Management of inpatient hyperglycemia by continuous glucose monitoring in insulin-treated patients with diabetes: Dexcom G6 Intervention Study

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Short Title: Dexcom G6 Interventional Study

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I. RESEARCH OBJECTIVES AND SPECIFIC AIMS

Diabetes is reported in 20-34% of hospitalized adult patients in general medicine and surgery units [1,2]. The annual incidence of diabetes as any listed diagnosis has more than doubled during the past 2 decades to a total of 7.2 million hospital discharges, for a total of 43.1 million hospital days among U.S. adults [3,4]. There is a large body of literature showing a strong association between diabetes and increased hospital mortality and morbidity [1,5-8]. Clinical guidelines have recommended the use of basal bolus insulin regimens as the preferred management approach of non-ICU patients with diabetes [9-11], as it has been shown to be effective in improving glycemic control and reducing hospital complications [12-14]. However, hypoglycemia is a common adverse event of insulin therapy [15-18], with incidence rates ranging between 12% and 35% in randomized studies in non-ICU settings [14,19]. The development of hypoglycemia, like hyperglycemia, has been associated with higher rates of hospital complications, higher health care resource utilization, and hospital mortality [10,16,20-22].

Bedside point-of-care (POC) capillary glucose monitoring is the standard of care to assess glycemic control in the hospital. Diabetes guidelines recommend bedside capillary POC testing before meals and at bedtime to assess glycemic control and to adjust insulin therapy in the hospital [9,10,23]. In contrast to POC testing, continuous glucose monitoring (CGM) measures interstitial glucose every 5-15 minutes, thus providing a more complete glycemic profile during 24-hours compared to standard POC glucose testing [24,25]. In a recent study of hospitalized patients with type 2 diabetes (T2D) treated with basal-bolus regimen, we reported increased detection of both hypo- and hyperglycemic events with the use of CGM compare to the standard-of-care POC glucose testing [24]. More than 50% of the hypoglycemic events occurred between dinner and breakfast suggesting that many of these episodes would be missed by standard POC testing. Schaupp et al [26] reported that the number of nocturnal hypoglycemic episodes <3.9 mmol/L (70 mg/dl) was 15-fold higher, and the number of episodes >13.9 mmol/L (250 mg/dl) detected by CGM during night was 12.5-fold higher [24] compared to capillary POC glucose testing in general medicine patients with T2D treated with a basal bolus insulin regimen for ≥ 3 days.

Despite evidence supporting the use of CGM devices in hospitalized patients [27,28], clinical guidelines have been inconclusive in recommending the use of CGM in the hospital due to the lack of safety and efficacy outcome studies [27,29,30]. In recent years, the improvement in the accuracy of CGM sensors, as well as lack of interference with acetaminophen [31] and need for calibration [32], the use of hypoglycemia and hyperglycemia alarm system, and the ability to transmit glucose data in real time to the hospital nursing station suggest that CGM technology could replace finger-stick blood glucose monitoring in insulin treated patients in the hospital. Accordingly, we propose a randomized controlled study comparing the use of POC testing (standard of care) and Dexcom G6 CGM in guiding insulin therapy in hospitalized patients with T1D and T2D.

We hypothesize that CGM, by providing a more complete 24-hour assessment of glucose values compared to POC testing, will represent a better tool to guide healthcare providers in adjusting insulin therapy during hospitalization and after hospital discharge in general medicine and surgery patients with T2D and T1D.

B. Specific Aims:

Aim 1. To determine differences in glycemic control, as measured by the percentage of time in range between 80-180 mg/dl (efficacy outcome) and frequency of hypoglycemia (safety outcome), between DexcomG6 CGM and POC BG testing in hospitalized patients with T1D and T2D treated with basal bolus insulin regimen. Adult patients with T1D and T2D requiring basal bolus insulin therapy will be randomized to POC testing (standard of care) or to Dexcom G6 CGM to guide daily insulin dose adjustment. All patients will receive POC testing before meals and bedtime as well as a Dexcom CGM device. Patients in the POC testing group will wear a blinded CGM and providers will adjust insulin dose based on POC results. Providers in the CGM group will adjust insulin dose based on daily glucose profile information.

Hypothesis: The use of CGM will result in similar glycemic control but will improve detection and reduce the frequency of clinically significant hypoglycemia (<54 mg/dl) and severe hyperglycemia (>250 mg/dl) compared to standard POC testing in insulin treated patients with T1D and T2D.

Aim 2. To examine differences in glycemic control after hospital discharge between Dexcom G6 CGM and POC BG testing in hospitalized patients with T1D and T2D. Patients enrolled in Aim 1 who will be discharged on insulin therapy (+/- oral agents) will be invited to participate in this prospective exploratory study. All patients, regardless of inpatient treatment arm, will be discharged with a blinded CGM device placed either on the abdomen or arm at physician discretion. The total duration of the study is 10 days. Downloading of the sensors will be performed prior to discharge and 10 days after hospital discharge.

