Continuous Glucose Monitoring in the Management of Hospitalized Patients with Hyperglycemia and Diabetes

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Dr. Guillermo Umpierrez

Personal/Professional Financial Relationships with Industry, Updated 2022

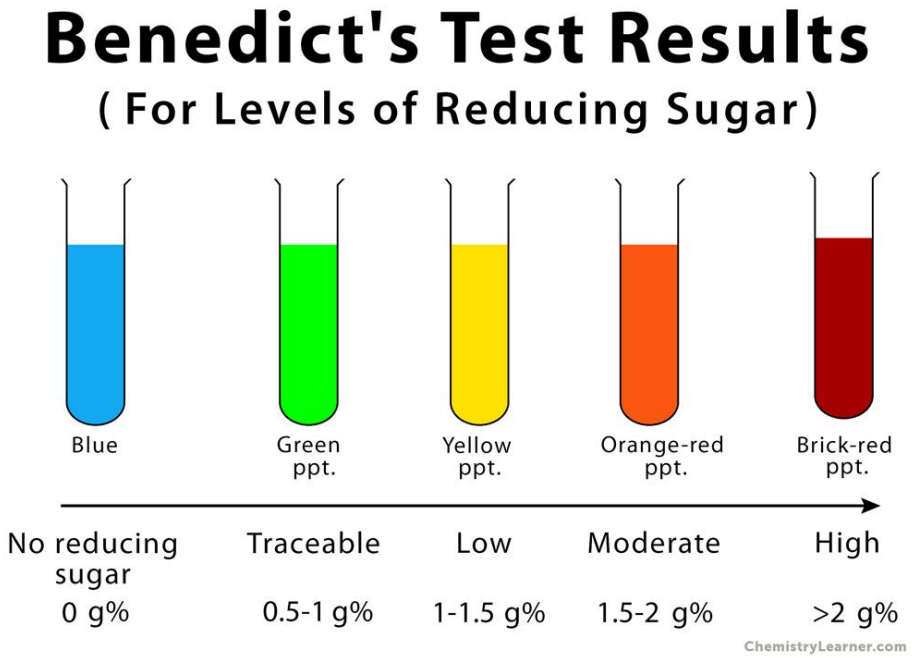
External Industry Relationships *	Company Name(s)	Role
Equity, stock, or options in biomedical industry companies or publishers		
Industry funds to Emory University for my research	Dexcom Abbott Bayer	Investigator-Initiated Research Projects
Industry Advisory/Consultant activities		

Agenda

- A history of glucose monitoring in the hospital
- Continuous glucose monitoring system era
  - Current evidence of CGM efficacy and safety
  - Clinical trials in ICU and Non-ICU settings
  - CMG use during COVID-19 pandemic
- Addressing challenges for CGM adoption

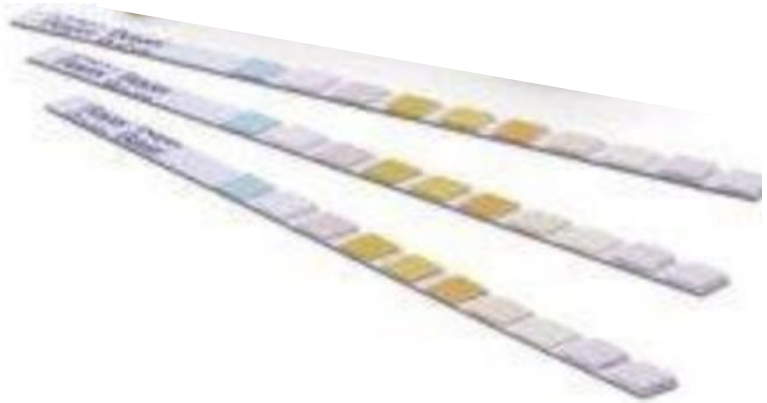
Urine Glucose Monitoring in Diabetes

1925 Glucose Testing for Sugar



8 drops of urine mixed in a test tube with 6 cc of Benedict's solution

1946 Miles Laboratory: "dip-and-read" urine test



Urine Glucose Monitoring in Diabetes

Advantages:

- Easy to perform
- Painless
- Stable methodology
- Widely available
- Not meter required
- Low cost

Disadvantages:

- Indirect measure of blood glucose
- Does not reflect blood glucose level at the time of testing
- No information about low blood glucose levels
- Medication interference

Self Blood Glucose Monitoring

The first patented blood glucose monitor was invented by Anton Hubert Clemens of the Ames Company (now known as the Bayer Corp.) in the mid 1960s.

Dry-reagent BG test-strip, 1964

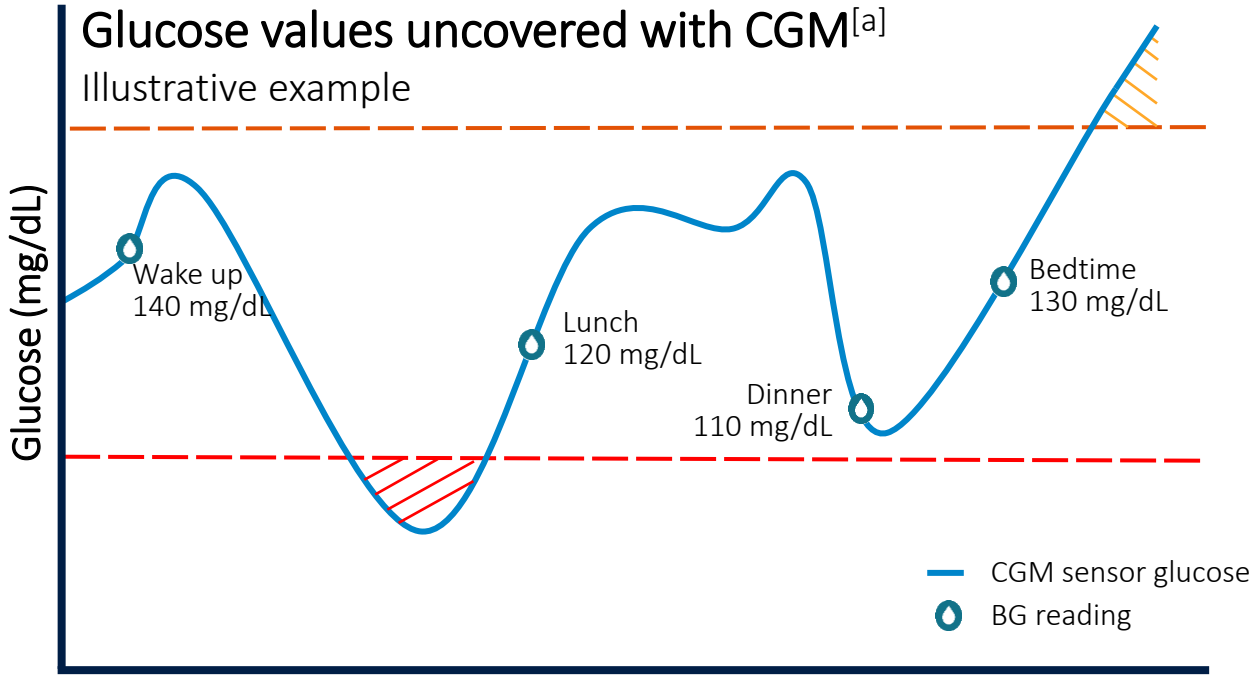
Self-Monitoring of Blood Glucose (SMBG)

- Uses/significance
  - Current standard for hospital glucose management
  - Measures blood glucose levels in real time
  - Assessment of hypo/hyperglycemia
  - Usefulness related to number of finger-sticks per day
    - ICU: Q1-2 hours during insulin infusion
    - Non-ICU: AC & HS
- Benefits/other considerations
  - Easy procedure with widespread adoption
  - Effective in adjusting treatment (standard of care)

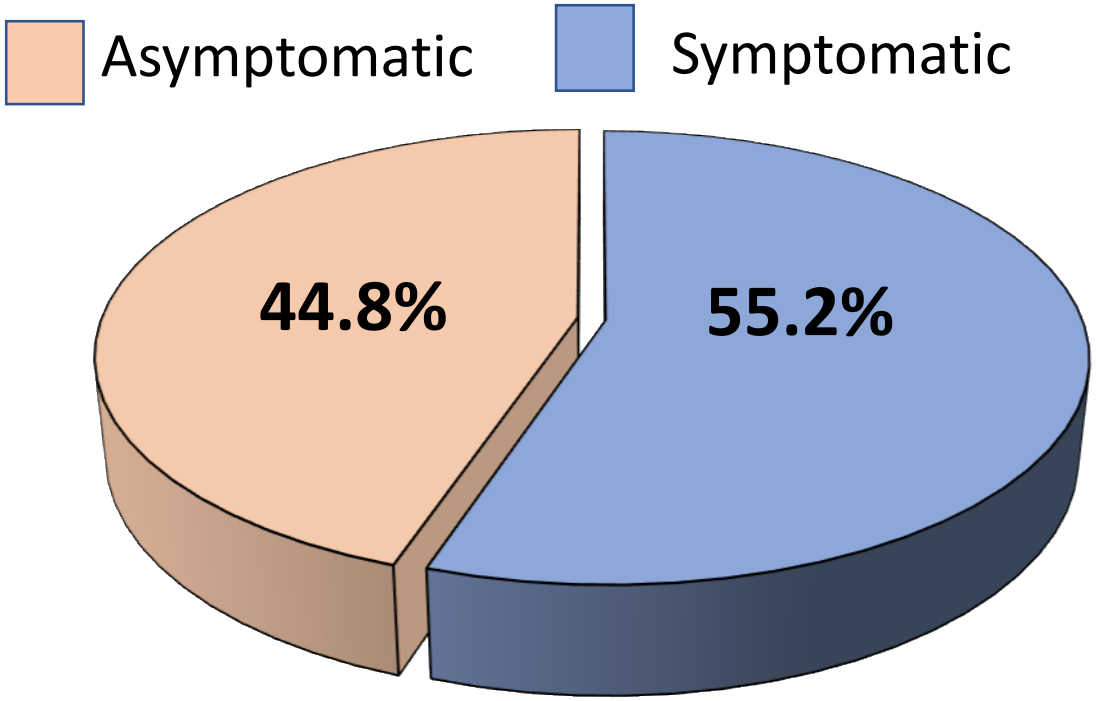
Limitations of POC Glucose testing: ***It Doesn't Tell the Whole Story***

- Only measures glucose levels in a single point in time
- Provides no indication of the direction or velocity of changing glucose levels
- Failure to recognize asymptomatic hypoglycemic events

POC testing can miss hyper- and hypoglycemic episodes



Asymptomatic hypoglycemia is common among insulin-treated inpatients with diabetes



Predictors of asymptomatic hypoglycemia

	OR	95% CI
Age < 50 yrs	1 (ref)	
- 50-58 yrs	1.73	(0.76-3.96)
- 59-64 yrs	2.55	(1.11-5.84)
- > 65 yrs	4.01	(1.62-9.92)
Male sex	2.08	(1.13-3.83)
GFR > 60 vs < 60 ml	0.70	(0.39-1.26)

Prospective observational study (n= 250) reported that 45% of insulin-treated non-ICU patients with BG <70 mg/dL had asymptomatic hypoglycemia. In multivariate analysis, older age and male gender were associated with higher risk of asymptomatic hypoglycemia.

