SUPPLEMENTARY DATA

Supplementary Methods for Sensitivity Analyses of Variability Based on Three Measurements in the Standard Glucose Treatment Group

Study subjects

Sensitivity analyses were performed to elucidate the effect of visit-to-visit glycaemic variability in the standard glucose treatment group, in which three measurements of HbA1c were available. After excluding 486 patients who experienced outcome events during the first 24 months and 532 with missing values of HbA1c, 4,551 patients in the standard glucose treatment group were included.

Glycaemic variability assessment

Fasting samples for HbA1c were taken at baseline, and 6, and 12 months and every year thereafter for HbA1c in the standard glucose treatment group. Visit-to-visit variability (VVV) of HbA1c was evaluated using 3 measurements at 6, 12 and 24 months. Measurements during the first 2 months were excluded in order to eliminate the effect of rapid reduction in HbA1c. Standard deviation (SD) was used as an index of VVV. For comparison, VVV of HbA1c was evaluated in the intensive glucose treatment group using three measurements at 6, 12 and 24 months. Effects of visit-to-visit glycaemic variability in randomised treatment groups were compared by adding an interaction term in the statistical model.

Supplementary Table 1. Spearman's Correlation Coefficients Between Measures of Visit-to-visit Variability, Maximum and Mean HbA1c (upper right triangle) /fasting glucose (lower left triangle, italic) Based on 5 Measurements in the Intensive Glucose Treatment Group.

	Mean	SD	Maximum	CV	VIM	RSD	ARV
Mean		0.56	0.93	0.42	0.11	0.46	0.50
SD	*0.57*		0.79	0.98	0.87	0.86	0.90
Maximum	*0.91*	*0.83*		0.68	0.42	0.67	0.70
CV	*0.32*	*0.95*	*0.63*		0.94	0.85	0.89
VIM	*0.06*	*0.83*	*0.42*	*0.96*		0.75	0.78
RSD	*0.52*	*0.89*	*0.75*	*0.84*	*074*		0.95
ARV	*0.53*	*0.91*	*0.76*	*0.86*	*0.75*	*0.96*	

SD, standard deviation; CV, coefficient of variation; VIM, variation independent of mean; RSD, residual standard deviation; ARV, average real variability

Visit-to-visit variability, maximum and mean HbA1c or fasting glucose were estimated using 5 measurements at 3, 6, 12, 18 and 24 months after randomisation.

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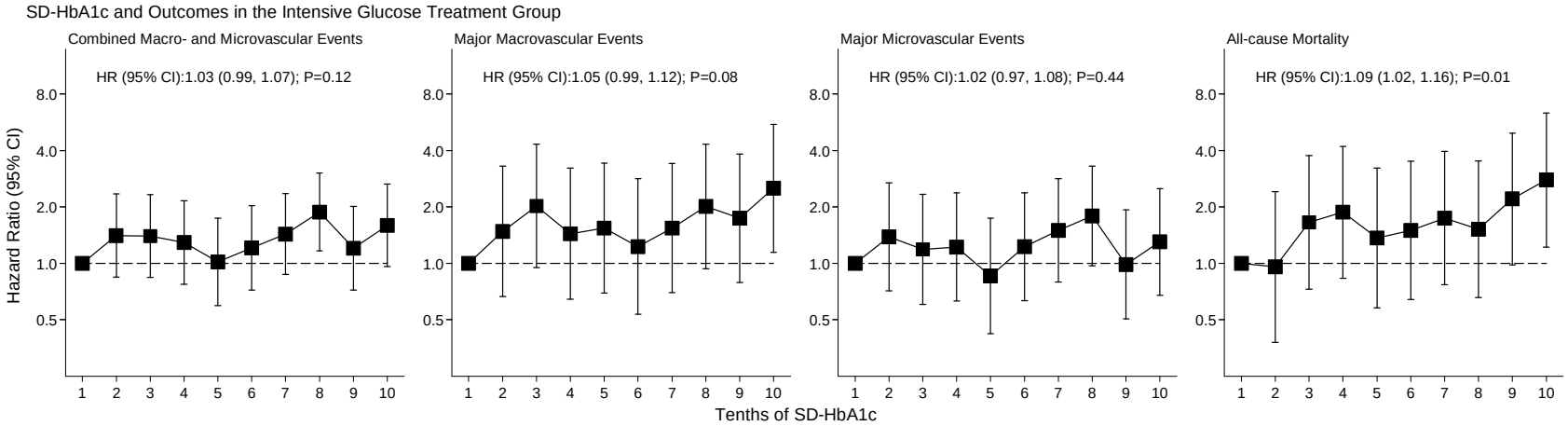
Supplementary Figure 1. The Effect of SD of HbA1c or Fasting Glucose Based on 5 Measurements during 6-30 Months on the Risks of Outcomes in the Intensive Glucose Treatment Group SD, standard deviation; SD-HbA1c, SD of HbA1c; SD-Glucose, SD of fasting glucose; HR, hazard ratio; CI, confidence interval HRs (95% CI) and P values were estimated for each 10-percentile point increase in SD of HbA1c or fasting glucose. Standard deviation was estimated using 5 readings at 6, 12, 18, 24 and 30 months after randomization. Patients were followed-up from 30 months to the end of the study.

