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REVIEW

A Review of Antithrombotic Treatment in Critical Limb Ischemia After Endovascular Intervention

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ABSTRACT

Endovascular intervention is often used to treat critical limb ischemia (CLI). Post-intervention treatment with antiplatelet and/or anticoagulant therapy has reduced morbidity and mortality due to cardiovascular complications. The purpose of this review is to shed light on the various pharmacologic treatment protocols for treating CLI following endovascular procedures. We reviewed the literature comparing outcomes after antithrombotic treatment for patients with CLI. We characterized antithrombotic therapies into three categories: (1) mono-antiplatelet therapy (MAPT) vs. dual antiplatelet therapy (DAPT), (2) MAPT vs. antiplatelet (AP) + anticoagulant (AC) therapy, and (3) AC vs. AP + AC therapy. Relevant results and statistics were extracted to determine differences in the rates of the following outcomes: (1) re-stenosis, (2) occlusion, (3) target limb revascularization (TLR), (4) major amputation, (5) major adverse cardiac events, (6) all-cause death, and (7) bleeding. Studies suggest that DAPT reduces post-surgical restenosis, TLR, and amputation for diabetic patients, without increasing major bleeding incidences, compared to MAPT. Also, AP + AC therapy provides overall superior efficacy, with no difference in bleeding incidences, compared to antiplatelet alone. Additionally, the effects were significant for restenosis, limb salvage, survival rates, and cumulative rate of above ankle amputation or death. These results suggest that treatment with DAPT and AP + AC might provide better outcomes than MAPT following the endovascular intervention for CLI, and that the ideal treatment may be related to the condition of the individual patient. However, the studies were few and heterogenous with small patient populations. Therefore, further large controlled studies are warranted to confirm these outcomes.

Keywords: Anticoagulant; Antiplatelet; Critical limb ischemia; Endovascular procedures; Peripheral artery disease

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INTRODUCTION

Critical limb ischemia (CLI) is an advanced stage of peripheral artery disease (PAD) and is defined by ischemic rest pain, a non-healing ulcer, or tissue loss for > 14 days [1, 2]. CLI is associated with a dramatic decline in quality of life, major amputations (above the ankle), increased cardiovascular events such as myocardial infarction and stroke, and mortality that occurs in up to 50% of patients within 5 years [3–5]. Prompt revascularization is the cornerstone of therapy for CLI and has a class I recommendation by all international guidelines [6]. Endovascular techniques developed over the past two decades have expanded the therapeutic options for patients with PAD [7, 8], and are used in approximately 80% of lower limb revascularization procedures [9, 10].

In select CLI patients, percutaneous transluminal angioplasty (PTA) is the recommended first-line therapy to avoid morbidities associated with vascular surgery [11]. In patients who are not suitable candidates for surgery, such as those with poor distal targets, insufficient saphenous veins for bypass grafting, and patients suffering with severe medical comorbidities, endovascular intervention may be the only option for saving the limb [6, 11]. The Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial suggested broadly similar outcomes in terms of amputation-free survival are associated with bypass surgery and balloon angioplasty in patients suffering from severe limb ischemia due to infra-inguinal disease and who are suitable for surgery and angioplasty. Other studies suggest that healthier patients (i.e., those with a life expectancy exceeding 2 years) may benefit from surgical intervention as an initial therapy for limb-threatening ischemia [12]. In contrast, Kudo et al. [13] suggested PTA as the first choice when life expectancy is less than 2 years and the patient is a candidate for either procedure. Importantly, endovascular intervention does not negate the need for bypass surgery and may be followed by surgery in certain cases.

Despite the benefits of endovascular intervention, recurrence rates remain high over a long duration [14, 15], which make the use of complementary antithrombotic treatment essential to prolong the recurrence-free duration and reduce the need for multiple interventions. However, high-level evidence of the effects of antithrombotic therapies is limited.

Recommendations regarding antithrombotic therapy for CLI patients based on sound evidences are lacking [1, 16–18]. The majority of published reviews focus on evaluating antithrombotic treatment for PAD in general and are not specific to CLI [19–25]. Additionally, few studies were specifically dedicated to CLI but instead were non-comprehensive and included a mixture of CLI and claudication patients [26, 27]. This may be due to the lack of reliable data regarding antithrombotic therapy for CLI following endovascular procedures because most studies are not stratified by the presence of CLI and may lack standardized follow-up procedures. In this study, we gathered and evaluated various antiplatelet and anticoagulant treatment strategies in patients with CLI who underwent endovascular revascularization from the literature. This review aims to (1) discuss the available literature for CLI patients, (2) to bring awareness to potentially safer and more effective treatment regimens, and (3) to call for further investigation for understudied treatments and evaluation of the potential effectiveness and safety of antithrombotic therapy for CLI patients.

METHODS

Study Design and Selection Criteria

A standardized electronic literature search in English was conducted in PubMed/MEDLINE, ScienceDirect, and Google Scholar using several combinations of the following keywords; “angioplasty”, “endovascular”, “antiplatelet”, “anticoagulants”, “platelet aggregation inhibition”, “critical limb ischemia”, “peripheral artery disease”, “individual antiplatelet or anticoagulant drug name or category such as aspirin, clopidogrel, cilostazol”, “antiplatelet or anticoagulant category or mechanism of action such as P2Y12/ADP inhibitor, direct thrombin

inhibitor, anti-factor Xa", "clinical trial", "prospective", and "retrospective".

