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REVIEW

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# Challenges and opportunities in the management of type 2 diabetes in patients with lower extremity peripheral artery disease: a tailored diagnosis and treatment review

Guillaume Mahé<sup>1,2,3\*</sup>, Victor Aboyans<sup>4,5</sup>, Emmanuel Cosson<sup>6,7</sup>, Kamel Mohammedi<sup>8,9</sup>, Gabrielle Sarlon-Bartoli<sup>10,11</sup>, Damien Lanéelle<sup>12,13</sup>, Tristan Mirault<sup>14,15</sup> and Patrice Darmon<sup>11,16</sup>

## Abstract

Lower extremity peripheral artery disease (PAD) often results from atherosclerosis, and is highly prevalent in patients with type 2 diabetes mellitus (T2DM). Individuals with T2DM exhibit a more severe manifestation and a more distal distribution of PAD compared to those without diabetes, adding complexity to the therapeutic management of PAD in this particular patient population. Indeed, the management of PAD in patients with T2DM requires a multidisciplinary and individualized approach that addresses both the systemic effects of diabetes and the specific vascular complications of PAD. Hence, cardiovascular prevention is of the utmost importance in patients with T2DM and PAD, and encompasses smoking cessation, a healthy diet, structured exercise, careful foot monitoring, and adherence to routine preventive treatments such as statins, antiplatelet agents, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. It is also recommended to incorporate glucagon-like peptide-1 receptor agonists (GLP-1RA) and sodium-glucose cotransporter-2 inhibitors (SGLT2i) in the medical management of patients with T2DM and PAD, due to their demonstrated cardiovascular benefits. However, the specific impact of these novel glucose-lowering agents for individuals with PAD remains obscured within the background of cardiovascular outcome trials (CVOTs). In this review article, we distil evidence, through a comprehensive literature search of CVOTs and clinical guidelines, to offer key directions for the optimal medical management of individuals with T2DM and lower extremity PAD in the era of GLP-1RA and SGLT2i.

**Keywords** Type 2 diabetes, Peripheral artery disease, Guidelines, Management, Glycemic control

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## Introduction

Type 2 diabetes mellitus (T2DM) stands out as a potent risk factor for lower extremity peripheral artery disease (PAD), with individuals with diabetes facing a two-fold higher risk of developing PAD compared to those without diabetes [1]. In comparison to individuals without diabetes, those with T2DM exhibit a more severe manifestation, partly related to concomitant neuropathy, as well as a more distal distribution of PAD, increasing the risk of complications [2, 3]. Patients with concomitant T2DM and PAD are at a high risk of cardiovascular events, including lower-limb events [2, 4]. Moreover, patients with PAD and T2DM are 2–10× more likely than non-diabetic patients to undergo an amputation [2, 5]. Indeed, approximately 70% of cases undergoing lower-extremity amputation in the United States are attributed to diabetes [6]. Diabetes-related amputations lead to profound functional disability, placing an immense economic burden on both patients and health systems [7]. Globally, 113 million individuals aged 40 years and older are living with PAD [8], of whom about 20–30% present with concomitant T2DM [9, 10].

Although T2DM may alter the clinical presentations of PAD, the diagnosis of PAD is often straightforward through non-invasive measures, such as the resting ankle-brachial index (ABI) and the toe-brachial index (TBI) [11, 12]. Conversely, the medical management of PAD, particularly in patients with T2DM, raises considerable challenges. While the focus has primarily been on managing major cardiac events in patients with T2DM, the care for PAD has experienced a more gradual progression in terms of evidence-based therapies [12, 13]. Notably, the benefits of novel glucose-lowering agents, such as glucagon-like peptide-1 receptor agonists (GLP-1RA) and sodium-glucose cotransporter-2 inhibitors (SGLT2i), for individuals with PAD remain overshadowed within the background of cardiovascular outcome trials (CVOTs). Existing data are often derived from post-hoc analyses of PAD subgroups, and offer, at best, low-grade evidence [14–18]. In addition, the types of medical and surgical specialties involved in PAD care vary significantly across the globe, and even within individual countries, leading to a heterogeneous and non-standardized patient pathway. The lack of standardized treatment protocols and organizational structures further contributes to the complexity of the management of patients with T2DM and PAD [19]. Therefore, pending the results of future clinical trials, multidisciplinary teams, including endocrinologists/diabetologists, vascular specialists, and primary care practitioners, have the opportunity to optimize the benefits gained from the existing treatment armamentarium in patients with both T2DM and PAD. In this review article, we distil evidence, through a comprehensive search of the literature and clinical guidelines,

to offer key directions for the optimal medical management of patients with T2DM and lower extremity PAD in the era of GLP-1RA and SGLT2i.

## Search strategy

Two industry-independent systematic literature searches were performed on MEDLINE (PubMed). The first search, which was conducted in October 2023, aimed to identify position statements, expert consensus, and societal guidelines on the treatment of PAD in patients with T2DM. The first search used the keywords: (“diabetes”) AND (“PAD” OR “peripheral artery disease” OR “peripheral arterial disease” OR “lower extremity arterial disease” OR “lower extremity artery disease” OR “LEAD”). In total, we found 15 clinical practice guidelines related to the therapeutic management of patients with T2DM and PAD (Table 1). The second search, which was conducted in November 2023, focused on identifying randomized controlled trials (RCTs) and CVOTs evaluating newer glucose-lowering agents for PAD, mainly GLP-1RA and SGLT2i. The second search included the keywords: (“PAD” OR “peripheral artery disease” OR “peripheral arterial disease” OR “amputation\*” OR “foot ulcer”) AND (“glucagon-like peptide-1” OR “glucagon-like peptide 1” OR “GLP-1” OR “GLP1” OR “GLP-1RA” OR “SGLT2” OR “SGLT2i” OR “sodium-glucose cotransporter 2” OR “sodium-glucose cotransporter-2” OR “liraglutide” OR “semaglutide” OR “dulaglutide” OR “exenatide” OR “lixisenatide” OR “efpeglenatide” OR “canagliflozin” OR “empagliflozin” OR “dapagliflozin” OR “ertugliflozin” OR “sotagliflozin”). In total, we found 15 CVOTs or RCTs evaluating GLP-1RA and SGLT2i for PAD (Table 2; Fig. S1).

## How does T2DM affect the pathophysiology of PAD?

The pathophysiology of PAD in patients with T2DM is similar to that in the non-diabetic population, except that the presence of concomitant diabetes mellitus can potentiate and accelerate the development and progression of PAD [9, 42]. The underlying T2DM metabolic abnormalities, namely chronic hyperglycemia, insulin resistance, and dyslipidemia, promote vascular inflammation, endothelial cell dysfunction, vasoconstriction, platelet activation, and thrombosis, all of which contribute to the progression of atherosclerotic lesions as well as microvascular damage in patients with T2DM [9, 42–45]. Endothelial dysfunction in T2DM can also be attributed to an overproduction of vasoconstrictors (e.g., endothelin-1) and prostanoids (e.g., thromboxane A2), contributing to abnormal vascular smooth muscle cell growth and migration [9, 46].

T2DM is considered as a proinflammatory state, associated with elevated levels of C-reactive protein and proinflammatory cytokines [9, 20, 47, 48]. This is further

**Table 1** Recommendations on the treatment of peripheral artery disease (PAD) in patients with type 2 diabetes mellitus (T2DM), as outlined by different clinical practice guidelines

Recommendation	ACC/ AHA [11]	ADA [20– 22]	ADFDG working group [23]	CCS [24]	CDS [25]	ESC/ ESVS [12, 13, 26–28]	GDS [29, 30]	SFMV/ SCVE [31]
Smoking cessation	X	X	X	X		X	X	X
Structured exercise therapy, in particular supervised exercise training	X	X		X		X	X	X
Mediterranean diet		X				X		X
Lipid-lowering agents: Statins, with additional lipid-lowering therapy with ezetimibe or a PCSK9 inhibitor if target lipid levels not achieved	X	X	X	X	X	X	X	X
Tight glycemc control (HbA1c < 7.0%)	X	X		X		X		X
Antihypertensive agents: ACEis or ARBs	X	X		X		X	X	X
Long-term antiplatelet therapy with clopidogrel or aspirin in patients with symptomatic PAD	X	X	X	X	X	X	X	X
Combination of rivaroxaban (2.5 mg twice daily) and aspirin (up to 100 mg once daily) in patients with symptomatic PAD at a low risk of bleeding		X		X		X	X	X
Revascularization in case of a lifestyle-limiting claudication or a chronic limb-threatening ischemia	X	X	X	X	X	X	X	X
Revascularization decisions based on individual factors (i.e., length, anatomic location, and extent of obstructive disease, availability of autogenous vein, patient comorbidities, local expertise)	X	X	X	X	X	X	X	X

ACC, American College of Cardiology; ACEi, angiotensin-converting enzyme inhibitor; ADA, American Diabetes Association; ADFDG, Australian Diabetes-related Foot Disease Guidelines; AHA, American Heart Association; ARB, angiotensin-receptor blocker; CCS, Canadian Cardiovascular Society; CDS, Chinese Diabetes Society; ESC, European Society of Cardiology; ESVS, European Society for Vascular Surgery; GDS, German Diabetes Society; HbA1c, glycated hemoglobin; PCSK9, proprotein convertase subtilisin/kexin type 9; SCVE, French Society for Vascular and Endovascular Surgery; SFMV, French Society of Vascular Medicine

compounded by hyperglycemia-induced activation of inflammatory pathways, which leads to the development of atherosclerosis [45, 46, 49]. T2DM is additionally associated with the enhanced production of advanced glycation end products that interact with their receptors to upregulate inflammatory transcription factors, leading to medial calcification and an increased leukocyte activity [43, 45, 49, 50]. Likewise, T2DM potentiates platelet aggregation, accelerates platelet turnover, and heightens blood coagulability by increasing the expression of tissue factor and decreasing antithrombin levels, contributing to a thrombotic environment [9, 51].

Overall, the interplay of all these aforementioned factors in individuals with T2DM accelerates the development and progression of atherosclerosis, which, coupled with diabetic microvascular complications, worsens the prognosis of PAD in the lower extremities (Fig. 1).

**Features of PAD in patients with T2DM**

Table 3 compares the typical features of lower extremity PAD in individuals with T2DM to those without T2DM. Compared to non-diabetic PAD, T2DM is associated with more distal lesions, and a more diffuse and multi-segmental pattern of PAD [2, 52, 53].

In patients with T2DM, PAD is commonly asymptomatic due to the presence of diabetic neuropathy [20]. This concomitant peripheral neuropathy may predispose patients with T2DM and PAD to present with advanced disease compared to patients without diabetes [2, 55]. Hence, those with T2DM and PAD are more likely to

develop chronic limb-threatening ischemia (CLTI) [5, 11, 56]. The coexistence of diabetes mellitus with peripheral neuropathy and PAD may also make the presentation of foot infection more subtle [11]. Besides neuropathy, other diabetic microvascular complications such as diabetic retinopathy are also associated with more severe PAD and CLTI [55, 57].

