Park Nicollet®
International Diabetes Center

The Role of CGM in the *Wide & Narrow* Spectrum of Diabetes

Richard M. Bergenstal, MD
International Diabetes Center
HealthPartners Institute
Minneapolis, MN

Disclosures: Richard M. Bergenstal, MD

I have no personal financial disclosures

- My employer, the non-profit HealthPartners Institute, contracts for my services, and I receive no personal income from the following activities:
  - I have participated in clinical research, been a member of a scientific advisory board, and served as a consultant for:
    - Abbott Diabetes Care, Ascensia, CeQur, Dexcom, Eli Lilly, Hygieia, Insulet, Johnson & Johnson, Medtronic, Novo Nordisk, Onduo, Roche, Sanofi, united Healthcare AND Zealand
  - My institution receives NIH/NIDDK funding: T1D (DCCT/EDIC) & T2D (GRADE) and Technology (SBIR with Hygieia) and automated insulin delivery systems (FLAIR)

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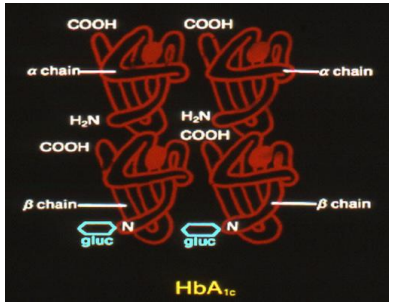
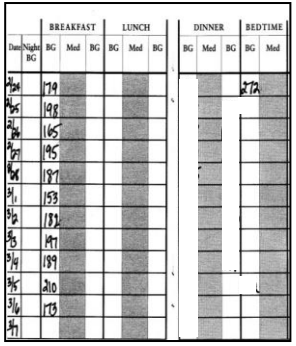
40-50 yr.

Hemoglobin A1c



40-50 yr.

Fingerstick Glucose Testing



15-20 yr.

Continuous Glucose Monitoring (CGM)

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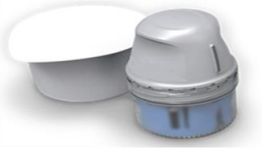
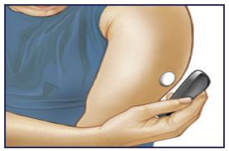
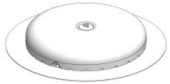
CGM Devices/Systems

Dexcom G6 and G6 Pro





Abbott FreeStyle Libre, Libre 2 and Libre Pro

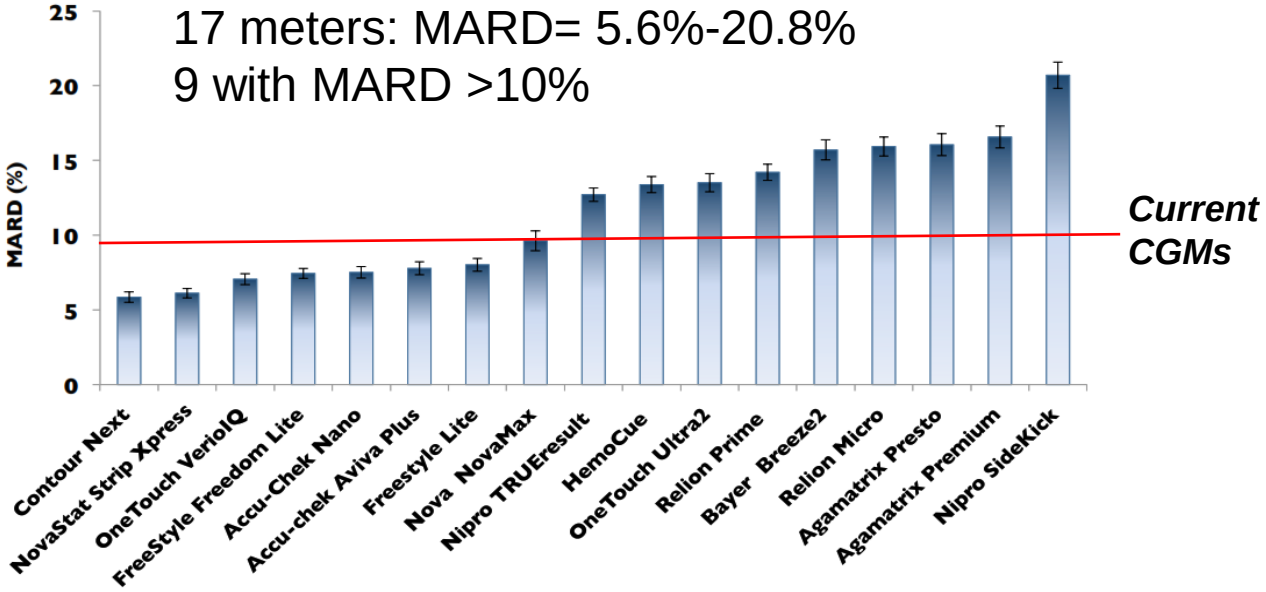


Eversense CGM (90 day) (Eversense E3-180 day system FDA approved)

Medtronic Guardian Sensor 3/ Guardian Connect CGM (iPro2)

Is CGM **accurate** enough?

Is SMBG much more accurate than CGM?



FDA U.S. FOOD & DRUG ADMINISTRATION

March 27, 2018 (iCGM)

FDA authorizes first fully interoperable CGM system

Ekhlaspour et al, JDST 2017

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THE LANCET

Comment

Continuous glucose monitoring: transforming diabetes management step by step

Richard M Bergenstal
International Diabetes Center at Park Nicollet

Wide and Narrow
Impact on
Diabetes Management

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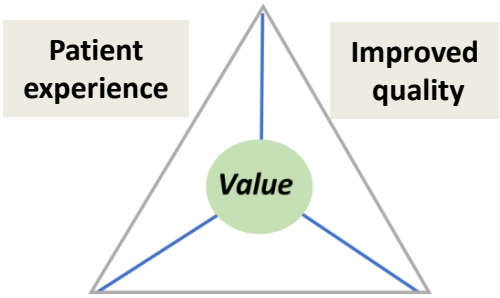
Published online February 16, 2018

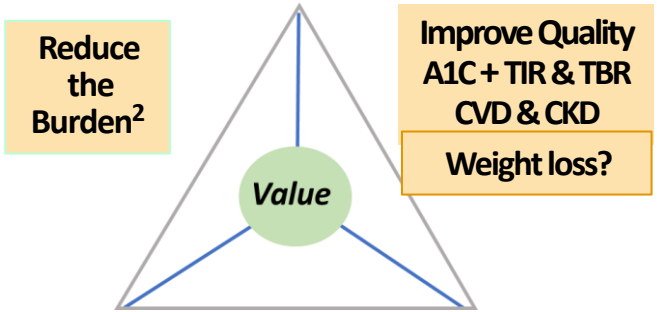
Triple Aim to Improve Healthcare Value (outcomes/cost)

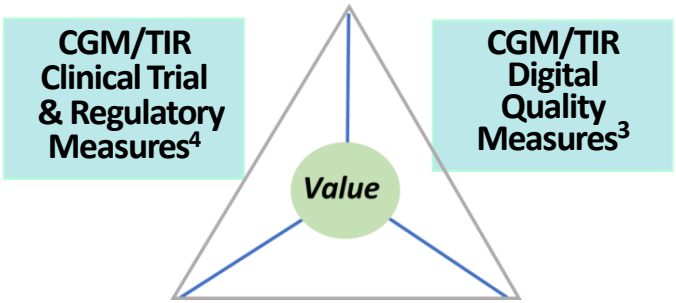
Healthcare *triple aim*[1]

