

GLP-1 Receptor Agonist Beyond Glycemic Control: Cardiometabolic Outcomes, Safety & Indications

Divya Patel¹, Ansari Rajialam Masuk², Dr. Harshdeep singh dabi³

Doctor of Pharmacy 3rd year student¹⁻², Assistant professor Department of pharmacology and pharmacy practice³

Saraswati Institute of Pharmaceutical Sciences, Dhanap, Gandhinagar, Gujarat, India^{1-2,3}

Corresponding Author: Divya Patel

ORCID ID: 0009-0007-3591-3706

Date of Submission: 04-02-2026

Date of Acceptance: 14-02-2026

Abstract

Because of their glucose-dependent insulinotropic activity, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) were first used to treat type 2 diabetes mellitus (T2DM). The therapeutic effects of GLP-1 RAs go beyond glucose management, according to mounting data from big cardiovascular outcome trials. Major adverse cardiovascular events, such as cardiovascular mortality, non-fatal myocardial infarction, and stroke, have been significantly reduced by a number of medicines in this class, especially in people with high cardiometabolic risk or established cardiovascular disease [1-4]. Additionally, GLP-1 RAs have positive effects on blood pressure, body weight, lipid markers, and systemic inflammation, all of which help to reduce cardiometabolic risk [5]. New research suggests that they can help control obesity, chronic renal disease, and heart failure with intact ejection fraction, even in those without diabetes [6-8]. Safety problems, including gastrointestinal issues, gallbladder illness, pancreatitis, and a rare risk of thyroid C-cell malignancies, require careful patient selection and monitoring [9]. With growing indications and clinical use, a thorough understanding of the pleiotropic effects, long-term safety, and appropriate therapeutic placement of GLP-1 RAs is required. This review critically evaluates existing evidence on the cardiometabolic outcomes, safety profile, and emerging applications for GLP-1 receptor agonists beyond glycemic control.

The evidence came from significant cardiovascular outcome trials, randomized clinical investigations, and recent meta-analyses.

Keywords: GLP-1 Receptor Agonists; Cardiometabolic Outcomes; Cardiovascular Disease; Obesity; Safety; Type-2 DM

I. Introduction

- Type 2 diabetes mellitus (T2DM) is a chronic, progressive metabolic condition that is distinguished not only by hyperglycemia but also by a number of cardiometabolic abnormalities such as obesity, hypertension, dyslipidemia, and systemic inflammation. These related disorders significantly raise the risk of cardiovascular disease (CVD), which is still the primary cause of morbidity and mortality among people with T2DM. Traditional glucose-centric therapy methods, while beneficial in decreasing glycemic indices, have had little effect on lowering cardiovascular outcomes, which points to the importance of medications that address the full cardiometabolic risk profile.
- GLP-1 is an incretin hormone released by intestinal L-cells in response to dietary intake. It stimulates glucose-dependent insulin secretion, inhibits incorrect glucagon release, slows stomach emptying, and induces satiety via central pathways. GLP-1 receptor agonists (GLP-1 RAs) were designed to take advantage of these physiological effects for glycemic control in T2DM, providing effective glucose lowering with a low risk of hypoglycemia as well as weight loss advantages. Early clinical trials demonstrated benefits beyond glucose management, motivating substantial research into their cardiometabolic potential.
- GLP-1 RAs' cardiovascular benefits were well proven in major, randomized cardiovascular outcome studies (CVOTs). Landmark studies such as LEADER, SUSTAIN-6, REWIND, and HARMONY. Significant decreases in major adverse cardiovascular events (MACE) were observed, including cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, especially in individuals with existing

CVD or high cardiovascular risk [1-4]. These findings represented a paradigm change, establishing GLP-1 RAs as disease-modifying agents rather than simply glucose-lowering medications.

- In addition to cardiovascular protection, GLP-1 RAs have beneficial effects on a variety of cardiometabolic markers. Trials and meta-analyses show consistent decreases in body weight, systolic blood pressure, and modest changes in lipid profiles [5]. These effects are partly mediated by appetite suppression, delayed stomach emptying, and improved insulin sensitivity, all of which contribute to a reduction in total cardiometabolic risk. GLP-1 RAs' anti-inflammatory and anti-atherogenic characteristics strengthen their involvement in cardiovascular prevention.
- Emerging evidence has broadened the therapeutic applications of GLP-1 RAs beyond diabetes. High-dose semaglutide and similar medicines have been approved for chronic weight management after demonstrating significant and sustained weight loss in obese individuals [6]. Renal outcome evaluations from CVOTs show a reduction in albuminuria progression and composite renal endpoints, indicating renoprotective effects independent of glycemic control [7]. Randomized trials have shown improvements in symptoms and functional ability for patients with heart failure with preserved ejection fraction (HFpEF), which is linked to obesity and metabolic dysfunction [8].
- Despite these advantages, safety issues remain critical. Gastrointestinal side effects are prevalent, especially during commencement and dosage escalation. Patients should be carefully selected and monitored due to potential hazards such as gallbladder illness, pancreatitis, and thyroid C-cell malignancies observed in animal trials [9]. As the number of indications grows and long-term use increases, knowing the balance of benefits and dangers becomes more important.

