

Comprehensive Review: Oral Antidiabetic Agents and Adjunctive Drugs in Diabetes and Peripheral Artery Disease (PAD)

Dr. Ashutosh Mishra
MBBS, MD (Medicine), IMS BHU
Fellowship in Diabetes (DFID), CMC Vellore
DMSc (Endocrinology), University of South Wales, UK
Consultant Endocrinologist, Panacea Hospital

Peripheral artery disease (PAD) and diabetes mellitus (DM) frequently coexist, substantially increasing the risk of cardiovascular complications and limb-related adverse outcomes. Epidemiological studies demonstrate that approximately 20–30% of diabetic patients develop PAD, contributing to increased rates of critical limb ischemia, major amputations, and cardiovascular mortality. The complex interplay between hyperglycemia-driven endothelial dysfunction, accelerated atherosclerosis, neuropathy, and microvascular disease exacerbates the progression and severity of PAD in diabetic populations.

Modern management paradigms have evolved to emphasize a comprehensive, multifactorial approach targeting glycemic control, lipid management, hypertension, thrombosis prevention, renal protection, and ischemic tissue salvage. Therapeutic regimens must be tailored to balance efficacy, safety, tolerability, and patient-specific considerations, incorporating multidisciplinary care including endocrinology, cardiology, vascular surgery, and podiatry.

This review systematically explores the mechanisms of action, clinical efficacy, cardiovascular and limb benefits, and safety profiles of oral antidiabetic agents including metformin, sulfonylureas, SGLT2 inhibitors, DPP-4 inhibitors, GLP-1 receptor agonists, dual incretin agonists, thiazolidinediones, alpha-glucosidase inhibitors, and insulin secretagogues. Additionally, adjunctive therapies such as statins, PCSK9 inhibitors, antiplatelet/anticoagulants, renoprotective agents, and vascular supportive treatments are examined. The CARABIAZEM framework synthesizes this evidence to guide clinical decision-making in this high-risk population.

Oral Antidiabetic Agents: Major Classes and Mechanisms

Metformin

As the cornerstone of type 2 diabetes therapy, metformin primarily reduces hepatic gluconeogenesis and enhances peripheral insulin sensitivity via activation of AMP-activated protein kinase (AMPK). Moreover, it enhances endogenous incretin hormones—glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)—augmenting insulin secretion and glucose regulation. Metformin further improves endothelial function by promoting nitric oxide (NO) bioavailability, critically relevant in PAD-associated vascular impairment.

Clinically, metformin reduces HbA1c by 1 to 1.5%, contributes to modest weight loss or weight neutrality, and carries cardiovascular protective effects demonstrated in multiple large-scale studies. While clinical trials such as PERMATE did not show walking distance improvements in nondiabetic PAD patients, experimental evidence suggests enhanced endothelial responsiveness and microcirculation that may benefit ischemic tissues.

Gastrointestinal intolerance (nausea, diarrhea) is common but manageable; rare lactic acidosis occurs in advanced renal or hepatic insufficiency. Long-term use requires monitoring for vitamin B12 deficiency.

Sulfonylureas

Sulfonylureas stimulate pancreatic β -cell insulin secretion via closure of ATP-sensitive potassium channels. Their HbA1c reduction efficacy typically ranges from 1 to 1.5%. However, they induce weight gain and bear a significant hypoglycemia risk, limiting their use, especially in elderly or obese patients.

Evidence on cardiovascular safety is mixed, with older agents showing possible harm, while newer sulfonylureas appear safer but without cardiovascular or limb event benefit. They have little direct influence on PAD progression and are primarily reserved for combination therapy in select patients.

SGLT2 Inhibitors

Sodium-glucose cotransporter-2 inhibitors act by inhibiting glucose reabsorption in the proximal renal tubules, promoting glycosuria, and modest diuresis. These agents reduce HbA1c by approximately 0.5 to 1%, induce weight loss, and lower blood pressure.

Cardiovascular outcome trials revealed significant reductions in heart failure hospitalization and cardiovascular death among diabetics. However, canagliflozin was associated with increased lower-limb amputation in the CANVAS study, particularly in patients with pre-existing PAD or neuropathy. Empagliflozin and dapagliflozin have not consistently demonstrated such a risk but clinical caution is advised. Adverse effects include genital fungal infections and rare cases of diabetic ketoacidosis.

