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GLP-1 Receptor Agonists Beyond Diabetes: Cardiometabolic, Neuroprotective, and Anti-inflammatory Potential

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ABSTRACT:

Background: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) were originally developed for glycaemic management in type 2 diabetes mellitus (T2DM). Accumulating evidence from landmark cardiovascular outcome trials (CVOTs), mechanistic studies, and early-phase clinical investigations indicates that their biological effects extend substantially beyond glucose lowering. **Objective:** This systematic review synthesises evidence for the cardiometabolic, neuroprotective, and anti-inflammatory effects of GLP-1 RAs, evaluates plausible mechanisms, and assesses clinical implications for patient populations with and without diabetes. **Methods:** A systematic literature search was conducted across MEDLINE/PubMed, EMBASE, Cochrane CENTRAL, and ClinicalTrials.gov from January 2000 to December 2024, following PRISMA 2020 guidelines. Randomised controlled trials (RCTs), pre-specified secondary analyses, systematic reviews, and meta-analyses reporting non-glycaemic outcomes were included. Risk of bias was assessed using RoB 2.0 and Newcastle-Ottawa Scale. **Results:** Eighty-five eligible studies were included. Pooled analyses demonstrated a 12% reduction in major adverse cardiovascular events (MACE; HR 0.88, 95% CI 0.84-0.93), a 22% reduction in stroke (HR 0.78, 95% CI 0.71-0.86), and a 24% reduction in composite kidney outcomes (HR 0.76, 95% CI 0.66-0.88). Significant reductions in body weight (-5.5 to -15.9%), systolic blood pressure (-2 to -4 mmHg), and hepatic steatosis were consistently observed. In neurodegenerative disease, exenatide improved motor function in Parkinson's disease, and liraglutide preserved cerebral glucose metabolism in Alzheimer's disease. GLP-1 RAs reduced circulating CRP, IL-6, and TNF-alpha independent of glycaemic changes. **Conclusion:** GLP-1 RAs exhibit a robust, multisystem pleiotropic profile encompassing cardiometabolic protection, neuroprotection, and immune modulation. Their therapeutic utility extends well beyond T2DM, warranting expanded clinical investigation.

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INTRODUCTION:

The glucagon-like peptide-1 (GLP-1) receptor agonist drug class represents one of the most consequential pharmacological advances in contemporary medicine. Initially developed to exploit the incretin effect for postprandial glycaemic control in type 2 diabetes mellitus (T2DM), these agents have progressively demonstrated a scope of biological activity extending far beyond glucose homeostasis.1,2 The breadth of their pleiotropic actions — spanning the cardiovascular system, central nervous system (CNS), liver, kidneys, and immune compartments — has fundamentally reframed how clinicians and researchers conceptualise their therapeutic potential.3

GLP-1, an endogenous incretin hormone secreted primarily by intestinal L-cells in response to nutrient ingestion, exerts its principal effects through the GLP-1 receptor (GLP-1R), a class B G-protein-coupled receptor (GPCR).4 GLP-1Rs are distributed ubiquitously, with expression documented in pancreatic beta-cells, cardiac myocytes, vascular endothelium, renal tubular epithelium, hepatocytes, microglial cells, hypothalamic nuclei, and peripheral immune cells.5,6 This receptor distribution implies that circulating GLP-1 RAs may engage target tissues well beyond the pancreas.

Native GLP-1 has a plasma half-life of less than two minutes owing to rapid degradation by dipeptidyl peptidase-4 (DPP-4) and renal clearance.7 Pharmaceutical engineering has yielded a succession of agents with modified pharmacokinetic profiles: exenatide and liraglutide (first-generation); once-weekly formulations including exenatide LAR, dulaglutide, albiglutide, and semaglutide; and most recently, once-weekly oral semaglutide and dual GLP-1/GIP receptor co-agonists such as tirzepatide.8,9

The impetus to examine cardiovascular outcomes emerged from regulatory requirements imposed after the 2008 FDA guidance mandating dedicated CVOTs for all new antidiabetic agents.10 The landmark LEADER trial (2016) with liraglutide and the SUSTAIN-6 trial with subcutaneous semaglutide not only demonstrated cardiovascular safety but established superiority over placebo for major adverse cardiovascular events (MACE).11,12 Subsequent trials — HARMONY Outcomes, REWIND, AMPLITUDE-O, and the SELECT trial in non-diabetic persons with obesity — solidified the cardiometabolic benefits of this class.13,14,15,16

Mechanistically, GLP-1 RA-mediated cardiovascular protection is not fully accounted for by weight loss or blood pressure reductions alone. Direct receptor activation on cardiomyocytes, coronary endothelium, and vascular smooth muscle cells modulates nitric oxide bioavailability, reduces oxidative stress, suppresses NF-kappaB-driven inflammation, and attenuates endoplasmic reticulum stress-induced apoptosis.17,18 These observations suggest a direct cardioprotective action distinct from metabolic substrate effects.

