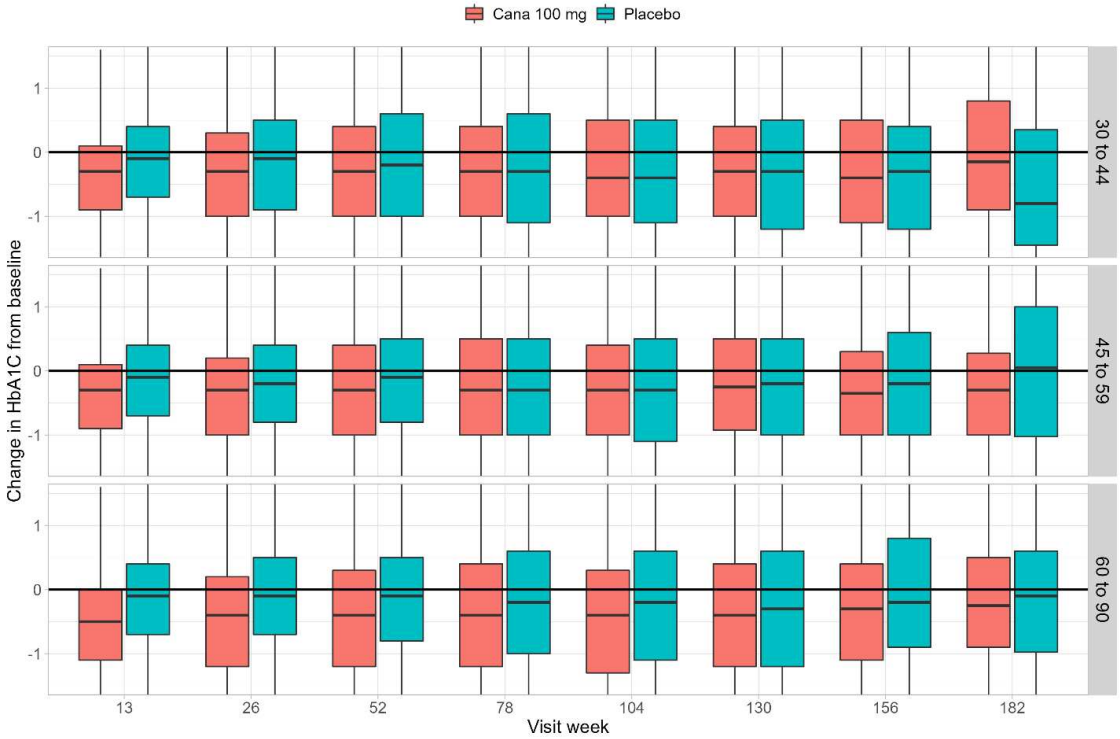
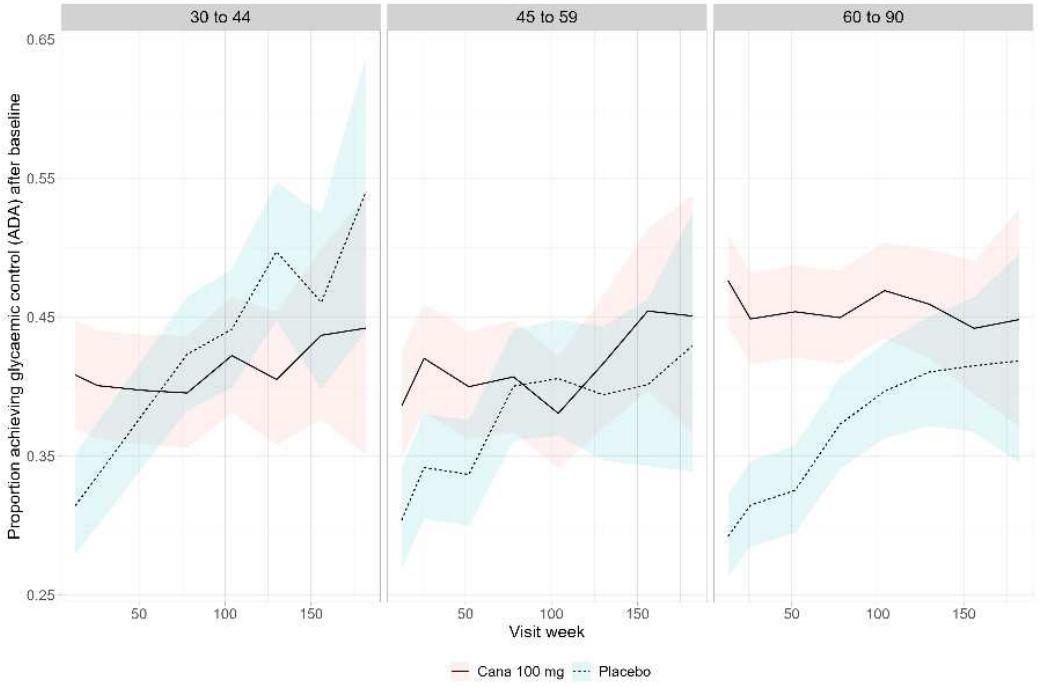
Supplementary Data