Adjustment was made for age, sex, randomized blood pressure lowering, region, duration of diabetes, baseline smoking status, baseline alcohol intake, systolic blood pressure, total cholesterol, log-transformed triglycerides, body mass index, baseline use of oral glucose lowering agents, baseline use of insulin and mean HbA1c or fasting glucose during 6-30 months.
The range of SD for each tenth group is <0.19(2.1), 0.19(2.1) to 0.25(2.7), 0.26(2.8) to 0.32(3.5), 0.33(3.6) to 0.39(4.3), 0.40(4.4) to 0.46(5.0), 0.47(5.1) to 0.55(6.0), 0.56(6.1) to 0.65(7.1), 0.66(7.2) to 0.80(8.7), 0.81(8.9) to 1.08(11.8), ≥1.08(11.8), respectively for HbA1c, and <0.45, 0.46 to 0.63, 0.64 to 0.79, 0.80 to 0.96, 0.97 to 1.13, 1.14 to 1.34, 1.35 to 1.59, 1.60 to 1.98, 1.99 to 2.65, ≥2.66, respectively for fasting glucose.



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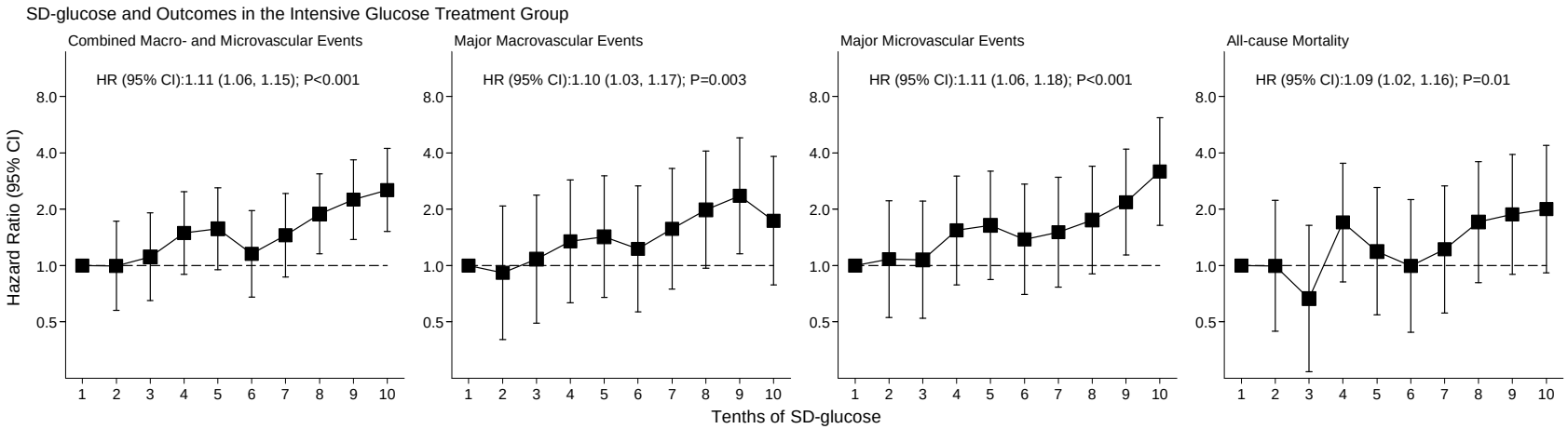

Supplementary Figure 2. The Effect of SD of HbA1c or Fasting Glucose on the Risks of Outcomes in the Models Including Imputation of Missing Values in the Intensive Glucose Treatment Group.
SD, standard deviation; SD-HbA1c, SD of HbA1c; SD-Glucose, SD of fasting glucose; HR, hazard ratio; CI, confidence interval
HRs (95% CI) and P values were estimated for each 10-percentile point increase in SD of HbA1c or fasting glucose.
SD and mean of HbA1c or fasting glucose was imputed among 720 patients using multiple imputation method.
Patients were followed-up from 24 months to the end of the study.
Adjustment was made for age, sex, randomized blood pressure lowering, region, duration of diabetes, baseline smoking status, baseline alcohol intake, systolic blood pressure, total cholesterol, log-transformed triglycerides, body mass index, baseline use of oral glucose lowering agents, baseline use of insulin and mean HbA1c or fasting glucose during 3-24 months.

