Design of FLAT-SUGAR: Randomized Trial of Prandial Insulin Versus Prandial GLP-1 Receptor Agonist Together With Basal Insulin and Metformin for High-Risk Type 2 Diabetes

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OBJECTIVE

Glycemic variability may contribute to adverse medical outcomes of type 2 diabetes, but prior therapies have had limited success in controlling glycemic fluctuations, and the hypothesis has not been adequately tested.

RESEARCH DESIGN AND METHODS

People with insulin-requiring type 2 diabetes and high cardiovascular risk were enrolled during a run-in period on basal-bolus insulin (BBI), and 102 were randomized to continued BBI or to basal insulin with a prandial GLP-1 receptor agonist (GLIPULIN) group, each seeking to maintain HbA_{1c} levels between 6.7% and 7.3% (50–56 mmol/mol) for 6 months. The primary outcome measure was glycemic variability assessed by continuous glucose monitoring; other measures were HbA_{1c}, weight, circulating markers of inflammation and cardiovascular risk, albuminuria, and electrocardiographic patterns assessed by Holter monitoring.

RESULTS

At randomization, the mean age of the population was 62 years, median duration of diabetes 15 years, mean BMI 34 kg/m^2, and mean HbA_{1c} 7.9% (63 mmol/mol). Thirty-three percent had a prior cardiovascular event, 18% had microalbuminuria, and 3% had macroalbuminuria. At baseline, the continuous glucose monitoring coefficient of variation for glucose levels was similar in both groups.

CONCLUSIONS

FLAT-SUGAR is a proof-of-concept study testing whether, in a population of individuals with type 2 diabetes and high cardiovascular risk, the GLIPULIN regimen can limit glycemic variability more effectively than BBI, reduce levels of cardiovascular risk markers, and favorably alter albuminuria and electrocardiographic patterns. We successfully randomized a population that has sufficient power to answer the primary question, address several secondary ones, and complete the protocol as designed.

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**The members of the Writing Committee of the FLAT-SUGAR Trial are listed in the APPENDIX.*

See accompanying articles, pp. 1610 and 1615.

Improving mean levels of glycemic control, as judged by assays for glycated hemoglobin (HbA_{1c}), has been shown to decrease risks of microvascular complications and cardiovascular disease (CVD) events for people with type 1 and type 2 diabetes (1,2). On the basis of these trials, HbA_{1c} levels $<$6.5% or 7% (47 or 53 mmol/mol) are proposed as standards for glycemic control (3,4). However, three subsequent trials suggested that targeting HbA_{1c} to this range may not lead to improved outcomes for people with long-standing type 2 diabetes (5–7). Of particular concern is the increase in CVD and all-cause mortality accompanying an intensive glycemic treatment strategy in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (6). The reasons for failure of the HbA_{1c}-based glycemic control strategies used in these more recent studies are not clear, but one possibility is that HbA_{1c} levels do not assess variability in plasma glucose levels; that is, HbA_{1c} does not directly reflect the frequency or severity of either hypoglycemic events or hyperglycemic increments after meals, both of which may cause physiologic changes that contribute to long-term risks. Possible mechanisms for such effects include systemic inflammation (8,9), oxidative stress (10), endothelial dysfunction (11,12), intimal-medial thickening (13), and cardiac ischemia or arrhythmias (14–16). Considerable literature linking various CVD risk markers with glycemic variability has been published (17,18).

Directly testing the hypothesis that glycemic variability contributes to adverse medical outcomes has been difficult due to limitations in available treatments and diagnostic tools. Other than α-glucosidase inhibitors, oral therapies have relatively weak effects on postprandial hyperglycemia. Of note, after failure of other treatments in people with long-standing type 2 diabetes, management of postprandial hyperglycemia with preprandial injections of rapid-acting insulin added to basal insulin is challenging and often ineffective (19,20). Efforts to maximize mealtime glycemic control by these means commonly fail to provide adequate control of postprandial glycemic increments while causing frequent hypoglycemia and weight gain.

However, new treatments for type 2 diabetes have been introduced. The shorter-acting GLP-1 receptor agonists (GLP-1RAs) exenatide and lixisenatide are of particular interest because of their ability to blunt postprandial glycemic increments (mainly by slowing gastric emptying) while also potentiating endogenous insulin secretion and suppressing inappropriate elevations of glucagon (21–25). Studies have shown that these agents, when used in combination with basal insulin and metformin, can flatten the postprandial glucose profile without increasing the risks of hypoglycemia and weight gain often associated with prandial insulin treatment (26–29). In addition, improved devices for continuous glucose monitoring (CGM) allow for more complete assessment of 24-h glycemic patterns (30–33).

