

DIFFERENTIAL LONGITUDINAL EFFECT OF GLUCOSE-LOWERING MEDICATIONS ON GLUCAGON AND C-PEPTIDE RESPONSES IN THE GLYCEMIA REDUCTION APPROACHES IN DIABETES: A COMPARATIVE EFFECTIVENESS (GRADE) STUDY

Steven E. Kahn, et al.

Supplemental Materials

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Table S1: Baseline characteristics of participants in the substudy by treatment group

	Glargine (n=184)	Glimepiride (n=195)	Liraglutide (n=163)	Sitagliptin (n=182)	p-value
Age (years)	57.3±9.3	57.6±10.2	57.7±9.7	58.0±10.6	0.932
Female	65 (35.3%)	79 (40.5%)	50 (30.7%)	55 (30.2%)	0.127
Race					0.842
American Indian/ Alaska Native	2 (1.1%)	6 (3.1%)	4 (2.5%)	8 (4.4%)	
Asia/Hawaiian/ Pacific Islander	4 (2.2%)	7 (3.6%)	6 (3.7%)	7 (3.8%)	
Black or African American	37 (20.1%)	36 (18.5%)	31 (19.0%)	27 (14.8%)	
White	124 (67.4%)	129 (66.2%)	111 (68.1%)	123 (67.6%)	
Other/Unknown	17 (9.2%)	17 (8.7%)	11 (6.7%)	17 (9.3%)	
Ethnicity					0.590
Non-Hispanic	152 (83.5%)	154 (80.2%)	137 (85.1%)	147 (80.8%)	
Hispanic	30 (16.5%)	38 (19.8%)	24 (14.9%)	35 (19.2%)	
Duration of Diabetes (years)	4.3±2.7	4.5±2.9	4.0±2.8	4.0±2.8	0.217
BMI (kg/m ²)	34.4±6.3	33.7±6.4	34.2±6.5	34.3±6.5	0.732
HbA1c (%)	7.4 [7.1, 7.8]	7.3 [7.1, 7.8]	7.4 [7.1, 7.9]	7.3 [7.0, 7.7]	0.447
Glucose (mmol/L)					
Fasting	8.1 [7.2, 9.1]	8.5 [7.4, 9.6]	8.3 [7.2, 9.4]	8.0 [7.3, 9.0]	0.148
30-minute	12.8 [11.2, 14.4]	13.2 [11.4, 14.7]	13.2 [11.4, 14.6]	13.0 [11.5, 14.5]	0.414
120-minute	15.7 [13.8, 17.1]	16.4 [14.6, 18.4]	15.7 [13.4, 17.5]	15.9 [14.0, 17.7]	0.035
Fasting glucagon (pmol/L)	10.0 [5.7, 13.4]	8.3 [5.6, 12.0]	9.4 [5.8, 13.4]	9.4 [6.5, 13.5]	0.287
Glucagon index (GGI; pmol/mmol)	0.01 [-0.43, 0.43]	-0.04 [-0.44, 0.26]	-0.12 [-0.36, 0.36]	-0.03 [-0.37, 0.32]	0.832
Fasting insulin (pmol/L)	114.0 [76.0, 172.5]	107.0 [68.5, 165.5]	106.0 [67.0, 169.0]	109.5 [75.3, 154.0]	0.553
Fasting C-peptide (nmol/L)	1.3 [1.0, 1.6]	1.3 [0.9, 1.7]	1.3 [0.9, 1.6]	1.3 [1.0, 1.7]	0.901
C-peptide index (CPI; nmol/mmol)	0.13 [0.09, 0.20]	0.11 [0.08, 0.17]	0.11 [0.07, 0.15]	0.12 [0.08, 0.19]	0.015
HOMA-S (%)	30.6 [24.3, 39.8]	31.1 [23.6, 40.3]	30.9 [24.4, 40.6]	29.8 [22.9, 40.1]	0.935

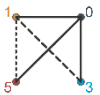
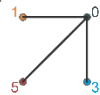
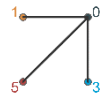
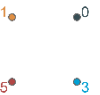
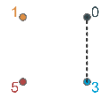
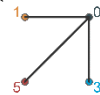
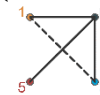
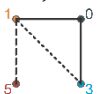
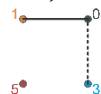
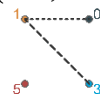
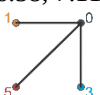
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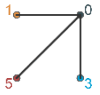
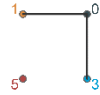
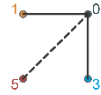
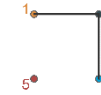
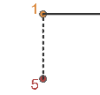
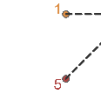
Table S2: Baseline characteristics of participants in the substudy compared to the remainder of the GRADE cohort

	Substudy Participants (n=724)	Other GRADE Participants (n=4323)	p-value
Age (years)	57.7±10.0	57.1±10.0	0.148
Female	249 (34.4%)	1588 (36.7%)	0.242
Race			0.409
American Indian/Alaska Native	20 (2.8%)	117 (2.7%)	
Asia/Hawaiian/Pacific Islander	24 (3.3%)	186 (4.3%)	
Black or African American	131 (18.1%)	869 (20.1%)	
White	487 (67.3%)	2827 (65.4%)	
Other/Unknown	62 (8.6%)	324 (7.5%)	
Ethnicity			0.564
Non-Hispanic	590 (82.3%)	3487 (81.3%)	
Hispanic	127 (17.7%)	802 (18.7%)	
Duration of Diabetes (years)	4.2±2.8	4.2±2.7	0.928
BMI (kg/m ²)	34.2±6.4	34.3±6.9	0.568
HbA1c (%)	7.4 [7.1, 7.8]	7.4 [7.1, 7.9]	0.049
Glucose (mmol/L)			
Fasting	8.2 [7.3, 9.3]	8.2 [7.2, 9.3]	0.935
30-minute	13.0 [11.4, 14.6]	12.9 [11.2, 14.5]	0.406
120-minute glucose	15.9 [13.9, 17.7]	15.9 [14.0, 17.9]	0.633
Fasting glucagon (pmol/L)	9.2 [5.9, 13.0]	NA	NA
Glucagon index (GGI; pmol/mmol)	-0.03 [-0.41, 0.34]	NA	NA
Fasting insulin (pmol/L)	130.0 [86.1, 194.0]	130.4 [84.9, 199.7]	0.922
Fasting C-peptide (nmol/L)	1.3 [1.0, 1.6]	1.3 [1.0, 1.6]	0.789
C-peptide index (CPI; nmol/mmol)	0.12 [0.08, 0.18]	0.12 [0.08, 0.17]	0.735
HOMA-%S	30.6 [23.4, 40.3]	31.0 [23.6, 41.1]	0.814

Data are summarized as mean±SD with p-value from an ANOVA F test or median [25th, 75th percentiles] with p-value from a Wilcoxon Rank Sum Test for continuous variables, and as n (%) with p-value from a Chi-square test for categorical variables. Glucose, insulin, C-peptide and glucagon values were winsorized, i.e., when values of variables were extreme (>6SD from the mean), they were reassigned a value 6SD from the mean.

