Continuous Glucose Monitoring: Technology and Clinical Need

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October 10, 2014

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Disclosures

- Investigator-initiated grant – DexCom
- Consultant
  - Abbott
  - Bayer
  - Medtronic
  - Merck
  - Sanofi

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Biostator
Glucose Controlled Insulin Infusion System

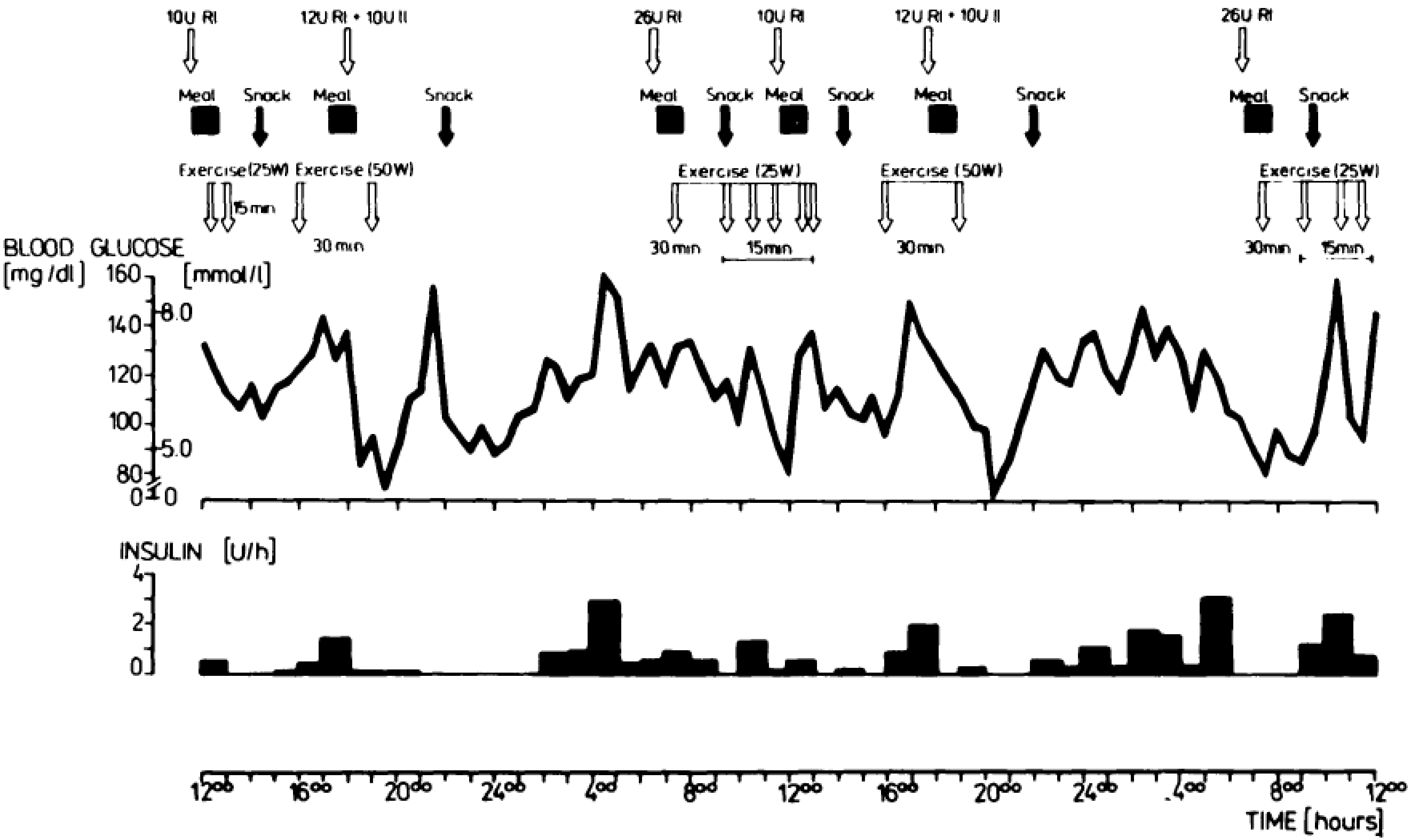

FIG. 2. Blood glucose profile of a patient treated by a combination of s.c. insulin injections plus feedback control by the Biostator for at least 50 h.

Ratzman KP Diab Care 5:11-17, 1982

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Time Perspective:
US FDA First Approvals CGM

YEAR	PRODUCT	TYPE of CGM	STATUS
1999	Medtronic (MiniMed)	Professional	Updated version available
2001	Cygnus GlucoWatch	Real-time	Not available
2005	Medtronic (MiniMed)	Real-time	Updated versions available, stand-alone and with pump
2006	DexCom	Real-time*	Updated versions available
2008	FreeStyle Navigator	Real-time	Not available in US

*settings may be adjusted for use as professional version, but approved for single patient use only

Currently available systems are subcutaneous and approved for sensor duration up to 7 days (sensor duration approval differs by product)

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The Parts of a CGM

- **Sensor**- obtains glucose information in **<u>interstitial fluid</u>**
- **Sensor insertion device**- to aid in effective sensor insertion

  -- sensors should be inserted **<u>subcutaneously</u>** where there is adequate fat which is usually in the abdomen or buttocks

  -- avoid areas of recent pump or sensor insertion sites

  -- consider that the sensor will be in place for several days
- **Transmitter**- attached to sensor, sends data to receiver
- **Receiver**- displays and stores immediate and recent glucose information, provides alarms and trends, history
  - stand-alone
  - integrated with insulin pump
- **Download/Upload software-** retrospective evaluation
- **Blood glucose meter** for calibration

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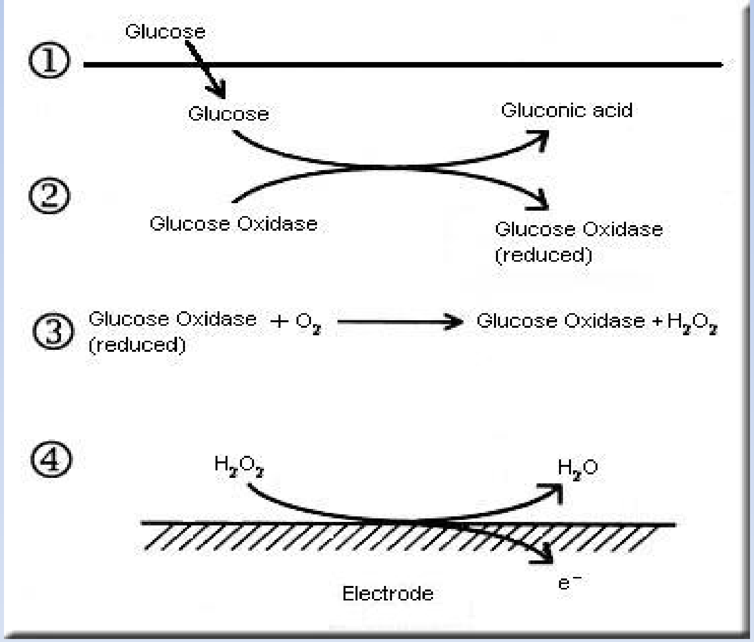
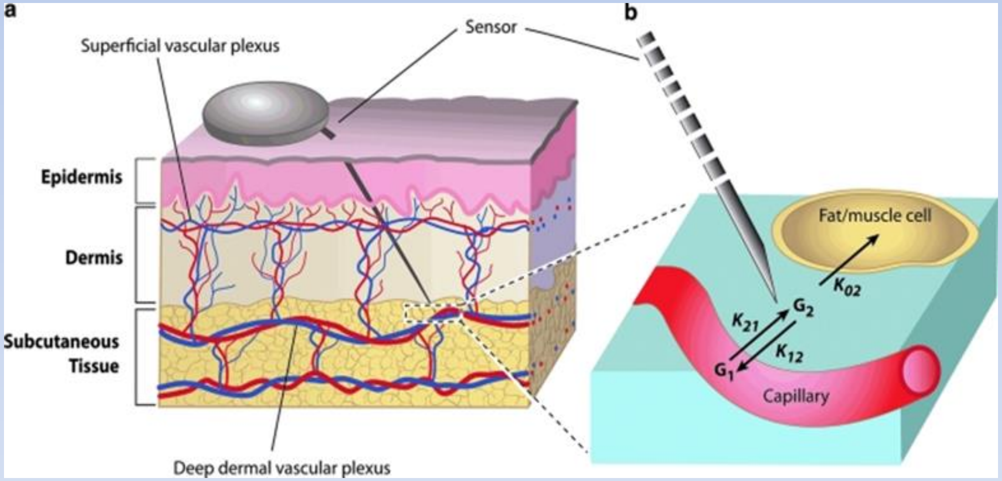
Sensor Technology

Current CGM measures the effect of glucose in the interstitial fluid (ISF)

- glucose diffuses across the capillary wall to the interstitial space and then through sensor membrane to site of glucose oxidase reaction on sensor





Diabetes Technol Ther. 2009; 11(S1): S-11–S-16.

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Sensor Technology

- Calibration is required so that the electrical signals produced by the glucose oxidase reaction can be converted to BG levels
  - Proprietary algorithms are used
- Current CGM - glucose updated every five minutes
- "Lag"-physiologic, device, sensor conditions in body
  - Blood flow, rate of diffusion plasma to ISF, glucose uptake by cells, sensor membrane and calculation/reporting time by CGM
  - calibration should not be done when there is a high rate of change in glucose such as in the first hour after eating or when a rapid change arrow appears on the display screen

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Physiological Factors that Affect Interstitial Fluid Glucose

- Tissue perfusion
- Glucose supply from the blood vessel
- Capillary permeability
- Metabolic rate of adjacent cells
- Other factors that influence cellular glucose uptake (e.g., insulin)
- Local temperature
- Oxygen tension in the interstitial space
- Other potential as yet unidentified factors

Cengiz E Diab Tech Ther 11 Suppl 1:S11-16, 2009.
Mensh BD J Diab Sci Tech 7: 863-870, 2013.

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Interfering Substances

SMBG

- Acetaminophen
- Ascorbic acid
- Uric acid
- Salicylic acid

CGM

- Acetaminophen
- Ascorbic acid
- Uric acid
- Paracetamol
- Isoniazid
- Salicylate
- Glutathione

All of these substances nonspecifically oxidize H_2O_2 and therefore interfere with the glucose oxidase-based BG test strips and glucose sensor electrodes

Cengiz E Diab Tech Ther 11 Suppl 1:S11-16, 2009

Alarms

- Project future hypo- and hyperglycemia depending on the threshold setting
- Thresholds can be customized for the patients
- SMBG should be used to confirm the alarm value
- Alarm fatigue is a significant problem:
  - Hypoglycemia alarm is set too high (90 mg/dl) increases sensitivity but decreases specificity
  - Hypoglycemia alarm is set too low (50 mg/dl) decreases sensitivity but increases specificity

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Differences

SMBG

- Measures capillary blood glucose
- Good correlation between capillary blood glucose and arterial/venous blood glucose, even during times of rapid change
- Difficult to get a complete picture of glycemic trends
- Static point in time – direction/magnitude of glucose change unknown
- Cannot alert user to out of range/potentially out of range blood sugars

CGM

- Measures glucose in the IF
- Lag time between IF glucose and blood glucose
  - Lag time increases during periods of rapid glycemic fluctuations
- Very helpful for seeing glycemic trends
- Gives directional arrows – can see where glucose is going
- Can alert user if BG is out of range/ will be out of range

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Reliability

SMBG

- General perception: OK
- Provides the basis for insulin administration
- Standard by which diabetes medications are adjusted

CGM

- General perception: good, but not accurate enough
- Good for trending information and to provide alerts/alarms
- Should not base insulin administration on sensor glucose alone – always double-check SG reading with a SMBG

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Indications for Diagnostic CGM

Inconsistency between glucose record diary and HbA1c
Assessing the frequency and severity of hyper- and hypoglycemia
Evaluation of the adequacy of timing and frequency of self-monitored blood glucose
Enhancing patient education and psychological motivation for optimal diabetes management

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Indications for Diagnostic CGM	Indications for Real-Time CGM
Inconsistency between glucose record diary and HbA1c	Improving diabetes management in patients with unstable diabetes
Assessing the frequency and severity of hyper- and hypoglycemia	Tracking and trending glucose thereby enabling patients to intervene and prevent unwanted glucose excursions
Evaluation of the adequacy of timing and frequency of self-monitored blood glucose	Assisting patients with hypoglycemia unawareness, repeated severe hypoglycemic episodes or undetected hypoglycemia
Enhancing patient education and psychological motivation for optimal diabetes management	Providing parents the ability to monitor their children in real-time

Diagnostic CGM

Clinic owns the equipment

Staff training

- –Sensor insertion
- –Patient teaching to protect site and perform BGs for later calibration
- –Upload process
- –Clean/disinfect, log equipment use

