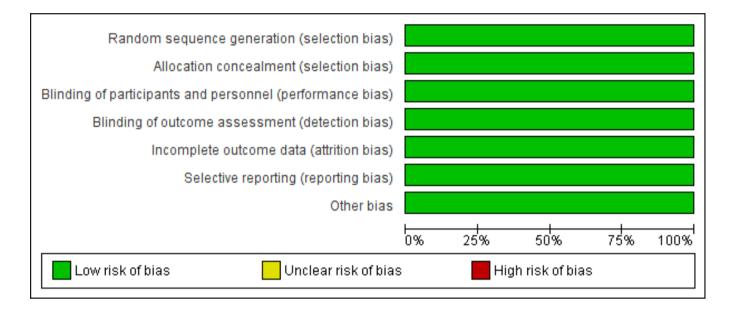
Supplementary Figures

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

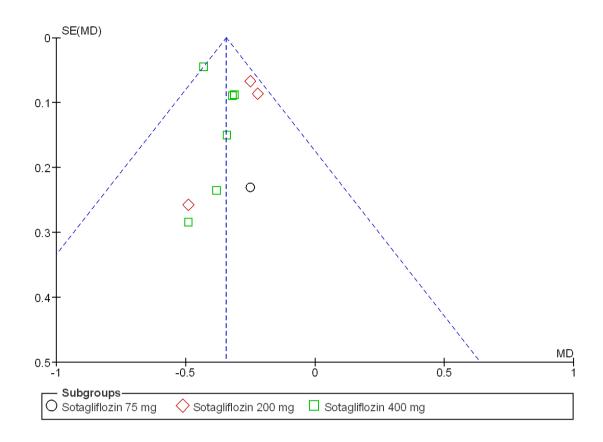
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Baker 2017(inTandem4)	•	•	•	•	•	•	•
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.

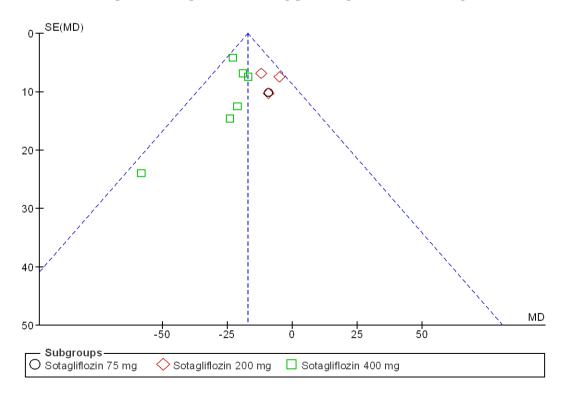


Supplementary Figure 3.

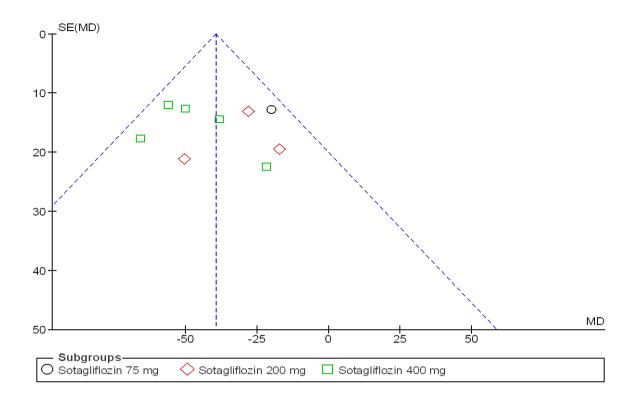
Panel A Funnel plot of comparison: HbA1c(%) outcome: HbA1c(%).



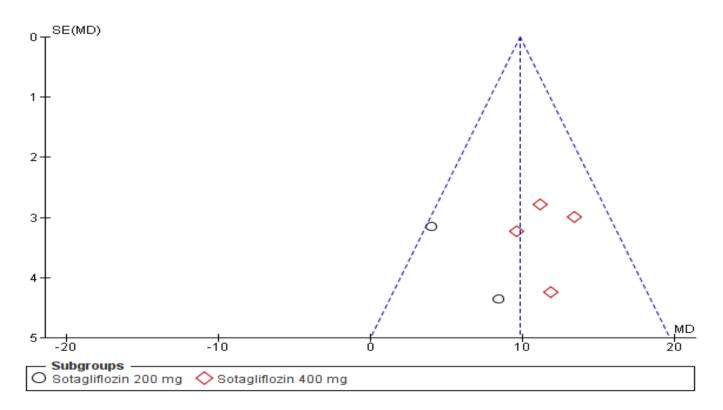
Panel B Funnel plot of comparison: Fasting plasma glucose (FPG; (mg/dL) outcome: FPG(mg/dL).