Table S3: Metabolic parameters determined longitudinally over five years by treatment group

	HbA1c (%)	Fasting glucose (mmol/L)	2-hour glucose (mmol/L)	Fasting glucagon (pmol/L)	30 minute glucagon (pmol/L)	Glucagon index (GGI) (pmol/mmol)	Fasting C-peptide (nmol/L)	30 minute C-peptide (nmol/L)	C-peptide index (CPI) (nmol/mmol)
Glargine									
Baseline	7.49	8.28	15.73	10.03	9.72	-0.116	1.35	2.03	0.15
(n=183)	(7.38, 7.59)	(8.07, 8.49)	(15.33, 16.13)	(9.66, 10.41)	(9.31, 10.14)	(-0.223, -0.008)	(1.32, 1.39)	(1.97, 2.09)	(0.14, 0.17)
Year 1	6.71	6.57	13.55	9.37	8.57	-0.258	0.97	1.73	0.18
(n=176)	(6.55, 6.87)	(6.23, 6.91)	(12.91, 14.20)	(8.62, 10.12)	(7.69, 9.46)	(-0.435, -0.081)	(0.91, 1.04)	(1.63, 1.84)	(0.15, 0.20)
Year 3	6.89	6.51	13.72	10.00	8.49	-0.333	0.90	1.61	0.14
(n=140)	(6.73, 7.04)	(6.12, 6.91)	(13.05, 14.39)	(8.97, 11.02)	(7.52, 9.47)	(-0.508, -0.159)	(0.82, 0.99)	(1.49, 1.73)	(0.12, 0.16)
Year 5	6.91	6.62	13.89	9.57	8.37	-0.283	0.87	1.65	0.16
(n=63)	(6.70, 7.12)	(6.11, 7.13)	(12.91, 14.87)	(7.53, 11.61)	(6.42, 10.33)	(-0.543, -0.024)	(0.74, 1.00)	(1.46, 1.84)	(0.13, 0.20)
Pairwise p-value plot¹									
Glimepiride									
Baseline	7.46	8.40	15.91	9.98	9.68	-0.121	1.35	2.01	0.15
(n=192)	(7.37, 7.56)	(8.21, 8.59)	(15.55, 16.28)	(9.61, 10.35)	(9.27, 10.09)	(-0.229, -0.012)	(1.32, 1.39)	(1.96, 2.07)	(0.13, 0.16)
Year 1	6.79	7.24	14.59	10.62	9.87(9.08,	-0.145	1.44	2.15	0.16
(n=182)	(6.63, 6.94)	(6.89, 7.60)	(13.98, 15.20)	(9.79, 11.45)	10.66)	(-0.328, 0.040)	(1.37, 1.51)	(2.04, 2.26)	(0.14, 0.19)
Year 3	6.97	7.34	15.21	9.78	9.48(8.63,	-0.045	1.35	2.08	0.15
(n=133)	(6.78, 7.15)	(6.95, 7.73)	(14.51, 15.91)	(8.84, 10.73)	10.33)	(-0.224, 0.135)	(1.28, 1.42)	(1.95, 2.20)	(0.12, 0.18)
Year 5	7.21	7.36	15.31	10.12	9.93(8.49,	-0.101	1.34	1.93	0.12
(n=47)	(6.83, 7.59)	(6.62, 8.11)	(14.08, 16.54)	(8.61, 11.62)	11.37)	(-0.379, 0.177)	(1.20, 1.48)	(1.74, 2.12)	(0.08, 0.15)
Pairwise p-value plot¹									
Liraglutide									
Baseline	7.49	8.29	15.76	9.97	9.73(9.29,	-0.076	1.35	2.00	0.14
(n=163)	(7.39, 7.59)	(8.07, 8.50)	(15.35, 16.17)	(9.56, 10.39)	10.17)	(-0.180, 0.028)	(1.32, 1.39)	(1.95, 2.06)	(0.13, 0.16)
Year 1	6.73	6.92	12.52	9.34	8.56(7.59,	-0.204	1.37	2.13	0.20
(n=145)	(6.53, 6.92)	(6.55, 7.28)	(11.75, 13.28)	(8.35, 10.32)	9.53)	(-0.463, 0.055)	(1.30, 1.45)	(2.01, 2.25)	(0.17, 0.23)
Year 3	6.89	7.27	13.05	9.33	8.34(7.32,	-0.229	1.33	2.05	0.17
(n=105)	(6.68, 7.11)	(6.77, 7.78)	(12.04, 14.07)	(8.30, 10.35)	9.36)	(-45.27, -0.47)	(1.24, 1.42)	(1.89, 2.21)	(0.14, 0.21)
Year 5	6.85	7.18	12.97	8.21	8.15	0.170	1.40	2.09	0.19
(n=39)	(6.58, 7.11)	(6.73, 7.64)	(11.47, 14.47)	(5.68, 10.75)	(5.29, 11.00)	(-0.296, 0.635)	(1.20, 1.59)	(1.82, 2.35)	(0.13, 0.24)
Pairwise p-value plot¹									

	HbA1c (%)	Fasting glucose (mmol/L)	2-hour glucose (mmol/L)	Fasting glucagon (pmol/L)	30 minute glucagon (pmol/L)	Glucagon index (GGI) (pmol/mmol)	Fasting C-peptide (nmol/L)	30 minute C-peptide (nmol/L)	C-peptide index (CPI) (nmol/mmol)
Sitagliptin									
Baseline	7.46	8.25	15.79	10.03	9.75	-0.071	1.35	2.03	0.15
(n=181)	(7.37, 7.55)	(8.07, 8.43)	(15.43, 16.14)	(9.66, 10.39)	(9.37, 10.12)	(-0.166, 0.025)	(1.32, 1.38)	(1.97, 2.08)	(0.14, 0.16)
Year 1	6.89	7.62	13.79	13.36	11.84	-0.379	1.30	2.13	0.20
(n=173)	(6.71, 7.07)	(7.31, 7.94)	(13.11, 14.48)	(12.35, 14.38)	(10.82, 12.87)	(-0.559, -0.198)	(1.23, 1.36)	(2.03, 2.24)	(0.17, 0.22)
Year 3	6.91	7.55	14.10	12.41	10.86	-0.390	1.25	2.05	0.19
(n=119)	(6.67, 7.15)	(7.08, 8.02)	(13.08, 15.11)	(11.18, 13.63)	(9.68, 12.05)	(-0.600, -0.181)	(1.17, 1.33)	(1.91, 2.20)	(0.16, 0.22)
Year 5	7.01	7.72	14.27	11.87	9.57	-0.779	1.26	1.87	0.19
(n=56)	(6.74, 7.28)	(7.13, 8.32)	(13.10, 15.44)	(10.00, 13.74)	(7.44, 11.70)	(-1.300, -0.258)	(1.11, 1.40)	(1.71, 2.03)	(0.12, 0.25)
Pairwise p-value plot¹									

