DRIVING CHANGE
& INNOVATION

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The Diamond Study:

Continuous Glucose Monitoring In Patients on Mulitple Daily Insulin Injections

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Disclosure Statement
Richard M. Bergenstal, MD

RMB has participated in *clinical research, a scientific advisory board or* served as a *consultant* for:

- Eli Lilly
- Novo Nordisk
- Sanofi
- Hygieia
- T1D Exchange (Helmsley Charitable Trust)
- Roche Diabetes Care
- J&J
- Abbott Diabetes Care
- Bayer Diabetes
- Medtronic Diabetes Care
- DexCom
- Astra Zeneca
- Merck
- Takeda

RMB inherited Merck stock and is a volunteer for ADA & JDRF

RMB's employer, non-profit Park Nicollet Institute, contracts for his services and **he receives no personal income from these activities**

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How About Patients using MDI

There are 6 million adult insulin users in the United States and > 5 million have T2D- few are on pumps

60-70% of adults with T1D use MDI

Here is what we know…

- Will injectors use a wearable technology?
- Will they be willing/able to make changes to obtain glycemic benefit?

CDC- National Diabetes Statistics Report, 2014

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4

Background on Insulin Treatment of Diabetes & CGM

- Most insulin treated patients with T1D & T2D have glucose levels above the target goal
- CGM offers improved glucose control as well as reduction of hypoglycemia and glucose variability
- Globally, most basal/bolus insulin is delivered by multiple daily injections
- Most previous CGM clinic research has addressed T1D patients using insulin pumps
- Information is needed to identify the patients who benefit from CGM including those on MDI

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CGM Benefits Diverse Users

- JDRF
- JDRF well-controlled
- EU Hypo reduction study
- STAR 3

Predominantly Pump Users

- SWITCH Study
- Gold
- **Diamond T1D cohort**
- **Diamond T2D cohort**

MDI

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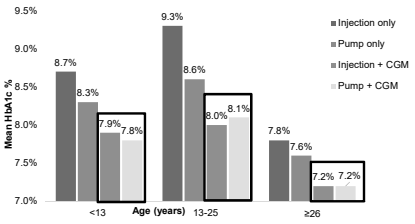
CGM Users Have Lower HbA1c Regardless of Insulin Delivery Method



Miller KM, et al. *Diabetes Care*. 2015;38:971-978.

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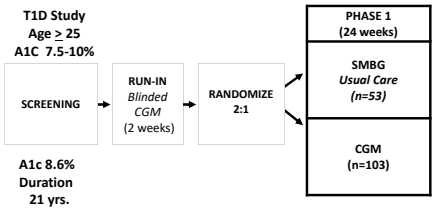
Study Design for DIaMonD (phase 1)



Primary outcome difference in mean HbA1c between treatment groups

Beck RW et al., *JAMA*. 2017;317(4):371-378.

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Study Designed to Limit Encounters to Allow Translation into Clinical Practice

- Weeks 1-3: Device Initiation
  - **CGM group:** clinic visit at Week 1 to troubleshoot device/use issues
  - **Both groups:** phone calls at Weeks 2 & 3
- Weeks 4 & 12: Diabetes Management Visits
  - Both groups: clinicians review glucose data & insulin adjustments *per usual care*
  - **Usual Care group:** clinic visits for blinded CGM placement at Weeks 11 & 23
- Week 24: End of Phase 1

29 clinical sites from across North America.

Beck RW et al., *JAMA*. 2017;317(4):371-378.

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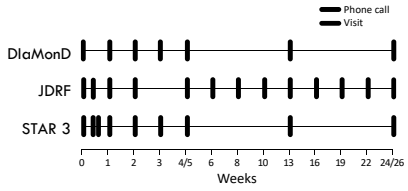
Encounter Frequency - DIaMonD vs JDRF & STAR 3



Beck RW et al., *JAMA*. 2017;317(4):371-378.
Bergenstal RM, et al. *N Engl J Med*. 2010;363:311-320.
JDRF CGM Study Group. *N Engl J Med*. 2008;359:1464-1476.

