University of Crete

School of Medicine

"The association of dysglycemia at hospital discharge with the risk of readmission and post-discharge mortality"

"Η Συσχέτιση της δυσγλυκαιμίας κατά την ημέρα εξαγωγής από το νοσοκομείο με τους δείκτες θνησιμότητας και επανα-εισαγωγής στο νοσοκομείο"

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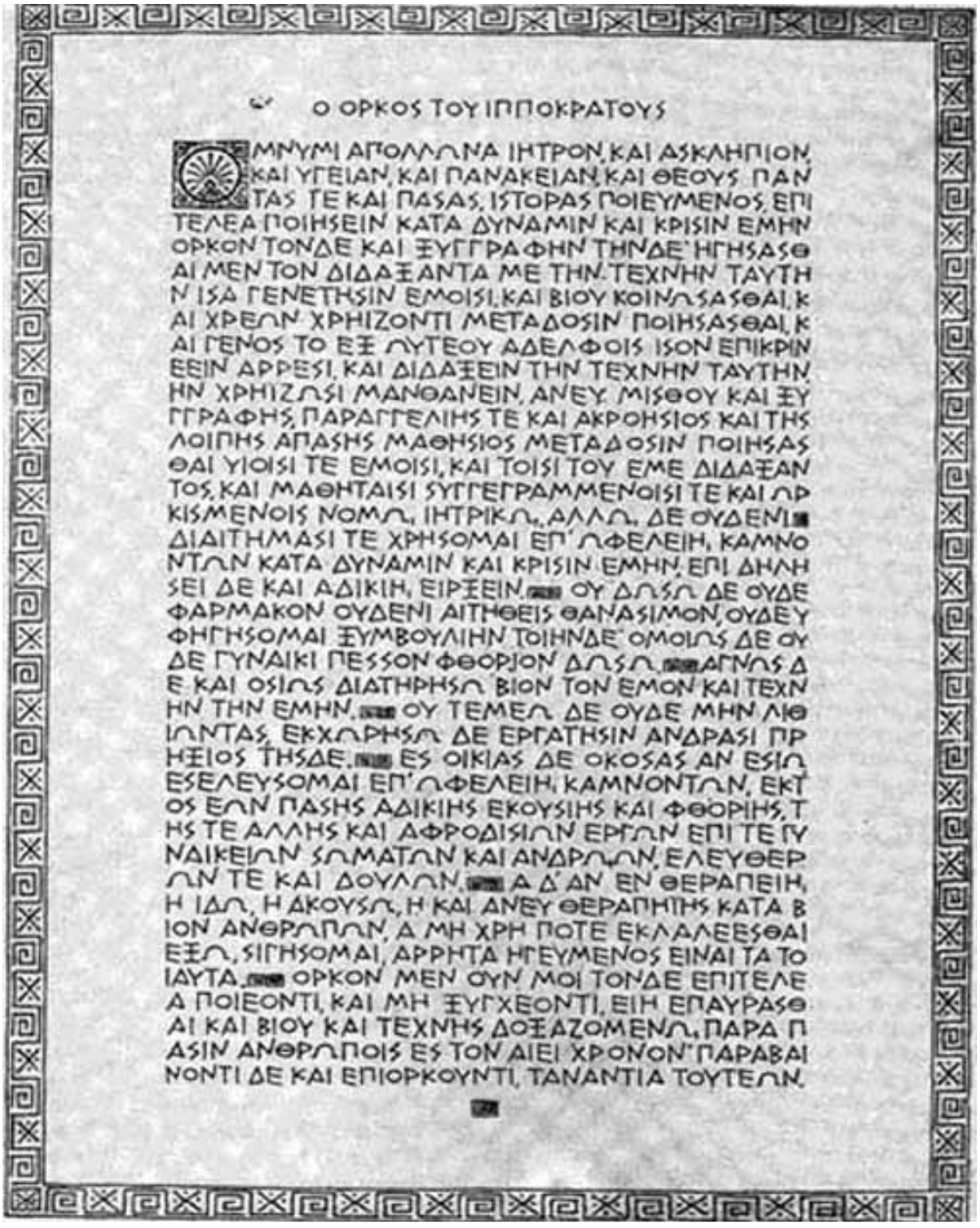

Ο ΟΡΚΟΣ ΤΟΥ ΙΠΠΟΚΡΑΤΟΥΣ

ΟΜΝΥΜΙ ΑΠΟΛΛΩΝΑ ΙΗΤΡΟΝ, ΚΑΙ ΑΣΚΛΗΠΙΟΝ, ΚΑΙ ΥΓΕΙΑΝ, ΚΑΙ ΠΑΝΑΚΕΙΑΝ, ΚΑΙ ΘΕΟΥΣ ΠΑΝΤΑΣ ΤΕ ΚΑΙ ΠΑΣΑΣ, ΙΣΤΟΡΑΣ ΠΟΙΕΥΜΕΝΟΣ, ΕΠΙΤΕΛΕΑ ΠΟΙΗΣΕΙΝ ΚΑΤΑ ΔΥΝΑΜΙΝ ΚΑΙ ΚΡΙΣΙΝ ΕΜΗΝ ΟΡΚΟΝ ΤΟΝΔΕ ΚΑΙ ΞΥΓΓΡΑΦΗΝ ΤΗΝΔΕ· ΗΓΗΣΑΣΘΑΙ ΜΕΝ ΤΟΝ ΔΙΔΑΞΑΝΤΑ ΜΕ ΤΗΝ ΤΕΧΝΗΝ ΤΑΥΤΗΝ ΙΣΑ ΓΕΝΕΤΗΣΙΝ ΕΜΟΙΣΙ, ΚΑΙ ΒΙΟΥ ΚΟΙΝΩΣΑΣΘΑΙ, ΚΑΙ ΧΡΕΩΝ ΧΡΗΙΖΟΝΤΙ ΜΕΤΑΔΟΣΙΝ ΠΟΙΗΣΑΣΘΑΙ, ΚΑΙ ΓΕΝΟΣ ΤΟ ΕΞ ΩΥΤΕΟΥ ΑΔΕΛΦΟΙΣ ΙΣΟΝ ΕΠΙΚΡΙΝΕΕΙΝ ΑΡΡΕΣΙ, ΚΑΙ ΔΙΔΑΞΕΙΝ ΤΗΝ ΤΕΧΝΗΝ ΤΑΥΤΗΝ, ΗΝ ΧΡΗΙΖΩΣΙ ΜΑΝΘΑΝΕΙΝ, ΑΝΕΥ ΜΙΣΘΟΥ ΚΑΙ ΞΥΓΓΡΑΦΗΣ, ΠΑΡΑΓΓΕΛΙΗΣ ΤΕ ΚΑΙ ΑΚΡΟΗΣΙΟΣ ΚΑΙ ΤΗΣ ΛΟΙΠΗΣ ΑΠΑΣΗΣ ΜΑΘΗΣΙΟΣ ΜΕΤΑΔΟΣΙΝ ΠΟΙΗΣΑΣΘΑΙ ΥΙΟΙΣΙ ΤΕ ΕΜΟΙΣΙ, ΚΑΙ ΤΟΙΣΙ ΤΟΥ ΕΜΕ ΔΙΔΑΞΑΝΤΟΣ, ΚΑΙ ΜΑΘΗΤΑΙΣΙ ΣΥΓΓΕΓΡΑΜΜΕΝΟΙΣΙ ΤΕ ΚΑΙ ΩΡΚΙΣΜΕΝΟΙΣ ΝΟΜΩ, ΙΗΤΡΙΚΩ, ΑΛΛΩ, ΔΕ ΟΥΔΕΝΙ ■ ΔΙΔΑΙΤΗΜΑΣΙ ΤΕ ΧΡΗΣΟΜΑΙ ΕΠ' ΩΦΕΛΕΙΗ, ΚΑΜΝΟΝΤΩΝ ΚΑΤΑ ΔΥΝΑΜΙΝ ΚΑΙ ΚΡΙΣΙΝ ΕΜΗΝ, ΕΠΙ ΔΗΛΗΣΕΙ ΔΕ ΚΑΙ ΑΔΙΚΙΗ, ΕΙΡΞΕΙΝ. ■ ΟΥ ΔΩΣΩ ΔΕ ΟΥΔΕ ΦΑΡΜΑΚΟΝ ΟΥΔΕΝΙ ΑΙΤΗΘΕΙΣ ΘΑΝΑΣΙΜΟΝ, ΟΥΔΕ ΥΦΗΓΗΣΟΜΑΙ ΞΥΜΒΟΥΛΙΗΝ ΤΟΙΗΝΔΕ· ΟΜΟΙΩΣ ΔΕ ΟΥΔΕ ΓΥΝΑΙΚΙ ΠΕΣΣΟΝ ΦΘΟΡΙΟΝ ΔΩΣΩ. ■ ΑΓΝΩΣ ΔΕ ΚΑΙ ΟΣΙΩΣ ΔΙΑΤΗΡΗΣΩ ΒΙΟΝ ΤΟΝ ΕΜΟΝ ΚΑΙ ΤΕΧΝΗΝ ΤΗΝ ΕΜΗΝ. ■ ΟΥ ΤΕΜΕΩ ΔΕ ΟΥΔΕ ΜΗΝ ΛΙΘΙΩΝΤΑΣ, ΕΚΧΩΡΗΣΩ ΔΕ ΕΡΓΑΤΗΣΙΝ ΑΝΔΡΑΣΙ ΠΡΗΞΙΟΣ ΤΗΣΔΕ. ■ ΕΣ ΟΙΚΙΑΣ ΔΕ ΟΚΟΣΑΣ ΑΝ ΕΣΙΩ ΕΣΕΛΕΥΣΟΜΑΙ ΕΠ' ΩΦΕΛΕΙΗ, ΚΑΜΝΟΝΤΩΝ, ΕΚΤΟΣ ΕΩΝ ΠΑΣΗΣ ΑΔΙΚΙΗΣ ΕΚΟΥΣΙΗΣ ΚΑΙ ΦΘΟΡΙΗΣ, ΤΗΣ ΤΕ ΑΛΛΗΣ ΚΑΙ ΑΦΡΟΔΙΣΙΩΝ ΕΡΓΩΝ ΕΠΙ ΤΕ ΓΥΝΑΙΚΕΙΩΝ ΣΩΜΑΤΩΝ ΚΑΙ ΑΝΔΡΩΩΝ, ΕΛΕΥΘΕΡΩΝ ΤΕ ΚΑΙ ΔΟΥΛΩΝ. ■ Α Δ' ΑΝ ΕΝ ΘΕΡΑΠΕΙΗ, Η ΙΔΩ, Η ΑΚΟΥΣΩ, Η ΚΑΙ ΑΝΕΥ ΘΕΡΑΠΗΙΗΣ ΚΑΤΑ ΒΙΟΝ ΑΝΘΡΩΠΩΝ, Α ΜΗ ΧΡΗ ΠΟΤΕ ΕΚΛΑΛΕΕΣΘΑΙ ΕΞΩ, ΣΙΓΗΣΟΜΑΙ, ΑΡΡΗΤΑ ΗΓΕΥΜΕΝΟΣ ΕΙΝΑΙ ΤΑ ΤΟΙΑΥΤΑ. ■ ΟΡΚΟΝ ΜΕΝ ΟΥΝ ΜΟΙ ΤΟΝΔΕ ΕΠΙΤΕΛΕΑ ΠΟΙΕΟΝΤΙ, ΚΑΙ ΜΗ ΞΥΓΧΕΟΝΤΙ, ΕΙΗ ΕΠΑΥΡΑΣΘΑΙ ΚΑΙ ΒΙΟΥ ΚΑΙ ΤΕΧΝΗΣ ΔΟΞΑΖΟΜΕΝΩ, ΠΑΡΑ ΠΑΣΙΝ ΑΝΘΡΩΠΟΙΣ ΕΣ ΤΟΝ ΑΙΕΙ ΧΡΟΝΟΝ· ΠΑΡΑΒΑΙΝΟΝΤΙ ΔΕ ΚΑΙ ΕΠΙΟΡΚΟΥΝΤΙ, ΤΑΝΑΝΤΙΑ ΤΟΥΤΕΩΝ.

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Disclaimer: The contents of the present proposal do not represent the views of the University of Crete, the University of Maryland, or the Veteran Affairs Health Care System.

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family community, has been an inspirational force for what I have accomplished and, more importantly, for what can be achieved.

Περίληψη

Οι ασθενείς με διαβήτη συχνά εμφανίζουν ακραίες τιμές γλυκόζης κατά την νοσηλεία τους στο νοσοκομείο. Είναι άγνωστο αν αυτά τα επεισόδια υπογλυκαιμίας ή υπεργλυκαιμίας κατά τη νοσηλεία, και ειδικά κατά τις τελευταίες ημέρες αυτής, μπορεί να επηρεάζουν την βραχυπρόθεσμη κλινική πορεία των ασθενών που τις εμφανίζουν. Ο στόχος της παρούσας διδακτορικής διατριβής ήταν να αξιολογηθεί εάν η υπογλυκαιμία και η αυξημένη μεταβλητότητα της γλυκόζης (GV) την τελευταία ημέρα νοσηλείας σχετίζονται με αυξημένη πιθανότητα επανεισαγωγης 30 ημερών και θνησιμότητα στις 30, 90 και 180 ημέρες μετά την έξοδο από το νοσοκομείο. Για να απαντήσουμε αυτά τα ερευνητικά ερωτήματα, συλλέξαμε δεδομένα σε εθνικό επίπεδο από τις Ηνωμένες Πολιτείες Αμερικής, τα οποία αντλήθηκαν από ηλεκτρονικές βάσεις δεδομένων που εστιάζουν σε νοσηλευόμενους ασθενείς με σακχαρώδη διαβήτη που νοσηλεύονται σε νοσοκομεία Veteran Affairs στις ΗΠΑ. Επειδή οι ασθενείς με σακχαρώδη διαβήτη έχουν πολλαπλές νοσηλείες στο νοσοκομείο, χρησιμοποιήσαμε προχωρημένα μοντέλα για τις στατιστικές αναλύσεις, GEE (Generalized Estimate Equations), τα οποία υπολογίζουν την επίδραση που έχουν στα αποτελέσματα οι πολλαπλές εισαγωγές στον ίδιο ασθενή. Τα πρωτόκολλα μελέτης εγκρίθηκαν από το Συμβούλιο Θεσμικής Αναθεώρησης του Πανεπιστημίου του Μέριλαντ (IRB) και την Επιτροπή Έρευνας και Ανάπτυξης Υποθέσεων Βετεράνων της Βαλτιμόρης. Τα αποτελέσματα των μελετών μας είναι καινοτόμα. Στην πρώτη μελέτη, δείξαμε ότι η υπογλυκαιμία και οι χαμηλές τιμές γλυκόζης κατά την τελευταία μέρα της νοσηλείας στο νοσοκομείο σχετίζονται με αυξημένο κίνδυνο για επανεισαγωγή 30 ημερών και θνησιμότητα 30, 90 και 180 ημερών μετά την έξοδο. Επιπλέον, επεκτείναμε τα ερευνητικά μας ερωτήματα και προσδιορίσαμε συγκεκριμένες τιμές χαμηλών τιμών γλυκόζης, κάτω από τις οποίες οι ασθενείς με σακχαρώδη διαβήτη διατρέχουν υψηλότερο κίνδυνο επανεισαγωγή και θνησιμότητας μετά το εξιτήριο.

Στη δεύτερη μελέτη, αξιολογήσαμε τον ρόλο της αυξημένη μεταβλητότητα της γλυκόζης κατά την τελευταία ημέρα νοσηλείας. Χρησιμοποιήσαμε τον συντελεστή διακύμανσης (CV) και την τυπική απόκλιση (SD) για να αντιπροσωπεύσουμε τις δύο πιο κοινές μετρήσεις της μεταβλητότητας της γλυκόζης. Διαπιστώσαμε ότι οι ασθενείς με διαβήτη και υψηλό CV ή SD την τελευταία ημέρα της νοσηλείας ήταν πιο πιθανό να εισαχθούν ξανά 30 ημέρες μετά το εξιτήριο. Τα ευρήματα αυτών των μελετών δημοσιεύτηκαν στο Journal of Clinical Endocrinology and Metabolism και στο BMJ Open Diabetes Research & Care και έλαβαν διεθνή αναγνώριση. Μετά την ολοκλήρωση των παραπάνω αναδρομικών-επιδημιολογικών μελετών, οι οποίες κατέδειξαν τη σημασία του γλυκαιμικού ελέγχου σε ασθενείς που νοσηλεύονται στο νοσοκομείο, εστιάσαμε σε κλινικές δοκιμές και παρεμβάσεις που μπορούν να οδηγήσουν σε βελτίωση του γλυκαιμικού ελέγχου κατά τη νοσηλεία. Η ομάδα μας ανέπτυξε έντονο ενδιαφέρον για τη χρήση τεχνολογιών και κυρίως συσκευών Continuous Glucose Monitoring (CGM) με καινοτόμους τρόπους για τη βελτίωση της φροντίδας των ασθενών με ΣΔ σε περιβάλλον νοσηλείας. Η σκέψη μας ήταν ότι χρησιμοποιώντας συσκευές CGM, θα μπορούσαμε να μειώσουμε την υπογλυκαιμία στο νοσοκομειακό περιβάλλον. Παρόλο που οι συσκευές CGM έχουν εγκριθεί για χρήση σε περιπατητικό περιβάλλον, η χρήση αυτών των συσκευών στο νοσοκομειακό περιβάλλον βρίσκεται σε ερευνητικό επίπεδο μόνο. Περιγράψαμε ένα νέο σύστημα παρακολούθησης, το οποίο ονομάσαμε Glucose Telemetry, το οποίο ξεπερνά πολλούς από τους περιορισμούς του CGM, καθώς είναι σε θέση να βοηθήσει τους ιατρούς να παρακολουθούν τις τιμές γλυκόζης από απόσταση. Αξιολογήσαμε το παραπάνω σύστημα σε πολλές απλές και πολυκεντρικές τυχαιοποιημένες κλινικές δοκιμές, αξιολογώντας την ικανότητά του να βελτιώνει τα γλυκαιμικά αποτελέσματα και εάν αυτή η παρέμβαση μπορεί να είναι εφικτή στο νοσοκομειακό περιβάλλον.

Abstract

Patients with diabetes often experience extreme glucose values during their hospitalization. It is unknown whether these episodes of hypoglycemia or hyperglycemia, especially during the last days of a hospitalization, may affect the short-term clinical course of patients who experience

them. The goal of the current Ph.D. proposal is to evaluate whether hypoglycemia and increased glucose variability (GV) on the last day of hospitalization are associated with increased 30-day readmissions and mortality at 30, 90, and 180 days following a hospital discharge.

We collected nationwide data, which were extracted from electronic databases focusing on hospitalized patients with diabetes admitted in Veteran Affairs hospitals in the USA. The study procedures, i.e., data collection, statistical analyses, and manuscript preparations, were partially conducted at the University of Maryland and the Baltimore VA Medical Center. Study protocols were approved by the University of Maryland Institutional Review Board (IRB) and the Baltimore Veterans Affairs Research and Development Committee.

The results of our studies are unique and innovative. In the first study, we demonstrated that hypoglycemia and low glucose values at hospital discharge are associated with increased risk for a 30-day readmission and 30-, 90-, and 180-day post-discharge mortality. Additionally, we expanded our research questions and identified specific cutoff low glucose values, below which patients with diabetes are at higher risk of readmission and post-discharge mortality.

In the second study, we evaluated the role of GV on the last day of hospitalization. We used the coefficient of variation (CV) and standard deviation (SD) to represent the two most common metrics of glucose variability. We identified that patients with diabetes and a high CV or SD on the last day of hospitalization were more likely to be readmitted 30 days after discharge. Overall, the findings of this proposal were published in the Journal of Clinical Endocrinology and Metabolism and at BMJ Open Diabetes Research & Care and received international recognition, as follows:

https://www.ncbi.nlm.nih.gov/pubmed/31042288

https://pubmed.ncbi.nlm.nih.gov/32398351/

https://www.medscape.com/viewarticle/912731

https://endocrinenews.endocrine.org/patients-with-diabetes-are-40-percent-more-likely-to-be-readmitted-to-the-hospital/

Following the completion of the above retrospective- epidemiological studies, which showed the importance of inpatient glycemic control, we focused on clinical trials and interventions that can lead to improving glycemic control during hospitalization. Our group developed a strong interest in utilizing technologies and mainly Continuous Glucose Monitoring (CGM) devices in innovative ways to improve care for patients with DM in the inpatient setting. Our thought was that by using CGM devices, we could decrease hypoglycemia in the hospital setting. Although CGM devices are approved for use in the ambulatory setting, the use of these devices in the hospital setting is considered investigational. We described a novel monitoring system, which we named Glucose Telemetry, which overcomes many of the CGM limitations, as it is able to provide remote glucose management. We have evaluated the above system in several single and multicenter randomized clinical trials, evaluating its ability to improve glycemic outcomes and whether this intervention can be feasible in the hospital setting.

Table of Contents

A1. Introduction -History of Diabetes

The history of diabetes in medicine dates back many years, with early descriptions of the disease dating as far back as Ancient Egypt [1]. In Ancient Egypt, diabetes was recognized as separate from other urinary conditions, and physicians attempted to treat it with dietary restrictions and herbal remedies. Around the 5th century BC, an Indian surgeon named Sushruta described diabetes and pointed out not only the sweet taste of the urine but its ability to attract the ants as well that the disease was affecting mainly the rich-upper castes. He also recognized that the disease was related to the excessive food consumption of rice, cereals, and sweets [1]. Similar descriptions have been reported from physicians from China (Chang Chung-Ching), Greece

(Rufus of Ephesus, Galen, Aretaeus), and Arab nations (Avicenna), as well as from other areas of the world. In the Middle Ages, diabetes was described as an evil condition and was often referred to as the "pissing evil" and was thought to be caused by a corrupted or "evil" humor in the body. The medieval scholar Dr. Maimonides (1138-1204) described in detail diabetes, including the symptoms of acidosis from uncontrolled hyperglycemia. Treatments during this time were often based on superstition and involved excessive phlebotomy or extreme dietary restrictions. It wasn't until the 19th century that significant advancements were made in our understanding of diabetes and its treatment.

One of the key figures in the history of diabetes research was the French physician Claude Bernard, who, in the mid-19th century, discovered that the liver plays a pivotal role in regulating blood glucose levels. Bernard's work laid the foundation for our modern understanding of diabetes and paved the way for further research. In the late 19th century, Oskar Minkowski and Joseph von Mering conducted experiments that linked diabetes mellitus to the pancreas, leading to the discovery of insulin-producing beta cells. In the early 20th century, scientists began to isolate and purify insulin. In 1921, Canadian researchers Frederick Banting and Charles Best from the University of Toronto successfully isolated and extracted insulin from dogs, leading to the first successful treatment of diabetes with insulin in humans. This discovery revolutionized the treatment of diabetes. Until this time, diabetes mellitus type 1 was considered a terminal disease [2], as this diagnosis almost certainly led to death.

Since the discovery of insulin, significant advancements have been made in treating and managing diabetes mellitus. In the 1930s-1950s, improved insulin and monitoring techniques were developed: Scientists worked extensively on refining insulin formulations, leading to the

development of longer-acting and more stable insulin products. In addition, blood and urine tests became standard for diagnosing and monitoring diabetes, providing more precise information about glucose levels and allowing better diabetes management. In the 1950s, the first oral medications for diabetes were introduced, providing an alternative to insulin injections for some patients with type 2 diabetes mellitus. In the 1970s, the development of home blood glucose monitoring devices allowed people with diabetes to better manage their condition at home. Notably, due to the initial significant cost, the first glucometers were thought to be only utilized at the physicians' office and not for home use. In the 1990s, the first genetically engineered insulin was introduced, providing a more consistent and reliable source of insulin. In the 1980s and the 1990s, important advances in insulin delivery were achieved as insulin pumps were introduced, offering a more continuous and flexible method of insulin delivery compared to injections. Continuous glucose monitoring (CGM) systems were developed, providing real-time data on blood glucose levels. More recently, in the 2000s, there was the development of new diabetes medications, such as DPP-4 inhibitors and GLP-1 receptor agonists, which offered alternatives to insulin for managing diabetes.

Overall, throughout history, diabetes management has evolved from a life-threatening/ terminal condition with limited treatment options to a more manageable chronic condition with a variety of therapeutic interventions and technologies. Research and innovation continue to shape the future of diabetes care.

A2. Types of Diabetes Mellitus

Although the majority of patients have type 2 diabetes mellitus and, to a lesser extent, type 1 diabetes mellitus, several other forms of diabetes have also been described [3]. Type 1 diabetes is

an autoimmune condition characterized by the immune system mistakenly attacking and destroying the insulin-producing beta cells in the pancreas. Islet cell autoantibodies and autoantibodies to glutamic acid decarboxylase (GAD), such as GAD-65, insulin, the tyrosine phosphatases islet antigen 2 (IA-2) and IA-2β, and zinc transporter 8 (ZnT8) have been identified as autoimmune markers for the diagnosis of type 1 diabetes [3]. The exact cause of this immune response is not entirely understood, but it is believed to involve a combination of genetic predisposition and environmental triggers. The onset of Type 1 diabetes is typically during childhood or adolescence, though it can occur at any age. Latent Autoimmune Diabetes in Adults (LADA) is a form of type 1 diabetes that occurs later in life among adult patients. Before the description of this condition, many patients with Latent Autoimmune Diabetes in Adults have been misdiagnosed with type 2 diabetes.

The main characteristic of the pathophysiology of Type 1 diabetes is an absolute insulin deficiency, requiring individuals to rely on external insulin for survival. The lack of insulin deficiency leads not only to elevated blood sugar levels but also to diabetic ketoacidosis. People with Type 1 diabetes must carefully and continuously adjust insulin doses, taking into consideration their dietary intake and physical activity to maintain blood glucose levels at the appropriate range and avoid hypoglycemia and hyperglycemia. Using glucometers and, most recently, Continuous Glucose Monitoring devices for monitoring blood glucose levels and multiple daily insulin injections or insulin pumps for insulin administration are standard components of managing Type 1 diabetes. Ongoing research focuses on understanding the autoimmune processes involved and developing interventions to prevent, delay, or reverse beta cell destruction.

Type 2 Diabetes:

Type 2 diabetes is the most common form of diabetes mellitus, accounting for almost 90-95% of all diabetes cases globally. Unlike Type 1 diabetes, Type 2 is characterized by insulin resistance but also insulin deficiency. The pathophysiology of type 2 diabetes includes various causes, among them genetics, lifestyle changes, and obesity. While there is a hereditary component, lifestyle choices such as poor diet, lack of physical activity, and obesity significantly increase the risk.

Type 2 diabetes often develops in adulthood, but there is an alarming rise in its occurrence among children and adolescents, mainly due to the global increase in childhood obesity. Initially managed through lifestyle modifications, including dietary changes and increased physical activity, diabetes medications may become necessary as the disease progresses. Oral or non-insulin diabetes medications such as metformin, sulfonylureas, and others aim to improve insulin sensitivity or enhance insulin production. In advanced stages, individuals may require insulin therapy alone or in combination with non-insulin diabetes medications. Lifestyle interventions, weight management, and regular exercise play crucial roles in managing Type 2 diabetes, regardless of the use of diabetes medications.

Gestational Diabetes:

Gestational diabetes mellitus occurs during pregnancy when insulin resistance and the inability to produce sufficient amounts of insulin to meet the increased needs lead to elevated blood glucose levels. This form of diabetes affects approximately 6-9% of pregnancies. Hormonal changes that occur during pregnancy can lead to insulin resistance, and for some women, this temporary condition may unmask an underlying predisposition to Type 2 diabetes. While gestational diabetes mellitus usually resolves after childbirth, affected women have a higher risk

of developing Type 2 diabetes later in their life. Managing gestational diabetes mellitus involves careful monitoring of blood glucose levels, dietary adjustments, and, in some cases, the use of diabetes medications. Insulin therapy may be necessary for those who cannot maintain target glucose levels with lifestyle modifications alone. Achieving tight glycemic control during pregnancy is crucial to prevent complications for both the mother and the newborn. Frequent clinic visits, monitoring blood sugar levels, and following a diabetes-focused treatment plan are essential components of care in patients with gestational diabetes mellitus.

Monogenic Diabetes:

Monogenic diabetes is a rare form of diabetes mellitus caused by mutations in a single gene, affecting insulin production and secretion. One form of monogenic diabetes is maturity-onset diabetes of the young (MODY), which usually presents in adolescence or early adulthood. Several types of MODY have been described. Neonatal diabetes is another form that manifests in the first six months of life. Monogenic diabetes accounts for only a small percentage of all diabetes cases, and its genetic basis differentiates it from more common forms. The specific genetic mutations involved in monogenic diabetes determine the age of onset, severity, and progression of the diabetes. Diagnosis of the monogenic forms of diabetes often involves genetic testing to identify the underlying genetic defect. Treatment varies but may include oral -non-insulin medications or, in some cases, insulin therapy. Understanding the genetic basis of monogenic diabetes is extremely important for tailoring treatment and providing accurate prognosis information to individuals and their families.