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors. The studies included in this review met the following criteria: (1) published between January 2000 and July 2019; (2) designed explicitly for CLI, including those that majorly include severe and late claudication cases (Rutherford class 3) that might overlap with CLI, or present results stratified for CLI patients; (3) antiplatelets and/or anticoagulants were administered following endovascular intervention, and the study was designed to compare different treatments; (4) recorded outcomes such as restenosis (recurrence of $\geq$ 50% diameter stenosis), occlusion, target limb revascularization (TLR), limb salvage, major amputation (above ankle area), major adverse cardiac events ("MACEs", such as cardiovascular death, myocardial infarction, angina, stroke, hospitalization for heart failure), all-cause death, and major bleeding (such as major bleeding, intracranial hemorrhage, require blood transfusion) or bleeding incidences; (5) patients were followed-up for at least 3 months; (6) studies including randomized clinical trials, retrospective studies, cohort studies with at least 20 patients or limbs per group.

We reviewed the titles and abstracts of articles identified in the literature as potentially suitable for inclusion in the review. Then, we evaluated the manuscript to confirm eligibility for inclusion in this review. Eight published studies met the inclusion criteria, and relevant data and statistics were extracted from the studies. The studies were summarized by the primary author, year of publication, endovascular intervention technique with or without stent, artery segment affected, treatment groups, number of patients/limbs, and the percentage of positive outcomes for each study. Studies were then categorized under three treatment groups; mono-antiplatelet (MAPT) vs. dual-antiplatelet (DAPT), MAPT vs. a combination of antiplatelet and anticoagulant (AP + AC), and anticoagulant vs. AP + AC.

RESULTS

Table 1 presents the antithrombotic drugs used in the studies included in the review, along with their mechanism of action. Table 2 provides details for the included studies.

Mono-Antiplatelet and Dual-Antiplatelet Therapy

Table 3 presents the effects of MAPT and DAPT on restenosis, occlusion, TLR, major amputation, MACEs, and all-cause death [28–30]. DAPT treatment showed promising effects for restenosis, TLR [31], and lower amputation rates in diabetic patients [32]. However, the data from Soga et al. [29] did not support the same restenosis outcome reported by Iida et al. [28], since there was no significant difference in the occurrence of restenosis following endovascular intervention for the same two treatment groups. A subgroup analysis was performed in one study which showed that, despite the lack of significant differences for the amputation rate between DAPT with aspirin plus clopidogrel

Table 1 Antithrombotic drugs and mechanism of action

Drugs	Mechanism of action
Antiplatelet	
Aspirin	Thromboxane A2 inhibitors
Cilostazol	Phosphodiesterase inhibitors
Clopidogrel	P2Y12/ADP receptor inhibitors
Tirofiban	P2Y12/ADP receptor inhibitors
Anticoagulant	
Batroxobin	Defibrinating agents
Bivalirudin	Direct thrombin inhibitor (IIb/IIIa inhibitor)
Dalteparin	Anti-factor Xa and thrombin
Sulodexide	Anti-factor Xa
Unfractionated heparin	Anti-factor Xa

Table 2 Inclusion criteria and baseline patient demographics

Author/year	Iida et al. [28]		Soga et al. [29]		Piaggesi et al. [49]		Tepe et al. [31]	
Number of CLI patients	CLI, n = 20, severe claudication, n = 120, stage II Rutherford, n = 51 (total n = 191)		60 (53 patients were randomized)		50		CLI, n = 27, severe claudication, n = 53 (total n = 80)	
Inclusion criteria	Patients with symptomatic PAD classified as greater than Rutherford 1 were screened by noninvasive tests to detect limb ischemia and de novo FP lesions		Patients with CLI who had an infrapopliteal disease were enrolled in the study before endovascular intervention. Other inclusion criteria were age > 20 years		Type 2 diabetes, presence of CLI according to criteria indicated in the Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC II) (rest pain and/or ischemic lesion in a patient with ankle pressure < 50 mmHg or transcutaneous oxygen tension [TcPO2] < 30 mmHg), and ability to give an informed consent, both about the PTA and the inclusion in a clinical trial		1. Age > 18 years and < 90 years 2. Chronic peripheral arterial disease in superficial femoral artery and/or popliteal artery stage Rutherford 3–5	
Patient baseline characteristics	Cilostazol group (n = 93)	Noncilostazol group (n = 98)	Cilostazol + aspirin group (n = 25)	Aspirin group (n = 25)	Sulodexide (n = 27)	Controls (n = 23)	True (n = 40)	Placebo (n = 40)
Age (years)	72 ± 9	73 ± 8	73 ± 10	73 ± 8	70 ± 8	71 ± 8	70 ± 8	70 ± 11
Males, n (%)	64 (69)	67 (68)	18 (72)	19 (76)	–	–	19	23
Body mass index (kg/m^2)	22 ± 3	22 ± 3	–	–	–	–	–	–
Hypertension, n (%)	75 (81)	80 (82)	20 (80)	24 (96)	–	–	31 (77.5)	31 (77.5)
Dyslipidemia, n (%)	41 (44)	49 (50)	10 (40)	15 (60)	–	–	25 (62.5)	25 (62.5)
Statin treatment, n (%)	30 (32)	38 (39)	–	–	–	–	–	–
Diabetes mellitus, n (%)	52 (56)	55 (56)	–	–	27 (100)	23 (100)	12 (30)	18 (45)
Glycosylated hemoglobin at baseline (%)	6.4 ± 1.7	6.2 ± 1.1	–	–	–	–	–	–
History of smoking, n (%)	41 (44)	47 (48)	7 (28)	13 (52)	–	–	15 (37.5%)	17 (42.5%)
End-stage renal disease on dialysis, n (%)	15 (16)	15 (15)	–	–	–	–	–	–
Coronary artery disease, n (%)	35 (38)	39 (40)	15 (60)	12 (48)	–	–	11 (27.5)	15 (37.5)
Cerebrovascular disease, n (%)	22 (24)	19 (19)	5 (20)	8 (32)	–	–	6 (15)	9 (22.5)
Rutherford classification, n (%)								
2	23 (25)	28 (29)	–	–	–	–	–	–
3	61 (65)	59 (60)	–	–	–	–	23 (57.5)	30 (75)
4	9 (10)	11 (11)	9 (36)	10 (40)	–	–	6 (15)	1 (2.5)
5			15 (60)	10 (40)	–	–	11 (27.5)	9 (22.5)
6			1 (4)	5 (20)	–	–	–	–

