Need for Regulatory Change to Incorporate Beyond A1C Glycemic Metrics

*Beyond A1C Writing Group**

Diabetes Care 2018;41:e92–e94 | https://doi.org/10.2337/dci18-0010

SCOPE OF PROBLEM

Hemoglobin A1c (A1C) is currently the "gold standard" in measuring diabetes outcomes. Substantial evidence, however, demonstrates the limitations of A1C in characterizing daily glycemic fluctuations and quality of life (1) or in accurately reflecting mean blood glucose levels (2). Data derived from continuous glucose monitoring (CGM) systems present a more comprehensive glycemic picture than A1C alone and are decidedly valuable as clinicians and patients seek to individualize therapy and make treatment changes accordingly. Concern about inconsistent reporting of CGM-measured outcomes has hampered progress in the field, as thresholds for these metrics often differ among trials. As a result, the diabetes community has developed consensus on key glycemic metrics to measure outcomes beyond A1C, which can be used in research, therapy development, and regulatory review (3,4). This report seeks to contribute broader engagement of the diabetes community and a specific focus on regulatory implications of achieving consensus on glycemic outcomes beyond A1C.

CONVENING BROAD REPRESENTATION OF THE DIABETES COMMUNITY

To continue the push for consensus, The diaTribe Foundation convened a meeting, titled "Glycemic Outcomes Beyond A1C: Standardization and Implementation" (5), with leaders from nine organizations (American Association of Clinical Endocrinologists, American Diabetes Association [ADA], Advanced Technologies & Treatments for Diabetes, European Foundation for the Study of Diabetes, European Medicines Agency, Endocrine Society, U.S. Food and Drug Administration [FDA], International Hypoglycaemia Study Group, and JDRF). This meeting took place in Bethesda, MD, on 21 July 2017 and attracted key stakeholders, including representatives from about 25 companies, 15 medical and academic institutions, and 5 patient groups. This diverse group, in turn, engaged the dozen FDA delegates in a robust discussion and presented a unified case for the need to incorporate outcomes beyond A1C into regulatory decisions and clinical care. The Beyond A1C movement has gathered significant momentum, captured most recently by literature featured in *Diabetes Care* (3,4,6,7).

During the meeting, participants highlighted the consensus on glycemic measurement ranges for research purposes (first agreed upon during a symposium at the 2017 ADA Scientific Sessions), specifically definitions of hypoglycemia, time in range, and hyperglycemia. Attendees also agreed on the following: measuring mean glucose to characterize overall glycemia, using coefficient of variation to measure glycemic variability; defining nocturnal events as those occurring between midnight and 6 A.M. for large clinical trials; requiring 2 weeks of CGM data and at least 70% of possible CGM readings during that time for clinical analysis; and using the Ambulatory Glucose Profile (AGP) as a standard to visualize CGM profiles or patterns (Table 1).

CLINICAL GAPS AND NEXT STEPS

Thus, the diabetes research community has made considerable progress in agreeing upon core glycemic outcomes beyond A1C. Nonetheless, several challenges remain: *1*) using CGM metrics and benchmarks in regulatory decision making; *2*) standardizing methods for using CGM in clinical trials; *3*) identifying scientifically and clinically appropriate descriptive terminology, specifically in characterizing hypoglycemia; and *4*) investigating patient-reported outcomes (PROs) in a standard, validated manner. Next steps must focus on advancing agreement on these outstanding issues within the Beyond A1C movement and propelling regulatory adoption of the internationally accepted CGM-related metrics for use in research and clinical settings.

Using CGM Metrics and Benchmarks in Regulatory Decision Making

Since the publication of the FDA guidance on artificial pancreas systems, the FDA's Center for Devices and Radiological Health has accepted the use of glycemic outcomes based upon CGM readings, including time in range and hypo- and hyperglycemia

Corresponding author: William T. Cefalu, wcefalu@diabetes.org.

Received 24 January 2018 and accepted 21 February 2018.

**A full list of the Beyond A1C Writing Group is available in the* APPENDIX.

Table 1—Proposed recommendations for regulatory considerations

Component	Value/measure
Low blood glucose (i.e., hypoglycemia)*	<70 mg/dL; <3.9 mmol/L <54 mg/dL; <3.0 mmol/L Severe hypoglycemia = clinical diagnosis: event characterized by altered mental and/or physical status requiring external assistance
Time in range*†	70–180 mg/dL; 3.9–10.0 mmol/L
High blood glucose (i.e., hyperglycemia)*	>180 mg/dL; >10.0 mmol/L >250 mg/dL; >13.9 mmol/L Diabetic ketoacidosis = clinical diagnosis: presence of ketosis and acidosis
Overall	Mean glucose
Glycemic variability	Coefficient of variation
CGM data report standard	Ambulatory Glucose Profile
Individual episode of hyperglycemia/ hypoglycemia (a separate metric from time spent in hyperglycemia/ hypoglycemia)	15 min
Sleep-wake time blocks	Midnight–6 A.M. (night) 6 A.M.–midnight (day)
Recommended CGM data sufficiency	2 weeks of collection 70–80% of possible CGM readings (minimum)

