

Using Real-World Data to Establish an Optimal Treatment Target for HbA1c in Diabetes Type 2



TriNetX

Manfred Stapff, Stephan Palm, Jennifer Stacey

TriNetX, Inc., Cambridge, MA, USA

BACKGROUND

Treatment of many diseases is a risk/benefit balancing act between positive and negative effects. As a surrogate parameter for treatment of diabetes mellitus type 2 (T2DM), Hemoglobin A1c (HbA1c) is used. Its target values are mostly based on findings in randomized clinical trials, which do not always reflect real-world medical practice. HbA1c target recommendations vary: A J-shaped curve for HbA1c has been discussed as results of meta-analyses (1), the possibility of “overtreatment”, especially in the elderly, has been suggested (2) and recent treatment guidelines have been loosened (3).

OBJECTIVES

This study intended to identify an optimal target HbA1c range using real-world data (RWD) from electronic medical records (EMRs) in patients over 50 years of age with T2DM:

- How do hemoglobin A1c values correlate with glucose values, hypoglycemic events, and diabetic complications?
- Is there an ideal target HbA1c value which can be recommended as the best balance between complications of diabetes and consequences of overtreatment, especially for the elderly?

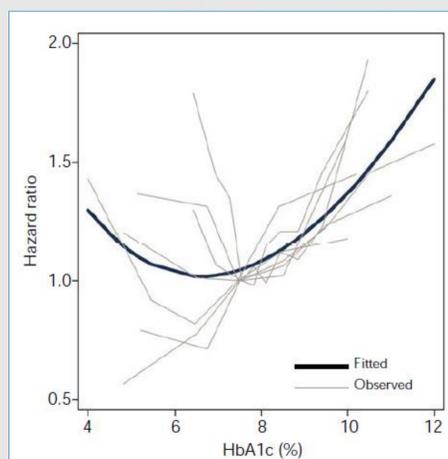


Figure 1: Suggested J-shaped curve for HbA1c and mortality: Metanalysis of studies plotted against the predicted curve from regression analysis for studies with HRs reported for more than four HbA1c categories.

Source: Literature (1)

METHODS

Data Source: We used TriNetX, a global health research network with the ability to perform real-time analyses on EMRs of >43 million patients, predominantly in the US (numbers as of January 2018). The network contained 2,575,870 patients with T2DM (IC10 code E11), of which 2,165,560 were over 50 years of age.

Patient Cohorts: 122,819 patients had stable HbA1c values as defined by having two values within predefined stratum limits at least 6 months apart from each other. The five strata were: HbA1c: < 5.5 | 5.5 - 6.49 | 6.5 - 7.49 | 7.5 - 8.49 | > 8.5 %

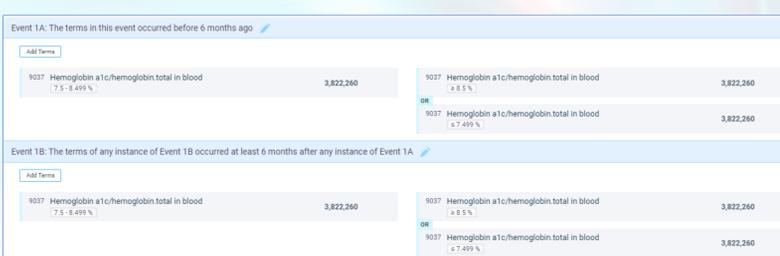


Figure 2: Definition of stable HbA1c value (example for stratum 7.5 – 8.49 %)

Outcome Definition: To define “hypoglycemic event” ICD10 codes E16.0, E16.1, E16.2, E11.64 or a blood glucose value below 70 mg/dL were used. ICD10 codes E11.65, E11.62, E11.61, E11.2, E11.4, or E11.5 were used to define diabetic complications (hyperglycemic event, diabetic ulcer, diabetic arthropathy, kidney complications, neurological complications, or circulatory complications, respectively).

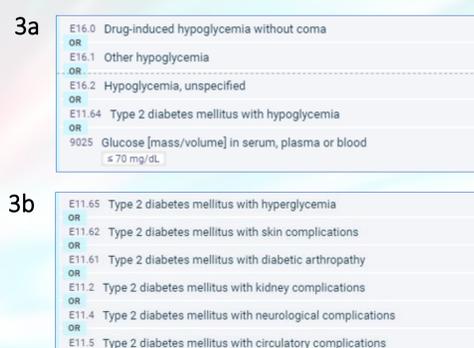


Figure 3: Definition hypoglycemic event (3a) and diabetic complication (3b).