The FLuctuATion reduction with inSUlin and Glp-1 Added togetheR (FLAT-SUGAR) study is using these methods to examine the hypothesis that glycemic variability is an important component of diabetes control that may influence diabetes complications. Three specific study questions are addressed. On a background of metformin and long-acting insulin therapy and with similar levels of HbA_{1c} attained, does mealtime treatment with exenatide compared with rapid-acting insulin *1*) reduce overall glycemic variability, *2*) reduce circulating levels of CVD markers, and *3*) reduce albuminuria or Holter-monitored electrocardiographic (ECG) abnormalities, two measures of tissue function relevant to diabetes? The results of the present proof-of-concept study are intended to guide the design of a larger, medical outcomes–driven trial testing a treatment strategy that reduces glucose variability better than traditional basal-bolus insulin (BBI) therapy. Because of this long-term objective, the population studied in FLAT-SUGAR was intended to be similar to that of the ACCORD trial.

RESEARCH DESIGN AND METHODS

Study Organization

FLAT-SUGAR is an Internet-based study (https://ccct.sph.uth.tmc.edu/flatsugar) with a public section as well as a password-protected section for use by clinical sites for randomization and data entry. All study documents are in the password-protected area of the Web site.

Logistical components of the trial include, besides the Clinical Trials Service Unit at the University of Washington in Seattle, Washington, a Data Coordinating Center at the University of Texas School of Public Health in Houston, Texas; a Drug Distribution Center at the Veterans Affairs Cooperative Studies Program in Albuquerque, New Mexico; and a Core Laboratory and a Holter ECG Reading and Analysis Center at the University of Washington. The organizational components of the study and their interrelationships are described in Supplementary Fig. 1. Clinical site investigators with expertise in intensive management of diabetes, including the use of CGM, and in clinical study management agreed to participate in this demanding protocol. These features permitted the ambitious goal of testing proof of concept for three separate study questions.

Study Design

The study is a multicenter comparison of two glycemic treatment strategies and comprised a screening period, an 8–12-week open-label run-in period, and a 26-week randomized, open-label treatment period (Supplementary Fig. 2).

Study Population Selected at Screening

A full description of inclusion and exclusion criteria is shown in Supplementary Table 1. Briefly, we identified an ACCORD-like population required to have type 2 diabetes and to need insulin therapy. Candidates for enrollment had to have either clinical CVD or evidence of increased CVD risk and to be clinically stable for the 3 months before enrollment. A subsample with some renal dysfunction was identified. Participants were provided no monetary incentive except a small reimbursement for transportation (gas mileage or fares), parking, and meals at the time of visits (total $10–50).

Run-in Period

The run-in procedure provided a stable clinical baseline, familiarized candidates to be randomized (CTR) with the study procedures, and identified those unable to adhere to study requirements. All CTR received instruction on an American Heart Association/American Diabetes Association meal plan and desirable exercises. If they had been using carbohydrate counting before the study, CTR were allowed to continue to do so as long as they met the HbA_{1c} goal. During this 8–12-week period, enrolled CTR used BBI therapy given by separate

injections with metformin and performed self-monitoring of blood glucose (SMBG) using the Bayer Contour meter three to four times daily as needed. All CTR were placed on basal insulin treatment using once- or twice-daily insulin glargine. If not previously taking metformin, CTR were required to start it with titration from 500 to 2,000 mg daily as tolerated. Medication dosages were adjusted by the investigators with a goal to maintain HbA_{1c} levels in the 6.7–8.0% (50–64 mmol/mol) range. All CTR were required to take one of three insulin rapid-acting analogs (RAAs): aspart, glulisine, or lispro. CGM (Dexcom SEVEN PLUS or G4), which was masked to CTR and investigators, and ambulatory ECG monitoring (Medicomp Holter) were performed for 7–10 days after at least 6 weeks of stable glycemic control. At the end of the run-in period, CTR had to meet eligibility for randomization, including tolerance of at least 500 mg metformin daily, performance of SMBG at least three times daily, maintenance of HbA_{1c} levels between 6.7 and 8.0% (50 and 64 mmol/mol), 7–10-day use of Holter devices, and successful 7–10-day use of CGM defined by a minimum 1,836 glucose values (85% of a goal 5-min CGM measurement for 7 days [2,160 total glucose values]). If CTR did not reach the goal 2,160 CGM measurements, they continued CGM to achieve the goal or were vetted for extenuating circumstances as long as they achieved 85% of goal CGM readings before randomization.