Diabetes *triple aim*

CGM *triple aim*







[1]Berwick D et al. *Health Affairs* 2008

[2] Reduce diabetes distress
Patient feels listened to

[3] TIR/TBR; GMI; Diabetes distress

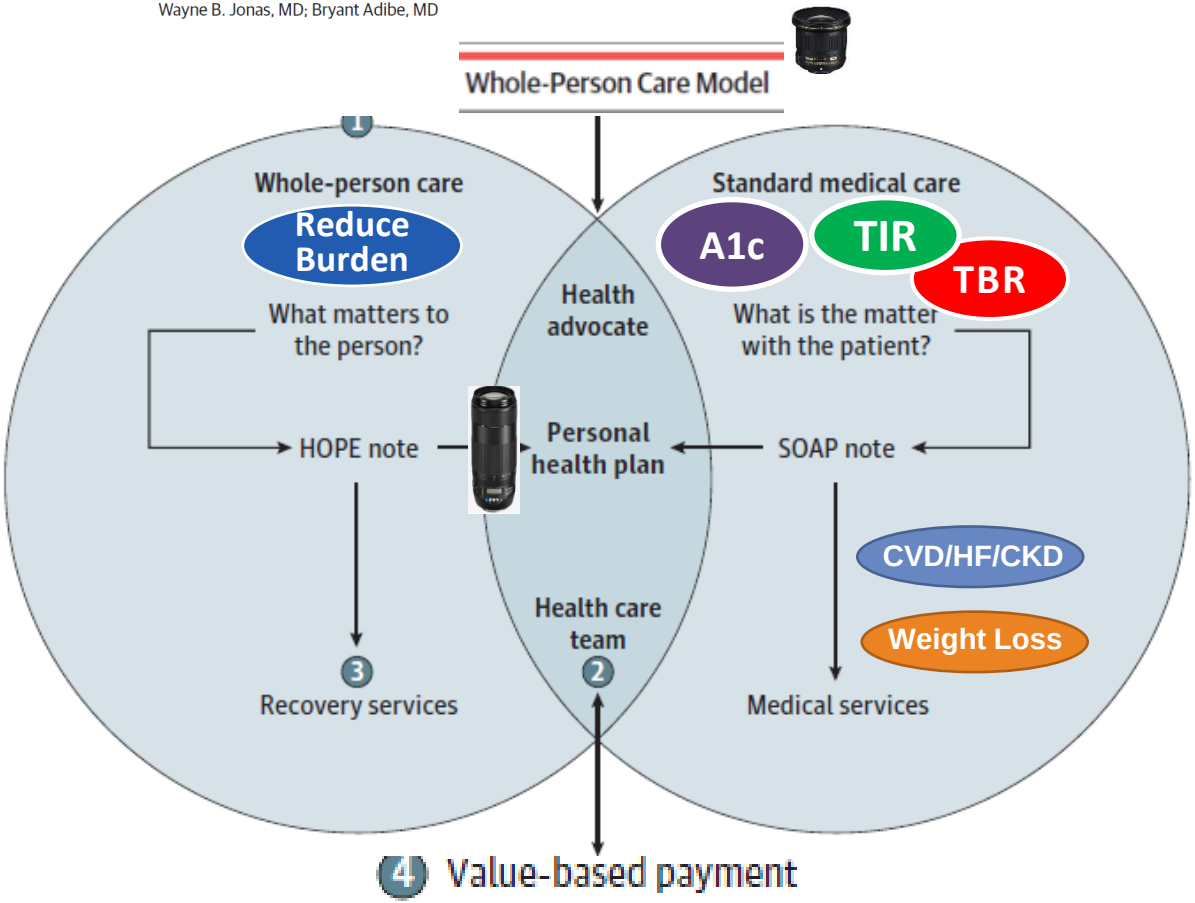
[4] CGM data in drug package insert

JAMA Health Forum™

Viewpoint

An Integrated Framework for Achieving National Health Goals

Wayne B. Jonas, MD; Bryant Adibe, MD



JAMA Health Forum.
2022;3(5):e221109
May 20, 2022

DCCT (1983-1993): Relationship of HbA1c to Risk of Microvascular Complications

The New England
Journal of Medicine

Volume 329 SEPTEMBER 30, 1993 Number 14

THE EFFECT OF INTENSIVE TREATMENT OF DIABETES ON THE DEVELOPMENT AND PROGRESSION OF LONG-TERM COMPLICATIONS IN INSULIN-DEPENDENT DIABETES MELLITUS

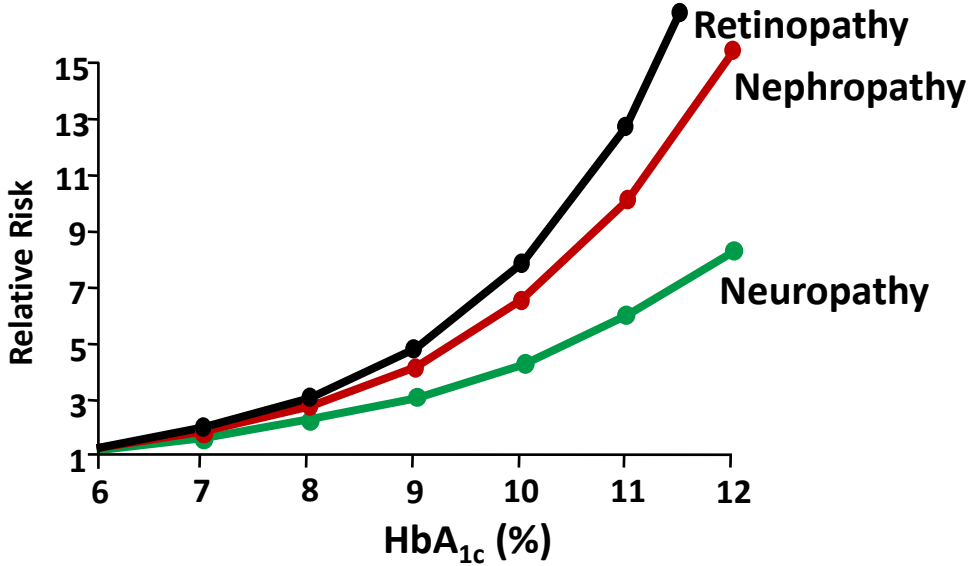
THE DIABETES CONTROL AND COMPLICATIONS TRIAL RESEARCH GROUP*

Abstract *Background.* Long-term microvascular and neurologic complications cause major morbidity and mortality in patients with insulin-dependent diabetes mellitus (IDDM). We examined whether intensive treatment with the goal of maintaining blood glucose concentrations close to the normal range could decrease the frequency and severity of these complications.

Methods. A total of 1441 patients with IDDM — 726 with no retinopathy at base line (the primary-prevention cohort) and 715 with mild retinopathy (the secondary-intervention cohort) were randomly assigned to intensive therapy administered either with an external insulin pump or by three or more daily insulin injections and guided by frequent blood glucose monitoring or to conventional therapy with one or two daily insulin injections. The patients were followed for a mean of 6.5 ye[illegible] ance and progression of retinopathy and other complications were assessed regularly.

Results. In the primary-prevention cohort, intensive therapy reduced the adjusted mean risk for the development of retinopathy by 76 percent (95 percent confidence interval, 62 to 85 percent), as compared with conventional therapy. In the secondary-intervention cohort, intensive therapy slowed the progression of retinopathy by 54 percent (95 percent confidence interval, 39 to 66 percent) and reduced the development of proliferative or severe nonproliferative retinopathy by 47 percent (95 percent confidence interval, 14 to 67 percent). In the two cohorts combined, intensive therapy reduced the occurrence of microalbuminuria (urinary albumin excretion of ≥40 mg per 24 hours) by 39 percent (95 percent confidence interval, 21 to 52 percent), that of albuminuria (urinary albumin excretion of ≥300 mg per 24 hours) by 54 percent (95 percent confidence interval, 19 to 74 percent), and that of clinical neuropathy by 60 percent (95 percent confidence interval, 38 to 74 percent). The chief adverse event associ[illegible] crease in severe hypoglycemia.

Conclusions. Intensive therapy effectively delays the onset and slows the progression of diabetic retinopathy, nephropathy, and neuropathy in patients with IDDM. (N Engl J Med 1993;329:977-86.)

