Clinical Chemistry 60:12
1510–1518 (2014)

Modeling of Effect of Glucose Sensor Errors on Insulin Dosage and Glucose Bolus Computed by LOGIC-Insulin

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BACKGROUND: Effective and safe glycemic control in critically ill patients requires accurate glucose sensors and adequate insulin dosage calculators. The LOGIC-Insulin calculator for glycemic control has recently been validated in the LOGIC-1 randomized controlled trial. In this study, we aimed to determine the allowable error for intermittent and continuous glucose sensors, on the basis of the LOGIC-Insulin calculator.

METHODS: A gaussian simulation model with a varying bias (0%–20%) and CV (−20% to +20%) simulated blood glucose values from the LOGIC-1 study (n = 149 patients) in 10 Monte Carlo steps. A clinical error grid system was developed to compare the simulated LOGIC-Insulin–directed intervention with the nominal intervention (0% bias, 0% CV). The severity of error measuring the clinical effect of the simulated LOGIC-Insulin intervention was graded as type B, C, and D errors. Type D errors were classified as acutely life-threatening (0% probability preferred).

RESULTS: The probability of all types of errors was lower for continuous sensors compared with intermittent sensors. The maximum total error (TE), defined as the first TE introducing a type B/C/D error, was similar for both sensor types. To avoid type D errors, TEs <15.7% for intermittent sensors and <17.8% for continuous sensors were required. Mean absolute relative difference thresholds for type C errors were 7.1% for intermittent and 11.0% for continuous sensors.

CONCLUSIONS: Continuous sensors had a lower probability for clinical errors than intermittent sensors at the same accuracy level. These simulations demonstrated the suitability of the LOGIC-Insulin control system for use with continuous, as well as intermittent, sensors.

Most critically ill patients have high blood glucose concentrations, independent of any history of diabetes. This hyperglycemia is associated with adverse outcomes in both adults and children treated in the intensive care unit (ICU),[3] and the observed relationship with adverse outcomes follows a J-shaped curve *(1, 2)*. Randomized controlled trials (RCTs) that evaluated the effects of normalizing blood glucose concentrations have shown mixed results. Although tight glycemic control (TGC) reduced morbidity and mortality in a single center *(3–5)* and in early implementation studies *(6, 7)*, TGC had either no effect or increased mortality in multicenter trials *(8–10)*. Unlike in the multicenter trials, the bedside execution of TGC in the Leuven single-center studies was highly standardized *(11)*. The frequent blood glucose measurements were done only on arterial blood by on-site blood gas analyzers. An intuitive paper-based protocol guided the well-trained nurses on insulin dosing. Insulin was only continuously infused by accurate syringe pumps through a central line.

The ICU community is now convinced that more attention should be paid to the accuracy of blood glucose meters and the adequacy of insulin dosage calculators *(12–14)*. The impact of sensor inaccuracy on insulin dosing errors may also be algorithm dependent. Consensus meetings *(13)* have been trying to define critical care–specific accuracy criteria, as the common accuracy norms (International Organization for Standardization 15197, CLIA, CLSI POCT12-A3) for time-intermittent blood glucose meters were not designed for the ICU setting *(15, 16)*. Continuous glucose monitoring (CGM) devices (and near-continuous devices) will play a role in blood glucose control in the ICU in the near future. However, norms on accuracy and clinical validation protocols for CGM devices are lacking. Clinical intervention trials to test the effect of sensor inaccuracy on blood glucose control may not be desirable. Computer modeling of sensor accuracy and bias

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Received May 9, 2014; accepted August 1, 2014.
Previously published online at DOI: 10.1373/clinchem.2014.227017

[3] Nonstandard abbreviations: ICU, intensive care unit; RCT, randomized controlled trial; TGC, tight glycemic control; CGM, continuous glucose monitoring; IQR, interquartile range; SE, severity of error; TE, total error; MARD, mean absolute relative difference; p75, 75th percentage (of the IQR).

for intermittent blood glucose meters and CGM devices has been proposed as an alternative *(17–19)*. Notably, the incidence of dangerous hypoglycemia episodes by overestimation of blood glucose concentrations, and consequently overdosing of insulin, need to be evaluated for intermittent and CGM sensors. Because more measurements are available, it can be expected that the accuracy requirements are lower for continuous glucose sensors compared with intermittent sensors. Boyd and Bruns recently performed a first simulation study that provided data to support this expectation in a virtual ICU setting, by use of the Yale and University of Washington algorithms in a virtual glucose regulation model *(20)*.

