Perioperative tight glucose control reduces postoperative adverse events in non-diabetic cardiac surgery patients

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Context: Tight glucose control (TGC) reduces morbidity and mortality in patients undergoing elective cardiac surgery, but only limited data about its optimal timing are available to date.

Objective: To compare the effects of perioperative (PERI) versus postoperative (POST) initiation of TGC on postoperative adverse events in cardiac surgery patients.

Design: Single center, single-blind, parallel-group, randomized controlled trial.

Settings: Academic tertiary hospital.

Participants: 2383 hemodynamically stable patients undergoing major cardiac surgery with expected postoperative ICU treatment for at least 2 consecutive days.

Intervention: Perioperatively or postoperatively initiated intensive insulin therapy with target glucose range 4.4–6.1 mmol/l.

Main Outcome Measures: Adverse events from any cause during postoperative hospital stay.

Results: In the whole cohort, perioperatively initiated TGC markedly reduced the number of postoperative complications (23.2 vs. 34.1%, 95% CI 0.60–0.78) in spite of only minimal improvement in glucose control (blood glucose 6.6±0.7 vs. 6.7±0.8 mmol/l, $p<0.001$; time in target range 39.3±13.7 vs. 37.3±13.8%, $p<0.001$). The positive effects of TGC on postoperative complications were driven by non-diabetic subjects (21.3 vs. 33.7%, 95% CI 0.54–0.74; blood glucose 6.5±0.6 vs. 6.6±0.8 mmol/, n.s.; time in target range 40.8±13.6 vs. 39.7±13.8%, n.s.), while no significant effect was seen in diabetic patients (29.4 vs. 35.1%, 95% CI 0.66–1.06) despite significantly better glucose control in the PERI group (blood glucose 6.9±1.0 vs. 7.1±0.8 mmol/l, $p<0.001$; time in target range 34.3±12.7 vs. 30.8±11.5%, $p<0.001$).

Conclusions: Perioperative initiation of intensive insulin therapy during cardiac surgery reduces postoperative morbidity in non-diabetic patients while having minimal effect in diabetic subjects.

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Abbreviations:

Elevated blood glucose is strongly associated with increased morbidity and mortality of patients with critical illness or a major surgical procedure (1–4). In 2001, the landmark Leuven trial performed in a surgical intensive care unit (SICU) (ICU) demonstrated that tight glucose control (TGC) using intravenous (IV) intensive insulin therapy (IIT) aimed at maintaining euglycemia (4.4–6.1 mmol/l) substantially reduced in-hospital mortality and the number of postoperative complications (5). Several other studies confirmed the positive effects of tight glucose control on selected postoperative outcomes (6–8), while other trials on more heterogeneous ICU populations did not show significant benefits (9, 10). The largest multicenter NICE-SUGAR trial even demonstrated increased mortality in patients on TGC most likely attributable to increased incidence of hypoglycemia (11). A recent meta-analysis including all major randomized trials in ICU showed a significant benefit of TGC in surgical but not nonsurgical ICU patients (12). Despite these rather inconsistent findings, the need to control elevated glucose levels in critically ill patients is generally accepted, although target ranges are mostly set higher than in the original Leuven trial.

While the concept of TGC has been studied intensively, the optimal timing of TGC initiation in surgical patients remains elusive despite the fact that excessive hyperglycemia during surgery was shown to be an independent predictor of perioperative morbidity and mortality (13, 14). Only few small studies comparing intraoperative vs. postoperative TGC initiation were published with rather inconsistent results (15, 16). A recent metananalysis of 5 randomized controlled trials comparing intensive and conventional insulin therapy during cardiac surgery could not show any benefit of the former except of reduced infection rates (17). It is thus currently unclear whether perioperative initiation of TGC affects the patients´ outcomes.

To this end, we performed a randomized controlled trial (RCT) comparing the effects of perioperative vs postoperative initiation of TGC on postoperative adverse events in cardiac surgery patients.

Materials and Methods

Trial design and population

We conducted a single center, single-blind, parallel-group, RCT involving adult cardiac surgery patients (age 18–90 years) in an academic tertiary hospital in Prague, Czech Republic between January 2007 and June 2012. The study was registered at Clinicaltrials.gov, number NCT01548963. Eligible participants were all hemodynamically stable patients undergoing major cardiac surgery with expected postoperative ICU treatment for at least 2 consecutive days. Exclusion criteria included allergy to insulin, mental incapacity, language barrier and refusal to participate in the study. Severe hemodynamic instability during the surgery, patient's rejection of further participation or his lost to follow-up were set as study discontinuation criteria. Informed consent was obtained from all participants before being enrolled into the trial. The study was approved by the Human Ethics Review Board of General University Hospital in Prague, Czech Republic and was performed in accordance with the guidelines proposed in the Declaration of Helsinki.