Randomized Treatment Period

Participants were randomized using electronic block randomization from the Data Coordinating Center at visit 3. Randomized participants continued with carefully supervised basal and mealtime therapy but were assigned either to continue BBI as in the run-in period or to replace the mealtime RAA with mealtime dosing of the GLP-1RA exenatide (Byetta) using a pen injector while continuing basal insulin glargine (GLIPULIN). Injections of either RAA or exenatide were generally taken just before all significant meals, but the timing could be adjusted according to participant preferences and glycemic patterns. A total daily dose of up to 20 μg exenatide was allowed, with distribution of 5- or 10-μg doses according to participant needs. In general, twice-daily or three times daily dosing was used with both regimens, depending on meal patterns. The investigators made titration decisions for basal and RAA insulin and for exenatide at all clinical visits as well as needed with supplementary telephone contact or electronic communications. The goal of titration was HbA_{1c} within a range of 6.7–7.3% (50–56 mmol/mol). Point-of-care HbA_{1c} was measured at each clinic visit for clinical glycemic management.

Clinical Measurements

Postrandomization visits occurred at baseline; 10 days; and 4, 12, 13, 19, 25, and 26 weeks (Supplementary Table 2). Clinical outcomes (blood pressure, heart rate, body weight, BMI, hip-waist circumference, adherence, and adverse events) were ascertained at baseline and 13 and 26 weeks. Baseline and 13- and 26-week visits included downloads of SMBG, CGM, and Holter data as well as Core Laboratory measurement of HbA_{1c}. Additional samples for Core Laboratory measurement of albumin/creatinine ratio, creatinine, alanine aminotransferase, inflammatory markers (levels of serum amyloid A [SAA], C-reactive protein [CRP], IL-6, and urinary 8-iso-prostaglandin F2α [8-iso-PGF2α] proteins) were also drawn at baseline and 13 and 26 weeks. Samples for assessments of adiponectin, 1,5-anhydroglucitol (1,5-AG), HDL proteomics, and serum metabolomics were performed on a 60-participant subset (30 per group) of the cohort.

ECG Monitoring Measurements

During each CGM monitoring period, a continuous Holter ECG monitor was also placed on each participant for 7–10 days. Each participant changed electrodes and batteries as needed and then returned the recorder for downloading at the research site after completion. All Holter data were uploaded and processed by Medicomp, Inc. Holter monitoring was performed together with CGM monitoring at prerandomization, 11–13 weeks, and 24–26 weeks. Other than the corrected QT interval (QTc), which was measured manually, all arrhythmias were quantified by Medicomp algorithms and verified by the Holter ECG Reading and Analysis Center at the University of Washington.

Processed Holter data were used to identify "panic" and "alert" rhythms. Panic rhythms were defined a priori as *1*) complete heart block, *2*) asystole (sinus pauses) of ≥5 s, *3*) sustained ventricular tachycardia or wide complex tachycardia with rate >150 beats/min (bpm) and duration ≥30 beats, or *4*) ventricular fibrillation. With any panic rhythm, the site was notified, and further evaluation or treatment was at the discretion of the primary investigator or the participant's physicians.

Alert rhythms were defined a priori as *1*) sustained supraventricular tachycardia (SVT) with rate ≥150 bpm and duration ≥30 s; *2*) sustained atrial fibrillation with rate ≥150 bpm and duration ≥30 s; *3*) sustained sinus tachycardia with rate ≥200 bpm and duration ≥5 min; *4*) sustained, marked bradycardia (sinus, idioventricular, or atrial fibrillation) with rate ≤35 bpm and duration ≥5 min; *5*) second-degree atrioventricular (AV) block types 1 and 2 or high-grade AV block, *6*) pauses with duration ≥3 and <5 s; and *7*) nonsustained ventricular tachycardia (NSVT) or wide complex tachycardia with rate ≥150 bpm and duration ≥5 beats and <30 beats.

Prespecified Holter-assessed end points were *1*) premature ventricular complexes (expressed as percent total beats per day); *2*) premature supraventricular complexes (expressed as percent total beats per day); *3*) QTc measured once daily using calipers when the heart rate was 60–100 bpm and the recording free of artifacts, with QTc calculated based on Bazett's formula using the average heart rate over the preceding 10 s and expressed as mean for all days of Holter recording performed at the prerandomization, 11–13-week, and 24–26-week visits; *4*) NSVT (expressed as number of beats per day and number of runs per day); *5*) SVT (expressed as number of beats per day and number of runs per day); *6*) sinus pauses >2.5 s (expressed as number of episodes per day); *7*) atrial fibrillation burden (expressed as percent of beats per day); and *8*) SVT burden (expressed as percent of beats per day).

