Modern Medical Management for PAD: A Shifting Paradigm?

Developments in PAD management that signal a fundamental change from treating symptoms alone to modifying disease progression and improving outcomes with comprehensive, guideline-directed medical therapy.

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Peripheral artery disease (PAD) is an increasingly prevalent atherosclerotic disease affecting approximately 236 million people worldwide.[1] PAD is associated with significant morbidity, including functional impairment, reduced quality of life (QOL), and elevated risk of major adverse cardiovascular events (MACE) and major adverse limb events (MALE).[1] Over the past 2 decades, the management of PAD has evolved from a strategy centered on symptom management and revascularization to one that emphasizes comprehensive, guideline-directed medical therapy (GDMT) as the foundation of care (Figure 1). Contemporary management prioritizes aggressive risk factor modification and evidence-based pharmacotherapy (Table 1)[2-19] to reduce MACE and MALE, prevent morbidity, and improve QOL.

LIPID-LOWERING THERAPIES: MOVING BEYOND STATINS

Hyperlipidemia is a common risk factor for development of PAD. Lipid-lowering therapy with high-intensity statin is the foundation of treatment, with a recently updated goal of lowering low-density lipoprotein cholesterol (LDL-C) to < 55 mg/dL for patients with clinical atherosclerotic cardiovascular (CV) disease.[20] This represents a departure from the previous LDL-C target of < 70 mg/dL, reflecting a shift toward more intensive lipid-lowering therapy to maximize risk reduction.[1] Multiple studies have shown that statin therapy is associated with a reduction in limb events and CV mortality in patients with PAD.[21] Despite this recommendation, statins are traditionally underprescribed in patients with PAD compared to other atherosclerotic diseases, including patients with coronary disease and/or cerebrovascular disease.[22,23]

In addition to statin therapy, newer proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have been shown to reduce MACE and MALE.[1] In a subgroup analysis of the FOURIER trial, evolocumab significantly reduced MACE in patients with symptomatic PAD and adverse limb outcomes, with a consistent relationship between lower achieved LDL-C levels and further reduction of MALE.[24] Similar benefits in reduction of MACE were seen for alirocumab in the ODYSSEY OUTCOMES trial.[25] Thus, it is recommended to utilize PCSK9 inhibitors in patients with PAD who have not achieved target LDL-C.[20]

Other alternative lipid-lowering therapies including ezetimibe and bempedoic acid may be utilized to reduce atherosclerotic risk. In a subgroup analysis of the IMPROVE-IT trial, which evaluated simvastatin plus ezetimibe versus placebo in patients with acute coronary syndrome, ezetimibe was associated with reduction of MACE in patients with PAD.[8,26] Although there are no randomized data to support the use of ezetimibe to prevent MALE in patients with PAD, observational studies suggest reduction of limb amputation.[27] In the CLEAR Outcomes trial, bempedoic acid significantly reduced the risk of MACE compared with placebo among statin-intolerant patients with established or high-risk CV disease,[9] and, in an analysis of patients with PAD, reduced MALE.[28]

Elevated lipoprotein(a) (Lp[a]) has emerged as an additional risk factor for development of atherosclerotic disease, with high Lp(a) levels demonstrating a two- to threefold increased risk of PAD.[29] In ODYSSEY OUTCOMES, a reduction in PAD events with alirocumab was associated with baseline quartile of Lp(a).[25] Although currently there are no targeted Lp(a)-lowering therapies available for prescription, multiple investigational therapeutic trials are currently underway to study their effect on MACE and MALE.[30]