Using reports for therapy change and diabetes education

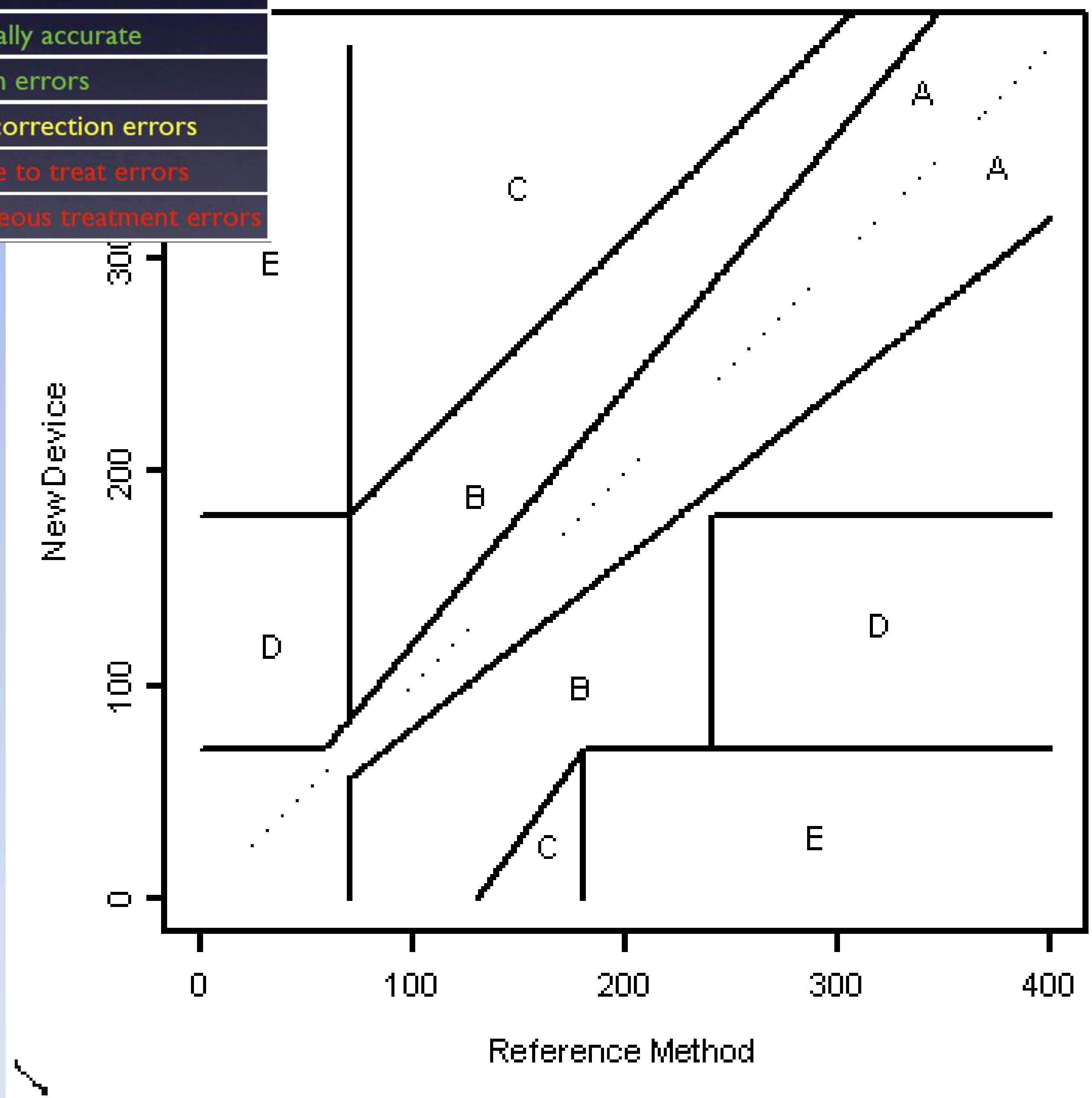
Plan time in schedule - CGM clinics or during regular visits

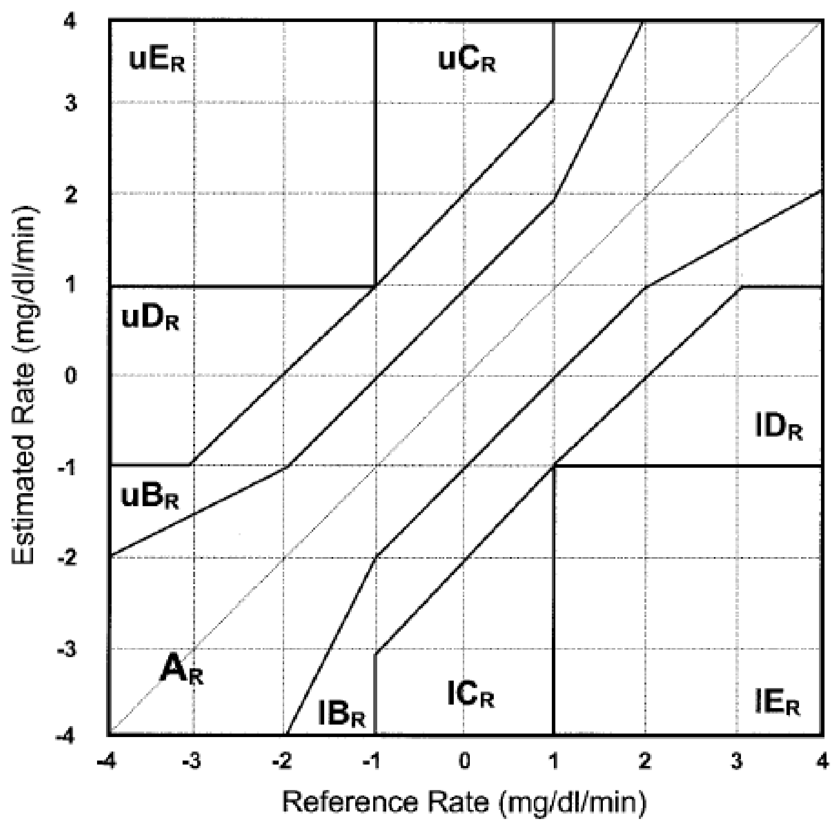
Diagnostic CGM	Real-Time CGM
Clinic owns the equipment	Patient owns equipment
Staff training –Sensor insertion –Patient teaching to protect site and perform BGs for later calibration –Upload process –Clean/disinfect, log equipment use	Stages: “Nuts and bolts” training to long-term use and success
Using reports for therapy change and diabetes education	Realistic expectations, understand benefits and potential limitations
Plan time in schedule - CGM clinics or during regular visits	Support to understand, make the most of CGM and prevent discontinuance of use

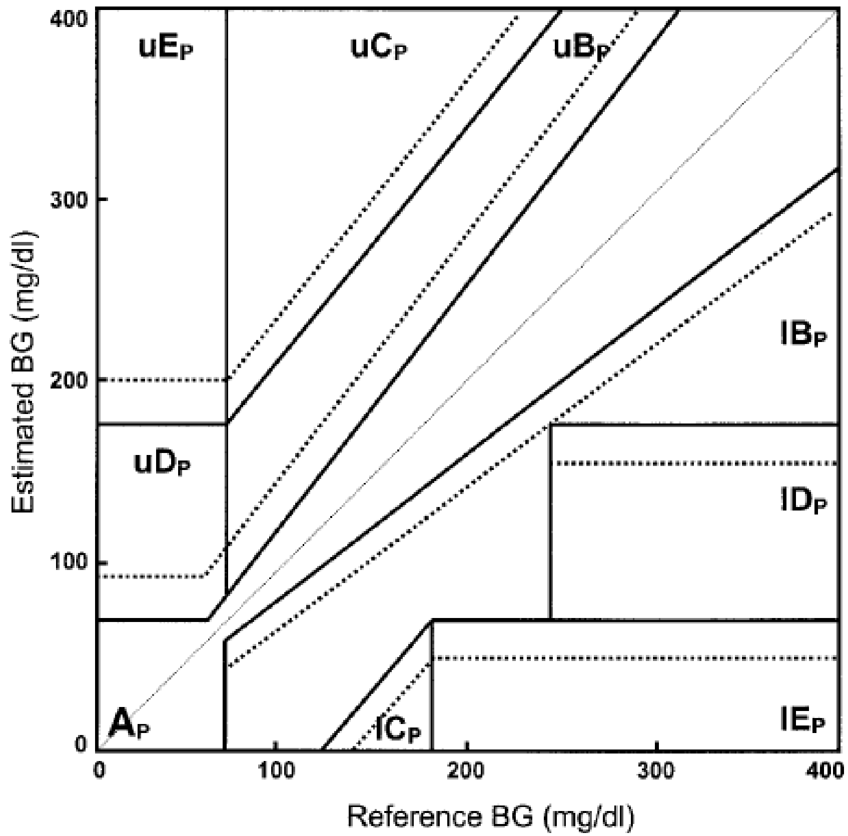
Accuracy

Gold Standard

Zone	
A	Clinically accurate
B	Benign errors
C	Overcorrection errors
D	Failure to treat errors
E	Erroneous treatment errors







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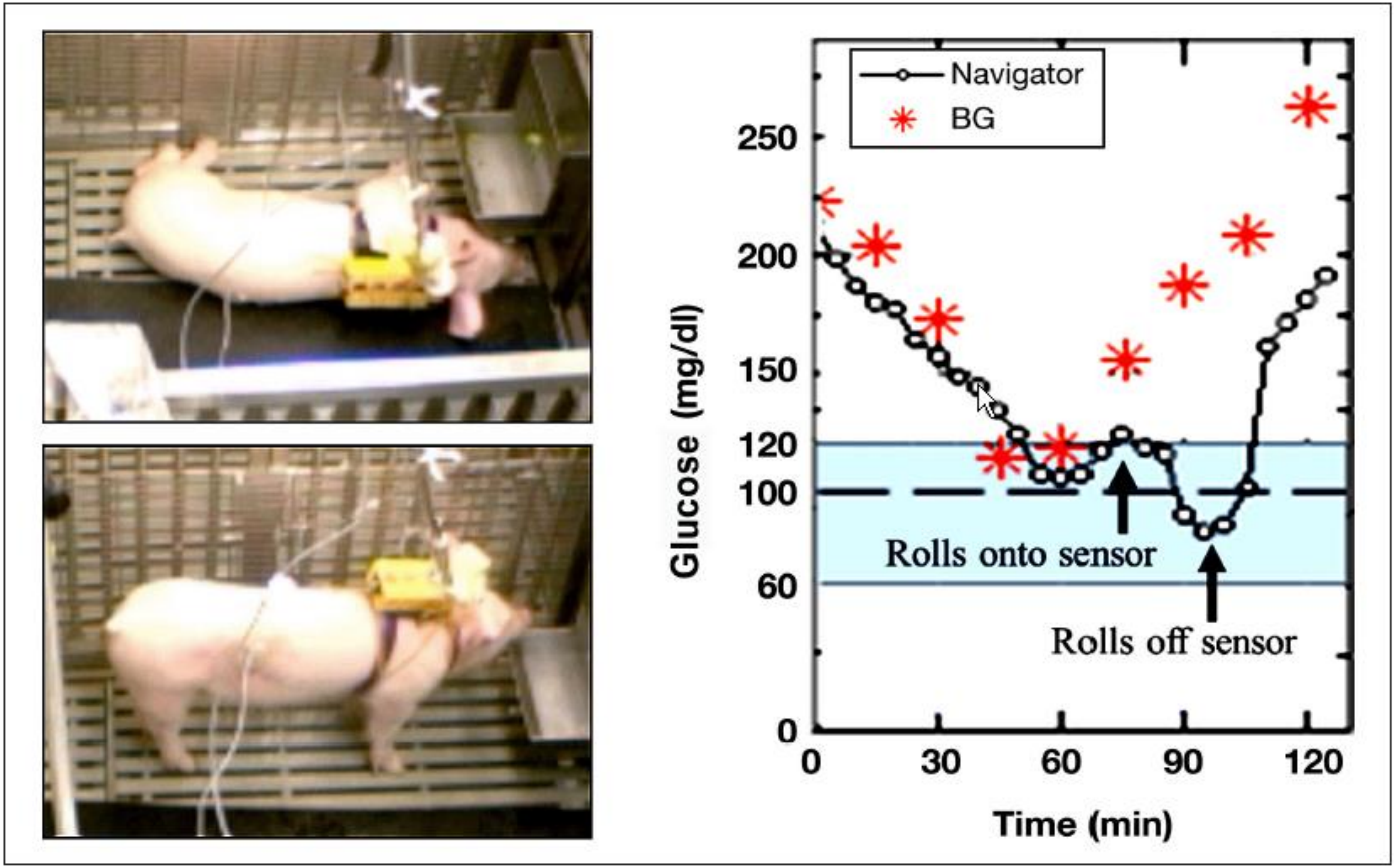
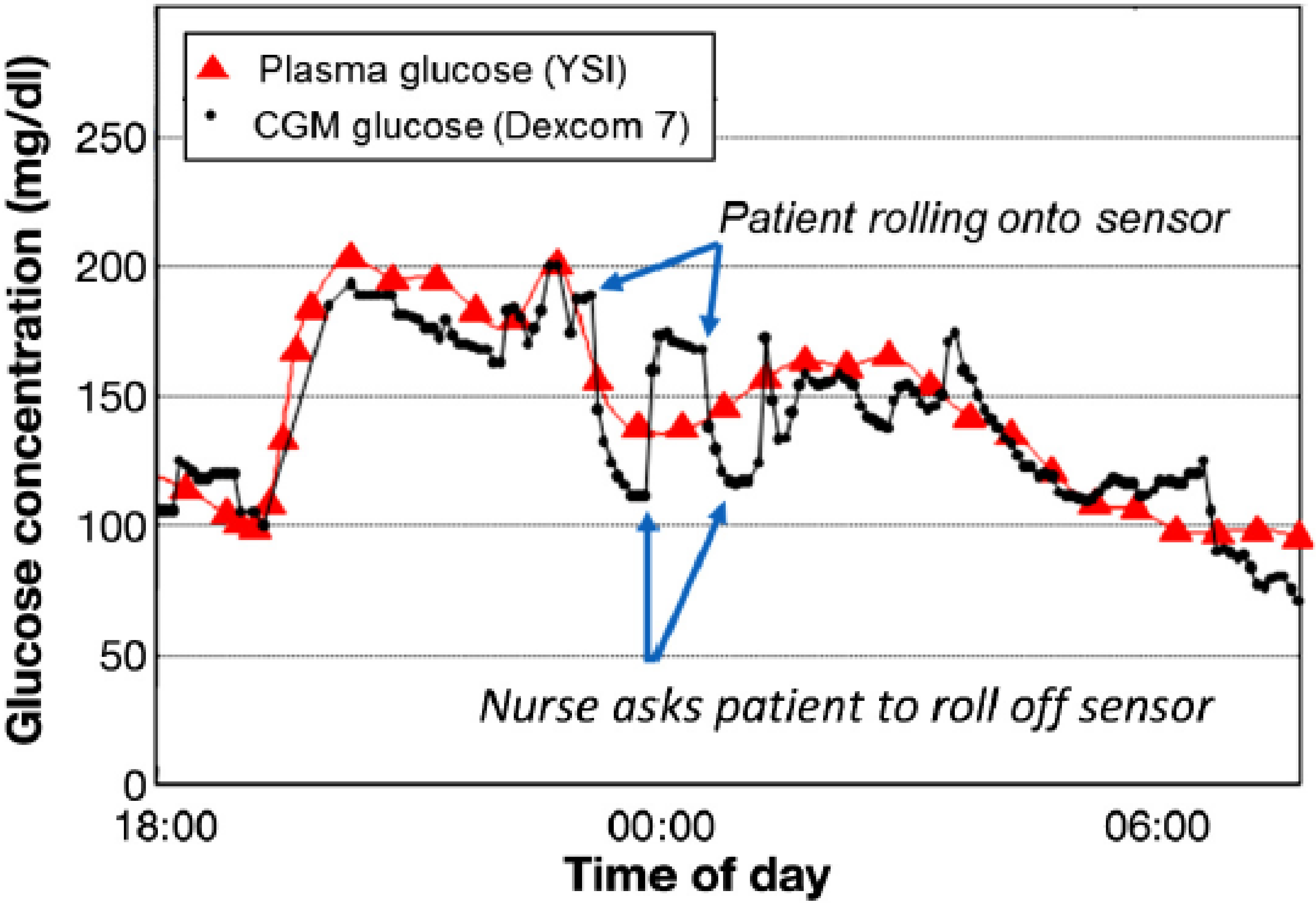
70.9% 93.9% 89.1%

