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Narrative Review

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Endothelial dysfunction as the mechanistic bridge between GLP-1 receptor agonism and cardiovascular protection: a narrative review

Abstract

Background: Endothelial dysfunction is the shared substrate of obesity, type 2 diabetes, and atherosclerotic cardiovascular disease. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) reduce major adverse cardiovascular events (MACE) by a margin that glycemic and weight effects do not fully account for, which has directed attention toward the vessel wall itself.

Objective: To appraise the preclinical and clinical evidence that GLP-1 RAs act directly on the vascular endothelium, and to define how much of the observed cardiovascular benefit this can reasonably explain.

Methods: Narrative review of PubMed/MEDLINE, Embase, and Web of Science through early 2026, prioritizing cardiovascular outcome trials, randomized studies of vascular function, network meta-analyses, and mechanistic work in human endothelial cells and atherosclerosis-prone animal models.

Findings: In experimental systems, GLP-1 RAs increase eNOS phosphorylation at Ser1177 and nitric oxide availability through AMPK/Akt and cAMP/PKA signaling; they lower NOX4-derived reactive oxygen species, endoplasmic reticulum stress, and NLRP3 inflammasome activity; they suppress ICAM-1, VCAM-1, and E-selectin via NF-κB inhibition; and they restore the number and functional capacity of endothelial progenitor cells. In patients, network meta-analyses show improvement in flow-mediated dilation exceeding that achieved with sulfonylureas or lifestyle modification, and coronary microvascular imaging studies report parallel gains in myocardial perfusion, although individual trials are not uniform. A modest, partly independent blood pressure-lowering effect has also been described. Across outcome trials, benefit is reproducible for human GLP-1 analogues and persists in a population without diabetes. A prespecified mediation analysis of SELECT attributed roughly one third of the MACE benefit to reduction in waist circumference, leaving the majority unexplained by adiposity. SURPASS-CVOT adds a complementary observation: tirzepatide was metabolically superior to dulaglutide yet not superior for MACE.

Conclusions: Endothelial protection is a coherent and probably contributory mechanism of GLP-1 RA cardioprotection. It is not yet an established one. The principal unresolved questions concern GLP-1 receptor expression in human endothelium and the translational validity of *in vitro* work performed at supraphysiologic concentrations — a caution echoed by independent 2025–2026 syntheses of this literature, not merely a position specific to this review.

Keywords: vascular endothelium, endothelial dysfunction, glucagon-like peptide-1, GLP-1 receptor agonists, nitric oxide, atherosclerosis, cardiovascular outcomes

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Abbreviations: AMPK, AMP-activated protein kinase; ASCVD, atherosclerotic cardiovascular disease; CVOT, cardiovascular outcome trial; eNOS, endothelial nitric oxide synthase; EPC, endothelial progenitor cell; FMD, flow-mediated dilation; GLP-1, glucagon-like peptide-1; GLP-1R, GLP-1 receptor; GLP-1 RA, GLP-1 receptor agonist; HFpEF, heart failure with preserved ejection fraction; HUVEC, human umbilical vein endothelial cell; ICAM-1, intercellular adhesion molecule-1; MACE, major adverse cardiovascular events; NO, nitric oxide; ROS, reactive oxygen species; T2D, type 2 diabetes; VCAM-1, vascular cell adhesion molecule-1.

Introduction

Obesity, type 2 diabetes (T2D), and cardiovascular disease travel together, and they do so because they share a target. More than half of diabetes-attributable deaths follow from macrovascular complications,[1,2] which makes cardiovascular disease the dominant prognostic determinant in T2D rather than a late complication of it.

The tissue where these three conditions converge is the endothelium. It stopped being regarded as a passive lining decades ago. Functionally it behaves as a distributed organ with autocrine, paracrine, and endocrine activity, setting vascular tone and regulating hemostasis, permeability, leukocyte traffic, and angiogenesis. Once injured, it becomes a proinflammatory, prothrombotic, proatherogenic surface, and that transition is detectable long before atherosclerosis declares itself clinically.[3]

GLP-1 receptor agonists (GLP-1 RAs) entered practice as glucose-lowering drugs and were later repositioned as weight-lowering ones. What moved them into cardiology was something the original development programs did not set out to demonstrate: a reproducible

reduction in major adverse cardiovascular events (MACE) whose magnitude sits uncomfortably above what the accompanying changes in glycated hemoglobin, blood pressure, lipids, and body weight would predict. That residual is the empirical basis for suspecting a direct vascular action, and the endothelium is the most credible place to look for it.[4,5]

This review has three aims. First, to summarize how endothelial dysfunction drives cardiovascular disease in the cardiometabolic patient. Second, to assemble the mechanistic and clinical evidence for endothelial effects of GLP-1 RAs. Third, and in our view the more useful contribution, to state plainly which parts of that argument are supported and which remain conjecture.

Methods

This is a narrative, non-systematic review. We searched PubMed/MEDLINE, Embase, and Web of Science from inception to early 2026 using combinations of the terms GLP-1 receptor agonist, liraglutide, semaglutide, dulaglutide, exenatide, tirzepatide, endothelium, endothelial dysfunction, nitric oxide, eNOS, flow-mediated dilation, atherosclerosis, and cardiovascular outcomes.

We gave priority to randomized cardiovascular outcome trials, randomized trials with vascular function endpoints, systematic reviews and network meta-analyses, and mechanistic studies performed in human endothelial cells or in atherosclerosis-prone animal models. Reference lists of retrieved articles were screened manually. Retracted publications were excluded, including a widely cited 2010 report on liraglutide and endothelial nitric oxide production that has since been withdrawn; readers should be aware that this paper still appears in the reference lists of several recent reviews.

Because the review is narrative, it does not follow PRISMA and is subject to selection bias. We have tried to limit that by stating the strength of each line of evidence explicitly (Table 4) rather than presenting all supporting studies with equal weight.

A primer for readers: interpreting the trial statistics in this review

This review leans heavily on hazard ratios (HR), odds ratios (OR), and confidence intervals (CI), and it is worth pausing on what these do and do not say, since the distinction matters for how the evidence in Sections 7 and 10 should be read.

A hazard ratio compares the instantaneous rate of an event between two groups over the course of a trial; an HR of 0.80 means the treated group experienced the event at 80% of the rate of the comparator group at any given moment, which is not the same as an 80% reduction in absolute risk. The 95% confidence interval is the range of effect sizes compatible with the observed data; when it excludes 1.0, the result is conventionally called statistically significant, but a CI that spans a wide range (for example, 0.57 to 1.11, as in PIONEER 6) signals a result that is imprecise rather than necessarily null, and readers should resist collapsing a wide, non-significant CI into a claim of no effect.

Composite endpoints such as three-point MACE (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) increase statistical power by pooling events, but they assume the components are of comparable clinical importance and are affected similarly by treatment, an assumption worth checking component by component, as we do in Table 3 and Section 7.4. A hard outcome, in the terminology used throughout this review, is one that is unambiguous and directly meaningful to the patient: death, myocardial infarction, stroke, kidney failure. A surrogate outcome, such as flow-mediated dilation or HbA1c, is a measurement that correlates with hard outcomes in observational data but has not necessarily been shown to mediate a treatment effect on them; Section 6 and Section 8 return to this distinction because much of the endothelial mechanistic literature relies on surrogates.

Finally, the number needed to treat (NNT), the number of patients who must be treated for the trial duration to prevent one event, translates a relative risk reduction into an absolute clinical magnitude and is often more useful at the bedside than the hazard ratio alone; we report NNTs where the source publications provide the absolute event rates needed to calculate them.

GLP-1 biology and the receptor question

GLP-1 is an incretin secreted by enteroendocrine L cells of the distal ileum and colon after nutrient intake. It circulates chiefly as GLP-1(7–36) amide and GLP-1(7–37), both cleaved rapidly by dipeptidyl peptidase-4 to GLP-1(9–36), which leaves the active peptide with a plasma half-life of only 1 to 2 minutes.

