The type 1 diabetes patient decision-making model for assessing the influence of hypo/hyper-alert settings on continuous glucose monitoring (CGM) nonadjunctive use

M. Vettoretti[1], A. Facchinetti[1], G. Sparacino[1] and C. Cobelli[1]

[1]Department of Information Engineering, University of Padova, Padova, Italy

1. INTRODUCTION

By using a **type 1 diabetes patient decision-making (T1D-DM) model** and in silico trials, we recently proved the safety and effectiveness of continuous glucose monitoring (CGM) nonadjunctive use, i.e. the use of CGM to make treatment decisions (results presented at the FDA Advisory Panel meeting of July 21st [1]). A further step is assessing how customizable **high alert** (HA) and **low alert** (LA) affect CGM nonadjunctive use performance.

2. AIM

The aim is to perform an in silico clinical trial with the T1D-DM model to assess how the setting of customizable HA and LA thresholds influences the glycemic control achieved by CGM nonadjunctive use compared to standard treatment based on SMBG.

3. THE T1D-DM MODEL

The T1D-DM model [2] simulates the blood glucose (BG) concentration of T1D subjects making treatment decisions based on glucose monitoring devices (SMBG or CGM). The model includes four components:

A. the **UVA/Padova simulator** of T1D patient metabolism [3]
B. models of **glucose monitoring devices** (both SMBG and CGM)
C. a model of the **patient's behavior** in making treatment decisions for different treatment scenarios
D. a model of **insulin** infusion **pump**

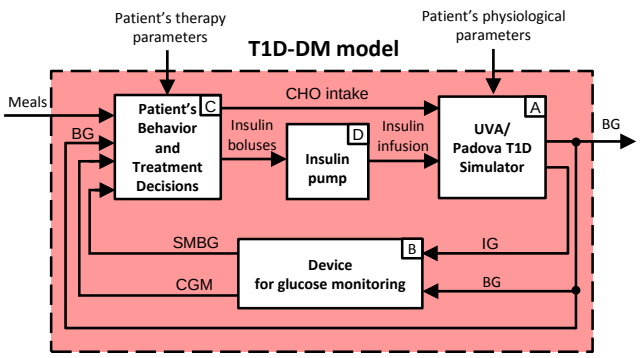

Fig. 1. Schematic representation of the T1D-DM model.

Implementation:

- SMBG and CGM measurements were simulated by models of the Bayer Contour Next USB [4] and the Dexcom G5 Mobile [5].
- The patient's behavior and treatment decision model was designed to reproduce treatments based on SMBG (Fig. 2, A) and nonadjunctive CGM use (Fig. 2, B).

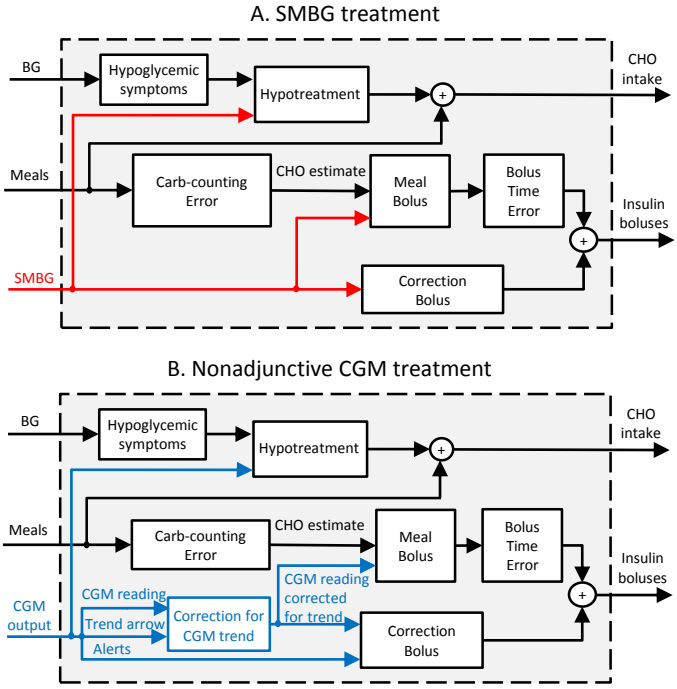

Fig. 2. Schematic representation of the patient's behavior and treatment decision model when treatments based on SMBG (A) and nonadjunctive CGM use (B) are simulated.

4. IN SILICO CLINICAL TRIAL AND METRICS

100 adult virtual subjects, 2 weeks, 2 treatment scenarios:

- **SMBG treatment** with different number of post-meal checks (PMC) per day, i.e. 0, 1, 2, 3.
- **Nonadjunctive CGM treatment** with 3 different LA thresholds, i.e. 80, 70 and 55 mg/dl, and 7 different HA thresholds, i.e. 180, 200, 250, 300, 350, 400 mg/dl and none.