Rate Error-Grid Zones	Point Error-Grid Zones: Hypoglycemia BG ≤ 70 mg/dl			Euglycemia 70<BG≤180mg/dl			Hyperglycemia BG > 180 mg/dl				
	A	D	E	A	B	C	A	B	C	D	E
A	57.4%	18.8%	0%	53.2%	23.4%	0.1%	55.9%	9.4%	0%	0.1%	0%
B	13.5%	5.1%	0%	11.6%	5.7%	0.1%	20.1%	3.7%	0%	0.1%	0%
uC	0%	0%	0%	0.6%	0.5%	0%	1.5%	0.6%	0%	0%	0%
lC	1.2%	0.4%	0%	0.4%	0.5%	0%	1.1%	0.3%	0%	0%	0%
uD	0.6%	1.4%	0%	1.0%	0.7%	0%	2.0%	0.8%	0%	0%	0%
lD	0.6%	0%	0%	1.0%	0.4%	0%	2.4%	0.3%	0%	0%	0%
uE	0%	0.2%	0%	0.1%	0.2%	0%	0.6%	0.3%	0%	0%	0%
lE	0.8%	0%	0%	0.4%	0.1%	0%	0.7%	0.1%	0%	0%	0%

Accurate Readings — Benign Errors — Erroneous Readings



Helton KL et al. J Diab Sci Tech 5:647-656, 2011



Helton KL et al. J Diab Sci Tech 5:647-656, 2011

MARD = Mean Absolute Relative Difference

YSI value – Sensor value = difference (in either direction)

- if YSI =100 mg/dl and CGM sensor = 80 mg/dl, the relative difference is -20 or 20%
- if YSI = 180 mg/dl and CGM sensor = 198 mg/dl, the relative difference is +18 mg/dl or 10%

Add all the values, e.g., 20% + 10% = 30%

Divide by the number of values, e.g., 30% ÷ 2 = 15%

MARD = 15%

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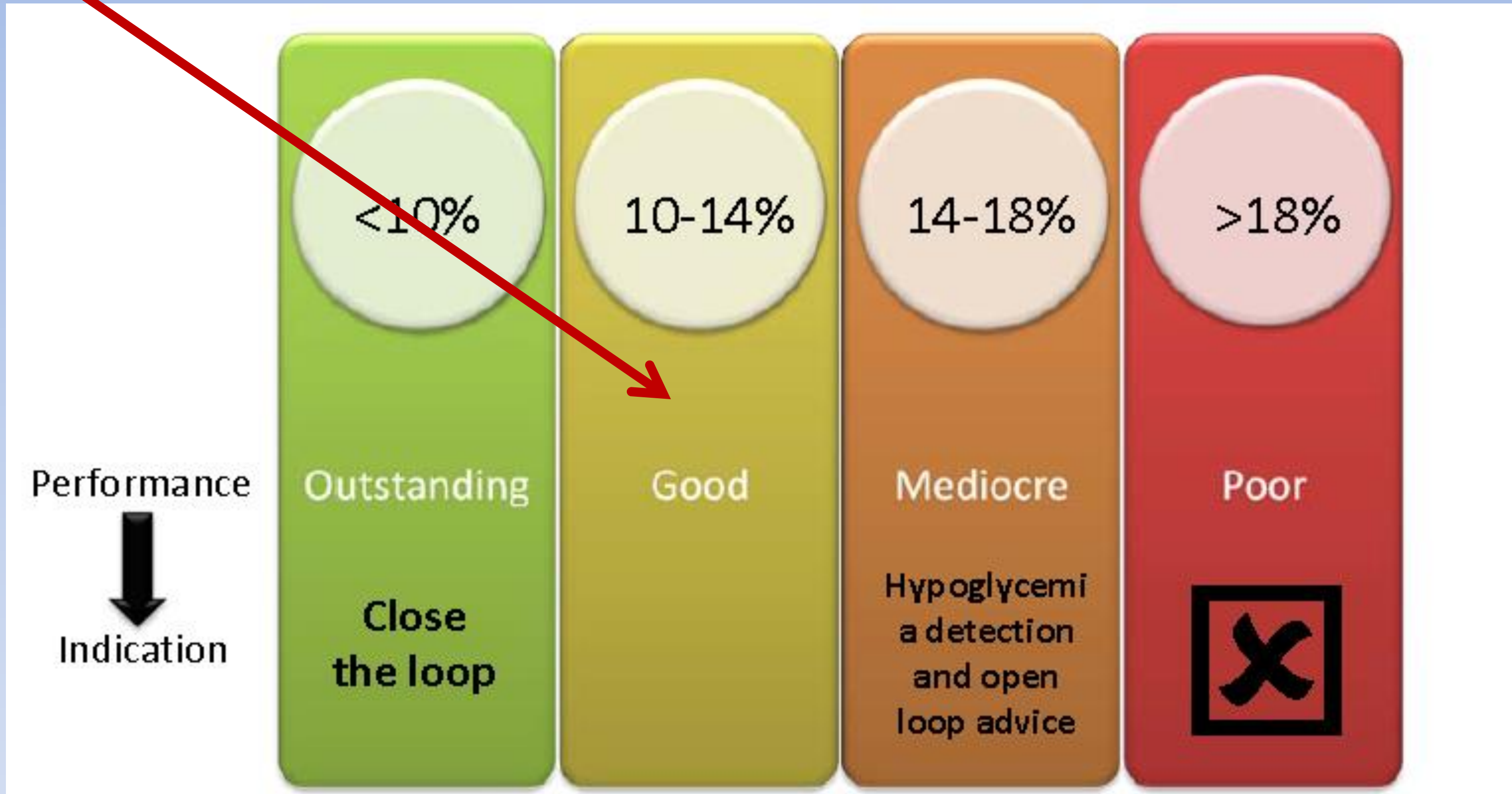
Sensor Performance by MARD

Intended Use/Accuracy Balance



Risk: Hypoglycemia	↓↓↓	↓↓	↓	↑↑
Benefit: Likelihood of achieving target	↑↑↑	↑↑	↑	↓

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Currently Available RT- CGM's

Medtronic

Dexcom G4 Platinum

Abbott FreeStyle Libre

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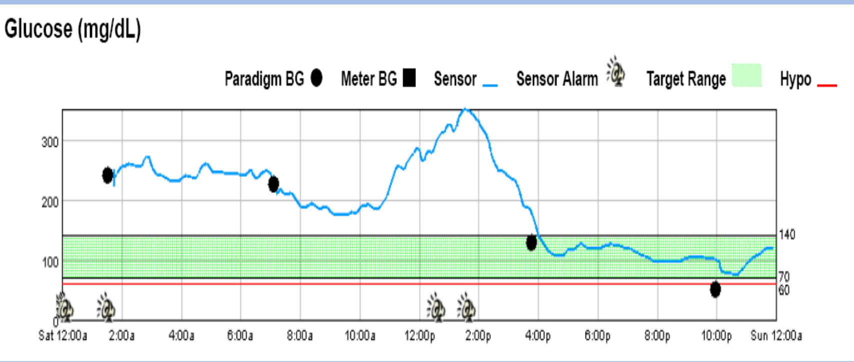
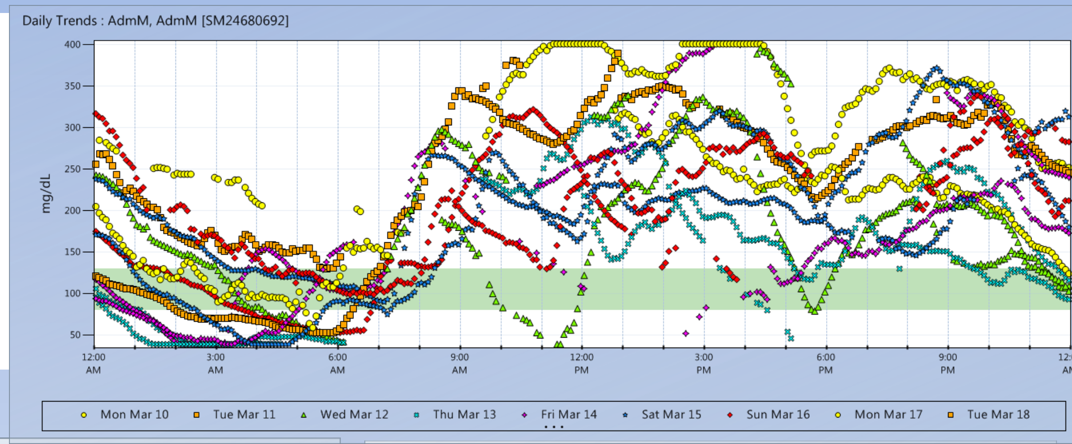
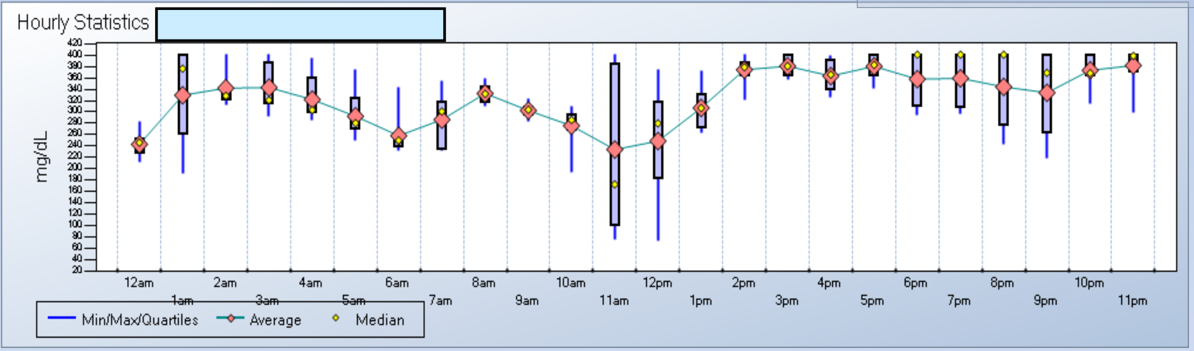
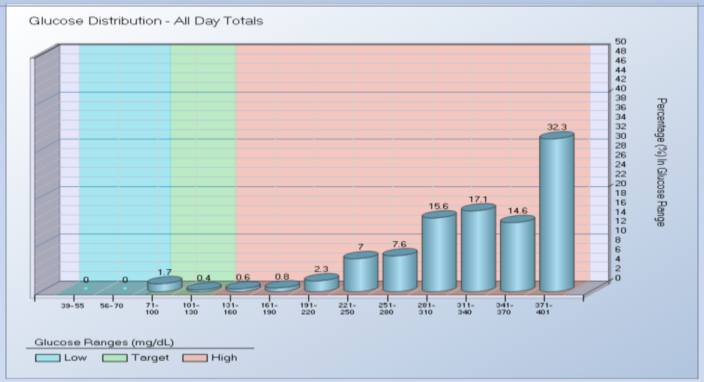
Multiplicity of Reports