Recently, we clinically validated the LOGIC-Insulin blood glucose algorithm in an RCT *(21)*. This software system, incorporating an advanced algorithm *(22)*, advises the bedside nurse on insulin dosage (or glucose bolus in the event of hypoglycemia) and the timing of the next blood sampling. A group of 300 critically ill patients were randomized according to blood glucose control performed by the nurse or guided by the LOGIC-Insulin software system. Blood glucose control by LOGIC-Insulin was tighter than that of nurses (lower glycemic penalty index *(23)*) and safer (lower number of hypoglycemic events). During the study, blood glucose concentrations were measured in undiluted blood, drawn from the arterial line, by accurate on-site blood gas analyzers and at a frequency determined by LOGIC-Insulin for the patients of the LOGIC arm [mean sampling interval of 2.2 (0.4) h]. In the patients allocated to the LOGIC-Insulin treatment group, insulin dosing and timing of blood glucose measurements were hence standardized. Both intermittent and CGM sensors were analyzed on the basis of the patient data from the LOGIC-1 RCT *(21)*. Bias and imprecision were added to these real-life glucose trajectories, and the treatment effect (due to these inaccurate glucose readings) was compared with the clinical treatment that was effectively given to the patient during the RCT (i.e., by use of the raw glucose readings without added bias or imprecision). The aim of this simulation study was to determine allowable accuracy levels for intermittent and CGM sensors in real-life patient data.

Materials and Methods

SIMULATIONS BY USE OF REAL-LIFE CLINICAL PATIENT DATA

The LOGIC-Insulin control system is a computerized algorithm that computes the most optimal insulin dose (or glucose bolus in case of hypoglycemia) to achieve normoglycemia in critically ill patients. Real-life patient data of 149 critically ill patients, originating from the LOGIC arm of the LOGIC-1 RCT and studied for a median time period of 1.9 days [interquartile range (IQR) 1.2–4.7 days] *(21)*, provided the foundation of this simulation study. Instead of simulating the glucose dynamics by use of a mathematical model *(20, 24–26)*, we recomputed insulin dosages and glucose boluses by the LOGIC-Insulin algorithm assuming less accurate glucose sensor values. The intermittent version of the algorithm was adapted for continuous glucose measurements so that trend information of the glucose trajectories could be computed more accurately. With CGM, the glucose values at the time points that the LOGIC-Insulin intervention was computed during the LOGIC-1 RCT, were averaged over the last 10 min of CGM glucose data instead of adopting just the actual blood glucose at that time point (which is the case for intermittent values). In this simulation study, we gradually modified the accuracy level of the glucose values. For both the intermittent and the continuous scenario, we kept the time points of the protocol-directed interventions the same as with the LOGIC-1 RCT, allowing us to compare the new (simulated) LOGIC-Insulin interventions with the original (nominal) LOGIC-Insulin interventions. We initially set up a clinical error grid system to clinically assess the differences between the original and new LOGIC-Insulin–directed interventions. The methodology has the advantage that real-life glucose dynamics, often missed by mathematical models, are included to better approach reality by use of simulations.

CLINICAL ERROR GRID SYSTEM

We clinically assessed the new LOGIC-Insulin interventions by use of a 3-dimensional error grid system. The first and second dimensions evaluate the absolute difference of insulin dose and glucose bolus. The third dimension compares the relative insulin change with respect to the previous (effectively administered) insulin dose. This third category gives information on the computed insulin dose that may be masked for the first category (absolute insulin dose). For example, an insulin dose difference of 2 U/h is called large if the previously delivered dosage was only 1.5 U/h, but is called small if the previous dose was 10 U/h. The third dimension indicates that the insulin dose error for the first case is potentially more dangerous than for the second case, as the difference of relative change is 133% for the first case and only 20% for the second case.

Next, the level of deviation for each category was compared to "acceptable" and "unacceptable" boundaries, varying as a function of glycemia. These boundaries were determined before the start of the study on the basis of normal data distributions observed in the LOGIC-RCT *(21)* and by consulting medical experts. Supplemental Appendix 1, which accompanies the online version of this article at http://www.clinchem.org/