**Pitfalls in the diagnosis of PAD in T2DM**

Various clinical practice guidelines recommend the annual examination of all patients with T2DM for the presence of PAD, even in the absence of foot ulceration. This examination should include a medical history, assessing exertional leg symptoms (intermittent claudication or other walking impairment, ischemic rest pain, and non-healing wounds), palpating peripheral pulses, and examining the skin’s appearance (color, temperature, and pilosity) [11, 13, 23, 25, 26, 58, 59]. Indeed, performing a thorough skin examination is important in patients with T2DM, as there are diabetic cutaneous manifestations associated with PAD, most commonly diabetic dermopathy [60]. In addition, features such as dry, cool, or fissured skin, absence of hair growth, and dystrophic toenails are frequently observed in patients with PAD [61]. Neuropathy, which is a major risk factor for tissue loss, should also be assessed using 10-g monofilaments and, if available, a tuning fork to assess vibration sense [26, 61]. Overall, such a thorough clinical evaluation is essential to detect masked PAD in patients with T2DM [26].

**Table 2** Analyses of cardiovascular outcome trials (CVOTs) assessing sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA) for peripheral artery disease (PAD)

Trial(s)	References	Study description	Follow-up	Main findings
<i>SGLT2i</i>				
CANVAS & CANVAS-Renal (canagliflozin)	Matthews et al. [32]	Post-hoc analysis of 2 double-blind, randomized trials involving 10,142 patients with T2DM and a history or a high risk of CV disease who received canagliflozin (100 or 300 mg/day orally) vs. matching placebo	Mean of 3.6 years (5.7 in CANVAS and 2.1 years in CANVAS-R)	Rates of amputations were 6.30 and 3.37 events per 1000 participant-years with canagliflozin vs. placebo (HR 1.97; 95% CI 1.41–2.75) Risk factors for amputation included: history of amputation (HR 16.27; 95% CI 10.65–24.63), history of peripheral vascular disease (HR 2.77; 95% CI 1.93–3.96), and history of neuropathy (HR 1.86; 95% CI 1.35–2.56)
CANVAS & CANVAS-Renal & CREDESCENCE (canagliflozin)	Yi et al. [14]	Post-hoc analysis of 3 double-blind, randomized trials in 14,543 patients with T2DM, of which 3514 had CKD without PAD and 1156 had CKD and PAD, who received canagliflozin (100 or 300 mg/day orally) vs. matching placebo	Median of 2.5 years	In those with CKD and PAD, canagliflozin reduced risk of MACE (HR 0.62; 95% CI 0.47–0.83), composite of HHF or CV death (HR 0.62; 95% CI 0.46–0.82), and composite of ESKD or doubling of serum creatinine (HR 0.51; 95% CI 0.33–0.79), with no heterogeneity of effect with canagliflozin between patients with and without PAD ( $p_{\text{interaction}} > 0.20$ ) No increase in serious AEs or lower-limb amputations was observed with canagliflozin in patients with CKD, regardless of PAD status ( $p = 0.33$ )
CANVAS & CANVAS-Renal & CREDESCENCE (canagliflozin)	Barracough et al. [33]	Post-hoc analysis of 3 double-blind, randomized trials in 14,543 patients with T2DM, of whom 3159 (21.7%) had PAD at baseline, who received canagliflozin vs. matching placebo	Median of 2.5 years	In patients with PAD, canagliflozin reduced MACE (HR 0.76; 95% CI 0.62–0.92), with similar MACE benefits in patients without PAD (HR 0.86; 95% CI 0.76–0.98) No difference in amputation risk by PAD status ( $p_{\text{interaction}}$ of 0.31), but there was an overall increased risk of amputation with canagliflozin (HR 1.50; 95% CI 1.19–1.89). This was due to increase seen in CANVAS program
CANVAS & CANVAS-Renal & CREDESCENCE (canagliflozin)	Arnott et al. [34]	Post-hoc analysis of 3 double-blind, randomized trials, involving 10,142 patients with T2DM in CANVAS and 4401 patients with T2DM in CREDESCENCE, to determine if there was an explanation as to why the effects of canagliflozin on amputation risk vary between CANVAS and CREDESCENCE	Median follow-up was 2.4 years in CANVAS and 2.5 years in CREDESCENCE	There were 133 amputations in CREDESCENCE and 187 amputations in CANVAS, with prior amputation as strongest predictor of future amputations Effect of canagliflozin on amputation risk was significantly different between CANVAS and CREDESCENCE ( $p_{\text{heterogeneity}}$ of 0.02), but this was not explained by participant or trial differences. There was no evidence that foot disease management protocols in CREDESCENCE ameliorated amputation risk
DAPA-HF & DELIVER (dapagliflozin)	Butt et al. [15]	Post hoc analysis of 2 randomized, double-blind trials in 11,005 patients with symptomatic HF, 809 (7.4%) of whom with history of PAD, who received dapagliflozin (10 mg/day orally) vs. matching placebo	Median of 1.8 years	Dapagliflozin, compared to placebo, reduced risk of worsening HF or CV death to same extent in patients with (HR 0.71; 95% CI 0.54–0.94) and without (HR 0.80; 95% CI 0.73–0.88) PAD, with no interaction between PAD and effect of treatment ( $p_{\text{interaction}}$ of 0.39) Amputation rate did not differ between dapagliflozin and placebo in those with (HR 0.87; 95% CI 0.43–1.75) or without PAD (HR 0.87; 95% CI 0.46–1.64)

**Table 2** (continued)

Trial(s)	References	Study description	Follow-up	Main findings
DECLARE-TIMI 58 (dapagliflozin)	Bonaca et al. [35]	Post hoc analysis of a double-blind, randomized trial involving 17,160 patients with T2DM and a history or a high risk of CV disease, including 1025 (6.0%) with a history of symptomatic lower extremity PAD, who received dapagliflozin (10 mg/day orally) vs. matching placebo	Median of 4.2 years	<p>Patients in placebo arm with PAD vs. those without PAD had a higher adjusted risk of CV death/HHF (HR 1.60; 95% CI 1.21–2.12; <math>p=0.001</math>), progression of kidney disease (HR 1.51; 95% CI 1.13–2.03; <math>p&lt;0.01</math>), and limb AEs (HR 8.37; 95% CI 6.45–10.87; <math>p&lt;0.001</math>)</p> <p>Overall, amputation risk was higher in those with vs. without PAD (5.6% vs. 1.1%; HR 4.47; 95% CI 2.86–7.00; <math>p&lt;0.001</math>). Predictors of amputation were PAD, longer T2DM duration, male sex, history of HF, higher baseline HbA1c, and non-use of statin and/or ezetimibe</p> <p>Benefit of dapagliflozin on HHF or CV death was consistent regardless of PAD status (PAD: HR 0.86; no PAD: HR 0.82; <math>P_{\text{interaction}}</math> of 0.79). Similarly, benefits for reductions in kidney complications with dapagliflozin vs. placebo were consistent (PAD: HR 0.78; no PAD: HR 0.76; <math>P_{\text{interaction}}</math> of 0.84)</p> <p>No differences between dapagliflozin vs. placebo in limb ischemic AEs (HR 1.07; 95% CI 0.90–1.26; <math>p=0.45</math>) and amputation (HR 1.09; 95% CI 0.84–1.40; <math>p=0.53</math>), with no significant interactions by presence of PAD or not (<math>p_{\text{interaction}}</math> of 0.30 and 0.093, respectively)</p>
EMPA-REG OUTCOME (empagliflozin)	Verma et al. [16]	Post hoc analysis of a double-blind, randomized trial involving 7020 patients with T2DM and established CV disease, 1461 (20.8%) of whom had PAD at baseline, who received empagliflozin (10 or 25 mg/day orally) vs. placebo	Median of 3.1 years	<p>In patients with PAD, empagliflozin vs. placebo reduced CV death by 43% (HR 0.57; 95% CI 0.37–0.88), all-cause death by 38% (HR 0.62; 95% CI 0.44–0.88), HHF by 44% (HR 0.56; 95% CI 0.35–0.92), and incident or worsening nephropathy by 46% (HR 0.54; 95% CI 0.41–0.71)</p> <p>In patients with PAD, rate of lower-limb amputations was 5.5% with empagliflozin and 6.3% with placebo (HR 0.84; 95% CI 0.54–1.32). In patients without PAD, rate of lower-limb amputations was 0.9% with empagliflozin and 0.7% with placebo (HR 1.30; 95% CI 0.69–2.4)</p>
EMPA-REG OUTCOME (empagliflozin)	Inzucchi et al. [36]	Post hoc analysis of a double-blind, randomized trial in 7,020 patients with T2DM and CV disease, who received empagliflozin vs. placebo, aimed to assess lower-limb amputations in EMPA-REG OUTCOME	Median of 3.1 years	<p>Lower-limb amputations were reported in 131 patients: 88/4,687 patients (1.9%) treated with empagliflozin and 43/2,333 (1.8%) treated with placebo. The incidence rate was 6.5 per 1000 patient-years in both groups. In the analysis of time to first event, the risk of lower-limb amputations was similar between empagliflozin and placebo (HR 1.00; 95% CI 0.70–1.44)</p>
VERTIS CV (ertugliflozin)	Cannon et al. [37]	Double-blind, randomized trial in 8,246 patients with T2DM and CV disease, 1,541 (18.7%) of whom had PAD, who received ertugliflozin (5 or 15 mg/day orally) vs. placebo	Median of 3.0 years	<p>MACE occurred in 653 of 5,493 patients (11.9%) in ertugliflozin group and in 327/2745 patients (11.9%) in placebo group (HR 0.97; 95% CI 0.85–1.11)</p> <p>Amputations were performed in 2.0% of ertugliflozin-treated patients and in 1.6% of patients receiving placebo. Vascular disorders occurred in 2.9% of ertugliflozin-treated patients and in 3.6% of patients receiving placebo</p>
SOLOIST-WHF (sotagliflozin*)	Bhatt et al. [38]	Double-blind trial, randomizing 1,222 patients with T2DM and worsening HF to 200 or 400 mg of oral sotagliflozin or placebo once daily	Median of 9.0 months	<p>Amputations were performed in 4/605 patients receiving sotagliflozin (0.7%) and 1/611 receiving placebo (0.2%)</p>
SOTA-CKD3 (sotagliflozin*)	Cherney et al. [39]	Double-blind trial, randomizing 787 patients with T2DM and an eGFR of 30–59 ml/min/1.73 m <sup>2</sup> to 200 or 400 mg of oral sotagliflozin or placebo once daily	52 weeks	<p>MACE occurred in 18/527 patients (3.4%) receiving sotagliflozin and in 9/260 patients (3.5%) receiving placebo</p> <p>Amputations were performed in 3/527 patients (0.6%) receiving sotagliflozin and in 3/260 patients (1.2%) receiving placebo</p>
SOTA-CKD4 (sotagliflozin*)	Cherney et al. [40]	Double-blind trial, randomizing 277 patients with T2DM and an eGFR of 15–30 ml/min/1.73 m <sup>2</sup> to 200 or 400 mg of oral sotagliflozin or placebo once daily	52 weeks	<p>MACE occurred in 7/184 patients (3.8%) receiving sotagliflozin and in 12/93 patients (12.9%) receiving placebo</p> <p>Amputations were performed in 3/184 patients (1.6%) receiving sotagliflozin and in 0/93 patients (0%) receiving placebo</p>