Table 2 continued

Author/year	Iida et al. [28]		Soga et al. [29]		Piaggesi et al. [49]		Tepe et al. [31]	
Fontaine classifications, *n* (%)								
II								
III/IV								
Baseline ankle BPI	0.71 ± 0.15	0.66 ± 0.14	0.74 ± 0.33	0.66 ± 0.14	0.31 ± 0.24	0.29 ± 0.18	0.61 ± 0.22	0.61 ± 0.33
Author/year	**Thott et al. [32]**		**Koppensteiner et al. [33]**		**Wang et al. [34]**		**Allie et al. [35]**	
Number of CLI patients	1941		CLI, *n* = 100 (total 275)		CLI, *n* = 60, severe claudication, *n* = 69 (total *n* = 129)		298	
Inclusion criteria	Patients with CLI undergoing primary endovascular intervention in the fem-pop segment (above/below knee). CLI was defined as ischemic rest pain, and or non-healing ischemic ulcer or gangrene (grade IV, V, and VI in the Rutherford classification)		Symptomatic patients with angiographically or sonographically documented femoropopliteal de novo or recurrent lesions scheduled for an interventional procedure at the Division of Angiology, University Hospital Zurich, were included		Patients with diabetes and symptomatic limb ischemia (Rutherford classification III or worse) who needed intraluminal and/or subintimal angioplasty for occlusive disease in the lower-limb vessels were eligible for this study and were enrolled at a single center		Patients with Rutherford classification 4–6 CLI and severe infrainguinal PAD who underwent PPI between January 1, 2000 and January 31, 2003 and were treated with a combination of bivalirudin and tirofiban	
Patient baseline characteristics	DAPT (*n* = 599)	Aspirin (*n* = 1342)	Controls (CLI, *n* = 56, total *n* = 138)	Dalteparin group (CLI, *n* = 44, total *n* = 137)	Controls (*n* = 71)	Batroxobin (*n* = 58)	Bivalirudin/tirofiban group (*n* = 149)	UFH control group (*n* = 149)
Age (years)	78 (70–84)	80 (71–85)	70 ± 11	69 ± 10	7 ± 7	70 ± 7	69 ± 11	68 ± 12
Males, *n* (%)	251 (42)	555 (41)	60	56	27 (45.0)	20 (39.22)	106 (71.1)	102 (68.5)
Body mass index (kg/m^2)	–	–	–	–	–	–	–	–
Hypertension, *n* (%)	488 (81)	1054 (79)	78	77	33 (55.0)	26 (51.0)	70 (46.9)	62 (41.9)
Dyslipidemia, *n* (%)	–	–	–	–	–	–	–	–
Statin treatment, *n* (%)	363 (60)	700 (52)	–	–	–	–	–	–
Diabetes mellitus, *n* (%)	242 (40)	603 (45)	32	30	–	–	116 (79.2)	112 (75.1)
Glycosylated hemoglobin at baseline (%)	–	–	–	–	7.6 ± 1.6	7.2 ± 1.3	–	–
History of smoking, *n* (%)	303 (51)	590 (44)	–	–	9 (15.0)	6 (11.8)	117 (78.5)	124 (83.2)
End-stage renal disease on dialysis, *n* (%)	–	–	–	–	–	–	–	–
Coronary artery disease, *n* (%)	237 (40)	645 (48)	42	39	–	–	32 (21.5)	35 (23.5)
Cerebrovascular disease, *n* (%)	59 (10)	169 (13)	18	15	–	–	–	–

Table 2 continued

Author/year	Thott et al. [32]		Koppensteiner et al. [33]		Wang et al. [34]		Allie et al. [35]	
Rutherford classification, *n* (%)								
2	–	–	–	–	–	–	–	–
3	–	–	–	–	33 (55.0)	28 (54.9)	–	–
4	–	Aspirin (n = 1342)	–	–	10 (16.7)	7 (13.7)	–	–
5	–	80 (71–85)	–	–	17 (28.3)	16 (31.4)	–	–
6	–	555 (41)	–	–			–	–
Fontaine classifications, *n* (%)		–						
II		1054 (79)	67 (48.6)	75 (54.7)				
III/IV			32 (23.2)	24 (17.5)				
Baseline ankle BPI	–	–	0.70 ± 0.18	0.66 ± 0.18	0.48 ± 0.18	0.48 ± 0.17	–	–

