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SPECIAL ARTICLE
Thrombosis and antithrombotic treatment

Antithrombotic treatment following revascularization for chronic limb-threatening ischaemia: a scientific statement of the European Society of Cardiology Working Group on Aorta and Peripheral Vascular Diseases and the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy

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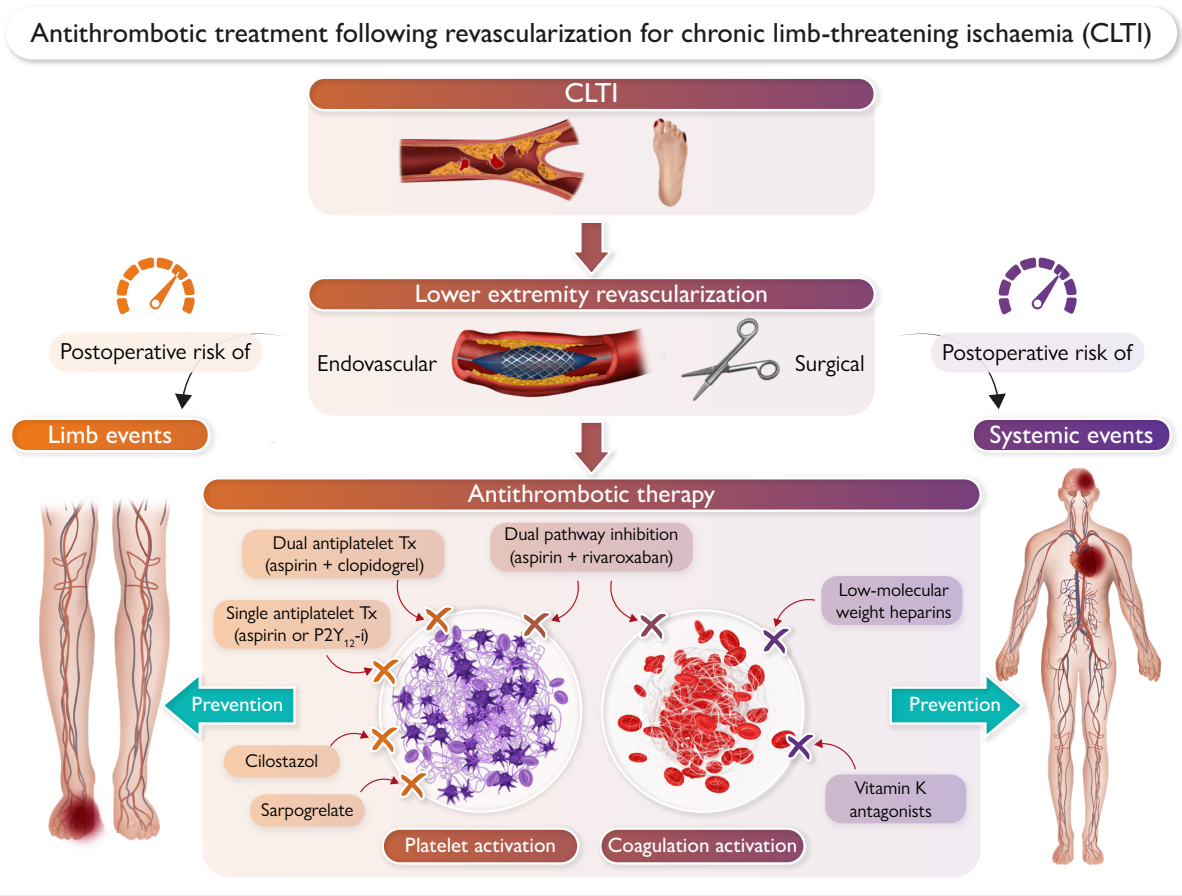
Graphical Abstract



Abstract

Chronic limb-threatening ischaemia (CLTI) is defined as ischaemic rest pain, or non-healing ulceration, requiring endovascular or surgical lower limb revascularization (LLR). Lower limb revascularization in CLTI entails a high risk of major adverse limb events (MALE) and major adverse cardiovascular events (MACE). This scientific statement addresses this risk based on a systematic review. A structured literature search was performed, and articles were independently evaluated by two investigators. In total, 1678 articles were identified, of which 34 were included in the final analysis. Only three randomized controlled trials (RCTs) addressed antithrombotic therapy in CLTI following LLR. None of these demonstrated superiority of any antithrombotic regimen over the other. Eight RCTs investigated antithrombotic therapy following LLR in populations with peripheral arterial disease including CLTI subgroups and suggest a benefit of dual antiplatelet therapy on limb events. One large RCT demonstrated that dual pathway inhibition with aspirin and vascular-dose rivaroxaban reduced the risk of MALE, MACE, and unplanned target limb revascularization. Data from 22 observational studies suggest a benefit of dual antiplatelet therapy on overall survival and amputation-free survival after LLR as compared with single antiplatelet therapy. Intensified antithrombotic treatment should be proposed in patients with CLTI following LLR to reduce the risk of MALE and MACE. Randomized controlled trials on antithrombotic therapy in patients with CLTI following LLR are scarce. Dual pathway inhibition is the only regimen for which an RCT demonstrated a reduction of MALE and MACE following LLR. Dual antiplatelet therapy appears to be associated with a reduced risk of MALE in CLTI following LLR.

Keywords Lower limb revascularization • Chronic limb-threatening ischaemia • Peripheral arterial disease • Vascular surgery • Peripheral percutaneous angioplasty • Stenting • Antithrombotic therapy

Introduction

Chronic limb-threatening ischaemia (CLTI) is the clinically most severe manifestation of peripheral arterial disease (PAD). Chronic limb-threatening ischaemia is defined as a critically low perfusion status of the lower limbs causing ischaemic rest pain, or non-healing ulceration, or gangrene.[1,2] Among patients with PAD, patients with CLTI are at heightened risk of limb loss and suffer an annual risk of amputation of 15%–20%.[3]

In addition to limb loss, patients with CLTI are at high risk of major adverse cardiovascular events (MACE). The risk of MACE associated with CLTI and more generally with PAD can be attributed to the concomitant occurrence of atherosclerotic lesions in the coronary and cerebrovascular circulation.[2] Within the spectrum of patients with PAD, CLTI patients face the highest risk of MACE and all-cause death.[4]

Hence, therapeutic goals in the management of CLTI are dual, aimed at minimizing the risk of both major adverse limb events (MALE) and MACE.[3] For limb salvage, a timely lower limb revascularization (LLR) with either an endovascular or a surgical approach is essential.[1,2] Especially, the early phase after LLR is endangered by a heightened risk of MALE and MACE.[5–7]

Optimization of antithrombotic treatment following LLR may contribute to a reduction in the risk of subsequent ischaemic events.[8] According to recent European Society of Cardiology (ESC) guidelines for the management of peripheral arterial and aortic diseases, the combination of aspirin (100 mg/day) and vascular-dose rivaroxaban (2.5 mg twice daily) should be considered following LLR of patients with PAD without high bleeding risk, while dual antiplatelet therapy (DAPT) is recommended for high-bleeding risk patients for up to 3 months following LLR.[2] Account must be taken of the fact that no CLTI-specific recommendation on antithrombotic treatment following LLR is provided.

The recommendation on dual pathway inhibition (DPI) with aspirin and vascular-dose rivaroxaban is based on the results of a large randomized controlled trial (RCT), the Vascular Outcomes Study of Acetylsalicylic Acid Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for Peripheral Artery Disease (VOYAGER-PAD) trial, which demonstrated a net benefit of DPI (vs aspirin plus placebo) following endovascular or surgical LLR.[9] It warrants mention, however, that the VOYAGER-PAD trial included a mixed population of patients with different clinical manifestations of PAD, in which patients with CLTI were a minority (23%).

The lack of robust evidence deriving from large RCTs specifically addressing antithrombotic therapy in patients with CLTI following LLR has led to considerable differences in antithrombotic treatment regimens in patients with CLTI following LLR across Europe. The great variability in antithrombotic treatment regimens applied for this vulnerable group of patients was captured by a survey performed by the Working Group on Aorta and Peripheral Vascular Diseases of the ESC, conducted in collaboration with various European and national scientific societies.[10]

According to the paucity of data from large RCTs directly investigating antithrombotic strategies in patients with CLTI following LLR, no specific recommendations on antithrombotic regimens are provided by recent ESC guidelines on the management of peripheral arterial and aortic diseases nor by surgical guidelines on antithrombotic therapy for vascular diseases.[2,11]

In this context, and against the background of a potentially increased platelet activation and reduced response to antiplatelet agents in CLTI,[12,13] a scientific statement on antithrombotic therapy, which targets platelet and coagulation pathways to reduce the high risk of MACE and MALE following LLR in patients with CLTI, is needed (*Graphical Abstract*).