**Table 2** (continued)

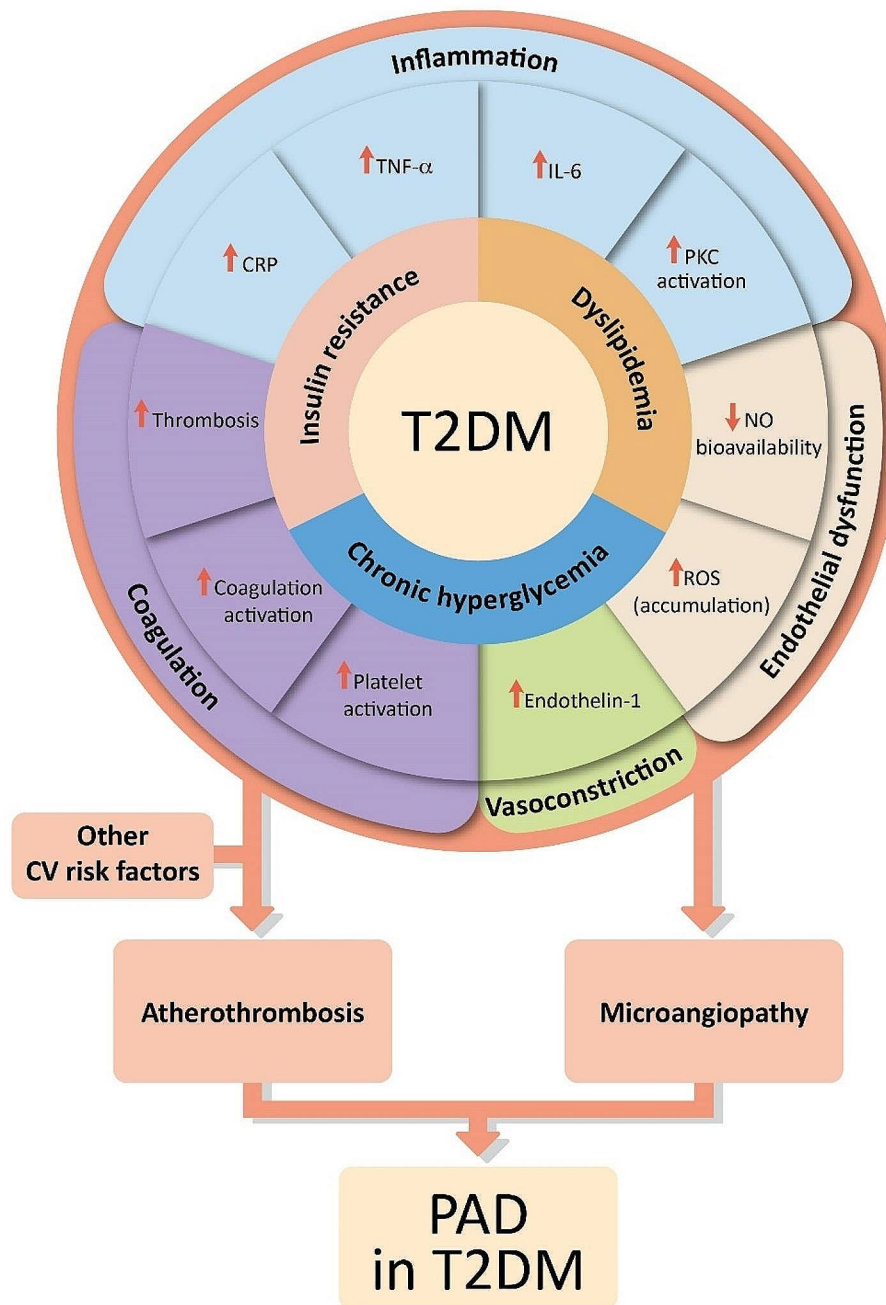
Trial(s)	References	Study description	Follow-up	Main findings
LEADER & SUSTAIN-6 (liraglutide and semaglutide)	Verma et al. [17]	Post hoc analysis of 2 randomized, double-blind trials in patients with T2DM at high CV risk or with CV disease. LEADER included 9,340 patients, 1,184 (12.7%) of whom had PAD, who received SC liraglutide ( $\leq 1.8$ mg/day) vs. placebo. SUSTAIN-6 included 3,297 patients, 460 (14.0%) of whom had PAD, who received SC semaglutide (0.5 or 1.0 mg/week) vs. placebo	Median of 3.8 years in LEADER and 2.1 years in SUSTAIN-6	Patients with PAD were at a ~35% increased risk of MACE vs. those without PAD (LEADER: HR 1.36; 95% CI 1.17–1.58; $p < 0.0001$ ; SUSTAIN-6: HR 1.33; 95% CI 0.94–1.83; $p = 0.09$ ) Effects of both therapies on MACE were consistently beneficial in patients with PAD (liraglutide: HR 0.77; 95% CI 0.58–1.01; semaglutide: HR 0.61; 95% CI 0.33–1.13) and without PAD (liraglutide: HR 0.89; 95% CI 0.79–1.00; semaglutide: HR 0.77; 95% CI 0.58–1.01; $p_{\text{interaction}}$ of 0.34 for liraglutide and 0.49 for semaglutide)
LEADER (liraglutide)	Dhatariya et al. [41]	Post hoc analysis of a double-blind, randomized trial in 9,340 patients with T2DM at high CV risk, aimed at assessing the impact of SC liraglutide (1.8 mg/day) vs. placebo on the incidence of DFUs and their sequelae	Median of 3.8 years	Similar rates of patients reported DFUs (176/4668 [3.8%] with liraglutide vs. 191/4,672 [4.1%] with placebo; HR 0.92; 95% CI 0.75–1.13; $p = 0.41$ ) Analysis of DFU-related sequelae demonstrated a significant reduction in amputations with liraglutide vs. placebo (HR 0.65; 95% CI 0.45–0.95; $p = 0.028$ ). However, there was no difference between treatments in DFU requiring peripheral revascularization (HR 0.87; 95% CI 0.48–1.58; $p = 0.64$ )
EXSCEL (exenatide)	Badjatiya et al. [18]	Post hoc analysis of a double-blind, randomized trial involving 14,752 patients with T2DM, 2,800 (19.0%) of whom had documented PAD, who received SC exenatide (2 mg/week) vs. placebo	Median of 3.2 years	Patients with PAD were less likely to be on a statin (65.8% vs. 75.3%), a $\beta$ -blocker (45.4% vs. 58.1%), an angiotensin-converting enzyme inhibitor (45.2% vs. 49.5%), or aspirin (57.3% vs. 65.0%) vs. patients without PAD Compared to patients without PAD, those with PAD had higher rates of MACE (13.6% vs. 11.4%; HR 1.13; 95% CI 1.00–1.27; $p = 0.047$ ), all-cause mortality (10.0% vs. 6.8%; HR 1.38; 95% CI 1.20–1.60; $p < 0.001$ ), and amputations (5.0% vs. 0.9%; HR 5.48; 95% CI 4.16–7.22; $p < 0.001$ ) Exenatide and placebo resulted in similar rates of amputations in those with PAD (5.0% with exenatide vs. 4.9% with placebo; HR 0.99; 95% CI 0.71–1.38) and in those without PAD (0.9% in both groups; HR 0.96; 95% CI 0.66–1.41; $p_{\text{interaction}}$ of 0.92). Patients treated with exenatide or placebo also had similar rates of MACE, regardless of PAD status ( $p_{\text{interaction}}$ of 0.42)

AE, adverse event; CANVAS, CANagliflozin cardioVascular Assessment Study; CI, confidence interval; CKD, chronic kidney disease; CRENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; CV, cardiovascular; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58; DELIVER, Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure; DFU, diabetic foot ulcer; eGFR, estimated glomerular filtration rate; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; ESKD, end-stage kidney disease; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; HbA1c, glycated hemoglobin; HF, heart failure; HHF, hospitalization for heart failure; HR, hazard ratio; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MACE, major adverse cardiovascular events; SC, subcutaneous; SOLOIST-WHF, Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; T2DM, type 2 diabetes mellitus; VERTIS CV, Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes; vs., versus

\*Sotagliflozin is a dual inhibitor of SGLT1 and SGLT2

In patients with clinical suspicion for PAD (e.g., in case of absent or diminished foot pulses), the diagnosis of PAD is established with the measurement of the resting ABI. Patients with  $ABI \leq 0.90$  are diagnosed with PAD [4, 11, 12, 31]. However, although ABI is currently the first choice for evaluating PAD, peripheral diabetic arteries frequently have medial and intimal calcifications, resulting in higher segmental and ankle pressures and consequently an elevated ABI ( $>1.40$ ) [52]. A retrospective study including 1162 patients with symptomatic PAD from a United States vascular laboratory showed that resting ABI had a reduced accuracy of 66% in patients with diabetes versus 81% in patients without diabetes

( $p < 0.001$ ) [62]. Hence, in patients with T2DM, it is recommended to also measure the TBI and toe pressure, because medial calcification rarely affects digital arteries. A  $TBI \leq 0.70$  is diagnostic of PAD [4, 11]. The toe pressure is normally 10 mmHg lower than the brachial pressure, a toe pressure  $< 40$  mmHg predicts impaired wound healing for ischemic ulcers, and a toe pressure  $< 30$  mmHg can be used as a hemodynamic diagnostic criterion for CLTI [52, 61]. Transcutaneous oxygen pressure ( $TcPO_2$ ) at rest or during exercise is another measure of skin perfusion that is not affected by calcification of the medial arteries, and can thus be also useful in patients with



**Fig. 1** Pathophysiology of lower extremity peripheral artery disease (PAD) in patients with type 2 diabetes mellitus (T2DM). Other cardiovascular (CV) risk factors may include advanced age, smoking, hypertension, longer duration of diabetes, neuropathy, retinopathy, and prior history of CV disease. Abbreviations CRP, C-reactive protein; IL, interleukin; NO, nitric oxide; PKC, protein kinase C; ROS, reactive oxygen species; TNF- $\alpha$ , tumor necrosis factor-alpha

T2DM. A resting TcPO<sub>2</sub> value <30 mmHg can be used as a hemodynamic diagnostic criterion for CLTI [31].