The purpose of this review is to extensively analyze the evidence supporting the use of GLP-1 receptor agonists for purposes other than glycemic control, with an emphasis on cardiometabolic outcomes, safety profile, and emerging therapeutic indications.

Physiology of the GLP-1 Receptor System

Glucagon-like peptide-1 (GLP-1) is an incretin hormone produced by intestinal L-cells after food consumption. It improves glucose-dependent insulin secretion, reduces glucagon release, slows stomach emptying, and induces satiety via central nervous system pathways [10, 11]. The GLP-1 receptor (GLP-1R), a class B G-protein-coupled receptor, is found in pancreatic β -cells, the gastrointestinal tract, kidneys, cardiovascular organs, and the brain [12]. Receptor activation activates cyclic adenosine monophosphate signaling, activating protein kinase A and Epac2 pathways, resulting in increased insulin production, β -cell survival, and decreased apoptosis [13].

GLP-1R signaling regulates hunger, autonomic balance, endothelial function, and inflammation, leading to cardiometabolic advantages beyond glycemic control [14].

Pharmacology of GLP-1 receptor agonists

GLP-1 receptor agonists (GLP-1 RAs) are synthetic peptides that resist degradation by dipeptidyl peptidase-4, resulting in a longer half-life and clinical efficacy [15]. Modifications can involve amino acid alterations, fatty-acid acylation for albumin binding, or fusion with immunoglobulin fragments [16]. These medicines have varying pharmacokinetic characteristics, allowing them to be classified as either short-acting or long-acting formulations.

Long-acting GLP-1 RAs activate receptors for persistent effects on fasting glucose, body weight, and cardiometabolic risk factors, while minimizing hypoglycemia from insulin-dependent action [17].