Study interventions

Study participants were randomly assigned to 2 treatment groups: PERI group with intraoperative and postoperative tight glucose control and POST group with only postoperative TGC. In PERI group intensive insulin therapy was initiated at any time from the beginning of cardiac surgery if blood glucose levels exceeded 6.1 mmol/l, while in POST group IIT was started after the admission to the postoperative ICU and everytime blood glucose during the operation exceeded 10 mmol/l an i.v. bolus of 1–2 IU of rapid-acting insulin was administered in order to keep glucose values under this threshold. In both groups TGC lasted until the end of the ICU stay or until oral intake was restored. Target blood glucose range was set at 4.4 – 6.1 mmol/l. For post hoc result analysis and to better reflect the current more moderate glucose control approach a second range of less stringent glucose control was defined as 4.4 – 8.3 mmol/l. For allocation of participants to one of the study groups, a simple randomization procedure according to a computer-generated list of random numbers was used. Only the study coordinator and the operation staff were aware of the treatment assignment, the patients themselves as well as the postoperative ICU staff and outcome assessors and data analysts were kept blinded to the treatment allocation.

Intensive insulin therapy protocols

Two protocols for TGC were employed during the trial: the primarily used Matias protocol, which is essentially a modified Leuven protocol with the addition of insulin boluses, was later replaced by the computer-based eMPC (enhanced model predictive control) protocol with variable sampling rate, which in previous trials proved to be superior in terms of efficacy as well as safety (18, 19). Both protocols were described in detail elsewhere (18). Human rapid-acting insulin (Actrapid HM, Novo Nordisk, Baegsvard, Denmark) was given via a central venous line as a continuous infusion alone or in combination with insulin boluses (when Matias protocol was applied). A standard concentration of 50 IU of insulin in 50 ml of 0.9% NaCl was used.

Blood glucose measurement and glucose infusion

Blood glucose samples were obtained from an arterial line whenever possible; otherwise, central venous line was used. Capillary samples were not used during the ICU stay, but became acceptable after the patient was discharged to standard ward. Blood glucose levels were assessed by a blood gas analyzer (ABL 700, Radiometer Medical, Copenhagen, Denmark – 86.9% of samples) or a standard point-of-care glucometer (ACCU-CHECK® Inform system, F. Hoffmann La-Roche AG, Basel, Switzerland – 13.1% of samples). Blood sampling rate was guided by the applied protocol. During operation, blood glucose was measured every 1 hour with the frequency increasing to every 30 minutes in the on-pump period. In all patients, infusion of 10% glucose solution with a glucose dose of 6.7 g per hour was

initiated upon the admission to postoperative ICU and was continued for approximately 18 hours, when oral food intake was reestablished. In patients on mechanical ventilation, glucose infusion lasted for 48 hours and was then replaced by standard enteral nutrition.

Data collection

Patient history and clinical parameters including age, sex, race, height, weight, BMI, EuroSCORE (the European System for Cardiac Operative Risk Evaluation), history of diabetes mellitus and type of surgery were collected prospectively. Blood glucose levels were recorded from the beginning of operation until the end of postoperative hospital stay. Perioperative and postoperative adverse events, medication and nutrition were continuously monitored and documented.

Outcome measures

The primary study endpoint was defined as number of adverse events from any cause during the postoperative hospital stay and included following newly developed organ dysfunctions: cardiovascular (low cardiac output syndrome, postoperatively initiated inotropic support or intra-aortic balloon counterpulsation, acute myocardial ischemia, moderate to severe arrhythmias, cardiopulmonary resuscitation (CPR)), respiratory (acute pneumonia, fluidothorax $>$ 300 ml, reintubation, acute respiratory distress syndrome (ARDS)/acute lung injury), neurological (stroke, transient ischemic attack), gastrointestinal (GI) (ileus, gastric ulcer, GI bleeding, hepatopathy, acute pancreatitis, need of parenteral nutrition), renal (acute kidney injury defined by RIFLE criteria – stage Injury and above) and infections defined by clinical picture and the need of systemic antibiotic therapy (detailed criteria of all selected adverse events are listed in *Supplement 1*). All events were evaluated according to the prespecified criteria by attending ICU physicians who were blinded to the treatment assignment. Parameters of glucose control (average blood glucose, time in, above and below target range, time in hyperglycemia $>$ 8.3 mmol/l, number of hypoglycemic episodes) and postoperative hospital stay length were set up as secondary endpoints. Severe hypoglycemia was defined as blood glucose under 2.2 mmol/l.