The ESC Working Group on Aorta and Peripheral Vascular Diseases and the ESC Working Group on Cardiovascular Pharmacotherapy aimed at compiling a scientific statement on antithrombotic therapy following LLR for CLTI based on a systematic literature review.

Methods

In this systematic review, we adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[14,15] A medical information specialist (Brigitte Wildner, University Library, Medical University Vienna) searched the databases CENTRAL, EMBASE, and MEDLINE on 14 October 2023. A finalizing search to update the initial search results was conducted on 25 March 2024.

The strategy and search terms are provided in the Supplementary data. The following groups of studies were considered eligible for the present review: (i) RCTs directly addressing antithrombotic therapy in patients with CLTI following surgical or endovascular LLR; (ii) RCTs on antithrombotic therapy in mixed populations of patients with PAD undergoing LLR and involving subgroups of patients with CLTI; and (iii) observational studies specifically reporting antithrombotic therapy in patients with CLTI receiving surgical or endovascular LLR.

Two investigators (O.S. and M.D.C.) independently performed the screening of titles and abstracts of all records. If titles and abstracts complied with the predefined inclusion criteria or if titles and abstracts were inconclusive, their respective full texts were retrieved and reviewed. In case of disagreement between the two reviewers, a third reviewer (R.D.C.) was consulted for the decision to include the respective record or not in the analysis. In addition, we also performed a manual search, including trials that were not captured by the structured search.

Results

In total, 1678 records were identified by a structured database search from CENTRAL, EMBASE, and MEDLINE and by an additional manual search (*Figure 1*). After removal of 327 duplicates, 1351 records entered the screening process. The screening of title and abstract led to the exclusion of 1255 articles. The remaining 96 articles underwent a full-text examination, leading to the exclusion of additional 62 articles. Finally, 34 articles reporting the outcomes of 33 studies were included in the final analysis. Of these, three RCTs directly addressed antithrombotic therapy following revascularization for CLTI, eight addressed antithrombotic therapy in mixed PAD patient populations undergoing LLR, including patients with CLTI (of these, two records referred to the same RCT[9,16]), and 22 observational studies focused on antithrombotic therapy in CLTI following LLR (*Figure 2*).

Randomized controlled trials on antithrombotic therapy following revascularization for chronic limb-threatening ischaemia

Three small RCTs specifically addressed antithrombotic therapy in patients with CLTI following surgical (two RCTs) or endovascular (one RCT) LLR (*Table 1*). In total, 445 patients (mean age 72 years, 63% male) were included. In a first RCT, DAPT with aspirin plus clopidogrel did not suggest significant differences compared with single antiplatelet therapy (SAPT) with aspirin and placebo as to the risk of myocardial infarction, in-hospital death, and intracranial haemorrhage in patients undergoing surgical LLR.[18] The rate of blood transfusions was significantly higher in patients on DAPT than in patients on aspirin alone. Conversely,

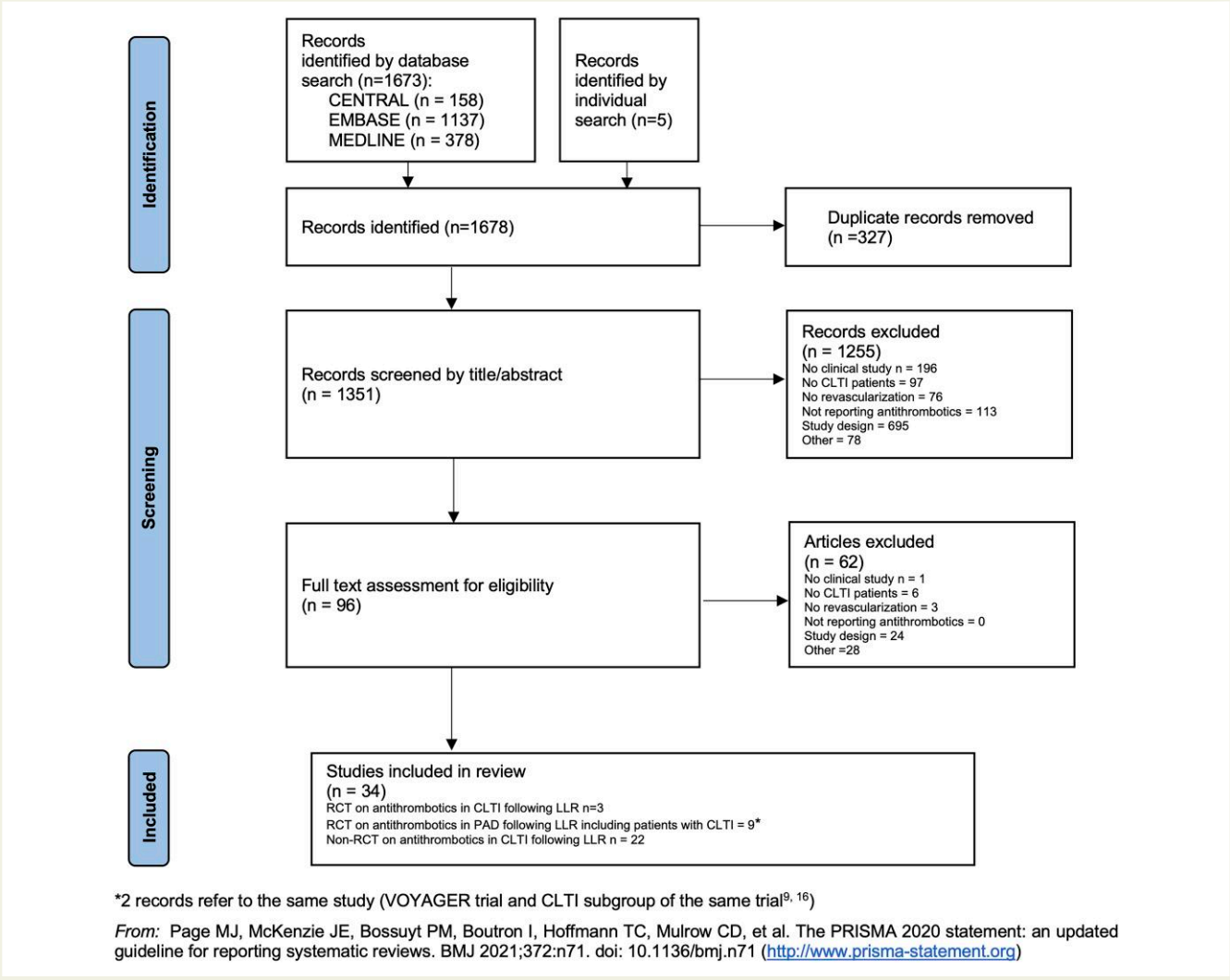


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram depicting the literature search and selection process; modified from Moher *et al*. and Page *et al*.[14,15] CLTI, chronic limb-threatening ischaemia; LLR, lower limb revascularization; PAD, peripheral arterial disease; RCT, randomized controlled trial

biomarkers of platelet activation and of myocardial injury were lower in patients on DAPT than in patients on SAPT. It needs to be noted that the primary outcome of this study was platelet-monocyte aggregation and the number of patient calculation was performed with this purpose.

A second RCT showed that the combination of aspirin with low-molecular-weight heparin (5.000 IU of dalteparin once daily) for 3 months after surgery did not result in improvements of primary graft patency, amputation rates, and cardiovascular mortality after 12 months of follow-up (in comparison with aspirin plus placebo).[19] No differences in bleeding complications were observed between patients receiving aspirin and dalteparin and patients receiving aspirin and placebo injections.

The Cilostazol for Below-the-Knee Artery Disease after Balloon Angioplasty in Patients With Severe Limb Ischemia (CABBAGE) trial compared a combined treatment of aspirin and cilostazol with aspirin monotherapy following below-the-knee angioplasty in patients with CLTI.[17] At the 3-month follow-up, no significant difference between groups was found regarding restenosis and MALE rates, as well as regarding bleeding events.

Summary

No RCT demonstrated any benefit on ischaemic events with intensified antithrombotic regimens compared with aspirin monotherapy in patients with CLTI undergoing surgical or endovascular LLR. A greater need of blood transfusions was suggested in patients with CLTI receiving DAPT (vs SAPT) after surgical LLR.