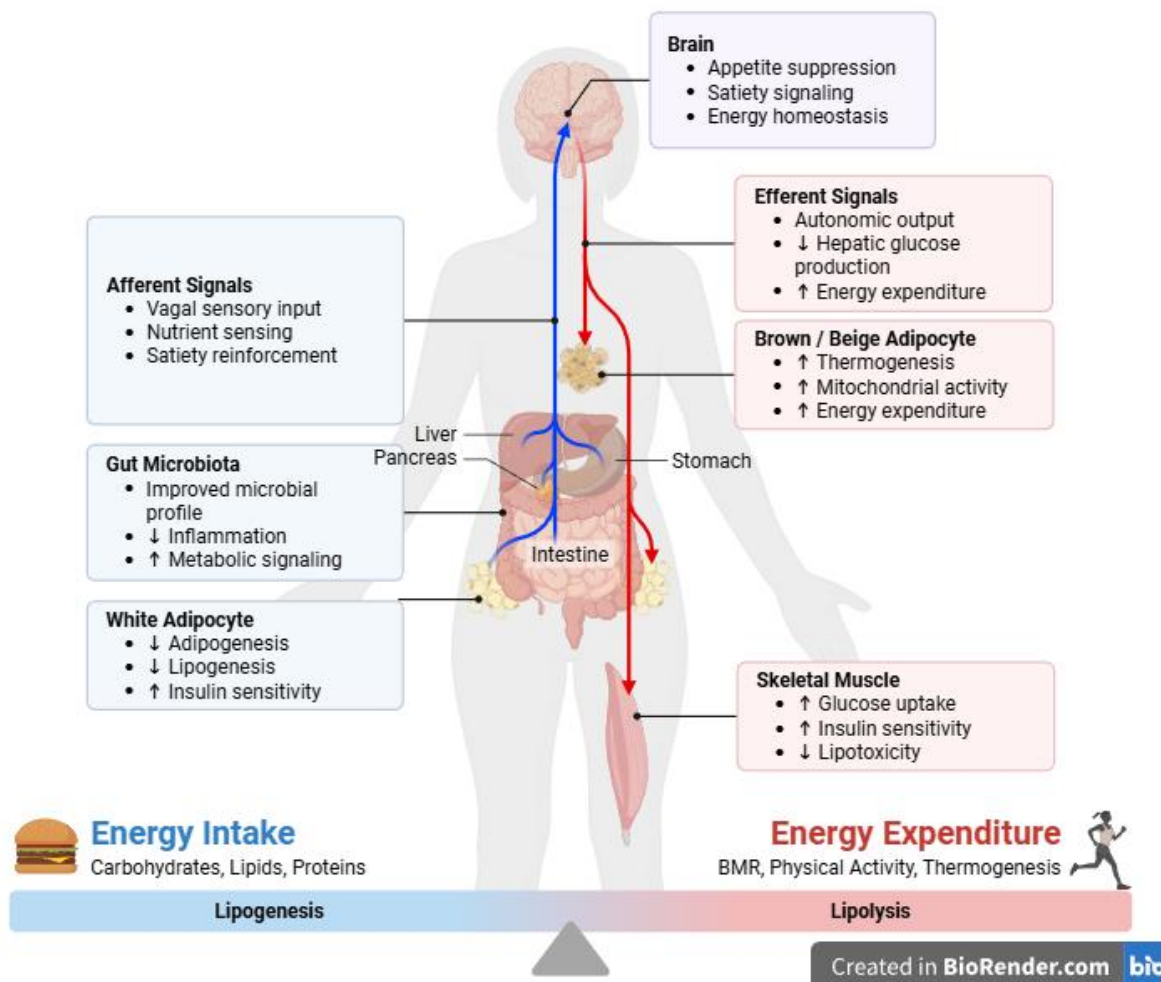


Figure 1: Integrated central and peripheral mechanisms of action of glucagon-like peptide-1 receptor agonists.

Glucagon-like peptide-1 receptor agonists regulate energy balance and metabolic homeostasis by activating coordinated central and peripheral pathways. Central stimulation of GLP-1 receptors in the brain reduces hunger, improves satiety signaling, and regulates energy homeostasis. Afferent neural impulses from the gastrointestinal tract, especially through vagal sensory pathways, carry nutrition sensing and satiety reinforcement to the central nervous system. Efferent autonomic signals carry central GLP-1-mediated actions to peripheral tissues, reducing hepatic glucose synthesis and increasing energy expenditure. GLP-1 receptor agonists modify gut microbiota composition, resulting in decreased inflammation and enhanced metabolic signaling. Stimulation of brown and beige adipocytes in adipose tissue increases thermogenesis and mitochondrial activity, whereas white adipocyte

stimulation reduces adipogenesis and lipogenesis while improving insulin sensitivity. GLP-1 receptor agonists improve glucose absorption and insulin sensitivity in skeletal muscle while lowering lipotoxicity. Collectively, these processes contribute to lower energy intake, higher energy expenditure, and overall cardiometabolic benefit in addition to glycemic management.

Source: Created by the author and adapted from published literature.

Cardiovascular Outcomes Beyond Glycemic Control

GLP-1 receptor agonists provide cardiovascular advantages in addition to decreasing blood sugar levels. Mechanistic investigations show improved endothelial nitric oxide bioavailability, reduced

oxidative stress, decreased vascular inflammation, and stability of atherosclerotic plaques [18,19]. Preclinical models indicate improved myocardial glucose uptake and mitochondrial efficiency [20].

Clinical evidence shows that reducing atherosclerotic events such as myocardial infarction

and ischemic stroke is more effective than hospitalizing for heart failure [21]. New research suggests that heart failure patients with retained ejection fraction may benefit from weight loss, reduced systemic inflammation, and enhanced cardiorespiratory fitness [22].