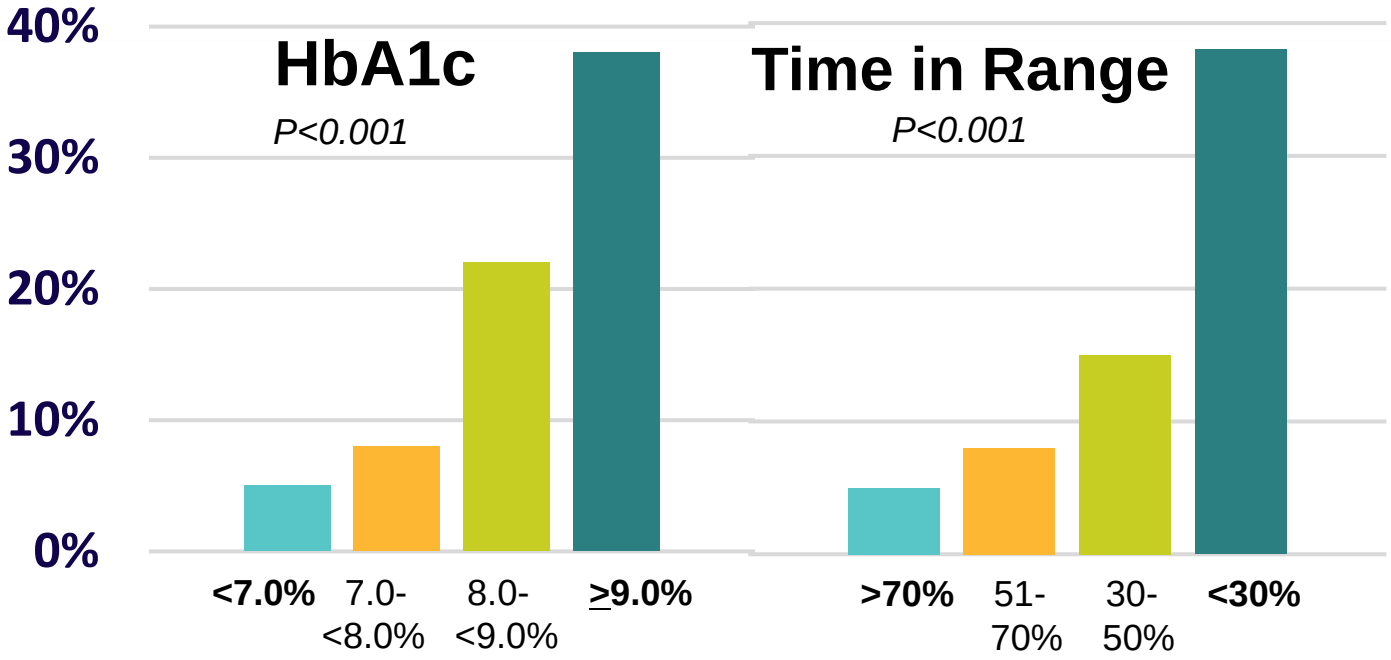


End DCCT 1993

"HbA1c Era"

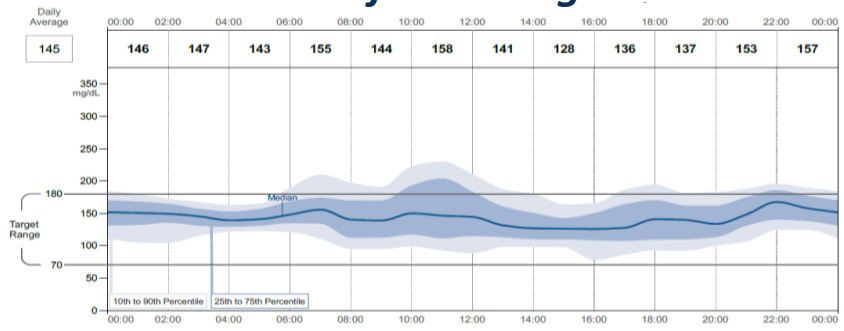
2021

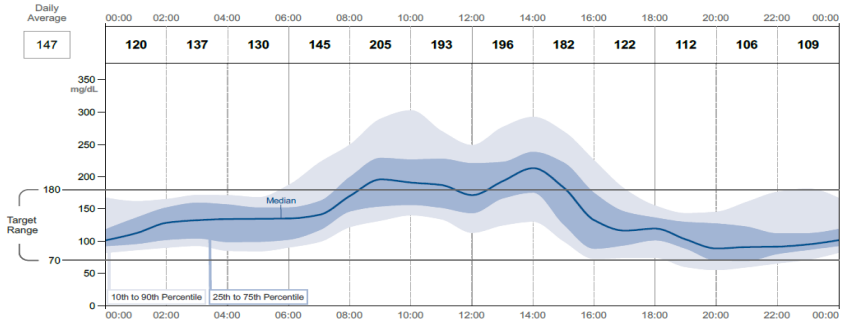
Retinopathy Progression According to HbA1c and Time in Range

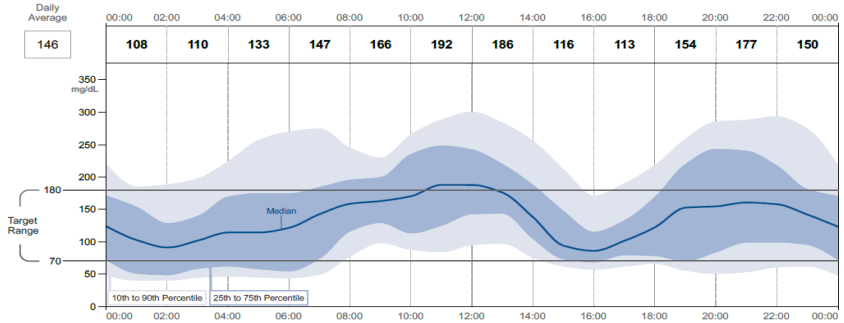


Retinopathy progression rate increased by:
32% for each 0.5% higher HbA1c and for 6.2 percentage points lower TIR

A1C or CGM for Management?







A1C (%)	% Time Hypo (< 70 mg/dL)	% Time TIR (70-180 mg/dL)
6.7%	1%	83%
6.7%	6%	69%
6.7%	9%	51%

CV= coefficient of variation

Wide Angle

CGM FIRST – for ALL PwT1D

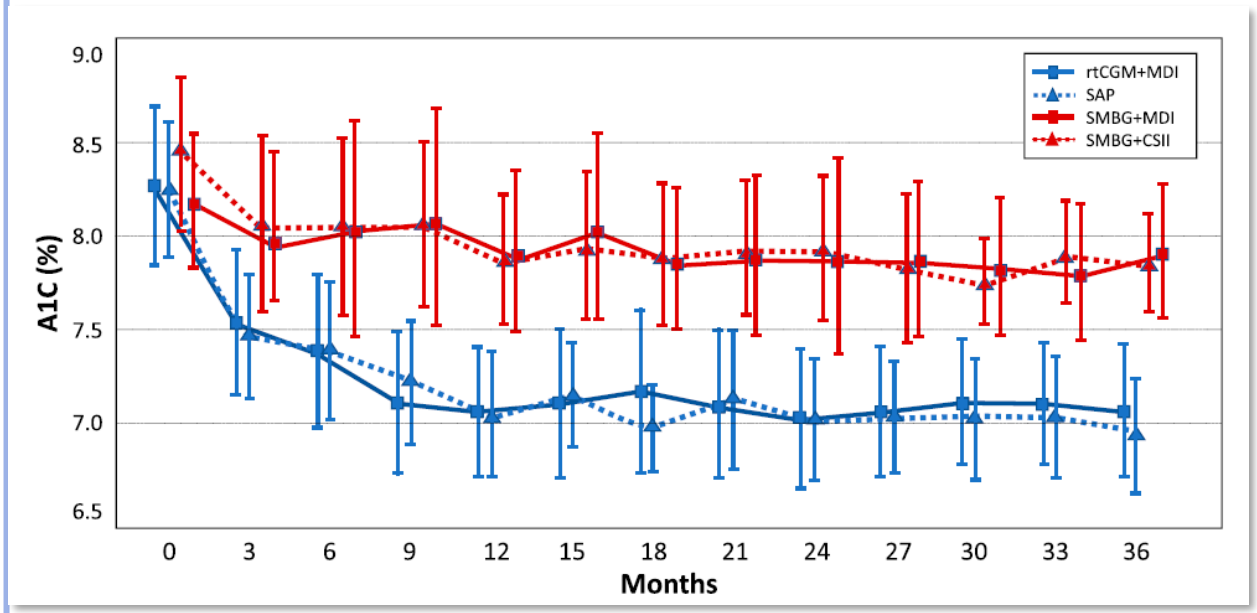
COMISAIR[1]

