LOGIC-Insulin Algorithm–Guided Versus Nurse-Directed Blood Glucose Control During Critical Illness

The LOGIC-1 single-center, randomized, controlled clinical trial

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OBJECTIVE—Tight blood glucose control (TGC) in critically ill patients is difficult and labor intensive, resulting in poor efficacy of glycemic control and increased hypoglycemia rate. The LOGIC-Insulin computerized algorithm has been developed to assist nurses in titrating insulin to maintain blood glucose levels at 80–110 mg/dL (normoglycemia) and to avoid severe hypoglycemia (<40 mg/dL). The objective was to validate clinically LOGIC-Insulin relative to TGC by experienced nurses.

RESEARCH DESIGN AND METHODS—The investigator-initiated LOGIC-1 study was a prospective, parallel-group, randomized, controlled clinical trial in a single tertiary referral center. A heterogeneous mix of 300 critically ill patients were randomized, by concealed computer allocation, to either nurse-directed glycemic control (Nurse-C) or algorithm-guided glycemic control (LOGIC-C). Glycemic penalty index (GPI), a measure that penalizes both hypoglycemic and hyperglycemic deviations from normoglycemia, was the efficacy outcome measure, and incidence of severe hypoglycemia (<40 mg/dL) was the safety outcome measure.

RESULTS—Baseline characteristics of 151 Nurse-C patients and 149 LOGIC-C patients and study times did not differ. The GPI decreased from 12.4 (interquartile range 8.2–18.5) in Nurse-C to 9.8 (6.0–14.5) in LOGIC-C ($P < 0.0001$). The proportion of study time in target range was 68.6 ± 16.7% for LOGIC-C patients versus 60.1 ± 18.8% for Nurse-C patients ($P = 0.00016$). The proportion of severe hypoglycemic events was decreased in the LOGIC-C group (Nurse-C 0.13%, LOGIC-C 0%; $P = 0.015$) but not when considered as a proportion of patients (Nurse-C 3.3%, LOGIC-C 0%; $P = 0.060$). Sampling interval was 2.2 ± 0.4 h in the LOGIC-C group versus 2.5 ± 0.5 h in the Nurse-C group ($P < 0.0001$).

CONCLUSIONS—Compared with expert nurses, LOGIC-Insulin improved efficacy of TGC without increasing rate of hypoglycemia.

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Tight blood glucose control (TGC) has been shown to improve the outcomes of critically ill patients in well-controlled single-center studies (1–3). In contrast, large, pragmatic multicenter trials have failed to reproduce these beneficial effects of TGC (4–6). The largest, most recent trial even showed an increase in mortality in the TGC group (6). Invariably, the incidence of hypoglycemia increased in patients allocated to the TGC groups. The general consensus in the clinical community is that persistent hyperglycemia cannot be tolerated in critically ill patients but that hypoglycemia, induced by intensive insulin therapy, should be avoided (7,8). Much more controversial are the target blood glucose levels in TGC. In highly standardized intensive care units (ICUs), with state-of-the-art blood glucose measurement technology and a nursing team that is well trained in and focused on TGC, the strict target level of 80–110 mg/dL may be feasible. In all other settings, a more lenient target may be recommended (9–11). Regardless of the target level of glycemic control, insulin infusion can always result in severe hypoglycemia. Frequent blood glucose measurements thus remain essential. This need increases the workload of the nursing staff. To strike the right balance among efficacy (avoiding persistent hyperglycemia), safety (avoiding hypoglycemia), and attainability (minimizing workload increase) different protocols have been developed. These protocols can be generic guidelines on paper, which allow intuitive and anticipative decision making by the nurses (12,13). Alternatively, the protocols can be based on elementary algorithms, either on paper or computerized, which allow less freedom for the nursing staff (14–26). In addition, more complex computer algorithms have been developed to allow effective and safe TGC (27,28). The LOGIC-Insulin algorithm, which is in this last category, advises the nurses on the appropriate insulin infusion rate (or use of a dextrose bolus in case of hypoglycemia) and on the interval of the next blood glucose measurement. The algorithm and the corresponding graphical user interface are integrated into the LOGIC-Insulin software. A visual alarm, built into the software, warns the nurse when new blood sampling is advised or in case of hypoglycemia. In the current study, we report the results of the head-to-head comparison of LOGIC-Insulin algorithm–guided TGC with expert nurse-directed TGC in a heterogeneous population of critically ill adult patients.