Cardona et al. BMJ Open Diab Res Care 2018;**6**:e000607

Continuous Glucose Monitoring (CGM) in the Hospital

- Invasive
  - Intravascular- venous and arterial
- Minimally invasive
  - Subcutaneous
- Non-invasive
  - Transdermal

- Sampling frequencies typically range from 1 to 15 minutes
- More than 15 continuous or semi-CGM devices have been reported

Wallia et al. J Diabetes Science Technology 2017
Umpierrez & Klonoff, Diabetes Care 2018

Invasive (Intravascular) CGM Technology

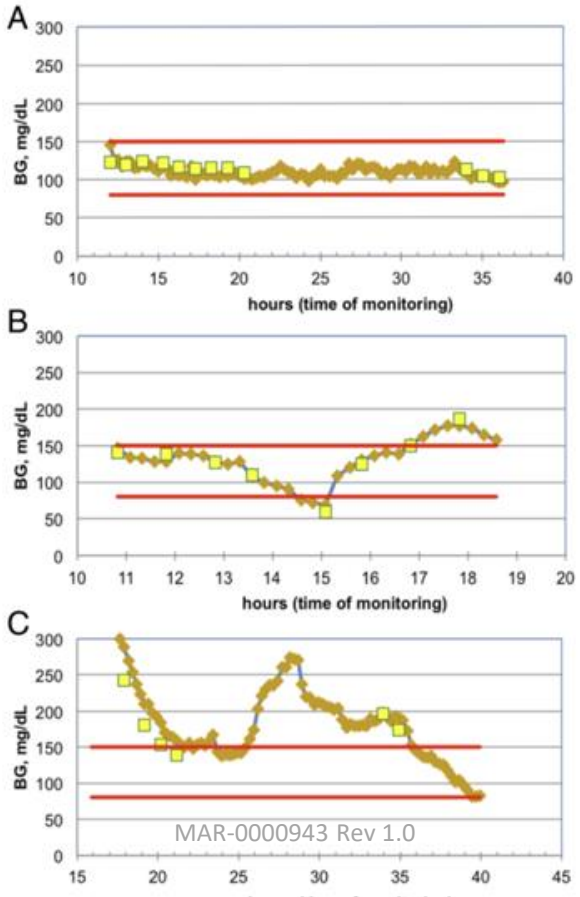
Righy Shinotsuka et al. Critical Care (2016) 20:380
DOI 10.1186/s13054-016-1547-3

Critical Care

RESEARCH Open Access

Manual versus Automated moNitoring Accuracy of GlucosE II (MANAGE II)

Cláudia Righy Shinotsuka[1], Alexandre Brasseur[1], David Fagnoul[1], Timothy So[2], Jean-Louis Vincent[1] and Jean-Charles Preiser[1*]



Representative individual tracings of patients in the unit utilizing the OptiScanner device compared to YSI. The device removes 0.12 ml sample every 15 minutes and analyzes glucose using infrared spectroscopy.

MARD 7.7%

OPTISCANNER

FDA Approved 2017

CGM Use in the ICU

Clinical Care/Education/Nutrition/Psychosocial Research

ORIGINAL ARTICLE

Real-Time Continuous Glucose Monitoring in Critically Ill Patients

A prospective randomized trial

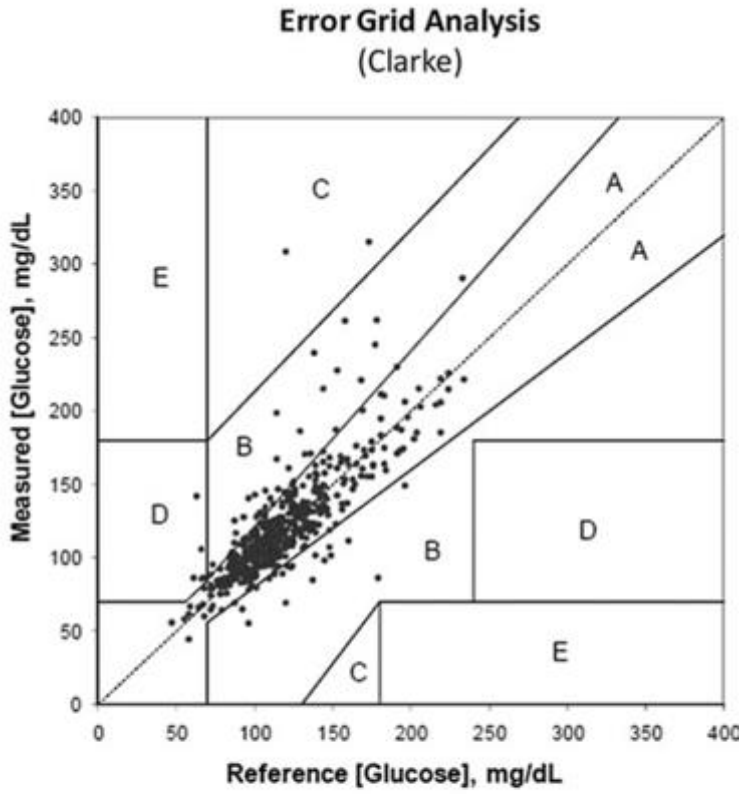
Holzinger et al. Diabetes Care 33:467-472, 2010

BMJ Open Diabetes Research & Care

Performance of the Medtronic Sentrino continuous glucose management (CGM) system in the cardiac intensive care unit

Kosiborod et al. BMJ DRC April 2014

Randomized Evaluation of Glycemic Control in the Medical Intensive Care Unit Using Real-Time CGM: REGIMEN Trial



EGA zone	A	B	C	D	E
Cases	454	60	2	5	0
Percentage (%)	87.1	11.5	0.4	1.0	0.0
Percentage (%)	98.6			1.4	

During 96 h of monitoring, glycemia reached target (80–110 mg/dL) in 37 (15%), was between 70 and 180 mg/dL in 91 (10%), and <60 mg/dL in 2 (2%) of the time

98.6% of data falling in Zones A and B of the error grid analysis

RT-CGM did not ameliorate glucose control or variability; neither did it reduce the number of hypoglycemic events,

DIABETES TECHNOLOGY & THERAPEUTICS. Volume 17, Number 12, 2015

REVIEW Open Access

Continuous glucose monitoring in the ICU: clinical considerations and consensus

- Compared to POC monitoring systems, CGMs offer benefit in the prevention of severe hyperglycemia and hypoglycemia by enabling insulin infusions to be adjusted more rapidly and potentially more accurately because trends in glucose concentrations can be more readily identified.
- Clinical guidelines recommend target blood glucose between 140 and 180 mg/dL for most patients in the intensive care unit (ICU).

Krinsley et al. Critical Care (2017) 21:197

CGM in the ICU: Technology limitations

- Intravascular CGMs carry risks of thrombus formation, catheter occlusion, and catheter related infections
- Lack of evidence on the accuracy during periods of arterial hypotension, hypothermia or hypoxia
- Substance interference (acetaminophen, ascorbic acid, mannitol, heparin, and salicylic acid) with some CGM devices
- Costs
- Limited data in favor of tight glycemic control in ICU

Umpierrez & Klonoff, Diabetes Care 2018

CGM Use in the ICU

Clinical Care/Education/Nutrition/Psychosocial Research

ORIGINAL ARTICLE

Real-Time Continuous Glucose Monitoring in Critically Ill Patients

A prospective randomized trial

A recent systematic review of 37 studies, both RCTs and observational studies, concluded that in terms of efficacy, the use of subcutaneous CGM systems does not seem to improve the glycemic control of critically ill patients in a clinically significant manner.

Kosiborod et al. BMJ DRC April 2014

Continuous Glucose Monitoring in the Operating Room and Cardiac Intensive Care Unit

Perez-Guzman et al. Diabetes Care March 2021

Diabetes & COVID-19

ICU Care

Continuous Glucose Monitoring in the Intensive Care Unit During the COVID-19 Pandemic

Agarwal et al. Diabetes Care 44:847-849, 2021

Remote Continuous Glucose Monitoring With a Computerized Insulin Infusion Protocol for Critically Ill Patients in a COVID-19 Medical ICU: Proof of Concept

Davis et al. Diabetes Care, Online February 9, 2021

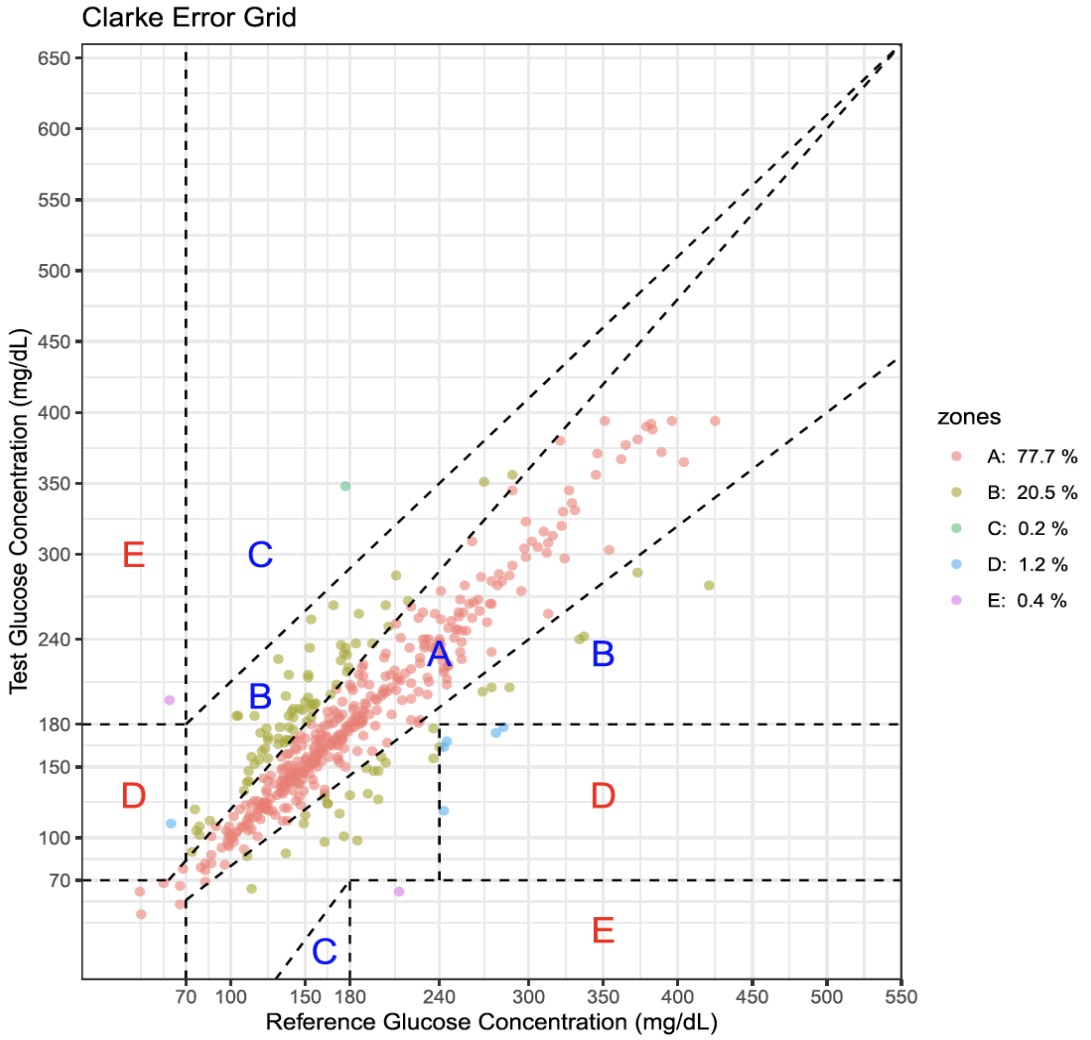
Remote Glucose Monitoring

Montefiore-Einstein during COVID-19: Real-World Logistics of Inpatient CGM

- Placement of sensor
  - Skilled endocrine NP
  - Proning trend → arm placement
- Placement of receiver
  - On door facing out, within 20 ft
  - Re-used receiver (after cleaning)
- Alerts (100-250 mg/dL, drop/rise)

Agarwal et al. Diabetes Care 44:847-849, 2021

Relationship between CGM and POC glucose values



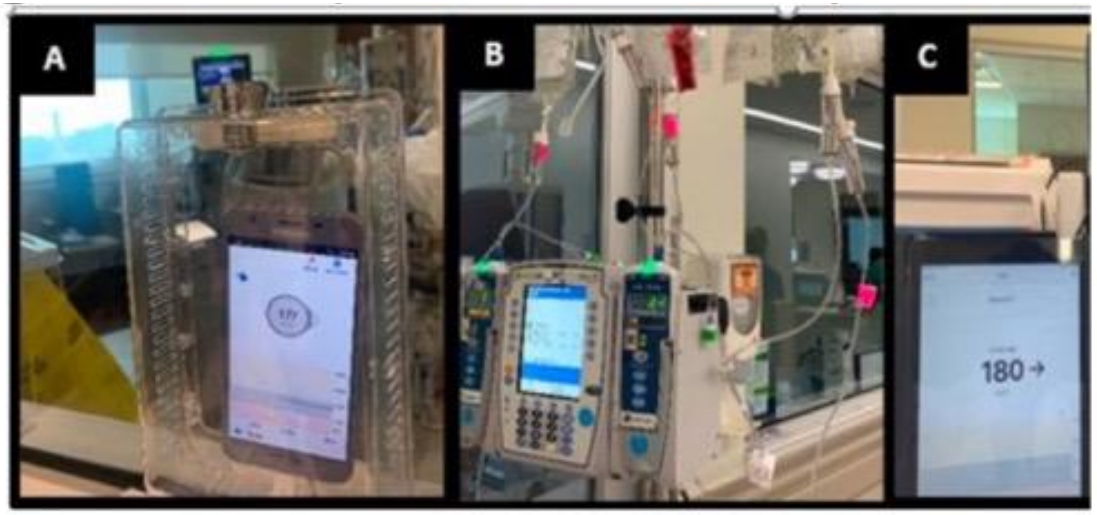
n	15/15%	20/20%	30/30%	40/40%	MARD	Median ARD
493	0.708	0.777	0.888	0.953	12.578	6.338

