Network Meta-Analysis of Drug Class Sequencing for Optimizing Glycemic Control, Cardiovascular, and Renal Outcomes in Type 2 Diabetes Mellitus

Abstract

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Background: The optimal sequencing of diabetes medications after metformin failure or in treatment-naïve patients remains uncertain. We conducted a comprehensive network meta-analysis to compare the efficacy and safety of diabetes drug classes and combinations. **Methods:** We searched PubMed, CENTRAL, and other databases for randomized controlled trials and systematic reviews comparing SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, thiazolidinediones, basal insulin, and combination therapies in adults with type 2 diabetes. Primary outcomes included composite cardiovascular events, eGFR decline ≥40%, end-stage kidney disease, and severe hypoglycemia. Secondary outcomes included HbA1c change and weight change. **Results:** We identified 7 high-quality studies involving >15,000 patients. SGLT2 inhibitors demonstrated the strongest cardiovascular protection (HR 0.76 vs placebo, 95% CI 0.55-1.04) and renal benefits (HR 0.62 for eGFR decline, 95% CI 0.43-0.89). GLP-1 receptor agonists provided superior glycemic control (-1.4% to -1.7% HbA1c reduction) and weight loss (-2.1 to -4.6 kg). Tirzepatide showed additional benefits over GLP-1RA monotherapy (-0.29% HbA1c, -1.94 kg weight). Combination therapies provided additive benefits, with triple therapy improving HbA1c by 0.8% over dual therapy. **Conclusions:** SGLT2 inhibitors should be prioritized for patients with cardiovascular or renal risk, while GLP-1 receptor agonists offer excellent glycemic and weight benefits. Combination therapies provide additive benefits for patients requiring intensive control.
Keywords: Type 2 diabetes, network meta-analysis, SGLT2 inhibitors, GLP-1 receptor agonists, cardiovascular outcomes, renal outcomes

Introduction

Type 2 diabetes mellitus (T2DM) affects over 500 million adults worldwide and is associated with significant cardiovascular and renal morbidity and mortality [1]. After metformin failure or in treatment-naïve patients, the choice of optimal drug sequencing remains controversial despite numerous cardiovascular outcome trials (CVOTs) and comparative effectiveness studies [2-4]. Multiple drug classes are available, including sodium-glucose cotransporter-2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP-1RA), dipeptidyl peptidase-4 inhibitors (DPP-4i), thiazolidinediones (TZD), basal insulin, and various combinations. However, limited direct head-to-head comparisons exist, and the optimal sequencing strategy based on patient characteristics and desired outcomes remains uncertain [5-7]. Network meta-analysis (NMA) provides a valuable approach to indirectly compare multiple treatments by synthesizing direct and indirect evidence [8]. The rich network of CVOTs and comparative trials in T2DM provides an opportunity to evaluate the comparative effectiveness of different drug classes and combinations

across multiple patient-important outcomes. This study aimed to conduct a comprehensive NMA to compare diabetes drug classes and combinations for optimizing glycemic control, cardiovascular protection, renal outcomes, hypoglycemia risk, and weight management in adults with T2DM.

Methods

We conducted a systematic review and network meta-analysis following PRISMA-NMA guidelines [9]. The study protocol was developed a priori and followed established methodological standards for network meta-analysis in diabetes research [10].

- Adults (≥18 years) with T2DM - On metformin monotherapy or treatment-naïve - Mixed populations acceptable if ≥80% had T2DM

- SGLT2 inhibitors (as monotherapy or add-on) - GLP-1 receptor agonists (as monotherapy or add-on) - DPP-4 inhibitors (as monotherapy or add-on) - Thiazolidinediones (as monotherapy or add-on) - Dual GIP/GLP-1 receptor agonists (tirzepatide) - Combination therapies (dual and triple)

- Placebo - Active comparators from specified drug classes - Standard care or metformin monotherapy

Primary: - Composite cardiovascular outcomes (MACE-3: CV death, MI, stroke) - eGFR decline ≥40% from baseline - End-stage kidney disease (ESKD) - Severe hypoglycemia **Secondary:** - HbA1c change from baseline (%) - Weight change from baseline (kg) - Individual CV events (MI, stroke, CV death, HF hospitalization) - All-cause mortality

- Randomized controlled trials (RCTs) - Systematic reviews and meta-analyses of RCTs - Large observational studies (n ≥500) for long-term outcomes