Hypothesis: Glucose monitoring by CGM will improve detection of clinically significant hypoglycemia (<54 mg/dl) and severe hyperglycemia (>250 mg/dl) compared to standard POC after hospital discharge in patients with T1D and T2D.

II. BACKGROUND AND STATUS OF WORK IN THE FIELD.

II.a. Inpatient glycemic control in non-ICU setting. Patients with diabetes have a three-fold greater chance of hospitalization compared to those without diabetes [33]. The annual incidence of diabetes as any listed diagnosis has more than doubled during the past 2 decades to a total of 7.2 million hospital discharges for a total of 43.1 million hospital days among U.S. adults affected [3,4]. Current guidelines recommend the use of intravenous insulin in the ICU and subcutaneous insulin regimens in non-ICU settings [10,34]. Although effective in improving glycemic control and in reducing hospital complications [14,35], intensive insulin therapy results in frequent hypoglycemia, reported in 12% to 30% of patients [13,36,37]. Thus, improving glycemic control while minimizing the rate of hypoglycemia is of major importance in the hospital, because both hyperglycemia and hypoglycemia have been shown to be independent risk factors of poor clinical outcomes and mortality [1,38,39].

II.b. Transition Care from Hospital to Home. Hospital discharge represents a critical time for ensuring a safe transition to the outpatient setting and reducing the need for emergency department visits and re-hospitalization. Few studies have addressed the management of patients with diabetes after hospital. In two recent randomized studies, we assessed the efficacy of an HbA1c based algorithm using glargine insulin for the management of patients with T2D [12]. Patients were discharged on a combination of oral antidiabetic drugs (OADs) and glargine insulin at 50% of hospital dose if their HbA1c was < 9%. Patients with an HbA1c ≥ 9% were discharged on a combination of OAD and glargine insulin at 80% of total daily hospital dose or on a basal bolus regimen with glargine and rapid-acting insulin analog before meals. The average HbA1c on admission of 8.75% decreased to 7.9% and 7.35% after 4 and 12 weeks of hospital discharge. The rate of hypoglycemia was ~32% in patients treated with oral agents plus basal insulin and greater than 40% in patients treated with basal bolus insulin regimen. These RCT studies and previous retrospective studies highlight the importance of BG monitoring and cautious use of insulin after hospital discharge.

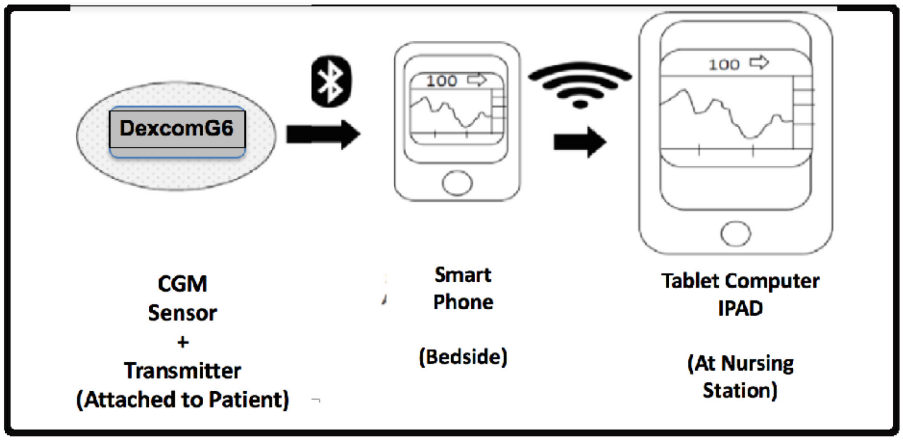
II.c. Advantages and limitations of CGM in non-ICU setting. Several studies have shown that the inpatient use of CGM is more effective in identifying trends toward hypoglycemia and hyperglycemia compared to standard POC glucose testing [24,25]. In a recent study, we reported increased detection of both hypo- and hyper-glycemic events with the use of CGM compare to the standard-of-care POC BG (23). More than 50% of the hypoglycemic events occurred between dinner and breakfast, suggesting that standard POC testing would miss many of these episodes. A recent panel of experts in inpatient diabetes care reported that CGM could more effectively identify hypoglycemia and hyperglycemia, allowing for better and safer management of patients with inpatient glycemic variability (22). Previous studies, however, used blinded CGM and therefore interventions to prevent impending hypoglycemia were not performed [25,26,40,41].

Previous studies with CGM technology in non-ICU settings have used "blinded" devices with glucometric values from the CGM compared retrospectively with the POC blood glucose testing. In these studies, CGM alarms were turned off, limiting any potential treatment actions based on the CGM glucose values. In the past, the CGM receiver/monitor was usually located in the patient's room necessitating nurses to enter frequently the patient's room to check CGM glucose values. In the present study, the blinded CGM will be a commercial G6 sensor/ applicator and a transmitter with modified firmware that stores glucose data. This is advantageous since there is no need for the subjects to use a receiver, which is the case with current CGM devices. For those in the real-time CGM group, referred to as the glucose telemetry service (GTS), glucose data will be transmitted

wirelessly from the DexcomG6 transmitter to a monitoring device located at a central nursing station. We anticipate that patients randomized to the CGM GTS will have less hypoglycemia as well as less severe hyperglycemia than patients randomized to POC group (standard of care).

