# 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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**ABSTRACT**

**Objective:** Tight blood glucose (TGC) control 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 between 80-110 mg/dL (normoglycemia) and to avoid severe hypoglycemia (<40 mg/dL). The objective was to clinically validate LOGIC-Insulin, compared to TGC-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 to algorithm-guided blood glucose control (LOGIC-C). Glycemic Penalty Index (GPI), a measure that penalizes hypo/hyperglycemic deviations from normoglycemia, was the efficacy outcome measure and incidence of severe hypoglycemia (<40 mg/dL) the safety outcome measure.

**Results:** Baseline characteristics of 151 Nurse-C patients and 149 LOGIC-C patients and study time did not differ. The GPI decreased from 12.4 (IQR 8.2-18.5) in Nurse-C to 9.8 (IQR 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 vs. 60.1±18.8% for Nurse-C patients (P=0.00016). The proportion of severe hypoglycemic events was decreased (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 LOGIC-C vs. 2.5±0.5 h in Nurse-C group (P<0.0001).

**Conclusions:** LOGIC-Insulin, compared with expert nurses, improved efficacy of TGC without increasing rate of hypoglycemia.

Tight blood glucose control (TGC) has been shown to improve the outcome of critically ill patients in well-controlled single center studies (1-3). In contrast, large, pragmatic multi-center 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 and 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 the target level of glycemic control, insulin infusion can always result in severe hypoglycemia. Hence, frequent blood glucose measurements remain essential. This increases the workload of the nursing staff. To strike the right balance between 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). Also more complex computer algorithms have been developed to allow effective and safe TGC (27, 28). The LOGIC-Insulin algorithm, belonging to this last category, advises the nurses on the appropriate insulin infusion rate (or a dextrose bolus in case of hypoglycemia) and on the time interval of the next blood glucose measurement. The algorithm and the corresponding graphical user interface are integrated in the so-called LOGIC-Insulin software. A visual alarm, built in the software, allows to warn the nurse when a new blood

sampling is advised or in case of hypoglycemia. In the present study we report the results of the head-to-head comparison of the LOGIC-Insulin algorithm-guided TGC with the 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 (see Supplemental Data 1). Likewise, all nurses were trained during a two months 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 in whom blood glucose control was deemed necessary, were screened for eligibility (Figure 1). Exclusion criteria were the following: not critically ill (oral food intake, not mechanically ventilated), no arterial line available, pregnant or breastfeeding, moribund, diabetes coma, inclusion into another RCT, previous inclusion in the LOGIC-1 trial (e.g. upon ICU re-admission when patient's condition unexpectedly deteriorated after discharge from ICU), age < 18 year and declined participation. Written informed consent was preoperatively obtained from the patient

him/herself in case of elective (cardiac) surgery. For emergency admissions, written, deferred informed consent by the closest family member or legal guardian was obtained within 24 hours. Consecutive patients were stratified into 2 categories (post-cardiac surgery or other ICU admissions). Patients were randomly allocated in a one-to-one ratio, using permuted blocks of 10 per stratum, to one of the two study interventions by a centralized computer system. Consequently, nurses had to be able to do blood glucose control either with the paper-based protocol (Nurse-C), either with the computerized LOGIC-Insulin algorithm (LOGIC-C). As the nurse/patient ratio was 1:2, possible combinations for each nurse were "Nurse-C & Nurse-C", "Nurse-C & LOGIC-C", and "LOGIC-C & LOGIC-C". Block-size was unknown to bed-side physicians and nurses. Outcome assessors, but not patients nor attending ICU-staff, were blinded for treatment allocation.

Study procedures

Blood glucose control, 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 with oral intake of carbohydrates, at discharge to the general ward or to another ICU, when the arterial line was removed, in case 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, Baegsvard, 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 up to 7 days after ICU-admission in combination with an electrolyte solution to deliver minimal nutritional support and to maintain hydratation. Enteral nutrition was started when possible, and if enteral nutrition was insufficient at 7 days in ICU, parenteral nutrition was initiated on day 8 to reach the caloric goal (29, 30).