Secondary Diabetes:

Secondary diabetes is a form of diabetes that occurs secondary to another medical condition or as a side effect of certain medications that predispose patients to diabetes. Underlying causes can

include pancreatic diseases, hormonal disorders (for example, Cushing's syndrome or acromegaly), and drug-induced diabetes (for example, atypical antipsychotic medications). The onset of secondary diabetes is related to the underlying condition, and its prevalence is relatively low compared to primary forms of diabetes. Treatment for secondary diabetes varies based on treating the primary/ underlying condition or, if it is medication-induced, adjusting or discontinuing the offending medication safely. For those with diabetes arising from another medical condition, management may also involve a combination of lifestyle modifications, medications, and, in some instances, insulin therapy. Comprehensive medical evaluation and collaboration between healthcare professionals from different specialties are crucial steps for identifying and managing secondary diabetes effectively.

Other Rare Forms:

In addition to monogenic and secondary diabetes, several other rare forms result from specific genetic mutations or metabolic abnormalities. Mitochondrial diabetes, for example, stems from mutations in mitochondrial DNA, affecting energy production in cells. These rare forms often have distinct clinical presentations, requiring specialized diagnostic approaches and focused treatments. Given the rarity of these forms of diabetes mellitus, a comprehensive understanding of the genetic and metabolic mechanisms involved is essential for accurate diagnosis and effective management. Treatment strategies may include addressing the underlying genetic defect, managing associated symptoms, and, in some cases, diabetes medications or insulin therapy. Research in this area is ongoing, and advances in genetic/personalized medicine hold promise for further insights into these rare forms of diabetes.

A3. Diabetes in the outpatient-ambulatory setting

Over 37.3 million people of all ages, or 11.3% of the US population, have known diabetes. It is also estimated that 8.5 million people are undiagnosed [4]. The number of people with diabetes has risen globally from 108 million in 1980 to 422 million in 2014 [5]. Several studies performed in an ambulatory setting have shown that abnormal glycemic control can lead to micro and macrovascular diabetes-related complications [6, 7]. Overall, there is a significant level of evidence to suggest that hypoglycemia, hyperglycemia, and increased glucose variability (GV) are associated with adverse clinical outcomes.

In addition, several important conditions have been identified, all of which can significantly impact the health of patients with diabetes: Many patients with diabetes are overweight or obese, are physically inactive, are current tobacco users, or have hypertension or dyslipidemia. These unfavorable metabolic traits can explain why diabetes has significant morbidity and mortality. Overall, diabetes is the leading noninfectious cause of blindness, the leading cause of non-traumatic lower limb amputations, represents one of the most common causes of renal failure and end-stage renal disease and is among the leading causes of cardiovascular and cerebrovascular disease [4].

A4. Diabetes in the inpatient setting

Unsurprisingly, the prevalence of diabetes among hospitalized patients is even higher. Many patients with diabetes have a history of multiple and severe medical conditions, frequently associated with microvascular and macrovascular complications leading to recurrent and prolonged hospitalizations. People with diabetes have a higher chance of hospital admission compared to those without diabetes [8, 9]. Overall, more than 25% of the patients who are admitted have a history of diabetes [10]. Only in 2018, 8.25 million hospital discharges were

reported with diabetes, which translated to increased hospital costs [4]. In 2017, the cost of hospitalizations for patients with diabetes in the U.S. was estimated to be close to $123 billion [11].

Although 25% of inpatients have diabetes, another 12-25% of hospitalized patients present with hyperglycemia (without a history of diabetes) [12, 13]. These subjects can be patients with previously undiagnosed diabetes and individuals with stress-induced hyperglycemia, manifesting during acute illness-hospitalization and resolving following hospital discharge. In summary, almost 40-50% of hospitalized patients in the US have either an underlying history of diabetes, undiagnosed diabetes, or stress-induced hyperglycemia.

A5. Importance of glycemic control in the inpatient setting

Improving glycemic control in the hospital setting is essential, as several observational studies have shown that abnormal glucose control in the inpatient setting is associated with adverse clinical outcomes. Among critically ill patients hospitalized in the Intensive Care Unit (ICU), those who developed hyperglycemia had a higher mortality rate than those who did not [14-16]. In a retrospective study that included 1826 patients admitted to the medical and surgical ICU, the group of patients who had overall mean glucose values of 80-99 mg/dl had a lower mortality rate of 10% compared to the group of patients who had mean glucose values >300 mg/dl and who were found to have a mortality of 43% [14]. This increased mortality risk seems independent of other important parameters, such as ICU length of stay or duration of the history of diabetes, which has also been associated with increased mortality. In addition to the increased risk of mortality, several additional- mainly observational studies- have found that hyperglycemia has

been associated with prolonged length of hospital stay, a higher number of nosocomial complications, increased risk of infections, and mortality [14-26].

Reducing inpatient hyperglycemia, therefore, represents an important goal. However, achieving normoglycemia can lead to hypoglycemia. Hypoglycemia can also be harmful, and several studies have shown that hypoglycemia is associated with increased mortality among hospitalized patients [27-29] as well as prolonged in hospital length of stay and higher hospital cost [28, 30]. Hypoglycemia in the hospital has been defined as any point-of-care (POC) blood glucose <70 mg/dl, while severe hypoglycemia has been defined as any POC blood glucose <40 mg/dl [31]. The prevalence of hypoglycemia events varies across different studies and how it was defined. A retrospective study that evaluated medical records of 2,174 hospitalized patients with diabetes reported hypoglycemic events in 9.5% of the hospitalized patients [32]. In randomized clinical trials, the prevalence of hypoglycemia has been reported from 3 to 30% of medical and surgical patients [31].

Inappropriate intensification of diabetes therapy and medical errors can lead to over-treatment and, eventually, the development of iatrogenic hypoglycemia [33, 34]. Subsequently, fear of hypoglycemia can lead to clinical inertia, defined as "the recognition of a problem with a patient's management but a failure to act" [35]. Clinical inertia in inpatient diabetes management is a well-recognized reason for the hyperglycemia under-treatment among hospitalized patients with diabetes [33, 36-40]. Lack of ownership or confidence in diabetes management are barriers to achieving optimal glucose control in the inpatient setting [36, 41, 42]. The fear of hypoglycemia can be partially justified by the existing strong associations of hypoglycemia with adverse clinical outcomes.

In addition to hypoglycemia, another metric of adverse clinical outcomes from dysglycemia has been identified. Glucose variability represents the fluctuation of glycemic control; the wider these values are, the higher the glucose variability. In vitro and in vivo studies have shown that high glucose variability levels are more likely to lead to oxidative stress than hyperglycemia,[43-46] neuronal damage, mitochondrial damage, and coagulation activity[46, 47].

Several metrics of GV have been reported, and there is a lack of standardization for the definition and method of measurement of glucose variability. Significant heterogeneity of GV indices is reported within the literature [47]; therefore, it is challenging to consolidate the available evidence to drive changes in clinical practice. Standard deviation (SD) is a simple method for assessing glucose variability. It represents the distribution of data around the mean blood glucose [46]and is helpful for the analysis of the intra-day variation of POC glucose values. The coefficient of variation (CV) has frequently been utilized as a metric to access GV [44, 48] and represents the most widely accepted method of glucose variability. A criticism of the CV is that the mean is used in its calculation. As a result, violations of normality of the distribution of glucose values or extreme concentrations can exaggerate the CV measurement. Other metrics of variability have been proposed, including but not limited to J-index, mean amplitude of glucose excursion (MAGE), mean absolute glucose (MAG), continuous overlapping net glycemic action (CONGA), the high and low blood glucose index (HBGI, LHBI), and mean of daily differences (MODD) [45, 46, 49]. A limitation of the above metrics is that they require many glucose values. As a result, they cannot be efficiently utilized for point glucose value measurements. These metrics are more appropriate for evaluating GV using continuous glucose monitoring (CGM) devices.

Several studies have reported an association between increased GV and adverse outcomes, including mortality, in critically ill hospitalized patients with infections or sepsis and congestive heart failure [44, 50-53]. In a large multicenter ICU study, increased GV was a stronger predictor of mortality than the average/mean glucose values. Another retrospective study evaluated the medical records of 935 subjects admitted under medicine or surgery in a non-critical care (general ward) setting [44]. The authors performed general estimating equations (GEE) and adjusted for multiple covariates, including age, race, service of care (medicine or surgery), previous diagnosis of diabetes, hemoglobin A1c, body mass index (BMI), use of regular insulin, and hypoglycemia incidence. Overall, they showed that for every 10 mg./dl increase in SD and 10-percentage point increase in CV, the length of a hospital stay increased by 4.4% and 9.7%, respectively. The relative risk for death was also increased by 8% for every 10 mg/dl increase in SD [44].

A6. Quality of care in the hospital setting

Providing the highest quality of care to hospitalized patients should be a priority for all inpatient care facilities. Patients are admitted to a hospital expecting an uncomplicated and as short a hospitalization as possible, eventually leading to a safe discharge. However, hospitalized patients may experience prolonged lengths of stay, developing nosocomial complications, including hospital-acquired infections, unexpected mortality, and unsafe discharge plans, leading to early hospital readmissions. Among those unfavorable clinical outcomes, **increased inpatient and post-hospital discharge mortality rates and high 30-day readmission rates** represent some of the most significant adverse clinical outcomes, which reflect poor quality of health care in hospitals and can lead to higher health care costs.

A7. Hospital readmissions, an important factor of health care quality in patients with diabetes

Hospital readmissions, especially when they occur soon after discharge, represent a significant factor leading to rising hospital costs and are a marker of poor-quality healthcare delivery [54, 55]. Among the various readmission rates, the 30-day readmission rate has been considered significant as the Centers for Medicare and Medicaid Services (CMS) Readmissions Reduction Program penalizes hospitals with higher than 30-day readmission rates [56]. Patients see early re-hospitalization as a failure of the healthcare system, as the safe transition of patients from the hospital to their homes cannot be achieved [55].

Patients with chronic and severe medical conditions are more likely to be readmitted to the hospital [57]. Among patients with diabetes, the 30-day readmission rate is higher and is reported to range between 14% and 22.7% [58-65]. Compared with patients without diabetes mellitus, patients with diabetes have 40% higher re-hospitalization rates, with 30-day readmission rates reported to range between 14% and 26% [54, 58-63, 66-71]. Notably, almost 30% of these patients are experiencing two or more readmissions per year [72], accounting for more than 50% of total hospitalizations and hospital costs [72]. The cost of 30-day readmissions is estimated to be nearly $25 billion [54].

A8. Risk factors for hospital readmissions among patients with diabetes

It is essential to identify factors that place a patient with diabetes at increased risk for 30-day readmission. Policies and interventions can be tailored toward those factors to reduce the high

readmission rates and improve the quality and safety of care among patients with diabetes [54]. In general, predisposing factors that can lead to an increased risk of readmission can be broadly divided into three major categories: socioeconomic, hospital-related, and patient-diabetes-related.

A8i. Socioeconomic risk factors associated with 30-day readmission rates

Male patients with diabetes and those who have a lower education level are more likely to be readmitted in 30 days compared to females or those who are at least college graduates [58, 59, 66]. Insurance status is associated with increased risk for 30 readmission [58, 61, 66, 73]. Patients with diabetes who have lower income and those who are unemployed, retired, or disabled have been found to have a higher risk for 30-day readmission compared to those who have higher income or are employed [60, 66]. There are inconsistent data to suggest any increased or decreased risk for 30-day readmission with increased age, race-ethnicity, or proximity to the hospital [54].

A8ii. Hospital-related risk factors associated with 30-day readmission rates

Patients with diabetes with many previous hospitalizations, as well as those who are admitted urgently-emergently, have been found not surprisingly to be at higher risk for 30-day readmission [58, 66]. Decreasing length of stay efforts have raised concerns that shortened hospitalizations may lead to increased readmission risk. In contrast, however, several studies have shown that prolonged stay is associated with increased risk for 30-day readmission [58-61]. As expected, discharge against medical advice, as well as discharge with an intravenous catheter

placed (versus without an intravenous catheter-self care), has been found to lead to increased risk for 30-day readmission [61].

A8iii. Patients and diabetes-related risk factors associated with 30-day readmission rates

Several studies have found that patients with diabetes and a higher comorbidity burden are at a higher risk for 30-day readmission [58-60, 73], regardless of underlying microvascular or macrovascular complications. The increased risk for re-hospitalization is not only associated with the micro- and macrovascular comorbidities related to diabetes but, in general, among those with a higher comorbidity index. Patients receiving glucocorticosteroids or being treated with insulin as part of their outpatient (pre-admission) medication regimen are also at a higher risk for 30-day readmission [66]. Interestingly, a randomized clinical trial found that receiving diabetes medication during hospitalization before discharge is associated with a decreased risk for 30-day readmission among patients with diabetes and poor glycemic control [61]. Glucose control was also evaluated as a risk factor for 30-day readmission. Among them, hyperglycemia or hypoglycemia at admission or 24 hours before admission [64] and hypoglycemia at any point of the hospital stay [73] were associated with an increased 30-day readmission rate.

A9. Patients with diabetes are at a higher risk of mortality following hospital discharge.

Hospitalized patients with diabetes are at high risk for readmission and experience higher post-discharge mortality [44, 74-79], which is at least partially related to their underlying comorbidities. Among hospitalized patients with significant underlying cardiac disease, patients with diabetes experience higher post-discharge mortality compared to those without a history of diabetes [74, 75, 80]. In a study that included more than 2,000 patients with a previous history of

myocardial infarction (MI), hypertension, congestive heart failure, intermittent claudication, and obesity, mortality during the 30 days after coronary artery bypass grafting (CABG) was 6.7% among those with diabetes and 3.0% among those without diabetes ($p<0.01$) [74]. Mortality between 30 days and two years after hospital discharge was 7.8% and 3.6% among the two groups, respectively ($P < 0.01$). Similarly, among those with a recent myocardial infarction, the group of patients with diabetes experienced higher post-discharge mortality rates (up to five years) compared with those without diabetes (55% for patients with diabetes compared to 30% for patients without diabetes, $p<0.01$) [75]. Among elderly patients hospitalized for hypoglycemia or hyperglycemia, the 30-day post-discharge mortality rate has been reported to be 5.4% and 4.4%, respectively, and 1-year mortality has been reported to be 17.1% and 19.9% [77].

Studies have examined the role of glucose control and post-hospital discharge mortality, focusing mainly on glucose values early in hospital admission or during the hospital stay. In one of these studies, the authors not only found that patients with diabetes had a higher one-year post-discharge mortality rate compared with patients without diabetes but also that patients with diabetes and average glucose values of greater than 200 mg/dl during the entire hospital stay had an increased one-year post-discharge mortality compared with those with lower glucose values [80]. Focusing only on glucose values at admission, glucose values during this early period of hospitalization >240 mg/dl in patients with diabetes and myocardial infarction have been associated with increased 30-day and one-year post-discharge mortality [78]. In addition, increased GV during the entire hospital stay has been independently associated with 90-day post-discharge mortality [44] in a large retrospective study that included patients with diabetes hospitalized in the non-ICU setting.

A10. Risk factors associated with abnormal glycemic control in the hospital setting

Studies have identified risk factors for abnormal glucose control during inpatient stays. Older age, insulin use, errors related to insulin therapy, low body mass index (BMI), several comorbidities (liver failure, acute/chronic kidney disease, malignancy, heart failure, sepsis), and poor nutrition intake are important risk factors for hypoglycemia [81-85]. The severity of illness [86], treatment with medications with hyperglycemic properties [87], inappropriate selection of diabetes medications [88, 89], lack of knowledge or ownership of diabetes management [36, 42], changes in nutrition/ carbohydrate intake without making adjustments to the insulin regimen [42, 90] are associated with hyperglycemia. Limited information is available about risk factors associated with increased glucose variability. A retrospective study evaluating the risk factors of GV among hospitalized patients in the ICU setting reported that patients experiencing increased GV were more likely to be older, had a higher burden of comorbid conditions, had higher illness severity, and received greater treatment intensity [91].

B. Purpose of the current Ph.D. proposal

Reducing hospital readmissions and post-discharge mortality are high priorities for quality health care [92]. As described above, previously published studies have focused on identifying different risk factors that can lead to a higher risk for readmission, among them the potential role of glucose control during hospitalization. Although some of the published studies have focused on the effect of glucose control at admission or during the entire hospital stay, very limited information, if any, is available on the role of low blood glucose concentration during the day of a hospital discharge (the final 24 hours of hospitalization) with clinical outcomes. The last day of

a hospital admission represents a unique period during a hospital stay when medication adjustments have usually been finalized, patients can tolerate a full diet, thus minimizing nutritional interruptions and abnormalities in glucose control, and the underlying conditions that necessitated hospitalization have been treated [92].

The current proposal aimed to examine the association of glucose concentrations among patients with diabetes during the last 24 hours of their hospital stays and identify the risk of 30-day readmissions and post-discharge mortalities [92]. The main aim of this work was to investigate whether there is an increased risk of readmission and post-discharge mortality among patients discharged with low glucose values. More importantly, the purpose of this Ph.D. application is to identify a specific lower glucose value threshold above which patients with diabetes can be safely discharged from the hospital without experiencing increased risk for either readmission or death. In addition, we wanted to evaluate whether increased GV at hospital discharge is associated with an increased risk of 30-day readmission.

C. Methods

C1. Study overview: data sources (for both cohorts)

To address these different research questions, we assembled two separate study cohorts, one for low glucose values, i.e., hypoglycemia, and one for glucose variability, focusing on the last day of hospitalization. These nationwide cohorts used data from the Veterans Affairs (VA) health system, which has detailed information about the clinical course and outcomes of patients with diabetes admitted from 01/01/2000-12/31/2014 [93]. We collected data up to 2014, as this was the last year the International Classification of Diseases (ICD)-9 codes were used. ICD-10 codes

were initiated after 2014. Data were from the VA central data warehouse (CDW), a comprehensive national administrative database containing multiple files related to demographic, clinical, and pharmacy utilization. Mortality data were obtained from VA vital status files, which provided death dates [93]. The University of Maryland Center Institutional Review Board and the Baltimore Veterans Administration Medical Research and Development Committee approved the proposal protocols.

C2. Creation for the first cohort (low glucose-hypoglycemia at hospital discharge)

The cohort creation for the low glucose concentration- hypoglycemia on the last day of the hospitalization involved several steps (**Figure 1**) [92]. First, we identified all VA nationwide admissions related to diabetes [93]. Diabetes was defined by two or more ICD-9 codes during the past two years from either inpatient stay or outpatient visits on separate days and/or prescriptions for diabetes medications in the current year [94]. We then excluded admission to psychiatric or long-term care (*n=273,549*) settings, hospitalizations ending with a transfer to a non-VA hospital (*n=54,992*), admissions with a length of stay ≥30 days (*n=34,006*), and hospitalizations with death during admission (*n=30,603*) [93]. We also excluded hospitalizations where point of care (POC) glucose concentrations on the last day of hospital stay were not reported and those with reported values <10 mg/dl (*n=457,312*), admissions with missing body mass index [(BMI), *n=17,748*], or duplicate admissions (*n=510*). We also excluded intensive care unit admissions, as this population of patients with diabetes is different from the patients with diabetes admitted to the general wards/non-critical care setting (*n=92,879*) [44]. We also excluded hospitalizations where it was impossible to determine the admitting service (medicine or surgery, n=3) or the hospital where the patients were admitted (n=*62*). Finally, as hyperglycemia may be associated with an increased readmission rate or post-discharge mortality,

we excluded subjects-hospitalizations with hyperglycemic values (average glucose ≥180 mg/dl, n= 496,005) on the day of discharge. Our final cohort included 843,978 admissions.

C3. Creation for the second cohort (GV at hospital discharge).

Similar to the above, the cohort was created by initially identifying all acute VA admissions among patients with diabetes, using the same criteria [94, 95]. Then we excluded admissions (**Figure 4**) to psychiatric or long-term care settings (n=273,549) and admissions ending with transfer to a non-VA hospital (n=54,992), as follow-up data was not available, admissions with LOS ≥ 30 days (n=34,006) or LOS< 1 day (n=59,474), and admissions with in-hospital deaths (n=30,603). We also excluded admissions where there were less than two glucose values (including only those with two or more glucose values) during the last 24 hours of the hospitalization, as neither SD nor CV can be computed, and glucose values collected within 5 minutes of previous glucose values as previously described (n=772,482) [44]. Additionally, 399 duplicate admissions were also excluded. Patients in the ICU were excluded as this represents a different population than those admitted to noncritical care settings (n=13,071).[44] Finally, we excluded admissions with missing body mass index (BMI) or with BMI < 14 or > 120 kg/m^2 (n=20,835), hospitalizations where it was not possible to determine the admitting service (medicine or surgery, n=1), or the hospital where the patients were admitted (n=85)[96]. The final cohort sample used for analysis was 1,042,150 admissions.

C4. Covariates collected for both studies

Several covariates were collected [92, 95]. The independent variables that we studied included age, sex, BMI, income, admission source (whether patients were admitted from home or long-term care facilities), type of admitting service (medicine or surgery), diabetes medications received during the last 24 hours of their hospital stay, and several different comorbid conditions as identified by Elixhauser and colleagues (**Tables 1**) [54, 93, 97]. We determined the length of hospital stay by subtracting the discharge day and time from the admission day and time to ascertain the last 24 hours of the hospitalization.

C5. Exposures

The exposure of interest for the first cohort (low glucose-hypoglycemia at hospital discharge) was minimum POC glucose concentration during the 24 hours before discharge. Hypoglycemia and severe hypoglycemia were defined as POC glucose values <70 mg/dl and <40mg/dl, respectively [31].

The exposure of interest for the second cohort was glucose variability, measured in two ways: coefficient of variation (CV) and standard deviation (SD). We divided CV and SD values into ten different groups (deciles), with the first and tenth deciles having the lowest and the highest measurements, respectively.

C6. Outcomes

We studied five outcome measures: 30-day readmission, 30-, 90-, 180-day mortality, and a composite 30-day readmission or mortality outcome. We defined readmissions as those that occurred within 30 days of the date of discharge from the index admission [93, 98]. Since DM

patients are at risk of multiple admissions [72], limiting our cohort to include only the first readmission would have led us to exclude a significant number of re-hospitalizations. Readmissions more than 30 days after an index admission were considered as new index admissions, as previously described [93, 98]. Mortality was defined as death that occurred 30-, 90- or 180 days following initial discharge. The composite outcome of the 30-day readmission or mortality was defined as readmission or death within 30 days following discharge from the hospital.

C7. Statistical Methods

For low glucose-hypoglycemia at hospital discharge (first cohort) analysis, we used Poisson regression to compute adjusted rates of the five outcomes of interest (mortality 30-, 90- or 180 days following discharge, 30-day readmission, and 30-day readmission or mortality). For each outcome, event rates were computed for every 10 mg/dl glucose concentration category reported on the last day of hospitalization. Seventeen glucose concentration categories were used for each of the five outcome measures. We used Liang and Zeger's general estimating equations (GEE) [99, 100] with an exchangeable covariance structure to account for the serial autocorrelation of repeated admissions obtained from the same patient. Absolute event rates were adjusted to reflect the sample mean for each covariate and were generated as follows. For continuous variables, the variable's mean was used in the adjustment. For categorical variables, the estimate was adjusted to reflect the prevalence of the variable in the population (e.g., sex: 97% male). In addition to computing absolute event rates, we used linear contrasts to compute relative event rates. For these computations, 100-109 mg/dl was used as the reference category, as this value is associated with lower rates of hospital complications and mortality [101].

From the list of collected covariates (**Table 1**), we selected those variables that were potential confounders of the association between glucose concentration and one or more of our five outcome measures. We defined a potential confounder as a covariate that, when added to the model which included the 17-glucose concentration categories, produced a 10% or greater change in the association of the log event rate of one or more of the five outcome measures and at least three or more glucose concentration categories. For each of our five outcome measures, we performed two analyses: i) analysis including only the potential confounders selected as described above [age, BMI, and BMI^2 (BMI centered at 30 kg/m^2 and its square to decrease the collinearity between un-centered BMI and its square)], admission source, admitting service, diabetes medications received on the last day of the hospitalization, and the presence of comorbidities including congestive heart failure, liver disease, fluid or electrolyte disorders, hypertension, metastatic cancer, renal failure, solid tumor without metastasis and myocardial infraction) and ii) analysis including age, BMI, BMI^2, sex, admission source, admitting service, diabetes medications, and all the comorbidities (**Table 1**).

To determine if there was a glucose concentration below which the event rates in our five outcome measures increased, we fitted the adjusted event rates to a piecewise linear continuous regression [102, 103] in which each adjusted event rate was weighted by the inverse of the estimate's variance. The regressions assumed that there would be two distinct linear relations between glucose concentration and each outcome (i.e., relations that can be described by two lines having distinct intercepts and slopes, one describing the "normal glucose values" and the second the "lower glucose values") and that the two linear relations met at a single glucose concentration referred to as the "knot." The analysis estimated multiple parameters, including (1) the location of the knot, the glucose concentration at which two lines meet, one line describing the relation of glucose below the knot "lower glucose values" to the outcome, the second line the

relation above the knot "normal glucose values," (2) the slope and intercept of the line in the range of the "lower glucose values," and (3) the slope and intercept of the line in the range of the "normal glucose values."

Similar analyses were conducted for the second cohort (Glucose Variability cohort). The event rates were computed for every decile group of CV and SD. General estimating equations (GEE) with a Poisson distribution and an exchangeable covariance structure were used to calculate adjusted rate ratios of the 30-day readmission while accounting for the correlation of repeated admissions obtained from the same patient and clustering in each center [99, 104]. We considered three models based on CV and SD deciles: (1) The minimally adjusted model, which controls for age, gender, and race; (2) The second model, which controls for all the variables collected (**Table 1**), except for hypoglycemia [age, gender, including income, BMI, admission source (whether patients were admitted from home or other facilities), admitting service, diabetes medications, year of admission and multiple comorbidities], (3) The third model which controls for all the variables in the second model including also hypoglycemia. We did not adjust for A1c as only 35.3% of patient admissions had an A1c obtained within 90 days of hospitalization. Bonferroni corrected P values adjusting for multiple testing were used to compare the covariates among three CV categories based on the calculated CV values (admissions with CV deciles 1-4, CV 5-7, and CV 8-10) in **Table 1**.

Statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc). A two-tailed $p<0.05$ was considered statistically significant.

D. Results

D1. Low glucose-hypoglycemia at hospital discharge study

The overall crude 30-day readmission rate was 17.3%, and the 30-, 90- and 180-day crude mortality rates were 2.3%, 6.0%, and 10%, respectively. 18.8% of the study cohort died or were readmitted within 30 days post-discharge. The mean age (**Table 1)** of patients at admission was 66.8±10.8 (mean±SD) years, with most of them admitted from home (94.7%) and hospitalized under medicine service (79.7%). The most common comorbid conditions were hypertension, either uncomplicated or complicated (53.4% and 19.3%, respectively), cardiac arrhythmias (23.4%), congestive heart failure [(CHF), 23%], renal failure (21.9%) and chronic obstructive pulmonary disease [COPD, (20.5%)]. Admissions with and without hypoglycemia (**Table 1**) differed significantly in several of the covariates we examined, an effect. However, that can be secondary to the large sample size of our cohort.

Most patients were discharged with minimum glucose values of 100-109 mg/dl (**Table 2**, 15.2%). As the glucose concentrations became progressively lower than 100 mg/dl, the fraction of subjects who experienced an event (**Table 2**) and the relative rate generally increased for all five outcomes (**Table 3**). The results were almost similar even in the fully adjusted model, where we adjusted for multiple covariates, including all the comorbidities we collected (**Tables 4 and 5**). Hypoglycemia and severe hypoglycemia during the last 24 hours of the inpatient stay were present in 9.1% and 0.6% of the admissions, respectively. The adjusted 30-day readmission rate, the combined 30-day readmission/mortality rate and the 30-, 90- and 180-day mortality rates were 18.5% (95% CI:18.2%-18.8%), 20.1% (95% CI:19.8%-20.4%), 1.8% (95% CI:1.7%-1.9%), 5.1% (95% CI:4.9%-5.2%) and 8.7% (95% CI:8.5%-8.9%) for admissions with

hypoglycemia and 20.3% (95% CI:19.2%-21.5%), 23.0% (95% CI:21.8%-24.2%), 2.8% (95% CI:2.5%-3.2%), 6.9% (95% CI:6.3%-7.5%), and 11.1% (95% CI:10.4%%-11.8%) for admissions with severe hypoglycemia, respectively. Admissions of patients with diabetes who had hypoglycemia during the last 24 hours of hospitalization had 39% [Rate Ratio: RR:1.39 (CI:1.32,147)], 30% [RR: 1.30 (1.26, 1.34)] and 27% [RR: 1.27 (1.24, 1.30) higher rates of dying within 30, 90, and 180 days after discharge, compared to those with glucose values from 100-109 mg/dl, respectively (**Table 3**). Furthermore, among those who experienced severe hypoglycemia, the rate was 124% [RR:2.24 (1.96-2.57)], 81% [RR: 1.81 (1.66-1.97)], and 66% [RR:1.66 (1.55-1.77)] higher. The rates of being readmitted in 30 days or experiencing either readmission or death in 30 days were 20% [RR: 1.20 (1.18, 1.23)] and 22% [RR:1.22 (1.20, 1.24)] higher among patients with hypoglycemia and 32% [RR: 1.32 (1.24-1.40)] and 39% [1.39 (1.32-1.46)] higher among those who developed severe hypoglycemia.