The Dexcom G6 CGM is a commercially available factory-calibrated sensor system [32], thus there is no need for POC BG testing for sensor calibration. Performance/accuracy data for 10-days have reported excellent correlation with glucose values reported by laboratory and POC testing. The benefits of factory-calibrated CGM sensors include replacing the need for finger-stick blood glucose monitoring and providing the benefits of real-time glucose values in adjusting insulin therapy during hospitalization and after discharge. The proposed prospective RCT will be the first to test the efficacy and safety of Dexcom G6 CGM in adjusting daily insulin dose in medicine and surgery patients with T1D and T2D in non-ICU settings.

DexcomG6 Glucose Telemetry System. The system includes 3 main devices, i) DEXCOM G6 CGM device (sensor, transmitter, ii) a smart phone, and iii) a tablet computer. As a first step glucose values obtained from the CGM sensor are sent to the CGM transmitter by Bluetooth technology and DEXCOM Share2 software application to a smart phone that serves as an intermediate-transmitting (routing) device. This study phone will be locked in a safe box located in the patient's room. With the help of commercial internet wireless network, glucose values from the smart phone will be transmitted wirelessly to a table computer (I-Pad) using the DEXCOM Follow application [https://www.dexcom.com/apps].



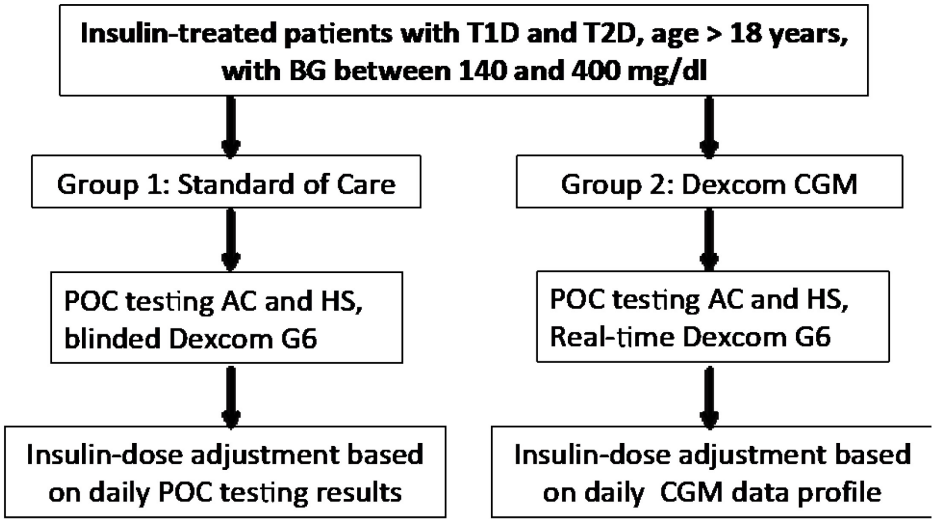
CGM alarm settings, and prevention of hypoglycemia protocol. Hypoglycemia alarms will be set to < 80 mg/dl (for prevention for low blood glucose levels). Nursing staff will be instructed to provide 15 grams of carbohydrates in response to a hypoglycemia alarm. For control group (blinded CGM) CGM alarms are turned off, however if the POC is found to be between <80 mg/dl, 15 grams of carbohydrates will be given as a preventive measurement to avoid clinically significant hypoglycemia.
Patients will receive education on the CGM technology by our research team. Similar education efforts are applied targeting nursing and medical staff, including how and when to remove or replace CGM sensors and transmitters and about the hypoglycemia prevention protocol. Treatment of hypoglycemia (POC <80 mg/dl) will be similar in both groups following a standard hospital protocol.

III. STUDY DESIGN AND METHODS

Aim 1. To determine differences in glycemic control, as measured by time in range between 80-180 mg/dl (efficacy outcome) and frequency of hypoglycemia (safety outcome), between DexcomG6 CGM and POC BG testing in hospitalized patients with T1D and T2D treated with basal bolus insulin regimen.

All patients with a known history of T1D and T2D admitted to general medicine and surgery units (non-ICU) receiving insulin therapy, will be considered as potential candidates for participation. Patients will be randomized to POC testing (standard of care group) or to Dexcom G6 (CGM group) to guide daily insulin dose adjustment. Patients in the POC testing group will wear blinded CGMs and providers will adjust insulin dose based on POC results before meals and bedtime (current standard of care). Providers in the CGM group will adjust insulin dose based on daily CGM glucose profile information.