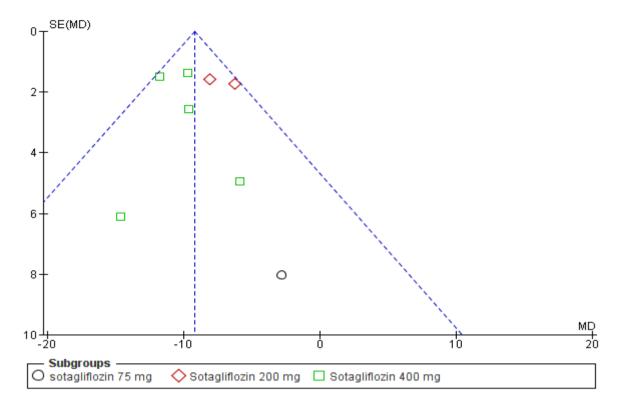
Panel C. Funnel plot of comparison: 2-hr postprandial plasma glucose(PPG) for outcome: 2hr-PPG.



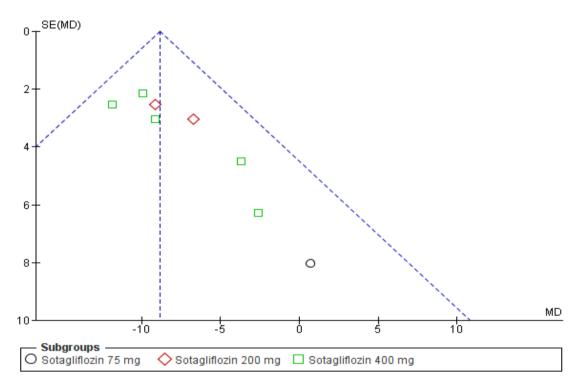
Panel D. Funnel plot of comparison: % time-in-range (70-180 mg/dL) for outcome: % time-in-range



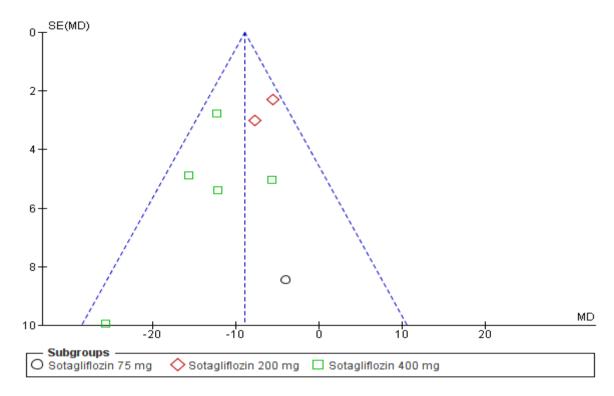
Panel E. Funnel plot of comparison: total daily insulin dose, outcome: total daily insulin dose(% change)



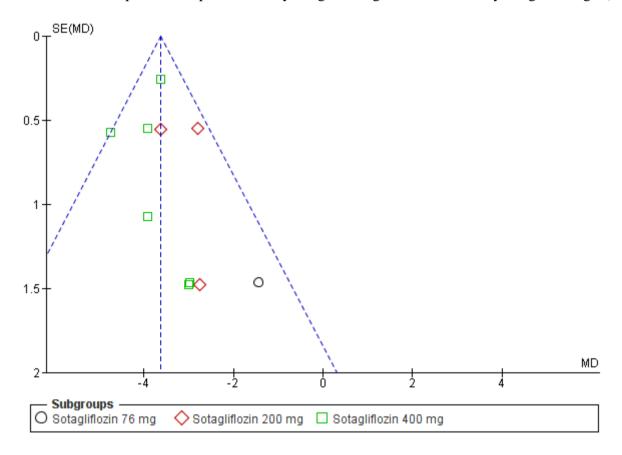
Panel F. Funnel plot of comparison: basal daily insulin dose, outcome: basal daily insulin dose(% change)



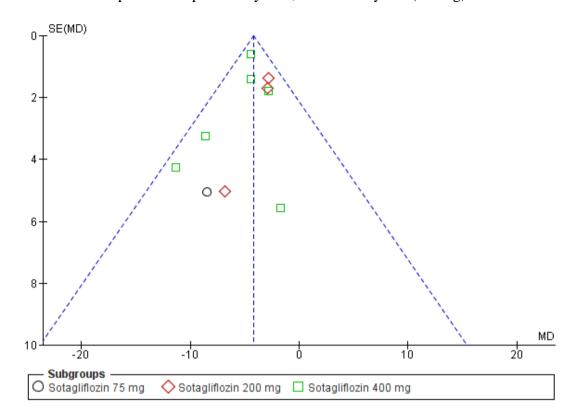
Panel G. Funnel plot of comparison: bolus daily insulin dose, outcome: bolus daily insulin dose(% change)