3 year follow up of 94 adults with **Type 1 diabetes** 4 treatment groups:

1. Real time CGM* + MDI†
2. SAP˜ (CGM + pump)
3. SMBG‡ + MDI
4. SMBG + pump

- Only **CGM groups** had significant improvements in **TIR** and ***significant reductions in TBR***
- A1C was lower in the rtCGM groups than SMBG groups

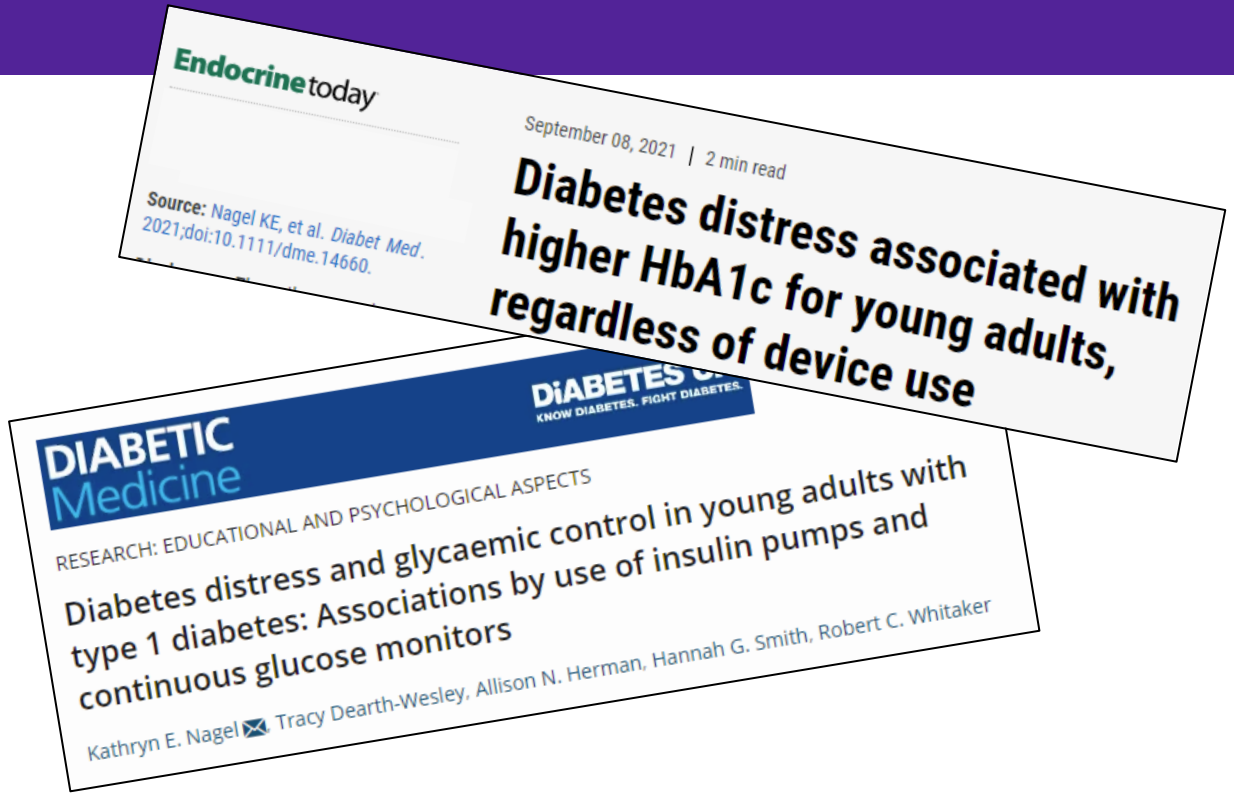
*Real time continuous glucose monitoring †Multiple dose injections ˜Sensor augmented pump ‡Self monitoring blood glucose

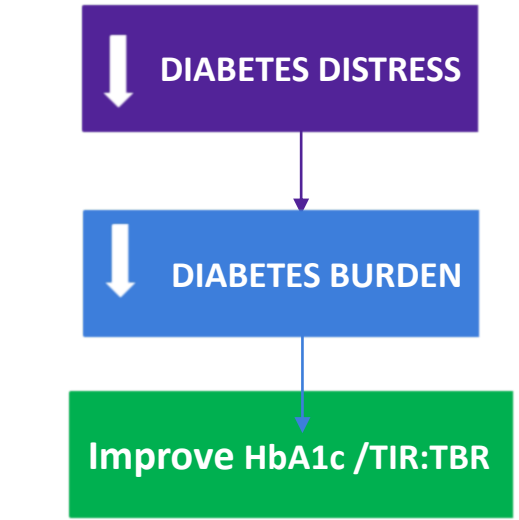


Note: 3 year non-randomized prospective real world clinical trial.

[1]Soupal J et al. Diabetes Care. 2020;43(1):37-43.

Minimizing diabetes distress: a key strategy to reduce the burden of diabetes





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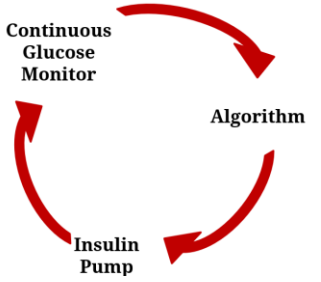
Nagel KE et al. Diabetes distress and glycaemic control in young adults with type 1 diabetes: Associations by use of insulin pumps and continuous glucose monitors. Diabet Med 2021;38:e14660.

Automated Insulin Delivery

Computerized control of insulin delivery based on data from a continuous glucose sensor

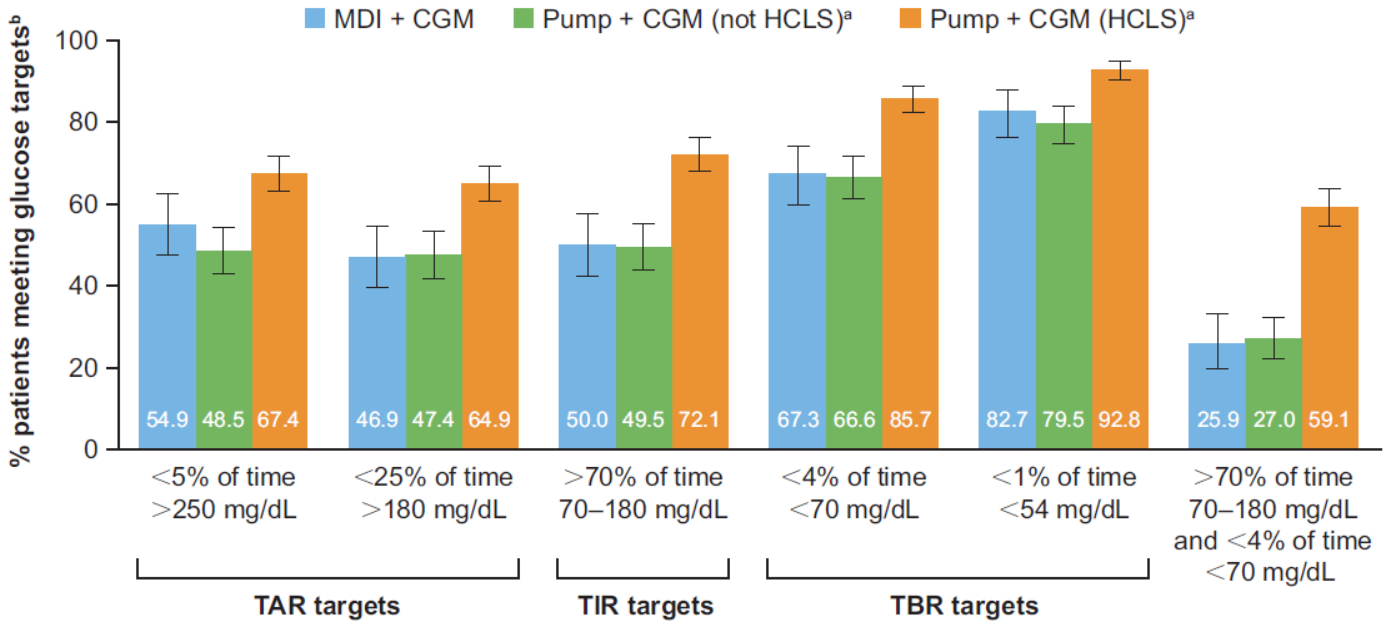


Insulin increased to reduce hyperglycemia

Insulin reduced to avoid hypoglycemia

T1D Exchange participants (N=926) on various approaches to insulin delivery willing to share their CGM data