Supplementary Figure 1. Change in HbA1c for the canagliflozin and placebo groups according to eGFR and study group. Box and whisker plots show median, interquartile range, minimum and maximum values.



Supplementary Figure 2. Proportion of participants achieving a moderate binary reduction of >0.5% in HbA1c according to randomized therapy, baseline eGFR strata in mL/min/1.73m^2, and study week. 95% confidence bands are demarcated by grey shading. Treatment effects on HbA1C were assessed using generalized linear mixed models with a logistic link function an unstructured covariance structure and a Toeplitz covariance structure variables for treatment, time, baseline eGFR strata, interactions for randomized treatment and time, baseline HbA1C value, and time with eGFR status. Cana 100 mg=Canagliflozin 100 mg daily.

Supplementary Table 1. Treatment effects on HbA1c-lowering at 13 weeks according to background diabetes therapy at baseline were assessed using linear mixed models with an unstructured covariance structure with the main effects of treatment, time, baseline eGFR status, baseline HbA1c. P value is for the 2-way interaction between treatment and background diabetes therapy at baseline.

	Change in HbA1c at 13 Weeks Canagliflozin vs. Placebo (%, 95% CI)	**P Interaction**
Overall	**-0.32 (-0.38, -0.26)**	**--**
Sulfonylurea yes	-0.30 (-0.41, -0.19)	0.65
Sulfonylurea no	-0.33 (-0.40, -0.26)	
GLP-1/DPP-4 inhibitor yes	-0.35 (-0.47, -0.23)	0.58
GLP-1/DPP-4 inhibitor-4 no	-0.31 (-0.38, -0.24)	
Metformin yes	-0.33 (-0.40, -0.25)	0.75
Metformin no	-0.31 (-0.39, -0.22)	
Insulin yes	-0.32 (-0.40, -0.25)	0.86
Insulin no	-0.31 (-0.41, -0.22)	
Number of medications		
One	-0.31 (-0.40, -0.21)	0.93
Two	-0.33 (-0.42, -0.24)	
≥Three	-0.31 (-0.44, -0.18)	
GFR 60-90 mL/min/1.73m^2	**-0.38 (-0.47, -0.29)**	--
Sulfonylurea yes	-0.33 (-0.49, -0.16)	0.37
Sulfonylurea no	-0.42 (-0.52, -0.31)	
GLP-1/DPP-4 inhibitor yes	-0.45 (-0.62, -0.28)	0.49
GLP-1/DPP-4 inhibitor-4 no	-0.37 (-0.47, -0.26)	
Metformin yes	-0.39 (-0.49, -0.28)	0.82
Metformin no	-0.36 (-0.53, -0.19)	
Insulin yes	-0.44 (-0.56, -0.33)	0.17
Insulin no	-0.31 (-0.45, -0.17)	
Number of medications		
One	-0.36 (-0.52, -0.20)	0.91
Two	-0.38 (-0.52, -0.25)	
≥Three	-0.44 (-0.63, -0.25)	
GFR 45-59 mL/min/1.73m^2	**-0.28 (-0.39, -0.18)**	--
Sulfonylurea yes	-0.28 (-0.46, -0.10)	0.93
Sulfonylurea no	-0.29 (-0.42, -0.16)	
GLP-1/DPP-4 inhibitor yes	-0.21 (-0.42, 0.002)	0.57
GLP-1/DPP-4 inhibitor-4 no	-0.30 (-0.42, -0.18)	
Metformin yes	-0.27 (-0.41, -0.13)	0.76
Metformin no	-0.30 (-0.46, -0.14)	
Insulin yes	-0.27 (-0.41, -0.14)	0.88
Insulin no	-0.30 (-0.46, -0.13)	
Number of medications		