Signaling proceeds through GLP-1R, a class B G protein-coupled receptor coupled to Gs, which activates adenylyl cyclase and raises intracellular cAMP with downstream engagement of PKA and Epac2. Beyond the pancreatic β cell, GLP-1R transcripts have been reported in cardiovascular tissue, kidney, lung, and central nervous system.[6]

Here the argument becomes less comfortable than most reviews concede. The precise cellular localization and functional weight of GLP-1R within the human cardiovascular system remain contested, and much of the older tissue-distribution literature rests on antibodies of poor specificity. Ban and colleagues showed nearly two decades ago that the cardioprotective and vasodilator actions of GLP-1 are mediated through both receptor-dependent and receptor-independent routes, with the supposedly inactive metabolite GLP-1(9–36) contributing to the latter.[7] Any mechanistic account that assumes a straightforward endothelial GLP-1R is, at present, assuming more than has been shown. Two more recent syntheses do not close this gap so much as restate it with newer data. A 2026 review tracing the field from clinical trial success to receptor-level mechanism concluded that functional GLP-1R signaling has been demonstrated convincingly in rodent and cultured-cell systems but not yet confirmed directly in human vascular endothelium.[8] Earlier surveys had already listed vascular endothelial cells among the tissues where GLP-1R transcript is detectable, alongside cardiomyocytes, lung, kidney, and the central nervous system,[9] but detectable transcript is not the same as demonstrated functional signaling, and that distinction is exactly what the receptor-dependent/independent split above is meant to capture.

Two pharmacologic strategies exploit the axis: DPP-4 inhibitors, which prolong endogenous GLP-1 action, and GLP-1 RAs, which mimic it while resisting enzymatic degradation. Within the agonist class, the distinction between human GLP-1 analogues and exendin-4-derived molecules carries practical consequences, as Section 8 sets out. Tirzepatide, a dual GIP/GLP-1 agonist, and compounds such as survodutide extend the class beyond GLP-1R agonism alone.[10] Table 1 summarizes the pharmacologic characteristics of the agents discussed in this review.

Citation: Borges NCC. Endothelial dysfunction as the mechanistic bridge between GLP-1 receptor agonism and cardiovascular protection: a narrative review. *J Cardiol Curr Res.* 2026;19(3):98–111. DOI: 10.15406/jccr.2026.19.00650

Table 1 Pharmacologic characteristics of GLP-1 receptor agonists and dual incretin agonists

Agent	Molecular origin	Route and frequency	Approximate half-life	Cardiovascular outcome evidence
Exenatide	Exendin-4	SC, twice daily	2–4 h	Not evaluated for CV superiority
Lixisenatide	Exendin-4	SC, once daily	≈3 h	ELIXA: neutral; safety established
Exenatide ER	Exendin-4, extended release	SC, once weekly	Release-limited	EXSCEL: did not meet superiority
Liraglutide	Human GLP-1 analogue, acylated	SC, once daily	≈13 h	LEADER: MACE reduction
Dulaglutide	Human GLP-1 analogue, Fc fusion	SC, once weekly	≈5 days	REWIND: MACE reduction, including lower-risk patients
Semaglutide	Human GLP-1 analogue, acylated	SC, once weekly	≈1 week	SUSTAIN-6 and SELECT: MACE reduction
Semaglutide	Same molecule with SNAC absorption enhancer	Oral, once daily	≈1 week	PIONEER 6 and SOUL: MACE reduction
Albiglutide	Human GLP-1, albumin fusion	SC, once weekly	≈5 days	Harmony Outcomes: MACE reduction; commercially withdrawn
Efpeglenatide	Exendin-4, Fc fusion	SC, once weekly	≈week	AMPLITUDE-O: MACE reduction
Tirzepatide	Dual GIP/GLP-1 agonist	SC, once weekly	≈5 days	SURPASS-CVOT: non-inferior to dulaglutide

CV, cardiovascular; ER, extended release; GIP, glucose-dependent insulinotropic polypeptide; MACE, major adverse cardiovascular events; SC, subcutaneous; SNAC, sodium N-(8-[2-hydroxybenzoyl]amino) caprylate. Half-lives are approximate and should be confirmed against current prescribing information.

Endothelial dysfunction: what has to be repaired

Loss of nitric oxide bioavailability

The defining lesion is a fall in nitric oxide (NO) availability. NO is generated by endothelial nitric oxide synthase (eNOS) in response to shear stress and agonists such as acetylcholine, and it restrains vascular smooth muscle proliferation, platelet aggregation, and leukocyte adhesion. When synthesis falls or oxidative degradation rises, vasodilator reserve is lost and vasoconstrictor tone predominates.[11]

The consequences extend past vasomotion. Reduced NO derepresses expression of the adhesion molecules ICAM-1, VCAM-1, and E-selectin, which recruit leukocytes to sites of endothelial injury. Recruited monocytes take up oxidized LDL, become foam cells, and initiate the atherosclerotic plaque.[12]

Oxidative stress

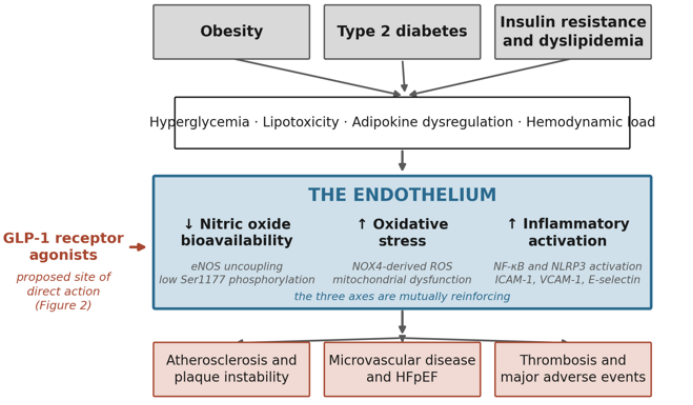
Reactive oxygen species (ROS) arising from NADPH oxidases, mitochondrial dysfunction, and uncoupled eNOS consume NO and oxidize membrane lipids and proteins. Hyperglycemia, smoking, and dyslipidemia amplify their production. ROS also degrade tight junction integrity, raise endothelial permeability, and admit inflammatory cells, establishing a self-sustaining cycle of injury, inflammation, and remodeling[13,14] that no single antioxidant intervention has yet interrupted convincingly in clinical trials.

Inflammation and endothelial-to-mesenchymal transition

Inflammation is both cause and consequence. TNF-α, IL-1β, IL-6, and chemokines such as MCP-1 are elevated and sustain immune cell recruitment. The chronic low-grade inflammation characteristic of diabetes, hypertension, and metabolic syndrome ultimately favors plaque destabilization and thrombosis.[15]

A more recently characterized contributor is endothelial-to-mesenchymal transition, in which endothelial cells lose VE-cadherin and acquire a fibrotic, migratory phenotype under the influence of hyperglycemia, TGF-β signaling, and inflammatory cytokines. Its relevance to plaque instability is biologically plausible and clinically unquantified.[16]

Taken together, endothelial dysfunction is not simply a marker of risk. It is the node at which hemodynamic, metabolic, and inflammatory injury converge, organized around three axes: NO deficiency, oxidative stress, and immune activation (Figure 1). A drug that acted on all three simultaneously would be expected to modify cardiovascular outcomes. Whether GLP-1 RAs do so directly is the question the remainder of this review addresses.



eNOS, endothelial nitric oxide synthase; HFpEF, heart failure with preserved ejection fraction; ICAM-1, intercellular adhesion molecule-1; NOX4, NADPH oxidase 4; ROS, reactive oxygen species; VCAM-1, vascular cell adhesion molecule-1.

Figure 1 Convergence of cardiometabolic risk factors on the endothelium. Obesity, type 2 diabetes, and insulin resistance act through a common set of injurious stimuli that impair three interdependent endothelial functions: nitric oxide generation, redox balance, and control of inflammatory activation. The resulting phenotype drives the clinical manifestations shown below. GLP-1 receptor agonists are proposed to act at the level of the endothelium itself, as detailed in Figure 2. eNOS, endothelial nitric oxide synthase; HFpEF, heart failure with preserved ejection fraction; ICAM-1, intercellular adhesion molecule-1; NOX4, NADPH oxidase 4; ROS, reactive oxygen species;VCAM-1, vascular cell adhesion molecule-1.

Key teaching points — Section 4

- Endothelial dysfunction is defined by three interdependent abnormalities: reduced nitric oxide bioavailability, increased oxidative stress, and heightened inflammatory activation.

