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Comparative Effectiveness of GLP-1 Receptor Agonists in Type 2 Diabetes: A Systematic Review

Dr Adesh D. Mishra[1], Dr Suneel Kumar Rohilla[2]*, Dr Md Faraz Qureshi[3]

[1]Associate professor, Dept of Pharmacology, Raipur Institute of Medical Sciences (RIMS), Raipur, Chhattisgarh, India

[2]Associate professor, Dept of Pharmacology, Pt B.D.Sharma PGIMS, Rohtak, Haryana, India

[3]Assistant professor, Dept of Pharmacology, Raipur Institute of Medical Sciences (RIMS), Raipur, Chhattisgarh, India

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KEYWORDS

Type 2 DM, GLP-1 receptor, Treatment adherence, Cost-effectiveness, Side effects

ABSTRACT:

Objective:

To systematically evaluate the comparative glycemic efficacy, weight reduction, cardiovascular outcomes, safety, and patient adherence of currently approved GLP-1RAs in the management of T2DM.

Methods:

Comprehensive literature searches of PubMed, Cochrane Library, Embase, and clinical trial databases were conducted up to mid-2025 to identify randomized controlled trials (RCTs), cardiovascular outcome trials (CVOTs), meta-analyses, and observational studies comparing GLP-1RAs. Outcomes extracted included reductions in HbA1c, body weight, occurrence of major adverse cardiovascular events, adverse drug reactions, and treatment adherence rates. Quality assessment used Cochrane and Newcastle-Ottawa tools.

Results:

Twenty-five RCTs and seven CVOTs met inclusion criteria. Semaglutide and tirzepatide consistently demonstrated the greatest HbA1c and weight reductions. Cardiovascular outcomes were notably improved with liraglutide, semaglutide, and dulaglutide. Gastrointestinal side effects were common but transient. Once-weekly and oral formulations showed improved adherence. Data heterogeneity limited head-to-head comparisons.

Conclusions:

GLP-1RAs differ in efficacy and safety profiles. Semaglutide offers superior glycemic and weight benefits, supported by robust cardiovascular evidence. Nevertheless, therapy should be individualized according to patient factors. Future studies should address long-term comparative effectiveness, cost-effectiveness, and personalized treatment strategies.

Introduction

Type 2 diabetes mellitus (T2DM), a condition that is becoming more and more of a global health problem, is characterized by persistent hyperglycemia caused by insulin resistance and pancreatic beta-cell dysfunction. By significantly increasing the risk of macrovascular events like myocardial infarction, stroke, and heart failure as well as microvascular repercussions including retinopathy, nephropathy, and neuropathy, the disorder contributes to high rates of morbidity and death worldwide.[1-7] Treatments that provide more than simply glucose reduction are replacing traditional therapy paradigms that only concentrate on glycemic control.[3]

For the treatment of type 2 diabetes, glucagon-like peptide-1 receptor agonists, or GLP-1RAs, have emerged as a ground-breaking family of drugs.[2] These compounds mimic the actions of the natural incretin hormone GLP-1 by increasing glucose-dependent insulin secretion and suppressing inappropriate glucagon release.[3,8] They also change how the appetite is regulated, which promotes fullness and effective weight control, and they delay the emptying of the stomach, which lowers postprandial glucose spikes. Together,

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these advantages help to enhance glycemic control and mitigate many of the condition's detrimental metabolic aftereffects.[9]

GLP-1RAs are particularly notable for their benefits to the cardiovascular system. Strong evidence from numerous large-scale randomized cardiovascular outcome trials has demonstrated that GLP-1RA therapy prevents major adverse cardiovascular events (MACE), such as myocardial infarction, stroke, and cardiovascular mortality. GLP-1RAs are currently the suggested treatment for T2DM patients who are at high risk for cardiovascular issues as a result of these findings.[2,6,10]

Many GLP-1RAs with various pharmacokinetic and pharmacodynamic characteristics are currently approved globally.[11] These medications vary in their molecular composition, duration of action, dose schedules (ranging from twice daily to once weekly or even oral forms), and individual efficacy profiles.[12-15] Despite the fact that all GLP-1RAs aid in weight loss and better glycemic management, recent studies suggest that the magnitude of these benefits, as well as the drugs' tolerance and cardiovascular prevention benefits, may differ.[13]

Practitioners must be able to use systematic comparative data to tailor therapy to each patient's unique profile while balancing effectiveness, safety, adherence potential, and patient preferences.[14] Given the complexity and diversity of available agents, this review synthesizes the most recent evidence, including head-to-head trial data, network meta-analyses, and real-world studies, to provide a comprehensive assessment of the relative efficacy of GLP-1RAs in the treatment of type 2 diabetes.[16-20] The information offered is intended to improve patient outcomes, aid in clinical decision-making, and help direct future research objectives in this rapidly evolving field.[21]

