning tablets for diseases of the arteries and veins outside the heart because there is no good way to clearly predict who is going to bleed, other than if they have bled before. We suggest ways medical professionals could try and think about bleeding and suggest that people at risk of bleeding from their stomach should be given tablets to reduce stomach acid to reduce the risk of bleeding from the blood thinners.

8.4. What antithrombotics are best for people with diseases of their arteries?

Most people with symptoms from narrowings of their arteries will need antiplatelet blood thinning tablets for life. People with narrowings in the arteries supplying blood to their brains should generally have one antiplatelet blood thinning tablet. This includes people having a procedure to open the narrowings in the arteries taking blood to the brain. If those people have had a small stroke, they should be given two antiplatelet blood thinning tablets for a period of time, then this should be dropped to one antiplatelet blood thinning tablet. Sometimes only one is used.

People with narrowings in their leg arteries may not need any blood thinning tablet if they have no symptoms in the leg. If they have symptoms, they should generally have an antiplatelet blood thinning tablet or may have an antiplatelet plus anticoagulant blood thinning tablet in combination. The choice will depend on the individual's risk balance of forming clots form their disease and bleeding from the tablets. People with narrowings in their leg arteries undergoing a procedure to open or bypass the narrowings may have one or two antiplatelet blood thinning tablets, an antiplatelet plus anticoagulant blood thinning tablet in combination, or a stronger anticoagulant blood thinning tablet on its own. The choice will again depend on the individual's balance of risks of forming clots from their disease and bleeding from the tablets.

People with a widening of the main artery in their stomach (an aortic aneurysm) should be offered an antiplatelet blood thinning tablet, which is usually aspirin. If the aneurysm needed to be repaired, the antiplatelet tablet would be continued afterwards for life.

People with diseases of their arteries sometimes have other reasons to be on blood thinning tablets. In that situation the vascular healthcare professional may need to talk to the healthcare professional who started the other medication or may just leave the person on that medication.

8.5. What antithrombotics are best for people with diseases of their veins?

Generally, people with clots in their veins will be offered an anticoagulant blood thinning tablet for a period of time, usually a few months. The length of time they are on the tablet will depend on how serious the clot was, their risk of forming another clot, and their risk of bleeding from the tablets. People having procedures on their veins may need a blood thinning injection, tablets, or nothing. Again, the risks of clotting and bleeding will need to be balanced carefully.

8.6. What are the main areas that need further research?

The risk balance between clots forming and bleeding for people with narrowings or widenings of their arteries still needs more research to understand which blood thinning tablets are best. This especially applies to people having operations for narrowings in the arteries supplying blood to their brains, and people having a keyhole intervention to open up narrowed arteries in the legs. More research into the best blood thinning tablets for people with widenings (aneurysms) of the arteries is still needed.

More research is also needed into the best blood thinning tablets for people having veins widened with stents, and for people with clots in the veins just under the skin in the legs, to understand which blood thinning tablet is best and how long they should be used for.

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APPENDIX A. SUPPLEMENTARY DATA

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