In the Nurse-C group blood glucose control was based on a paper guideline for TGC (12, see Supplemental Data 1). It has not been 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 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 – 4 h.

The LOGIC-Insulin algorithm guided blood glucose control in the LOGIC-C group. Fundamentals of this algorithm had been earlier described in detail (31) after which further developments have been realized in Matlab (R2008a The MathWorks Inc, Natick, MA, USA). The software advised 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 on-admission variables) for the initial phase and five main phase-II variables (patient profile, blood glucose, insulin dose sequence, nutrition and steroid pharmaca) for the second phase. The patient profile is defined by the reason for ICU admission, the prior history of diabetes and the body mass index, whereas the on-admission variables are set by the severity of illness, the blood glucose level and the nutrition, all on admission. Further, the model coefficients corresponding to the phase-II variables are adapted

based on the incoming closed-loop measurements (every sampling episode) and, if appropriate, on an internal glucose control performance evaluation system (every 24 hours). This control system assesses the level of blood glucose control and the required blood sampling frequency, in the previous 24 hours. 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 imposed robustness 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 hours depending on the (observed and predicted) glycemia stability. Blood glucose measurements coincide as early as possible with the routine blood gas analysis schedule that the nurses are used to. 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 regarding 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, both in the hyperglycemic and the hypoglycemic range. 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 blood glucose control.

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, during the intervention. Likewise, the incidence of hypoglycemia below 60 mg/dL and below the conventional cutoff of 70 mg/dL was assessed.

The other markers of efficacy of glycemic control were the mean blood glucose level, the hyperglycemic index (HGI, 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, while the time 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. Also the number of days that patients received steroids was counted. Clinical outcome measures were the length of ICU and hospital stay, as well as the

hospital mortality. Patients, who had been discharged from hospital before 90 days post-randomization, were regarded as survivors.

As the LOGIC-Insulin software served as an "advising" system, the nurse had the possibility to overrule the given advice. Overrules were defined as absolute insulin dose differences > 0.1 IU/h 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 non-inferiority (equivalence) trial since we assumed that it would be difficult to outperform the TGC expertise of the Leuven nursing staff. According to prior studies, the blood glucose control performance of the Leuven nurses resulted in an average GPI of 26 (standard deviation (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. Based on a 5% confidence level (alpha error) and a 97% statistical power (beta 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 intention-to-treat basis. An additional per-protocol analysis was done to exclude the patients in whom severe protocol violations occurred: for the LOGIC-C group, when inadvertently the LOGIC-Insulin software had not been used during

an entire nursing shift (> 8 h) and for the Nurse-C group, when the LOGIC-Insulin software had been used during an entire nursing shift (> 8 h) (36).

No subgroup analyses were planned. Variables were summarized as frequencies and percentages, mean and SD or median and interquartile range (IQR), as appropriate. Data were compared using Chi-square (Fisher's exact) test, Student's T-test, and non-parametrical (Wilcoxon/Mann-Whitney U) tests, as appropriate. For all endpoints, differences were considered statistically significant whenever the two-sided P-value was lower than 0.05, without correction for multiple testing. For the statistical analyses Statview (version 5.0.1 SAS Institute Inc, Cary, NC, USA) and Matlab were used.

## RESULTS

### Study intervention

In a 4 months' time frame 300 patients were randomized and included into the intention-to-treat analysis (Table 1). In 9 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. In one patient the Nurse-C was switched to LOGIC-C for more than 8 h. These patients were excluded in the per-protocol analysis (Figure 1 and Supplemental Data 2).

Blood glucose control

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. Despite being 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 blood glucose control (HGI, 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.

While no episodes of severe hypoglycemia occurred in the LOGIC-C group, severe hypoglycemic events were observed in the Nurse-C arm (4 patients with one event and 1 patient with two events). The proportion of hypoglycemic measurements below 60 mg/dL was also halved in the LOGIC-C group. These reductions were not statistically confirmed at patient level. However, a significant decrease of glucose readings below the conventional cutoff of 70 mg/dL was found both at patient level as well as sample level. The sampling interval was decreased by 12% in the LOGIC-C group, indicating a slight increase of the workload for the nurses.