Statistical analysis

To detect an overall difference of 10% in postoperative complications between the treatment groups with a two-sided 0.1% significance level and a power of 99%, a sample size of 2400 patients in the whole cohort was necessary assuming a baseline postoperative morbidity of 30%. To include this number of patient a 3-year inclusion period with 800 patients a year was anticipated. One interim analysis was performed after 1400 patients had been enrolled with the P value maintained at 0.1%, confirming the formerly calculated sample size. Numerical data from both groups were compared using Student's *t* test or Mann-Whitney Rank Sum Test as appropriate. Categorical data were analyzed with a two sample proportion test using standard approximation. The difference between primary endpoints was expressed as relative risk reduction with a 95% confidence interval (CI). The significance level was set at $P = .05$. To correct for baseline bias an adjustment analysis using logistic regression or negative binomial regression and analysis of variance (ANOVA) or likelihood ratio (LR) test, as appropriate, was performed.

Results

Baseline characteristics of study subjects

A total number of 2383 subjects were randomized into the trial between January 2007 and December 2010, 1134 in the PERI and 1249 in the POST group. The detailed enrollment process is depicted in the Consort diagram (*Figure 1*). Patients in the POST group were slightly older with a higher prevalence of diabetes mellitus and chronic kidney disease together with higher EuroSCORE. Other baseline parameters including BMI (body mass index (BMI)), left ventricular (LV) ejection fraction and baseline creatinine were comparable between both groups (Table 1).

When divided according to the presence of diabetes mellitus, baseline profile of nondiabetic subjects in both PERI and POST group reflected the situation in the whole cohort with no difference in most of the baseline parameters except of CKD prevalence. In contrast, subjects with diabetes showed increased age and EuroSCORE, decreased BMI and slightly reduced LV EF, but had no difference in the number of CKD patients in POST as compared to PERI group (Table 1).

Types of surgery

Elective operations dominated the spectrum of surgical procedures, with acute operations being performed in approx. 10 – 15% of all subjects. Coronary artery by-pass grafting (CABG) was the most prevalent type of surgery. Other types included aortic, mitral and tricuspidal valve repair or replacement, thoracic aortic surgery and pulmonary endarterectomy (Table 1).

Glucose control

During the ICU stay, only minimal differences in main parameters of glucose control were observed between both study cohorts favoring almost exclusively the PERI group, including average blood glucose, time in hyperglycemia as well as the number of hypoglycemic episodes (Table 2). These differences were even less pronounced in the nondiabetic subgroup with comparable average ICU glycemia and time in target range and reduced number of hypoglycemic episodes. In contrast, subjects with diabetes mellitus showed slightly tighter glucose control in the PERI group as demonstrated by decreased ICU as well as intraoperative glycemia and longer time spent in target range, with no significant difference in the occurrence of hypoglycemia, even though time under target range was increased in the PERI group. Episodes of severe hypoglycemia ($<$2.2 mmol/l) were kept comparably low in all study subgroups (Table 2). During the operation period i.v. insulin was administered to 95.1% of all subjects in PERI group (94.1% in the nondiabetic and 98.1% in the