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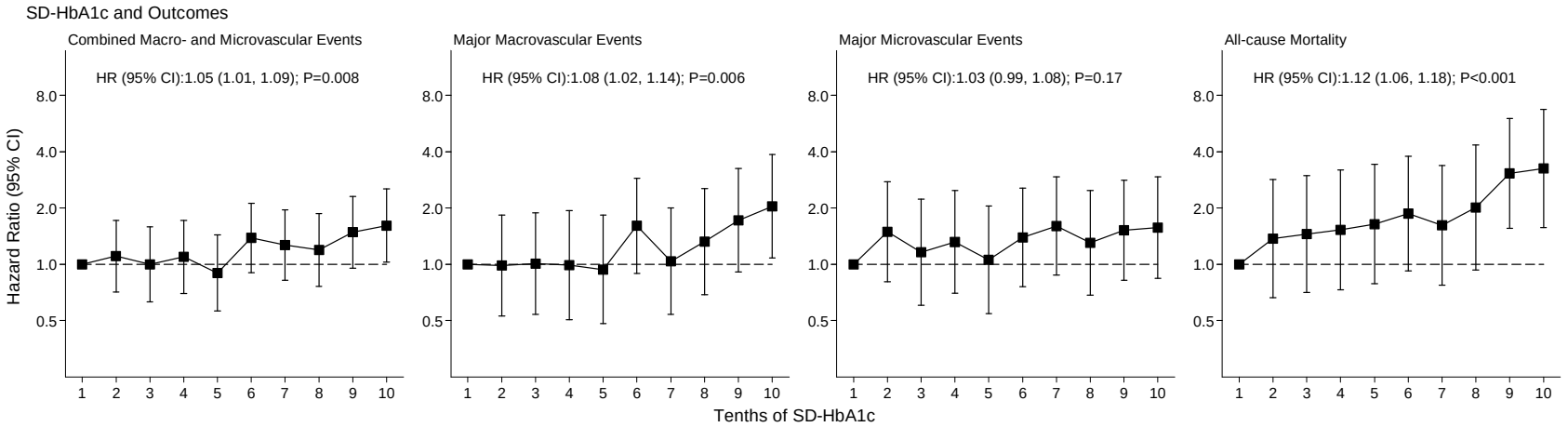
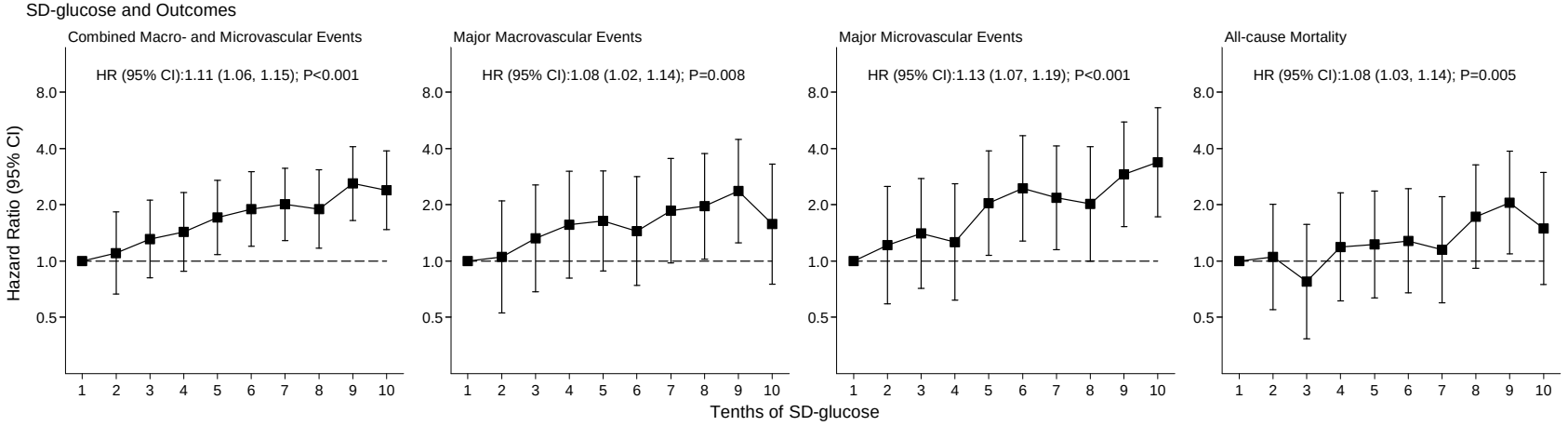




SUPPLEMENTARY DATA

Supplementary Table 2. The Effects of SD of HbA1c or Fasting Glucose on Outcomes by Subgroups Defined by Change in HbA1c from 3 to 24 Months within the Range of -0.3(-3.3) to 0.3% (3.3mmol/mol) or Larger.

	SD-HbA1c					SD-glucose			
	N of events/patients	HR (95% CI)	P for trend	P for heterogeneity		N of events/patients	HR (95% CI)	P for trend	P for heterogeneity
Combined macro- and microvascular events									
Change in HbA1c									
-0.3 to 0.3%	114 / 1246	1.06 (0.97-1.14)	0.19			114 / 1246	1.14 (1.05-1.23)	0.001	
<-0.3 or >0.3%	402 / 3153	1.04 (0.99-1.09)	0.08	0.90		402 / 3153	1.10 (1.06-1.15)	<0.001	0.29
Major macrovascular events									
Change in HbA1c									
-0.3 to 0.3%	58 / 1246	1.11 (1.00-1.22)	0.047			58 / 1246	1.10 (0.99-1.23)	0.08	
<-0.3 or >0.3%	176 / 3153	1.11 (1.05-1.18)	0.001	0.93		176 / 3153	1.07 (1.00-1.14)	0.05	0.35
Major microvascular events									
Change in HbA1c									
-0.3 to 0.3%	63 / 1246	1.02 (0.92-1.14)	0.66			63 / 1246	1.19 (1.07-1.32)	0.002	
<-0.3 or >0.3%	246 / 3153	1.04 (0.98-1.10)	0.25	0.79		246 / 3153	1.13 (1.07-1.20)	<0.001	0.54
All-cause mortality									
Change in HbA1c									
-0.3 to 0.3%	55 / 1246	1.11 (0.99-1.25)	0.07			55 / 1246	1.08 (0.96-1.21)	0.22	
<-0.3 or >0.3%	156 / 3153	1.12 (1.04-1.21)	0.003	0.92		156 / 3153	1.04 (0.97-1.11)	0.27	0.76

SD, standard deviation; SD-HbA1c, SD of HbA1c; SD-glucose, SD of fasting glucose; HR, hazard ratio; CI, confidence interval

HRs (95% CI) and P values were estimated for each 10-percentile point increase in SD of HbA1c or fasting glucose.

Patients were followed-up from 24 months to the end of the study.