RESULTS

- 122,810 patients fulfilled the HbA1c stability criteria and could be stratified into one of the five strata. The majority of patients (62,330) had HbA1c values between 5.5 and 6.49% on two occasions at least 6 months apart from each other.
- 25,380 patients had HbA1c over 8.5%, and only 200 patients below 4.5%.
- With exception of the low HbA1c stratum (<4.5%), mean age, gender and concomitant hypertension did not differ significantly across the strata. (See Table 1).
- Median glucose values correlated well with HbA1c, from 110 mg/dL with HbA1c < 4.5% to 209 mg/dL with HbA1c > 8.5%.
- The incidence of hypoglycemic events were the highest in the two lowest HbA1c strata, indicative of a higher hypoglycemic risk if T2DM is “overtreated”.
- The frequency of diabetic complications increased with HbA1c values above 6.5% as to be expected.
- Surprisingly, the lowest HbA1c stratum (<4.5%) showed a higher diabetic complication rate than the median strata (4.5 – 6.5%), which could be contributed to “overtreated” severe cases or just a consequence of the low sample size in this stratum.
- Similarly, the percentage of patients on insulin showed a J-shaped curve, too, which may confirm the hypothesis of “overtreatment” of severe cases.
- However, the J-shape did not change when patients on insulin were removed from the cohort.
- Overall, patients in the HbA1c stratum of 5.5 – 6.49% had the lowest risk of experiencing a hypoglycemic event and also the lowest diabetic complication rate (See Figure 4).

Table 1: Patient distribution in HbA1c strata.

	n, all	200	8,410	62,330	21,780	4,710	25,380
HbA1c		< 4.5	4.5 - 5.49	5.5 - 6.49	6.5 - 7.49	7.5 - 8.49	> 8.5
mean age	67	67	70	71	70	63	
% female	46%	53%	57%	53%	49%	51%	
% with hypertension	70%	83%	86%	86%	85%	86%	

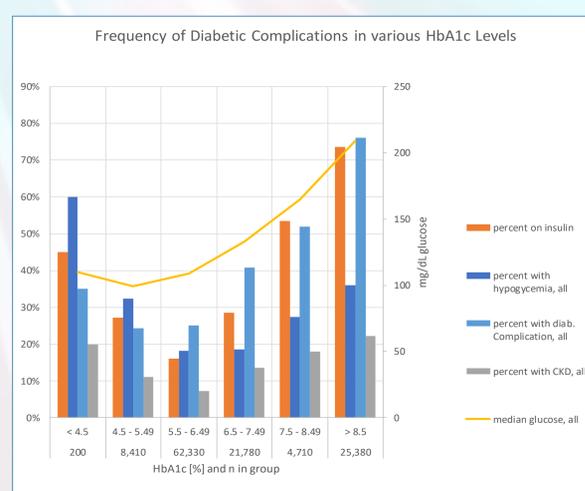


Figure 4: J-shaped curve of HbA1c strata, risk of hypoglycemia, and diabetic complications.

CONCLUSIONS

- Real-world data confirmed an excellent correlation between HbA1c and median glucose values.
- The data suggest a J-shaped curve with a range of HbA1c 5.5 – 6.5 % displaying the lowest frequency of both, hypoglycemic events (“overtreatment”) and diabetic complications.
- To our knowledge this is the first study proposing an optimal HbA1c treatment target for T2DM based on a large set of real-world data.

REFERENCES

1. Luke W. The HbA1c and All-Cause Mortality Relationship in Patients with Type 2 Diabetes is J-Shaped: A Meta-Analysis of Observational Studies. The Review of DIABETIC STUDIES Vol 11 No 2 2014
2. Lipska KJ. Potential Overtreatment of Diabetes Mellitus in Older Adults With Tight Glycemic Control. JAMA Intern Med. 2015;175(3):356-362
3. Quaseem A. et.al. Hemoglobin A1c Targets for Glycemic Control With Pharmacologic Therapy for Nonpregnant Adults With Type 2 Diabetes Mellitus: A Guidance Statement Update From the American College of Physicians. Ann Intern Med. doi:10.7326/M17-0939