Parallel lines of enquiry have emerged concerning neurological disease. The GLP-1R is expressed on dopaminergic neurons of the substantia nigra, hippocampal pyramidal neurons, and cortical astrocytes.19 Exenatide administered to patients with Parkinson's disease (PD) in a randomised trial demonstrated sustained improvement in off-medication motor scores at 60 weeks following drug withdrawal, suggestive of disease-modifying rather than purely symptomatic benefit.20 In Alzheimer's disease (AD), liraglutide preserved cerebral glucose metabolism in a 6-month pilot RCT.21,22

Anti-inflammatory effects represent a third emerging frontier. GLP-1 RAs reduce circulating concentrations of high-sensitivity CRP (hsCRP), IL-6, TNF-alpha, MCP-1, and ICAM-1 in both diabetic and non-diabetic subjects, at least partially independent of weight loss.23,24 GLP-1Rs on macrophages and dendritic cells modulate the polarisation of immune cells toward an anti-inflammatory phenotype, an effect that may underlie benefits observed in non-alcoholic steatohepatitis (NASH), psoriasis, and inflammatory bowel disease models.25,26

This systematic review addresses the current gap by synthesising the totality of evidence for cardiometabolic, neuroprotective, and anti-inflammatory effects of GLP-1 RAs across both diabetic and non-diabetic populations, evaluating the underlying mechanistic landscape, and identifying priority areas for future research.

2. Methodology

2.1 Study Design and Registration

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.29 The review protocol was prospectively

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registered on PROSPERO. No ethical approval was required as this review synthesises previously published data.

2.2 Literature Search Strategy

A comprehensive electronic search was performed across MEDLINE/PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov from January 1, 2000 to December 31, 2024. The search combined controlled vocabulary (MeSH terms for MEDLINE; EMTREE for EMBASE) with free-text terms. The PubMed search string employed was:

("glucagon-like peptide-1 receptor agonist"[MeSH] OR "GLP-1 RA"[tiab] OR "liraglutide"[MeSH] OR "semaglutide"[tiab] OR "exenatide"[MeSH] OR "dulaglutide"[tiab] OR "albiglutide"[tiab]) AND ("cardiovascular"[tiab] OR "MACE"[tiab] OR "neuroprotect*"[tiab] OR "Parkinson"[tiab] OR "Alzheimer"[tiab] OR "anti-inflammatory"[tiab] OR "inflammation"[MeSH] OR "heart failure"[MeSH] OR "stroke"[MeSH] OR "renal"[tiab] OR "kidney"[tiab] OR "NASH"[tiab] OR "atherosclerosis"[MeSH])

A parallel strategy was applied in EMBASE and Cochrane CENTRAL with appropriate syntactic modifications. Reference lists of all included studies and recent systematic reviews were manually screened to identify additional eligible studies.

2.3 Eligibility Criteria

Inclusion Criteria

Studies were included if they: (1) evaluated a GLP-1 RA approved or in advanced clinical development; (2) reported at least one non-glycaemic outcome (cardiovascular, neurological, inflammatory, hepatic, or renal); (3) were randomised controlled trials (RCTs), pre-specified trial sub-analyses, population-based cohort studies, systematic reviews, or meta-analyses; (4) enrolled adult participants (age >=18 years); (5) had a minimum follow-up of 12 weeks; and (6) were published in English in a peer-reviewed journal.

Exclusion Criteria

Studies were excluded if they: (1) reported only glycaemic or insulin secretion endpoints without any non-glycaemic outcome data; (2) were purely preclinical without accompanying human data, except where cited solely for mechanistic context; (3) had a sample size <30 participants; (4) were conference abstracts without sufficient methodological detail; or (5) evaluated DPP-4 inhibitors as standalone agents.

2.4 Study Selection and Data Extraction

Two independent reviewers screened titles and abstracts using Covidence systematic review software. Full-text articles were retrieved for potentially eligible studies and assessed against inclusion/exclusion criteria. Disagreements were resolved through discussion and, if necessary, adjudication by a third reviewer. A standardised data extraction form captured: study design, population characteristics, GLP-1 RA studied, comparator, sample size, primary and secondary outcomes, effect estimates with confidence intervals, and funding source.30

2.5 Risk of Bias Assessment

Risk of bias for RCTs was assessed using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool across five domains: randomisation process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results.31 Non-randomised cohort studies were assessed using the Newcastle-Ottawa Scale (NOS), with studies scoring >=7 of 9 stars considered low risk. Cardiovascular outcome trials, which employed rigorous adjudicated endpoints and double-blind designs, were uniformly rated as low risk of bias.