Study Diagram:



We will randomize a total of 185 (the first 5 participants will not be included in the analysis but will be used ensure the technology is working appropriately without any sensor or connectivity issues. If issues are identified, corrections will be made at this time so as to not affect the integrity of the study) male and female subjects >18 years with T1D and T2D treated with basal bolus insulin regimen and with expected hospitalization longer than 3 days. Due to the design of this study, there will be no run-in period. Upon arrival to the emergency department or medical or general surgical wards, subjects will be screened. Patients admitted with acute or chronic medical illnesses, emergency or elective surgical procedures and trauma would be included in the study.

Standard of Care Group: Glucose monitoring by POC testing will be performed before meals and at bedtime. Results will be uploaded in the electronic medical record (EMR) system. The research team together with the PCP team will adjust daily insulin orders based on POC readings (standard of care) [10,14,43] In addition, patients will wear a 'blinded' CGM (no results will be visualized by patients, nursing staff, PCP or research teams).

CGM Group: Patients will wear a real-time Dexcom G6 CGM, which provide BG readings every 5 minutes for up to 10 days. In addition, patients will undergo POC testing before meals and bedtime per hospital protocol. Insulin therapy will be titrated based on daily CGM printouts, which will include BG readings, glycemic excursions, hypoglycemia and severe hyperglycemia values throughout the day. Patients will wear a CGM in the current approved insertion site, the abdomen, and in the upper arm, both during hospitalization (up to 10 days).

Primary and Secondary Research Outcomes:

The primary aim is difference between POC testing (standard of care) and CGM in glycemic control (efficacy outcome) and hypoglycemic events (safety outcome) during hospitalization:

1) Glycemic control, as measured by time in range between 80-180 mg/dl (efficacy outcome)
2) Clinically significant hypoglycemia <54 mg/dl (safety outcome)

Secondary outcomes include differences between groups in any of the following measures:

1. Nocturnal hypoglycemia < 70 mg/dl and < 54 mg/dl (between 22:00 and 06:00)
2. Number of hypoglycemia events (< 70 and 54 mg/dl)
3. Duration or time in hypoglycemia (minutes) during the day and night
4. Frequency and duration of time in hyperglycemia > 250 mg/dl
5. Percentage of BG readings within target BG of 80 and 180 mg/dl
6. Glycemic variability calculated by Standard Deviation, and MAGE
7. Differences in BG by CGM devices placed in the abdomen and upper extremity
8. Number of sensor removal for procedures/imaging, sensors failures, sensors dislodgments

9. After discharge: time in range (TIR), frequency of and time in hypoglycemia (TIHypo), frequency of and time in hyperglycemia (TIHyper), glycemic variability (GV)

Inclusion Criteria:

1. Males and females ≥ 18 years admitted to a general medicine or surgical services.
2. Diagnosis of: T1D or T2D receiving insulin therapy during hospital admission.
3. Subjects must have a randomization BG < 400 mg/dL without laboratory evidence of diabetic ketoacidosis (bicarbonate < 18 mEq/L, pH < 7.30, or positive serum or urinary ketones).
4. Patients with expected hospital length-of-stay of 2 or more days

Exclusion Criteria:

1. Patients with acute illness admitted to the ICU or expected to require admission to the ICU.
2. Patients expected to require MRI procedures during hospitalization.
3. Patients with clinically relevant hepatic disease (diagnosed liver cirrhosis and portal hypertension), corticosteroid therapy (equal to a prednisone dose ≥5 mg/day) , end-stage renal disease (dialysis), or anasarca.
4. Mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study.
5. Female subjects who are pregnant or breast-feeding at time of enrollment into the study.
6. COVID-19 infection

Subjects who are later found to be COVID-19 positive after enrollment, will be withdrawn from the study. If the infection appears 48 hours after enrollment, it will be documented as a complication as described in the data collection forms.

CGM Data Accuracy analysis:

Interstitial glucose values collected by CGM will be paired with POC BG (closed values within 15 min range). Patients with ≥ 2 days of sensor data, and with a minimum of 70% of CGM readings over used days will be included in the comparison analysis. A minimum of approximately 70% of possible CGM readings over used days appears to generate a report that enables optimal analysis and decision-making; standard reporting and visualization of CGM data are important [44,45]. CGM metrics will include overall MARD (mean absolute relative difference) and MAD (mean absolute difference), as well as the percentage of sensor values that fall within either 30 mg/dl of the POC testing or 30% glucose concentration. Similar calculations will be performed for 20 mg/dl/20% and 10 mg/dl/10% stratified by glucose values < 70 mg/dl, 70-140 mg/dl, >140-180 mg/dl and > 180 mg/dl [45]. The MARD reflects accuracy of the CGM glucose reading compared to the reference POC reading. This is the current standard for assessing accuracy of glucometer readings. Lower MARD indicates smaller differences between the CGM and meter value; a higher MARD value indicates larger differences. A three way and direct head-to-head comparison of data from the abdomen, upper arm and POC BG will be compared.