Randomized controlled trials on antithrombotic therapy following revascularization for peripheral arterial disease (combining patients with and without chronic limb-threatening ischaemia)

In eight RCTs, antithrombotic therapy was assessed after surgical or endovascular LLR in broader patient populations with PAD, combining claudicants with patients suffering from CLTI (*Table 2*). These trials (three on surgical LLR, four on endovascular LLR, and one on

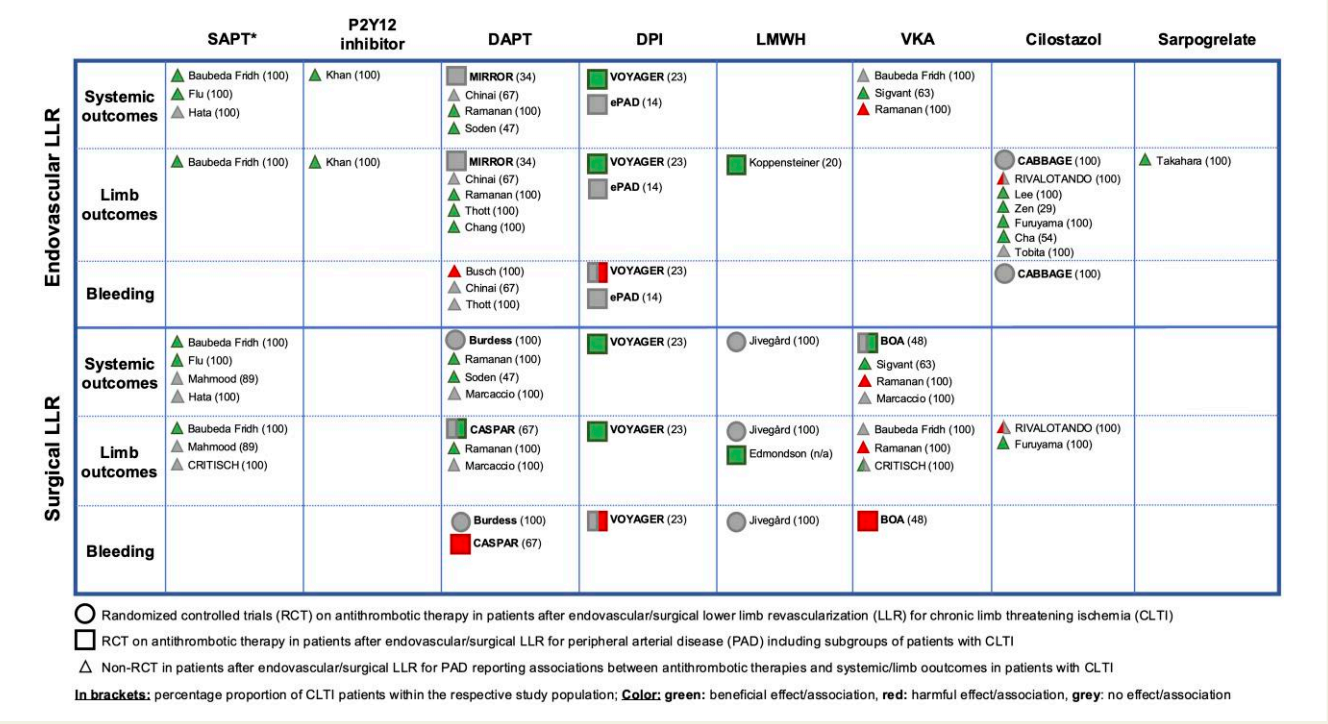


Figure 2 Population, design, and results of the studies included in the present review. DAPT, dual antiplatelet therapy; DPI, dual pathway inhibition; LMWH, low-molecular weight heparin(s); LLR, lower limb revascularization; SAPT, single antiplatelet therapy; VKA, vitamin K antagonists

both) comprised data on 10 903 patients. Of these RCTs, three specifically report data on the respective subgroups of patients with CLTI.[16,22,24]

Dual antiplatelet therapy vs single antiplatelet therapy

Following surgical LLR, there was no benefit of DAPT (aspirin plus clopidogrel) in comparison with aspirin plus placebo on the occurrence of a combined endpoint of graft occlusion, graft revascularization or replacement, amputation, and death [hazard ratio (HR) 0.98, 95% confidence interval (CI) 0.78–1.23].[25] A benefit of DAPT vs aspirin plus placebo was only found in the subgroup of patients with infrapopliteal prosthetic bypass grafts (HR 0.65, 95% CI 0.45–0.95, $P = .025$), while no benefit was found in patients with venous grafts (HR 1.25, 95% CI 0.95–1.67). In addition, among patients with venous grafts, DAPT (vs aspirin plus placebo) was associated with a higher incidence of mild and moderate bleeding events (mild bleeding: 12.1% with DAPT vs 5.4% with aspirin plus placebo, $P = .004$; moderate bleeding: 3.7% with DAPT vs 0.7% with aspirin, $P = .004$), while no significant difference was observed among prosthetic graft recipients. No CLTI-specific findings are reported in this trial.

No RCT compared DAPT with SAPT in patients with CLTI undergoing endovascular LLR. In a mixed PAD population (34% of patients with CLTI), one small RCT reported that DAPT with aspirin and clopidogrel for 6 months was associated with lower target lesion revascularization rates as compared with aspirin monotherapy (2% vs 8%, $P = .04$) and higher levels of platelet inhibition, although 30% of patients were found to be clopidogrel resistant.[27] However, no sustained benefit of DAPT was observed at 1 year of follow-up.[20] Data on the CLTI subgroup were not reported in this trial.

Ticagrelor vs clopidogrel

One RCT compared two DAPT regimens in a mixed PAD population (55% of patients with CLTI) undergoing femoropopliteal drug-eluting stent implantation with stent obstruction evaluated by intravascular imaging by means of frequency-domain optical coherence tomography. The association of aspirin and ticagrelor showed no significant differences compared with aspirin and clopidogrel on in-stent restenosis (assessed as net percentage volume obstruction) and stent re-endothelialization (assessed as percentage of uncovered stent struts).[21] Ticagrelor use was associated with greater inhibition of platelet reactivity as compared with clopidogrel 3 months after LLR. Neither clinical outcomes nor data on the CLTI population were specifically reported.

Anticoagulants vs antiplatelet regimens

In one RCT, the use of low-molecular-weight heparin (dalteparin) vs aspirin plus dipyridamole after surgical LLR resulted in higher graft patency in the subgroup of patients with CLTI. Here, however, the proportion of CLTI among the entire population patients was not provided.[24]

In a comparably larger RCT (2690 patients with PAD), oral anticoagulation with vitamin K antagonists [target international normalized ratio (INR) 3.0–4.5] did not result in fewer graft occlusions compared with aspirin after surgical LLR (HR 0.95; 95% CI 0.82–1.11).[26] A benefit of vitamin K antagonists on graft patency was, however, observed among patients with vein grafts (HR 0.69; 95% CI 0.54–0.88), while a detrimental effect was observed among non-venous graft recipients (HR 1.26; 95% CI 1.03–1.55). Importantly, vitamin K antagonists doubled the risk of major bleeding in the overall population, even excluding

Table 1 Randomized controlled trials on antithrombotic therapy in patients after lower limb revascularization for chronic limb-threatening ischaemia

Study	Number of CLTI/PAD patients *N/N* (%[a])	Comparator arm	Experimental arm	Follow-up duration	Endpoints	Limb outcomes	Systemic outcomes
Endovascular LLR							
CABBAGE[17]	53/53 (100)	Aspirin	Aspirin + cilostazol	3 months	Primary patency, MALE, bleeding	Cilostazol: No difference in primary patency No difference in MALE	Cilostazol: No difference in all bleeding
Surgical LLR							
Burdess *et al.*[18]	108/108 (100)	Aspirin + placebo	DAPT	3 days	Markers of myocardial injury and platelet activation (plasma troponin concentration, platelet-monocyte aggregation, platelet P-selectin expression), bleeding events (major life-threatening bleeding, major non-life-threatening bleeding, minor bleeding) up to 2 days following surgery	Not reported.	DAPT: Lower markers of platelet activation and myocardial injury (platelet monocyte aggregates $P = .0019$, platelet p-selectin $P = .0035$, plasma troponin $P < .001$)[b] No difference in periprocedural myocardial infarction. No difference in bleeding Increase in blood transfusions (RR 2.3; $P = .04$)
Jivegård *et al.*[19]	284/284 (100)	Aspirin + placebo	Aspirin + dalteparin	12 months	Primary graft patency, healing from ulcerations, patients' acceptability of injections, late graft failure, myocardial infection, stroke, re-procedures, death	Dalteparin: No difference primary graft patency	Dalteparin: No difference in ischaemic adverse events No difference in all bleeding.

DAPT, dual antiplatelet therapy; LLR, lower limb revascularization; MALE, major adverse limb events; PTA, percutaneous transluminal angioplasty; RR, relative risk.
[a]Percentage proportion of patients with CLTI.
[b]The primary outcome of this study was platelet-monocyte aggregation and the number of patient calculation was performed in this purpose.