Data for each parameter are mean [95% CI] from a GEE model with adjustment for age, sex, race, baseline BMI, and baseline HOMA2-%S. Each set of six pairwise comparisons of visit means within treatment groups was adjusted using the Holm step-down correction.¹ Level of significance for pairwise visit comparison is indicated by line type (no line: $p > 0.05$; short-dash: $p \leq 0.05$; long-dash: $p \leq 0.01$; solid: $p \leq 0.001$)

Table S4: Association of α - and β -cell function with the primary metabolic outcome by treatment group

A. Models with α -cell function alone

	Fasting glucagon (HR, CI)		Glucagon index (GGI) (HR, CI)	
	At Baseline	At Follow-up	At Baseline	At Follow-up
Glargine	1.11 (0.84, 1.38)	1.06 (0.81, 1.30)	0.91 (0.71, 1.10)	1.02 (0.82, 1.21)
Glimepiride	1.01 (0.79, 1.23)	1.03 (0.81, 1.25)	0.97 (0.82, 1.12)	0.95 (0.78, 1.13)
Liraglutide	1.16 (0.90, 1.42)	1.16 (0.88, 1.45)	1.27 (0.95, 1.59)	0.94 (0.74, 1.14)
Sitagliptin	1.04 (0.72, 1.36)	1.16 (0.81, 1.51)	1.06 (0.77, 1.34)	1.11 (0.86, 1.36)
Overall	1.07 (0.95, 1.20)	1.08 (0.96, 1.22)	1.01 (0.91, 1.12)	0.99 (0.91, 1.09)

Joint α -cell p-value: baseline: p=0.55, follow-up p=0.37

B. Models with β -cell function alone

	Fasting C-peptide (HR, CI)		C-peptide index (CPI) (HR, CI)	
	At Baseline	At Follow-up	At Baseline	At Follow-up
Glargine	1.01 (0.71, 1.31)	1.12 (0.78, 1.47)	0.84 (0.64, 1.03)	0.75 (0.54, 1.00)
Glimepiride	1.08 (0.79, 1.37)	1.25 (0.96, 1.54)	1.01 (0.81, 1.21)	0.90 (0.70, 1.11)
Liraglutide	0.89 (0.59, 1.18)	0.94 (0.75, 1.13)	0.94 (0.70, 1.17)	0.92 (0.73, 1.12)
Sitagliptin	0.90 (0.59, 1.22)	1.18 (0.83, 1.52)	0.77 (0.57, 1.00)	0.75 (0.56, 0.94)
Overall	0.98 (0.81, 1.18)	1.12 (0.98, 1.27)	0.88 (0.80, 0.97)	0.83 (0.75, 0.92)[‡]

Joint β -cell p-value: baseline p=0.04, follow-up p<0.001

C. Models with both α - and β -cell function

	Fasting glucagon (HR, CI)		Glucagon index (GGI) (HR, CI)		Fasting C-peptide (HR, CI)		C-peptide index (CPI) (HR, CI)	
	At Baseline	At Follow-up	At Baseline	At Follow-up	At Baseline	At Follow-up	At Baseline	At Follow-up
Glargine	1.10 (0.82, 1.37)	1.06 (0.82, 1.29)	0.93 (0.74, 1.12)	1.04 (0.83, 1.24)	1.00 (0.70, 1.31)	1.12 (0.81, 1.43)	0.85 (0.66, 1.05)	0.75 (0.53, 1.00)
Glimepiride	0.98 (0.75, 1.20)	0.99 (0.77, 1.22)	0.98 (0.81, 1.14)	0.96 (0.77, 1.15)	1.11 (0.79, 1.42)	1.26 (0.94, 1.57)	1.01 (0.79, 1.23)	0.91 (0.69, 1.14)
Liraglutide	1.20 (0.93, 1.47)	1.21 (0.91, 1.51)	1.30 (1.01, 1.63)	0.93 (0.72, 1.15)	0.85 (0.54, 1.16)	0.89 (0.66, 1.12)	0.91 (0.71, 1.11)	0.93 (0.74, 1.12)
Sitagliptin	1.05 (0.70, 1.41)	1.12 (0.77, 1.46)	1.12 (0.77, 1.47)	1.06 (0.78, 1.35)	0.91 (0.58, 1.24)	1.15 (0.80, 1.51)	0.77 (0.55, 1.00)	0.75 (0.56, 0.95)
Overall	1.06 (0.94, 1.19)	1.07 (0.95, 1.20)	1.04 (0.94, 1.15)	0.99 (0.91, 1.09)	0.97 (0.81, 1.17)	1.10 (0.97, 1.26)	0.88 (0.79, 0.97)	0.83 (0.75, 0.92)[‡]

Joint α -cell p-value: baseline p=0.55, follow-up p=0.45

Joint β -cell p-value: baseline p=0.04, follow-up p<0.001

The hazard ratio per 1SD increase and its 95% CI are in parentheses. Bolded values indicate the estimate is significantly different from zero at p<0.05. A superscript [‡] indicates p<0.001. The p-values for the within treatment group HR's are Holm adjusted for 4 tests. Tests of interaction with treatment were not significant in any of the models. Joint p-values are based on a 2df test of both components of α - or β -cell function within the model.

Table S5: Association of α - and β -cell function with the secondary metabolic outcome by treatment group

A. Models with α -cell function alone

	Fasting glucagon (HR, CI)		Glucagon index (GGI) (HR, CI)	
	Baseline	Follow-up	Baseline	Follow-up
Glargine	1.20 (0.81, 1.60)	1.19 (0.84, 1.55)	0.86 (0.60, 1.13)	0.94 (0.71, 1.17)
Glimepiride	1.11 (0.88, 1.33)	1.15 (0.85, 1.45)	1.09 (0.82, 1.36)	1.18 (0.88, 1.48)
Liraglutide	1.01 (0.74, 1.27)	1.07 (0.80, 1.35)	1.12 (0.70, 1.54)	1.07 (0.80, 1.34)
Sitagliptin	0.95 (0.66, 1.25)	1.14 (0.80, 1.47)	0.92 (0.61, 1.22)	1.33 (0.94, 1.72)
Overall	1.07 (0.95, 1.21)	1.14 (1.00, 1.30)	1.01 (0.89, 1.15)	1.14 (1.01, 1.27)

Joint α -cell p-value: baseline: p=0.56, follow-up p=**0.04**

B. Models with β -cell function alone

	Fasting C-peptide (HR, CI)		C-peptide index (CPI) (HR, CI)	
	At Baseline	At Follow-up	At Baseline	At Follow-up
Glargine	0.99 (0.60, 1.38)	1.19 (0.80, 1.57)	0.88 (0.55, 1.21)	0.70 (0.34, 1.07)
Glimepiride	1.01 (0.65, 1.37)	1.29 (0.93, 1.65)	1.05 (0.82, 1.28)	0.86 (0.63, 1.09)
Liraglutide	0.73 (0.30, 1.16)	0.90 (0.63, 1.16)	1.01 (0.70, 1.32)	0.94 (0.68, 1.20)
Sitagliptin	1.16 (0.64, 1.68)	1.29 (0.84, 1.74)	0.90 (0.62, 1.18)	0.77 (0.53, 1.01)
Overall	0.97 (0.75, 1.25)	1.17 (1.00, 1.36)	0.97 (0.85, 1.09)	0.83 (0.72, 0.95)[‡]