Safety Measurements

At each visit and phone contact (Supplementary Table 2), CTR and randomized participants were questioned to elicit reportable adverse events. Hypoglycemic events were identified by symptoms reported and review of diaries and

meter downloads. To further ensure safety, CGM data from the prerandomization, 11–13-week, and final 24–26-week collections were analyzed. Predetermined hypoglycemia detected by CGM was reported by the Data Coordinating Center to the study site for the following: *1*) a serious event, defined as ≥4% of readings <40 mg/dL (2.2 mmol/L) with at least 2,160 readings over a 7–10-day period, or *2*) a significant event, defined as 2 to <4% of readings <40 mg/dL (2.2 mmol/L) or >5% of readings <50 mg/dL (2.8 mmol/L) with at least 2,160 readings over a 7–10-day period. The investigator could reevaluate the participant status then make appropriate changes as needed. Holter monitor recordings were screened and sites notified if panic rhythms were identified. Serious adverse events as well as unanticipated adverse device or medication adverse events were reported by the site investigators, reviewed by the study safety officer, coded using the Medical Dictionary for Regulatory Activities, and reported to the pharmaceutical companies for U.S. Food and Drug Administration–mandated surveillance process. Safety data also were summarized and reported to the Data and Safety Monitoring Board.

Statistical Analysis

A complete description of all the outcomes in FLAT-SUGAR are listed in hierarchical order in Table 1.

Primary Outcome

Change in the coefficient of variation (CV) of glucose values by CGM was the primary outcome for this trial. The CV of the CGM is the SD of the glucose values divided by the mean. To estimate a sample size for FLAT-SUGAR, unpublished data were taken from a previous randomized clinical trial of CGM (JDRF Continuous Glucose Sensor Trial) in participants with type 1 diabetes (R. Beck, personal communication). The control group for the JDRF trial (n = 58 adults aged >25 years) had a baseline HbA_{1c} of 6.7–8.0% (50–64 mmol/mol) and wore a masked CGM at baseline and 6 months. At baseline, the group mean CV CGM value, calculated as the mean of individual mean CV CGM values, was 38, with an SD of 8 and similar values at baseline. Values followed an approximately normal distribution. Assuming a two-sample two-tailed t test with a type I error of 0.05, a sample size of 110 participants (55 per group) would give 90% power to detect a difference of a mean change of 5 CV (SD 8) units between the control and treatment groups. In addition to the conventional two-sample t test, an ANCOVA model adjusting for the baseline value and clinical site was performed. If the residual values from the ANCOVA indicated nonnormality, a Wilcoxon rank sum test was used. To account for potential dropouts and noncompliance with CGM use, this value was increased by ~20 to a sample size of 130 (65 per group). This sample size covers a range of possible estimates in differences of CV of 3–6 and SD of CV of 4–8. With a power of 85%, the sample size is 92 (108 allowing for 15% dropout), and with a power of 80%, the sample size is 82 (96 allowing for 15% dropout). Analyses followed the intention-to-treat principle.

Secondary Outcomes

Because there is no gold standard to assess glycemic variability, especially in individuals with type 2 diabetes, we also examined other reported indices, including *1*) relative improvement from baseline of at least 20% of CV CGM; *2*) percent of CGM readings 70–180 mg/dL (3.9–10.0 mmol/L), <70 mg/dL (≤3.9 mmol/L) (hypoglycemia), and >180 mg/dL (10.0 mmol/L) (hyperglycemia); *3*) SD; *4*) mean amplitude of glycemic excursions (MAGE); *5*) continuous overall net glycemic action (CONGA); *6*) mean of daily differences (MODD); *7*) interquartile range; and *8*) mean glucose values at 48 h.

