Tight glucose control - the tighter the better?

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Abstract - Glucose control using insulin therapy is implemented in most intensive care units (ICU). While some studies show that glucose control results in better outcomes in critically ill patients, it is associated with an increase in hypoglycaemia. The optimal blood glucose value (BG) is the subject of debate. In this review, we address the outcomes in morbidity and mortality of insulin protocols in the ICU aimed at different BG target ranges. There is not sufficient evidence to recommend very strict BG regulation, though moderate glycaemic control might still result in mortality and morbidity benefit of critically ill patients. Less variability of BG might be beneficial. It is hard to identify clear differentiation of treatment effects in diagnostic subgroups. Implementation of glycaemic control is associated with a highly variable increase in hypoglycaemic rate and increase in number of BG measurements. Prudence dictates hypoglycaemia should be avoided as much as possible. Practical considerations on the work floor should be taken into account while choosing a BG target range that can be safely and effectively achieved.

Keywords - Tight glucose control, glucose regulation, target range, intensive care, hypoglycaemia

Introduction
Hyperglycaemia occurs frequently in critically-ill patients; even a modest degree of hyperglycaemia is associated with an increase in mortality [1]. Since the landmark study of Van den Berghe et al. [2] demonstrated that tight glucose control (TGC) resulted in lower mortality in one centre, some form of TGC has been implemented in most intensive care units (ICU). The effects of TGC are related to metabolic control, as reflected by normoglycaemia, rather than the infused insulin dose or parenteral glucose load [3]. Potential mechanisms for the benefits of TGC may be the prevention of immune dysfunction, reduction of systemic inflammation, and protection of the endothelium and of mitochondrial ultrastructure and function [4-6]. Lack of confirmation by multicentre trials and fear of the associated increase in hypoglycaemia has led to international debate. Two multicentre trials on the effects of TGC have been suspended [7, 8]. Recently, the results of the very large multicentre NICE-SUGAR trial were published.

Meanwhile, guidelines recommend controlling of hyperglycaemia in patients with severe sepsis [9]. The optimal blood glucose (BG) target range is the subject of debate. High levels of BG that have traditionally been accepted are associated with increased mortality, while low levels approaching the hypoglycaemic range have their own complications. Although the original Leuven studies [2, 6] were aimed at a BG target range of 4.4-6.1 mmol/l, this is associated with an increase in rate of hypoglycaemia. For this reason, several ICUs aim at a more liberal target range. On the other hand, stricter glycaemic control might result in better outcomes that might not be offset by possible adverse effects of an increase in hypoglycaemia. Finding the optimal range for glycaemic control is now the challenge. Furthermore, BG variability may be another factor, as strongly fluctuating BG in the accepted range is associated with impaired outcome [10]. In this review, we address the outcomes in the morbidity and mortality of insulin protocols in the ICU that are aimed at different BG target ranges. We will discuss whether subgroups of patients who profit most from TGC can be defined, and the risks of hypoglycaemia associated with glycaemic control.

Methods
We performed a search of the PubMed databases up to July 2008. Full papers of clinical trials on the effects of implementation of glycaemic control were searched using the following terms: ‘hyperglycaemia’, ‘glucose control’, ‘insulin protocol’, ‘tight glycemic control’, ‘strict glucose regulation’, ‘ICU’, ‘intensive care’, ‘critically ill’ and ‘critical illness’. Papers were limited to human adults, clinical trial, meta-analysis and randomized controlled trial. Language restrictions were not applied. From the 226 titles, 32 abstracts were selected resulting in 16 potentially relevant papers. Nine additional papers were retrieved from the references and personal bibliography. After scrutinizing these 25 papers, 8 were excluded, because they did not concern original studies [3, 5, 11-15], or did not have a control group for TGC [16]. In this review we included 13 controlled trials, 1 subanalysis focused on the review question [2, 4, 6, 7, 17-26] and supplementary evidence for a target range from three observational studies [27-29].