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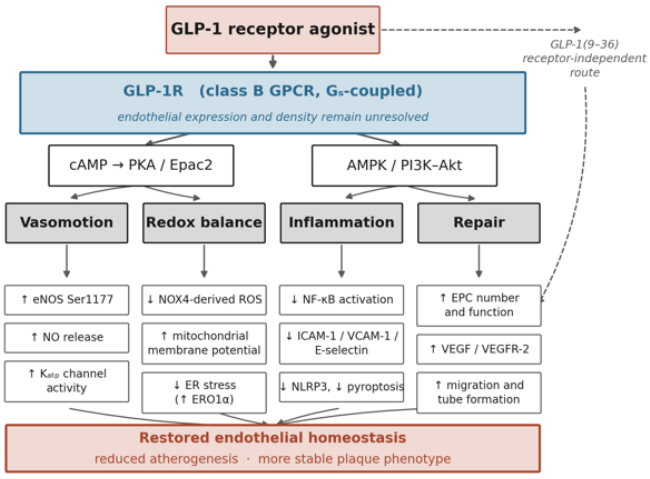
- These three axes are mutually reinforcing rather than independent, which is why interventions that act on only one axis tend to produce modest clinical effects.
- Endothelial dysfunction precedes angiographically detectable atherosclerosis and is therefore a plausible early therapeutic target, not only a late-stage marker.
- Endothelial-to-mesenchymal transition is a newer concept in this pathway and its clinical weight, unlike the classical triad, remains largely unquantified in humans.

Preclinical evidence for endothelial actions

Figure 2 maps the signaling pathways discussed in this section onto the four effector arms through which GLP-1 receptor agonists have been proposed to act on the endothelium.



Solid arrows denote pathways with direct experimental support; the dashed arrow denotes the receptor-independent route attributed to the GLP-1(9–36) metabolite. Evidence strength for each effector arm is graded in Table 4.

EPC, endothelial progenitor cell; ER, endoplasmic reticulum; eNOS, endothelial nitric oxide synthase; NO, nitric oxide.

Figure 2 Proposed molecular mechanisms of GLP-1 receptor agonist action on the vascular endothelium. Receptor engagement raises intracellular cAMP with downstream PKA and Epac2 signaling, and activates AMPK and PI3K–Akt, converging on four effector arms: vasomotion, redox balance, inflammation, and repair. Solid arrows denote pathways with direct experimental support; the dashed arrow denotes the receptor-independent route attributed to the GLP-1(9–36) metabolite. Evidence strength for each effector arm is graded in Table 4. EPC, endothelial progenitor cell; ER, endoplasmic reticulum; eNOS, endothelial nitric oxide synthase; NO, nitric oxide.

Restoration of the eNOS/NO axis

Experimental data converge on increased NO production and eNOS phosphorylation after GLP-1 RA exposure. In ApoE−/− mice, liraglutide raised endothelium-derived NO, inferred from an enhanced contractile response to L-NAME.[17] Parallel *in vitro* work showed increased eNOS expression and activity mediated by AMPK and PI3K/Akt, with the GLP-1R/cAMP/PKA axis implicated in upregulation of endothelial NO production.[10]

In human umbilical vein endothelial cells (HUVECs), GLP-1 exposure raised eNOS activity and Ser1177 phosphorylation within minutes; prolonged exposure increased eNOS protein without a corresponding rise in mRNA, which points to post-transcriptional regulation. Work with exenatide demonstrated direct endothelial protection through AMPK/Akt/eNOS signaling in a GLP-1R-dependent manner, since the effect was abolished by the antagonist exendin(9–39).[18] This last point matters: receptor dependence established pharmacologically in a cell line is the strongest form of mechanistic evidence currently available for the class, and it remains cell-line evidence.

Relevant to the ischemic setting, exenatide enhances ATP-sensitive potassium channel activity, which contributes to improved vasomotor responsiveness after ischemia-reperfusion injury.[19]

Redox and endoplasmic reticulum stress

GLP-1 RAs lower ROS production, recover mitochondrial membrane potential, and improve oxygen consumption in endothelial cells. These changes are accompanied by faster leukocyte rolling velocity and reduced leukocyte adhesion, which are functional rather than merely biochemical readouts.[20]

At the molecular level, exendin-4 activates AMPK and upregulates ERO1α, improving protein-folding capacity and suppressing endoplasmic reticulum stress and ROS overproduction.[21] GLP-1 RAs also inhibit NOX4-dependent ROS generation and reduce NLRP3 inflammasome activation, both established mediators of diabetic endothelial injury.[22] Liraglutide attenuates TRIB3/NF-κB signaling, reducing oxidative stress and pyroptosis in HUVECs cultured under high glucose.[23]

Anti-inflammatory effects and adhesion molecule regulation

Liraglutide suppresses TNF-α-induced ICAM-1 and VCAM-1 expression in endothelial cells through NF-κB inhibition.[17] Exenatide lowers soluble ICAM-1 and VCAM-1 in patients with T2D, which extends the observation from cell culture to circulating biomarkers in humans.[24] In vascular macrophages, exendin-4 suppresses lipopolysaccharide-induced proinflammatory gene expression by activating cAMP/PKA and blocking NF-κB nuclear translocation.[25,26]

One finding deserves particular attention from cardiologists: semaglutide has been reported to shift the secretory profile of epicardial adipose tissue toward an antithrombotic and anti-inflammatory phenotype, in part through downregulation of FABP4. Given the anatomic continuity between epicardial fat and the coronary adventitia, a paracrine route to the coronary endothelium is plausible. The supporting evidence is currently limited to a small number of studies and should be treated as hypothesis-generating.

Endothelial repair, progenitor cells, and angiogenesis

Bone marrow-derived endothelial progenitor cells (EPCs) contribute to endothelial repair and post-ischemic angiogenesis, and their number and function are reduced by oxidative stress, advanced glycation end products, and inflammation, all of which are increased in diabetes.[27]

Clinical studies in T2D report that dulaglutide raises circulating EPC counts and improves their proliferative, adhesive, migratory, and tubulogenic capacity, with inverse correlations to IL-6, TNF-α, C-reactive protein, and advanced glycation end products.[28] Mechanistically, hyperglycemia reduces GLP-1R expression in EPCs, impairing function and promoting apoptosis, and restoring GLP-1 signaling with exendin-4 reverses these changes. GLP-1 RAs additionally stimulate endothelial VEGF expression with VEGFR-2 activation and downstream PLCγ/ERK and PI3K/Akt signaling, translating into greater proliferation, migration, and tube formation *in vitro*.[21]

A blood pressure-lowering effect, operating partly independent of the mechanisms above, has also been described. GLP-1 RAs produce modest reductions in systolic blood pressure, typically in the range of

2 to 5 mmHg, through mechanisms proposed to include natriuresis and attenuation of renin-angiotensin-aldosterone system activity in addition to weight loss itself; whether this reflects a direct renal tubular or vascular smooth muscle action, an endothelial effect, or is largely downstream of weight loss remains actively debated, and the magnitude is too small on its own to account for the cardiovascular outcome trial results.[29]

Atherogenesis and plaque phenotype

In preclinical models, GLP-1 RAs reduce plaque area, monocyte and macrophage accumulation, and lesion vulnerability. Semaglutide reverses Western diet-induced aortic gene expression patterns related to leukocyte trafficking, lipid handling, and extracellular matrix turnover.[10] The resulting plaque phenotype is less inflamed and more stable, with suppression of matrix metalloproteinases and preservation of the fibrous cap. There is also a signal toward reduced thrombotic risk through inhibition of platelet aggregation, although whether this is endothelium-dependent has not been resolved.

Key teaching points — Section 5

- The strongest mechanistic evidence for a direct endothelial action is receptor dependence shown pharmacologically: exendin(9–39) abolishes the AMPK/Akt/eNOS effect of exenatide, which is the closest this literature comes to a causal experiment.
- Four effector arms are consistently described across independent laboratories: nitric oxide signaling, redox and endoplasmic reticulum stress, adhesion molecule and inflammatory suppression, and endothelial progenitor cell repair.
- Almost all of this evidence comes from HUVECs, rodent models, or small human mechanistic studies; direct confirmation in human coronary or resistance-vessel endothelium is still missing.
- The epicardial adipose tissue finding (FABP4 downregulation) is the most anatomically compelling but least replicated mechanism in this section, and should be presented to trainees as hypothesis-generating rather than established.

Human vascular physiology

Flow-mediated dilation (FMD) of the brachial artery remains the reference non-invasive measure of endothelium-dependent function, quantifying the change in arterial diameter during reactive hyperemia.[30]

Systematic reviews and network meta-analyses of glucose-lowering agents report that GLP-1 RAs improve FMD relative to placebo, and outperform sulfonylureas and lifestyle intervention, including in patients with T2D and no overt cardiovascular disease.[31,32] One network meta-analysis found no measurable heterogeneity across included trials ($I^2 = 0\%$), which is reassuring but also unusual for a vascular function endpoint and may reflect the small number of contributing studies.