RESEARCH DESIGN AND METHODS

Study design

The protocol and consent forms were approved by the institutional review board of the University Hospitals Leuven (ML6079) and the Belgian Federal Agency for Medicines and Health Products (80M0437). The study had an investigator-initiated, single-center, prospective, randomized, controlled, parallel-group design and was performed in a 56-bed ICU of a tertiary referral university hospital. The nurse/patient ratio in the ICU was 1:2. All nurses were proficient in TGC according to the Leuven paper-based protocol (Supplementary Table 1). Likewise, all nurses were trained during a 2-month period in using the LOGIC-Insulin software.

Patients were recruited from 22 August 2011 to 16 December 2011. In that period, all critically ill adults admitted to the ICU and for whom TGC was deemed necessary were screened for eligibility (Fig. 1). Exclusion criteria were the following: not critically ill (oral food intake, not mechanically ventilated), no arterial line available, pregnant or breastfeeding, moribund, in diabetic coma, included in another randomized controlled trial, previously included in the LOGIC-1 trial (e.g., on ICU readmission when patient's condition unexpectedly deteriorated after discharge from the ICU), aged <18 years, and declined participation. Written informed consent was obtained preoperatively from the patient himself or herself in case of elective (cardiac) surgery. For emergency admissions, deferred written, informed consent by the closest family member or legal guardian was obtained within 24 h. Consecutive patients were stratified into two categories (after cardiac surgery or other ICU admissions). Patients were randomly allocated by a centralized computer system in a 1:1 ratio, with permuted blocks of 10 per stratum, to either of the two study interventions. Consequently, nurses had to be able to perform TGC with either the paper-based protocol (Nurse-C group), or the computerized LOGIC-Insulin algorithm (LOGIC-C group). Because the nurse/patient ratio was 1:2, possible group combinations for each nurse were Nurse-C and Nurse-C, Nurse-C and LOGIC-C, and LOGIC-C and LOGIC-C. Block size was unknown to bedside physicians and nurses. Outcome assessors, but not patients or attending ICU-staff, were blinded for treatment allocation.
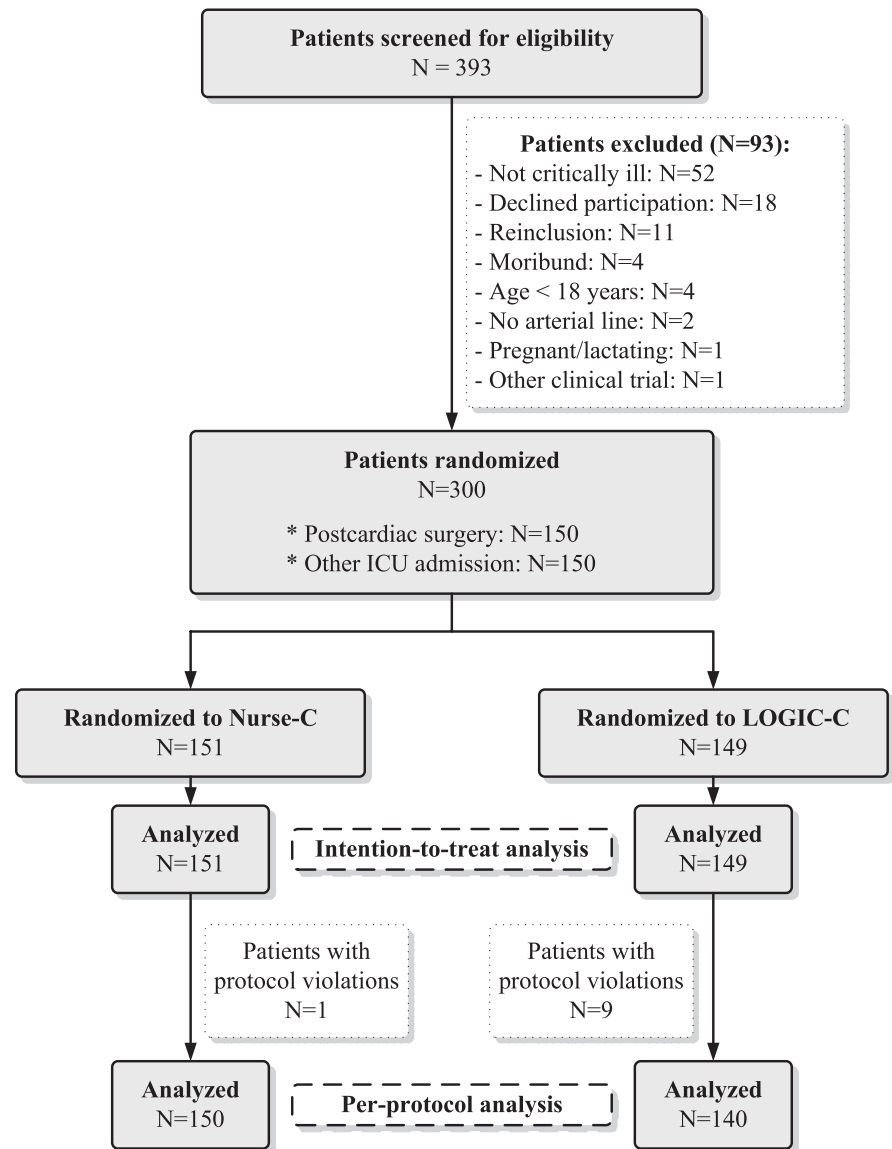