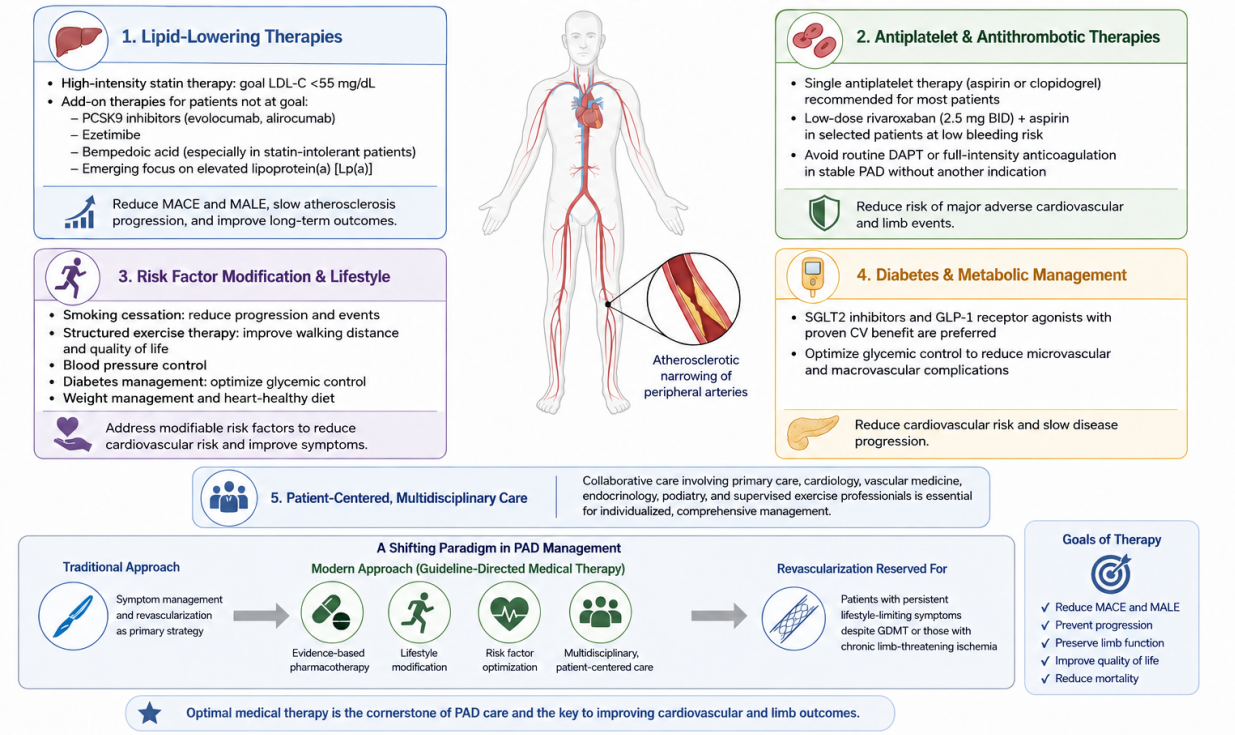

Figure 1. Modern medical management for PAD emphasizes comprehensive medical therapy, including intensive lipid-lowering, antithrombotic therapy, risk factor modification, exercise, and cardiometabolic treatment to reduce CV and limb events, improve function, and complement revascularization when needed. BID, twice daily; DAPT, dual antiplatelet therapy. Created with assistance from ChatGPT-5.6 Sol.

ANTITHROMBOTIC AND ANTIPLATELET THERAPY: BREAKTHROUGHS IN DUAL-PATHWAY INHIBITION

In patients with symptomatic PAD, current guidelines recommend single antiplatelet therapy with either aspirin or clopidogrel for reduction of MACE.[1] The CAPRIE trial demonstrated modest benefit of clopidogrel 75 mg daily compared to aspirin 325 mg daily in patients with recent ischemic stroke, recent myocardial infarction (MI), or symptomatic PAD.[2] This benefit was most pronounced in the PAD subgroup, forming the basis for contemporary guideline recommendations that generally favor clopidogrel over aspirin as the preferred single antiplatelet agent in patients with symptomatic PAD.[1] In patients with asymptomatic PAD, the role of antiplatelet therapy is less clear because the clinical trial assessing the question did not enroll a PAD population by typical diagnostic standards.[31]