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

The daily insulin dose was found to be 21.6 (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 carbohydrates did also not differ between the two groups (28.7 (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 carbohydrates and the number of patients (receiving steroids) in the study as a function of the study duration.

Protocol compliance

A minor overruling of the LOGIC-Insulin advice only occurred in 27 patients, accounting for 0.73% blood glucose measurements. In 21 patients nurses did a major overruling of the software (0.46% blood glucose measurements). One out of the 25 major overrules was justified in order 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 length of stay in the ICU did not differ between treatment groups (Nurse-C: 4 (2-7) days vs LOGIC-C: 4 (2-7) days, P=0.84). Patients in the Nurse-C group (14 (9-27) days) had a similar length of stay in the hospital compared to the LOGIC-C group (16 (10-33) days, P=0.24). While ICU mortality was comparable between the treatment groups (Nurse-C: 6.6% vs LOGIC-C: 8.1%, P=0.66), there was a non-significant trend (P=0.081) towards a higher hospital mortality in the LOGIC-C group (12.8%) compared to the Nurse-C group (6.6%). Seven patients died in the post-ICU period 27 (15-30) days after stop of the study in the LOGIC-C group. Switch to palliative care due to poor prognosis after protracted care on the general ward was the cause of death in 5/7 patients. The two other patients died acutely due to pneumonia with (septic) shock. No Nurse-C patients died in the post-ICU period.

## CONCLUSION

The use of the computerized LOGIC-Insulin algorithm improved TGC, while decreasing the incidence of hypoglycemia, in comparison with expert-nurse directed blood glucose control. However, the better and safer glycemic control went together 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 had improved their efficacy of blood glucose control during the LOGIC-1 study may have contributed. This is reflected in an important reduction of the GPI in the Nurse-C group in comparison with earlier described GPI values (32, 35). As such a Hawthorne effect was expected, the clinical study was conceived as an equivalence trial. This allows us to conclude that for the primary endpoint the LOGIC-Insulin software is, at a minimum, truly on par with a gold standard blood glucose control 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 experienced a severe hypoglycemic event (< 40 mg/dL). The incidence of severe hypoglycemia (at patient level) in the Nurse-C group during the study was in line with the rate of 3.5% during the EPaNIC study in which the Leuven ICUs participated (29). In the latter study, the incidence of severe hypoglycemia was higher in the patients who did not receive early parenteral nutrition, compared to those who did. For the current LOGIC-Insulin 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 a similar blood glucose control (37). Under these conditions and at that time, the tested software algorithm did not improve blood glucose control in the KU Leuven intensive care. However, a direct comparison between computerized algorithms will only be possible when they have found their way to general, clinical ICU practice. Inherently, present studies on computerized algorithms will have paper-based protocols as comparator as the latter are the current standard-of-care.

The LOGIC-Insulin software nevertheless 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 blood glucose control 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 blood glucose control and avoidance of hypoglycemia (40).

The current study has limitations though. Due to its single-center design, the external validity and generalizability of the LOGIC-1 results are lower. LOGIC-Insulin still has to be tested in a large, pragmatic multi-center clinical trial in which the centers' level of expertise in blood glucose control will be less. Also, to comply with recent recommendations on blood glucose control, 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, as this is the major concern of intensive care nurses and physicians. As the shortage of nurses will prolong, all efforts should be done to minimize the workload increase for the nursing staff. The integration of a clinically robust blood glucose control 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 blood glucose control (avoiding persistent hyperglycemia) without increasing the rate of hypoglycemia in comparison with blood glucose control by the expert Leuven nursing team.

## AUTHORS' CONTRIBUTIONS

TVH designed the LOGIC-Insulin control system, contributed to the clinical study, analyzed data and co-wrote the manuscript. DM designed and led the clinical study, co-researched data and wrote the manuscript. PJW designed the database and contributed to the clinical study. JH, EV and JB participated in the clinical study. BDM participated in the engineering pre-study. GVdB co-designed the study and reviewed/edited the manuscript. All authors contributed to the writing of the draft manuscript. They read and approved the final manuscript.