Figure 1—*Patients in the study. All patients admitted to the ICU from 22 August 2011 onward and in whom TGC was deemed necessary were screened for eligibility. Of those, 300 patients (150 patients after cardiac surgery and 150 patients with another reason for ICU admission) were effectively randomized and analyzed in the ITT analysis. Severe protocol violations occurred in 10 patients, who were excluded in the per protocol analysis.*

Study procedures

TGC with the target glucose range of 80–110 mg/dL, started in both treatment groups immediately from admission to the ICU. TGC was discontinued in both groups when the patient started oral intake of carbohydrates, at discharge to the general ward or to another ICU, when the arterial line was removed, if the patient switched to palliative care, or when recurrent severe hypoglycemic episodes (<40 mg/dL) were observed. The maximum study duration was set at 14 days for both treatment groups.

Blood glucose levels were measured in undiluted blood, drawn from the arterial line, by an on-site blood gas analyzer (ABL 700; Radiometer Medical, Copenhagen, Denmark). Insulin (Actrapid HM; Novo Nordisk, Bægsvard, Denmark), in concentration of 50 IU in 50 mL 0.9% NaCl, was continuously infused through a central venous catheter by the Perfusor Space syringe infusion system (BBraun, Melsungen, Germany). Patients received dextrose 5% at 30–40 mL/h as long as 7 days after ICU admission, in combination with an electrolyte solution to deliver minimal nutritional support and to maintain hydration. Enteral nutrition was started when possible, and if enteral nutrition was insufficient at 7 days in

the ICU, parenteral nutrition was initiated on day 8 to reach the caloric goal (29,30).

In the Nurse-C group, TGC was based on a paper guideline for TGC as described in detail elsewhere (12) (see Supplementary Table 1). It is not conceived as a strict "if-then" protocol, but rather as guide for the nursing team. The paper guideline allows intuitive and anticipative decision making, resulting in effective glycemic control as shown in the Leuven clinical trials (1,2). Every 4 h the blood glucose level is measured as part of a routine blood gas analysis. Depending on the stability of glycemia and caloric intake, extra blood glucose measurements are taken. In general, the sampling interval varies between 1 and 4 h.

The LOGIC-Insulin algorithm guided TGC in the LOGIC-C group. Fundamentals of this algorithm have been earlier described in detail (31). Since that description, further developments have been realized in Matlab (R2008a; The MathWorks Inc, Natick, MA). The software advises the nurse on the insulin dosage (or a dextrose bolus in case of hypoglycemia) as well as on the next blood sampling interval. The LOGIC-Insulin control system is founded on a robust, biphasic and adaptive patient model comprising two main phase I variables (patient profile and admission variables) for the initial phase and five main phase II variables (patient profile, blood glucose, insulin dose sequence, nutrition, and steroid medication) for the second phase. The patient profile is defined by the reason for ICU admission, the previous history of diabetes, and the BMI, whereas the admission variables are set by the severity of illness, the blood glucose level, and the nutrition, all determined on admission. Further, the model coefficients corresponding to the phase II variables are adapted on the basis of the incoming closed-loop measurements (every sampling episode) and, if appropriate, of an internal glucose control performance evaluation system (every 24 h). This control system assesses the level of blood glucose control and the required blood sampling frequency in the previous 24 h. Visual alarms on sampling time, hypoglycemia, and nutrition dose entry errors are also included in the software.