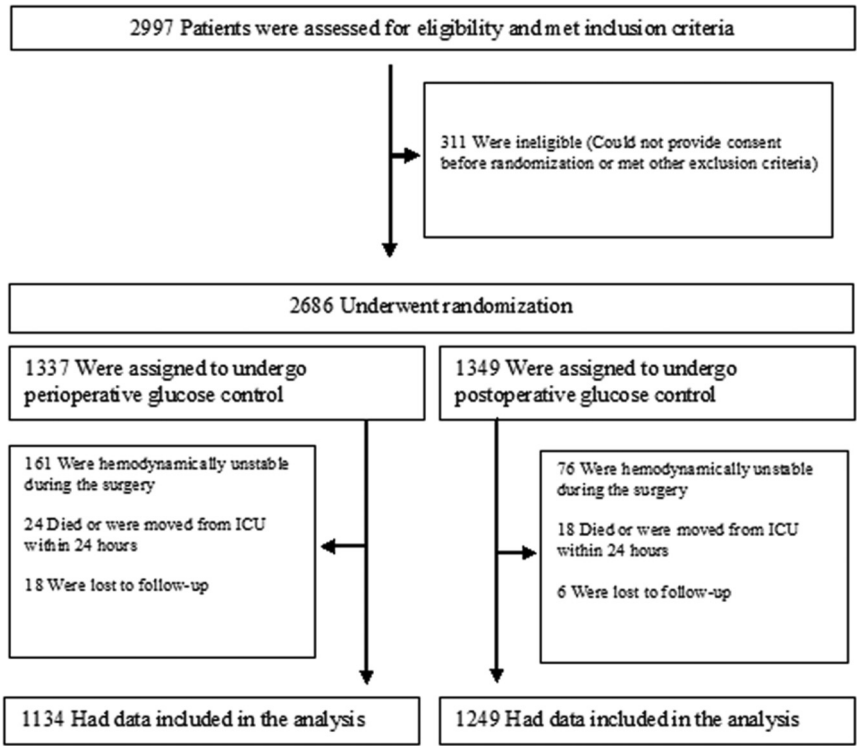

Figure 1. Assessment, randomization and follow-up of study patients

diabetic subgroup) and to 22.7% of subjects in the POST group (11.9% in the nondiabetic and 51.6% in the diabetic subgroup), respectively.

Perioperative morbidity and mortality

In the whole cohort, the number of patients with postoperatively developed organ complications was significantly reduced in the PERI as compared to the POST group (23.2 vs. 34.1%, relative risk [RR] 0.68, 95% CI [CI] 0.60 – 0.78). This decrease was driven by all types of dysfunctions except of the respiratory ones, with neurological and infectious complications showing the maximum reduction (Table 3). Favorable effects of intraoperatively initiated TGC were even more pronounced in nondiabetic subjects achieving a risk reduction of 37% of developing any kind of postoperative complication (21.3 of PERI vs. 33.7% of POST subjects, RR 0.63, CI 0.54 – 0.74). Analogously to the whole cohort, only newly onset dysfunctions of the respiratory tract did not differ between PERI and POST subgroups, while cardiovascular, renal, GI, neurological and infectious complications were decreased to a similar or even greater extent than in the whole group (Table 4). Among subjects with DM, however, no difference could be seen between PERI and POST group in the incidence of postoperative complications of all types except of the cardiovascular ones (Table 4). When adjusted for baseline differences in age, prevalence of diabetes mellitus and chronic kidney disease, logistic EUROSCORE, percentage of elective procedures, CABG, off-pump surgery and extracorporeal circulation between PERI and POST group all the results still retained their significance with the exception of renal complications in the whole cohort and GI adverse events in the nondiabetic group which both slightly failed to cross the $P < .05$ threshold (RR 0.55–1.01, $P = .055$ for renal and RR 0.34–1.00, $P = .05$ for GI complications).

Intraoperative initiation of TGC showed no effect on the whole postoperative length of stay (LOS) or the duration of the ICU treatment in the whole cohort (Table 3) as well as the nondiabetic subgroup (Table 4), whereas it reduced both ICU and total hospital stay in the diabetic group (Table 4). Perioperative mortality did not differ significantly between any of the studied groups (Tables 3 and 4).

Discussion

In the present trial, we show that perioperative initiation of TGC reduces postoperative complications and improves outcomes predominantly in nondiabetic patients undergoing cardiac surgery. Although excessive hyperglycemia during surgery is a well-established and independent predictor of perioperative morbidity and mortality (13, 14, 20), only limited data assessing the effects of its lowering are available to date. Lazar et al demonstrated that the administration of glucose-insulin-potassium (GIK) infusion aimed at maintaining blood glucose levels between 6.7 and 10 mmol/l decreases episodes of recurrent ischemia and wound infections and improves 2-year survival as compared with a sliding scale insulin protocol with target range < 13.9 mmol/l in subjects undergoing CABG (21). Similarly, GIK infusion with target glucose levels of 6.0–10.0 mmol/l improved myocardial contractile function and decreased inotropic support in a study by Koskenkari et al (22). However, the first RCT to comprehensively assess the value of intraoperative TGC which included 400 patients receiving either TGC aiming at blood glucose between 4.4 and 5.5 mmol/l or conventional treatment with glycemic target under 11.1 mmol/l during CABG implantation failed to show any significant difference in the composite outcome (death, deep sternal wound infection, prolonged infection, cardiac arrhythmias, stroke and renal failure) between both groups. In fact,

Table 1. Baseline characteristics of study subjects.