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DIaMond Type 1 Phase 1 Results

Beck RW et al., *JAMA*. 2017;317(4):371-378.

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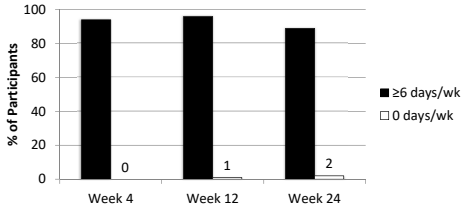
CGM Usage ≥6 Days/Week



Beck RW et al., *JAMA*. 2017;317(4):371-378.

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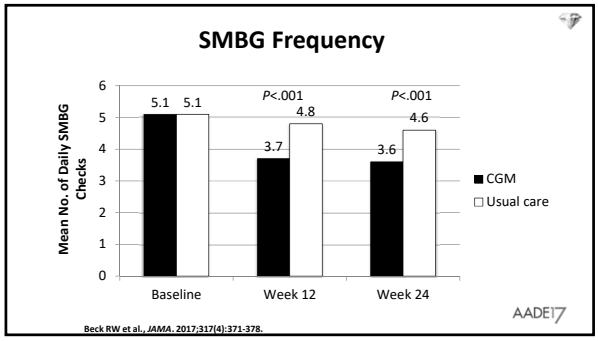
SMBG Frequency
Mean No. of Daily SMBG Checks
5.1
5.1
P<.001
3.7
4.8
P<.001
3.6
4.6
CGM
Usual care
Baseline
Week 12
Week 24
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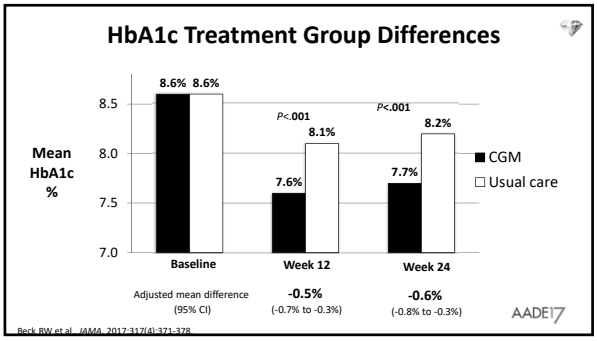
Beck RW et al., JAMA. 2017;317(4):371-378.


HbA1c Treatment Group Differences
Mean HbA1c %
8.6%
8.6%
P<.001
7.6%
8.1%
P<.001
7.7%
8.2%
CGM
Usual care
Baseline
Week 12
Week 24
Adjusted mean difference (95% CI)
-0.5% (-0.7% to -0.3%)
-0.6% (-0.8% to -0.3%)
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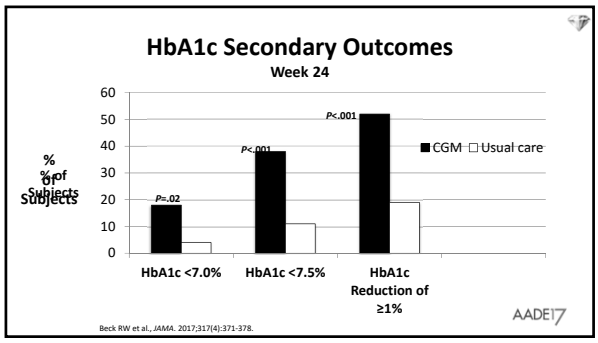
Beck RW et al. JAMA. 2017;317(4):371-378.