Table 2 Randomized controlled trials on antithrombotic therapy in patients after lower limb revascularization for peripheral arterial disease including subgroups of patients with chronic limb-threatening ischaemia

Study	Number of CLTI/PAD patients *N/N* (%[a])	Comparator arm	Experimental arm	Follow-up duration	Endpoints	Limb outcomes	Systemic outcomes
Endovascular LLR							
MIRROR[20]	27/80 (34)	Aspirin + placebo	DAPT	12 months	Primary endpoint: Platelet activation markers and rate of clopidogrel resistance Secondary endpoint: Target lesion revascularization, restenosis	DAPT: No benefit on target lesion revascularization or restenosis No CLTI-specific results provided	DAPT: No benefit on mortality No CLTI-specific results provided
Ducci *et al.*[21]	22/40 (55)	DAPT	Aspirin + ticagrelor	12 months	Neointimal proliferation and platelet reactivity	Ticagrelor: No difference in neointimal proliferation No CLTI-specific results provided	Ticagrelor: Lower platelet reactivity (lower platelet reactive units $P < .001$) No CLTI-specific results provided
Koppensteiner *et al.*[22]	56/275 (20)	Aspirin	Aspirin + dalteparin (3 months)	12 months	Occurrence of restenosis	Dalteparin: Lower restenosis rate (CLTI subgroup: $P = .01$)	Not reported
ePAD[23]	29/203 (14)	DAPT	DPI (Aspirin + edoxaban 60 mg od)	6 months	Primary endpoint: Bleeding (TIMI and ISTH criteria) Secondary endpoint: Restenosis or reocclusion	DPI: No benefit on restenosis/reocclusion at 6 months (RR 0.89, 95% CI 0.59–1.34). No benefit on the composite of restenosis/reocclusion and target lesion revascularization at 6 months (RR 0.82, 95% CI 0.53–1.18). No benefit on the composite of restenosis/reocclusion, target lesion revascularization and amputation at 6 months (RR 0.82, 95% CI 0.56–1.18) No CLTI-specific results provided	DPI: No difference in clinically relevant non-major bleeding (ISTH, RR 1.39, 95% CI 0.58–3.31) No difference in major/life-threatening bleeding (RR 0.20, 95% CI 0.02–1.70) No difference in the composite of MACE, restenosis/reocclusion, target lesion revascularization and amputation at 6 months (RR 0.80, 95% CI 0.55–1.15) No CLTI-specific results provided
Surgical LLR							
Edmondson *et al.*[24]	200/Proportion of CLTI patients not reported	Aspirin + dipyridamole	Dalteparin	12 months	Bypass graft patency	Dalteparin: Higher graft patency after salvage surgery (CLTI subgroup with salvage surgery: 1-year graft patency 78% vs 64%, $P = .0006$)	Not reported
CASPAR[25]	567/851 (67)	Aspirin + placebo	DAPT	24 months	Primary endpoint: Composite of graft occlusion, surgical or endovascular LLR, above the ankle amputation, death Secondary endpoint: individual occurrence of graft occlusion, surgical or endovascular LLR, above the ankle amputation, death, myocardial infarction, or stroke Safety endpoint: GUSTO bleeding events	DAPT: Benefit on primary composite end-point in subgroup of patients with prosthetic bypass ($P = .025$) Benefit on amputations in subgroup of patients with prosthetic bypass ($P = .034$) No benefit on primary composite endpoint in the whole population No CLTI-specific results provided	DAPT: More GUSTO bleeding in subgroup of patients with venous bypass ($P < .001$) No CLTI-specific results provided

Continued

Table 2 *Continued*

Study	Number of CLTI/PAD patients *N/N* (%[a])	Comparator arm	Experimental arm	Follow-up duration	Endpoints	Limb outcomes	Systemic outcomes
BOA[26]	1295/2690 (48)	Aspirin	VKA (phenprocoumon or acenocoumarol, INR target 3.0–4.5)	12 months	Primary endpoint: graft occlusion Secondary endpoint: composite of vascular death, non-fatal myocardial infarction, non-fatal stroke, amputation; individual occurrence of death from any cause, death from vascular causes, myocardial infection, stroke, major amputation, vascular intervention, major hemorrhage	VKA: Benefit on risk of venous graft occlusions (HR 0.69, 95% CI 0.54–0.88) No benefit on total graft occlusions No CLTI-specific results provided	VKA: More bleeding (4.7% vs 2.5%)
Endovascular or surgical LLR							
VOYAGER[9] (CLTI subgroup[16])[b]	1533/6564 (23)	Aspirin + placebo	DPI (aspirin + rivaroxaban 2.5 mg bid)	36 months	Primary endpoint: Composite of acute limb ischaemia, major amputation, myocardial infarction, stroke, cardiovascular death Secondary endpoint: Acute limb ischaemia, amputation, myocardial infarction, stroke, coronary heart disease death; unplanned index limb revascularization for recurrent limb ischaemia; hospitalization for peripheral or coronary event; cardiovascular death; all-cause mortality, venous thromboembolism Safety endpoint: TIMI major bleeding, ISTH major bleeding, BARC major bleeding	DPI: Benefit on acute limb ischaemia, major amputation for vascular cause, myocardial infarction, stroke from any cause, death from any cause (HR 0.86, 95% CI 0.76–0.96, $P = .01$) Benefit on acute limb ischaemia, major amputation for vascular cause, myocardial infarction, ischaemic stroke, death from any cause (HR 0.89, 95% CI 0.79–0.99, $P = .03$) Benefit on secondary endpoint (HR 0.80, 95% CI 0.71–0.91, $P < .001$) Benefit on unplanned index-limb revascularizations (HR 0.88, 95% CI 0.79–0.99, $P = .03$) CLTI-specific results: DPI: Benefit on unplanned index limb revascularization after endovascular LLR (HR 0.79, 95% CI 0.56–1.00, $P = .049$) No benefit on unplanned index limb revascularization after surgical LLR (HR 0.83, 95% CI 0.55–1.25, $P = .37$)	DPI: Benefit on primary endpoint (HR 0.85, 95% CI 0.76–0.96, $P = .009$) Benefit on hospitalization for coronary or peripheral thrombotic event (HR 0.72, 95% CI 0.62–0.85, $P < .001$) More ISTH major bleeding (HR 1.42, 95% CI 1.10–1.84, $P = .007$) No difference in TIMI or BARC major bleeding events

CI, confidence interval; CLTI, chronic limb-threatening ischaemia; DAPT, dual antiplatelet therapy (aspirin + clopidogrel); DPI, dual pathway inhibition; EP, endpoint; HR, hazard ratio; INR, international normalized ratio; LLR, lower limb revascularization; MALE, major adverse limb events; PAD, peripheral arterial disease; PTA, percutaneous transluminal angioplasty; RR, relative risk; VKA, vitamin K antagonists.

[a]Percentage proportion of patients with CLTI.

[b]Two publications (one publication comprising results of CLTI subgroup; two records in PRISMA flow chart; *Figure 1*).

postoperative haemorrhage (HR 1.96; 95% CI 1.42–2.71). While 48% of participants had CLTI, no specific results were reported in this subgroup.

Dual pathway inhibition vs dual/single antiplatelet therapy

In a first small RCT, the combination of edoxaban with aspirin was compared with DAPT for 3 months in 203 patients with PAD (14% patients with CLTI) following LLR.[23] The primary endpoint (bleeding rates) did not differ between both groups, nor was there a between-group difference in secondary endpoints (freedom from a composite of restenosis, reocclusion, target lesion revascularization, amputation, and MACE).[23]

The first large-scale RCT on DPI, the VOYAGER-PAD trial, compared the combination of aspirin and vascular-dose rivaroxaban with aspirin alone after surgical or endovascular LLR.[9] In this trial, comprising 23% of patients with CLTI, DPI use was associated with a reduction in the composite endpoint of acute limb ischaemia, major amputation for vascular causes, myocardial infarction, ischaemic stroke, or death from cardiovascular causes (HR 0.85, 95% CI 0.76–0.96) in comparison with patients receiving aspirin plus placebo, which was primarily attributed to a reduction of acute limb ischaemia (HR 0.67, 95% CI 0.55–0.82).

A *post hoc* analysis of the CLTI subgroup showed a lower rate of unplanned index limb revascularization in patients receiving DPI (vs aspirin plus placebo) after endovascular LLR (HR 0.75, 95% CI 0.56–1.00, $P = .049$), but not after surgical LLR (HR 0.83, 95% CI 0.55–1.25).[16]

Importantly, DPI was associated with more major bleeding events than aspirin plus placebo, but with no increase in fatal or intracranial bleeding. Concomitant use of clopidogrel after endovascular revascularization was here limited to <30 days, due to increased rates of major bleeding events with longer durations.[28] No heterogeneity was observed on bleeding risk between endovascular and surgical revascularization.[29]

Summary

In RCTs combining patients with and without CLTI, DPI with aspirin and vascular-dose rivaroxaban appears to be the strategy with the highest potential of a net benefit after surgical and endovascular LLR. After surgical LLR, DAPT is not superior over SAPT in preventing graft occlusion, graft revascularization or replacement, amputation, and death. In infrapopliteal prosthetic bypass grafts, DAPT may be beneficial on graft patency and amputation rates. In venous bypass grafts, vitamin K antagonists (target INR 3.0–4.5) result in higher graft patency (in comparison with aspirin), but increase the risk of bleeding.

