Continuous glucose monitoring to Assess glycemia in chroNic kiDneY disease – ChANging glucosE management

(An interventional trial)

Protocol
September 28, 2015

Short title:
CANDY-CANE

Investigators:
Maryam Afkarian, MD, PhD
Ian de Boer, MD, MS (PI)
Irl Hirsch, MD
Joshua Neumiller, PharmD
Dace Trence, MD
Katherine Tuttle, MD

Supported by:
American Diabetes Association
Providence Sacred Heart Medical Center and Children's Hospital
MedTronic (equipment and supplies)
Abbott (equipment and supplies)

Sponsor of IND:
N/A

Abstract

Chronic kidney disease (CKD) is a common and morbid complication of diabetes. Poor glycemic control underlies most cases of diabetes and CKD, but clinicians and patients have virtually no high-quality information to guide glucose management once this develops. Diabetes and CKD fundamentally alters the ascertainment and treatment of hyperglycemia due to changes in hemoglobin kinetics, limitations to the menu of available medications, decreased catabolism of insulin and oral hypoglycemic medications, and – in end stage renal disease – direct effects of renal replacement therapy on blood glucose and insulin secretion. This constellation of changes is widely believed to increase the risk of hypoglycemia, which may in turn contribute to the markedly elevated levels of systemic inflammation and oxidative stress observed in diabetes and CKD and the high rates of arrhythmia and sudden death observed in this population. New medications that lower glucose with reduced risk of hypoglycemia are insufficiently evaluated among patients with CKD, who have frequently been excluded from clinical trials.

This is a proof-of-concept clinical trial testing the effects of linagliptin *versus* glipizide on glucose variability among people with type 2 diabetes and stage 3-4 CKD. In a cross-over design, each enrolled participant will receive 28 days of each study medication. Study medications will be provided in a randomly assigned order without blinding. The primary study outcome is glucose time in range, measured by ablinded continuous glucose monitoring for the last 6 days of each 28-day treatment period. Secondary outcomes include indices of glycemic variability, hypoglycemia, and biomarkers of systemic inflammation, oxidative stress, and albuminuria. The overall goal of this research is to identify safe and effective treatments to control glycemia among patients with diabetes and CKD.

1. Study Objectives

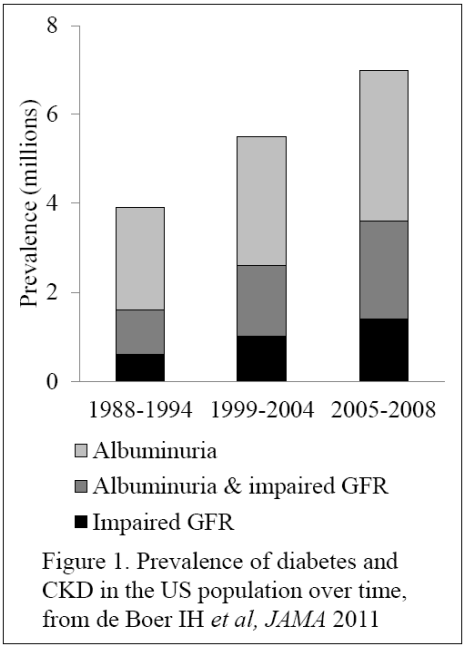

Figure 1. Prevalence of diabetes and CKD in the US population over time, from de Boer IH *et al, JAMA* 2011

Chronic kidney disease (CKD) is a common and devastating complication of diabetes. Specifically, albuminuria or reduced glomerular filtration rate (GFR) occurs in approximately 40% of patients with type 2 diabetes and markedly increases risks of cardiovascular disease (CVD) and death. Poor glycemic control underlies most cases of diabetic CKD, but clinicians and patients have virtually no high-quality information to guide glycemia management once CKD develops. CKD fundamentally alters the ascertainment and treatment of hyperglycemia due to changes in hemoglobin kinetics, limitations to the menu of available medications, and decreased catabolism of insulin and oral hypoglycemic medications. This constellation of changes is widely believed to increase glucose variability and the risk of severe hypoglycemia, which may in turn contribute to the markedly elevated levels of systemic inflammation and oxidative stress and the high rates of CVD and death observed among people with diabetes and CKD. New medications that lower glucose with reduced risk of hypoglycemia are insufficiently evaluated among patients with CKD, who have been frequently excluded from clinical trials.