Regulation of GLP-1 Receptor Agonist

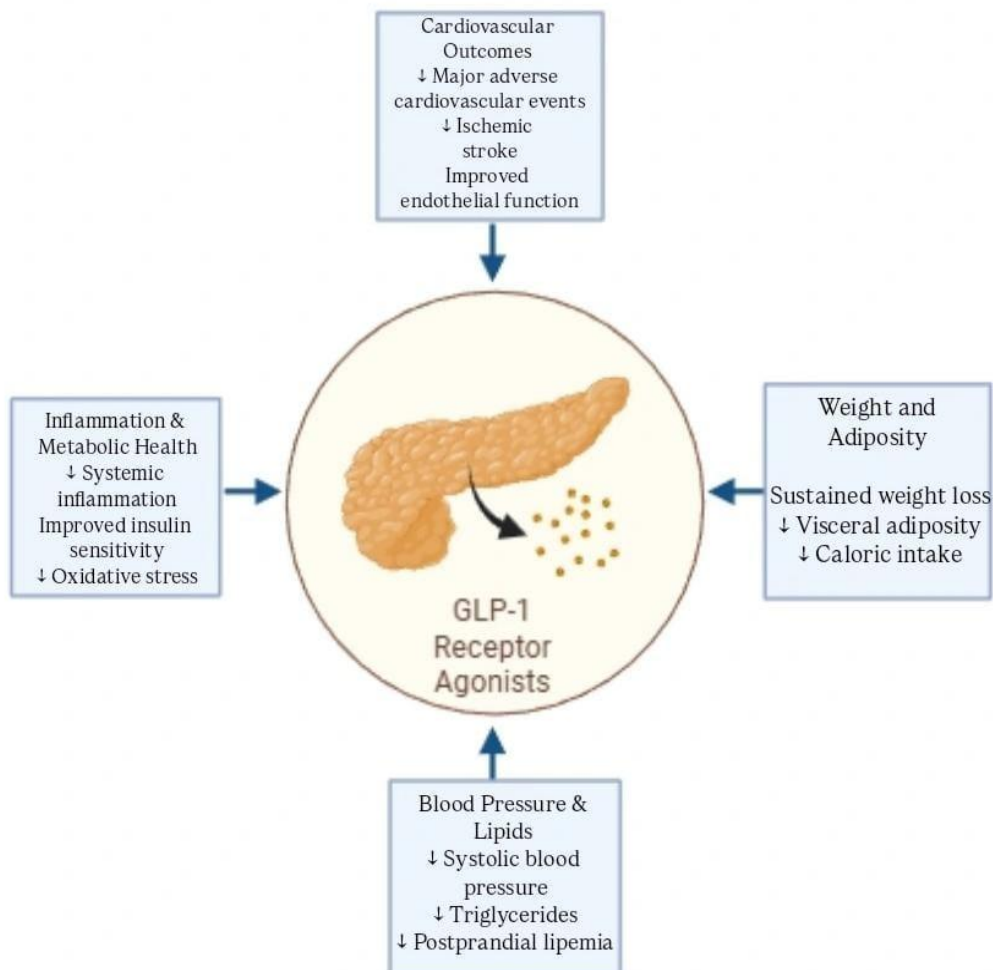


Figure 2: Cardiometabolic effects of glucagon-like peptide-1 receptor agonists beyond glycemic control.

Glucagon-like peptide-1 receptor agonists provide pleiotropic cardiometabolic advantages via

mechanisms other than glucose reduction. These include lower rates of major adverse cardiovascular

events and ischemic stroke, as well as improved endothelial function. GLP-1 receptor agonists improve long-term weight loss by reducing calorie intake and decreasing visceral adiposity. Systolic blood pressure, triglyceride levels, and postprandial lipemia have all improved. Furthermore, these medicines reduce systemic inflammation, increase insulin sensitivity, and lower oxidative stress. These combined benefits contribute to overall cardiometabolic risk reduction in persons with and without type 2 diabetes.

Source: Created by the author and adapted from published literature.

Metabolic benefits beyond glucose lowering
 Weight Reduction

GLP-1 RAs promote long-term weight loss by

regulating appetite, satiety, and reward-related eating behaviors via hypothalamic and mesolimbic pathways [23,24].

Blood pressure and lipids

Weight loss, natriuresis, and better arterial compliance have been shown to consistently lower systolic blood pressure [25]. Lowering triglycerides and postprandial lipemia helps reduce cardiovascular risk [26].

Hepatic and Renal Effects

GLP-1 RAs improve hepatic steatosis by inhibiting de novo lipogenesis and increasing fatty acid oxidation [27]. Renal advantages include reduced albuminuria and slowing of estimated glomerular filtration rate decline through anti-inflammatory and hemodynamic effects [28].

Table 1: Pharmacological characteristics and clinical profile of glucagon-like peptide-1 receptor agonists

Drug	Molecular type	Dosing frequency	Route	Mean HbA1c reduction (%)	Mean weight loss (kg)	CV benefit	Key adverse effects
Exenatide	Exendin-4 analog	Twice daily / once weekly	SC	0.8–1.5	2-3	Neutral	Nausea, vomiting
Liraglutide	Human GLP-1 analog	Once daily	SC	1.0–1.8	3-4	Yes	GI intolerance
Semaglutide	Human GLP-1 analog	Once weekly / oral daily	SC / Oral	1.2–2.0	5–10	Yes	Nausea, diarrhea
Dulaglutide	Human GLP-1 analog	Once weekly	SC	1.0–1.5	2–4	Yes	GI symptoms
Albiglutide	Human GLP-1 dimer	Once weekly	SC	0.6–1.0	1–2	Yes	Injection-site reactions
Lixisenatide	Exendin-4 analog	Once daily	SC	0.8–1.2	2–3	Neutral	Nausea

Abbreviations: CV, cardiovascular; GI, gastrointestinal; HbA1c, glycated hemoglobin; SC, subcutaneous. Values represent approximate ranges derived from phase III trials and cardiovascular outcome studies.

