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SPECIAL ARTICLE

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

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The aim of this collaborative document is to provide an update for clinicians on best antithrombotic strategies in patients with aortic and/or peripheral arterial diseases. Antithrombotic therapy is a pillar of optimal medical treatment for these patients at very high cardiovascular risk. While the number of trials on antithrombotic therapies in patients with aortic or peripheral arterial diseases is substantially smaller than for those with coronary artery disease, recent evidence deserves to be incorporated into clinical practice. In the absence of specific indications for chronic oral anticoagulation due to concomitant cardiovascular disease, a single antiplatelet agent is the basis for long-term antithrombotic treatment in patients with aortic or peripheral arterial diseases. Its association with another antiplatelet agent or low-dose anticoagulants will be discussed, based on patient's ischaemic and bleeding risk as well therapeutic paths (e.g. endovascular therapy). This consensus document aims to provide a guidance for antithrombotic therapy according to arterial disease localizations and clinical presentation. However, it cannot substitute multidisciplinary team discussions, which are particularly important in patients with uncertain ischaemic/bleeding balance. Importantly, since this balance evolves over time in an individual patient, a regular reassessment of the antithrombotic therapy is of paramount importance.

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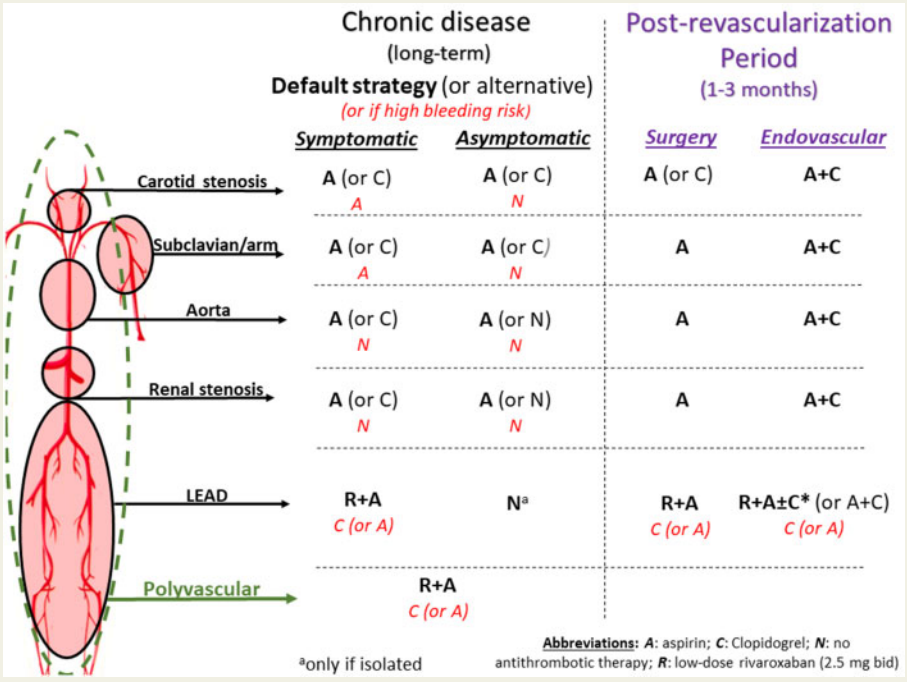
Graphical Abstract



Summary of optimal and alternative antithrombotic strategies in patients with peripheral arterial disease. [a]In the absence of any other vascular disease. [b]The addition of clopidogrel on top of low-dose aspirin and rivaroxaban can be decided case by case, taking into consideration type and length of stent, disease severity, and bleeding risk. If clopidogrel is added, it should be limited to 1 month to limit bleeding complications.[100] [c]There are no data for a head-to-head comparison between R + A vs. A + C strategies. The latter has been empirically implemented and recommended for endovascular therapy,[1] while the R + A has been recently assessed in a randomized trial.[80] Also, the R + A strategy can be prolonged beyond the post-revascularization period with benefits on MACE and MALE.

Keywords Antithrombotic therapy • Anticoagulant • Antiplatelet drug • Peripheral arterial disease • Aorta • Lower-extremity artery disease • Carotid artery • Vertebral artery • Subclavian artery • Renal artery • Mesenteric artery • Thrombosis

Introduction

In 2017, the European Society of Cardiology (ESC), in collaboration with the European Society for Vascular Surgery, released guidelines on the diagnosis and management of peripheral arterial diseases (PADs).[1] They highlighted the importance of antithrombotic therapy to prevent major adverse cardiovascular events (MACE) and emphasized major gaps in evidence with respect to risk reduction associated with newer antithrombotic treatments. Since then, results from major randomized controlled trials (RCTs) as well as registries have dramatically modified the landscape of antithrombotic options in these patients. In addition, peripheral events, frequently grouped as major adverse limb events (MALE), have gained increasing attention. Therefore, the three working groups involved in the present collaborative document sensed the urgency to give clinicians a holistic roadmap to optimize antithrombotic management in patients with aortic disease and/or PADs, with a focus on the post-procedural and chronic phases of these diseases. The document is presented by arterial territory and ends with the management of patients requiring chronic oral anticoagulants for associated conditions and the assessment of bleeding risk in vascular patients.

Carotid, vertebral, and subclavian arteries

Key messages: Antithrombotic therapies for carotid, subclavian, or vertebral artery disease

- Long-term antiplatelet therapy with aspirin or clopidogrel is proposed in patients with symptomatic or asymptomatic carotid stenosis.
- Dual antiplatelet therapy (DAPT) (aspirin + ticagrelor or clopidogrel) may be proposed in patients with symptomatic carotid stenosis in the early phase of minor stroke or transient ischaemic attack (TIA).

- DAPT (aspirin + clopidogrel) is proposed in patients undergoing carotid stenting, for at least 1 month.
- SAPT should be maintained in patients scheduled for CEA.
- Long-term low-dose rivaroxaban plus aspirin may be proposed in patients with asymptomatic carotid stenosis or in those with history of carotid revascularization, who are considered at very-high risk because of associated comorbidities (especially polyvascular patients), provided bleeding risk is not high.*
- In the absence of specific evidence, it is reasonable to apply the same antithrombotic strategies proposed for carotid artery disease to vertebral and subclavian artery diseases.

