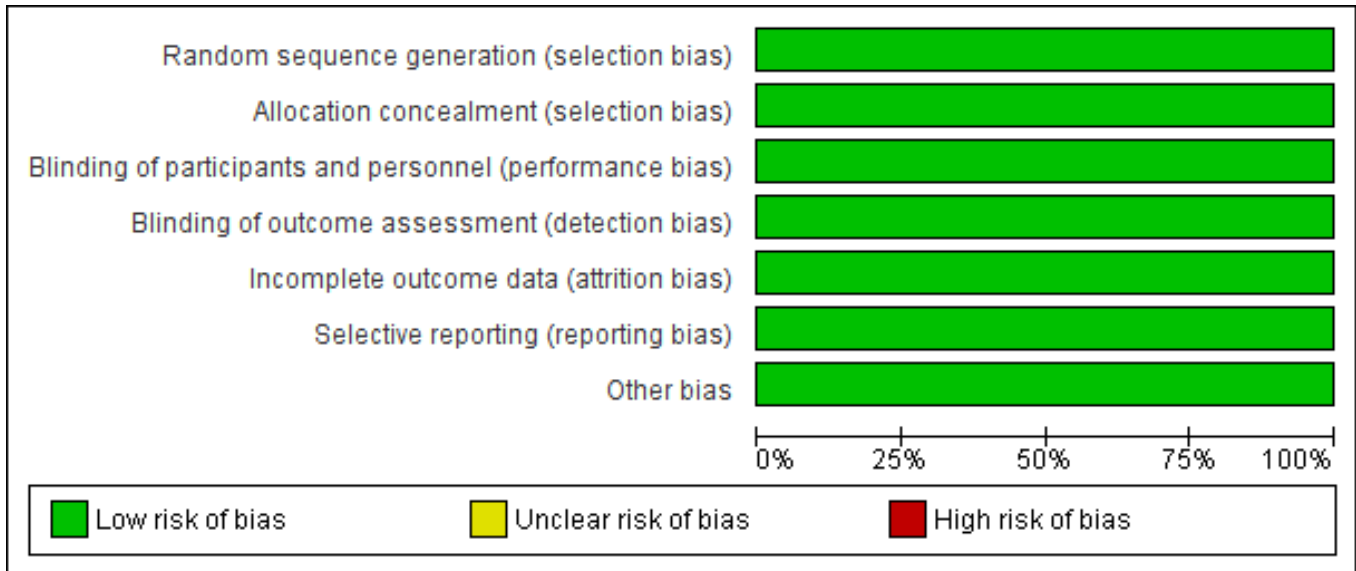


# Supplementary Figures

**Supplementary Figure 1. Risk of bias summary:** risk of bias item for each included RCT according to Cochrane Risk-of-Bias Tool

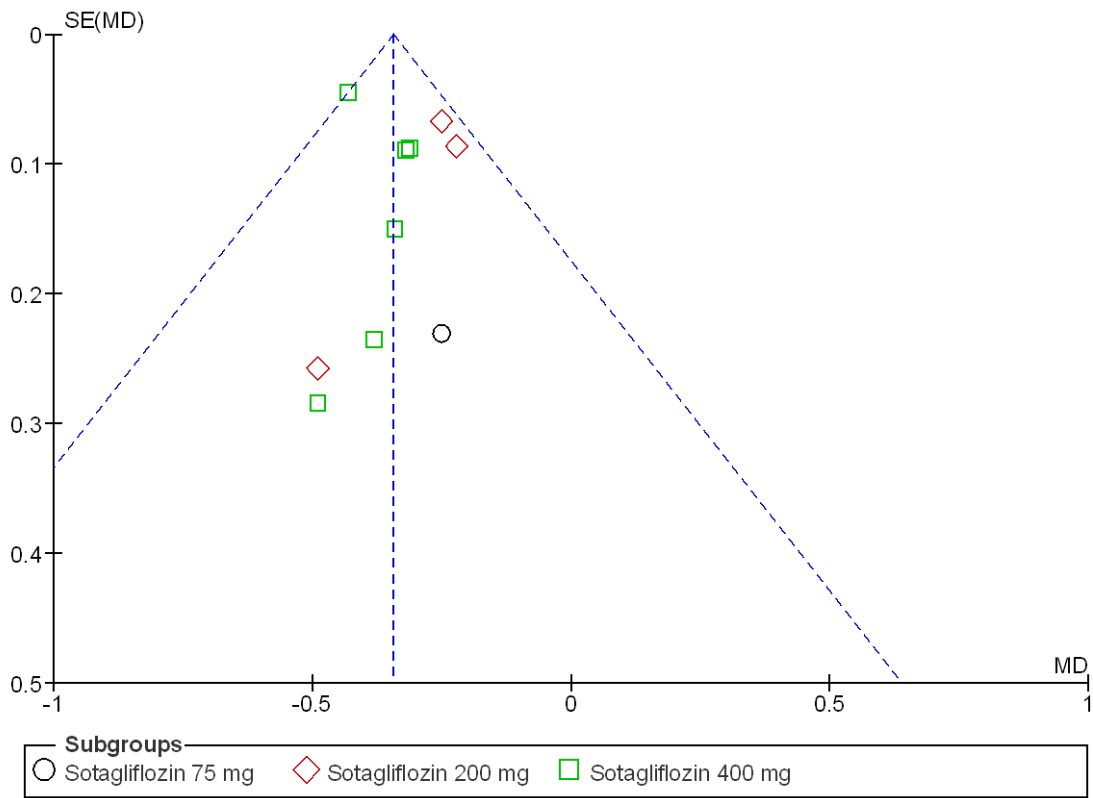
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Baker 2017(inTandem4)	+	+	+	+	+	+	+
Bode 2017	+	+	+	+	+	+	+
Buse 2018 (inTandem1)	+	+	+	+	+	+	+
Danne 2018(inTandem2)	+	+	+	+	+	+	+
Garg 2017(inTandem3)	+	+	+	+	+	+	+
Sands 2015	+	+	+	+	+	+	+

**Supplementary Figure 2. Risk of bias graph:** each risk of bias item is presented as percentages across all included RCTs.

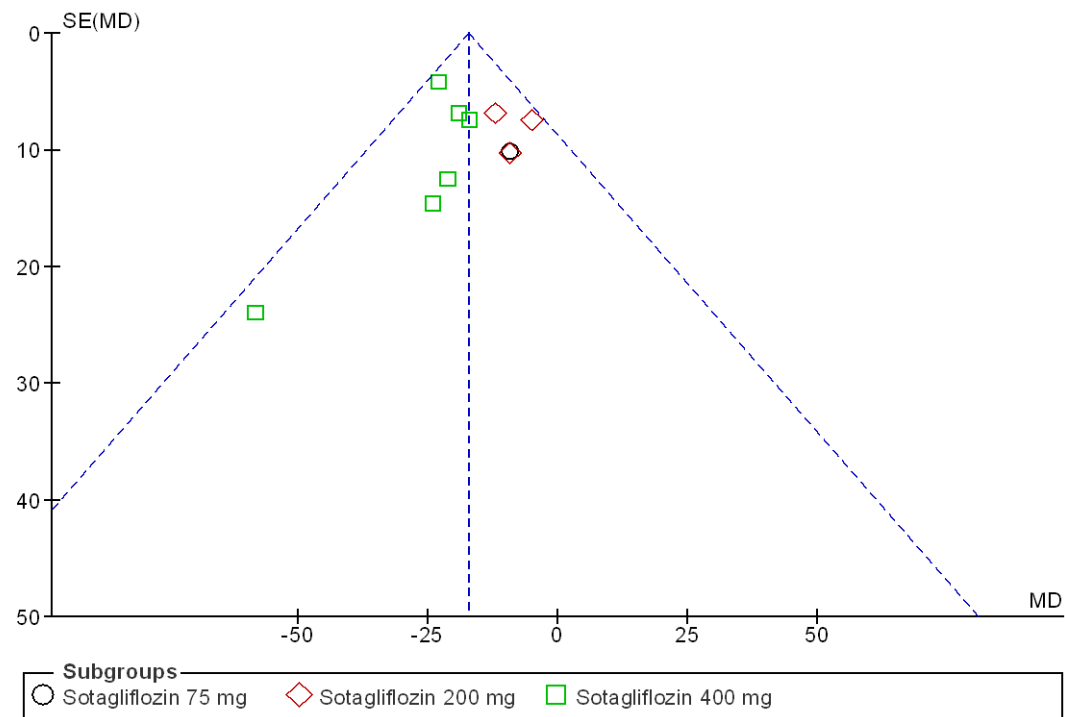


### Supplementary Figure 3.

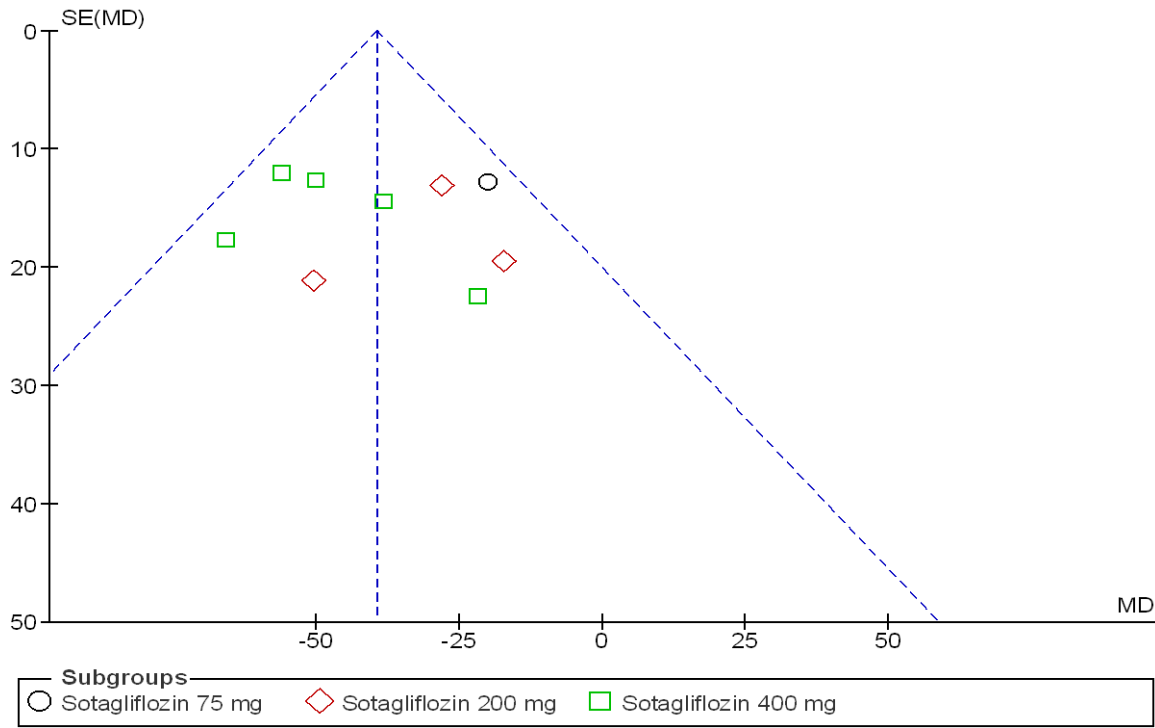
**Panel A** Funnel plot of comparison: HbA1c(%) outcome: HbA1c(%)



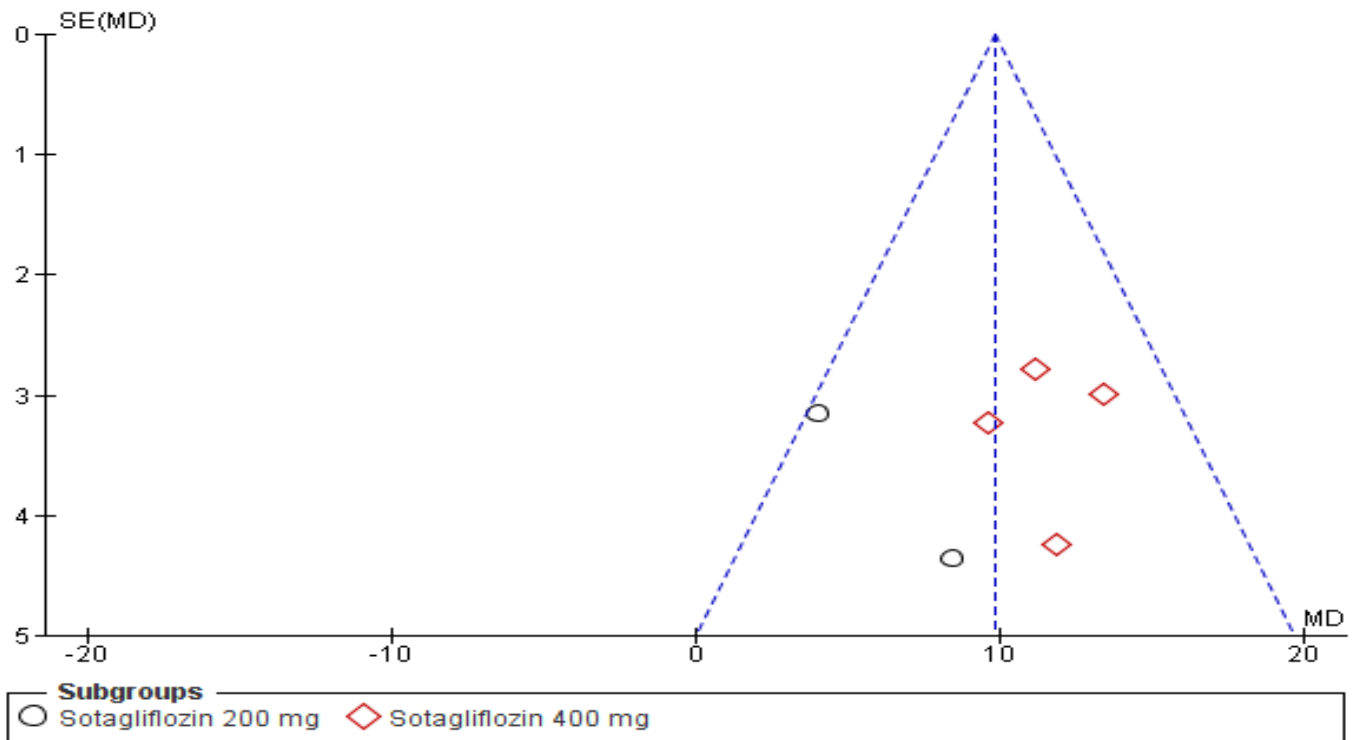
**Panel B** Funnel plot of comparison: Fasting plasma glucose (FPG; (mg/dL) outcome: FPG(mg/dL).