CGM – alarms and hypoglycemia protocol. We will use a real-time Dexcom CGM device with a modified transmitter able to store and transmit glucose data to different devices including a notebook/IPAD or computer desk located at the nursing station. **The hypoglycemia alarm** will be set at 80 mg/dl to alert the nursing staff and providers that a patient is at risk of hypoglycemia. If this occurs, the nursing staff will meet patient in the room to assess clinical status and signs/symptoms of hypoglycemia and will perform a POC glucose testing to confirm glucose values. Nursing staff will be instructed to document POC at the time and provide 15 grams of carbohydrates to treat and prevent a serious hypoglycemic event.

Patients in the Standard of Care group will wear a blinded CGM and without alarms, but BG levels will be recorded (in a blinded fashion). If a POCT BG value is <80 mg/dl, 15 grams of carbohydrates will be given as a preventive measurement to avoid clinically significant hypoglycemia.

An additional CGM alarm will be set up if BG>250mg/dL for one (1) hour. The alarms will be set up only for the research team following the participants assigned to real-time intervention. The research physician will determine if treatment changes need to be done and notify the nursing staff of such changes that require immediate attention.

Treatment randomization. Patients will be randomized using a computer-generated randomization table. Treatment randomization/assignment will be coordinated by the statistician Dr. Limin Peng. A research person (not actively involved in recruitment) at each institution will follow a computer-generated block randomization table based on glucose levels (BG≤200 or BG>200 mg/dL) at randomization.

Recommended Basal Bolus Insulin Protocol.
Patients will be treated with a basal bolus insulin regimen as previously reported [12,13].
During the first day of study enrollment POC BG values will be used to start insulin dosing in both groups.

T1D TREATMENT PROTOCOL

- Patients will be T1D will be treated with basal bolus insulin regimen, given 50% basal (glargine or detemir) and 50% of rapid acting insulin (lispro or aspart) before meals. This will be adjusted at physician's discretion based on the patient's home insulin regimen.

T2D TREATMENT PROTOCOL

Patients T2D Treated with Insulin Prior to Admission

- Discontinue oral antidiabetic drugs on admission.
- Subjects treated with insulin prior to admission will receive 80% of the total daily dose (TDD) given as basal bolus regimen with basal insulin (glargine, detemir or degludec) once daily plus rapid-acting insulin (lispro or aspart) before meals.
- Half of TDD will be given as basal and half as rapid-acting insulin.
- Basal insulin will be given once daily, at the same time of the day.
- Rapid-acting insulin will be given in three equally divided doses before each meal. To prevent hypoglycemia, if a subject is not able to eat, prandial insulin will be held.

Insulin Naïve T2D Patients Treated with Oral Agents or GLP1-RA Prior to Admission

- Discontinue oral antidiabetic drugs on admission.
- Starting total daily insulin dose:
  - 0.4 U/Kg/day when randomization BG between 140-200 mg/dL
  - 0.5 U/Kg/day when randomization BG between 201-400 mg/dL
  - 0.5 U/Kg/day if HbA1C: 7.5% to 8.4%
  - 0.6 U/Kg/day for HbA1C≥8.5%
  - Reduce TDD to 0.3 units per kg in patients ≥ 70 years of age and/or with an eGFR < 60 ml/min.
- Half of TDD will be given as basal insulin (glargine, detemir or degludec) once daily plus rapid-acting insulin (lispro or aspart) before meals.
- Basal insulin will be given once daily, at the same time of the day.
- Rapid-acting insulin will be given in three equally divided doses before each meal. To prevent hypoglycemia, if a subject is not able to eat, prandial insulin dose will be held.

To make daily insulin adjustments, POCT BG values will be used in the standard of care group. For those in the CGM group, the previous 24 hour glucose profile will be used to adjust insulin. The following guidelines will be used for insulin adjustment, at the physician discretion:

- Fasting glucose will be defined as average BG from 00:00 – 06:00AM. Basal insulin will be adjusted based on this level.

– Prandial adjustments – increase in dose is recommended if peak BG within 4 hours after a meal is >180mg/dL.

Basal Insulin adjustment.

- Daily basal (glargine, detemir or degludec) insulin dose will be adjusted as follow:
  - If the fasting and pre-dinner BG is between 100 - 140 mg/dl in the absence of hypoglycemia the previous day: no change
  - If the fasting and pre-dinner BG is between 141 - 200 mg/dl in the absence of hypoglycemia: increase basal insulin by 10% every day
  - If the fasting and pre-dinner BG is between 201 - 280 mg/dl in the absence of hypoglycemia: increase basal insulin by 20% every day
  - If the fasting and pre-dinner BG is >281 mg/dl in the absence of hypoglycemia the previous day: increase basal insulin (glargine) dose by 30% every day
  - If the fasting and pre-dinner BG is between 70 - 99 mg/dl in the absence of hypoglycemia: decrease TDD (basal and prandial) insulin dose by 10% every day
  - If BG <70 mg/dL, the insulin TDD (basal and prandial) should be decreased by 20%.
  - If BG <40 mg/dL, the insulin TDD (basal and prandial) should be decreased by 30-40%.