More recent clinical trials have demonstrated the benefit of dual-pathway inhibition with use of antithrombotic agents such as low-dose rivaroxaban in addition to antiplatelet therapy with aspirin. In the landmark COMPASS trial, aspirin plus low-dose rivaroxaban 2.5 mg twice daily reduced MACE in patients with stable coronary artery disease and/or PAD compared to aspirin alone.[3] Subgroup analysis demonstrated treatment with rivaroxaban and aspirin compared with aspirin alone also reduced MALE, including major amputation.[32] This trial marked a pivotal advance in the medical management of PAD, as findings provided the first robust evidence that pharmacologic therapy could substantially reduce MALE, including acute limb ischemia and major vascular amputation in addition to CV events. Prior to COMPASS, pharmacologic therapies had primarily focused on CV risk reduction, with limited evidence supporting their ability to prevent limb events. These findings were further supported by the VOYAGER PAD trial in 2020, which demonstrated similar limb benefits of this regimen in patients with recent lower extremity revascularization.[4] Together, COMPASS and VOYAGER PAD establish dual-pathway inhibition as a cornerstone of contemporary PAD management, shifting the therapeutic paradigm from symptom-directed treatment to comprehensive prevention of both CV and limb ischemic events.

DIABETES MANAGEMENT: MORE THAN GLYCEMIC CONTROL

Diabetes is a known risk factor for the development of PAD and adverse limb events, including amputation, by accelerating atherosclerosis and contributing to ulcer formation with poor wound healing and neuropathy.[33,34] Although guidelines do not mention specific glycemic targets, it is recommended that glycemic control follows standard recommendations.[1]

Two classes of medications have emerged as primarily beneficial for the reduction of MACE in patients with PAD: sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs).[1] In the EMPA-REG OUTCOME trial, the SGLT2 inhibitor empagliflozin significantly reduced MACE.[10] Although dapagliflozin did not demonstrate a significant reduction in MACE in DECLARE-TIMI 58, it was associated with lower rates of CV death and heart failure (HF) hospitalization.[11] Canagliflozin reduced MACE in the CANVAS program; however, this benefit was accompanied by an increased risk of lower extremity amputation not seen with empagliflozin or dapagliflozin, prompting the FDA to issue a boxed warning.[12] Although this finding was not reproduced in the subsequent CREDENCE trial, trial protocol held canagliflozin for patients at high risk for amputation and incorporated more intensive foot surveillance.[35] The FDA removed the boxed warning in 2020, but canagliflozin continues to carry a precaution regarding amputation risk in susceptible patients. Subsequent meta-analyses did not demonstrate an increased risk of amputation with other SGLT2 inhibitors, supporting the preferential use of empagliflozin or dapagliflozin in patients with PAD when SGLT2 inhibitor therapy is indicated.[36,37]

GLP-1 AND THE CHANGING CARDIOMETABOLIC LANDSCAPE

In addition to SGLT2 inhibitors, GLP-1 RAs have transformed CV prevention by reducing atherosclerotic events

TABLE 1. PHARMACOLOGIC THERAPIES IN PAD: KEY CLINICAL TRIALS

Treatment	Medication	Key Studies (Year)	Population
Antithrombotic agents	Clopidogrel 75 mg once daily	CAPRIE (1996)[2]	RCT; N = 19,185 (~25% PAD) Recent ischemic stroke, recent MI, or symptomatic PAD
	Aspirin daily + rivaroxaban 2.5 mg twice daily	COMPASS (2017)[3]	RCT; N = 27,395 (7,470 with PAD; 4,129 with symptomatic PAD) Stable atherosclerotic disease (CAD, PAD, carotid disease)
		VOYAGER PAD (2020)[4]	RCT; N = 6,564 Symptomatic PAD with recent lower extremity revascularization
Lipid-lowering therapies	Statins	HPS (2007)[5]	N = 6,748 Patients with PAD
	PCSK9 inhibitors	FOURIER (2017)[6]	RCT; N= 27,564 (~ 13.2% PAD) Established ASCVD on statin with baseline LDL > 70 mg/dL
		ODYSSEY OUTCOMES (2018)[7]	RCT; N = 18,924 Recent ACS with LDL > 70 mg/dL on statin therapy
	Ezetimibe	IMPROVE-IT (2015)[8]	RCT; N = 18,144 (1,001 with PAD) Recent ACS
	Bempedoic acid	CLEAR Outcomes (2023)[9]	RCT; N = 13,970 (1,624 with PAD) Established CVD or high-risk primary prevention