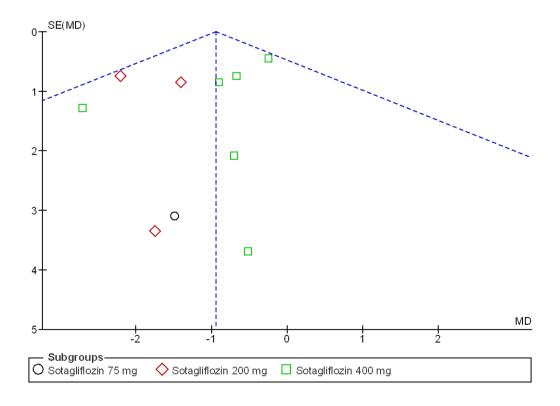
Panel H. Funnel plot of comparison: body weight changes, outcome: body weight changes(%)



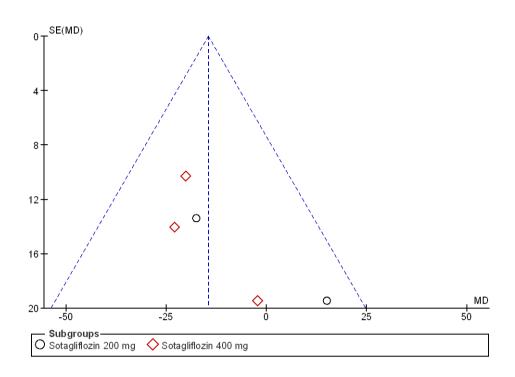
Panel I. Funnel plot of comparison: sys BP, outcome: sys BP(mmHg)



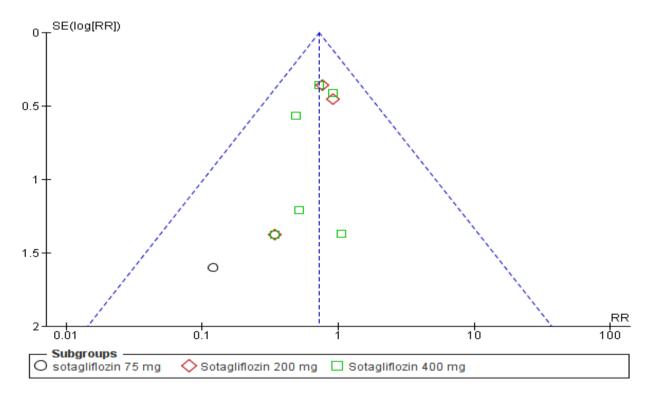
Panel L. Funnel plot of comparison: eGFR changes, outcome: eGFR changes(ml/min/1.73 m2)



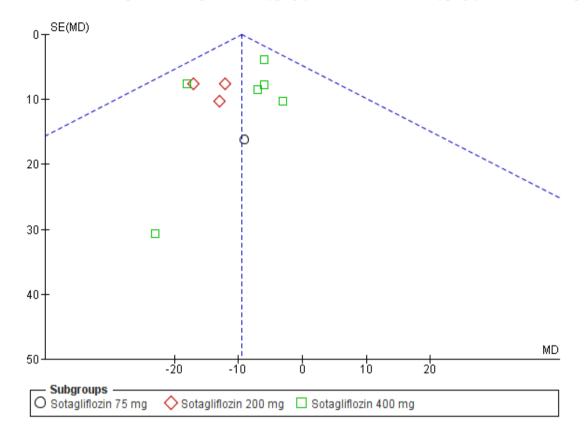
Panel M. Funnel plot of comparison: urinary A/C ratio, outcome: albumin/creatinine ratio(mg/g).



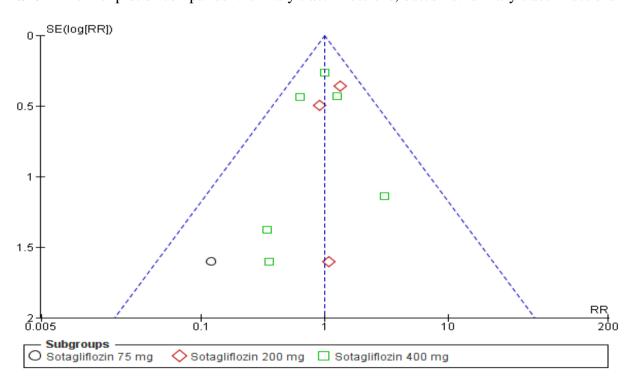
Panel N. Funnel plot of comparison: severe hypoglycemia, outcome: severe hypoglycemia.