Methods

Search Strategy and Study Selection

A comprehensive and systematic search was conducted for pertinent information in a number of significant biological and clinical trial databases, including PubMed, Embase, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov. The search encompassed all relevant papers published up until June 2025. The search terms included keywords and medical subject headings (MeSH) associated with type 2 diabetes and GLP-1 receptor agonists, such as “GLP-1 receptor agonists,” “type 2 diabetes,” “glycemic control,” and “cardiovascular outcomes,” in addition to specific drug names like liraglutide, semaglutide, dulaglutide, exenatide, and tirzepatide.

Only high-quality observational studies involving adult patients (≥18 years) with type 2 diabetes, cardiovascular outcome trials (CVOTs), randomized controlled trials (RCTs), and meta-analyses met the inclusion requirements. Research that satisfied the inclusion criteria either directly contrasted two or more GLP-1RAs or GLP-1RAs with other antidiabetic drugs or a placebo. Studies that reported relevant clinical outcomes, including weight change, the incidence of major adverse cardiovascular events (MACEs), safety profiles, adherence metrics, and a decrease in HbA1c, were included. Studies that solely focused on type 1 diabetes, animal or in vitro models, reviews, editorials, and papers written in languages other than English were disqualified in order to ensure primary clinical relevance and consistency.

Data Extraction and Quality Assessment

Two independent reviewers carefully collected relevant data from each included study using a predefined and consistent data extraction form in order to ensure consistency and minimize errors. The data that was extracted included study demographics (year of publication, design, sample size, and duration), intervention characteristics (specific GLP-1 receptor agonist used, dosage, and comparator treatments), and patient baseline profiles (age, sex, duration of diabetes, baseline glycemic control, and comorbidities). Clinical outcomes that were retrieved were changes in body weight and HbA1c, incidence rates of major adverse cardiovascular events (MACE), adverse events related to medication, and patient adherence rates. The rigorous process included cross-checking by both reviewers to ensure data integrity, and any conflicts were resolved by arbitration or consensus by a third reviewer. This careful data extraction allowed for a comprehensive and accurate synthesis of the relative efficacy and safety profiles of many GLP-1 receptor agonists in type 2 diabetes.

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Data Synthesis

Due to the substantial clinical and methodological variation among the included studies, a narrative synthesis methodology was primarily employed to integrate and synthesize data. Finding patterns, trends, and connections within and between disparate datasets is made possible by narrative synthesis, which describes and interprets study findings in an orderly, textual fashion. This method is particularly helpful when variations in research populations, treatments, outcome measures, and study designs render quantitative meta-analysis impracticable. By carefully organizing and evaluating the data via narrative synthesis, a comprehensive understanding of the relative effectiveness of many GLP-1 receptor agonists was achieved. Furthermore, when sufficient data were available to provide indirect comparisons and rank-order treatments based on safety and effectiveness, network meta-analyses from previously published research were incorporated. The integration of narrative and statistical synthesis ultimately facilitated nuanced clinical decision-making by guaranteeing robustness while accounting for the diversity and complexity of the data.

Results

Study Characteristics

A wide range of patient populations were covered by the 32 studies that were included in the systematic review, including 7 cardiovascular outcome trials (CVOTs) and 25 randomized controlled trials (RCTs). With sample sizes ranging from around 200 to 9,000 people, these trials offer a strong foundation of data for assessing GLP-1 receptor agonists.[18] Participants' baseline glycated hemoglobin (HbA1c) usually fell between 7.5% and 9.5%, indicating moderate to poor glycemic control before starting treatment. Participants in the study had varying cardiovascular risk profiles, ranging from relatively low-risk individuals to those with a history of cardiovascular disease [Marso et al., 2016; Gerstein et al., 2019].[11,14] The mean duration of diabetes among study subjects was between 5 and 12 years, reflecting established disease.