Adjustment was made for age, sex, randomized blood pressure lowering, region, duration of diabetes, baseline smoking status, baseline alcohol intake, systolic blood pressure, total cholesterol, log-transformed triglycerides, body mass index, baseline use of oral glucose lowering agents, baseline use of insulin and mean HbA1c or fasting glucose during 3-24 months

SUPPLEMENTARY DATA

Supplementary Table 3. The Effect of Visit-to-visit Variability in HbA1c Based on 5 Measurements on the Risks of Outcomes in the Intensive Glucose Treatment Group.

	Model 1		Model 2		Model 3	
	HR (95%CI)*	P	HR (95%CI)*	P	HR (95%CI)*	P
Combined macro- and microvascular events						
Mean	1.43 (1.34, 1.54)	<0.0001	1.37 (1.27, 1.48)	<0.0001	-	-
SD	1.33 (1.25, 1.42)	<0.0001	1.28 (1.19, 1.37)	<0.0001	1.12 (1.02, 1.22)	0.02
Maximum	1.44 (1.34, 1.54)	<0.0001	1.38 (1.28, 1.48)	<0.0001	1.23 (1.02, 1.47)	0.03
CV	1.28 (1.19, 1.38)	<0.0001	1.23 (1.14, 1.32)	<0.0001	1.11 (1.02, 1.21)	0.02
VIM	1.14 (1.05, 1.24)	0.001	1.10 (1.02, 1.20)	0.02	1.11 (1.02, 1.20)	0.02
RSD	1.28 (1.20, 1.37)	<0.0001	1.24 (1.16, 1.33)	<0.0001	1.10 (1.01, 1.19)	0.02
ARV	1.31 (1.22, 1.40)	<0.0001	1.26 (1.17, 1.35)	<0.0001	1.11 (1.02, 1.21)	0.02
Major macrovascular events						
Mean	1.26 (1.12, 1.41)	0.0001	1.20 (1.07, 1.36)	0.003	-	-
SD	1.30 (1.17, 1.44)	<0.0001	1.25 (1.13, 1.39)	<0.0001	1.21 (1.06, 1.38)	0.005
Maximum	1.32 (1.18, 1.47)	<0.0001	1.26 (1.12, 1.42)	<0.0001	1.45 (1.12, 1.88)	0.006
CV	1.28 (1.15, 1.43)	<0.0001	1.23 (1.10, 1.38)	0.0002	1.18 (1.05, 1.34)	0.007
VIM	1.20 (1.07, 1.35)	0.002	1.17 (1.04, 1.32)	0.008	1.17 (1.04, 1.32)	0.008
RSD	1.29 (1.17, 1.42)	<0.0001	1.25 (1.13, 1.38)	<0.0001	1.20 (1.07, 1.35)	0.003
ARV	1.30 (1.18, 1.44)	<0.0001	1.26 (1.13, 1.39)	<0.0001	1.21 (1.07, 1.37)	0.002
Major microvascular events						
Mean	1.54 (1.41, 1.67)	<0.0001	1.48 (1.35, 1.62)	<0.0001	-	-
SD	1.36 (1.25, 1.48)	<0.0001	1.30 (1.19, 1.42)	<0.0001	1.08 (0.96, 1.21)	0.20
Maximum	1.52 (1.40, 1.65)	<0.0001	1.46 (1.33, 1.59)	<0.0001	1.13 (0.90, 1.43)	0.30
CV	1.29 (1.18, 1.42)	<0.0001	1.23 (1.12, 1.36)	<0.0001	1.07 (0.96, 1.20)	0.20
VIM	1.10 (0.99, 1.22)	0.07	1.06 (0.95, 1.19)	0.27	1.07 (0.95, 1.19)	0.26
RSD	1.30 (1.20, 1.41)	<0.0001	1.26 (1.15, 1.37)	<0.0001	1.06 (0.96, 1.18)	0.26
ARV	1.34 (1.23, 1.46)	<0.0001	1.29 (1.19, 1.41)	<0.0001	1.09 (0.98, 1.22)	0.10
All-cause mortality						
Mean	1.37 (1.21, 1.54)	<0.0001	1.29 (1.14, 1.47)	<0.0001	-	-
SD	1.41 (1.27, 1.56)	<0.0001	1.39 (1.25, 1.54)	<0.0001	1.34 (1.18, 1.53)	<0.0001
Maximum	1.45 (1.29, 1.62)	<0.0001	1.40 (1.24, 1.57)	<0.0001	1.74 (1.35, 2.25)	<0.0001
CV	1.39 (1.25, 1.55)	<0.0001	1.37 (1.23, 1.53)	<0.0001	1.31 (1.16, 1.48)	<0.0001
VIM	1.29 (1.15, 1.45)	<0.0001	1.29 (1.15, 1.44)	<0.0001	1.30 (1.15, 1.46)	<0.0001
RSD	1.41 (1.28, 1.54)	<0.0001	1.38 (1.25, 1.52)	<0.0001	1.33 (1.19, 1.49)	<0.0001
ARV	1.44 (1.31, 1.59)	<0.0001	1.42 (1.28, 1.57)	<0.0001	1.38 (1.22, 1.55)	<0.0001

SD, standard deviation; CV, coefficient of variation; VIM, variation independent of mean; RSD, residual standard deviation; ARV, average real variability; HR, hazard ratio; CI, confidence interval

Model 1 was adjusted for age, sex, and randomized blood pressure lowering.