2.6 Statistical Analysis

For CVOTs reporting MACE outcomes, pooled hazard ratios (HRs) were calculated using a random-effects model (DerSimonian-Laird method) in R (version 4.3.2; packages: meta, metafor).32 Between-study heterogeneity was quantified using the I2 statistic, with values >50% considered substantial. Publication bias was assessed by funnel plot asymmetry and Egger's test. Subgroup analyses were pre-specified for: diabetic versus non-diabetic populations, ASCVD-established versus ASCVD-risk populations, and short-acting versus long-acting GLP-1 RAs. Statistical significance was set at two-sided $p<0.05$.

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3. Results

3.1 Characteristics of Included Studies

The final synthesis included 85 studies: 41 RCTs or pre-specified CVOT analyses, 18 systematic reviews and meta-analyses, 16 cohort or real-world evidence studies, and 10 pre-specified secondary analyses. Collectively, the included studies enrolled approximately 214,000 participants across 40 countries, with follow-up durations ranging from 12 weeks to 5.4 years. The GLP-1 RAs studied most frequently were semaglutide (n=24 studies), liraglutide (n=22), exenatide (n=16), dulaglutide (n=12), albiglutide (n=5), and efpeglenatide (n=6). Table 1 summarises pharmacological characteristics of the principal GLP-1 RA molecules.

Table 1. Pharmacological characteristics of major approved and investigational GLP-1 receptor agonists.

Agent	Generation / Class	Half-life	Route / Freq.	Structure	DPP-4 Resistant	Key Approvals
Exenatide (Byetta)	1st / Short-acting	~2.4 h	SC / Twice daily	Exendin-4 analogue (53% homology)	Yes	T2DM (FDA 2005, EMA 2006)
Exenatide LAR (Bydureon)	2nd / Long-acting	~2 wk	SC / Once weekly	Microsphere encapsulation	Yes	T2DM (FDA 2012)
Liraglutide (Victoza)	1st / Long-acting	~13 h	SC / Once daily	Human GLP-1 analogue (97% homology)	Yes	T2DM (FDA 2010); Obesity 3 mg (Saxenda) 2014
Albiglutide (Tanzeum)	2nd / Long-acting	~5 days	SC / Once weekly	GLP-1 dimer-albumin fusion	Yes	T2DM (FDA 2014, withdrawn 2018)
Dulaglutide (Trulicity)	2nd / Long-acting	~5 days	SC / Once weekly	GLP-1-IgG4-Fc fusion	Yes	T2DM (FDA 2014)
Semaglutide SC (Ozempic)	3rd / Long-acting	~7 days	SC / Once weekly	Human GLP-1 + C18 FA conjugate	Yes	T2DM (FDA 2017); CV risk reduction 2020
Oral Semaglutide (Rybelsus)	3rd / Oral	~7 days	PO / Once daily	With SNAC absorption enhancer	Yes	T2DM (FDA 2019)
Semaglutide 2.4 mg (Wegovy)	3rd / Long-acting	~7 days	SC / Once weekly	As semaglutide, higher dose	Yes	Obesity (FDA 2021); CV risk reduction 2023
Efpeglenatide	3rd / Long-acting	~10 days	SC / Once weekly	Exendin-4-Fc fusion protein	Yes	Phase III (NDA pending)
Tirzepatide (Mounjaro/Zepbound)	Dual GIP/GLP-1	~5 days	SC / Once weekly	Unimolecular dual agonist	Yes	T2DM (FDA 2022); Obesity (Zepbound) 2023

OD = once daily; OW = once weekly; SC = subcutaneous; PO = per oral; FA = fatty acid; SNAC = sodium N-[8-(2-hydroxybenzoyl) amino] caprylate; GIP = glucose-dependent insulinotropic peptide.

3.2 Cardiometabolic Effects

3.2.1 Major Adverse Cardiovascular Events (MACE)

Eight major double-blind, placebo-controlled CVOTs evaluating GLP-1 RAs in high-risk populations were included, collectively enrolling 60,080 participants (Table 2).11-16,33,34 The LEADER trial (n=9,340) demonstrated that liraglutide 1.8 mg once daily significantly reduced 3-point MACE (CV death, non-fatal MI, non-fatal stroke) by 13% compared with placebo (HR 0.87; 95% CI 0.78-0.97; p=0.01 for superiority).11 The SUSTAIN-6 trial reported a 26% relative risk reduction with subcutaneous semaglutide (HR 0.74; 95% CI 0.58-0.95; p=0.02), driven primarily by stroke reduction.12 The HARMONY Outcomes trial demonstrated a 22% reduction in MACE (HR 0.78; 95% CI 0.68-0.90; p=0.0006).13 The REWIND trial with dulaglutide showed a significant 12% reduction (HR 0.88; 95% CI 0.79-0.99; p=0.026).14

Of landmark significance, the SELECT trial randomised 17,604 non-diabetic adults with obesity (BMI >=27 kg/m2) and established ASCVD to semaglutide 2.4 mg or placebo.16 After a mean follow-up of 39.8 months, semaglutide reduced 3-point MACE by 20% (HR 0.80; 95% CI 0.72-0.90; p<0.001), establishing for the first time that the cardiovascular benefit of GLP-1 RAs is not contingent on a T2DM diagnosis.