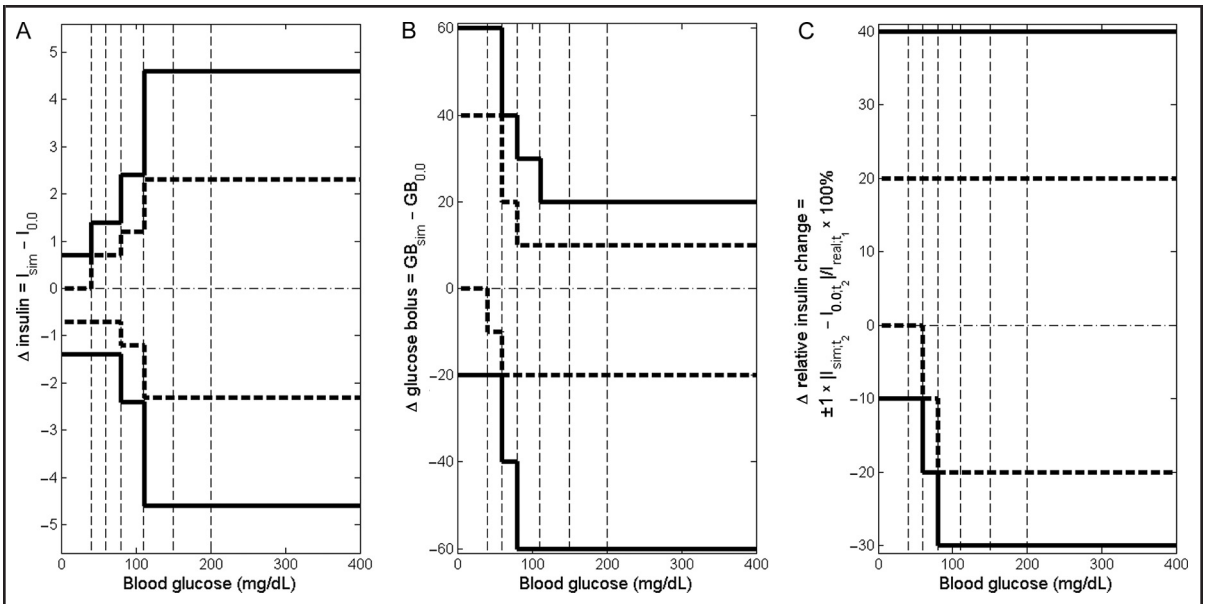

Fig. 1. Clinical error grid system from three different perspectives.

(A), Δ absolute insulin dose (I). (B), Δ absolute glucose bolus (GB). (C), Δ relative insulin change (RI). The acceptable and unacceptable boundaries are presented by the dashed and solid lines, respectively.

content/vol60/issue12, describes in detail the origin of these boundaries, which are visualized in Fig. 1. Deviations that fell between the acceptable and unacceptable boundaries were categorized as errors that should be avoided but without being a direct life-threatening situation. Deviations falling outside the unacceptable boundaries were regarded as potentially severe life-threatening (hypoglycemia) errors. All deviations were numerically transformed to an error code per category (E_1, E_2, and E_3; see Table 1). The sum of these 3 error codes, called the severity of error (SE) and obtained for each simulated LOGIC-Insulin intervention, was related to a type of error:

- Type A errors: none or inconsequential, $0 \leq SE < 3$;
- Type B errors: severe but not life-threatening, $SE \geq 3$;
- Type C errors: potentially life-threatening, $SE \geq 6$;
- Type D errors: acutely life-threatening, $SE \geq 10$.

The type D class of errors is present only in case of highly inappropriate treatment of hypoglycemia (e.g., administration of a substantial amount of insulin when absolutely not indicated during a true hypoglycemic episode and/or no delivery of glucose bolus when appropriate).

ACCURACY MODEL

We performed simulations for both intermittent and CGM sensors. The glucose measurements in the LOGIC-RCT *(21)* (use of on-site blood gas analyzer ABL 700, Radiometer Medical) were interpolated as a piecewise cubic hermite polynomial with time interval set at 5 min to obtain a continuous glucose signal. Sensor inaccuracies were modeled by adding relative assay bias, expressed as a positive or negative fraction, and imprecision, expressed as CV multiplied by a random number drawn from a gaussian distribution with mean of zero and standard deviation equal to 1, to the observed glucose signal *(17)*. Bias was varied from −20% to +20% in increments of 5% and from −10% to +10% in increments of 1%, whereas CV was varied from 0% to 10% in increments of 1% and from 10% to 20% in increments of 5%. We ignored other analytical errors (such as nonlinear bias and drift) and user errors in this model.

By use of 10 Monte Carlo simulations with a uniform distribution, a total of 15 720 960 LOGIC-Insulin–directed interventions were generated for the intermittent sensor study and the same number of data points for the CGM sensor study. All of these interventions were compared to the original LOGIC-Insulin interventions and evaluated as explained above, resulting in a type A, B, C, or D error for each intervention. The probability that an error type occurred, combining all 10 Monte Carlo simulations, was computed for each (virtual) sensor type [characterized by a bias and CV value and expressed as a total error (TE) value: TE = absolute(bias) + 1.96 * CV].