The overall goal of our research is to improve the management and clinical outcomes of patients with diabetes and CKD. The goal of this study is to test whether a dipeptidyl peptidase-4 inhibitor, compared with a sulfonylurea, improves time in normoglycemia and reduces glycemic variability and hypoglycemic exposure.

Hypothesis a: Linagliptin, compared with glipizide, increases time in normoglycemia and decreases glycemic variability and hypoglycemic exposure, at a similar level of mean glycemia.

Hypothesis b: Linagliptin, compared with glipizide, reduces systemic inflammation, oxidative stress, and albuminuria, at a similar level of mean glycemia.

2. Background and Rationale

2.1. Chronic kidney disease is common. Chronic kidney disease (CKD), defined by elevated urine albumin excretion ("albuminuria") and/or impaired glomerular filtration rate (GFR),[1-4] is a tremendous problem from the perspectives of individual patients and the public health. CKD occurs in 40% or more of patients with type 2 diabetes.[1-6] We demonstrated that the prevalence of diabetes and CKD in the United States increased by 34% to 6.9 million persons over the last 20 years, driven by the increasing prevalence of diabetes itself (**Figure 1**, manuscript included with application).[6] Diabetes is the leading cause of end stage renal disease (ESRD) requiring dialysis or kidney transplantation in the developed world.[7]

2.2. Kidney disease identifies persons with diabetes at high risk of cardiovascular disease and death. Recent provocative data suggest that kidney disease captures all excess mortality risk associated with type 1 diabetes.[8,9] Surprisingly, using data from the Third National Health and Nutrition Examination Survey linked to the National Death Index, we found that kidney disease

also captured almost all excess mortality risk in type 2 diabetes.[10] Specifically, kidney disease was associated with markedly increased 10-year cumulative mortality, particularly among people with diabetes, but diabetes was not associated with increased mortality risk absent kidney disease (**Figure 2**). These data expand on work by our group and others demonstrating that albuminuria and impaired GFR are strong, independent, and additive risk factors for cardiovascular disease (CVD) and death among persons with diabetes.[11-16]

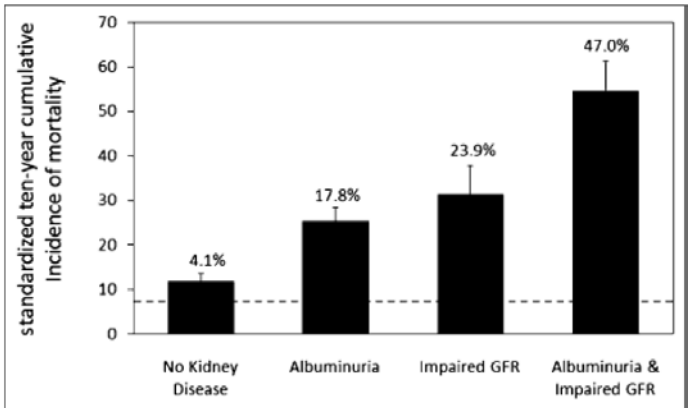

Figure 2. Ten-year cumulative incidence of mortality in the US population among people with type 2 diabetes, by kidney disease status, standardized to population age, gender and race and compared to people with neither diabetes nor CKD (dotted line). From Afkarian M *et al, JASN* 2013.

2.3. Kidney disease fundamentally alters glucose homeostasis, increasing the risk of hypoglycemia. Impaired GFR leads to a number of important perturbations in glucose homeostasis. These include decreased insulin catabolism, impaired metabolism and excretion of glucose-lowering medications (leading to prolonged sulfonylurea half-life and a contraindication to metformin use), decreased renal gluconeogenesis, malnutrition (in advanced DKD), and a blunted counter-regulatory response. [1-4,17-21] Mounting data suggest that these changes lead to increased risk of hypoglycemia. Moen *et al* reported that inpatient and outpatient veterans with diabetes and CKD experienced double the incidence rates of laboratory glucose <70 mg/dL compared to veterans with diabetes and normal estimated GFR.[22] Glucose <70 mg/dL was associated with markedly increased short-term mortality. A recent population-based Canadian study of diabetes and CKD reported a U-shaped association of hemoglobin A1c with all-cause mortality, again suggesting adverse effects of hypoglycemia.[23] In the ACCORD trial, albuminuria and reduced estimated GFR (even with limited ranges) were associated with markedly increased risks of hypoglycemia, particularly with intensive glucose-lowering.[24]