*In the absence of: prior history of intracerebral haemorrhage or ischaemic stroke, history of other intracranial pathology, recent gastrointestinal bleeding or anaemia due to possible gastrointestinal blood loss, other gastrointestinal pathology associated with increased bleeding risk, liver failure, bleeding diathesis or coagulopathy, extreme old age or frailty, or renal failure requiring dialysis or with eGFR <15 mL/min/1.73 m^2.

Antithrombotic treatment therapy in carotid artery disease

Carotid plaques are potential sources of embolic stroke and are associated with increased risk of cardiovascular events beyond stroke. Since no trial has investigated single antiplatelet therapy (SAPT, e.g. aspirin) to reduce cardiovascular events in patients with non-stenotic carotid plaques, this document will focus on patients with carotid artery stenosis (luminal narrowing >50%).

Asymptomatic carotid artery disease

Antithrombotic treatment in patients with asymptomatic carotid stenosis remains controversial. The ACB study, the only trial in this setting, failed to show the superiority of aspirin vs. placebo but was limited in size (*Table 1*).[3] In observational studies, SAPT, consisting mainly of low-dose aspirin, was associated with reduced risk of MACE, although data were conflicting for moderate stenosis (i.e. 50%–75%).[12–14] DAPT, combining aspirin and clopidogrel, was of no benefit over SAPT.[15] The ESC guidelines suggest long-term SAPT in patients with asymptomatic ≥50% carotid artery stenosis, if bleeding risk is low.[1]

More recently, the COMPASS trial randomized patients with chronic coronary and/or peripheral artery disease into three arms: dual pathway inhibition (DPI) combining aspirin 100 mg o.d. + rivaroxaban 2.5 mg bid vs. rivaroxaban 5 mg bid vs. aspirin 100 mg o.d.[16] Overall, a significant decrease in MACE was reported in patients allocated to DPI vs. aspirin alone (*Table 1*), with a similar trend, albeit not statically significant likely due to the limited sample size, observed among the 1919 patients with either history of carotid revascularization or asymptomatic ≥50% stenosis.[16] Specific data on the subgroup with asymptomatic carotid stenosis were not reported.

Symptomatic carotid artery disease

Symptomatic carotid stenosis is associated with a high risk of early recurrence of cerebrovascular ischaemic events.[17] In patients with cerebrovascular accidents related to large arterial disease, SAPT (aspirin or clopidogrel) was more effective in reducing recurrent events than oral anticoagulation with vitamin K antagonists (VKA).[2,3,18,19] A subgroup analysis of the SOCRATES trial with ipsilateral atherosclerotic stenosis demonstrated significantly lower rates of MACE in patients receiving ticagrelor vs. aspirin (*Table 1*).[4]

Regarding DAPT in the early phase of symptomatic carotid stenosis, the combination of aspirin and clopidogrel reduces the risk of asymptomatic cerebral embolization and stroke.[20–23] It also reduces the risk of stroke recurrence after minor stroke ischaemic attack and TIA.[24,25] More recently, the THALES trial (n = 11 016) showed a significant 17% risk of death or stroke reduction when using ticagrelor + aspirin vs. aspirin alone in patients with minor stroke or high-risk TIA.[26] In a pre-specified subgroup analysis of patients with ipsilateral extra/intracranial stenosis >30%, the risk reduction was even more substantial (*Table 1*), with a very high benefit/risk ratio.[5] Data on the efficacy of dipyridamole to reduce stroke are inconsistent, without specific results with carotid stenosis.[27–29]

Antithrombotic therapy in carotid stenting

After carotid stenting, DAPT (aspirin + clopidogrel) is the standard of treatment, while the optimal duration is debated.[11] Two small RCTs have compared SAPT and DAPT in carotid artery stenting (CAS), for a total of 150 patients, and both trials were prematurely interrupted due to unacceptable neurologic event rate in the SAPT arm (3 vs. 0 strokes and 11 vs. 1 TIA).[30] Given the experience with coronary stenting, most operators favour empirically DAPT after CAS for at least 1 month. In a Taiwanese nationwide registry,[31] the 6-month rates of ischaemic stroke, composite vascular events, or death were similar among 2829 patients with DAPT durations of <30, 30–41 and ≥42 days. In a single-centre series of patients undergoing CAS, the addition of cilostazol has been proposed on the top of DAPT, in case of platelet resistance to clopidogrel to reduce magnetic resonance imaging-detected ischaemic lesions,[32] but the extension of that study found no significant reduction in clinical events.[33]

Antithrombotic treatment in carotid surgery

In patients undergoing carotid endarterectomy (CEA), the reduction in peri-procedural and long-term ischaemic events under aspirin has been evidenced in trials (*Table 1*) and real-life registries.[6–9,34] Low-dose aspirin was superior to high-dose aspirin on 30-day risk of MACE.[10]

The addition of a second antiplatelet agent has consistently been reported to reduce neurological events vs. aspirin alone in patients with recent TIA/stroke.[35] In a meta-analysis collecting data of three RCTs comparing DAPT to SAPT in carotid interventions (only one with CEA), no difference in fatal stroke was found after CEA

