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Title Page:

Chronic kidney disease and hypoglycemia in people with type 2 diabetes

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Supplemental Table 1. Hypoglycemia incidence using alternative definitions of hypoglycemia

Consecutive measurements <70 mg/dL required to diagnosis hypoglycemia	CANDY Study			INITIATION Study	
	CKD (N = 81)	Controls (N = 24)	p-value*	End of study (N = 78)	p-value**
1 measurement					
N events	312	96		233	
N (%) participants with at least 1 event	59 (73)	17 (71)		52 (71)	
Duration of episode (minutes)	91 (73)	100 (82)	0.69	96 (61)	0.68
Nadir glucose (mg/dL)	59 (4)	55 (8)	0.07	60 (5)	0.35
Rate (episodes per 30 days)	7.3 (0.0-14.6)	5.9 (0.0-13.6)	0.97	10.5 (0.0-21.9)	0.04
2 measurements					
N events	292	93		229	
N (%) participants with at least 1 event	57 (70)	17 (71)		52 (71)	
Duration of episode (minutes)	98 (74)	104 (89)	0.81	96 (61)	0.87
Nadir glucose (mg/dL)	58 (4)	55 (8)	0.10	60 (5)	0.08
Rate (episodes per 30 days)	5.3 (0.0-13.0)	5.9 (0.0-14.6)	0.92	10.5 (0.0-18.5)	0.03
3 measurements					
N events	255	80		220	
N (%) participants with at least 1 event	56 (69)	16 (67)		51 (70)	
Duration of episode (minutes)	100 (56)	116 (86)	0.51	104 (76)	0.76
Nadir glucose (mg/dL)	58 (4)	55 (7)	0.16	59 (6)	0.13
Rate (episodes per 30 days)	5.3 (0.0-11.7)	5.9 (0.0-10.9)	0.97	10.1 (0.0-18.5)	0.01
6 measurements					
N events	201	63		176	
N (%) participants with at least 1 event	52 (64)	15 (62)		48 (66)	
Duration of episode (minutes)	126 (59)	130 (80)	0.86	128 (88)	0.91
Nadir glucose (mg/dL)	55 (6)	52 (6)	0.12	57 (6)	0.17
Rate (episodes per 30 days)	4.8 (0.0-10.1)	3.5 (0.0-8.9)	0.97	8.7 (0.0-14.3)	0.01
12 measurements					
N events	129	42		120	

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N (%) participants with at least 1 event	49 (60)	14 (58)		42 (58)	
Duration of episode (minutes)	154 (67)	153 (83)	0.96	153 (85)	0.95
Nadir glucose (mg/dL)	53 (7)	50 (7)	0.19	54 (6)	0.38
Rate (episodes per 30 days)	2.5 (0.0-6.0)	2.4 (0.0-6.8)	0.86	4.5 (0.0-13.1)	0.005

Glucose measurements were recorded by continuous glucose monitoring every 5 minutes. The number of consecutive measurements <70 mg/dL required to define a discrete episode of hypoglycemia was varied to assess impact of the definition on hypoglycemia incidence. The primary definition required at least 3 consecutive measurements, or approximately 15 minutes (and at least 10 minutes). Participants were required to have three consecutive measurements \geq 70 mg/dL prior to being at risk for an additional hypoglycemia episode, except when two measurements <70 mg/dL were required to diagnose hypoglycemia (in which case two measurements \geq 70 mg/dL were required prior to being at risk for an additional hypoglycemia episode).

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Supplemental Table 2. Sensitivity analysis assessing glycemia outcomes among CANDY and INITIATION participants who did not report use of acetaminophen or paracetamol.