Remote CGM with computerized guided CII (Glucommander)

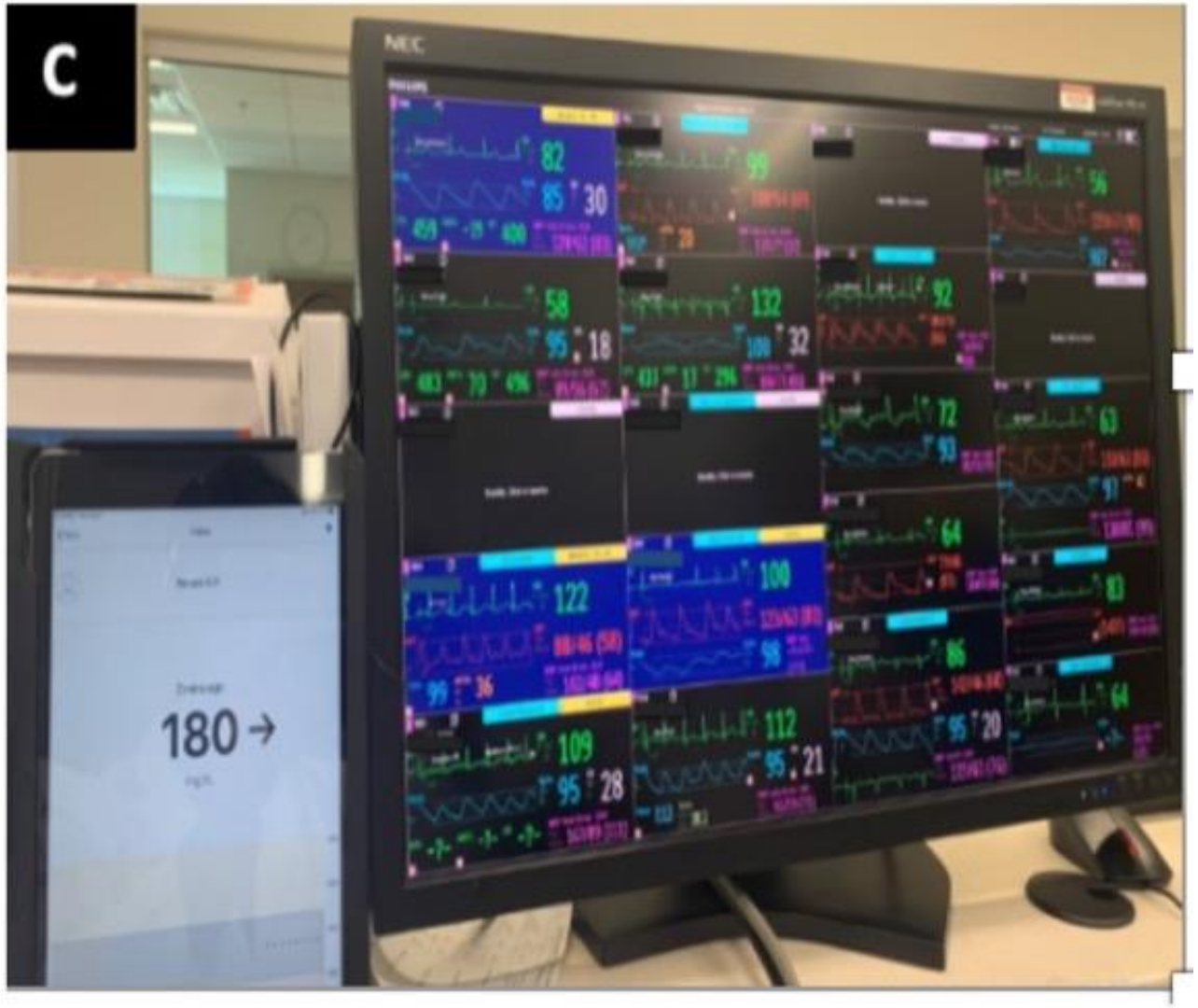
Remote CGM (G6) + POC q6hr + Glucommander

+ Electronic Health Record Documentation/Validation

Remote CGM with computerized guided CII (Glucommander)



Davis et al. Diabetes Care 2021



Davis et al. Diabetes Care 2021

CGM in non-ICU settings

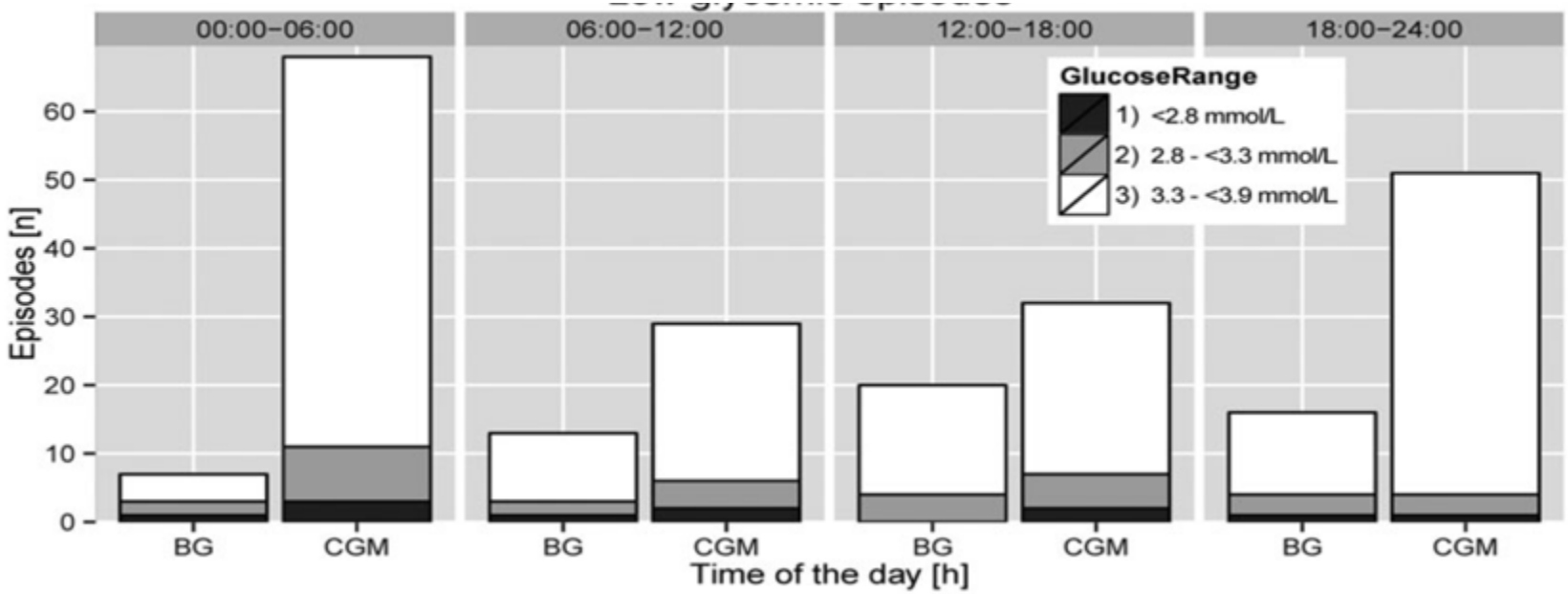
Clinical Trials using CGM in Non-ICU Settings

Author, Year	Population	Sample Size	# of sites	Type of CGM	Performance Measurement	Comparator
Schaupp, 2015	General Ward	84	1	iPro	Accuracy	Capillary BG
Gomez, 2015	General Ward	38	1	iPro-2	Accuracy	Capillary BG
Gu, 2017	Ward	81	8	Sensor Augmented Pump	Performance Measurement	MDI with Blinded CGM
Galindo, 2020	General Ward	100	1	Libre	Accuracy	Capillary BG
Davis, 2021	General Ward	205	2	Dexcom G6	Accuracy	Capillary BG
Spanakis, 2022	General Ward	162	#2	Dexcom G6	Glycemic control	Capillary BG

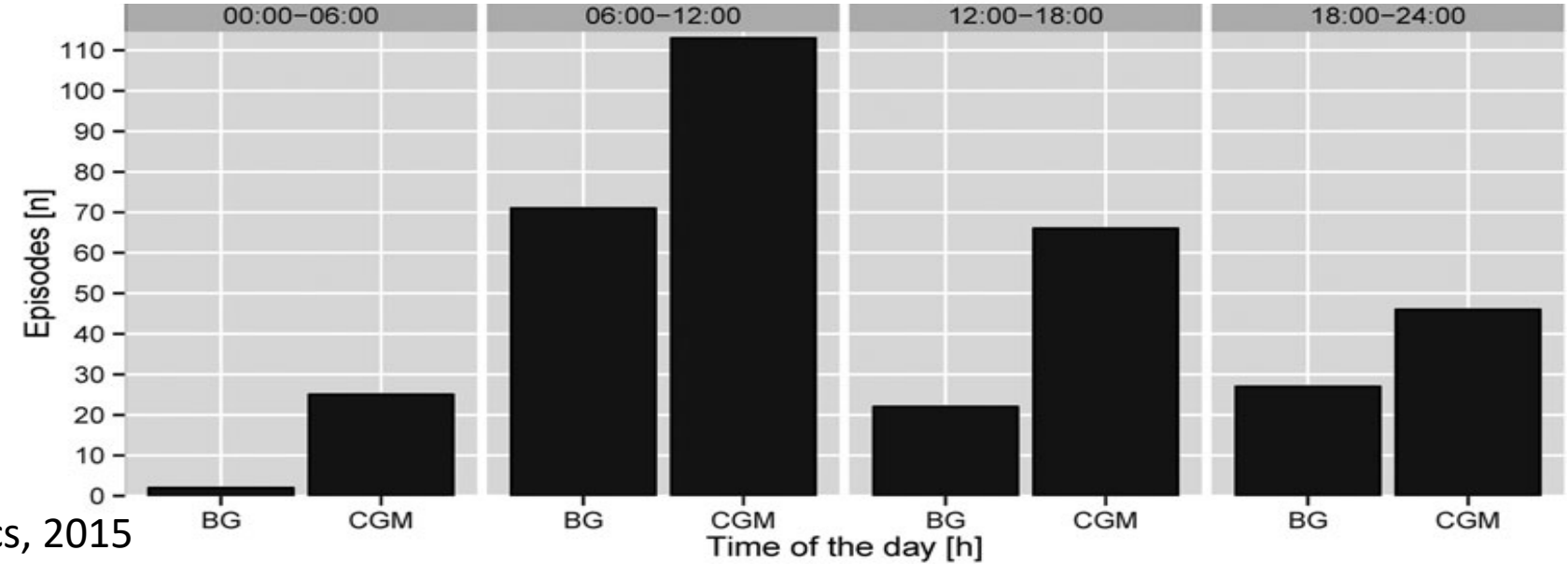
Schaup, et al. Diabetes Technol Ther 2015;17:611-618; 4. Gomez etal. J Diabetes Sci Technol 2015;10:325-329; 5. Gu, et al. Diabetes Metab 2017;43:359-363; Galindo et al. Diabetes care 2020; Davis et al. Diabetes Care 202; Spanakis et al. Diabetes Care 2022