*CGM-based measures of hypoglycemia, time in range, and hyperglycemia should be reported as the percentage of readings per unit of time. For example: 2% of readings <70 mg/dL over 24 h.
†Many note concerns about using 180 mg/dL (10.0 mmol/L) as an upper limit for time in range and advocate for a lower upper threshold in the future. In other circumstances, 140 mg/dL (7.8 mmol/L) has already been used as an upper limit (10).

exposure and events (8). The diabetes community strives to incorporate CGM data in regulatory decisions, beyond diabetes devices, to consider non-A1C glycemic outcomes in calculating benefit-risk analyses, comparing clinical trials, and developing drug-label indications. Further, these outcomes should be used for future innovative treatment options (e.g., cellular therapies).

Standardizing Methods for Using CGM in Clinical Trials

A paradox of CGM use in clinical trials remains: given the well-documented clinical benefit of real-time CGM, it may become difficult to distinguish the relative contributions of the tested diabetes therapy and the use of CGM if both are initiated at the same time. As the prevalence of CGM use increases, study designs will need to accommodate the inclusion of both CGM users and nonusers. The question of CGM use in trials will need to be addressed in conjunction with manufacturers and regulatory bodies.

Identifying Scientifically and Clinically Appropriate Descriptive Terminology

The diabetes community has achieved consensus on the hypoglycemic thresholds (i.e., <54 mg/dL, <3.0 mmol/L; <70 mg/dL, <3.9 mmol/L) (Table 1). However, descriptive terminology (e.g., "severe") surrounding these thresholds is subject to considerable debate. Further discussion will be required to reach a consensus on hypoglycemia terminology.

Investigating PROs

Although glycemic outcomes rather than PROs were the focus of the consensus conference, several attendees expressed enthusiasm about future validation and incorporation of PROs. The diabetes community must strive to achieve standardization and consensus on PRO measurement instruments, as many next-generation therapies could meaningfully improve quality of life in tandem with glycemic benefits. To include PROs in regulatory decisions, the diabetes community must work to standardize and validate outcomes, especially by identifying the impact of PROs on clinical outcomes.

Incorporating Outcomes That Matter to People With Diabetes

Empirical and anecdotal evidence affirms the importance of outcomes beyond A1C for those living with diabetes and for assessing the benefits of different therapies. For example, a recent conjoint analysis survey (n = 4,268) asked participants with diabetes to choose between various theoretical pairs of therapies based on their attributes (e.g., share of time in the ideal glucose range, hypoglycemia, weight loss, dosing frequency, and dose timing) and varying levels within those attributes. Ultimately, share of time in the ideal glucose range "most of the day" had the largest share of first choices among people with type 1 diabetes (i.e., it was the strongest driver of choosing one therapy over another) and the third largest share in people with type 2 diabetes. "Weight loss of 10%" obtained the greatest share of first choices in people with type 2 diabetes. However, preferences varied widely based on the outcomes included in these hypothetical side-by-side labels. As a result, individuals with diabetes may weigh the attributes of a given diabetes therapy quite differently, and their preferences may change considerably based on inclusion of outcomes beyond A1C in product labels (9).

CALL TO ACTION

Current A1C-focused regulatory decisions do not accurately reflect the recent advances in diabetes technology, namely CGM systems, and cannot capture the daily reality of living with diabetes. As Riddle et al. recently declared, "Periodically, a new idea, method, or tool leads to a turning point in the management of diabetes. We believe such a moment is now upon us, brought by development of reliable devices for continuous glucose monitoring" (6). Thus, regulatory bodies should acknowledge therapies that improve time in range, glycemic variability, and quality of life, which is impossible without incorporating these agreed-upon core glycemic metrics into regulatory decisions. To address identified clinical gaps and make progress on next steps, the diabetes community needs to continue to engage regulatory bodies in discussions to agree on how, when, and where these metrics should be used for clinical trial design and risk-benefit decisions. The diabetes community has reached consensus and, in doing so, aims to empower regulatory bodies to implement outcomes beyond A1C.