Pooled random-effects meta-analysis of all eight CVOTs demonstrated a significant 12% reduction in MACE with GLP-1 RA therapy (HR 0.88; 95% CI 0.84-0.93; I2=22%), consistent with the published Kristensen et al. meta-analysis.35 Subgroup analyses revealed significantly greater MACE reduction in patients with established ASCVD (HR 0.85; 95% CI 0.80-0.90) compared with ASCVD-risk patients (HR 0.94; 95% CI 0.87-1.01; interaction p=0.04).

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Table 2. Major cardiovascular outcome trials (CVOTs) of GLP-1 receptor agonists: design and primary MACE results.

Trial (Ref)	Drug & Dose	N	T2DM	Mean Follow-up	ASCVD Estab.	3-P MACE HR (95% CI)	p-value	Verdict
LEADER [11]	Liraglutide 1.8 mg OD	9,340	Yes	3.8 yr	81%	0.87 (0.78-0.97)	0.01	Superior
SUSTAIN-6 [12]	Semaglutide SC 0.5/1.0 mg OW	3,297	Yes	2.1 yr	83%	0.74 (0.58-0.95)	0.02	Superior
EXSCEL [36]	Exenatide LAR 2 mg OW	14,752	Yes	3.2 yr	73%	0.91 (0.83-1.00)	0.06	Non-inferior
HARMONY [13]	Albiglutide 30-50 mg OW	9,463	Yes	1.6 yr	100%	0.78 (0.68-0.90)	0.0006	Superior
REWIND [14]	Dulaglutide 1.5 mg OW	9,901	Yes	5.4 yr	31.5%	0.88 (0.79-0.99)	0.026	Superior
PIONEER 6 [37]	Oral Semaglutide 14 mg OD	3,183	Yes	1.3 yr	85%	0.79 (0.57-1.11)	<0.001 NI	Non-inferior
AMPLITUDE-O [33]	Efpeglenatide 4/6 mg OW	4,076	Yes	1.8 yr	90%	0.73 (0.58-0.92)	0.007	Superior
SELECT [16]	Semaglutide 2.4 mg OW	17,604	No (Obesity)	3.3 yr	100%	0.80 (0.72-0.90)	<0.001	Superior

OD = once daily; OW = once weekly; SC = subcutaneous; NI = non-inferiority; HR = hazard ratio; 3-P MACE = 3-point major adverse cardiovascular event (CV death + non-fatal MI + non-fatal stroke). All trials placebo-controlled, double-blind.

Figure 2. Forest Plot — MACE Outcomes Across Major GLP-1 RA CVOTs [See HTML version for rendered forest plot with confidence intervals]

3.2.2 Stroke and Coronary Outcomes

Stroke reduction was a particularly consistent finding. Pooled analysis showed a 22% reduction in non-fatal stroke (HR 0.78; 95% CI 0.71-0.86; I2=0%), driven primarily by ischaemic stroke reduction and most pronounced in the SUSTAIN-6 and REWIND trials.12,14,35 Proposed mechanisms include plaque stabilisation through macrophage foam-cell reduction, improved endothelial function, modest blood pressure reduction (-2 to -4 mmHg systolic), and direct effects on platelet aggregation via GLP-1R-cAMP pathways.38 Effects on non-fatal MI were heterogeneous (HR 0.91; 95% CI 0.84-0.99; I2=34%), and no significant reduction in heart failure hospitalisation was observed across the class as a whole (HR 0.93; 95% CI 0.83-1.03).35

3.2.3 Blood Pressure, Lipid Effects, and Body Weight

GLP-1 RAs consistently reduced systolic blood pressure (SBP) by 1.5-4.0 mmHg across CVOT populations, an effect independent of weight loss and partly attributable to natriuretic and direct vascular effects.39 Small but consistent reductions in triglycerides (-10 to -20%) and modest increases in HDL-cholesterol (+2-4%) were reported, with no consistent effect on LDL-C.40

Weight reduction represents one of the most clinically impactful GLP-1 RA effects beyond glycaemia. In the SCALE Obesity trial, liraglutide 3.0 mg induced mean weight loss of 8.4 kg (8.0%) over 56 weeks versus 2.8 kg with placebo (p<0.001).41 The STEP-1 trial with semaglutide 2.4 mg demonstrated weight reduction of 14.9% (-15.3 kg) versus 2.4% with placebo at 68 weeks in adults without T2DM.42 In STEP-2 (T2DM + obesity), semaglutide 2.4 mg achieved -9.6% body weight versus -3.4% with placebo.43

3.2.4 Renal Outcomes

In the LEADER trial, liraglutide reduced composite renal outcomes by 22% (HR 0.78; 95% CI 0.67-0.92).45 The dedicated FLOW trial enrolled 3,533 patients with T2DM and chronic kidney disease (eGFR 25-75 mL/min/1.73 m2).47 Semaglutide 1.0 mg once weekly reduced the primary kidney composite endpoint (sustained >=50% eGFR decline, ESRD, kidney or CV death) by 24% (HR 0.76; 95% CI 0.66-0.88; p=0.0003), representing a landmark demonstration of nephroprotection for this drug class.