For all the outcomes (**Figure 2**), there was a progressive increase in the adjusted event rates (red circles with 95% confidence intervals) below the knot (determined by piecewise linear continuous regression), marking the point of intersection of the two lines (blue lines) smoothing the relation in the "lower glucose values" and "normal glucose values." For all five outcome measures, the slope of the line below the knot obtained by fitting the adjusted event rates to a piecewise continuous regression was negative and statistically significant. For three of the five outcome measures, the slope above the knot was not statistically significantly different from zero (**Table 6**). For all five outcome measures, the slope below the knot was statistically significantly different from the slope above the knot (**Table 6**). Overall, the knots were located at 92.9 mg/dl for the 30-day readmission rate, 45.2 mg/dl for the 30-day mortality rate, 65.8 mg/dl for 90-day mortality, 67.3 mg/dl for 180-day mortality and 87.2 mg/dl for 30-day readmission or mortality.

The location of the knots and the slopes in “lower glucose values” and “normal glucose values” were similar when we adjusted for multiple covariates (**Figure 3, Table 7**).

D2. Glucose Variability at hospital discharge study

The final cohort included 1,042,150 unique admissions over the 14-year study observation period. In **Table 8**, we present baseline characteristics of the admissions of patients with diabetes, divided into three categories based on the calculated CV values (admissions with CV 1-4, CV 5-7, and CV 8-10). Overall, the mean age of patients at admission was 66.5±10.8 (mean±SD) years, with the majority being male (97.2%) and Caucasian (71.64%). 94.4% were admitted from home and hospitalized under medical service (80.7%). The most common comorbid conditions included congestive heart failure [CHF (24.2%], cardiac arrhythmia (22.9%), renal failure (22.9%), and chronic obstructive pulmonary disease [COPD, 21.8%]. The overall median LOS was 3.9 days (interquartile range: 2.2-6.9), and 7.35% of admissions of patients with diabetes exhibited hypoglycemia in the last 24 hours of hospitalization. The mean number of point-of-care glucose values in the previous inpatient stay was 3.9±0.95. Admissions among the three groups differed significantly in several covariates we examined. This effect could be secondary due to the large sample size of our cohort. One notable observation, however, is that admissions in the 8-10 CV categories, which had the highest GV measurements, had increased incidence of hypoglycemia (19.4%) compared to admissions in the 5-7 CV (3.5%) and 1-4 CV (1.3%) categories (**Table 8**).

In **Tables 9 and 10,** we present 30-day readmission rate ratios (RR) of deciles of CV and SD, using the first decile with the lowest variability as the reference group. For both CV and SD, as

GV on the last day of admission increased, the 30-day readmission rate ratio increased. For the CV analysis (**Table 9**), after adjustment for age, gender, and race (model 1), admissions in the fourth to tenth CV deciles had an increased 30-day readmission rate compared to those in the first CV category. Admissions with CV values in the tenth CV category had the highest 30-day readmission rate ratio [RR: 1.23 (1.20-1.26), p<0.0001]. In contrast, admissions with CV values in the lowest deciles (CV 2-3) did not experience a statistically significant increase in the 30-day readmission rate compared to those in the first CV category. In model 2, in which we adjusted for almost all covariates we collected (except for hypoglycemia), admissions with CV in the fifth to tenth CV categories had a statistically significant progressive increase in the 30-day readmission rate. The results were similar in model 3, where we adjusted for all the variables in model 2 and included hypoglycemia. Overall, compared to the reference first CV category, after adjusting for all the covariates, admissions with the highest CV values in the tenth category had an increased 30-day readmission rate [model 3, RR: 1.08 (1.05-1.10), p<0.0001].

Similarly, when we used SD as a measurement of GV (**Table 10**), admissions with SD in the third to tenth categories (models 1 and 2) and admissions with SD in the fourth to tenth categories (model 3) had a higher 30-day readmission rate compared to the first SD category. After adjusting for all the covariates, including hypoglycemia (model 3), admissions with the SD values in the tenth category had the highest 30-day readmission rate [RR: 1.11 (1.09-1.14), p<0.0001].

E. Discussion

With this Ph.D. application, we evaluated the association of minimum glucose value-hypoglycemia and increased GV during the last 24 hours of hospitalization with 30-day readmission and post-discharge mortality rates in patients with diabetes. We identified several glucose thresholds (knots), where below those glucose concentrations, there was an increased risk of developing one of the outcomes of interest: 92.9 mg/dl for 30-day readmission, 45.2 mg/dl, 65.8 mg/dl and 67.3 for 30-, 90- and 180-day for post-discharge mortality, and 87.2 mg/dl for the combined outcome of 30-day readmission or post-discharge mortality [92]. We also identified that admissions of patients with diabetes with the highest GV during the last 24 hours of the inpatient stay, using CV and SD measurements, had an increased risk for 30-day readmission [92]. This association persisted despite adjustment for multiple covariates, notably including adjustment for hypoglycemia during the last 24 hours of hospitalization. The results from our cohort studies may shed light on two potentially modifiable risk factors for reducing 30-day readmissions: low glucose values and increased GV on the hospital discharge day.

Hospital readmissions within 30 days have drawn national policy attention due to the increased cost of hospitalizations and concerns about the poor quality of care, although the latter is debated [54, 98]. Therefore, research on potentially modifiable factors to reduce readmissions is paramount. In our cohort, the readmission rate among patients with diabetes was 17.3%, consistent with previous reports [58-65, 67, 68]. Studies have tried to identify risk factors for readmission in patients with diabetes [54, 58-62, 64, 73, 105]. Previous studies have focused on the effect of glucose values at admission [64] or during the entire hospital stay [73] but not on glycemic control during the last day of hospitalization.

In our first analysis, even low-normal glucose values between 70-93 mg/dl were associated with a higher 30-day readmission rate. The reasons for the increased risk of readmission for this glucose category (70-93 mg/dl) are unknown. We hypothesize that patients with diabetes with glucose levels close to the hypoglycemia range before discharge are more likely to develop even lower glucose values after discharge. This hypothesis may be difficult to explore because hypoglycemic events can be transient, albeit sufficient to lead to severe adverse events (such as falls, arrhythmias, and seizures), resulting in hospital readmissions and increased mortality. Evidence from the VADT, ADVANCE, and ACCORD trials showed an increased association of severe hypoglycemia with mortality and major macrovascular and microvascular events [106-109]. Our data suggest that in analogy to the outpatient setting, hospitalized patients with diabetes who have glucose concentrations close to the hypoglycemia range are at risk of readmissions and complications after discharge.

The prevalence of hypoglycemia after discharge is unknown, and few studies have focused on optimal glycemic management following hospitalization. In a randomized clinical trial, hypoglycemia (<70 mg/dL) after hospitalization was reported in 22% of patients discharged on oral antidiabetic drugs (OADs), 30% on OAD plus basal insulin, 44% on basal-bolus insulin, and 25% on basal insulin only [110]. Transitioning care from the inpatient to the outpatient setting is often challenging, leading to adverse events, poor glycemic control, increased emergency room visits, and higher hospital readmission rates and costs [110, 111]. As clinical studies are lacking, large randomized clinical trials are needed to evaluate the impact of improved glycemic control after discharge on clinical outcomes and the effectiveness of innovative strategies on the transition of care [110].

In the second analysis, we additionally showed an independent association of higher GV on the last day of hospitalization with increased 30-day readmission. This is the first nationwide study to determine whether increased GV is associated with increased risk for hospital readmissions. Evidence from studies performed in the outpatient setting has shown that higher GV increases the risk of adverse clinical outcomes. The effect of GV on oxidative stress and endothelial dysfunction is thought to be equal to or greater than that attributed to persistent hyperglycemia. It is postulated to contribute to the development of micro- and macrovascular diabetes complications [46]. Within the inpatient setting, several studies have examined increased GV with adverse outcomes, revealing associations with prolonged length of stay [44] and increased mortality in both ICU and non-critical care settings.[44, 48, 50, 53, 112].

It is unknown how a higher GV on the last day of hospitalization may contribute to an increased risk of 30-day readmission. Although we did not have access to post-discharge glycemic values, one potential explanation is that high GV predisposes patients to post-discharge hypoglycemia or to significant hyperglycemia, which may lead to readmission. In our study, we found that those admissions of patients with the highest GV also had the highest incidence of hypoglycemia during the last 24 hours of the hospital stay, which is consistent with previous observations. It is known that blood glucose disturbances precede severe hypoglycemia [113], and increased GV has been previously identified as a predictor of hypoglycemia.[49, 114, 115] The transition of care from the inpatient to the outpatient setting signifies a vulnerable and challenging time with a greater risk of dysglycemia, as well as healthcare utilization such as emergency room visits or readmissions.[96, 110, 111] As patients with diabetes have multiple and often sub-optimally controlled comorbidities, they have an inherently higher risk for frequent readmissions [10, 72].

Our analyses have several strengths. Overall, our study population cohorts represent one of the most extensive studies that examined readmission rates and post-discharge mortality in patients with diabetes. We also utilized national data, not regional data, to examine readmission rates in an integrated health system. Although we may have missed admissions and re-hospitalizations to non-VA hospitals, analyzing data from the VA Health Care System, a "closed" health system where most veterans are admitted and readmitted, is one of the most robust ways to examine readmission rates. Given the comprehensive and extensive nature of the Veterans Health Administration data sources, we included data from almost 1 million admissions of patients with diabetes and a broad set of covariates and risk factors in this analysis (**Tables 1 and 8**).

Our study has some limitations to consider when interpreting the results. Like previously published studies that used administrative data from the Veterans Affairs Health Care System, our analysis is restricted to a single healthcare system (90). Although we could include nationwide data from the VA hospitals in our research, admissions, and readmissions to non-VA hospitals were not obtained. Our study population, veterans admitted between 2000 and 2014, may differ from the general US population as they were more likely to be male, elderly, and have chronic illnesses. Despite these differences, our ability to adjust for demographic data and an extensive list of comorbid conditions leads us to believe that our findings apply to the general population. Additionally, our study did not try to distinguish preventable readmissions from other readmissions. As previous publications have pointed out, although the use of administrative data to determine the preventability of readmissions has been employed, preventability is subjective, and administrative data may not be the best method for this purpose [93, 116].

F. New directions after the conduction of the above epidemiological studies

Following the completion of the above retrospective epidemiological studies, which showed the importance of inpatient glycemic control, we focused on clinical trials and interventions that can improve glycemic control during hospitalization. Medical centers have implemented protocols focused on preventing and treating inpatient hypoglycemia and its serious complications [117, 118]. However, current hypoglycemia protocols for the hospital are limited by the infrequency of point-of-care (POC) capillary glucose testing, leading to gaps where low glucose values may be undetected/undocumented [119].

Our group developed a strong interest in utilizing technologies, mainly Continuous Glucose Monitoring (CGM) devices, in innovative ways to improve care for patients with DM in the inpatient setting. We thought that by using CGM devices, we could decrease hypoglycemia in the hospital setting.

Before our work [118], many studies evaluated the use of CGM devices among hospitalized patients with diabetes mellitus [119]. Most of these previously performed studies have been conducted in the intensive care unit (ICU) setting. Only a few have examined the use of CGM devices in patients with diabetes mellites in the non-ICU setting [119-121]. Among those studies conducted in the general wards, CGM devices detected more hypoglycemic episodes than POC capillary glucose testing [119, 121-123]. Despite providing a better assessment of glycemic control, the use of CGM devices has not been widely adopted as prospective studies using real-time glucose monitoring at that had not been lacking. Prior studies used "blinded" CGM, and therefore, interventions to prevent impending hypoglycemia were not performed [119, 121-123]. Another major limitation of the CGM devices was the technology used: Glucose values were captured in the CGM device and not transmitted to the nursing station to allow nursing staff and providers to detect and prevent hypoglycemia. Even with un-blinded/real-time CGM use,

hypoglycemia alarms were only visible and audible at the bedside. As a result, nurses frequently entered the patient's room to monitor glucose values on the CGM receiver. Without this information being readily available to nursing staff in a centralized location, CGM technology is likely not a practical or efficient way to monitor a large number of hospitalized patients with diabetes.

F1. Development of the "Glucose Telemetry System"

A few years ago, we pioneered an innovative technique using CGM devices by transmitting glucose data wirelessly from the bedside to the Baltimore Veterans Affairs Medical Center nursing station, describing a novel monitoring system that overcomes many of the above limitations [118]. This system consisted of a) DEXCOM G4 CGM (DEXCOM, San Diego, CA, USA) sensor and transmitter, which used a CGM device that has been approved by the FDA to be used in the ambulatory-outpatient setting (**but not for the hospital setting, which is still considered investigational and not FDA approved**). Then, we used Bluetooth technology and the DEXCOM Share 2 application (DEXCOM, San Diego, CA, USA) to send glucose values from the CGM device to an Apple iPhone located in the patient's room, which served as an intermittent transmitting (routing) device. We utilized the commercially available wireless internet network (Verizon Network, similar to Cosmote or Vodaphone in Greece) as well as another software application (DEXCOM Follow application, San Diego, CA, USA) to send glucose values wirelessly from the iPhone to the iPad located centrally at the nursing station on the same floor. By utilizing this system (**Figure 5**), glucose values could be transmitted from the patient's bed (bedside) to the nursing station, achieving remote glucose monitoring.

F2. Pilot study of the Glucose telemetry System

As a next step, we evaluated the feasibility and effectiveness of the Glucose Telemetry System. Below, we provide the description and evaluation of the Glucose Telemetry System, which is from our manuscript published a couple of years ago [118].

We performed a single-arm clinical study, and our Glucose Telemetry System monitored all subjects. We recruited adult patients (>18 years old) with type 2 diabetes mellitus at higher risk for hypoglycemia, who were admitted to general medicine service at the Baltimore Veterans Affairs Medical Center (BVAMC) and who were expected to stay in the hospital for longer than two days. Patients were considered to be at higher risk for hypoglycemia if they had one or more of the following risk factors of hypoglycemia [82-84]: outpatient insulin use > 0.6 u/kg/day, age ≥ 67, body mass index (BMI) ≤ 27, chronic kidney disease (serum creatinine > 2 mg/dl), history of liver failure, active malignancy, congestive heart failure, cerebrovascular event, or sepsis. The ethics committees of the University of Maryland and BVAMC approved the protocol and the study.

All subjects were managed with a basal-bolus insulin regimen with glargine (Lantus, Sanofi Aventis, Gentilly, France) once daily and aspart (Novolog, Novo Nordisk, Bagsvaerd, Denmark) before meals. The study team adjusted insulin based on previously published studies [124]. Nurses were educated daily about the features of the Glucose Telemetry System and trained to calibrate the CGM devices (the Dexcom G4 system required calibration at that time) as well as when and how to remove/replace the CGM sensors and transmitters (if needed). A low alarm threshold was set on the iPad at a glucose value of 85 mg/dl, resulting in an audible alarm from the central iPad device. As the Follow application provided the opportunity to choose an

alarm from many different types, we allowed the nursing staff to select which type of alarm they would like to use. By placing the iPad in a central location at the nursing station, even nursing staff that were not involved in the care of the study participants were able to notify the assigned nurse when the alarm activated. Nurses were instructed to perform a Point of Care (finger stick) capillary glucose testing to confirm hypoglycemia and to provide at least 10 grams of carbohydrates to the patient when CGM alarmed a glucose value <85 mg/dl as a preventive action of hypoglycemia.

The primary outcomes of interest were the number of hypoglycemic episodes, hypoglycemic event rate (defined as hypoglycemic episodes/per patient per day under CGM), and time spent in hypoglycemia. Hypoglycemic episodes, clinically significant hypoglycemic episodes, and severe hypoglycemic episodes were defined as glucose concentrations detected by CGM <70 mg/dl, <54 mg/dl, and <40 mg/dl, respectively, for at least 20 minutes [125],[31].

With the pilot study, we recruited five insulin-treated patients with type 2 diabetes mellitus, whose glucose was monitored by the Glucose Telemetry System. Overall, participants were elderly with an average age of 70.8 ± 6.2 (mean ± SD), BMI of 33.1 ± 9.3 kg/m2, and a duration of diabetes mellitus of 22 ± 12.9 years.

Regarding glucose management, two patients had three alarm events when CGM glucose values were <85 mg/dl. In each case, nursing staff provided treatment per the hypoglycemia prevention protocol and successfully prevented hypoglycemia <70 mg/dl. Both patients received oral carbohydrates as per protocol. In one patient who had two episodes, CGM readings revealed decreasing glucose levels for a total of 30 minutes, reaching a nadir of 71 mg/dL before eventually increasing after treatment. On both occasions, POC capillary blood glucose revealed

blood glucose of 75 mg/dl and 83 mg/dl. The second subject had 1 episode of glucose value of 83 mg/dl at 00:38 am; the GTS notified the nursing unit, but POC glucose testing was not performed. Treatment was provided, and glucose values increased to levels >85 mg/dl 15 minutes later.

Two patients experienced a single hypoglycemic event despite GTS monitoring. The first episode occurred after a patient received prandial insulin and was transferred to radiology for an imaging study, interrupting his meal. The duration of hypoglycemia was 25 min, including when the patient became hypoglycemic, the time until he received treatment, and the time until hypoglycemia resolved. Glucose values from CGM were as low as 68 mg/dl (POC capillary glucose testing was 63 mg/dl simultaneously). The second case occurred post-dinner due to decreased appetite and poor nutritional intake. The hypoglycemia alarm went off. However, the nursing staff failed to act, as she managed another patient requiring emergency treatment. In this case, the patient was hypoglycemic for 50 minutes. CGM recorded glucose values as low as 56 mg/dL with a POC capillary blood glucose value of 55 mg/dL, which was checked at that time. The overall hypoglycemia event rate was 0.1 events per patient per day under CGM. Neither of the participants experienced clinically significant hypoglycemic or severe hypoglycemic episodes. Overall time spent in hypoglycemia <70 mg/dl was 0.30% ± 0.39, time spent within BG target of 70-179 mg/dl was 64.68% ± 15.39, and time spent in hyperglycemia ≥180 mg/dl or and ≥300 mg/dl was 35.02% ± 15.5 and 2.86% ± 5.6, respectively. No CGM glucose value was below 54 mg/dl in any of the participants. Average glucose and coefficient of variation (CV) were 167.5 ± 19.6 mg/dl and 30.13% ± 6.26, respectively. Two study patients required more than 1 CGM sensor during their hospital stay. Per manufacturer recommendations, one required removing the sensor due to a CT scan imaging procedure, and the other subject experienced sensor failure. Overall, each participant required 1 or 2 (mean 1.4) CGM sensors during the

entire hospital stay. Overall, participants were monitored with CGM devices for an average of 4 ± 1.6 days, requiring an average daily insulin dose of 0.36 units/ kg ± 0.23 units/kg.

Overall, this pilot study showed that our intervention, the Glucose telemetry System, was feasible and could potentially mitigate hypoglycemia in the hospital setting.

F2. Randomized clinical trials evaluating the role of Real-time CGMs/ Glucose telemetry Systems in the hospital setting

Following the pilot study results, we submitted grant applications as a first step, with which we were seeking funding to conduct large randomized clinical trials. We were successful in securing funding from the Veterans Affairs Research Office. Our primary aim of this grant application, a randomized clinical trial, is to determine whether the Glucose Telemetry System can decrease hypoglycemia in the hospital setting. Our proposal has several secondary aims: We want to evaluate that by using Glucose Telemetry and reducing hypoglycemia, we will improve important clinical outcomes (such as decreasing the length of hospital stay) without causing worsening hyperglycemia.

Following the COVID-19 declaration, and similar to what has occurred with many randomized clinical trials internationally, our study was halted shortly after an interim analysis was completed because of safety concerns related to the COVID-19 pandemic, as per IRB and data safety monitoring board recommendations. We decided, however, to proceed with publishing our interim analysis results. These results are described below and are from our manuscript, published in 2020 [126], almost immediately after the COVID-19 declaration. The rationale was that during the COVID-19 pandemic, especially in the first couple of years, CGM devices have

been used in the hospital, even without efficacy data. Providers have implemented inpatient use of CGM devices, although this use in the hospital is still considered investigational. Although the primary aim of our study was to reduce hypoglycemia, Glucose Telemetry could serve as a method of remote glucose monitoring, which could reduce the need for frequent entry of staff into patient rooms (typically four to six times daily to check POC). This would reduce personal protective equipment utilization and decrease the risk of exposure and transmission between patients and hospital staff. By reducing the time nursing staff spend checking POC (and entering the patients' rooms), the extra time could be reallocated to caring for patients with more emergent and critical needs [126].

We recruited hospitalized patients with type 2 diabetes mellitus who were at high risk for hypoglycemia (based on risk factors as described in the pilot study) [126]. After informed consent was obtained, eligible participants were stratified based on their number of risk factors for inpatient hypoglycemia (two or fewer or three or more risk factors). They were randomized to Glucose Telemetry (intervention/unblinded group) or POC blood glucose testing (POC/standard-of-care/blinded group). Nursing staff were requested to obtain a POC for hypoglycemia alarms as permitted and to provide at least 15 g of carbohydrates (15–16 g using glucose tablets/glucose gel/juice) for impending hypoglycemia. Nurses were instructed to give another 15 g if inadequate response in the glucose value occurred. Although our study focused on preventing hypoglycemia and not hyperglycemia, high-glucose alerts were set at 400 mg/dL because we believed turning the high alerts off would be unethical. Participants in the standard-of-care group used blinded CGM systems to collect CGM geometric data. CGM alerts were turned off for this group, and if the POC was <85 mg/dL, 15 g of carbohydrates (as described above) were given to the participant as a preventive measure for hypoglycemia. As per standard of care, if the POC was <70 mg/dL, the hypoglycemia treatment protocol was initiated in both

groups. If the patient had hypoglycemia and could eat, nurses provided 15 g carbohydrates per os. If the patient could not swallow or eat or developed severe hypoglycemia, they were started on D50 (dose range 20–25 mL). If there was no intravenous access, then glucagon 1 mg intramuscularly was suggested to be used. Nurses were also trained in using CGM devices, such as removing sensors and transmitters as needed (before computed tomography scan or MRI). All participants were managed with basal-bolus (glargine-aspart) insulin regimens during their inpatient stay. Insulin initiation and titration were performed per protocol or as clinically indicated [124].

The primary outcome was the reduction of hypoglycemia in the inpatient setting. To evaluate clinical efficacy, we adapted CGM metrics proposed for ambulatory patients [125, 127]. The primary outcome was the difference in hypoglycemic events per patient, defined as CGM glucose values <70 mg/dL for >15 min. Secondary outcomes were the percentage of time spent in the hypoglycemic range <70 mg/dL and hypoglycemic event rates (defined as the number of hypoglycemic events/patient/day). Additional secondary outcomes included differences in clinically significant hypoglycemic events per patient (defined as CGM glucose values <54 mg/dL for >15 min) and percentage of time below range (TBR) <54 mg/dL. We also examined whether there was any difference in nocturnal hypoglycemic events per patient (defined as hypoglycemic events <70 mg/dL or clinically significant hypoglycemic events <54 mg/dL occurring between midnight and 6:00 A.M.) and prolonged episodes of hypoglycemia (defined as hypoglycemia <70 mg/dL or clinically significant hypoglycemia <54 mg/dL for >120 min). Although our trial was not focused on improving hyperglycemia, a secondary outcome was to evaluate whether there was increased hyperglycemia by preventing hypoglycemia. To evaluate this, we calculated the percentage of time above range (TAR) >180–250 mg/dL and TAR >250 mg/dL as well as time in range (TIR) 70–180 mg/dL [127]. We also examined whether there was

any difference in glucose variability (using the coefficient of variation [CV]) between the two groups.

Overall, 82 patients with type 2 diabetes consented to participate in this trial; 10 participants were not included in the analysis, leaving 36 subjects in each group for the final analysis. The clinical and demographic characteristics were similar, with no statistically significant differences between the two groups. Overall, the mean age was 68 ± 10 (mean ± SD) years, median (IQR) BMI was 32.0 kg/m2 (26.8-36.3), and subjects were predominantly admitted for cardiovascular (27.7%) or infectious (25.0%) disease-related conditions. Mean eGFR was 57.6 mL/min/1.73m2 in the Glucose Telemetry group and 67.7 mL/min/1.73m2 in the control group (p=0.82). Participants had a long duration of diabetes (median [IQR] of 18 years [11.5-25.5)]), and the majority were managed before admission with basal: bolus insulin regimens either alone (43.1%) or in combination with *per os* and/or glucagon-like peptide receptor agonists (20.8%). No patients received enteral nutrition, and seven subjects received steroids (3 in the Glucose Telemetry group versus 4 in the control group, *p*=NS).

For our primary outcome (Table 11), participants in the Glucose telemetry group experienced 60.4% fewer hypoglycemic events (<70 mg/dL) compared to the POC group (0.67 events/patient, 95%CI 0.34-1.30 versus 1.69 events/patient, 95%CI 1.11-2.58, *p*=0.024) with an absolute risk reduction (ARR) of 1.02. In both groups, there were 1.18 hypoglycemic events/patient with a total of 85 events (24 in the Glucose Telemetry group and 61 in the POC group). There was a reduction in the percentage of time in the hypoglycemic range <70 mg/dl in the Glucose Telemetry group compared to the POC group (0.40%, 95%CI 0.18%-0.92% versus 1.88%, 95%CI 1.26%-2.81%, *p*=0.002). The rate of hypoglycemic events was also lower in the

intervention group compared to the standard of care group (0.12 hypoglycemic events/patient/day, 95%CI 0.06-0.24 versus 0.35 events/patient/day, 95%CI 0.23-0.54, p=0.011).

The Glucose Telemetry group experienced fewer clinically significant hypoglycemic events (<54 mg/dL compared to the POC group (0.08 events/patient, 95%CI 0.03-0.26 versus 0.75 events/patient, 95%CI 0.51-1.09, p=0.003). There was also a decrease in TBR< 54 mg/dl for the intervention group compared to the control group (0.05%, 95%CI 0.01%-0.43% versus 0.82%, 95%CI 0.47%-1.43%, p=0.017). There were 21.3 minutes per day and 102.3 minutes per admission (using median LOS) saved from hypoglycemia <70 mg/dL and 11.1 minutes per day and 53.2 minutes per admission saved from hypoglycemia <54 mg/dL. Notably, subjects in the Glucose Telemetry group had no prolonged hypoglycemic episodes <70 mg/dL or < 54 mg/dL compared to participants in the POC group (0.2 episodes/patient <70 mg/dL and 0.4 episodes/patient <54 mg/dL). In contrast, there was no statistically significant difference in the number of nocturnal hypoglycemic events <70 mg/dL (0.19, 95%CI 0.09-0.41 versus 0.33, 95%CI 0.19-0.59, p=0.26) or clinically significant nocturnal hypoglycemic events <54 mg/dL (0.03, 95%CI 0.01-0.24 versus 0.11, 95% CI 0.04-0.33, p=0.26) between the two groups.

The main purpose of our trial was a reduction in hypoglycemia and not a reduction in hyperglycemia, and insulin increases were made based on POC versus CGM data. Therefore, we did not find any significant difference in TIR 70-180 mg/dL (59.12%, 95% CI 52.47%-66.61% in the intervention group versus 54.69% 95% CI 47.96%-62.37% in the control group, p=0.39), TAR>180-250 mg/dL (29.88%, 95% CI 26.11%-34.19% in the intervention group versus 30.10%, 95% CI 26.11%-34.70% in the control group, p=0.94) or TAR>250 mg/dL (10.60%, 95% CI 7.15%-15.73% in the intervention group versus 13.33%, 95% CI 9.20%-19.37% in the

control group, p=0.41). There was no difference in glucose variability measured by CV (26.09%, CI24%-28.19% intervention group versus 27.89%, CI25.41%-30.36% in the control group, p=0.28) between the two groups. Mean glucose was 183.3 mg/dL and 180 mg/dL in the RT-CGM/GTS and control groups, respectively (p=0.69).