Table 1—Primary and secondary outcomes

Outcome hierarchy	Measurement class	Measurement type (source)	Outcome measure
Primary outcome	Glycemic control	Glycemic variability (CGM)	• CV CGM
Secondary outcomes	Glycemic variability	Glycemic variability (CGM)	• SD in glucose levels • MAGE • CONGA • MODD
		Other glycemic indices	• % glucose within 71–180 mg/dL by CGM • Hypoglycemia (clinical)
	Biomarkers	Systemic inflammation (serum)	• IL-6 • CRP • SAA
		Oxidative stress (urine)	• 8-iso-PGF2α
		Diabetic kidney disease (urine)	• Albumin/creatinine ratio
	Weight control	Body weight (vital signs)	• Body weight • BMI
	Rhythm disturbance	Arrhythmias (Holter monitor)	• QTc By randomized group • Arrhythmias By randomized group: Supraventricular arrhythmias Ventricular arrhythmias
Tertiary outcomes	Glycemia	Hyperglycemia (serum)	• 1,5-AG
	Adipocyte biology	Adipokine (serum)	• Adiponectin
	Plasma lipoprotein	HDL proteins (plasma)	• HDL proteomics
	Systemic metabolism	Metabolites (serum)	• Metabolomics

RESULTS

Between August 2012 and January 2014, the 12 clinical sites screened 255 individuals, and 131 eligible candidates entered the run-in period (Supplementary Table 3). Of these, 102 were eligible after the run-in. The leading causes of ineligibility were HbA_{1c} out of range (n = 101), dropout (n = 12), and C-peptide level out of range (n = 17). All 102 participants agreed to be randomized to either BBI or GLIPULIN. Baseline characteristics of randomized participants were balanced between treatment groups (Table 2) and closely resembled those of the ACCORD cohort. Sixty-three percent were male, 81% were Caucasian, mean age was 62 years, and 33% had a prior CVD event. At randomization, mean BMI was 34 kg/m^2, blood pressure 130/73 mmHg, HbA_{1c} 7.9% (63 mmol/mol), and creatinine 79.56 μmol/L. Microalbuminuria was present in 18% and macroalbuminuria in 3% of participants at randomization.

Table 2—Characteristics of participants at randomization

Variable	GLIPULIN (n = 52)	BBI (n = 50)	Total (n = 102)	ACCORD glycemia trial (n = 10,251)
Age (years)	62 (8)	63 (7)	62 (8)	62 (7)
Female sex	31	44	37	39
Median duration of diabetes (years)	15 (9)	16 (7)	15 (8)	10
Previous cardiovascular event	39	28	33	35
Previous congestive heart failure	8	0	4	5
Race or ethnic group				
White non-Hispanic	83	80	81	63
Black non-Hispanic	12	14	13	19
Hispanic	2	6	4	7
Other	4	0	2	11
Weight (kg)	101.3 (14.2)	99.7 (17.8)	100.5 (16.0)	93.4
BMI (kg/m^2)	34.2 (5.0)	33.7 (5.1)	33.9 (5.1)	32.2 (5.5)
Waist circumference (cm)	113.9 (16.6)	112.8 (14.1)	113.4 (15.4)	106.8
Blood pressure (mmHg)				
Systolic	131.7 (13.6)	129.1 (15.2)	130.4 (14.4)	136.4
Diastolic	73.5 (11.3)	73.1 (9.8)	73.3 (10.5)	74.9
Heart rate (bpm)	70.5 (10.5)	72.4 (10.4)	71.4 (10.4)	72.7
Blood				
HbA_{1c} (mmol/mol)	64 (4)	63 (3)	63 (4)	67 (12)
HbA_{1c} (%)	8.0 (0.4)	7.9 (0.3)	7.9 (0.4)	8.3 (1.1)
C-peptide (nmol/L)	0.80 (0.07)	0.73 (0.10)	0.77 (0.07)	NA
Creatinine (μmol/L)	79.56 (17.68)	79.56 (17.68)	79.56 (17.68)	79.56
Alanine aminotransferase (μkat/L)	37.6 (22.8)	32.4 (14.8)	35.0 (19.3)	NA
Urine				
Albumin/creatinine ratio (mg/g)	3.95 (7.83)	4.52 (16.94)	4.23 (13.05)	NA
<3.4	75	84	80	69
3.4–34	21	14	18	25
>34	4	2	3	7
Glucose-lowering medications (prescreening)				
Insulin	100	100	100	35
Basal insulin only	27	24	26	NA
Prandial insulin only	2	6	4	NA
Basal + one or more prandial injections	62	58	60	NA
Premixed insulin one or two injections	4	6	5	NA
Metformin	89	90	89	60
Secretagogue	21	26	24	51
Thiazolidinedione	6	2	4	19
GLP-1RA	0	8	4	0
DPP-4 inhibitor	2	4	3	0
CV CGM	31.9 (6.1)	30.0 (6.1)	31.0 (6.1)	NA

Data are mean (SD) or %. DPP-4, dipeptidyl peptidase-4; NA, not available.