The objective was to find the maximum allowable total error (TE_{max}) of a glucose sensor that would still

Table 1. Error code to be determined per LOGIC-Insulin intervention at time point *t* by comparing the simulated interventions (with added error) to the nominal interventions (0% bias, 0% CV).[a]

Intervention	Error code
Category 1	
$\Delta I < LB_{U1}$	$E_1 = 3$
$LB_{U1} \leq \Delta I < LB_{A1}$	$E_1 = 1$
$LB_{A1} \leq \Delta I \leq UB_{A1}$	$E_1 = 0$
$UB_{A1} < \Delta I \leq UB_{U1}$	$E_1 = 1$
$UB_{U1} < \Delta I$	
BG ≥70 mg/dL	$E_1 = 3$
BG <70 mg/dL	$E_1 = 10$
Category 2	
$\Delta GB < LB_{U2}$	
BG ≥50 mg/dL	$E_2 = 3$
BG <50 mg/dL	$E_2 = 10$
$LB_{U2} \leq \Delta GB < LB_{A2}$	$E_2 = 1$
$LB_{A2} \leq \Delta GB \leq UB_{A2}$	$E_2 = 0$
$UB_{A2} < \Delta GB \leq UB_{U2}$	$E_2 = 1$
$UB_{U2} < \Delta GB$	$E_2 = 3$
Category 3	
$\Delta RI < LB_{U3}$	$E_3 = 3$
$LB_{U3} \leq \Delta RI < LB_{A3}$	$E_3 = 1$
$LB_{A3} \leq \Delta RI \leq UB_{A3}$	$E_3 = 0$
$UB_{A3} < \Delta RI \leq UB_{U3}$	$E_3 = 1$
$UB_{U3} < \Delta RI$	$E_3 = 3$

Category 1, Δ absolute insulin dose: $\Delta I_t = I_{sim;t} - I_{0.0;t}$; [ΔI] = IU/h. Category 2, Δ absolute glucose bolus: $\Delta GB_t = GB_{sim;t} - GB_{0.0;t}$; [ΔGB] = mL glucose 50%. Category 3, Δ relative insulin change: $\Delta RI_{t+1} = \pm 1 \times \left| \frac{I_{sim;t+1} - I_{0.0;t+1}}{I_{real;t}} \right| \times 100\%$; [ΔRI] = %. BG, blood glucose; LB, lower boundary; UB, upper boundary; A, acceptable; U, unacceptable.

allow safe use of a less accurate glucose signal by the LOGIC-Insulin control system. Therefore, the probability of type D errors was set at 0% and of type C errors as <0.01%. In a final step, the TE_{max} found at the individual intervention level was related to the mean absolute relative difference (MARD), averaged over the 10 Monte Carlo simulations. MARD is often reported by glucose sensor manufacturers and summarizes the sensor performance at the patient group level.

Results

Fig. 2 presents the relationship between the probability of type B, C, and D errors and the TE (expressed as a combination of bias and CV) of the glucose measurements for both intermittent and CGM devices. The probability of all types of errors is generally lower for continuous sensors compared with intermittent sensors. Indeed, the probability that a specific error type occurs for the same total error is higher with intermittent glucose sensors than with continuous sensors.

The severity of error is augmented from type B errors to type C errors to type D errors, as clarified in the definitions above. Therefore, type B errors are expected to occur more often than type C and D errors, independent of the measurement frequency of the glucose sensor (intermittent/continuous).

The analyses with bias and imprecision as independent parameters are presented in the online Supplemental Data. Contour plots for type A, B, C, and D errors are characterized by a constant probability of appearance as a function of CV (%) and bias (%). As can be expected, the probability of all types of errors increases with higher bias and CV values for both intermittent and continuous glucose sensors (see online Supplemental Figs. 1 and 2). Contour plots of type D errors are rather flat and positive for CGM devices compared with intermittent sensors. This indicates that mainly positive bias errors (i.e., consistent overestimation of the glucose measurements) cause the most dangerous errors in case of continuous measurements. Thus, the effect of imprecision is rather limited for type D errors. Consistently underestimated glucose observations lead to more defensive blood glucose control and hyperglycemia, accordingly. Although the effect of positive bias mainly causes type D errors in case of continuous measurements, imprecision and even negative bias cannot be neglected (for example in case of type C errors).

Assuming zero bias, the probability of type C errors is 0.03% under a fixed TE condition (TE 10%, CV 5.1%) for intermittent glucose measurements (see online Supplemental Fig. 3). Increasing the measurement frequency (continuous glucose measurements, see online Supplemental Fig. 4) returns a >6-fold reduction of this type C error probability to <0.005%.