	Whole cohort		Non-diabetic subjects		Diabetic subjects	
	PERI	POST	PERI	POST	PERI	POST
Number of patients	1134	1249	869	910	265	339
Females (n, %)	323 (28.6)	372 (29.8)	243 (28.0)	263 (28.9)	80 (30.7)	109 (32.2)
Age (years)	64.7 ± 11.1	**66.6 ± 9.7**‡	64.4 ± 11.5	65.8 ± 10.0	65.8 ± 9.3	**68.8** ± **8.3**‡
BMI (kg/m^2)	28.4 ± 5.6	28.2 ± 4.3	27.8 ± 5.6	27.9 ± 4.3	30.3 ± 5.4	**29.0** ± **4.3***
Diabetes mellitus (n, %)	265 (23.4)	**339 (27.1)***	0	0	265	339
Neurological disease (n, %)	108 (9.5)	106 (8.5)	79 (9.1)	64 (7.0)	29 (10.9)	42 (12.4)
COPD (n, %)	157 (13.8)	193 (15.5)	109 (12.5)	142 (15.6)	48 (18.1)	51 (15.0)
Chronic kidney disease (n, %)	43 (3.8)	**78 (6.2)**†	24 (2.8)	**46 (5.1)***	19 (7.2)	32 (9.4)
Renal replacement therapy (n, %)	9 (0.8)	14 (1.1)	6 (0.7)	9 (1.0)	3 (1.1)	5 (1.5)
Smoker (n, %)	250 (22.0)	270 (21.6)	200 (23.0)	214 (23.5)	50 (18.9)	56 (16.5)
Baseline creatinine (μmol/liter)	99.4 ± 61.9	99.3 ± 53.5	95.9 ± 52.6	97.1 ± 48.3	110.9 ± 84.8	105.2 ± 65.1
LV EF (%)	55.8 ± 13.3	55.2 ± 13.8	55.8 ± 13.2	55.8 ± 13.6	55.8 ± 13.6	**53.6 ± 14.4***
Additive EuroSCORE	3.8 ± 2.2	**4.2 ± 2.3**‡	3.8 ± 2.1	4.0 ± 2.3	3.8 ± 2.2	**4.7** ± **2.4**‡
Logistic EuroSCORE	7.2 ± 9.6	**8.5 ± 12.2***	7.3 ± 10.0	8.0 ± 11.8	6.8 ± 8.1	**9.8** ± **13.1**‡
Elective surgery (n, %)	**1005 (88.6)** †	1048 (83.9)	**758 (87.2)** *	761 (83.6)	**247 (93.2)** †	287 (84.6)
CABG (n, %)	790 (69.7)	**966 (77.3)** ‡	564 (64.9)	**672 (73.8)** ‡	226 (85.3)	294 (86.7)
Aortic valve replacement (n, %)	236 (20.8)	237 (19.0)	211 (24.3)	200 (22.0)	25 (9.4)	37 (10.9)
Mitral valve replacement (n, %)	143 (12.6)	139 (11.1)	121 (13.9)	107 (11.8)	22 (8.3)	32 (9.4)
Other surgery types (n, %)	**106 (9.3)**†	75 (6.0)	**100 (11.5)**†	63 (6.9)	6 (2.3)	12 (3.5)
Off-pump surgery (n, %)	412 (36.3)	**506 (40.5)***	342 (39.4)	361 (39.7)	70 (26.4)	**145 (42.8)** ‡
Extracorporeal circulation (n, %)	**722 (63.7)***	743 (59.5)	527 (60.6)	549 (60.3)	**195 (73.6)** †	194 (57.2)
Extracorporeal circulation duration (min)	127.8 ± 82.4	**135,1 ± 77.2***	136.2 ± 75.7	137.9 ± 82.2	105.0 ± 95.5	**127.7 ± 60.1**‡

Data are expressed as mean ± SD or absolute number with relative percentage. $^*P < 0.05$, $^\dagger P < 0.01$, $^\ddagger P < 0.001$. PERI – perioperatively initiated tight glucose control, POST – postoperatively initiated tight glucose control, BMI – body mass index, COPD – chronic obstructive pulmonary disease, LV EF – left ventricular ejection fraction, EuroSCORE – European System for Cardiac Operative Risk Evaluation, CABG – coronary artery by-pass graft.

Table 2. ICU glucose control (from the beginning of operation to the end of ICU stay).