Summary of findings
Randomized controlled trials on the effects of TGC
Six single-centre [2, 4, 6, 17, 19,22] and three multicentre...
randomized controlled studies [7, 23-24] have compared TGC with normoglycaemia (see table). The original Leuven trial shows mortality and morbidity benefit in TGC-patients [2]. In contrast, the most recent and largest multicentre trial show increased mortality in TGC [24]. Five studies [2, 4, 6, 17, 19] show better outcomes in terms of morbidity for TGC. The studies were reviewed, ranged in order of increasing target BG and achieved BG results.

A two-centre study, set up to compare strict TGC (4-6 mmol/l) versus medium TGC (6-8 mmol/l) during the first 48 hours of ICU stay, achieved no difference in median BG and this resulted in an identical mortality in the patients [23].

The two Leuven studies [2,6] aimed for BG of 4.4-6.1 mmol/l compared to standard therapy at that time, insulin started in case of BG>12 and aimed at BG<10 mmol/l. A reduction of mean morning BG resulted in an apparent risk reduction in IC mortality of 42% [2]. In the medical ICU, comparable reduction of mean morning BG lowered mortality only in the predefined subgroup of patients with a ICU length of stay (LOS) of at least three days [6]. TGC did result in lower morbidity in the whole intention-to-treat group, in terms of incidence of new renal failure, duration of mechanical ventilation and ICU stay. The NICE-SUGAR trial compared TGC with moderate glycaemic control and did not confirm this benefit of TGC: mortality in the control group with moderate glycaemic control (BG 8-10 mmol/l) was lower than in the TGC-group [24]. A small RCT, aiming at the same target BG, could not show a significantly better survival for TGC-treated patients [22]. A multicentre trial targeted at the same BG was suspended because of an increase in hypoglycaemia, and no demonstrated differences in mortality or morbidity outcomes [7].

In two smaller trials a slightly higher BG was aimed for – target 4.4-6.7 mmol/l – [4, 17]; TGC did not result in a decrease in mortality either, though the infection rate was lowered.

In another study, glycaemic control was more liberal with a BG target between 6.1 and 7.8 mmol/l [19]. No benefit was seen in mortality, but fewer glycaemic control patients had evidence of vascular damage.

In summary, most evidence seems to have been delivered by the recently completed multicentre trial, demonstrating a survival benefit of moderate glycaemic control (BG 8-10 mmol/l) compared with TGC (BG 4.4-6.1 mmol/l). The mortality benefit of any glycaemic control is shown by only one single centre RCT which aimed at a BG of 4.4 – 6.1 mmol/l compared with traditional control of high BG. Three other RCTs show decreasing morbidity as a result of TGC with the same target range - again, compared with high BG - whereas in one RCT with a more liberal target range of 6.1 – 7.8 mmol/l, resulted in a reduction in morbidity.

**Historically controlled cohort studies**

Of four before and after cohort studies [18, 20, 21, 25], the largest study shows statistically significant mortality gain as well as morbidity benefit in the glycaemic control cohort [21]. In order of increasing target and achieved BG, these are the results. In a study of the effects of TGC targeted at BG 4.4-6.1 mmol/l, no differences were shown in mortality or morbidity [25]. Though ICU mortality is said to be lowered by TGC with a comparable target range, this is of unknown statistical significance [20]. The largest study used a more liberal target range of BG <7.8 mmol/l [21]. This was associated with a significant decrease in mortality and morbidity. In a smaller study on the effects of glycaemic control aimed at 5-8 mmol/l mortality and morbidity were identical [20]. This leaves only the large cohort study, aimed at BG <7.8 mmol/l [21], to show better outcomes for glycaemic control.

**Subgroup analyses of randomized controlled trials**

A subgroup analysis of the pooled data from the two Leuven studies [2,6] compared three strata of achieved BG control [26]. A gradual decrease in risk of ICU and hospital mortality, occurrence of new renal failure and new critical illness polyneuropathy (CIPNP) are reported with mean BG decreasing to <6.1 mmol/l.