Fig. 3 shows the probability of type C and D errors as a function of the TE for intermittent (Fig. 3A) and continuous (Fig. 3B) glucose measurements in more detail. Assuming a 10% total error, representing a mixture of bias and/or imprecision returns a mean probability of type C errors of 0.015% for intermittent and 0.0049% for continuous measurements. Compared with the previous TE 10% probabilities (where zero bias was assumed), these probabilities are halved for intermittent measurements and similar for CGM devices. The probability of appearance of type C errors depends merely on the imprecision and less on the bias for intermittent sensors. This is also confirmed by the

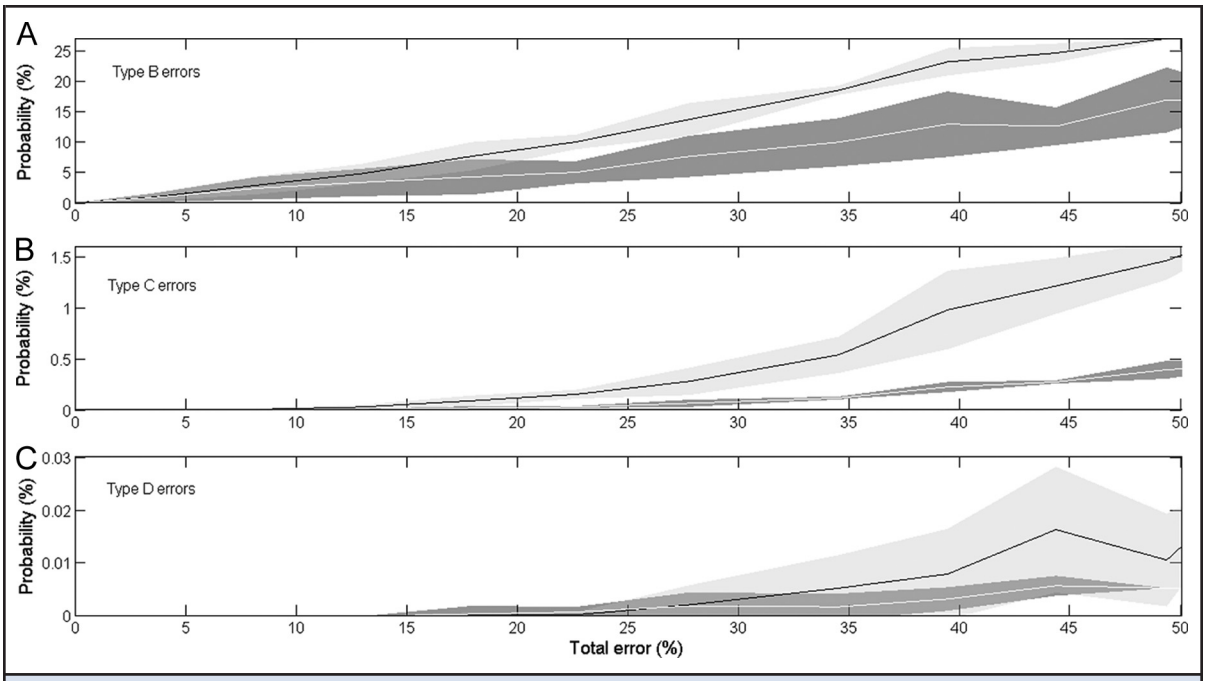

Fig. 2. Probability [mean (SD)] of type B (panel A), C (panel B), and D (panel C) errors as a function of the total error of the sensor.

The probability that an error type occurred, combining all 10 Monte Carlo simulations, was computed for each sensor type under study. In a following phase, and for reasons of clarity, all different sensor types were grouped (5% TE intervals), and the mean probability (SD) per subgroup is presented as a function of the mean TE per subgroup. Means (and SDs) for intermittent glucose sensors are represented by the black line (light gray shaded area) and, for continuous glucose sensors, by the white line (dark gray shaded area).

rather vertical contour plots presented in online Supplemental Fig. 3.

The maximum allowable total error (TE_{max}, indicating the zero probability of type D errors) was 15.7% for intermittent glucose sensors and 17.8% for CGM devices (Fig. 3, A and B). Transforming these (individual) TE_{max} values toward the MARD summary parameter equals an IQR range of 5.7%–12.2% (median 7.9%) for intermittent glucose sensors and 6.5%–13.8% (median 8.9%) for CGM devices (Fig. 4). The condition of an allowable probability of $<0.01\%$ type C errors returns TE_{max} values on average of 9.1% and 14.1% for intermittent and continuous glucose sensors, respectively. Transforming these values to MARD ranges gives 3.3%–7.1% (median 4.6%) for intermittent sensors and 5.2%–11.0% (median 7.1%) for CGM devices.

