**Comparative analysis of diuretic classes on cardiorenal** **outcomes in GLP-1 receptor agonist therapy among individuals with obesity, with and without type 2 diabetes**

**Aim:** To investigate mortality and cardiorenal outcomes when GLP-1 receptor agonists (GLP-1 RAs) are combined with commonly prescribed medications in individuals with obesity, with and without type 2 diabetes (T2D).

**Methods:** We conducted target trial emulation using a US healthcare database (N = 4,552,535) with 1:1 propensity-score matching. Eligible participants with obesity (BMI≥30kg/m²) who initiated GLP-1RAs were followed for up to 5 years. Drug interactions were quantified using Bliss independence model and mapped to Nash equilibrium matrices. Primary outcome was all-cause mortality; secondary outcomes included MACE and MAKE.

**Results:** Among individuals with T2D, GLP-1RA/hydrochlorothiazide reduced mortality (HR 0.81, 95%CI 0.71-0.93), MACE (HR 0.67, 95%CI 0.60-0.75) and kidney events (HR 0.64, 95%CI 0.52-0.78) with dose-dependent benefits. In contrast, GLP-1RA/furosemide increased mortality 3.05-fold (95%CI 2.65-3.52) and MAKE 2.87-fold (95%CI 2.52-3.25). This risk elevation was more pronounced in individuals without T2D (mortality HR 5.81, 95%CI 3.14-10.74).

**Conclusion:** Diuretic selection critically modifies GLP-1RA outcomes, with hydrochlorothiazide enhancing cardiorenal protection while furosemide combinations raise significant safety concerns. These findings have immediate implications for clinical practice and warrant prospective validation.