Stat	Totals	12am	1am	2am	3am	4am	5am	6am	7am	8am	9am	10am	11am
# of Readings	2912	149	144	150	153	141	132	96	83	86	95	101	107
Average	196	164	123	105	97	89	89	103	147	222	241	246	238
Min	Low	52	Low	Low	Low	Low	42	41	75	111	91	50	Low
Quartile 25	121	95	70	45	43	53	54	88	111	161	193	205	185
Median	194	156	118	103	87	73	91	101	137	230	238	230	244
Quartile 75	267	227	176	155	131	126	117	111	183	275	278	312	286
Max	High	317	252	245	238	208	155	202	265	344	350	394	High
Std. Dev.	93	72	61	59	53	42	35	34	46	63	60	85	87
Est. Std. Dev.	108	98	79	82	65	54	47	17	53	84	63	79	75
IQR	146	132	107	110	88	73	63	23	72	114	84	107	101
SE Mean	2	6	5	5	4	4	3	3	5	7	6	8	8
%CV	48	44	49	56	55	47	39	33	31	28	25	35	37

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Multiplicity of Reports

- Can be overwhelming at first
- Every report isn't necessary or useful to review for all patients
- Select those reports that are most important for what are the priorities for that patient
  - Hypoglycemia
  - Overall glycemic control
  - Variability

Clinical Use

- Improve overall glycemic control
- Reduce number of hypoglycemic events
- Reduce glycemic variability
- Empower and educate patients in diabetes management
- Use in partially and fully closed-loop (artificial pancreas)

Improvement in Glycemic Excursions With a Transcutaneous, Real-Time Continuous Glucose Sensor

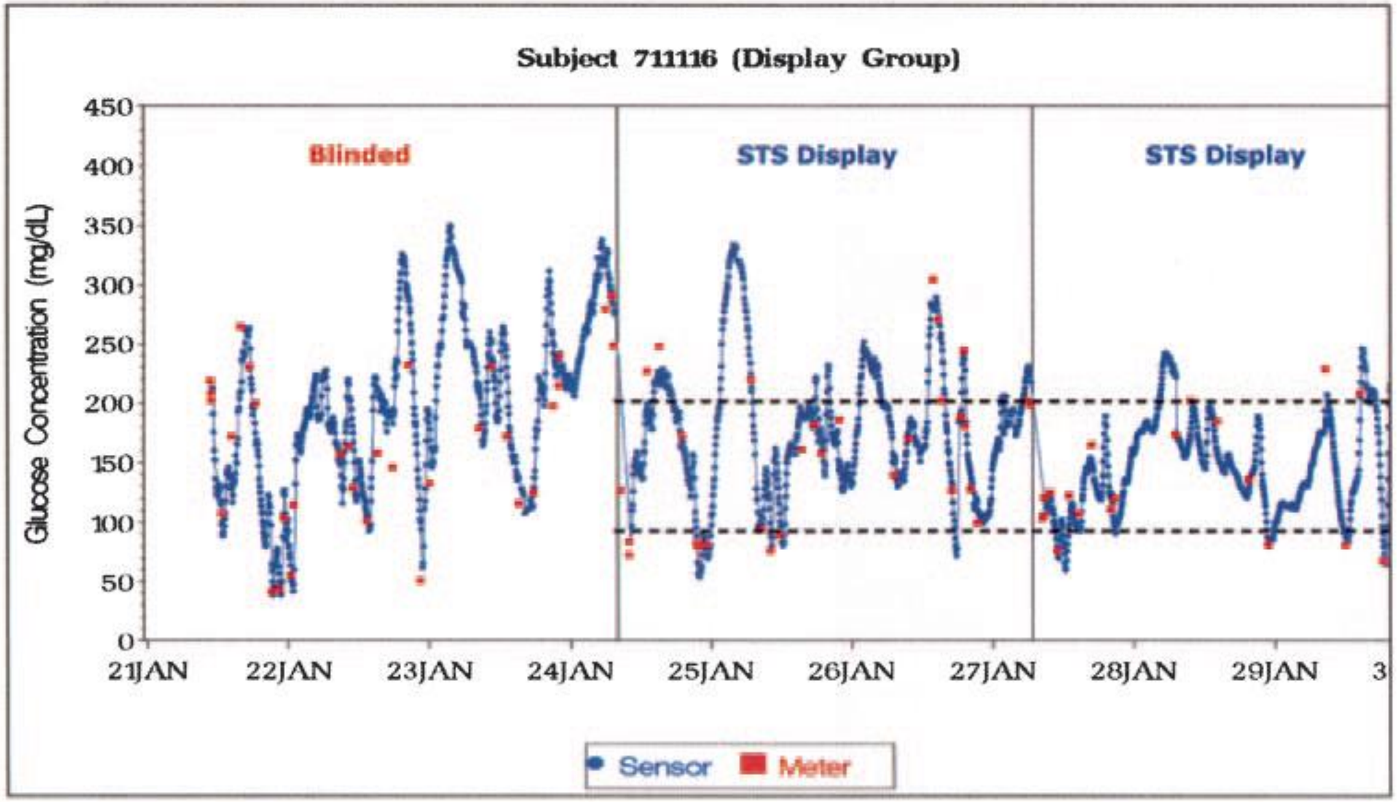
A randomized controlled trial

Satish Garg, MD[1]
Howard Zisser, MD[2]
Sherwyn Schwartz, MD[3]
Timothy Bailey, MD[4]
Roy Kaplan, MD[5]
Samuel Ellis, PharmD[1]
Lois Jovanovic, MD[2]

Period 1:
Median Glucose (min, max) = 200 mg/dl (42, 350)
Mean Glucose ± Stdev = 200 ± 69 mg/dl

Period 2:
Median Glucose (min, max) = 176 mg/dl (54, 334)
Mean Glucose ± Stdev = 178 ± 57 mg/dl

Period 3:
Median Glucose (min, max) = 148 mg/dl (60, 264)
Mean Glucose ± Stdev = 150 ± 42



Society

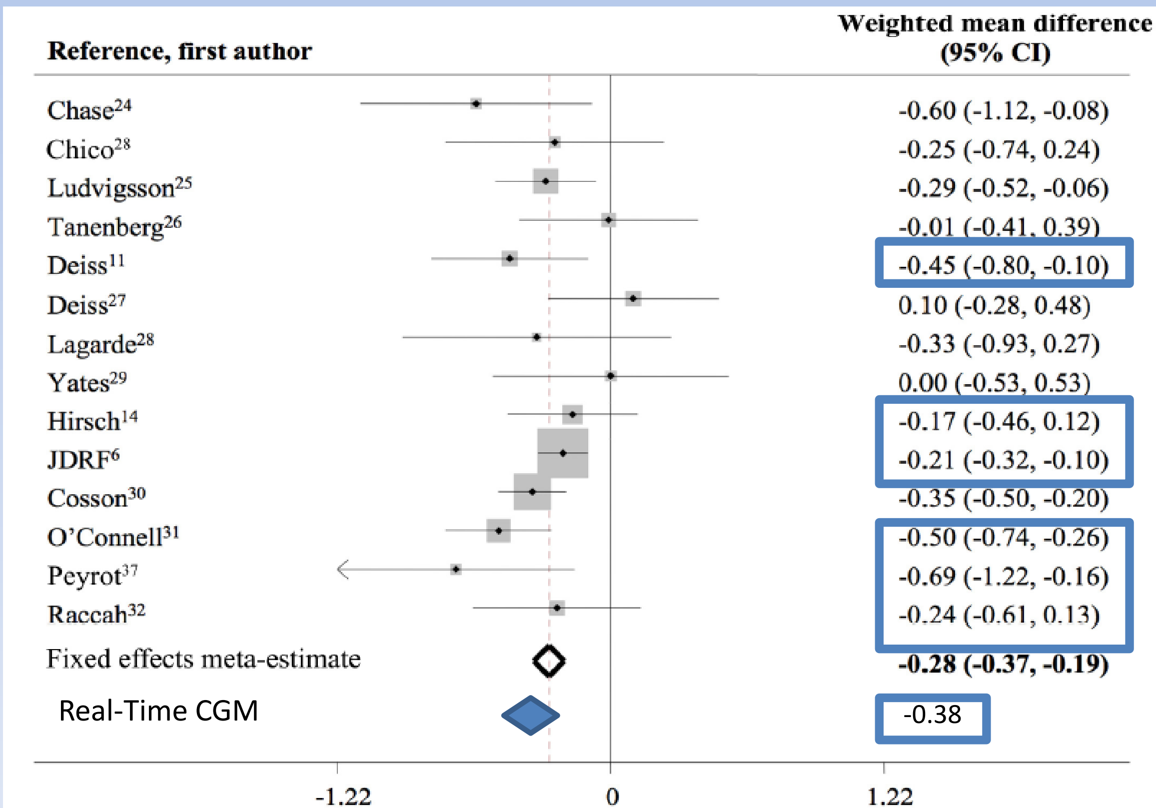
Garg S *et al. Diab Care* 29:44-50, 2006.

Journal of Diabetes Science and Technology
Volume 6, Issue 5, September 2012

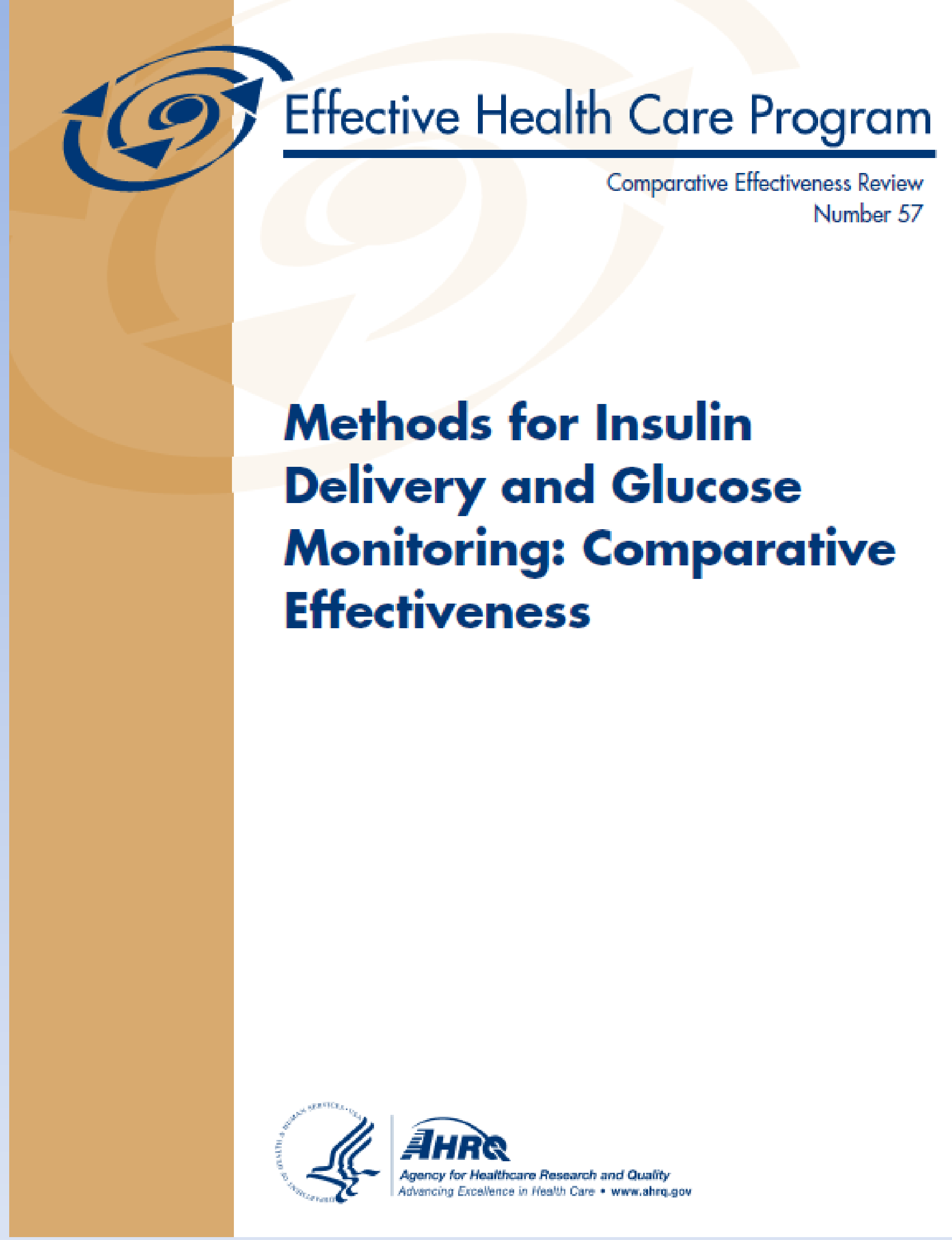
ORIGINAL ARTICLE

Comparative Analysis of the Efficacy of Continuous Glucose Monitoring and Self-Monitoring of Blood Glucose in Type 1 Diabetes Mellitus