HbA1c Secondary Outcomes
Week 24
% of Subjects
P=.02
P<.001
P<.001
CGM
Usual care
HbA1c <7.0%
HbA1c <7.5%
HbA1c Reduction of ≥1%
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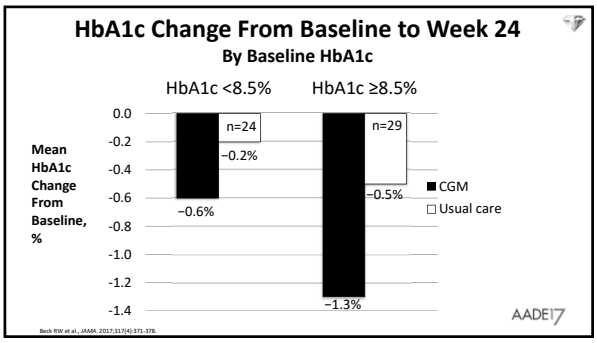
Beck RW et al., JAMA. 2017;317(4):371-378.


HbA1c Change From Baseline to Week 24
By Baseline HbA1c
HbA1c <8.5%
HbA1c ≥8.5%
Mean HbA1c Change From Baseline, %
n=24
−0.2%
−0.6%
n=29
−0.5%
−1.3%
CGM
Usual care
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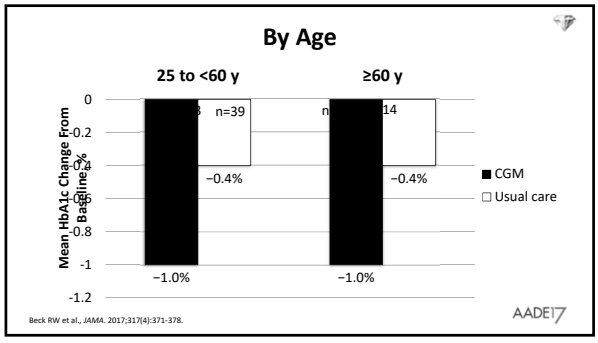
Beck RW et al., JAMA. 2017;317(4):371-378.


By Age
25 to <60 y
≥60 y
Mean HbA1c Change From Baseline, %
n=39
−0.4%
−1.0%
−0.4%
−1.0%
CGM
Usual care
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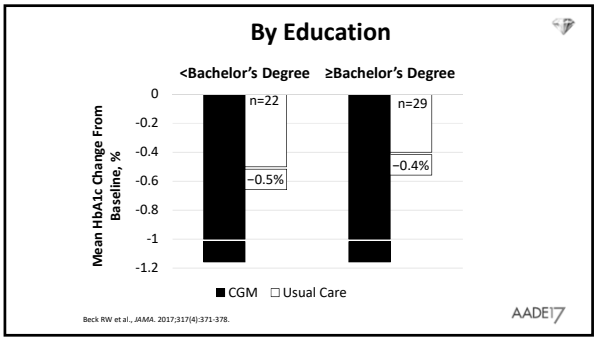
Beck RW et al., JAMA. 2017;317(4):371-378.


By Education
<Bachelor's Degree
≥Bachelor's Degree
Mean HbA1c Change From Baseline, %
n=22
−0.5%
n=29
−0.4%
CGM
Usual Care
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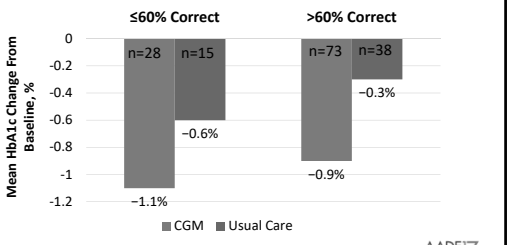
Beck RW et al., JAMA. 2017;317(4):371-378.

By Diabetes Numeracy Test



Beck RW et al., *JAMA*. 2017;317(4):371-378.

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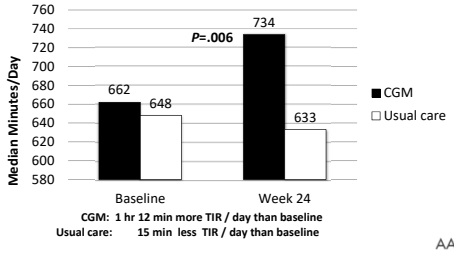
CGM-Measured Time-in-Range 70-180 mg/dL (3.9-10mmol/L)



CGM: 1 hr 12 min more TIR / day than baseline
Usual care: 15 min less TIR / day than baseline

Beck RW et al., *JAMA*. 2017;317(4):371-378.

