Empagliflozin, a potent, selective sodium glucose cotransporter 2 inhibitor, inhibits renal glucose reabsorption, leading to glucosuria and improved fasting and postprandial glucose. Due to its renal mechanism of action (MOA), we hypothesized that glucose lowering with empagliflozin is independent of β-cell function and insulin resistance. Using pooled data from three 24-week trials that investigated empagliflozin 10 mg (n=632) and empagliflozin 25 mg (n=626) versus placebo (n=622) as monotherapy or add-on to metformin (MET) or MET+sulfonylurea, we investigated the influence of baseline HbA1c, body mass index (BMI), HOMA-B and HOMA-IR on change from baseline in HbA1c using 2-way interaction models.

Empagliflozin significantly reduced HbA1c from baseline versus placebo at week 24; in a model without interaction, mean HbA1c reductions versus placebo were -0.65% with empagliflozin 10 mg and -0.70% with empagliflozin 25 mg. Baseline HbA1c had a significant influence on the treatment effect (p<0.001 for interaction). There were no interactions between treatment and baseline BMI (p=0.606), HOMA-B (p=0.384) or HOMA-IR (p=0.199). In a model including baseline HbA1c by treatment interaction, predicted reductions in HbA1c versus placebo at week 24 (%) in patients with baseline HbA1c 7.5%, 8.0%, 8.5%, 9.0%, 9.5% and 10.0% were -0.48, -0.65, -0.82, -0.99, -1.16 and -1.32 with empagliflozin 10 mg, respectively, and -0.55, -0.71, -0.86, -1.02, -1.18 and -1.33 with empagliflozin 25 mg, respectively. In summary, treatment effects of empagliflozin on HbA1c reductions appear to be driven by baseline HbA1c and to be independent of baseline β-cell function, insulin sensitivity and BMI.