This information describes all patients for each study. The studies included in the review have data analysis for CLI-only in most studies, as presented in Tables 3, 4, 5, and 6

BPI Brachial Pressure Index

– not explicitly mentioned

compared to aspirin, DAPT was associated with significantly lower amputation rates than MAPT (HR 0.26; 95% CI 0.13–0.52; $p < 0.001$), but not a higher bleeding rate, in diabetic patients with CLI following endovascular femoropopliteal stenting [32]. Subgroup analyses for disease, stent, and arterial segment did not reveal significantly different results between the two treatment groups [32].

Mono-Antiplatelet and Mono-Antiplatelet Plus Anticoagulant Therapy

Table 4 shows the effectiveness of MAPT vs. AP + AC and the safety (bleeding) differences between the two are presented in Table 5. For all the efficacy parameters evaluated, there was evidence of better therapeutic outcomes in AP + AC group compared to the MAPT group in all studies. However, significant values were achieved for restenosis [33], limb salvage, survival rate, and cumulative rate of major amputation and death [34]. Interestingly, the therapeutic effects of aspirin and aspirin plus dalteparin on occlusion rates revealed no significance when data were evaluated for PAD, but a subgroup analysis of claudication and CLI showed significantly better occlusion outcome for aspirin plus dalteparin [33]. Furthermore, while restenosis rates for aspirin vs. aspirin plus batroxobin showed no significant differences between the two groups, subgroup analysis for infra-popliteal lesions showed significantly higher restenosis rates in aspirin than in aspirin plus batroxobin (p = 0.0026) and also for lesions > 10 cm (p = 0.0016) [34]. There were no differences in the bleeding incidences between MAPT and AP + AC groups [33, 34] (Table 5).

Anticoagulant and Antiplatelet Plus Anticoagulant Therapy

Table 5 shows one study [35] that evaluated the efficacy of AC vs. AP + AC, which showed differences between the two groups despite evidence of better limb salvage rates with AP + AC than AP alone. There were no differences in the bleeding complications between the two treatment groups (Table 6).

Table 3 Mono antiplatelet vs. dual antiplatelet

Study	Type	Endovascular intervention	Artery	Treatment	Dose/duration	Follow-up (months)	Number of patients/limbs	Rates (%)	*p* value or HR	Subgroup analysis
Restenosis (recurrence of ≥ 50% diameter stenosis)										
Iida et al. [28]	RCT	PTA with provisional nitinol stenting	Femoro-popliteal	Aspirin	Aspirin (100 mg/day) alone or + cilostazol (200 mg/day)	12	38/77	49	0.001	
				Aspirin + cilostazol			15/75	20		
Tepe et al. [31]	RCT	PTA with or without stenting	Femoro-popliteal	Aspirin + placebo	Placebo or clopidogrel (300 mg) + 500 mg aspirin before intervention. Daily dose of 75 mg placebo or clopidogrel + 500 mg or 100 mg of aspirin, respectively for 6 months post-intervention	6	13/33	39.4	n.s.	
				Aspirin + clopidogrel			14/35	40		
Soga et al. [29]	RCT	Balloon angioplasty	Infra-popliteal	Aspirin	Aspirin (100 mg/day) alone or + cilostazol (200 mg/day)	3	20/25	81	n.s.	
				Aspirin + cilostazol		3	21/25	82		
Occlusion										
Iida et al. [28]	RCT	PTA with provisional nitinol stenting	Femoro-popliteal	Aspirin	Aspirin (100 mg/day) alone or + cilostazol (200 mg/day)	12	7/77	9	n.s.	
				Aspirin + cilostazol			4/75	5		
Tepe et al. [31]	RCT	PTA with or without stenting	Femoro-popliteal	Aspirin + placebo	Placebo or clopidogrel (300 mg) + 500 mg aspirin before intervention. Daily dose of 75 mg placebo or clopidogrel + 500 mg or 100 mg of aspirin, respectively for 6 months post-intervention	6	1/33	3	n.s.	
				Aspirin + clopidogrel			3/35	8.6		
Target limb revascularization (TLR)										
Iida et al. [28]	RCT	PTA with provisional nitinol stenting	Femoro-popliteal	Aspirin	Aspirin (100 mg/day) alone or + cilostazol (200 mg/day)	12	34/85	40	0.001	
				Aspirin + cilostazol			14/82	17		
Tepe et al. [31]	RCT	PTA with or without stenting	Femoro-popliteal	Aspirin + placebo	Placebo or clopidogrel (300 mg) + 500 mg aspirin before intervention. Daily dose of 75 mg placebo or clopidogrel + 500 mg or 100 mg of aspirin, respectively for 6 months post-intervention	6	8/40	20	0.04	
				Aspirin + clopidogrel			2/40	5		
Major amputation (above ankle amputation)										
Iida et al. [28]	RCT	PTA with provisional nitinol stenting	Femoro-popliteal	Aspirin	Aspirin (100 mg/day) alone or + cilostazol (200 mg/day)	12	2/98	2	n.s.	
				Aspirin + cilostazol			0/82	0		
Thott et al. [32]	Retrospective	PTA or SAP with or without stent	Femoro-popliteal	Aspirin	Doses were not provided; variable duration for clopidogrel, not specified for aspirin	12	228/1342	17	HR 0.77 (95% CI 0.59–0.99)	Superior effect of aspirin + clopidogrel in diabetics (HR 0.26; 95% CI 0.13–0.52; $p < 0.001$)
				Aspirin + clopidogrel			77/599	13		