Observational studies on antithrombotic therapy following revascularization for chronic limb-threatening ischaemia

Aspirin vs no aspirin

Several observational studies addressed the use of aspirin following LLR for CLTI (*Table 3*). In a cohort of 10 617 CLTI patients undergoing endovascular or surgical LLR (mean age 76.8 years, 51% female), the use of aspirin was associated with a lower risk of amputation (HR 0.77, 95% CI 0.69–0.87, $P < .001$) and of the combined endpoint of amputation or death (0.69, 95% CI 0.65–0.73, $P < .001$), as compared with no antiplatelet therapy.[43] Two smaller studies (in total 207 patients) on aspirin use in CLTI patients after endovascular and surgical LLR suggested an association of aspirin with fewer cardiac adverse events, while no association was observed between aspirin and graft failure or vascular death after surgical revascularization.[39,41] Importantly, at longer-term follow-up (10 years), the prescription of antiplatelet therapy after surgical or endovascular LLR did not appear to be an independent predictor of overall mortality.[42] Accordingly, a study on a mixed population of 18 742 lower extremity artery disease patients undergoing endovascular or surgical LLR (63% of patients suffering from CLTI, with a mean age of 77 years, 51% being female) reported that the use of aspirin did not affect the composite endpoint of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death.[47]

Dual antiplatelet therapy vs single antiplatelet therapy

A prospective single-centre study assessed the pharmacodynamic response to DAPT with aspirin plus clopidogrel in patients with CLTI (mean age 73 years, 38% female) and demonstrated a high prevalence of high-on-treatment platelet reactivity following endovascular LLR.[13] While the occurrence of MALE and MACE did not differ between patients with CLTI with and without high-on-treatment platelet reactivity, the risk of bleeding was lower in patients with high-on-treatment platelet reactivity.

Comparing DAPT with SAPT after endovascular LLR for CLTI, no difference was observed with respect to the risk of amputation, survival, or bleeding in a retrospective study on 625 patients with CLTI (mean age 70 years, 37% female).[30]

Several outcome analyses derive from the database of the Vascular Quality Initiative of the US Society of Vascular Surgery: two retrospective analyses consistently demonstrated higher survival rates in patients on DAPT as compared with patients receiving SAPT following endovascular LLR.[45,46] The first analysis included only patients with CLTI ($n = 50\,890$, mean age 68 years, 41% female). Here, DAPT was associated with improved overall survival and improved amputation-free survival after surgical and endovascular LLR, while it was not related to major amputation after LLR.[46] In the second analysis of the Vascular Quality Initiative included a mixed population of PAD patients (claudication and CLTI). Here, 57 041 patients undergoing LLR (28% bypass) were included. Of 15 985 bypasses (69% for critical limb ischaemia), the survival benefit of patients receiving DAPT was only observed in the CLTI subgroup.[45]

Analysing different components of medical management in other 11 466 CLTI patients undergoing LLR (mean age 68 years, 43% female), it was concluded that DAPT is independently associated with limb salvage (HR 0.81, 95% CI 0.77–0.86).[32]

Dual antiplatelet therapy was also associated with a lower risk of amputation (HR 0.56, 95% CI 0.36–0.86) without increased risk of bleeding (HR 1.08, 95% CI 0.79–1.47) among 1941 patients with diabetes and CLTI (median age 79 years, 58% female) undergoing femoropopliteal stent implantation.[31] Regarding DAPT duration, no differences were observed between patients receiving DAPT for <100 days and patients on DAPT for longer time.

Three antiplatelet strategies, i.e. aspirin monotherapy, $P2Y_{12}$-inhibitor monotherapy, and DAPT, were compared in another analysis of the US Vascular Quality Initiative involving 11 503 patients with CLTI (mean age 68 years, 43% female) undergoing endovascular LLR.[33] In comparison with aspirin, $P2Y_{12}$-inhibitor monotherapy was associated with higher 3-year overall survival rates (HR 0.82, 95% CI 0.68–0.98, $P = .03$), amputation-free survival (HR 0.75, 95% CI 0.65–0.86, $P < .001$), and limb salvage (HR 0.74, 95% CI 0.60–0.91, $P = .004$). No difference was found between $P2Y_{12}$-inhibitor monotherapy and DAPT with respect to 3-year overall survival (HR 0.94, 95% CI 0.77–1.14), amputation-free survival rates (HR 0.92, 95% CI 0.78–1.07), and limb salvage rates (HR 0.80, 95% CI 0.64–1.00, $P = .06$).

Dual antiplatelet therapy was compared with SAPT after surgical LLR among 1812 patients with CLTI (mean age 71 years, 30% female) receiving infrapopliteal bypass grafts: no difference was found between groups in terms of MALE, mortality, major amputation, or reintervention rates.[40]

Table 3 Observational studies in patients after lower limb revascularization for peripheral arterial disease involving patients with chronic limb-threatening ischaemia

Study	Number of CLTI/ PAD patients *N/N* (%[a])	Objective	Follow-up duration	Antithrombotic strategy	Limb outcomes	Systemic outcomes
Endovascular LLR						
Busch *et al.*[13]	71/71 (100)	High on treatment platelet reactivity in CLTI patients on DAPT and its impact at 6 months on MALE and major adverse cardiac and cerebrovascular events	6 months	DAPT	DAPT: Prevalence of high on treatment platelet reactivity in CLTI patients on DAPT after LLR 64.8% No high on treatment platelet reactivity effect on MALE and major adverse cardiac and cerebrovascular events	DAPT: Related to higher bleeding rate in patients on DAPT and high on treatment platelet reactivity (HR 0.32, 95% CI 0.1079–0.9396, $P = .0217$)
Chinai *et al.*[30]	-/625 (67[a])	Impact of DAPT vs SAPT on amputation-free survival	29 months	DAPT	DAPT: Not related to amputation-free survival (OR 0.8, 95% CI 0.5–1.2, $P = .3$)	DAPT: Not related to survival ($P = .9$) Not related to major bleeding ($P = .1$)
Thott *et al.*[31]	1941/1941 (100)	Effect of DAPT vs SAPT on amputation and bleeding rates in diabetic patients with CLTI following LLR	24 months	DAPT	DAPT: Lower risk of amputation after endovascular LLR (HR 0.56, 95% CI 0.36–0.86)	DAPT: Not related to risk of bleeding
Chang *et al.*[32]	11 466/11 466 (100)	Effect of optimal medical therapy (and DAPT) on overall survival, amputation-free survival, and limb salvage following LLR	24 months	DAPT	DAPT: related to improved amputation free survival (HR 0.86, 95% CI 0.82–0.90, $P < .001$) and improved limb salvage after endovascular LLR (HR 0.81, 95% CI 0.77–0.86, $P < .007$)	Not reported
Khan *et al.*[33]	11 503/11 503 (100)	Impact of aspirin vs P2Y12 inhibitor monotherapy vs DAPT on amputation-free survival and overall survival	3.8 years	P2Y12 monotherapy or DAPT	P2Y12 monotherapy vs aspirin: Related to limb salvage (HR 0.74, 95% CI 0.60–0.9, $P = .004$). Related to improved amputation free survival (HR 0.75, 95% CI 0.65–0.86, $P < .001$). P2Y12 monotherapy vs DAPT: Not related to in limb salvage. Not related to amputation free survival.	P2Y12 monotherapy vs aspirin: Related to improved overall survival (HR 0.82, 95% CI 0.68–0.98, $P = .03$) P2Y12 monotherapy vs DAPT: Not related to overall survival
Lee *et al.*[34]	172 172/ (100)	Association of cilostazol with patency and clinical outcomes after LLR	24 months	SAPT or DAPT ± cilostazol	Cilostazol: related to improved primary patency (HR 0.2, 95% CI 0.11–0.26, $P < .001$)	Not reported
Zen *et al.*[35]	137/475 (29)	Effect of Cilostazol on patency after femoropopliteal drug eluting stent implantation	12 months	SAPT or DAPT ± cilostazol	Cilostazol: related to lower restenosis rates (OR 0.5, 95% CI 0.3–0.8, $P = .008$) Not related to MALE	Not reported
Cha *et al.*[36]	536/990 (54)	Effect of Cilostazol on MALE after endovascular LLR	24 months	Cilostazol + DAPT	Cilostazol + DAPT: related to lower incidence of MALE in CLTI subgroup (17.5% vs 25.7%, $P = .056$)	Not reported
Tobita *et al.*[37]	28/231 (12)	Effect of cilostazol on restenosis after endovascular LLR	12 months	Cilostazol	Cilostazol: Not related to risk of restenosis after LLR in CLTI subgroup (OR 0.00, 95% CI 0.00-inf, $P > .99$)	Not reported
Takahara *et al.*[38]	386/386 (100)	Effect of sarpogrelate on clinical outcomes after endovascular LLR	21 months	Sarpogrelate	Sarpogrelate: related to improved amputation-free survival (HR 0.57, 95% CI 0.34–0.97, $P = .036$)	Not reported
Surgical LLR						
Mahmood *et al.*[39]	101/113 (89)	Efficacy of aspirin in maintaining bypass graft patency	24 months	Aspirin		Not reported