Emerging and Expanding Indications

GLP-1 RAs are now being used to address obesity in non-diabetic individuals, in addition to type 2 diabetes [29]. Current research suggests potential roles in metabolic dysfunction-related steatotic liver disease, chronic renal disease, and heart failure with maintained ejection fraction [30,31]. GLP-1-signaling has a significant role in a variety of

physiological conditions, including polycystic ovarian syndrome, post-transplant metabolic syndrome, and neurodegenerative illnesses [32].

Safety and Tolerability Profiles

GLP-1 RAs are generally well-tolerated. Common gastrointestinal side effects include nausea, vomiting, and diarrhea, which are typically

temporary [33]. Large-scale research has not found a causal link between pancreatitis and pancreatic cancer [34]. Rapid weight loss has led to a slight

increase in gallbladder-related events [35]. Thyroid C-cell hyperplasia in rats has not been confirmed in human studies [36].

Table 2: Safety, tolerability, contraindications, and drug interactions of glucagon-like peptide-1 receptor agonists

Category	Clinical details	Notes / precautions
Common adverse effects	Nausea, vomiting, diarrhea, constipation	Dose-dependent; improve with gradual titration
Serious adverse effects	Pancreatitis (rare), gallbladder disease	Discontinue if suspected pancreatitis
Hypoglycemia	Rare as monotherapy	Risk increases with insulin or sulfonylureas
Cardiovascular safety	Neutral or beneficial	Avoid in unstable heart failure unless evidence supports
Renal safety	Transient worsening of renal function	Mainly due to dehydration from GI effects
Thyroid safety	Risk of medullary thyroid carcinoma	Contraindicated in MEN-2 or personal/family history
Gastrointestinal disorders	Gastroparesis	Avoid in severe gastroparesis
Pregnancy & lactation	Insufficient safety data	Not recommended
Drug interactions	Delayed absorption of oral drugs	Monitor drugs with narrow therapeutic index
Use with insulin	Increased hypoglycemia risk	Reduce insulin dose when initiating GLP-1 RA

Abbreviations: MEN-2, multiple endocrine neoplasia type 2; GI, gastrointestinal.

GLP-1 receptor agonists should be initiated at low doses with gradual escalation to minimize gastrointestinal adverse effects.

Drug interactions and contraindications

GLP-1 RAs have few clinically meaningful medication interactions. Delayed gastric emptying can impact the absorption of medicines with narrow therapeutic indices [37]. When insulin and sulfonylureas are used together, the dose may need to be adjusted to reduce the risk of hypoglycemia.

Contraindications include a personal or family history of medullary thyroid cancer, multiple endocrine neoplasia type 2, and severe gastroparesis [38].

Challenges and Limitations

Barriers to widespread use include high costs, restricted accessibility, injections, and gastrointestinal intolerance [39]. Individual variability in cardiometabolic response and insufficient long-term safety data indicate the

necessity for customized treatment strategies and longer surveillance [40].

Future Perspectives

Future advancements include oral GLP-1 RAs with enhanced bioavailability, dual and triple incretin receptor agonists, and precision-medicine techniques to identify optimal responders [41,42]. Early incorporation of GLP-1 RAs into cardiometabolic disease preventive strategies could significantly alter therapy paradigms.

Recent advances in GLP-1 receptor agonist therapy

Over the last decade, the therapeutic landscape for glucagon-like peptide-1 receptor agonists (GLP-1 RAs) has changed dramatically, changing these medicines from glucose-lowering treatments to broad-spectrum cardiometabolic therapies. A significant recent achievement is the development of dual and multi-incretin receptor agonists, which take advantage of synergistic interactions between incretin pathways. Dual agonists that target both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors have shown higher metabolic efficacy than selective GLP-1 receptor agonists. These agents achieve improved glycemic control and significant

weight loss via complementary mechanisms such as increased insulin secretion, appetite suppression, improved adipose tissue remodeling, and increased energy expenditure, indicating a paradigm shift towards physiologically integrated incretin-based pharmacotherapy [41].

Another significant achievement is the effective translation of oral GLP-1 receptor agonists, which addresses one of the fundamental drawbacks of peptide-based therapies: parenteral delivery. Oral semaglutide, when combined with an absorption enhancer, has shown glycemic and weight-loss efficacy comparable to injectable GLP-1 receptor agonists, enhancing patient acceptance and long-term adherence [42,43]. This invention is especially important for chronic cardiometabolic diseases that necessitate ongoing pharmaceutical intervention.