We also evaluated the role of real-time CGM devices, such as the Glucose Telemetry System, with another clinical trial. In this multicenter study, we recruited low and high-risk hypoglycemia patients with either type 1 or type 2 diabetes mellitus. We utilized CGM devices not only to prevent hypoglycemia but also to guide providers in adjusting insulin based on the CGM (as well as POC) glucose values. The study is described below and is from our manuscript published in 2022 [128]. This multicenter, noninferiority, open-label randomized study was conducted in three hospitals in the U.S., including Grady Memorial Hospital and Emory University Hospital in Atlanta, GA, and the University of Maryland Medical Center in Baltimore, MD.

We screened subjects >18 years of age with type 1 or type 2 diabetes admitted to general medical and surgical services [128]. We enrolled patients with glucose levels <400 mg/dL without laboratory evidence of diabetic ketoacidosis and with an anticipated length of hospitalization >72 hours after enrollment. Key exclusion criteria included patients with acute illness who required or were expected to require ICU admission or had a planned MRI during hospitalization, clinically relevant hepatic disease (diagnosed liver cirrhosis and portal hypertension), corticosteroid therapy (equivalent to prednisone dose >5 mg/day), end-stage renal disease (dialysis), anasarca, pregnancy, or any mental condition rendering the patient unable to understand the nature, scope, and possible consequences of the study. Following the coronavirus

disease 2019 (COVID-19) pandemic declaration, a modification was submitted to exclude individuals hospitalized with COVID-19 infection.

Subjects were randomly assigned to one of two groups: a standard of care with participants wearing a blinded Dexcom G6 CGM with insulin dose adjusted based on capillary POC glucose monitoring (POC group) or to the real-time CGM (RT-CGM) group with insulin adjustment based on daily CGM profile. Participants in the intervention group were monitored by RT-CGM glucose telemetry system (GTS), as described previously [118, 126]. Hypoglycemia alarms were set at 80 mg/dL on the iPad tablet placed at the nursing station to prevent hypoglycemia. An additional CGM alarm was set if glucose levels were >250 mg/dL for at least one hour. The alarm notified the research team, who determined if medication adjustments were necessary, which were then relayed to the primary team for implementation. Participants in the control group wore blinded CGM devices, which are CGM systems with alarms turned off and were only used to record CGM glucose values during the hospital stay. If the glucose value by POC testing was <80 mg/dL, 15 g of carbohydrates was given as a preventive measure to avoid clinically significant hypoglycemia. Subjects in both groups had POC testing before meals, at bedtime, and when clinically indicated. Starting insulin dosage and daily insulin adjustment orders were similar in both groups and followed a previously reported basal-bolus insulin regimen [129]. Insulin dose recommendations for insulin initiation or titration were based on the protocol and made by a board-certified endocrinologist. These recommendations were ultimately relayed to clinical nurses, who administrated insulin to the hospitalized patients. The nursing staff administrated corrective insulin, following the protocol without further communication with providers or the study team.

Primary endpoints included differences in the percentage of time in range (TIR) 70–180 mg/dL and hypoglycemia, defined as the percentage of time below range (TBR) <70 mg/dL and <54 mg/dL. Other secondary outcomes included differences in the percentage of time above range (TAR) >180 mg/dL and >250 mg/dL, total number of hypoglycemic episodes <70 mg/dL and <54 mg/dL [127], and number of hypoglycemic episodes per participant. We also evaluated if there was a difference in nocturnal hypoglycemia by evaluating the difference in number of events <70 mg/dL and <54 mg/dL and in the percentage of TBR <70 mg/dL and <54 mg/dL occurring between 12:00 midnight and 6:00 A.M. Furthermore, we evaluated whether there was a difference in the reoccurrence of hypoglycemia <70 mg/dL and <54 mg/dL, occurring during the day or nocturnal hours, and a difference in mean daily glucose values. We examined differences in glycemic variability measured by the mean amplitude of glycemic excursion (MAGE), coefficient of variation (CV), and SD.

We consented to 185 eligible general medicine and surgery patients. Of them, nine subjects in the control group and three subjects in the intervention group were excluded due to lack of CGM data (one subject), sensor failure (one subject), or administrative withdrawal (one subject refused to wear the CGM device after abdominal surgery). Overall, 173 subjects completed the study and had CGM data: 85 subjects were randomly assigned to the standard of care (POC group) and 88 subjects to the intervention (CGM) group. Among them, six subjects in the standard of care and five in the intervention group were excluded because of a hospital stay <24 hours after CGM placement. In the final analysis, we included 162 subjects. There were no significant differences in age, sex, race, BMI, type and duration of diabetes, admission HbA_{1c}, blood glucose at the time of the randomization, diabetes outpatient regimen, or primary admitting diagnosis between groups.

There were no significant differences in TIR 70–180 mg/dL among subjects managed in the CGM group compared with those managed by the POC standard of care (54.51% ± 27.72 vs. 48.64% ± 24.25; *P* = 0.14) **Table 12**. There were no differences in mean daily glucose (183.2 ± 40 vs. 186.8 ± 39 mg/dL; *P* = 0.36) or total daily insulin dose (40.7 ± 29.5 vs. 36.1 ± 28.1 units/day; *P* = 0.33). There were non-statistically significant differences in TAR >180 mg/dL (44.80% ± 27.89 vs. 49.21% ± 25.50; *P* = 0.26) and in TAR >250 mg/dL (16.24% ± 19.63 vs. 17.08% ± 17.59; *P* = 0.45) for participants in the CGM intervention and POC group, respectively.

We observed a non-significant reduction in TBR <70 mg/dL (0.69% ± 2.15 vs 2.15% ± 5.91, p=0.43) and the TBR <54 mg/dL (0.32% ± 1.33 vs 1.00% ± 3.74, p=0.35) in the CGM group compared to POC group (Table 12). A similar trend was observed in the percent of patients with CGM values <70 mg/dL (36% vs. 39% p=0.68) or <54mg/dL (14% vs 24%, p=0.12), as well as in the number of hypoglycemic events per patient <70 mg/dL (0.65 ± 1.26 vs. 1.15 ± 2.24 events/patient, p=0.36) and <54 mg/dL (0.22 ± 0.59 vs 0.56 ±1.46 events/patient, p=0.11) between CGM and POC groups. In terms of nocturnal hypoglycemia, we observed non-statistically significant reductions in percentage of TBR <70 mg/dL (0.22% ± 0.84 vs. 0.76% ± 2.67, p=0.90), percentage of TBR <54 mg/dL (0.13% ± 0.75 vs. 0.35% ± 1.57, p=0.35), in the number of hypoglycemic events per patient <70 mg/dL (0.20 ± 0.49 vs. 0.34 ±0.83 events/patient, p=0.71) or <54 mg/dL (0.08 ± 0.36 vs. 0.23 ± 0.72 events per patient, p=0.14).

Participants in the CGM group with one hypoglycemic event < 70 mg/dL had fewer recurrent hypoglycemic events <70 mg/dL (1.80 ± 1.54 vs 2.94 ± 2.76 events/patient, p=0.04) and a lower percentage of TBR <70 mg/dL (1.89% ± 3.27 vs 5.47% ± 8.49, p=0.02) compared to the control POC group. The incidence-rate ratio for inpatient hypoglycemia <70 mg/dL was estimated as 0.53 (95% CI, 0.31-0.92). The group difference in the percentage of TBR <70 mg/dL was also confirmed by the Zero-inflated Beta regression (p<0.001), which accounts for diabetes status for the zero-inflation component. Similarly, subjects in the CGM group who experienced nocturnal hypoglycemia <70 mg/dL had less nocturnal reoccurrence of hypoglycemic events <70 mg/dL (1.21 ± 0.43 vs 1.93 ± 0.92 events/patient, p=0.02) and lower percentage of TBR <70 mg/dL (1.30% ± 1.71 vs 4.27% ± 5.15, p=0.004), compared to the control POC group. Among those who experienced hypoglycemia <54 mg/dL, RT-CGM intervention led to less frequent hypoglycemic events with an estimated incidence ratio for hypoglycemia <54 mg/dL of 0.37 (95% CI: 0.17-0.83). There were no differences in glycemic variability between the POC group and CGM group, as measured by the coefficient of variation (27%±8 vs. 26%±9, p=0.33), standard deviation (50.4 mg/dl ± 16.2 mg/dl versus 46.8 mg/dl ±18 mg/dl, p=0.28) and mean amplitude of glycemic excursion (65.02±39.10 vs 61.24±32.41, p=0.73).

F3. Clinical studies evaluating the Accuracy of Real-time CGMs (compared to POC) in the hospital setting

In addition to performing studies evaluating the role of CGM devices in improving glucose control, we were also involved in studies that evaluated the accuracy of CGM devices in the hospital setting. One of them is presented below, and the description is from our manuscript published in 2021 [130]. With this study which represents one of the largest accuracy CGM

devices in the hospital setting, we combined data from three inpatient clinical studies (NCT03877068, NCT03508934, and NCT03832907) conducted at four urban hospitals (Emory University Midtown, Grady Memorial, University of Maryland Medical Center and the Baltimore Veterans Affairs Medical Center), which all of them used the factory-calibrated Dexcom G6 CGM system (Dexcom, San Diego, CA). This study aimed to analyze matched pairs of CGM and capillary POC glucose values to assess CGM accuracy in the hospital setting. All studies received Institutional Review Board approval by participating institutions.

Data from non-critically ill medical or surgical patients (n=218) with type 1 (T1) and type 2 (T2) diabetes treated with basal and/or rapid-acting insulin and with admission BG <400 mg/dL were included [130]. Patients were recruited from general medical and surgical units. Basic demographic and inpatient clinical data were obtained from the electronic health record, and all analyzed CGM sensors were placed on the abdomen. POC BG values were obtained by hospital calibrated Nova StatStrip[131] (Grady Memorial Hospital), Accu-Chek Inform II glucose meters [132] (Emory University Midtown Hospital and University of Maryland Medical Center), and Abbott Precision XceeedPro [133] (Baltimore VA Medical Center). POC glucose values were checked per hospital protocol, as clinically indicated, if there was a concern for hypoglycemia or the clinical team deemed this necessary for patient care. A total of 4,067 matched pairs of CGM and capillary POC glucose values were analyzed. CGM-POC glucose pairs were matched by time, using the sensor glucose value within the following 5-minute window of the POC glucose measurement to account for CGM lag time.[134, 135] Matched pairs with POC glucose values outside of the CGM reading range (BG <40 mg/dL or >400 mg/dL) were excluded. To assess accuracy during the first 12- and 24-hours of sensor life, patients requiring any sensor change (n=61) were excluded.

Mean absolute relative difference (MARD) was used as the main accuracy measure. Secondary measures included median absolute relative difference (ARD) and the percentage of CGM readings within ±15 mg/dL of POC reference values ≤ 100mg/dL or ±15% of POC values > 100mg/dL (%15/15). Analogous measurements for %20/20 and %30/30 were also calculated, consistent with the Food and Drug Administration (FDA) accuracy requirements for approval of nonadjunctive factory-calibrated CGM systems.[136, 137] MARD and median ARD were analyzed during the first 12- and 24-hours of wear and during the entire hospital stay, as well as by glucose ranges (<70 mg/dL, 70–180 mg/dL, 180-250 mg/dL, and >250 mg/dL), renal function (eGFR <30, 30-59, 60-90, and >90 mL/min/1.73m^2) and hemoglobin level (<7, 7-10, 10-14, and >14 g/dL) on admission. An exploratory accuracy analysis within different body mass index (BMI) categories was also performed. The overall percentage of CGM values within %15/15, %20/20, and %30/30 was also analyzed across different glucose ranges. Clinical reliability was assessed using Clarke error grid analyses.

MARD and median ARD were determined as the average relative difference between the CGM and POC glucose-matched pairs and expressed as a percentage. Statistical methods for CGM performance analysis were based on recommendations by Clarke and Kovatchev.[138] To determine the accuracy of sensor values compared to POC testing in population subgroups, analyses were based on glucose ranges, renal function, and hemoglobin categories. We also calculated the accuracy according to sensor life (first 12 and first 24 hours). Data are presented as mean (± SD) for continuous and count (percentage) for categorical variables. Error grid analyses were determined with the R package "ega," designed for Clarke or Parkes error grid

analysis (https://cran. r- project.org/web/packages/ega/ega.pdf). Additional analyses were conducted with SAS.

Characteristics of the included study population are outlined in Table 13. The mean age of patients was 60.6 ± 12 years, with an average body mass index of 33.4 ± 9.0 kg/m^2. Most patients had type 2 diabetes (96%) with a mean duration of diabetes of 15.9 ± 10.3 years and admission hemoglobin A1c of 9.1 ± 2.2%. Most patients were admitted to a primary medical service (88%). Mean enrollment BG was 203.6 ± 69.8 mg/dL with a median length of hospital stay of 5 (IQR 3, 8) days. The average daily glucose by POC testing was 178.7 ± 39.6 mg/dL and 176.7 ± 43.4 mg/dL by CGM.

The MARD was 12.8% and median ARD 10.1% [IQR 4.6, 17.6] during the hospital stay for all available matched pairs (n=4,067), with lower accuracy during the first 12- and 24- hours (n=263, MARD 16.4% median ARD 12.5% [IQR 5.6, 23.2]) and n= 627, MARD 14.4% and median ARD 11.1% [IQR 5.3, 20.0], respectively), Table 14. For further evaluation, CGM accuracy data was stratified by subgroups according to POC glucose categories, hemoglobin, and renal function ranges. The assessment of MARD and median ARD according to POC glucose level strata showed similar accuracy within target range of 70-180 mg/dL (n=2423; MARD 13.0%, median ARD 10.2% [IQR 4.5, 18.1]) and mild-moderate hyperglycemia (POC BG 181-250 mg/dL, n=1103, MARD 11.8%, median ARD 10.0% [IQR 4.7, 16.7]; and severe hyperglycemia POC BG >250 mg/dL, n=475, MARD 12.1%, median ARD 9.4% [4.4, 16.1]) A higher MARD and median ARD observed in hypoglycemia [POC glucose 50-70mg/dL, n=52; MARD 18.8%, median ARD 14.5% [IQR 6.9, 27.3]). Additionally, CGM showed consistent accuracy according to different admission hemoglobin (Hgb) ranges (Hgb 7-10 g/dL, n=1024,

MARD 12.9%, median ARD 10.2% [4.5, 18.0]; Hgb 10.1-14 g/dL, n=2543, MARD 12.8%, median ARD 10.2% [4.7, 17.6]; Hgb >14 g/dL, n=428, MARD 11.7%, median ARD 9.3% [4.1, 15.6]), down to a hemoglobin value less than 7 g/dL where a higher MARD and median ARD were observed (n=72, MARD 17.8 %, median ARD 15.8% [IQR 8.9, 23.5]).

Comparable accuracy metrics were also observed across admission renal function categories based on eGFR, including eGFR values lower than 30 mL/min/1.73m^2 (eGFR >90, n=950, MARD 13.2%, median ARD 10.8% [IQR 4.7, 18.8]; eGFR 60-90, n=1134, MARD 12.2%, median ARD 10.1% [IQR 5.1, 16.5]; eGFR 30-59, n=1079, MARD 13.3%, median ARD 10.1% [IQR 4.4, 18.1]; and eGFR <30, n=904, MARD 12.5%, median ARD 9.8% [IQR 4.3, 17.4]).

In an exploratory analysis of this retrospective matched-pair data, accuracy metrics were analyzed by BMI categories (≤30 kg/m^2, between 30-40 kg/m^{2,} and >40 kg/m^2). Overall accuracy metrics between BMI categories were comparable, though the MARD and median ARD trending slightly lower as BMI increased (BMI ≤30 kg/m^2, n=1459, MARD 13.3%, median ARD 10.0% [IQR 4.7, 17.9]; 30< BMI ≤40 kg/m^2, n=1662, MARD 12.6%, median ARD 10.4% [IQR 4.8, 17.7]; BMI >40 kg/m^2, n=946, MARD 12.4%, median ARD 9.8% [IQR 4.3, 17.0]).

The proportion of CGM values within ±15, 20 and 30% of POC reference values for glucose levels >100 mg/dL and ±15, 20 or 30 mg/dL for POC glucose levels ≤100 mg/dL (%15/15, %20/20, %30/30) increased between the first 12-hours (57.0, 69.2, 85.9%) and 24-hours (63, 75.6, 89.2%) of sensor life. The overall proportion of CGM values meeting %15/15, %20/20, %30/30 criteria were 68.7, 81.7, 93.8%, respectively (Table 14).

A Clarke error grid (CEG) analysis of all matched pair data showed good clinical reliability with 98.7% of values falling in CEG Zones A+B (Zone A, 80.9%; Zone B, 17.8%; Zone C, 0.1%; Zone D, 1.1%, Zone E, 0.0%). CEG analysis during the first 12 hours of sensor life revealed 98.8% of values in Zones A+B (Zone A, 81.8%; Zone B, 17.0%; Zone C, 0.1%; Zone D, 1.1%, Zone E, 0.0%) while the first 24-hours showed 98.7% values in Zones A+B (Zone A, 82.0%; Zone B, 16.7%; Zone C, 0.1%; Zone D, 1.2%, Zone E, 0.0%).

G. Ongoing and future studies

In addition, our group has been part of large multicenter studies, further exploring the use of CGM devices in the hospital setting. In one of them, a six center Randomized Clinical Trial [TIGHT (TIME In Glucose Hospital Target, NCT05135676)], we want to evaluate whether glucose management with CGM devices (without the use of Glucose Telemetry or any remote CGM glucose management system) can achieve a mean glucose of 90-130 mg/dL without increasing hypoglycemia. More specifically, we recruit individuals with diabetes who are hospitalized (non-ICU) for an eligible condition and are randomly assigned to receive standard therapy (glucose target 140-180 mg/dL per ADA guidelines) or intensive therapy (glucose target 90-130 mg/dL and CGM used for monitoring). The main inclusion criteria are adult patients (Aged >= 18 years old) with type 2 diabetes (either previous diagnosis or a new diagnosis of type 2 diabetes), with a Hemoglobin A1c (HbA1c) >= 7.0% (laboratory-measured at or since hospital admission or within prior 3-months), who have at one blood glucose measurement >180 mg/dL since admission, who are insulin-treated in the hospital (insulin already initiated since

admission or planned to be initiated) and are expected to stay in the hospital at least for 3 additional days, following randomization. The study has several exclusion criteria, with the most notable of them being admission to the Intensive Care Unit and having a diagnosis of Type 1 diabetes or atypical forms of diabetes (including pancreatectomy and pancreatitis) and stress hyperglycemia.

We use real-time CGM devices in the Intensive Target Group and masked-blinded CGM devices (for comparison reasons) in the Standard Target Group. Two co-primary outcomes were assessed via a hierarchical approach, including a treatment group comparison of mean glucose (superiority) followed by a non-inferiority comparison of hypoglycemia evaluating time below range <54 mg/dL measured with CGM devices. Several other secondary outcomes will be evaluated, such as CGM metrics during daytime only (06:00 AM to 00:00 AM), CGM Metrics by nighttime only (00:00 AM to 06:00 AM), CGM metrics related to hypoglycemia and CGM metrics related to hyperglycemia as well as CGM metrics related to Glucose Variability.

In addition, our group is involved in one of the most important studies on CGM devices in the hospital setting. This study, which is currently ongoing, is testing the accuracy of the DEXCOM CGM devices compared to serum glucose values (and more precisely using arterialized venous blood sample measurements) by utilizing the Yellow Spring Instruments techniques (YSI study, NCT04879693). Yellow Spring Instruments Instruments have been used excessively in the outpatient setting, and all the POC glucometers and CGM devices have received FDA approvals based on the above method of glucose evaluation. Although several studies have evaluated the accuracy of CGM devices in the hospital setting [139, 140], they were limited as they used POC as a comparator. POC has many disadvantages. One of the significant limitations is that not all of

the glucometers have the same accuracy. As a result, accuracy results can be affected by the comparator (different glucometers).

This study is the first to evaluate the accuracy of the CGM devices in the inpatient setting, utilizing Yellow Spring Instruments and comparing CGM glucose values with the blood sample measurements (NCT04879693). The study's objective is to establish the performance of the CGM devices compared to a laboratory reference measurement. We recruit adult (18 years of age and older) patients who are admitted to the hospital in a non-ICU setting (General Wards), are expected to stay for at least 48 hours, are receiving any diabetes treatment during the hospital stay, and are willing to wear up to 3 CGM devices in different places of their body (Two in the abdomen and one on the back of the arm or one on each arm and one on the abdomen). There are several exclusion criteria (NCT04879693); among them, the most important are patients admitted to the Intensive Care Unit and patients who have End Stage Renal Disease on hemodialysis (as the accuracy of the CGM devices has not been evaluated in this population). The effectiveness of the System will be evaluated by comparison of CGM values to a laboratory reference, Yellow Spring Instrument (YSI), using arterialized venous sample measurements. Performance will be evaluated in terms of point and rate accuracy of the System in reference to YSI. The safety profile of the System will be characterized by the incidence of device-related Adverse Events (AEs) experienced by study subjects. This study is extremely important: If the results are positive, CGM devices can receive FDA regulatory approval, allowing them to utilize CGM devices officially in the hospital setting.

H. Discussion/ Importance of our work on CGM devices in the hospital setting

Close monitoring of glucose values in the hospital is necessary to achieve glycemic control and prevent adverse outcomes associated with dysglycemia. CGM devices provide an easier method for monitoring blood glucose levels more frequently than labor-intensive capillary POC testing and other more cumbersome techniques (i.e., venous glucose sampling) [126]. Recently, the COVID-19 pandemic set into motion the rapid transition of CGM to the hospital setting to address these unmet needs in glucose monitoring during a time when minimizing bedside encounters became paramount [126, 140]. Due to the COVID-19 pandemic, providers have implemented inpatient use of CGM devices, which is still considered investigational. The RT-CGM/ Glucose Telemetry System was used and found to be beneficial in this environment. RT-CGM/ Glucose Telemetry System as a method of glucose monitoring was used to reduce the need for frequent entry of staff into patient rooms (typically 4-6 times daily to check POC), with a gold to reduce personal protective equipment (PPE) utilization and decreased risk of exposure and transmission between patients and hospital staff [126]. Lastly, the use of CGMs in the hospital was able, by reducing the time that nursing staff spent checking POC, to reallocate time to care for patients with more emergent and critical needs. It is estimated that each POC test requires 5 minutes on average to perform [121, 141]. This benefit, which would alleviate overburdened nursing staff under normal circumstances, was emphasized due to the pandemic crisis. Even in the absence of COVID-19 declaration, our intervention could be potentially utilized among hospitalized patients who are in isolation, not only for COVID-19 infection but for other infectious causes (i.e., Tuberculosis, Methicillin-resistant Staphylococcus aureus, Vancomycin Resistant Enterococcus among others).

There were several steps in implementing the Glucose Telemetry System [126]: training nursing staff on GGM devices- Glucose Telemetry System and providing technical support as needed, selecting a commercially available internet network with consistent signal, ensuring minimal interruption in glucose transmission between iPhone and iPad, securing the devices with an anti-theft iPad case at the nursing station and a locked safe box wired to a permanently affixed object at the bedside containing the iPhone and portable battery are some examples of implementation procedures.

Currently, utilization of CGM devices lacks FDA approval for hospital use, and there is an absence of safety and efficacy evidence [121, 142, 143]. For general medical wards, where most patients with diabetes are hospitalized, very few studies have been performed before our work, and they were primarily observational, evaluating CGM accuracy [119, 120, 122, 123]. These studies revealed that CGM devices were more likely to detect hypoglycemia compared to POC. A limitation was using "blinded" CGM devices, where CGM glucose values were not viewable to providers or patients. As a result, interventions to prevent hypoglycemia could not be performed based on the CGM data. With our interventional randomized controlled clinical trials, we used RT-CGM systems (Glucose Telemetry System), performed in the general wards, to reduce inpatient hypoglycemia. We focused on reducing inpatient hypoglycemia as it is associated with prolonged length of stay, higher hospital charges, and increased risk for readmission and mortality [28-30, 92]. Severe hypoglycemic events have led institutions to develop inpatient diabetes management teams to implement hospital protocols and procedures to reduce this risk [117]. We believe that the proposed intervention of RT-CGM/Glucose Telemetry System and simplified hypoglycemia prevention protocols could serve as valuable tools to modify existing institutional hypoglycemia prevention protocols. The strength of our studies was

the evaluation of RT-CGM/Glucose telemetry Systems in the general wards, a setting where glucose monitoring is more limited (4-6 times per day), in contrast to the ICU where glucose values can be intensively monitored, checked hourly if needed [144].

Following the publication of the above studies, there was national and international interest in our work. The most notable was from the Endocrine Society, which published new recommendations about the management of hyperglycemia and diabetes in the hospital setting [145]. With this updated manuscript, the Endocrine Society now recommends using CGM devices in the hospital setting in conjunction with POC glucose testing, a change from the previous recommendation [31].

Overall, CGM devices can be a promising tool for inpatient glucose monitoring, helping to reduce the care burden associated with bedside POC glucose monitoring [130]. RT-CGM/ Glucose telemetry System combined with a simplified hypoglycemia prevention protocol can decrease hypoglycemia among insulin-treated patients with type 2 diabetes [126]. Like cardiac telemetry, a system used for patients at high risk for arrhythmia, we believe that future RT-CGM systems could be utilized to monitor hospitalized patients with diabetes at high risk for hypoglycemia [126].

I. Conclusions

In conclusion, with this VA nationwide cohort study that included a large cohort of individuals with diabetes, we identified the following significant findings: patients with diabetes with

hypoglycemia or near normal glucose values on the last day of their inpatient stay were at a higher risk of 30-day readmission and post-discharge mortality and patients with diabetes with a higher GV on the last day of hospitalization were at a higher risk for 30-day readmission. More importantly, glucose concentrations below 92.9 mg/dl and 67.3 mg/dl had higher rates of 30-day readmissions and mortality, respectively, and glucose levels <87.2 mg/dl were associated with higher combined 30-day readmissions or mortality compared to patients with glucose >100 mg/dl. Following this work, we focused on clinical trials and interventions to improve glycemic control during hospitalization. We developed a new system, the Glucose Telemetry System, which is based on CGM devices. We evaluated the feasibility and effectiveness of this intervention in the inpatient setting, and we are currently involved in studies evaluating the accuracy of the CGM devices in this environment with the ultimate goal of receiving regulatory approvals in the hospital setting.