Table 1 Trials on antithrombotic therapy in patients with carotid artery disease

Trial (acronym or 1st author, year)	Type and aim	Comparison	*N*	Setting (indication)	Primary endpoint	Main hypothesis validated?
Carotid artery stenosis: symptomatic and asymptomatic						
AITIA, 1977[2]	Multicenter RCT: aspirin in TIA	A_{1300mg} vs. placebo	178	Subgroup of pts with TIA related to carotid artery disease	Composite: cerebral or retinal infarction, or death @ 2 yrs	Yes (A vs. placebo: event probability 11.8% vs. 26.3%; $P = 0.04$)
ACB, 1995[3]	Multicenter RCT: aspirin in asymptomatic carotid artery stenosis	A_{325mg} vs. placebo	372	Pts with ≥50% asymptomatic carotid artery stenosis	Composite: stroke, TIA; MI, UA, or death @ 2.4 yrs	No (HR 0.988, 95% CI 0.667–1.464, $P = 0.95$)
SOCRATES, 2017 (subgroup analysis)[4]	Multicenter RCT: ticagrelor in high-risk TIA or non-severe ischaemic stroke	$Ticagrelor_{180mg}$ vs. A_{100mg}	3081	Subgroup of pts with high risk TIA or non-severe ischaemic stroke and ipsilateral atherosclerotic stenosis	Composite: stroke, MI, or death @ 3 months	Yes (HR 0.68, 95% CI 0.53–0.88, $P = 0.003$)
COMPASS, 2018 (carotid subgroup)[7]	Multicentre RCT: AT strategies in chronic CAD or PAD	$R_{2.5\,mg\,x2} + A_{100mg}$ vs. $R_{5mg\,x2}$ vs. A_{100mg} alone	27 395 (Carotid: 1919)	Carotid subgroup: history of carotid revasc. or asymptomatic ≥50% carotid stenosis	Composite: stroke, MI, or cardiovascular death @ 21 mo.	Yes for overall study [R + A vs. A HR 0.72 (0.57–0.90)], $P = 0.0047$, no interaction in the carotid group.
THALES, 2020 (subgroup analysis)[5]	Multicenter RCT: ticagrelor + aspirin in high-risk TIA or minor ischaemic stroke	$Ticagrelor_{180mg} + A_{100mg}$ vs. A_{100mg}	2351	Subgroup of pts with high risk TIA or non-severe ischaemic stroke and ipsilateral atherosclerotic stenosis (>30%)	Composite of stroke, or death @ 30 days	Yes (HR 0.73, 95% CI 0.56–0.96, $P = 0.023$)
Carotid revascularization						
AITIA-surgery, 1978[6]	Multicenter RCT: aspirin after CEA	A_{1300mg} vs. Placebo	130	Pts after elective CEA	Composite: cerebral or retinal infarction, or death @ 2 years	No (A vs. Placebo: 22.3% vs. 18.5%; $P = 0.70$)
Boysen, 1988[7]	Multicenter RCT: aspirin after CEA	A_{50mg} vs. Placebo	301	Pts after elective CEA	Composite: stroke, TIA, MI, or vascular death @ 27 months	No (A vs. Placebo: RR 0.89, 95% CI 0.57–1.38)
Kretschmer, 1990[8]	Single-centre RCT: aspirin in elective CEA	A_{1000mg} vs. no APT	66	Pts with symptomatic or asymptomatic carotid stenosis undergoing CEA	Mortality @ 3 years	Yes (A vs. no treatment: 12.5% vs. 32.4%, $P < 0.021$)
Lindblad, 1993[9]	Multicenter RCT: aspirin in elective CEA	A_{75mg} vs. Placebo	232	Pts with symptomatic or asymptomatic carotid stenosis undergoing CEA	Stroke or death @ 6 months	Yes: Disabling stroke A 1.7% vs. placebo 9.6%, $P = 0.01$, Death: A 3.4% vs. placebo 8.7%, $P = 0.11$
ACE, 1999[10]	Multicenter RCT: low- vs. high-dose aspirin in elective CEA	$A_{81–325mg}$ vs. $A_{650–1300mg}$	2849	Pts with symptomatic or asymptomatic carotid stenosis undergoing CEA	Composite: stroke, MI, or death @ 3 months	Yes (High-dose A vs. low-dose A: RR 1.34, 95% CI 1.03–1.75, $P = 0.03$)
Dalainas, 2006[11]	Single-centre RCT: DAPT in carotid stenting	$A_{325\ mg}$ vs. $A_{325\ mg}$ + $Ticlopidine_{500mg}$	100	Pts with symptomatic or asymptomatic carotid stenosis undergoing carotid stenting	TIA or Stroke @ 1 month	Yes (A vs. A + ticlopidine: 16% vs. 2%, $P < 0.05$)

A, aspirin; APT, antiplatelet treatment; CEA, Carotid endarterectomy; DAPT, Dual antiplatelet therapy; RCT, Randomized controlled trial; SAPT, single antiplatelet therapy; TIA, transient ischaemic attack.

between DAPT and SAPT, but a significantly higher risk of major bleeding and neck haematoma with DAPT.[30] A pooled analysis of two recent large RCTs comparing DAPT vs. aspirin alone in patients with stroke or TIA[24,25] demonstrated a significant reduction in MACE within the first 21 days [5.2% vs. 7.8%; hazard ratio (HR) 0.66; 95% confidence interval (CI) 0.56–0.77], without a significant increase in major bleeding events.[36] No specific results in stroke secondary to carotid disease were reported.

In asymptomatic patients undergoing CEA, a retrospective study including 28 683 procedures showed that DAPT was associated with a 39% risk reduction in neurological events vs. aspirin alone [odds ratio (OR) 0.61; 95% CI 0.43–0.87], at the cost of higher rate of bleeding requiring reoperation (OR 1.71; 95% CI 1.20–2.42).[37] The single small RCT of DAPT vs. SAPT in asymptomatic patients was underpowered for clinical endpoints; it demonstrated that a single 75 mg dose of clopidogrel (on top of aspirin) the night before surgery reduced significantly embolization rates within the first 3 post-operative hours.[38] In a recent meta-analysis including that RCT[38] and six retrospective observational studies[37,39–43] comparing DAPT ($n = 8536$) to SAPT ($n = 27\,320$) during CEA, the former did not reduce 30-day mortality, stroke, or TIA but increased major bleeding events (1.27% vs. 0.83%; $P = 0.0003$) and neck haematomas (8.19% vs. 6.77%; $P = 0.001$).[30]

Antithrombotic treatment in patients with vertebral and subclavian artery stenosis

The evidence on the use of antithrombotic agents in case of vertebral or subclavian artery stenosis is lacking, but their use is reasonable given the overall cardiovascular risk in these patients (see Supplementary material online).[44,45]

Aortic diseases

Key messages: Antithrombotic therapies in aortic diseases

- Long-term SAPT should be proposed in patients with severe/complex aortic plaques.*
- Following an embolic event possibly related to a complex aortic plaque, DAPT may be proposed.
- SAPT may be proposed in patients with an aortic aneurysm (AA) to reduce general cardiovascular risk, without convincing proof of reducing aneurysmal growth.
- There is no validated long-term antithrombotic therapy in patients following acute aortic syndromes. Beyond the acute phase, antithrombotic therapy should be maintained if clearly indicated (e.g. anticoagulation for mechanical valve or atrial fibrillation). However, close monitoring with imaging techniques is mandatory.
- Long-term SAPT can be proposed after (T)EVAR, based on patient's risk characteristics.

*See Supplementary material online, *table S1*.