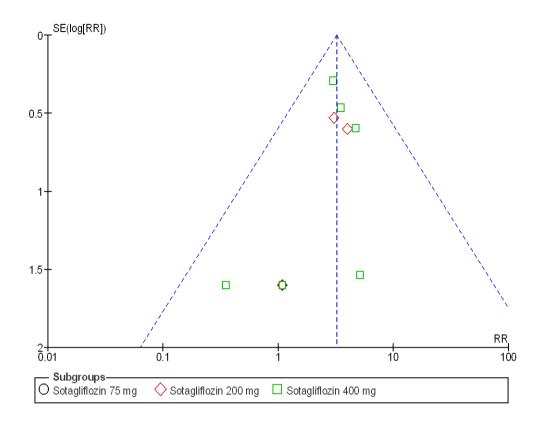
Panel O. Funnel plot of comparison: hypoglycemia, outcome: hypoglycemia (events per patient-year).



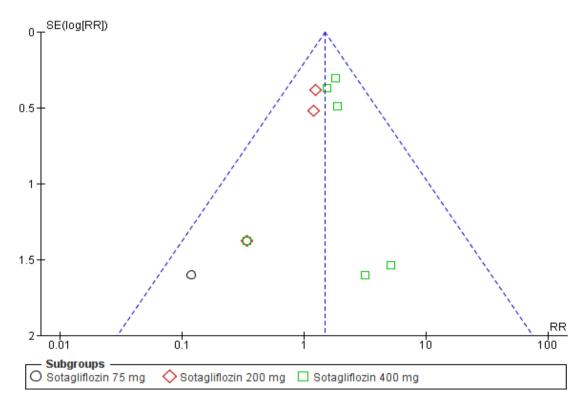
Panel P. Funnel plot of comparison: urinary tract infections, outcome: urinary tract infections.



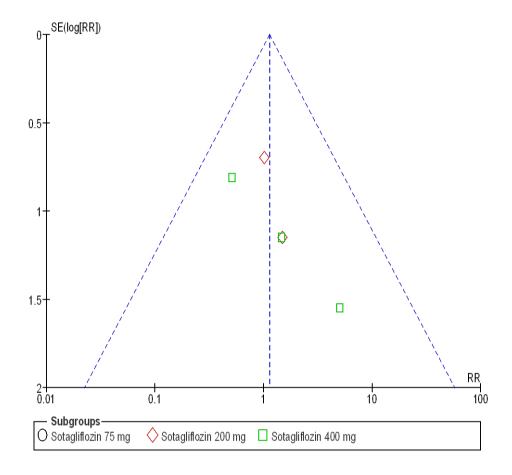
Panel Q. Funnel plot of comparison: genital tract infections, outcome: genital tract infections.



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

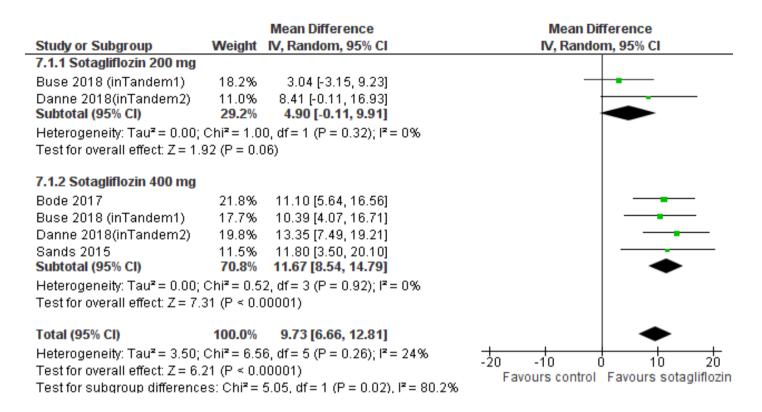


Panel S. Funnel plot of comparison: MACE, outcome: MACE



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

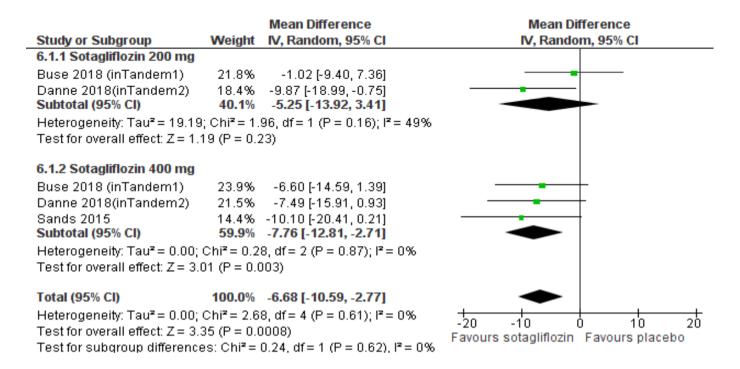
Panel A: outcome: time-in-range (%)