J. Figures and Tables

Figure 1. Low glucose-hypoglycemia at hospital discharge cohort creation

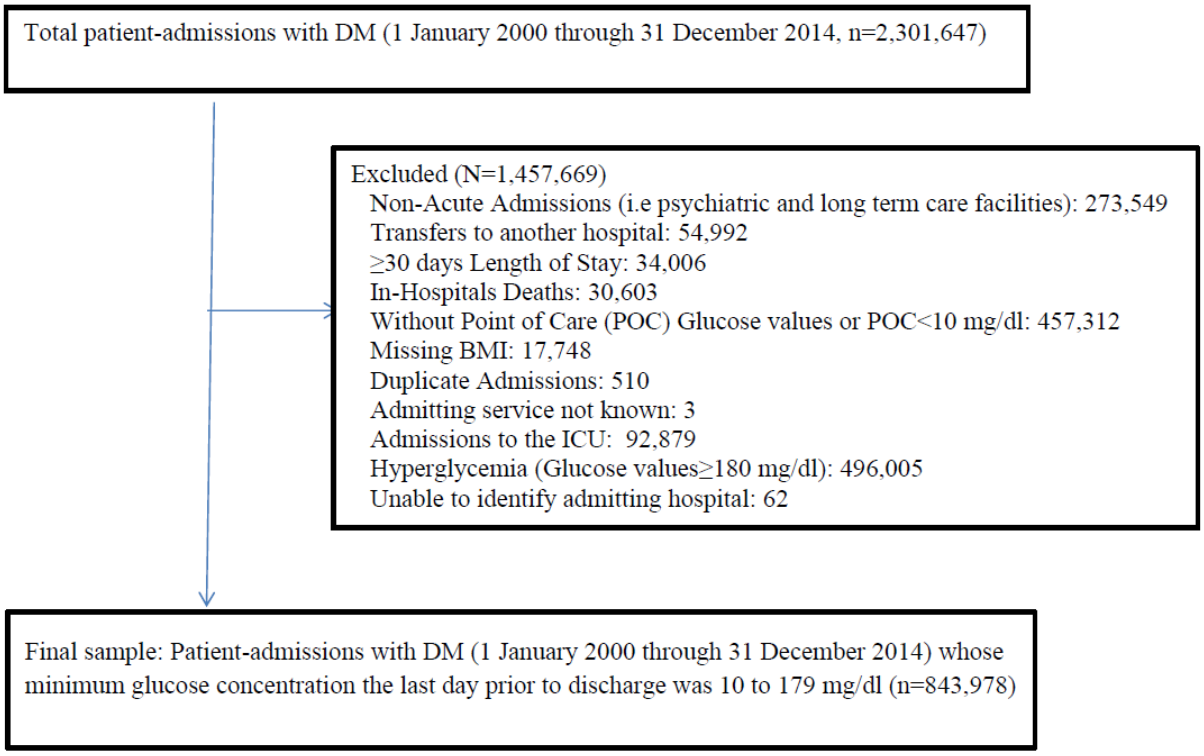

Table 1. Characteristics of all admissions (Low glucose-hypoglycemia at hospital discharge cohort)

Variable	All admissions (N=843,978)	Without hypoglycemia (N=767,338)	With hypoglycemia (N=76,640)	p
*Age (SD), years	66.8 (10.8)	66.5 (10.8)	66.8 (10.8)	<0.001
Male Sex (%)	819,178 (97.0%)	744,579 (97.0%)	74,599 (94.3%)	<0.001
**BMI (kg/m²)	29.7 (25.8-34.6)	29.8 (25.8-34.6)	28.8 (24.7-33.7)	<0.001
**Income ($)	$16,064 ($8,962-$31,322)	$16,062 ($8,961-$31,321)	$16,068 ($9,000-$31,234)	0.97
**Length of Stay (days)	3.8 (2.0-6.8)	3.8 (2.0-6.8)	3.9 (2.0-7.0)	<0.001
Admission source n (%)				0.02
From Home	799,047 (94.7%)	726,416 (94.7%)	72,631 (94.8%)	
From other hospitals	21,236 (2.5%)	19,414 (2.5%)	1,822 (2.4%)	
From Nursing homes	23,695 (2.8%)	21,508 (2.8%)	2,187 (2.8%)	
Admitting service n (%)				<0.001
Medicine	672,247 (79.7%)	608,836 (79.3%)	63,411 (82.7%)	
Surgery	171,731 (20.3%)	158,502 (20.7%)	13,229 (17.3%)	
DM Medications				<.001
Insulin	421978 (50.0%)	380,170 (49.5%)	41,808 (54.5%)	
NIM	83,345 (9.9%)	76,549 (10.0%)	6,796 (8.9%)	
Insulin and NIM	163,100 (19.3%)	142,397 (18.6%)	20,703 (27.0%)	
None	175,555 (20.8%)	168,222 (21.9%)	7,333 (9.6%)	
Comorbid Conditions				
Alcohol Abuse	40,247 (4.7%)	37,034 (4.8%)	3,213 (4.2%)	<0.001
Blood loss Anemia	7,577 (0.9%)	6,939 (0.9%)	638 (0.8%)	0.04
Cardiac Arrhythmia	197,147 (23.4%)	180501 (23.5%)	16646 (21.7%)	<0.001
Congestive Heart Failure	193,926 (23.0%)	173,863 (22.7%)	20,063 (26.2%)	<0.001
COPD	173,102 (20.5%)	157,399 (20.5%)	15,703 (20.5%)	0.88
Coagulopathy	22,949 (2.7%)	21,079 (2.8%)	1,870 (2.4%)	<0.001
Deficiency Anemia	37,126 (4.4%)	33,341(4.4%)	3,785 (4.9%)	<0.001
Depression	102,615 (12.2%)	93,746 (12.2%)	8,869 (11.6%)	<0.001
Drug Abuse	17,643 (2.1%)	15,875 (2.1%)	1,768 (2.3%)	<0.001
Fluid- Electrolyte Disorder	134,572 (15.9%)	120,206 (15.7%)	14,366 (18.7)	<0.001
HIV/AIDS	3,840 (0.5%)	3,463 (0.5%)	377 (0.5%)	0.11
Hypothyroidism	56,590 (6.7%)	51,429 (6.7%)	5,161 (6.7%)	0.73
Hypertension				<0.001
Complicated	163,235 (19.3%)	163,235 (18.8%)	19,173 (25.0%)	
Not complicated	450,213 (53.4%)	413,430 (53.9%)	36,783 (48.0%)	
Liver Disease	55,310 (6.6%)	50,510 (6.6%)	4,800 (6.3%)	0.006
Lymphoma	9,503 (1.1%)	8,729 (1.1%)	774 (1.0%)	0.001
Metastatic Cancer	19,961 (2.4%)	18,421 (2.4%)	1,540 (2.0%)	<0.001
Solid Tumor Non-Metastatic	70,223 (8.3%)	64,698 (8.4%)	5,525 (7.2%)	<0.001
Myocardial Infraction	50,444 (6.0%)	45,875 (6.0%)	4,569 (6.0%)	0.86
Neurological Disorder	36,510 (4.3%)	33,433 (4.4%)	3,077 (4.0%)	<0.001
Paralysis	15,740 (1.9%)	14,607 (1.9%)	1,133 (1.5%)	<0.001
Peptic Ulcer Disease	6,868 (0.8%)	6,276 (0.8%)	592 (0.8%)	<0.001
Peripheral Vascular Disease	81,860 (9.7%)	73,062 (9.5%)	8,798 (11.5%)	<0.001
Psychosis	21,301 (2.5%)	19,494 (2.5%)	1,807 (2.4%)	0.002
Pulmonary Circulatory Disorder	25,732 (3.1%)	23,401 (3.1%)	2,331 (3.0%)	0.91
Renal Failure	184,784 (21.9%)	162,963 (21.2%)	21,821 (28.5%)	<0.001
Rheumatologic Diseases	10,538 (1.3%)	9,528 (1.2%)	1,010 (1.3%)	0.07
Valvular Disorder	40,473 (4.8%)	37,043 (4.8%)	3,430 (4.5%)	<0.001

Data are n (%), *: Mean,**: Median, SD: Standard deviation, BMI: Body Mass Index, DM: Diabetes Mellitus, COPD: Chronic Obstructive pulmonary disease, HIV: Human Immunodeficiency Virus, AIDS: AIDS: Acquired Immune Deficiency Syndrome, NIM: Non-Insulin Medications.

Table 2. Event rates of the five outcomes allocated by glucose category obtained the last 24 hours of the inpatient stay ((Low glucose-hypoglycemia at hospital discharge cohort)

Glucose Category (mg/dl)		30-Day Readmission		30-Day Readmission or Mortality		30-Day Mortality		90-Day Mortality	
	Admissions	Events	Rate (%), (95% CI)	Events	Rate (%), (95% CI)	Events	Rate (%), (95% CI)	Events	Rate (%), (95% CI)
10-19	134	35	19.9 (13.9, 28.4)	44	25.6 (19.2, 34.2)	15	7.4 (4.7, 11.6)	19	9.3 (6.3, 13.8)
20-29	871	185	17.4 (15, 20.3)	223	21.3 (18.8, 24.2)	52	3.4 (2.7, 4.4)	103	7.7 (6.5, 9.2)
30-39	3661	797	18.3 (17, 19.6)	896	20.7 (19.5, 22.1)	148	2.5 (2.2, 2.9)	348	6.6 (6.0, 7.2)
40-49	11,032	2,427	18.0 (17.3, 18.8)	2663	20.0 (19.3, 20.8)	355	2.0 (1.8, 2.2)	924	5.8 (5.4, 6.1)
50-59	23,346	4,832	16.9 (16.4, 17.4)	5286	18.7 (18.2, 19.2)	697	1.9 (1.7, 2.0)	1689	5.0 (4.8, 5.3)
60-69	37,596	7,278	15.8 (15.4, 16.2)	7902	17.3 (17.0, 17.7)	921	1.5 (1.4, 1.6)	2469	4.6 (4.4, 4.7)
70-79	56,997	10,427	14.9 (14.6, 15.2)	11261	16.3 (16.0, 16.6)	1307	1.4 (1.3, 1.5)	3478	4.2 (4.1, 4.4)
80-89	88,946	15,561	14.2 (14.0, 14.5)	16840	15.5 (15.3, 15.8)	1923	1.3 (1.2, 1.4)	5350	4.1 (4.0, 4.2)
90-99	119,396	20,210	13.8 (13.6, 14.0)	21920	15.1 (14.9, 15.3)	2520	1.3 (1.2, 1.3)	6936	3.9 (3.8, 4.0)
100-109	128,530	21,471	13.7 (13.5, 13.9)	23312	15.0 (14.8, 15.2)	2773	1.3 (1.2, 1.3)	7417	3.9 (3.8, 4.0)
110-119	118,706	19,670	13.6 (13.4, 13.8)	21527	15.0 (14.8, 15.2)	2679	1.3 (1.3, 1.4)	7035	3.9 (3.8, 4.0)
120-129	94,273	15,991	14.0 (13.8, 14.2)	17447	15.4 (15.1, 15.6)	2154	1.3 (1.2, 1.4)	5555	3.9 (3.8, 4.0)
130-139	69,524	11,751	14.0 (13.8, 14.3)	12948	15.6 (15.3, 15.8)	1707	1.4 (1.3, 1.5)	4163	3.9 (3.8, 4.0)
140-149	46,216	7,665	13.9 (13.5, 14.2)	8448	15.3 (15.0, 15.7)	1146	1.4 (1.3, 1.5)	2759	3.8 (3.7, 4.0)
150-159	26,262	4,293	13.6 (13.2, 14.1)	4798	15.3 (14.9, 15.8)	699	1.5 (1.4, 1.6)	1572	3.9 (3.7, 4.0)
160-169	12,776	2,160	14.1 (13.5, 14.7)	2389	15.7 (15.0, 16.3)	323	1.4 (1.3, 1.6)	724	3.7 (3.5, 3.9)
170-179	5,712	954	14.1 (13.2, 15.1)	1055	15.8 (14.8, 16.7)	132	1.4 (1.2, 1.6)	266	3.2 (2.9, 3.6)

[a]: Adjusted for age, BMI, BMI^2, admission source, admitting service, diabetes medications, comorbidities (cardiac arrhythmia, congestive hea disorder, hypertension, metastatic cancer, solid tumor without metastasis, renal failure, weight loss).
[b]: The number of admissions is the same for each of the five outcomes.

Table 3. Event rate ratios of the five outcomes allocated by glucose category obtained the last 24 hours of the inpatient stay (Low glucose-hypoglycemia at hospital discharge cohort)

Glucose Category (mg/dl)	30-Day Readmission	30-Day Readmission or Mortality	30-Day Mortality	90-Day Mortality	180-Day Mortality
	RR (95% CI)	**RR, (95% CI)**	**RR, (95% CI)**	**RR, (95% CI)**	**RR, (95% CI)**
10-19	1.45 (1.02, 2.08)	1.71 (1.28, 2.28)	5.82 (3.69, 9.18)	2.40 (1.62, 3.55)	1.91 (1.39, 2.63)
20-29	1.28 (1.10, 1.49)	1.42 (1.25, 1.62)	2.72 (2.11, 3.50)	1.99 (1.68, 2.36)	1.71 (1.49, 1.96)
30-39	1.34 (1.24, 1.44)	1.38 (1.30, 1.48)	1.98 (1.69, 2.32)	1.70 (1.55, 1.86)	1.60 (1.50, 1.72)
40-49	1.32 (1.26, 1.38)	1.34 (1.29, 1.39)	1.57 (1.42, 1.74)	1.48 (1.40, 1.57)	1.44 (1.38, 1.50)
50-59	1.24 (1.20, 1.28)	1.25 (1.21, 1.29)	1.46 (1.35, 1.58)	1.30 (1.24, 1.36)	1.26 (1.22, 1.30)
60-69	1.15 (1.12, 1.19)	1.16 (1.13, 1.19)	1.19 (1.11, 1.28)	1.17 (1.13, 1.22)	1.15 (1.12, 1.19)
70-79	1.09 (1.06, 1.12)	1.09 (1.06, 1.11)	1.11 (1.04, 1.18)	1.09 (1.05, 1.12)	1.08 (1.05, 1.11)
80-89	1.04 (1.02, 1.06)	1.04 (1.02, 1.06)	1.03 (0.97, 1.08)	1.06 (1.03, 1.09)	1.06 (1.04, 1.09)
90-99	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)	0.99 (0.94, 1.04)	1.01 (0.98, 1.04)	1.03 (1.01, 1.05)
100-109	Reference	Reference	Reference	Reference	Reference
110-119	0.99 (0.97, 1.01)	1.00 (0.98, 1.02)	1.03 (0.98, 1.08)	1.01 (0.98, 1.04)	1.00 (0.98, 1.02)
120-129	1.02 (1.00, 1.05)	1.03 (1.01, 1.05)	1.03 (0.97, 1.08)	0.99 (0.96, 1.02)	0.99 (0.97, 1.01)
130-139	1.03 (1.00, 1.05)	1.04 (1.02, 1.06)	1.09 (1.03, 1.16)	1.00 (0.97, 1.04)	0.98 (0.96, 1.00)
140-149	1.01 (0.99, 1.04)	1.02 (1.00, 1.05)	1.09 (1.02, 1.16)	0.99 (0.95, 1.03)	0.95 (0.92, 0.98)
150-159	1.00 (0.96, 1.03)	1.02 (0.99, 1.06)	1.18 (1.09, 1.27)	0.99 (0.95, 1.04)	0.93 (0.90, 0.96)
160-169	1.03 (0.98, 1.08)	1.05 (1.00, 1.09)	1.11 (1.00, 1.24)	0.95 (0.89, 1.01)	0.91 (0.87, 0.95)
170-179	1.03 (0.96, 1.11)	1.05 (0.99, 1.12)	1.07 (0.91, 1.25)	0.83 (0.75, 0.91)	0.77 (0.72, 0.84)
<70	1.20 (1.18, 1.23)	1.22 (1.20, 1.24)	1.39 (1.32, 1.47)	1.30 (1.26, 1.34)	1.27 (1.24, 1.30)
<40	1.32 (1.24-1.40)	1.39 (1.32-1.46)	2.24 (1.96-2.57)	1.81 (1.66-1.97)	1.66 (1.55-1.77)

[a]: Adjusted for age, BMI, BMI^2, admission source, admitting service, diabetes medications, comorbidities (cardiac arrhythmia, congestive heart failure, fluid or electrolyte disorder, hypertension, metastatic cancer, solid tumor without metastasis, renal failure, weight loss), **RR:** Rate ratios

Table 4. Event rates of the five outcomes allocated by glucose category obtained the last 24 hours of the inpatient stay (Low glucose-hypoglycemia at hospital discharge cohort)

Glucose Category (mg/dl)		30-Day Readmission		30-Day Readmission or Mortality		30-Day Mortality		90-Day Mortality	
	Admissions	Events	Rate (%), (95% CI)	Events	Rate (%), (95% CI)	Events	Rate (%), (95% CI)	Events	Rate (%), (95% CI)
10-19	134	35	19.9 (13.9, 28.4)	44	25.6 (19.2, 34.1)	15	7.3 (4.7, 11.4)	19	9.3 (6.3, 13.7)
20-29	871	185	17.3 (14.9, 20.2)	223	21.1 (18.6, 24.0)	52	3.2 (2.5, 4.1)	103	7.2 (6.1, 8.6)
30-39	3,661	797	18.2 (16.9, 19.6)	896	20.6 (19.4, 22.0)	148	2.4 (2.1, 2.8)	348	6.4 (5.8, 7.0)
40-49	11,032	2,427	18.0 (17.2, 18.7)	2663	19.9 (19.2, 20.7)	355	1.9 (1.7, 2.1)	924	5.6 (5.3, 5.9)
50-59	23,346	4,832	16.9 (16.4, 17.4)	5286	18.7 (18.2, 19.2)	697	1.8 (1.6, 1.9)	1689	4.8 (4.6, 5.0)
60-69	37,596	7,278	15.7 (15.4, 16.1)	7902	17.3 (16.9, 17.7)	921	1.4 (1.4, 1.5)	2469	4.4 (4.2, 4.5)
70-79	56,997	10,427	14.9 (14.6, 15.2)	11261	16.2 (15.9, 16.5)	1307	1.3 (1.3, 1.4)	3478	4.0 (3.9, 4.2)
80-89	88,946	15,561	14.2 (13.9, 14.4)	16840	15.5 (15.2, 15.7)	1923	1.2 (1.2, 1.3)	5350	4.0 (3.9, 4.1)
90-99	119,396	20,210	13.8 (13.6, 14.0)	21920	15.0 (14.8, 15.3)	2520	1.2 (1.1, 1.2)	6936	3.8 (3.7, 3.9)
100-109	128,530	21,471	13.6 (13.4, 13.8)	23312	14.9 (14.7, 15.1)	2773	1.2 (1.2, 1.3)	7417	3.7 (3.6, 3.8)
110-119	118,706	19,670	13.5 (13.3, 13.7)	21527	14.9 (14.7, 15.1)	2679	1.2 (1.2, 1.3)	7035	3.7 (3.7, 3.8)
120-129	94,273	15,991	14.0 (13.7, 14.2)	17447	15.3 (15.1, 15.5)	2154	1.2 (1.2, 1.3)	5555	3.7 (3.6, 3.8)
130-139	69,524	11,751	14.0 (13.7, 14.3)	12948	15.5 (15.2, 15.8)	1707	1.3 (1.3, 1.4)	4163	3.7 (3.6, 3.9)
140-149	46,216	7,665	13.8 (13.5, 14.1)	8448	15.3 (14.9, 15.6)	1146	1.3 (1.2, 1.4)	2759	3.7 (3.6, 3.8)
150-159	26,262	4,293	13.6 (13.1, 14.0)	4798	15.2 (14.8, 15.7)	699	1.4 (1.3, 1.5)	1572	3.7 (3.5, 3.8)
160-169	12,776	2,160	14.0 (13.4, 14.7)	2389	15.6 (14.9, 16.2)	323	1.3 (1.2, 1.5)	724	3.5 (3.3, 3.7)
170-179	5,712	954	14.0 (13.1, 15.0)	1055	15.6 (14.7, 16.6)	132	1.3 (1.1, 1.5)	266	3.0 (2.7, 3.3)

[a]: Adjusted for age, BMI, BMI^2, sex, admission source, admitting service, diabetes medications, comorbidities [hypothyroidism, lymphoma, li pulmonary circulatory disorder, renal failure, peripheral vascular disease, vascular disorder, cardiac arrhythmia, neurological disorder, fluid o deficiency anemia, alcohol abuse, drug abuse, depression, COPD, psychoses, blood loss anemia, coagulopathy, rheumatologic diseases (rheu vascular disease), HIV/AIDS, peptic ulcer, CHF, metastatic cancer, solid tumor without metastasis, myocardial infarction].
[b]: The number of admissions is the same for each of the five outcomes.

Table 5. Event rate ratios of the five outcomes allocated by glucose category obtained the last 24 hours of the inpatient stay (Low glucose-hypoglycemia at hospital discharge cohort)

Glucose Category (mg/dl)	30-Day Readmission	30-Day Readmission or Mortality	30-Day Mortality	90-Day Mortality	180-Day Mortality
	RR (95% CI)	RR, (95% CI)	RR, (95% CI)	RR, (95% CI)	RR, (95% CI)
10-19	1.46 (1.02, 2.08)	1.72 (1.29, 2.29)	6.04 (3.86, 9.47)	2.49 (1.70, 3.66)	1.96 (1.42, 2.69)
20-29	1.27 (1.09, 1.48)	1.41 (1.24, 1.61)	2.62 (2.03, 3.39)	1.93 (1.62, 2.30)	1.66 (1.45, 1.91)
30-39	1.33 (1.24, 1.44)	1.38 (1.30, 1.48)	1.99 (1.70, 2.34)	1.71 (1.56, 1.87)	1.60 (1.50, 1.72)
40-49	1.32 (1.26, 1.38)	1.34 (1.29, 1.39)	1.59 (1.43, 1.77)	1.49 (1.41, 1.59)	1.44 (1.38, 1.51)
50-59	1.24 (1.20, 1.28)	1.25 (1.21, 1.29)	1.46 (1.35, 1.58)	1.30 (1.24, 1.36)	1.26 (1.21, 1.30)
60-69	1.15 (1.12, 1.19)	1.16 (1.13, 1.19)	1.19 (1.11, 1.28)	1.17 (1.13, 1.22)	1.15 (1.12, 1.19)
70-79	1.09 (1.06, 1.12)	1.09 (1.06, 1.11)	1.10 (1.04, 1.17)	1.08 (1.05, 1.12)	1.08 (1.05, 1.11)
80-89	1.04 (1.02, 1.06)	1.04 (1.02, 1.06)	1.03 (0.97, 1.09)	1.06 (1.03, 1.09)	1.07 (1.04, 1.09)
90-99	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)	0.99 (0.94, 1.04)	1.01 (0.98, 1.04)	1.03 (1.01, 1.05)
100-109	Reference	Reference	Reference	Reference	Reference
110-119	0.99 (0.97, 1.01)	1.00 (0.98, 1.02)	1.02 (0.97, 1.08)	1.00 (0.98, 1.03)	1.00 (0.98, 1.02)
120-129	1.02 (1.00, 1.05)	1.03 (1.01, 1.05)	1.02 (0.97, 1.08)	0.99 (0.96, 1.02)	0.99 (0.97, 1.01)
130-139	1.03 (1.00, 1.05)	1.04 (1.02, 1.06)	1.09 (1.03, 1.16)	1.00 (0.97, 1.04)	0.98 (0.96, 1.00)
140-149	1.01 (0.99, 1.04)	1.02 (1,.00, 1.05)	1.09 (1.02, 1.16)	0.99 (0.95, 1.02)	0.95 (0.92, 0.97)
150-159	1.00 (0.96, 1.03)	1.02 (0.99, 1.05)	1.16 (1.08, 1.26)	0.98 (0.94, 1.03)	0.92 (0.89, 0.95)
160-169	1.03 (0.98, 1.08)	1.04 (1.00, 1.09)	1.10 (0.99, 1.22)	0.94 (0.88, 1.00)	0.90 (0.86, 0.95)
170-179	1.03 (0.96, 1.10)	1.05 (0.99, 1.11)	1.04 (0.89, 1.23)	0.81 (0.73, 0.90)	0.76 (0.71, 0.82)

[a]: Adjusted for age, BMI, BMI^2, sex, admission source, admitting service, diabetes medications, comorbidities [hypothyroidism, lymphoma, liver disease, paralysis, pulmonary circulatory disorder, renal failure, peripheral vascular disease, vascular disorder, cardiac arrhythmia, neurological disorder, fluid or electrolyte disorder, deficiency anemia, alcohol abuse, drug abuse, depression, COPD, psychoses, blood loss anemia, coagulopathy, rheumatologic diseases (rheumatoid arthritis/collagen vascular disease), HIV/AIDS, peptic ulcer, CHF, metastatic cancer, solid tumor without metastasis, myocardial infarction]. **RR:** Rate ratios

Table 6. Slopes Above and Below the Knot from Piecewise Continuous Regression (Low glucose-hypoglycemia at hospital discharge cohort)

	Below Knot		Above knot		Difference between slops
Outcome	Slope ($x10^{-4}$)	p	Slope ($x10^{-4}$)	p	p
30-day Readmission	-7.70	<0.001	0.01	0.97	<0.001
30-day Readmission or Mortality	-12.00	<0.001	0.88	0.38	<0.001
30-day Mortality	-15.80	<0.001	-0.10	0.72	<0.001
90-day Mortality	-8.8	<0.001	-0.60	0.02	<0.001
180-day Mortality	-10.50	<0.001	-1.50	<0.001	<0.001

[a]: Adjusted for age, BMI, BMI^2, admission source, admitting service, diabetes medications, comorbidities (cardiac arrhythmia, congestive heart failure, fluid or electrolyte disorder, hypertension, metastatic cancer, solid tumor without metastasis, renal failure, weight loss).

Table 7. Slopes Above and Below the Knot from Piecewise Continuous Regression Analysis (Low glucose-hypoglycemia at hospital discharge cohort)

	Below Knot		Above knot		Difference between slops
Outcome	Slope ($x10^{-4}$)	p	Slope ($x10^{-4}$)	p	p
30-day Readmission	-7.60	<0.001	0.04	0.93	<0.001
30-day Readmission or Mortality	-11.90	<0.001	0.81	0.15	<0.001
30-day Mortality	-22.10	<0.001	-0.30	0.17	<0.001
90-day Mortality	-10.0	<0.001	-0.50	<0.001	<0.001
180-day Mortality	-10.20	<0.001	-1.50	<0.001	<0.001

[a]: Adjusted for age, BMI, BMI^2, sex, admission source, admitting service, diabetes medications, comorbidities [hypothyroidism, lymphoma, liver disease, paralysis, pulmonary circulatory disorder, renal failure, peripheral vascular disease, vascular disorder, cardiac arrhythmia, neurological disorder, fluid or electrolyte disorder, deficiency anemia, alcohol abuse, drug abuse, depression, COPD, psychoses, blood loss anemia, coagulopathy, rheumatologic diseases (rheumatoid arthritis/collagen vascular disease), HIV/AIDS, peptic ulcer, CHF, metastatic cancer, solid tumor without metastasis, myocardial infarction].

