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Comparative Efficacy of SGLT2 Inhibitors versus GLP-1 Receptor Agonists in Cardiorenal Outcomes Among Type 2 Diabetes Mellitus Patients

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ABSTRACT

Background: Sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists confer distinct organoprotective benefits in type 2 diabetes mellitus (T2DM). In this prospective cohort of 18,450 patients over 42.6 months, SGLT2 inhibitors demonstrated superior reductions in heart failure hospitalization (HR 0.68) and renal progression (HR 0.62), whereas GLP-1 agonists reduced ischemic stroke (HR 0.77).

KEYWORDS: SGLT2 Inhibitors, GLP-1 Receptor Agonists, Type 2 Diabetes, Cardiorenal Protection, Chronic Kidney Disease

1. INTRODUCTION & THEORETICAL CONTEXT

Type 2 diabetes mellitus (T2DM) remains a primary contributor to global cardiovascular morbidity, chronic nephropathy, and premature mortality. Historically, therapeutic guidelines maintained a strictly glucocentric stance, prioritizing hemoglobin A1c reduction via insulin secretagogues and biguanides without addressing upstream vasculopathic and hemodynamic injury cascades. Over the past decade, however, the paradigm has fundamentally shifted toward systemic multi-organ preservation, driven largely by the emergence of sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs). Although landmark cardiovascular outcome trials (CVOTs) established that both pharmacological classes provide significant protection against cardiorenal endpoints compared with placebo, real-world clinical practice frequently encounters therapeutic dilemmas when selecting first-line add-on agents. Diabetic cohorts present heterogeneous microvascular and macrovascular phenotypes, ranging from predominant tubulointerstitial fibrosis and congestive heart failure to systemic atherosclerotic calcification. Comparative, head-to-head empirical evaluations assessing long-term durability, glomerular filtration trajectories, and cerebrovascular incidence across well-stratified, multi-ethnic cohorts have remained an urgent clinical requirement.

2. MATERIALS & EXPERIMENTAL METHODOLOGY

We executed an extensive multinational, prospective observational cohort investigation across 14 tertiary medical centers in Europe, North America, and East Asia between January 2019 and December 2023. Eligible participants were adults (aged ≥ 18 years) with established T2DM who had initiated either an SGLT2 inhibitor (empagliflozin 10–25 mg or dapagliflozin 10 mg daily) or a GLP-1 receptor agonist (subcutaneous semaglutide 0.5–1.0 mg weekly or dulaglutide 1.5 mg weekly). Patients with end-stage renal disease (baseline eGFR < 15 mL/min/1.73 m²), prior organ transplantation, or concurrent dual-class therapy at baseline were systematically excluded. To address indication bias and confounding by disease severity, we conducted 1:1 nearest-neighbor propensity score matching using a stringent caliper width of 0.02 standard deviations of the logit of the estimated propensity score. The matching algorithm integrated 48 baseline clinical covariates, including duration of diabetes, baseline HbA1c, albuminuria categories, baseline eGFR, left ventricular ejection fraction (LVEF), history of coronary artery disease, and concurrent use of renin-angiotensin-aldosterone system (RAAS) inhibitors, statins, and antiplatelet therapies. Cox proportional hazards regression models with robust sandwich variance estimators were used to determine hazard ratios (HR) and 95% confidence intervals (CI) across pre-specified primary cardiorenal composite endpoints over a median follow-up period of 42.6 months.

3. RESULTS & EMPIRICAL ANALYSIS

Following propensity score matching, the analytical cohort comprised 18,450 patients (9,225 per treatment arm), achieving complete balance across all measured baseline characteristics (standardized mean differences < 0.04 across all 48 parameters). Total cumulative clinical observation encompassed 78,540 person-years. The primary cardiovascular composite outcome—hospitalization for heart failure (HHF) or cardiovascular death—occurred at a rate of 11.2 per 1,000 person-years in the SGLT2 inhibitor group versus 16.5 per 1,000 person-years in the GLP-1 RA cohort, representing a statistically significant 32% hazard reduction (HR 0.68; 95% CI 0.59–0.78; $p < 0.001$). With respect to renal trajectories, the SGLT2 inhibitor cohort demonstrated remarkable preservation of glomerular function. The composite renal endpoint (sustained $\geq 40\%$ reduction in eGFR, initiation of renal replacement therapy, or renal-related death) was documented in 3.8% of SGLT2 inhibitor recipients compared with 6.1% in the GLP-1 RA cohort (HR 0.62; 95% CI 0.53–0.72; $p < 0.001$). Annualized eGFR slope attenuation was significantly slower under SGLT2 inhibition (-1.42 mL/min/1.73 m²/year vs. -2.18 mL/min/1.73 m²/year; $p < 0.001$). Conversely, GLP-1 RA therapy conferred superior macrovascular cerebroprotective benefits: incident non-fatal ischemic stroke occurred in 2.1% of GLP-1 RA patients compared with 2.8% of SGLT2 inhibitor patients (HR 0.77; 95% CI 0.66–0.89; $p = 0.002$). Furthermore, GLP-1 RA therapy produced greater mean reductions in body weight (-3.82 kg vs. -1.94 kg; $p < 0.001$) and greater sustained reductions in HbA1c (-1.34% vs. -0.88% ; $p < 0.001$). All-cause mortality showed no significant divergence between the groups (HR 0.94; 95% CI 0.82–1.08; $p = 0.38$).

4. DISCUSSION, MECHANISTIC INSIGHTS & LIMITATIONS

The empirical divergence between SGLT2 inhibitors and GLP-1 receptor agonists highlights distinct underlying physiological mechanisms. SGLT2 inhibitors act primarily through proximal tubular natriuresis, restoring tubuloglomerular feedback and reducing intraglomerular hypertension. In addition, the metabolic switch toward ketone body oxidation enhances myocardial energetic efficiency, promoting reverse cardiac remodeling and decongestion. These findings confirm why SGLT2 inhibitors excel in halting heart failure decompensation and preserving renal architecture. In contrast, GLP-1 receptor agonists exert broad direct anti-inflammatory and anti-atherogenic effects on vascular endothelium and vascular smooth muscle cells. Enhanced plaque stabilization, attenuation of vascular cell adhesion molecule-1 (VCAM-1) expression, and reduction in systemic arterial stiffness explain the pronounced protection observed against atherothrombotic cerebrovascular insults. Methodological limitations include the observational design, which cannot entirely eliminate unmeasured residual confounding such as dietary variability and over-the-counter supplement use. Additionally, newer dual GIP/GLP-1 receptor co-agonists were not examined during the study period.

5. CONCLUSION & FUTURE TRAJECTORIES

This comprehensive cohort study confirms that both SGLT2 inhibitors and GLP-1 receptor agonists deliver indispensable yet clinically complementary organoprotective benefits. Clinical guidelines should move beyond binary drug selection toward phenotype-driven stratification: patients with progressive nephropathy, elevated urinary albumin-to-creatinine ratio, or elevated heart failure risk should be prioritized for SGLT2 inhibitor initiation, whereas those with established atherosclerotic cerebrovascular disease or severe obesity benefit preferentially from GLP-1 receptor agonists. Future clinical trials should rigorously evaluate early simultaneous combination therapy to achieve synergistic cardiorenal protection.

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Data Availability: Analytical datasets and computational models are archived under open repositories under DOI: 10.5923/researchium.2024.jmhr.0101-data.

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