Supplemental insulin. Rapid-acting insulin will be administered following the "supplemental/correction insulin scale" protocol.

- If a patient is able and expected to eat most of his/her meals, supplemental insulin will be administered before meals and at bedtime following the "usual" dose of the insulin scale protocol.
- If a patient is not able to eat, supplemental insulin will be administered every 6 hours following the "sensitive" dose of the supplemental insulin scale protocol.
- **Table indicates number of units to be added to scheduled insulin dose.**

BEFORE MEAL, Supplemental Sliding Scale Insulin (number of units) - Add to scheduled insulin dose.
****Check appropriate column and cross out other columns**

***BG (mg/dL)**	**☐ Insulin Sensitive**	**☐ Usual**	**☐ Insulin Resistant**
< 141	No sliding scale (supplemental)insulin		
141 – 180	2	3	4
181 – 220	3	4	6
221 – 260	4	5	8
261 – 300	5	6	10
301 – 350	6	8	12
351 – 400	7	10	14
> 400	8	12	16

BEDTIME sliding scale: **Supplemental Sliding Scale Insulin dose at bedtime starting at BG > 220 mg/dL**

***BG (mg/dL)**	**☐ Insulin Sensitive**	**☐ Usual**	**☐ Insulin Resistant**
< 220	No sliding scale (supplemental) insulin		
221 – 260	1	2	4
261 – 300	2	3	5
301 – 350	3	4	6
351 – 400	4	5	7
> 400	5	6	8

*BG by POCT will be used in the standard of care group and CGM values at time of insulin administration will be used for those in the Dexcom CGM group.

Hospital Diabetes Education.

1. Diabetes education if not received within 1 year of admission
2. Use of glucose meters for home glucose self-monitoring
3. Keeping BG records, and will receive a logbook to record glucose tests results
4. Training on placement and care of CGM Dexcom G6
5. Hypoglycemia prevention, recognition and management

Aim 2. To examine differences in glycemic control after hospital discharge between Dexcom G6 CGM and POC BG testing in hospitalized patients with T1D and T2D.

During the hospital stay, patients will be instructed on CGM placement and care. The CGM system training sessions will be performed by a diabetes educator. The diabetes educator will educate patients on how CGM system differs from capillary SMBG, reinforcing the need for continued SMBG. Patients interested in participating in the study and willing to and able to use the CGM device will be recruited. A new CGM (blinded) will be placed prior to discharge. Patients will be asked to return for a clinic visit after 10 days of discharge (sooner or later depending on participant's schedule). Downloading of the sensors will be performed at the day of discharge and during follow up visit after hospital discharge.

Insulin Discharge Algorithm[12]:

Patients will be discharged following a standard protocol taking in consideration preadmission treatment (oral agents or insulin) and HbA1c value on admission as previously reported [12].

Patients with poorly controlled diabetes (HbA1c >7.5%) enrolled in Aim 1 will be invited to participate in this open label prospective outpatient study. The total duration of the study is 10 days.

- Patients with admission Hba1c < 7.5% will be discharged on their preadmission antidiabetic regimen.
- Patients on oral agents prior to admission with an HbA1c between 7.5% and <10% will be discharged on oral agents plus basal insulin (glargine, detemir, degludec) at 50% of the daily hospital dose.
- Patients on oral agents prior to admission with an admission A1C ≥ 10% will be discharged on their oral agents plus basal insulin at 80% of daily hospital dose.
- Patients on oral agents plus basal insulin (NPH, glargine, detemir) prior to admission with an admission A1C between 7.5% and <10% will be discharged on their oral agents plus basal insulin at 50% of daily hospital dose.
- Patients on oral agents plus basal insulin (NPH, glargine, detemir) prior to admission with an admission A1C ≥ 10% will be discharged on their oral agents plus basal insulin at 80% of daily hospital dose.
- Patients treated with basal bolus regimen prior to admission will be discharged on 80% of their preadmission TDD with basal insulin once daily and rapid-acting insulin before meals.

Follow-up Care:

- Duration of post discharge study: ~10 days (participant can return sooner or later depending on his/her schedule)
- New CGM (blinded) sensor will be placed (abdomen or arm at investigator's discretion) before discharge. If primary care team is planning to discharge over the weekend: participants will get new blinded sensor on Friday evening prior to discharge. The real time CGM will be left in the abdomen to continue to monitor during hosptial stay. Participant will be asked to return on the following business working day to remove real time CGM. Blinded sensor (placed before discharge) will be removed at 10 day follow up visit after discharge.
- Patients will be asked to continue checking their blood glucose by regular POCT and will return to the outpatient clinic visit at 10 days after discharge (sooner or later depending on participant's availability and schedule.