Another feature of the LOGIC-Insulin algorithm is its robustness, imposed by taking into account the (possible) inaccuracy of the glucose sensor in the computation of the insulin dose. The advised sampling interval varies from 1 to 4 h,

depending on the (observed and predicted) glycemia stability. Blood glucose measurements coincide as early as possible with the routine blood gas analysis schedule to which the nurses are accustomed. Finally, the LOGIC-Insulin software is run from a central server in the hospital onto thin client bedside computers. The nurses in charge of the patient operate the program.

When positioning the LOGIC-Insulin algorithm with respect to other known protocols, a distinction can be made with respect to the algorithm's predictive capacity, complexity, and incorporation of typical critical illness features. Whereas protocols such as Endotool (26), Glucommander (20), GRIP (24), and SPRINT (19) are mainly based on feedback algorithms, the LOGIC-Insulin and eMPC (27) algorithms combine both feedback and predictive mechanisms, estimating the effect of future disturbances.

Outcome measures

The primary outcome measure of the LOGIC-1 study was the glycemic penalty index (GPI), a marker of efficacy of glycemic control (32,33), during the intervention. The GPI is an index (ranging from 0 to 100) derived from the blood glucose values that are outside the target level of 80–110 mg/dL, in both the hyperglycemic and the hypoglycemic ranges. The weight of the penalty score of a blood glucose measurement is proportional to the level of deviation from normoglycemia. The GPI is the average of all penalties that are individually assigned to all blood glucose values, based on an optimized smooth penalty function. GPI values less than 23 are deemed to reflect effective TGC.

The most important secondary (safety) outcome measure was the incidence of

severe hypoglycemia (<40 mg/dL) during the intervention, either as the proportion of patients who had one or more episodes of severe hypoglycemia or as the proportion of severe hypoglycemic events of all blood glucose measurements. Likewise, the incidences of hypoglycemia <60 mg/dL and also at the conventional cutoff <70 mg/dL were assessed.

The other markers of efficacy of glycemic control were the mean blood glucose level, the hyperglycemic index (denoting the area under the glucose curve above the upper limit of the target range, i.e., 110 mg/dL, divided by the study time) (34), the time to reach the target range (80–110 mg/dL), and the percentage of time in this target range. This percentage was computed by linearly interpolating the monitored time-discrete glucose signal, adding the time zones in the target range, dividing this sum by the total study time, and finally multiplying this result by 100. The daily difference between the minimum and maximum blood glucose was used as a marker of blood glucose variability, whereas the interval between blood glucose measurements served as a marker of workload for the nursing team.

Patient-specific daily insulin infusion rate and daily total amount of carbohydrates (parenteral and enteral) were calculated. The number of days that each patient received steroids was also counted. Clinical outcome measures were ICU and hospital stays and the in-hospital mortality. Patients who were discharged from the hospital before 90 days after randomization were regarded as survivors.

Because the LOGIC-Insulin software served as an advising system, the nurse

Table 1—Baseline characteristics

	Nurse-C	LOGIC-C
Total patients	151	149
Age (years)	62 (14)	65 (15)
Male	93 (62%)	88 (59%)
BMI (kg/m^2)	25.9 (4.8)	26.5 (5.5)
Diabetes	32 (21.2%)	32 (21.5%)
Apache II score	24 (10)	23 (10)
Admission type		
After cardiac surgery	74 (49.0%)	76 (51.0%)
Transplantation	25 (16.6%)	19 (12.8%)
Medical	23 (15.2%)	26 (17.4%)
Other surgery	29 (19.2%)	28 (18.8%)

Data are means (SD) or N (%).

had the ability to overrule the given advice. Overrules were defined as absolute insulin dose differences >0.1 and <1 IU/h for minor overrules and ≥1 IU/h for major overrules. The major overrules were also qualitatively analyzed.