In addition to measuring the ABI and the TBI, Doppler waveform analysis of the ankle arteries is recommended in patients with T2DM and suspected PAD to detect occlusive disease despite calcified arteries [4, 26, 31]. In a retrospective, community-based study from Australia performed in 396 patients with suspected PAD, which

used color duplex ultrasound as the reference standard, the sensitivity of continuous-wave Doppler waveform analysis was unaffected by the presence of diabetes (83% in patients with diabetes and 81% in those without diabetes) [63]. Similarly, the specificity of continuous-wave Doppler was unaffected by diabetes (88% in patients with diabetes and 90% in those without diabetes) [63]. Doppler waveform analysis has also been found to be useful



**Table 3** Characteristics of peripheral artery disease (PAD) in patients with type 2 diabetes mellitus (T2DM) compared with patients without T2DM

Patients with PAD without T2DM	Patients with PAD and T2DM
<i>Anatomical aspects</i> [2, 50, 53, 54]	
Anatomical localization mainly proximal (aorta, iliac, femoral, and popliteal arteries)	Anatomical localization mainly distal (popliteal, tibial, and fibular arteries)
Focal pattern of PAD	Diffuse, multisegmental, and bilateral pattern of PAD
Less extensive arterial wall calcification, which is often more localized and intimal	Extensive arterial wall calcification often observed, which is more circumferential and medial
Collateral arterial bed rather well-developed	Impaired collateral arterial bed often observed
<i>Clinical features</i> [2, 9, 20, 53, 55]	
Typical PAD presentation such as intermittent claudication	More frequent asymptomatic presentation or atypical symptoms such as leg fatigue or slow walking velocity
Individuals are generally more aware of foot wounds	Higher risk of non-healing foot wounds, consequently leading to an increased risk of infections
Progression may be slow and often correlates more directly with lifestyle factors (e.g., smoking, hyperlipidemia)	Faster progression with a higher risk of gangrene, chronic limb-threatening ischemia, and amputations
Ankle-brachial index (ABI) and other non-invasive tests are more reliable for diagnosing PAD	Due to medial arterial calcification, ABI may be falsely elevated (underdiagnosis)
Treatment response can be more predictable	Might have a less favorable response to certain treatments (e.g., angioplasty), and may require more aggressive medical management

in evaluating PAD severity and for the detection of CLTI [64]. In patients with T2DM with confirmed PAD by an  $ABI \leq 0.90$ , a  $TBI \leq 0.70$ , and/or monophasic/biphasic Doppler waveform morphology, additional non-invasive imaging with duplex ultrasound, magnetic resonance angiography, or computed tomographic angiography can be performed to characterize the arterial lesions present and to develop an individualized treatment plan [4, 11, 31]. Figure 2 summarizes our overall diagnostic algorithm of PAD in patients with T2DM.

To aid in the early detection of PAD in individuals with T2DM, the American Diabetes Association recommends screening for asymptomatic PAD using the ABI in patients with T2DM at high risk for PAD, including any of the following: age  $\geq 50$  years, diabetes duration  $\geq 10$  years, comorbid microvascular disease, clinical evidence of foot complications, or any end-organ damage from diabetes [21]. However, the usefulness of screening PAD using the ABI and the TBI among patients with T2DM without any symptoms or wound problems remains a topic of debate. There are no randomized trials comparing PAD screening versus no screening in patients with

T2DM. Moreover, the United States Preventive Services Task Force suggested that in patients with T2DM who are already at high risk for cardiovascular disease (CVD), screening for PAD with an ABI is unlikely to alter effective management decisions and improve clinical outcomes [65]. Nevertheless, screening for PAD using the ABI is justifiable in patients with T2DM, given that PAD is a public health issue that is often underrecognized, and not performing this non-invasive and readily available diagnostic test is potentially harmful in individuals at high risk for PAD [66].

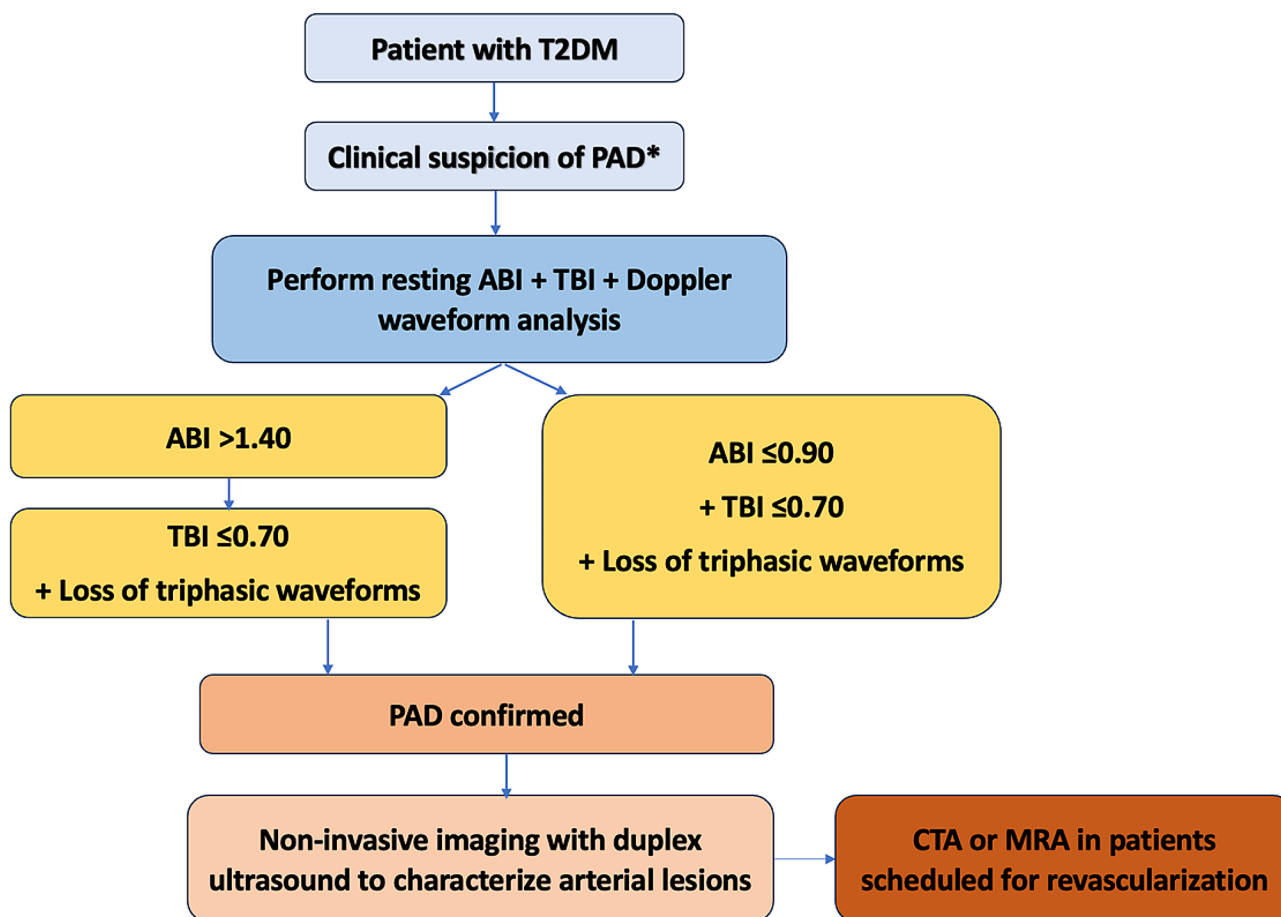
### Does T2DM make a difference in the therapeutic approach of PAD?

#### *What do treatment guidelines recommend?*

The therapeutic approach of PAD in individuals with T2DM is consistent across different clinical practice guidelines, as summarized in Table 1. Given that the combination of T2DM and PAD is associated with a very high cardiovascular risk [67], general cardiovascular prevention is of the utmost importance and encompasses non-pharmacological measures such as smoking cessation, a healthy diet, and structured exercise [12, 13]. In addition, pharmacological therapy includes antihypertensive drugs, lipid-lowering agents, glucose-lowering agents, and antithrombotic agents [23, 58].

It is recommended to target systolic blood pressure between 120 and 130 mmHg and diastolic blood pressure below 80 mmHg in patients with T2DM, while avoiding orthostatic hypotension in older ( $>65$  years) and frail patients [26]. Aggressive management of dyslipidemia in patients with T2DM and PAD is also necessary, with a  $\geq 50\%$  reduction from baseline for low-density lipoprotein (LDL) cholesterol and a recommended target value  $<1.4$  mmol/L ( $<55$  mg/dL) [26]. Regardless of baseline LDL cholesterol levels, clinical practice guidelines recommend statin therapy in all patients with PAD for the prevention of major adverse cardiovascular events (MACE) (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke) and major adverse limb events (MALE) (limb ischemia, amputation, or PAD-related revascularization) [11–13, 23, 24, 29, 30]. On top of general prevention, statins are also indicated in patients with PAD to improve walking distance [11, 12, 68]. In patients with PAD who do not achieve their target LDL cholesterol on statin therapy alone, additional lipid-lowering therapy with ezetimibe (a cholesterol absorption inhibitor) and a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor is recommended [21, 26]. PCSK9 inhibition has been found to significantly reduce the risk of MACE in patients with PAD [69, 70].

As a secondary prophylaxis in patients with T2DM and symptomatic PAD, all clinical practice guidelines advocate single antiplatelet therapy, either aspirin (75–100 mg



**Fig. 2** Diagnostic approach for lower extremity peripheral artery disease (PAD) in patients with type 2 diabetes mellitus (T2DM). *Abbreviations* ABI, ankle-brachial index; CTA, computed tomography angiography; MRA, magnetic resonance angiography; TBI, toe-brachial index. \*Recommended annual clinical evaluation (medical history, feet inspection, assessing PAD symptoms, monofilament test)

per day) or clopidogrel (75 mg per day), to reduce the risk of MACE [11–13, 24, 29, 30]. Of note, long-term dual antiplatelet therapy (aspirin plus clopidogrel) is not recommended in patients with T2DM and symptomatic PAD, as it may increase the risk of bleeding without providing substantial additional cardiovascular benefits [11, 12]. However, a combination of low-dose rivaroxaban (2.5 mg twice daily) and aspirin (100 mg once daily) should be considered in patients with symptomatic PAD at a low risk of bleeding [26, 27]. Compared with aspirin alone, the addition of rivaroxaban to aspirin reduced the risk of MACE and MALE in patients with symptomatic PAD [71–73].

When intermittent claudication impairs everyday life activities, or if a patient with T2DM and symptomatic PAD develops CLTI, revascularization is recommended to restore direct blood flow to at least one of the foot arteries [11, 12, 20, 23, 24, 29, 30]. Importantly, any revascularization procedure should be part of a comprehensive care plan that addresses other issues encountered in patients with T2DM and PAD including:

prompt treatment of any concurrent foot infection, regular wound debridement, biomechanical offloading (if inappropriate plantar pressures are detected), control of blood glucose, assessment and improvement of nutritional status, treatment of edema and other comorbidities, as well as exercise rehabilitation [11, 13, 74].

**Role of glucose-lowering agents in T2DM and PAD**

The risk of both microvascular and macrovascular complications of T2DM is strongly associated with hyperglycemia [75]. In the EUCLID (Examining Use of ticagrelor in peripheral artery Disease) trial, every 1% increase in glycated hemoglobin (HbA1c) was associated with a 14% increased risk for MACE in patients with symptomatic PAD and T2DM [76]. Hence, the achievement of a HbA1c level <7.0% (<53 mmol/mol) is recommended in patients with T2DM and PAD to reduce microvascular complications, and should be considered for reducing macrovascular complications in the long term [11, 12, 20, 24, 26]. Target HbA1c levels should nevertheless be individualized in accordance with age, T2DM duration,

and patient comorbidities, while avoiding hypoglycemic episodes [26].