Individual trials are less uniform than the pooled estimates suggest, and the discrepancy is informative (Table 2). The earliest human evidence came from a small crossover study in which native GLP-1 infusion improved FMD in patients with T2D and stable coronary artery disease,[33] an early proof of concept that motivated the subsequent trials of GLP-1 RAs specifically. In the ENDIS trial, 89 adults with type 1 diabetes and no cardiovascular disease were randomized to semaglutide, empagliflozin, or control; at 12 weeks FMD improved in both active arms with no difference between drugs, accompanied by a fall in peripheral resistance.[34] By contrast, the SAIS2 trial found no advantage of liraglutide over insulin glargine on FMD.[35] Exenatide extended-release improved both FMD and carotid intima-media thickness in patients with T2D.[36]

Table 2 Human studies of endothelial function and vascular structure with GLP-1 receptor agonists

Study	Design	Population	Intervention	Vascular result
Nyström [33]	Crossover, mechanistic	T2D with stable coronary artery disease	Native GLP-1 infusion	Improved brachial FMD
SAIS2 (Nomoto[35])	Randomized, open-label	T2D	Liraglutide vs insulin glargine	No between-group difference in FMD
Di Paolo[36]	Prospective	T2D	Exenatide extended release	Improved FMD and carotid intima-media thickness
ENDIS[34]	Randomized, 3-arm, n = 89	Type 1 diabetes without cardiovascular disease	Semaglutide vs empagliflozin vs control	FMD improved 1.9-fold (semaglutide) and 2.0-fold (empagliflozin) versus control; no difference between drugs (P = 0.745); peripheral resistance fell with semaglutide
Hachuła[24]	Prospective	T2D with atherosclerosis	GLP-1 RA (class)	Reduced adhesion molecules and MCP-1
Kim[31]	Network meta-analysis	T2D	Glucose-lowering agents (class comparison)	GLP-1 RA superior to sulfonylurea and lifestyle for FMD; $I^2 = 0\%$
Wang[32]	Bayesian network meta-analysis	T2D	Antidiabetic drug classes	Favors GLP-1 RA for endothelial function

FMD, flow-mediated dilation; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MCP-1, monocyte chemoattractant protein-1; T2D, type 2 diabetes.

A separate line of human evidence, using coronary microvascular imaging rather than brachial FMD, points in a similar direction. A 2025 review of GLP-1 receptor agonists and myocardial perfusion concluded that GLP-1R activation is associated with improved myocardial blood flow and microvascular function in patients with metabolic syndrome or T2D, based largely on imaging measures of perfusion reserve, though the authors themselves flagged substantial inconsistency across studies attributable to differences in imaging modality, population, and outcome definition[37] — the same methodological heterogeneity that limits the FMD literature above.

The pattern is best read as a genuine but modest class effect on endothelial function whose measurable size depends heavily on the

comparator, the baseline degree of dysfunction, and the duration of exposure. It is worth remembering that FMD is a surrogate that has never been validated as a treatment-effect mediator in a cardiovascular outcome trial.

Cardiovascular outcome trials

Following the 2008 regulatory requirement for cardiovascular safety data on new glucose-lowering agents, a sequence of outcome trials evaluated GLP-1 RAs in patients with T2D.[38-45] Designed for non-inferiority, several returned a superiority signal (Table 3, Figure 3).

Table 3 Cardiovascular outcome trials of GLP-1 receptor agonists and dual incretin agonists

Trial	Agent	Population	3-point MACE	Comment
ELIXA	Lixisenatide	T2D, recent acute coronary syndrome	HR 1.02	Safety established; no benefit
LEADER	Liraglutide	T2D, high CV risk (81% established CVD)	HR 0.87 (0.78–0.97)	All-cause mortality HR 0.85
SUSTAIN-6	Semaglutide SC	T2D, high CV risk	HR 0.74 (0.58–0.95)	Driven by 39% fewer non-fatal strokes
EXSCEL	Exenatide once weekly	T2D, broad risk spectrum	HR 0.91 (0.83–1.00)	Discontinuation approximately 43%
Harmony Outcomes	Albiglutide	T2D with ASCVD	HR 0.78 (0.68–0.90)	Agent commercially withdrawn
REWIND	Dulaglutide	T2D, only 31% established CVD	HR 0.88 (0.79–0.99)	Suggests benefit in primary prevention
PIONEER 6	Oral semaglutide	T2D, high CV risk	HR 0.79 (0.57–1.11)	Non-inferiority; CV death HR 0.49
AMPLITUDE-O	Efpeglenatide	T2D with CVD or CKD	HR 0.73 (0.58–0.92)	Exendin-based molecule
SELECT	Semaglutide 2.4 mg	BMI ≥ 27 kg/m^2, established CVD, no diabetes	HR 0.80 (0.72–0.90)	17,604 patients; first CV indication without T2D
SOUL	Oral semaglutide 14 mg	T2D with ASCVD, CKD, or both	HR 0.86 (0.77–0.96)	9,650 patients; median follow-up 47.5 months
SURPASS-CVOT	Tirzepatide vs dulaglutide	T2D with ASCVD	HR 0.92 (95.3% CI 0.83–1.01)	Non-inferiority met; all-cause mortality HR 0.84

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; HR, hazard ratio; MACE, major adverse cardiovascular events; SC, subcutaneous; T2D, type 2 diabetes. Hazard ratios are versus placebo except SURPASS-CVOT, which used an active comparator.

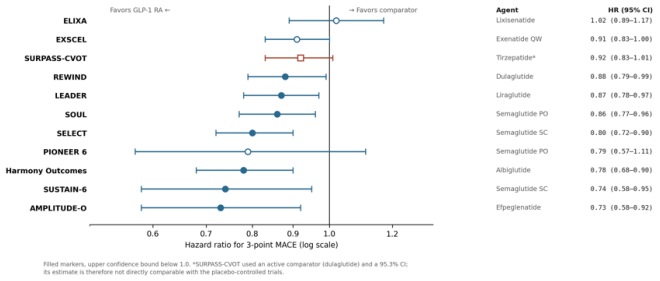


Figure 3 Hazard ratios for three-point major adverse cardiovascular events across cardiovascular outcome trials of GLP-1 receptor agonists and dual incretin agonists. Estimates are ordered by point estimate. Filled markers indicate an upper confidence bound below 1.0. SURPASS-CVOT used an active comparator (dulaglutide) and a 95.3% confidence interval, and is therefore not directly comparable with the placebo-controlled trials.

SELECT and the uncoupling of benefit from weight

SELECT randomized 17,604 patients with a body mass index of at least 27 kg/m^2 and established cardiovascular disease, without diabetes, to once-weekly semaglutide 2.4 mg or placebo, and reported a 20% reduction in MACE.[46] As proof that the benefit does not require glycemic control, it is the single most important trial in this literature.

A prespecified analysis of adiposity measures went further and is, mechanistically, the more interesting paper. Among semaglutide-treated patients there was no linear relationship between weight loss at week 20 and subsequent MACE; reduction in waist circumference, by contrast, predicted lower risk at both 20 and 104 weeks. Mediation analysis estimated that approximately 33% of the treatment effect was mediated through waist circumference reduction (HR 0.86, 95% CI 0.77–0.97 after adjustment for time-varying change).[47] In the placebo arm, weight loss was paradoxically associated with higher event rates, a pattern consistent with reverse causation from unrecognized illness.

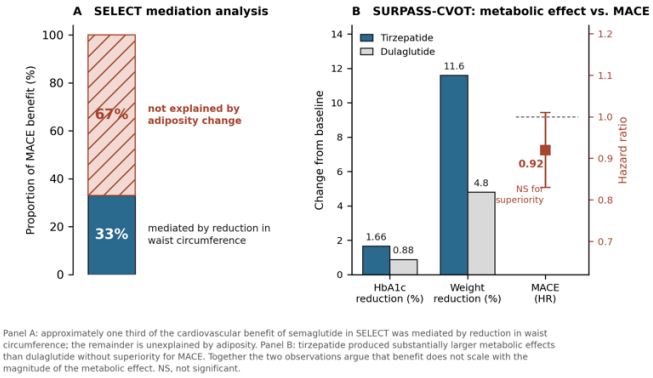
Two thirds of the effect therefore remains unaccounted for by adiposity (Figure 4A). That residual is precisely the space that direct vascular actions would occupy, although a residual is an absence of explanation, not evidence for a particular one, and the analysis was not designed to adjudicate between competing mechanisms. Renal, hemodynamic, and anti-inflammatory pathways compete for the same unexplained variance.