		Whole cohort		Non-diabetic subjects		Diabetic subjects	
		PERI	POST	PERI	POST	PERI	POST
No. of patients		1134	1249	869	910	265	339
Average blood glucose (mmol/liter)	Whole period	6.6 ± 0.7	**6.7 ± 0.8**‡	6.5 ± 0.6	6.6 ± 0.8	6.9 ± 1.0	**7.1 ± 0.8**‡
	Intraoperative period	7.0 ± 1.4	**7.4 ± 1.5**‡	6.8 ± 1.1	**7.0 ± 1.2**‡	7.7 ± 1.9	**8.3 ± 1.8**‡
Time in TGC target range (4.4–6.1 mmol/liter, %)		**39.3 ± 13.7**‡	37.3 ± 13.8	40.8 ± 13.6	39.7 ± 13.8	**34.3 ± 12.7**‡	30.8 ± 11.5
Time in GC range (4.4–8.3 mmol/liter, %)		**79.3 ± 13.3**‡	75.8 ± 14.4	**82.5 ± 11.1**‡	79.7 ± 12.5	**68.8 ± 14.6**‡	65.2 ± 13.9
Time above target range (>8.3 mmol/liter, %)		14.5 ± 12.2	**17.2 ± 13.5**‡	12.5 ± 10.2	**13.9 ± 11.8***	21.1 ± 15.6	**26.1 ± 13.8**‡
Time below target range (<4.4 mmol/liter, %)		6.2 ± 5.7	**7.0 ± 5.8**‡	5.0 ± 5.2	**6.4 ± 5.6**‡	**10.1 ± 5.7**†	8.7 ± 5.9
Moderate hypoglycemia 2.2–3.2 mmol/liter (n of measurements/all measurements, %)		508/56 319 (0.9)	**703/62 855 (1.1)** ‡	267/40 766 (0.7)	**419/45 100 (0.9)** ‡	241/15 553 (1.5)	266/17 755 (1.5)
Severe hypoglycemia < 2.2 mmol/liter (n of measurements/all measurements, %)		44/56 319 (0.1)	61/62 855 (0.1)	20/40 766 (0.1)	33/45 100 (0.1)	24/15 553 (0.2)	28/17 755 (0.2)

Data are expressed as mean ± SD or absolute number with relative percentage. $^*P < 0.05$, $^\dagger P < 0.01$, $^\ddagger P < 0.001$. PERI – perioperatively initiated tight glucose control, POST – postoperatively initiated tight glucose control, TGC – tight glucose control, GC – glucose control.

Table 3. Perioperative morbidity and mortality - whole cohort.

		PERI	POST	AD or RR (95% CI)
No. of patients		1134	1249	115
Hospital stay length (days)		11.7 ± 8.1	12.2 ± 9.4	0.5 (-0.2 – 1.2)
ICU stay length (hours)		117.5 ± 132.1	115.5 ± 117.7	2.0 (-12.2 – 8.1)
Perioperative mortality (n of patients, %)		37 (3.3)	48 (3.8)	0.85 (0.56 – 1.29)
Perioperative morbidity (n of patients, %)		263 (23.2)	**426 (34.1)**‡	**0.68 (0.60 – 0.78)**
Complications (n of events, %)	Cardiovascular	135 (11.9)	**257 (20.6)**‡	**0.58 (0.48 – 0.70)**
	Respiratory	72 (6.3)	94 (7.5)	0.84 (0.63 – 1.13)
	Renal	88 (7.8)	**131 (10.5)***	**0.74 (0.57 – 0.96)**
	Gastrointestinal	33 (2.9)	**66 (5.3)**†	**0.55 (0.37 – 0.83)**
	Neurological	30 (2.6)	**82 (6.6)**‡	**0.40 (0.27 – 0.61)**
	Infectious	36 (3.2)	**89 (7.1)**‡	**0.45 (0.31 – 0.65)**

Data are expressed as mean ± SD or absolute number with relative percentage. The difference between the groups was expressed as absolute difference (AD) for numerical data or relative risk (RR) for categorical data, both with 95% confidence interval (CI). The AD and RR values are unadjusted. $^*P < 0.05$, $^\dagger P < 0.01$, $^\ddagger P < 0.001$. PERI – perioperatively initiated tight glucose control, POST – postoperatively initiated tight glucose control.

intraoperative TGC significantly increased the number of strokes and tended to increase overall mortality, raising thus concerns about the efficacy and safety of tight glucose control during surgical procedures (16).

In contrast to these data, perioperatively initiated TGC in our study markedly decreased postoperative complications with an overall risk reduction of 32%. Except of confirming the previously established association between perioperative TGC and the reduction of cardiovascular and infectious complications, our data also show a strong

Table 4. Perioperative morbidity and mortality - non-diabetic and diabetic subjects.