The choice of glucose-lowering agents in patients with PAD should also be individualized to the key product characteristics, the patient's wishes, preferences, and financial support/drug coverage [24]. However, it is recommended to include GLP-1RA or SGLT2i in the medical management of patients with T2DM and PAD, since they have demonstrated cardiovascular benefits [22, 26, 29, 30]. GLP-1RA show in particular great promise for treating PAD in patients with T2DM, since they may have systemic microcirculatory benefits in the peripheral vascular district, including reduced inflammation and oxidative stress, improved endothelial function, vasodilatation, and anti-atherosclerotic effects [77–82]. In a recent open-label RCT of 55 patients with T2DM and PAD, the administration of liraglutide improved peripheral perfusion, suggesting that it may prevent the clinical progression of PAD [83]. The main mechanisms supporting the cardiorenal protective effects of SGLT2i include the correction of cardiorenal risk factors, metabolic adjustments ameliorating myocardial substrate utilization, and optimization of ventricular loading conditions through effects on diuresis, natriuresis, and vascular function [84, 85]. Both GLP-1RA and SGLT2i are well-tolerated, with gastrointestinal symptoms and polyuria being the most common side effects of GLP-1RA and SGLT2i, respectively [86]. They are also associated with weight loss, which is mainly due to loss of fat mass. However, the concomitant loss of lean mass warrants attention and requires prevention strategies to preserve skeletal muscle and improve physical function [87].

Of note, before the breakthrough of GLP-1RA and SGLT2i, a few studies showed that metformin reduced the risk of MALE and MACE in patients with T2DM [88, 89], including in those with PAD [90]. However, the same risk reduction of MACE was found in patients with T2DM treated with dulaglutide (a GLP-1RA) and metformin compared to those treated with dulaglutide alone, questioning the need for metformin [91, 92].

CVOT analyses provide insights into the cardiovascular benefits and safety profile of GLP-1RA and SGLT2i in PAD (Table 2). Importantly, SGLT2i have been shown to be beneficial in patients with chronic kidney disease (CKD) and/or heart failure—two frequent comorbidities in patients with PAD—regardless of the presence of diabetes [14, 15]. However, in a recent meta-analysis of 20 RCTs evaluating the effectiveness of SGLT2i in reducing the risk of PAD in 59,952 patients with T2DM, the use of SGLT2i did not significantly change the incidence of PAD compared to placebo or oral glucose-lowering agents (relative risk [RR], 0.98; 95% confidence interval [CI] 0.78–1.24) [93]. Subgroup analysis further revealed that the risk of incident PAD did not differ between the

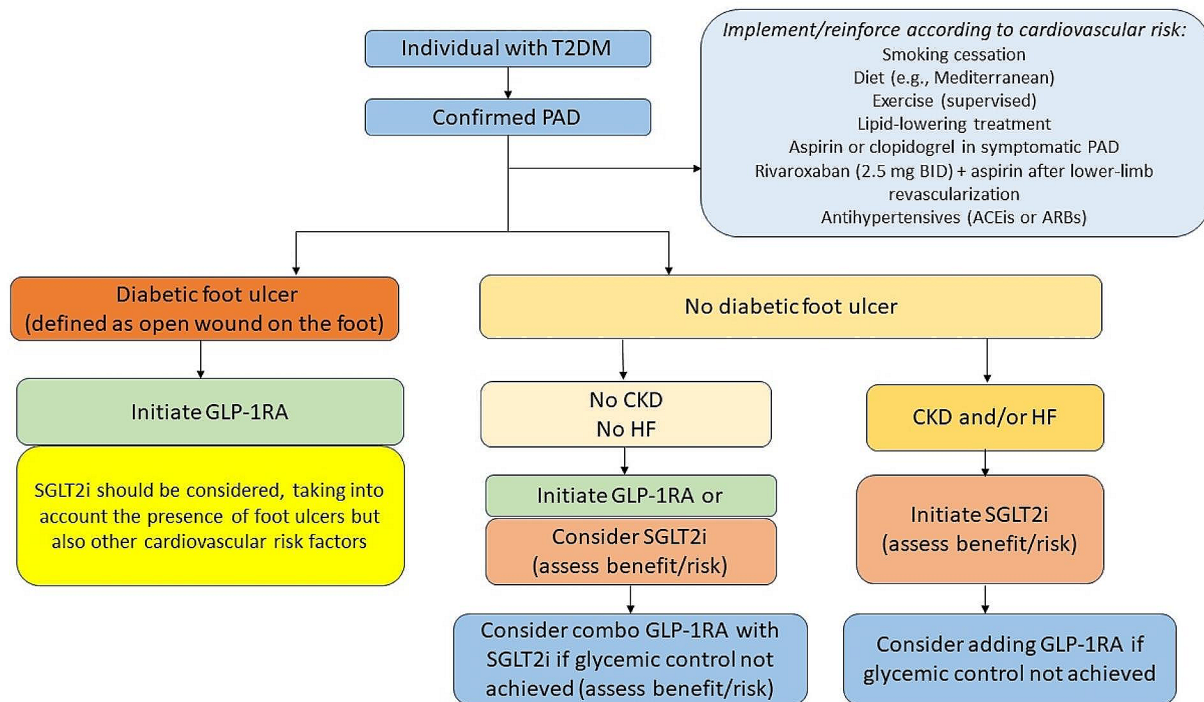
four evaluated SGLT2i: canagliflozin (RR, 1.18; 95% CI 0.70–1.99), dapagliflozin (RR, 0.86; 95% CI 0.58–1.27), empagliflozin (RR, 1.16; 95% CI 0.75–1.79), and ertugliflozin (RR, 0.83; 95% CI 0.49–1.40) [93]. SGLT2i were also not associated with an increased risk of restenosis in a real-world study from Japan among 157 patients with T2DM undergoing femoropopliteal endovascular therapy with drug coated balloon for symptomatic PAD [94].

Regarding the safety of SGLT2i, in a real-world study using three nationwide United States databases, including 96,128 adults with CKD and T2DM who newly filled prescriptions for SGLT2i versus GLP-1RA, SGLT2i compared with GLP-1RA were associated with a higher risk of lower-limb amputations (hazard ratio [HR], 1.65; 95% CI 1.22–2.23) and of non-vertebral fractures (HR 1.30; 95% CI 1.03–1.65) [95]. Moreover, in the CANVAS (CANagliflozin cardioVascular Assessment Study) program including 10,142 patients with T2DM at high cardiovascular risk, canagliflozin was associated with a 1.97-fold increased risk (95% CI 1.41–2.75) of lower-limb amputations [32]. Identified independent predictors of amputation were prior amputations, male sex, non-Asian ethnicity, history of peripheral vascular disease, history of neuropathy, albuminuria, and increased HbA1c at baseline [32]. However, in the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial including 4,401 patients with T2DM and CKD, similar amputation rates were found in the canagliflozin and placebo groups (HR 1.11; 95% CI 0.79–1.56) [96]. Moreover, no increased amputation risk was observed in CVOTs using other SGLT2i [15, 16, 35–38, 97].

Overall, it is advisable to conduct a thorough screening for risk factors for amputations when initiating SGLT2i. These risk factors include a history of amputations, neuropathy, high HbA1c at baseline, and diabetic foot ulcers (DFUs) [32]. It is also advised to be cautious with the use of SGLT2i in patients with an active DFU and to carefully weigh the individual benefit-risk balance (Fig. 3). Recent evidence also highlights an increased risk of amputation in patients with PAD or at high risk for PAD who are under diuretics [98]. Thus, the addition of SGLT2i on top of diuretics should be discussed case by case.

Comparisons between GLP-1RA and SGLT2i are scarce, with no available data from RCTs. The impact of GLP-1RA on the progression of PAD in patients with T2DM was evaluated in real-world studies [99, 100]. Compared to SGLT2i, the use of GLP-1RA was associated with a significantly lower risk of MALE, which was driven by a lower incidence of CLTI (HR 0.83; 95% CI 0.68–1.02) [100].

In terms of CVOT findings, a post-hoc analysis of LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), performed



**Fig. 3** Glucose-lowering management approach for lower extremity peripheral artery disease (PAD) in patients with type 2 diabetes mellitus (T2DM). Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BID, twice daily; CKD, chronic kidney disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; SGLT2i, sodium-glucose cotransporter-2 inhibitor

in 9340 patients with T2DM at high cardiovascular risk, found that treatment with liraglutide did not increase the risk of DFUs (defined as an open wound on the foot) and was associated with a significantly lower risk of DFU-related amputations compared to placebo (HR 0.65; 95% CI 0.45–0.95) [41]. Semaglutide was also associated with a lower need for coronary and peripheral revascularization compared to placebo (HR 0.65; 95% CI 0.50–0.86) in SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes) conducted in 3297 patients with T2DM at high cardiovascular risk [101]. In a more recent post-hoc analysis of both LEADER and SUSTAIN-6, liraglutide and semaglutide reduced MACE, with consistent cardiovascular efficacy regardless of PAD status [17]. EXSCCEL (Exenatide Study of Cardiovascular Event Lowering) is another CVOT evaluating exenatide in 14,752 patients with T2DM with or without CVD including PAD [102]. Treatment with exenatide or placebo resulted in similar rates of non-traumatic amputations in those with PAD (HR 0.99; 95% CI 0.71–1.38) and in those without PAD (HR 0.96; 95% CI 0.66–1.41). Exenatide was also associated with a significantly lower all-cause mortality in patients with T2DM and PAD (HR 0.77; 95% CI 0.61–0.98) [18].

STRIDE is an ongoing trial (NCT04560998) that is investigating the effect of subcutaneous once-weekly

semaglutide on walking ability compared to placebo in patients with T2DM and symptomatic PAD with intermittent claudication. STRIDE is expected to provide valuable insights into the functional outcomes of GLP-1RA for individuals with T2DM and PAD. Similarly, additional data is anticipated from the long-term placebo-controlled SOUL trial (NCT03914326) investigating the effects of oral semaglutide on MACE and MALE in patients with T2DM and CKD or CVD, including individuals with symptomatic PAD.

Figure 3 summarizes our directions in the pharmacological treatment algorithm of PAD in patients with T2DM, including the incorporation of GLP-1RA and SGLT2i. Of note, based on individual metabolic control and cardiovascular and renal risk factors, the association of a GLP-1RA with a SGLT2i could be considered [22, 103]. Although SGLT2i in patients with CKD or heart failure could be beneficial, it is essential that when initiating SGLT2i alone or in combination with GLP-1RA, a thorough individual evaluation of the benefit-risk profile is conducted to mitigate any potential risk of amputations.

**Perspectives for optimizing PAD management in patients with T2DM**

Despite the availability of various clinical practice guidelines for the therapeutic management of patients with

T2DM and PAD and their overall consistency, there can be gaps in their implementation in real-life clinical practice [104]. Suboptimal rates of evidence-based therapies have also been noted among patients with T2DM and PAD. In a real-world analysis of a large claims database from the United States, performed in 543,938 patients with T2DM and atherosclerotic CVD, including 294,092 (54.1%) patients with PAD, the use of GLP-1RA and SGLT2i was found to be low (<9%) [105]. Similarly, CAPTURE, a non-interventional, cross-sectional, multinational study conducted in 9823 adults with T2DM (36.5% with CVD including PAD), revealed that GLP-1RA and/or SGLT2i were used by 21.9% of participants, with comparable rates among patients with and without CVD (21.5% and 22.2%, respectively) [106]. Furthermore, in a meta-analysis of 86 studies investigating the rates of prescription of vasculoprotective therapies in patients with PAD, the pooled literature estimates for the utilization of antiplatelets, statins, and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers were 75%, 56%, and 53%, respectively, indicating important treatment gaps [107].