One	-0.33 (-0.50, -0.16)	0.65
Two	-0.28 (-0.46, -0.11)	
≥Three	-0.18 (-0.40, 0.03)	
GFR 30-44 mL/min/1.73m^2	**-0.26 (-0.37, -0.15)**	--
Sulfonylurea yes	-0.27 (-0.47, -0.07)	0.92
Sulfonylurea no	-0.26 (-0.39, -0.13)	
GLP-1/DPP-4 inhibitor yes	-0.35 (-0.58, -0.11)	0.44
GLP-1/DPP-4 inhibitor-4 no	-0.24 (-0.36, -0.11)	
Metformin yes	-0.22 (-0.40, -0.04)	0.62
Metformin no	-0.28 (-0.42, -0.14)	
Insulin yes	-0.24 (-0.36,-0.11)	0.45
Insulin no	-0.33 (-0.55, -0.11)	
Number of medications		
One	-0.25 (-0.41, -0.09)	0.92
Two	-0.29 (-0.45, -0.12)	
≥Three	-0.23 (-0.53, 0.08)	

	OR (95% Confidence Interval)						
		Study Week					
eGFR group (mL/min/1.73m)	**Overall**	**13**	**26**	**52**	**78**	**104**	**130**
>0.5% Reduction in Hemoglobin A1C							
All[1]	1.21 (1.10 - 1.34)	1.74 (1.54 - 1.98)	1.52 (1.34 - 1.72)	1.39 (1.22 - 1.58)	1.11 (0.98 - 1.27)	1.08 (0.94 - 1.22)	1.00 (0.86 - 1.17)
60 to 90[2]	1.47 (1.27 - 1.70)	2.20 (1.81 - 2.68)	1.77 (1.46 - 2.15)	1.72 (1.42 - 2.10)	1.37 (1.13 - 1.67)	1.34 (1.10 - 1.64)	1.22 (0.97 - 1.53)
45 to 59	1.12 (0.94 - 1.33)	1.44 (1.14 - 1.82)	1.40 (1.11 - 1.76)	1.31 (1.04 - 1.66)	1.03 (0.81 - 1.30)	0.90 (0.70 - 1.15)	1.10 (0.83 - 1.45)
30 to 44	0.99 (0.83 - 1.18)	1.51 (1.19 - 1.90)	1.32 (1.05 - 1.67)	1.08 (0.85 - 1.36)	0.89 (0.70 - 1.13)	0.93 (0.73 - 1.18)	0.69 (0.52 - 0.91)
>0.3% Reduction in Hemoglobin A1C							
All[1]	1.26 (1.15 - 1.39)	1.82 (1.61 - 2.06)	1.53 (1.36 - 1.73)	1.38 (1.22 - 1.57)	1.10 (0.97 - 1.25)	1.11 (0.98 - 1.27)	1.07 (0.92 - 1.25)
60 to 90[3]	1.51 (1.31 - 1.75)	2.29 (1.89 - 2.77)	1.89 (1.56 - 2.29)	1.60 (1.32 - 1.94)	1.38 (1.13 - 1.67)	1.34 (1.10 - 1.64)	1.28 (1.02 - 1.60)
45 to 59	1.17 (0.99 - 1.38)	1.56 (1.24 - 1.96)	1.41 (1.12 - 1.77)	1.41 (1.12 - 1.78)	1.01 (0.80 - 1.28)	0.91 (0.72 - 1.16)	1.11 (0.84 - 1.47)
30 to 44	1.04 (0.88 - 1.23)	1.54 (1.23 - 1.93)	1.23 (0.98 - 1.54)	1.10 (0.87 - 1.38)	0.87 (0.69 - 1.10)	1.04 (0.81 - 1.32)	0.80 (0.61 - 1.07)

Supplementary Table 2. Odds of achieving a moderate reduction in HbA1c (>0.5%) or minimal significant change (>0.3%) in HbA1c with canagliflozin or placebo by eGFR category and study week. [1]P<0.001 for overall treatment effect. [2]P=0.001 for interaction of treatment and eGFR strata on outcome of >0.5% reduction in eGFR. [4]P=0.002 for interaction of treatment and eGFR stratum on outcome of >0.3% reduction in HbA1c.