Continued

Table 3 *Continued*

Study	Number of CLTI/PAD patients *N/N* (%[a])	Objective	Follow-up duration	Antithrombotic strategy	Limb outcomes	Systemic outcomes
					Aspirin: No association between aspirin use and graft failure or vascular death	
Marcaccio *et al.*[40]	1812/1812 (100)	Effect of different antithrombotic regimes on clinical outcomes and infrapopliteal bypass patency	36 months	SAPT, DAPT, or AC + AP	DAPT vs SAPT: Not related to MALE. Not related to major amputation. Not related to re-intervention AC and AP vs SAPT: Not related to MALE Not related to major amputation Not related to re-intervention	DAPT vs SAPT: Not related to mortality AC and AP vs SAPT: Not related to mortality
Endovascular or surgical LLR						
Flu *et al.*[41]	106/106 (100)	Factors influencing morbidity and mortality after LLR	30 days	AP	Not reported	AP: Related to lower rate of cardiac adverse events (53% vs 88%, $P < .0001$)
Hata *et al.*[42]	459 (100)	Factors influencing mortality after LLR	10 years	AP	Not reported.	AP: No association to mortality (73.1% vs 74.9%, $P = .62$).
Baubeta Fridh *et al.*[43]	10 617/10 617 (100)	Factors influencing risk of amputation and mortality after LLR	2.7 years	Aspirin or AC	Aspirin: Related to lower risk of amputation (HR 0.77, 95% CI 0.69–0.87, $P < .001$) AC: Not related to risk of amputation (HR 1.02, 95% CI 0.86–1.20, $P = .849$)	Aspirin: Related to lower risk of combined EP (amputation or death) (HR 0.69, 95% CI 0.65–0.73, $P < .001$) AC: Related to lower risk of combined EP (amputation or death) (HR 0.90, 95% CI 0.81–0.99, $P = .024$)
CRITISCH[44]	1200/1200 (100)	Factors influencing clinical outcomes after LLR for CLTI	12 months	SAPT, DAPT, or AC	AC: related to improved amputation-free survival after surgical LLR with bypass (HR 0.52, 95% CI 0.30–0.92, $P = .025$) Not related to amputation-free survival after surgical LLR with patchplasty (HR 0.39, 95% CI 0.14–1.13, $P = .084$) AP: Not related to amputation-free survival after surgical LLR with bypass (HR 0.58, 95% CI 0.32–1.03, $P = .062$)	Not reported
Soden *et al.*[45]	27 042/57 041 (47)	Effect of different antithrombotic regimes on survival	60 months	DAPT	Not reported	DAPT: Related to improved survival after surgical LLR for CLTI (DAPT vs SAPT HR 0.86, 95% CI 0.78–0.95, $P = .003$) Related to improved survival after endovascular LLR for CLTI (DAPT vs SAPT HR 0.89, 95% CI 0.82–0.96, $P = .004$)
Ramanan *et al.*[46]	50 890/50 890 (100)	Effect of different antithrombotic regimes on postoperative major amputation at 30 days and 1 year. Secondary outcomes: survival at 30 days and 1 year, amputation free survival at 30 days and 1 year, target legion reintervention at 1 year, and target thrombosis at 1 year.	12 months	DAPT or AC	DAPT: Related to reduced 30-day major amputation after endovascular LLR ($P = .002$) Related to improved 30-day amputation-free survival after endovascular LLR ($P < .0001$) Related to improved 1-year amputation-free survival after surgical and endovascular LLR	DAPT: Related to reduced 30-day mortality after endovascular LLR ($P < .0001$) Related to reduced 1-year mortality after surgical and endovascular LLR (both $P < .0001$)

Continued

Table 3 *Continued*

Study	Number of CLTI/ PAD patients *N/N* (%[a])	Objective	Follow-up duration	Antithrombotic strategy	Limb outcomes	Systemic outcomes
					(both $P < .0001$) Related to reduced 1-year target lesion reinterventions after endovascular LLR ($P = .04$) Not related to 30-day amputation-free survival after surgical LLR Not related to 30-day major amputation rates after surgical LLR Not related to 1-year major amputation rates after surgical and endovascular LLR Not related to 1-year major amputation rates after surgical and endovascular LLR Not related to 30-days target lesion reinterventions after endovascular LLR Not related to 30-days and 1-year target thrombosis after surgical LLR	Not related to 30-day mortality after surgical LLR AC: Related to lower 1-year survival after surgical ($P = .03$) and endovascular ($P < .0001$) LLR Related to increased risk of 1-year major amputation after surgical LLR ($P < .0001$) Not related to increased risk of 1-year major amputation after endovascular LLR ($P = .1566$)
Sigvant *et al.*[47]	11 783/18 742 (63)	Effect of medical treatment on clinical outcomes in PAD after revascularization	36 months	AC	Not reported	AC: Related to lower risk of composite EP (myocardial infarction, stroke, cardiovascular death HR 0.84, 95% CI 0.75–0.94, $P = .002$)
Rockhold *et al.*[48]	141/141 (100)	Effect of type of anticoagulation (warfarin, DOAC) on MACE, MALE, and bleeding events	12 months	Warfarin, DOAC	Warfarin vs DOAC: No difference in MALE after LLR (RR 1.09, 95% CI 0.53–2.25, $P = .72$)	Warfarin vs DOAC: Warfarin related to higher rates of ISTH major bleeding events after LLR (RR 3.76, 95% CI 1.07–13.19, $P = .015$) No difference in MACE after LLR (RR 2.35, 95% CI 0.60–9.18, $P = .18$) No difference in all-cause mortality after LLR (RR 1.63, 95% CI 0.70–3.78, $P = .15$)
RIVALUTANDO[49]	287/287 (100)	Factors influencing risk of amputation, restenosis and mortality after LLR (e.g. cilostazol)	12 months	DAPT ± cilostazol	Cilostazol: Related to higher risk of restenosis (HR 3.08, 95% CI 1.65–4.02, $P = .001$) Related to higher risk of reintervention (HR 3.1, 95% CI 1.34–4.79, $P = .005$) Not related to limb salvage	Not reported
Furuyama *et al.*[50]	104/104 (100)	Factors influencing ulcer healing after LLR in CLTI	3 months	Cilostazol	Cilostazol: related to improved ulcer healing-impaired ulcer healing without cilostazol (HR 3.482, 95% CI 1.321–9.674, $P = .0114$)	Not reported

Listed studies specifically report associations between antithrombotic therapies and limb outcomes and/or systemic outcomes in the respective CLTI (sub)populations.
AC, anticoagulation; AP, antiplatelet; CI, confidence interval; CLTI, chronic limb-threatening ischaemia; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; HR, hazard ratio; LLR, lower limb revascularization; MACE, major adverse cardiovascular events; MALE, major adverse limb events; PAD, peripheral arterial disease; RR, relative risk; SAPT, single antiplatelet therapy.
[a]Percentage proportion of patients with CLTI.