Aortic plaques

Aortic plaques are observed in 40%–50% of middle-aged individuals.[46] The disease severity is quantified based on plaque thickness and the presence of ulceration/mobile components (Supplementary material online, *Table S1*).[47] The size and complexity of aortic arch plaques are associated with cerebrovascular events (OR: 4–9 in plaques ≥4 mm or complex),[48] but can also cause peripheral events. Despite antithrombotic therapies, the annual incidence of stroke recurrence is up to 12%.[49]

Primary prevention

Given the high prevalence of aortic plaques among adults, the lack of evidence for aspirin use in asymptomatic patients with aortic plaques, and doubts on benefit/risk ratio of aspirin in primary prevention, it is not reasonable to prescribe aspirin for simple aortic plaques. SAPT, preferably clopidogrel[18,50] or low-dose aspirin,[51] can be suggested in severe/complex plaques. Anticoagulation[51] or DAPT[50] is not indicated as they are of no benefit while they increase the bleeding risk.

Secondary prevention

After an embolic TIA/stroke or peripheral event related to aortic plaque, SAPT with aspirin or clopidogrel is recommended. DAPT or VKA (INR 2–3) can be discussed, but the level of evidence is low or inconclusive.[51,52] Further studies are needed to determine optimal duration of antithrombotic treatment, as the benefit appears more pronounced within the first weeks after stroke while long-term bleeding risk remains elevated. The choice of antithrombotic therapy should follow the current guidelines irrespective of the presence of aortic plaques.[53] In cryptogenic stroke, rivaroxaban 15 mg o.d.[54] or dabigatran 110–150 mg bid[55] were not found to be superior to low-dose aspirin. Specific data on stroke secondary to aortic plaques are missing.

Aortic aneurysms

Patients with AAs, either thoracic or abdominal (AAA), are at increased risk of MACE.[56–58] Thus, despite the absence of dedicated studies, SAPT (aspirin or clopidogrel) may be reasonable for patients without contraindication.[59] Anticoagulants are not indicated as they are associated with a higher bleeding risk.[60] In case of intraluminal thrombus or occlusive aneurysm, anticoagulation can be considered, in light of the role of the mural thrombus in aneurysmal progression.[61] In an RCT in 144 aspirin-naive patients with small AAA, no difference in aneurysmal growth at 1 year was found between ticagrelor and placebo.[56]

Acute aortic syndromes

After the acute phase of aortic dissection, antithrombotic treatment can be necessary in one-third of cases for associated conditions (coronary artery disease, atrial fibrillation, stroke, mechanical aortic valve prosthesis, pulmonary or peripheral embolism). This treatment presents a favourable effect on the thrombosis onset or extension[62] and has not been associated with major complications (e.g. aortic

growth, rupture, or death).[63] No longitudinal study has assessed the role of antithrombotic therapy after intramural haematoma, while case series suggest that anticoagulation does not impact intramural haematoma progression. Close monitoring with imaging techniques should be performed in all patients following acute aortic syndromes. If the evolution is unsatisfactory, endovascular or surgical treatment should be considered.[64,65]

Antithrombotic therapy after (thoracic) endovascular aortic replacement

There are limited data on the antithrombotic treatment after (thoracic) endovascular aortic replacement [(T)EVAR+]. However, SAPT (e.g. aspirin) is advised to avoid cardiovascular events over time.[66] Only in one study with 28 patients, De Bruin *et al.*[67] administered DAPT prior to EVAR, without describing the combination duration. In patients undergoing both (T)EVAR and percutaneous coronary intervention, DAPT has not been associated with increased rate of bleeding, endoleak or recurrent dissection.[68,69] Anticoagulation has been associated with a higher rate of complications including endoleak, re-intervention, late conversion surgery, or mortality.[70]

Endograft thrombus lining is present in >20% of cases after (T)EVAR, two-third of which remain stable or disappear.[71] It results from the complex interaction of systemic haemorheological factors (coagulation disorders or heparin-induced thrombocytopenia), hemodynamics at the level of the prosthesis or device-related characteristics (polyester-covered stent-grafts or aorto-uni-iliac endograft).[72] It has not been associated with thromboembolic comp lications, thus, conservative treatment using SAPT remains consensual. Lifelong oral anticoagulation is reserved for patients at low bleeding risk with thromboembolic events or growing thrombus. In patients at high bleeding risk, anticoagulation interruption and relining with a new endograft is advised.[73]

Lower-extremity artery disease

Figure 1 and *Table 2* summarize trials on antithrombotic therapies in patients with LEAD.[16,18,74–86]

Key messages: Antithrombotic therapy in patients with LEAD

There is no proven benefit to support the use of aspirin in patients with asymptomatic lower extremity artery disease (LEAD) and no significant coronary artery disease or PAD in other territories.

Asymptomatic LEAD in patients with other clinical atherosclerotic disease (e.g. CAD) confers an increased risk of cardiovascular events. Intensified antithrombotic approach using rivaroxaban 2.5 mg bid on top of aspirin may be proposed in this setting, in the absence of high bleeding risk.

Antiplatelet therapy is the mainstay of antithrombotic strategy in patients with symptomatic LEAD. Rivaroxaban 2.5 mg bid should be proposed on top of low-dose aspirin in stable patients with chronic symptomatic LEAD, without conditions at high risk of bleeding.*

If SAPT is planned, clopidogrel may be preferred over aspirin.

There is no clear evidence in favour of long-term DAPT in chronic symptomatic LEAD.

Clopidogrel on top of aspirin is not proven to have beneficial effect on graft patency and is associated with increased bleeding risk in patients following vascular surgery.

Low-dose aspirin and rivaroxaban 2.5 mg bid should be proposed in patients undergoing revascularization (surgical or endovascular) for LEAD with no increased risk of bleeding.*

*History of intra-cranial haemorrhage or ischaemic stroke, or other intracranial pathology, recent gastrointestinal bleeding or anaemia due to possible gastrointestinal blood loss, other gastrointestinal pathology associated with increased bleeding risk, liver failure, bleeding diathesis or coagulopathy, extreme old age or frailty, or renal failure with eGFR <15 mL/min/1.73 m^2.

Long-term antithrombotic treatment for asymptomatic lower extremity artery disease

Asymptomatic LEAD, identified by low ankle-brachial index, is at increased risk of MACE and MALE.[78,87] However, two trials failed to show benefit of long-term aspirin in this setting (*Table 2*).[74,75] In the COMPASS trial, among patients included based on CAD, 1422 had also asymptomatic LEAD.[88] In this group, the favourable results of DPI regarding MACE (HR 0.73; 95% CI 0.45–1.18), and MALE (HR 0.74; 95% CI 0.46–1.18) were similar to the whole trial, with no interaction. Nevertheless, the results cannot be extrapolated to patients with asymptomatic LEAD and no associated clinical atherosclerotic disease.