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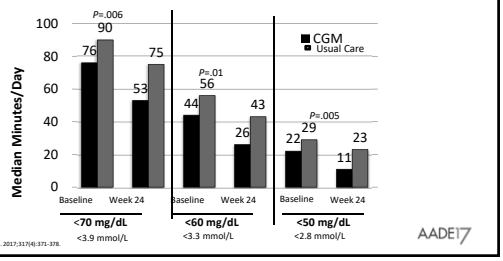
CGM-Measured Hypoglycemia – <50 to <70mg/dL (2.8-3.9 mmol/L)



Beck RW et al., *JAMA*. 2017;317(4):371-378.

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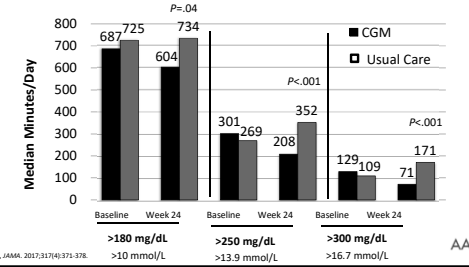
CGM-Measured Hyperglycemia – >180 to >300 mg/dL (10 - 16.7 mmol/L)



Beck RW et al., *JAMA*. 2017;317(4):371-378.

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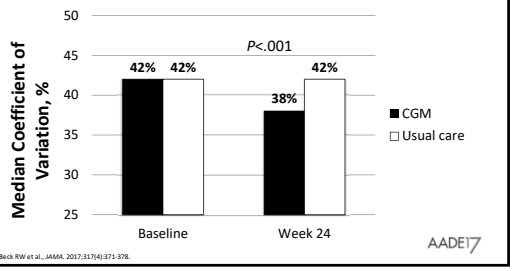
Glucose Variability



Beck RW et al., *JAMA*. 2017;317(4):371-378.

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DIaMonD Trial Phase 2 Extension: Adding CSII

A Randomized Trial Comparing:
CSII vs MDI in T1D Patients CGM

Beck RW et al. Initiation of Insulin Pump in Adults with T1D on MDI… Lancet Diabetes and Endocrinology July 12, 2017 epub ahead of print

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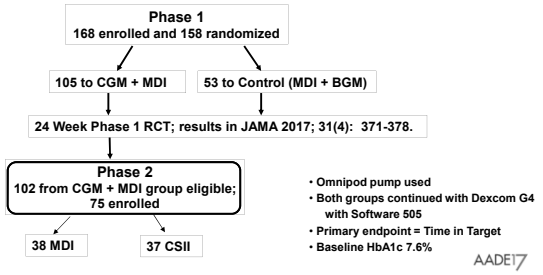
DIaMonD Phase 2 Methodology



- Omnipod pump used
- Both groups continued with Dexcom G4 with Software 505
- Primary endpoint = Time in Target
- Baseline HbA1c 7.6%

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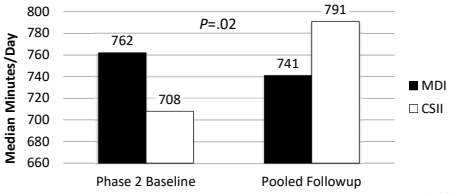
CGM-Measured Time-in-Range 70-180 mg/dL (3.9-10mmol/L) – Phase 2



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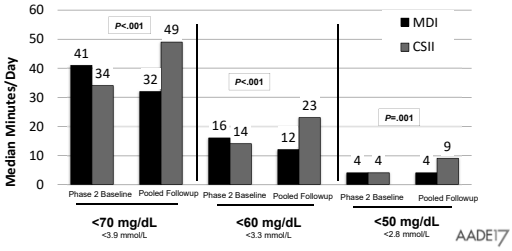
CGM-Measured Hypoglycemia – 50-70mg/dL (2.8-3.9 mmol/L) – Phase 2