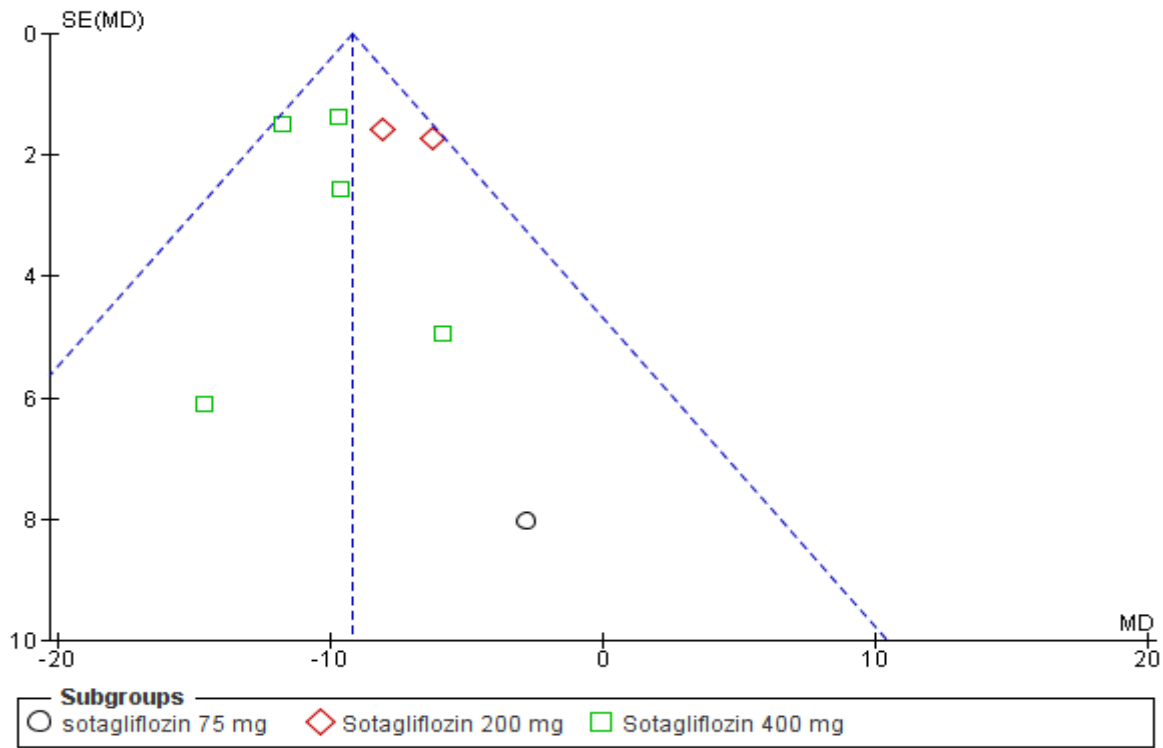
**Panel C.** Funnel plot of comparison: 2-hr postprandial plasma glucose(PPG) for outcome: 2hr-PPG.



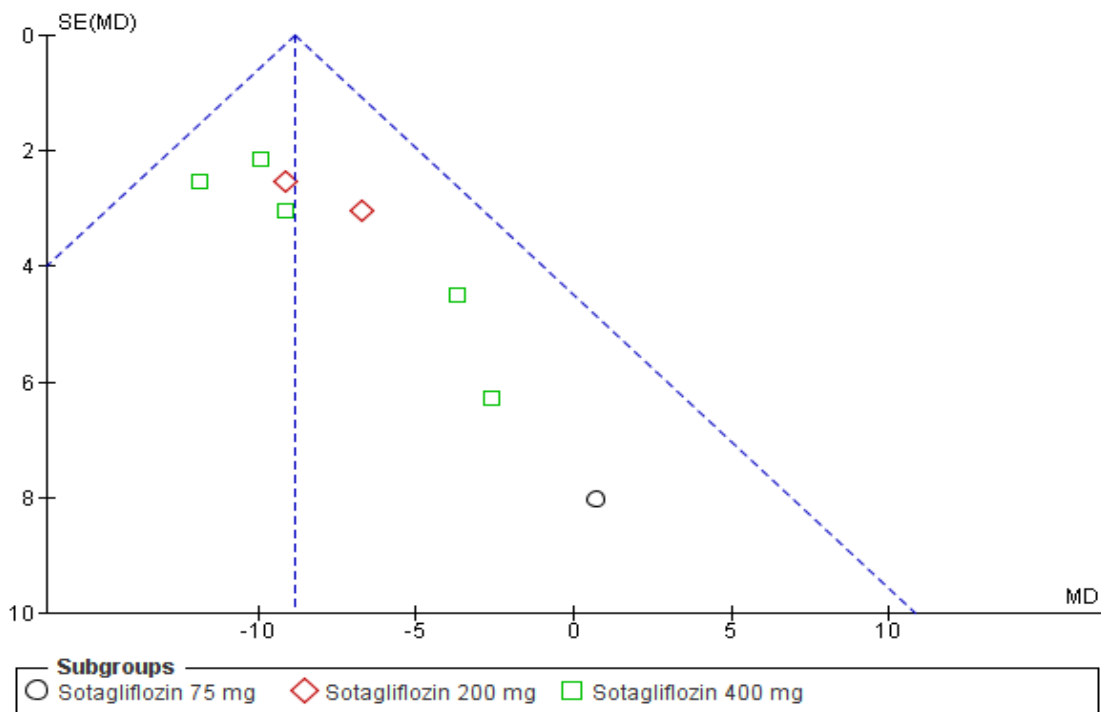
**Panel D.** Funnel plot of comparison: % time-in-range (70-180 mg/dL) for outcome: % time-in-range



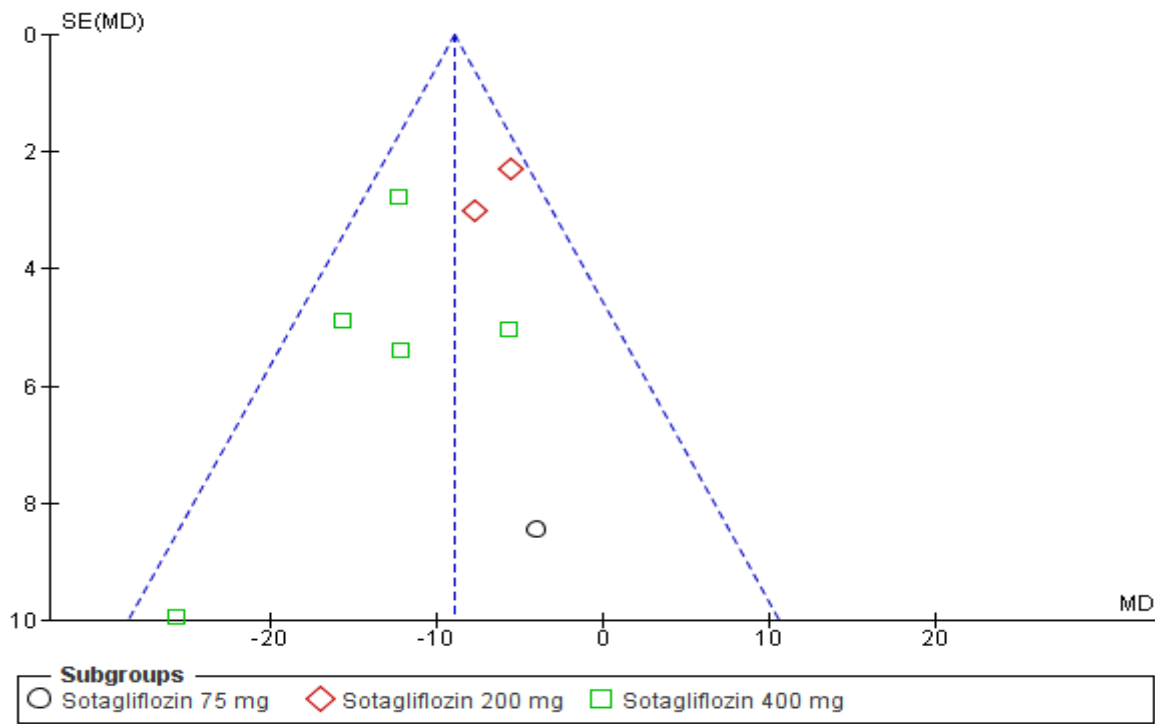
**Panel E.** Funnel plot of comparison: total daily insulin dose, outcome: total daily insulin dose(% change)



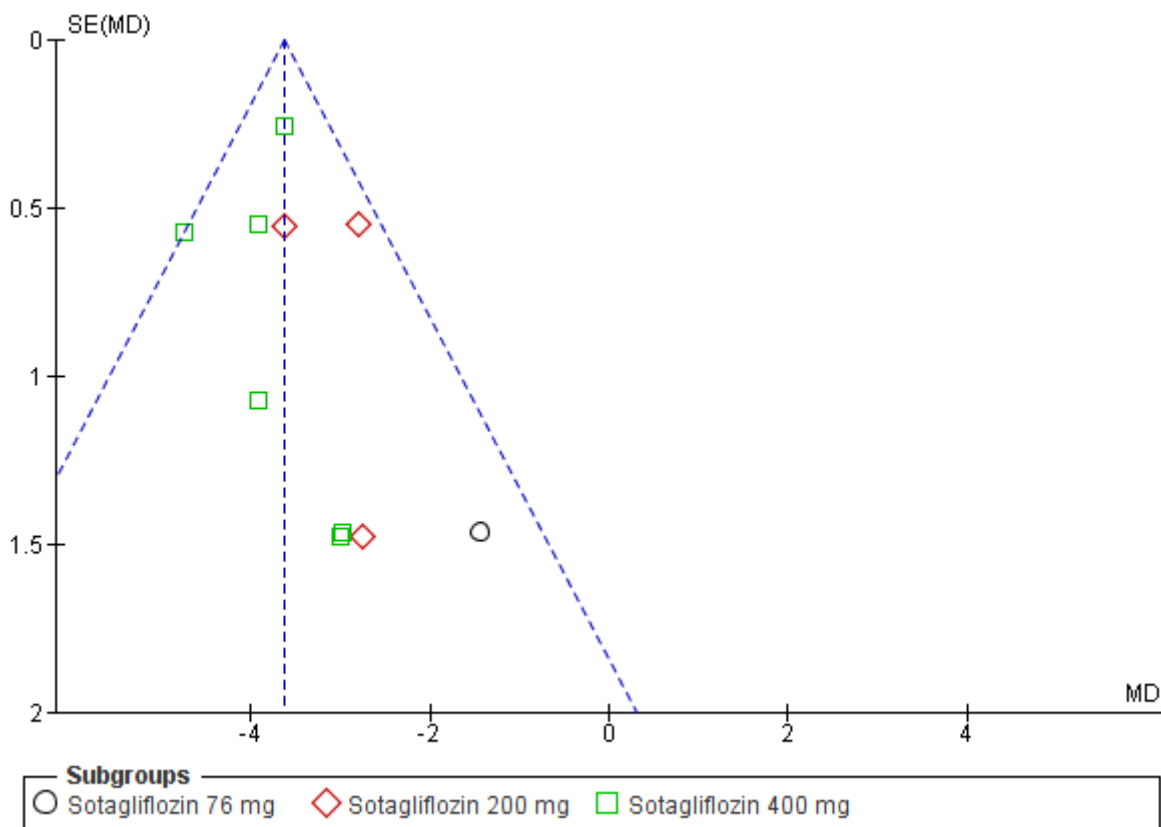
**Panel F.** Funnel plot of comparison: basal daily insulin dose, outcome: basal daily insulin dose(% change)