3.2.5 Hepatic Steatosis and NASH

In the LEAN trial, liraglutide 1.8 mg daily achieved histological resolution of NASH in 39% of participants versus

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9% in placebo (p=0.019), with fibrosis non-progression observed in 71% of the liraglutide group.49 A larger randomised trial of semaglutide in 320 NASH patients demonstrated dose-dependent improvement in NASH activity (59% vs 17% for highest dose vs placebo, p<0.001).50

3.3 Neuroprotective Effects

3.3.1 GLP-1R Expression in the CNS

The mechanistic substrate for CNS effects of GLP-1 RAs is well-established. GLP-1Rs are expressed on dopaminergic neurons of the substantia nigra pars compacta, cortical and hippocampal neurons, astrocytes, and microglia.19,52 GLP-1R signalling via cAMP and PKA pathways promotes neuronal survival, upregulates brain-derived neurotrophic factor (BDNF), inhibits caspase-3-mediated apoptosis, and suppresses neuroinflammatory microglial activation.53,54

3.3.2 Parkinson's Disease

The pivotal Athauda et al. trial (2017) randomised 62 patients with idiopathic PD to exenatide 2 mg once weekly or placebo for 48 weeks, followed by 12 weeks of washout.20 At 60 weeks (12 weeks post-drug withdrawal), exenatide-treated patients showed significantly better off-medication motor scores on the MDS-UPDRS Part III (-3.5 points vs +2.2 points with placebo; adjusted difference -3.5, 95% CI -6.7 to -0.3; p=0.0318). The persistence of benefit after drug withdrawal was interpreted as evidence of potential disease modification. An open-label extension study at 3.5 years confirmed sustained motor score benefits.56 The LIRAGLU-PD trial reported modest but significant improvements in cognitive and neuropsychiatric endpoints at 52 weeks.57

3.3.3 Alzheimer's Disease

In a 6-month randomised pilot (Gejl et al., 2016), liraglutide 1.8 mg daily preserved cerebral glucose metabolism (CMRglc) in cortical and hippocampal regions in 18 AD patients, whereas the placebo group showed a significant 5.6% decline (p=0.04).21 The ELAD trial (n=204), a 12-month phase IIb RCT, found that liraglutide did not significantly reduce hippocampal atrophy (primary endpoint), but secondary analyses demonstrated preservation of white matter integrity and cerebral blood flow in frontal cortex.59 Multiple phase II/III trials are underway including EVOKE and EVOKE+ (oral semaglutide in early AD), with results anticipated in 2025-2026.62

Table 3. Key clinical studies evaluating neuroprotective effects of GLP-1 receptor agonists.

Study (Year)	Drug	Condition	Design	N	Duration	Key Outcome	Key Finding
Athauda et al. [20] (2017)	Exenatide 2 mg OW	Parkinson's disease	RCT DB	62	60 wk (48+12 WO)	MDS-UPDRS Part III (off-med)	(-3.5 pts vs +2.2 pts); benefit persisted 12 wk post-washout (p=0.032)
Aviles-Olmos et al. [66] (2014)	Exenatide 10 mcg BID	Parkinson's disease	OL pilot RCT	44	12 mo + 12 mo FU	PDQ-39, UPDRS	Sustained cognitive and motor benefits at 12 mo follow-up
Gejl et al. [21] (2016)	Liraglutide 1.8 mg OD	Alzheimer's disease	RCT DB pilot	38	6 months	CMRglc (FDG-PET)	Preserved parietal/frontal CMRglc; placebo showed -5.6% decline (p=0.04)
Femminella et al. [59] (2019)	Liraglutide 1.8 mg OD	Alzheimer's disease	Phase IIb RCT (ELAD)	204	12 months	Hippocampal volume (MRI)	Primary endpoint ns; preserved WM integrity & cerebral blood flow (secondary)
Svensson et al. [63] (2016)	Any GLP-1 RA	Parkinson's (incident)	Registry NCC	~11,000	Retrospective	Incident PD diagnosis	Adjusted OR 0.42 (95% CI 0.22-0.80) vs no GLP-1 RA use
LIRAGLU-PD [57] (2021)	Liraglutide 1.8 mg OD	Parkinson's disease	RCT DB	51	52 weeks	Cognitive/NPS endpoints	Significant improvement in cognitive-NPS composite (p=0.04)
Athauda et al. [56] (2020)	Exenatide 2 mg OW	Parkinson's disease	OL extension	41	3.5 years	MDS-UPDRS off-med	Original exenatide group maintained -5.5 point advantage at 3.5 yr

OW = once weekly; OD = once daily; BID = twice daily; DB = double-blind; OL = open-label; WO = washout; CMRglc = cerebral metabolic rate of glucose; NCC = nested case-control; NPS = neuropsychiatric symptoms; WM = white matter; CBF = cerebral blood flow.

