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Background: Sodium glucose co-transporter-2 (SGLT2) inhibitors designed to treat type 2 diabetes show special benefits on reducing body weight and heart failure risks. So far, only three SGLT2 inhibitors have marketed globally and more SGLT2 inhibitors are undergoing clinical development.

Objectives: Establish a quantitative relationship of PK exposure, glucose-corrected urinary glucose excretion (UGE), and HbA1c for SGLT2 inhibitors in T2DM patients to support new SGLT2 inhibitor development.

Methods: Drug concentrations, UGE values with corresponding fasting glucose concentrations and HbA1c data meeting pre-set criteria were collected from PubMed database. Non-linear mixed effect modeling method was utilized to construct the relationship. One or two-compartmental PK model with transit function and linear elimination characteristics followed by an empirical Emax model were utilized to demonstrate PK-UGE dynamics. UGE-HbA1c relationship in placebo group was analyzed for each of three categories (naïve, add-on and others) separately. An exponential structure (Kplacebo) with maximum decreasing extent (Pmax) describing glucose decrease under placebo treatment and a linear function (Splacebo) describing disease progression was used to simulate placebo effects. HbA1c was predicted using an exponential function (Kdrug, describing saturation of drug effect) timing glucose-normalized UGE. Final models were assessed by precision of parameter estimates, diagnostic plots and visual predictive checks (VPC).

Results: Ninety-six articles with 880 drug concentrations, 27 glucose-corrected UGE levels and 1212 HbA1c data points were analyzed. PK-UGE models shared same Emax (0.606 L) with EC50 of 56.6, 2310, and 841 ng/mL for Dapagliflozin, Canagliflozin, Empagliflozin respectively. Kdrug was estimated to be 0.203 weeks⁻¹, which suggested 5-week continuous treatment of SGLT2 inhibitors could show an obvious drug effect for HbA1c. Diagnostic plots and VPC checks showed good agreement and adequate accuracy in models.

Conclusions: The quantitative drug exposure-biomarker-response relationship was constructed, which offers insight into long-term SGLT2 inhibitors efficacy prediction.