Discussion

This simulation study, which used true clinical data from critically ill patients in whom TGC was done by the LOGIC-Insulin control system *(21)*, showed that less stringent allowable error criteria may be needed for continuous than for intermittent glucose sensors. It also confirms the conclusion by Boyd and Bruns that quality specifications of intermittent glucose sensors may be different for CGM devices *(20)*. As the likelihood for all insulin-dosing errors rises with increasing glucose sensor inaccuracy (bias and imprecision) for both intermittent and CGM sensors, more attention should be paid to the performance of blood glucose meters and the origins of potential inaccuracy in daily clinical practice in the ICU. In this simulation study, we found that severe errors (type C) are often caused by imprecision for intermittent sensors. In contrast, a consistent positive bias, in particular for CGM devices, is the main reason for most severe, acutely life-threatening insulin dosing errors (type D).

Defining the required accuracy level for a glucose sensor depends on the number of errors that are allowed for adequate and safe clinical use. For reasons of safety, we initially limited the allowable count of type D errors to zero. On the basis of this criterion, the maximum allowable total error for CGM devices was found

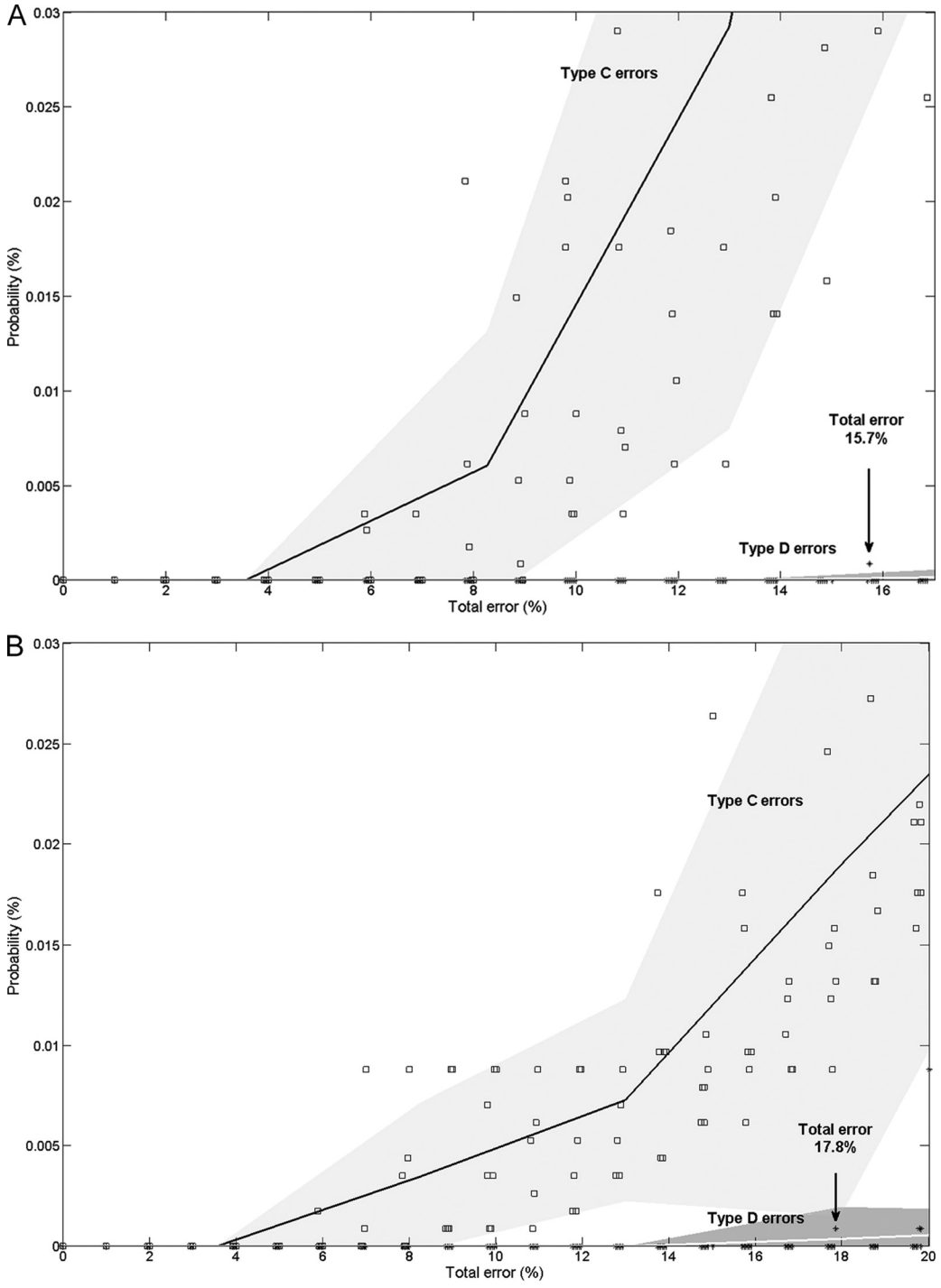

Fig. 3. Detail of Fig. 2.