The practical corollary is nonetheless firm. Because benefit was independent of baseline adiposity and of the magnitude of weight loss, prescribing rules anchored to BMI thresholds or to weight-loss response are difficult to justify from these data.

SOUL and the oral formulation

SOUL tested oral semaglutide 14 mg in 9,650 patients with T2D and ASCVD, chronic kidney disease, or both. Over a median 47.5 months, MACE occurred in 12.0% of the semaglutide group versus 13.8% of the placebo group (HR 0.86, 95% CI 0.77–0.96; P = 0.0028), with the reduction in non-fatal myocardial infarction contributing most of the effect.[48] Benefit was consistent irrespective of concomitant

SGLT2 inhibitor use, which supports additive rather than overlapping mechanisms and aligns with current guideline recommendations for combined therapy in T2D with established cardiovascular disease.



Panel A: approximately one third of the cardiovascular benefit of semaglutide in SELECT was mediated by reduction in waist circumference; the remainder is unexplained by adiposity. Panel B: tirzepatide produced substantially larger metabolic effects than dulaglutide without superiority for MACE. Together the two observations argue that benefit does not scale with the magnitude of the metabolic effect. NS, not significant.

Figure 4 Two lines of evidence that cardiovascular benefit is not proportional to metabolic effect. (A) In the SELECT mediation analysis, approximately one third of the reduction in major adverse cardiovascular events was mediated by reduction in waist circumference, leaving two thirds unexplained by adiposity. (B) In SURPASS-CVOT, tirzepatide produced substantially larger reductions in HbA1c and body weight than dulaglutide without achieving superiority for major adverse cardiovascular events. NS, not significant.

Heart failure and dual incretin agonism

Early trials in heart failure with reduced ejection fraction were neutral or inconclusive. The picture changed in obesity-related heart failure with preserved ejection fraction (HFpEF). STEP-HFpEF showed improvement in symptoms, physical limitation, and exercise capacity with semaglutide, accompanied by weight loss and reduced C-reactive protein.[49] SUMMIT showed that tirzepatide reduced a composite of death and worsening heart failure in patients with obesity-related HFpEF, with parallel gains in functional status.[50] A prespecified analysis of SELECT extended this picture to atherosclerotic disease: among 4,286 patients with a history of heart failure at enrollment, semaglutide reduced MACE and the composite heart failure endpoint regardless of whether heart failure was present at baseline, and regardless of ejection fraction subtype, with no significant heterogeneity between HFpEF and HFrEF.[51]

SURPASS-CVOT compared tirzepatide with dulaglutide, an active comparator with previously established cardiovascular efficacy in REWIND, in 13,165 patients with T2D and ASCVD. After a median of four years the primary endpoint occurred in 12% versus 13% (HR 0.92; P = 0.003 for non-inferiority, P = 0.09 for superiority). All-cause mortality was 16% lower with tirzepatide (HR 0.84), and metabolic effects were substantially larger: HbA1c fell by 1.66% versus 0.88% at 36 months, and body weight by 11.6% versus 4.8%.[52]

This result repays careful reading (Figure 4B). A drug that was clearly metabolically superior was not superior for MACE. Whatever produces the cardiovascular benefit of incretin-based therapy, it does not scale linearly with the intensity of the metabolic effect. That observation is congruent with, though not proof of, a mechanism operating at the vessel wall.

Stroke: a consistent and probably underappreciated signal

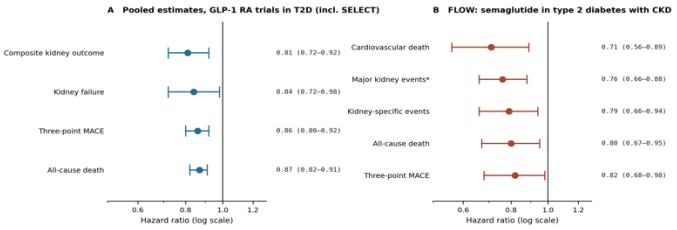
Stroke reduction deserves separate treatment because it is one of the more reproducible hard-outcome signals in this literature and because it aligns mechanistically with the endothelial and antithrombotic actions described in Section 5. An early meta-analysis of seven cardiovascular outcome trials (56,004 participants with T2D) found GLP-1 RA use associated with a 15% lower risk of non-fatal stroke, a 19% lower risk of fatal stroke that did not reach significance, and a 16% lower risk of total stroke;[53] critically, the magnitude of stroke reduction did not correlate with the degree of HbA1c or weight lowering achieved, which foreshadows the SELECT and SURPASS-CVOT dissociation discussed above.

A subsequent eight-trial meta-analysis restricted to cardiovascular outcome trials found a comparable reduction in total stroke risk (relative risk approximately 0.83) with no significant effect on hemorrhagic stroke specifically, suggesting the benefit is concentrated in the ischemic subtype, consistent with an antiatherothrombotic and antiplatelet mechanism rather than a generic reduction in bleeding risk.[54] A more recent pooled analysis incorporating SELECT and FLOW data, extending the evidence base to patients without diabetes and to those with chronic kidney disease, reported stroke incidence reduced by 15% (OR 0.85, 95% CI 0.77–0.93) and non-fatal stroke by 13%,[55] reinforcing that this is not an effect specific to glycemic control.

For the practicing cardiologist evaluating secondary stroke prevention in a patient with diabetes or obesity, this body of evidence is arguably as clinically actionable as the MACE data more commonly cited, yet it receives comparatively little emphasis in cardiology teaching relative to the myocardial infarction and heart failure literature.

All-cause mortality: the pooled picture across the class

Individual trials are underpowered for all-cause mortality as a standalone endpoint, which makes pooled analysis particularly informative here. A 2025 meta-analysis pooling randomized trials of GLP-1 receptor agonists in type 2 diabetes, including a post-hoc inclusion of SELECT, found significant reductions in three-point MACE (HR 0.86, 95% CI 0.80–0.92), all-cause death (HR 0.87, 0.82–0.91), a composite kidney outcome (HR 0.81, 0.72–0.92), and kidney failure specifically (HR 0.84, 0.72–0.98), with no evidence of heterogeneity between the SELECT population and the type 2 diabetes trials.[56] (Figure 5A).



Panel A: pooled hazard ratios from a 2025 meta-analysis of randomized GLP-1 receptor agonist trials in type 2 diabetes, with post-hoc inclusion of SELECT (Badve et al., Lancet Diabetes Endocrinol 2025). Panel B: prespecified outcomes of the FLOW trial, the first dedicated kidney outcome trial of a GLP-1 receptor agonist, stopped early for efficacy (median follow-up 3.4 years). CKD, chronic kidney disease; MACE, major adverse cardiovascular events. *Composite of ≥50% eGFR decline, kidney failure, or kidney/cardiovascular death.

Figure 5 Hard outcomes beyond three-point MACE. (A) Pooled hazard ratios from a 2025 meta-analysis of randomized GLP-1 receptor agonist trials in type 2 diabetes, with post-hoc inclusion of SELECT, for a composite kidney outcome, kidney failure, three-point MACE, and all-cause death. (B) Prespecified outcomes of the FLOW trial, the first dedicated kidney outcome trial of a GLP-1 receptor agonist, in type 2 diabetes with chronic kidney disease, stopped early for efficacy.

A separate 2026 systematic review restricted to high-cardiovascular-risk populations reached a concordant conclusion: several individual trials showed non-significant or borderline effects for myocardial infarction, stroke, or cardiovascular death considered in isolation, but pooling the data revealed significant reductions in both MACE and all-cause mortality, with directional consistency

across trial designs, drug formulations (subcutaneous and oral), and patient populations.[57] The authors interpreted this consistency as evidence that the cardiovascular benefit is a class effect rather than a property of any single molecule, a conclusion that sits in some tension with the trial-by-trial heterogeneity discussed in Section 8 and that we think should be read as a statement about the pooled central estimate rather than a claim that every individual agent is equally effective.