Long-term antithrombotic treatment for symptomatic LEAD

In symptomatic LEAD, antiplatelet drugs improve cardiovascular prognosis (*Table 2*).[12,16,18,76,78,79,87] Current guidelines recommend low-dose aspirin or clopidogrel.[1] In the CAPRIE study, clopidogrel was superior to aspirin in reducing MACE in patients with clinical LEAD (HR 0.74; 95% CI 0.64–0.91).[18] The EUCLID trial enrolled 13 885 patients with symptomatic LEAD and found no difference in MACE between ticagrelor and clopidogrel.[79] In addition, the risk of acute limb ischaemia did not differ between the two groups.[89]

Regarding DAPT, the CHARISMA trial (*Table 2*) showed a non-significant trend for MACE reduction in the subgroup of 3096 LEAD patients under aspirin + clopidogrel vs. aspirin alone.[76]

Vorapaxar was tested on top of aspirin and/or clopidogrel in the TRA2P-TIMI 50 trial.[90] In 20 170 patients with history of myocardial infarction or symptomatic LEAD, a significant 17% risk reduction of

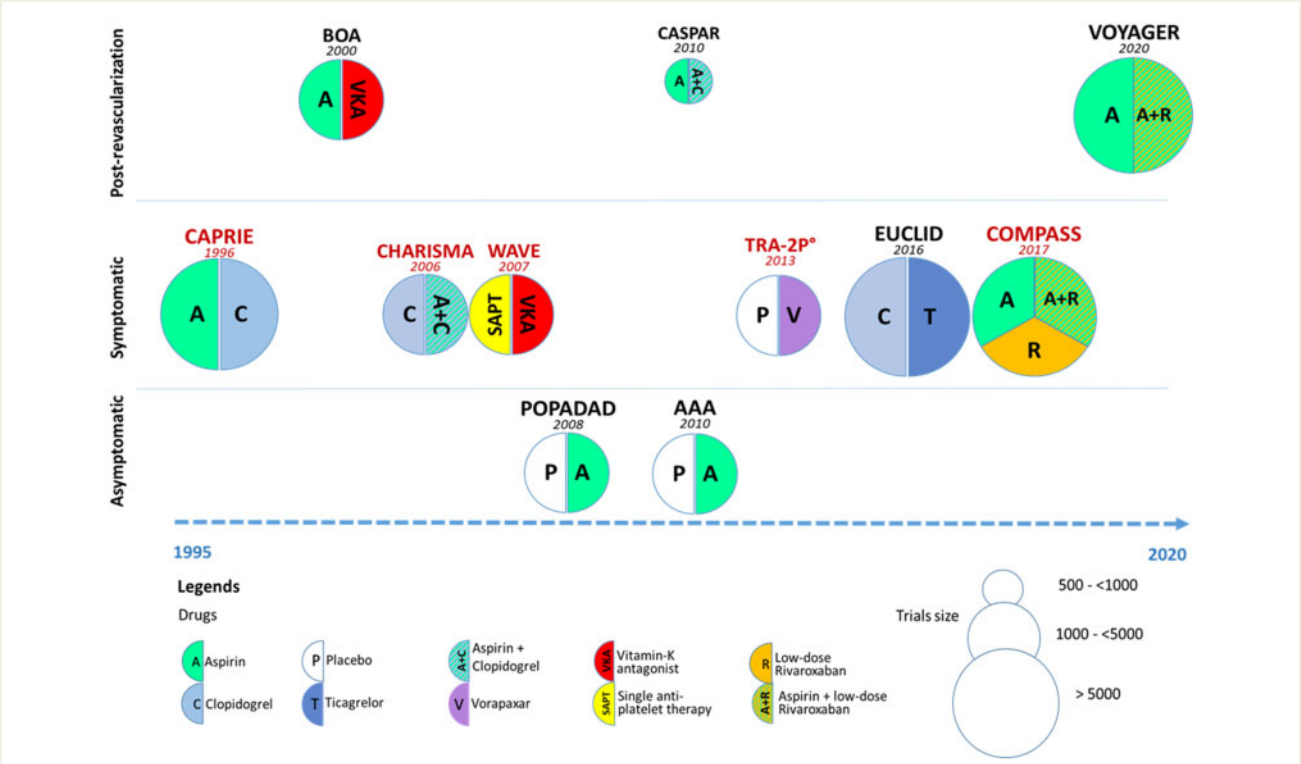


Figure 1 Major trials on antithrombotic therapies in lower-extremities artery disease including >500 patients. Trial title in black: included exclusively patients with lower-extremities artery disease. Trial titles in red: presence of lower-extremities artery disease was an inclusion criteria among others.

MACE was reported, without heterogeneity between the two groups (*Table 2*). In those with LEAD, a significant reduction in ALI and amputation was found under vorapaxar, at the cost of significant excess of major and intracranial bleeding (*Table 2*).[78] This drug is not available in the European market.

The COMPASS trial reported a significant reduction in MACE and MALE under rivaroxaban 2.5 mg bid + aspirin in the overall study population of CAD and/or PAD ($n = 27\,395$),[88] as well as in those with symptomatic LEAD.[16] This combination resulted in an increase in major bleeding (but neither fatal nor intracranial bleeding), but the benefits outweighed the risks, especially in patients with diabetes, renal dysfunction, heart failure, or polyvascular disease.[91,92]

Antithrombotic therapy after surgical bypass procedures

About one-third of lower extremity vein grafts develop conduit and/or anastomotic lesions, threatening their patency. Venous bypass thrombosis occurs mostly within the first year.[93] The risk is greater with smaller calibre conduits, non-saphenous veins, and when anastomosis is infra-popliteal. While antiplatelet agents are commonly used, there is no robust evidence on which antithrombotic strategy is most effective to maintain vein graft patency.[81–83] The CASPAR trial showed no benefit of aspirin + clopidogrel vs. aspirin alone in patients undergoing below knee bypass graft after 1-year follow-up (*Table 2*).[83] Warfarin can be considered in patients at low bleeding risk but with high risk conduits (e.g. poor runoff, or redo procedure) based on a weak evidence for improved patency (Bypass Oral anticoagulants or Aspirin trial) (*Table 2*).[82]