Glycemic Control

HbA1c levels were significantly lowered by all GLP-1 receptor agonists, confirming their effectiveness as glucose-lowering medications. Compared to liraglutide and dulaglutide, which demonstrated reductions of around 1.2% and 1.1%, respectively, semaglutide consistently had the largest mean absolute HbA1c decrease of about 1.5%. With HbA1c decreases near 2.0%, tirzepatide, a new dual GLP-1/GIP receptor agonist, demonstrated even higher effectiveness. Because they affect gastric emptying, short-acting GLP-1RAs were particularly effective at lowering postprandial glucose excursions, while long-acting agents demonstrated better control over fasting glucose levels, offering a supplemental therapeutic effect [Marso et al., 2016; Gerstein et al., 2019].[11,14]

Weight Management

One significant side effect of GLP-1RAs, weight reduction, differed greatly between the agents under study. Most notable weight reductions, frequently between 5 and 15 kg, were linked to semaglutide and tirzepatide. Compared to liraglutide and dulaglutide, which usually resulted in weight reductions of 3 to 5 kg, this impact was noticeably better.[22] The fact that weight reduction is sustained over extended periods of time emphasizes the usefulness of GLP-1RAs in treating the comorbidities of type 2 diabetes associated with obesity [Marso et al., 2016][11].

Cardiovascular Outcomes

Major CVOTs, including LEADER (evaluating liraglutide), SUSTAIN-6 (semaglutide), REWIND (dulaglutide), and HARMONY (albiglutide), consistently demonstrated that GLP-1RAs reduce the relative risk of major adverse cardiovascular events (MACE) by a range of 12-26%.[23,24] The beneficial effects extended beyond MACE to reductions in cardiac death, stroke incidents, and hospitalization due to heart failure. Emerging outcome data for tirzepatide suggest similar cardiovascular protective effects, although more extensive data are pending [Marso et al., 2016; Gerstein et al., 2019].[11,14]

Safety Profile

In all GLP-1RA investigations, gastrointestinal side events—mostly temporary nausea and vomiting—were the most commonly reported. Gradual dosage increase often reduced these dose-dependent adverse effects. GLP-1RAs had a little risk of hypoglycemia, unless they were used with insulin or sulfonylureas.[25] Crucially, no study or meta-analysis found a verified rise in the

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incidence of medullary thyroid cancer or pancreatitis, confirming the generally positive safety profile of this treatment class [Marso et al., 2016].[11]

Adherence and Patient Preferences

In contrast to more frequent dose regimens, the availability of long-acting, once-weekly injectable formulations improved patient comfort and satisfaction and increased adherence to GLP-1RA treatment.[26,27] By removing injection-related obstacles, oral semaglutide has shown increased patient acceptability and possible adherence, significantly expanding the utility of the medication class [Gerstein et al., 2019].[14]

Cost-Effectiveness

Cost-effectiveness assessments show good economic profiles when taking into consideration GLP-1RAs' capacity to lower hospital admissions and problems associated to diabetes, despite their higher initial drug costs when compared to conventional antidiabetic medicines. GLP-1RAs are therefore a wise investment in long-term diabetes management that might eventually result in lower medical costs [Marso et al., 2016].[11]

Discussion

This comprehensive review emphasizes the significant therapeutic value of GLP-1 receptor agonists (GLP-1RAs) in the treatment of type 2 diabetes mellitus (T2DM), which have a number of benefits beyond glycemic control.[28-30] These drugs accomplish their therapeutic objectives in several ways, including promoting satiety, delaying stomach emptying, blocking inappropriate glucagon release, and boosting glucose-dependent insulin secretion. When combined, these mechanisms lead to clinically meaningful weight loss as well as notable decreases in HbA1c, which is crucial for T2DM patients who often experience obesity and insulin resistance.[31,32]

Due to their consistent superior efficacy over previous drugs, tirzepatide and semaglutide have emerged as the leaders in this therapeutic class. Semaglutide, a once-weekly GLP-1RA, has shown remarkable results in clinical trials, reducing HbA1c levels of up to 1.5–2% and causing notable weight loss, often exceeding 10% [Marso et al., 2016].[11] Tirzepatide, a dual GLP-1 and GIP receptor agonist, has demonstrated even more efficacy in head-to-head testing, indicating that it might be able to reinterpret therapy objectives in the management of type 2 diabetes [Rosenstock et al., 2021].[20] In addition to enhancing metabolic profiles, these advantages target obesity, a significant cause of insulin resistance and cardiovascular morbidity.[33]

Important cardiovascular outcome studies (CVOTs) like LEADER, SUSTAIN-6, and REWIND have shown the cardiovascular beneficial effect of GLP-1RA therapy. These studies consistently demonstrated reductions in major adverse cardiovascular events (MACE), including nonfatal myocardial infarction, nonfatal stroke, and cardiovascular mortality, especially in high-risk populations [Gerstein et al., 2019; Gerstein et al., 2024].[14,22] These findings have led to changes in clinical guidelines, which now prioritize GLP-1RAs for patients with elevated cardiovascular risk or existing atherosclerotic cardiovascular disease (ASCVD). By providing both cardiovascular protection and metabolic control, this repositions the medicines as dual-action treatments.[34-36]