Statistical analyses

The study was conceived as a noninferiority (equivalence) trial, because we assumed that it would be difficult to outperform the TGC expertise of the Leuven nursing staff. According to previous studies, the TGC performance of the Leuven nurses resulted in an average GPI of 26 (SD 11) (35) for the Leuven medical ICU and in an average GPI of 22 (SD 14) for the Leuven surgical ICU (32). Pilot observations allowed us to arbitrarily define the minimal clinically important difference as a lowering of the GPI by 5 points. On the basis of a 5% confidence level (α error) and a 97% statistical power (β error level 3%), the study required 147 patients in each arm of the study (GPI lowering from 22 ± 14 to 17 ± 10) (www.dssresearch.com). To take into account withdrawals, the study was set up for 300 patients (150 in each arm).

All analyses were performed on intent to treat (ITT) basis. An additional per protocol analysis was done to exclude the cases in which severe protocol violations occurred: for the LOGIC-C group, when the LOGIC-Insulin software had inadvertently not been used during an entire nursing shift (>8 h) and for the Nurse-C group when the LOGIC-Insulin software had inadvertently been used during an entire nursing shift (>8 h) (36).

No subgroup analyses were planned. Variables were summarized as frequencies and percentages, mean (SD), or median and interquartile range (IQR), as appropriate. Data were compared with χ^2 (Fisher exact) tests, Student t tests, and nonparametric (Wilcoxon and Mann-Whitney U) tests as appropriate. For all end points, differences were considered statistically significant whenever the two-sided P value was <0.05, without correction for multiple testing. For the statistical analyses, StatView (version 5.0.1; SAS Institute Inc, Cary, NC) and Matlab were used.

RESULTS

Study intervention

In a 4-months time frame, 300 patients were randomized and included in the ITT analysis (Table 1). For nine patients of the LOGIC-C group, the algorithm was not used during at least one nursing shift of 8 h. During these periods, the patients were inadvertently switched to the Nurse-C group. For one patient, the Nurse-C protocol was switched to LOGIC-C for more than 8 h. These 10 patients were excluded in the per protocol analysis (Fig. 1 and Supplementary Table 2).

TGC

Table 2 summarizes the outcome measures of the study. Study duration and mean blood glucose level during the intervention did not differ between the treatment groups. The GPI, the primary outcome measure, was 2.6 points lower in the LOGIC-C group than in the Nurse-C group. Although this was a highly significant statistical difference, it did not exceed the a priori presumed minimal clinically important difference of 5 points. All other markers of efficacy of TGC (hyperglycemic index, time in target, time to reach target) were also better in the LOGIC-C group. Moreover, blood glucose variability was decreased in the LOGIC-C group.

Although no episodes of severe hypoglycemia occurred in the LOGIC-C group, six severe hypoglycemic events were observed in the Nurse-C arm (four patients with one event each and one patient with two events). The proportion of hypoglycemic measurements >60 mg/dL was also halved in the LOGIC-C group. These reductions were not statistically confirmed at the patient level. A significant decrease of glucose readings below the conventional cutoff of 70 mg/dL, however, was found both at patient levels as well as sample levels. The sampling interval was decreased by 12% in the LOGIC-C group, indicating a slight increase in workload for the nurses.

In the per protocol analysis, all differences between the treatment groups, except the daily difference between minimum and maximum glycemia, were maintained (see Supplementary Table 2).

The daily insulin dose was found to be a median of 21.6 (IQR 13.8–37.3) IU/day for the Nurse-C group and 20.0 (13.7–34.6) IU/day for the LOGIC-C group ($P = 0.40$). The total amount of carbohydrate intake also did not differ between the two groups (median 28.7 [IQR 22.9–36.8] g/day for Nurse-C and 29.7 [22.8–50.0] for LOGIC-C; $P = 0.29$). Finally, the proportional number of days that patients received steroids was similar (30.9% for Nurse-C and 27.1% for LOGIC-C; $P = 0.12$). Figure 2 shows the blood glucose, the insulin infusion rate, the total amount of carbohydrate intake, and the number of patients receiving steroids in the study as a function of the study duration for each group.