Table 3 continued

Study	Type	Endovascular intervention	Artery	Treatment	Dose/duration	Follow-up (months)	Number of patients/limbs	Rates (%)	*p* value or HR	Subgroup analysis
Tepe et al. [31]	RCT	PTA with or without stenting	Femoro-popliteal	Aspirin + placebo	Placebo or clopidogrel (300 mg) + 500 mg aspirin before intervention. Daily dose of 75 mg placebo or clopidogrel + 500 mg or 100 mg of aspirin, respectively for 6 months post-intervention	6	6/33	18.2	n.s.	
				Aspirin + clopidogrel			6/35	17.1		
Soga et al. [29]	RCT	Balloon angioplasty	Infra-popliteal	Aspirin	Aspirin (100 mg/day) alone or + cilostazol (200 mg/day)	3	1/25	4	n.s.	
				Aspirin + cilostazol			1/25	4		
Major adverse cardiac events										
Iida et al. [28]	RCT	PTA with provisional nitinol stenting	Femoro-popliteal	Aspirin	Aspirin (100 mg/day) alone or + cilostazol (200 mg/day)	12	9/98	9	n.s.	
				Aspirin + cilostazol			11/93	12		
Tepe et al. [31]	RCT	PTA with or without stenting	Femoro-popliteal	Aspirin + placebo	Placebo or clopidogrel (300 mg) + 500 mg aspirin before intervention. Daily dose of 75 mg placebo or clopidogrel + 500 mg or 100 mg of aspirin, respectively for 6 months post-intervention	6	15/40	37.5	n.s.	
				Aspirin + clopidogrel			12/40	30		
Soga et al. [29]	RCT	Balloon angioplasty	Infra-popliteal	Aspirin	Aspirin (100 mg/day) alone or + cilostazol (200 mg/day)	3	1/25	4	n.s.	
				Aspirin + cilostazol			1/25	4		
All-cause death										
Thott et al. [32]	Retrospective	PTA or SAP with or without stent	Femoro-popliteal	Aspirin	Doses were not provided; variable duration for clopidogrel, not specified for aspirin	12	571/1342	43	HR 0.72[a] (95% CI 0.61–0.86)	
				Aspirin + clopidogrel			172/599	29		
Iida et al. [28]	RCT	PTA with provisional nitinol stenting	Femoro-popliteal	Aspirin	Aspirin (100 mg/day) alone or + cilostazol (200 mg/day)	12	4/98	4	n.s.	
				Aspirin + cilostazol			7/93	8		
Tepe et al. [31]	RCT	PTA with or without stenting	Femoro-popliteal	Aspirin + placebo	Placebo or clopidogrel (300 mg) + 500 mg aspirin before intervention. Daily dose of 75 mg placebo or clopidogrel + 500 mg or 100 mg of aspirin, respectively, for 6 months post-intervention	6	1/40	2.5	n.s.	
				Aspirin + clopidogrel			0/40	0		
Soga et al. [29]	RCT	Balloon angioplasty	Infra-popliteal	Aspirin	Aspirin (100 mg/day) alone or + cilostazol (200 mg/day)	3	1/25	4		
				Aspirin + cilostazol			0/25	0		