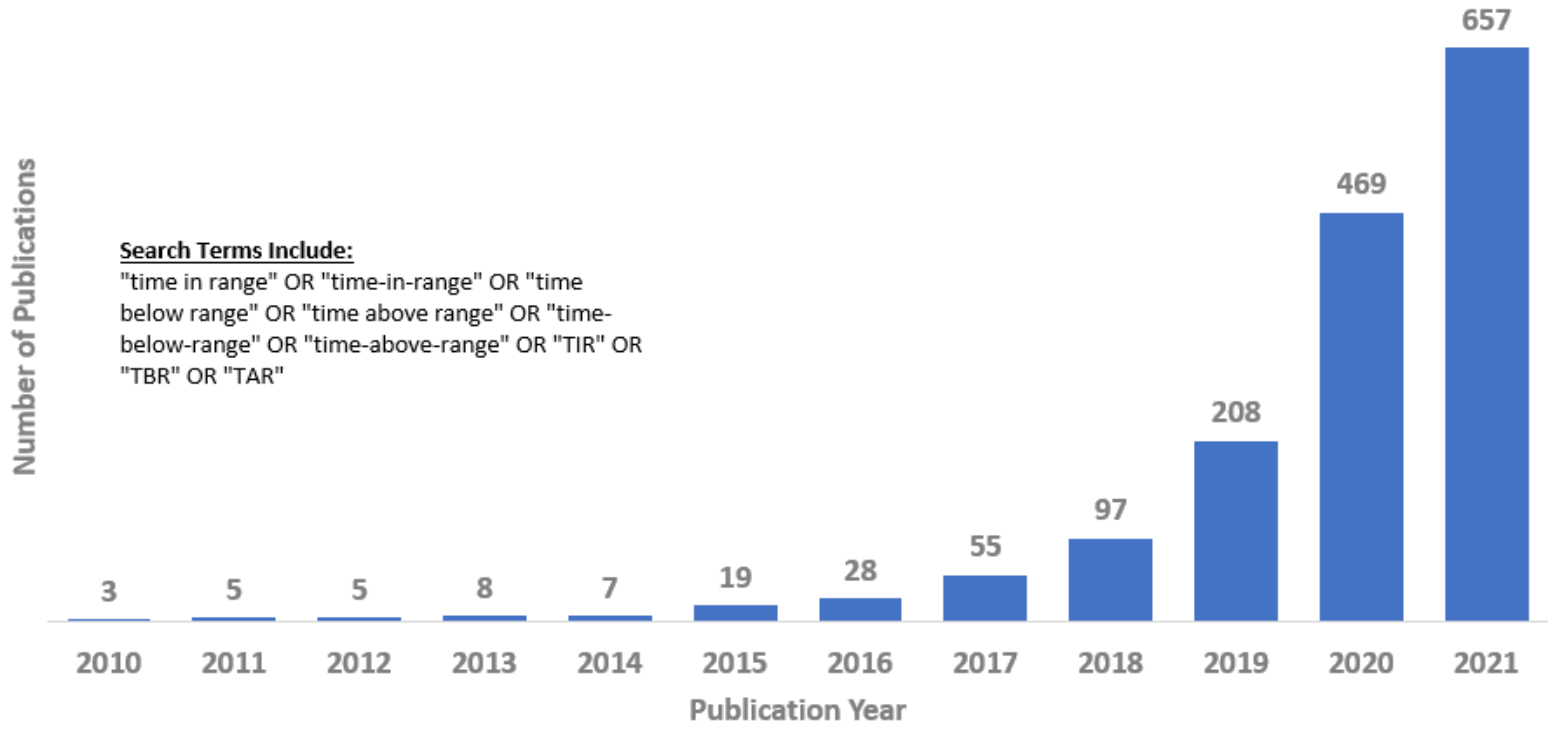
Figure 6. Proportion of Patients Meeting Various Glucose Targets



Laffel L. et al. Gaps Remain in Achieving Target Type 1 Diabetes Glycemic Goals Despite Advanced Technologies
Poster #652 ADA Sci Sessions June 2022

Time In Range as a Clinical Outcome: Results of a Longitudinal Analysis of the Literature and Clinical Trials

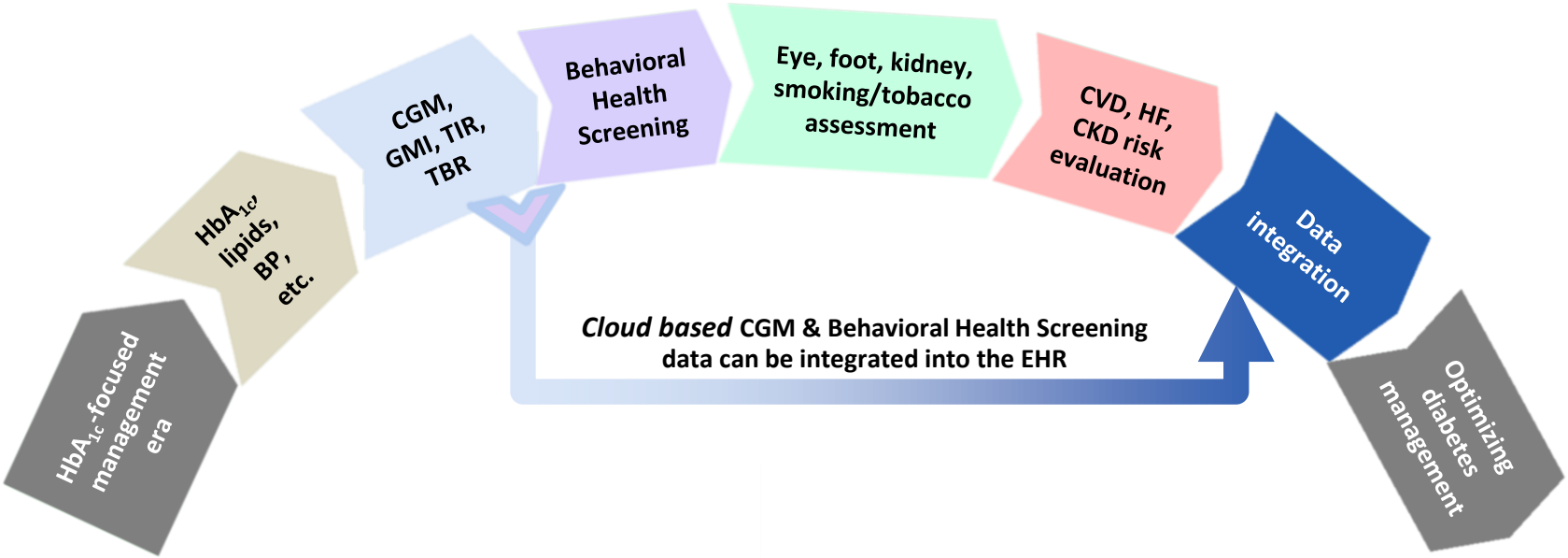
Figure 1: Number of Publications Reporting Time-in-Range as a Clinical Outcome



Patel P, et al. ADA 2022

Rethinking diabetes care in the digital age

Building a Bridge Toward Optimal Diabetes Management



Modified from R Bergenstal presentation at NCQA Digital Quality Summit July, 2021
Rethinking Diabetes Care In The Digital Age. Findings from the 2021 Digital Quality Summit.
Available at: https://www.ncqa.org/wp-content/uploads/2022/02/NCQA-DQS-WhitepaperRethinkDiabetes.pdf Accessed 9 March 2022