		Non-diabetic subjects			Diabetic subjects		
		PERI	POST	AD or RR (95% CI)	PERI	POST	AD or RR (95% CI)
No. of patients		869	910	41	265	339	74
Hospital stay length (days)		11.6 ± 7.9	11.6 ± 8.4	0.01 (-0.7 – 0.8)	12.0 ± 8.7	**13.6 ± 11.4***	**1.7 (0.1 – 3.3)**
ICU stay length (hours)		120.3 ± 133.7	115.8 ± 118.9	4.5 (-16.4 – 7.3)	108.4 ± 126.5	**114.7 ± 114.6†**	**6.3 (2.0 – 19.0)**
Perioperative mortality (n of patients, %)		19 (2.2)	33 (3.6)	0.60 (0.35 –1.05)	18 (6.8)	15 (4.4)	1.54 (0.79 – 2.99)
Perioperative morbidity (n of patients, %)		185 (21.3)	**307 (33.7)‡**	**0.63 (0.54–0.74)**	78 (29.4)	119 (35.1)	0.84 (0.66 – 1.06)
Complications (n of events, %)	Cardiovascular	109 (12.5)	**193 (21.2)‡**	**0.59 (0.48 – 0.73)**	26 (9.8)	**64 (18.9)†**	**0.52 (0.34 – 0.80)**
	Respiratory	56 (6.4)	69 (7.6)	0.85 (0.60 – 1.19)	16 (6.0)	25 (7.4)	0.82 (0.45 – 1.50)
	Renal	54 (6.2)	**92 (10.1)†**	**0.61 (0.45 – 0.85)**	34 (12.8)	39 (11.5)	1.12 (0.72 – 1.72)
	Gastrointestinal	22 (2.5)	**46 (5.1)†**	**0.50 (0.30 – 0.83)**	11 (4.2)	20 (5.9)	0.70 (0.34 – 1.44)
	Neurological	8 (0.9)	**60 (6.6)‡**	**0.14 (0.07 – 0.29)**	22 (8.3)	22 (6.5)	1.28 (0.72 – 2.26)
	Infectious	24 (2.7)	**60 (6.6)‡**	**0.42 (0.26 – 0.67)**	12 (4.5)	29 (8.6)	0.53 (0.28 – 1.02)

Data are expressed as mean ± SD or absolute number with relative percentage. The difference between the groups was expressed as absolute difference (AD) for numerical data or relative risk (RR) for categorical data, both with 95% confidence interval (CI). The AD and RR values are unadjusted. $^{*}P < 0.05$, $^{\dagger}P < 0.01$, $^{\ddagger}P < 0.001$. PERI – perioperatively initiated tight glucose control, POST – postoperatively initiated tight glucose control.

beneficial effect of early TGC initiation on other adverse event types including neurological, renal and GI. Strikingly, this substantial risk reduction was associated with very little overall glucose control improvement in the PERI group throughout the ICU stay. Obviously, the differences in glucose levels were slightly more pronounced in the intraoperative period, but whether this was the primary mechanism, by which postoperative complications in the PERI group were reduced, remains questionable (especially considering the fact that the nondiabetic subgroup, that profited the most from perioperative initiation of TGC, showed the least improvement in glucose control and vice versa). The marginally increased incidence of hypoglycemia, a factor associated with higher morbidity and mortality in subjects on TGC, in the POST group might also not fully explain the reduction in postoperative outcomes. It might be speculated that early administration of insulin already during the surgery could have to some extent moderated the developing operation-induced stress response by other than glucose-lowering effects, including anti-inflammatory, antioxidant, antithrombotic, and vasodilatatory (23–25). On the other hand, this would seem to be in contrast with a subanalysis of the Leuven study that showed that blood glucose, rather than insulin, is responsible for the positive effects of TGC (26). The proposed hypothesis notwithstanding, the exact mechanisms by which intraoperatively initiated IIT reduced the number of postoperative complications remain yet to be fully elucidated. Nevertheless, our data indicate that the intraoperative phase of cardiac surgery might possess more significance to postoperative outcomes than previously thought and that the exact timing of insulin infusion might be one of the key elements contributing to the efficacy of the TGC regimen.