The following information will be collected after discharge:

1. Glycemic control:
    a. Mean daily blood glucose by CGM and POC testing
    b. Time in range (80-180 mg/dl)
    c. Frequency of overall clinically significant hypoglycemia (<54 mg/dl) and severe hyperglycemia (>250 mg/dl).
    d. Nocturnal hypoglycemia < 70 mg/dl and < 54 mg/dl (between 22:00 and 06:00)
    e. Duration or time in hypoglycemia (minutes) during the day and night
    f. Frequency and duration of time in hyperglycemia > 240 mg/dl
    g. Percentage of BG readings within target BG of 80 and 180 mg/dl (time in range)
    h. Glycemic variability calculated by Standard Deviation, and MAGE

2. Diabetes treatment:
    a. Number of patients receiving insulin
    b. Insulin dosage (unit/day)
    c. Use of oral agents

3. Clinical Outcome:
    a. Hospital readmissions
    b. Emergency room visits

Study Sites:
The study will be conducted in three academic institutions: Grady Memorial Hospital (Umpierrez G and Davis, G), Midtown Emory Hospital (Migdal, A), and at the University of Maryland and VA Maryland Health Care System (PI: Ilias Spanakis).

IV. Statistical Methods
The present study is one of two projects aimed to investigate the role of CGM (Dexcom G6 CGM) in the management of patients with diabetes in non-ICU setting receiving basal bolus insulin treatment. These prospective studies will explore the efficacy of CGM compared to standard POC glucose testing in assessing glucose control (efficacy) and hypoglycemic events (safety) as well as in guiding insulin therapy in patients with diabetes during admission and after hospital discharge. Professor Limin Peng, PhD at the School of Public Health at Emory University will conduct statistical analyses.

The primary efficacy endpoint is glycemic control measured by mean daily BG concentration and time in range between patients managed by POC testing (standard of care) and CGM. To show non-inferiority between POC and CGM in terms of glycemic control, we set the equivalence margin of 18 mg/dl (1 mOsm/l), from a view that a difference <18 mg/dl is usually not considered as clinically significant (12, 14, 16). Based on the results

from Rabbit medicine and surgery trials, it is reasonable to assume the standard deviation of mean daily BG is bounded above by 45 mg/dl. Assuming the true BG difference between the treatment groups is zero, and using one-sided, two-sample t-tests, we require 78 subjects for each treatment group to achieve 80% power. Accounting for 10% attrition rate, we would need 90 patients per treatment group, which means 180 subjects in total, to achieve >80% power in Aim 1.

We will report baseline characteristics by hospital service (medicine and surgery), diabetes type, and risk factors for hypoglycemia. The rates of incidence of hypoglycemia will be calculated based on the data obtained by CGM and POC. Comparisons will be made with the use of Wilcoxon tests (or Kruskal– Wallis tests) and Chi-square tests (or Fisher's exact test) as appropriate. Multivariate linear regression will be conducted to assess the difference in continuous secondary outcomes between the two groups while other relevant covariates. To be eligible for analysis at least 70% of CGM values need to be available per day, with at least 2 eligible days of data per subject in each study arm (inpatient and outpatient). Glucose patterns will be analyzed based on the Ambulatory Glucose Profile, recently endorsed by an international expert as a standardized approach for CGM interpretation [44]. Hospital glucose values after the first day of insulin treatment will be included in the analysis to allow us to have a full 24-hrs glucose profile and to avoid analyzing day-1 CGM values which may have lower accuracy. For clinical accuracy, CGM and POC BG will be paired and will be plot in the Clarke Error Grid [46,47]. Paired CGM and POC BG falling in the Zone A will be defined as "accurate", and in Zone B as "acceptable", with remaining values considered "not acceptable" if falling in Zone C, D, or E.

A total of 180 insulin treated patients will be included in this prospective study. Based on previous studies by our unit, we anticipate that 80% of patients will complete the inpatient and ambulatory arms of the study [13,48].

V. Methods and Procedures Applied to Human Subjects:

Potential Risk to Human Subjects

Hypoglycemia. The risk of hypoglycemia in non-ICU patients treated with basal-bolus insulin is between 12%–35% [14,19,37,49]. In this analysis, hypoglycemia is defined as a BG or IG < 70 mg/dL. Clinical significant hypoglycemia is defined as BG or IG < 56 mg/dl. Severe hypoglycemia is defined as BG or IG < 40 mg/dL.

Use of CGM. No major risks are expected with the use of the CGM device. Pain and bleeding with insertion is minimal. Skin irritation may occur in those sensitive to adhesives. Other potential risks and drawbacks of using CGM described in the literature including unrealistic expectations and overly aggressive correction of elevated glucose levels. Patients will be protected from this after discharge as all discharge CGMs will be blinded with insulin adjustments being made based on POC BG standard of care.