The practical implication is that the mortality benefit of this class, unlike the MACE benefit, only becomes visible at the level of aggregated evidence; no single completed trial other than FLOW[58] (Section 7.6) has been definitively powered to detect an all-cause mortality difference on its own.

Renal outcomes: the FLOW trial

FLOW is the first cardiovascular outcome trial in this class designed with a primary kidney endpoint, and it belongs in this review because the renal microvasculature is, mechanistically, endothelium acting under some of the highest shear and filtration stress in the body; the same NO, oxidative stress, and inflammatory pathways described in Section 4 operate in the glomerular and peritubular capillary bed.

The trial randomized 3,533 adults with T2D and chronic kidney disease (estimated glomerular filtration rate of 50 to 75 mL/min/1.73m^2 with a urinary albumin-to-creatinine ratio of 300 to 5,000 mg/g, or an eGFR of 25 to 50 with a UACR of 100 to 5,000, all on background renin-angiotensin system inhibition) to subcutaneous semaglutide 1.0 mg weekly or placebo. The trial was stopped early at a prespecified interim analysis for clear efficacy after a median follow-up of 3.4 years.[58]

The primary outcome, a composite of at least 50% eGFR decline, kidney failure, or death from kidney or cardiovascular causes, occurred in 331 of 1,767 semaglutide-treated participants versus 410 of 1,766 on placebo, a 24% relative risk reduction (HR 0.76, 95% CI 0.66–0.88; P = 0.0003). The kidney-specific component of the composite was reduced similarly (HR 0.79, 0.66–0.94), death from cardiovascular causes was reduced by 29% (HR 0.71, 0.56–0.89), and all-cause mortality fell by 20% (HR 0.80, 0.67–0.95) (Figure 5B). A prespecified analysis of the ischemic and heart-failure components found that semaglutide reduced the composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke by 18% (HR 0.82, 0.68–0.98), consistently across estimated glomerular filtration rate categories, urine albumin-to-creatinine ratio strata, and KDIGO risk classification, with no significant treatment-by-severity interaction (all P-interaction > 0.13).[59]

Two features of FLOW are particularly relevant to the argument of this review. First, benefit was consistent regardless of concomitant SGLT2 inhibitor use (24% relative risk reduction in both stratified subgroups), which parallels the SOUL finding in Section 7.2 and argues for genuinely additive, non-overlapping mechanisms between the two drug classes at the level of the nephron and the vessel wall. Second, semaglutide slowed the rate of eGFR decline over the trial by 1.16 mL/min/1.73m^2 per year relative to placebo, a structural rather than purely hemodynamic signal that is difficult to attribute to glycemic or blood-pressure effects alone and is more parsimoniously explained by a direct action on the renal microvascular endothelium and glomerular filtration barrier, though FLOW was not designed to adjudicate the underlying mechanism.[60]

Peripheral artery disease: the STRIDE trial

Peripheral artery disease (PAD) is atherosclerosis made directly visible as a functional deficit, and until 2025 no pharmacotherapy had convincingly improved walking capacity in this population. STRIDE addressed this gap directly. The trial randomized 792 patients with T2D and symptomatic PAD with intermittent claudication (Fontaine stage IIa, ankle-brachial index ≤ 0.90 or toe-brachial index ≤ 0.70) across 112 sites in 20 countries to subcutaneous semaglutide 1.0 mg weekly or placebo for 52 weeks.[61]

The primary endpoint was the ratio to baseline of maximum walking distance on a constant-load treadmill at week 52. The estimated median ratio to baseline was 1.21 with semaglutide versus 1.08 with placebo, a between-group treatment ratio of 1.13 (95% CI 1.06–1.21; P = 0.0004), corresponding to a mean absolute improvement in walking distance of approximately 40 meters in the semaglutide group against a baseline maximum walking distance of only about 185 meters, a clinically substantial gain for a population the investigators described as severely disabled despite early-stage disease classification. Pain-free walking distance, symptom burden, and quality-of-life measures improved in parallel, and there were no treatment-related deaths.

STRIDE has generated legitimate methodological debate. Published correspondence in the Lancet noted that pain-free walking distance, a secondary endpoint, may be confounded by diabetic peripheral neuropathy, which can blunt claudication pain independently of vascular status; the trial investigators responded that the primary endpoint was maximum walking distance, not pain-free distance, and that both measures improved significantly regardless.[62] We think this exchange is worth presenting to trainees precisely because it illustrates how even a positive, well-conducted trial invites scrutiny of endpoint selection, which is the same posture this review has taken toward the CVOTs in Section 8.

Mechanistically, STRIDE is difficult to explain through glycemic control alone (PAD improvement was not proportional to HbA1c change) and sits comfortably alongside the endothelial repair and anti-inflammatory mechanisms of Section 5, applied to the lower-extremity macrocirculation and microcirculation rather than the coronary bed.

Ongoing outcome trials

Two gaps in the current evidence base are being addressed directly. SURMOUNT-MMO (NCT05556512) is the first dedicated cardiovascular outcome trial of tirzepatide against placebo, rather than an active comparator, in adults with obesity but without diabetes, encompassing both primary and secondary prevention cohorts. Its primary endpoint is a five-component composite that explicitly includes heart failure events alongside the traditional ischemic components, reflecting the recognition that obesity-related cardiovascular risk operates substantially through a hemodynamic and heart-failure pathway distinct from atherosclerotic MACE.[63] Results are not yet available at the time of writing.

Second, triple agonists (GIP/GLP-1/glucagon receptor) such as retatrutide are in earlier-phase development with metabolic effects that exceed those of tirzepatide, but no cardiovascular outcome data yet exist for this subclass; the SURPASS-CVOT and SURMOUNT-MMO experience with dual agonism, where metabolic superiority did not straightforwardly translate into proportionally larger MACE reduction, is a reasonable prior against assuming triple agonists will automatically outperform existing agents on hard cardiovascular endpoints, though this remains speculative pending trial data.

Key teaching points — Section 7

- MACE reduction is only one of several hard-outcome signals now available for this class; stroke, all-cause mortality, major

kidney events, and walking capacity in peripheral artery disease each have dedicated or pooled trial evidence.

- FLOW is the strongest single-trial evidence in this review for a mechanism beyond glycemic control: a 24% reduction in a hard kidney composite endpoint, stopped early for efficacy, with benefit independent of SGLT2 inhibitor use.
- STRIDE extended the evidence base to a functional, patient-reported outcome (walking distance) in a population defined by macrovascular disease of the lower extremity, complementing the coronary- and cerebrovascular-focused CVOTs.
- Pooled meta-analytic estimates are more precise than any individual trial for all-cause mortality and stroke, but pooling also obscures genuine molecule-level heterogeneity, a tension this review returns to explicitly in Section 8.

Critical appraisal: what the evidence does not establish

We think four caveats should temper any causal claim, and we state them before the clinical implications rather than after.

The receptor problem

Localization and density of GLP-1R in human endothelium are unresolved. Cardioprotective and vasodilator actions of GLP-1 occur through both receptor-dependent and receptor-independent routes, with GLP-1(9–36) implicated in the latter. Mediation through non-canonical receptors, or entirely indirect effects via reduced circulating cytokines, improved insulin sensitivity, lower epicardial adipose volume, or reduced afterload, has not been excluded. This is not a minority view within the field: two comprehensive 2025 reviews spanning mechanism to clinical translation reached a similar conclusion, that outcome data have moved faster than resolution of the underlying vascular receptor biology, and that the gap constrains mechanistic interpretation more than it constrains clinical practice.[64,65]

Supraphysiologic exposure *in vitro*

A substantial portion of the mechanistic literature uses concentrations well above those achieved clinically, where off-target engagement and artifact become likely. Dose-response work in vivo is largely absent, and until it exists the extrapolation from HUVEC data to human coronary endothelium is an assumption.

Within-class heterogeneity

Human GLP-1 analogues show more consistent cardioprotection than exendin-4-derived agents, plausibly reflecting differences in receptor affinity, immunogenicity, and pharmacokinetics. This may partly explain the neutral EXSCEL result, compounded by discontinuation approaching 43%. AMPLITUDE-O complicates the story, since efpeglenatide is exendin-based and did show benefit. The class-versus-molecule question is not settled.

Surrogate validity

Despite the central pathophysiologic position of endothelial dysfunction, its clinical use as a prognostic or diagnostic instrument remains marginal. FMD, arterial stiffness indices, and biomarkers of endothelial activation have predictive value in research settings but are not incorporated into routine risk stratification, and none has been shown to mediate a treatment effect on hard outcomes. Improving FMD is not the same as preventing infarction.