Figure 2. Relation of 17-glucose concentration categories to mortality, readmission, and readmission or mortality (Low glucose-hypoglycemia at hospital discharge cohort)

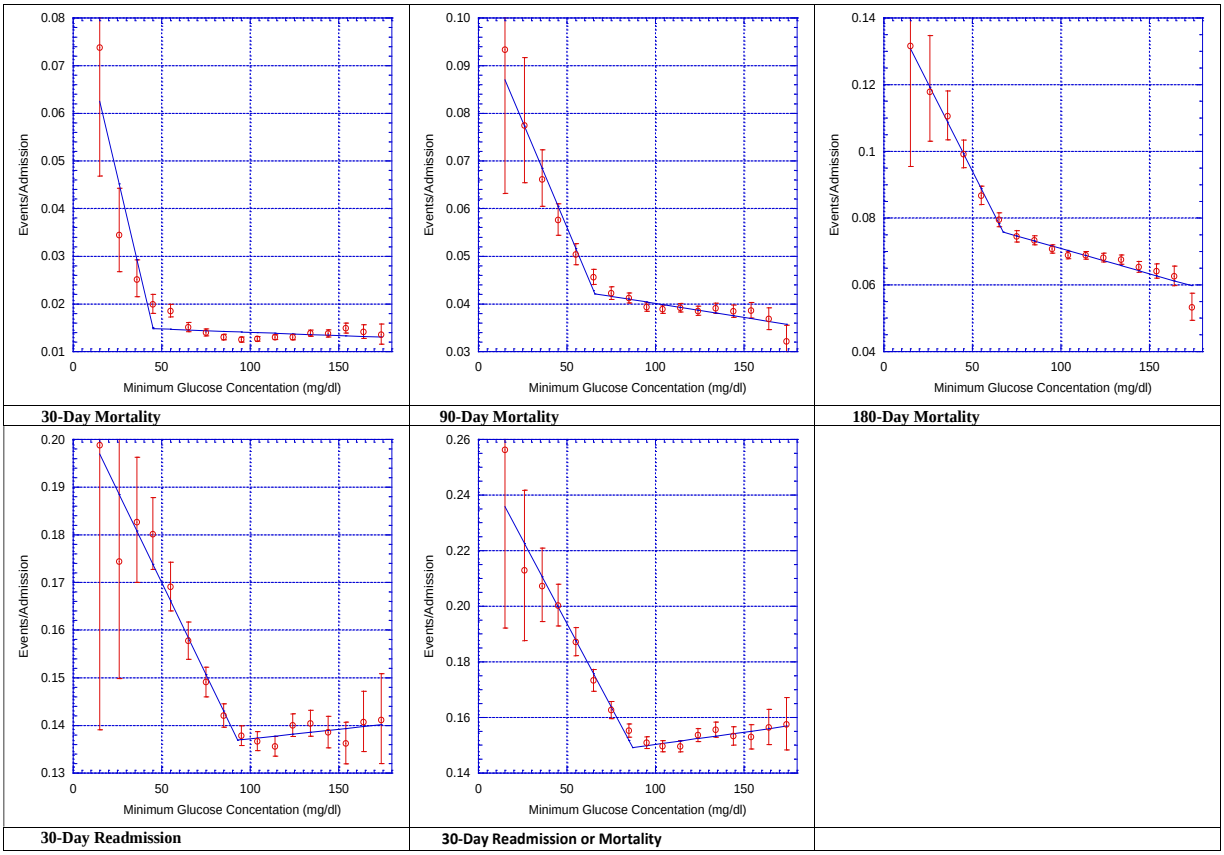

Figure 3. Relation of 17-glucose concentration categories to mortality, readmission, and readmission or mortality, adjusted for multiple covariates (Low glucose-hypoglycemia at hospital discharge cohort)

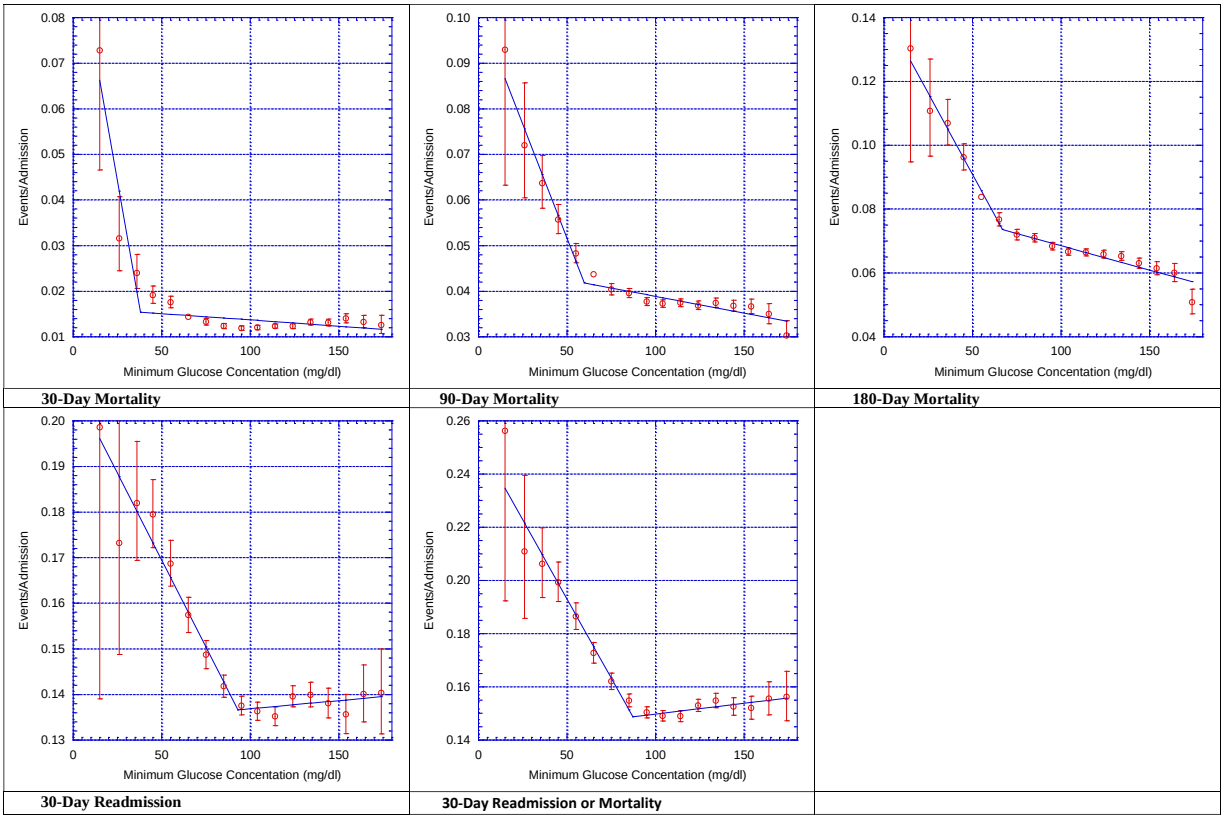

Figure 4. Study flow diagram. Glucose Variability cohort. (DM: Diabetes Mellitus, LOS: Length of stay, ICU: Intensive care unit)

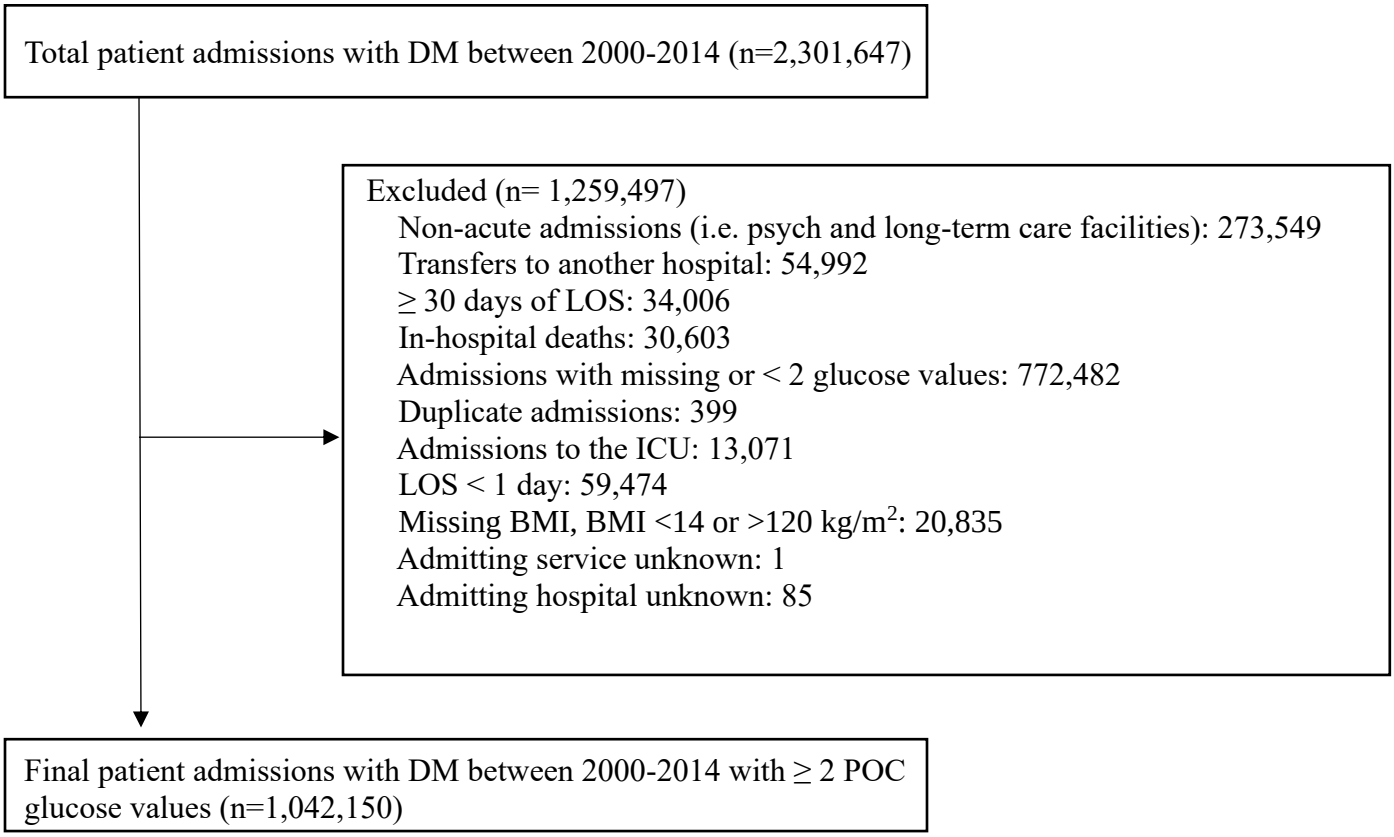

Table 8. Characteristics of Admissions of Patients with Diabetes Mellitus (Glucose Variability Cohort)

Variable	All Admissions (N=1,042,150)	GV (CV 1-4) (N=416,885)	GV (CV 5-7) (N=312,624)	GV (CV 8-10) (N=312,641)	Adjusted P
*Age (years)	66.5 (10.8)	66.1 (10.7)	66.6 (10.7)	66.8 (10.9)	<0.001
HbA1C	7.8 (1.9)	7.5 (1.8)	7.7 (1.9)	8.1 (2.1)	<0.001
Male Sex, n (%)	1,012,466 (97.2)	404,389 (97)	303,904 (97.2)	304,173 (97.3)	<0.001
**BMI (kg/m^2)	29.8 (25.7-34.8)	30.4 (26.3-35.4)	30.0 (25.9-34.9)	28.9 (24.8-33.7)	<0.001
Race, n (%)					<0.001
White	746,704 (71.7)	302,472 (72.6)	224,713 (71.9)	219,519 (70.2)	
Black	205,090 (19.7)	79,399 (19)	60,370 (19.3)	65,321 (20.9)	
Asian/American Indian/Pacific	18,957 (1.8)	7,563 (1.8)	5,767 (1.84)	5,627 (1.8)	
Other/Unknown	71,399 (6.9)	27,451 (6.6)	21,774 (7)	22,174 (7.1)	
Income, n (%)					<0.001
< $20,000	601,841 (57.8)	240,379 (57.7)	180,234 (57.7)	181,228 (60)	
$20,001-$40,000	343,421 (33.0)	136,717 (32.8)	103,299 (33.0)	103,405 (33.1)	
$40,001-$60,000	56,350 (5.4)	22,866 (5.5)	16,912 (5.4)	16,572 (5.3)	
>$60,001	40,538 (3.9)	16,923 (4.1)	12,179 (3.9)	11,436 (3.7)	
**LOS (days)	3.9 (2.2-6.9)	3.9 (2.2-6.7)	3.9 (2.2-6.8)	4.00 (2.3-7.00)	<0.001
***Hypoglycemia, n (%)	76,621 (7.4)	5,203 (1.3)	10,902 (3.5)	60,516 (19.4)	<0.001
Year of Admission, n (%)					<0.001
Before 2005	204,954 (19.7)	81,411 (19.5)	59,462 (19.0)	64,081 (20.5)	
2006-2010	431,271 (41.4)	167,179 (40.1)	128,592 (41.1)	135,500 (43.3)	
2011-2015	405,925 (39.0)	168,295 (40.4)	124,570 (39.9)	113,060 (36.2)	
Admission source, n (%)					0.48
Nursing Home	29,777 (2.9)	11,833 (2.8)	9,108 (2.9)	8,836 (2.8)	
Transfers from OSH	28,122 (2.7)	11,133 (2.7)	8,642 (2.8)	8,347 (2.7)	
Home/Outpatient	984,251 (94.4)	393,919 (94.5)	294,874 (94.3)	295,458 (94.5)	
Admitting Service, n (%)					<0.001
Medicine	841,242 (80.7)	322,961 (77.5)	254,065 (81.3)	264,216 (84.5)	
Surgery	200,908 (19.3)	93,924 (22.53)	58,559 (18.7)	48,425 (15.5)	
DM Medications, n (%)					<0.001
Insulin	635,152 (61.0)	235,609 (56.5)	193,937 (62)	205,606 (65.8)	
NIM	57,026 (5.5)	29,019 (7)	16,540 (5.3)	11,467 (3.7)	
NIM & Insulin	232,960 (22.4)	85,470 (20.5)	69,867 (22.4)	77,623 (24.8)	
None	117,012 (11.2)	66,787 (16)	32,280 (10.3)	17,945 (5.7)	
Comorbid Conditions, n (%)					
Alcohol Abuse	52,701 (5.1)	21,273 (5.1)	15,739 (5)	15,689 (5)	1.0
Blood Loss Anemia	9,240 (0.9)	3604 (0.9)	2,821 (0.9)	2,815 (0.0)	1.0
Cardiac Arrhythmia	239,084 (22.9)	94,426 (22.7)	73,068 (23.4)	71,590 (22.9)	<0.001
CHF	252,302 (24.2)	91,616 (22)	77,377 (24.8)	83,309 (26.7)	<0.001
COPD	226,848 (21.8)	86,918 (20.9)	67,995 (21.8)	71,935 (23)	<0.001
Coagulopathy	30,557 (2.9)	11,902 (2.9)	9,436 (3)	9,219 (3)	0.008
Deficiency Anemia	46,229 (4.4)	17,127 (4.1)	13,884 (4.4)	15,218 (4.9)	<0.001
Depression	128,659 (12.4)	52,794 (12.7)	38,313 (12.3)	37,552 (12)	<0.001
Drug Abuse	23,302 (2.2)	8,810 (2.1)	6,757 (2.2)	7,735 (2.5)	<0.001
Fluid/Electrolyte	181,170 (17.4)	67,928 (16.3)	54,448 (17.4)	58,794 (18.8)	<0.001
HIV/AIDS	4,366 (0.4)	1,725 (0.41)	1,346 (0.43)	1,295 (0.41)	1.0
Hypothyroidism	70,271 (6.7)	27,787 (6.7)	21,222 (6.8)	21,262 (6.8)	1.0
Hypertension (Complicated)	210,652 (20.2)	72,536 (17.4)	64,401 (20.6)	73,715 (23.6)	<0.001
Liver Disease	72,858 (7.0)	28,344 (6.8)	22,293 (7.1)	22,221 (7.1)	<0.001
Lymphoma	11,900 (1.1)	4,708 (1.1)	3,633 (1.2)	3,559 (1.1)	1.0
Metastatic Cancer	25,685 (2.5)	11,231 (2.7)	7,667 (2.5)	6,787 (2.2)	<0.001
Solid Tumor Non-Met	86,514 (8.3)	37,739 (9.1)	25,651 (8.2)	23,124 (7.4)	<0.001
Myocardial Infarction	64,594 (6.2)	24,958 (6)	19,635 (6.3)	20,001 (6.4)	<0.001
Neurological Disorder	43,784 (4.2)	17,713 (4.3)	13,187 (4.2)	12,884 (4.1)	0.93
Obesity	89,885 (8.6)	41,097 (9.9)	27,182 (8.7)	21,606 (6.9)	<0.001
Paralysis	15,558 (1.5)	6,723 (1.6)	4,787 (1.5)	4,048 (1.3)	<0.001
Peptic Ulcer Disease	8,129 (0.8)	3,315 (0.8)	2,450 (0.8)	2,364 (0.8)	1.0
PVD	102,132 (9.8)	38,293 (9.2)	30,793 (9.9)	33,046 (10.6)	<0.001
Psychosis	26,010 (2.5) 33,094	10,334 (2.5)	7,761 (2.5)	7,915 (2.5)	1.0
Pulm/Circ Disease	(3.2) 238,635 (22.9)	12,561 (3)	10,192 (3.3)	10,341 (3.3)	<0.001
Renal Failure	13,559 (1.3)	81,843 (19.6)	72,712 (23.3)	84,080 (26.9)	<0.001
Rheumatoid Arthritis	48,174 (4.6)	4,938 (1.2)	4,027 (1.3)	4,594 (1.5)	<0.001
Valvular Disease	21,410 (2.0)	18,657 (4.5)	14,721 (4.7)	14,796 (4.7)	<0.001
Weight Loss		8,065 (1.9)	6,513 (2.1)	6,832 (2.2)	<0.001

*Mean (standard deviation) **Median (interquartile range), ***Hypoglycemia within past 24 hours

GV: Glucose Variability, CV: Coefficient of Variation, BMI: Body Mass Index, LOS: Length of Stay, OSH: Outside Hospital, DM: Diabetes Mellitus, NIM: Non-Insulin Medications, CHF: Congestive Heart Failure, COPD: Chronic Obstructive Pulmonary Disease, HIV: Human Immunodeficiency Virus, AIDS: Acquired Immunodeficiency Syndrome, Non-met: Non-Metastatic, PVD: Peripheral Vascular Disease, Pulm/Circ: Pulmonary or Circulatory disorders.

Table 9. Event RR of the 30-day Readmission by CV Decile Category, obtained in the Last 24 Hours of Inpatient Stay (Glucose Variability Cohort)

Decile Category: *CV%	**Model 1:RR (95% CI)**	**P**	**Model 2: RR (95% CI)**	**P**	**Model 3: RR (95%CI)**	**P**
1st: 3.6 (2.0-4.9)	1.00 ref		1.00 ref		1.00 ref	
2nd: 8.2 (7.2-9.2)	1.00 (0.98-1.02)	0.88	1.00 (0.98-1.02)	0.81	1.00 (0.98-1.02)	0.80
3rd: 12.0 (11.1-12.9)	1.02 (1.00-1.04)	0.06	1.01 (0.99-1.03)	0.44	1.01 (0.99-1.03)	0.45
4th: 15.6 (14.7-16.5)	1.03 (1.01-1.05)	**0.0004**	1.01 (0.99-1.03)	0.25	1.01 (0.99-1.03)	0.27
5th: 19.4 (18.4-20.3)	1.06 (1.04-1.08)	**< 0.0001**	1.02 (1.00-1.04)	**0.03**	1.02 (1.00-1.04)	**0.03**
6th: 23.4 (22.4-24.5)	1.08 (1.06-1.10)	**< 0.0001**	1.03 (1.01-1.05)	**0.002**	1.03 (1.01-1.05)	**0.003**
7th: 28.1 (26.9-29.4)	1.10 (1.08-1.12)	**<0.0001**	1.04 (1.02-1.06)	**< 0.0001**	1.04 (1.02-1.05)	**<0.0001**
8th: 33.9 (32.3-35.6)	1.15 (1.13-1.18)	**<0.0001**	1.07 (1.05-1.09)	**<0.0001**	1.07 (1.05-1.09)	**<0.0001**
9th: 41.8 (39.5-44.4)	1.16 (1.13-1.19)	**<0.0001**	1.07 (1.04-1.09)	**<0.0001**	1.06 (1.03-1.08)	**<0.0001**
10th: 56.2 (51.2-64.1)	1.23 (1.20-1.26)	**<0.0001**	1.10 (1.08-1.13)	**<0.0001**	1.08 (1.05-1.10)	**<0.0001**

Model 1: Adjusting for age, gender, race
Model 2: Adjusting for age, gender, race (Model 1) and length of stay, DM medication groups, income, BMI, year of admission, admission source, admitting service, comorbidities
Model 3: Adjusting for age, gender, race, length of stay, DM medication groups, income, BMI, year of admission, admission source, admitting service, comorbidities (Model 2) and hypoglycemia
RR: Rate Ratio, **CV:** coefficient of variation, **DM:** diabetes mellitus, **BMI:** body mass index
*Median (IQR)

Table 10. Event RR of the 30-day Readmission by SD Decile Category, obtained in the last 24 hours of Inpatient Stay

Decile Category: *SD mg/dL	**Model 1:RR (95%CI)**	**P**	**Model 2: RR (95%CI)**	**P**	**Model 3: RR (95%CI)**	**P**
1st: 5.1 (2.8-7.1)	1.00 ref		1.00 ref		1.00 ref	
2nd: 12.1 (10.6-13.7)	1.02 (0.99-1.04)	0.16	1.00 (0.99-1.03)	0.55	1.01 (0.99-1.03)	0.59
3rd: 18.4 (16.8-19.8)	1.04 (1.02-1.07)	**0.0002**	1.02 (1.00-1.04)	**0.049**	1.02 (1.00-1.04)	0.07
4th: 24.5 (22.9-26.2)	1.08 (1.06-1.10)	**<0.0001**	1.04 (1.02-1.06)	**<0.0001**	1.04 (1.02-1.06)	**<0.0001**
5th: 31.1 (29.5-33.0)	1.10 (1.07-1.12)	**<0.0001**	1.05 (1.03-1.07)	**<0.0001**	1.04 (1.02-1.06)	**<0.0001**
6th: 38.7 (36.7-40.7)	1.11 (1.08-1.13)	**<0.0001**	1.05 (1.02-1.07)	**<0.0001**	1.04 (1.02-1.06)	**0.0001**
7th: 47.6 (45.3-50.2)	1.14 (1.12-1.16)	**<0.0001**	1.07 (1.05-1.09)	**<0.0001**	1.06 (1.04-1.08)	**<0.0001**
8th: 59.1 (55.9-62.6)	1.15 (1.13-1.18)	**<0.0001**	1.07 (1.04-1.09)	**<0.0001**	1.06 (1.04-1.09)	**<0.0001**
9th: 75.7 (70.7-81.4)	1.20 (1.17-1.23)	**<0.0001**	1.10 (1.07-1.12)	**<0.0001**	1.09 (1.06-1.11)	**<0.0001**
10th: 109.6 (97.3-129.6)	1.27 (1.23-1.30)	**<0.0001**	1.13 (1.10-1.15)	**<0.0001**	1.11 (1.09-1.14)	**<0.0001**

Model 1: Adjusting for age, gender, race
Model 2: Adjusting for age, gender, race (Model 1) and length of stay, DM medication groups, income, BMI, year of admission, admission source, admitting service, comorbidities
Model 3: Adjusting for age, gender, race, length of stay, DM medication groups, income, BMI, year of admission, admission source, admitting service, comorbidities (Model 2) and hypoglycemia
RR: Rate Ratio, **SD:** Standard Deviation **DM:** diabetes mellitus, **BMI:** body mass index
*Median (IQR)

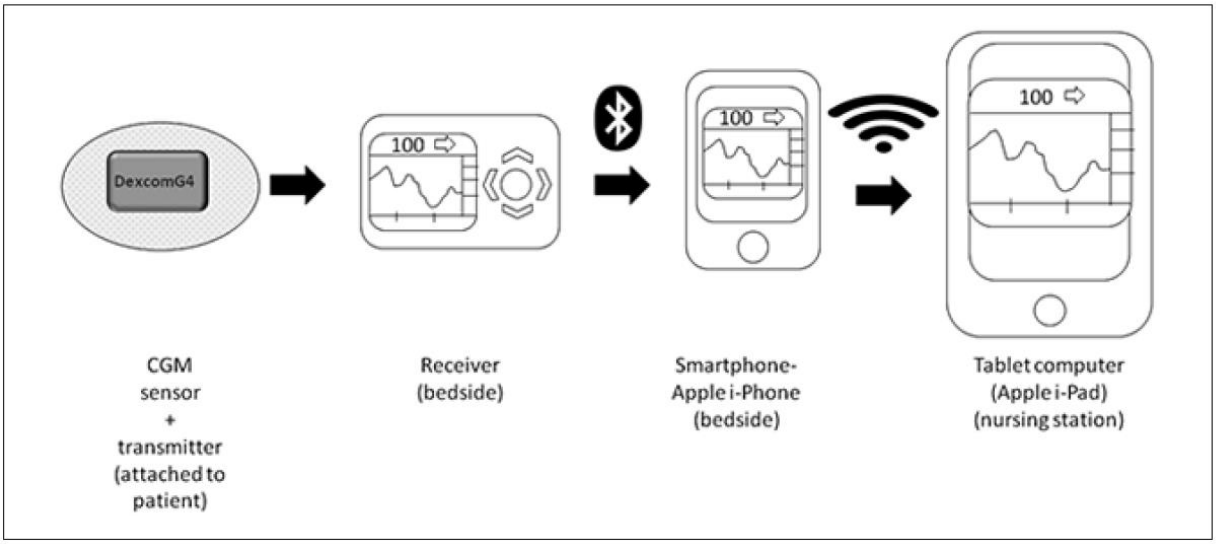

Figure 5. The Glucose Telemetry system (GTS) [118]

Table 11. Glycemic Outcomes (From [126])			
	RT-CGM/GTS group (n=36)	POC group (n=36)	P value
Hypoglycemic events / per patient < 70 mg/dL < 54 mg/dL	 0.67 (0.34-1.30) 0.08 (0.03-0.26)	 1.69 (1.11-2.58) 0.75 (0.51-1.09)	 0.024 0.003
Nocturnal hypoglycemic events / per patient < 70 mg/dL < 54 mg/dL	 0.19 (0.09-0.41) 0.03 (0.01-0.24)	 0.33 (0.19-0.59) 0.11 (0.04-0.33)	 0.26 0.26
Hypoglycemic events (< 70mg/dL) / per patient/ per day	0.12 (0.06-0.24)	0.35 (0.23-0.54)	0.011
Percentage of TBR < 70 mg/dL (%)	0.40 (0.18-0.92)	1.88 (1.26-2.81)	0.002
Percentage of TBR < 54 mg/dL (%)	0.05 (0.01-0.43)	0.82 (0.47-1.43)	0.017
Percentage of TIR 70-180 mg/dL (%)	59.12 (52.47-66.61)	54.69 (47.96-62.37)	0.39
Percentage of TAR >180-250 mg/dL (%)	29.88 (26.11-34.19)	30.10 (26.11-34.70)	0.94
Percentage of TAR > 250 mg/dL (%)	10.60 (7.15-15.73)	13.33 (9.20-19.37)	0.41
CV (%)	26.09 (24-28.19)	27.89 (25.41-30.36)	0.28

Data are mean (95% CI). TBR: time below range, TIR: time in range, TAR: time above range, CV: coefficient of variation, CI: confidence interval

Table 12. Glycemic control, insulin therapy, and hospital clinical outcomes (From [128])

	Overall (N=162)	POC-Guided (N=79)	CGM-Guided (N=83)	P value
Glycemic Control				
TIR %, 70 -180 mg/dL	51.65 ± 26.2	48.64 ± 24.2	54.51 ± 27.7	0.14
TBR % < 70 mg/dL	1.40 ± 4.45	2.15 ± 5.91	0.69 ± 2.15	0.43
TBR %< 54 mg/dL	0.65 ± 2.79	1.00 ± 3.74	0.32 ± 1.33	0.35
TAR % > 180 mg/dL	46.95 ± 26.76	49.21 ± 25.50	44.80 ± 27.89	0.26
TAR % > 250 mg/dL	16.65 ± 18.61	17.08 ± 17.59	16.24 ± 19.63	0.45
Mean daily Glucose, mg/dL	184.9 ± 40	186.8 ± 39	183.2 ± 40	0.36
Glycemic Variability				
Coefficient of variation	27± 8	27± 8	26± 9	0.33
Standard deviation, mg/dL	48.6± 18.0	50.4 ± 16.2	46.8 ±18.0	0.28
Mean amplitude glycemic excursion	63.08 ± 35.74	65.02 ± 39.10	61.24 ± 32.41	0.73
Hypoglycemia				
Events per patient <70 mg/dL	0.90 ± 1.82	1.15 ± 2.24	0.65 ± 1.26	0.36
Events per patient <54 mg/dL	0.38 ± 1.11	0.56 ± 1.46	0.22 ± 0.59	0.11
Nocturnal hypoglycemia, TBR % <70 mg/dL	0.48 ± 1.97	0.76 ± 2.67	0.22 ± 0.84	0.90
Nocturnal hypoglycemia, TBR % <54 mg/dL	0.24 ± 1.22	0.35 ± 1.57	0.13 ± 0.75	0.35
Nocturnal hypoglycemic events per patient <70 mg/dL	0.27 ± 0.68	0.34 ± 0.83	0.20 ± 0.49	0.71
Nocturnal hypoglycemic events per patient <54 mg/dL	0.15 ± 0.56	0.23 ± 0.72	0.08 ± 0.36	0.14
Recurrent hypoglycemia, TBR % <70 mg/dL	3.71 ± 6.67	5.47 ± 8.49	1.89 ± 3.27	0.02*
Recurrent hypoglycemia, TBR % <54 mg/dL	3.37 ± 5.68	4.12 ± 6.85	2.17 ± 2.97	0.28
Recurrent hypoglycemic events per patient <70 mg/dL	2.38 ± 2.30	2.94 ± 2.76	1.80 ± 1.54	0.04*
Recurrent hypoglycemic events per patient <54 mg/dL	2.00 ± 1.81	2.32 ± 2.21	1.50 ± 0.67	0.63
Recurrent nocturnal hypoglycemia, TBR % <70 mg/dL	2.79 ± 4.06	4.27 ± 5.15	1.30 ± 1.71	0.004*
Recurrent nocturnal hypoglycemia, TBR % <54 mg/dL	2.52 ± 3.32	2.71 ± 3.78	2.14 ± 2.47	0.76
Recurrent nocturnal hypoglycemic events per patient <70 mg/dL	1.57 ± 0.79	1.93 ± 0.92	1.21 ± 0.43	0.02*
Recurrent nocturnal hypoglycemic events per patient <54 mg/dL	1.67 ± 0.98	1.80 ± 1.14	1.40 ± 0.55	0.73

Table 13. Patient Characteristics (Accuracy CGM Study [130]).

Age, years	60.6 ± 12.0
Sex, n (%)	
Male	147 (67)
Female	71 (33)
BMI, kg/m^2	33.4 ± 9.0
Race, n (%)	
Black	159 (73)
White	52 (24)
Hispanic	6 (2.8)
Other	1 (0.5)
Type 2 Diabetes, n (%)	209 (96)
Duration of Diabetes, years	15.9 ± 10.3
Admission Service, n (%)	
Medicine	192 (88)
Surgery	26 (12)
Admission Hemoglobin A1c, %	9.1 ± 2.2
Enrollment BG, mg/dL	203.6 ± 69.8
Median LOS (post-enrollment), days [IQR]	5 [3, 8]
Grouped Admission Diagnosis, n (%)	
Cardiovascular	76 (35)
Infectious	66 (30)
Neurologic	21 (9.6)
Pulmonary	17 (7.8)
Other (DM-related, GI, surgical, gynecologic, renal)	52 (24.3)
Legend: BG, blood glucose; BMI, body mass index; DM, diabetes mellitus; GI, gastrointestinal; IQR, interquartile range; LOS, length of stay	

Table 14. CGM Reliability by Sensor Age (Accuracy CGM Study [130]).