2.4. Evidence evaluating glucose control strategies in diabetes and CKD is lacking. Ironically, despite the fact that poor glycemic control underlies most cases of diabetic CKD, little is known regarding the impact of CKD on optimal glycemia targets and therapeutic strategies. Intensive diabetes therapy clearly reduces the risk of developing CKD,[25-30] and many people with diabetes develop CKD in large part due to poor glycemic control. However, clinical trials ascertaining the risks and benefits of tight glycemic control have systematically excluded people with prevalent CKD.[24-32] As a result, guidelines for clinical care commonly extrapolate treatment principles and hemoglobin A1c targets from studies that include few or no participants with kidney disease.[4] This may be unsafe. In ACCORD, post-hoc analysis suggests that the widely publicized adverse effect of intensive glucose lowering on mortality was confined to participants with CKD at baseline.[33] High-quality data on the benefits and in particular the risks of lowering blood glucose are needed to determine appropriate treatment strategies for patients with diabetes and CKD.

2.5. Continuous glucose monitoring offers a novel approach to study glycemia in CKD. Rapid advancements in technology have facilitated the use of continuous glucose monitoring (CGM) for clinical care and research.[34,35] CGM makes measurements of interstitial glucose concentration that accurately reflect blood glucose.[36] These measurements have become the gold

standard for measuring average glycemia and glycemic variability in high-quality studies such as the A1c-Derived Average Glucose (ADAG) Study,[37-40] STAR-3,[41] and the JDRF Sensor Study.[42] CGM has been applied in a number of small studies of CKD, mostly ESRD (**Table 1**).[43-51] These studies demonstrated that CGM is accurate in the setting of even advanced. In comparison, a larger, more detailed study with longer periods of CGM could additionally define glycemic variability and ascertain the determinants and consequences of hypoglycemia in CKD.

Table 1. Published studies of continuous glucose monitoring (CGM) among persons with kidney disease

First author	Participants	N	CGM duration	Correlation of CGM with blood glucose	Other
Riveline	T2D, HD	19	4d	0.90	Poor correlation of mean CGM glc & HbA1c
Jung	T2D, HD	9	6d	0.8-0.9	Hypoglycemia predominantly during & after HD
Kazempour	T2D, HD	17	48h	N/A	Frequent hypoglycemia, low glucose after HD
Mirani	T2D, HD	12	72h	N/A	Higher glucose variability after HD
Sobngwi	HD without diabetes	14	48h	N/A	CGM reflected blood glucose profile well, glucose concentrations were lower after HD
Marshall	CAPD	8	72h	0.91	Glucose variability correlated with dialysate
Skubala	CAPD	30	72h	N/A	Mean glucose dependent on dialysate glucose
Vos	DM, CKD	25	48h	N/A	Mean CGM glucose correlated better with glycated albumin than hemoglobin A1c
Lo	T2D, CKD	43*	6d	N/A	GGM glc correlated well with HbA1c in stage 3 but not stage 4-5 CKD, affected by EPO use

HD = hemodialysis; CAPD = continuous ambulatory peritoneal dialysis; CKD = chronic kidney disease not yet on dialysis; Correlation of CGM with blood glucose using venous phlebotomy; *subset (N<43) used CGM

2.6. Inflammation and oxidative stress may link CKD, hypoglycemia, and death. High glucose variability leads to periods of hypoglycemia and increases systemic inflammation and oxidative stress.[52-54] Patients with diabetes and CKD are known to have high levels of systemic

inflammation and oxidative stress, and these biologic processes likely contribute to the excess CVD risk observed in this population.[55-58] In particular, hypoglycemia may predispose to subclinical ventricular arrhythmia.[59-61] A markedly increased risk of sudden cardiac death is a major cause of increased cardiovascular death among persons with CKD.[62] Taken together, these data suggest that hypoglycemia may contribute to the high levels of inflammation, oxidative stress, and sudden cardiac death observed in diabetes and CKD.