CGM in Non-ICU Patients with T2D

Hypoglycemia
< 2.8 mmol/L



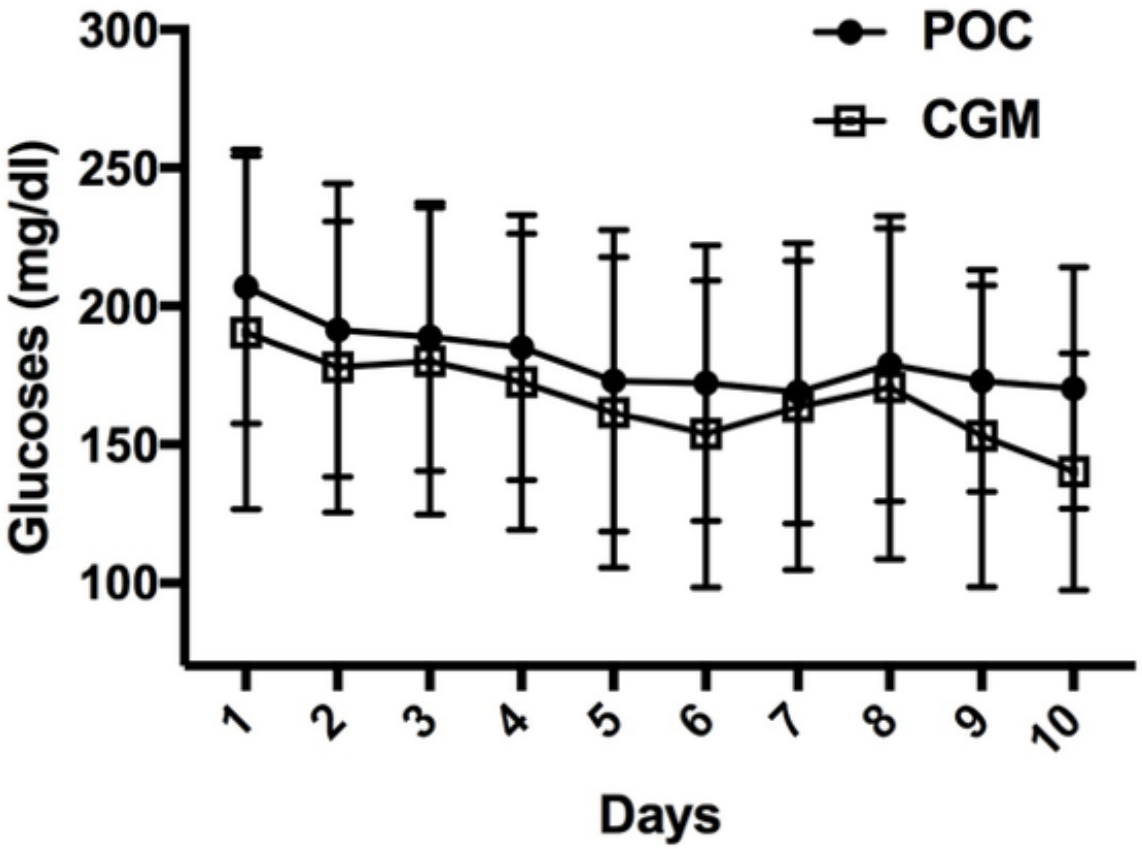
Hyperglycemia
>13.9 mmol/L



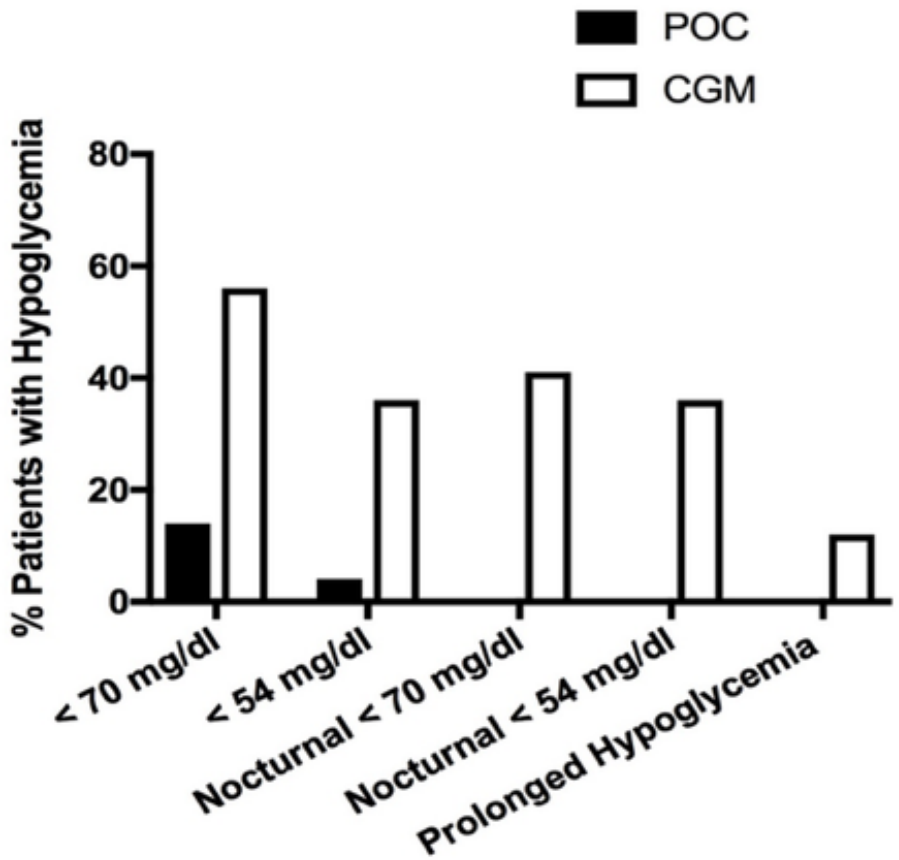
Schaupp et al.
Diabetes Technology & Therapeutics, 2015

Freestyle Libre Pro Flash CGMS vs. POC Capillary Glucose Testing in Hospitalized Patients with T2D

Mean Hospital Daily Glucose



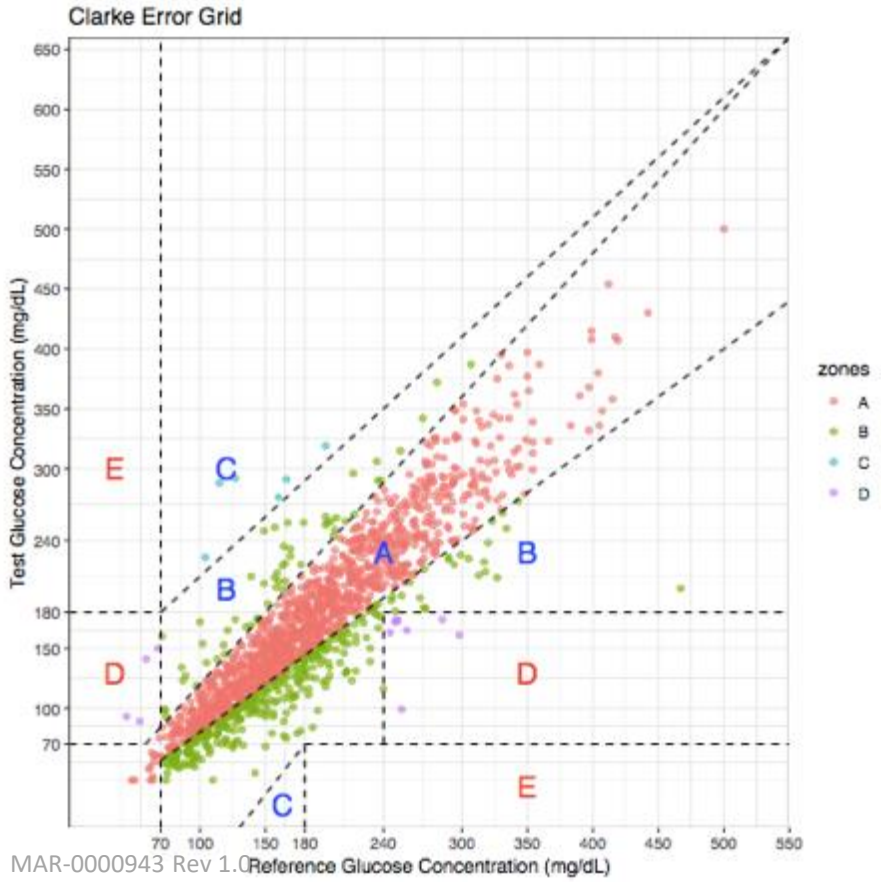
Hypoglycemia by POC and CGM



Galindo & Umpierrez et al. Diabetes Care, August 2020

Freestyle Libre Pro Flash CGMS vs. POC Capillary Glucose Testing in Hospitalized Patients with T2D

Clarke Error Grid analysis

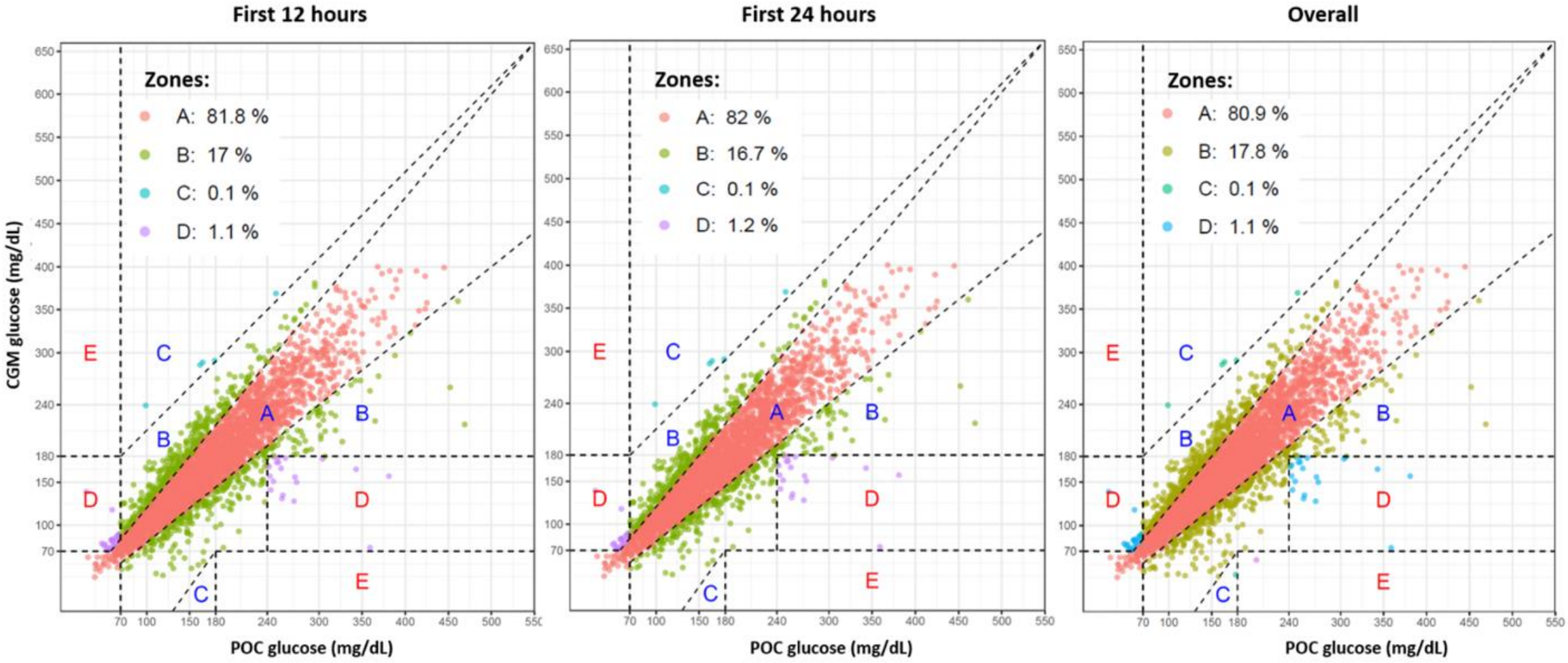


Glucose Range (mg/dL)	Matched Pairs (n)	MARD (%)
Overall	1576	14.8
51-69	13	27.9
70-180	829	16.7
>180	731	12.1
>250	253	11.4

Galindo et al. Diabetes Care 2020

Accuracy of Dexcom G6 CGM in Non-Critically Ill Hospitalized Patients with Diabetes