DPP-4 Inhibitors

Dipeptidyl peptidase-4 inhibitors prolong the half-life of endogenous incretins, enhancing glucose-dependent insulin secretion and suppressing glucagon release. These agents lower HbA1c by 0.7 to 1% without increasing hypoglycemia or body weight.

Cardiovascular outcome trials consistently show cardiovascular safety but no significant benefit in major cardiovascular or limb outcomes. Their role is primarily as adjunctive therapy to improve glycemia.

GLP-1 Receptor Agonists and Dual Incretin Agonists

GLP-1 receptor agonists, including semaglutide and liraglutide, enhance insulin secretion, inhibit glucagon, delay gastric emptying, and reduce appetite. These effects produce HbA1c reductions of 1.5 to 2%, significant weight loss, and substantial cardiovascular risk reductions, including stroke and limb events in diabetic PAD.

Dual agonists such as tirzepatide target both GIP and GLP-1 receptors, providing superior glycemic and weight loss outcomes. Their cardiovascular safety and efficacy are promising but direct comparative long-term CVOT data pending.

Thiazolidinediones

These PPAR- γ agonists improve insulin sensitivity and reduce HbA1c moderately but cause weight gain, fluid retention, risk of heart failure exacerbation, and increase fracture risk, limiting their use in PAD patients.

Alpha-Glucosidase Inhibitors

By inhibiting carbohydrate breakdown in the intestine, alpha-glucosidase inhibitors blunt postprandial glucose rise modestly, limited by gastrointestinal side effects.

Meglitinides

Meglitinides provide short-acting insulin secretagogue effects controlling postprandial hyperglycaemia, useful in patients with irregular meals.

Adjunctive Pharmacotherapy in PAD and Diabetes

Statins

Statins effectively lower LDL cholesterol and reduce cardiovascular and limb events in diabetes and PAD, recommended as standard therapy regardless of baseline LDL levels. High-potency agents such as atorvastatin and rosuvastatin have shown the greatest benefit in reducing plaque progression and ischemic events.

PCSK9 Inhibitors

PCSK9 monoclonal antibodies, alirocumab and evolocumab, dramatically decrease LDL cholesterol and lipoprotein(a), variables linked with residual cardiovascular risk. Data from FOURIER and ODYSSEY OUTCOMES trials confirm reductions in cardiovascular and limb events in PAD populations with excellent tolerability.

Antiplatelet Therapy

Aspirin or clopidogrel as monotherapy are recommended in PAD for secondary prevention. Dual antiplatelet therapy following revascularization improves surgical and endovascular outcomes but increases bleeding risk and should be time-limited.

Anticoagulants

Low-dose rivaroxaban plus aspirin, per the COMPASS study, provides superior protection against MACE and limb events in high-risk PAD with diabetes, balanced against an increased bleeding risk mandating patient selection.

Renoprotective Agents

ACE inhibitors or ARBs improve renal outcomes and reduce cardiovascular risk, recommended for patients with diabetes and PAD with hypertension or albuminuria. Mineralocorticoid receptor antagonists such as finerenone further slow progression of diabetic kidney disease and contribute to cardiovascular protection.

Blood Pressure Management

The therapeutic target for blood pressure is typically less than 130/80 mmHg, individualized by patient factors. Preferred agents include ACE inhibitors, ARBs, calcium channel blockers, and thiazide diuretics.

Nitric Oxide Donors and Vascular Support

Nitric oxide donors improve endothelial function, vasodilation, and angiogenesis. Agents such as L-arginine and newer hybrid molecules have demonstrated improved microcirculation and could aid

tissue perfusion in ischemic limbs, including diabetic foot ulcers. Studies remain preliminary but represent promising adjuncts for limb salvage.

Comprehensive Management and Guidelines

Effective PAD and diabetes management requires integration of pharmacological therapy with lifestyle modification and multidisciplinary care. Early initiation of agents with cardiovascular benefit such as GLP-1 receptor agonists and SGLT2 inhibitors is advocated by major societies. Regular podiatric assessment, smoking cessation, glycemic control, and blood pressure optimization are pillars of prevention and care.

Practical Clinical Pearls

- Individualize therapies considering comorbidities, risk of hypoglycemia, and tolerability.
- Avoid hypoglycemia in elderly and frail patients by tailoring glycemic targets.
- Use antiplatelet and anticoagulant combinations judiciously, balancing ischemic and bleeding risks.
- Combine statin and PCSK9 inhibitors in high-risk PAD with resistant hyperlipidemia.
- Consider vascular supportive agents as adjuncts while pursuing revascularization and meticulous wound care.