Model 2 was adjusted for variables in model 1 plus region, duration of diabetes, baseline smoking status, baseline alcohol intake, systolic blood pressure, total cholesterol, log-transformed triglycerides, body mass index, baseline use of oral glucose lowering agents, and baseline use of insulin in addition to model 1.

Model 3 was adjusted for all variables in model 2 and mean HbA1c during the first 24 months.

*HRs represent per 1 SD increase.

SUPPLEMENTARY DATA

Supplementary Table 4. The Effect of Visit-to-visit Variability in Fasting Glucose Based on 5 Measurements on the Risks of Outcomes in the Intensive Glucose Treatment Group.

	Model 1		Model 2		Model 3	
	HR (95%CI)*	P	HR (95%CI)*	P	HR (95%CI)*	P
Combined macro- and microvascular events						
Mean	1.21 (1.12, 1.31)	<0.0001	1.16 (1.07, 1.25)	0.0005	-	-
SD	1.31 (1.22, 1.40)	<0.0001	1.26 (1.18, 1.36)	<0.0001	1.27 (1.16, 1.39)	<0.0001
Maximum	1.28 (1.19, 1.38)	<0.0001	1.23 (1.14, 1.34)	<0.0001	1.46 (1.24, 1.72)	<0.0001
CV	1.32 (1.23, 1.43)	<0.0001	1.28 (1.19, 1.39)	<0.0001	1.26 (1.16, 1.36)	<0.0001
VIM	1.29 (1.20, 1.39)	<0.0001	1.26 (1.17, 1.36)	<0.0001	1.27 (1.17, 1.37)	<0.0001
RSD	1.27 (1.18, 1.36)	<0.0001	1.23 (1.14, 1.32)	<0.0001	1.21 (1.11, 1.32)	<0.0001
ARV	1.27 (1.19, 1.36)	<0.0001	1.23 (1.15, 1.32)	<0.0001	1.21 (1.11, 1.32)	<0.0001
Major macrovascular events						
Mean	1.15 (1.02, 1.29)	0.03	1.12 (0.99, 1.27)	0.08	-	-
SD	1.17 (1.05, 1.31)	0.006	1.15 (1.02, 1.29)	0.02	1.12 (0.96, 1.30)	0.15
Maximum	1.19 (1.06, 1.34)	0.003	1.17 (1.04, 1.32)	0.01	1.30 (1.01, 1.68)	0.04
CV	1.19 (1.06, 1.33)	0.004	1.16 (1.03, 1.31)	0.02	1.14 (1.00, 1.29)	0.046
VIM	1.17 (1.04, 1.32)	0.008	1.15 (1.02, 1.30)	0.02	1.15 (1.02, 1.30)	0.02
RSD	1.17 (1.04, 1.30)	0.007	1.15 (1.02, 1.29)	0.02	1.12 (0.97, 1.29)	0.13
ARV	1.16 (1.04, 1.30)	0.009	1.14 (1.01, 1.28)	0.03	1.10 (0.96, 1.27)	0.17
Major microvascular events						
Mean	1.21 (1.10, 1.34)	0.0002	1.15 (1.03, 1.27)	0.011	-	-
SD	1.38 (1.27, 1.50)	<0.0001	1.33 (1.21, 1.46)	<0.0001	1.39 (1.24, 1.56)	<0.0001
Maximum	1.31 (1.19, 1.44)	<0.0001	1.25 (1.13, 1.38)	<0.0001	1.57 (1.28, 1.92)	<0.0001
CV	1.41 (1.29, 1.55)	<0.0001	1.37 (1.24, 1.50)	<0.0001	1.35 (1.22, 1.49)	<0.0001
VIM	1.38 (1.26, 1.52)	<0.0001	1.34 (1.22, 1.48)	<0.0001	1.35 (1.23, 1.49)	<0.0001
RSD	1.32 (1.21, 1.44)	<0.0001	1.27 (1.16, 1.39)	<0.0001	1.27 (1.14, 1.42)	<0.0001
ARV	1.33 (1.22, 1.45)	<0.0001	1.29 (1.17, 1.41)	<0.0001	1.30 (1.16, 1.45)	<0.0001
All-cause mortality						
Mean	1.20 (1.06, 1.35)	0.005	1.15 (1.01, 1.31)	0.03	-	-
SD	1.27 (1.13, 1.42)	<0.0001	1.23 (1.09, 1.39)	0.0007	1.22 (1.05, 1.42)	0.01
Maximum	1.28 (1.14, 1.44)	<0.0001	1.25 (1.10, 1.41)	0.0005	1.55 (1.20, 2.00)	0.0008
CV	1.25 (1.11, 1.41)	0.0002	1.21 (1.07, 1.37)	0.003	1.18 (1.04, 1.35)	0.01
VIM	1.20 (1.06, 1.35)	0.003	1.16 (1.03, 1.32)	0.02	1.17 (1.03, 1.32)	0.02
RSD	1.26 (1.13, 1.40)	<0.0001	1.22 (1.09, 1.37)	0.0009	1.20 (1.04, 1.38)	0.01
ARV	1.24 (1.11, 1.38)	0.0001	1.19 (1.06, 1.34)	0.004	1.15 (1.00, 1.33)	0.052

SD, standard deviation; CV, coefficient of variation; RSD, residual standard deviation; ARV, average real variability; VIM, variation independent of mean; HR, hazard ratio; CI, confidence interval

Model 1 was adjusted for age, sex, and randomized blood pressure lowering.