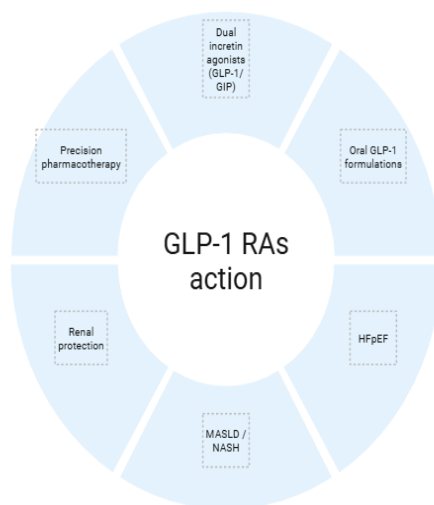
Recent research has expanded the clinical application of GLP-1 receptor agonists to non-diabetic cardiometabolic illnesses, highlighting their disease-modifying potential. Randomized clinical trials have demonstrated that semaglutide markedly enhances symptoms, functional capacity, and health-related quality of life in individuals with heart failure and preserved ejection fraction, irrespective of diabetes status [8]. Furthermore, emerging data supports the significance of GLP-1 receptor agonists in metabolic dysfunction-associated steatotic liver disease, with receptor activation reducing hepatic fat formation, suppressing inflammatory pathways, and improving insulin sensitivity [44].

Advances in cardiorenal outcome research have added to the growing therapeutic profile of GLP-1 receptor agonists. Contemporary studies

show prolonged decreases in albuminuria and a slower drop in estimated glomerular filtration rate, indicating renoprotective effects that go beyond glucose management [31]. Improvements in endothelial function, vascular inflammation, and atherosclerotic plaque stability continue to support their role in long-term cardiovascular risk reduction, establishing GLP-1 receptor agonists as agents capable of modifying disease progression rather than simply improving surrogate metabolic markers [36,41].

GLP-1-based therapy's future course is becoming more and more in line with precision pharmacology. Predictors of therapeutic response, such as baseline body mass index, sex-specific differences, genetic variability, and gut-brain hormonal transmission, are the subject of current research. These insights could lead to better tolerability, optimum dose titration, and customized medication selection [41,45]. At the same time, next-generation GLP-1 receptor agonists with longer half-lives, better safety profiles, and increased receptor selectivity are being developed, expanding their use in cardiometabolic disorders [43].

All things considered, these recent developments demonstrate how GLP-1 receptor agonists have evolved into adaptable cardiometabolic drugs with a growing range of indications, including diabetes, obesity, cardiovascular disease, and metabolic organ failure. Their place in modern clinical practice is probably going to be further redefined by ongoing outcome-driven research and pharmaceutical innovation.



Created in BioRender.com bito

Figure 3. Recent advances and emerging therapeutic applications of glucagon-like peptide-1 receptor agonists.

Recent advances in GLP-1 receptor agonist therapy include the creation of dual and multi-incretin receptor agonists, oral peptide formulations, and long-acting delivery systems. In addition to glycemic management, GLP-1 receptor agonists have been shown to benefit obesity, heart failure with intact ejection fraction, metabolic dysfunction-associated steatotic liver disease, and chronic kidney disease. Precision pharmacotherapy advancements aim to improve patient selection and tailored dosing strategies.

Source: Created by the author and adapted from published literature.

II. Conclusion

GLP-1 receptor agonists have progressed from glucose-lowering medications to complete cardiometabolic drugs. Their shown benefits for cardiovascular outcomes, body weight, and renal and hepatic markers highlight their growing clinical importance. Continued study will help to refine their location across a wide range of cardiometabolic illnesses.

Conflict of Interest

Regarding this study, the author discloses no conflicts of interest.

Acknowledgment

The author admits that several tables and figures were modified from previously published works solely for scholarly purposes. No commercial use is intended, and all sources have been appropriately attributed.

