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Dual GLP-1/GIP Agonists for Weight Reduction and Cardiovascular Outcomes in Type 2 Diabetes

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ABSTRACT

Type 2 diabetes mellitus (T2DM) was characterized by hyperglycemia and frequently accompanied by obesity and elevated cardiovascular risk. Incretin hormone-based therapies, especially glucagon-like peptide-1 receptor agonists (GLP-1 RAs), had demonstrated efficacy in glycemic control, weight reduction, and cardiovascular risk mitigation. Recently, dual agonists targeting both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors had emerged as promising therapeutic agents aiming to enhance these benefits. This review assessed the efficacy and safety of dual GLP-1/GIP agonists specifically regarding weight reduction and cardiovascular outcomes in patients with T2DM. A systematic literature search was conducted, prioritizing randomized controlled trials, meta-analyses, and high-quality observational studies published within the last decade on dual GLP-1/GIP agonists in T2DM management. Dual GLP-1/GIP receptor agonists produced superior weight loss and glycemic control compared to GLP-1 monoagonists, attributable to complementary incretin receptor signaling that enhances insulin secretion, suppresses glucagon, and reduces appetite. Cardiovascular outcome trials demonstrated noninferiority to established GLP-1 RAs and suggest potential additional cardioprotective effects, although evidence for superiority remains inconclusive. These dual agonists also exerted beneficial effects on risk factors such as lipid profiles and blood pressure. However, data heterogeneity and evolving trial designs merit cautious interpretation. Dual GLP-1/GIP agonists represented a significant advance in T2DM treatment, offering enhanced weight reduction and promising cardiovascular benefits. Further large-scale and long-term studies are warranted to fully characterize their cardiovascular protective profile and optimize clinical application.

Keywords: Type 2 diabetes, Dual GLP-1/GIP agonists, Weight reduction, Cardiovascular outcomes, Incretins

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a prevalent metabolic disorder characterized by insulin resistance, pancreatic β-cell dysfunction, and chronic hyperglycemia [1-5]. The pathophysiology of T2DM involves multiple biochemical pathways, notably the dysregulation of incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which normally potentiate postprandial insulin secretion and maintain glucose homeostasis. Increasing evidence underscores their critical role in modulating systemic metabolic functions beyond glucose regulation, including effects on appetite and cardiovascular physiology [6-9].

Obesity is a common comorbidity in T2DM and contributes to disease progression and increased cardiovascular morbidity and mortality [10-16]. Weight control remains a cornerstone in managing T2DM, given its profound impact on insulin sensitivity and cardiovascular risk [17-20]. Therapies targeting incretin pathways, such as GLP-1 receptor agonists (GLP-1 RAs), have demonstrated efficacy in reducing body weight and improving cardiovascular outcomes. However, the therapeutic potential of the complementary incretin GIP has gained attention, as it exhibits distinct receptor-mediated effects that may potentiate metabolic improvements when combined with GLP-1 signaling. This review is to critically evaluate current evidence on dual GLP-1/GIP receptor agonists as therapeutic agents in T2DM, focusing on their effects on weight reduction and cardiovascular outcomes, aiming to elucidate their mechanistic advantages, clinical efficacy, limitations, and future prospects [21-26].

Molecular Mechanisms of Dual GLP-1/GIP Agonists

Dual GLP-1/GIP receptor agonists activate both the GLP-1 receptor (GLP-1R) and the GIP receptor (GIPR), two key incretin receptors expressed in pancreatic β-cells and various peripheral tissues. GLP-1R agonism enhances glucose-dependent insulin secretion, suppresses glucagon release, delays gastric emptying, and reduces appetite through central neuroendocrine pathways. GIPR stimulation primarily augments insulin release and influences lipid metabolism. Whereas isolated GIP agonism showed limited efficacy in T2DM due to receptor downregulation in hyperglycemic states, combined agonism synergistically restores β-cell function and improves metabolic control [27-29].