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

		Mean Difference	Mean Difference	
Study or Subgroup	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
5.1.1 Sotagliflozin 200 mg				
Buse 2018 (inTandem1)	22.2%	-4.90 [-16.03, 6.23]		
Danne 2018(inTandem2)	17.6%	-11.92 [-24.97, 1.13]		
Subtotal (95% CI)	39.8%	-7.85 [-16.32, 0.61]	•	
Heterogeneity: Tau² = 0.00;	$Chi^2 = 0.64$	4, df = 1 (P = 0.42); I ^z = 0%		
Test for overall effect: $Z = 1$.	82 (P = 0.0	17)		
5.1.2 Sotagliflozin 400 mg				
Buse 2018 (inTandem1)	17.5%	-17.50 [-30.63, -4.37]		
Danne 2018(inTandem2)	26.3%	-21.20 [-30.97, -11.43]		
Sands 2015	16.4%	-19.90 [-33.55, -6.25]		
Subtotal (95% CI)	60.2%	-19.89 [-26.68, -13.09]	•	
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 2 (P = 0.91); I² = 0%				
Test for overall effect: $Z = 5$.	74 (P < 0.0	00001)		
Total (95% CI)	100.0%	-15.09 [-21.40, -8.79]	•	
Heterogeneity: Tau ² = 14.50); Chi² = 5.:	56, df = 4 (P = 0.23); I ² = 28%		
Test for overall effect: Z = 4.	69 (P < 0.0	00001)	-20 -10 0 10 20	
Test for subgroup differences: Chi ² = 4.72, df = 1 (P = 0.03), I ² = 78.8%			Favours sotagliflozin Favours control	

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

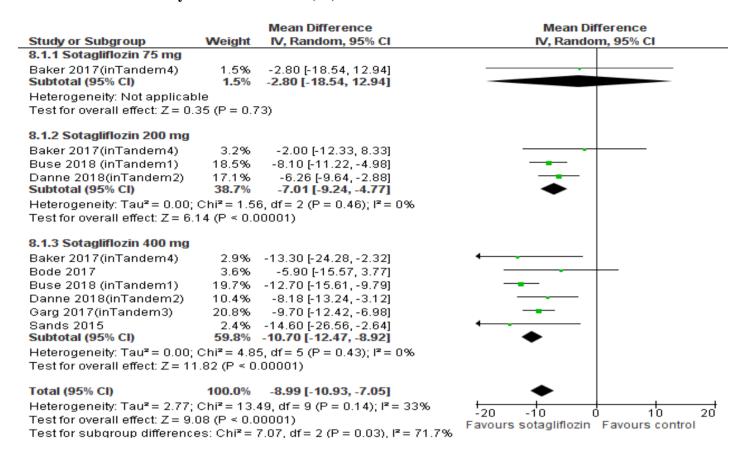


Panel D: outcome: mean amplitude of glucose excursion (MAGE) (mg/dL)