Efforts to bridge these treatment gaps can include continuing medical education for healthcare providers, as well as patient education. A barrier to the initiation of novel glucose-lowering therapies, particularly GLP-1RA, is their administration via injections. There is hence a necessity to encourage pharmacists and nurse practitioners to offer patient education on these injectable treatments. Patients should also be educated on the importance of inspecting their feet daily, proper footwear, proper nail hygiene, and the importance of seeking medical attention for any foot problems like cuts, sores, or changes in the color or temperature of the feet [11].

The optimal management of PAD in patients with T2DM requires a dedicated multidisciplinary collaboration, involving endocrinologists/diabetologists, vascular surgeons, cardiologists, podiatrists, primary care specialists, and other healthcare professionals [13, 25]. Nather et al. [108] from Singapore evaluated the effectiveness of a hospital multidisciplinary team in improving the management of diabetic foot problems. They found that the introduction of a multidisciplinary team reduced the average length of hospital stay from 20.4 to 12.2 days and the major amputation rate from 31.2 to 11.0%. In a similar study from China, the introduction of a multidisciplinary team, coordinated by an endocrinologist and a podiatrist for managing diabetic foot problems, was associated with a reduction in the frequency of major amputations from 9.5 to <5% [109]. Overall, both studies highlight the effectiveness of a multidisciplinary approach in improving patient care, reducing complications, and potentially saving healthcare costs [108, 109]. It is also important that all patients with T2DM, even those without a DFU,

have their peripheral arteries examined at least annually through a medical history and pedal pulse palpation [110].

### Strengths and limitations

This review article is strengthened by the inclusion of multiple data sources, incorporating both clinical practice guidelines and RCTs/CVOTs, to provide a comprehensive overview of the current evidence on PAD management in patients with T2DM. In addition, the conducted systematic searches were thorough and industry-independent, ensuring a broad and unbiased inclusion of relevant literature. Nevertheless, as with any literature review, there is a risk of publication bias. Moreover, the quality of the included studies can vary, which can affect the overall strength of the evidence presented.

### Conclusions

PAD, characterized by atherosclerosis in the arteries of the lower extremities, is highly prevalent in patients with T2DM. The management of PAD in patients with T2DM requires a multidisciplinary and individualized approach that addresses both the overarching metabolic disturbances inherent to diabetes and the specific vascular complications of PAD. While there are several societal guidelines for the diagnosis and treatment of PAD in patients with T2DM, it is important to acknowledge that these guidelines are primarily based on data from the general population. To better tailor recommendations and improve care for this particular population, there is a pressing need for robust, T2DM-specific PAD clinical trials, primarily focusing on novel glucose-lowering agents known for their cardiovascular benefits, including GLP-1RA and SGLT2i. The initiation of such focused research efforts is essential to inform and refine clinical practices, optimizing patient outcomes in this complex interplay of systemic metabolic dysfunction and localized vascular impairment.

### Abbreviations

ABI	Ankle-brachial index
ACC	American College of Cardiology
ACEi	Angiotensin-converting enzyme inhibitor
ADA	American Diabetes Association
ADFDG	Australian Diabetes-related Foot Disease Guidelines
AE	Adverse event
AHA	American Heart Association
ARB	Angiotensin-receptor blocker
CANVAS	CANagliflozin cardioVascular Assessment Study
CCS	Canadian Cardiovascular Society
CDS	Chinese Diabetes Society
CI	Confidence interval
CKD	Chronic kidney disease
CLTI	Chronic limb-threatening ischemia
CRENCE	Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation
CRP	C-reactive protein
CVD	Cardiovascular disease
CVOT	Cardiovascular outcome trial

DAPA-HF	Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure
DECLARE-TIMI 58	Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58
DELIVER	Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure
DFU	Diabetic foot ulcer
eGFR	Estimated glomerular filtration rate
EMPA-REG OUTCOME	Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients
ESC	European Society of Cardiology
ESKD	End-stage kidney disease
ESVS	European Society for Vascular Surgery
EUCLID	Examining Use of ticAgreLor In peripheral artery Disease
EXSCEL	Exenatide Study of Cardiovascular Event Lowering
GDS	German Diabetes Society
GLP-1RA	Glucagon-like peptide-1 receptor agonist
HbA1c	Glycated hemoglobin
HF	Heart failure
HHF	Hospitalization for heart failure
HR	Hazard ratio
IL	Interleukin
LDL	Low-density lipoprotein
LEAD	Lower extremity arterial disease
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results
MACE	Major adverse cardiovascular events
MALE	Major adverse limb events
NO	Nitric oxide
PAD	Peripheral artery disease
PCSK9	Proprotein convertase subtilisin/kexin type 9
PKC	Protein kinase C
RCT	Randomized controlled trial
ROS	Reactive oxygen species
RR	Relative risk
SC	Subcutaneous
SCVE	French Society for Vascular and Endovascular Surgery
SFMV	French Society of Vascular Medicine
SGLT2i	Sodium-glucose cotransporter-2 inhibitor
SOLOIST-WHF	Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure
SUSTAIN-6	Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes
T2DM	Type 2 diabetes mellitus
TBI	Toe-brachial index
TcPO <sub>2</sub>	Transcutaneous oxygen pressure
TNF-α	Tumor necrosis factor-alpha
VERTIS CV	Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes
vs.	Versus

## Supplementary Information

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Supplementary Material 1.

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## Availability of data and materials

No datasets were generated or analysed during the current study.

## Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Competing interests

GM reports consulting fees from Novartis and Amgen; honoraria for lectures and presentations from Amarin, Aspen, Bayer, BMS-Pfizer, Leo Pharma, and Perimed; and advisory board participation for Novo Nordisk and Sanofi. VA reports honoraria and institutional funding from Amarin, Amgen, AstraZeneca, Boehringer Ingelheim, Organon, Novo Nordisk, and Vifor. EC declares consulting fees, honoraria for lectures, presentations, or speaker bureaus from Abbott, AlphaDiab, Ascencia, Lilly, LVL Médical, Medtronic, MSD, Novartis, Novo Nordisk, Roche Diagnostics, Sanofi-Aventis, as well as grants from AstraZeneca, LVL Médical, and Roche Diagnostics outside the submitted work. KM reports consulting fees from Novo Nordisk; honoraria for lectures, presentations, or speaker bureaus from Novo Nordisk, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Sanofi, LifeScan, Abbott, and Bayer; and advisory board participation for Novo Nordisk, Sanofi, and Amarin. GSB reports honoraria for lectures, presentations, or speaker bureaus from Amgen, BMS, Leo Pharma, Novartis, Novo Nordisk, Pfizer, Sanofi, and Servier. DL reports honoraria for lectures, presentations, or speaker bureaus from Amgen, Aspen, Bayer, BMS, Leo Pharma, Pfizer, and Sanofi. TM reports receiving honoraria from Bayer, Incyte, Amarin, Novartis, and Novo Nordisk; and receiving non-financial support from Abbott, Alexion Pharma, Amgen, Bayer, Boehringer Ingelheim, BMS, Incyte, MSD, and Pfizer. PD reports consulting fees, honoraria for lectures, presentations, or speaker bureaus from Novo Nordisk, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Menarini, Sanofi, Abbott, MSD, and Bayer; and advisory board participation for Novo Nordisk, Eli Lilly, Menarini, and Boehringer Ingelheim.