Long-term patency of infra-inguinal prosthetic grafts is lower than venous ones.[93] Subgroup analysis of the CASPAR trial suggested that DAPT confers benefit for prosthetic graft occlusion, revascularization, amputation or death without increasing significantly major bleeding.[83] VKAs did not improve prosthetic graft patency, though they were slightly beneficial in venous conduits.[82,94] A single centre retrospective study suggested that VKAs could be associated with prolonged patency of at risk prosthetic grafts due to poor run off (*Table 2*).[95]

Antithrombotic therapy after endovascular procedures

The choice, dose, and duration of antithrombotic drug therapy in relation to endovascular procedures is unclear. A Cochrane meta-analysis including 3529 patients evaluated antithrombotic drugs for prevention of restenosis or reocclusion.[96] No reduction was found with aspirin plus dipyridamole vs. aspirin plus placebo (OR 0.69; 95% CI 0.44–1.10). DAPT is often used after endovascular procedures with large variability regarding its duration, usually between 1 and

Table 2 Trials on antithrombotic therapy in patients with lower-extremities artery disease

Trial (acronym or 1st author, year)	Type and aim	Comparison	*N*	Setting (indication)	Primary endpoint	Main hypothesis validated?
Long-term AT therapy in asymptomatic LEAD						
POPAPAD, 2008[74]	Multicentre RCT, A in diabetic and asymptomatic LEAD	A_{100mg} vs. placebo	1276	Diabetic pts with ABI <0.99	CV death, non-fatal MI or stroke, or major amputation	No: Efficacy: HR 0.98 (0.76–1.26)
AAA, 2010[75]	Multicentre RCT	A_{100mg} vs. placebo	3350	Asymptomatic with ABI < 0.95	Fatal/nonfatal ACS or stroke or revascularization	No: Efficacy: HR 1.03 (0.84–1.27)
Long-term AT therapy in symptomatic LEAD						
CAPRIE, 1996 (LEAD subgroup)[18]	Multicentre RCT: A vs. C in chronic CVD	C vs. A_{325mg}	19 185 (LEAD: 6452)	Symptomatic LEAD	MACE (MI, stroke, CV death)	Yes: in LEAD: C reduced MACE risk 23.8 % vs. A ($P = 0.01$).
CHARISMA, 2006 (LEAD subgroup)[76]	Multicentre RCT: DAPT in chronic CVD or pts at high risk	$A_{75–162mg}$ + C vs. A + placebo	15 603 (LEAD: 2838)	Symptomatic LEAD	MACE	No; A + C vs A alone: HR 0.85 (0.66–1.08); $P = 0.18$
WAVE, 2007[77]	Multicentre RCT: benefit of Warfarin + A in pts with PAD	APT + warfarin (INR 2–3) vs. SAPT (A or C or ticlopidine)	2161 (LEAD: 1767)	Symptomatic LEAD or carotid or subclavian disease	1° EP: MACE Co-1° EP: MACE + urgent peripheral/coronary revasc	No 1°EP RR 0.92 (0.73–1.16); $P = 0.48$ Co-1°EP RR 0.91 (0.74–1.12; $P = 0.37$
TRA-2°P, 2013 [R] (LEAD subgroup)[78]	Multicentre RCT. Vorapaxar on top of APT in atherosclerosis	Vorapaxar vs. placebo	3787	Symptomatic LEAD	MACE 2nd EP: MALE (ALI, peripheral revasc.)	No for MACE: HR 0.94 (0.78–1.14), Yes for MALE: ALI: HR 0.58 (0.39–0.86); $P = 0.006$ peripheral revasc.: HR 0.84 (0.73–0.97); $P = 0.017$
EUCLID, 2017[79]	Multicentre RCT ticagrelor in LEAD	Ticagrelor vs. clopidogrel	13 887	Symptomatic LEAD	MACE	No: HR = 1.02 (0.92–1.13); P = ns
COMPASS, 2018 (LEAD subgroup)[16]	Multicentre, RCT to compare AT strategies in chronic CAD or PAD	$R_{2.5\,mg\ x2}$ + A_{100mg} vs. $R_{5mg\ x2}$ vs. A_{100mg} alone	27 395 (LEAD: 5551)	History of revasc. or symptomatic PAD or asymptomatic LEAD with CAD	MACE (secondary outcome: MALE)	Yes for overall study. Yes for LEAD: R + A vs. A: HR 0.70 (0.56–0.88), $P = 0.002$
After revascularization						
VOYAGER, 2020[80]	Multicentre RCT: DPI after peripheral revasc.	$R_{2.5\,mg\ bid}$ + A_{100mg} vs. A_{100mg} (± C)	6564 pts with symptomatic LEAD	Symptomatic LEAD with peripheral revascularization (surgery or EVT)	ALI, vascular-related major amputation, MI, ischaemic stroke or CV death	Yes: HR 0.85 (0.76–0.96), $P = 0.009$

Continued

Table 2 *Continued*

Trial (acronym or 1st author, year)	Type and aim	Comparison	*N*	Setting (indication)	Primary endpoint	Main hypothesis validated?
Bypass surgery						
Sarac *et al.*, 1998[81]	Single-centre RCT: effectiveness of OAC with A after bypass	Warfarin vs. Warfarin + A_{325mg}	56 (64 vein bypasses)	CLTI/severe claudication	Graft occlusion	Yes: 3 yrs cumulative primary patency warfarin vs. A 74% vs. 51%; $P = 0.04$.
BOA, 2000[82]	Multicentre RCT to compare OAC vs. A after bypass	Warfarin (INR 3 - 4.5) vs. A_{80mg}	2650	LEAD	Graft occlusion	No: 308 warfarin vs. A HR 0.95 (0.82–1.11); vein grafts: HR 0.69 (0.54–0.88); non-venous grafts: HR 1.26 (1.03–1.55)
CASPAR, 2010[83]	Multicentre RCT: benefit of DAPT after limb bypass	$A_{75–100mg}$ + C vs. A alone	851	LEAD, below the knee venous and prosthetic bypass	Graft occlusion or index bypass revasc. or index leg amputation or death	No: Primary EP: HR 0.98; 0.78–1.23
Endovascular revascularization						
Iida *et al.*, 2008[84]	Single-centre, open RCT comparing 2 post-angioplasty APT strategies	Cilostazol + A_{100mg} vs. Ticlopidine + A	127	Fem-pop EVT	Treated segment patency 2nd EP: TLR	Yes: 24-mo patency: Cilostazol + A: 82% vs. Ticlopidine + A 60%. TLR 82% vs. 70%; $P = 0.0036$
MIRROR, 2012[85]	Single-centre RCT: DAPT in lower limb angioplasty	A_{100mg} + C vs. A alone	80	EVT	Platelet activation markers. 2nd EP: TLR	Yes: Markers were reduced: ß-TG 365,5 vs. 224.5; $P = 0.03$. TLR 6 mts 8/40 vs. 2/40; $P = 0.04$
ePAD, 2018[86]	Multicentre open RCT: edoxaban vs. clopidogrel on top of aspirin after fem-pop EVT	$Edox_{60mg}$ + A_{100mg} vs. + C + A_{100mg}	203	Fem-pop EVT	Restenosis/reocclusion	No: 6-mo restenosis/occlusion: HR 0.89 (0.59–1.34)