A fifth limitation applies to this review itself. It is narrative, not systematic, and its reference selection is therefore subject to bias. Table 4 is offered as partial compensation: each mechanism is graded by the level of evidence actually supporting it.

Table 4 Proposed endothelial mechanisms of GLP-1 receptor agonists, graded by strength of supporting evidence

Mechanism	Principal evidence base	Translational confidence
eNOS Ser1177 phosphorylation and increased nitric oxide	HUVEC and rodent studies; receptor dependence demonstrated with exendin(9–39)	Moderate to high in vitro; unconfirmed in human coronary endothelium
Reduced NOX4-derived ROS and improved mitochondrial function	Cell culture and diabetic animal models; some human leukocyte–endothelium data	Moderate
Suppression of ICAM-1, VCAM-1, and E-selectin via NF-κB	Cell culture, ApoE−/− mice, and reduced soluble adhesion molecules in patients	Moderate to high; human biomarker data supportive
Restoration of endothelial progenitor cell number and function	Small clinical studies with dulaglutide and supporting mechanistic work	Moderate; small samples, surrogate endpoints
VEGF/VEGFR-2-driven angiogenesis	In vitro tube formation and animal models	Low to moderate; clinical relevance unclear
Plaque stabilization and reduced matrix metalloproteinase activity	Animal models; human carotid intima-media thickness data	Moderate
Shift in epicardial adipose secretome (FABP4)	Limited human tissue studies	Low; hypothesis-generating
Improved flow-mediated dilation in patients	Randomized trials and network meta-analyses, with inconsistent individual results	Moderate as a class effect; not validated as a mediator of outcomes
Reduced platelet aggregation	Preclinical only; mechanism undetermined	Low

eNOS, endothelial nitric oxide synthase; FABP4, fatty acid-binding protein 4; HUVEC, human umbilical vein endothelial cell; ICAM-1, intercellular adhesion molecule-1; NOX4, NADPH oxidase 4; ROS, reactive oxygen species; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor.

Table 5 Safety signals associated with GLP-1 receptor agonists relevant to cardiovascular practice

Adverse effect	Approximate frequency	Evidence and regulatory status	Practical implication
Nausea, vomiting, diarrhea	Common (up to 40–50% during titration)	Consistent across all trials; leading cause of discontinuation (~43% in EXSCEL)	Slow dose titration; do not equate early GI intolerance with lack of cardiovascular benefit
Cholelithiasis / cholecystitis	Uncommon, increased versus placebo	Consistent signal across trials; plausibly related to rate of weight loss	Counsel on biliary symptoms, particularly with rapid weight loss
Acute pancreatitis	Rare	Labeled precaution; no consistent significant excess in largest CVOTs	Relative caution with prior pancreatitis history
Diabetic retinopathy complications	Uncommon; HR ~1.76 in SUSTAIN-6	Attributed to rapid glycemic improvement; less prominent with gradual titration	Baseline ophthalmologic assessment in patients with established retinopathy
Non-arteritic anterior ischemic optic neuropathy (NAION)	Very rare; up to 1 in 10,000 users per EMA	WHO global alert and EMA label update, 2025; MHRA safety update, 2026; pooled HR 2.62 (1.81–3.80); not yet added to US labeling	Counsel on sudden unilateral vision loss; discontinue and refer urgently if confirmed
Thyroid C-cell tumors	Not confirmed in humans	Dose- and duration-dependent signal in rodent studies only; class-wide labeled contraindication in MEN2 / personal or family history of medullary thyroid carcinoma	Screen for contraindicating history before initiation

CVOT, cardiovascular outcome trial; EMA, European Medicines Agency; GI, gastrointestinal; HR, hazard ratio; MEN2, multiple endocrine neoplasia type 2; MHRA, Medicines and Healthcare products Regulatory Agency; NAION, non-arteritic anterior ischemic optic neuropathy; WHO, World Health Organization. Frequencies and risk estimates are approximate and should be confirmed against current product labeling, which varies by regulatory jurisdiction.

Key teaching points — Section 8

- Receptor-independent effects, attributed to the GLP-1(9–36) metabolite, mean that a clean mechanistic story requiring only endothelial GLP-1R is not yet supported by the evidence.
- Concentrations used in most *in vitro* mechanistic work exceed clinical exposure, which limits how directly those findings can be extrapolated to patients.
- Human GLP-1 analogues and exendin-4-derived molecules do not behave identically in outcome trials, and AMPLITUDE-O is a genuine counterexample to any simple molecule-class rule.
- No vascular surrogate used in this literature, including flow-mediated dilation, has been formally validated as a mediator of hard cardiovascular outcomes.

Clinical implications

Three points follow for practice.

The cardiovascular benefit of GLP-1 RAs should not be framed as a consequence of glycemic control. SELECT demonstrated it in patients without diabetes, and the mediation analysis showed that most of the effect is not explained by adiposity either. The indication is cardiovascular; the metabolic effects are concomitant rather than causal in any simple sense.

Agent selection matters. Outcome evidence for MACE reduction is solid for liraglutide, semaglutide (subcutaneous and oral), and dulaglutide, and neutral for lixisenatide and once-weekly exenatide. Treating the class as interchangeable is not supported by the trial data, whatever the shared mechanism may eventually prove to be.

Combination with SGLT2 inhibitors is reasonable. In SOUL, benefit was independent of background SGLT2 inhibitor therapy, consistent with guideline recommendations for additive use in patients with T2D and established cardiovascular disease.

For readers practicing in Brazil and elsewhere in Latin America, two further considerations apply. Liraglutide, dulaglutide, subcutaneous and oral semaglutide, and tirzepatide are available, but access is constrained by cost and by limited public-system coverage, which restricts translation of this evidence to the patients at highest absolute risk. Latin American populations were also under-represented in the pivotal trials. Prescribers should consult the current position statements of the Brazilian Society of Cardiology, the Brazilian Diabetes Society, and the Brazilian Society of Endocrinology and Metabolism for indication and reimbursement guidance, which are updated more frequently than the primary literature.

Safety considerations relevant to the cardiologist

A review focused on cardiovascular benefit risks presenting an incomplete picture unless it also states, plainly, what the same trials and post-marketing data show about harm. Five areas are relevant to cardiology practice specifically.

Gastrointestinal effects and treatment discontinuation

Nausea, vomiting, diarrhea, and constipation are the most common adverse effects across the class and the principal driver of discontinuation, which reached approximately 43% in EXSCEL and is a practical barrier to sustaining the cardiovascular benefits documented in Section 7. Slow dose titration mitigates but does not eliminate this problem; cardiologists co-managing these patients should anticipate it rather than treat early gastrointestinal intolerance as a reason to abandon a drug with demonstrated hard-outcome benefit.

Gallbladder disease and pancreatitis

Cholelithiasis and cholecystitis occur more frequently with GLP-1 RAs, plausibly related to the rate of weight loss itself rather than a direct pharmacologic effect on biliary physiology. Acute pancreatitis has been reported in cardiovascular outcome trials at low absolute rates and without a consistent significant excess over placebo in the largest trials, but it remains a labeled precaution, and a history of pancreatitis is a relative caution in most prescribing guidance.

Citation: Borges NCC. Endothelial dysfunction as the mechanistic bridge between GLP-1 receptor agonism and cardiovascular protection: a narrative review. *J Cardiol Curr Res.* 2026;19(3):98–111. DOI: 10.15406/jccr.2026.19.00650

Diabetic retinopathy

SUSTAIN-6 reported a significant excess of retinopathy complications with semaglutide (HR approximately 1.76 versus placebo), thought to reflect rapid glycemic improvement rather than a direct drug effect, a phenomenon well described with insulin and other agents that produce fast HbA1c reduction in patients with pre-existing retinopathy. This did not recur to the same degree in subsequent trials with more gradual titration, but baseline ophthalmologic assessment and monitoring during the first months of therapy is reasonable in patients with established retinopathy.

Non-arteritic anterior ischemic optic neuropathy (NAION)

This is the most consequential new safety signal to emerge since the SELECT and SOUL publications and had not yet reached regulatory consensus at the time earlier drafts of this review were prepared. In June 2025, the World Health Organization issued a global medical product alert on semaglutide and NAION, following a European Medicines Agency Pharmacovigilance Risk Assessment Committee review that classified NAION as a very rare side effect potentially affecting up to 1 in 10,000 users, with a recommendation to update product information accordingly;[66] the United Kingdom's MHRA issued a corresponding drug safety update in February 2026.