Joint β -cell p-value: baseline p=0.82, follow-up p=**0.004**

C. Models with both α - and β -cell function

	Fasting glucagon (HR, CI)		Glucagon index (GGI) (HR, CI)		Fasting C-peptide (HR, CI)		C-peptide index (CPI) (HR, CI)	
	At Baseline	At Follow-up	At Baseline	At Follow-up	At Baseline	At Follow-up	At Baseline	At Follow-up
Glargine	1.20 (0.80, 1.60)	1.15 (0.81, 1.50)	0.87 (0.59, 1.16)	0.91 (0.61, 1.21)	0.98 (0.53, 1.42)	1.15 (0.77, 1.53)	0.93 (0.62, 1.24)	0.71 (0.36, 1.05)
Glimepiride	1.11 (0.88, 1.33)	1.15 (0.86, 1.43)	1.09 (0.82, 1.35)	1.20 (0.89, 1.50)	1.01 (0.68, 1.35)	1.28 (0.90, 1.66)	1.05 (0.79, 1.32)	0.84 (0.59, 1.09)
Liraglutide	1.09 (0.81, 1.37)	1.15 (0.80, 1.49)	1.13 (0.68, 1.58)	1.06 (0.80, 1.31)	0.73 (0.28, 1.17)	0.86 (0.58, 1.14)	0.99 (0.67, 1.31)	0.96 (0.68, 1.23)
Sitagliptin	0.89 (0.61, 1.17)	1.08 (0.78, 1.39)	0.92 (0.58, 1.27)	1.29 (0.86, 1.72)	1.23 (0.65, 1.81)	1.26 (0.79, 1.74)	0.89 (0.61, 1.17)	0.80 (0.55, 1.05)
Overall	1.07 (0.95, 1.20)	1.12 (0.99, 1.28)	1.01 (0.89, 1.16)	1.12 (0.99, 1.26)	0.96 (0.75, 1.25)	1.14 (0.97, 1.33)	0.97 (0.85, 1.10)	0.83 (0.72, 0.96)

Joint α -cell p-value: baseline p=0.58, follow-up p=0.07

Joint β -cell p-value: baseline p=0.84, follow-up p=**0.01**

The hazard ratio per 1SD increase and its 95% CI are in parentheses. Bolded values indicate the estimate is significantly different from zero at p<0.05. A superscript [‡] indicates p<0.001. The p-values for the within treatment group HR's are Holm adjusted for 4-tests. Tests of interaction with treatment were not significant in any of the models. Joint p-values are based on a 2df test of both components of α -cell or β -cell function within the model.

Table S6: Changes in glycemic outcomes per 1 standard deviation (1SD) increase in fasting and glucose-induced changes in glucagon and 1SD increase in fasting and glucose-induced changes C-peptide over time and by treatment group

Outcome Variable	Group	Visit Year	Effect per 1 SD increase			
			Fasting glucagon	Glucagon index (GGI)	Fasting C-peptide	C-peptide index (CPI)
Fasting glucose	Glargine	1	0.03	0.16	0.92[‡]	-0.31
		3	0.09	0.21	0.95[‡]	-0.54[‡]
		5	0.36[†]	0.61[†]	1.17[‡]	-0.01
		Overall	0.16	0.33[‡]	1.01[‡]	-0.29[†]
	Glimepiride	1	0.17	0.27	0.22	-0.32
		3	0.12	0.14	0.58[*]	-0.40[*]
		5	-0.40	0.29	1.49[‡]	0.09
		Overall	-0.04	0.23	0.76[‡]	-0.21
	Liraglutide	1	0.28	0.04	0.53[*]	-0.21
		3	0.55	0.13	0.94[‡]	-0.35
		5	0.14	-0.56[*]	-0.30[*]	-0.22
		Overall	0.32	-0.13	0.39[‡]	-0.26[*]
	Sitagliptin	1	0.10	0.27	0.52[‡]	-0.12
		3	-0.07	0.03	0.51[*]	-0.67
		5	0.44	0.06	0.39	-0.12
		Overall	0.16	0.12	0.47[‡]	-0.31[†]
	All Treatments	1	0.15	0.19[†]	0.55[‡]	-0.24[‡]
		3	0.17	0.13	0.74[‡]	-0.49[‡]
		5	0.14	0.10	0.69[‡]	-0.07
		Overall	0.14[*]	0.16[†]	0.63[‡]	-0.28[‡]