CGM Data at Baseline

A graphic representation of the 24-h mean of the means for all randomized participants is shown in Fig. 1. The lowest mean value occurred between 5:00 and 10:00 A.M., with a prominent increment after the first meal and smaller increments later in the day. All participants completed the minimum number of CGM measurements, although 10 did not achieve the goal CGM of 2,160 readings. The mean value for CV CGM at baseline in the BBI group (n = 49 completed) was 30.1 ± 6.0 and in the GLIPULIN group (n = 52), 31.9 ± 6.1 (P not significant for the difference). Only 2% of all CGM readings were <70 mg/dL (3.9 mmol/L); ~23% were >180 mg/dL (10 mmol/L). Mean values of MAGE, CONGA, and MODD are shown in Table 3. These secondary glycemic outcomes were compared with the final levels at the end of the trial.

ECG and Holter Monitoring Values at Baseline

A total of 102 participants had a baseline continuous Holter monitor placed before randomization for a mean monitoring duration of 8 days per participant. The total number of rhythm disturbances was relatively few during the monitoring period. No panic rhythms were detected. Six alert rhythms were identified during the prerandomization Holter recordings using a priori definitions. For participants assigned to the BBI group, detected rhythms were sustained atrial fibrillation (one occurrence in one participant) and NSVT (one occurrence in three participants). For participants assigned to the GLIPULIN group, detected rhythms were second-degree AV block (one occurrence in one participant) and a sinus pause between 3 and 5 s (one occurrence in one participant).

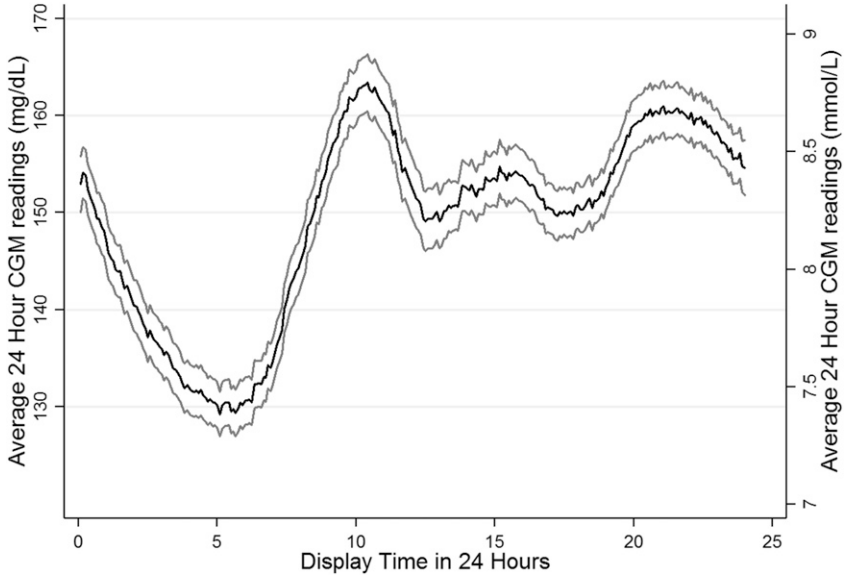

Figure 1—Graph of mean of means of 24-h CGM readings (for all 102 participants) before randomization in FLAT-SUGAR. Error curves represent the SD.

CONCLUSIONS

The FLAT-SUGAR study differs from previous studies of glycemic variability in several important ways, including its operational structure, the therapeutic methods used, and the population studied. Although an investigator-initiated study, FLAT-SUGAR has a complex design, involves geographically dispersed clinical centers, and uses centralized facilities for operational management, data handling, laboratory measurements, and drug and device supply and support (Supplementary Fig. 1). Financial support was provided primarily by a single commercial entity, with significant additional amounts provided from two other companies. Several other companies provided support in the form of in-kind donations of study drugs and equipment (details provided in DUALITY OF INTEREST).

It became clear in the 1990s that glycemic control as assessed by HbA_{1c} was a major risk factor for microvascular and neuropathic complications (1,2). However, over the next two decades, there has been support for the concept that these results arise from factors other than the mean glucose alone, which is captured by HbA_{1c} (12,17). Given the evidence that both hyperglycemia and hypoglycemia activate inflammation and oxidative stress, we hypothesized that the variability of glucose could be another risk factor for diabetes-related complications. The triumvirate of glucose variability, hyperglycemia, and hypoglycemia, with interactions among these components, has been identified and reviewed by Monnier et al. (34). In Fig. 2, we summarize the mechanisms potentially linking these aspects of glycemic control to oxidative stress and inflammatory mechanisms.

