CLOSER LOOK

MEMORANDUM

ATTD International Consensus Meeting on Time-in-Range (TIR) - February 19, 2019

Executive Highlights

- **Following previous workshops and consensus publications, a group of diabetes clinician and researcher luminaries congregated in Berlin to arrive at a further consensus on targets for CGM metrics for different patient groups.** A big thank you to Profs. Moshe Phillip and Tadej Battelino for organizing and running this critical meeting.
- **Surprising some, the group decided to collapse type 1 and type 2 diabetes targets (so they were the same), and jettisoned measures of glycemic variability from the primary target-setting venture.** The recommendation divided patients into "people with diabetes," "people with frail diabetes," "pregnant women with type 1 diabetes," and "pregnant women with type 2 diabetes/gestational diabetes." This focus on simplicity will certainly help to grease the skids of adoption. See the table below for all of the recommended targets and times therein.
- **The group also agreed that:** (i) A minimum of the equivalent of 10 full days of CGM data (i.e., minimum 70% coverage of a 14-day period) is required to generate a representative CGM profile; and (ii) a ~5% increase/decrease in time-in-range constitutes a clinically meaningful change.
- **The Writing Committee's goal is to have a manuscript published before ADA.**

Hello from Berlin, Germany, where Profs. Tadej Battelino and Moshe Phillip led a meeting of the minds on time-in-range and glycemic variability, seeking to answer the questions: (i) What CGM-based metrics matter and are most practical for implementation in clinical practice; and (ii) where should the target for each of these metrics be set for different groups of patients?

*****NOTE THAT THE FOLLOWING RECOMMENDATIONS HAVE NOT YET BEEN FINALIZED. THE WRITING COMMITTEE AIMS TO REFINE AND PUBLISH BEFORE ADA IN JUNE*****

While the Writing Committee still has to finalize the recommendations and some of the terminology has yet to be ironed out, the targets are summarized in the following table:

Diabetes Group	Time-in-Range Target	Time Below Range Target	Time Above Range Target
People with diabetes (type 1 and type 2)	≥70% (Range: 70-180 mg/dl)	<4% time below 70 mg/dl <1% time below 54 mg/dl	(minimize time in hyperglycemia)
People with "frail" diabetes* (type 1 and type 2)	≥50% (Range: 70-180 mg/dl)	<1% time below 70 mg/dl	≥90% time below 250 mg/dl**
Type 1 pregnancy	≥70% (Range: 63-140 mg/dl)	<4% time below 63 mg/dl	<25% time above 140 mg/dl
Type 2 pregnancy/ gestational diabetes	≥85% (Range: 63-140 mg/dl)	<4% time below 63 mg/dl	<10% time above 140 mg/dl

		(Only for those treated with insulin or SUs)	

* Frailty defined as a person who "can't carry out the abilities of daily living without risk or is terminally ill."

** We'd recommend "<10% time above 250 mg/dl" for greater harmonization with other recommendations.

In addition to those key target metrics, the group has preliminarily agreed on parameters related to the minimum amount of CGM data needed to form a representative profile and clinically meaningful increases in time-in-range:

- **14 days of CGM data should be required to generate a representative CGM profile.** 10 days is also acceptable (equivalent to ~70% sensor wear for 14 days), but 14 days is ideal. An asterisk may also be added because, as Profs. Stephanie Amiel and Roman Hovorka pointed out, four weeks of data is preferable to reliably detect hypoglycemia exposure.
- **A ~5% increase/decrease (one hour per day) constitutes a clinically meaningful change in time-in-range.** Dr. Roy Beck and Dr. Robert Vigersky (et al.) have both looked at CGM data sets, finding that a 10% change in time-in-range correlates with a ~0.5% and ~0.8% change in A1c, respectively. Assuming a linear relationship, this suggests that a 5% change in time-in-range would result in a 0.25%-0.4% change in A1c. Of course, in reality, the relationship is curvilinear, meaning an improvement in time-in-range improves A1c to a greater extent when baseline A1c is higher. E.g., in Dr. Beck's analysis, for those with a baseline A1c ≥8%, a 10% change in time-in-range correlated with a 1% change in A1c; for those with baseline A1c 7%-8%, a 10% change in time-in-range correlated with a 0.4% change in A1c. We'd add that a 10% time-in-range change - 2 hours per day - adds up to one full month per year in range.

Notably absent from the table are any target recommendations for measures of glycemic variability. After much debate, the group determined that while measures like standard deviation (SD) and coefficient of variation (CV) are certainly useful - and should continue to be used in the research setting - they don't really inform clinical practice. Clinicians like Drs. Beck, Stu Weinzimer, and Rich Bergenstal characterized CV as a useful marker, but not a parameter that they need on top of hypoglycemia and time-in-range; said Dr. Beck, "If you're looking quickly at the AGP and you see CV is >40%, it means you need to drill down…I put CV there with mean glucose, something there to look at, but you don't need it. Similarly, though Dr. Kovatchev made a strong, evidence-backed case for the use of the low blood glucose index (LBGI) as the primary measure of hypoglycemia (or perhaps in conjunction with CV in a composite metric), it was not ultimately adopted for this consensus. This decision boiled down to three main reasons: Simplicity, the advantage of using continuous variables, and a very high correlation between LBGI and time <70 mg/dl. However, attendees still see a role for LBGI in research and population management.