2.7 Linagliptin is shown to reduce blood glucose in Type 2 diabetes patients. Linagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor proven to reduce blood glucose among patients with type 2 diabetes and normal GFR, with an incidence of clinical hypoglycemia that is lower than that of sulfonylureas (SU).[63] Linagliptin is primarily eliminated through non-renal routes and does not require dose adjustment with impaired GFR. In CKD, fixed-dose Linagliptin reduces hemoglobin A1c (compared with placebo) without a significant increase in clinically-recognized hypoglycemia.[64,65]

2.8. Summary: why we should study glycemia in people with diabetes and CKD now. It is critical to optimize treatment among patients with type 2 diabetes and CKD because they represent a large population at markedly increased risk of CVD and death. Risks and benefits of glucose-lowering strategies may differ in CKD because CKD fundamentally alters glucose homeostasis and its ascertainment and treatment. In particular, hypoglycemia and its biologic sequelae may be particularly common and detrimental in this population. However, virtually no high-quality data are available to guide glucose management in patients with CKD. CGM offers a novel opportunity to define fundamental aspects of impaired glucose homeostasis in CKD, including glycemic variability and hypoglycemia incidence rates, risk factors, and sequelae. Moreover, application of new diabetes treatments to patients with CKD may help prevent hypoglycemia in this high-risk population.

3. Study Methods

3.1 Overview This is a proof-of-concept clinical trial testing the effects of linagliptin *versus* glipizide on glucose variability among patients with type 2 diabetes and stage 3-4 CKD. Linagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor proven to reduce blood glucose among patients with type 2 diabetes and normal GFR, with an incidence of clinical hypoglycemia that is lower than that of sulfonylureas (SU).[63] Linagliptin is primarily eliminated through non-renal routes and does not require dose adjustment with impaired GFR. In CKD, fixed-dose Linagliptin reduces hemoglobin A1c (compared with placebo) without a significant increase in clinically-recognized hypoglycemia.[64,65] We hypothesize, among patients with type 2 diabetes and CKD, that Linagliptin, compared to Glipizide (a SU), will increase glucose time in range (TIR) (ascertained using CGM) while reducing glycemic variability and time below range (TBR) and exerting similar effects on mean glycemia. Results may have direct implications for patient care, suggesting that use of linagliptin as a SU-sparing agent may improve patient safety, and will provide a useful framework for future studies targeting glycemic control while minimizing hypoglycemia in the CKD population.

3.2 Study Design This is a cross-over trial in which each participant is treated with both linagliptin and glipizide, one medication at a time. Cross-over trials increase power and reduce cost by studying each participant on each treatment and comparing changes within each individual, as opposed to across individuals. We have successfully completed a crossover trial of similar size and duration with excellent recruitment and retention.[66] The main limitation of cross-

over trials is the potential for treatment carry-over, in which effects of treatment from the first treatment period extend into the subsequent treatment period(s). Because the effects of linagliptin and glipizide on glucose are rapid, we have little concern for carry-over effects on glucose as measured by CGM, our primary outcome. (Hemoglobin A1c and other longer-term glycemic markers will only be evaluated in secondary, exploratory analyses.) Given rapid effects, we will have short treatment periods (4 weeks), which will enhance retention and adherence. A wash-out phase is not appropriate for this study because carry-over effects are not expected and withdrawal of both glucose-lowering medications would lead to relative hyperglycemia

3.3 Study population This clinical trial will enroll 24 participants with type 2 diabetes and an estimated GFR 15-59 mL/min/1.73m^2 who are currently using a SU to control blood glucose. We will further restrict eligibility to participants with hemoglobin A1c < 8%, for whom we expect substantial times in each of normoglycemia, hypoglycemia, and hyperglycemia. Eligibility criteria is described in table 2. When available, eligibility laboratory data will be obtained from the electronic medical record, or from the results of previous research studies (such as CANDY); values within 3 months will be considered acceptable.

3.4 Recruiting

We will primarily recruit participants from the CANDY study, approaching the eligible subset of these participants at the last CANDY study visit. The CANDY study is a longitudinal observational study of patients with type 2 diabetes and stage 3/4 CKD. The aims of CANDY are to characterize glucose variability, hypoglycemia and hyperglycemia using continuous glucose monitoring and to explore the biologic sequelae of glucose variability and hypoglycemia in diabetes with CKD. The inclusion and exclusion criteria for both CANDY and CANDY-CANE are similar, making CANDY participants ideal candidates for the CANDY-CANE trial.