	CGM vs Capillary POC (first 12 hours)	**CGM vs Capillary POC (first 24 hours)**	**CGM vs Capillary POC (entire hospitalization)**
Paired readings, n	258	614	4067
MARD, %	16.4	14.4	12.8
Median ARD, % (IQR)	12.8 (5.6, 23.2)	11.1 (5.3, 20.4)	10.1 (4.6, 17.6)
%15/15, %20/20, %30/30	57.0, 69.0, 86.0	63.0, 75.2, 89.1	68.7, 81.7, 93.8

K. Publications

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"Association of glucose concentrations at hospital discharge with readmissions and mortality: A nationwide cohort study."

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Abbreviations: VA: Veteran Affairs, CMS: Centers for Medicare and Medicaid Services, DM: Diabetes Mellitus, ICD: International Classification of Diseases, CDW: Central Data Warehouse, POC: Point of Care, BMI: Body Mass Index, GEE: General Estimating Equation, CHF: Congestive Heart Failure, COPD: Chronic Obstructive Pulmonary Disease, OAD: oral antidiabetic drugs

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Conflict of Interest Disclosures

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Abstract

Context: Low blood glucose concentrations during the discharge day may affect 30-day readmission and post hospital discharge mortality rates.

Objective: To investigate whether patients with diabetes and low glucose values during the last day of hospitalization are at increased risk of readmission or mortality.

Design: Minimum point of care glucose values were collected during the last 24 hours of the hospitalization. We used adjusted rates of 30-day readmission rate, 30-day, 90-day, and 180-day mortality rate and combined 30-day readmission/mortality rate to identify minimum glucose thresholds above which patients can be safely discharged.

Setting: Nation-wide cohort study including 843,978 admissions of patients with diabetes at the Veteran Affairs hospitals over a 14-year period.

Main Outcomes: 30-day readmission rate, 30-day, 90-day, and 180-day mortality rate and combined 30-day readmission/mortality rate.

Results: The rate ratios (RR) increased progressively for all five outcomes as the minimum glucose concentrations progressively decreased below the 90-99 mg/dl category, compared to the 100-109 mg/dl category: 30-day readmission RR 1.01 to 1.45, 30-day readmission/mortality RR 1.01 to 1.71, 30-day mortality RR 0.99 to 5.82, 90-day mortality RR 1.01 to 2.40, 180-day mortality 1.03 to 1.91. Patients with diabetes experienced greater 30-day readmission rate, 30-, 90- and 180-day post-discharge mortality and higher combined 30-day readmission/mortality with glucose levels <92.9 mg/dl, <45.2 mg/dl, 65.8 mg/dl and 67.3 mg/dl and <87.2 mg/dl, respectively.

Conclusions: Patients with diabetes who had hypoglycemia or near normal glucose values during the last day of hospitalization had higher rates of 30-day readmission and post discharge mortality.

Reducing hospital readmissions is a high-priority for quality health care. The Centers for Medicare and Medicaid Services (CMS) Readmissions Reduction Program penalizes hospitals with excessive 30-day readmission rates [56]. Compared to patients without diabetes mellitus (DM), patients with DM have 40% higher re-hospitalization rates, with 30-day readmission rates reported to range between 14% and 26% [54, 58-63, 66-71]. Notably almost 30% of them experience two or more re-admissions per year [72]. In 2012 [146] and also in 2017 [11] the cost of hospitalizations for DM patients in the U.S. was close to $123 billion. Assuming a 20% readmission rate the cost of 30-day readmissions is estimated to be close to $25 billion [54].

Studies have identified risk factors for readmissions among DM patients [54, 58-62, 64, 73, 105], although little is known about the effect of glycemic control and the readmission risk. Hyperglycemia at admission or 24-hours prior to admission [64] and hypoglycemia at any point of the hospital stay [73] have been associated with increased 30-day readmission rates. Inpatient hypoglycemia at any time of the hospital stay among patients with and without DM is also associated with higher post discharge mortality [76]. Several studies have reported that patients with DM have increased morality compared to patients without DM [29, 76, 147, 148]. In a recently published study that included hospitalized patients with and without diabetes, hypoglycemia was associated with increased short and long term mortality [29].

The majority of the published studies have focused on the effect of glucose control at admission or during the hospital stay. Limited information, if any, is available on whether low blood

glucose concentration during the day of hospital discharge (last 24 hours of hospitalization) -a potentially modifiable factor -is associated with adverse clinical outcomes, such as 30-day readmission and post discharge mortality. The final day of the hospitalization represents a unique period during the inpatient stay when medications adjustments have been almost finalized, patients are able to tolerate a full diet- minimizing nutritional interruptions and abnormalities in glucose control- and the underlying conditions that necessitated hospitalization have been treated.

The purpose of the current study was to examine the association of minimum glucose values in DM patients during the last 24 hours of hospital stay and the risk of 30-day readmission and post discharge mortality. More importantly the main aim of this work was to investigate whether there is a specific lower glucose value threshold above which DM patients can be safely discharged from the hospital without experiencing increased risk for either readmission or death.

Methods

Study overview/ Data Sources

This nationwide cohort study used data obtained from the Veterans Affairs (VA) health system detailing the clinical course and outcomes of DM patients admitted from 01/01/2000-12/31/2014 [93]. The study period ended in 2014, which was the last full year that International Classification of Diseases (ICD)-9 codes were used. We obtained the data from the VA Central Data Warehouse (CDW), a comprehensive national administrative database containing VA clinical, pharmacy and utilization files. The VA Vital Status file provided dates of death [93]. The study was approved by the University of Maryland Center Institutional Review Board and the Baltimore Veterans Administration Medical Research and Development Committee.

The cohort creation involved several steps, as previously described [93, 94] (**Figure 1**). First, we identified all VA nationwide admissions [93] of DM patients, defined by 2 or more ICD-9 codes during past 2 years from either inpatient stay or outpatient visits on separate days, and/or prescriptions for DM medications in the current year [94]. We excluded hospitalizations to psychiatric or long-term care (*n=273,549*) settings, admissions ending with a transfer to a non-VA hospital (*n=54,992*), admissions with a length of stay ≥30 days (*n=34,006*) and hospitalizations with death during admission (*n=30,603*) [93]. We also excluded admissions where point of care (POC) glucose concentrations were not reported and those with reported values <10 mg/dl (*n=457,312*), admissions with missing body mass index [(BMI), *n=17,748*], or duplicate admissions (*n=510*). We also excluded intensive care unit admissions, as this population of DM patients is different from the DM patients admitted to the general wards/non critical care setting (*n=92,879*) [44]. We also excluded hospitalizations where it was not possible to determine the admitting service (medicine or surgery, *n=3*) or the hospital that the patients were admitted (n=*62*). Finally, as hyperglycemia may be associated with increased rate of readmission or post discharge mortality, which was outside the scope of this report, we excluded subjects who were discharged with hyperglycemic values (average glucose ≥180 mg/dl, *n= 496,005*). Our final cohort included 843,978 admissions.

Covariates

The independent variables that we studied included age, sex, BMI, income, admission source (whether patients were admitted from home or long term care facilities), type of admitting service (medicine or surgery), DM medications received during the last 24 hours of their hospital stay, and several different co-morbid conditions as identified by Elixhauser and colleagues (**Table 1**) [54, 93, 97]. We determined length of hospital stay by subtracting the discharge day and time from the admission day and time, to ascertain the last 24 hours of the hospitalization.

Outcomes and Exposures

Our exposure of interest was minimum POC glucose concentration during the 24-hour period prior to discharge. Hypoglycemia and severe hypoglycemia were defined as POC glucose value <70 mg/dl and <40mg/dl, respectively [31]. We studied five outcome measures: 30-day readmission, 30-, 90-, 180-day mortality, and a composite outcome of 30-day readmission or mortality [93, 98]. We defined readmissions if they occurred within 30 days of the date of discharge from the index admission [93, 98]. Since DM patients are at risk of multiple admissions [72] limiting our cohort to include only the first readmission, would have led us to exclude a significant number of re-hospitalizations. Readmissions more than 30 days after an index admission were considered as new index admissions, as previously described [93, 98]. Mortality was defined as death which occurred 30-, 90- or 180-days following initial discharge. The composite outcome of the 30-day readmission or mortality was defined as readmission or death within 30 days following discharge from the hospital.

Statistical Methods

We used Poisson regression to compute adjusted rates of the five outcomes of interest (mortality 30-, 90- or 180-days following discharge, 30-day readmission and 30-day readmission or mortality). For each of the outcomes event rates were computed for every 10 mg/dl glucose concentration categories reported of the last day of hospitalization. Overall seventeen glucose concentration categories were used for each of the five outcome measures. We used general estimating equations (GEE) of Liang and Zeger [99, 100] with an exchangeable covariance structure to account for the serial autocorrelation of repeated admissions obtained from the same patient. Absolute events rates were adjusted to reflect the sample mean for each covariate and were generated as following. For continuous variables, the mean of the variable was used in the adjustment. For categorical variables, the estimate was adjusted to reflect the prevalence of the

variable in the population (e.g. sex: 97% male). In addition to computing absolute event rates, we used linear contrasts to compute relative event rates. For these computations 100-109 mg/dl was used as the reference category as this value has been shown to be associated with lower rates of hospital complications and mortality [101].

From the list of collected covariates (**Table 1**) we selected those variables that were potential confounders of the association between glucose concentration and one or more of our five outcome measures. We defined a potential confounder as a covariate that, when added to the model which included the 17-glucose concentration categories, produced a 10% or greater change in the association of the log event rate of one or more of the five outcome measures and at least three or more glucose concentration categories. For each of our five outcome measures we performed two analyses: i) an analysis including only the potential confounders selected as described above [age, BMI and BMI^2 (BMI centered at 30 kg/m^2 and its square to decrease the collinearity between un-centered BMI and its square)], admission source, admitting service, DM medications received on the last day of the hospitalization, and the presence of comorbidities including congestive heart failure, liver disease, fluid or electrolyte disorders, hypertension, metastatic cancer, renal failure, solid tumor without metastasis and myocardial infraction) and ii) an analysis including age, BMI, BMI^2, sex, admission source, admitting service, DM medications and all the comorbidities (**Table 1**).

To determine if there was a glucose concentration below which the event rates in our five outcome measures increased, we fitted the adjusted event rates to a piecewise linear continuous regression [102, 149] in which each adjusted event rate was weighted by the inverse of the estimate's variance. The regressions assumed that there would be two distinct linear relations between glucose concentration and each outcome (i.e. relations that can be described by two

lines having distinct intercepts and slopes, one describing the “normal glucose values” and the second the “lower glucose values”), and that the two linear relations met at a single glucose concentration referred to as the “knot”. The analysis estimated multiple parameters including, (1) the location of the knot, the glucose concentration at which two lines meet, one line describing the relation of glucose below the knot “lower glucose values” to outcome, the second line the relation above the knot “normal glucose values”, (2) the slope and intercept of the line in the range of the “lower glucose values”, and (3) the slope and intercept of the line in the range of the “normal glucose values”. Statistical analyses were performed by using SAS software version 9.4 (SAS Institute Inc). A two-tailed $p<0.05$ was considered statistically significant.

Results

The final cohort consisted of 843,978 admissions over 14 years of observation. The overall crude 30-day readmission rate was 17.3% and the 30-, 90- and 180-day crude mortality rates were 2.3%, 6.0% and 10%, respectively. A total of 18.8% of the study cohort died or readmitted within 30 days post discharge. The mean age (**Table 1)** of patients at admission was 66.8±10.8 (mean±SD) years, with most of them admitted from home (94.7%) and hospitalized under medicine service (79.7%). The most common co-morbid conditions were hypertension, either uncomplicated or complicated (53.4% and 19.3% respectively), cardiac arrhythmias (23.4%), congestive heart failure [(CHF), 23%], renal failure (21.9%) and chronic obstructive pulmonary disease [COPD, (20.5%)]. Admissions with and without hypoglycemia (**Table 1**) differed significantly in several of the covariates that we examined, an effect however that can be secondary to the large sample size of our cohort.

Most patients were discharged with minimum glucose values of 100-109 mg/dl (**Table 2**, 15.2%). As the glucose concentrations became progressively lower than 100 mg/dl, the fraction

of subjects who experienced an event (**Table 2**), and the relative rate generally increased for all five outcomes (**Table 3**). The results were almost similar even in in the fully adjusted model, where we adjusted for multiple covariates, among them all the co-morbidities that we collected (**Tables 4 and 5**). Hypoglycemia and severe hypoglycemia during the last 24 hours of the inpatient stay was present in 9.1% and 0.6% of the admissions, respectively. The adjusted 30-day readmission rate, the combined 30-day readmission/mortality rate and the 30-, 90- and 180-day mortality rates were 18.5% (95% CI:18.2%-18.8%), 20.1% (95% CI:19.8%-20.4%), 1.8% (95% CI:1.7%-1.9%), 5.1% (95% CI:4.9%-5.2%) and 8.7% (95% CI:8.5%-8.9%) for admissions with hypoglycemia and 20.3% (95% CI:19.2%-21.5%), 23.0% (95% CI:21.8%-24.2%), 2.8% (95% CI:2.5%-3.2%), 6.9% (95% CI:6.3%-7.5%), and 11.1% (95% CI:10.4%%-11.8%) for admissions with severe hypoglycemia, respectively. Admissions of DM patients who had hypoglycemia during the last 24 hours of hospitalization had a 39% [Rate Ratio: RR:1.39 (CI:1.32,147)], 30% [RR: 1.30 (1.26, 1.34)] and 27% [RR: 1.27 (1.24, 1.30) higher rate of dying within 30, 90 and 180 days after discharge, compared to those that had glucose values between 100-109 mg/dl respectively (**Table 3**). Furthermore, among those that experienced severe hypoglycemia, the rate was 124% [RR:2.24 (1.96-2.57)], 81% [RR: 1.81 (1.66-1.97)] and 66% [RR:1.66 (1.55-1.77)] higher. The rate of being readmitted in 30 days or experiencing either readmission or death in 30 days was 20% [RR: 1.20 (1.18, 1.23)] and 22% [RR:1.22 (1.20, 1.24)] higher among patients with hypoglycemia and 32% [RR: 1.32 (1.24-1.40)] and 39% [1.39 (1.32-1.46)] among those who developed severe hypoglycemia.

For all the outcomes (**Figure 2**), there was a progressive increase in the adjusted event rates (red circles with 95% confidence intervals) below the knot (determined by piecewise linear continuous regression), marking the point of intersection of the two lines (blue lines) smoothing the relation in the “lower glucose values” and “normal glucose values”. For all five outcome

measures, the slope of the line below the knot obtained by fitting the adjusted event rates to a piecewise continuous regression was negative and statistically significant. For three of the five outcome measures, the slope above the knot was not statistically significantly different from zero (**Table 6**). For all five outcome measures, the slope below the knot was statistical significantly different from the slope above the knot (**Table 6**). Overall, the knots were located at 92.9 mg/dl for 30-day readmission rate, 45.2 mg/dl for 30-day mortality rate, 65.8 mg/dl for 90-day mortality, 67.3 mg/dl for 180-day mortality and 87.2 mg/dl for 30-day readmission or mortality. The location of the knots and the slopes in "lower glucose values" and "normal glucose values" where similar when we adjusted for multiple covariates (**Figure 3, Table 7**).

Discussion

In the present study, we evaluated the association of minimum glucose values during the last 24 hours of the hospitalization with 30-day readmission and post discharge mortality rates in patients with DM. We identified several glucose thresholds (knots), where below those glucose concentrations there was an increased risk of developing one of the outcomes of interest: 92.9 mg/dl for 30-day readmission, 45.2 mg/dl, 65.8 mg/dl and 67.3 for 30-, 90- and 180-day for post discharge mortality, and 87.2 mg/dl for the combined outcome of 30-day readmission or post discharge mortality.

Hospital readmissions within 30 days have drawn national policy attention due to the increased cost of hospitalizations and concerns about poor quality of care, although the latter is debated [54, 98]. In our cohort, the rate of readmission in DM patients was 17.3%, consistent with previous reports [58-65, 67, 68]. Studies have tried to identify risk factors for readmission in DM patients [54, 58-62, 64, 73, 105]. Previous studies have focused either on the effect of glucose values either at admission [64] or during the entire hospital stay [73], but not on the glycemic

control during the last day of hospitalization. In our analysis, even low-normal glucose values between 70-93 mg/dl, were associated with a higher 30-day readmission rate. The reasons for the increased risk for readmission for this glucose category (70-93 mg/dl) is unknown. We hypothesize that DM patients with glucose levels close to the hypoglycemia range prior to discharge are more likely to develop even lower glucose values after discharge. This hypothesis may be difficult to explore because hypoglycemic events can be transient, albeit sufficient enough to lead to severe adverse events (such as falls, arrhythmias, seizures) resulting in hospital readmissions and increased mortality. Evidence from the VADT, ADVANCE and ACCORD trials showed an increased association of severe hypoglycemia with mortality, major macrovascular and microvascular events [106-109]. Our data suggest that in analogy to the outpatient setting, hospitalized DM patients with glucose concentrations close to the hypoglycemia range are at risk of readmissions and complications after discharge.

Patients with DM have a higher risk of post discharge mortality compared to patients without DM [44, 74-79]. The cause for increased mortality is multifactorial as patients with DM frequently have multiple co-morbidities and are hospitalized with more severe medical conditions compared to individuals without DM. In addition, they are at risk of hypoglycemia, which is a well-known risk factor associated with adverse clinical outcomes. In our study, we showed that glucose values <67.3 mg/dl during the last 24 hours of the hospitalization are associated with increased risk of post-discharge mortality.

The prevalence of hypoglycemia after discharge is unknown and few studies have focused on the optimal glycemic management following hospitalization. A recent randomized clinical trial, hypoglycemia (<70 mg/dL) after hospitalization was reported in 22% of patients discharged on oral antidiabetic drugs (OADs), 30% on OAD plus basal insulin, 44% on basal-bolus insulin, and

25% on basal insulin only [110]. The transition of care from the inpatient to the outpatient setting is often challenging, leading to adverse events, poor glycemic control, increased emergency room visits, higher hospital readmission rates and costs [110, 111]. As clinical studies are lacking, large randomized clinical trials are needed to evaluate the impact of improved glycemic control after discharge on clinical outcomes and the effectiveness of innovative strategies on the transition of care [110].

The study has several strengths. Our cohort represents one of the largest studies that examined readmission rates and post discharge mortality in DM patients. This is the first study using national data to examine readmission rates in an integrated health system. Although we may have missed admissions and re-hospitalizations to non-VA hospitals, we believe that analyzing data from the VA Health Care System, a "closed" health system where the majority of veterans are admitted and readmitted, represents one of the most robust ways to examine readmission rates. Another strength of the study is the extensive VHA data sources that allowed us to include numerous covariates and risk factors (**Table 1**).

Our study has some limitations to consider when interpreting the results. Similar to previously published studies that used administrative data from the Veterans Affairs Health Care System, our analysis is restricted to a single health care system [93]. Although we were able to include in our analysis nationwide data from the VA hospitals, admissions and readmissions to non-VA hospitals were not obtained. Our study population, veterans that were admitted between 2000 to 2014, may be different than the general US population as were more likely to be male, elderly and have chronic illness. Despite these differences, our ability to adjust for demographic data and an extensive list of comorbid conditions leads us to believe that our findings are applicable to the general population. As several studies have shown an increased risk of readmission and

mortality in patients with DM compared to patients without DM [29, 54, 58-63, 66-71, 76, 147, 148], we limited our analysis to patients/admissions with a diagnosis of diabetes. Therefore, our findings cannot be generalized and can only be applicable in this group of individuals. Additionally, our study did not try to distinguish preventable readmissions from other readmissions. As previous publications have pointed out, although use of administrative data to determine preventability of readmissions has been employed, preventability is subjective and administrative data may not be the best method to be utilized for this purpose [93, 116].

In conclusion, the results of this VA nationwide cohort study that included 843,978 admissions indicate that patients with DM, who had hypoglycemia or near normal glucose values at the last day of the inpatient stay were at a higher risk for of 30-day readmission and post discharge mortality. More specifically glucose concentrations lower than 92.9 mg/dl and 67.3 mg/dl had higher rates of 30-day readmissions and mortality respectively; and that glucose levels <87.2 mg/dl was associated with higher combined 30-day readmissions or mortality compared to patients with glucose >100 mg/dl. Future prospective studies need to be performed which will lead to alternative-safest discharge planning. Potential approaches which may reduce the risk for readmission or death after discharge are: Delaying patient release from the hospital until normoglycemia is achieved, modifying outpatient DM medications or advice patients to perform frequent glucose monitoring or use continuous glucose monitoring (CGM) devices.

Author Contributions:

E.K.S. and J.D.S. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. E.K.S. conceived and designed the study, provided guidance for the statistical analysis and wrote the manuscript. G.E.U., T.S., M.Z., S.S. and J.C.F. made critical revisions to the manuscript for important intellectual content.

J.D.S. performed the statistical analyses and made critical revisions to the manuscript for important intellectual content. The authors had access to all the study data and take full responsibility of the accuracy of the analysis; All authors approve the manuscript.

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"Association of glucose variability at the last day of hospitalization with 30-day readmission in adults with diabetes"

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Abbreviations: GV: Glucose Variability, VA: Veterans Affairs, SD: Standard Deviation, CV: Coefficient of Variation, CMS: Centers for Medicare and Medicaid, HRRP: Hospital Readmissions Reduction Program, DM: Diabetes Mellitus, LOS: Length of Stay, ICU: Intensive Care Unit, BMI: Body Mass Index, POC: Point-of-Care, GEE: General Estimating Equations, CHF: Congestive Heart Failure, Chronic Obstructive Pulmonary Disease (COPD), RR: Rate-Ratios

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Conflict of Interest Disclosures

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ABSTRACT

Objective: To evaluate whether increased GV during the last day of inpatient stay is associated with increased risk of 30-day readmission in patients with diabetes.

Research Design and Methods: A comprehensive list of clinical, pharmacy and utilization files were obtained from the Veterans Affairs (VA) Central Data Warehouse to create a nationwide cohort including 1,042,150 admissions of patients with diabetes over a 14-year study observation period. Point-of-care glucose values during the last 24 hours of hospitalization were extracted to

calculate GV [measured as standard deviation (SD) and coefficient of variation (CV)]. Admissions were divided into 10 categories defined by progressively increasing SD and CV.

The primary outcome was 30-day readmission rate, adjusted for multiple covariates including demographics, comorbidities, and hypoglycemia.

Results: As GV increased, there was an overall increase in the 30-day readmission rate ratio. In the fully adjusted model, admissions with CV in the 5^{th}-10^{th} CV categories and admissions with SD in the 4^{th}-10^{th} categories had a statistically significant progressive increase in 30-day readmission rates, compared to admissions in the 1^{st} (lowest) CV and SD categories. Admissions with the greatest CV and SD values (10^{th} category) had the highest risk for readmission [RR: 1.08 (1.05-1.10), $p<0.0001$ and RR: 1.11 (1.09-1.14), $p<0.0001$ for CV and SD respectively].

Conclusions: Patients with diabetes who exhibited higher degrees of GV on the final day of hospitalization had higher rates of 30-day readmission.

Significance of this Study

What is already known about this subject?

- Hospital readmissions represent a high-priority quality indicator for the healthcare delivery system.
- Increased glucose variability (GV) has been linked to adverse outcomes in the hospital, such as prolonged length of stay.
- Hypoglycemia in the last 24 hours of hospitalization has been associated to increased 30-day readmissions.

What are the new findings?

- Admissions of DM patients with the highest GV in the last 24 hours of the inpatient stay were associated to an increase in 30-day readmission rate ratios.
- This association persisted even after adjustment of multiple covariates, including hypoglycemia in the last 24 hours of the inpatient stay.

How might these results change the focus of research or clinical practice?

- The observed association between increased GV in the last 24 hours of hospitalization with higher rates of 30-day readmission may reveal a potentially independent and modifiable factor to reduce hospital readmissions.

INTRODUCTION

Hospital readmissions, a high-priority quality indicator for the healthcare delivery system, has remained an important quality metric due to the significant economic burden, high prevalence, and preventability.[54] The Centers for Medicare and Medicaid (CMS) hospital readmissions reduction program (HRRP) penalizes hospitals with higher readmission rates by reducing payments.[56, 63]

Patients with diabetes mellitus (DM) have high 30-day readmission rates, ranging from 14-26%.[54, 58-63, 66-71] In both 2012 and 2017, an estimated $123 billion of healthcare costs incurred was attributed to the hospitalizations of patients with DM,[150, 151] with 30-day readmissions costs estimated at $20 billion.[152] Therefore, identifying underlying causes and potentially modifiable risk factors for readmissions is imperative as it may improve quality of care and reduce the cost of inpatient care in patients with DM.

Numerous risk factors for hospital readmissions have been described in patients with DM, including burden of comorbidities, ethnic/racial minority, hospital-related and socioeconomic factors, among others.[54, 152] However, there is limited data available regarding the impact of inpatient dysglycemia (defined as hyperglycemia, hypoglycemia and increased glucose variability) on readmission risk. Hyperglycemia at time of admission or 24 hours before admission [66] and hypoglycemia during hospitalization have been associated with higher 30-day readmission rates.[153]

Glucose variability (GV), another marker of dysglycemia, refers to the magnitude of glucose fluctuations that occur around the mean glucose, and is increasingly considered as an indicator of poor glycemic control.[44, 154] Increased GV and hyperglycemia are known to be associated with adverse outcomes presumed to be secondary to their impact on oxidative stress,[43-46] neuronal damage, mitochondrial damage, and coagulation activity.[46, 47] Increased GV during hospitalization is associated with a higher risk for poor clinical outcomes in the non-critical care setting such as prolonged length of stay (LOS) and increased post-discharge mortality,[44] as well as increased mortality in the intensive care unit (ICU) setting.[45] There is presently no gold standard for measurement of GV [45, 49] and several indices have been described.[45, 46] The most widely used measure is standard deviation (SD) [45] along with the coefficient of variation, (CV) another valid and frequently utilized measure for GV.[44]

The majority of the published studies have examined the effect of glucose control during the entire hospital stay on adverse outcomes. There is limited information about the relationship between glucose control during the last day of hospitalization and the risk for readmission. In a nationwide cohort study we examined 843,978 admissions among patients with DM and we reported a strong association of lower glucose values during the last 24 hours of hospitalization with adverse clinical outcomes, including higher 30-day readmission rates.[96]

To our knowledge no previous studies have examined the relationship between GV during the last day of the hospitalization and risk of hospital readmission in patients with DM. Therefore,

we evaluated whether increased GV during the last 24 hours of hospitalization, a potentially modifiable risk factor, is associated with increased 30-day readmission rates.

METHODS

Study overview and data sources

This nationwide cohort study utilized data obtained from the Veterans Affairs (VA) health system of DM patients admitted between January 1, 2000 to December 31, 2014.[93, 96] The study ended in 2014, as this was the final year in which ICD-9 codes were used. Data was obtained from the VA Central Data Warehouse, a national administrative data repository which stores comprehensive clinical, pharmacy, and utilization records and VA Vital Status File for dates of death.[93] This study was approved by the University of Maryland Institutional Review Board and the Baltimore VA Research and Development Committee.

The cohort was created by initially identifying all acute VA admissions among DM patients. DM patients were identified by either the presence of ≥ 2 ICD-9 codes during the past 2 years from an inpatient stay or outpatient visit on separate days and/or had prescriptions for DM within the current year.[94] We excluded admissions (**Figure 1**) to psychiatric or long-term care settings (n=273,549) and admissions ending with transfer to a non-VA hospital (n=54,992), as follow-up data was not available, admissions with LOS ≥ 30 days (n=34,006) or LOS< 1 day (n=59,474), and admissions with in-hospital deaths (n=30,603). We also excluded admissions where there were less than two glucose values (including only those with two or more glucose values) during

the last 24 hours of the hospitalization, as neither SD or CV can be computed, and glucose values collected within 5 minutes of previous glucose values as previously described (n=772,482).[44]

Additionally, 399 duplicate admissions were also excluded. Patients in the ICU were excluded as this represents a different population than those admitted to noncritical care settings (n=13,071).[44] Finally, we excluded admissions with missing body mass index (BMI) or with BMI < 14 or > 120 kg/m^2 (n=20,835), hospitalizations where it was not possible to determine the admitting service (medicine or surgery, n=1) or the hospital where the patients were admitted (n=85).[96] The final cohort sample used for analysis was 1,042,150 admissions.

Covariates

Independent variables analyzed for this study included age, gender, race, BMI, income, year of admission, admission source (whether patients were admitted from home or other facilities), admitting service (medicine or surgery), hemoglobin A1c (A1c) obtained 90 days prior to the admission, DM medications used during the last 24 hours of hospitalization, and several comorbid conditions as previously defined by Elixhauser et al. (**Table 1**).[97] Hypoglycemia in the hospital was defined as glucose values <70 mg/dl.[155] Length of hospital stay was calculated by subtracting the discharge day and time from the admission day and time, to ascertain the last 24 hours of the hospitalization.