Despite their promise, therapeutic decision-making needs to remain individualized. Patient-specific factors, including as comorbidities, renal function, gastrointestinal tolerability, preferred methods of administration, and budgetary concerns, have a significant impact on the choice of therapy.[37] Gastrointestinal side effects as nausea, vomiting, and diarrhea may hinder adherence even though they are often transient and dose-dependent, highlighting the importance of patient counseling, gradual dosage titration, and monitoring methods [Buse et al., 2020].[38] Expanding treatment options and potentially increasing patient satisfaction and compliance include the introduction of oral semaglutide and the development of multiple formulations, ranging from twice-daily injections to once-weekly preparations [Nauck et al., 2019].[39]

Nonetheless, a number of flaws in the current body of evidence necessitate careful consideration. Heterogeneity in research design, patient demographics, and outcome variables complicates direct comparisons between different GLP-1RAs. Moreover, additional long-term, head-to-head trials are required to ascertain tirzepatide's relative benefit over established GLP-1RAs, despite the drug's previously unprecedented efficacy [Frias et al., 2021].[40] Furthermore, even while clinical

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studies provide reliable effectiveness and safety data, there is still a lack of empirical data on adherence, persistence, and long-term safety across a range of groups. Observational studies, registry data, and post-marketing tracking will be crucial to confirm the duration of benefit and identify rare or delayed negative effects.[20]

Combining GLP-1RAs with other newly developed antidiabetic medications, such as sodium-glucose cotransporter-2 (SGLT2) inhibitors, presents intriguing opportunities for the future. Initial research suggests that there might be synergistic effects on glycemic control, weight loss, renal protection, and cardiovascular outcomes [American Diabetes Association, 2024].[19] As comprehensive evaluations across different patient categories, clinical contexts, and healthcare systems continue to develop, well-designed randomized controlled trials (RCTs) will be necessary to optimize combination approaches.[2,4,10]

Finally, patient-centered treatment is necessary to maximize therapeutic impact. Decision-making that considers patient preferences, treatment burden, and quality of life enhances adherence and overall satisfaction in addition to clinical success. In order to increase long-term success, shared decision-making models are needed, where patients evaluate the benefit-risk profile of each medication option, considering factors like cost, expected outcomes, frequency of administration, and potential side effects [Davies et al., 2022].[17]

Conclusion

GLP-1 receptor agonists (GLP-1RAs), which have potent effects on lowering glycated hemoglobin (HbA1c), promoting weight loss, and safeguarding the cardiovascular system, have radically changed the way type 2 diabetes mellitus (T2DM) is treated. By mimicking the activities of natural incretin hormones, these compounds work together to improve glycemic control and reduce the issues related to obesity by increasing glucose-dependent insulin secretion, decreasing glucagon release, controlling hunger, and delaying stomach emptying. Semaglutide and tirzepatide in particular have demonstrated better performance among GLP-1RAs. Semaglutide typically produces the largest decreases in HbA1c and body weight in clinical trials; however, tirzepatide, a dual GLP-1/glucose-dependent insulinotropic polypeptide receptor agonist, has even better glycemic and weight loss effects. These developments have increased the number of therapy options available to patients who often struggle to meet glycemic goals with conventional medications. Despite the promising therapeutic features of these medications, tailored therapy selection is essential to optimize efficacy and safety for a variety of patient populations. The decision is influenced by a number of patient circumstances, such as concurrent cardiovascular or renal disease, tolerance profiles, the mode and frequency of administration (oral vs. injectable), and cost considerations. For example, drugs having data from cardiovascular outcome studies would be more beneficial for patients with cardiovascular risk factors, while patients who are terrified of injections might select oral semaglutide. The gastrointestinal side effects that are commonly associated with GLP-1RAs must be properly controlled in order to increase adherence.

Treatment outcomes may be considerably improved by next-generation multi-receptor agonists that target the GLP-1, GIP, and glucagon receptors as well as innovative formulations including oral GLP-1RAs. By using complementary processes, these new medications aim to enhance glucose regulation and weight control. Clinical trial data must be integrated with real-world data from current and upcoming studies to improve comparative effectiveness and guide customized, patient-centered treatment approaches. This expanding research will help doctors balance the benefits and drawbacks, ensure equitable access, and create tailored treatments that effectively treat multifactorial metabolic dysfunction in type 2 diabetes.

GLP-1RAs are a groundbreaking discovery that offer a number of benefits beyond lowering blood sugar levels, including as weight control, cardiometabolic protection, and the potential to change the way type 2 diabetes is treated and improve long-term outcomes.

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