We were delighted by the group's approach to generating a simple and concise set of target recommendations, always keeping in mind that the targets must be easy to teach and remember. Still, it was a bit of a surprise when the day finished with targets for just four macro-groups: (non-frail) people with diabetes, "frail" people with diabetes, type 1 diabetes pregnancy, and type 2 diabetes pregnancy/gestational diabetes. Going into the meeting, preliminary materials had suggested breaking different groups out by age (e.g., pediatrics, geriatrics), therapy (e.g., MDI, basal and/or SFUs, orals/GLP-1s), and presence of comorbidities; exiting, essentially all of those groups had been collapsed, as had type 1 and type 2 diabetes. The target of 70%+ time-in-range was selected for the non-frail groups because it approximates the DCCT-validated target of A1c <7%, and also because it is what is typically seen in studies of type 1s on automated insulin delivery. [The latter point raises the question of what will happen to guidelines when next-gen AID brings people to 80%+ time-in-range.] This broad agreement certainly required some compromises here and there; for example, though gestational diabetes experts Drs. Murphy and Kirsten Nørgaard felt that the data better supported a target of <5% for time in hypoglycemia, they ultimately coalesced on 4% so that the recommendations better aligned across groups.

While we see the obvious pros associated with easily-recalled and translated guidelines and advocating for widespread individualization, it is not necessarily feasible to expect a 30-year-old upper class type 1 woman on hybrid closed loop, a four-year-old type 1 on SAP, an adolescent type 1 on MDI, a type 2 on an SU, and a type 2 on metformin to achieve the same time in and below range. Parents of the infant may be frustrated by unobtainable goals, and the type 2 on metformin may be satisfied with 70% time-in-range, when her goal could perhaps be more ambitious. Attendees argued that this is where the patient-doctor relationship enters - targets should ultimately be tailored to the specific patient, and patients should be encouraged to make incremental steps toward a goal, even if they are still far away. Prof. Amiel proposed that setting the same aspirational goal for each therapeutic group does make sense because, "If a therapy doesn't work, switch the therapy, not the target."

The consensus-making process was lively and collaborative, and we were particularly moved by Prof. Battelino's opening remarks (plus an interjection from Dr. Irl Hirsch). Prof. Battelino claimed that it is "our professional and ethical duty" to arrive at a consensus that is acceptable to healthcare providers, make a strong effort to implement it into routine use, make it accepted/adopted/used by people with diabetes, and to make new treatment modalities that work for people with diabetes. Based on survey data, Dr. Hirsch underscored just how vital and difficult getting healthcare providers to accept consensus will be: 0% of non-endocrinologists, 59% of endocrinologists, and 65% of people with diabetes are ready to go beyond A1c. Our work is cut out for us on the education front! But Prof. Battelino is not deterred - he recalls when the DCCT came out in NEJM and 90% of his diabetologist colleagues didn't believe it, and then when diabetologists later argued in Diabetes Care that BGMs only confuse patients. How can every one of us accelerate acceptance and adoption of these metrics and targets, as well as CGM, to help people with diabetes live better, healthier lives?

- **FDA's Dr. Courtney Lias encouraged clinicians and researchers to establish metrics and targets with clinical relevance for the sake of this meeting, but drew a line in the sand between these targets and regulatory acceptance:** "[Expert opinion] is important, but not sufficient to support a new surrogate endpoint. We want data." This data to which she is referring would have to support the claim that a surrogate endpoint is correlated with clinical outcomes related to the sponsor's proposed purpose.
    - **Dr. Lias also advised sponsors to take CGM inaccuracies into account in their study designs: "**Really look at some of the uncertainty in point accuracy you're getting in studies. If you look at the regulation for iCGM, that's literally the best they can do right now. SMBG is better at point values. Of course, SMBG can't do everything that CGM can do. But if you're just looking at a glucose value from CGM, each individual value is not as accurate. I recommend modeling inaccuracy, putting that into your design, especially in a drug trial where you want to measure a range using CGM; building in what is the inaccuracy of that estimate. It'd probably be confidence or variation."
- **Over the course of the meeting, Medtronic's Dr. Vigersky and Dexcom's Dr. David Price shared some interesting tidbits on real-world time-in-ranges from their user bases:**
    - **Dexcom users spend ~3% per day <70 mg/dl.**
    - **Type 1 Medtronic Guardian Connect users spend 4% <70 mg/dl; type 1 Medtronic SAP users spend ~3.5% <70 mg/dl.**
    - **Type 2s on Medtronic SAP spend 1.1% time <70 mg/dl.**

-- by Brian Levine and Kelly Close