BP, blood pressure; CVD, cardiovascular disease; CKD, chronic kidney disease; GMI, glucose management indication (formerly estimated HbA_{1c});
HF, heart failure; TIR, Time in range (70–180mg/dL); TBR, Time below range (<70 mg/dL)

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Time in Range in Relation to All-Cause and Cardiovascular Mortality in Patients With Type 2 Diabetes: A Prospective Cohort Study

Jingyi Lu,[1] Chunfang Wang,[2] Yun Shen,[1] Lei Chen,[2] Lei Zhang,[1] Jinghao Cai,[1] Wei Lu,[1] Wei Zhu,[1] Gang Hu,[3] Tian Xia,[2] and Jian Zhou[1]

Diabetes Care 2021 Feb; 44(2): 549-555

- 6,225 T2D – CGM (72 hrs)
- Followed 10 years (2005-2015)
- Association baseline TIR & Mortality
  - All cause & CV mortality

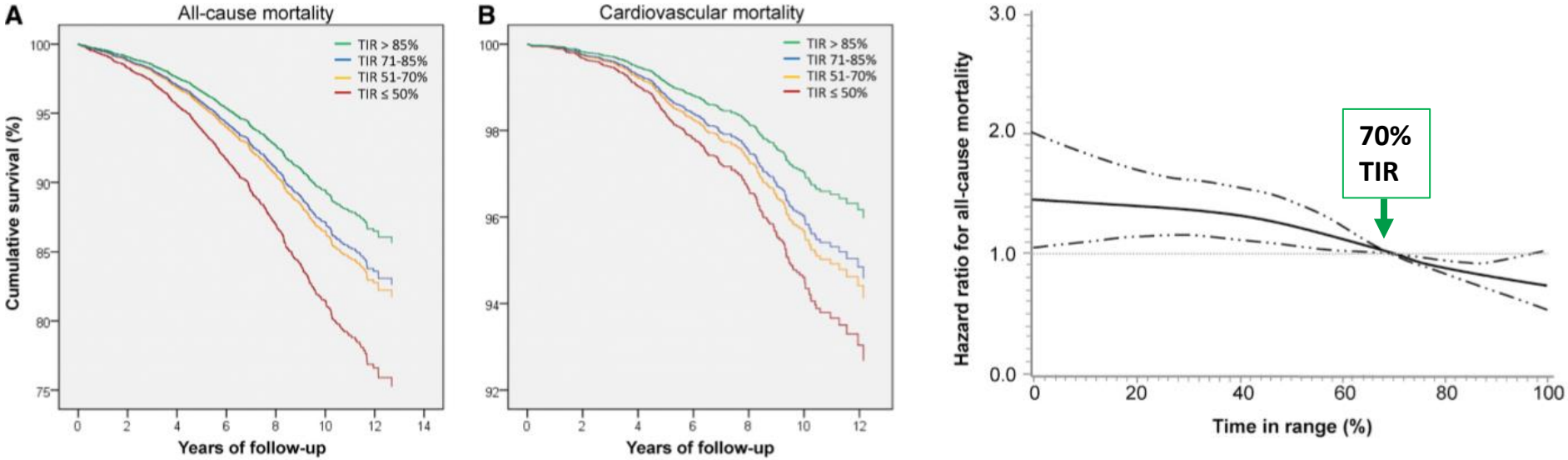

Figure 1—Multivariate-adjusted cumulative survival curves of all-cause (*A*) and cardiovascular (*B*) mortality by different levels of TIR. Adjusted for age, sex, BMI, diabetes duration, systolic blood pressure, triglyceride, HDL cholesterol, LDL cholesterol, smoking status, history of cancer and CVDs, and using antihypertensive drugs, aspirin, and statins.

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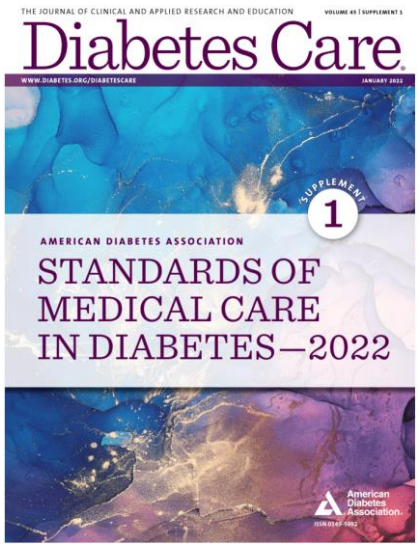
AGP Report Recommended



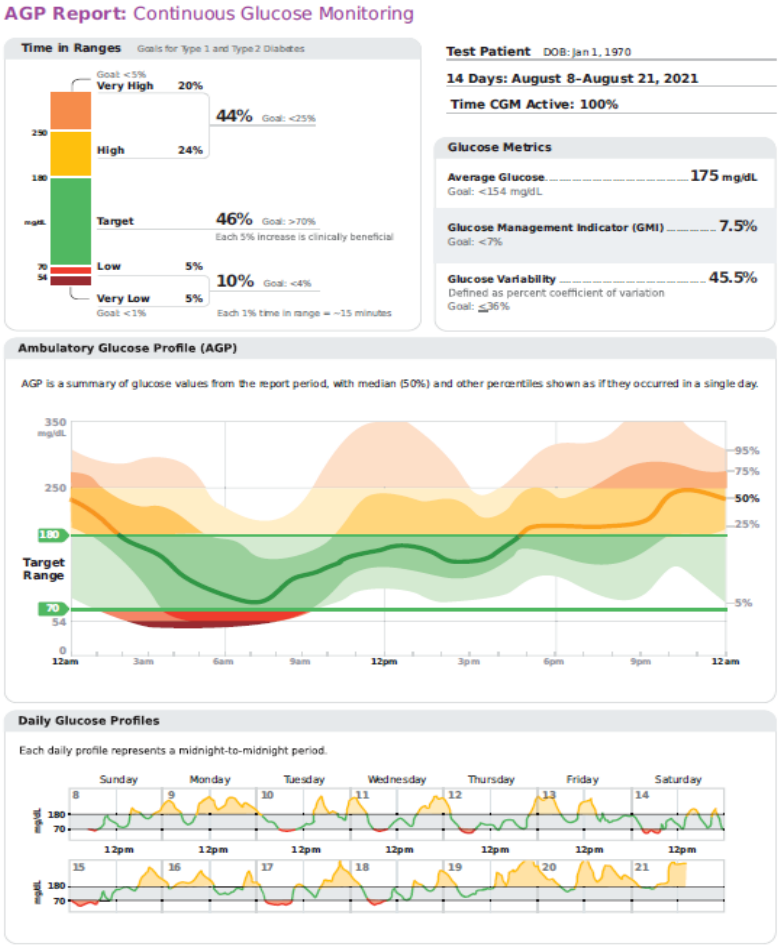


Figure 6.1—Key points included in standard ambulatory glucose profile (AGP) report. Reprinted from Holt et al. (33).