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## References

1. Adou C, Magne J, Gazere N, Aoudia M, Chastaingt L, Abovans V. Global epidemiology of lower extremity artery disease in the 21st century (2000–2021): a systematic review and meta-analysis. *Eur J Prev Cardiol.* 2024;31(7):803–11.
2. Jude EB, Oyibo SO, Chalmers N, Boulton AJ. Peripheral arterial disease in diabetic and nondiabetic patients: a comparison of severity and outcome. *Diabetes Care.* 2001;24(8):1433–7.
3. Mohammadi K, Woodward M, Hirakawa Y, Zoungas S, Colagiuri S, Hamet P, et al. Presentations of major peripheral arterial disease and risk of major outcomes in patients with type 2 diabetes: results from the ADVANCE-ON study. *Cardiovasc Diabetol.* 2016;15(1):129.
4. Criqui MH, Matsushita K, Abovans V, Hess CN, Hicks CW, Kwan TW, et al. Lower extremity peripheral artery disease: contemporary epidemiology, management gaps, and future directions: a scientific statement from the American Heart Association. *Circulation.* 2021;144(9):e171–91.
5. Bhandari N, Newman JD, Berger JS, Smilowitz NR. Diabetes mellitus and outcomes of lower extremity revascularization for peripheral artery disease. *Eur Heart J Qual Care Clin Outcomes.* 2022;8(3):298–306.
6. Geiss LS, Li Y, Hora I, Albright A, Rolka D, Gregg EW. Resurgence of diabetes-related nontraumatic lower-extremity amputation in the young and middle-aged adult U.S. population. *Diabetes Care.* 2019;42(1):50–4.
7. Stewart CC, Berhaneselase E, Morshed S. The burden of patients with lower limb amputations in a community safety-net hospital. *J Am Acad Orthop Surg.* 2022;30(1):e59–66.
8. GBD 2019 Peripheral Artery Disease Collaborators. Global burden of peripheral artery disease and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Glob Health.* 2023;11(10):e1553–65.
9. Marso SP, Hiatt WR. Peripheral arterial disease in patients with diabetes. *J Am Coll Cardiol.* 2006;47(5):921–9.
10. Barnes JA, Eid MA, Creager MA, Goodney PP. Epidemiology and risk of amputation in patients with diabetes mellitus and peripheral artery disease. *Arterioscler Thromb Vasc Biol.* 2020;40(8):1808–17.
11. Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, et al. 2016 AHA/ACC Guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation.* 2017;135(12):e726–79.
12. Abovans V, Ricco JB, Bartelink MEL, Björck M, Brodmann M, Cohnert T, et al. 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries. Endorsed by: the European Stroke Organization (ESO) the Task Force for the diagnosis and treatment of peripheral arterial diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *Eur Heart J.* 2018;39(9):763–816.
13. Fritridge R, Chuter V, Mills J, Hincliffe R, Azuma N, Behrendt CA et al. The intersocietal IWGDF, ESVS, SVS guidelines on peripheral artery disease in people with diabetes and a foot ulcer. *Diabetes Metab Res Rev.* 2023;40(3):e3686. <https://doi.org/10.1002/dmrr.3686>
14. Yi TW, Wong MMY, Neuen BL, Arnott C, Poirier P, Seufert J, et al. Effects of canagliflozin on cardiovascular and kidney events in patients with chronic kidney disease with and without peripheral arterial disease: integrated analysis from the CANVAS program and CREDENCE trial. *Diabetes Obes Metab.* 2023;25(7):2043–7.
15. Butt JH, Kondo T, Yang M, Jhund PS, Docherty KF, Vaduganathan M, et al. Heart failure, peripheral artery disease, and dapagliflozin: a patient-level meta-analysis of DAPA-HF and DELIVER. *Eur Heart J.* 2023;44(24):2170–83.
16. Verma S, Mazer CD, Al-Omran M, Inzucchi SE, Fitchett D, Hehne U, et al. Cardiovascular outcomes and safety of empagliflozin in patients with type 2 diabetes mellitus and peripheral artery disease: a subanalysis of EMPA-REG OUTCOME. *Circulation.* 2018;137(4):405–7.
17. Verma S, Al-Omran M, Leiter LA, Mazer CD, Rasmussen S, Saevereid HA, et al. Cardiovascular efficacy of liraglutide and semaglutide in individuals with diabetes and peripheral artery disease. *Diabetes Obes Metab.* 2022;24(7):1288–99.
18. Badjatiya A, Merrill P, Buse JB, Goodman SG, Katona B, Iqbal N, et al. Clinical outcomes in patients with type 2 diabetes mellitus and peripheral artery disease: results from the EXSCEL Trial. *Circ Cardiovasc Interv.* 2019;12(12):e008018.
19. Dhand S. Multidisciplinary approach to PAD: Who's on your team? *Semin Intervent Radiol.* 2018;35(5):378–83.
20. American Diabetes Association. Peripheral arterial disease in people with diabetes. *Diabetes Care.* 2003;26(12):3333–41.
21. American Diabetes Association Professional Practice Committee. 10. Cardiovascular disease and risk management: standards of care in diabetes-2024. *Diabetes Care.* 2024;47(Suppl 1):S179–218.
22. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 10. Cardiovascular disease and risk management: standards of care in diabetes-2023. *Diabetes Care.* 2023;46(Suppl 1):S158–90.
23. Chuter V, Quigley F, Tosenovsky P, Ritter JC, Charles J, Cheney J, et al. Australian guideline on diagnosis and management of peripheral artery disease: part of the 2021 Australian evidence-based guidelines for diabetes-related foot disease. *J Foot Ankle Res.* 2022;15(1):51.
24. Abramson BL, Al-Omran M, Anand SS, Albalawi Z, Coutinho T, de Mestral C, et al. Canadian Cardiovascular Society 2022 guidelines for peripheral arterial disease. *Can J Cardiol.* 2022;38(5):560–87.
25. Wang A, Lv G, Cheng X, Ma X, Wang W, Gui J, et al. Guidelines on multidisciplinary approaches for the prevention and management of diabetic foot disease (2020 edition). *Burns Trauma.* 2020;8:tkaa017.
26. Marx N, Federici M, Schütt K, Müller-Wieland D, Ajan RA, Antunes MJ, et al. 2023 ESC guidelines for the management of cardiovascular disease in patients with diabetes. *Eur Heart J.* 2023;44(39):4043–140.
27. Abovans V, Bauersachs R, Mazzolai L, Brodmann M, Palomares JFR, Debus S, et al. Antithrombotic therapies in aortic and peripheral arterial diseases in 2021: a consensus document from the ESC working group on aorta and peripheral vascular diseases, the ESC working group on thrombosis, and the ESC working group on cardiovascular pharmacotherapy. *Eur Heart J.* 2021;42(39):4013–24.
28. Nordanstig J, Behrendt CA, Baumgartner I, Belch J, Bäck M, Fritridge R, et al. European Society for Vascular Surgery (ESVS) 2024 clinical practice guidelines on the management of asymptomatic lower limb peripheral arterial disease and intermittent claudication. *Eur J Vasc Endovasc Surg.* 2024;67(1):9–96.
29. Balletshofer B, Ito W, Lawall H, Malyar N, Oberländer Y, Reimer P, et al. Position paper on the diagnosis and treatment of peripheral arterial disease (PAD) in people with diabetes mellitus. *Exp Clin Endocrinol Diabetes.* 2019;127(S 01):S105–13.
30. Balletshofer B, Böckler D, Diener H, Heckenkamp J, Ito W, Katoh M, et al. Position paper on the diagnosis and treatment of peripheral arterial disease (PAD) in people with diabetes mellitus. *Exp Clin Endocrinol Diabetes.* 2022;130(S 01):S127–36.
31. Mahé G, Boge G, Bura-Rivière A, Chakfé N, Constans J, Goueffic Y, et al. Disparities between international guidelines (AHA/ESC/ESVS/ESVM/SVS) concerning lower extremity arterial disease: consensus of the French Society of Vascular Medicine (SFMV) and the French Society for Vascular and Endovascular Surgery (SCVE). *Ann Vasc Surg.* 2021;72:1–56.
32. Matthews DR, Li Q, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, et al. Effects of canagliflozin on amputation risk in type 2 diabetes: the CANVAS program. *Diabetologia.* 2019;62(6):926–38.
33. Barraclough JY, Yu J, Figtree GA, Perkovic V, Heerspink HJL, Neuen BL, et al. Cardiovascular and renal outcomes with canagliflozin in patients with peripheral arterial disease: data from the CANVAS Program and CREDENCE trial. *Diabetes Obes Metab.* 2022;24(6):1072–83.
34. Arnott C, Huang Y, Neuen BL, Di Tanna GL, Cannon CP, Oh R, et al. The effect of canagliflozin on amputation risk in the CANVAS program and the CREDENCE trial. *Diabetes Obes Metab.* 2020;22(10):1753–66.
35. Bonaca MP, Wiviott SD, Zelniker TA, Mosenzon O, Bhatt DL, Leiter LA, et al. Dapagliflozin and cardiac, kidney, and limb outcomes in patients with and without peripheral artery disease in DECLARE-TIMI 58. *Circulation.* 2020;142(8):734–47.

36. Inzucchi SE, Iliev H, Pfarr E, Zinman B. Empagliflozin and assessment of lower-limb amputations in the EMPA-REG OUTCOME trial. *Diabetes Care*. 2018;41(1):e4–5.
37. Cannon CP, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med*. 2020;383(15):1425–35.
38. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med*. 2021;384(2):117–28.
39. Cherney DZI, Ferrannini E, Umpierrez GE, Peters AL, Rosenstock J, Powell DR, et al. Efficacy and safety of sotagliflozin in patients with type 2 diabetes and stage 3 chronic kidney disease. *Diabetes Obes Metab*. 2023;25(6):1646–57.
40. Cherney DZI, Ferrannini E, Umpierrez GE, Peters AL, Rosenstock J, Carroll AK, et al. Efficacy and safety of sotagliflozin in patients with type 2 diabetes and severe renal impairment. *Diabetes Obes Metab*. 2021;23(12):2632–42.
41. Dhatriya K, Bain SC, Buse JB, Simpson R, Tarnow L, Kaltoft MS, et al. The impact of liraglutide on diabetes-related foot ulceration and associated complications in patients with type 2 diabetes at high risk for cardiovascular events: results from the LEADER trial. *Diabetes Care*. 2018;41(10):2229–35.
42. Mohammedi K, Woodward M, Hirakawa Y, Zoungas S, Williams B, Lisheng L, et al. Microvascular and macrovascular disease and risk for major peripheral arterial disease in patients with type 2 diabetes. *Diabetes Care*. 2016;39(10):1796–803.
43. Fadini GP, Albiero M, Bonora BM, Avogaro A. Angiogenic abnormalities in diabetes mellitus: mechanistic and clinical aspects. *J Clin Endocrinol Metab*. 2019;104(11):5431–44.
44. Golledge J. Update on the pathophysiology and medical treatment of peripheral artery disease. *Nat Rev Cardiol*. 2022;19(7):456–74.
45. Mauricio D, Gratacós M, Franch-Nadal J. Diabetic microvascular disease in non-classical beds: the hidden impact beyond the retina, the kidney, and the peripheral nerves. *Cardiovasc Diabetol*. 2023;22(1):314.
46. Paneni F, Beckman JA, Creager MA, Cosentino F. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part I. *Eur Heart J*. 2013;34(31):2436–43.
47. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA*. 2001;286(3):327–34.
48. Nativel M, Schneider F, Saulnier PJ, Gand E, Ragot S, Meilhac O, et al. Prognostic values of inflammatory and redox status biomarkers on the risk of major lower-extremity artery disease in individuals with type 2 diabetes. *Diabetes Care*. 2018;41(10):2162–9.
49. Deng H, Li B, Shen Q, Zhang C, Kuang L, Chen R, et al. Mechanisms of diabetic foot ulceration: a review. *J Diabetes*. 2023;15(4):299–312.
50. Kim TI, Guzman RJ. Medial artery calcification in peripheral artery disease. *Front Cardiovasc Med*. 2023;10:1093355.
51. Kakouros N, Rade JJ, Kourliouros A, Resar JR. Platelet function in patients with diabetes mellitus: from a theoretical to a practical perspective. *Int J Endocrinol*. 2011;2011:742719.
52. Gibbons GW, Shaw PM. Diabetic vascular disease: characteristics of vascular disease unique to the diabetic patient. *Semin Vasc Surg*. 2012;25(2):89–92.
53. Mahé G, Ouedraogo N, Leftheriotis G, Vielle B, Picquet J, Abraham P. Exercise treadmill testing in patients with claudication, with and without diabetes. *Diabet Med*. 2011;28(3):356–62.
54. Mercier C, Brazeau T, Lamoureaux J, Boisvert E, Robillard S, Breton V, et al. Diabetes impaired ischemia-induced PDGF (platelet-derived growth factor) signaling actions and vessel formation through the activation of Scr homology 2-containing phosphatase-1. *Arterioscler Thromb Vasc Biol*. 2021;41(9):2469–82.
55. Behroozian A, Beckman JA. Microvascular disease increases amputation in patients with peripheral artery disease. *Arterioscler Thromb Vasc Biol*. 2020;40(3):534–40.
56. Lee MS, Rha SW, Han SK, Choi BG, Choi SY, Ali J, et al. Comparison of diabetic and non-diabetic patients undergoing endovascular revascularization for peripheral arterial disease. *J Invasive Cardiol*. 2015;27(3):167–71.
57. Foussard N, Saulnier PJ, Potier L, Ragot S, Schneider F, Gand E, et al. Relationship between diabetic retinopathy stages and risk of major lower-extremity arterial disease in patients with type 2 diabetes. *Diabetes Care*. 2020;43(11):2751–9.
58. Hinchliffe RJ, Forsythe RO, Apelqvist J, Boyko EJ, Frittridge R, Hong JP, et al. Guidelines on diagnosis, prognosis, and management of peripheral artery disease in patients with foot ulcers and diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev*. 2020;36(Suppl 1):e3276.
59. Mohammedi K, Woodward M, Zoungas S, Li Q, Harrap S, Patel A, et al. Absence of peripheral pulses and risk of major vascular outcomes in patients with type 2 diabetes. *Diabetes Care*. 2016;39(12):2270–7.
60. Trihan JE, Lanéelle D, Metcalfe N, Perez Martin A, Frances P. Diabetes-associated dermatological manifestations in primary care and their association with vascular complications. *J Diabetes Metab Disord*. 2020;19(2):989–96.
61. Conte MS, Bradbury AW, Kolh P, White JV, Dick F, Frittridge R, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. *Eur J Vasc Endovasc Surg*. 2019;58(15):S1–Se10933.
62. AbuRahma AF, Adams E, AbuRahma J, Mata LA, Dean LS, Caron C, et al. Critical analysis and limitations of resting ankle-brachial index in the diagnosis of symptomatic peripheral arterial disease patients and the role of diabetes mellitus and chronic kidney disease. *J Vasc Surg*. 2020;71(3):937–45.
63. Tahan PE, Sebastian M, Barwick AL, Chuter VH. How sensitive and specific is continuous-wave doppler for detecting peripheral arterial disease in people with and without diabetes? A cross-sectional study. *Diab Vasc Dis Res*. 2018;15(5):396–401.
64. Trihan JE, Mahé G, Croquette M, Coutant V, Thollot C, Guillaumat J, et al. Accuracy of acceleration time of distal arteries to diagnose severe peripheral arterial disease. *Front Cardiovasc Med*. 2021;8:744354.
65. Guirguis-Blake JM, Evans CV, Redmond N, Lin JS. Screening for peripheral artery disease using the ankle-brachial index: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2018;320(2):184–96.
66. Olin JW, Halperin JL. US Preventive Services Task Force recommendation statement regarding screening for peripheral artery disease with the ankle-brachial index: déjà vu all over again. *Lancet*. 2018;392(10153):1160–2.
67. Sprenger L, Mader A, Larcher B, Mächler M, Vonbank A, Zanolin-Purin D, et al. Type 2 diabetes and the risk of cardiovascular events in peripheral artery disease versus coronary artery disease. *BMJ Open Diabetes Res Care*. 2021;9(2):e002407.
68. Momsen AH, Jensen MB, Norager CB, Madsen MR, Vestersgaard-Andersen T, Lindholt JS. Drug therapy for improving walking distance in intermittent claudication: a systematic review and meta-analysis of robust randomised controlled studies. *Eur J Vasc Endovasc Surg*. 2009;38(4):463–74.
69. Bonaca MP, Nault P, Giugliano RP, Keech AC, Pineda AL, Kanevsky E, et al. Low-density lipoprotein cholesterol lowering with evolocumab and outcomes in patients with peripheral artery disease: insights from the FOURIER trial (further cardiovascular outcomes research with PCSK9 inhibition in subjects with elevated risk). *Circulation*. 2018;137(4):338–50.
70. Schwartz GG, Steg PG, Szarek M, Bittner VA, Diaz R, Goodman SG, et al. Peripheral artery disease and venous thromboembolic events after acute coronary syndrome: role of lipoprotein(a) and modification by alirocumab: prespecified analysis of the ODYSSEY OUTCOMES randomized clinical trial. *Circulation*. 2020;141(20):1608–17.
71. Bonaca MP, Bauersachs RM, Anand SS, Debus ES, Nehler MR, Patel MR, et al. Rivaroxaban in peripheral artery disease after revascularization. *N Engl J Med*. 2020;382(21):1994–2004.
72. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med*. 2017;377(14):1319–30.
73. Kaplovitch E, Eikelboom JW, Dyal L, Aboyns V, Abola MT, Verhamme P, et al. Rivaroxaban and aspirin in patients with symptomatic lower extremity peripheral artery disease: a subanalysis of the COMPASS randomized clinical trial. *JAMA Cardiol*. 2021;6(1):21–9.
74. Ruiz-Canela M, Estruch R, Corella D, Salas-Salvado J, Martínez-González MA. Association of Mediterranean diet with peripheral artery disease: the PRE-DIMED randomized trial. *JAMA*. 2014;311(4):415–7.
75. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;321(7258):405–12.
76. Low Wang CC, Blomster JI, Heizer G, Berger JS, Baumgartner I, Fowkes FGR, et al. Cardiovascular and limb outcomes in patients with diabetes and peripheral artery disease: the EUCLID trial. *J Am Coll Cardiol*. 2018;72(25):3274–84.
77. Caruso P, Maiorino MI, Bellastella G, Esposito K, Giugliano D. Pleiotropic effects of GLP-1 receptor agonists on peripheral artery disease: Is there any hope? *Diabetes Metab Res Rev*. 2023;39(7):e3627.
78. Rizzo M, Abate N, Chandalia M, Rizvi AA, Giglio RV, Nikolic D, et al. Liraglutide reduces oxidative stress and restores heme oxygenase-1 and ghrelin levels in patients with type 2 diabetes: a prospective pilot study. *J Clin Endocrinol Metab*. 2015;100(2):603–6.