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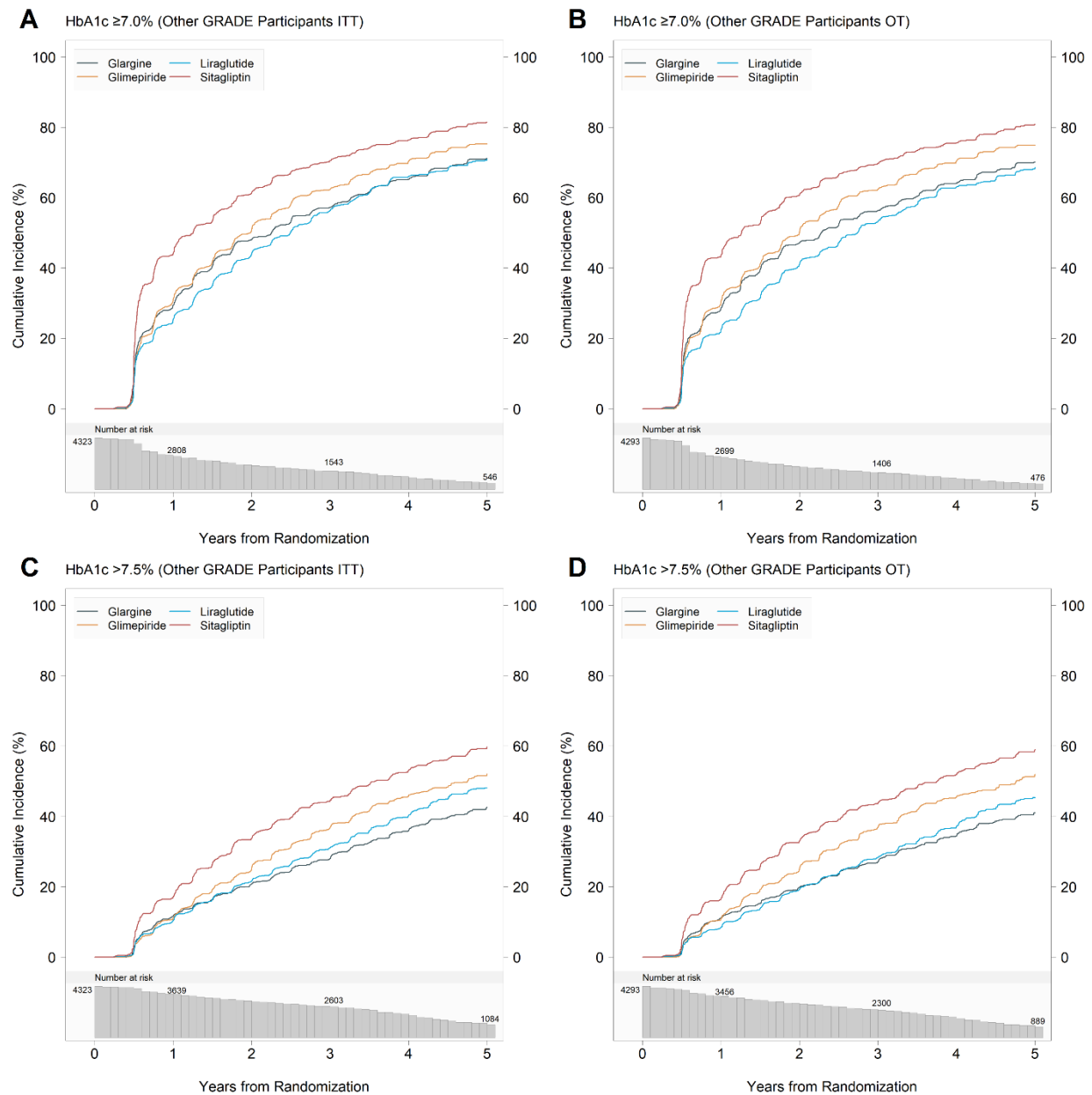
Outcome Variable	Group	Visit Year	Effect per 1 SD increase			
			Fasting glucagon	Glucagon index (GGI)	Fasting C-peptide	C-peptide index (CPI)
2-hr glucose	Glargine	1	-0.02	0.13	1.01[†]	-0.52
		3	0.06	0.30	1.39[‡]	-0.90[†]
		5	0.35	1.22[†]	1.38[‡]	0.05
		Overall	0.13	0.55*	1.26[‡]	-0.45
	Glimepiride	1	0.24	0.34	0.33	-1.15[‡]
		3	0.14	0.20	1.13*	-0.96[†]
		5	-0.00	1.63	2.70[†]	-0.02
		Overall	0.13	0.73*	1.39[‡]	-0.71
	Liraglutide	1	0.51	0.48	0.05	-0.84[‡]
		3	1.26*	0.29	0.17	-0.91[†]
		5	-0.05	-1.05	-0.23	-0.38
		Overall	0.57	-0.09	-0.00	-0.71[‡]
	Sitagliptin	1	0.31	0.57	0.41	-0.69[†]
		3	-0.03	0.09	0.59	-1.74[†]
		5	0.66	-0.28	0.51	-0.64
		Overall	0.31	0.13	0.51	-1.02[‡]
	All Treatments	1	0.26	0.38[†]	0.45[†]	-0.80[‡]
		3	0.36	0.22	0.82[‡]	-1.12[‡]
		5	0.24	0.38	1.09[‡]	-0.25
		Overall	0.26*	0.32[†]	0.62[‡]	-0.84[‡]

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Outcome Variable	Group	Visit Year	Effect per 1 SD increase			
			Fasting glucagon	Glucagon index (GGI)	Fasting C-peptide	C-peptide index (CPI)
HbA1c (%)	Glargine	1	0.06	0.06	0.17*	-0.11
		3	0.03	0.09	0.10	-0.25‡
		5	0.10	0.17	0.18	-0.14
		Overall	0.06	0.11	0.15†	-0.17†
	Glimepiride	1	0.06	0.03	0.07	-0.19†
		3	-0.00	0.08	0.33‡	-0.20*
		5	0.15	0.19	0.61†	-0.03
		Overall	0.07	0.10	0.34‡	-0.14
	Liraglutide	1	0.07	-0.03	0.05	-0.15
		3	0.18	0.10	0.06	-0.17
		5	0.09	-0.19	-0.13	-0.18
		Overall	0.11	-0.04	-0.01	-0.17†
	Sitagliptin	1	0.15*	0.25†	0.08	-0.18
		3	0.03	0.07	0.15	-0.35
		5	0.08	-0.05	0.17	-0.01
		Overall	0.09	0.09	0.13*	-0.18†
	All	1	0.09*	0.07*	0.09†	-0.15‡
		3	0.06	0.09*	0.16‡	-0.24‡
		5	0.11	0.03	0.21‡	-0.09
		Overall	0.07†	0.07†	0.12‡	-0.18‡

The cells with significant changes are bolded with p-value superscripts: *0.01≤p≤0.05; †0.001≤p<0.01; ‡p<0.001; no superscript means p>0.05. P-values were Holm corrected for 12 tests in visit by year subgroups, for 3 tests in visit subgroups (labeled Year 1, Year 3, Year 5), for the 4 overall tests within treatment subgroups (labeled Overall) and are unadjusted in the combined treatments (labeled Overall).

Figure S1: Cumulative incidence of the primary and secondary metabolic outcomes for the GRADE cohort not in the glucagon substudy



Cumulative incidence of the primary (A and B) and secondary metabolic outcomes (C and D) using intention-to-treat (A and C) and on-treatment (B and D) analytical approaches. The histogram at the bottom of each plot presents the number of participants still at risk over time.

Approach to Randomization of GRADE Participants for the Glucagon Substudy **10/20/2020**

Overall Description

The plan is to perform glucagon assays on the 0 and 30-minute samples from all the OGTTs of 724 participants. The Central Biochemistry Laboratory (CBL) has budgeted for 8890 samples, so this ceiling must not be exceeded. Some of the selected samples may be unavailable or of poor quality and will need to be replaced after review.

Since we will want to assess treatment effects, the selected participants must have data from a baseline OGTT and at least one subsequent OGTT, ideally year 1 to assess early effects. The available OGTTs must include 0 and 30-minute samples.

Finally, the power calculations require at least 100 participants with a primary outcome in each group, or at least 400 total. With a sample size of 724, it is a virtual certainty that this minimum will be exceeded.

Storage Consent

The participants signed and potentially updated a consent form indicating whether samples could be stored. Since glucagon will be done on stored samples, this information determines which samples can be used.

Eligible Participants and Assays

We need to identify participants with 0 and 30-minute samples. Looking at who has glucose values is unreliable because the CBL stopped running samples in November 2017. Instead, we will use the OGTT forms, which record which blood samples were collected, and only keep visits for which both the 0 and 30-minute samples were collected. In addition, because the mass spec assay used a large amount of the available samples from baseline and 1 year, we will exclude the participants from the mass spec pilot study. Finally, since the assay will be done on stored samples, we need to restrict the selection to those.

The availability and completeness of the OGTTs for the 5047 participants are summarized below (incomplete means that the 0 and 30-minute time points were not both collected):

In mass spec pilot	20 (0.4%)
Samples not stored	287 (5.7%)
Baseline OGTT incomplete	229 (4.5%)
No OGTT after baseline	184 (3.6%)
No Year 1 OGTT	58 (1.1%)
Year 1 OGTT incomplete	149 (3.0%)
Complete baseline and year 1 OGTT	4120 (81.6%)

Keeping the participants with stored samples at least from the baseline and year 1 OGTTs leaves 4120 participants. These participants have an average of 3.18 OGTTs.