Clarke Error Grid Analysis by Sensor Age



N= 205

T2D patients in general medicine & surgery wards

Error Grid Analysis: Zones A and B: 98.7%

Davis, Umpierrez et al. Diabetes Care 2021

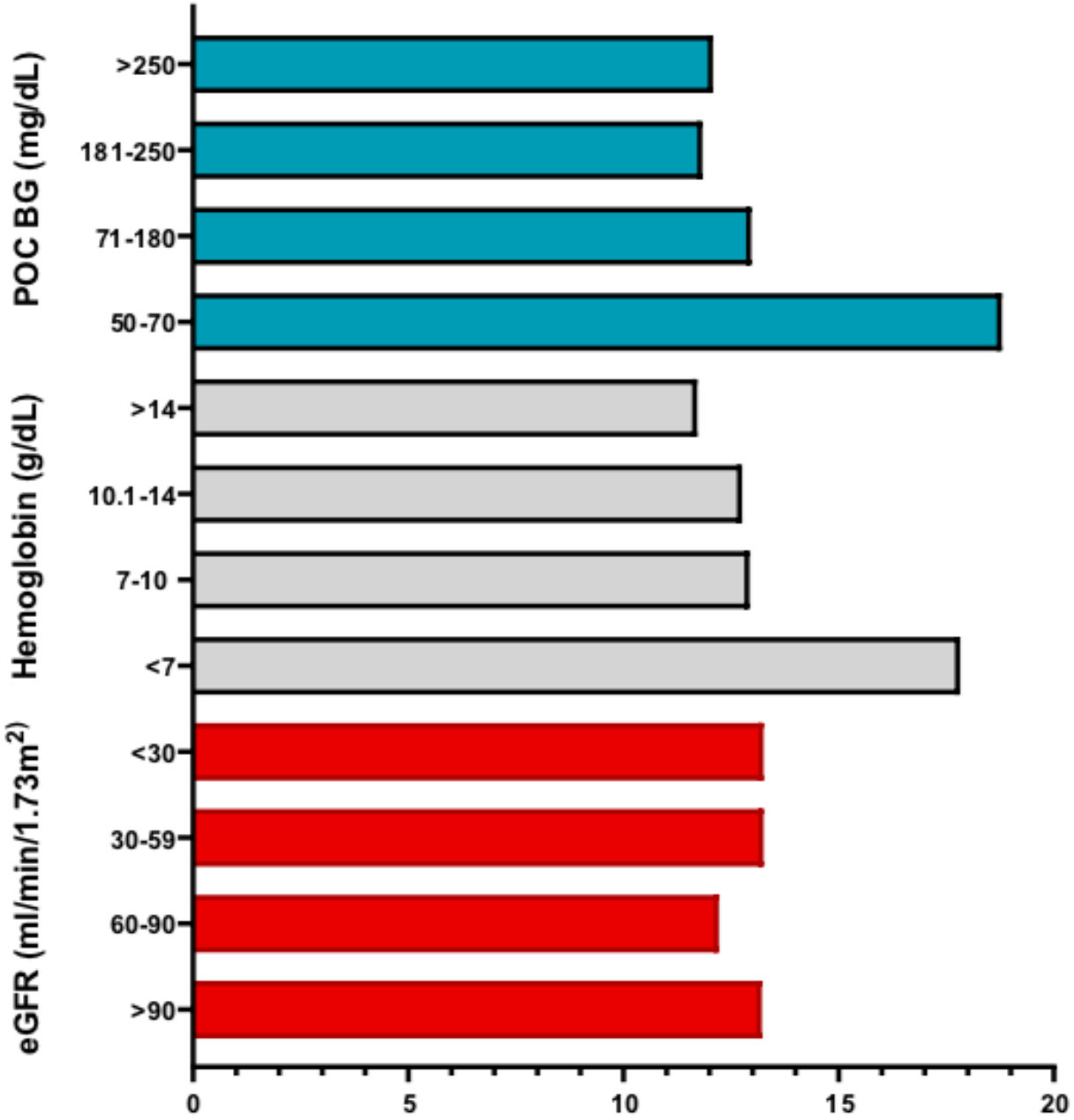
Mean absolute relative difference (MARD) reported by glucose range, hemoglobin value and eGFR category

Dexcom G6

Hospital Accuracy Study,
CGM vs POC

N= 205
Insulin-treated patients with T2D in general medicine and surgery wards

Comparable accuracy metrics were also observed across Race, BMI, GFR, and abdomen vs arm placement



Davies et al. Diabetes Care

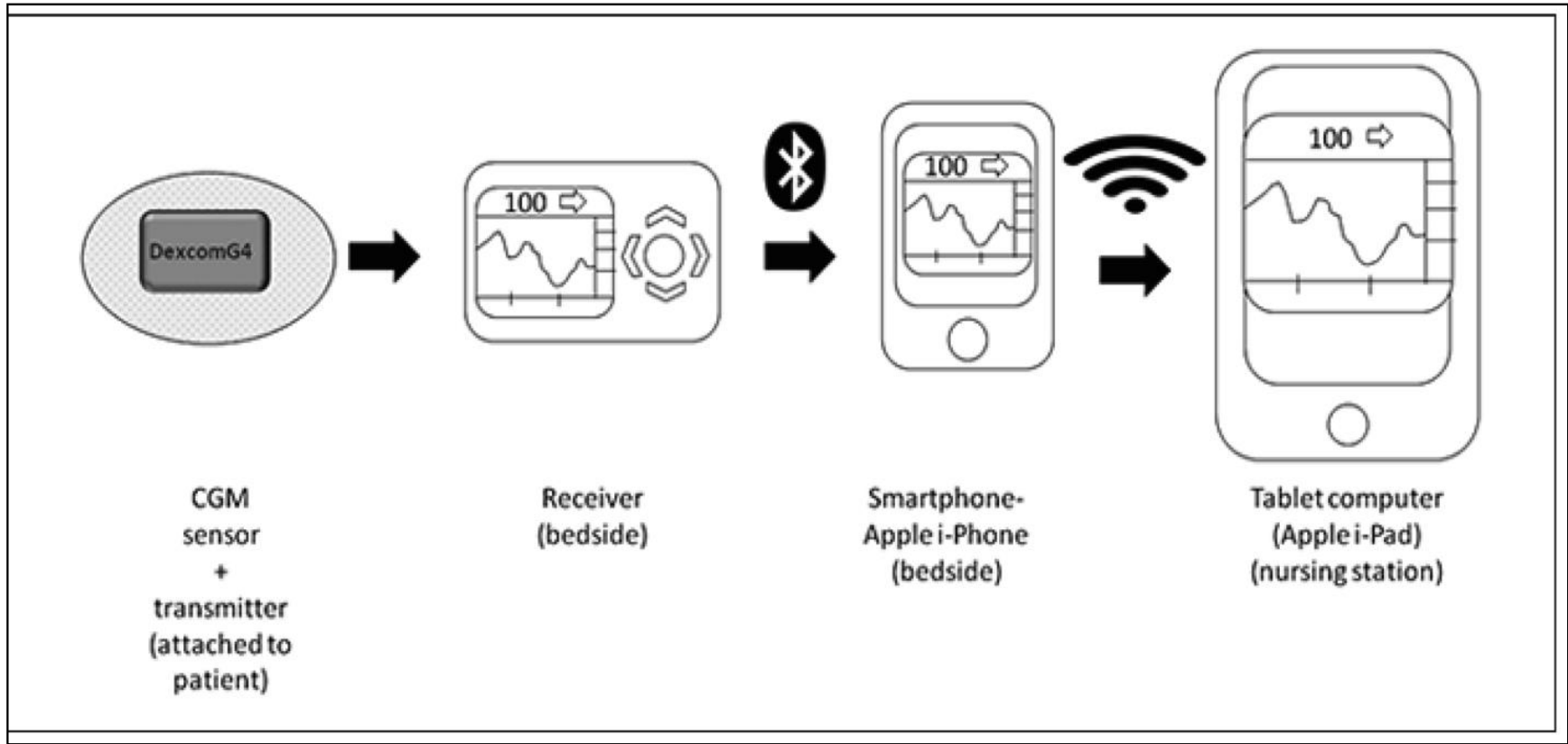
Glucose Telemetry System

The Effect of Continuous Glucose Monitoring in Preventing Inpatient Hypoglycemia in General Wards: The Glucose Telemetry System

Journal of Diabetes Science and Technology
1–6

Spanakis et al.
Baltimore VAMC, University of Maryland

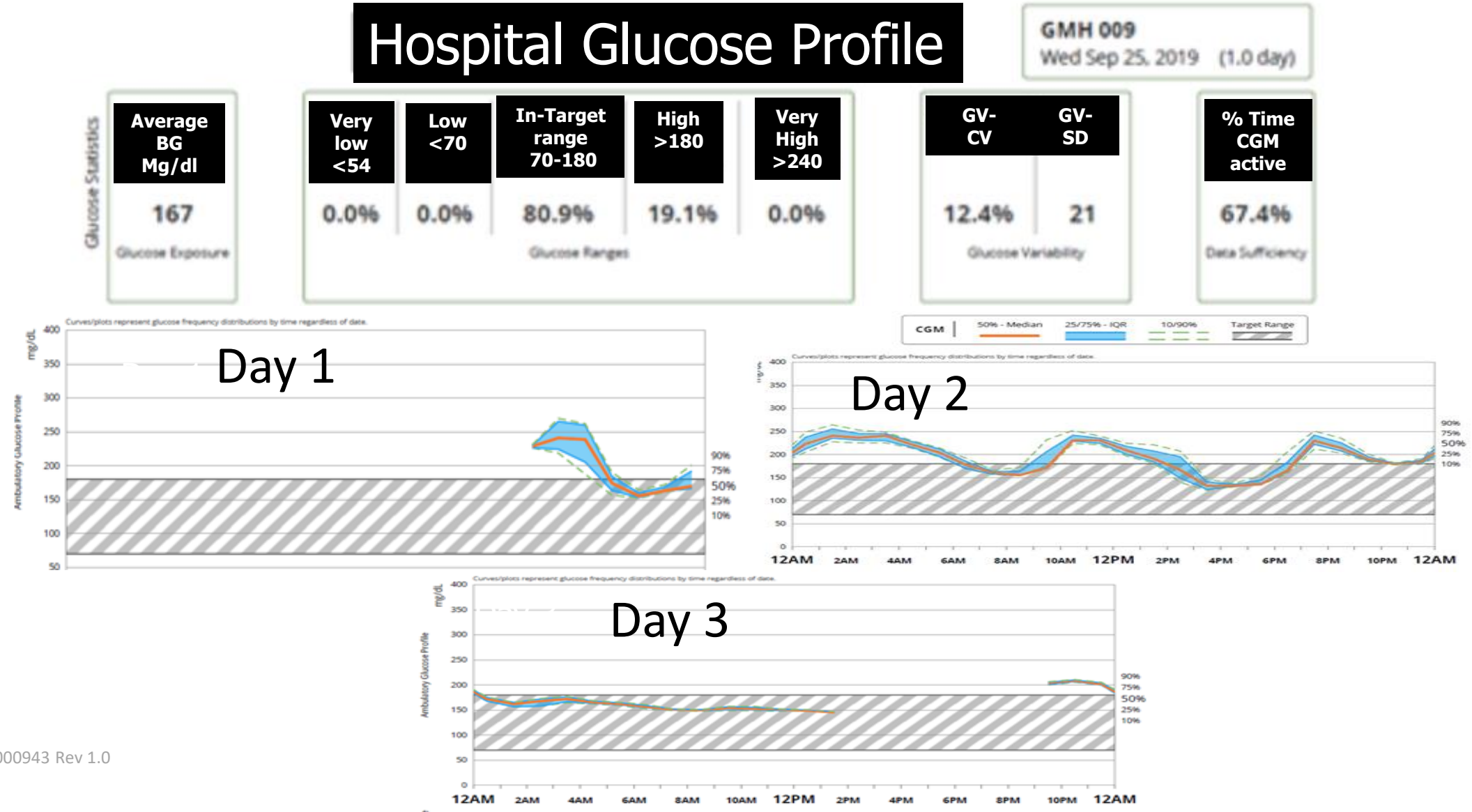
Pilot study.
BG results < 85 mg/dl were transmitted to nursing station allowing early intervention to prevent hypoglycemia.