Protocol compliance

A minor overruling of the LOGIC-Insulin advice occurred in only 27 patients, accounting for 0.73% of blood glucose

Table 2—Study TGC data (ITT analysis)

	Nurse-C ($N = 151$)	LOGIC-C ($N = 149$)	P value
Study period (days)	1.9 (1.1–3.7)	1.9 (1.2–4.7)	0.42
Blood glucose (mg/dL)	107 (11)	106 (9)	0.36
Minimum blood glucose (mg/dL)	28	45	
Maximum blood glucose (mg/dL)	328	272	
GPI	12.4 (8.2–18.5)	9.8 (6.0–14.5)	<0.0001
Hyperglycemic index (mg/dL)	4.2 (1.5–7.4)	2.5 (1.2–4.4)	0.0028
Time in target range (%)	60.1 (18.8)	68.6 (16.7)	0.00016
Time to reach target range (h)	2.9 (1.0–6.2)	1.9 (0–3.8)	0.0035
Mean of maximum change in glycemia per day (mg/dL)	37 (27–46)	31 (24–45)	0.045
Hypoglycemia (patients)			
<70 mg/dL	73 (48.3%)	48 (32.2%)	0.0048
<60 mg/dL	27 (17.9%)	21 (14.1%)	0.43
<40 mg/dL	5 (3.3%)	0 (0%)	0.060
Hypoglycemia (samples)			
<70 mg/dL	170 (3.8%)	142 (2.3%)	<0.0001
<60 mg/dL	52 (1.2%)	39 (0.6%)	0.0071
<40 mg/dL	6 (0.1%)	0 (0%)	0.015
Sampling interval (h)	2.5 (0.5)	2.2 (0.4)	<0.0001

Data are median (IQR), mean (SD), or N (%).

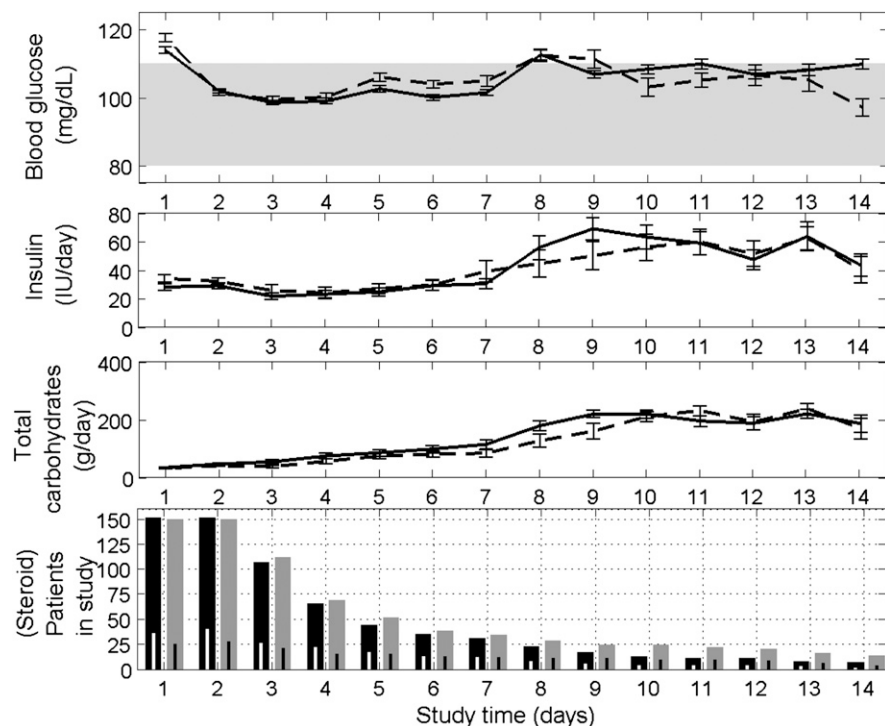**Figure 2**—*Blood glucose* (top), *insulin infusion* (second to top), *and total carbohydrates* (third to top) *are all expressed as means (± SEM) and as a function of study time. Dashed lines indicate the Nurse-C group; solid lines indicate the LOGIC-C group. The shaded area in the* top *panel denotes the target blood glucose range (80–110 mg/dL). The* bottom *panel expresses the number of patients in the study, with black bars indicating the Nurse-C group, gray bars indicating the LOGIC-C, and the respective numbers of patients receiving steroids indicated by white lines in black bars for Nurse-C and black lines in gray bars for LOGIC-C.*

measurements. In 21 patients, nurses did a major overruling of the software (0.46% of blood glucose measurements). Of the 25 major overrules, 1 was justified to avoid hypoglycemia; the other overrules were explained by a clinical context unknown to the software (e.g., inadvertent change of nutrition without informing the software or a disconnected insulin infusion line).