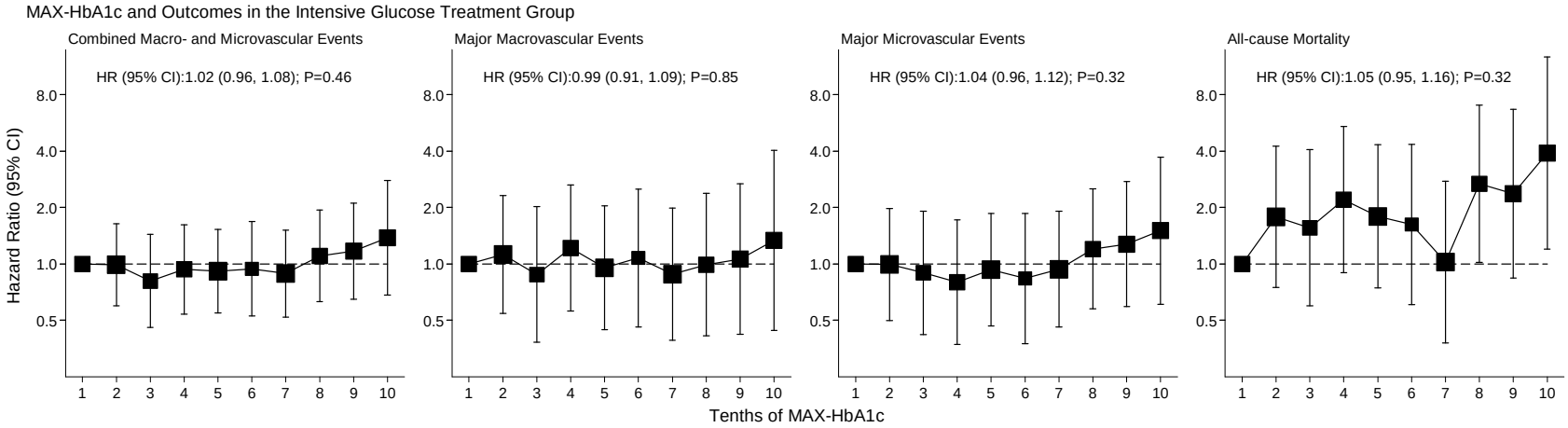
Model 2 was adjusted for variables in model 1 plus region, duration of diabetes, baseline smoking status, baseline alcohol intake, systolic blood pressure, total cholesterol, log-transformed triglycerides, body mass index, baseline use of oral glucose lowering agents, and baseline use of insulin in addition to model 1.

Model 3 was adjusted for all variables in model 2 and mean fasting glucose during the first 24 months.

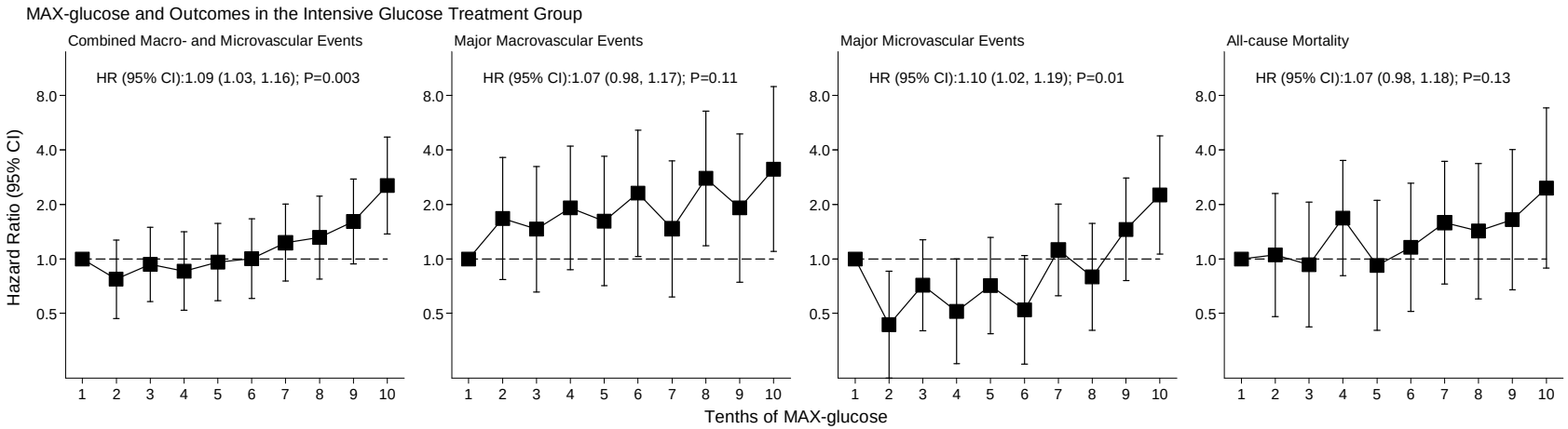
*HRs represent per 1 SD increase.