Table 2. Eligibility criteria

Inclusion criteria:
Type 2 diabetes
eGFR 15-59 mL/min/1.73 m^2
Hemoglobin A1c < 8%
Age ≥ 18 years
Current use of sulfonylurea

Exclusion criteria:
BMI > 40 kg/m^2
Actively using CGM for clinical care
End stage renal disease needing dialysis
Kidney transplant
History of acute pancreatitis
Pregnant
Unable to provide informed consent

Should additional participants be required, we will recruit these patients through mechanisms used for recruiting in the CANDY trial. For example, if needed we will recruit from Nephrology, Diabetes, and primary care clinics associated with the University of Washington, Harborview Medical Center, and Providence Medical Research Center/Sacred Heart Center in Spokane. Patients will be pre-screened through either the Mindscape or Orca computerized medical record system to access their records for limited information prior to obtaining their consent to determine eligibility. We will approach these potential participants at clinic visits after introduction by clinical staff OR by sending a mailed invitation postcard. In addition, we will advertise this study to patients seen in other Seattle-area Nephrology and Diabetes clinics

through distribution of the study brochure. Patients from these other Seattle-area clinics will self-refer for screening if they are interested.

3.5 Intervention Throughout the 8 weeks (total) of this trial, we will ask all participants to discontinue use of their prevalent SU but maintain other glucose-lowering medications (e.g. insulin) at unchanged doses. We will then prescribe linagliptin for 4 weeks and glipizide for 4 weeks, in a randomly determined order. DPP-4 inhibitors are an attractive class of medications to lower blood glucose among patients at high risk of hypoglycemia because they enhance the actions of endogenous insulin, with little effect on insulin secretion or action when a source of oral glucose is absent. DDP-4 inhibitors may also have beneficial effects on microvascular complications, including CKD, independent of glucose.[67,68] Linagliptin is particularly attractive for patients with CKD because it is primarily eliminated through non-renal routes and does not require dose adjustment or increased monitoring for adverse effects, even with advanced CKD.[64,65] We will administer linagliptin at its standard fixed dose of 5 mg daily. For comparison, we will administer glipizide at a fixed dose of 5 mg daily. We selected glipizide because it has a relatively short half-life and is therefore commonly used in patients with CKD. While individuals will differ in their hypoglycemic responses to these medications and doses, we anticipate that mean glycemia will change to a similar extent with each intervention when averaged across participants. In addition, we will adjust for mean CGM blood glucose when comparing differences in hypoglycemia and glucose variability.

3.5.1 Randomization Each participant will be prescribed linagliptin for 4 weeks and glipizide for 4 weeks. The order of these interventions will be randomly assigned by the Northwest Kidney Center Pharmacy, which will dispense all study medications. There will be no stratification or blocking.

3.5.2 Blinding Participants will not be blinded to treatment assignment in order to reduce cost and maximize patient safety. However, data for the primary study outcome (time in range measured by CGM) will masked to participants, and study staff and investigators will be given only coded treatment assignments ("A" and "B") until data analyses are completed. In this setting, lack of participant blinding is unlikely to bias results.

4. Study procedures.

Each participant will undergo blinded CGM for the last 6 days of each 4-week treatment period (**Figure 3**). During each CGM period, participants will also be asked to self-monitor blood glucose concentrations, and blood and urine samples will be collected for measurements of inflammation, oxidative stress, and albuminuria.

Figure 4. Medtronic continuous glucose monitor

4.1. Continuous glucose monitoring.

We will use Medtronic Enlite glucose sensors coupled to iPro2 recorders (**Figure 4**). The Enlite is an advanced glucose sensor, offering accurate glucose monitoring over days of use.

An Enlite will be provided to participants at study visits 2 and 4. Study staff will insert the sensor into the subcutaneous tissue of the abdomen with the use of a disposable introducer needle. The sensor is attached to the iPro2 recorder, which with its predecessor (iPro recorder) has proved reliable in numerous clinical studies as a masked glucose

sensor. Participants will be instructed in the use of the device including collection of self-monitored blood glucose concentrations for device calibration using a study-provided glucose meter. A guide booklet will be provided for the participant to take home. The participant will be instructed to contact the site staff if any appreciable skin reaction occurs or for any other concerns or questions. Participants will return all CGM equipment after 6 days, and study personnel will upload the data. Participants who do not obtain an adequate amount of CGM glucose values will be asked to repeat use of the CGM so that a sufficient amount of data is obtained. CGM data will be masked to participants, study staff, and investigators.