Supplementary Table 3. Risk of primary composite endpoint and secondary kidney composite with canagliflozin compared with placebo according to use of non-SGLT2 diabetes medications at baseline.

Outcome	Model	HR (95% CI)
Primary composite	**Unadjusted**	**0.67 (0.57-0.80)**
	Sulfonylurea yes	0.57 (0.40-0.81)
	Sulfonylurea no	0.71 (0.58-0.86)
	GLP-1/DPP-4 inhibitor yes	0.75 (0.49-1.14)
	GLP-1/DPP-4 inhibitor-4 no	0.66 (0.55-0.80)
	Metformin yes	0.64 (0.50-0.83)
	Metformin no	0.70 (0.56-0.88)
	Insulin yes	0.71 (0.59-0.87)
	Insulin no	0.57 (0.40-0.80)
	Number of medications	
	One	0.69 (0.54-0.89)
	Two	0.63 (0.49-0.82)
	≥Three	0.71 (0.43-1.18)
	Week 13 HBA1C	**0.71 (0.60-0.84)**
	Sulfonylurea yes	0.60 (0.42-0.86)
	Sulfonylurea no	0.73 (0.60-0.89)
	GLP-1/DPP-4 inhibitor yes	0.79 (0.52-1.22)
	GLP-1/DPP-4 inhibitor-4 no	0.69 (0.57-0.83)
	Metformin yes	0.68 (0.53-0.87)
	Metformin no	0.72 (0.57-0.91)
	Insulin yes	0.74 (0.61-0.90)
	Insulin no	0.60 (0.43-0.85)
	Number of medications	
	One	0.72 (0.56-0.92)
	Two	0.67 (0.52-0.87)
	≥Three	0.75 (0.46-1.24)
	Time-varying HBA1C	**0.68 (0.57-0.80)**
	Sulfonylurea yes	0.58 (0.40-0.82)
	Sulfonylurea no	0.70 (0.58-0.85)

	GLP-1/DPP-4 inhibitor yes	0.75 (0.49-1.15)
	GLP-1/DPP-4 inhibitor-4 no	0.66 (0.55-0.80)
	Metformin yes	0.65 (0.51-0.84)
	Metformin no	0.70 (0.55-0.87)
	Insulin yes	0.71 (0.59-0.87)
	Insulin no	0.57 (0.40-0.80)
	Number of medications	
	One	0.69 (0.54-0.89)
	Two	0.64 (0.49-0.83)
	≥Three	0.72 (0.44-1.18)
	Time-varying HBA1C Spline	**0.68 (0.58-0.81)**
	Sulfonylurea yes	0.58 (0.41-0.83)
	Sulfonylurea no	0.71 (0.58-0.86)
	GLP-1/DPP-4 inhibitor yes	0.76 (0.49-1.16)
	GLP-1/DPP-4 inhibitor-4 no	0.67 (0.56-0.81)
	Metformin yes	0.65 (0.51-0.84)
	Metformin no	0.71 (0.56-0.89)
	Insulin yes	0.72 (0.59-0.87)
	Insulin no	0.58 (0.41-0.82)
	Number of medications	
	one	0.70 (0.55-0.91)
	two	0.65 (0.50-0.84)
	≥ three	068 (0.41-1.13)
Kidney composite	**Unadjusted**	**0.66 (0.53-0.81)**
	Sulfonylurea yes	0.54 (0.34-0.85)
	Sulfonylurea no	0.69 (0.54-0.87)
	GLP-1/DPP-4 inhibitor yes	0.71 (0.43-1.17)
	GLP-1/DPP-4 inhibitor-4 no	0.64 (0.51-0.81)
	Metformin yes	0.56 (0.40-0.77)
	Metformin no	0.74 (0.56-0.97)
	Insulin yes	0.69 (0.54-0.88)
	Insulin no	0.56 (0.36-0.86)
	Number of medications	
	One	0.72 (0.53-0.97)