Baraka Floyd, M.D., M.Sc.,[1] Prakash Chandra, M.D.,[2] Stephanie Hall, M.P.H.,[1]
Christopher Phillips, M.D., M.P.H.,[1] Ernest Alema-Mensah, Ph.D.,[1] Gregory Strayhorn, M.D., Ph.D.,[1]
Elizabeth O. Ofili, M.D., M.P.H.,[1] and Guillermo E. Umpierrez, M.D.[2]



Real-Time CGM



Effective Health Care Program

Comparative Effectiveness Review
Number 57

Methods for Insulin Delivery and Glucose Monitoring: Comparative Effectiveness

AHRQ
Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

Golden S. Agency for Healthcare Research and Quality Comparative Effectiveness Review Number 57 Report 12-EHC036-EF, 2012.

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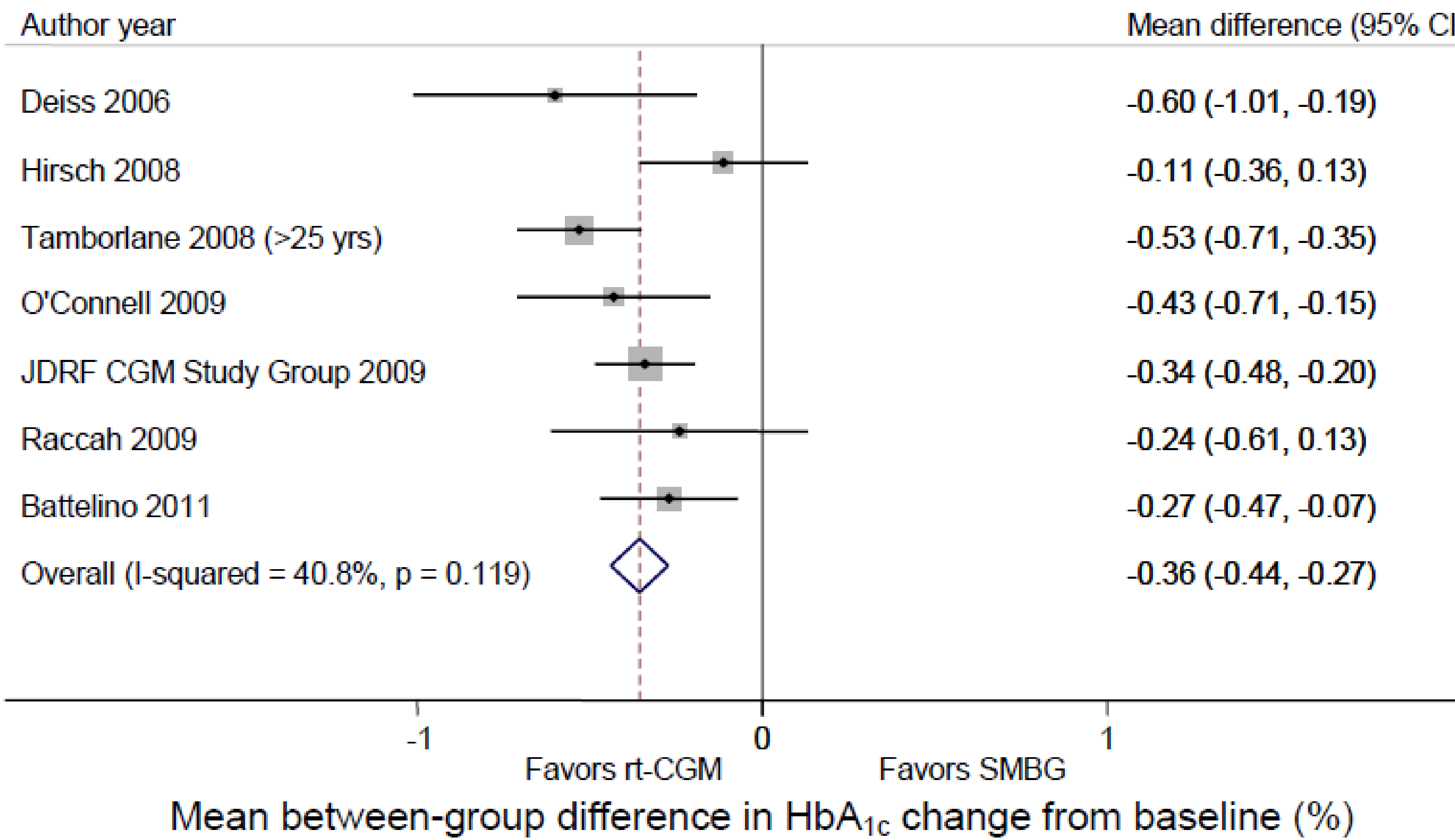
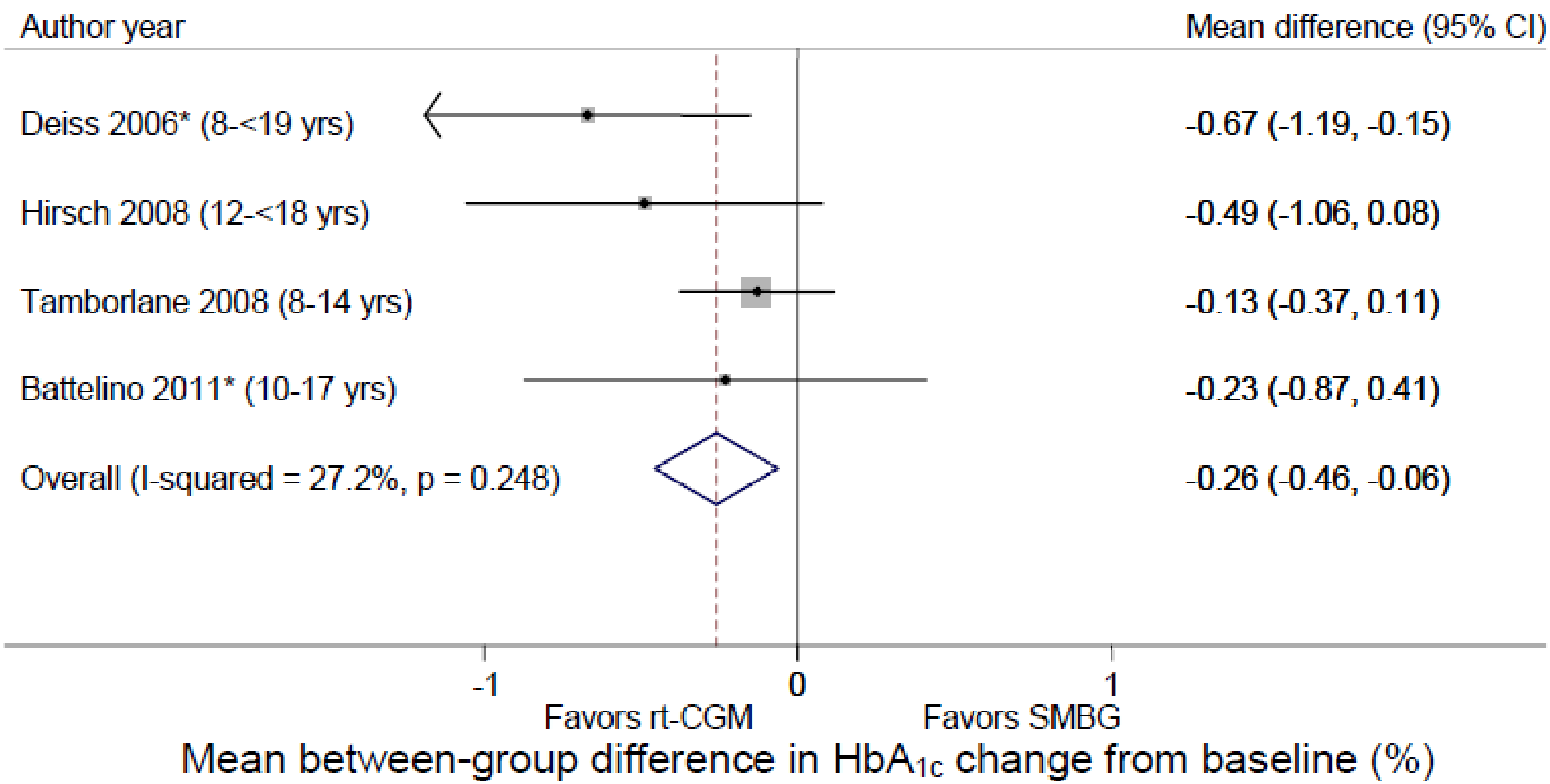
Figure 30. Between-group difference between rt-CGM and SMBG in how HbA_{1c} changed from baseline among adults with type 1 diabetes in studies where compliance was greater than 60%



Golden S. Agency for Healthcare Research and Quality Comparative Effectiveness Review Number 57 Report 12-EHC036-EF, 2012.

Figure 31. Between-group difference between rt-CGM and SMBG in how HbA_{1c} changed from baseline among children and adolescents with type 1 diabetes

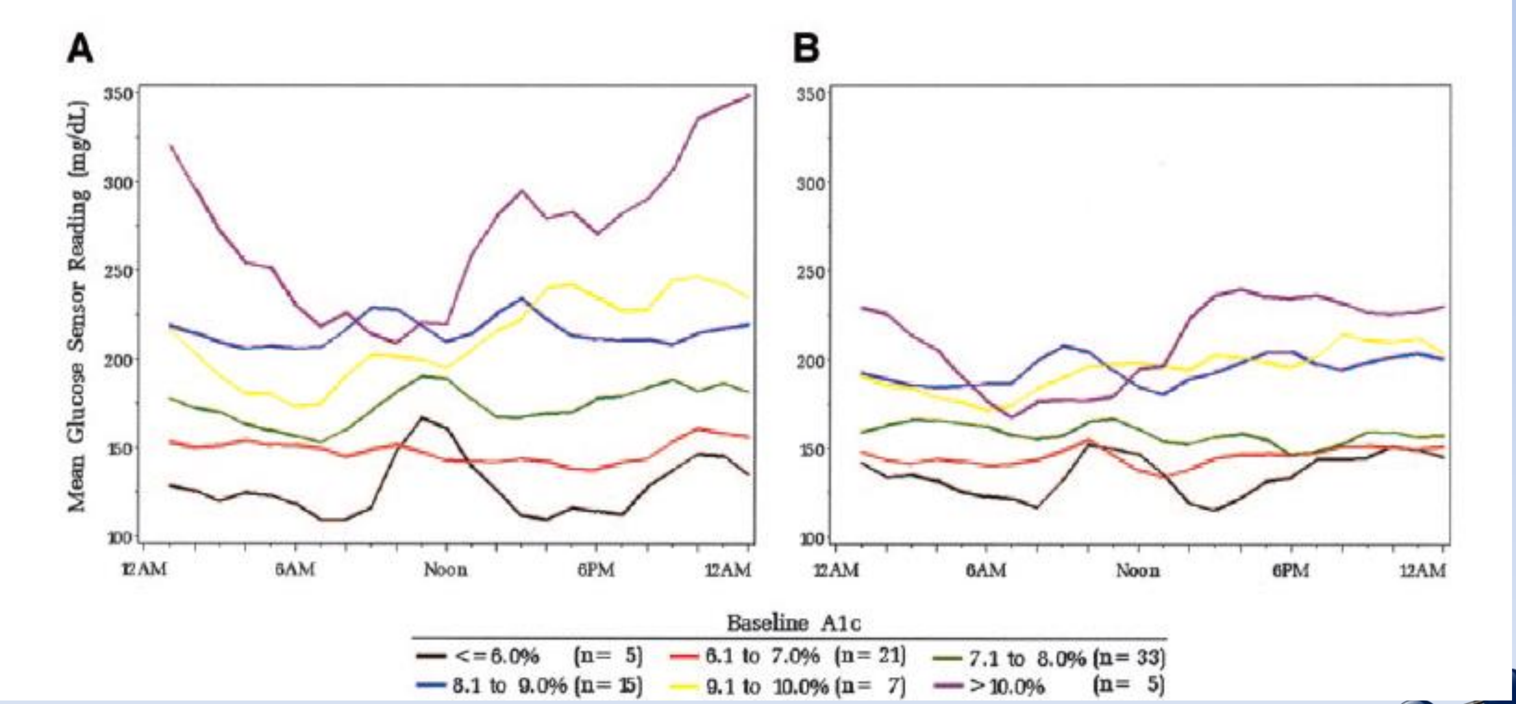


Golden S. Agency for Healthcare Research and Quality Comparative Effectiveness Review Number 57 Report 12-EHC036-EF, 2012.