Simulations are run twice, first assuming **normal awareness of hypoglycemia** (i.e. symptoms start at BG>50 mg/dl), then assuming **impaired awareness of hypoglycemia** (i.e. symptoms start at BG≤50 mg/dl).

Metrics:

$\Delta T_{70\text{-}180}$ [h/day], $\Delta T_{<70}$ [min/day], $\Delta T_{<50}$ [min/day], $\Delta T_{>180}$ [h/day] and $\Delta T_{>250}$ [h/day] i.e. the difference between time in 70-180 mg/dl, time below 70 mg/dl, time below 50 mg/dl, time above 180 mg/dl and time above 250 mg/dl with nonadjunctive CGM and the worst-case SMBG scenario.

One-tailed sign test (5% significance level) to determine if median $\Delta T_{70\text{-}180}$ is significantly <0 and median $\Delta T_{<70}$, $\Delta T_{<50}$, $\Delta T_{>180}$ and $\Delta T_{>250}$ are significantly >0.

5. RESULTS

The worst-case SMBG scenario is the one with PMC=0 for time in 70-180 mg/dl, time above 180 and 250 mg/dl, the one with PMC=3 for time below 70 and 50 mg/dl.

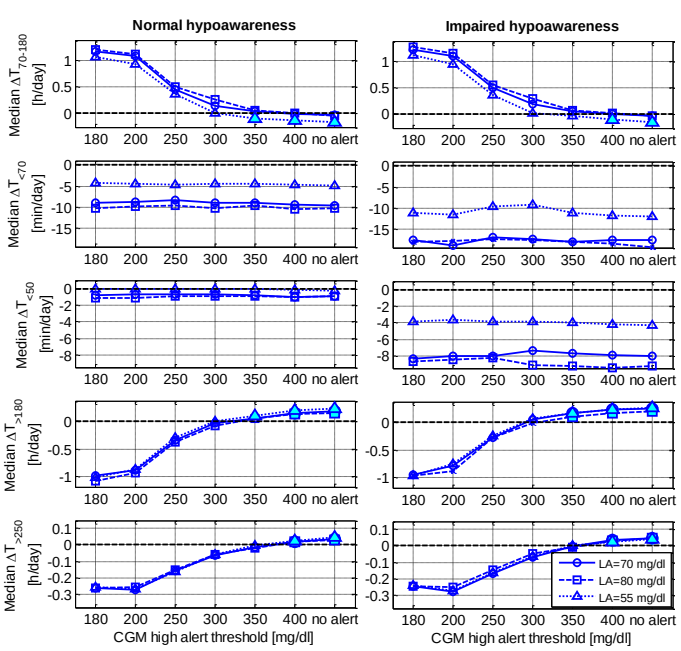

Fig. 3. Median $\Delta T_{70\text{-}180}$, $\Delta T_{<70}$, $\Delta T_{<50}$, $\Delta T_{>180}$ and $\Delta T_{>250}$ calculated in 100 adult virtual subjects with normal (left) and impaired (right) hypoawareness. In each panel, blue curves represent the metric's median value on varying HA threshold with LA threshold equal to 80 (dashed line with squares), 70 (solid line with circles) and 55 mg/dl (dotted line with triangles). Filled markers indicate the alert settings for which median $\Delta T_{70\text{-}180}$ is statistically significantly <0, and median $\Delta T_{<70}$, $\Delta T_{<50}$, $\Delta T_{>180}$ and $\Delta T_{>250}$ are statistically significantly >0.

Nonadjunctive CGM compared to worst-case SMBG scenario:

- never deteriorates time below 70 and 50 mg/dl for any alerts;
- significantly deteriorates time above 180 mg/dl for HA≥350 mg/dl, time above 250 mg/dl for HA≥400 mg/dl;
- significantly deteriorates time in 70-180 mg/dl for HA≥350, in normal hypoawareness, and HA≥400 mg/dl, in impaired hypoawareness.

Best glycemic control is achieved with LA=80 mg/dl, HA=180 mg/dl.

6. CONCLUSIONS

The trial demonstrated that nonadjunctive CGM use, compared to SMBG, drives to equivalent or reduced time in hypoglycemia for all the alert settings, with major benefits for patients with impaired hypoawareness. Conversely, time in hyperglycemia is reduced only when HA is close to 180 mg/dl and significantly increased when HA is not used or very high (e.g. 400 mg/dl).

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CONTACT: Martina Vettoretti, martina.vettoretti@dei.unipd.it

ATTD Advanced Technologies & Treatments for Diabetes

DEPARTMENT OF INFORMATION ENGINEERING UNIVERSITY OF PADOVA