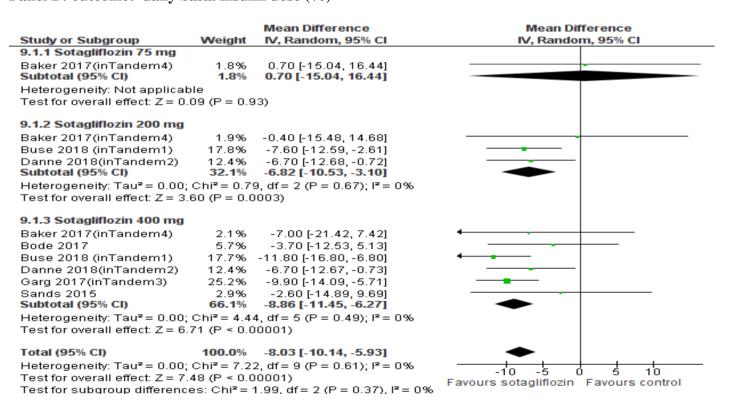
		Mean Difference	Mean Difference	
Study or Subgroup	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
31.1.1 Sotagliflozin 200 mg	3			
Buse 2018 (inTandem1)	22.2%	-4.50 [-24.40, 15.40]		
Danne 2018(inTandem2) Subtotal (95% CI)	19.1% 41.4 %		-	
Heterogeneity: Tau² = 78.79	5; Chi² = 1.	71, $df = 1$ (P = 0.19); $I^2 = 41\%$		
Test for overall effect: Z = 1.	.42 (P = 0.1	16)		
31.1.2 Sotagliflozin 400 mg	g			
Buse 2018 (inTandem1)	23.4%	-21.57 [-40.97, -2.17]		
Danne 2018(inTandem2)	21.4%	-23.74 [-44.01, -3.47]		
Sands 2015	13.8%	-27.50 [-52.76, -2.24]		
Subtotal (95% CI)	58.6 %	-23.76 [-36.01, -11.50]	•	
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 2 (P = 0.94); I² = 0%				
Test for overall effect: Z = 3	.80 (P = 0.0	0001)		
Total (95% CI)	100.0%	-19.52 [-28.91, -10.14]	•	
Heterogeneity: Tau ^z = 0.00; Chi ^z = 2.95, df = 4 (P = 0.57); I^z = 0% Test for overall effect: Z = 4.08 (P < 0.0001) Test for subgroup differences: Chi ^z = 0.74, df = 1 (P = 0.39), I^z = 0%			-50 -25 0 25 50 Favours sotagliflozin Favours control	

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 (%)

		Mean Difference	Mean Difference
Study or Subgroup	Weight	IV, Random, 95% CI	IV, Random, 95% CI
10.1.1 Sotagliflozin 75 mg			
Baker 2017(inTandem4)	3.2%	-4.00 [-20.56, 12.56]	
Subtotal (95% CI)	3.2%	-4.00 [-20.56, 12.56]	
Heterogeneity: Not applicab	le		
Test for overall effect: $Z = 0$.	47 (P = 0.6)	4)	
10.1.2 Sotagliflozin 200 mg	ı		
Baker 2017(inTandem4)	3.6%	-1.20 [-16.61, 14.21]	
Buse 2018 (inTandem1)	25.5%	-5.50 [-10.01, -0.99]	
Danne 2018(inTandem2)	18.1%	-7.70 [-13.61, -1.79]	
Subtotal (95% CI)	47.3%	-6.05 [-9.54, -2.56]	→
Heterogeneity: Tau² = 0.00;			
Test for overall effect: $Z = 3$.	40 (P = 0.0	007)	
10 1 3 Sotagliflozin 100 ma			
10.1.3 Sotagliflozin 400 mg		40.001.00.00.0.701	
Baker 2017(inTandem4)	3.2%	-13.60 [-29.99, 2.79]	<u> </u>
Bode 2017	8.1%	-5.60 [-15.48, 4.28]	
Buse 2018 (inTandem1)	8.5%		
Danne 2018(inTandem2)	7.2%	-12.10 [-22.63, -1.57]	
Garg 2017(inTandem3) Sands 2015		-12.30 [-17.74, -6.86] -25.60 [-45.07, -6.13]	<u> </u>
Subtotal (95% CI)		-12.38 [-16.15, -8.61]	•
Heterogeneity: Tau ² = 0.00;			•
Test for overall effect: $Z = 6$.			
restroi overali ellect. Z = o.:	45 (1 ~ 0.0	0001)	
Total (95% CI)	100.0%	-9.14 [-12.17, -6.12]	•
Heterogeneity: Tau² = 4.02;	$Chi^2 = 10.9$	34, df = 9 (P = 0.28); I² = 18%	-20 -10 0 10 20
Test for overall effect: $Z = 5$.	93 (P < 0.0	0001)	-20 -10 0 10 20 Favours sotagliflozin Favours control
Test for subgroup difference	es: Chi² = 6	6.17 , df = 2 (P = 0.05), $I^2 = 67.6\%$	1 avours sotagimozini i avours control