A, Aspirin; ACS, acute coronary syndrome; AT, antithrombotic strategy APT, antiplatelet therapy; C, Clopidogrel; CLTI, Chronic limb-threatening ischaemia; CV, cardiovascular; CVD, cardiovascular death; DAPT, dual antithrombotic therapy; Edox, edoxaban; EP, endpoint; EVT, endovascular therapy; Fem-pop, femoro-popliteal; HR, hazard-ratio; LEAD, lower extremity artery disease; MI, myocardial infarction; Mo, months; OAC, oral anticoagulant; Pts, patients; R, rivaroxaban; RCT, randomized clinical trial; Revasc, revascularization; SAPT, single antiplatelet therapy; Yrs, years.

3 months.[97] The ESC guidelines on PAD recommend DAPT (aspirin + clopidogrel) for at least 1 month after infra-inguinal stent implantation.[1] Stenting of infra-popliteal arteries is often followed by a longer DAPT duration, without available evidence.

DAPT duration is primarily based on extrapolation from coronary stenting which might not be adequate: higher residual platelet reactivity in response to adenosine diphosphate and arachidonic acid were found in LEAD vs. CAD patients.[98] Patients undergoing peripheral angioplasty may have a weaker response to aspirin and clopidogrel compared to percutaneous coronary intervention patients.[98] The MIRROR trial randomized 80 patients undergoing femoro-popliteal endovascular intervention in two arms: aspirin vs. DAPT.[85] At 6 months, there was a significant reduction in target lesion revascularization (TLR) in the DAPT group (*Table 2*). The patients received thereafter aspirin alone and the initial difference in TLR was no longer apparent at 12 months. A recent retrospective analysis of 693 patients receiving endovascular revascularization showed that DAPT ≥6 months was an independent predictor of reduced risk for MACE (HR 0.61; 95% CI 0.40–0.93) and MALE (HR 0.55; 95% CI 0.38–0.77), without significant increase in major bleeding.[99] In one RCT, cilostazol plus aspirin improved 3-year vascular patency vs. ticlopidine plus aspirin (*Table 2*).[84] Yet, cilostazol is currently not labelled for antithrombotic properties in Europe.

Dual pathway inhibition after peripheral revascularization

The VOYAGER-PAD trial assessed safety and efficacy of DPI (rivaroxaban 2.5 mg bid + aspirin) vs. aspirin, initiated within 10 days after revascularization, in 6564 patients undergoing surgical or endovascular lower-extremity revascularization (*Table 2*).[80] Additional clopidogrel was allowed at investigators discretion for up to 6 months. Over a median follow-up of 28 months, the primary efficacy endpoint (acute limb ischaemia (ALI), major amputation, myocardial infarction (MI), ischaemic stroke, or cardiovascular death) rate was significantly reduced under DPI vs. aspirin (15.5% vs. 17.8%, $P = 0.009$). Regarding safety, TIMI major bleeding, occurred in 2.65% in the DPI group and in 1.87% in the aspirin group ($P = 0.07$). Projecting the results to a population of 10 000 patients, the DPI strategy would have prevented 181 primary efficacy events at the cost of 29 TIMI major bleeding events per year. Approximately 50% of patients also received clopidogrel in both arms of the trial, mostly after endovascular therapy. The beneficial effect of the DPI was independent of clopidogrel (primary endpoint: HR 0.85; 95% CI 0.71–1.01 with clopidogrel, vs. HR 0.86; 95% CI 0.73–1.01 without clopidogrel). The primary safety outcome did not differ in both situations (HR 1.32; 95% CI 0.78–2.24 with clopidogrel, vs. HR 1.55; 95% CI 0.88–2.73 without clopidogrel). Major bleeding (ISTH criteria) risk was higher when clopidogrel was given for more than 1 month and increasing over time.[100] Since the addition of clopidogrel was not randomized, there are currently no data for a head-to-head comparison between DPI and DAPT (aspirin + clopidogrel) strategies. The latter has been empirically implemented for endovascular therapy and secondarily recommended based on expert opinion, while the former has been validated in the VOYAGER trial.[80] Also, the DPI strategy can be prolonged without any change beyond the post-revascularisation period with proven benefits on MACE and MALE in the COMPASS trial.[16]

Renal and mesenteric arteries

Key messages: Antithrombotic therapies in renal and mesenteric artery diseases

- SAPT is indicated for cardiovascular prevention in patients with atherosclerotic renal or mesenteric artery stenosis.
- DAPT, for at least 1 month, is proposed after renal or mesenteric artery stenting.

Data on antithrombotic therapies in patients who suffer from renal or mesenteric artery atherosclerotic disease are scarce, but their use is reasonable based on the elevated cardiovascular risk in patients with any atherosclerotic disease (see Supplementary material online).[101–105]

Patients with peripheral arterial disease and concomitant indication for oral anticoagulation

Key messages: Antithrombotic strategies in patients with PAD and other indications requiring anticoagulation.

- When full-dose OACs are indicated for other conditions in patients with chronic PAD, the addition of antiplatelet therapy should generally be avoided because of bleeding risk, unless a recent percutaneous revascularization was performed.[106]
- SAPT in addition to OAC may be prescribed in patients at high thrombotic risk, taking the bleeding risk into consideration.