Relationship of Fasting and Hourly Blood Glucose Levels to HbA_{1c} Values

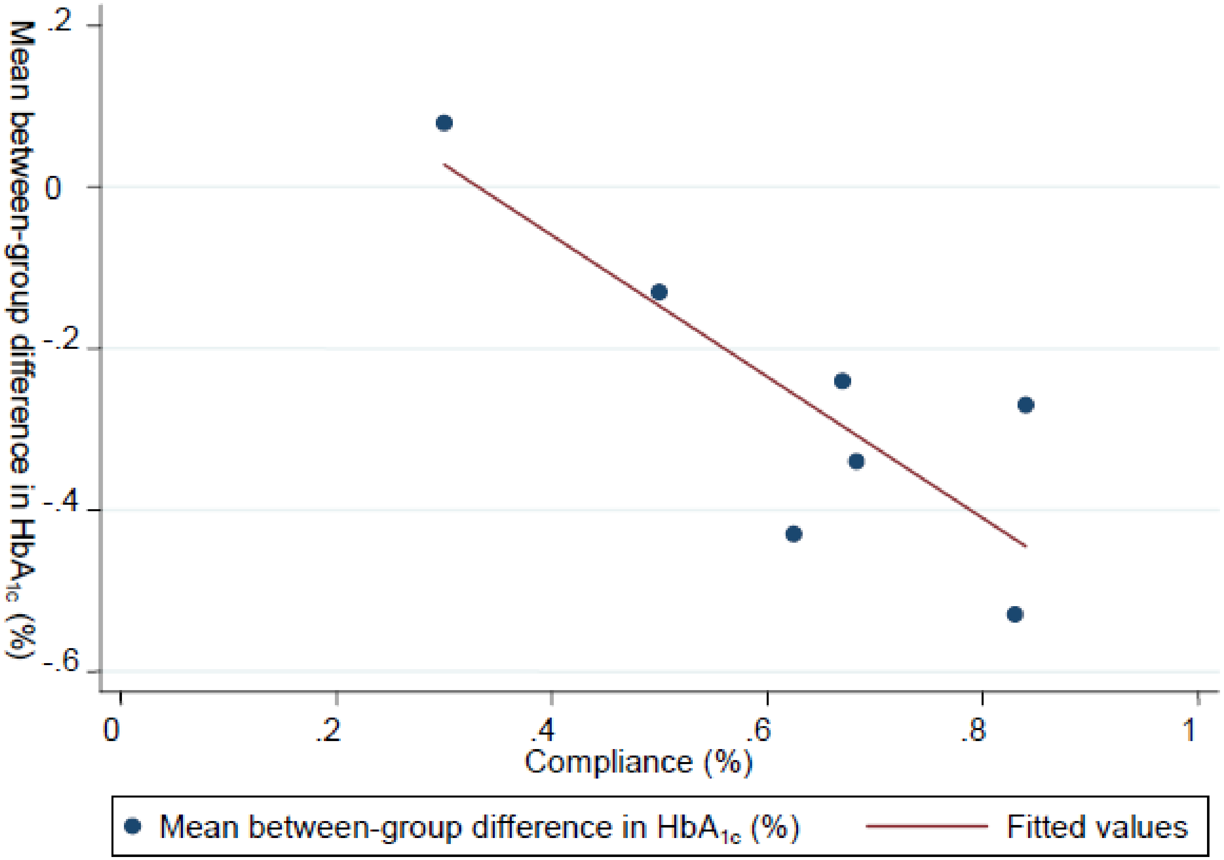
Safety, accuracy, and improvements in glucose profiles obtained using a 7-day continuous glucose sensor

SATISH GARG, MD[1]
LOIS JOVANOVIC, MD[2]



Diab Care 29: 2644-2649, 2006

Figure 29. Compliance with sensor and mean between-group difference between rt-CGM and SMBG in how HbA_{1c} (%) changed from baseline



HbA_{1c} = hemoglobin A_{1c}; rt-CGM = real-time continuous glucose monitoring; SMBG = self monitoring of blood glucose

BMJ

BMJ 2011;343:d3805 doi: 10.1136/bmj.d3805

RESEARCH

Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data

John C Pickup *professor of diabetes and metabolism*[1], Suzanne C Freeman *medical statistics student*[2 3], Alex J Sutton *professor of medical statistics*[2]

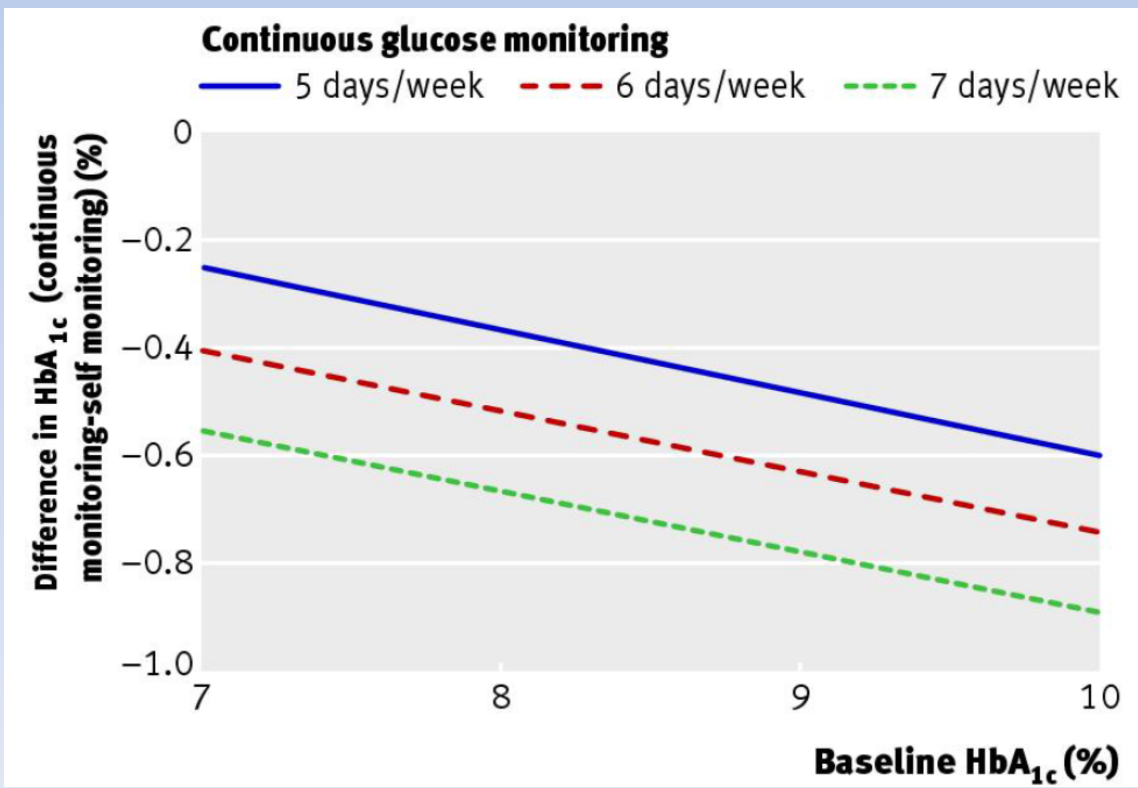


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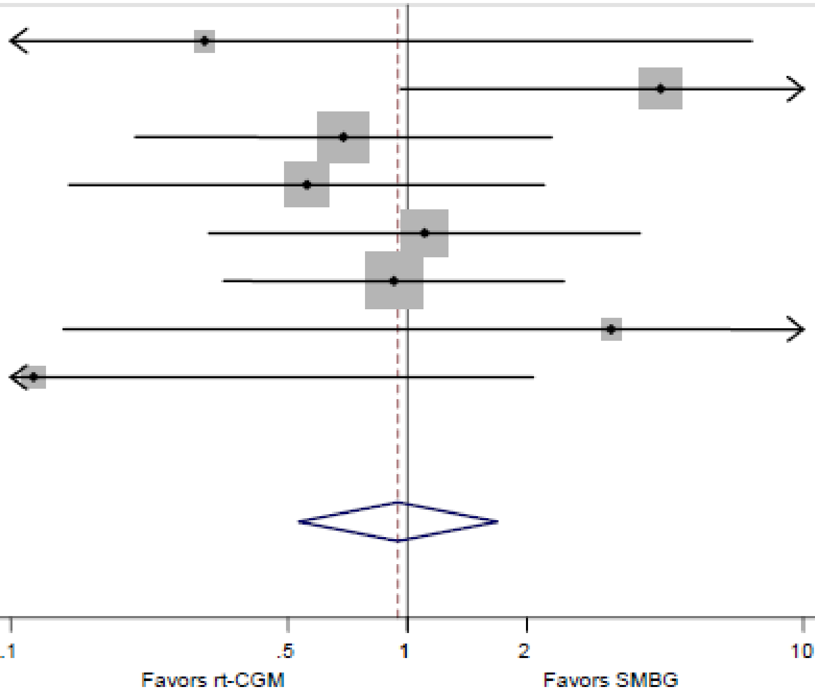
Figure 33. Pooled relative risk of severe hypoglycemia in rt-CGM versus SMBG interventions among patients with type 1 diabetes

Author year	RR (95% CI)	# events rt-CGM	N rt-CGM	# events SMBG	N SMBG
Deiss 2006	0.31 (0.01, 7.39)	0	52	1	48
Hirsch 2008	4.36 (0.96, 19.81)	8	66	2	72
Tamborlane 2008 (8-14 yrs)	0.69 (0.21, 2.32)	4	56	6	58
Tamborlane 2008 (15-24 yrs)	0.56 (0.14, 2.22)	3	57	5	53
Tamborlane 2008 (>25 yrs)	1.11 (0.32, 3.87)	5	52	4	46
JDRF CGM Study Group 2009	0.93 (0.34, 2.49)	7	67	7	62
Raccah 2009	3.27 (0.14, 78.58)	1	55	0	60
Kordonouri 2010	0.11 (0.01, 2.08)	0	76	4	78
O'Connell 2009	(Excluded)	0	26	0	29
Battelino 2011	(Excluded)	0	62	0	58
Overall	0.95 (0.53, 1.69)				



Pooled Relative Risk and 95% Confidence Intervals of Severe Hypoglycemia

CI = confidence interval; RR = relative risk; rt-CGM = real-time continuous glucose monitor; SMBG = self monitoring of blood glucose

Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95% confidence intervals for each study. The diamond at the bottom of the graph indicates the 95% confidence interval for the random-effects pooled estimate.