n.s. not significant
[a] Univariate analysis

Table 4 Mono antiplatelet vs. antiplatelet + anticoagulant

Study	Type	Endovascular intervention	Artery	Treatment	Dose/treatment	Follow-up (months)	Number of patients/ limbs	Rates (%)	Statistical significance	Subgroup analysis
Restenosis (recurrence of ≥ 50% diameter stenosis)										
Wang et al. [34]	RCT	Intraluminal and/or subintimal angioplasty	Femoro-popliteal and infra-popliteal	Aspirin	Aspirin (100 mg/day) from admission day to at least 12 months if no side effects. Batroxobin (5 IU/0.5 ml), 2 doses before and 4 doses post-procedure	12	74/267 (lesion)	27.7	n.s.	Infra-popliteal lesion showed significant difference ($p = 0.0026$) between aspirin [42.7%] and aspirin plus batroxobin [27.7%], and for lesion > 10 cm (aspirin [54%]) and aspirin plus batroxobin [34.8%]) ($p = 0.0016$)
				Aspirin + batroxobin		12	45/246 (lesion)	18.3		
Koppensteiner et al. [33]	RCT	PTA	Femoro-popliteal	Aspirin	Aspirin (100 mg/day) 1 day before procedure + dalteparin (5000 IU/day) for 2 days postoperatively. Patients were randomized post-operatively to receive aspirin (100 mg/day) alone or + dalteparin (2500 IU/day) for 3 months	12	27/38	72	0.01	
				Aspirin + dalteparin			15/33	45		
Occlusion										
Wang et al. [34]	RCT	Intraluminal and/or subintimal angioplasty	Femoro-popliteal and infra-popliteal	Aspirin	Aspirin (100 mg/day) from admission day to at least 12 months if no side effects. Batroxobin (5 IU/0.5 ml), 2 doses before and 4 doses post-procedure	12	41/267 (lesion)	15.4	n.s.	
				Aspirin + batroxobin			28/244 (lesion)	11.4		
Major amputation (above ankle amputation)										
Wang et al. [34]	RCT	Intraluminal and/or subintimal angioplasty	Femoro-popliteal and infra-popliteal	Aspirin	Aspirin (100 mg/day) from admission day to at least 12 months if no side effects. Batroxobin (5 IU/0.5 ml), 2 doses before and 4 doses post-procedure	12	11/60	18.3	n.s.	
				Aspirin + batroxobin			3/51	5.9		
Piaggesi et al. [49]	Observational	PTA with or without stenting	n.m.	Aspirin or clopidogrel	Aspirin 100 mg/day, or clopidogrel 75 mg/day (if aspirin-intolerant). In case of stenting, patients received both indefinitely, alone, or + sulodexide 25 mg bid per os (upon discharge)	6	3/23	13.04	n.s.	
				Aspirin or clopidogrel + sulodexide			3/27	11.11		
Limb salvage and survival rates										
Wang et al. [34]	RCT	Intraluminal and/or subintimal angioplasty	Femoro-popliteal and infra-popliteal	Aspirin	Aspirin (100 mg/day) from admission day to at least 12 months if no side effects. Batroxobin (5 IU/0.5 ml), 2 doses before and 4 doses post-procedure	12	–	78.30	0.0414	
				Aspirin + batroxobin			–	92.2		

Table 4 continued

Study	Type	Endovascular intervention	Artery	Treatment	Dose/treatment	Follow-up (months)	Number of patients/limbs	Rates (%)	Statistical significance	Subgroup analysis
All-cause death										
Wang et al. [34]	RCT	Intraluminal and/or subintimal angioplasty	Femoro-popliteal and infra-popliteal	Aspirin	Aspirin (100 mg/day) from admission day to at least 12 months if no side effects. Batroxobin (5 IU/0.5 ml), 2 doses before and 4 doses post-procedure	12	2/60	3.30	n.s.	
				Aspirin + batroxobin			1/51	2		
Cumulative rate of above ankle amputation or death										
Wang et al. [34]	RCT	Intraluminal and/or subintimal angioplasty	Femoro-popliteal and infra-popliteal	Aspirin	Aspirin (100 mg/day) from admission day to at least 12 months if no side effects. Batroxobin (5 IU/0.5 ml), 2 doses before and 4 doses post-procedure	12	13/60	21.7	0.0284	
				Aspirin + batroxobin			3/51	5.9		

n.m. not mentioned, *n.s.* not significant

DISCUSSION

Based on this review of post-endovascular antiplatelet and anticoagulant treatment regimens for patients with CLI, patients should receive antiplatelet therapy, particularly DAPT. This regimen showed no increase in major bleeding incidences compared to MAPT, and reduced post-surgical restenosis, TLR, and amputations for diabetic patients [28, 31]. Also, the combination of antiplatelet and anticoagulant was shown to have overall superior efficacy, with no difference in bleeding incidences, compared to antiplatelet alone. The effects were significant for restenosis [33], limb salvage, survival rates, and cumulative rates of above ankle amputation or death [34]. In addition, patients who undergo infra-popliteal endovascular intervention or with arterial injury > 10 cm might benefit the most from treatment with AP + AC [34]. However, the antithrombotic regimen is best determined based on an individual basis.

Guidelines for antithrombotic therapy in patients with PAD and CLI are variable and inconclusive [1, 19, 41, 42]. The European Society of Cardiology (ESC) recommends the use of MAPT (aspirin) for angioplasty (class I recommendations) [19, 42]. The American College of Chest Physicians recommends the use of MAPT (aspirin or clopidogrel) after angioplasty (grade 1A) [16, 19]. The Society for Vascular Surgery recommends a minimum of 30 days of aspirin and clopidogrel following infrainguinal endovascular procedures (grade 2B) [19, 41]. The consensus across the majority of the studies, however, is that there is a lack of evidence to support one specific treatment regimen [19–22, 26, 27].

DAPT with aspirin and clopidogrel was suggested for at least 1 month following stent implantation, regardless of stent type, or with aspirin and ticagrelor in PAD patients with previous myocardial infarction [16]. We found that treatment with DAPT following endovascular intervention seems superior to MAPT treatment for the prevention of restenosis in femoropopliteal segments in CLI [28], but not in infra-popliteal segments [29], suggesting that DAPT effects in CLI might be influenced by