Other antiplatelet drugs

The role of cilostazol was assessed in six observational studies (in total 1294 CLTI patients, mean age ranging from 69 to 75 years, female proportion from 23% to 34%). Three of these studies included only CLTI populations (563 patients), while three included mixed populations with PAD (731 CLTI patients). The association between cilostazol use and lower rates of restenosis and MALE after endovascular LLR was inconsistent among studies.[34–37,49] However, CLTI patients not receiving cilostazol after endovascular or surgical LLR showed higher risk of failed ulcer healing (HR 3.482, 95% CI 1.321–9.674, $P = .011$) and lower amputation-free survival (HR 2.99, 95% CI 1.213–3.736, $P = .008$).[50]

One study assessed the use of the selective serotonin-2A (5-HT_{2A}) receptor antagonist sarpogrelate in 386 patients with CLTI (mean age 71 years, 33% female) undergoing endovascular LLR and reported improved amputation-free survival rates in comparison with patients without sarpogrelate.[38]

Oral anticoagulants

The use of oral anticoagulants (OACs) among 10 617 patients with CLTI undergoing endovascular or surgical LLR was associated with a lower risk of the combined endpoint of amputation or death (HR 0.90, 95% CI 0.81–0.99, $P = .024$), while no association was observed with the risk of amputation only (HR 1.02, 95% CI 0.86–1.20).[43] Among the 1200 patients with CLTI patients enrolled in the German Registry of First-Line Treatments in Patients With Critical Limb Ischemia (CRITISCH), anticoagulation was associated with better amputation-free survival after bypass surgery (HR 0.52, 95% CI 0.30–0.92, $P = .025$), but not after femoral patchplasty (HR 0.39, 95% CI 0.14–1.13).[44] The use of oral anticoagulation after endovascular or surgical LLR was associated with a lower risk of the composite endpoint of myocardial infarction, stroke, or cardiovascular death (HR 0.84, 95% CI 0.75–0.94, $P = .002$) among 18 742 patients, mostly suffering from CLTI (63%).[47]

In contrast, an analysis of the Vascular Quality Initiative on 50 890 patients with CLTI (mean age 68 years, 41% female) reported lower 1-year survival rates in patients who were discharged on anticoagulants after endovascular (HR 1.27, 95% CI 1.19–1.36, $P < .0001$) or surgical LLR (HR 1.17, 95% CI 1.06–1.30, $P = .03$).[46] In this analysis, the use of OACs was related to a higher risk of major amputation after surgical (HR 1.57, 95% CI 1.35–1.83, $P < .0001$), but not endovascular LLR (HR 1.15, 95% CI 0.95–1.39). Finally, a small study on 141 CLTI patients undergoing LLR reported no differences in mortality, MACE, or MALE between patients receiving vitamin K antagonists as compared with patients receiving direct OACs; however, major bleeding events were more common among patients receiving vitamin K antagonists (relative risk 3.76, 95% CI 1.07–13.19, $P = .015$).[48]

Summary

In observational studies, aspirin is associated with lower mortality and MACE rates (vs no antiplatelet therapy) in patients with CLTI undergoing LLR. Dual antiplatelet therapy is associated with higher overall survival and amputation-free survival after surgical and endovascular LLR as compared with SAPT, at the cost of a higher risk of bleeding, without differences between patients receiving DAPT for <100 days and patients on DAPT for longer time. Data on the effects of oral anticoagulation and of cilostazol on both limb and systemic events are inconsistent.

Discussion

This scientific statement of the ESC Working Group on Aorta and Peripheral Vascular Diseases and the ESC Working Group on Cardiovascular Pharmacotherapy is based on a systematic review, which is the first one focusing on antithrombotic therapy in the high-risk population of patients with CLTI following surgical or endovascular LLR.

While recent ESC guidelines for the management of peripheral arterial and aortic diseases contain recommendations for the antithrombotic treatment in patients with PAD following LLR, no statement is provided for the vulnerable group of patients with CLTI following LLR.[2] Similarly, current surgical guidelines from the European Society for Vascular Surgery on antithrombotic therapy for vascular diseases do not specify antithrombotic treatment concepts for patients with CLTI after LLR.[11]

In recent years, three systematic reviews addressed antithrombotic management of patients with PAD following LLR.[51] A first comprehensive systematic review and network meta-analysis analysed different antiplatelet agents following LLR.[51] However, this systematic review did not specifically address patients with CLTI and was finalized before the publication of the VOYAGER-PAD study. The results of the VOYAGER-PAD study were captured by a more recently published systematic review on antithrombotic treatment in PAD following LLR, which also did not specifically address patients with CLTI.[52] Finally, a third systematic review suggested an association between adenosine diphosphate receptor inhibitor high on-treatment platelet reactivity and worse clinical outcomes after LLR without showing CLTI-specific outcomes.[53]

Against this background, the focus on the post-interventional or post-surgical period of patient CLTI is clinically and scientifically relevant. In the current systematic review, only three small RCTs were captured directly addressing antithrombotic therapy following LLR for CLTI. None of these trials demonstrated that a specific antithrombotic strategy provides a significant benefit on MACE or MALE. The generalizability of these three RCTs is limited by the modest sample size of each trial and the inhomogeneity of the underlying LLR approaches (surgical LLR: two RCTs; endovascular LLR: one RCT). Moreover, it needs to be noted that these RCTs, as well as other studies captured by our structured literature search, have been conducted several years ago, while LLR strategies have substantially improved over time. Aiming at providing a most comprehensive picture of the existing evidence, we decided not to limit the search strategy to any specific time period. Therefore, the key finding of this systematic review is the urgent need for a large-scale RCT on antithrombotic therapies in patients with CLTI undergoing revascularization to establish an evidence-based treatment approach for this high-risk patient group.[7]

The high rate of adverse systemic and limb events in patients with CLTI is related to arterial thrombosis and hypoperfusion of the limbs, as well as to a generalized inflammatory state in patients who often have polyvascular disease. Chronic limb-threatening ischaemia represents the end stage of atherosclerosis in the limbs and the failure of preventive measures. Surgical and endovascular revascularization procedures disrupt vascular endothelium and atherosclerotic plaques and often introduce prosthetic materials (stents and vascular grafts), leading to activation of platelets and coagulation, with the possible occurrence of thrombosis and vascular occlusion.[54–57] A higher expression of vessel wall procoagulants is prompted by a generalized status of vascular inflammation, as demonstrated by high levels of C-reactive protein in such patients.[58] Thus, the occurrence of thrombosis depends on the intertwined activation of vascular wall cells, platelets, and coagulation, with thrombin playing a crucial role.

Table 4 Randomized controlled trials on antithrombotic treatment in patients with chronic limb-threatening ischaemia following lower limb revascularization (listed on ClinicalTrials.gov)

Study title	ClinicalTrials.gov ID	Population	Design	Comparator arm	Experimental arm	Primary endpoint	Status[a]
Pilot Study to Examine the Use of Rivaroxaban After Angioplasty for Critical Limb Ischaemia (RIVAL-PAD)	NCT02260622	Patients with CLTI after angioplasty	RCT	DAPT	DPI (aspirin + rivaroxaban 2.5 mg bid)	The primary outcome is a combined endpoint consisting of any reintervention (surgical procedures to revascularize), above ankle amputation and restenosisat one year	Completed[b]
Comparison of Cilostazol-based Triple Antiplatelet Therapy Versus Dual Antiplatelet Therapy for Outcomes of below-the Knee Endovascular Intervention in Patients With Critical Limb Ischaemia (TAP CLI Study)	NCT02829151	Patients with CLTI after below-the-knee endovascular intervention	RCT	DAPT	DAPT + cilostazol	A composition event of all-cause death, myocardial infarction, stroke, repeat revascularization of the target lesion, and unexpected amputation of the target limb between both groups	Status unknown
Efficacy and Safety of Apixaban in Reducing Restenosis and Limb Loss in PAD Patients. (AGRIPPA)	NCT04229264	Patients with CLTI after below-the-knee endovascular intervention	RCT	DAPT	DPI (aspirin + apixaban 2.5 mg bid)	Restenosis of the treated infrapopliteal artery, major amputation, clinical driven-target lesion revascularization, major cardiovascular events	Status unknown

AC, anticoagulation; AP, antiplatelet; CLTI, chronic limb-threatening ischaemia; DAPT, dual antiplatelet therapy; DPI, dual pathway inhibition; PAD, peripheral arterial disease; RCT, randomized controlled trial.
[a]As retrieved from ClinicalTrials.gov.
[b]Results of 20 patients presented at 2018 Canadian Society of Vascular Surgery Annual Meeting.