Source of Funding: NIL

References

- [1]. **Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., et al.** Liraglutide and cardiovascular outcomes in type 2 diabetes. *New England Journal of Medicine*. 2016;375(4):311-322.
- [2]. **Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D., Freddy G. Eliaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S.et al.** Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *New England Journal of Medicine*. 2016;375(19):1834-1844.
- [3]. **Prof Hertz C Gerstein, MD. Prof Helen M Colhoun, MD. Prof Gilles R Dagenais, MD. Rafael Diaz, MD. Mark Lakshmanan, MD. Prof Prem Pais, MD. et al.** Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND). *The Lancet*. 2019;394(10193):121-130.
- [4]. **Prof Adrian F Hernandez, MD. Jennifer B Green, MD. Salim Janmohamed, MB. Prof Ralph B D'Agostino, Sr, PhD. Prof Christopher B Granger, MD. Nigel P Jones, MA. et al.** Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease. *The Lancet*. 2018;392(10157):1519-1529.
- [5]. **Michael A. Nauck, Daniel R. Quast, Jakob Wefers, Juris J. Meier.** GLP-1 receptor agonists in the treatment of type 2 diabetes—state of the art. *Molecular Metabolism*. 2021;46: 101102.
- [6]. **Michael A. Nauck, Daniel R. Quast, Jakob Wefers, Juris J. Meier, et al.** Once-weekly semaglutide in adults with overweight or obesity. *New England Journal of Medicine*. 2021;384(11):989-1002.
- [7]. **Johannes F.E. Mann, M.D. David D. Ørsted, M.D., Ph.D. Kirstine Brown-Frandsen, M.D. Steven P. Marso, M.D., Neil R. Poulter, F.Med.Sci., Søren Rasmussen, Ph.D., et al.** Liraglutide and renal outcomes in type 2 diabetes. *New England Journal of Medicine*. 2017;377(9):839-848.
- [8]. **Mikhail N. Kosiborod, M.D. Steen Z. Abildstrøm, Ph.D. Barry A. Borlaug, M.D. Javed Butler, M.D. Søren Rasmussen, Ph.D. Melanie Davies, M.D. G. Kees Hovingh, M.D., Ph.D. et al.** Semaglutide in patients with heart failure with preserved ejection fraction. *New England Journal of Medicine*. 2023;389(12):1069-1084.
- [9]. **Daniel J. Drucker, Steven I. Sherman, Richard M. Bergenstal, John B. Buse.** Safety of incretin-based therapies: a review of the scientific evidence. *Journal of Clinical Endocrinology and Metabolism*. 2019;104(11):4503-4523.
- [10]. **Daniel J. Drucker.** The biology of incretin hormones. *Cell Metabolism*. 2006;3(3):153–165.