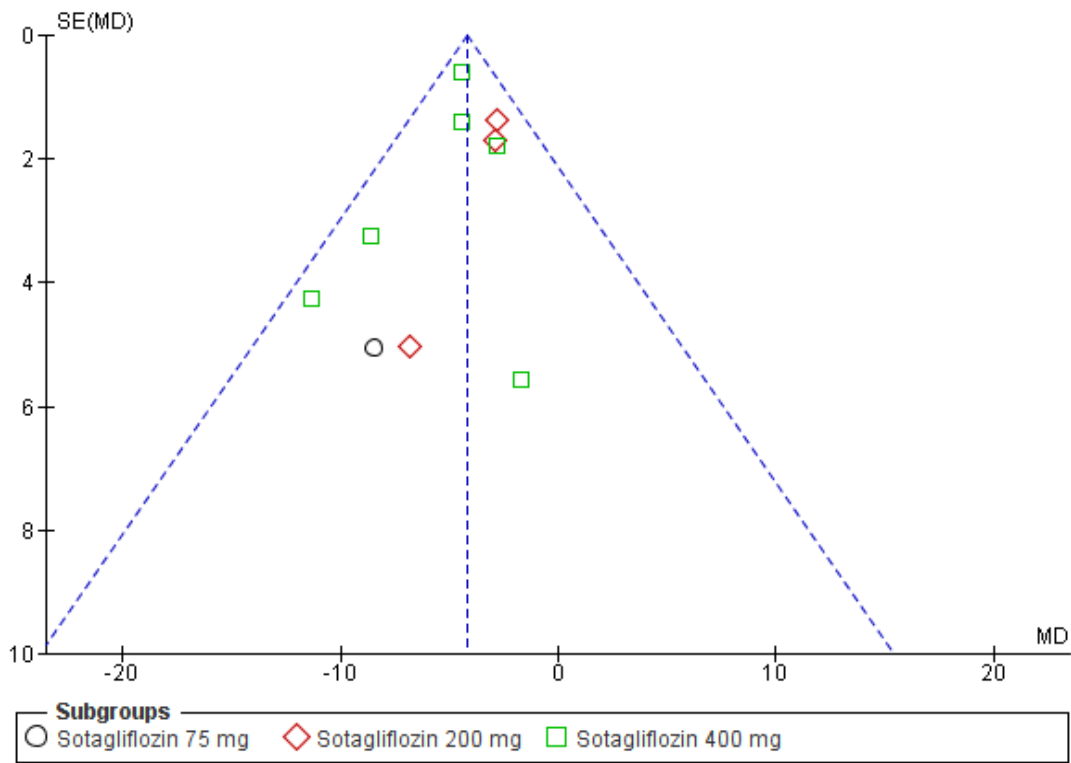
**Panel G.** Funnel plot of comparison: bolus daily insulin dose, outcome: bolus daily insulin dose(% change)



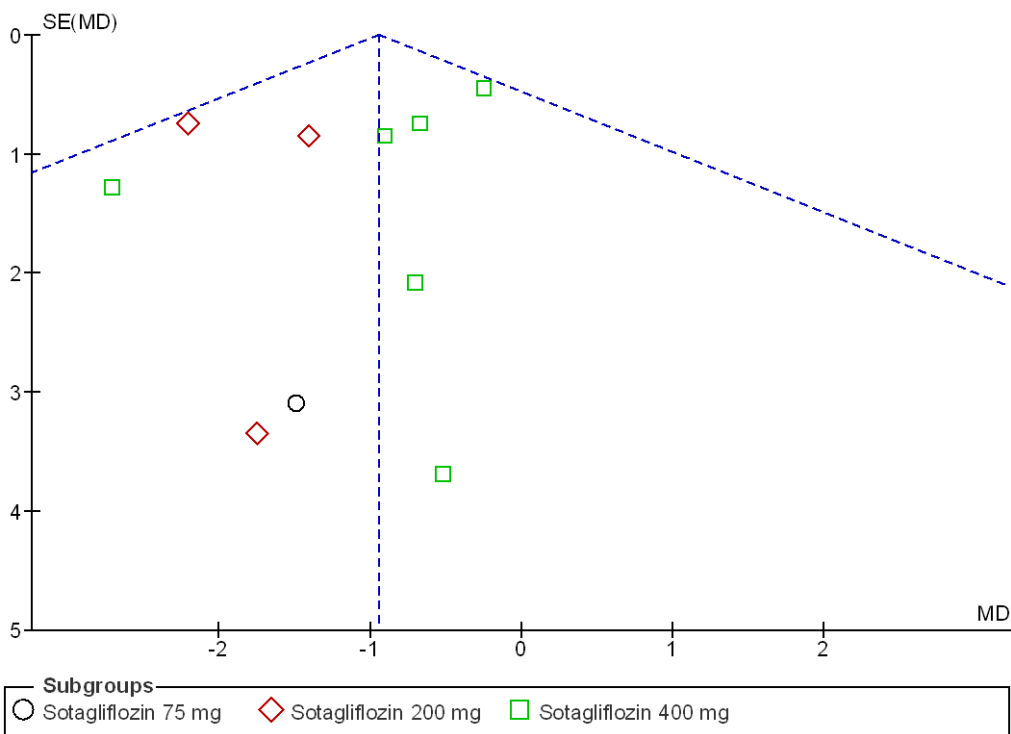
**Panel H.** Funnel plot of comparison: body weight changes, outcome: body weight changes(%)



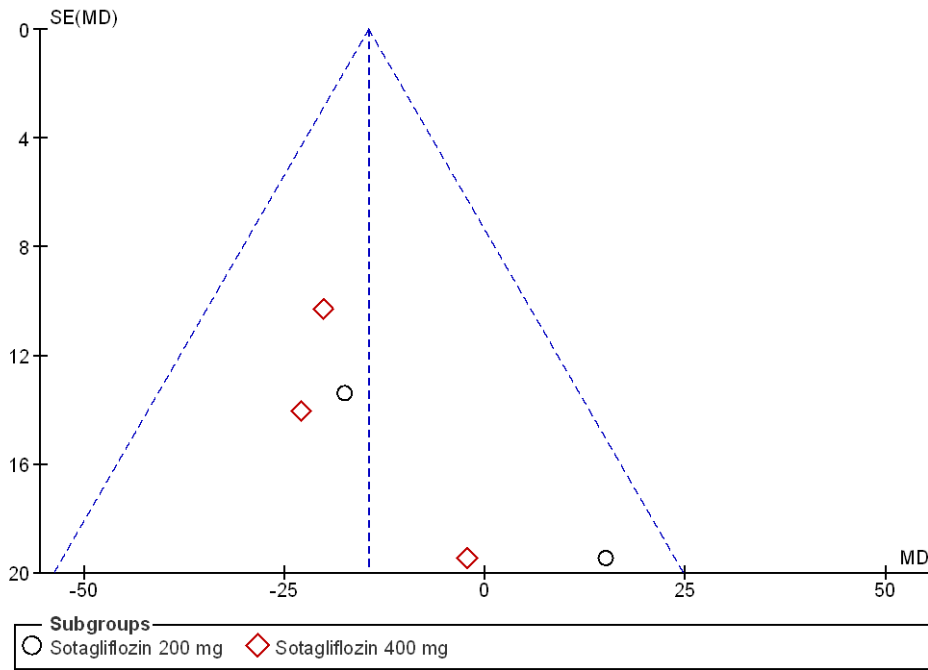
**Panel I.** Funnel plot of comparison: sys BP, outcome: sys BP(mmHg)



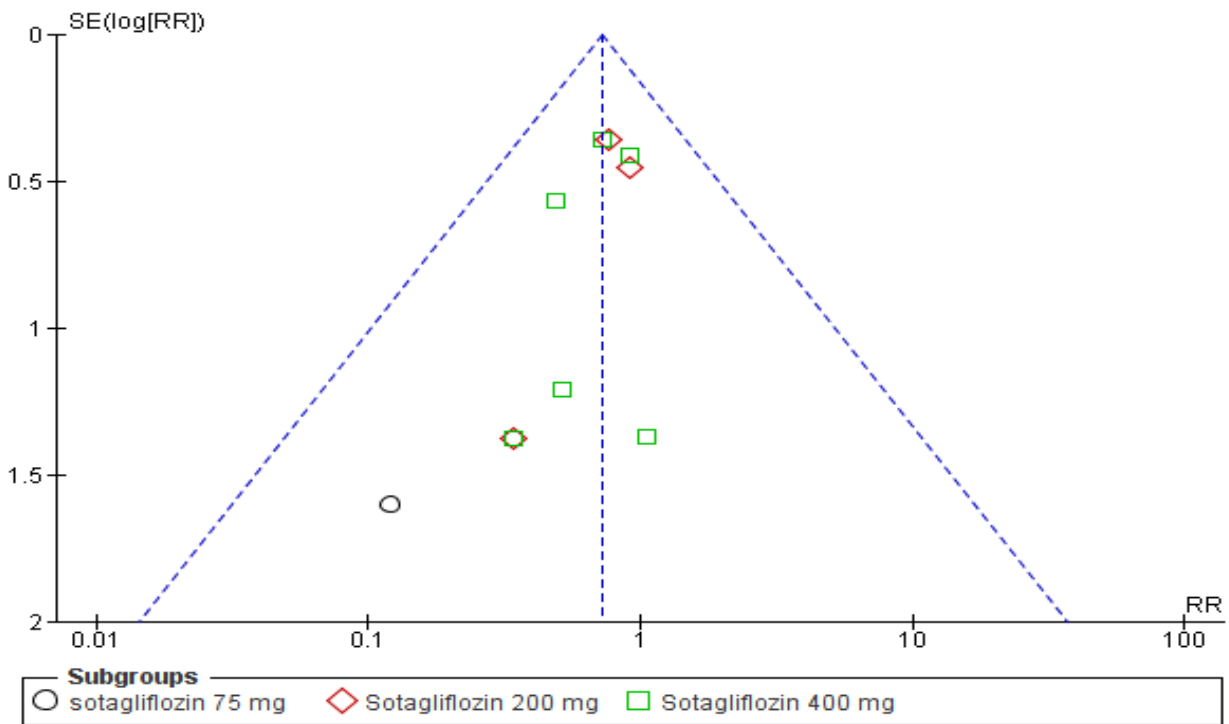
**Panel L.** Funnel plot of comparison: eGFR changes, outcome: eGFR changes(ml/min/1.73 m2)