Exposures and outcomes

Exposures of interest for this study were measures of GV, measured by the CV and SD. CV and SD were calculated from point-of-care (POC) glucose values measured (minimum ≥2 values) during the last 24 hours of hospitalization.[44] We divided CV and SD values into 10 different groups (deciles) with the 1st decile and the 10th decile having the lowest and the highest measurements, respectively. Our outcome measure was the 30-day readmission, defined as a rehospitalization which occurred within 30 days from the discharge date of the index admission.[93, 98] As DM patients are at risk for multiple admissions (and therefore readmissions),[72] we did not only include the first readmission, as this approach would have led to exclusion of a significant number of rehospitalizations. All readmissions that occurred more than 30 days from the index hospitalization were considered new index admissions, as previously described.[93, 96, 98]

Statistical methods

The event rates were computed for every decile group of CV and SD. General estimating equations (GEE) with a Poisson distribution and an exchangeable covariance structure were used to compute adjusted rate ratios of the 30-day readmission while accounting for the correlation of repeated admissions obtained from the same patient and clustering in each center.[99, 104]

We considered three models based on CV and SD deciles: (1) The minimally adjusted model, which controls for age, gender, and race; (2) The second model which controls for all the variables collected (**Table 1**), except for hypoglycemia [age, gender, including income, BMI, admission source (whether patients were admitted from home or other facilities), admitting

service, DM medications, year of admission and multiple comorbidities]; (3) The third model which controls for all the variables in the second model including also hypoglycemia. We did not adjust for A1c as only 35.3% of patient-admissions had an A1c obtained within 90 days of the hospitalization. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute). Bonferroni corrected P values adjusting for multiple testing were used to compare the covariates among three CV categories based on the calculated CV values (admissions with CV deciles 1-4, CV 5-7 and CV 8-10) in **Table 1**. A two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

The final cohort included 1,042,150 unique admissions over the 14-year study observation period. In **Table 1**, we present baseline characteristics of the admissions of patients with DM, divided into three different categories based on the calculated CV values (admissions with CV 1-4, CV 5-7 and CV 8-10). Overall the mean age of patients at admission was 66.5±10.8 (mean±SD) years, with the majority being male (97.2%) and Caucasian (71.64%). 94.4% of them were admitted from home and were hospitalized under medicine service (80.7%). The most common comorbid conditions included congestive heart failure [CHF (24.2%], cardiac arrhythmia (22.9%), renal failure (22.9%) and chronic obstructive pulmonary disease [COPD, 21.8%]. Overall median LOS was 3.9 days (interquartile range: 2.2-6.9) and 7.35% of admissions of DM patients exhibited hypoglycemia in the last 24 hours of hospitalizations. The mean number of point-of-care glucose values during the last of the inpatient stay was 3.9±0.95. Admissions among the 3 groups differed significantly in several of the covariates that we examined, an effect that can be secondary to the large sample size of our cohort. One notable

observation however is that admissions in the 8-10 CV categories, which had the highest glucose variability measurements, had increased incidence of hypoglycemia (19.4%) compared to admissions in the 5-7 CV (3.5%) and 1-4 CV (1.3%) categories (**Table 1**).

Table 1. Characteristics of Admissions of Patients with Diabetes Mellitus

Variable	All Admissions (N=1,042,150)	GV (CV 1-4) (N=416,885)	GV (CV 5-7) (N=312,624)	GV (CV 8-10) (N=312,641)	Adjusted P
*Age (years)	66.5 (10.8)	66.1 (10.7)	66.6 (10.7)	66.8 (10.9)	<0.001
HbA1C	7.8 (1.9)	7.5 (1.8)	7.7 (1.9)	8.1 (2.1)	<0.001
Male Sex, n (%)	1,012,466 (97.2)	404,389 (97)	303,904 (97.2)	304,173 (97.3)	<0.001
**BMI (kg/m^2)	29.8 (25.7-34.8)	30.4 (26.3-35.4)	30.0 (25.9-34.9)	28.9 (24.8-33.7)	<0.001
Race, n (%)					<0.001
White	746,704 (71.7)	302,472 (72.6)	224,713 (71.9)	219,519 (70.2)	
Black	205,090 (19.7)	79,399 (19)	60,370 (19.3)	65,321 (20.9)	
Asian/American Indian/Pacific	18,957 (1.8)	7,563 (1.8)	5,767 (1.84)	5,627 (1.8)	
Other/Unknown	71,399 (6.9)	27,451 (6.6)	21,774 (7)	22,174 (7.1)	
Income, n (%)					<0.001
< $20,000	601,841 (57.8)	240,379 (57.7)	180,234 (57.7)	181,228 (60)	
$20,001-$40,000	343,421 (33.0)	136,717 (32.8)	103,299 (33.0)	103,405 (33.1)	
$40,001-$60,000	56,350 (5.4)	22,866 (5.5)	16,912 (5.4)	16,572 (5.3)	
>$60,001	40,538 (3.9)	16,923 (4.1)	12,179 (3.9)	11,436 (3.7)	
**LOS (days)	3.9 (2.2-6.9)	3.9 (2.2-6.7)	3.9 (2.2-6.8)	4.00 (2.3-7.00)	<0.001
***Hypoglycemia, n (%)	76,621 (7.4)	5,203 (1.3)	10,902 (3.5)	60,516 (19.4)	<0.001
Year of Admission, n (%)					<0.001
Before 2005	204,954 (19.7)	81,411 (19.5)	59,462 (19.0)	64,081 (20.5)	
2006-2010	431,271 (41.4)	167,179 (40.1)	128,592 (41.1)	135,500 (43.3)	
2011-2015	405,925 (39.0)	168,295 (40.4)	124,570 (39.9)	113,060 (36.2)	
Admission source, n (%)					0.48
Nursing Home	29,777 (2.9)	11,833 (2.8)	9,108 (2.9)	8,836 (2.8)	
Transfers from OSH	28,122 (2.7)	11,133 (2.7)	8,642 (2.8)	8,347 (2.7)	
Home/Outpatient	984,251 (94.4)	393,919 (94.5)	294,874 (94.3)	295,458 (94.5)	
Admitting Service, n (%)					<0.001
Medicine	841,242 (80.7)	322,961 (77.5)	254,065 (81.3)	264,216 (84.5)	
Surgery	200,908 (19.3)	93,924 (22.53)	58,559 (18.7)	48,425 (15.5)	
DM Medications, n (%)					<0.001
Insulin	635,152 (61.0)	235,609 (56.5)	193,937 (62)	205,606 (65.8)	
NIM	57,026 (5.5)	29,019 (7)	16,540 (5.3)	11,467 (3.7)	
NIM & Insulin	232,960 (22.4)	85,470 (20.5)	69,867 (22.4)	77,623 (24.8)	
None	117,012 (11.2)	66,787 (16)	32,280 (10.3)	17,945 (5.7)	
Comorbid Conditions, n (%)					
Alcohol Abuse	52,701 (5.1)	21,273 (5.1)	15,739 (5)	15,689 (5)	1.0
Blood Loss Anemia	9,240 (0.9)	3604 (0.9)	2,821 (0.9)	2,815 (0.0)	1.0
Cardiac Arrythmia	239,084 (22.9)	94,426 (22.7)	73,068 (23.4)	71,590 (22.9)	<0.001
CHF	252,302 (24.2)	91,616 (22)	77,377 (24.8)	83,309 (26.7)	<0.001
COPD	226,848 (21.8)	86,918 (20.9)	67,995 (21.8)	71,935 (23)	<0.001
Coagulopathy	30,557 (2.9)	11,902 (2.9)	9,436 (3)	9,219 (3)	0.008
Deficiency Anemia	46,229 (4.4)	17,127 (4.1)	13,884 (4.4)	15,218 (4.9)	<0.001
Depression	128,659 (12.4)	52,794 (12.7)	38,313 (12.3)	37,552 (12)	<0.001
Drug Abuse	23,302 (2.2)	8,810 (2.1)	6,757 (2.2)	7,735 (2.5)	<0.001
Fluid/Electrolyte	181,170 (17.4)	67,928 (16.3)	54,448 (17.4)	58,794 (18.8)	<0.001
HIV/AIDS	4,366 (0.4)	1,725 (0.41)	1,346 (0.43)	1,295 (0.41)	1.0
Hypothyroidism	70,271 (6.7)	27,787 (6.7)	21,222 (6.8)	21,262 (6.8)	1.0
Hypertension (Complicated)	210,652 (20.2)	72,536 (17.4)	64,401 (20.6)	73,715 (23.6)	<0.001
Liver Disease	72,858 (7.0)	28,344 (6.8)	22,293 (7.1)	22,221 (7.1)	<0.001
Lymphoma	11,900 (1.1)	4,708 (1.1)	3,633 (1.2)	3,559 (1.1)	1.0
Metastatic Cancer	25,685 (2.5)	11,231 (2.7)	7,667 (2.5)		<0.001
Solid Tumor Non-Met	86,514 (8.3)	37,739 (9.1)	25,651 (8.2)		<0.001

Myocardial Infarction	64,594 (6.2)	24,958 (6)	19,635 (6.3)	6,787 (2.2)	<0.001
Neurological Disorder	43,784 (4.2)	17,713 (4.3)	13,187 (4.2)	23,124 (7.4)	0.93
Obesity	89,885 (8.6)	41,097 (9.9)	27,182 (8.7)	20,001 (6.4)	<0.001
Paralysis	15,558 (1.5)	6,723 (1.6)	4,787 (1.5)	12,884 (4.1)	<0.001
Peptic Ulcer Disease	8,129 (0.8)	3,315 (0.8)	2,450 (0.8)	21,606 (6.9)	1.0
PVD	102,132 (9.8)	38,293 (9.2)	30,793 (9.9)	4,048 (1.3)	<0.001
Psychosis	26,010 (2.5) 33,094	10,334 (2.5)	7,761 (2.5)	2,364 (0.8)	1.0
Pulm/Circ Disease	(3.2) 238,635 (22.9)	12,561 (3)	10,192 (3.3)	33,046 (10.6)	<0.001
Renal Failure	13,559 (1.3)	81,843 (19.6)	72,712 (23.3)	7,915 (2.5)	<0.001
Rheumatoid Arthritis	48,174 (4.6)	4,938 (1.2)	4,027 (1.3)	10,341 (3.3)	<0.001
Valvular Disease	21,410 (2.0)	18,657 (4.5)	14,721 (4.7)	84,080 (26.9)	<0.001
Weight Loss		8,065 (1.9)	6,513 (2.1)	4,594 (1.5)	<0.001
				14,796 (4.7)	
				6,832 (2.2)	

*Mean (standard deviation) **Median (interquartile range), ***Hypoglycemia within past 24 hours
GV: Glucose Variability, CV: Coefficient of Variation, BMI: Body Mass Index, LOS: Length of Stay, OSH: Outside Hospital, DM: Diabetes Mellitus, NIM: Non-Insulin Medications, CHF: Congestive Heart Failure, COPD: Chronic Obstructive Pulmonary Disease, HIV: Human Immunodeficiency Virus, AIDS: Acquired Immunodeficiency Syndrome, Non-met: Non-Metastatic, PVD: Peripheral Vascular Disease, Pulm/Circ: Pulmonary or Circulatory disorders.

In **Tables 2 and 3** we present 30-day readmission rate-ratios (RR) of deciles of CV and SD, using the fist decile with the lowest variability as the reference group. For both CV and SD, as glucose variability on the last day of admission increased, the 30-day readmission rate-ratio increased. For the CV analysis (**Table 2**), after adjustment for age, gender and race (model 1), admissions that were in the 4^{th}-10^{th} CV deciles had an increased 30-day readmission rate compared to those admissions that were in the 1^{st} CV category. Admissions with CV values in the 10^{th} CV category had the highest 30-day readmission rate ratio [RR: 1.23 (1.20-1.26), p<0.0001]. In contrast, admissions with CV values in the lowest deciles (CV 2-3) did not experience a statistically significant increase in the 30-day readmission rate comparing to those in the 1^{st} CV category. In model 2, in which we adjusted for almost all covariates that we collected (except for hypoglycemia), admissions with CV in the 5^{th}-10^{th} CV categories had a statistically significant progressive increase in the 30-day readmission rate. The results were similar in model 3, where we adjusted for all the variables in model 2 and included hypoglycemia. Overall, compared to the reference 1^{st} CV category, after adjusting for all the covariates, admissions with the highest CV values in the 10^{th} category had an increased 30-day readmission rate [model 3, RR: 1.08 (1.05-1.10), p<0.0001].

Table 2. Event RR of the 30-day Readmission by CV Decile Category, obtained in the Last 24 Hours of Inpatient Stay

Decile Category: *CV%	**Model 1:RR (95% CI)**	**P**	**Model 2: RR (95% CI)**	**P**	**Model 3: RR (95%CI)**	**P**
1st: 3.6 (2.0-4.9)	1.00 ref		1.00 ref		1.00 ref	
2nd: 8.2 (7.2-9.2)	1.00 (0.98-1.02)	0.88	1.00 (0.98-1.02)	0.81	1.00 (0.98-1.02)	0.80
3rd: 12.0 (11.1-12.9)	1.02 (1.00-1.04)	0.06	1.01 (0.99-1.03)	0.44	1.01 (0.99-1.03)	0.45
4th: 15.6 (14.7-16.5)	1.03 (1.01-1.05)	**0.0004**	1.01 (0.99-1.03)	0.25	1.01 (0.99-1.03)	0.27
5th: 19.4 (18.4-20.3)	1.06 (1.04-1.08)	**< 0.0001**	1.02 (1.00-1.04)	**0.03**	1.02 (1.00-1.04)	**0.03**
6th: 23.4 (22.4-24.5)	1.08 (1.06-1.10)	**< 0.0001**	1.03 (1.01-1.05)	**0.002**	1.03 (1.01-1.05)	**0.003**
7th: 28.1 (26.9-29.4)	1.10 (1.08-1.12)	**<0.0001**	1.04 (1.02-1.06)	**< 0.0001**	1.04 (1.02-1.05)	**<0.0001**
8th: 33.9 (32.3-35.6)	1.15 (1.13-1.18)	**<0.0001**	1.07 (1.05-1.09)	**<0.0001**	1.07 (1.05-1.09)	**<0.0001**
9th: 41.8 (39.5-44.4)	1.16 (1.13-1.19)	**<0.0001**	1.07 (1.04-1.09)	**<0.0001**	1.06 (1.03-1.08)	**<0.0001**
10th: 56.2 (51.2-64.1)	1.23 (1.20-1.26)	**<0.0001**	1.10 (1.08-1.13)	**<0.0001**	1.08 (1.05-1.10)	**<0.0001**

Model 1: Adjusting for age, gender, race
Model 2: Adjusting for age, gender, race (Model 1) and length of stay, DM medication groups, income, BMI, year of admission, admission source, admitting service, comorbidities
Model 3: Adjusting for age, gender, race, length of stay, DM medication groups, income, BMI, year of admission, admission source, admitting service, comorbidities (Model 2) and hypoglycemia
RR: Rate Ratio, **CV:** coefficient of variation, **DM:** diabetes mellitus, **BMI:** body mass index
*Median (IQR)

Similarly, when we used SD as a measurement of glucose variability (**Table 3**), admissions with SD in the 3rd-10th categories (models 1 and 2) and admissions with SD in the 4th-10th categories (model 3) had a higher 30-day readmission rate compared to the 1st SD category. After adjusting for all the covariates including hypoglycemia (model 3), admissions with the SD values in the 10th category had the highest 30-day readmission rate [RR: 1.11 (1.09-1.14), p<0.0001].

Table 3. Event RR of the 30-day Readmission by SD Decile Category, obtained in the last 24 hours of Inpatient Stay

Decile Category: *SD mg/dL	**Model 1:RR (95%CI)**	**P**	**Model 2: RR (95%CI)**	**P**	**Model 3: RR (95%CI)**	**P**
1st: 5.1 (2.8-7.1)	1.00 ref		1.00 ref		1.00 ref	
2nd: 12.1 (10.6-13.7)	1.02 (0.99-1.04)	0.16	1.00 (0.99-1.03)	0.55	1.01 (0.99-1.03)	0.59
3rd: 18.4 (16.8-19.8)	1.04 (1.02-1.07)	**0.0002**	1.02 (1.00-1.04)	**0.049**	1.02 (1.00-1.04)	0.07
4th: 24.5 (22.9-26.2)	1.08 (1.06-1.10)	**<0.0001**	1.04 (1.02-1.06)	**<0.0001**	1.04 (1.02-1.06)	**<0.0001**
5th: 31.1 (29.5-33.0)	1.10 (1.07-1.12)	**<0.0001**	1.05 (1.03-1.07)	**<0.0001**	1.04 (1.02-1.06)	**<0.0001**
6th: 38.7 (36.7-40.7)	1.11 (1.08-1.13)	**<0.0001**	1.05 (1.02-1.07)	**<0.0001**	1.04 (1.02-1.06)	**0.0001**
7th: 47.6 (45.3-50.2)	1.14 (1.12-1.16)	**<0.0001**	1.07 (1.05-1.09)	**<0.0001**	1.06 (1.04-1.08)	**<0.0001**
8th: 59.1 (55.9-62.6)	1.15 (1.13-1.18)	**<0.0001**	1.07 (1.04-1.09)	**<0.0001**	1.06 (1.04-1.09)	**<0.0001**
9th: 75.7 (70.7-81.4)	1.20 (1.17-1.23)	**<0.0001**	1.10 (1.07-1.12)	**<0.0001**	1.09 (1.06-1.11)	**<0.0001**

10th: 109.6 (97.3-129.6)	1.27 (1.23-1.30)	**<0.0001**	1.13 (1.10-1.15)	**<0.0001**	1.11 (1.09-1.14)	**<0.0001**

Model 1: Adjusting for age, gender, race
Model 2: Adjusting for age, gender, race (Model 1) and length of stay, DM medication groups, income, BMI, year of admission, admission source, admitting service, comorbidities
Model 3: Adjusting for age, gender, race, length of stay, DM medication groups, income, BMI, year of admission, admission source, admitting service, comorbidities (Model 2) and hypoglycemia
RR: Rate Ratio, **SD:** Standard Deviation **DM:** diabetes mellitus, **BMI:** body mass index
*Median (IQR)

DISCUSSION

In this study, we evaluated the association of GV during the last 24 hours of hospitalization with 30-day readmission rates among a large cohort of adults with diabetes admitted in the non-critical care setting. We identified that admissions of DM patients with the highest GV during the last 24 hours of the inpatient stay, using CV and SD measurements, had an increased risk for 30-day readmission. This association persisted despite adjustment for multiple covariates, notably including adjustment for hypoglycemia during the last 24 hours of hospitalization.

Evidence from studies performed in the outpatient setting has shown that higher GV increases risk of adverse clinical outcomes. The effect of GV on oxidative stress and endothelial dysfunction is thought to be equal or greater than that attributed to persistent hyperglycemia, and is postulated to contribute to the development of micro- and macrovascular DM complications.[46] Within the inpatient setting several studies have examined increased GV with adverse outcomes, revealing associations with prolonged length of stay [44] and increased mortality in both ICU and non-critical care settings.[44, 48, 50, 53, 112]

To our knowledge, this is the first nationwide study aiming to determine whether increased GV is associated with increased risk for hospital readmissions. Hospital readmissions within 30-days post-discharge has drawn national attention with federal policy reform due to the rising healthcare expenditure, high prevalence, and preventability.[54] Therefore, research focused on exploring potentially modifiable factors to reduce readmissions is of utmost importance. The effect of glucose control at admission or throughout the inpatient stay on readmission has been evaluated,[153] but not during the final day of the hospitalization. Recently, we have reported an association of lower glucose values on the last inpatient day with increased rate of 30-day readmission.[96] In the present analysis, we have additionally showed an independent association of higher GV on the last day of hospitalization with increased 30-day readmission. The results from our cohort studies may shed light on two potentially modifiable risk factors for reducing 30-day readmissions.

It is unknown how higher GV on the last day of hospitalization may contribute to increased risk of 30-day readmission. Although we did not have access to post discharge glycemic values, one potential explanation is that high GV predisposes patients to post-discharge hypoglycemia or to significant hyperglycemia, which may lead to readmission. In our study we found that those admissions of patients with the highest GV also had the highest incidence of hypoglycemia during the last 24 hours of the hospital stay, which is consistent with previous observations. It is known that blood glucose disturbances precede severe hypoglycemia [113] and increased GV has been previously identified as a predictor of hypoglycemia.[49, 114, 115] The transition of care from inpatient to the outpatient setting signifies a vulnerable and challenging time with greater risk of dysglycemia, as well as healthcare utilization such as emergency room visits or

readmissions.[96, 110, 111] As patients with DM have multiple and often sub-optimally controlled comorbidities, they have an inherently higher risk for frequent readmissions.[10, 72]

Despite the growing evidence of an association of GV with poor clinical outcomes, it remains debatable whether GV should be considered a treatment target.[156-158] Lack of standardization for the definition and method of measurement of GV contributes to this uncertainty. Within the literature there is significant heterogeneity of GV indices reported,[47] therefore the consolidation of the available evidence to drive changes in clinical practice is difficult. SD, a simple method for assessing GV, represents the distribution of data around the mean blood glucose,[46] and is useful for analysis of intra-day variation of POC glucose values. Other metrics of variability have been proposed including but not limited to J-index, mean amplitude of glucose excursion (MAGE), mean absolute glucose (MAG), Continuous Overlapping Net Glycemic Action (CONGA), the High and Low Blood Glucose Index (HBGI, LHBI) and Mean of Daily Differences (MODD).[45, 46, 49] A criticism of the CV is that the mean is used in its calculation and as a result, violations of normality of the distribution of glucose values or extreme concentrations can exaggerate the CV measurement. Although this is a valid criticism, each of the other metrics have their own limitations.[46] We used the CV which has been frequently reported.[44, 48] Although an imperfect metric of variability, our study shows that the CV is related to 30-day readmission and suggests further studies should be conducted to determine if reducing variability lowers the rate of readmission. Recently, several studies have reported on the benefits of continuous glucose monitoring (CGM) over point of care capillary glucose testing in assessing glycemic control and GV in hospitalized patients. Future studies

using this technology will help us to confirm our findings on the importance of GV on hospital outcome and readmission risk.

Our study has several strengths. To our knowledge, this cohort is one of the largest studies evaluating readmission rates in patients with DM using national data. Additionally, the VA Health Care System is a "closed" health system where most veterans receive all of their health care including, including treatment during hospitalizations thus assuring a robust method to accurately measure readmissions. Given the comprehensive and extensive nature of the Veterans Health Administration data sources, we were able to include data for more than 1 million admissions of patients with diabetes and a broad set of covariates and risk factors in this analysis (**Table 1**).

There are limitations to our study that should be considered. Consistent with previously published studies utilizing Veterans Health Administration data sources, our analysis is restricted to this single health care system.[93] Although we included nationwide data, it excluded readmissions to non-VA hospitals. Additionally, our patient population may not be representative of the general population given veterans are more likely to be male, elderly, and have multiple comorbid conditions. However, since we adjusted for social-demographic data and comorbidities, we have minimized the impact of these differences and we believe the results can be extrapolated to the general DM population. Glucose variability can be influenced by the nutritional intake during an inpatient stay, which was not collected in our study, and perhaps is a limitation. We did not distinguish the preventable readmissions from other readmissions. Though

preventability of readmissions has been evaluated using administrative data previously, it is subjective and therefore may not represent the most optimal method to study this objective.[93, 116] Identifying high GV as a potentially modifiable risk factor in the last 24 hours utilizing point-of-care glucose values alone may be challenging. Methods in detecting high GV in the inpatient setting in a reliable and efficient way need to be explored. Consideration of CGM use in the hospital setting would ensure collection of accurate glucometric data, including CV and SD. Current ongoing prospective studies using CGM technology (NCT NCT03508934 and NCT03877068) are investigating the use of CGM in the hospital setting and after discharge, and should provide a more complete information on GV on clinical outcome and readmission risk. Lastly, we limited our analysis on the effect of GV during the last day of the hospitalization on readmission and did not examine the overall effect during the entire hospital stay.

In conclusion, the results of this VA nationwide cohort observation study including 1,042,150 admissions of patients with DM indicate that patients with higher GV on the last day of hospitalization were at a higher risk for 30-day readmission. Although the increased 30-day readmission risk could also be secondary to underlying medical conditions, inpatient diabetes medications or other risk factors unrelated to glucose variability, our extensive analyses, adjusting for multiple covariates indicate that increased GV during the last day of the hospitalization can be considered as a potential risk factor for early readmission. Further prospective studies are needed to fully explore whether reducing GV can decrease the risk for 30-day readmission.

Author Contribution Statement:

E.K.S. and M.Z had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. E.K.S. conceived and designed the study, provided guidance for the statistical analysis and wrote the manuscript. G.E.U made critical revisions to the study design and manuscript and takes responsibility for the integrity of the data and the accuracy of the data analysis. M.Z performed the statistical analyses and made critical revisions to the manuscript for important intellectual content. L.G.S, T.S., J.D.S, G.N, J.C.F and M.F.M. made critical revisions to the manuscript for important intellectual content. The authors had access to all the study data and take full responsibility of the accuracy of the analysis; All authors approve the manuscript.

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H3. Abstract submitted at the 79th American Diabetes Association Meeting

"The association of low glucose values at hospital discharge with 30-day readmission rate and post discharge mortality in patients with DM."

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Abstract

Objective 30-day readmission rate and post discharge mortality reflect the quality of the health care system. There is lack of knowledge whether low glucose values at the last day of the inpatient stay are associated with increased risk of readmission or mortality.

Design Nation-wide cohort study including 836,189 admissions of patients with DM admitted in the non ICU setting in Veteran Affairs hospitals, over a 14 year period. Poisson regression analysis to evaluate whether glucose values at the last 24 hours of the hospital stay are associated with 30-day readmission rate, 30-day, 90-day, and 180-day mortality rate and combined 30-day readmission/mortality rate.

Results The final cohort consisted of 836,189 DM admissions over 14 years. 30-day readmission rate was 17.2% and the 30-, 90- and 180-day mortality rate were 2.3%, 6.1% and 10% respectively. 18.8% died or readmitted in 30 days. There was a sharp increase of the event rates with glucose values below 98 mg/dl, 29.3 mg/dl ,57.3 mg/dl, 68.3 mg/dl and 86.4 mg/dl for 30-day readmission rate, 30-day, 90-day, and 180-day mortality rate and combined 30-day readmission/mortality rate respectively (**Figure 2**).

Conclusions In a nation-wide study, DM patients that have lower glucose values at the last day of hospitalization in the non ICU setting are at a higher risk for 30-day readmission or post discharge mortality.

H4. Abstract submitted at the 79th American Diabetes Association Meeting

The association of glucose variability during the last day of hospitalization and 30-day readmission in adults with diabetes

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Objective: Thirty-day hospital readmission (**30-day RA**) rates are a metric of healthcare quality. Limited data is available, whether increased glucose variability (GV) during the last day of hospital stay is associated with an increased risk of 30-day RA.

Design: Nationwide cohort of 1,042,859 admissions of patients with diabetes in the non-critical care setting in 129 Veteran Affairs hospitals, between 2001-2014. Coefficient of Variation (CV) was measured using glucometer data and was used as measurement of GV, divided into ten equal categories. Covariates, including demographics, socio-economic factors and up to 30 comorbidities were collected. Poisson regression was used to determine if CV during the last stay day of the hospitalization was associated with 30-day RA.

Results: After adjusting for age, gender and race (**Model 1**), there was a gradual increase in 30-day RA ratio among admissions with higher CV. Following adjusting for all the covariates collected (**Model 2**), only admissions with the highest CV demonstrated an increased 30-day RA. The rate ratios and 95% CIs were 1.049 (1.026, 1.073, $p<0.0001$), 1.038 (1.015,1.061, $p=0.0011$), 1.065 (1.042,1.089, $p<0.0001$), for the 8^{th}, 9^{th} and the 10^{th} tentiles respectively, compared to those with CV in the 1^{st} tentile. In **Model 3**, after adjusting for covariates used in Model 2 and for hypoglycemia, results remained statistically significant for those admissions

with the highest CV [rate ratios and 95% CIs are 1.044 (1.021,1.068, p=0.0001), 1.028 (1.006,1.052, p=0.014), 1.042 (1.018,1.067, p=0.0005) for the 8^{th}, 9^{th} and the 10^{th} tentiles].

Conclusions: Higher glucose variability during the last day of hospitalization was associated with increased 30-day RA rates after adjustment for multiple covariates and hypoglycemia.

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