Glycemic Targets:

Standards of Medical Care in Diabetes - 2022. *Diabetes Care* 2022;45(Suppl. 1)

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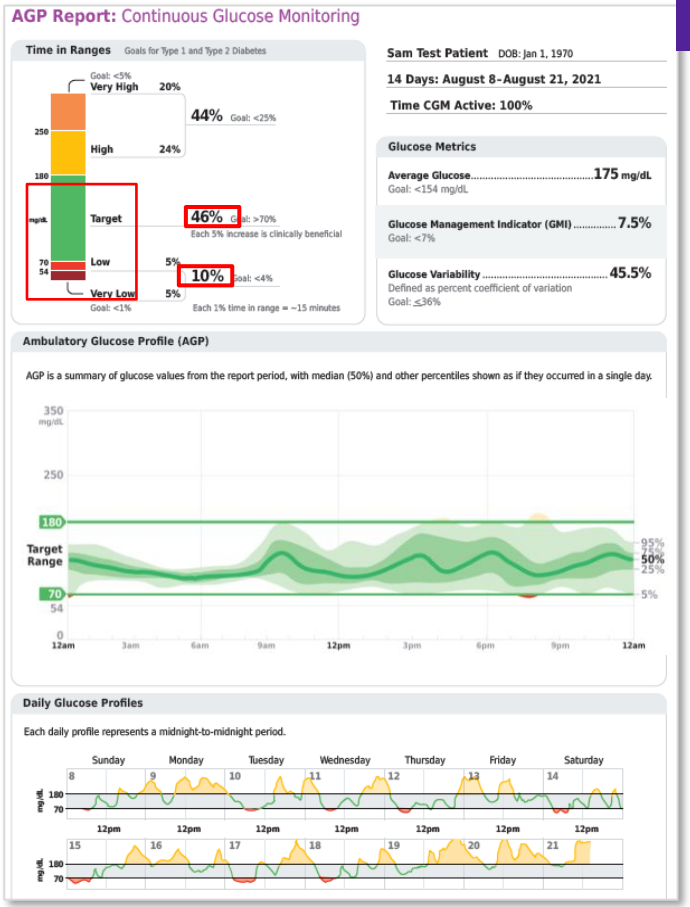
CGM Clinician Guided Management



1. Is there a glucose control problem?

More Green, Less Red

2. Where is the problem?

FNIR

Flat Narrow In Range

3. Continue to titrate on a timely basis

Titrate, Titrate, Titrate

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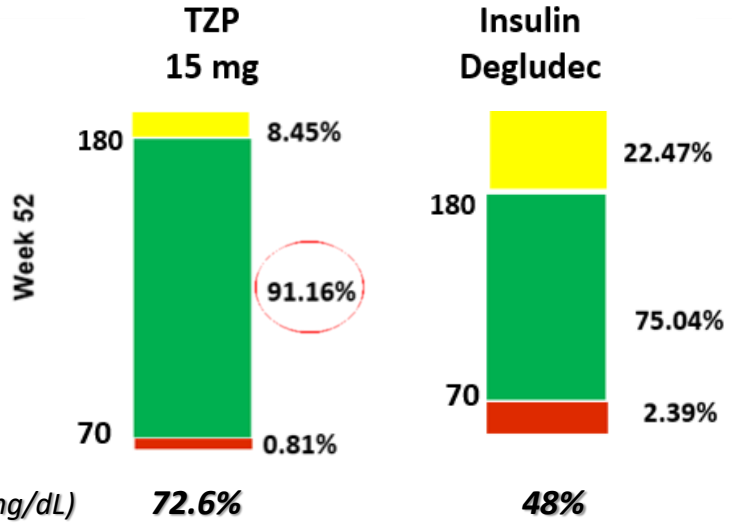
Bergenstal RM, Simonson GD, Heinemann L, More Green, Less Red:
How Color Standardization May Facilitate Effective Use of CGM *J Diabetes Sci Technol* 2022;16:3–6

SURPASS-3: *Tir*zepatide vs insulin degludec

SURPASS-3 CGM substudy: TIR at 52 weeks



Do we need to add ***Time in Tight Range*** **(TITR) 70-140 mg/dL**
to the current *Time in Range* (TIR) 70-180 mg/dL

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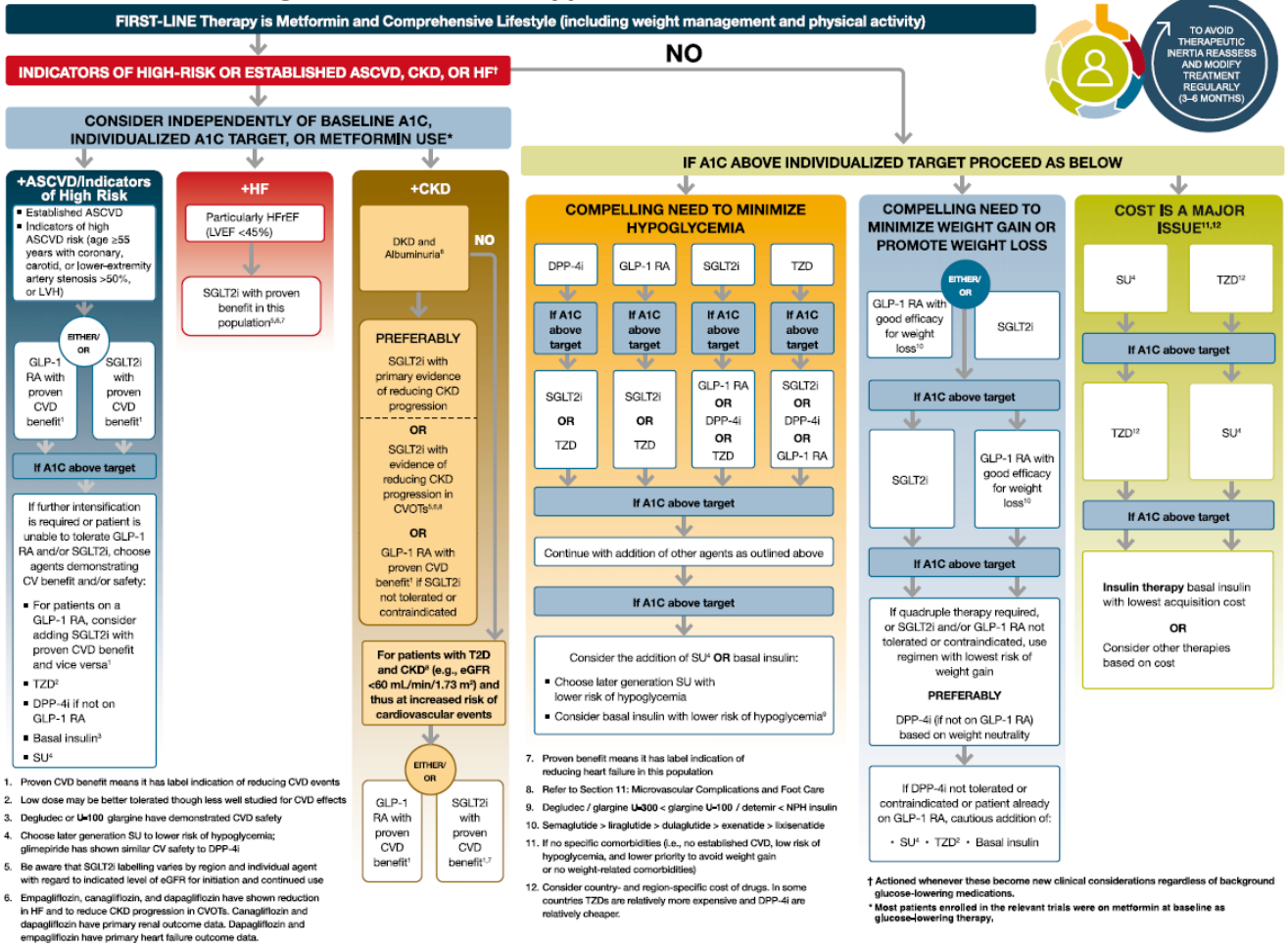
Battelino T, Bergenstal R. Rodriguez A. et al. Lancet DE Apr 2022 online first

Glucose-lowering medication in type 2 diabetes: ADA Standards of Care in Diabetes - 2021



1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or U-100 glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.
* Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

2021
Non-Glycemic (CVD/HF/CKD) & Glycemic

2022
Non-Glycemic (CVD/HF/CKD) & Glycemic & Weight Loss

More:

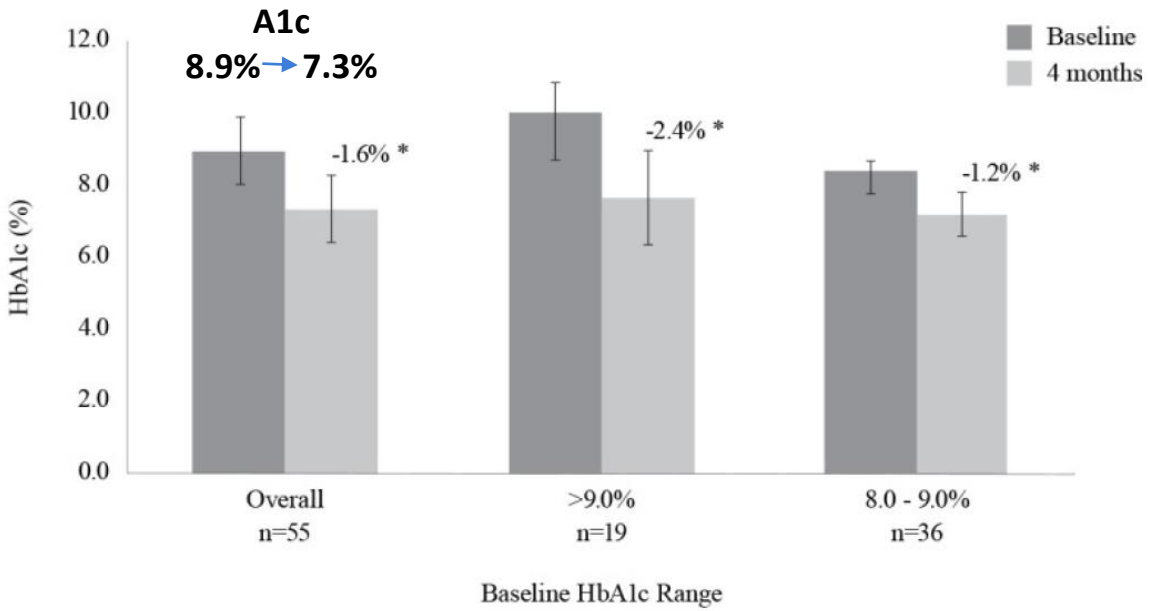
- **GLP-1 RA^{+}, SGLT2i**

Role of CGM guided management?

Figure 9.1—: 2021 ADA Professional Practice Committee (PPC) adaptation of Davies et al. and Buse et al.

Does remote monitoring of digital CGM data improve outcomes?

Patients with T2D followed in a CGM-based virtual diabetes clinic (Onduo)



CGM, continuous glucose monitoring; SD, standard deviation

Majithia AR et al. *J Med Internet Res* 2020;22:e21778. doi: 12.2196/21778

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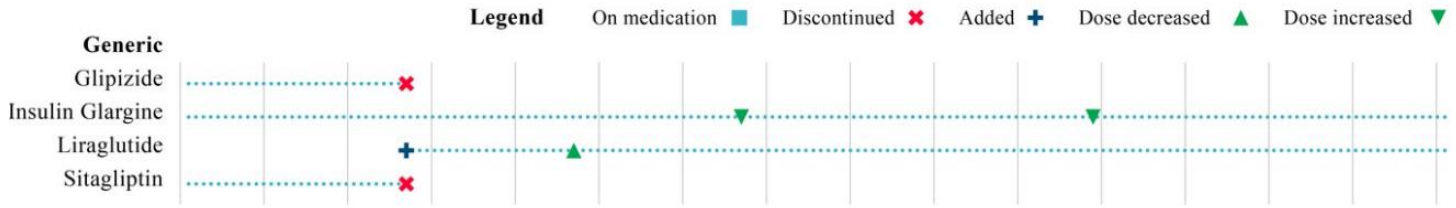
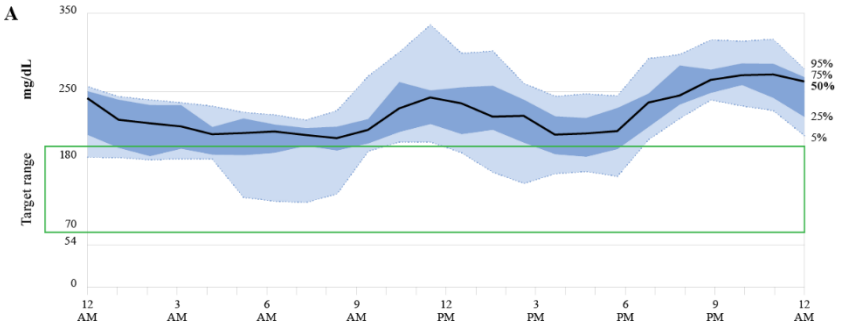
Does remote monitoring of digital CGM data improve outcomes?

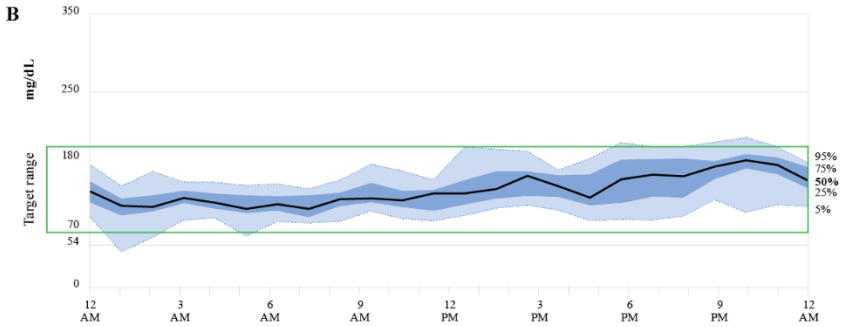
Timely access to guideline-based diabetes medications and technologies



Baseline



4 months on CGM



CGM, continuous glucose monitoring

Majithia AR et al. *JMIR Form Res* 2022 doi: 10.2196/31629 [Epub ahead of print]

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The EKG Informing the Future of CGM

Eric J. Topol, MD, Scripps Research Translational Institute
The Lancet Vol 397: February 27, 2021

Digital medicine

What's lurking in your electrocardiogram?

For decades one of my favourite tasks in medicine has been reading 12-lead electrocardiograms (ECGs). I've always thought the wealth of information provided was impressive—

Discussed that papers that showed how ECG could tell you

- **Gender**
- **Anemia**
- **CV outcome prediction**

AGP – EKG of glucose management

Digital medicine

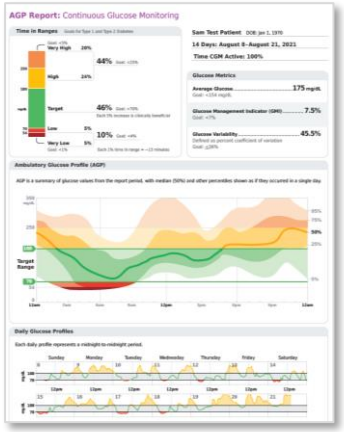
What's lurking in your *continuous glucose monitor?* *

For a decade one of my favorite tasks in medicine has been looking for patterns in the CGM/AGP report. I think CGM/AGP will transform diabetes management-

*** CGM has been used to show:**
Different people have very different glycemic responses to the same foods

Hall H, et. al. Glucotypes reveal new patterns of glucose dysregulation. *PLoS Biol.* 2018;16(7):e2005143
Berry SE et al. Human postprandial responses to food and potential for precision nutrition. Nat Med. 2020 Jun;26(6):964-973.

In Summary: *CGM using AGP* and taking a wide and narrow perspective is achieving both the *CGM & Diabetes Triple Aim*



Wide

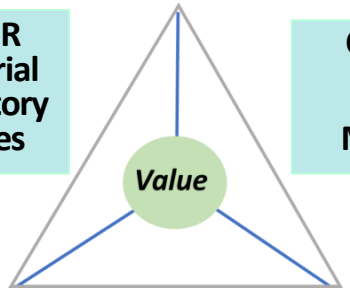
&

Narrow

CGM *triple aim*

CGM/TIR Clinical Trial & Regulatory Measures

CGM/TIR Digital Quality Measures

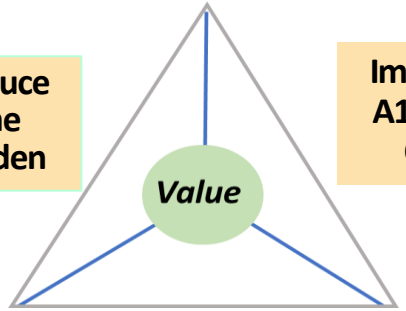


CGM/TIR Guided Clinical Care Strategies

Diabetes *triple aim*

Reduce the Burden

Improve Quality A1C + TIR & TBR CVD & CKD



Reduce therapeutic inertia

Thank you!