Get A Random Sample

The subset of participants for the glucagon substudy is a simple random sample of 724 participants from the 4120 eligible GRADE participants. The percentage of participants with a primary outcome among the eligibles is 71.29%. With this, the probability that a sample of size $N=724$ contains at least 400 participants with a primary outcome is essentially 1. The number of participants with the primary metabolic outcome in the selected sample is:

	Glargine	Glimepiride	Liraglutide	Sitagliptin
No Primary	59 (32.1%)	52 (26.7%)	51 (31.3%)	47 (25.8%)
Primary	125 (67.9%)	143 (73.3%)	112 (68.7%)	135 (74.2%)

The corresponding percentages in the full GRADE cohort are:

	Glargine	Glimepiride	Liraglutide	Sitagliptin
No Primary	422 (33.8%)	346 (27.9%)	424 (34.1%)	300 (23.9%)
Primary	825 (66.2%)	895 (72.1%)	818 (65.9%)	957 (76.1%)

Balance

Table S2 compares the participants included in the glucagon sample to the remaining randomized participants. The sample seems representative of the GRADE participants, with only minor differences.

GRADE Research Group (April 30, 2021)

Designations: Principal Investigator (PI); Co-Principal Investigator (Co-PI); Co-Investigator (Co-I); Study Coordinator (SC); Recruitment/Retention Coordinator (RC); Research Staff (RS)

Current Clinical Centers

Albert Einstein College of Medicine: Crandall, JP (PI); McKee, MD (Co-PI, past); Behringer-Massera, S (Co-I, past); Brown-Friday, J (SC); Xhori, E (RC, past); Ballentine-Cargill, K (RS); Duran, S (RS); Estrella, H (RS); Gonzalez de la torre, S (RS, past); Lukin, J (RS, past)

Atlanta VA Medical Center: Phillips, LS (PI); Burgess, E (Co-I); Olson, D (Co-I); Rhee, M (Co-I); Wilson, P (Co-I); Raines, TS (SC); Boers, J (SC); Costello, J (SC); Maher-Albertelli, M (SC); Mungara, R (SC); Savoye, L (SC, past); White, CA (SC); Gullett, C (SC, past); Holloway, L (SC, past); Morehead, F (SC, past); Person, S (SC, past); Sibymon, M (SC, past); Tanukonda, S (SC, past); Adams, C (RC, past); Ross, A (RC, past)

Baylor College of Medicine: Balasubramanyam, A (PI); Gaba, R (Co-I); Gonzalez Hattery, E (SC); Ideozu, A (SC); Jimenez, J (SC); Montes, G (RC); Wright, C (RS, past)

Baylor Scott & White Research Institute (Baylor Research Institute): Hollander, P (PI); Roe, E (Co-I, past); Jackson, A (SC); Smiley, A (SC); Burt, P (SC, past); Estrada, L (RS); Chionh, K (RS, past)

Case Western Reserve University/Cleveland VA/MetroHealth Medical Center: Ismail-Beigi, F (PI); Falck-Ytter, C (Co-PI); Sayyed Kassem, L (Co-PI); Sood, A (Co-PI, past); Tiktin, M (Co-I, SC); Kulow, T (SC); Newman, C (SC); Stancil, KA (SC); Cramer, B (SC, past); Iacoboni, J (SC, past); Kononets, MV (SC, past); Sanders, C (SC, past); Tucker, L (SC, past); Werner, A (SC, past); Maxwell, A (RS); McPhee, G (RS); Patel, C (RS); Colosimo, L (RS, past); Krol, A (RS, past)

Columbia University Medical Center: Goland, R (PI); Pring, J (SC); Alfano, L (SC); Kringas, P (SC, past); Hausheer, C (RC, past); Tejada, J (RC, past); Gumpel, K (RS, past); Kirpitch, A (RS, past); Schneier, H (RS, past)

Duke University Medical Center: Green, JB (PI); AbouAssi, H (Co-I); Chatterjee, R (Co-I); Feinglos, MN (Co-I, past); English Jones, J (SC, RC); Khan, SA (SC, RC); Kimpel, JB (SC, past); Zimmer, RP (SC, past); Furst, M (RC, past); Satterwhite, BM (RS); Thacker, CR (RS); Evans Kreider, K (RS, past)

Indiana University: Mariash, CN (PI); Mather, KJ (PI, past); Ismail, HM (Co-I); Lteif, A (Co-I, past); Mullen, M (SC); Hamilton, T (SC, past); Patel, N (SC, past); Riera, G (RC); Jackson, M (RC, past); Pirics, V (RC, past); Aguillar, D (RS, past); Howard, D (RS, past); Hurt, S (RS, past)

International Diabetes Center: Bergenstal, R (PI); Carlson, A (Co-I); Martens, T (Co-I); Johnson, M (SC); Hill, R (SC); Hyatt, J (SC); Jensen, C (SC); Madden, M (SC); Martin, D (SC); Willis, H (SC); Konerza, W (RS); Yang, S (RS); Kleeberger, K (RS, past); Passi, R (RS, past)

Kaiser Permanente Northwest: Fortmann, S (PI); Herson, M (Co-I); Mularski, K (Co-I); Glauber, H (Co-I, past); Prihoda, J (Co-I, past); Ash, B (SC); Carlson, C (SC); Ramey, PA (SC); Schield, E (SC); Torggrimson-Ojerio, B (SC); Arnold, K (SC, past); Kauffman, B (SC, past); Panos, E (SC, past); Sahnaw, S (RC); Bays, K (RS); Berame, K (RS); Cook, J (RS); Ghioni, D (RS); Gluth, J (RS); Schell, K (RS); Criscola, J (RS, past); Friason, C (RS, past); Jones, S (RS, past); Nazarov, S (RS, past)

Kaiser Permanente of Georgia: Barzilay, J (PI); Rassouli, N (Co-PI); Puttnam, R (Co-I);

Ojoawo, B (SC); Nelson, R (RC); Curtis, M (SC, past); Hollis, B (SC, past); Sanders-Jones, C (SC, past); Stokes, K (SC, past); El-Haqq, Z (RS, past); Kolli, A (RS, past); Tran, T (RS, past)

Massachusetts General Hospital: Wexler, D (PI); Larkin, ME (Co-I, SC); Meigs, J (Co-I); Chambers, B (SC, past); Dushkin, A (SC, past); Rocchio, G (SC, past); Yepes, M (SC, past); Steiner, B (RC); Dulin, H (RC, past); Cayford, M (RS); Chu, K (RS); DeManbey, A (RS); Hillard, M (RS); Martin, K (RS); Thangthaeng, N (RS); Gurry, L (RS, past); Kochis, R (RS, past); Raymond, E (RS, past); Ripley, V (RS, past); Stevens, C (RS, past)