**Panel M.** Funnel plot of comparison: urinary A/C ratio, outcome: albumin/creatinine ratio(mg/g).

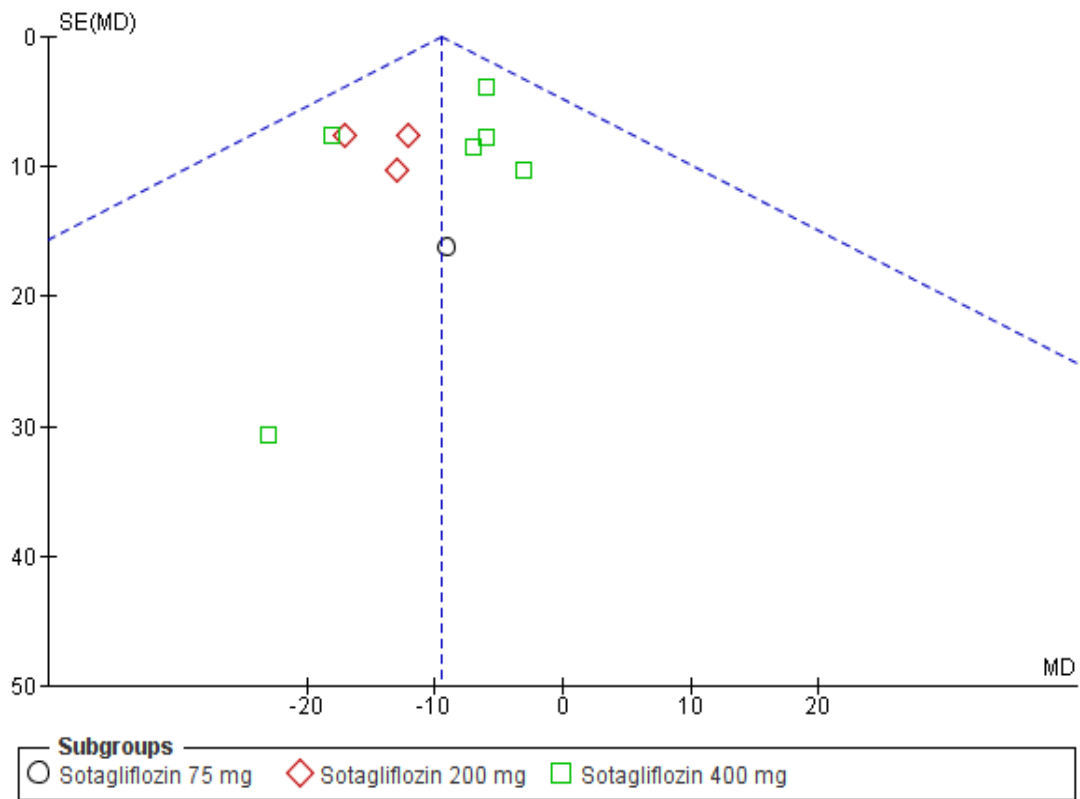


**Panel N.** Funnel plot of comparison: severe hypoglycemia, outcome: severe hypoglycemia.

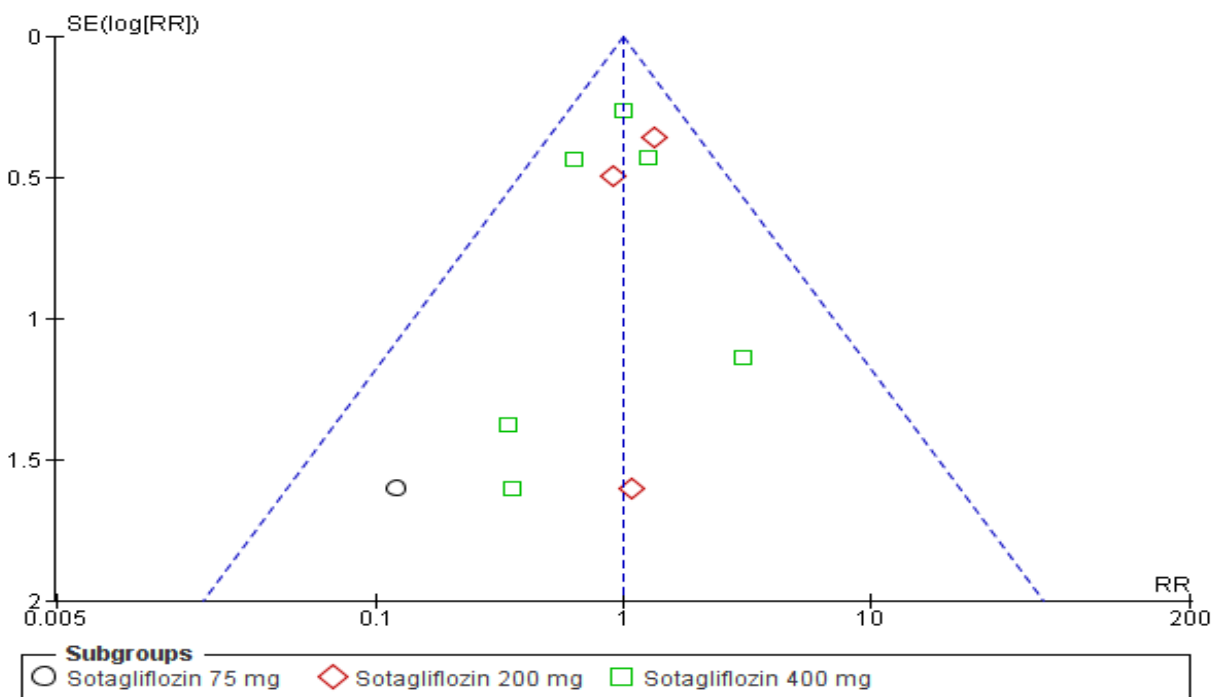




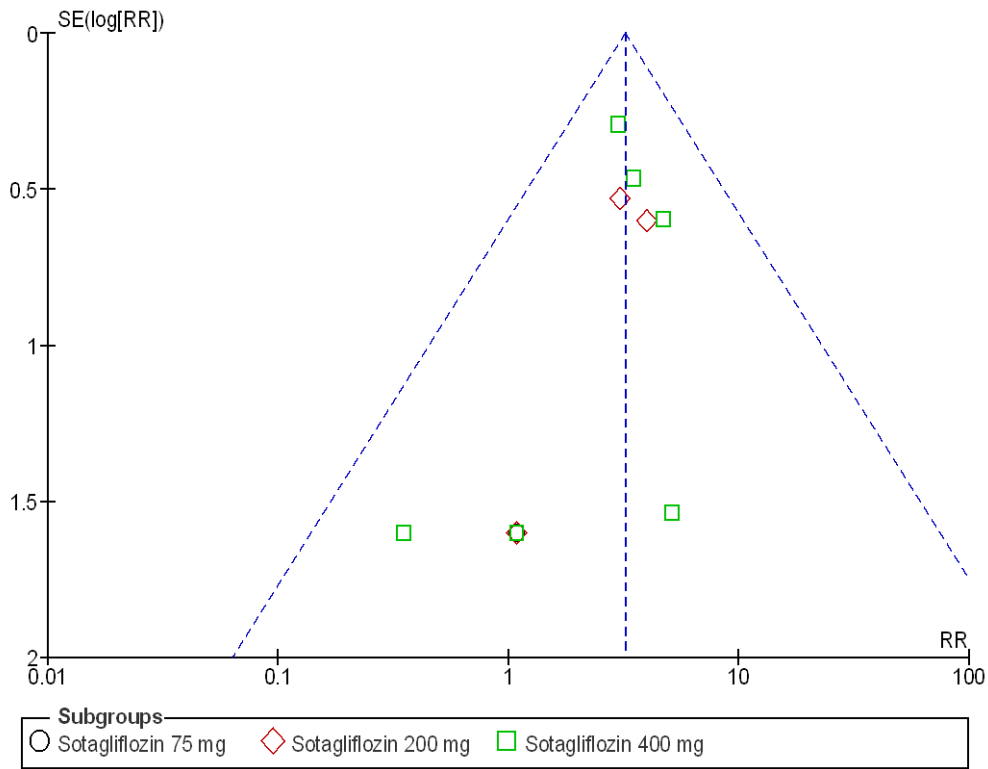
**Panel O.** Funnel plot of comparison: hypoglycemia, outcome: hypoglycemia (events per patient-year).



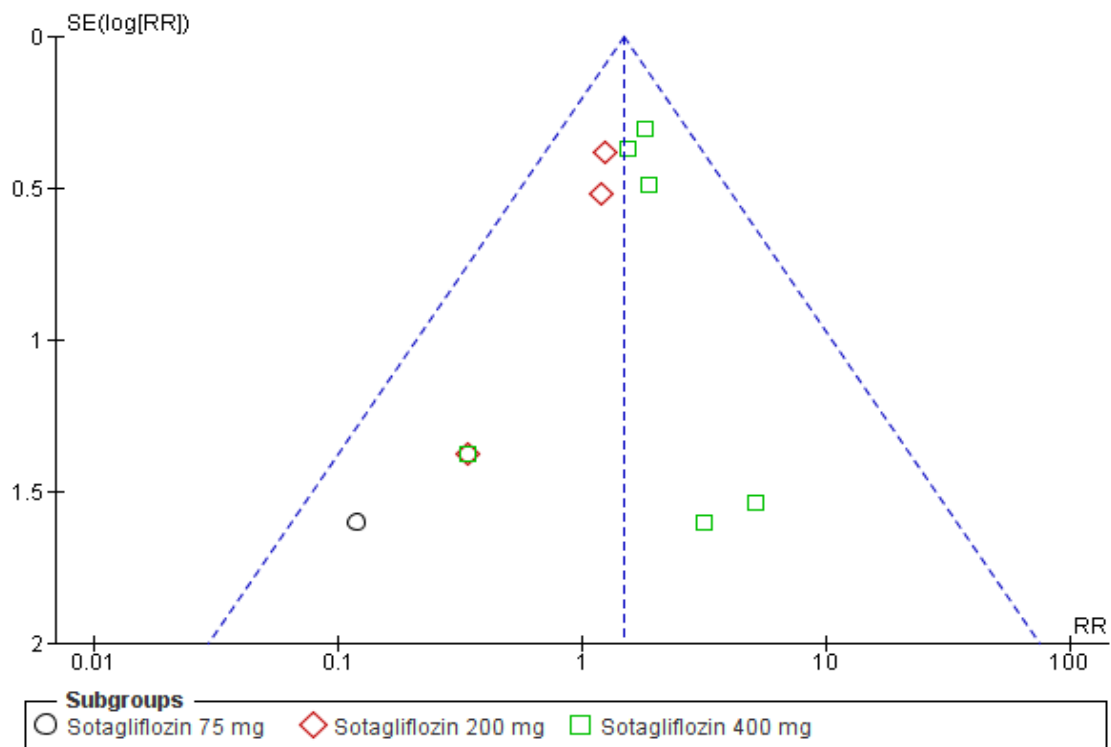
**Panel P.** Funnel plot of comparison: urinary tract infections, outcome: urinary tract infections.



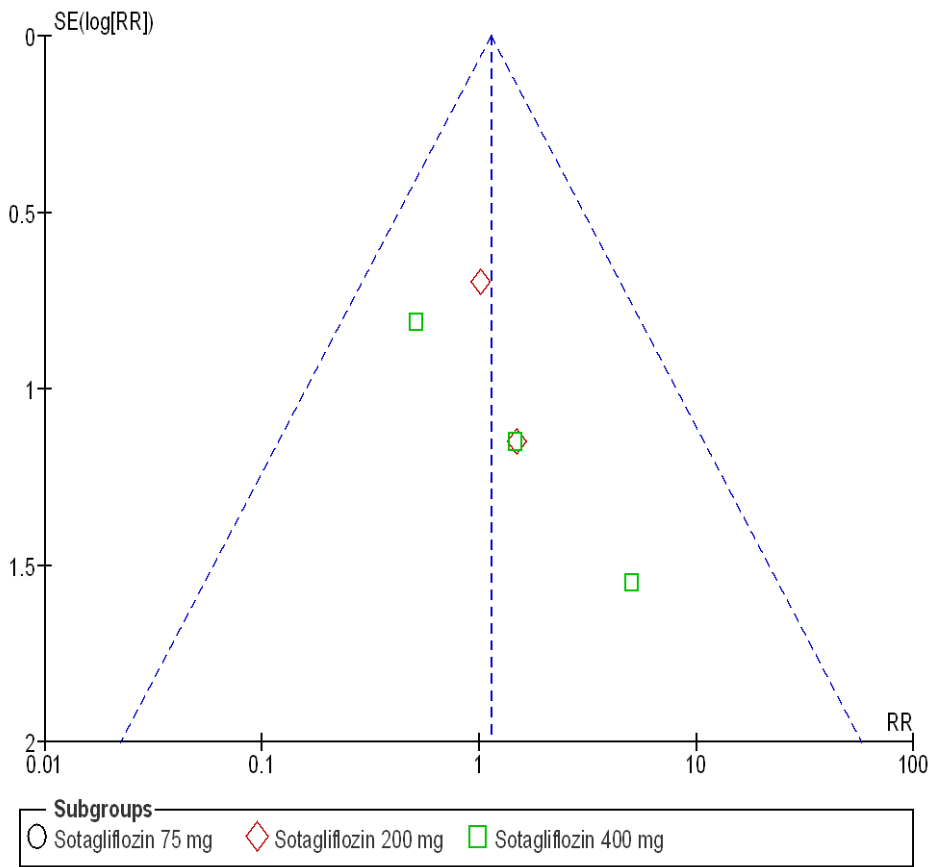
**Panel Q.** Funnel plot of comparison: genital tract infections, outcome: genital tract infections.