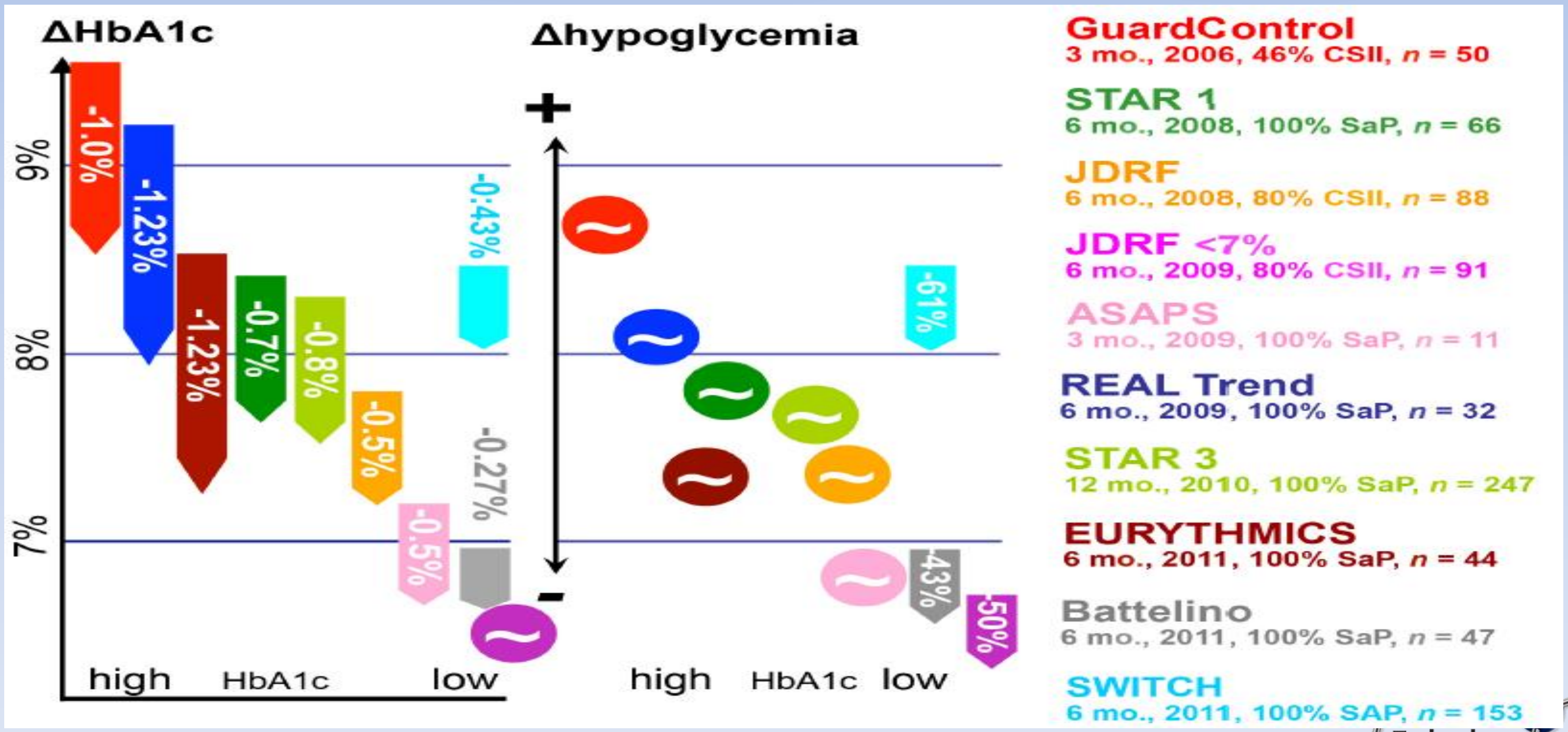
Test for heterogeneity: Q = 7.91 with 7 degrees of freedom ($p = 0.34$)

I-squared = 12 percent

Golden S. Agency for Healthcare Research and Quality Comparative Effectiveness Review Number 57 Report 12-EHC036-EF, 2012.

Continuous Glucose Monitoring: Evidence and Consensus Statement for Clinical Use

Andreas Liebl, M.D.,[1] Helmut R. Henrichs, M.D.,[2] Lutz Heinemann, Ph.D.,[3]
Guido Freckmann, M.D.,[4] Eberhard Biermann, M.D.,[5] and Andreas Thomas, Ph.D.,[6]
for the Continuous Glucose Monitoring Working Group of the
Working Group Diabetes Technology of the German Diabetes Association



J Diab Sci Tech 7: 500-519, 2013.

Real-Time Continuous Glucose Monitoring Significantly Reduces Severe Hypoglycemia in Hypoglycemia-Unaware Patients With Type 1 Diabetes

Pratik Choudhary, MBBS, MRCP, MP[1,3]
Sharmin Ramasamy, MBBS, MRCP[2]
Louisa Green, BSC[3]
Geraldine Gallen, RGN[3]
Siobhan Pender, RGN[2]
Anna Brackenridge, MBBS, MRCP, MD[2]
Stephanie A. Amiel, MBBS, MD, FRCP[1,3]
John C. Pickup, BM, DPhil, FRCP[1,2]

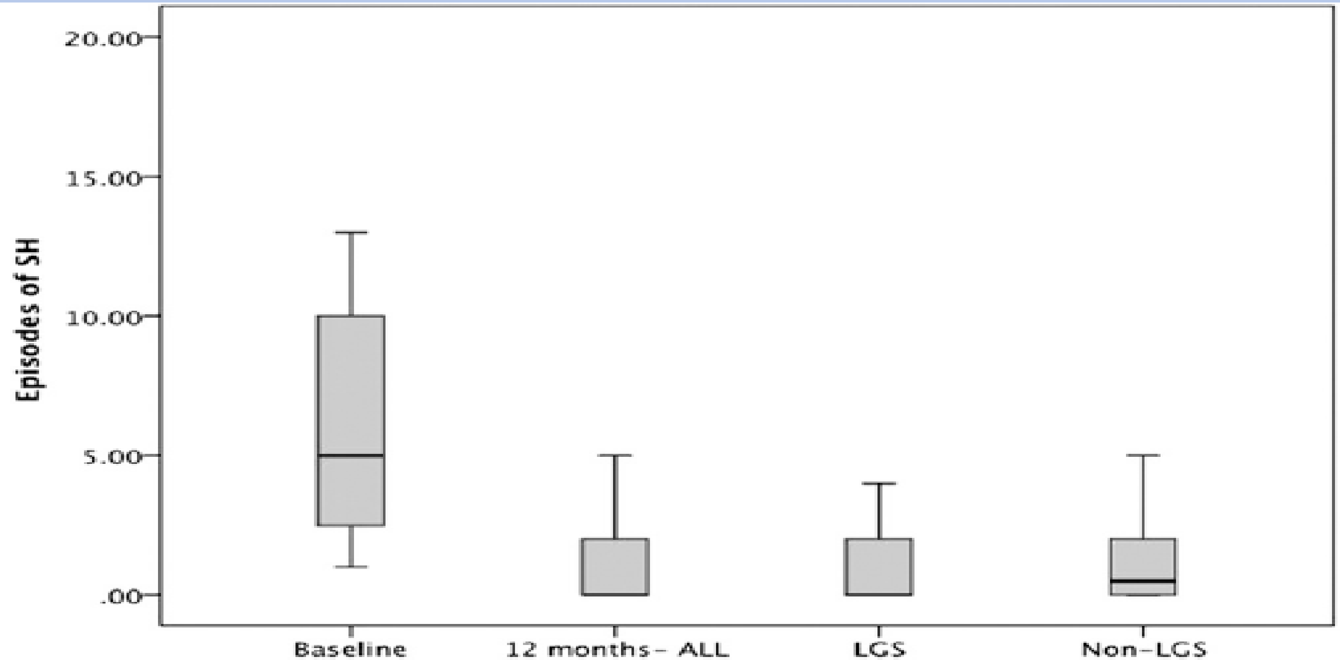


Figure 1—*Annual rates of SH, requiring third-party help at baseline and 12 months after starting CGM. Also shown are the 12-month rates divided into those treated with or without LGS. SH, severe hypoglycemia.*

Diab Care 36:4160-4162, 2013.

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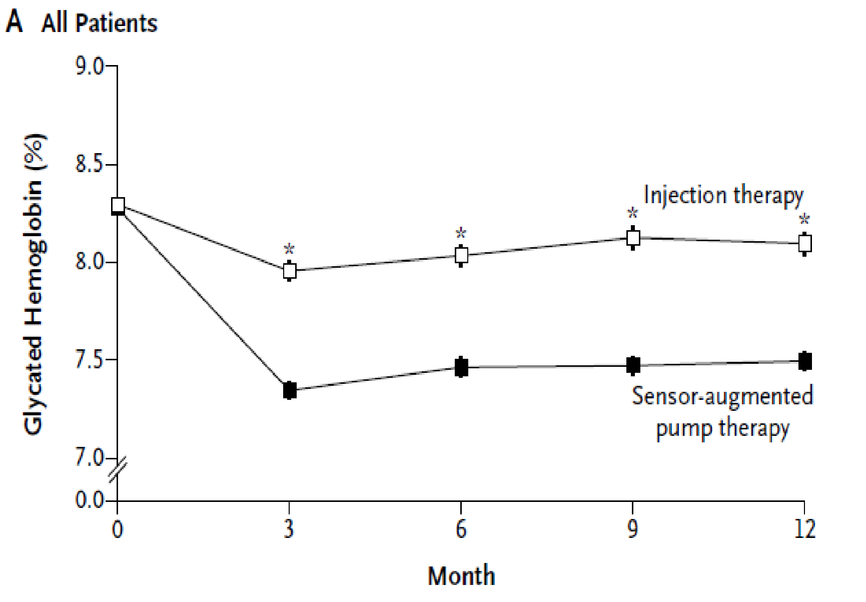
Effectiveness of Sensor-Augmented Insulin-Pump Therapy in Type 1 Diabetes

Richard M. Bergenstal, M.D., William V. Tamborlane, M.D.,
Andrew Ahmann, M.D., John B. Buse, M.D., Ph.D., George Dailey, M.D.,
Stephen N. Davis, M.D., Carol Joyce, M.D., Tim Peoples, M.A.,
Bruce A. Perkins, M.D., M.P.H., John B. Welsh, M.D., Ph.D.,
Steven M. Willi, M.D., and Michael A. Wood, M.D., for the STAR 3 Study Group*



Variable	All Patients		
	Sensor-Augmented Pump Therapy (N=247)	Injection Therapy (N=248)	P Value
Severe hypoglycemia			
No. of events	32	27	0.58
No. of patients	21	17	
Rate per 100 person-yr	13.31	13.48	0.84

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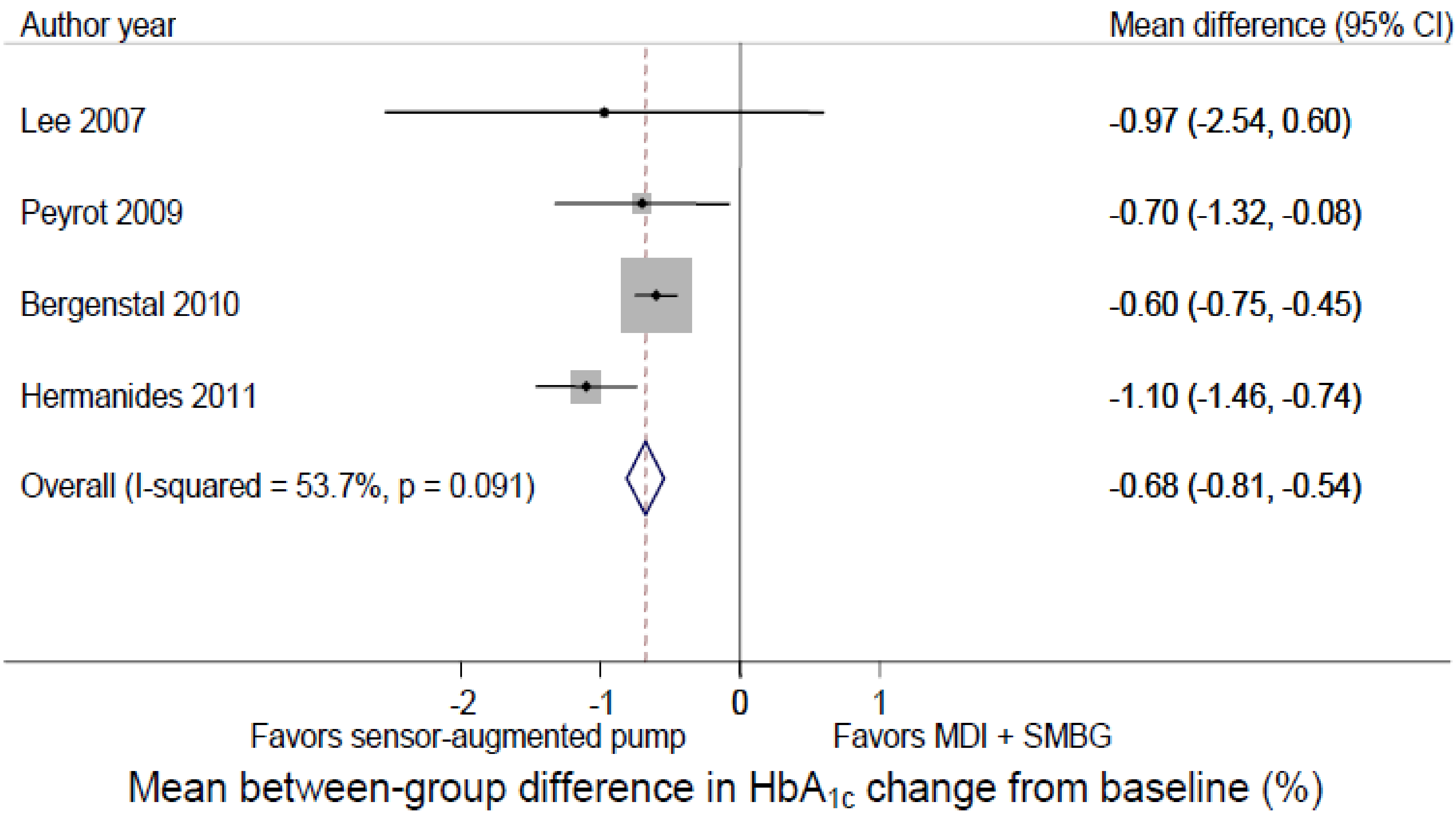
N Eng J Med 363: 311-320, 2010.

Figure 35. Between-group difference between sensor-augmented pumps and MDI/SMBG in how HbA_{1c} changed from baseline among patients with type 1 diabetes



No difference in mild or severe hypoglycaemia

Golden S. Agency for Healthcare Research and Quality Comparative Effectiveness Review Number 57 Report 12-EHC036-EF, 2012.