Table 5 Anticoagulant vs. antiplatelet + anticoagulant

Study	Type	Endovascular intervention	Artery	Treatment	Dose/duration	Follow-up (months)	Number of patients/limbs	Rates (%)	*p* value
Restenosis (recurrence of ≥ 50% diameter stenosis									
Allie et al. [35]	Retrospective	PTA with or without stent, thrombectomy, laser, or combination	Femoro-popliteal/infra-popliteal	Unfractionated heparin Bivalirudin and tirofiban + unfractionated heparin	Bivalirudin (0.75 mg/kg bolus) followed by 1.75 mg/kg/h infusion for procedure duration, and tirofiban with 10 mcg/kg/min 30 min bolus with a peri- and post-PPI 0.1 mcg/kg/min continuous drip for 12 h. A historical matched UFH monotherapy control group was used. UFH was administered at a bolus dose of 50–100 U/kg, with a target activated clotting time (ACT) > 250 s	6	31/149 24/149	16.1 21.4	n.s.
Limb salvage rate									
Allie et al. [35]	Retrospective	PTA with or without stent, thrombectomy, laser, or combination	Femoro-popliteal/infra-popliteal	Unfractionated heparin Bivalirudin and tirofiban + unfractionated heparin	Bivalirudin (0.75 mg/kg bolus) followed by 1.75 mg/kg/h infusion for procedure duration, and tirofiban with 10 mcg/kg/min 30 min bolus with a peri- and post-PPI 0.1 mcg/kg/min continuous drip for 12 h. A historical matched UFH monotherapy control group was used. UFH was administered at a bolus dose of 50–100 U/kg, with a target activated clotting time (ACT) > 250 s	6	132/149 140/149	89 94	0.053
All-cause death									
Allie et al. [35]	Retrospective	PTA with or without stent, thrombectomy, laser, or combination	Femoro-popliteal/infra-popliteal	Unfractionated heparin Bivalirudin and tirofiban + unfractionated heparin	Bivalirudin (0.75 mg/kg bolus) followed by 1.75 mg/kg/h infusion for procedure duration, and tirofiban with 10 mcg/kg/min 30 min bolus with a peri- and post-PPI 0.1 mcg/kg/min continuous drip for 12 h. A historical matched UFH monotherapy control group was used. UFH was administered at a bolus dose of 50–100 U/kg, with a target activated clotting time (ACT) > 250 s	6	9/149 7/149	6 4.6	n.s.

n.s. not significant

Table 6 Major bleeding and other bleeding

Study	Study type	Endovascular intervention	Artery	Treatment	Dose/duration	Time point (months)	Number of patients (major bleeding)	Number of patients (other bleeding)	Other bleeding rates (%)	Other bleeding (*p* value or HR)
Mono antiplatelet vs. dual antiplatelet										
Thott et al. 2017 [32]	Retrospective	PTA or SAP with or without stent	Femoro-popliteal	Aspirin	Doses not provided; variable duration for clopidogrel, not specified for aspirin	12	–	148/1342	11	HR 1.12 (95% CI 0.85–1.49)
				Aspirin + clopidogrel			–	72/599	12	
Tepe et al. [31]	RCT	PTA with or without stenting	Femoro-popliteal	Aspirin + placebo	Placebo or clopidogrel (300 mg) + 500 mg aspirin before intervention. Daily dose of 75 mg placebo or clopidogrel + 500 mg or 100 mg of aspirin, respectively for 6 months post-intervention	6	0	2/40	5	n.s.
				Aspirin + clopidogrel			0	1/40	2.5	
Soga et al. [29]	RCT	Balloon angioplasty	Infra-popliteal	Aspirin	Aspirin (100 mg/day) alone or + cilostazol (200 mg/day)	3	–	0/25	0	n.s.
				Aspirin + cilostazol			–	1/25	4	
Mono antiplatelet vs. antiplatelet + anticoagulant										
Wang et al. [34]	RCT	Intraluminal and/or subintimal angioplasty	Femoro-popliteal and infra-popliteal	Aspirin	Aspirin (100 mg/day) from admission day to at least 12 months if no side effects. Batroxobin (5 IU/0.5 ml), 2 doses before and 4 doses post-procedure	12	0	3/60	5	n.s.
				Aspirin + batroxobin			0	5/51	10	
Koppensteiner et al. [33]	RCT	PTA	Femoro-popliteal	Aspirin	Aspirin (100 mg/day) 1 day before procedure + dalteparin (5000 IU/day) for 2 days postoperatively. Patients were randomized post-operatively to receive aspirin (100 mg/day) alone or + dalteparin (2500 IU/day) for 3 months	12	0	–	–	n.s.
				Aspirin + dalteparin			0	–	–	

n.s. not significant

arterial segment as well as follow-up duration. We also found that TLR was lower in DAPT-treated groups compared to MAPT-treated groups [28, 31]. However, in contrast to the superior effects of aspirin plus clopidogrel over aspirin in the context of TLR when treated for 6 months [31], this advantage disappeared at 1 year after intervention when clopidogrel was discontinued at 6 months [43], suggesting the need to treat patients with DAPT for a longer duration than 6 months after endovascular intervention. However, there have been no follow-up studies to address this issue, and further investigations are warranted to determine appropriate treatment duration.