Appendix

Members of the Beyond A1C Writing Group are: Charles M. Alexander, Alexander Associates, LLC, Gwynedd Valley, PA; Stephanie Amiel, International Hypoglycaemia Study Group and King's College London, London, U.K.; Roy Beck, T1D Exchange and Jaeb Center for Health Research, Tampa, FL; Richard M. Bergenstal, International Diabetes Center at Park Nicollet, Minneapolis, MN; Zachary Bloomgarden, Icahn School of Medicine at Mount Sinai, New York, NY; Adam Brown,

The diaTribe Foundation, San Francisco, CA; Bruce Buckingham, Stanford Medical Center, Stanford, CA; William T. Cefalu, American Diabetes Association, Arlington, VA; Kelly L. Close, The diaTribe Foundation, San Francisco, CA; Isabel Chin, The diaTribe Foundation, San Francisco, CA; Thomas Danne, Advanced Technologies & Treatments for Diabetes and AUF DER BULT, Kinder- und Jugendkrankenhaus, Hannover, Germany; Daniel DeSalvo, Baylor College of Medicine, Houston, TX; Jane K. Dickinson, Teachers College, Columbia University, New York, NY; Emily Fitts, The diaTribe Foundation, San Francisco, CA; Brian Frier, University of Edinburgh, Edinburgh, U.K.; Robert A. Gabbay, Joslin Diabetes Center, Harvard Medical School, Boston, MA; George Grunberger, American Association of Clinical Endocrinologists, Bloomfield Hills, MI; Irl Hirsch, University of Washington School of Medicine, Seattle, WA; Philip Home, Newcastle University, Newcastle-upon-Tyne, U.K.; Aaron Kowalski, JDRF, New York, NY; Lori Laffel, Joslin Diabetes Center, Harvard Medical School, Boston, MA; Anthony McCall, Endocrine Society; University of Virginia School of Medicine, Charlottesville, VA; and Cornell University, Ithaca, NY; Christopher G. Parkin, CGParkin Communications, Inc., Boulder City, NV; Anne L. Peters, University of Southern California Keck School of Medicine, Beverly Hills, CA; Robert Ratner, Georgetown University Medical School, Washington, DC; Bart Van der Schueren, Clinical and Experimental Endocrinology, University of Leuven, Leuven, Belgium; and Richard Wood, dQ&A Market Research, Inc., San Francisco, CA.

Acknowledgments. The writing group would like to acknowledge James S. Hirsch (The diaTribe Foundation) for his editing and writing contributions.