	CANDY Study			INITIATION Study	
	CKD (N = 68)	Controls (N = 22)	p-value*	End of study (N = 71)	p-value**
Observation time					
Total time (days)	737.4	253.5		443	
Average time per participant (days)	10.8 (2.3)	11.5 (2.6)		6.2 (0.8)	
Mean blood glucose (mg/dL)	169.0 (38.0)	156.8 (31.5)		154.9 (30.3)	
Level 1 hypoglycemia (<70 mg/dL)					
N events	218	64		210	
N (%) participants with at least 1 event	47 (69)	14 (64)		49 (69)	
Duration of episode (minutes)	96 (51)	118 (92)	0.42	106 (77)	0.47
Nadir glucose (mg/dL)	57 (4)	55 (8)	0.38	59 (6)	0.11
Rate (episodes per 30 days)	5.6 (0.0-11.5)	3.7 (0.0-8.9)	0.59	9.9 (0.0-18.3)	0.02
Level 2 hypoglycemia (<54 mg/dL)					
N events	61	16		76	
N (%) participants with at least 1 event	31 (46)	9 (41)		26 (37)	
Time in range					
Time in hypoglycemia (minutes <54 mg/dL per day)	6 (12)	6 (12)	0.99	13 (29)	0.08
10PM – 10AM	5 (10)	5 (10)		11 (27)	
10AM – 10PM	1 (5)	1 (4)		2 (7)	
Time in hypoglycemia (minutes <70 mg/dL per day)	28 (38)	25 (36)	0.68	49 (72)	0.03
10PM – 10AM	23 (32)	19 (28)		39 (64)	
10AM – 10PM	5 (12)	6 (12)		10 (21)	
Time in range (minutes 70-180 mg/dL per day)	888 (320)	1018 (319)	0.10	975 (266)	0.05
Time above range (minutes >180 mg/dL per day)	524 (333)	397 (325)	0.12	415 (273)	0.03
Glycemic variability					
SD of glucose readings, mean (SD)	51.8 (13.9)	43.9 (12.3)	0.02	49.6 (14.2)	0.36

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IQR of glucose readings, mean (SD)	70.5 (21.4)	59.0 (19.5)	0.02	70.0 (23.3)	0.89
CV% of glucose readings, mean (SD)	30.8 (6.0)	28.0 (5.7)	0.06	32.1 (7.6)	0.26

Cell contents are N (%), mean (SD), or median (IQR). SD = standard deviation; CV = coefficient of variation. * p-value compares CANDY participants with CKD to CANDY controls. ** p-value compares CANDY participants with CKD to INITATION study controls.

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Supplemental Table 3. Sensitivity analysis assessing glycemia outcomes in CANDY, excluding the second observation period for 18 CANDY participants (15 with chronic kidney disease, 3 control) who were informed of their results from the first observation for safety.

	CANDY Study		
	CKD (N = 81)	Controls (N = 24)	p-value*
Observation time			
Total time (days)	807.4	257.1	
Average time per participant (days)	10.0 (3.0)	10.7 (3.0)	
Mean blood glucose (mg/dL)	169.8 (40.3)	158.0 (30.5)	
Level 1 hypoglycemia (<70 mg/dL)			
N events	224	71	
N (%) participants with at least 1 event	53 (65)	16 (67)	
Duration of episode (minutes)	102 (62)	114 (88)	0.62
Nadir glucose (mg/dL)	58 (4)	55 (8)	0.21
Rate (episodes per 30 days)	5.2 (0.0-12.0)	4.8 (0.0-11.2)	0.99
Level 2 hypoglycemia (<54 mg/dL)			
N events	58	21	
N (%) participants with at least 1 event	33 (41)	10 (42)	
Time in range			
Time in hypoglycemia (minutes <70 mg/dL per day)	29 (39)	27 (36)	0.84
10PM – 10AM	24 (35)	19 (27)	
10AM – 10PM	5 (12)	8 (15)	
Time in range (minutes 70-180 mg/dL per day)	883 (323)	1003 (313)	0.11
Time above range (minutes >180 mg/dL per day)	528 (337)	410 (318)	0.12
Glycemic variability			
SD of glucose readings, mean (SD)	51.9 (13.8)	46.0 (15.3)	0.10
IQR of glucose readings, mean (SD)	71.7 (23.6)	63.9 (25.3)	0.18
CV% of glucose readings, mean (SD)	30.8 (6.2)	29.3 (6.9)	0.35

Cell contents are N (%), mean (SD), or median (IQR). SD = standard deviation; CV = coefficient of variation. * p-value compares CANDY participants with CKD to CANDY controls.