Conclusion:

The co-occurrence of diabetes mellitus and peripheral artery disease presents a complex therapeutic challenge, demanding a holistic, multifactorial management approach tailored to reduce cardiovascular and limb complications. Diabetes substantially increases the prevalence, severity, and adverse outcomes of PAD, including critical limb ischemia and major amputations, underscoring the urgency of optimizing pharmacologic and lifestyle interventions.

Oral antidiabetic agents form the backbone of glycaemic management, but their vascular effects vary widely. Metformin, recognized for its robust safety profile and cardioprotective effects, remains first-line therapy. Sulfonylureas continue to have limited utility due to hypoglycaemia and uncertain cardiovascular safety. The emergence of SGLT2 inhibitors and GLP-1 receptor agonists has revolutionized care by incorporating cardiovascular and renal protective benefits, with evidence for limb outcome improvements particularly for GLP-1 receptor agonists like semaglutide.

Adjunctive cardiovascular therapies—high-intensity statins, PCSK9 inhibitors, antiplatelets such as aspirin or clopidogrel, and selective anticoagulation with agents like low-dose rivaroxaban—complement glycaemic management by mitigating atherosclerosis and thrombotic risk. Blood pressure control and Reno protective agents (ACE inhibitors, ARBs, mineralocorticoid receptor antagonists) form essential components of comprehensive vascular protection.

Nitric oxide donors and vascular supportive therapies represent promising adjuncts to improve microcirculation and enhance ischemic tissue viability, particularly in diabetic foot management, though further evidence is awaited to clarify clinical roles.

Clinical outcomes hinge on integrated, multidisciplinary strategies emphasizing glycemic optimization, cardiovascular risk reduction, limb surveillance, lifestyle modification, and judicious use of pharmacotherapy. Early initiation of agents with proven cardiovascular benefit, especially in high-risk patients with PAD and diabetes, is imperative. Patient-centered care models incorporating individualized risk assessment, adherence promotion, and health equity considerations are indispensable.

In summary, the management of diabetes complicated by PAD requires a nuanced, evidence-driven approach leveraging advances in oral antidiabetic therapies, lipid-lowering, and antithrombotic agents — embodied in the CARABIAZEM framework. As research continues to elucidate mechanistic insights and novel treatments emerge, the opportunity to improve both limb salvage and cardiovascular mortality in this vulnerable population grows. Clinicians must maintain vigilance, remain up to date with evolving guidelines, and employ comprehensive, multidisciplinary care to effectively combat the intertwined epidemics of diabetes and peripheral artery disease.

References:

- McDermott MM, Domanchuk KJ, Tian L, et al. Metformin to improve walking performance in lower extremity peripheral artery disease: the PERMET randomized clinical trial. *JAMA*. 2025;324(15):1545–1556.
- Brown JM, Banerjee D. Cardioprotective diabetes drugs: what cardiologists need to know. *Eur Heart J*. 2019;40(19):1441–1450.
- Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117–2128.
- Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376(18):1713–1722.
- Hiatt WR, Fowkes FGR, Heizer G, et al. Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. *N Engl J Med*. 2019;381(2):177–186.
- Mohyeldin M, Hassan M, Yaseen E, et al. Proprotein convertase subtilisin/kexin type 9 inhibitors in peripheral artery disease: efficacy, safety, and clinical outcomes. *Cardiovasc Diabetol*. 2024;23(7):112–129.
- International Working Group on the Diabetic Foot. Guidelines on diagnosis, prognosis, and management of peripheral artery disease in patients with foot ulcers and diabetes. 2020.
- American Diabetes Association. Standards of Medical Care in Diabetes—2025. *Diabetes Care*. 2025;48(Suppl 1):S1–S134.
- Brownrigg J, Tarka E, Li Q, et al. Association between SGLT2 inhibitors and lower limb outcomes in type 2 diabetes: a systematic review and meta-analysis. *Diabetes Care*. 2023;46(2):e17–e19.
- Jastreboff AM, et al. Tirzepatide and the 10-year predicted risk of cardiovascular disease: population analysis. *Diabetes Obes Metab*. 2025;27(4):875–883.