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**DISCLOSURE SUMMARY**

TVH, BDM and GVdB are inventors on EP1487518; BDM and GVdB are inventors on US2005171503. Further, the authors declare not to have any conflict of interest.

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**TABLES**

**Table 1** Baseline characteristics

| | | Nurse-C | LOGIC-C |
|---|---|---|---|
| Number of patients | | 151 | 149 |
| Age – years, mean (SD) | | 62 (14) | 65 (15) |
| Male – N (%) | | 93 (62%) | 88 (59%) |
| BMI –kg/m², mean (SD) | | 25.9 (4.8) | 26.5 (5.5) |
| Diabetes Mellitus – N (%) | | 32 (21.2%) | 32 (21.5%) |
| Apache II –mean (SD) | | 24 (10) | 23 (10) |
| Admission type | Post-cardiac surgery - N (%) | 74 (49.0%) | 76 (51.0%) |
| | Transplantation - N (%) | 25 (16.6%) | 19 (12.8%) |
| | Medical - N (%) | 23 (15.2%) | 26 (17.4%) |
| | Other surgery - N (%) | 29 (19.2%) | 28 (18.8%) |

**Table 2** Study blood glucose control data (Intention-to-treat analysis).

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

**FIGURES**

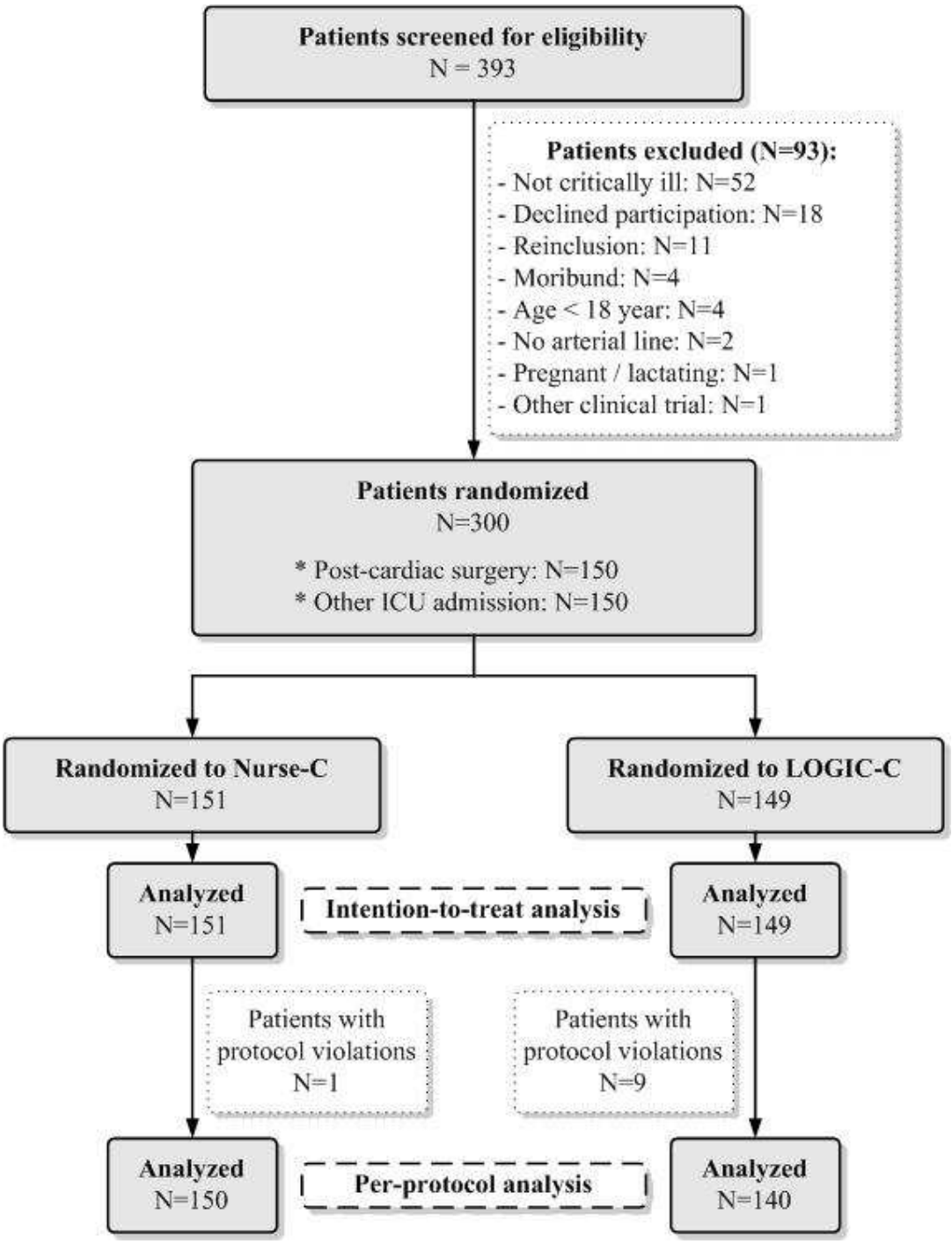


**Figure 1:**

Patients in the study. All patients admitted to the ICU from 22 August 2011, onward and in whom blood glucose control was deemed necessary were screened for eligibility. Of those,

300 patients (150 patients with post-cardiac surgery and 150 patients with another reason for ICU admission) were effectively randomized and analyzed in the intention-to-treat analysis. Severe protocol violations occurred in 10 patients, who were excluded in the per-protocol analysis.

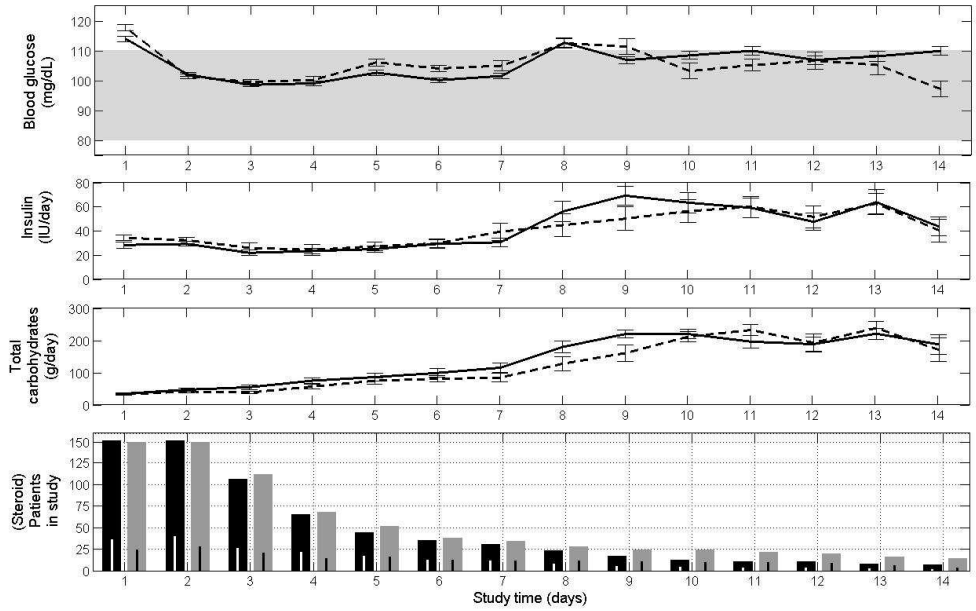


**Figure 2:**

Blood glucose (top panel), Insulin infusion (second panel), Total carbohydrates (third panel), all expressed as means ± standard error mean and as a function of study time (dashed line: Nurse-C, solid line: LOGIC-C). 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 (black bars: Nurse-C, grey bars: LOGIC-C) and the respective number of patients receiving steroids (white line in black bars for Nurse-C, black line in grey bars for LOGIC-C).