Table 5 Gaps in evidence

Issues remaining unsolved
Optimal antithrombotic therapy in patients with chronic limb-threatening ischaemia undergoing lower limb revascularization
Tailored antithrombotic therapy in patients with chronic limb-threatening ischaemia undergoing lower limb revascularization depending on endovascular method of revascularization (use of atherectomy, drug-eluting devices, types of stents/scaffolds)
Differentiation of antithrombotic therapy in patients with chronic limb-threatening ischaemia undergoing lower limb revascularization depending on anatomy (above-the-knee, below-the-knee, multisegmental)
Bleeding risk scores specifically addressing patients with chronic limb-threatening ischaemia following lower limb revascularization
Gender and ethnicity differences in the risk of systemic events and limb events following lower limb revascularization for chronic limb-threatening ischaemia

Activation of both platelets and of the coagulation cascade has been implicated in the genesis of ischaemic events at sites distant from the local intervention in patients with PAD.[54,55,59] Revascularization itself contributes to increased platelet activation and aggregation, along with the initiation of the coagulation process.[56,57] Furthermore, a reduced response to antiplatelet agents has been reported after revascularization in up to 27% of patients with CLTI, probably related to a heightened inflammatory status.[60] The increased platelet activation in CLTI and the reduced response to antiplatelet agents after LLR underline the possible need for tailoring antithrombotic treatment, especially in the post-revascularization period.[12,13]

Despite the documented increased risk of local and systemic thrombotic events in patients with CLTI as compared with patients with intermittent claudication, no study has so far compared different antithrombotic regimens between patients with CLTI and patients with claudication following LLR. Some studies mixed both PAD populations and have not even reported the results in patients with CLTI apart from those observed in claudicants. Against this background, our review shows that DAPT with aspirin and clopidogrel is the most frequently used antithrombotic regimen for CLTI patients undergoing LLR, in agreement with contemporary clinical practice reflected in a recent survey among the members of the ESC Working Group on Aorta and Peripheral Vascular Diseases.[10]

Recently, DPI has become an important alternative to DAPT, based on the results of the VOYAGER-PAD trial, which—over several years—has been the largest RCT providing robust evidence for a potential net benefit of an intensified antithrombotic regimen following LLR in PAD.[9] As shown here, DPI is the only antithrombotic strategy that consistently reduced the risk of limb and systemic events in patients undergoing LLR, although it should be noted that only 23% of the study population in the trial suffered from CLTI. Regarding the entire study population, the benefit of DPI was consistently observed after both endovascular and surgical LLR[29] and was independent of the concomitant use of clopidogrel in patients undergoing endovascular LLR.[28] In this context, it should be noted that the protocol of the VOYAGER-PAD trial allowed the concomitant use of clopidogrel for up to 30 days (or up to a maximum of 60 days, if justified by the investigator).[9] Of all patients randomized in VOYAGER-PAD, 50.6% concomitantly received clopidogrel for a median period of 29 days.[28] Of patients, who underwent endovascular LLR, 69% received DAPT at randomization, 55.5% were on concomitant clopidogrel for ≤30 days, and 42.3% received clopidogrel for >30 days (31 days median duration of concomitant use of clopidogrel).[61] In these patients, the benefit of DPI was independent of the concomitant use of clopidogrel.[61]

Nevertheless, the trial design allows no final conclusion on a direct head-to-head comparison of DPI vs DAPT after LLR. A trial directly comparing these two intensified antithrombotic strategies in patients with CLTI following LLR appears to be now warranted and timely. The recently initiated UK-based Clopidogrel, Aspirin, and Rivaroxaban after revascularization with angioplasty (CLARITY) trial (UK National Institute for Health and Care Research Award ID NIHR154252), which assigns patients with CLTI after endovascular LLR to clopidogrel alone or to DAPT or to DPI, has the potential to contribute much needed data in this field. Beyond this trial, data from recently completed and ongoing trials will further elucidate knowledge on optimal antithrombotic therapy in the high-risk group of patients with CLTI following LLR (*Table 4*).

One important aspect of intensified antithrombotic regimens that warrants mention is the risk of bleeding, especially in frail populations, such as patients with CLTI. Hence, the potential reduction of MALE and MACE by optimized antithrombotic treatment always needs to be weighted against the bleeding risk. Recently published ESC guidelines on the management of peripheral arterial and aortic diseases recommend the implementation of predefined anticoagulation strategies at different degree when associated with an increased risk of bleeding (renal impairment with a glomerular filtration rate < 15 mL/min/1.73 m^2, dialysis, acute coronary syndrome < 30 days, history of intracranial haemorrhage, stroke or transient ischaemic attack, active or clinically significant bleeding).[2] These recommendations address patients with chronic symptomatic PAD after revascularization without specification for patients with CLTI.

To further specify the estimation of bleeding risk in patients with PAD following revascularization, the OAC3-PAD risk score was developed from data deriving from a large German healthcare database.[62] The OAC3-PAD risk score, which, in the meantime, has undergone external validation, involves the presence of CLTI as one, among eight parameters, which identifies patients with PAD at risk of bleeding following LLR.[63–66] In this context, it needs to be acknowledged that the OAC3-PAD risk score was developed for patients following LLR for PAD, and it still needs to be evaluated to which extent this score would allow a risk stratification within the high-risk group of patients with CLTI.

Beyond the primary question of the optimal antithrombotic therapy in patients with CLTI undergoing LLR, several gaps in evidence need to be addressed in future studies (*Table 5*). First, should antithrombotic therapy be tailored to the technique of endovascular LLR (atherectomy, drug-eluting devices, bioresorbable scaffolds)? Second, should antithrombotic therapy be adapted depending on the anatomic site of intervention, such as iliac, femoropopliteal, crural arteries, or multisegmental revascularization? Third, are there sex-, genetic-, or ethnicity-related differences in the risk of systemic and limb adverse events that warrant different antithrombotic strategies?[67] Is there a role of additional $P2Y_{12}$ inhibitors, such as ticagrelor, in the post-revascularization phase of patients with CLTI? Lastly, should we design and adopt bleeding risk scores specific to patients with CLTI to individualize antithrombotic therapy?

The lack of good quality, adequately powered RCTs, the heterogeneity of antithrombotic regimens investigated, and the heterogeneity in endpoint definitions at the present time prevent the possibility to perform a meta-analysis of the available studies. In its absence, this

systematic review on antithrombotic therapy in patients with CLTI undergoing LLR summarizes the available data and highlights major gaps in evidence (*Table 5*).

Conclusions

In patients with CLTI following LLR, an intensified antithrombotic treatment should be proposed to reduce the risk of MALE and MACE. This systematic review highlights the lack of good quality evidence regarding antithrombotic therapy in patients with CLTI undergoing either surgical or endovascular LLR. Based on the few available randomized studies, mostly performed in mixed populations comprising both claudicants and CLTI patients, as well as on observational studies performed in CLTI cohorts, DAPT with aspirin and clopidogrel appears to offer advantages over SAPT on ischaemic limb events. Dual pathway inhibition is the only regimen, for which a large RCT, which included patients with CLTI, demonstrated a reduction in the risk of both major limb and cardiovascular adverse events, following surgical and endovascular LLR.

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Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

O.S. declares no conflict of interest for this contribution. M.D.C. reports personal speaker fees from Sanofi, Daiichi Sankyo, and Medtronic and a travel grant from Sanofi. L.M. reports grants or contracts from Novartis and Amgen. A.B.-R. reports personal consulting fees from Bayer and personal payment or honoraria for lectures, presentations, speaker bureaus, and manuscript writing or educational events from Bayer, BMS/Pfizer, and Novartis. C.H. reports research grants to his institution from iThera, AgeLess Sciences, the European Union (EURAMET), Lipton; research grants from BBSRC for PhD studentship; research grant from MRC; and participation in the SUCCESS study from MedAlliance. C.H. reports travel support for lectures from Bayer and the Royal Society of Medicine. C.H. is a member of the European Society of Vascular Medicine board, the chairperson-elect of the ESC Working Group on Aorta and Peripheral Vascular Diseases, the president of the Royal Society of Medicine Vascular Medicine Council, and a member of the board of the UEMS Division of Vascular Medicine. J.R.P. declares no conflict of interest for this contribution. J.C.A.M. reports personal consulting fees from Bayer Healthcare, Boehringer Ingelheim, Novartis, and Amarin; personal payment or honoraria for lectures, presentations, speaker bureaus, and manuscript writing or educational events from AstraZeneca, Bayer Healthcare, Servier, Novartis, Boehringer Ingelheim, Daiichi, Menarini, Bial, and Amarin. J.C.A.M. reports having received support from Servier to attend ESC Congress 2023 and ESC Congress 2024. S.S. reports research funding from C.R. Bard and consulting fees from iThera Medical, Boston Scientific, and Cook Medical. S.S. received payment or honoraria for lectures, presentations, speaker bureaus, and manuscript writing or educational events and support for attending meetings and/or travel from Cook Medical and Boston Scientific. S.S. reports her participation on a Data Safety Monitoring Board or Advisory Board for Boston Scientific. M.B. declares no conflict of interest for this contribution. V.A. reports personal consulting fees from Amarin, AstraZeneca, Bayer, Boehringer Ingelheim, and Novo Nordisk. V.A. is editor-in-chief of the European Journal of Preventive Cardiology. R.D.C. reports consulting fees from Sanofi, Milestone, Daiichi Sankyo, Janssen, Pfizer, Bristol-Myers Squibb, and Menarini; payment or honoraria for lectures, presentations, speaker bureaus, and manuscript writing or educational events; and support for attending meetings and/or travel from Sanofi, Milestone, Daiichi Sankyo, Janssen, Pfizer, Bristol-Myers Squibb, Menarini, and Amarin. R.D.C. reports supports for attending meetings and/or travel from Amarin and Daiichi Sankyo. R.D.C. reports his participation on a Data Safety Monitoring Board or Advisory Board for Daiichi-Sankyo (NOAH-AFNET6).

Data Availability

The underlying data will be shared on reasonable request.

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