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DIaMonD Phase 2 Results

- CGM adherence was excellent at 96% wear time of ≥6 days/week
- Time in target (70-180mg/dL) increased by 78 minutes with CSII
  - Time in hyperglycemia decreased in CSII group by ~ 1 hour
  - Time in hypoglycemia increased in CSII group
- HbA1c change was not statistically different between groups
  - MDI group increased HbA1c by 0.1% and CSII group by 0.3%
- Daily insulin dose decreased with CSII, yet increase in boluses/day
- Adverse events
  - MDI group – 1 severe hypoglycemia episode
  - CSII group – 1 DKA episode and 1 hospitalization due to hyperglycemia without DKA

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The Impact of Continuous Glucose Monitoring on Markers of Quality of Life in Adults With Type 1 Diabetes: Further Findings From the DIAMOND Randomized Clinical Trial

William H. Polonsky,[1,2] Danielle Hessler,[3] Katrina J. Ruedy,[4] and Roy W. Beck,[4] for the DIAMOND Study Group

June 2017

Diabetes Care 2017;40:736–741 | https://doi.org/10.2337/dc17-0133

CONCLUSIONS

CGM contributes to significant improvement in diabetes-specific QOL (i.e., diabetes distress, hypoglycemic confidence) in adults with T1D, but not with QOL measures not specific to diabetes (i.e., well-being, health status). CGM satisfaction was associated with most of the QOL outcomes but not with glycemic outcomes.

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DIaMonD Study: Multiple Daily Injections and Continuous Glucose Monitoring in Type 2 Diabetes

Beck RW et al. CGM vs Usual Care in T2D Patients on MDI: A Randomized Trial In Press: Annals Internal Medicine 2017

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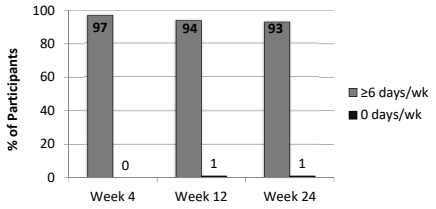
Baseline Characteristics- *Typical of T2D Population*

Characteristic	All Patients (n=158)
Baseline HbA1c Mean age	8.5% 60 ± 10 years
Mean T2D duration	18 years
Mean SMBG	3/day
Mean BMI	36
≥ 1 severe hypo / DKA in past 12 months	2% / 0%
C-Peptide ≥ 0.2 ng/ml	92%

31

CGM Usage ≥6 Days/Week In T2 MDI Subjects



93% were using CGM ≥ 6 days a week in month 6

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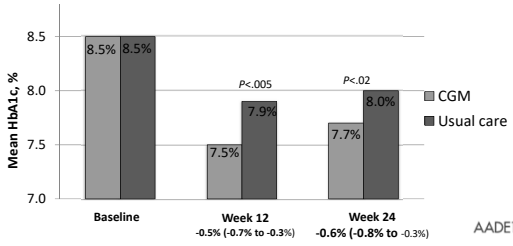
32

HbA1c Treatment Group Differences – T2 Subjects on MDI



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33

HbA1c Outcomes – T2 Subjects on MDI

	24 Weeks		
Secondary Outcomes	**CGM Group (N=79)** *n (%)*	**Control Group (N=79)** *n (%)*	**Adjusted Odds Ratio (95% Confidence Interval) [*P* value]**
Reduction in HbA1c ≥0.5%	56 (**73%**)	37 (**49%**)	2.7 (1.3 to 5.5) [0.009]
Reduction in HbA1c ≥1%	30 (**39%**)	21 (**28%**)	1.6 (0.7 to 3.4) [0.23]
Relative reduction in HbA1c ≥10%	40 (**52%**)	24 (**32%**)	2.2 (1.1 to 4.4) [0.03]