Protection against Risks

We will follow safeguards to minimize the risk to our subjects: a) we will carefully monitor capillary BG at the bedside using a hand-held glucose meter, b) only experienced nurses/or phlebotomist will draw blood samples, and c) women of reproductive age who are sexually active will undergo a urine pregnancy tests prior to participation in the study. To prevent significant clinical events, no patients with history of significant liver, renal impairment or cardiac failure will be recruited in this study.

We expect that approximately 10% in the inpatient setting and ~20% in the outpatient (post-discharge) arm will experience one or more episodes of hypoglycemia. To minimize the risk of hypoglycemia, the starting dose will be reduced in the basal bolus insulin regimen (TDD: 0.4 units per kg of body weight), in addition, in patients ≥ 70 years of age and/or eGFR < 60 ml/min the TTD will be further reduce to 0.3 units/kg. To avoid hypoglycemia, the total daily dose of insulin will be decreased by 10% for BG between 70-99 mg/dl and by 20% after each episode of hypoglycemia (BG < 70 mg/dl). In addition, in patients treated with insulin at home, the TDD of insulin will be reduced by 20% on admission and the attending physician may further reduce insulin dose in the presence of severe hypoglycemia.

CGM – alarms and hypoglycemia protocol. We will use a Dexcom CGM "blinded" device with a modified transmitter able to store and transmit glucose data to different devices including a notebook/IPAD or computer desk located at the nursing station. **The use of hypoglycemia alarm** set at 80 mg/dl will alert nursing staff and

providers that a patient maybe at risk of hypoglycemia. If this occurs, the nursing staff will meet patient in the room to assess clinical status and signs/symptoms of hypoglycemia and will perform a POC glucose testing. A carbohydrate load of 15 grams will be provided to patients to avoid clinically significant hypoglycemia.

Clinically significant hypoglycemia defined as POC <80 will be treated per hospital protocol in both groups.

Nursing staff should perform a POCT BG if the patient complains of symptoms of hypoglycemia, even in the absence of CGM alarms. POCT BG should be treated accordingly.

Insertion of the CGM sensor will be performed per manufacturer instructions and following an aseptic technique. After insertion of the sensors, providers will ensure proper hemostasis is achieved. Sensors will be removed if prolonged bleeding or severe pain occurs.

Recruitment and Consent. Coordinators will screen for potential participants from the electronic medical record. Subjects will be provided with sufficient information on the practice of glucose monitoring before providing written consent. The process of obtaining informed consent will follow the standard procedures of Emory University. This protocol will be submitted for approval by the Emory IRB.

Potential Benefits to Human Subjects. Subject participating in this trial will not receive any direct benefits during the hospital stay, since treatment decision will be made based on POC BG (standard of care). In the outpatient arm, investigators will analyze glucose profiles in a more detailed manner with potential for better treatment modifications.

Inclusion of children. No patients under the age of 18 will be recruited in this study.

Confidentiality. Informed consent will follow the procedure of Emory University Institutional Review Board. Every potential participant will be informed in writing and verbally with the important and key points of the study. One of the investigators or research coordinators will obtain a witnessed informed consent prior to inclusion of a patient into the study. Data collection records with personal identifiers will be stored in locked file cabinets. Presentation of the study results at regional or scientific meetings or in publications will not identify subjects. Access to research and confidential records will be limited to clinical investigators, coordinators and the IRB at Emory University.

Payment for Participation. Participation in this study is voluntary. Patients will receive one hundred dollars ($100.00) during the hospital stay, if patient withdraws before discharge, compensation will be provided at $10 per day during the inpatient stay and no more than $100. Seventy-five dollars ($75.00) at the 10 day clinic visit after discharge. Total compensation will be one hundred and seventy-five dollars ($175.00).

Financial Obligation. No additional cost to patients or to the institution will be incurred for research purposes. Research studies will be performed at no cost to study subjects. CGM will be provided by the sponsor at no cost to participants.

Research Injuries. If a patient is injured because of taking part in this study, Dr. Umpierrez and investigators, along with the medical facility will make medical care available to the patient at the patient's own cost. Financial compensation for such things as lost wages, disability or discomfort due to an injury related to the study is not available.

Financial Conflict of Interests. None of the investigators in this study have any outside activities that may represent a conflict of interest. None of the investigators have an economic interest in an outside entity, or act as officers, directors, employees or consultants with such an entity, whose financial interest may be affected by this research study.

Informed Consent. After identification of eligible patients these individuals will be provided basic information regarding the study and, if interested, they will then be screened by research staff using the inclusion/exclusion criteria delineated elsewhere in this protocol. The consent form, potential risks and benefits, and the rights of research participants will be explained to the participant by the investigators or research coordinator. Individuals will be asked if they have any questions, and research staff will answer these questions. The principal investigator will also be available to answer questions that participants may have during the consent procedure or during the time a participant is enrolled in the study. The consent form will be

completed in accordance with the IRB guidelines of Emory University. A signed copy of the consent form will be provided to the participant and a copy will be placed in the file that is maintained for each participant in the study office.

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