MedStar Health Research Institute/ MedStar Baltimore: Park, J (PI); Aroda, V (PI, past); Ghazi, A (Co-PI); Magee, M (Co-I); Rensing, Ann (Co-I); Loveland, A (SC); Hamm, M (SC); Hurtado, M (SC); Kuhn, A (SC); Leger, J (SC); Manandhar, L (SC); Mwicigi, F (SC); Sanchez, O (SC); Young, T (SC)

Miami VA Healthcare System/University of Miami: Garg, R (PI), Lagari-Libhaber, V (PI); Florez, HJ (PI, past); Valencia, WM (PI, past); Marks, J (Co-PI, past); Casula, S (Co-I); Oropesa-Gonzalez, L (SC); Hue, L (SC, past); Cuadot, A (SC, past); Nieto-Martinez, R (SC, past); Riccio Veliz, AK (SC, past); Gutt, M (RC, past); Kendal, YJ (RS, past); Veciana, B. (RS, past)

Oregon Health & Science University: Ahmann, A (PI); Aby-Daniel, D (Co-I); Joarder, F (Co-I); Morimoto, V (Co-I); Sprague, C (Co-I); Yamashita, D (Co-I); Cady, N (SC); Rivera-Eschright, N (SC); Kirchhoff, P (SC, past); Morales Gomez, B (RC); Adducci, J (RC, past); Goncharova, A (RC, past)

Pacific Health Research and Education Institute/VA Pacific Islands: Hox, SH (PI); Petrovitch, H (Co-PI); Matwichyna, M (SC); Jenkins, V (SC, past); Broadwater, L (RS); Ishii, RR (RS); Bermudez, NO (RS; past)

Pennington Biomedical Research Center: Hsia, DS (PI); Cefalu, WT (PI, past); Greenway, FL (Co-I); Waguespack, C (Co-I); King, E (SC); Fry, G (SC); Dragg, A (SC); Gildersleeve, B (SC); Arceneaux, J (SC); Haynes, N (SC, past); Thomassie, A (SC, past); Pavlionis, M (SC, past); Bourgeois, B (RC, past); Hazlett, C (RS)

San Diego VA Medical Center: Mudaliar, S (PI); Henry, R (PI, past); Boeder, S (Co-I, past); Pettus, J (Co-I, past); Diaz, E (SC); Garcia-Acosta, D (SC); Maggs, S (SC); DeLue, C (SC, past); Stallings, A (SC, past); Castro, E (RC, past); Hernandez, S (RC, past)

Southwestern American Indian Center: Krakoff, J (PI); Curtis, JM (Co-I); Killeen, T (SC); Khalid, M (SC); Joshevama, E (RC, past); Diaz, E (RS); Martin, D (RS); Tsingine, K (RS); Karshner, T (RS, past)

St. Luke's-Roosevelt Hospital: Albu, J (Co-PI); Pi-Sunyer, FX (Co-PI, past); Frances, S (Co-I); Maggio, C (SC, past); Ellis, E (RC); Bastawrose, J (RC, past); Gong, X (RS)

SUNY Downstate Medical Center/New York Hospital-Queens: Banerji, MA (PI); August, P (Co-I); Lee, M (Co-I); Lorber, D (Co-I); Brown, NM (SC, RC); Josephson, DH (SC); Thomas, LL (SC, RC); Tsovian, M (SC, RC); Cherian, A (SC, RC, past); Jacobson, MH (RS); Mishko, MM (RS)

The University of North Carolina Diabetes Care Center: Kirkman, MS (PI); Buse, JB (Co-I); Diner, J (Co-I); Dostou, J (Co-I); Machineni, S (Co-I); Young, L (Co-I); Bergamo, K (Co-I, past); Goley, A (Co-I, past); Kerr, J (Co-I, past); Largay, JF (Co-I, past); Guarda, S (SC); Cuffee, J (SC, past); Culmer, D (SC, past); Fraser, R (RC); Almeida, H (RC, past); Coffey, S (RC, past); Debnam, E (RC, past); Kiker, L (RC, past); Morton, S (RC, past); Josey, K (RS); Fuller, G (RS, past)

University of Alabama Birmingham: Garvey, WT (PI); Cherrington, AL (Co-PI); Dyer, D (SC); Lawson, MCR (SC); Griffith, O (SC, past); Agne, A (RC); McCullars, S (RC)

University of Cincinnati/Cincinnati VA Medical Center: Cohen, RM (PI); Craig, J (SC); Rogge, MC (SC; past); Burton, K (SC, past); Kersey, K (SC, RC, past); Wilson, C (SC, past);

Lipp, S (RC, past); Vonder Meulen, MB (RC, past); Adkins, C (RS); Onadeko, T (RS)

University of Colorado-Denver/VA: Rasouli, N (PI); Baker, C (Co-I); Schroeder, E (Co-I, past); Razzaghi, M (Co-I); Lyon, C (Co-I, past); Penaloza, R (Co-I, past); Underkofler, C (SC); Lorch, R (SC); Douglass, S (SC, past); Steiner, S (SC, past)

University of Iowa: Sivitz, WI (PI); Cline, E (SC); Knosp, LK (SC); McConnell, J (SC, past); Lowe, T (RC)

University of Michigan: Herman, WH (PI); Pop-Busui, R (Co-PI); Tan, MH (Co-I); Martin, C (SC); Waltje, A (SC, RC); Katona, A (SC); Goodhall, L (SC, past); Eggleston, R (RC, past); Kuo, S (RS); Bojescu, S (RS, past); Bule, S (RS, past); Kessler, N (RS, past); LaSalle, E (RS, past); Whitley, K (RS, past)

University of Minnesota: Seaquist, ER (PI); Bantle, A (Co-I); Harindhanavudhi, T (Co-I); Kumar, A (Co-I); Redmon, B (Co-I); Bantle, J (Co-I, past); Coe, M (SC); Mech, M (SC); Taddese, A (RC); Lesne, L (RS); Smith, S (RS)

University of Nebraska Medical Center/Omaha VA: Desouza, C (PI); Kuechenmeister, L (Co-I); Shivaswamy, V (Co-I); Burbach, S (SC); Rodriguez, MG (SC); Seipel, K (SC); Alfred, A (SC, past); Morales, AL (SC, past); Eggert, J (RS); Lord, G (RS); Taylor, W (RS, past); Tillson, R (RS, past)

University of New Mexico: Schade, DS (PI); Adolphe, A (Co-PI); Burge, M (Co-PI, past); Duran-Valdez, E (SC); Martinez, J (RC, past); Bancroft, A (RS); Kunkel, S (RS); Ali Jamaledin Ahmad, F (RS, past); Hernandez McGinnis, D (RS, past); Pucchetti, B (RS, past); Scripsick, E (RS, past); Zamorano, A (RS, past)

UT Health San Antonio: DeFronzo, RA (PI); Cersosimo, E (Co-PI); Abdul-Ghani, M (Co-I); Triplitt, C (Co-I); Juarez, D (SC); Mullen, M (SC); Garza, RI (SC, past); Verastiqui, H (SC, past); Wright, K (RC, past); Puckett, C (RS)