- [11]. **Jens Juul Holst.** The physiology of glucagon-like peptide 1. *Physiological Reviews.* 2007;87(4):1409–1439.
- [12]. **Laurent L. Baggio, Daniel J. Drucker.** Biology of incretins: GLP-1 and GIP. *Gastroenterology.* 2007;132(6):2131–2157.
- [13]. **Jonathan E. Campbell, Daniel J. Drucker.** Pharmacology, physiology, and mechanisms of incretin hormone action. *Cell Metabolism.* 2013;17(6):819–837.
- [14]. **Daniel J. Drucker.** Mechanisms of action and therapeutic application of glucagon-like peptide-1. *Cell Metabolism.* 2018;27(4):740–756.
- [15]. **Michael A. Nauck.** Update on developments with glucagon-like peptide-1 receptor agonists. *Diabetes Technology and Therapeutics.* 2016;18(Suppl 1): S2–S10.
- [16]. **Lars Bjerre Knudsen, Jesper Lau.** The discovery and development of liraglutide and semaglutide. *Frontiers in Endocrinology.* 2019; 10:155.
- [17]. **Jens J. Meier.** GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. *Nature Reviews Endocrinology.* 2012;8(12):728–742.
- [18]. **Mina H. Noyan-Ashraf, Daniel J. Drucker.** Cardiovascular actions of incretin hormones. *Circulation Research.* 2011;108(8):909–922.
- [19]. **Angelo Avogaro, Gian Paolo Fadini.** Cardiovascular effects of glucagon-like peptide-1 receptor agonists. *Nature Reviews Cardiology.* 2014;11(6):353–367.
- [20]. **Katherine Ban, Mina H. Noyan-Ashraf, Jürgen Hofer, et al.** Cardioprotective and vasodilatory actions of glucagon-like peptide-1 receptor agonists. *Circulation.* 2008;117(18):2340–2350.
- [21]. **Subodh Verma, Darren K. McGuire.** The role of glucagon-like peptide-1 receptor agonists in cardiovascular risk reduction. *Diabetes Care.* 2020;43(2):289–296.
- [22]. **Silvio E. Inzucchi, Darren K. McGuire.** New drugs for the treatment of diabetes and heart failure. *The Lancet Diabetes and Endocrinology.* 2018;6(6):473–486.
- [23]. **Olivia M. Farr, Maria A. Tsoukas, Christos S. Mantzoros.** Glucagon-like peptide-1 and appetite regulation. *Endocrine Reviews.* 2016;37(4):347–374.
- [24]. **Liesbeth van Bloemendaal, Jeroen S. Ten Kulve, Susanne E. la Fleur, et al.** GLP-1 receptor activation in the brain: implications for eating behaviour. *Nature Reviews Endocrinology.* 2014;10(8):437–448.
- [25]. **Feng Sun, Shanshan Wu, Sheng Guo, et al.** Effect of glucagon-like peptide-1 receptor agonists on blood pressure: a meta-analysis. *Diabetes Research and Clinical Practice.* 2015;110(1):26–37.
- [26]. **Zin Zin Htike, Francesco Zaccardi, Dimitrios Papamargaritis, et al.** Efficacy and safety of GLP-1 receptor agonists on lipid metabolism. *Diabetes, Obesity and Metabolism.* 2017;19(3):329–339.
- [27]. **Matthew J. Armstrong, Philip Gaunt, Guruprasad P. Aithal, et al.** Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis. *The Lancet.* 2016;387(10019):679–690.
- [28]. **Michaël H.A. Muskiet, Laura Tonneijck, Marlies M. Smits, et al.** GLP-1 and renal physiology. *Diabetes Care.* 2017;40(2):280–286.
- [29]. **John P. H. Wilding.** GLP-1 receptor agonists for the treatment of obesity. *BMJ (British Medical Journal).* 2021;373: n1380.
- [30]. **Kenneth Cusi.** Treatment of patients with type 2 diabetes and non-alcoholic fatty liver disease. *Diabetologia.* 2016;59(6):1112–1120.
- [31]. **Johannes F. E. Mann, Michaël H.A. Muskiet.** GLP-1 receptor agonists and kidney protection. *Clinical Journal of the American Society of Nephrology.* 2021;16(2):308–310.
- [32]. **Christian Hölscher.** Neuroprotective effects of glucagon-like peptide-1 receptor agonists. *Neuroscience and Biobehavioral Reviews.* 2014; 47:299–315.
- [33]. **Katrin Bettge, Matthias Kahle, Mohamed S. Abd El Aziz, et al.** Occurrence of nausea with glucagon-like peptide-1 receptor agonists. *Diabetes, Obesity and Metabolism.* 2017;19(3):336–347.
- [34]. **Matteo Monami, Irene Dicembrini, Edoardo Mannucci.** Safety of glucagon-like peptide-1 receptor agonists. *Current Diabetes Reports.* 2014;14(2):444.
- [35]. **Marlies M. Smits, Laura Tonneijck, Michaël H.A. Muskiet, et al.** GLP-1 based therapies and risk of gallbladder disease. *Diabetes Care.* 2016;39(4): e53–e54.
- [36]. **Birgit Gier, Peter C. Butler.** Glucagon-like peptide-1 receptor agonists and thyroid cancer risk. *Diabetes Care.* 2012;35(Suppl 2): S265–S270.

- [37]. **Mette Christensen, Filip K. Knop.** Effects of glucagon-like peptide-1 receptor agonists on gastric emptying. *Diabetes, Obesity and Metabolism.* 2012;14(6):531–544.
- [38]. **Michael A. Nauck, Jens J. Meier.** Incretin-based therapies: safety and contraindications. *Diabetes Care.* 2019;42(Suppl 1): S180–S187.
- [39]. **Melanie J. Davies, Vanita R. Aroda, Barbara S. Collins, et al.** Management of hyperglycemia in type 2 diabetes: positioning of GLP-1 receptor agonists. *Diabetes Care.* 2022;45(6):1362–1379.
- [40]. **William T. Cefalu, Matthew C. Riddle.** Real-world evidence for glucagon-like peptide-1 receptor agonists. *Diabetes Care.* 2020;43(11):2661–2663.
- [41]. **Michael A. Nauck, Daniel R. Quast.** Cardiometabolic effects of dual incretin receptor agonists. *Trends in Endocrinology and Metabolism.* 2021;32(6):401–414.
- [42]. **Daniel J. Drucker.** Advances in oral peptide therapeutics. *Nature Reviews Drug Discovery.* 2020;19(4):277–289.
- [43]. **Melanie J. Davies, Vanita R. Aroda, Barbara S. Collins, Francesco Cosentino, Jonathan E. Shaw, Kamlesh Khunti.** Management of hyperglycemia in type 2 diabetes, 2022: A consensus report by the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care.* 2022;45(11):2753–2786.
- [44]. **Kenneth Cusi.** Treatment of patients with type 2 diabetes and metabolic dysfunction-associated steatotic liver disease. *Diabetologia.* 2016;59(6):1112–1120.
- [45]. **Michael A. Nauck, Jens J. Meier.** Incretin-based therapies: safety, efficacy and future perspectives. *Diabetologia.* 2018;61(5):1016–1023.