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34

Effect of Baseline HbA1c on CGM Benefit with T2 MDI Subjects

Baseline HbA1c	Change in HbA1c From Baseline		*P* value
	CGM Group	Usual Care Group	
≥ 7.5%	**-0.9%** (n=79)	**-0.5%** (n=79)	0.02
≥ 8.0%	**-0.9%** (n=63)	**-0.6%** (n=57)	0.05
≥8.5%	**-1.1%** (n=39)	**-0.7%** (n=39)	0.02
≥ 9.0%	**-1.4%** (n=17)	**-0.7%** (n=21)	0.04

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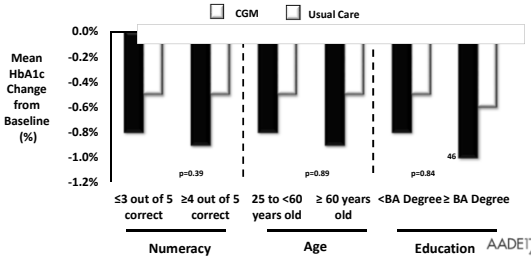
Diamond Study – Similar HbA1c Reduction Observed in T2 Subsets



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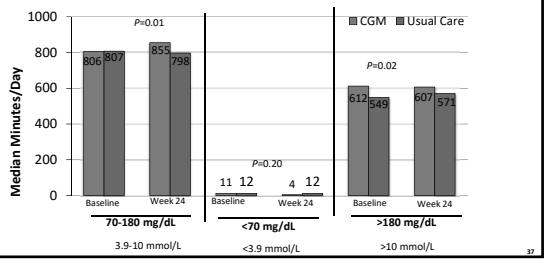
Glycemic Results with T2D MDI and CGM Subjects: Minutes/Day



Insulin and Medication Changes

	Baseline		24 Weeks		
	CGM Group (N=79)	Usual Care Group (N=79)	CGM Group (N=77)	Usual Care Group (N=75)	*P* value
Total Daily Insulin Dose *units/kg/day (mean ± SD)*	**1.2** ± 0.6	1.0 ± 0.5	**1.3** ± 0.7	1.1 ± 0.5	
Change in Total Daily Insulin Dose *(mean ± SD)*			**+0.1** ± 0.3	0.0 ± 0.3	0.06
% Using Non-insulin Glucose Lowering Meds	71%	66%	65%	64%	
N of Participants Adding Non-insulin Glucose Lowering Meds			2	2	

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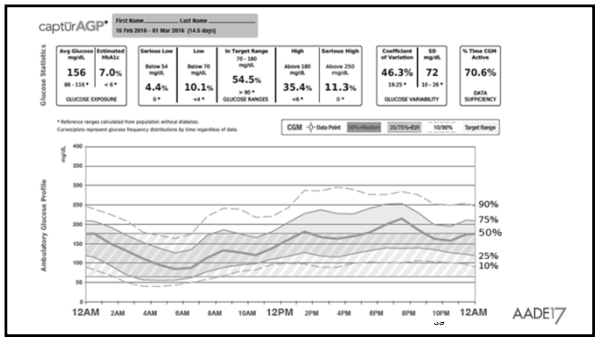
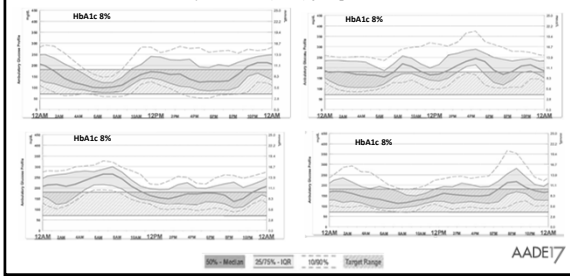
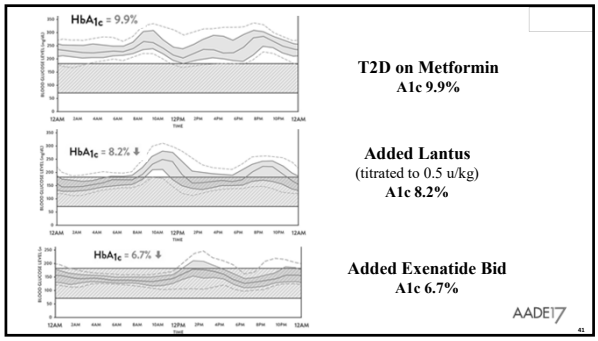


