CLOSER LOOK

MEMORANDUM

DCCT time-in-range analysis published in Diabetes Care, linking time in 70-180 mg/dl to complications; a major victory for BeyondA1c validation - October 25, 2018

Executive Highlights

- ***Diabetes Care* has published time-in-range analysis using fingerstick glucose data from DCCT:** Validation of Time in Range as an Outcome Measure for Diabetes Clinical Trials (Drs. Roy Beck, Rich Bergenstal et al.). The compelling data shows a clear, consistent association between time spent in the range of 70-180 mg/dl and the development/progression of retinopathy and microalbuminuria. Obviously CGM was not used in DCCT, so taking seven-point fingerstick data was the only option here. Dr. Roy Beck first presented the data at ADA 2018 and shows more in-depth analysis here.
- **This landmark publication offers important validation for time-in-range, linking it to long-term complications** in one of the most famous diabetes trials ever conducted. The authors provide a very strong conclusion: "Based on these results, a compelling case can be made that TIR is strongly associated with the risk of microvascular complications and should be an acceptable end point for clinical trials."

In a tremendous victory for the BeyondA1c movement, *Diabetes Care* published a very important article online yesterday: "Validation of Time in Range as an Outcome Measure for Diabetes Clinical Trials" (Dr. Roy Beck, Dr. Richard Bergenstal, Dr. Tonya Riddlesworth, Dr. Craig Kollman, Dr. Zhaomian Li, Adam Brown, Kelly Close).

The compelling DCCT analysis, first presented by Dr. Roy Beck at ADA 2018, shows a clear, consistent association between time-in-range (70-180 mg/dl) and the development/progression of retinopathy and microalbuminuria - see the pictures below. Since CGM was not used in DCCT, the clever analysis did the next-best thing: assessing time-in-range based on seven-point fingerstick data taken once every three months during DCCT.

Time-in-range was 52% in the DCCT intensive treatment group vs. 31% with conventional treatment ($p<0.001$), corresponding to a mean glucose of 160 mg/dl vs. 233 mg/dl.

Further, time-in-range was just 32% in those that developed the retinopathy and microalbuminuria outcomes vs. 42%-44% in those who didn't. Notably, the hazard rate for developing retinopathy was *increased by 64%* for each 10 percentage points lower time-in-range. Compared to the group with time-in-range ≥50%, those at <30% had a nearly seven-fold higher risk of developing retinopathy - wow. The same was true for developing microalbuminuria: for each 10 percentage points lower time-in-range, the hazard rate was increased by 40%.

Every table and graphic in this article is fascinating, and we especially appreciate the article's conclusion: "Based on these results, a compelling case can be made that TIR is strongly associated with the risk of microvascular complications and should be an acceptable end point for clinical trials. Although hemoglobin A1c remains a valuable outcome metric in clinical trials, TIR and other glycemic metrics - especially when measured with continuous glucose monitoring - add value as outcome measures in many studies." Hear, hear! We were honored to be co-authors on this publication.

We hope to see this paper widely used to support the value of CGM endpoints in clinical trials, to encourage payers that time-in-range is an important endpoint, and perhaps to urge FDA that drugs and devices could be *indicated* for improving time-in-range.

- **This DCCT analysis cannot answer another interesting question: What is the outcomes difference once time-in-range levels get above 70%, 80%, and 90%?** As seen in the graph below, very few DCCT patients had a time-in-range >70%, and even in 2018, very few people with diabetes are hitting such targets now, as we understand it. Still, as CGM, automated insulin delivery, and perhaps SGLT-2 inhibitors become more widely used in type 1 diabetes, this sort of sensitivity analysis will be valuable to see - e.g., by linking TIR data to healthcare claims, costs, hospitalizations, etc. We note that more stable insulins and more frequent BGM and CGM have almost certainly contributed to better TIR in recent years. We know it can improve significantly.