Although it is agreed that the CV may not completely capture glucose variability, this variable was identified as the most practical outcome for monitoring partly because we had previous data that allowed for an estimate of sample size for this study. Other measures of glycemic variability were also included in the analytic plan (Table 1). The primary purpose for FLAT-SUGAR was to determine whether separating glycemic variability while maintaining similar HbA_{1c} levels in a population of obese patients with type 2 diabetes and at high risk for or with known CVD is possible. A positive study would lead us to perform a definitive study with a relevant clinical outcome. Additional prespecified measures of outcome were ECG measurements collected by Holter monitoring, albuminuria, and various measures of inflammation and oxidative stress that may support a link between glycemic variability and tissue injury.

The study questions posed about the potential to reduce glycemic variability and the effect of this effort on physiologic and medical outcomes could not have been tested without availability of the shorter-acting GLP-1RAs that may blunt postprandial glycemic increments in type 2 diabetes more effectively than prandial insulin or long-acting GLP-1s. Although important reductions of glycemic variability have been shown with use of twice-daily injections of exenatide (35), FLAT-SUGAR tested the potential for an even-greater reduction of variability with injections of exenatide at low doses up to three times daily with meals. Similarly, use of currently available devices for CGM allows for collection of complete daily profiles to document the changes of glycemic profiles obtained by the two treatment methods. Although most of the evidence supporting a role for glycemic variability in the pathogenesis of diabetes complications has come, up to now, from epidemiologic studies or short-term

Table 3—Metrics of variability from CGM

	Baseline (n = 102)	mg/dL	mmol/L
CV CGM	31.03 (6.07)	—	—
% CGM readings within 70–180 mg/dL (3.9–10 mmol/L)	74.32 (11.84)	—	—
Hypoglycemia (% readings <70 mg/dL [3.9 mmol/L])	2.49 (3.01)	—	—
Hyperglycemia (% readings >180 mg/dL [10 mmol/L])	23.19 (12.13)	—	—
Mean glucose	—	149.27 (17.25)	8.28 (0.96)
SD	—	46.37 (10.65)	2.57 (0.59)
MAGE	—	85.93 (19.05)	4.77 (1.06)
CONGA	—	59.12 (15.89)	3.28 (0.88)
MODD	—	45.89 (12.52)	2.55 (0.69)
Interquartile range	—	59.97 (14.48)	3.33 (0.80)

Data are mean (SD). Mean glucose is the average of 48-h CGM values for each patient.