Preclinical studies revealed that dual agonists improve β-cell survival and function via cAMP-mediated and ERK-dependent pathways, distinct from GLP-1R signaling alone, suggesting additive cytoprotective effects. Moreover, dual agonism modulates appetite regulation through hypothalamic centers differently from GLP-1 monoagonists, resulting in greater reductions in food intake and body weight. Evidence indicates the dual approach also influences adipose tissue metabolism, increasing energy expenditure and lipolysis [30-34].

While GLP-1 agonists have well-established cardiovascular protective mechanisms improving endothelial function, reducing inflammation, and modulating cardiac remodeling emerging data suggest that GIP may contribute additional benefits by enhancing lipid metabolism and attenuating atherosclerotic progression, though mechanistic clarity remains incomplete. Dual agonism, therefore, harnesses complementary pathways to optimize glycemic control and cardiovascular risk factor modulation [35-40].

In summary, the molecular rationale for dual GLP-1/GIP agonists rests on their synergistic enhancement of insulin secretion, appetite suppression, β-cell preservation, and metabolic homeostasis, thereby offering superior therapeutic potential over GLP-1 single agonists.

Analytical and Experimental Methods in Evaluating Dual Agonists

Assessment of dual GLP-1/GIP agonists encompasses robust clinical trial methodologies, including randomized controlled trials (RCTs), pharmacokinetic/pharmacodynamic analyses, and cardiovascular outcome trials (CVOTs). Phase 2 and 3 trials commonly employ double-blind, placebo- or active comparator-controlled designs, measuring endpoints such as HbA1c reduction, weight change, and major adverse cardiovascular events (MACE) [10].

Biochemical assessment includes glucose tolerance tests, insulin/C-peptide assays, and incretin hormone measurements to quantify insulinotropic effects [41-45]. Imaging and biomarker evaluations assess cardiovascular remodeling and inflammation. Trial meta-analyses pool heterogeneous data, necessitating rigorous quality assessment to mitigate bias from variable trial durations and populations [46-50].

Notably, the SURPASS series and other pivotal trials utilize head-to-head comparisons of dual agonists like tirzepatide against established GLP-1 RAs (e.g., dulaglutide). Clinical endpoints include MACE incidence, heart failure hospitalizations, lipid profiles, and renal outcomes, alongside patient-reported outcomes and adverse event monitoring [51-55].

Limitations include varying patient baseline risk, short follow-up periods in some trials, and differing titration protocols affecting generalizability. Despite these challenges, the accumulating evidence base offers comprehensive insight into the dual agonists' efficacy profile.

In conclusion, current experimental methodologies provide rigorous evaluation frameworks for dual GLP-1/GIP agonists, although longer-term and real-world studies are warranted to consolidate cardiovascular risk reduction evidence.

Clinical and Pathophysiological Implications

In clinical practice, dual GLP-1/GIP agonists address multiple facets of T2DM pathophysiology: control of hyperglycemia, weight reduction, and mitigation of cardiovascular risk factors. Clinical trials demonstrate their superiority over GLP-1 RAs alone in reducing HbA1c by approximately 0.8% to 1% and inducing weight loss up to 17% in obese individuals with T2DM within months of therapy initiation. These benefits appear mediated by enhanced β-cell function, decreased appetite, and favorable lipid metabolism shifts [56-60].

Cardiovascular outcome data are evolving. Dual agonists have shown noninferiority to GLP-1 RAs in MACE reduction, with some analyses suggesting possible additional mortality and renal benefits. This contrasts with single-agent GLP-1 RAs, which have definitive evidence from multiple CVOTs for cardioprotection, including improved endothelial function and reduced inflammation. However, dual agonists may approach a therapeutic ceiling for cardiovascular benefit in populations receiving optimized care [61-66].

Further, weight loss achieved partly explains improvements in blood pressure, lipid profiles, and inflammatory markers, relevant to cardiovascular risk mitigation. Their impact on heart failure outcomes remains under investigation, with some observational data indicating neutral or modest benefit [67].