Two	0.62 (0.45-0.86)
≥Three	0.56 (0.31-1.03)
Week 13 HBA1C	**0.68 (0.55-0.84)**
Sulfonylurea yes	0.55 (0.35-0.87)
Sulfonylurea no	0.71 (0.56-0.90)
GLP-1/DPP-4 inhibitor yes	0.75 (0.45-1.25)
GLP-1/DPP-4 inhibitor-4 no	0.66 (0.52-0.83)
Metformin yes	0.58 (0.42-0.80)
Metformin no	0.75 (0.57-0.99)
Insulin yes	0.71 (0.56-0.90)
Insulin no	0.57 (0.37-0.88)
Number of medications	
One	0.74 (0.54-0.998)
Two	0.64 (0.46-0.89)
≥Three	0.59 (0.32-1.08)
Time-varying HBA1C	**0.65 (0.53-0.81)**
Sulfonylurea yes	0.54 (0.34-0.84)
Sulfonylurea no	0.69 (0.54-0.87)
GLP-1/DPP-4 inhibitor yes	0.71 (0.43-1.17)
GLP-1/DPP-4 inhibitor-4 no	0.64 (0.51-0.81)
Metformin yes	0.55 (0.40-0.77)
Metformin no	0.74 (0.56-0.97)
Insulin yes	0.69 (0.54-0.88)
Insulin no	0.54 (0.35-0.84)
Number of medications	
One	0.72 (0.53-0.97)
Two	0.61 (0.44-0.85)
≥Three	0.56 (0.31-1.03)
Time-varying HBA1C Spline	**0.66 (0.54-0.81)**
Sulfonylurea yes	0.55 (0.35-0.86)
Sulfonylurea no	0.69 (0.55-0.88)
GLP-1/DPP-4 inhibitor yes	0.72 (0.43-1.18)
GLP-1/DPP-4 inhibitor-4 no	0.65 (0.52-0.82)
Metformin yes	0.56 (0.40-0.77)

Metformin no	0.75 (0.57-0.99)
Insulin yes	0.69 (0.55-0.88)
Insulin no	0.56 (0.36-0.86)
Number of medications	
One	0.73 (0.54-0.99)
Two	0.62 (0.44-0.86)
≥Three	0.54 (0.30-1.002)

Outcome	**No Change in HbA1C** HR (95% CI)	**HbA1C** change HR (95% CI)	$P_{interaction}$
Moderate Change			
Primary composite	0.69 (0.56 - 0.85)	0.62 (0.47 - 0.82)	0.54
Kidney composite	0.68 (0.52 - 0.88)	0.58 (0.41 - 0.82)	0.47
CV death and HF hospitalization	0.68 (0.53 - 0.87)	0.61 (0.44 - 0.85)	0.63
Doubling of creatinine	0.62 (0.46 - 0.83)	0.52 (0.35 - 0.76)	0.47
ESKD	0.72 (0.53 - 0.98)	0.59 (0.40 - 0.88)	0.44
Cardiovascular Death	0.74 (0.53 - 1.04)	0.67 (0.43 - 1.03)	0.70
MACE	0.83 (0.66 - 1.05)	0.70 (0.51 - 0.95)	0.39
Minimally Significant Change			
Primary composite	0.67 (0.53 - 0.85)	0.66 (0.51 - 0.85)	0.94
Kidney composite	0.66 (0.49 - 0.88)	0.62 (0.45 - 0.85)	0.78
CV death and HF hospitalisation	0.63 (0.48 - 0.82)	0.69 (0.51 - 0.93)	0.64
Doubling of creatinine	0.61 (0.44 - 0.84)	0.55 (0.39 - 0.78)	0.68
ESKD	0.69 (0.49 - 0.96)	0.66 (0.46 - 0.94)	0.85
CV Death	0.72 (0.50 - 1.03)	0.73 (0.49 - 1.08)	0.95
MACE	0.82 (0.64 - 1.06)	0.73 (0.55 - 0.97)	0.55

Supplementary Table 4. Risk of primary and secondary outcomes according to achievement of moderate change (>0.5%) or minimally significant change (>0.3%) in HbA1c at week 13. Cox model for time to outcome and including treatment HbA1C change, and an interaction between treatment and glycemic change category. Coefficients (and 95% Cis) are the treatment effect per HbA1C change status HR-hazard ratio. CI-confidence interval. MACE-major adverse cardiovascular events.