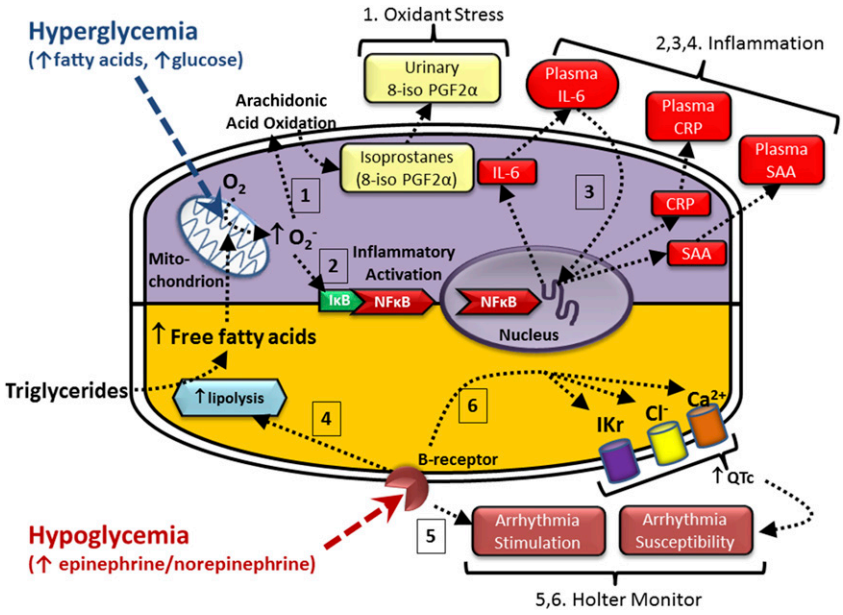

Figure 2—Selected, potential biological consequences of hyper- and hypoglycemia assessed in FLAT-SUGAR. Hyperglycemia (and/or fatty acids) may uncouple mitochondrial respiration, leading to *1*) increased oxidative stress, as assessed by measuring urinary 8-iso-PGF2α, a product of arachidonic acid oxidation; *2*) increased inflammatory activation, as assessed by measuring plasma levels of IL-6, CRP, and SAA resulting from translocation to the nucleus of the transcription factor nuclear factor-κB; and *3*) secondary activation of additional CRP and SAA expression by circulating IL-6. Hypoglycemia may also stimulate inflammatory activation secondarily, leading to an adrenergic counterregulatory response resulting in epinephrine- and/or norepinephrine-mediated stimulation of β-receptor–mediated *4*) lipolysis, with increased intracellular fatty acids and inflammation also assessed through plasma IL-6, CRP, and SAA levels; *5*) direct stimulation of arrhythmias, as assessed by Holter monitoring; and *6*) effects on multiple (e.g., potassium [IKr], chloride [Cl^-], calcium [Ca^{2+}]) ion channels, resulting in an increase in the QTc, which predisposes to arrhythmia and is assessed by Holter monitoring. IκB, inhibitor of κB.

physiologic studies of surrogate measures, FLAT-SUGAR may provide more direct interventional evidence. If, as intended, equivalent HbA_{1c} levels are attained with BBI and GLIPULIN treatment, the effects of reduced glycemic variability may be assessed, although direct effects of the exenatide or prandial insulin treatments cannot be excluded. The array of biomarkers included in the study will provide insights into a variety of postulated mechanisms.

The population selected for FLAT-SUGAR is a high-risk subgroup of people with type 2 diabetes. That the participants needed both basal insulin and additional prandial treatment ensures a relatively long duration of diabetes, and clinical markers of CVD risk are apparent at randomization. Comparison of baseline characteristics of the FLAT-SUGAR and ACCORD populations at baseline confirms considerable similarity between the two. Because microalbuminuria was present in 18% and a prior CVD event had occurred in 33% of those randomized in FLAT-SUGAR, assessment of changes in albuminuria and occurrence of ECG abnormalities will be of great interest. Demonstration of differences in these measures between the groups assigned to BBI and GLIPULIN could provide justification for a larger and longer study including these and other medical end points.

Despite these novel features, FLAT-SUGAR has important limitations. A true control group is not feasible. This limitation introduces the difficulty of distinguishing between the effects of reduced glycemic variability and nonglycemic effects of exenatide or prandial insulin (36). There could be direct tissue effects or ones resulting from nonglycemic metabolic effects or from weight changes. Finally, the study is, by necessity, unblinded.

Because the study requires an intensive treatment schedule with frequent visits, multiple interactions with highly specialized staff, and frequent measures of outcomes including both CGM and Holter monitoring, conclusions from the results cannot be reliably generalized to a broader population of less motivated or less carefully monitored people. Additionally, the protocol is not consistent with usual clinical practice in adding a GLP-1RA after BBI therapy, which has proven insufficiently effective. However, the goal is not to replicate practice but to test the hypothesis that glucose variability can be differentiated in this population.

In summary, FLAT-SUGAR is a proof-of-concept study aiming to verify the ability of a novel combination therapy regimen of basal insulin with a short-acting GLP-1RA to decrease glycemic variability and to then investigate whether this decrease in variability correlates with biochemical and clinical predictors of adverse medical outcomes. We successfully recruited, as intended, a trial population that resembles that of the ACCORD study population in which intensive glycemic therapy proved to be potentially hazardous. The randomized groups in FLAT-SUGAR were evenly matched. The number of participants recruited provides sufficient power to answer the primary study question and to address a number of secondary questions of interest. Validation of the treatment approach tested in FLAT-SUGAR and identification of the best clinical variables for further investigation could justify and assist in planning a larger medical outcomes trial.

Appendix

Writing Committee. Jeffrey L. Probstfield, Division of Cardiology, University of Washington (co-chair, co-principal investigator); Irl Hirsch, Diabetes Care Center, University of Washington (co-principal investigator); Kevin O'Brien, Division of Cardiology, University of Washington; Barry Davis, School of Public Health, University of Texas Health Science Center at Houston; Richard Bergenstal, International Diabetes Center, Park Nicollet; Connie Kingry, Division of Cardiology, University of Washington; Dori Khakpour, Diabetes Care Center, University of Washington; Sarah Pressel, School of Public Health, University of Texas Health Science Center at Houston; Kelley R. Branch, Division of Cardiology, University of Washington; and Matthew Riddle, Section of Diabetes, Oregon Health & Science University (co-chair).

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