and offering improvements in cardiometabolic risk factor management and functional status. Both the SUSTAIN-6 CV and LEADER outcome trials, which assessed semaglutide and liraglutide, respectively, included patients with known PAD and demonstrated significant reductions in MACE.[13,14] Beyond CV risk reduction, GLP-1 RAs also confer limb-specific benefits. The STRIDE trial demonstrated significant improvement in walking distance with semaglutide compared to placebo in patients with type 2 diabetes and symptomatic PAD with intermittent claudication.[15] These findings are particularly notable given that, aside from cilostazol, effective medical therapies targeting claudication symptoms have historically been scarce. With larger and longer-term studies, GLP-1 RAs have been shown to address both CV risk reduction and functional impairment, further expanding the role of medical therapy in contemporary PAD management.

Beyond their CV benefits, GLP-1 RAs are increasingly prescribed for the treatment of other metabolic disorders such as obesity, chronic kidney disease, obstructive sleep apnea, and metabolic dysfunction-associated steatohepatitis.[17] Since its initial FDA approval in 2005, GLP-1 use has significantly increased. Studies have shown that approximately 1 in 8 people in the United States have reported current or past GLP-1 usage.[38] Their rapid adoption extends their influence beyond individual patient care to the future of clinical investigation. As GLP-1 RAs become part of routine background therapy among trial participants, the landscape of PAD clinical trials will change. Future PAD trials will begin to evaluate novel therapies on top of GLP-1 RAs rather than in their absence, requiring careful interpretation of both CV and limb outcomes within an evolving standard of care. Furthermore, background therapy may lower baseline CV and metabolic risk and reduce trial event rates, ultimately requiring larger and longer studies or more targeted higher-risk cohorts while shifting expectations for incremental treatment effects.

	Result	CV Benefit	Limb Benefit
	RRR ~8.7% in favor of clopidogrel 75 mg daily vs aspirin 325 mg daily (95% CI, 0.3-16.5; *P* = .043)	↓ ACE (PAD subgroup showed the largest benefit)	_
	Aspirin + rivaroxaban 2.5 mg twice daily ↓ primary outcome vs aspirin alone (HR, 0.76; 95% CI, 0.66-0.86; *P* < .001)	↓ MACE	↓ MALE in subgroup analysis
	Aspirin + rivaroxaban 2.5 mg twice daily ↓ primary outcome vs aspirin alone (HR, 0.85; 95% CI, 0.76-0.96; *P* = .009)	↓ MACE	↓ MALE
	RRR ~22% with simvastatin vs placebo (95% CI, 15-29; *P* < .001)	↓ MACE	↓ amputation in observational studies
	↓ LDL ~59%; evolocumab ↓ primary endpoint (HR, 0.85; 95% CI, 0.79-0.92; *P* < .001)	↓ MACE	↓ MALE in subgroup analysis
	↓ LDL ~55%; alirocumab ↓ primary endpoint (HR, 0.85; 95% CI, 0.78-0.93; *P* < .001)	↓ MACE	? benefit (possible in high Lp[a])
	↓ LDL ~24%; simvastatin + ezetimibe ↓ primary outcome vs simavastatin alone (HR, 0.936; 95% CI, 0.89-0.99; *P* = .016)	Modest ↓ MACE	? benefit in observational studies
	Bempedoic acid ↓ primary endpoint vs placebo (11.7% vs 13.3%; HR, 0.87; 95% CI, 0.79-0.96; *P* = .004)	↓ MACE	↓ MALE in subgroup analysis