SUPPLEMENTARY DATA

Supplementary Figure 3. The Effect of Maximum of HbA1c/Fasting Glucose among 5 measurements during 6-30 months on the Risks of Outcomes in the Intensive Glucose Treatment Group.
MAX, maximum; MAX-HbA1c, maximum of HbA1c; MAX-glucose, maximum of fasting glucose; HR, hazard ratio; CI, confidence interval
HRs (95% CI) and P values were estimated for each 10-percentile point increase in maximum of HbA1c/fasting glucose.
Maximum value was the highest among 5 measurements at 6, 12, 18, 24 and 30 months after randomization. Patients were followed-up from 30 months to the end of the study.
Adjustment was made for age, sex, randomized blood pressure lowering, region, duration of diabetes, baseline smoking status, baseline alcohol intake, systolic blood pressure, total cholesterol, log-transformed triglycerides, body mass index, baseline use of oral glucose lowering agents, baseline use of insulin and mean HbA1c or fasting glucose during 6-30 months.
The range of maximum value for each tenth group is <6.3(45), 6.3(45) to 6.5(48), 6.6(49) to 6.8(51), 6.9(52) to 7.0(53), 7.1(54) to 7.2(55), 7.3(56) to 7.5(58), 7.6(60) to 7.8(62), 7.9(63) to 8.2(66), 8.3(67) to 9.1(76), ≥9.2(77), respectively for HbA1c, and <6.4, 6.5 to 7.1, 7.2 to 7.6, 7.7 to 8.1, 8.2 to 8.7, 8.8 to 9.2, 9.3 to 9.9, 10.0 to 10.9, 11.0 to 12.7, ≥12.8, respectively for fasting glucose.