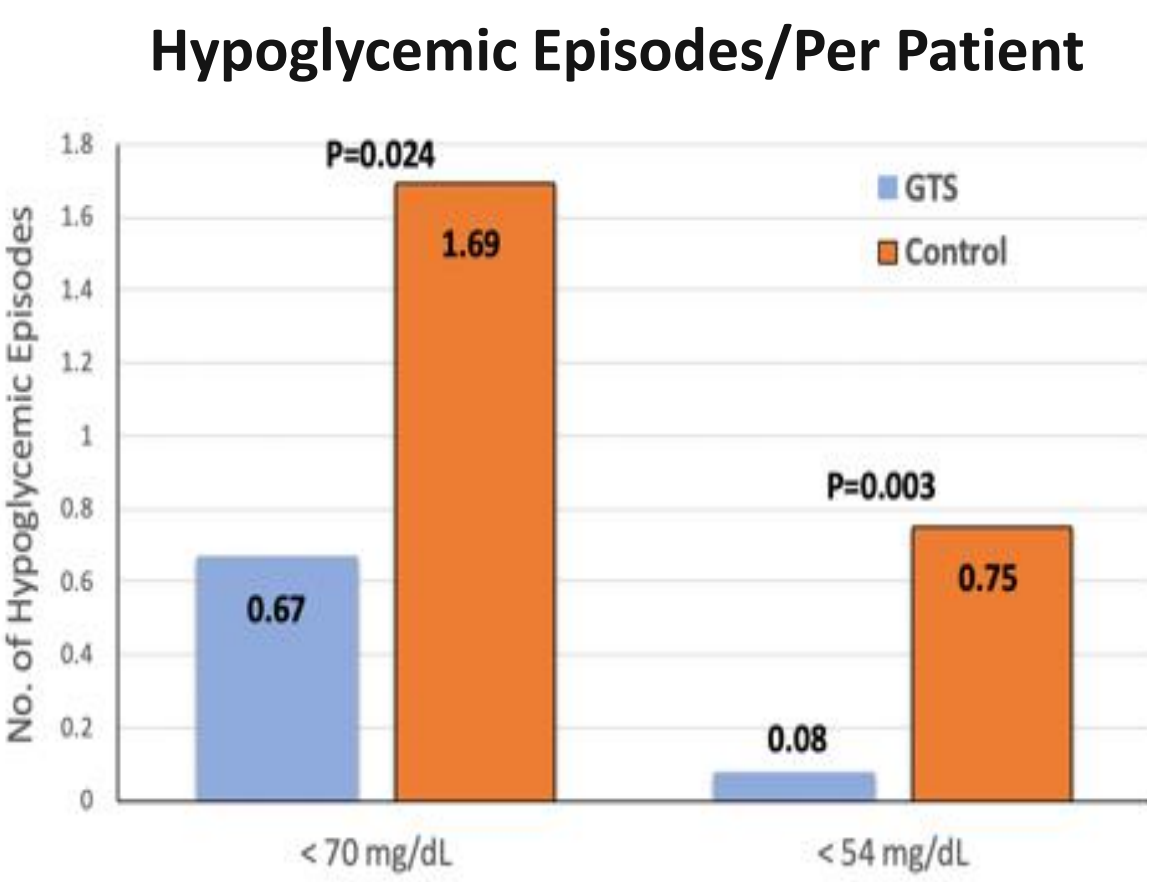
NCT02904512

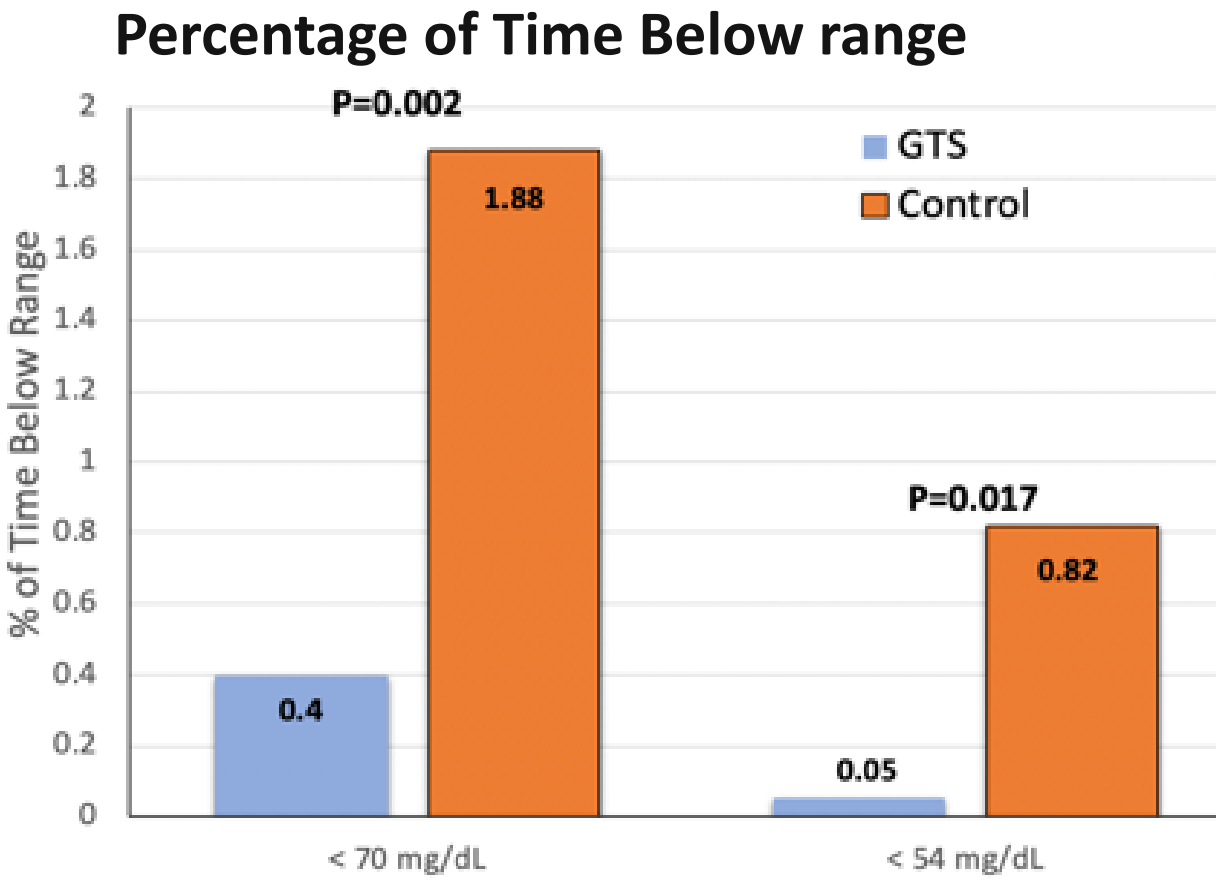
CGM Hospital Use

CGM Hospital Use: Intervention Study



Reducing Inpatient Hypoglycemia in the General Wards Using rtCGM -- the Glucose Telemetry System, an RCT

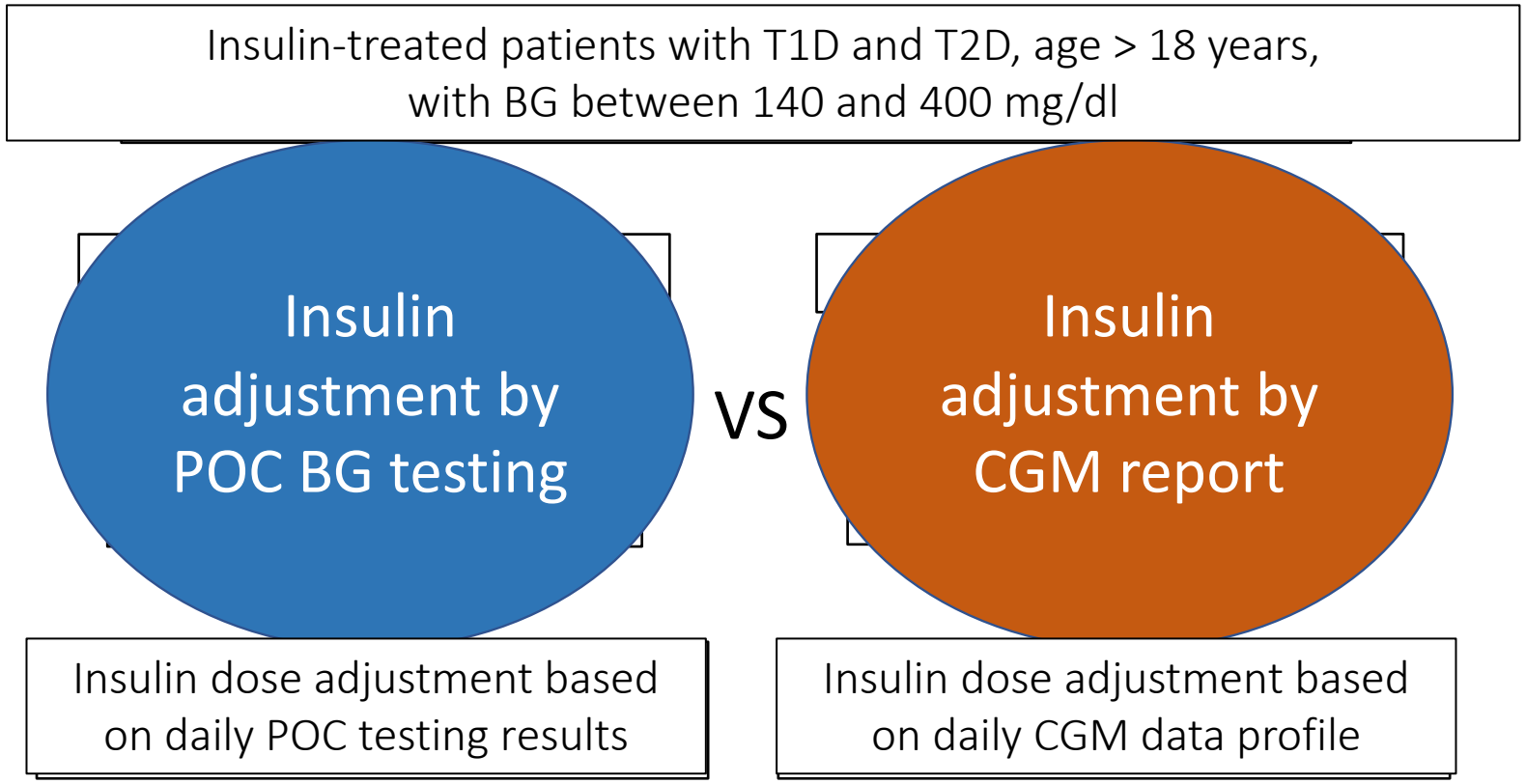




Singh et al. Diabetes Care 43:2736-2743, 2020

Management of Inpatient Hyperglycemia by CGM in Insulin-Treated Patients With Diabetes

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

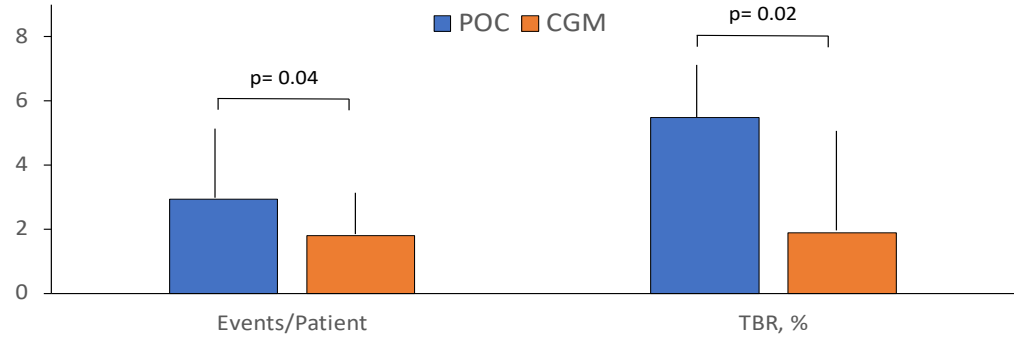


- Umpierrez et al. unpublished.