TABLE 1. PHARMACOLOGIC THERAPIES IN PAD: KEY CLINICAL TRIALS (CONT'D)

Treatment	Medication	Key Studies (Year)	Population
Diabetes	SGLT2 inhibitors	EMPA-REG OUTCOME (2015)[10]	RCT; N = 7,020 (~20.8% with PAD, N = 1,461) Type 2 diabetes with established CVD
		DECLARE-TIMI 58 (2019)[11]	RCT; N = 17,160 Type 2 diabetes with established ASCVD or multiple risk factors
		CANVAS (2017)[12]	Pooled data from CANVAS and CANVAS-R RCT; N = 10,142 Type 2 diabetes with established CVD or risk factors
	GLP-1 RAs	SUSTAIN-6 (2016)[13]	RCT; N = 3,297 (~14% PAD, N = 460) Type 2 diabetes with established CVD or high CV risk
		LEADER (2016)[14]	RCT; N = 9,340 (~12.7% PAD, N = 1,184) Type 2 diabetes with high CV risk
		STRIDE (2025)[15]	RCT; N = 792 Type 2 diabetes and PAD with intermittent claudication
Anti-inflammatory therapies	Colchicine	LoDoCo2 (2020)[16]	RCT; N = 5,522 Chronic coronary disease
	Canakinumab	CANTOS (2017)[17]	RCT; N = 10,061 Prior MI and elevated hs-CRP on statin
Antihypertensive therapies	ACE inhibitor	HOPE (2000)[18]	RCT; N = 9297 (~25% PAD) High CV risk without known HF
PDE3 inhibitor	Cilostazol	Money et al (1998)[19]	RCT; N = 239 Stable symptomatic intermittent claudication

Abbreviations: ACD, absolute claudication distance; ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CV, cardiovascular; CVD; cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; HR, hazard ratio; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); MACE, major adverse cardiovascular event; MALE, major adverse limb event; MI, myocardial infarction; PAD, peripheral artery disease; PCSK9, proprotein convertase subtilisin/kexin type 9; PDE3, phosphodiesterase 3 inhibitor; RCT, randomized controlled trial; RR, relative risk; RRR, relative risk reduction; SGLT2, sodium-glucose cotransporter 2.

ANTI-INFLAMMATORY THERAPIES: A POTENTIAL NEW TARGET?

Inflammation is increasingly recognized as a key contributor to the development and progression of atherosclerotic disease, including PAD.[39] Prior observational studies have demonstrated a relationship between elevated inflammatory markers, including C-reactive protein (CRP) and interleukin-6 (IL-6), and the development of PAD.[40-42] These findings have garnered interest in developing targeted anti-inflammatory therapies to reduce residual CV risk beyond conventional lipid-lowering therapies. In the CANTOS trial, canakinumab, an IL-1β inhibitor, significantly reduced the rate of CV events compared to placebo independent of lipid lowering in patients with prior MI and elevated high-sensitivity CRP.[17] Similarly, the LoDoCo2 trial also demonstrated beneficial effects of low-dose colchicine in reduction of CV events in patients with stable chronic coronary disease.[16] These findings establish inflammation as a potential therapeutic target in atherosclerotic disease. Although neither CANTOS nor LoDoCo2 specifically enrolled patients with PAD, their findings provide biological rationale for evaluating anti-inflammatory therapy in this high-risk population that experiences substantial residual risk despite contemporary GDMT. The ongoing LEADER-PAD trial is the first randomized controlled trial evaluating whether low-dose colchicine reduces MACE and MALE in patients with symptomatic PAD.[43] If positive, anti-inflammatory therapy could represent another important advance in the evolution of PAD management by targeting residual inflammatory risk in addition to thrombosis, cardiometabolic risk, and dyslipidemia.