Another striking finding of our study was the fact that the reduction of postoperative morbidity connected with intraoperative initiation of TGC was driven predominantly by nondiabetic subjects. These findings are in line with some of the previously published data showing stronger association of hyperglycemia with increased mortality risk in nondiabetics than in persons with diabetes (27, 28) and less benefit of tight glucose control in subjects with DM (6, 29). The reason for this difference might be an adaptive response to hyperglycemia in diabetic patients due to their chronic exposure to higher glucose levels, while in nondiabetics such mechanisms are missing (30). Another factor that might have contributed to the different outcomes in individuals with and without DM was the presence of hypoglycemia, as the number of moderately hypoglycemic subjects (2.2 – 3.2 mmol/l) was significantly reduced in nondiabetic PERI subgroup as compared to POST group, while being conversely increased in diabetic subjects. However, the incidence of severe hypoglycemia was comparable throughout all subgroups. Finally, the fact that more than 50% of subjects in the diabetic POST subgroup received i.v. insulin during the operation (albeit only in the amount of a single bolus of 1–2 IU and with the target glucose being under 10 mmol/l) might have to some extent diluted any positive effects of intraoperative insulin administration in the diabetic PERI group.

Although our study was not powered to assess mortality, this parameter certainly comprises the most important safety signal for any intervention. Increased number of deaths, though statistically nonsignificant (4 vs. 0, n.s.), raised concerns about the safety of intraoperative TGC in the study by Gandhi et al (16). Here we did not find any significant difference in perioperative mortality between any of the PERI and POST subgroups. The length of postoperative stay as one of the secondary endpoints did not differ between the subgroups either in the whole cohort or in nondiabetics, while being slightly prolonged in the diabetic POST group. These results largely confirm findings by Gandhi et al, who also could not observe any shorten-

ing of the LOS in association with intraoperative TGC (16).

As tight glucose control per se increases the potential risk of hypoglycemia, safety is one of the primary concerns connected to TGC. Compared with the intensive arms of NICE-SUGAR and the original van den Berghe trial with similar glucose targets as in our study, both PERI and POST group showed lower incidence of severe hypoglycemia (<2.2 mmol/l – 3.2 and 4.2% of subjects for PERI and POST vs. 5.1% in van den Berghe 2001 and 6.8% in NICE-SUGAR) (5, 11). Somehow surprisingly, intraoperative initiation of TGC in our study slightly decreased the number of moderate hypoglycemic episodes (2.2 – 3.3 mmol/l) and reduced time spent under the target range as compared with postoperative initiation in the nondiabetic subgroup, while the rates of severe hypoglycemia were comparable across all groups. Our current data do not enable us to unravel the exact mechanisms responsible for this positive effect, although one possible explanation could be that in subjects without previous history of diabetes mellitus perioperative insulin administration prevented early glycemic rises and stabilized glucose profile which resulted in decreased occurrence of hypoglycemia. Nevertheless, the obtained results indicate that intraoperative initiation of TGC is a safe procedure with minimal additional hypoglycemic risk for the patient as compared with postoperative initiation.

Several limitations could have partially affected the results of the present study as well as their further applicability. Despite the inclusion efforts several baseline characteristics differed slightly between the groups including older age, increased prevalence of diabetes mellitus and chronic kidney disease, lower percentage of elective procedures, higher proportion of CABG and off-pump surgery and worse prognosis as assessed by the additive and logistic EuroSCORE in the POST group. Nevertheless, the differences between the groups remained valid after statistical adjustment for these baseline inconsistencies. The higher drop-out rate due to hemodynamic instability during surgery in the PERI group as well as administration of low corrective bolus insulin doses during intraoperative period in part of the POST group could constitute another source of potential bias. It also should be mentioned, that the subgroup analysis between diabetic vs. nondiabetic patients has not been planned in the original protocol and therefore has to be considered exploratory with all potential limitations. The selected target range reflects more the original Leuven trial than current, less stringent recommendations, partially owing to the pre-NICE-SUGAR design of the trial and partially due to the unclear situation regarding optimal target ranges for different ICU subgroups with some metaanalytic data indicating benefits of tighter glucose targets in cardiac surgery subjects (12, 31). As this trial was not designed to compare different target ranges, we are not able to draw any relevant conclusions to this question. Nevertheless, the lower mortality rates in both PERI and POST group as compared to both Leuven and NICE-SUGAR trials suggest that our approach was safe. The absence of postdischarge follow-up due to complicated logistics comprises another limitation of the study. In contrast, the use of 2 different protocols for TGC should not have affected the outcomes, as only one protocol was used at a given time and the number of patients treated by a particular protocol was comparable in each group.

In summary, we have demonstrated that intraoperative initiation of tight glucose control using intensive insulin therapy substantially reduces the incidence of postoperative complications without affecting mortality or postoperative LOS in nondiabetic patients undergoing cardiac surgery while having little effect in subjects with DM.

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