**Panel R.** Funnel plot of comparison: diarrhea, outcome: diarrhea

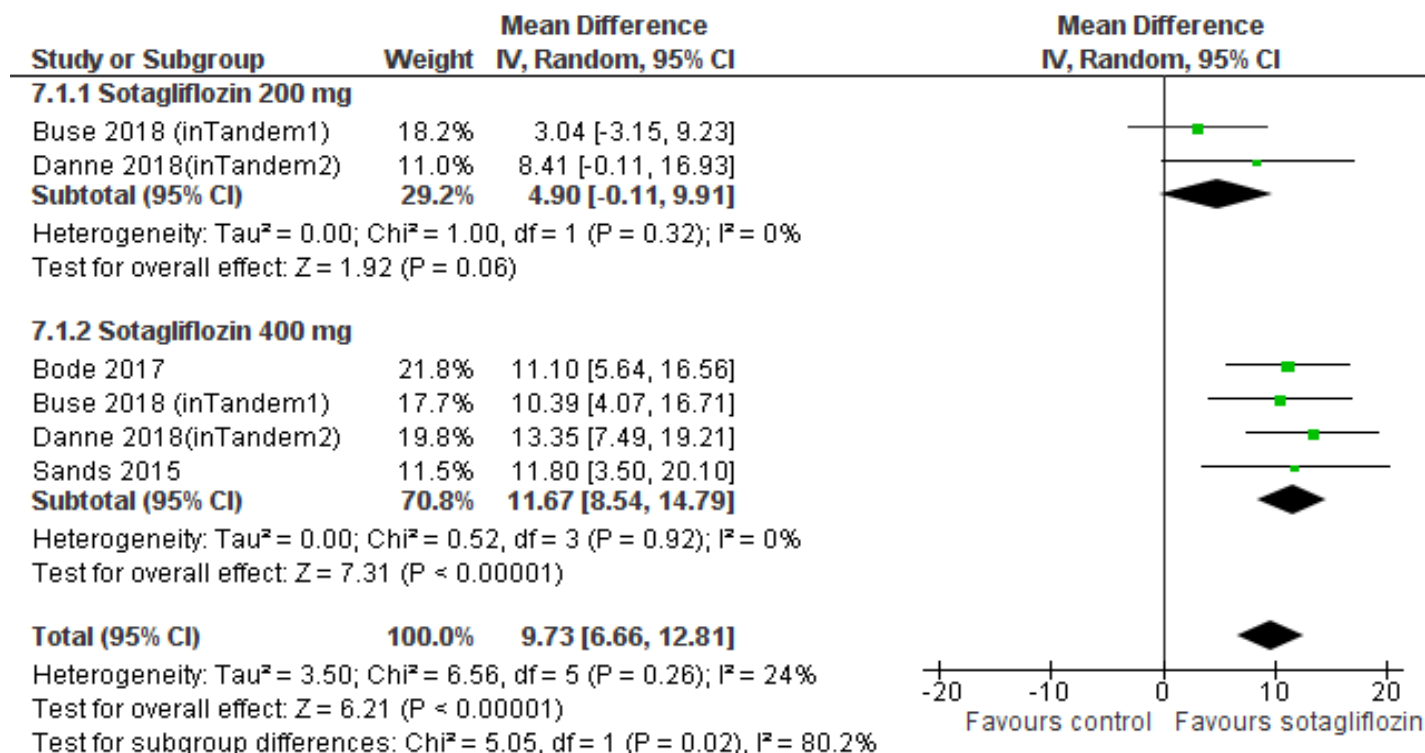


**Panel S.** Funnel plot of comparison: MACE, outcome: MACE

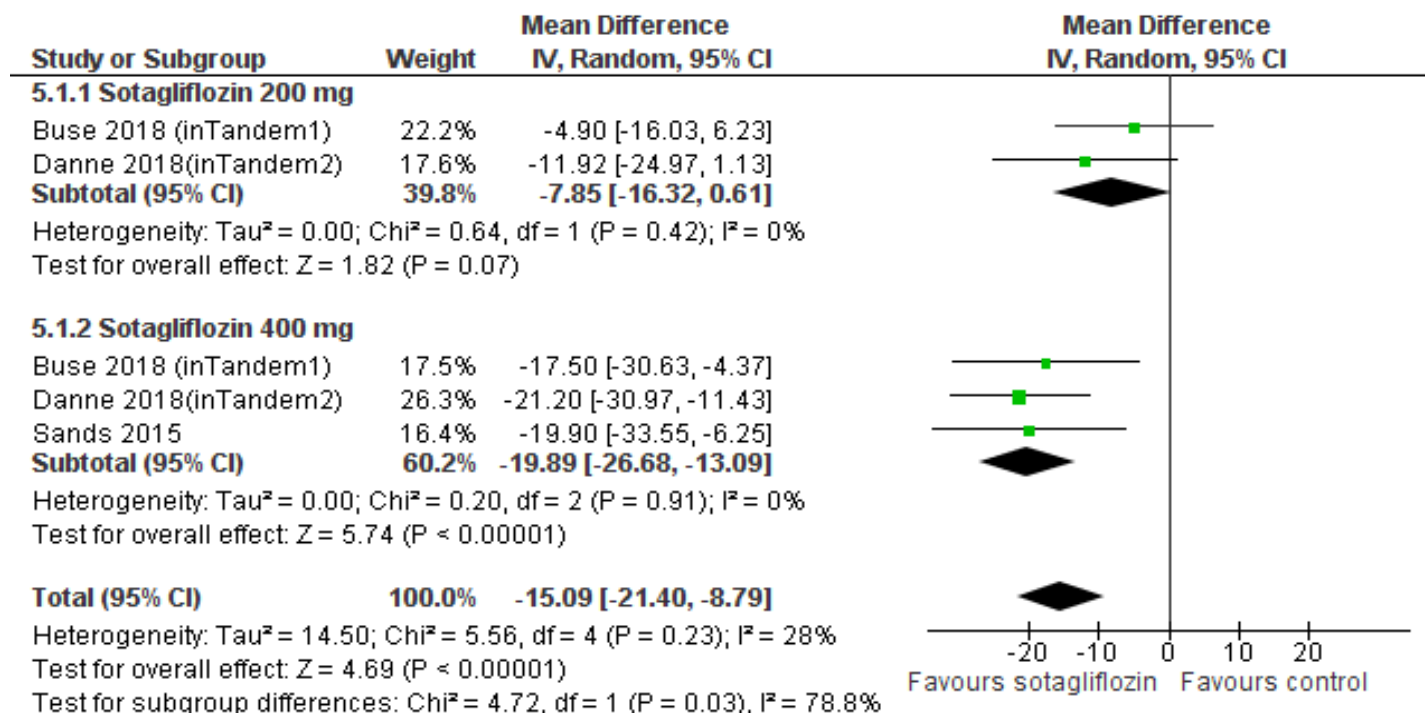


**Supplementary Figure 4. Forest plot of comparison: Sotagliflozin, outcome: Continuous Glucose Monitoring (CGM) parameters.**

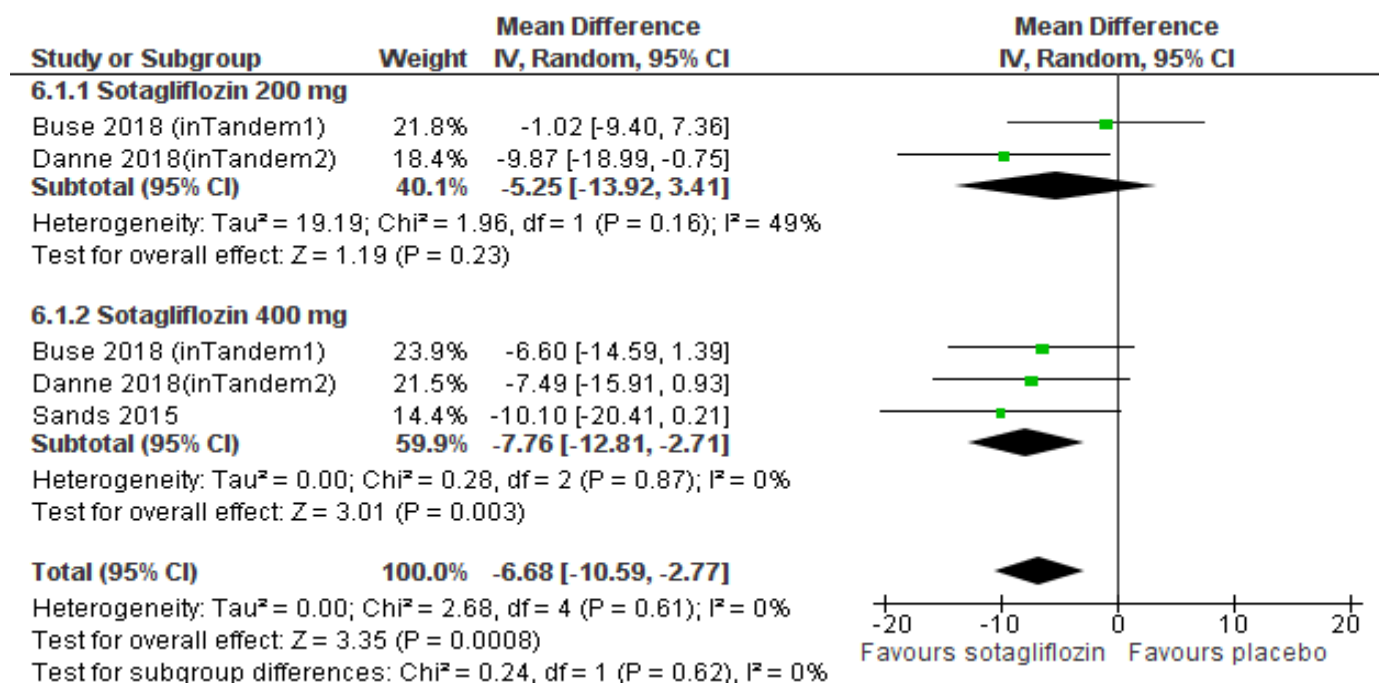
**Panel A: outcome: time-in-range (%)**



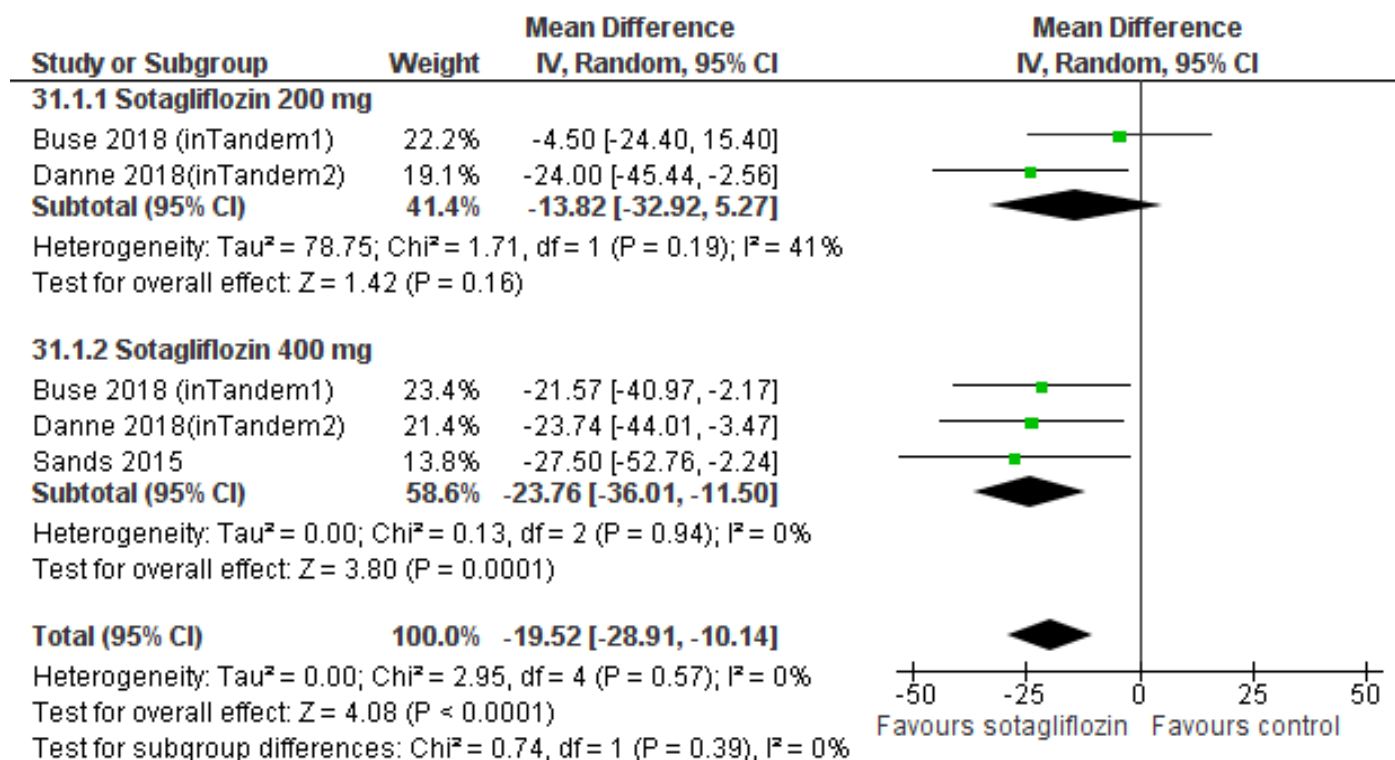
**Panel B: outcome: average daily glucose (mg/dL)**