Limitations include gastrointestinal adverse effects leading to treatment discontinuation and limited long-term safety data. Patient heterogeneity also influences response magnitude.

Thus, dual GLP-1/GIP agonists provide a multifaceted approach to T2DM management that integrates glycemic and cardiovascular risk reduction, representing a significant advancement in personalized therapy [68].

Therapeutic and Translational Aspects

The therapeutic translation of dual GLP-1/GIP agonism centers on agents like tirzepatide, now clinically approved for T2DM management. Tirzepatide combines balanced agonism at GLP-1R and GIPR, producing robust glucose lowering and weight loss superior to GLP-1 RAs such as semaglutide or dulaglutide. Clinical guidelines increasingly recognize dual agonists as second-line agents post-metformin failure, particularly in patients with overweight and elevated cardiovascular risk [18].

Translational research explores optimizing dosing regimens, minimizing side effects, and expanding indications including obesity without diabetes. Additionally, dual agonists are investigated in combination therapies with sodium-glucose cotransporter-2 inhibitors (SGLT2i) for additive cardiovascular and renal protection [19].

Challenges remain in cost-effectiveness, accessibility, and patient adherence due to injectable administration. Strategies to develop oral formulations and extended-release delivery systems are active research areas. Biomarker-guided patient selection to maximize benefit while minimizing adverse effects represents a precision medicine frontier.

Consequently, dual GLP-1/GIP agonists embody a promising therapeutic paradigm with translational potential extending beyond glucose control towards comprehensive metabolic and cardiovascular risk management.

Gaps, Controversies, and Future Research Directions

Despite promising clinical data, uncertainty persists regarding the incremental cardiovascular benefits of dual GLP-1/GIP agonists over established GLP-1 RAs. The SURPASS-CVOT trial showed noninferiority but narrowly missed statistical superiority for major cardiovascular events, suggesting a possible therapeutic ceiling or trial design limitations. Further large-scale, long-duration cardiovascular outcome studies are necessary to clarify this issue [20].

Mechanistic understanding of GIP's role in cardiovascular physiology remains incomplete, with some preclinical data indicating pro-atherogenic properties under certain contexts, complicating interpretation. Additionally, heterogeneity in patient populations, concomitant therapies, and endpoints complicate meta-analytic synthesis [21].

Other research gaps include the long-term safety profile, effects on heart failure and arrhythmias, and potential utility in non-diabetic obesity and metabolic syndrome. Investigations into combination therapies and personalized treatment algorithms are ongoing to optimize efficacy and minimize adverse effects.

Future research priorities, therefore, encompass elucidating mechanistic pathways, confirming cardiovascular outcome benefits in diverse populations, and developing novel dual agonist formulations to improve patient experience and adherence.

CONCLUSION

Dual GLP-1/GIP receptor agonists represent a significant advancement in T2DM treatment by offering superior glycemic control and weight reduction compared to traditional GLP-1 RAs. Their complementary receptor activation synergizes insulinotropic, anorectic, and metabolic effects, potentially translating into enhanced cardiovascular risk reduction. Clinical trials demonstrate noninferiority to established GLP-1 therapies for major cardiovascular events, with suggestive evidence for additional benefits on mortality and renal function. However, the clinical magnitude of cardiovascular protection beyond GLP-1 RA monotherapy remains to be definitively established, highlighting the need for longer-term and broader trials with diverse populations. The therapeutic promise of dual agonists is tempered by the need to address adverse events, treatment accessibility, and cost concerns, alongside expanding mechanistic insights into GIP's cardiovascular effects. Continued investigation should emphasize personalized approaches, long-term safety, and new formulations to maximize patient benefit. Overall, dual GLP-1/GIP agonists hold the potential to reshape the therapeutic landscape of T2DM, particularly for patients with obesity and elevated cardiovascular risk. A robust, large-scale cardiovascular outcomes trial with extended follow-up should be prioritized to definitively evaluate dual GLP-1/GIP agonists' cardioprotective efficacy and safety in diverse type 2 diabetes populations.

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