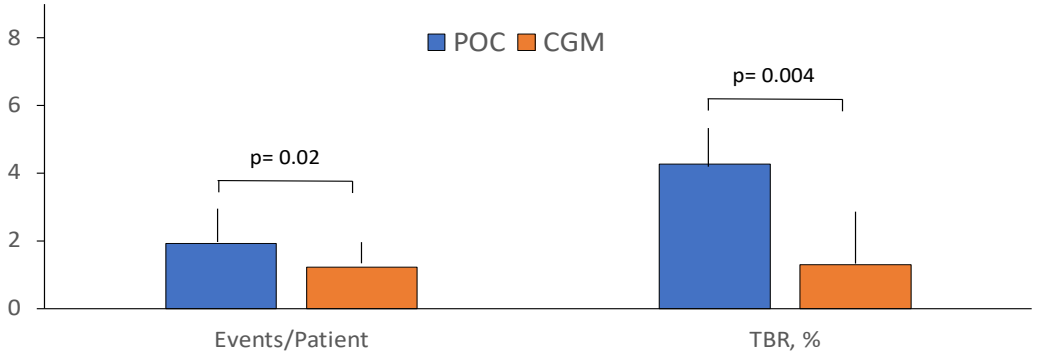
CGM-Guided Insulin Administration in Hospitalized Patients with Diabetes: A Randomized Clinical Trial

	POC (n=79)	CGM (n=83)	P value
Type 1, n (%) Type 2, n (%)	7 (9) 72 (91)	10 (12) 73 (88)	0.61
TIR %, 70 -180 mg/dL	48.64± 24.2	54.5 ± 27.7	0.14
TBR % <70 mg/dL	2.15 ± 5.9	0.69 ± 2.1	0.43
Recurrent hypo, TBR % <70 mg/dL	5.47 ± 8.4	1.89 ± 3.3	0.02
Recurrent hypo events/patient	2.94 ± 2.7	1.80 ± 1.5	0.04
Recurrent nocturnal hypo TBR %	4.27 ± 5.1	1.30 ± 1.7	0.004
Recurrent nocturnal hypo events patient	1.93 ± 0.9	1.21 ± 0.4	0.02

Recurrent Overall Hypoglycemic Events by Point-of-Care and RT-CGM



Recurrent Nocturnal Hypoglycemic Events by Point-of-Care and RT-CGM



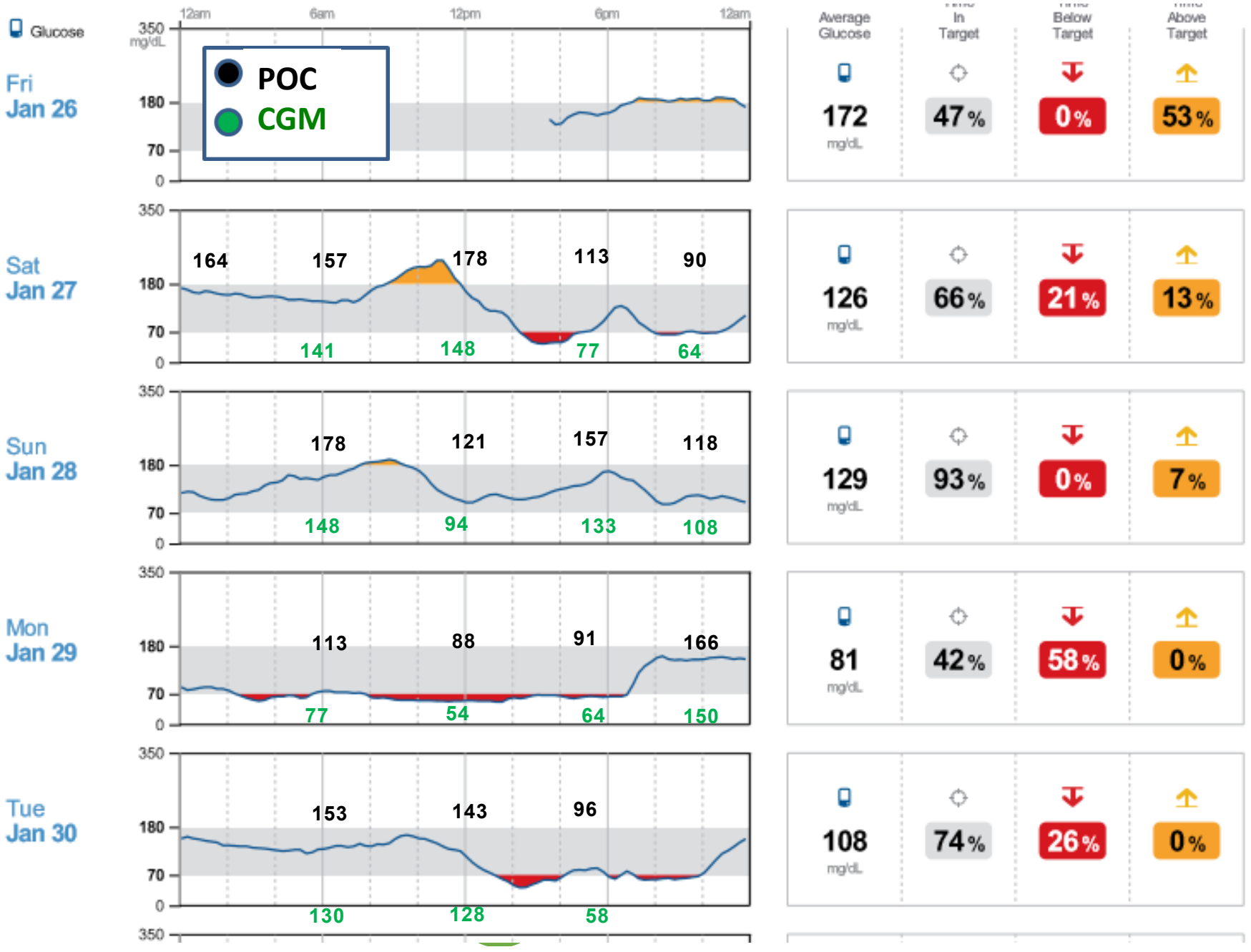
Spanakis et al. Diabetes Care 2022 Oct **1;45(10):2369-2375**

CGM Use in the Hospital: Challenges

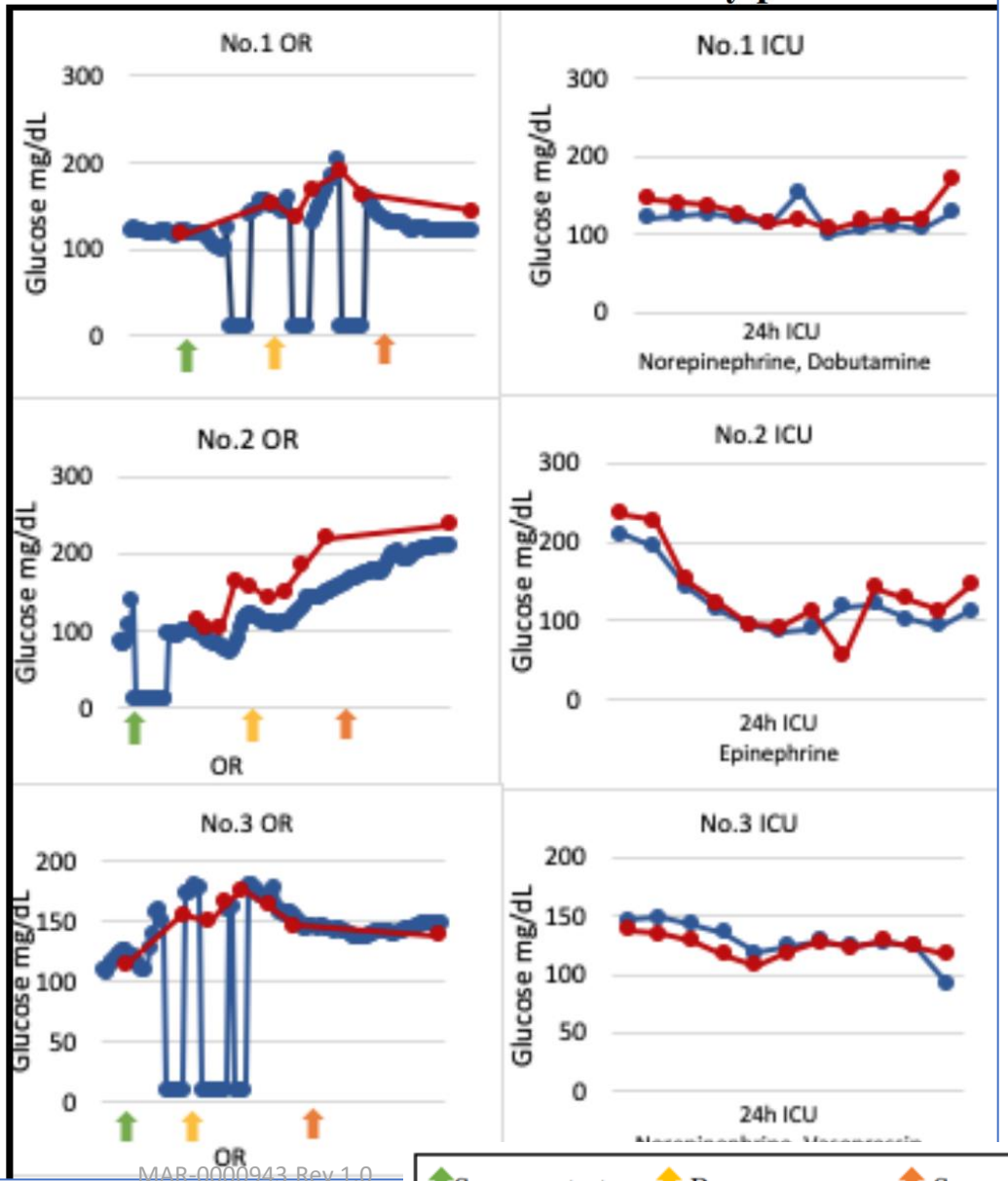
- No FDA approval in non-ICU settings
- New technology, not commonly used by PCPs and hospitalists
- Lack of evidence on the accuracy during periods of arterial hypotension, hypothermia or hypoxia
- Real-time data transmission to nursing staff and EMR
- Interference (acetaminophen, maltose, ascorbic acid, dopamine) with some CGM devices
- Costs
- Limited data in favor of tight glycemic control in ICU