**Panel C: outcome: Standard Deviation (SD) around average daily glucose (mg/dL)**

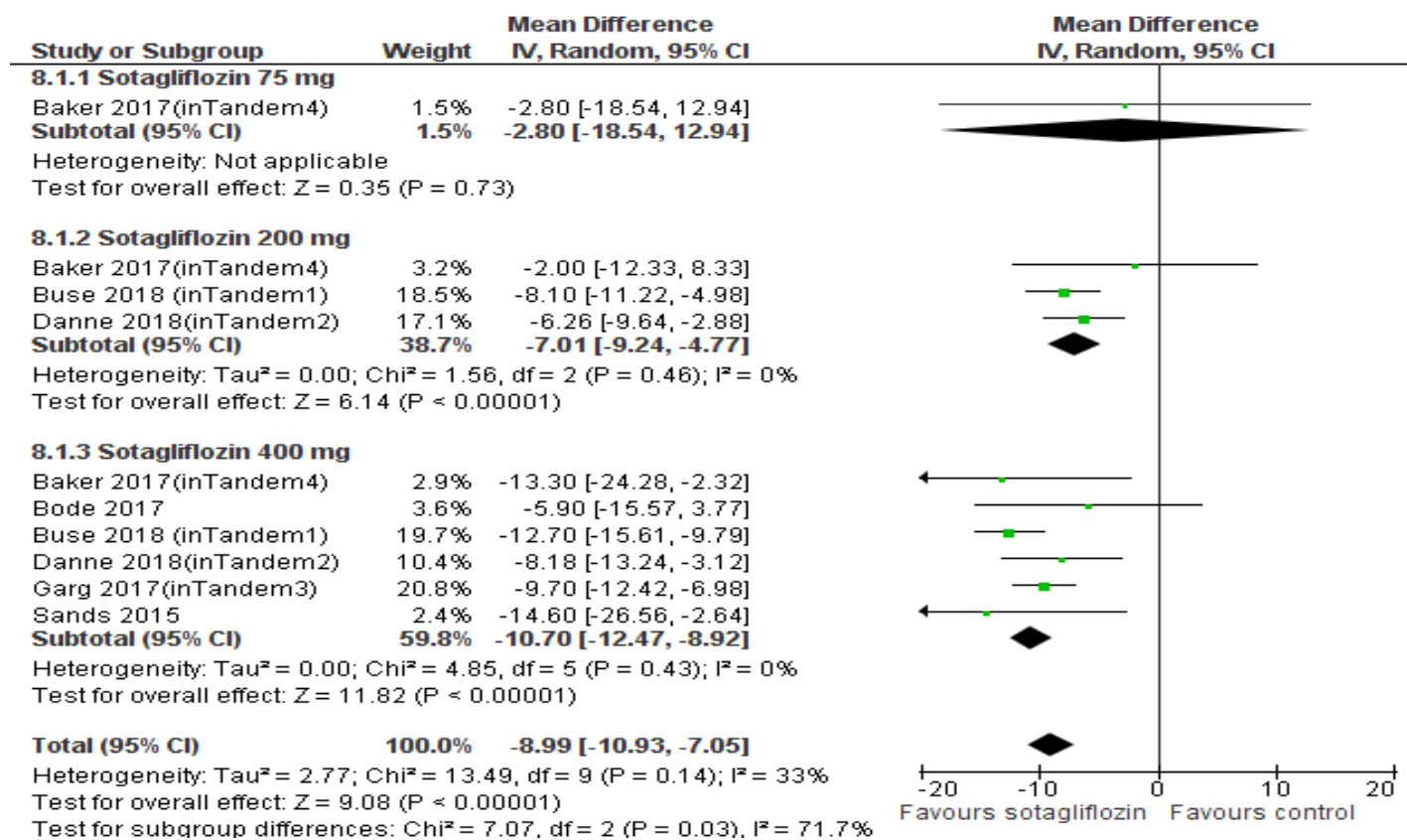


**Panel D: outcome: mean amplitude of glucose excursion (MAGE) (mg/dL)**

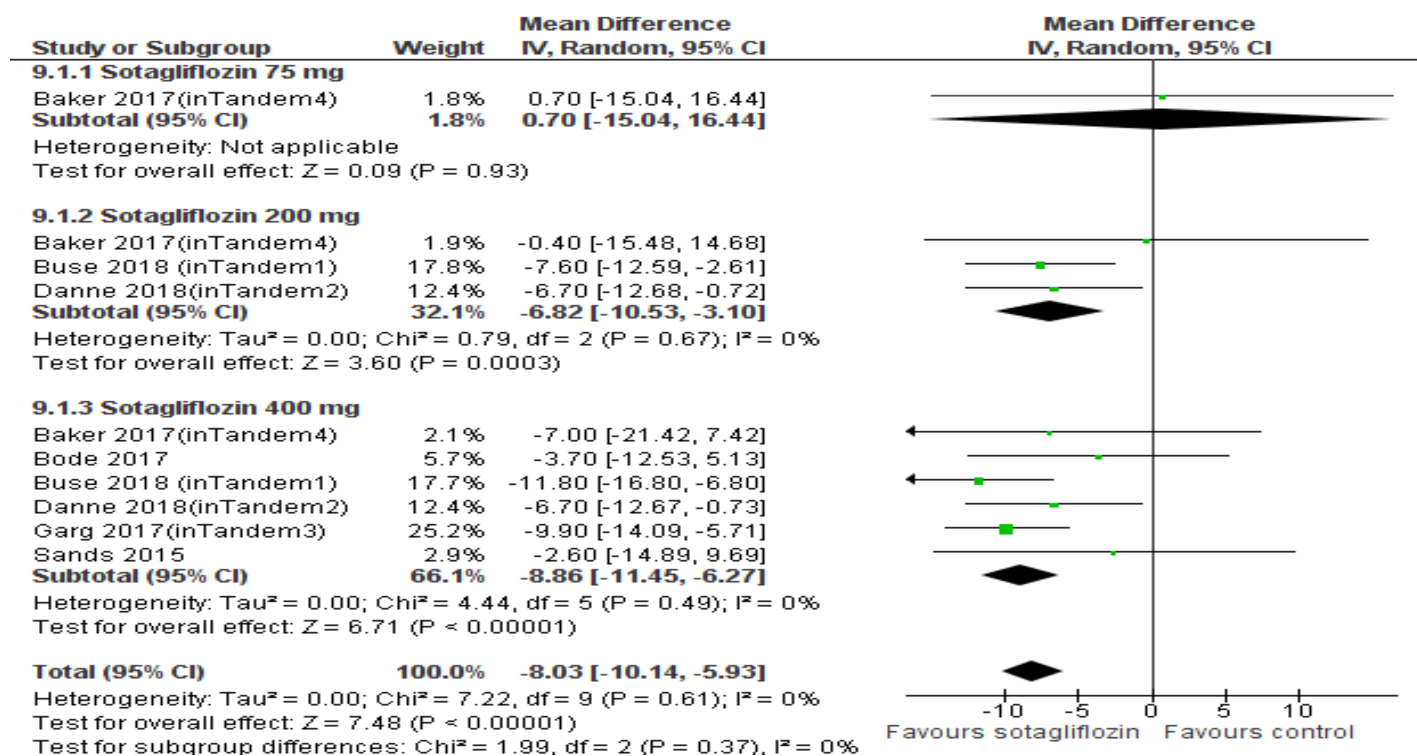


**Supplementary Figure 5. Forest plot of comparison: Sotagliflozin, outcome: Daily total, basal and bolus insulin dose (%) changes from baseline.**

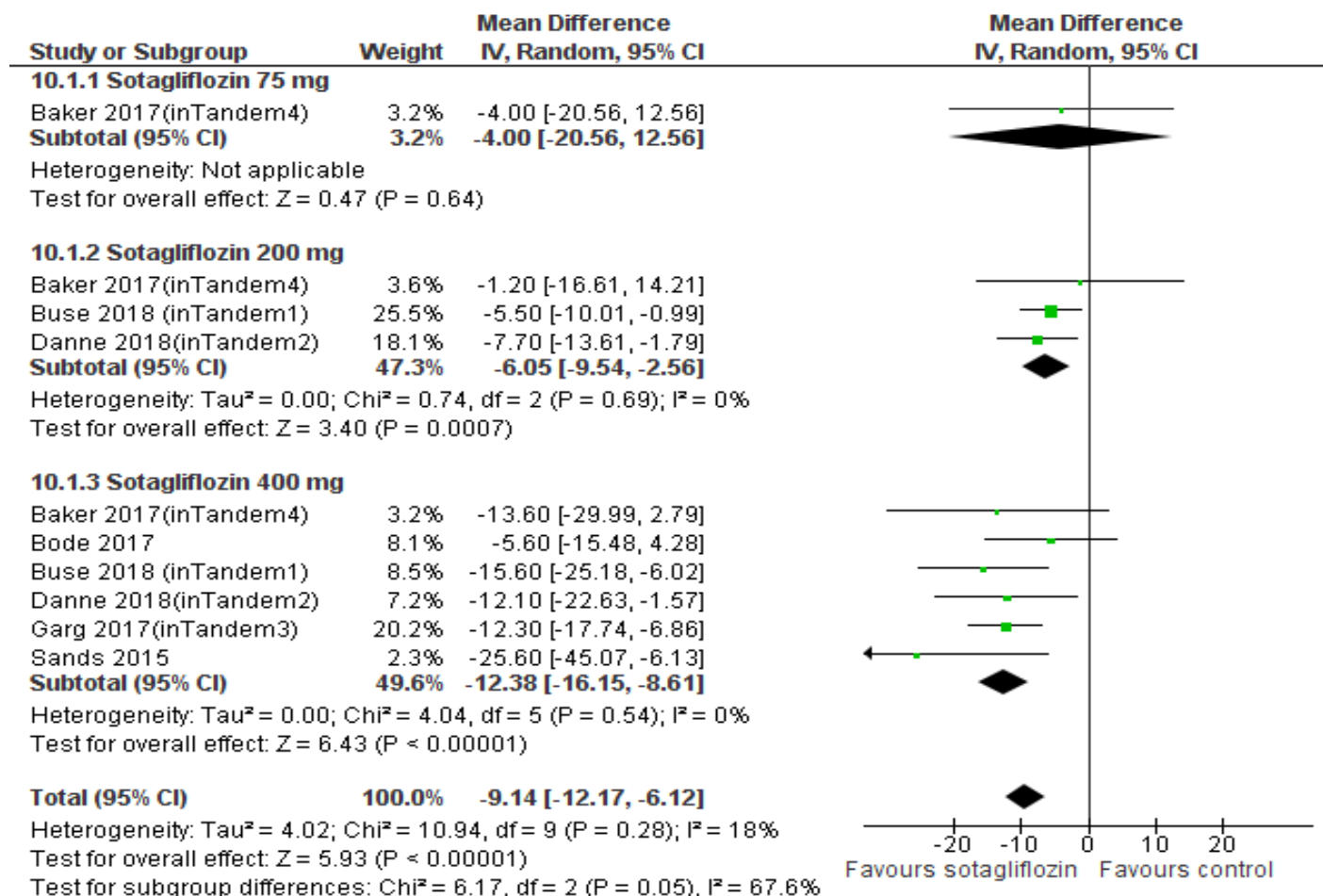
**Panel A: outcome: daily total insulin dose (%)**