4.2. Self-monitored blood glucose. Participants will be asked to monitor blood glucose concentrations for calibration purposes. Participants will be provided with a Blood Glucose Meter and test strips. They will be asked to perform at least 4 finger-stick blood glucose measurements per day. Data from the Blood Glucose Meter will be directly uploaded at the end of the trial.

4.3. Blood and urine collections. At least 3 nonfasting blood samples will be collected at study visits 3 and 5. Whole blood, serum and plasma samples will be aliquoted, and stored at -80°C as per Kidney Research Institute protocols. Spot urine collections will also be collected from patients at study visits 3 and 5.

4.4. Inflammation and oxidative stress. Oxidative stress and inflammation are increased in diabetes and in chronic kidney disease and are likely to contribute to the pathogenesis of cardiovascular disease. We chose to measure two established markers of oxidative stress and two established markers of inflammation for this study. In addition, banked samples will be available for novel cardiovascular biomarker assays that are currently under development or will be developed in the future. Plasma and urine F_2-isoprostanes (biomarkers of oxidative stress) will be measured by GC-MS as initially described by Roberts and Morrow[69] in the University of Washington Mass Spectrometry Core Resource. As biomarkers of inflammation, plasma C-reactive protein (CRP) concentrations will be determined by nephelometry and plasma interleukin-6 will be measured by ELISA (Biosource International) in the KRI laboratory.

4.5. Hemoglobin A1c and other measurements of glycemic control. Hemoglobin A1c will be measured in real time by the University of Washington (UW) Clinical Laboratory and repeated by the University of Missouri. Measurement at UW is by HPLC, and quality control is verified daily with results calibrated to the DCCT laboratory as recommended by the NGSP. At the University of Missouri, Hemoglobin A1c will be measured using the Tosoh G8 analyzer, which employs an ion-exchange HPLC method and is one of the NGSP Secondary Reference Laboratory methods. The G8 is one of the most precise instruments for HbA1c analysis available and has shown long term CV at the University of Missouri of <0.5%. Hemoglobin A1c poorly reflects glycemic variability and therefore may not correlate well with risk of hypoglycemia.[38] Moreover, existing evidence suggests that hemoglobin A1c correlates with average glycemia poorly in patients with kidney disease). Therefore, we will also measure glycated albumin and fructosamine concentrations. Glycated Albumin will be measured at the University of Missouri using the Lucica GA-L enzymatic glycated albumin assay kit on the Roche C311 analyzer (CV 3-5%). Fructosamine will be measured at the University of Missouri using the Roche Fructosamine assay on the Roche C311 analyzer (CV 3-5%). 1,5-anhydroglucitol will be measured at UW using an enzymatic colorimetric assay (GlycoMark)

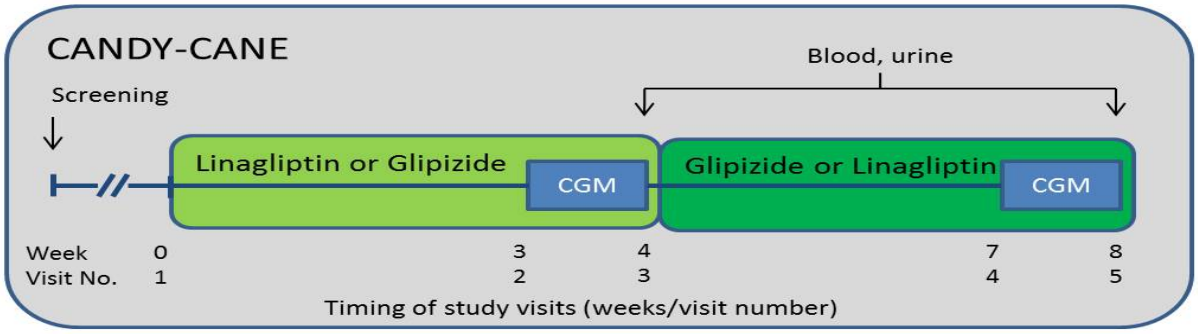

Figure 3. Timing of study visits. CANDY-CANE is an 8-week cross-over clinical trial. Continuous glucose monitoring (CGM) is performed during 6-day periods.