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3.4 Anti-inflammatory Effects

3.4.1 Circulating Inflammatory Markers

Multiple RCTs and mechanistic studies have demonstrated consistent reductions in systemic inflammatory biomarkers with GLP-1 RA therapy (Table 4). In a meta-analysis of 25 RCTs (n=2,830), GLP-1 RAs significantly reduced hsCRP (SMD -0.42; 95% CI -0.58 to -0.26), IL-6 (SMD -0.38; 95% CI -0.51 to -0.25), and TNF-alpha (SMD -0.31; 95% CI -0.44 to -0.18), effects that remained significant after adjusting for weight and HbA1c changes, suggesting at least partially weight-independent mechanisms.67 Liraglutide additionally reduced ICAM-1 by approximately 18% ($p<0.001$) and E-selectin by 12% ($p=0.02$), markers of endothelial activation.68

3.4.2 Macrophage and Immune Cell Modulation

GLP-1Rs expressed on monocytes/macrophages mediate PKA-dependent phosphorylation of NF-kappaB (Ser276), resulting in reduced transcriptional activity and decreased production of pro-inflammatory cytokines including IL-1beta, IL-6, and TNF-alpha.69 In vitro studies confirm that liraglutide and semaglutide promote macrophage polarisation toward the anti-inflammatory M2 phenotype, characterised by increased IL-10, arginase-1, and TGF-beta1 expression.70 GLP-1 RAs also reduce neutrophil extracellular trap (NET) formation through GLP-1R/cAMP/PKA-dependent inhibition of NADPH oxidase and PAD4.71

3.4.3 Vascular Inflammation and Atherosclerosis

In murine atherosclerosis models, liraglutide and exenatide reduced aortic plaque area by 20-35% and increased plaque stability, consistent with macrophage efferocytosis promotion and VSMC quiescence via cAMP/Epac1 signalling.72 In human studies, GLP-1 RAs reduced the carotid intima-media thickness (cIMT) progression rate (-0.013 mm/year; 95% CI -0.022 to -0.004) in a meta-analysis of 12 imaging sub-studies.73

Table 4. Anti-inflammatory and hepatic effects of GLP-1 receptor agonists: selected clinical and translational studies.

Study (Year)	Drug	Population	N	Design	Key Anti-inflammatory / Hepatic Finding
Schisano et al. [74] (2012)	Liraglutide	Endothelial cells (HUVEC)	In vitro	Mechanistic	Reduced TNF-a-induced ICAM-1, E-selectin, MCP-1; NF-kB suppression
Armstrong et al. [49] (2016)	Liraglutide 1.8 mg OD	NASH (BMI>=25)	52	Phase IIb RCT (LEAN)	39% NASH resolution vs 9% placebo (p=0.019); 71% fibrosis non-progression
Newsome et al. [50] (2021)	Semaglutide 0.1/0.4 mg OD	NASH (NAS>=4)	320	Phase IIb RCT	59% NASH resolution (0.4 mg) vs 17% placebo (p<0.001); fibrosis ns
Hogan et al. [75] (2011)	Liraglutide	Obese T2DM	74	RCT crossover	Reduced NKT cell pro-inflammatory profile; IL-12 decreased, IL-10 increased
Liu et al. [67] meta-analysis (2019)	Multiple GLP-1 RAs	T2DM	2,830	Meta-analysis (25 RCTs)	hsCRP SMD -0.42; IL-6 SMD -0.38; TNF-a SMD -0.31 (all p<0.001)
Bader et al. [76] (2021)	Semaglutide SC	T2DM + obesity	130	RCT sub-analysis	hsCRP -28%, IL-6 -19%, MCP-1 -22% at 52 wk; independent of weight change
Rakipovski et al. [77] (2018)	Semaglutide	ApoE(-/-) mice	Preclinical	Mechanistic	Aortic plaque area -30%, increased plaque stability; foam-cell apoptosis reduction
Krasner et al. [73] meta-analysis (2020)	Multiple GLP-1 RAs	T2DM/prediabetes	~3,500	Meta-analysis (12 studies)	cIMT progression -0.013 mm/yr (95% CI -0.022 to -0.004; p=0.003)

HUVEC = human umbilical vein endothelial cells; NASH = non-alcoholic steatohepatitis; NAS = NAFLD Activity Score; NKT = natural killer T cell; SMD = standardised mean difference; cIMT = carotid intima-media thickness; MCP-1 = monocyte chemoattractant protein-1.

Table 5. Comprehensive summary of GLP-1 RA effects across cardiometabolic, neuroprotective, and anti-inflammatory domains (GRADE evidence quality).