Discrepancy dilemma

54#y/o#male,#diabetic#foot#ulcer,#S/P#BKA

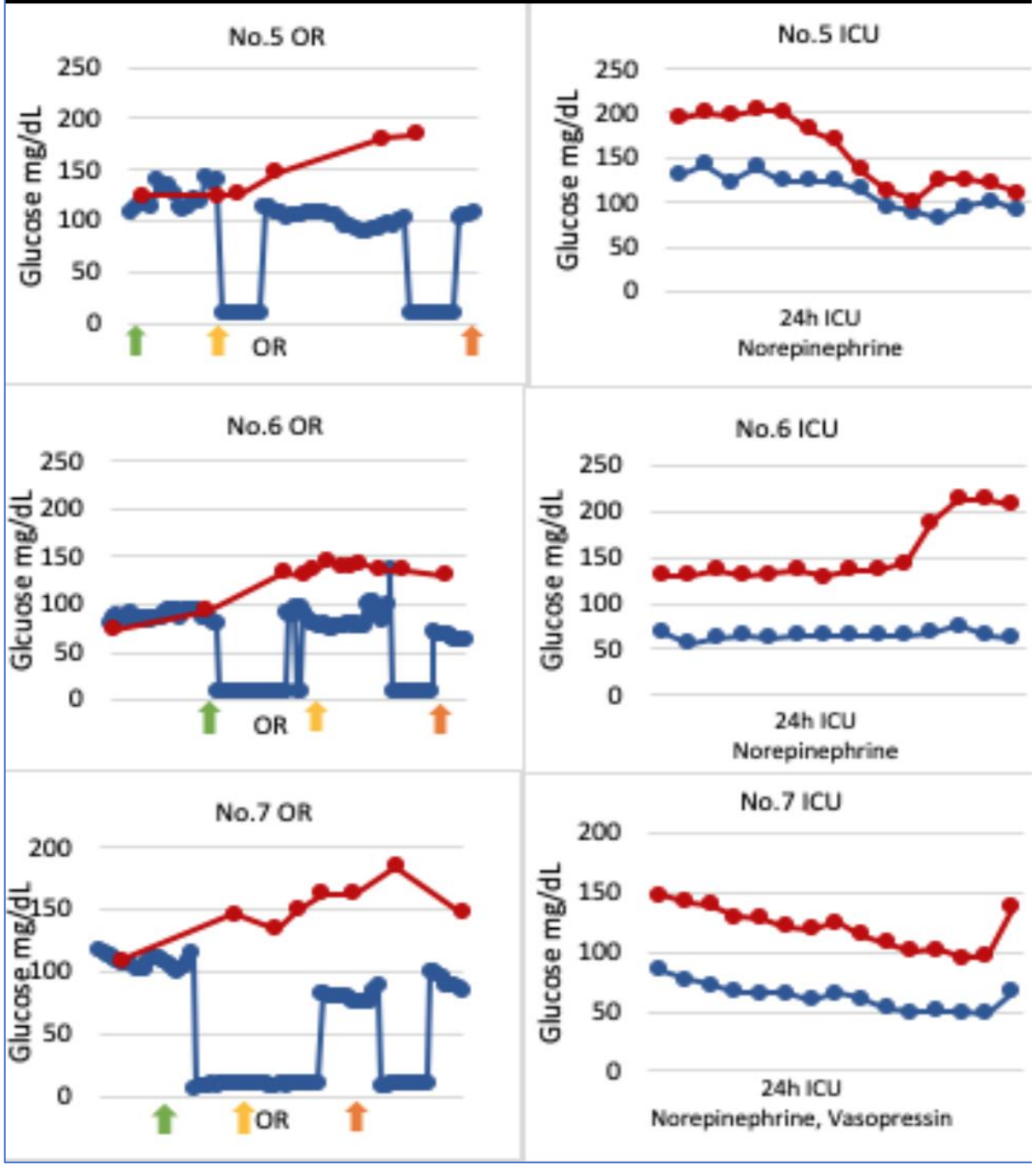


Panel C. OR CGM with Sensor Recovery post-CABG



Surgery start Bypass on Surgery end

Panel D. Non-recovering Sensors Post-CABG



CGM Use in Non-ICU Settings: Summary

- Available data from clinical studies suggest:
  - The use of CGM in patients with T2D can provide a more complete picture of the patient's glycemic status than POC testing
  - CGM provides a better direction of change, magnitude of change and warnings to predict both low and high BG levels compared to POC testing
  - Reduction of overall hypoglycemia diurnal and nocturnal
  - Reduction of hypoglycemia reoccurrence compared to POC testing

Wallia et al. Journal of Diabetes Science and Technology 2016
Umpierrez & Klonoff. Diabetes Care, 2018
Spanakis et al . Diabetes Care 2022

Future Directions

- Need appropriate studies for FDA approval (vs. YSI or laboratory)
- Education and training programs for hospital personnel is needed
- Develop simplified systems for data transmission from bedside to nursing station
- Need pharmaco-economic analysis
- Accurate CGM systems combined with automatic insulin dosing systems will facilitate glycemic control and reduction of hypoglycemia and hyperglycemia patients with diabetes.

Umpierrez & Klonoff. Diabetes Care 2018

Why a Hybrid Protocol in the ICU?

Allows validation of each device within each patient

Allows for continued validation

Facilitate reduced frequency of POC

Davis et al. Diabetes Care 2021

The Eversense System

Sensor

Smart Transmitter

Mobile App

Sensor that lasts up to 3 months

No weekly sensor insertion

No open wound

Removable and rechargeable

On-body vibe alerts

Gentle-on-skin adhesive

No extra device to carry

iOS and Android platform

Alarm settings & reports

FDA approved implantable CGM sensor- 90 day use

Closed-loop insulin delivery in inpatients with type 2 diabetes: a randomized, parallel-group trial

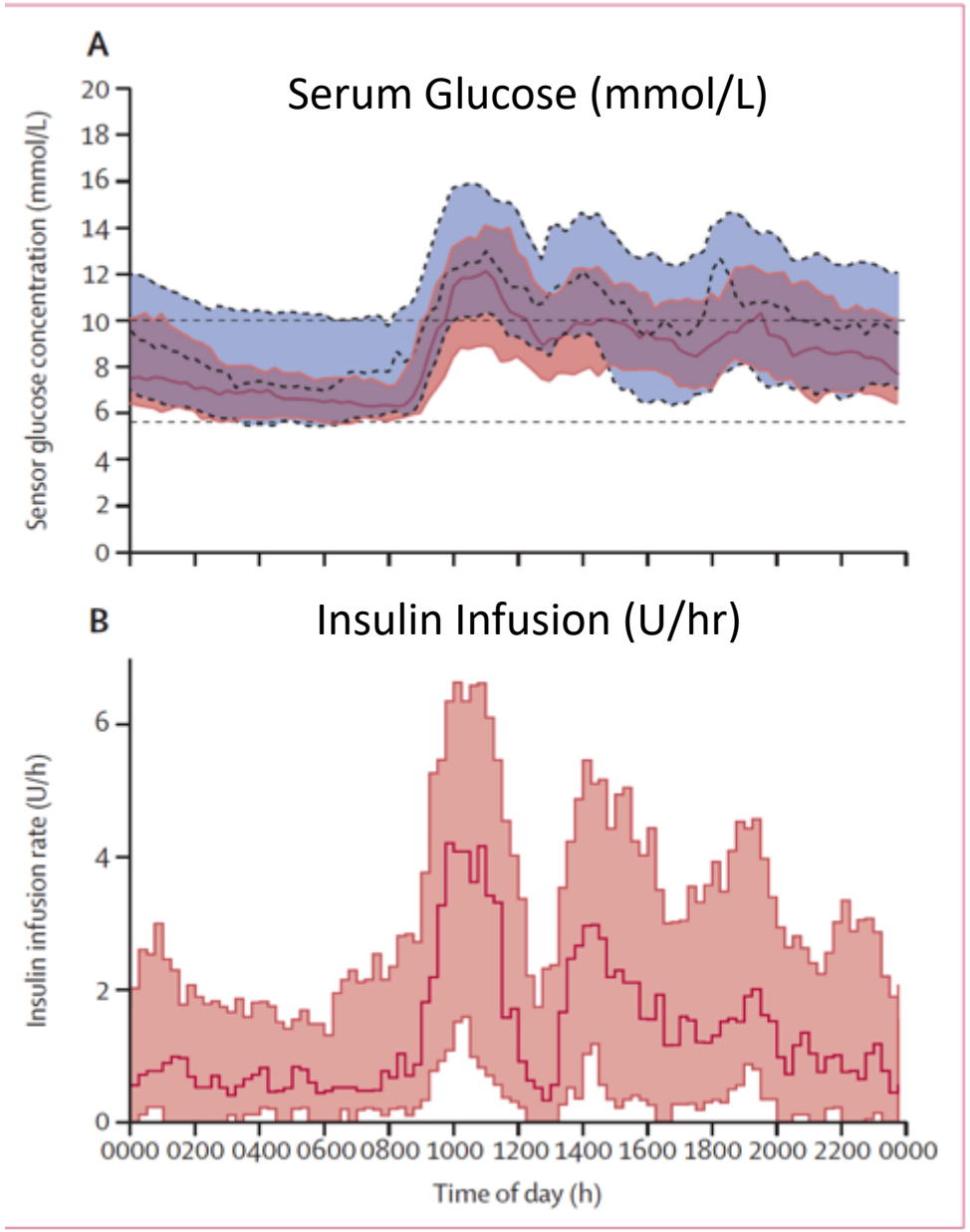
N= 40 patients, 20 in close loop, 20 control group

Higher proportion of time spent in the target glucose in the closed-loop group (59.8%) than control (38.1%)- difference 21.8% [95% CI 10.4–33.1]; p=0.0004).

No episodes of severe hypoglycemia or hyperglycemia with ketonemia in either group.

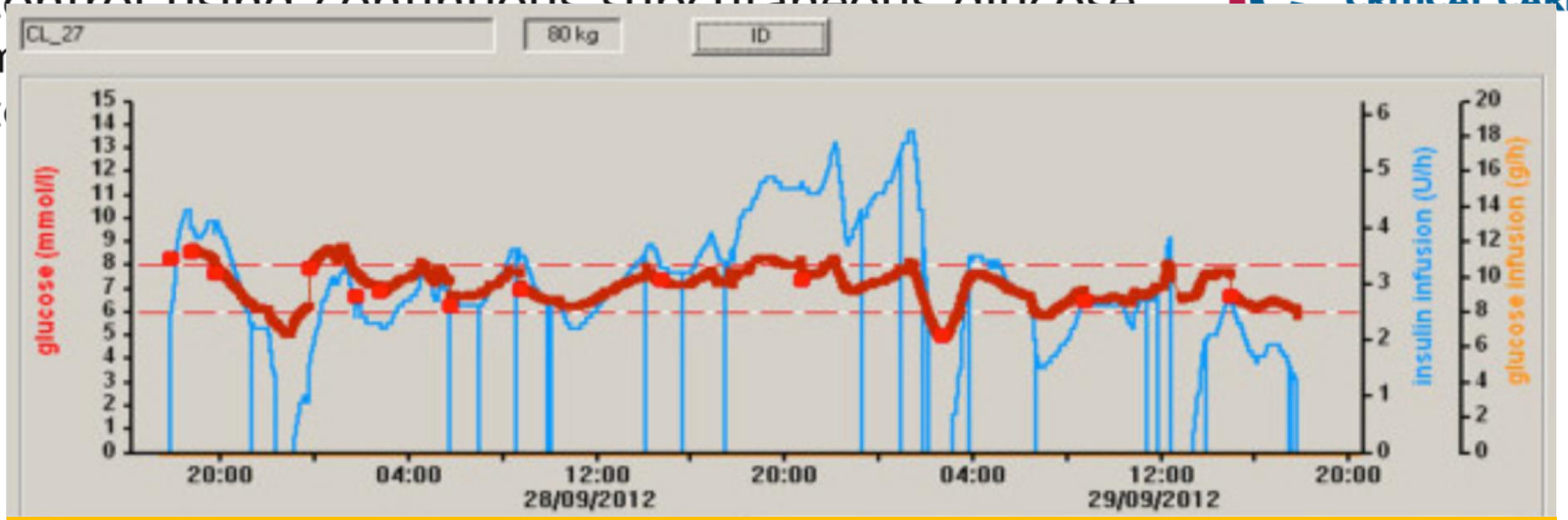
Interpretation Closed-loop insulin delivery without meal-time boluses is effective and safe in insulin-treated adults with type 2 diabetes in the general ward.

Median sensor glucose concentration and insulin delivery



Thabit et al. Lancet Diabetes & Endocrinol 5:117-24, 2017

Feasibility of fully automated closed-loop glucose control using continuous subcutaneous glucose m c



Fully automated closed-loop control based on SC glucose measurements is feasible and may provide efficacious and hypoglycemia-free glucose control in critically ill adults.

Leelarathna et al. Critical Care 2013, 17:R159

2016 Expert Panel and 2022 ADA Standards of Care

"CGM…has the potential to detect hyper- and hypoglycemia [in the hospital], that would otherwise be missed by POC.[a] However, expansion of CGM into US hospitals has been limited by the lack of RCTs comparing rtCGM with POC in hospital settings…"

ADA Standards of Care note insufficient data to recommend widespread use of CGM for hospitalized patients[b]

- ADA, American Diabetes Association; RCT, randomized controlled trial.
- a. Wallia A, et al. J Diabetes Sci Technol. 2017;11:1036-1044; b. American Diabetes Association. Diabetes Care. 2022;45(suppl 1):S244-S253.

Grady/Emory Hospital Diabetes Research Team

Grady/Emory Faculty

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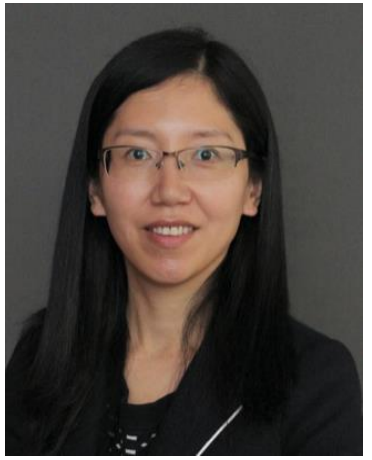

David Reyes

Thank You

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Conclusions -- rtCGM in the Hospital

- **Offers a remote digital solution to care management**
- **Provides continuous individualized feedback for rapid interventions**
- **Allows intelligent modification in pharmacotherapy**
- **Requires some ongoing validation to ensure accuracy**

Gothong C, et al. Curr Opin Endocrinol Diabetes Obes. 2022;29:1-9.