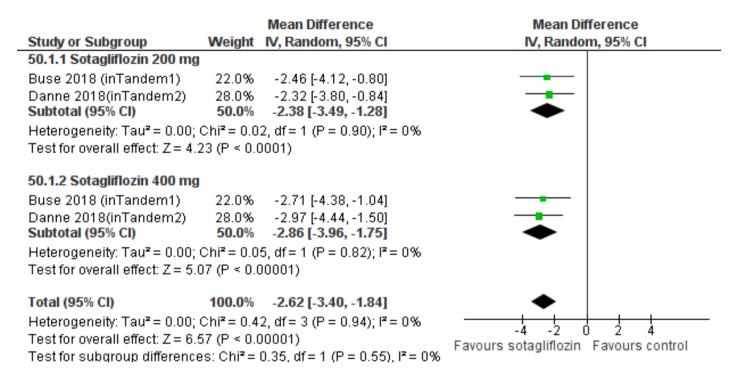
Supplementary Figure 6. Forest plot of comparison: Sotagliflozin, outcome: daily urinary

glucose excretion (UGE) (g/24 hr)

		Mean Difference	Mean Differen	ce	
Study or Subgroup	Weight	IV, Random, 95% CI	IV, Random, 95	% CI	
35.1.1 Sotagliflozin 75 mg	I				
Baker 2017(inTandem4) Subtotal (95% CI)		41.70 [22.81, 60.59] 41.70 [22.81, 60.59]	-	•	
Heterogeneity: Not applica	ıble				
Test for overall effect: Z = 4	I.33 (P < 0	.0001)			
35.1.2 Sotagliflozin 200 m	g				
Baker 2017(inTandem4) Subtotal (95% CI)		57.70 [38.03, 77.37] 57.70 [38.03, 77.37]		•	
Heterogeneity: Not applica	ıble				
Test for overall effect: Z = 5	5.75 (P < 0	.00001)			
35.1.3 Sotagliflozin 400 m	g				
Baker 2017(inTandem4)	18.6%	70.70 [50.51, 90.89]			
Sands 2015	41.6%	60.00 [49.76, 70.24]		-	
Subtotal (95% CI)	60.2%	62.19 [53.06, 71.32]		•	
Heterogeneity: Tau ² = 0.00; Chi ² = 0.86, df = 1 (P = 0.35); I ² = 0%					
Test for overall effect: Z = 1	3.35 (P ≤	0.00001)			
T-4-1 (05% CI)	400.0%	F7 70 147 72 67 071		•	
Total (95% CI)		57.79 [47.72, 67.87]		•	
Heterogeneity: Tau ² = 36.23; Chi ² = 4.53, df = 3 (P = 0.21); I ² = 34%					
Test for overall effect: Z = 11.24 (P < 0.00001) Favours sotadiflozin Favours control					
Test for subgroup differences: Chi ² = 3.67, df = 2 (P = 0.16), I ² = 45.5%					

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/1.73m²)

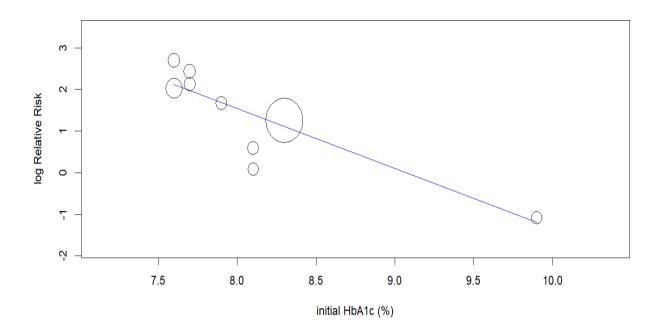


Panel B: outcome: eGFR changes from baseline during week 24-52 (ml/min/1.73m²)

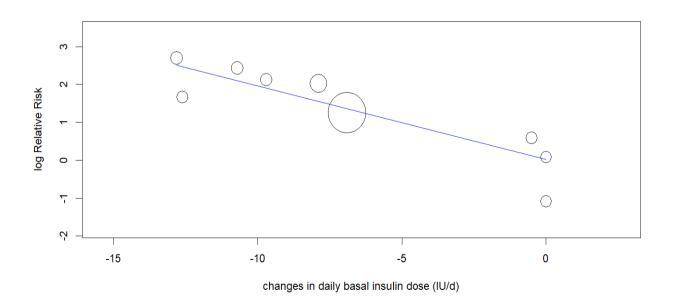
		Mean Difference	Mean Difference		
Study or Subgroup	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
51.1.1 Sotagliflozin 200 mg	ı				
Buse 2018 (inTandem1)	23.0%	1.18 [-0.48, 2.84]	 •		
Danne 2018(inTandem2) Subtotal (95% CI)	27.0% 50.0 %	0.12 [-1.36, 1.60] 0.59 [-0.52, 1.69]			
Heterogeneity: Tau ^z = 0.00;	$Chi^2 = 0.87$	7, df = 1 (P = 0.35); I ^z = 0%			
Test for overall effect: $Z = 1$.	04 (P = 0.3	(0)			
51.1.2 Sotagliflozin 400 mg	l				
Buse 2018 (inTandem1)	22.9%	1.63 [-0.04, 3.30]			
Danne 2018(inTandem2)	27.1%	2.30 [0.83, 3.77]			
Subtotal (95% CI)	50.0 %	2.01 [0.90, 3.11]	-		
Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 1 (P = 0.55); l² = 0%					
Test for overall effect: Z = 3.56 (P = 0.0004)					
Total (95% CI)	100.0%	1.30 [0.35, 2.25]	-		
Heterogeneity: Tau² = 0.30; Chi² = 4.39, df = 3 (P = 0.22); l² = 32%					
Test for overall effect: Z = 2.69 (P = 0.007)			Favours control Favours sotagliflozin		
Test for subgroup differences: $Chi^2 = 3.17$, $df = 1$ (P = 0.08), $I^2 = 68.5\%$			r avours control if avours sotagimozin		