4.6. Schedule of study measurements. This study consists of one screening visit and 5 study visits. Additional telephone and in-person contacts may be scheduled as needed to trouble-shoot or repeat CGM.

4.6.1. Screening Visit. The screening visit will last less than an hour and will assess eligibility criteria for the study. During the visit, informed consent will be administered by the study staff. The visit will include a focused medical history including review of the electronic medical record, an inventory of current and recent medications, and a blood draw to determine eligibility if necessary. If subjects have participated in the CANDY study, eligibility will be determined at the end of the CANDY study, and measurements used for that study may be used to determine eligibility.

4.6.2. Study Visit 1 At the first study visit, a complete medical history and medication inventory will be taken. The subject will be administered a medical history questionnaire. Height, weight and vital signs (blood pressure, heart rate) will be taken. The subject will be assigned the order of study medications and the first medication will be prescribed. The subject will pick up their first medication from the pharmacy and begin taking the medication. Adverse effects will be assessed.

4.6.2. Study Visit 2 At the second study visit, the CGM device will be introduced by the study staff. They will explain its purpose and functions in detail, place the CGM device, and thoroughly describe plans for trouble-shooting the CGM device. The study staff will also provide a study glucose meter and test strips for self-monitored blood glucose (SMBG) testing, explain expectations for tracking SMBG at home, provide logs for SMBG, and demonstrate proper use of the logs. Adverse effects will be assessed.

4.6.3. Study Visit 3 At the third study visit, the CGM device will be removed from the subject by the study staff, and the SMBG log will be turned in to the study staff. The subject will cease taking the first study medication on this day, and return any remaining prescription to the study staff. The visit will include a blood draw, and spot urine collection.. The subject will pick up their second medication from the pharmacy and begin taking the medication the following morning. Adverse effects will be assessed.

4.6.4. Study Visit 4 At the fourth study visit, the CGM device will be reintroduced by the study staff. They will place the CGM device, and thoroughly describe plans for trouble-shooting the CGM device. The study staff will also provide a study glucose meter and test strips for self-

monitored blood glucose (SMBG) testing, explain expectations for tracking SMBG at home, provide logs for SMBG, and demonstrate proper use of the logs. Adverse effects will be assessed.

4.6.5. Study Visit 5 At the fifth study visit, the CGM device will be removed from the subject by the study staff, and the SMBG log will be turned in to the study staff. The subject will cease taking the second study medication on this day, and return any remaining prescription to the study staff. The visit will include a blood draw, and spot urine collection. Adverse effects will be assessed.

24-hour contact information will be given to all participants for questions that arise during the CGM periods. Participants who do not complete at least 4 days of CGM will be asked to repeat measurements or will be replaced by an alternate participant

Table 3. Schedule of Procedures

Procedure	Screening	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Informed Consent	**X**					
Medication inventory	**X**					
Medical History	**X**	**X**				
Blood draw	***X**			**X**		**X**
Medical History Questionnaire		**X**				
Physical measurements (height, weight, vital signs)		**X**				
Randomization		**X**				
Medication Prescribed		**X**		**X**		
Urine-spot				**X**		**X**
CGM Provided			**X**		**X**	
CGM Returned				**X**		**X**
Log provided			**X**		**X**	

Log returned				**X**		**X**
AE		**X**	**X**	**X**	**X**	**X**

** Blood draw at the screening visit will be completed only if creatinine and hemoglobin A1c values are not otherwise available within 90 days prior to the screening visit.*

5. Statistical analysis

5.1 Data analysis. All analyses will be performed according to intention-to-treat, meaning that all participants who contribute data during treatment with linagliptin and glipizide will be included in analyses regardless of adherence or adverse effects. The primary study outcome will be glucose time in range (TIR, proportion of CGM glucose readings 70-180 mg/dL), a clinically relevant outcome that can be tested with high power because of its broad anticipated range within the study population and precise ascertainment using CGM.[35,70,71] We will summarize time in range by treatment assignment, along with secondary outcomes including TBR (< 70 mg/dL), hypoglycemia characteristics (episode number, nadir glucose, awareness, clinical severity), time above range (TAR), standard deviation of blood glucose concentration, mean blood glucose concentration, biomarkers of inflammation and oxidative stress, and urine albumin excretion rate. We will test differences in these outcomes by treatment assignment using linear regression (for continuous outcomes, using log transformation as needed) or using Poisson regression (for rate data). Models will be adjusted for mean CGM blood glucose to account for potential differential effects of linagliptin and glipizide on mean blood glucose.