University of Texas-Southwestern Medical Center: Raskin, P (PI); Rhee, C (Co-I, past); Abraham, S (SC); Jordan, LF (SC); Sao, S (SC); Morton, L (SC, past); Smith, O (SC, past); Osornio Walker, L (RC, past); Schnurr-Breen, L (RC, past); Ayala, R (RS); Kreymer, RB (RS); Sturgess, D (RS, past)

VA Puget Sound Health Care System/University of Washington: Utzschneider, KM (PI); Kahn, SE (Co-I); Alarcon-Casas Wright, L (Co-I); Boyko, EJ (Co-I); Tsai, EC (Co-I); Trencce, DL (Co-I, past); Trikudanathan, S (Co-I, past); Fattaleh, BN (SC); Montgomery, BK (SC, past); Atkinson, KM (RS); Koizedub, A (RS); Concepcion, T (RS, past); Moak, C (RS, past); Prikhodko, N (RS, past); Rhothisen, S (RS, past)

Vanderbilt University: Elasy, TA (PI); Martin, S (SC); Shackelford, L (RC, RS, past); Goidel, R (RS); Hinkle, N (RS); Lovell, C (RS); Myers, J (RS); Lipps Hogan, J (RS, past)

Washington University: McGill, JB (PI); Salam, M (Co-I); Schweiger, T (SC, RC); Kissel, S (SC, RC, past); Recklein, C (SC, past); Clifton, MJ (RS)

Yale University/Fair Haven Community Health Center/West Haven VA Medical Center: Tamborlane, W (PI); Camp, A (Co-I); Gulanski, B (Co-I); Inzucchi, SE (Co-I); Pham, K (Co-I); Alguard, M (SC, RC); Gatcomb, P (SC); Lessard, K (SC); Perez, M (SC); Iannone, L (RC); Magenheimer, E (RC); Montosa, A (RC)

Study Units

NIH/NIDDK (Sponsor): Cefalu, WT (Director, Division of Diabetes, Endocrinology and Metabolic Diseases); Fradkin, J (Director, Division of Diabetes, Endocrinology and Metabolic Diseases, past); Burch, HB (Project Scientist); Bremer, AA (Project Scientist, past)

Chairman's Office, Massachusetts General Hospital, Harvard Medical School: Nathan, DM (Study Chair, Study Co-PI)

Executive Committee: Nathan, DM (Study Chair, Study Co-PI); Lachin, JM (U01 Contact PI, Study Co-PI); Buse, JB (Co-I); Kahn, SE (Co-I); Krause-Steinrauf, H (Co-I, Project Director); Larkin, ME (Co-I, SC); Tiktin, M (Co-I, SC); Wexler, D (PI); Burch, HB (Program Scientist); Bremer, AA (Project Scientist, past)

Coordinating Center, The George Washington University Biostatistics Center: Lachin, JM (U01 Contact PI, Study Co-PI); Krause-Steinrauf, H (Co-I, Project Director); Younes, N (Co-I); Bebu, I (RS); Butera, N (RS); Buys, CJ (RS); Fagan, A (RS); Gao, Y (RS); Ghosh, A (RS); Gramzinski, MR (RS); Hall, SD (RS); Kazemi, E (RS); Legowski, E (RS); Liu, H (RS); Suratt, C (RS); Tripputi, M (RS); Arey, A (RS, past); Backman, M (RS, past); Bethupu, J (RS, past); Lund, C (RS, past); Mangat Dhaliwal, P (RS, past); McGee, P (RS, past); Mesimer, E (RS, past); Ngo, L (RS, past)

Central Biochemical Laboratory, University of Minnesota Advanced Research and Diagnostic Laboratory: Steffes, M (PI); Seegmiller, J (Co-I); Saenger, A (Co-I, past); Arends, V (SC); Gabrielson, D (SC, past)

Drug Distribution Center, VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center: Conner, T (PI); Warren, S (PI, past); Day, J (RS); Huminik, J (RS); Scrymgeour, A (RS)

ECG Reading Center, EPICARE, Wake Forest University: Soliman, EZ (PI); Pokharel, Y (PI, past); Zhang, ZM (Co-I, past); Campbell, C (SC); Hu, J (SC); Keasler, L (SC); Hensley, S (SC, past); Li, Y (RS)

Economic Evaluation and Assessment Center:

University of Michigan: Herman, WH (PI); Kuo, S (RS); Martin, C (SC); Waltje, A (SC, RC); Mihalcea, R (RS); Min, DJ (RS); Perez-Rosas, V (RS); Prosser, L (RS); Resnicow, K (RS); Ye, W (RS)

Centers for Disease Control and Prevention: Shao, H (RS); Zhang, P (RS)

Neurocognitive Coordinating Center, Columbia University Medical Center: Luchsinger, J (PI); Sanchez, D (SC); Assuras, S (RS)

QWB Reading Center, University of California San Diego Health Services Research Center: Groessl, E (PI); Sakha, F (SC); Chong, H (SC, past); Hillery, N (RS)

Collaborators

Cardiovascular Adjudication Advisor: Everett, BM (Brigham and Women's Hospital)

Collaborating Investigators (Recruitment Sites): Abdouch, I (University of Nebraska Medical Center/Omaha VA); Bahtiyar, G (SUNY Downstate Medical Center); Brantley, P (Pennington Biomedical Research Center (LSU)); Broyles, FE (Swedish Medical Center); Canaris, G (University of Nebraska Medical Center/Omaha VA); Copeland, P (Massachusetts General Hospital); Craine, JJ (UW Valley Medical Center); Fein, WL (Swedish Medical Center); Gliwa, A (SUNY Downstate Medical Center); Hope, L (SUNY Downstate Medical Center); Lee, MS (SUNY Downstate Medical Center); Meiners, R (Pennington Biomedical Research Center (LSU)); Meiners, V (Pennington Biomedical Research Center (LSU)); O'Neal, H (Pennington Biomedical Research Center (LSU)); Park, JE (UW Valley Medical Center); Sacerdote, A (SUNY Downstate Medical Center); Sledge, Jr., E (Pennington Biomedical Research Center)

(LSU)); Soni, L (SUNY Downstate Medical Center); Steppel-Reznik, J (Massachusetts General Hospital); Turchin, A (Massachusetts General Hospital)

Beta-Cell Ancillary Study: Brooks-Worrell, B (University of Washington); Hampe, CS (University of Washington); Palmer, JP (University of Washington); Shojaie, A (University of Washington)

Continuous Glucose Monitoring Substudy: Higgins, J (Massachusetts General Hospital; Harvard Medical School)

Emotional Distress Substudy: Golden, S (Johns Hopkins University); Gonzalez, J (Yeshiva University; Albert Einstein College of Medicine); Naik, A (Baylor College of Medicine); Walker, E (Albert Einstein College of Medicine)

National Diabetes Education Program (NDEP) Substudy: Doner Lotenberg, L (Hager Sharp); Gallivan, JM (National Institutes of Health); Lim, J (Hager Sharp); Tuncer, DM (National Institutes of Health)

Recruitment Ancillary Study: Behringer-Massera, S (The Mount Sinai Hospital, Beth Israel Medical Center)