Patients with PAD may have other conditions requiring transient/permanent anticoagulation. Patients with LEAD are at increased risk of AF,[107] an arrhythmia observed in >10% of patients hospitalized for LEAD and associated with increased risk of stroke, amputation and mortality.[108,109] Patients with AF and PAD have per definition a CHA_2DS_2-VASc score ≥1 and so qualify for OAC. Comparing rivaroxaban to warfarin in patients with AF, the ROCKET AF showed similar benefits in terms of primary outcome in those with LEAD, with increased bleeding with rivaroxaban vs. VKA (HR 1.40; 95% CI 1.06–1.86, interaction $P = 0.037$).[110] However, no significant difference in major bleeding was found with rivaroxaban vs. VKA in patients with CAD or LEAD in a retrospective study (HR 1.13; 95% CI 0.84–1.52),[111] as well as with apixaban vs. VKA in the LEAD

Table 3 **Factors associated with increased risk of bleeding in patients with lower-extremities artery disease**

Study	Setting	Bleeding definition	External validation	Predictive variables										
				Age	Female gender	Ethnicity/ global region	Diabetes	HTN or BP	Smoking	Hchol	Heart failure	Bleeding history	Underlying therapies	Others
Studies proposing bleeding scores for patients with LEAD														
REACH registry[118]	68 236 pts with or at risk of atherothrombosis	Non-fatal ICH, bleeding leading to hospitalization and transfusion	Yes	×			×	×	×	×	×		Antithrombotic therapies	
Spiliopoulos *et al.*[119]	530 pts with endovascular therapy for LEAD	Minor and major bleeding	No	×	×			×					DAPT	Obesity, antegrade access
COMPASS trial[121]	27 390 pts with CAD/PAD	ISTH criteria (major)	Yes	×	×	×	×	×	×	×	×	×	Antithrombotic therapies	Polyvascular disease
Other studies														
Cea Soriano *et al.*[122]	28 484 pts with LEAD in UK primary care	ICH	No					×	×			×	Anticoagulant therapy	
		GI bleeding											NSAIDs, antiplatelet therapy	Peptic ulcer disease
EUCLID trial[123]	13 885 pts with symptomatic LEAD	TIMI criteria (major)	No	×		×							Beta-blockers	Rutherford class

BP, blood pressure; CAD, coronary artery disease; DAPT, dual-antiplatelet therapy; GI, gastrointestinal; Hchol, hypercholesterolaemia; HTN, hypertension; ICH, intra-cranial haemorrhage; ISTH, international society on thrombosis and haemostasis; LEAD, lower-extremities artery disease; NSAIDs, non-steroid anti-inflammatory drugs; PAD, peripheral arterial diseases; pts, patients; TIMI, thrombolysis in myocardial infarction.

subgroup of the ARISTOTLE trial (HR 1.05; 95% CI 0.69–1.58).[112] In a nationwide cohort study in Taiwan, lower bleeding rates were reported with non-VKA oral anticoagulants (NOACs) vs. VKA (HR 0.64; 95% CI 0.50–0.80), possibly related to the lower doses used in Chinese patients.[113] In the absence of specific trials in patients with AF and PAD, NOACs remain preferred to VKAs.[114]

There is no solid rationale to add antiplatelet therapy (APT) to OACs in AF patients with PAD. A study including 14 199 hospitalized patients with AF, heart failure and coexisting CAD or PAD showed that adding APT to VKA did not reduce ischaemic events vs. VKA alone, but increased the bleeding risk.[106] In an RCT for CAD patients with AF, the addition of APT on top of OAC in AF patients with CAD did not reduce MACE but increased bleeding.[115] We therefore suggest to avoid routine addition of APT in patients with PAD requiring full dose OACs.

In case of peripheral stenting, evidence on the optimal antithrombotic regimen is lacking. We suggest short–term SAPT in patients receiving full dose OACs. The duration of this combination should be as limited as possible (1 month), depending on the clinical indication and bleeding risk; in case of high bleeding risk, the lowest NOAC dose approved for stroke prevention should be applied.[114] Recently, a meta–analysis of the four RCTs comparing the combination of a NOAC and clopidogrel vs. triple therapy with VKA, aspirin and clopidogrel in patients undergoing coronary stenting showed that dual therapy reduces bleeding by 34%, albeit increasing the stent thrombosis risk by 59%.[116] Notably, major and/or clinically relevant bleeding events were >3 times more frequent than ischaemic events. Extrapolating this evidence to PADs, a condition for which the risk of occlusive stent thrombosis is generally lower, we suggest treating AF patients undergoing peripheral artery stenting with a NOAC plus clopidogrel for 1 month, adding 1-month aspirin (i.e. triple therapy) only in selected cases at highest risk of stent thrombosis (e.g. previous stent thrombosis, severe slow flow at the end of intervention). Conversely, if bleeding risk is high, OAC alone should be prescribed.

Bleeding risk in patients with PAD

Bleeding risk evaluation is necessary before antithrombotic therapies initiation. Patients with PAD are generally at higher risk of bleeding as compared to average CAD patients.[117,118] although data on the bleeding risk in patients with PAD are limited. Scores such as HAS-BLED showed poor prognostic performances in these patients.[119] Recently the Academic Research Consortium High Bleeding Risk (ARC-HBR) score has been validated as a bleeding prediction tool in CAD patients undergoing percutaneous coronary intervention,[120] but not yet assessed in PADs. Few attempts have been made to propose bleeding risk scores for PAD patients, summarized in *Table 3*.[118,119,121–123] Only one study assessed the interest of proton pump inhibitors to reduce gastrointestinal bleeding in patients with PAD: the COMPASS trial found no significant decrease in upper gastrointestinal events as a composite primary endpoint (HR 0.88; 95% CI 0.67–1.15), but showed reduction in bleeding secondary to gastrointestinal lesions under pantoprazole as a secondary endpoint (HR 0.52; 95% CI 0.28–0.94).[124]

Conclusions

Over the last few years, several trials have led to a substantial progress in knowledge on antithrombotic therapy in PAD patients. The *Graphical abstract* summarizes schematically the optimized strategies according to disease localization. Nevertheless, complex situations with questionable ischaemic/bleeding risk ratio should be discussed case by case in a multidisciplinary team, taking patient's preferences into consideration. Since ischaemic and bleeding risks do change over time in an individual patient, regular reassessment of the antithrombotic choices remains of paramount importance.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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