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

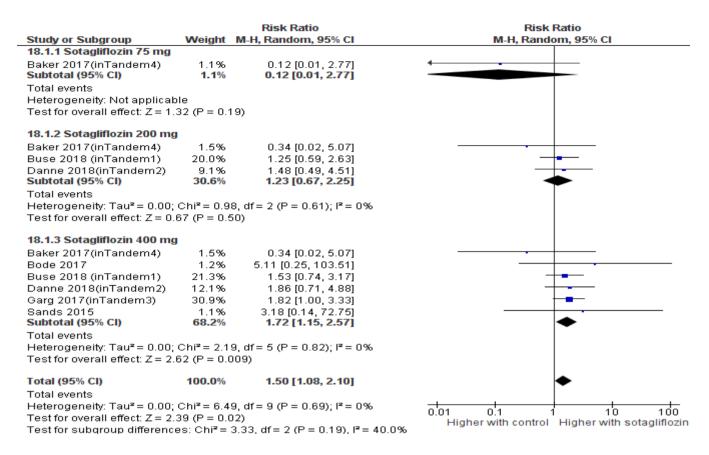


Panel B: effect of changes in daily basal insulin dose (IU/d) from baseline on the RR of DKA

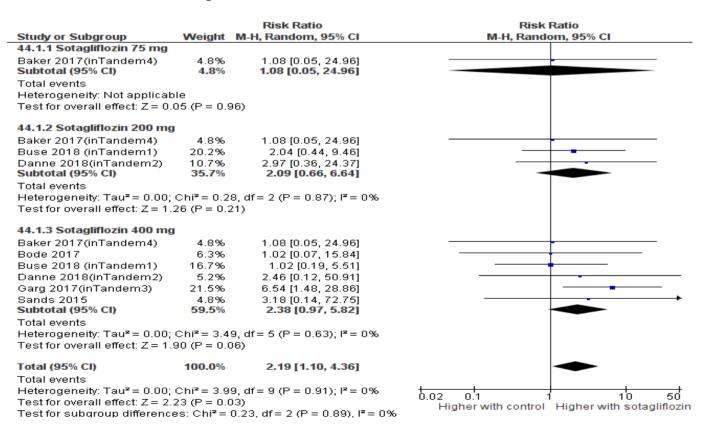


Supplementary Figure 9. Forest plot of comparison: Sotagliflozin, outcome: diarrhea and volume depletion events

Panel A: outcome: diarrhea

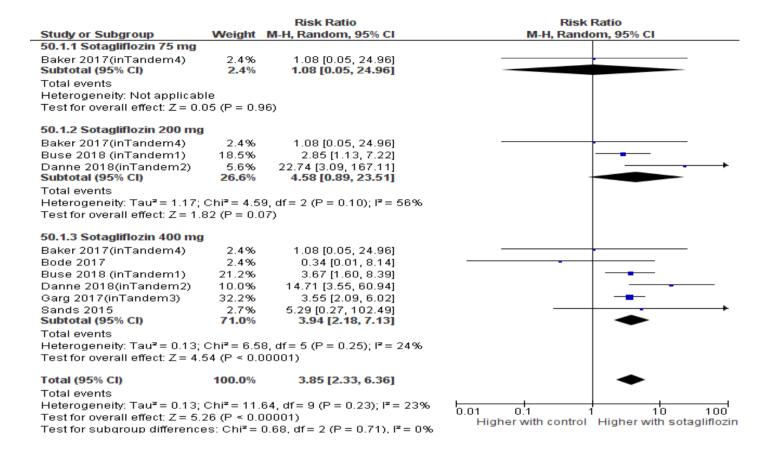


Panel B: outcome: volume depletion events



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)