(A), Probability [mean (SD)] of type C (black line and light gray shaded area) and D (white line and dark gray shaded area) errors as a function of the total error of time-intermittent glucose sensors. (B), Probability [mean (SD)] of type C (black line and light gray shaded area) and D (white line and dark gray shaded area) errors as a function of the total error of continuous glucose sensors. The squares and the stars represent, respectively, the probabilities that a type C or type D error occurred for a specific sensor type under study (characterized by a bias and CV value and expressed as TE value) combining all 10 Monte Carlo simulations.

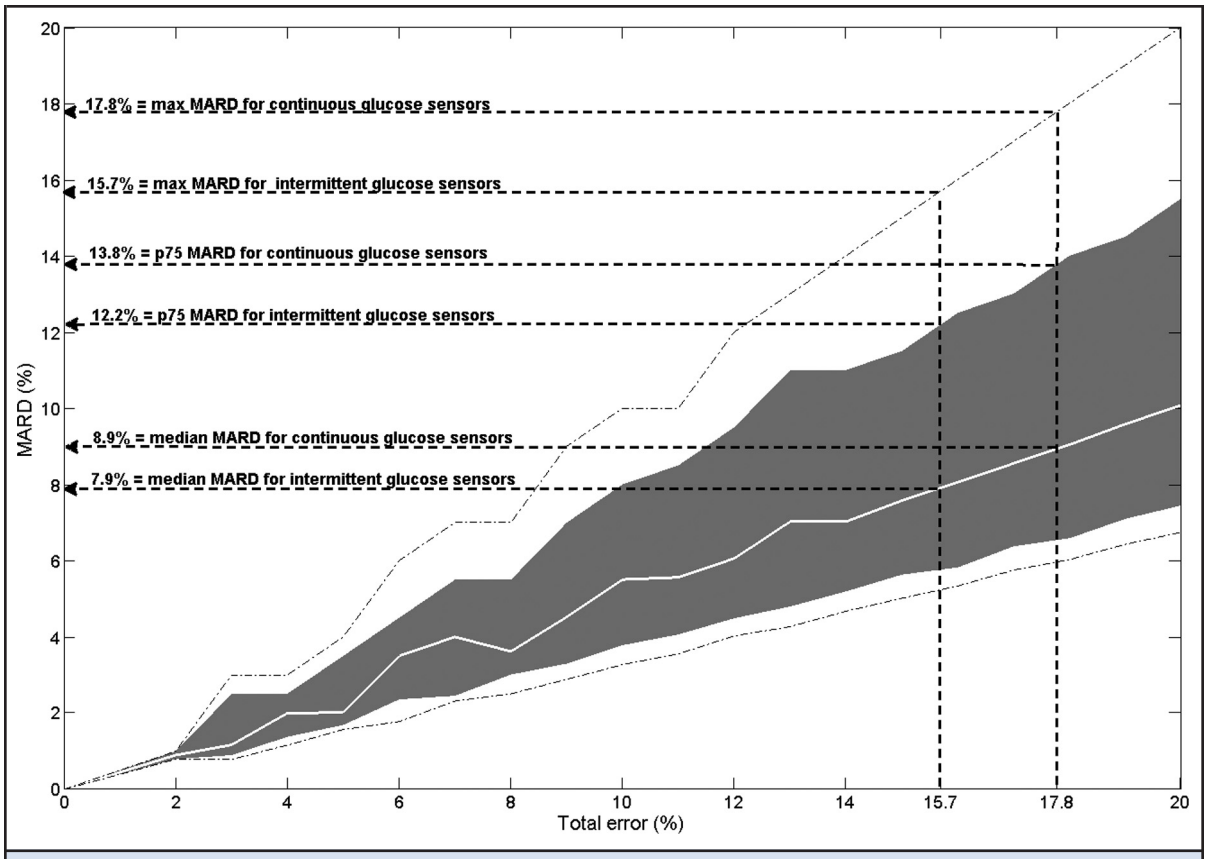

Fig. 4. Median MARD (white line), with shaded area representing the IQR range, as a function of TE of a glucose sensor and averaged over each previous 2% TE interval.

The dashed lines represent the minimum/maximum MARD per TE interval. max, Maximum.

to be larger than for intermittent glucose sensors, but the difference (2.1%) between intermittent and continuous sensors was relatively small. The benefit of CGM devices was more pronounced (difference 5.0%) for maintaining the rate of type C errors at <0.01%. This indicates that glucose control with LOGIC-Insulin algorithm permits the use of less accurate CGM devices, compared with intermittent glucose sensors. Accordingly, accuracy requirements for CGM devices could be lower than for intermittent glucose sensors, as already suggested by Boyd and Bruns *(20)*. However, probabilities for errors are hard for clinicians to interpret.