4 patients with T1D on MDI – HbA1c at a central lab of 8.0%

14 days of CGM (AGP) just prior to the HbA1c





DIaMonD Trial In Older Adults with T1D or T2D

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In Older Adults, Use of CGM Significantly Improved HbA1c, Time Spent in Target and Glycemic Variability

	CGM			Control			P value
	Baseline (N=63)	12 Weeks (N=61)	24 Weeks (N=58)	Baseline (N=53)	12 Weeks (N=52)	24 Weeks (N=50)	
Mean glucose, mg/dL	175±25	167±27	168±29	179±30	178±28	180±28	0.01
Glycemic Variability, Coefficient of Variation %	34 (28, 42)	33 (28, 37)	31 (28, 36)	34 (29, 38)	33 (28, 38)	33 (27, 39)	0.02
Time spent: 70-180 mg/dL, min/day	796±236	892±256	889±251	753±253	767±265	732±252	<0.001
Time spent: >250 mg/dL, min/day	172 (83, 281)	93 (30, 180)	89 (37, 208)	208 (112, 294)	180 (81, 251)	179 (83, 316)	0.006
Time spent: <60 mg/dL, min/day	10 (1, 38)	4 (0, 15)	3 (0, 15)	8 (1, 23)	4 (0, 27)	4 (0, 24)	0.11

97% of the 61 older adults patients wore CGM >6 days/week in 6 months.

Ruedy K et al. Journal of Diabetes Science and Technology. May, 2017.

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Summary: CGM in MDI Users in DIaMonD

- High adherence to CGM for type 1 and type 2
- HbA1c significantly reduced compared with control group
  - Reduced 0.6% in type 1 cohort
  - Reduced 0.3% in type 2 cohort
  - Consistent reduction in all sub-groups
  - Benefit appeared larger at highest HbA1c
- In T1DM time in range increased, time hypoglycemic or hyperglycemic decreased
- In T2DM time in range increased and time hyperglycemic decreased

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44

Conclusions and Comments Regarding What the DIaMonD Study Has Shown Us

- T1D & T2D patients on MDI who have not been exposed to technology:
  - Will embrace and use CGM consistently
  - Gain significant benefit from CGM
- These trials demonstrate basic expectations
  - Individualization of provider involvement is likely to improve results
  - Optimal incorporation of education in this process warrants added clinical research

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Expanded indication for the use of CMG

- CGM may become more widely used following the **Medicare approval** of a new category called: **"Therapeutic CMG"** which applies if:
  - The beneficiary has diabetes mellitus; **and**,
  - The beneficiary has been using a home blood glucose monitor (BGM) and performing frequent (four or more times a day) BGM testing; **and**,
  - The beneficiary is insulin-treated with multiple daily injections (MDI) of insulin or a continuous subcutaneous insulin infusion (CSII) pump; **and**,
  - The beneficiary's insulin treatment regimen requires frequent adjustment by the beneficiary on the basis of therapeutic CGM testing results.

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Acknowledgments

Steering Committee

Katrina Ruedy, MPSH & Roy Beck, MD, PhD –
Jaeb Center for Health Research

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OHSU

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International Diabetes Center

Howard Wolpert, MD –
Joslin Diabetes Center

Bill Polonsky, PhD –
Behavioral Diabetes Institute

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Jaeb Center for Health Research

HbA1c Central Lab

Santica Marcovina, PhD, ScD & Jessica Harting –
NW Lipid Research Laboratories

29 clinical study sites

TO ALL STUDY PARTICIPANTS!!

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47