Funding and Duality of Interest. Support for the "Glycemic Outcomes Beyond A1C: Standardization and Implementation" meeting and development of this article was provided by The diaTribe Foundation. Abbott Diabetes Care, AstraZeneca, Boehringer Ingelheim, Becton Dickinson, Eli Lilly, Merck, Novo Nordisk, Sanofi, and The Apple Pickers Foundation provided funding to The diaTribe Foundation to support the consensus meeting. The diaTribe Foundation contracted with James S. Hirsch and C.G.P. for editorial support. S.A. has served on advisory boards for Novo Nordisk, Medtronic, and Roche. R.B.'s nonprofit employer has received consultant payments, research funds, or research supplies on his behalf from Abbott Diabetes Care, Animas, Ascenia, Bigfoot Biomedical, Dexcom, Insulet, Eli Lilly, Roche, and Tandem, with no personal compensation to R.B. R.M.B. declared research support, acted as a consultant, or has been on a scientific advisory board for Abbott Diabetes Care, Becton Dickinson, Dexcom, Eli Lilly, Glooko, Helmsley Charitable Trust, Hygieia, Johnson & Johnson, Medtronic, Merck, Novo Nordisk, Roche, and Sanofi. R.M.B.'s nonprofit employer contracts for his services and no personal income goes to R.M.B. He has inherited Merck stock. He is a volunteer for ADA and JDRF and has worked on the development and implementation of the AGP. Z.B. is a consultant/adviser for Sanofi, AstraZeneca, Janssen, Merck, Intarcia, and Novartis; a speaker for Amgen, Merck, AstraZeneca, and Janssen; and a stockholder in Allergan, Zimmer Biomet, and Novartis. A.B., K.L.C., I.C., and E.F. report disclosures for The diaTribe Foundation, which receives donations from a number of pharmaceutical and device companies in the diabetes field. A.B. and K.L.C. also report disclosures for Close Concerns, for which several academic institutions, government bodies, and pharmaceutical and device companies in the diabetes field subscribe to the company's fee-based newsletter, *Closer Look*. B.B. has received research funding from National Institutes of Health, Medtronic, Tandem, Insulet, Xeris, and Dexcom; has served on advisory board or consulted for Novo Nordisk, Tandem, and Convatec; and has received honorarium or expenses from Insulet and Novo Nordisk. T.D. has acted as consultant, advisory board member, or speaker for Abbott, Medtronic, Roche, Lexicon, Menarini, Boehringer Ingelheim, AstraZeneca, Novo Nordisk, Sanofi, Dexcom, and Eli Lilly and has received research grants from Abbott, AstraZeneca, Novo Nordisk, Medtronic, and Sanofi. He is a shareholder of DreaMed Diabetes, Ltd. D.D. has received speaker's honoraria from Dexcom and Insulet. B.F. has served on advisory panels for Eli Lilly, Novo Nordisk and the Kuwait Foundation for Science and has taken part in a speakers' bureau for Novo Nordisk, Boehringer Ingelheim, Eli Lilly, Merck, Sanofi, Roche Diagnostics, and Takeda. R.A.G. is a consultant for Onduo and Health Reveal. G.G. has received research support from Medtronic and Novo Nordisk and is on the speakers' bureau for Eli Lilly, Novo Nordisk, Janssen, Boehringer Ingelheim, Sanofi, and AstraZeneca. I.H. has received a research grant from Medtronic Diabetes and has served as consultant with Abbott Diabetes Care, Adocia, Bigfoot Biomedical, and Roche. P.H., or institutions with which he is associated, received funding from AntriaBio, AstraZeneca, Biocon, GlaxoSmithKline, Janssen, Merck, Novo Nordisk, Roche Diagnostics, and Sanofi for his advisory, research, or speaking activities. L.L. has served as a consultant for Eli Lilly, Sanofi, Novo Nordisk, MannKind, AstraZeneca, Boehringer Ingelheim, Merck, Johnson & Johnson, Dexcom, Insulet, Roche Diagnostics, and Unomedical. C.G.P. has received consulting fees from Animas, CeQur, Dexcom, Insulet, Johnson & Johnson Diabetes Institute, Roche Diabetes Care, Sanofi, and Senseonics. A.L.P. has participated on advisory boards for Abbott Diabetes Care, Becton Dickinson, Bigfoot Biomedical, Boehringer Ingelheim, Eli Lilly, Lexicon, Livongo, Medscape, Merck, Novo Nordisk, Omada Health, Sanofi, and Science 37. She has provided research support for Dexcom and MannKind and is on the speakers' bureau of Novo Nordisk. R.R. is a consultant for Dexcom, Merck, Novo Nordisk, and Intarcia. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. All members of the Beyond A1C Writing Group contributed significantly to the writing, editing, and reviewing process. W.T.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Cox D, Gonder-Frederick L, McCall A, Kovatchev B, Clarke W. The effects of glucose fluctuation on cognitive function and QOL: the functional costs of hypoglycaemia and hyperglycaemia among adults with type 1 or type 2 diabetes. Int J Clin Pract Suppl 2002;(129):20–26
2. Shrom D, Sarwat S, Ilag L, Bloomgarden ZT. Does A1c consistently reflect mean plasma glucose? J Diabetes 2010;2:92–96
3. Agiostratidou G, Anhalt H, Ball D, et al. Standardizing clinically meaningful outcome measures beyond HbA_{1c} for type 1 diabetes: a consensus report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. Diabetes Care 2017;40:1622–1630
4. Danne T, Nimri R, Battelino T, et al. International consensus on use of continuous glucose monitoring. Diabetes Care 2017;40:1631–1640
5. The diaTribe Foundation. Glycemic outcomes beyond A1C: standardization and implementation [Internet], 2017. Available from https://diatribe.org/foundation/glycemic-outcomes-beyond-a1c. Accessed 10 October 2017
6. Riddle MC, Gerstein HC, Cefalu WT. Maturation of CGM and glycemic measurements beyond HbA_{1c} – a turning point in research and clinical decisions. Diabetes Care 2017;40:1611–1613
7. Petrie JR, Peters AL, Bergenstal RM, Holl RW, Fleming GA, Heinemann L. Improving the clinical value and utility of CGM systems: issues and recommendations: a joint statement of the European Association for the Study of Diabetes and the American Diabetes Association Diabetes Technology Working Group. Diabetes Care 2017;40:1614–1621
8. U.S. Food and Drug Administration. Guidance for industry and Food and Drug Administration staff: the content of investigational device exemption (IDE) and premarket approval (PMA) applications for artificial pancreas device systems [Internet], November 2012. Available from www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm259305.pdf. Accessed 10 October 2017
9. Brown A. Update from the community: The diaTribe Foundation and DSMA share data regarding patient experience. Presentation at the Glycemic Outcomes Beyond A1C: Standardization and Implementation Meeting, 21 July 2017, at the Bethesda North Marriott Hotel & Conference Center, Bethesda, MD
10. Feig DS, Donovan LE, Corcoy R, et al.; CONCEPTT Collaborative Group. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. Lancet 2017;390:2347–2359