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Supplemental Table 4. Associations of clinical characteristics with blood glucose coefficient of variation among 81 CANDY study participants with type 2 diabetes and chronic kidney disease

	N	Mean (SD), minutes/day	Difference (95%CI), minutes/day	Adjusted difference (95%CI), minutes/day
Age (years)				
<60	12	33.0 (7.1)	0 (Ref.)	0 (Ref.)
60-69	28	29.9 (5.2)	-3.1 (-7.4, 1.2)	-3.4 (-7.4, 0.7)
70-79	34	31.0 (6.2)	-2.0 (-6.3, 2.4)	-1.7 (-5.9, 2.6)
≥80	7	28.7 (4.4)	-4.3 (-9.2, 0.6)	-5.0 (-9.9, -0.1)
eGFR (mL/min/1.73m ²)				
45-59	28	29.9 (6.7)	0 (Ref.)	0 (Ref.)
30-44	30	32.3 (5.1)	2.4 (-0.6, 5.4)	2.4 (-0.3, 5.2)
<30	23	29.7 (5.7)	-0.1 (-3.4, 3.2)	0.1 (-3.2, 3.4)
HbA1c category				
<7.0%	25	29.9 (6.8)	0 (Ref.)	0 (Ref.)
7.0-7.9%	27	31.6 (5.8)	1.7 (-1.6, 5.1)	1.2 (-2.1, 4.6)
≥8.0%	28	30.7 (5.3)	0.8 (-2.4, 4.1)	0.2 (-3.5, 3.9)
HbA1c, per 1% increment			0.2 (-0.7, 1.1)	0.2 (-0.7, 1.2)
GMI category				
<7.0%	28	29.5 (5.1)	0 (Ref.)	0 (Ref.)
7.0-7.9%	39	32.0 (6.7)	2.5 (-0.3, 5.3)	3.1 (0.3, 5.9)
≥8.0%	14	29.6 (4.2)	0.1 (-2.8, 2.9)	0.5 (-2.2, 3.3)
GMI, per 1% increment			-0.5 (-1.7, 0.7)	-0.3 (-1.6, 1.0)
Insulin dose (units/kg/day)				
No insulin	9	25.3 (3.7)	0 (Ref.)	0 (Ref.)
0.01 – 0.5	38	31.4 (5.3)	6.1 (3.2, 8.9)	5.2 (1.8, 8.6)
0.51 – 1.0	23	30.8 (6.9)	5.5 (1.9, 9.1)	4.8 (0.9, 8.8)
> 1.0	11	32.7 (5.2)	7.4 (3.7, 11.1)	6.6 (2.5, 10.8)
Insulin dosage, per SD (0.44) increment			1.5 (0.4, 2.7)	1.4 (0.2, 2.7)
Duration of diabetes				
< 10 years	8	28.4 (5.6)	0 (Ref.)	0 (Ref.)
10-19 years	30	30.5 (5.3)	2.1 (-2.0, 6.2)	1.0 (-3.3, 5.3)
≥ 20 years	40	31.7 (6.4)	3.3 (-0.8, 7.4)	3.9 (-0.4, 8.2)
BMI				
<30	21	30.4 (3.8)	0 (Ref.)	0 (Ref.)
30-34	33	30.9 (7.1)	0.6 (-2.3, 3.5)	-0.2 (-2.9, 2.5)
35-39	18	31.3 (4.8)	1.0 (-1.7, 3.7)	0.1 (-2.9, 3.2)
≥40	9	29.6 (7.6)	-0.7 (-5.6, 4.2)	-0.8 (-6, 4.4)
Medications				

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Insulin				
None	9	25.3 (3.7)	0 (Ref.)	0 (Ref.)
Any	72	31.4 (5.8)	7.1 (3.4, 10.7)	5.9 (1.9, 9.9)
Insulin secretagogues				
No	63	31.1 (5.9)	0 (Ref.)	0 (Ref.)
Yes	18	29.3 (6.0)	1.3 (-1.9, 4.5)	0.8 (-2.4, 4.0)
Other glucose lowering agents				
No	52	30.7 (6.1)	0 (Ref.)	0 (Ref.)
Yes	29	30.7 (5.7)	-0.2 (-2.8, 2.3)	-0.5 (-3.2, 2.1)

Adjusted differences are adjusted for age, sex, and race.

Supplemental Figure 1. CONSORT flow diagram of CANDY study