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Threshold-Based Insulin-Pump Interruption for Reduction of Hypoglycemia

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Suspends insulin delivery below a pre-set threshold only if the patient does not intervene and restarts after two hours

N Engl J Med 369:224-32, 2013

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Low Alerts: Hypoglycemia, Predictive, Suspend

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Inclusion Criteria

- 16 to 70 years of age
- Type 1 diabetes of at least 2 years' duration
- Glycated hemoglobin value of 5.8% to 10.0%
- Used insulin-pump therapy for more than 6 months
- During run-in:
  - Wore sensors ≥ **80%** of the time
  - Had at **least two nocturnal hypoglycemic** events for > 20 consecutive minutes in the absence of a pump interaction

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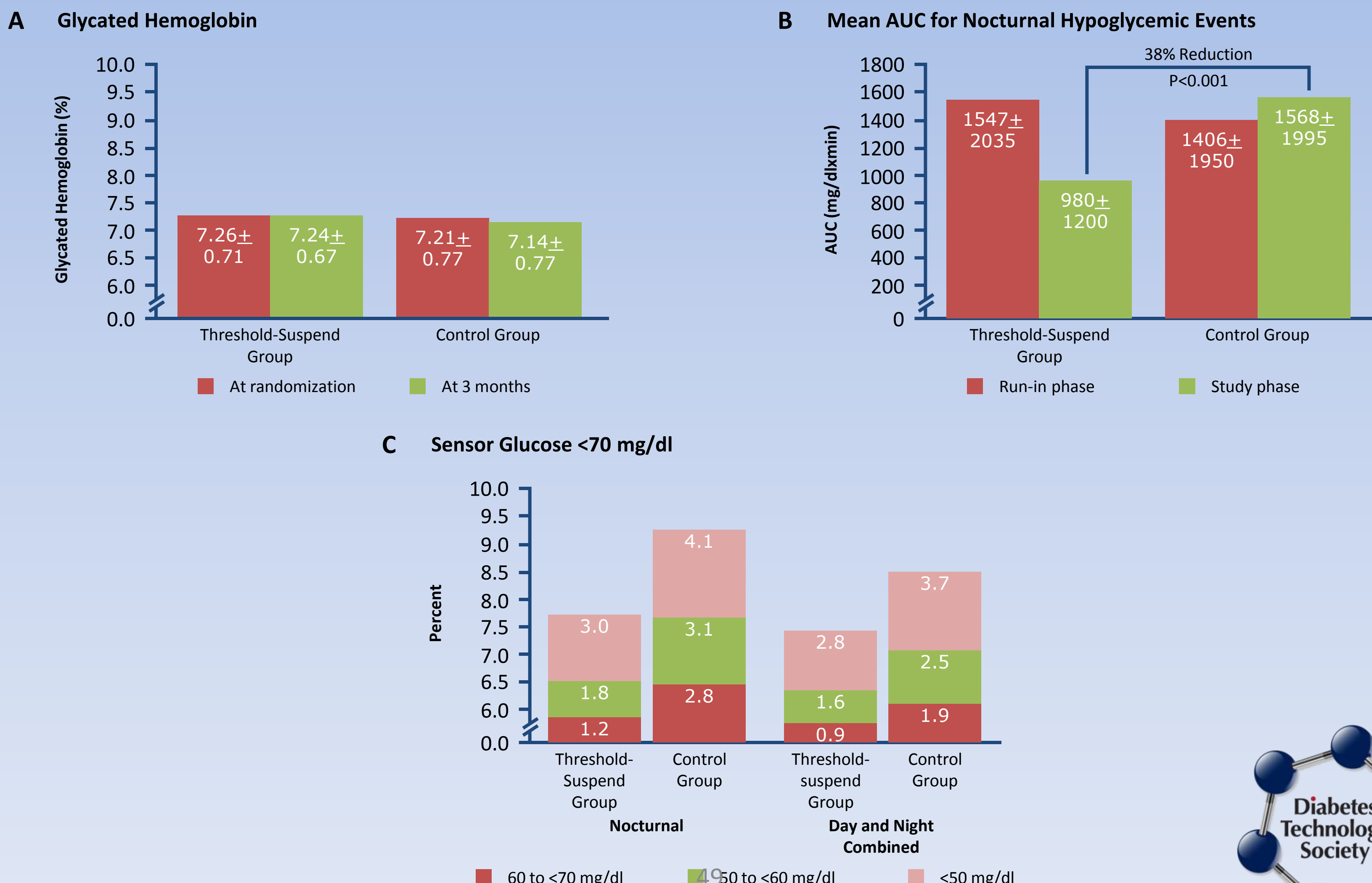
Table 1. Baseline Characteristics of the Patients Who Underwent Randomization.*

Characteristic	Threshold-Suspend Group (N=121)	Control Group (N=126)
Age (yr)		
Mean	41.6±12.8	44.8±13.8
Range	16–69	16–70
Duration of diabetes (yr)	27.1±12.5	26.7±12.7
Male sex (%)	38.0	39.7
Weight (kg)	79.6±15.9	79.1±15.1
Body-mass index†	27.6±4.7	27.1±4.3
Glycated hemoglobin at randomization (%)	7.26±0.71	7.21±0.77

* Plus–minus values are means ±SD. There were no significant differences between the groups.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.



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A Randomized Trial of a Home System to Reduce Nocturnal Hypoglycemia in Type 1 Diabetes

Diabetes Care 2014;37:1885–1891 | DOI: 10.2337/dc13-2159

*David M. Maahs,[1] Peter Calhoun,[2] Bruce A. Buckingham,[3] H. Peter Chase,[1] Irene Hramiak,[4] John Lum,[2] Fraser Cameron,[5] B. Wayne Bequette,[5] Tandy Aye,[3] Terri Paul,[4] Robert Slover,[1] R. Paul Wadwa,[1] Darrell M. Wilson,[3] Craig Kollman,[2] and Roy W. Beck,[2] for the In Home Closed Loop Study Group**

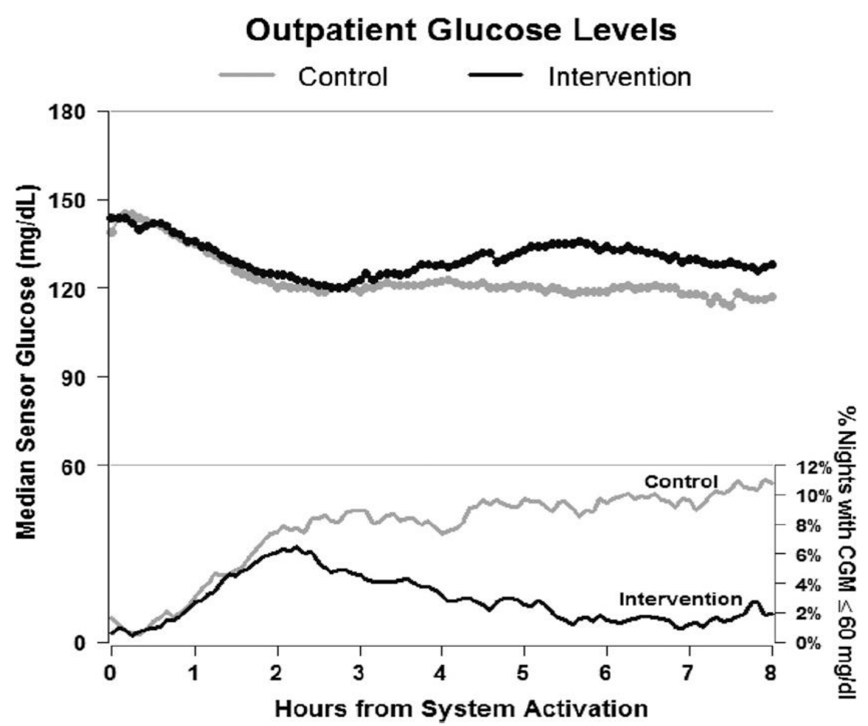
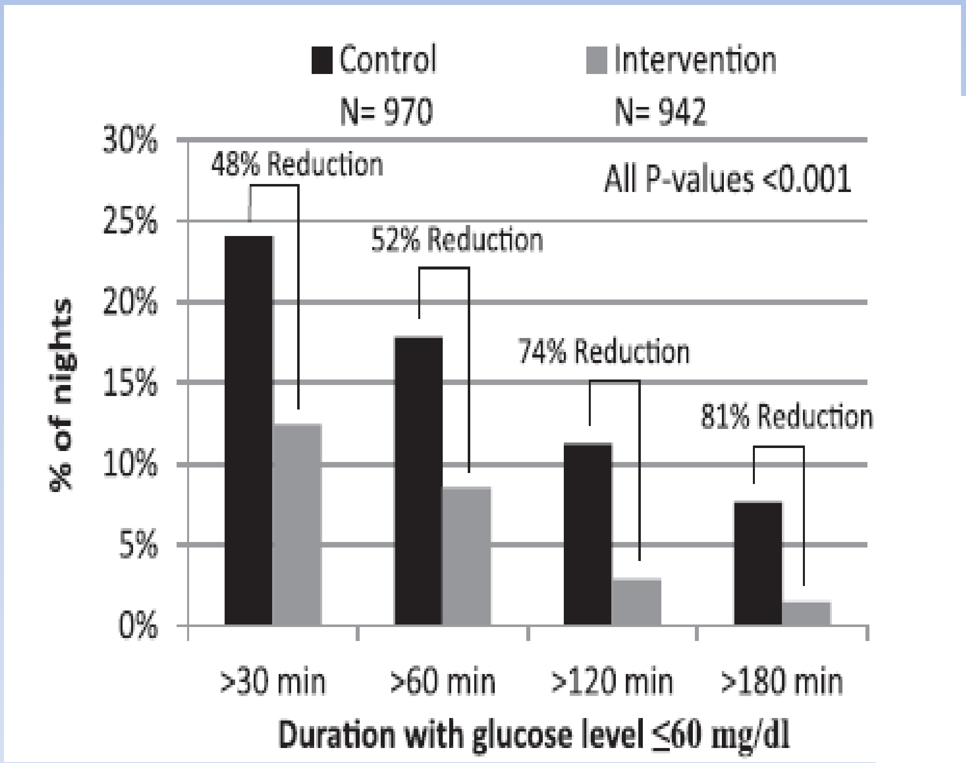
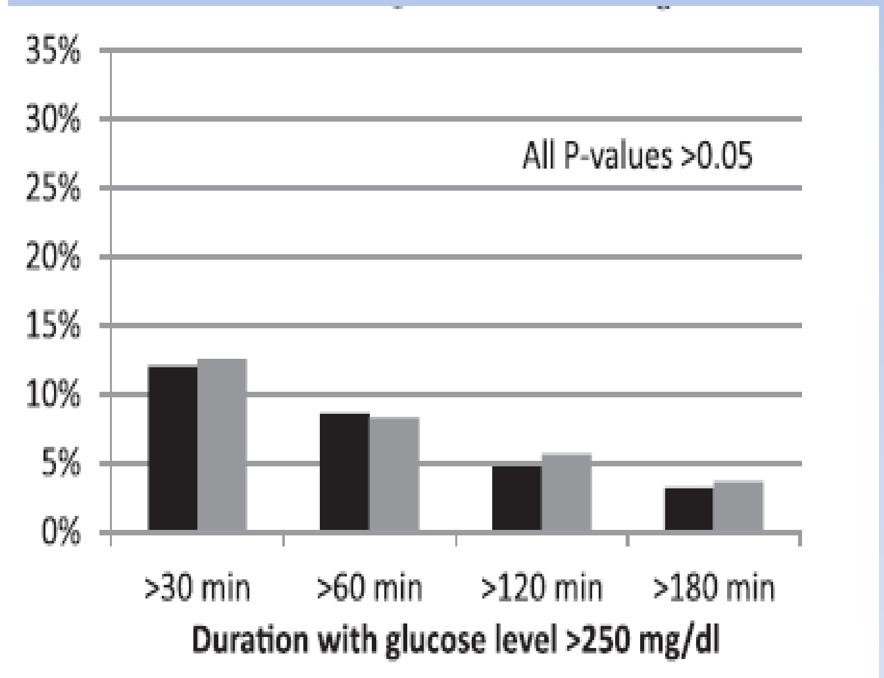


Figure 3—Sensor glucose levels overnight. The *top portion* of the figure shows the median glucose level across all nights in each treatment arm. The *bottom portion* of the figure shows the frequency of glucose level ≤60 mg/dL across all nights in each treatment arm.

Predictive Low Glucose Suspend System

Duration of Overnight Hypoglycaemia (L) and Hyperglycemia (R)





Clinical Use

- Improve overall glycemic control
  - YES
- Reduce number of hypoglycemic events
  - Not yet proven
- Reduce glycemic variability
  - YES
- Empowers and educates patients in diabetes management
  - YES
- Use in partially/fully closed-loop (artificial pancreas)
  - YES/COMING SOON

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Thanks for Your Attention

Any Questions?

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