**Panel B: outcome: daily basal insulin dose (%)**

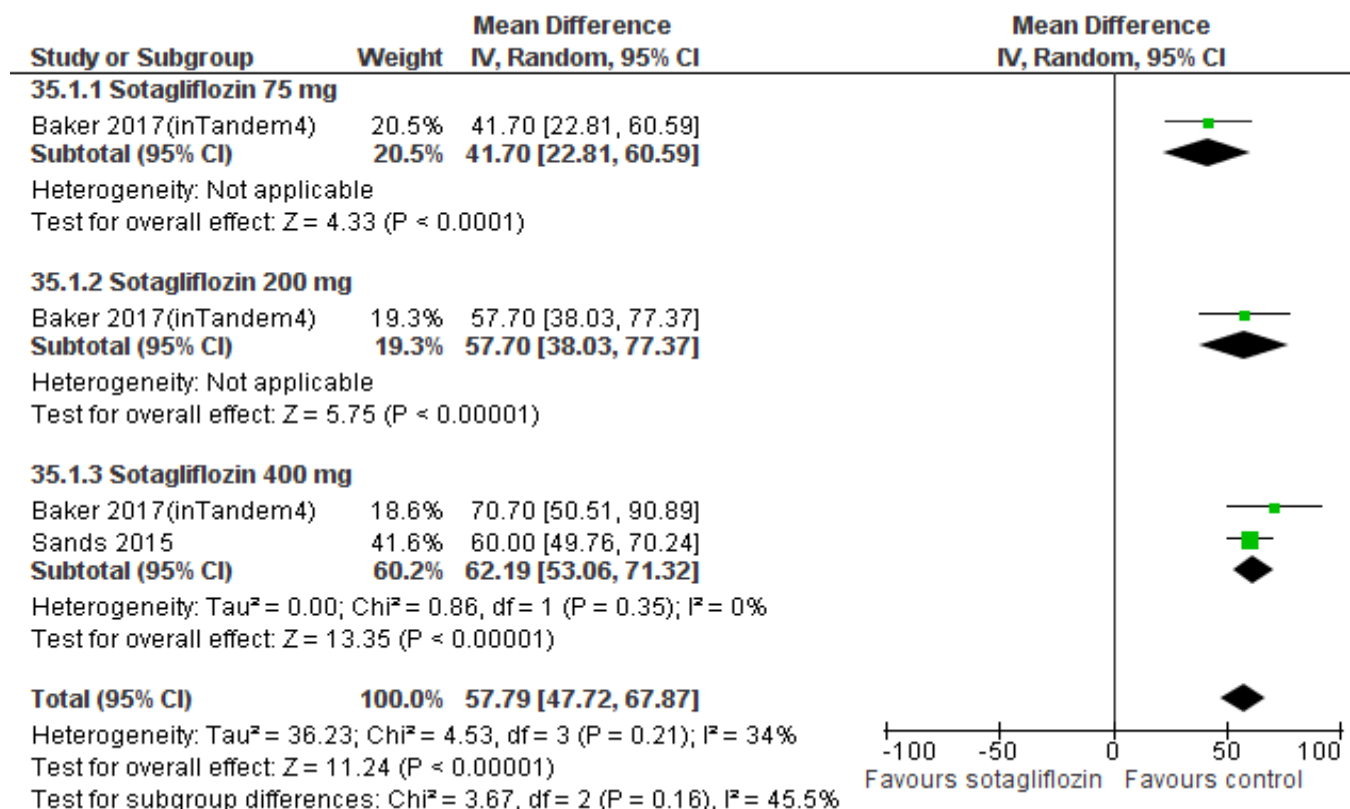


**Panel C: outcome: daily bolus insulin dose (%)**



**Supplementary Figure 6. Forest plot of comparison: Sotagliflozin, outcome: daily urinary**

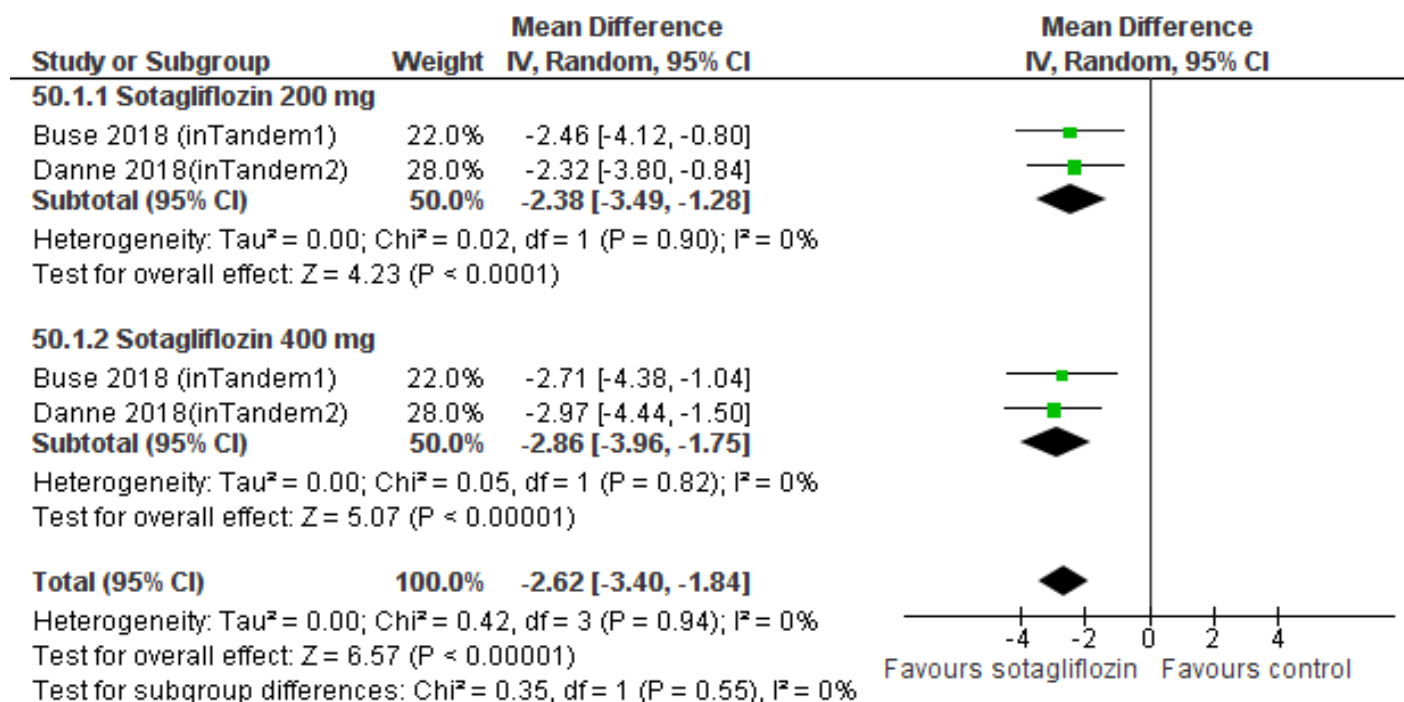
**glucose excretion (UGE) (g/24 hr)**



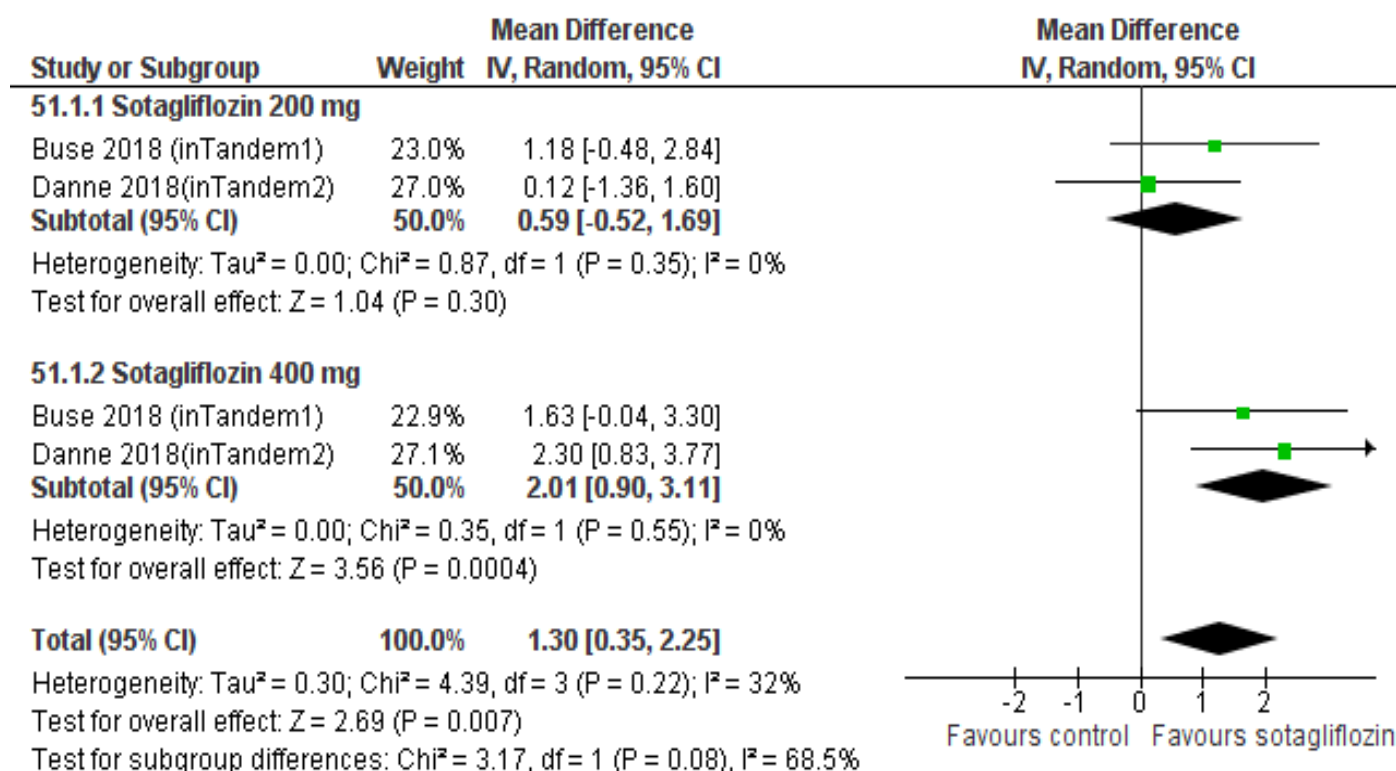


**Figure 7. Forest plot of comparison: Sotagliflozin vs. placebo, outcomes: eGFR changes over week 0-52: pooled analysis of inTandem1 and inTandem2 trials**

**Panel A: outcome: eGFR changes from baseline during week 0-24 (ml/min/1.73m<sup>2</sup>)**

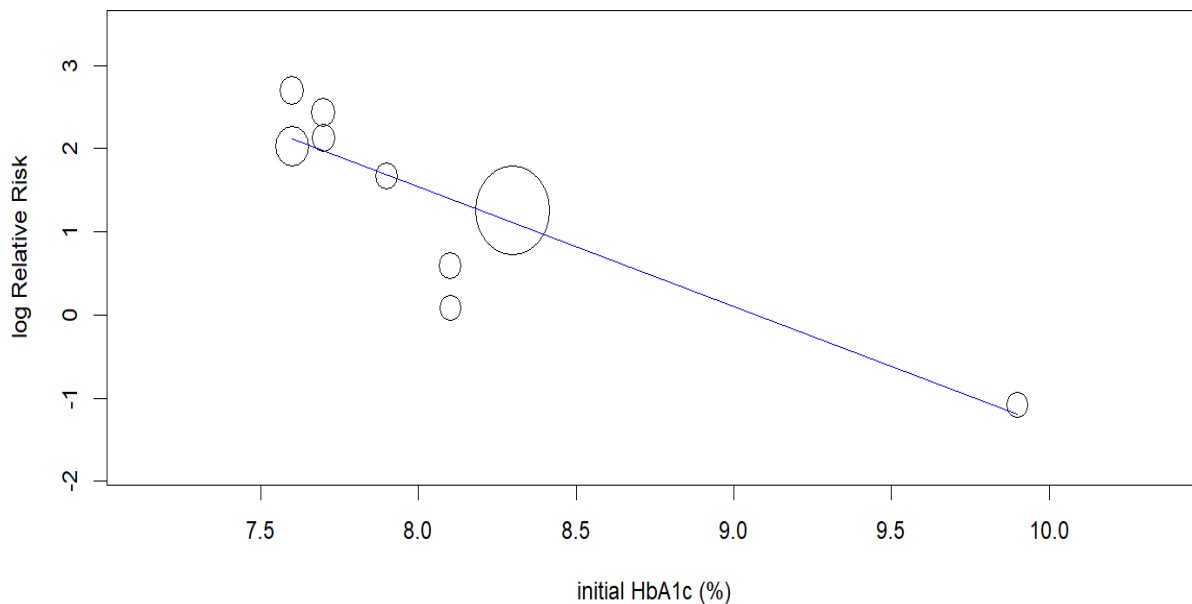


**Panel B: outcome: eGFR changes from baseline during week 24-52 (ml/min/1.73m<sup>2</sup>)**

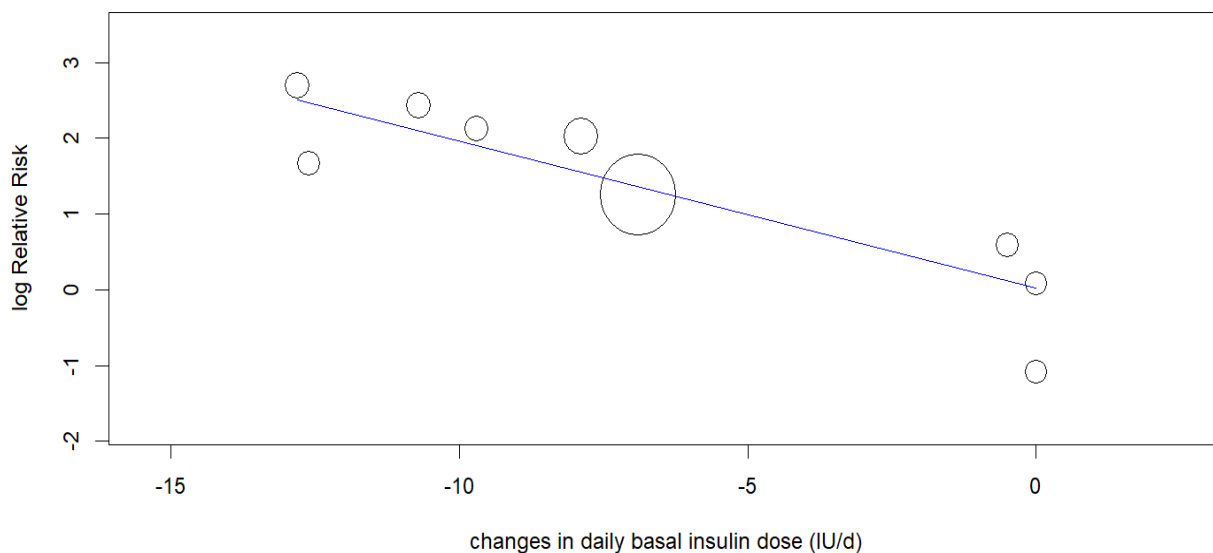


**Supplementary Figure 8. Meta-regression analysis:** regression plot of the effect of initial HbA1c(%) (**panel A**) and of changes in daily basal insulin dose(expressed as IU/d) from baseline (**panel B**) in relation to the risk (expressed as log risk ratio) of diabetic ketoacidosis (DKA). Each circle represents one comparison group, with the size of each circle representing the weight given to the group in meta-regression.