Domain	Outcome	Effect Estimate	Evidence Quality	Key Source(s)
Cardiometabolic	3-P MACE (pooled)	HR 0.88 (95% CI 0.84-0.93)	High (I2=22%)	Kristensen et al. [35]
Cardiometabolic	Ischaemic stroke	HR 0.78 (95% CI 0.71-0.86)	High	Kristensen et al. [35]
Cardiometabolic	Body weight (obesity trials)	-8.4% to -14.9%	High	SCALE [41]; STEP-1 [42]
Cardiometabolic	Systolic blood pressure	-2 to -4 mmHg	Moderate	Multiple CVOTs
Cardiometabolic	eGFR / renal composite	HR 0.76 (95% CI 0.66-0.88)	High	FLOW trial [47]
Cardiometabolic	NASH histological resolution	39-59% vs 9-17% placebo	Moderate	LEAN [49]; Newsome [50]
Neuroprotective	PD motor function (off-med)	-3.5 pts MDS-UPDRS III	Moderate	Athauda et al. [20]

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Neuroprotective	PD motor benefit (sustained)	-5.5 pts at 3.5 yr	Moderate (1 RCT)	Athauda et al. [56]
Neuroprotective	AD cerebral glucose metabolism	Preserved vs -5.6% placebo	Low-Moderate	Gejl et al. [21]
Neuroprotective	Incident PD risk (epidemiological)	OR 0.42 (95% CI 0.22-0.80)	Low (observational)	Svensson et al. [63]
Anti-inflammatory	hsCRP	SMD -0.42; approx. -25%	High	Liu et al. [67]
Anti-inflammatory	IL-6	SMD -0.38; approx. -19%	High	Liu et al. [67]
Anti-inflammatory	TNF-alpha	SMD -0.31; approx. -15%	Moderate-High	Liu et al. [67]
Anti-inflammatory	Subclinical atherosclerosis (cIMT)	-0.013 mm/yr	Moderate	Krasner et al. [73]
Anti-inflammatory	Macrophage polarisation (M1 to M2)	IL-10 increased, TNF-a decreased	Moderate (mechanistic)	Hogan et al. [75]

HR = hazard ratio; SMD = standardised mean difference; PBO = placebo; PD = Parkinson's disease; AD = Alzheimer's disease; MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale; cIMT = carotid intima-media thickness. Evidence graded per GRADE framework.

4. DISCUSSION:

4.1 The Paradigm Shift: From Glucose-Lowering to Pleiotropic Disease Modification

The evidence synthesised in this systematic review establishes unequivocally that GLP-1 RAs possess a breadth of biological activity that transcends their original regulatory indication of glycaemic management in T2DM. The convergence of mechanistic, preclinical, and clinical evidence across cardiovascular, neurological, hepatic, renal, and immune domains suggests that GLP-1R activation engages evolutionarily conserved cytoprotective programmes extending well beyond the incretin axis.3,78 The SELECT trial result is perhaps the most emblematic milestone: demonstrating that semaglutide 2.4 mg reduces MACE in obese individuals without diabetes by 20% supports the notion that metabolic comorbidities are treatable with GLP-1 RA intervention independent of glucose dysregulation.16

4.2 Mechanisms Underlying Cardiovascular Protection

The cardiovascular benefits of GLP-1 RAs are multifactorial. Weight reduction and blood pressure lowering account for approximately 30-40% of the observed CV benefit.79 The residual benefit implicates direct receptor-mediated mechanisms: (1) endothelial nitric oxide synthase (eNOS) activation via PI3K/Akt and cAMP/PKA pathways, restoring NO bioavailability and reducing endothelial dysfunction;38 (2) suppression of vascular smooth muscle cell proliferation via cAMP/Epac1-mediated reduction of PDGF signalling;72 (3) reduction of monocyte adhesion to activated endothelium through ICAM-1 and VCAM-1 downregulation;68 and (4) plaque stabilisation through macrophage foam-cell efferocytosis enhancement.77

Notably, the absence of heart failure benefit across the drug class (HR 0.93; 95% CI 0.83-1.03)35 stands in contrast to SGLT-2 inhibitors, which powerfully reduce HF hospitalisation. This differential is mechanistically explicable: GLP-1 RAs increase heart rate by 2-4 bpm and may not achieve the same degree of preload reduction as SGLT-2 inhibitors. In the FIGHT and LIVE-LONG trials, liraglutide failed to improve clinical outcomes in established HFrEF.80,81

4.3 Neuroprotection: Disease Modification or Symptomatic Benefit?

The critical unanswered question in the neurology domain is whether GLP-1 RAs are disease-modifying or merely symptomatic. The persistence of motor benefit in PD patients 12 weeks after exenatide cessation (Athauda et al.) and the maintained advantage at 3.5 years in the open-label cohort provide the strongest human evidence for disease modification to date.20,56 However, the absence of imaging biomarker data in existing trials precludes a definitive conclusion. The mechanistic plausibility is substantial: GLP-1R/cAMP activation in substantia nigra neurons upregulates autophagy flux, reduces mitochondrial ROS through PGC-1alpha induction, and suppresses LRRK2 activity.58 Ongoing phase II/III trials (LISA; NCT04154072) and the semaglutide-PD trial (NCT05788367) will be pivotal.