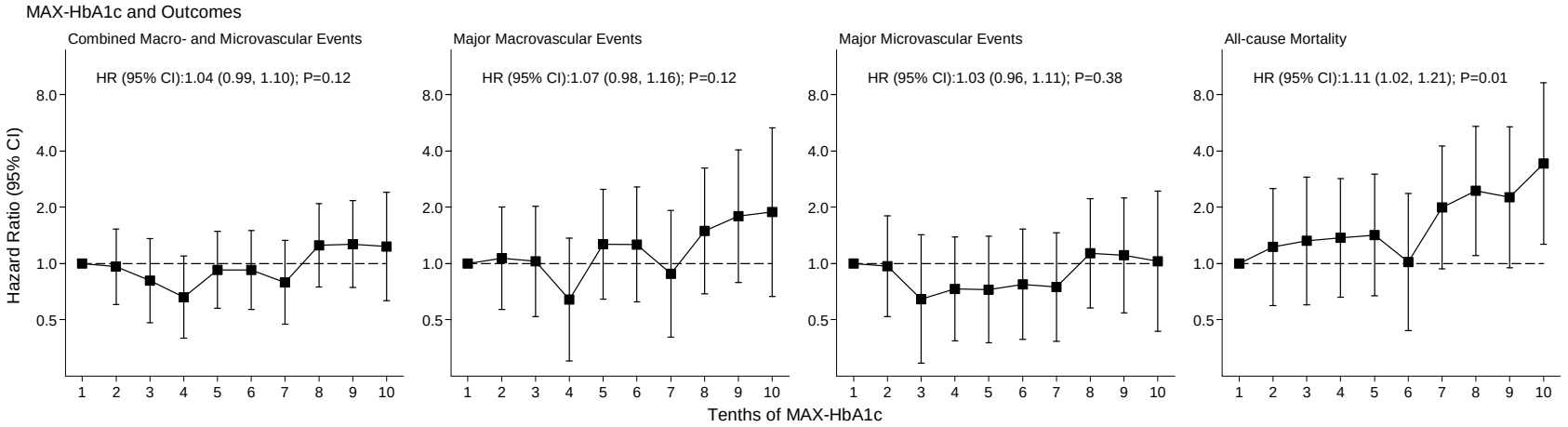


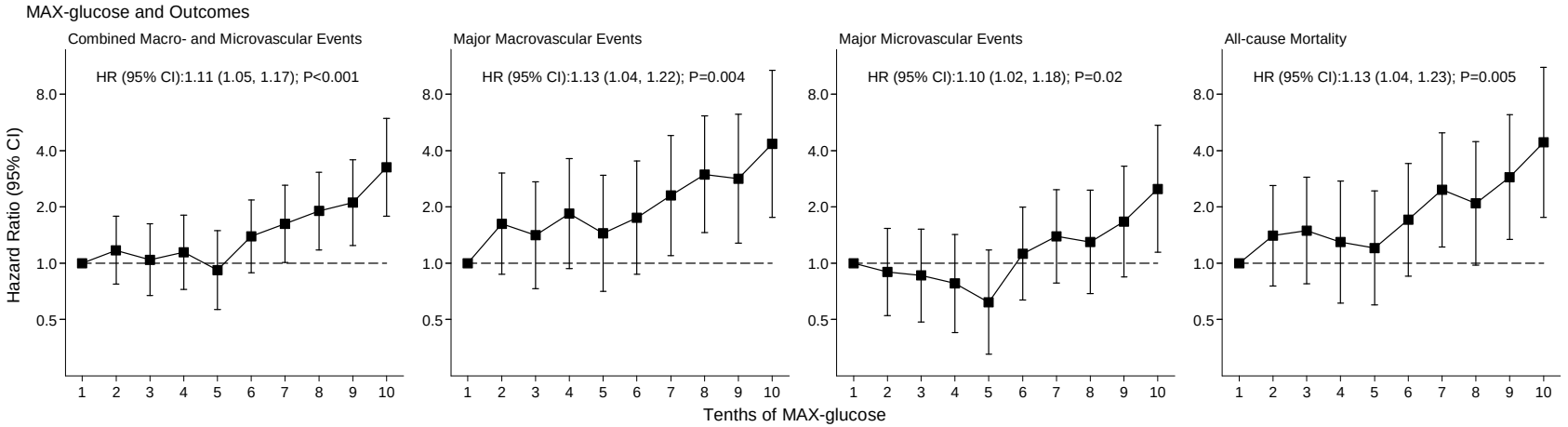
SUPPLEMENTARY DATA



Supplementary Figure 4. The Effect of Maximum of HbA1c or Fasting Glucose on the Risks of Outcomes in the Models Including Imputation of Missing Values in the Intensive Glucose Treatment Group.
MAX, maximum; MAX-HbA1c, maximum of HbA1c; MAX-glucose, maximum of fasting glucose; HR, hazard ratio; CI, confidence interval
HRs (95% CI) and P values were estimated for each 10-percentile point increase in maximum of HbA1c or fasting glucose.
Maximum and mean of HbA1c or fasting glucose was imputed among 720 patients using multiple imputation method.
Patients were followed-up from 24 months to the end of the study.
Adjustment age, sex, randomized blood pressure lowering, region, duration of diabetes, baseline smoking status, baseline alcohol intake, systolic blood pressure, total cholesterol, log-transformed triglycerides, body mass index, baseline use of oral glucose lowering agents, baseline use of insulin and mean HbA1c or fasting glucose during 3-24 months.

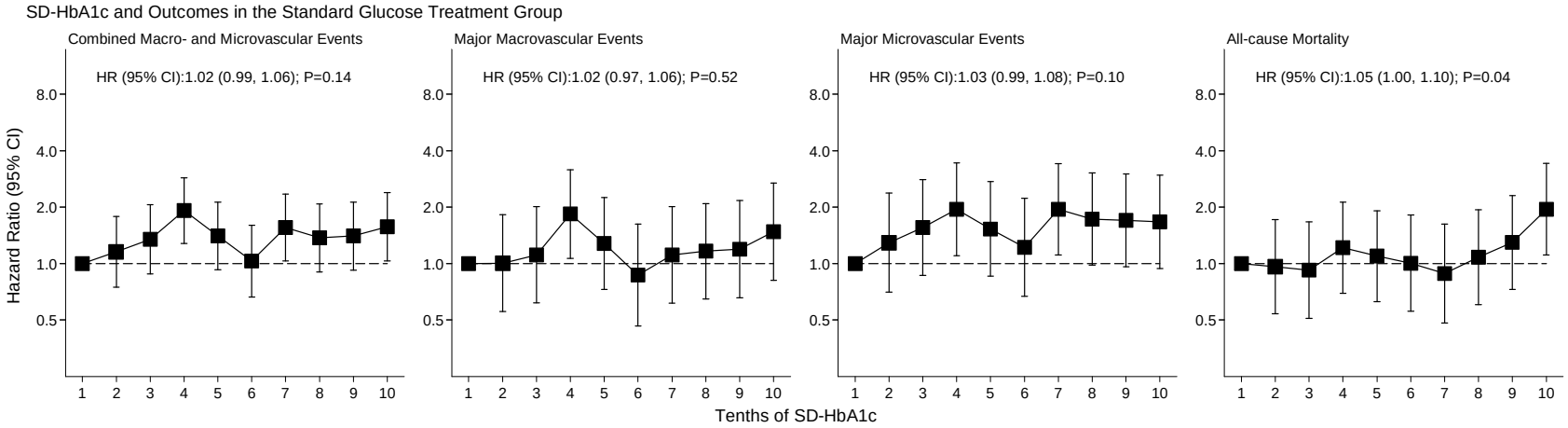
SUPPLEMENTARY DATA





SUPPLEMENTARY DATA

Supplementary Figure 5. The Effect of SD of HbA1c Based on 3 Measurements on the Risks of Outcomes in Standard Glucose Treatment Group (Upper) and in Intensive Glucose Treatment Group (Lower).
SD, standard deviation; SD-HbA1c, SD of HbA1c; HR, hazard ratio; CI, confidence interval
HRs (95% CI) and P values were estimated for each 10-percentile point increase in SD-HbA1c.
Standard deviation was estimated using 3 readings at 6, 12, and 24 months after randomization.
Adjustment age, sex, randomized blood pressure lowering, region, duration of diabetes, baseline smoking status, baseline alcohol intake, systolic blood pressure, total cholesterol, log-transformed triglycerides, body mass index, baseline use of oral glucose lowering agents, baseline use of insulin and mean HbA1c during the first 24 months.
The range of SD for each tenth group is <0.15(1.6), 0.15(1.6) to 0.22(2.4), 0.23(2.5) to 0.30(3.3), 0.31(3.4) to 0.37(4.0), 0.38(4.2) to 0.46(5.0), 0.47(5.1) to 0.57(6.2), 0.58(6.3) to 0.70(7.7), 0.71(7.8) to 0.89(9.7), 0.90(9.8) to 1.22(13.3), ≥1.23(13.4), respectively in standard glucose treatment group, and <0.15(1.6), 0.15(1.6) to 0.20(2.2), 0.21(2.3) to 0.25(2.7), 0.26(2.8) to 0.34(3.7), 0.35(3.8) to 0.43(4.7), 0.44(4.8) to 0.52(5.7), 0.53(5.8) to 0.65(7.1), 0.66(7.2) to 0.81(8.9), 0.82(9.0) to 1.11(12.1), ≥1.12(12.2), respectively in intensive glucose treatment group.
The average of SD-HbA1c was 0.56 (6.1) in the intensive glucose treatment group and 0.61(6.7) in the standard glucose treatment group.
For all outcomes, there were no heterogeneity between randomised groups (all P>0.05 for homogeneity).



SUPPLEMENTARY DATA