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

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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 “over-treatment”, 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?

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 2,755,870 patients with T2DM (ICD code E11), of which 2,165,560 were over 50 years of age.

Patient Cohort: 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%

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 “over-treated”.
- 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 stratum (4.5 – 6.5%), which could be contributed to “over-treated” 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 “over-treatment” 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).

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 (“over-treatment”) 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
2. Lipska KJ. Potential Overtreatment of Diabetes Mellitus in Older Adults With Tight Glycemic Control. JAMA Intern Med. 2015;175(3):356-362

Figure 1: Suggested J-shaped curve for HbA1c and mortality: Meta-analysis of studies plotted against the predicted curve from regression analysis for studies with HbA1c values exceeding four HbA1c categories. Source: Literature (1)

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

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

Table 1: Patient distribution in HbA1c strata.

Table 2: Frequency of Diabetic Complications in various HbA1c Levels.