5.2 Power. Using the cross-over study design, two-sided alpha of 0.05, and glucose time in range (TIR quantified as proportion of time) as primary outcome, and assuming a TIR standard deviation of 19.5% (similar to published values[70,71]) and within-person correlation of TIR 0.7, we calculated a need for 24 participants (each studied on linagliptin and on glipizide) to detect a 10% difference in TIR between treatment assignments with 90% power. Notably, power depends on the difference in TIR between treatment groups, rather than mean TIR (which we expect to be between 25% and 50%), as long as mean TIR is not near zero. Because the effect size (10% difference in TIR) and within-person correlation of TIR are not known in this population, we also present power for different combinations of these variables using a fixed sample size of 24 in **Table 4**. We have excellent power for the most likely range of standard deviation and for clinically relevant treatment effects.

Table 4. Power for intervention study

	Within-person correlation of time in range		
Difference in time in range (%)	0.6	0.7	0.8
8%	62%	74%	89%
10%	80%	****90%****	98%
12%	92%	97%	> 99%

14%	98%	> 99%	> 99%

6. Safety and adverse events

6.1. Definitions

6.1.1. Adverse Event. An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

6.1.2. Serious Adverse Event. Adverse events are classified as serious or non-serious. A serious adverse event is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious. All adverse events that do not meet any of the criteria for serious will be regarded as non-serious adverse events.

6.1.3. Adverse Event Reporting Period. Adverse events will be reported if they occur between the time that informed consent is granted through 30 days following the last study visit.

6.1.4. Post-study Adverse Event. All unresolved adverse events will be followed by the PI until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator will instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator will notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor will also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

6.1.5. Abnormal Laboratory Values. A clinical laboratory abnormality will be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

6.1.6. Hospitalization, Prolonged Hospitalization or Surgery. Any adverse event that results in hospitalization or prolonged hospitalization will be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery will be documented as an adverse event if the condition meets the criteria for and adverse event. Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

6.2. Recording of Adverse Events. At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form. All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document. All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

6.3. Reporting of Serious Adverse Events. Reports of all serious adverse events with a reasonable possibility of being related to the study (including follow-up information) will be submitted to the IRB, according to the IRB policy, within 10 working days. Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's binder. Adverse events with a reasonable possibility of being related to the study which are not serious will be reported to the IRB as components of annual reports. Because this is an observational study, no data safety and monitoring board will be created for this trial. Adverse events and recruitment will be monitored by the PI and reported to the IRB, as described above.

7. Data Handling and Record Keeping

7.1. Confidentiality. Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts will be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

7.2. Records Retention. All study data will be de-identified and stored in secured electronic files and/or a locked file cabinet within a locked room. Data including personal identifiers (i.e. screening data) will be kept separately in a secure, locked location.

8. Study Monitoring, Auditing, and Inspecting

8.1. Study Monitoring Plan. The PI will allocate adequate time for such monitoring activities. The PI will also ensure that any sponsor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. diagnostic laboratory), and has adequate space to conduct a monitoring visit, if requested.

8.2. Auditing and Inspecting. The PI will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The PI will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

9. Ethical Considerations

This protocol and any amendments will be submitted to the IRB, in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

10. Study Finances

10.1. Funding Source. This study is financed by the American Diabetes Association (Grant 4-14-CKD-20) and supplies are furnished by Medtronic.

10.2. Conflict of Interest. Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All investigators will follow the Institutional conflict of interest policy.

10.3. Subject Payments. Participants will be compensated $25 for each main study visit (study visits 1-5), for a total of $125 if all study visits are completed.

10.4. Publication Plan. Funding sources will be acknowledged in publications, but funding sources will not be involved in decisions regarding what or how to publish study results in any way.

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