Clinical outcome
The median stay in the ICU did not differ between treatment groups (Nurse-C 4 [IQR 2–7] days vs. LOGIC-C 4 [2–7] days; $P = 0.84$). Patients in the Nurse-C group (median 14 [IQR 9–27] days) had a similar hospital stay to the LOGIC-C group (16 [10–33] days; $P = 0.24$). Although in-ICU mortality was comparable between the treatment groups (Nurse-C 6.6% vs. LOGIC-C 8.1%; $P = 0.66$), there was a nonsignificant trend ($P = 0.081$) toward a higher in-hospital mortality in the LOGIC-C group (12.8%) than in the Nurse-C group (6.6%). Seven patients died in the post-ICU period a median of 27 (IQR 15–30) days after stop of the

study in the LOGIC-C group. Switch to palliative care as a result of poor prognosis after protracted care on the general ward was the cause of death in five of these seven patients. The two other patients died acutely of pneumonia with (septic) shock. No Nurse-C patients died in the post-ICU period.

CONCLUSIONS—The use of the computerized LOGIC-Insulin algorithm improved TGC while decreasing the incidence of hypoglycemia relative to expert nurse–directed TGC. The better and safer glycemic control did, however, come with a slight increase in workload for the nursing team.

Additionally, the difference in the GPI did not exceed the a priori defined threshold for clinical significant difference. The fact that the nurse team improved their efficacy of TGC during the LOGIC-1 study may have contributed to this lack of difference. This is reflected in an important reduction of the GPI in the Nurse-C group in comparison with earlier described GPI values (32,35). Because such a Hawthorne effect was expected,

the clinical study was conceived as an equivalence trial. This allows us to conclude that for the primary end point the LOGIC-Insulin software is, at a minimum, truly on par with the gold standard of TGC by expert nurses. All other markers of efficacy of blood glucose control were better in the LOGIC-C group.

Moreover, the safety of the algorithm was demonstrated by the reduction of the hypoglycemic events below the conventional cutoff of 70 mg/dL. Also, no patients in the LOGIC-C group had any severe hypoglycemic events (<40 mg/dL). The incidence of severe hypoglycemia (at the patient level) in the Nurse-C group during the study was in line with the rate of 3.5% during the Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients (EPaNIC) study in which the Leuven ICUs participated (29). In the latter study, the incidence of severe hypoglycemia was higher among the patients who did not receive early parenteral nutrition than among those who did. In the current LOGIC-1 study, none of the patients received early parenteral nutrition. In a previous study, which compared an enhanced software model predictive control algorithm with standard care, the higher parenteral carbohydrate intake in Leuven at that time was suggested to stabilize blood glucose levels, allowing a much lower sampling frequency for similar TGC (37). Under these conditions and at that time, the tested software algorithm did not improve blood glucose control in the Catholic University Leuven ICU; however, a direct comparison between computerized algorithms will only be possible when they have found their way into general, clinical ICU practice. Inherently, present studies on computerized algorithms will have paper-based protocols as comparators, because the latter are the current standard of care.

The LOGIC-Insulin software required more frequent blood glucose measurements than in the nurse-directed protocol; however, the obtained sampling interval of 2.2 h falls in the 2–3 h range that is applicable in routine glucose management protocols in at least three ICUs across Europe (38). In the future, clinically validated computerized algorithms for TGC will be integrated with continuous glucose monitoring sensors in a semi-closed loop system to allow nurses to handle the increased information output from the sensor and to decrease the workload of the frequent blood draws (39). A

synergistic effect can then be expected on efficacy of TGC and avoidance of hypoglycemia (40).

The current study does, however, have limitations. Because of its single-center design, the external validity of and the ability to generalize the LOGIC-1 results are lower. LOGIC-Insulin still has to be tested in a large, practical multicenter clinical trial in which the centers' level of expertise in TGC will be less. In addition, to comply with recent recommendations on TGC, different target ranges will have to be included in the software (7,39). Furthermore, future studies will need to be statistically powered to detect differences in the incidence of severe hypoglycemia, because this is the major concern of intensive care nurses and physicians. Because the shortage of nurses is expected to be prolonged, all efforts should be made to minimize any workload increase for the nursing staff. The integration of a clinically robust TGC algorithm with an accurate and reliable continuous glucose sensor might be a solution in the future.

In conclusion, the LOGIC-Insulin algorithm improved the efficacy of TGC (avoiding persistent hyperglycemia) without increasing the rate of hypoglycemia in comparison with TGC by the expert Leuven nursing team.

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