	Result	CV Benefit	Limb Benefit
	Empagliflozin ↓ primary outcome vs placebo (10.5% vs 12.1%; HR, 0.86; 95% CI, 0.74-0.99; *P* = .04 for superiority)	↓ MACE	_
	Dapagliflozin did not ↓ MACE (HR, 0.93; 95% CI, 0.84-1.03; *P* = .17) but did ↓ CV death or hospitalization for HF (HR, 0.83; 95% CI, 0.73-0.95; *P* = .005)	No difference in MACE; ↓HF hospitalization	_
	Canagliflozin ↓ primary outcome vs placebo (HR, 0.86; 95% CI, 0.75-0.97; *P* < .001)	↓ MACE	_
	Semaglutide ↓ primary outcome vs placebo (HR, 0.74; 95% CI, 0.58-0.95; *P* = .02)	↓ MACE	_
	Liraglutide ↓ primary outcome vs placebo (HR, 0.87; 95% CI, 0.78-0.97; *P* < .001)	↓ MACE	_
	Semaglutide ↑ walking distance vs placebo (estimated treatment ratio, 1:13; 95% CI, 1·06-1·21; *P* = .0004)	_	↑ walking distance
	Colchicine ↓ primary endpoint vs placebo (HR, 0.69; 95% CI, 0.57-0.83; P < .001)	↓ MACE	Under investigation (LEADER-PAD trial)
	Canakinumab 150 mg ↓ primary endpoint (HR, 0.85; 95% CI, 0.74-0.98; *P* = .021)	↓ MACE	_
	Ramipril ↓ primary outcome vs placebo (RR, 0.78; 95% CI, 0.70-0.86; *P* < .001)	↓ MACE	_
	Cilostazol had a 47% increase in ACD compared with 12.9% for the placebo group (*P* < .001)	_	↑ walking distance

ADDRESSING CLAUDICATION IN THE MODERN ERA

Supervised exercise therapy (SET) is recommended for patients with chronic symptomatic PAD to improve functional status, walking distance, and QOL.[1,44,45] Studies have demonstrated that SET in combination with endovascular revascularization provides more benefit than SET alone.[46,47] While SET programs are considered optimal, utilization is poor.[48] Community and home-based exercise programs are considered alternatives when SET is either not available or accessible.[1,49] Recent advances in digital health, including wearable activity monitors, remote monitoring, and mobile applications, are an active area of investigation in PAD and may reshape the future of exercise therapy.[50-52]

Before GLP-1 RAs were shown to improve functional capacity, cilostazol, a phosphodiesterase-3 (PDE-3) inhibitor that induces arterial vasodilation, was the only medication recommended for the treatment of symptomatic PAD.[53] Compared to placebo, cilostazol significantly increased maximal walking distance by around 40 m.[53] This is broadly comparable to the effects of semaglutide in the STRIDE trial.[15] However, cilostazol is contraindicated in patients with HF due to adverse outcomes with other PDE-3 inhibitors in this population.[54] In contrast, GLP-1 RAs have proven benefits in reducing HF outcomes.[55] This is particularly relevant given the high coprevalence of HF in patients with PAD.[56] Both pharmacologic therapies demonstrate considerably modest gains when compared to SET, which can improve walking distance 150 to 300 m in some stud-

ies.[57] Overall findings suggest that pharmacologic therapy should be used in conjunction with targeted exercise therapy for improvement of symptoms and functional status. Future research may focus on integrating digital health technologies with pharmacologic therapies to optimize functional outcomes.

CONCLUSION

Management of PAD has evolved from a symptom-focused approach to one centered on comprehensive vascular risk reduction. Beyond established advances in lipid lowering and antithrombotic therapy, recent evidence demonstrating reductions in MALE with dual-pathway inhibition, improvement in functional outcomes with GLP-1 RAs, and growing interest in anti-inflammatory therapy have expanded the therapeutic landscape. Together, these developments signal a fundamental shift in PAD management from treating symptoms alone to modifying disease progression and improving both CV and limb outcomes. The results of the ongoing LEADER-PAD trial and longer-term studies evaluating the effects of GLP-1 RAs on limb outcomes will continue to shape the future direction of the field. ■

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