The MARD values of the simulated glucose sensors, expressed in ranges, give a more practical interpretation of the above results. Intermittent glucose sensors with a fixed TE_{max} criterion of 15.7% returned a range of MARDs. In general, p75 of these MARDS (the 75th percentage of the IQR for MARD) was 12.2% (which may be used as a MARD threshold). The generated MARDs for continuous devices that met the TE_{max} criterion (17.8%) gave a p75 of 13.8%. Taking into account the condition for type C errors, the requirements are even stricter: 75% of the MARDs (with TE 9.1% and 14.1% for intermittent and CGM devices, respectively) are smaller than 7.1% for intermittent and 11.0% for CGM devices. It can be debated whether the type C criterion (error rate <0.01%) is too strict or too loose, but a zero probability of type D errors should be attained. From this simulation study, the maximum MARD that corresponds to the TE_{max} is the absolute minimum requirement a glucose sensor must meet: 15.7% for intermittent glucose sensors and 17.8% for CGM devices. For comparison, the gold standard for glycemic measurements in the ICU, blood gas analyzers, returned an MARD of 3.8% in a recent study *(27)*.

This study has several strengths. First, real-life clinical patient data were used. This allowed the acquisition of realistic glucose trajectories including complex dynamics, which are rarely incorporated in mathematical models. Second, the exact knowledge of the insulin dosing algorithm used during the clinical study made it possible to recompute the insulin doses (and glucose boluses) for dif-

ferent (simulated) glucose measurements and to compare to the original doses. Third, these insulin dosages (and glucose boluses) were assessed by use of a clinical error grid system to transform dosage errors into a clinically interpretable severity of error.

There are also some limitations. Foremost, the accuracy requirements found are only justified for the LOGIC-Insulin glucose control system. Use of other control systems may require different accuracy criteria, depending on the robustness of the algorithm. Robust algorithms may deal with inaccurate glucose measurements more easily than loose protocols *(28)*. Accordingly, accuracy requirements of glucose sensors are control-algorithm specific. Hence, simulation studies per algorithm are needed to determine how accurate glucose sensors should be for use with a specific algorithm.

Second, to be in line with previous simulation studies *(17, 29, 30)*, we simulated the glucose signal using 2 parameters: bias and imprecision. Hence, the pre- and postanalytical errors (such as calibration errors, user errors, and CGM drift errors), which may be important, were not covered. Accordingly, it is advisable to adopt a stricter maximum MARD for a blood glucose meter to deal with use in clinical practice.

Third, although the MARD is a quick method to assess glucose sensor accuracy, there is no consensus on the gold standard glucose metric. The value of MARD as a quality measure for glucose sensors further depends on the study design: number of patients, reference glucose sensor with which the test sensor is compared, and number of paired glucose samples per glycemic range. MARD should always be used in combination with more qualitative evaluation techniques such as Bland–Altman *(31, 32)* and Glycensit *(33)*. Such methodologies allow an analysis as a function of the blood glucose concentration and make a distinction between over- and underestimated glucose readings. Alternatively, the MARD can also be computed per glycemic range, aiming to detect any possible differences between the hypo-, normo-, and hyperglycemic range.

In conclusion, less stringent accuracy requirements appear to be needed for CGM devices. Our data suggest that the MARD should preferably be smaller than 7.1% for intermittent glucose sensors and 11.0% for CGM devices and never be higher than 15.7% for intermittent glucose sensors and 17.8% for CGM devices. However, the findings from simulation studies need to be confirmed in clinical trials with the combination of an accurate glucose sensor (time-intermittent/continuous) with a clinically validated glucose control system, looking at patient-centered outcome measures *(12, 34)*.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.*

Authors' Disclosures or Potential Conflicts of Interest: *Upon manuscript submission, all authors completed the author disclosure form. Disclosures and/or potential conflicts of interest:*

Employment or Leadership: None declared.
Consultant or Advisory Role: None declared.
Stock Ownership: None declared.
Honoraria: None declared.
Research Funding: Supported by the Agency for Innovation by Science & Technology IWT-TBM program (100793), and KU Leuven IOF-HB-10/039, and KU Leuven IOF-HB-13/027. B. De Moor, GOA/10/09 and iMinds Medical Information Technologies SBO 2014; G. Van den Berghe, Methusalem program of Flemish government (METH08/07) and ERC Advanced grant (AdvG-2012–321670; D. Mesotten, Senior Clinical Fellowship from Research Foundation–Flanders.
Expert Testimony: None declared.
Patents: None declared.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

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