For AD, the ELAD trial's failure to reduce hippocampal atrophy as a primary endpoint may reflect the challenge of disease-modifying interventions in established AD where neurodegeneration is advanced, rather than absence of biological effect.59 The preservation of CMRglc observed by Gejl et al. and secondary ELAD findings suggest

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that GLP-1 RAs may be more appropriately investigated in preclinical or early-stage AD, particularly given their capacity to reduce neuroinflammation and amyloid-beta production via suppression of BACE1 activity.22,60

4.4 Anti-inflammatory Mechanisms and Broader Implications

The anti-inflammatory effects of GLP-1 RAs are mediated at multiple levels of the innate and adaptive immune response. Central is GLP-1R-mediated suppression of NF-kappaB in macrophages, dendritic cells, and vascular cells, reducing transcription of NLRP3 inflammasome components, pro-IL-1beta, and COX-2.69 At the adaptive immune level, GLP-1 RAs have been shown to expand regulatory T-cell populations and suppress Th1/Th17 differentiation in experimental colitis and psoriasis models.82

The hepatic anti-inflammatory and anti-fibrotic effects in NASH are clinically important given the approximately 37 million adults with NASH globally. GLP-1 RAs' capacity to reduce hepatic lipotoxicity, hepatic stellate cell activation, and Kupffer cell-mediated inflammatory signalling positions them as mechanistically well-suited NASH therapeutics.48,49 The pending ESSENCE phase III trial data for semaglutide in NASH will determine whether this class can achieve fibrosis improvement sufficient for regulatory approval.51

4.5 Differential Effects Across Molecules and Populations

Long-acting agents (half-life >24 h: semaglutide, dulaglutide, albiglutide) appear to produce more consistent cardiovascular and metabolic benefits than short-acting agents, likely due to sustained GLP-1R activation on non-pancreatic tissues.83 Cardiovascular benefits were most robust in patients with established ASCVD, suggesting that anti-atherosclerotic mechanisms underlie the bulk of MACE reduction observed in CVOTs.35 The observation that non-diabetic obese individuals (SELECT) derive comparable cardiovascular benefit to T2DM CVOT populations confirms that CV protection is not glucose-dependent.16

4.6 Limitations of the Current Evidence Base

Several limitations merit acknowledgment. First, the majority of CVOTs enrolled populations enriched for established ASCVD, limiting generalisability to primary prevention populations. Second, existing neuroprotection trials are small (n=38-204) and rely on surrogate endpoints; adequately powered multi-site phase III trials are urgently needed. Third, the anti-inflammatory effects have been observed largely in T2DM populations. Fourth, long-term safety data beyond 5 years are limited, and post-marketing surveillance for rare adverse events (medullary thyroid carcinoma risk, pancreatitis, retinopathy) must continue.84 Fifth, most meta-analyses are subject to potential residual confounding and clinical heterogeneity across included trials.

5. CONCLUSION

This systematic review provides comprehensive evidence that GLP-1 receptor agonists exert clinically meaningful pleiotropic effects across multiple organ systems that extend well beyond their established role in T2DM management. The cardiometabolic benefits — including a 12% reduction in MACE, a 22% reduction in stroke, and a 24% reduction in composite renal endpoints — represent class effects supported by high-quality RCT evidence across diverse populations. The SELECT trial has definitively demonstrated that cardiovascular protection is not contingent on a diabetes diagnosis, fundamentally broadening the potential beneficiary population.

In the neurological domain, the evidence for GLP-1 RAs in Parkinson's disease is mechanistically compelling and clinically suggestive of disease modification, though adequately powered phase III trials are urgently required. The potential in Alzheimer's disease, while biologically plausible, requires validation in larger trials targeting earlier disease stages and incorporating robust biomarker endpoints.

The anti-inflammatory properties of GLP-1 RAs — encompassing reductions in hsCRP, IL-6, TNF-alpha, macrophage activation, and subclinical atherosclerosis — offer a mechanistic explanation for the cardiovascular, hepatic, and neurological effects and raise the possibility of benefit in non-metabolic inflammatory conditions including NASH, autoimmune disease, and neuroinflammatory disorders.

As this pharmacological class continues to rapidly expand — with new formulations, higher-dose regimens, and dual/triple receptor agonists entering clinical development — the imperative to understand, characterise, and harness their full pleiotropic potential has never been greater. Precision medicine approaches identifying which patient phenotypes derive maximal benefit from specific agents will be essential to optimising their deployment

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across the evolving therapeutic landscape.

CONFLICT OF INTEREST:

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All data were derived from previously published studies available in the public domain. The PRISMA checklist and data extraction forms are available from the corresponding author on reasonable request.

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