Studies investigating anticoagulation therapy for endovascular intervention for PAD, whether alone or in combination with antiplatelet therapy, are limited. The combination of rivaroxaban and aspirin reduced the risk of (CV) death, stroke, MI, acute limb ischemia, vascular amputation, and mortality compared to aspirin alone in patients with established vascular diseases [44]. Although the rivaroxaban and aspirin increased bleeding relative to aspirin alone, there was no significant excess of severe bleeding. These results agree with studies regarding the combination of antiplatelet and anticoagulant following endovascular intervention for CLI [33, 34]. The development of restenosis, which leads to increased amputation rates following endovascular procedures, might be attributed to the development of both short-term (via elastic recoil) and long-term (via arterial remolding) changes in the treated vasculature [19, 36–38, 45]. The disturbance of blood flow may result from the use of a stent, leading to endothelial injury, which promotes platelet aggregation and disturbs the production of anti-thrombotic factors and vasodilatory factors as well as the activation of coagulation cascade, all of which lead to thrombus formation, proliferation of vascular smooth muscle, and consequently stenosis [19, 38–40]. These substances may also cause reduced lumen diameter because they promote proliferation of vascular smooth muscle, and their migration into the intima causes reduction in lumen diameter. Additionally, activation of the coagulation cascade at the site of endothelial injury promotes thrombus formation and may contribute directly to intimal hyperplasia and stenosis [19, 39, 40]. Thus, treatment with antiplatelet/anticoagulant can interfere with the progression of this pathophysiology and protect from the development of long-term complications such as restenosis and reocclusion following endovascular intervention by inhibiting platelet aggregation and activation and disrupting tissue factor stimulation of the coagulation cascade.

Prothrombotic derangement with reduced fibrinolysis and platelet hyperactivity is particularly prominent in CLI, likely because atherosclerosis is the most common cause of CLI. These events may extend to affect the outcome of the postoperative (endovascular or surgical bypass) treatment with antithrombotic drugs [46]. This phenomenon might partly explain the low incidence rate of bleeding in the studies included in this report, although further studies are needed to confirm this finding. Nonetheless, AP + AC can interfere with the progression of this pathophysiology and protect from the development of long-term restenosis and re-occlusion following endovascular intervention via inhibiting platelet aggregation and activation as well as disrupting tissue factor stimulation of the coagulation cascade. The AP + AC treatment regimen seems promising for CLI cases undergoing endovascular procedures and warrant further investigation, particularly for infra-popliteal endovascular intervention or with arterial injury > 10 cm [34].

CLI-specific antiplatelet/anticoagulant therapy is mainly extrapolated from studies of patients with asymptomatic PAD or claudication [27, 47]. Azarbal et al. suggested the extrapolation of PAD to CLI is reasonable since the studies contain both PAD and CLI patients [27]; however, there are challenges with this extrapolation. For instance, the efficacy of aspirin in patients with CLI remains elusive and may be related to underrepresentation of CLI in clinical trials of PAD, inefficient aspirin metabolism (i.e., aspirin resistance), and inappropriate dosing [27, 48]. Additionally, aspirin resistance may be a consequence of more rapid recovery of platelet aggregability following each

dose of aspirin in PAD, with accelerated platelet turnover [48]. Similarly, although dual antiplatelet therapy with aspirin and clopidogrel is frequently used in patients with CLI after endovascular or surgical revascularization, there is little evidence for the efficacy of this strategy. Importantly, endovascular and surgical intervention for CLI seem to cause a prothrombotic derangement with reduced fibrinolysis and platelet hyperactivity [46]. Also, studies addressing the role of antithrombotic treatment for CLI and PAD have many weaknesses preventing proper recommendations based on solid evidence [19, 27]. Issues that need to be addressed in future studies include the lack of standardization and harmonization of data collection, heterogeneity of patient demographics, underpowered statistical analyses, and non-consistent reporting of bleeding incidences, and also the lack of proper subgroup analyses for diseases, presence or absence of stents, injured arterial segments, and injury lengths. In this review, the values of subgroup analyses were shown for artery segment [34] and disease (diabetes) [32]. However, the most striking evidence for the value of subgroup analyses was the study showing no difference between aspirin alone and aspirin plus dalteparin on occlusion rates for PAD, but the subgroup analysis for CLI showed significantly better occlusion outcomes for aspirin plus dalteparin [33]. These results suggest the necessity of exclusively evaluating the antithrombotic effect in CLI patients after endovascular intervention, or at least stratifying data for CLI in PAD studies, since antithrombotic treatment after endovascular intervention for PAD might not necessarily be effective for CLI and vice versa. These limitations preclude the development of recommendations for antithrombotic therapy after endovascular intervention.

The study has some limitations. This review included both randomized trials and retrospective studies. Different combinations of drugs and follow-up durations within each treatment group were used across studies. The number of studies, number of patients, endovascular procedure, and follow-up duration varied across groups. Statistical methods varied across the studies and subgroup analyses were not consistently performed. The review included data on studies published over a period of over 10 years, so various aspects of these surgical procedures may have evolved during this time, thereby affecting outcomes. However, we believe that this study will be of great value for practitioners treating patients with CLI as the studies used in this review were mostly specific for CLI patients. This review also underscores the potential differences in antithrombotic treatment outcomes for PAD versus CLI, necessitating the need to develop studies exclusively investigating strategies to treat CLI patients.

CONCLUSIONS

Antithrombotic treatments improve patient outcomes following endovascular intervention for CLI by minimizing complications without increasing bleeding, particularly in patients treated with the combination of DAPT and AP + AC. However, these observations are based on few studies with heterogenous data reporting, necessitating well-designed prospective randomized trials with appropriate subgroup analyses to compare and validate the seemingly superior efficacy and safety of DAPT or AP + AC over MAPT reported in the literature.

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