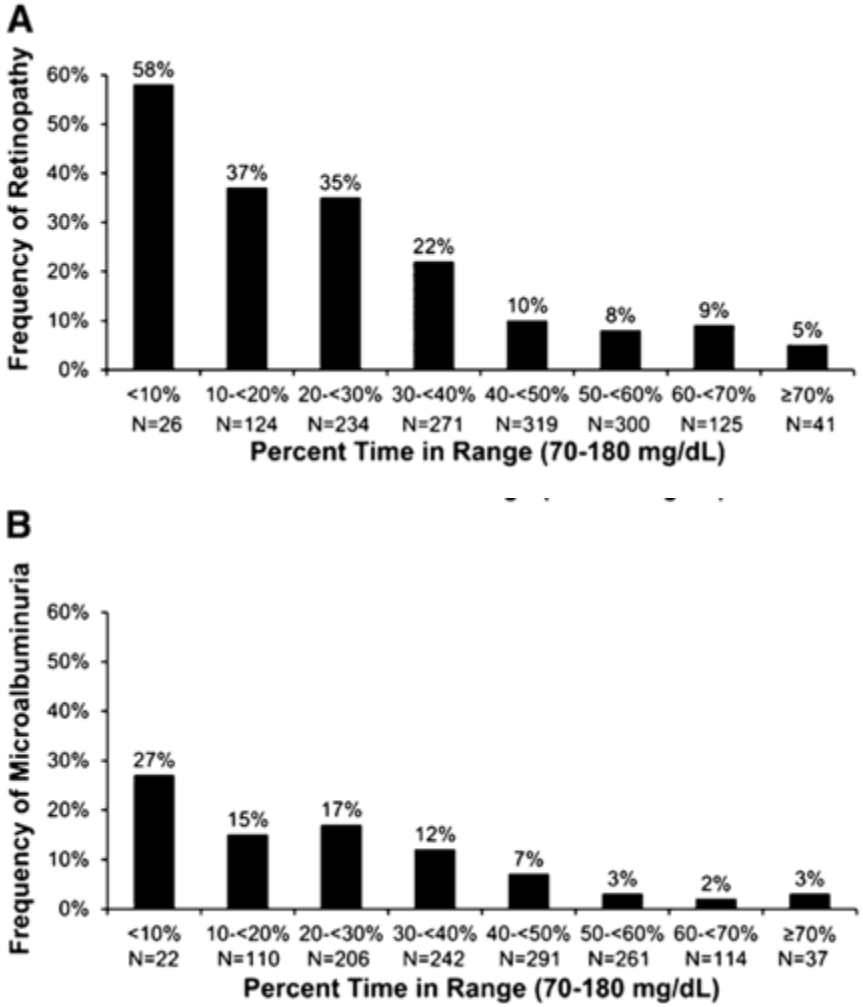

Table 1—Hazard ratios for development of retinopathy and microalbuminuria outcomes according to TIR

	Retinopathy outcome				Microalbuminuria outcome			
TIR	*N*	*N* (%) with outcome	Unadjusted HR (95% CI)*	Adjusted HR (95% CI)†	*N*	*N* (%) with outcome	Unadjusted HR (95% CI)*	Adjusted HR (95% CI)†
Overall								
≥50%	466	36 (8)	1.00	1.00	412	10 (2)	1.00	1.00
40 to <50%	319	32 (10)	1.54 (0.94–2.55)	1.61 (0.97–2.65)	291	20 (7)	2.44 (1.05–5.67)	2.40 (1.03–5.58)
30 to <40%	271	59 (22)	3.38 (2.22–5.15)	3.37 (2.20–5.15)	242	29 (12)	4.74 (2.16–10.40)	4.39 (2.01–9.58)
<30%	384	144 (38)	6.23 (4.25–9.13)	6.93 (4.69–10.24)	338	57 (17)	6.68 (3.35–13.29)	6.98 (3.49–13.96)
Primary cohort								
≥50%	228	8 (4)	1.00	1.00	222	3 (1)	1.00	1.00
40 to <50%	159	10 (6)	2.43 (0.91–6.53)	2.43 (0.90–6.54)	153	4 (3)	1.25 (0.19–8.41)	1.24 (0.18–8.36)
30 to <40%	131	25 (19)	7.08 (3.09–16.23)	6.51 (2.82–15.02)	123	6 (5)	3.68 (1.00–13.47)	3.61 (0.98–13.21)
<30%	208	64 (31)	11.29 (5.13–24.85)	11.16 (5.05–24.64)	200	23 (12)	7.35 (2.22–24.26)	7.24 (2.19–23.94)
Secondary cohort								
≥50%	238	28 (12)	1.00	1.00	190	7 (4)	1.00	1.00
40 to <50%	160	22 (14)	1.30 (0.73–2.31)	1.38 (0.77–2.45)	138	16 (12)	2.91 (1.05–8.02)	2.92 (1.05–8.08)
30 to <40%	140	34 (24)	2.39 (1.43–3.97)	2.50 (1.50–4.17)	119	23 (19)	5.11 (1.91–13.65)	4.76 (1.79–12.68)
<30%	176	80 (45)	4.95 (3.16–7.77)	5.72 (3.60–9.09)	138	34 (25)	6.93 (2.90–16.59)	6.78 (2.83–16.25)

Strata based on TIR averaged over the entire DCCT study period. HR, hazard ratio. *From discrete Cox proportional hazards regression models. *P* value, computed using TIR as a time-dependent continuous variable, is <0.001 for each cohort. †From discrete Cox proportional hazards regression models stratified by the ETDRS level of retinopathy at baseline and adjusted for the pre-DCCT glycemic exposure represented by the preexisting duration of diabetes separately for the primary and secondary cohorts. *P* value, computed using TIR as a time-dependent continuous variable, is <0.001 for each cohort. An additional model which included age and sex as covariates produced similar results.

Table 3—Summary of glucose metrics according to treatment group

	Treatment group	
	Intensive (*n* = 711)	Conventional (*n* = 729)
% TIR	52 ± 10	31 ± 12
Mean glucose (mg/dL)	160 ± 30	233 ± 47
% Time >180 mg/dL	34 ± 12	64 ± 15
% Time >250 mg/dL	13 (8, 20)	41 (30, 53)
AUC 180 mg/dL	23 (15, 35)	71 (49, 97)
HBGI	8 (6, 11)	21 (16, 27)
A1C (%)	7.3 ± 1.0	9.1 ± 1.3
% Time <70 mg/dL	13 (9, 17)	5 (2, 8)
% Time <54 mg/dL	5 (3, 7)	2 (1, 3)
Coefficient of variation (%)	53 ± 7	46 ± 7

Values shown are mean ± SD or median (quartiles) as appropriate for the distribution. For treatment group comparison of each metric, *P* value <0.001 from a linear regression model adjusted for the baseline value. Due to skewed distributions, van der Waerden scores were used for % time >250 mg/dL, AUC 180 mg/dL, HBGI, % time <70 mg/dL, and % time <54 mg/dL. AUC, area under the curve.

--by Adam Brown and Kelly Close