**Panel A:** effect of initial HbA1c (%) on the RR of DKA

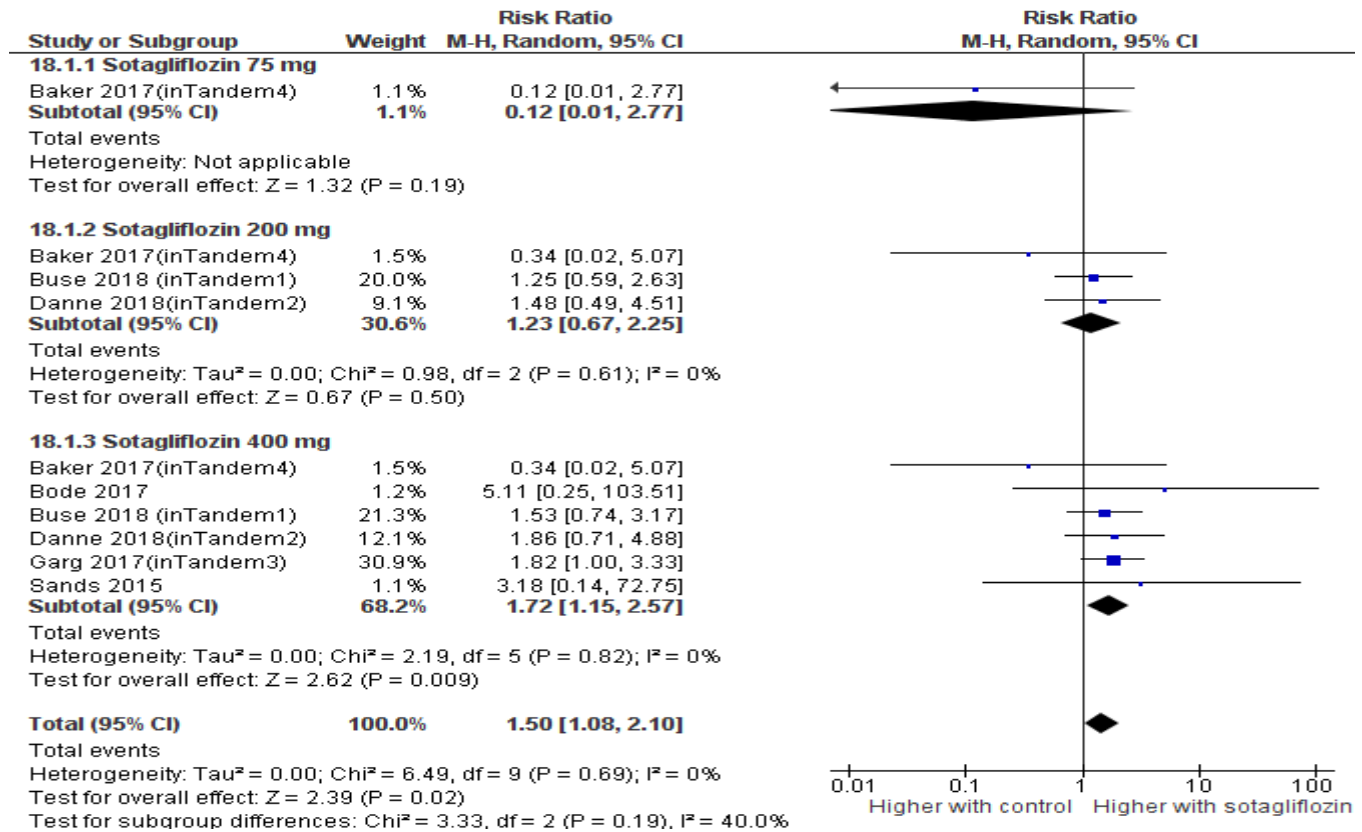


**Panel B:** effect of changes in daily basal insulin dose (IU/d) from baseline on the RR of DKA

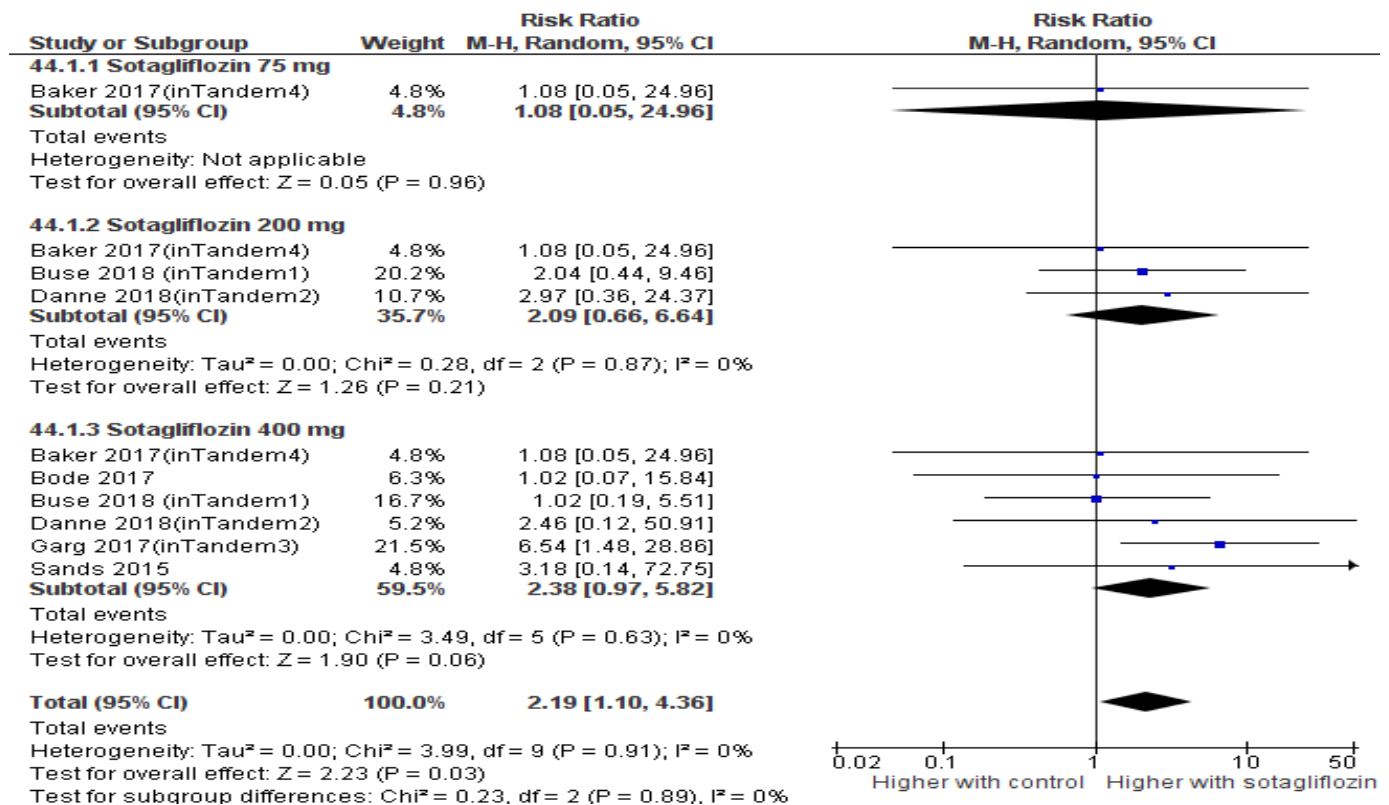


**Supplementary Figure 9. Forest plot of comparison: Sotagliflozin, outcome: diarrhea and volume depletion events**

**Panel A: outcome: diarrhea**

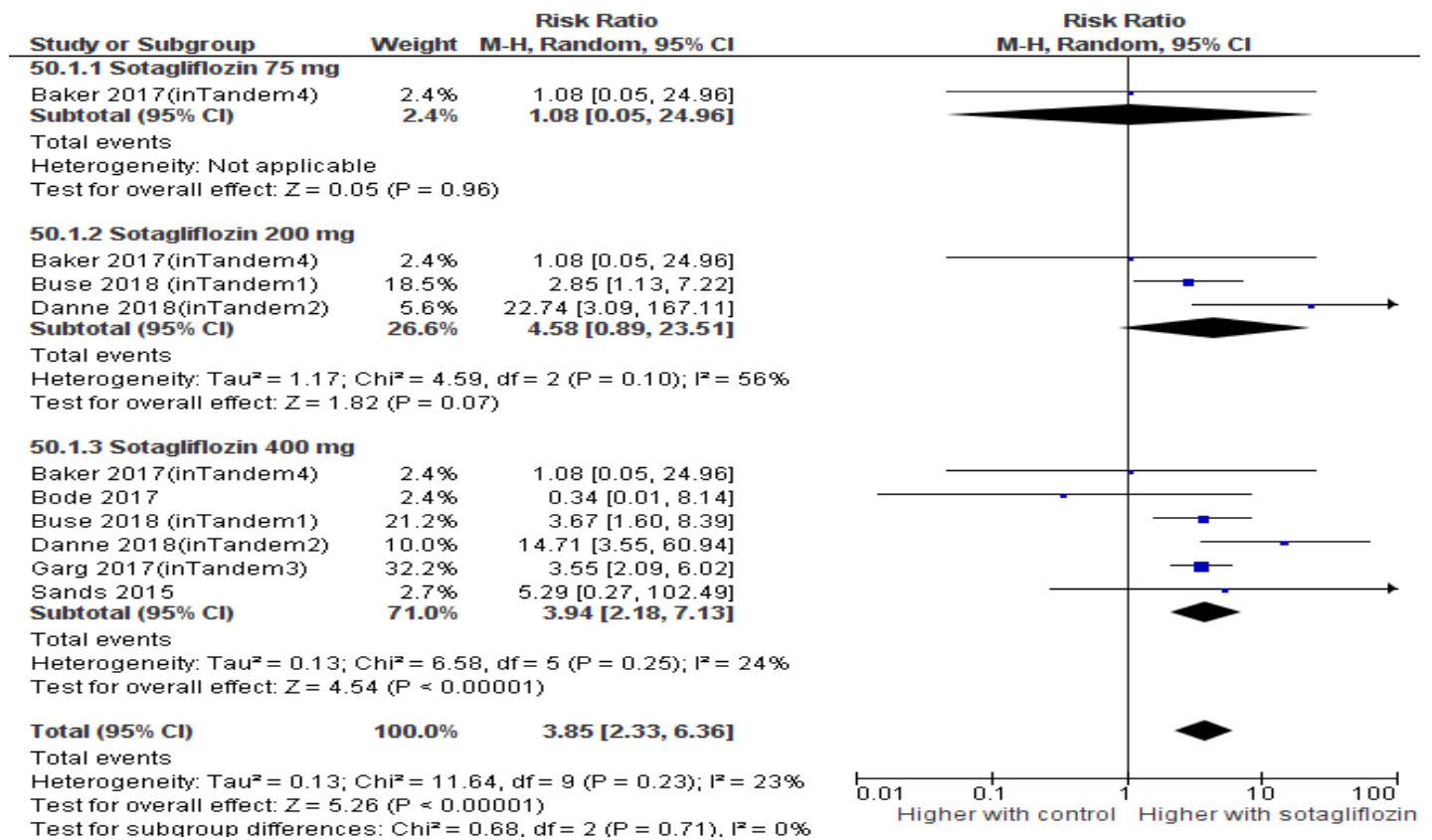


**Panel B: outcome: volume depletion events**



**Supplementary Figure 10. Forest plot of comparison: Sotagliflozin, outcome: incidence of acidosis-related and of major adverse cardiovascular events (MACE).**

**Panel A: outcome: acidosis-related adverse events**



**Panel B: outcome: major adverse cardiovascular events (MACE)**