79. Rizzo M, Rizvi AA, Patti AM, Nikolic D, Giglio RV, Castellino G, et al. Liraglutide improves metabolic parameters and carotid intima-media thickness in diabetic patients with the metabolic syndrome: an 18-month prospective study. *Cardiovasc Diabetol.* 2016;15(1):162.
80. Patti AM, Nikolic D, Magan-Fernandez A, Giglio RV, Castellino G, Chianetta R, et al. Exenatide once-weekly improves metabolic parameters, endothelial dysfunction and carotid intima-media thickness in patients with type-2 diabetes: an 8-month prospective study. *Diabetes Res Clin Pract.* 2019;149:163–9.
81. Patti AM, Rizvi AA, Giglio RV, Stoian AP, Ligi D, Mannello F. Impact of glucose-lowering medications on cardiovascular and metabolic risk in type 2 diabetes. *J Clin Med.* 2020;9(4):912.
82. Giglio RV, Pantea Stoian A, Al-Rasadi K, Banach M, Patti AM, Ciaccio M, et al. Novel therapeutical approaches to managing atherosclerotic risk. *Int J Mol Sci.* 2021;22(9):4633.
83. Caruso P, Maiorino MI, Longo M, Porcellini C, Matrone R, Digitale Selvaggio L, et al. Liraglutide for lower limb perfusion in people with type 2 diabetes and peripheral artery disease: the STARDUST randomized clinical trial. *JAMA Netw Open.* 2024;7(3):e241545.
84. Salvatore T, Galiero R, Caturano A, Rinaldi L, Di Martino A, Albanese G, et al. An overview of the cardiorenal protective mechanisms of SGLT2 inhibitors. *Int J Mol Sci.* 2022;23(7):3651.
85. Scisciola L, Taktaz F, Fontanella RA, Pesapane A, Surina, Cataldo V, et al. Targeting high glucose-induced epigenetic modifications at cardiac level: the role of SGLT2 and SGLT2 inhibitors. *Cardiovasc Diabetol.* 2023;22(1):24.
86. Rolek B, Haber M, Gajewska M, Rogula S, Pietrasik A, Gąsecka A. SGLT2 inhibitors vs. GLP-1 agonists to treat the heart, the kidneys and the brain. *J Cardiovasc Dev Dis.* 2023;10(8):322.
87. Sargeant JA, Henson J, King JA, Yates T, Khunti K, Davies MJ. A review of the effects of glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter 2 inhibitors on lean body mass in humans. *Endocrinol Metab (Seoul).* 2019;34(3):247–62.
88. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet.* 1998;352(9131):854–65.
89. Kooy A, de Jager J, Lehert P, Bets D, Wulfelég MG, Donker AJ, et al. Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. *Arch Intern Med.* 2009;169(6):616–25.
90. Tan S, Goudot G, Arnoux A, Tran Y, Maïssoro H, Poenou G, et al. Occurrence of major local lower limb events in type 2 Diabetic patients with lower extremity arterial disease: impact of metformin. *Ann Vasc Surg.* 2023;90:153–61.
91. Ferrannini G, Gerstein H, Colhoun HM, Dagenais GR, Diaz R, Dyal L, et al. Similar cardiovascular outcomes in patients with diabetes and established or high risk for coronary vascular disease treated with dulaglutide with and without baseline metformin. *Eur Heart J.* 2021;42(26):2565–73.
92. Sattar N, McGuire DK. Prevention of CV outcomes in antihyperglycaemic drug-naïve patients with type 2 diabetes with, or at elevated risk of, ASCVD: to start or not to start with metformin. *Eur Heart J.* 2021;42(26):2574–6.
93. Tsai PC, Chuang WJ, Ko AM, Chen JS, Chiu CH, Chen CH, et al. Neutral effects of SGLT2 inhibitors in acute coronary syndromes, peripheral arterial occlusive disease, or ischemic stroke: a meta-analysis of randomized controlled trials. *Cardiovasc Diabetol.* 2023;22(1):57.
94. Takahara M, Soga Y, Fujihara M, Iida O, Kawasaki D. Sodium-glucose cotransporter 2 inhibitor use in patients with diabetes mellitus undergoing endovascular therapy for symptomatic peripheral artery disease. *Cardiovasc Diabetol.* 2023;22(1):273.
95. Fu EL, D'Andrea E, Wexler DJ, Paterno E, Paik JM. Safety of sodium-glucose cotransporter-2 inhibitors in patients with CKD and type 2 diabetes: population-based US Cohort Study. *Clin J Am Soc Nephrol.* 2023;18(5):592–601.
96. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med.* 2019;380(24):2295–306.
97. Nuffield Department of Population Health Renal Studies Group; SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. *Lancet.* 2022;400(10365):1788–801.
98. Ba K, Sow MA, Magne J, Salle L, Lacroix P, Chastaingt L, et al. Risk of amputation under diuretics in patients with or at risk of lower extremity arterial disease: a systematic review and meta-analysis. *Arch Cardiovasc Dis.* 2023;116(6–7):357–63.
99. Lin DS, Lee JK, Chen WJ. Major adverse cardiovascular and limb events in patients with diabetes treated with GLP-1 receptor agonists vs DPP-4 inhibitors. *Diabetologia.* 2021;64(9):1949–62.
100. Lin DS, Yu AL, Lo HY, Lien CW, Lee JK, Chen WJ. Major adverse cardiovascular and limb events in people with diabetes treated with GLP-1 receptor agonists vs SGLT2 inhibitors. *Diabetologia.* 2022;65(12):2032–43.
101. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2016;375(19):1834–44.
102. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2017;377(13):1228–39.
103. Gourdy P, Darmon P, Dievart F, Halimi JM, Guerci B. Combining glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) in patients with type 2 diabetes mellitus (T2DM). *Cardiovasc Diabetol.* 2023;22(1):79.
104. Mahe G, Brodmann M, Capodanno D, Ceriello A, Cuisset T, Delgado V, et al. Current management and screening of peripheral and coronary artery disease in people with diabetes mellitus in Europe. The PADDIA/CADDIA survey. *Diabetes Res Clin Pract.* 2022;184:109214.
105. Weng W, Tian Y, Kong SX, Ganguly R, Hersloev M, Brett J, et al. The prevalence of cardiovascular disease and antidiabetes treatment characteristics among a large type 2 diabetes population in the United States. *Endocrinol Diabetes Metab.* 2019;2(3):e00076.
106. Mosenzon O, Alguwaihes A, Leon JLA, Bayram F, Darmon P, Davis TME, et al. CAPTURE: a multinational, cross-sectional study of cardiovascular disease prevalence in adults with type 2 diabetes across 13 countries. *Cardiovasc Diabetol.* 2021;20(1):154.
107. Hackam DG, Vyas MV. Utilization of vasculoprotective therapy for peripheral artery disease: a systematic review and meta-analysis. *Am J Med.* 2018;131(11):1332–e93.
108. Nather A, Siok Bee C, Keng Lin W, Xin-Bei Valerie C, Liang S, Tambyah PA, et al. Value of team approach combined with clinical pathway for diabetic foot problems: a clinical evaluation. *Diabet Foot Ankle.* 2010;1:5731.
109. Wang C, Mai L, Yang C, Liu D, Sun K, Song W, et al. Reducing major lower extremity amputations after the introduction of a multidisciplinary team in patient with diabetes foot ulcer. *BMC Endocr Disord.* 2016;16(1):38.
110. Hingorani A, LaMuraglia GM, Henke P, Meissner MH, Loretz L, Zinszer KM, et al. The management of diabetic foot: a clinical practice guideline by the society for vascular surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine. *J Vasc Surg.* 2016;63(2 Suppl):s3–21.

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