The underlying evidence is mixed in magnitude but consistent in direction. A retrospective matched cohort study from a single academic neuro-ophthalmology registry found a substantially elevated risk (reported as a large relative increase in a high-risk referral population), while a larger multicenter analysis across 14 databases in the OHDSI network, encompassing 37.1 million adults with T2D, found a smaller but still positive association.[67,68] A 2026 systematic review and meta-analysis pooling the available evidence reported a hazard ratio of 2.62 (95% CI 1.81–3.80) for NAION with semaglutide compared with control medications, with risk becoming statistically significant only after approximately two years of exposure, a time-dependency that is itself informative and argues against acute idiosyncratic reaction as the sole mechanism.[69]

NAION causes sudden, typically irreversible, painless monocular vision loss and currently has no effective treatment, which is why the absolute risk, low as it is, warrants explicit patient counseling rather than silent acceptance as background noise. As of this writing, NAION has not been added to United States prescribing labels, creating a transatlantic regulatory discrepancy that is itself worth flagging to trainees as an example of how safety evidence can outpace, or diverge across, regulatory response. Patients should be advised to seek urgent ophthalmologic evaluation for any sudden unilateral vision change during treatment, and semaglutide should be discontinued if NAION is confirmed, per current EMA guidance.

Thyroid C-cell tumors

Rodent studies with GLP-1 RAs have shown a dose- and duration-dependent increase in thyroid C-cell tumors, a finding not confirmed in human epidemiologic data to date but that carries forward as a class-wide labeled contraindication in patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2. This distinction, between an animal-model signal that shapes labeling and a confirmed human risk, is a useful teaching point in its own right about how regulatory caution and clinical evidence can diverge.

Key teaching points — Section 10

- Gastrointestinal intolerance, not a cardiovascular adverse effect, is the leading real-world threat to the benefits described in Section 7, because it drives discontinuation.
- NAION is the safety signal most likely to change practice in the near term: WHO and EMA have classified it as a very rare but serious risk as of 2025–2026, with a pooled hazard ratio around 2.6 and a latency of roughly two years before the risk becomes apparent.
- Thyroid C-cell tumor risk is a rodent-model finding that drives labeling caution but has not been confirmed in human data; this asymmetry between preclinical signal and clinical evidence is worth teaching explicitly.
- Retinopathy worsening early in treatment is most plausibly a consequence of rapid glycemic improvement rather than a direct pharmacologic effect on the retina, analogous to what is seen with insulin.

Research priorities

Five questions would move this field from plausibility toward proof.

First, in vivo dose-response studies at clinically achievable concentrations, which would settle whether the effects described in cell culture occur at therapeutic exposure.

Second, definitive mapping of GLP-1R in human vascular tissue using single-cell transcriptomics and validated detection reagents, which would resolve the receptor question that currently underlies every mechanistic claim.

Third, prespecified vascular endpoints embedded in outcome trials, so that FMD or endothelial biomarkers can be tested formally as mediators rather than assumed to be.

Fourth, trials in populations not yet studied: primary prevention, advanced chronic kidney disease, heart failure across the ejection fraction spectrum, and dual or triple agonists.

Fifth, head-to-head comparisons and real-world cohorts in under-represented populations, including Latin America, where baseline risk profiles and treatment access differ materially from the trial populations.

Conclusions

Endothelial dysfunction is the pathophysiologic link between obesity, T2D, and cardiovascular disease. GLP-1 receptor agonists act at several levels of vascular regulation simultaneously: they restore eNOS/NO signaling, attenuate oxidative and endoplasmic reticulum stress, suppress adhesion molecule expression through NF-κB inhibition, improve endothelial progenitor cell number and function, favor a more stable plaque phenotype, and produce a modest, partly independent reduction in blood pressure.

The clinical evidence is consistent with that profile. MACE reduction persists in patients without diabetes, is only partly mediated by reduction in adiposity, and does not track the magnitude of the metabolic effect. Coronary microvascular imaging now offers a second, independent line of human evidence alongside brachial flow-mediated dilation, though it shares the same cross-study heterogeneity. Endothelial protection is therefore a coherent and probably contributory mechanism.

Citation: Borges NCC. Endothelial dysfunction as the mechanistic bridge between GLP-1 receptor agonism and cardiovascular protection: a narrative review. *J Cardiol Curr Res.* 2026;19(3):98–111. DOI: 10.15406/jccr.2026.19.00650

It is not an established one. The receptor biology in human endothelium remains unresolved — recent 2025–2026 mechanistic and clinical syntheses of this literature reach the same conclusion, which suggests this is a genuine limit of current knowledge rather than a gap specific to this review. Most mechanistic work has been performed at concentrations that do not correspond to clinical exposure, and no vascular surrogate has been validated as a mediator of hard outcomes. Stating this openly seems to us more useful than asserting a mechanism the data do not yet support.

For the practicing cardiologist the operational message is unchanged by that uncertainty. GLP-1 receptor agonists should be regarded as cardiovascular risk-reducing agents, selected on the basis of molecule-specific outcome evidence, rather than as glucose-lowering or weight-lowering drugs with an incidental cardiac benefit.

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Conflicts of interest

The author declares no conflicts of interest.

Author contributions

Ney Carter do Carmo Borges was responsible for conceptualization, literature appraisal, interpretation, drafting, critical revision, and final approval of the manuscript.

Data availability

Not applicable. No new data were generated or analyzed for this narrative review.

Ethics approval

Not applicable. This review did not involve human participants or animal subjects.

Use of artificial intelligence

Generative artificial intelligence was used for language editing and manuscript formatting. The author critically reviewed and approved the entire manuscript and assumes full responsibility for its accuracy, originality, and integrity.

Originality of Figures

Figures 1 to 5 are original artwork prepared by the author. No previously published material has been adapted or reproduced, and no permissions are required.

Glossary of terms for trainees

This glossary is provided as a teaching aid and is not part of the peer-reviewed scientific content of the manuscript; editors may wish to remove it before typesetting, or retain it as supplementary educational material depending on journal policy.

AMPK. AMP-activated protein kinase, a cellular energy sensor activated by a rising AMP:ATP ratio; in the endothelium, its activation is linked to increased eNOS activity and reduced oxidative stress.

Composite endpoint. A single outcome that combines two or more distinct clinical events (for example, cardiovascular death, myocardial infarction, and stroke in three-point MACE) to increase statistical power; interpretation requires checking whether all components move in the same direction.

eNOS (endothelial nitric oxide synthase). The enzyme responsible for producing nitric oxide in endothelial cells; its activity is regulated in part by phosphorylation at serine residue 1177 (Ser1177).

Flow-mediated dilation (FMD). A non-invasive ultrasound measurement of brachial artery diameter change in response to increased blood flow (reactive hyperemia), used as a surrogate marker of endothelial function.

GLP-1R. The glucagon-like peptide-1 receptor, a class B G protein-coupled receptor; its precise distribution in human vascular tissue remains incompletely mapped, which is a recurring theme throughout this review.

Hard outcome. A clinical event that is unambiguous and directly meaningful to the patient, such as death, myocardial infarction, or stroke, as distinct from a surrogate or biomarker outcome.

Hazard ratio (HR). A measure comparing the rate of an event between two groups over time; an HR below 1.0 favors the treatment group. See Section 2.1 for a fuller discussion.

MACE. Major adverse cardiovascular events, most commonly defined as the composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke (three-point MACE).

Mediation analysis. A statistical approach that estimates what proportion of a treatment's overall effect on an outcome is explained by its effect on an intermediate variable, such as the proportion of semaglutide's cardiovascular benefit in SELECT explained by waist circumference reduction.

NAION. Non-arteritic anterior ischemic optic neuropathy, a form of ischemic damage to the optic nerve causing sudden, typically irreversible, painless vision loss; see Section 10.4.

Non-inferiority trial. A trial designed to show a new treatment is not unacceptably worse than a comparator, using a prespecified margin, rather than to show it is superior; several GLP-1 RA cardiovascular outcome trials were designed this way and some subsequently also demonstrated superiority.

Surrogate outcome. A measurement, such as FMD or HbA1c, that correlates with hard outcomes but has not necessarily been proven to mediate a treatment's effect on them.

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