**Observational studies**

Supplemental evidence for a certain level of glycaemic control comes from observational cohort studies. Failure to control BG to a target level of mean BG <7 mmol/l was an independent predictor of ICU death in a single-centre cohort study [28]. The proportion of time in six strata of BG control of 523 mixed ICU-patients was analyzed [26]. OR for mortality was not significantly different for each strata in which most time was spent.

In a multicentre study, lower ICU and hospital mortality was associated with a progressively lower achieved mean BG down to <7.9 mmol/l [27]. This study showed that variation in BG significantly and independently predicted mortality and even more so than did mean BG [27].

**Discussion**

The benefit of TGC, suggested by the single centre Leuven studies [2,6], is not confirmed by the recently published multicentre trial [24]. The factors that might explain this disparity are not clear. Local features of the Leuven population or standard of care may play a role, for instance predominately parenteral nutrition in this centre versus mainly enteral nutrition in the multicentre trial. Workload and protocol performances could play a role, as in Leuven glucose was regulated by extra staff, whereas in the NICE-SUGAR trial this was done by the regular staff as part of their duties, aided by a computerized protocol. None of these studies reports BG variability results, which might be another factor. Notably, the glycaemic management in the control group was stricter in the multicentre trial than at the time of the Leuven study. It is possible, that glycaemic control to certain extent might still benefit patients, but maybe not up to the very strict range.

**Target range for glycaemic control**

The most robust evidence comes from the largest multicentre trial which demonstrates the mortality benefit of glycaemic control aimed at BG of 8-10 mmol/l versus 4.5-6 mmol/l [24]. Two large controlled studies show a mortality and a morbidity benefit of glycaemic control, one aiming at BG 4.4-6.1, and one targeted at BG <7.8 mmol/l [2, 21]. Morbidity benefit is shown in two other studies with a BG target range 4.4-6.1 to 6.7 mmol/l [6, 17], and
another with a target range of 6.1-7.8 mmol/l [19]. These results seem to suggest, moderate glycaemic control might be beneficial and preferable to very strict regulation.

The size of the studies and the difference in the glucose control achieved influence the measured outcome effects of glycaemic control, as well as the target range. Circumstantial evidence for benefit of a certain BG target range is provided by subanalyses and uncontrolled observational studies. Subanalyses of the Van den Bergh trials show that mean BG <6.1 mmol/l is associated with the lowest mortality and occurrence of new renal insufficiency and CIPNP [3,26]. Two observational studies show mortality benefit with mean BG <7 mmol/l [29] or <7.9 mmol/l [27]. Though these results suggest increasing benefit with decreasing target range of glycaemic control to a certain extent, this study and to-be-published findings of an Amsterdam group show limiting the variability in BG per patient might be an even more important factor in the beneficial effects of glycaemic control than achieved mean BG [10, 27]. Of course, conclusions are hard to draw from these observational data.

International sepsis guidelines in which limiting hyperglycaemia using intravenous insulin is recommended, are more conservative; they suggest a protocol aimed at keeping BG to at least <8.3 mmol/l [9]. This weak recommendation is said to be based on low quality evidence, consisting of observational studies that show an association between increasing hyperglycaemia and increasing mortality [30] and a nonsignificant tendency of decreasing mortality with lowering BG [28]. An intermediate target level for BG of 7.8-10 mmol/l has been suggested by others, because of concerns about increased rate of hypoglycaemia [31]. The performance of the glycaemic control protocol, staffing, facilities and other practical circumstances influence the ability to limit hypoglycaemia and BG variability. If these are optimal, we think it premature to abandon glycaemic control, but it might be prudent to strive to moderate BG ranges, for instance somewhere in the range of 7-10 mmol/l.

Subgroups of patients benefiting from glycaemic control

The effects of glycaemic control on outcome may be different for certain subgroups of patients. Identifying patients who profit most from glycaemic control can help to prevent potential harm of the associated increase in hypoglycaemia in the patients who may benefit less from glycaemic control. It is not immediately apparent which patients profit most from glycaemic control. Among the reviewed studies, proof of benefit of glycaemic control tends to be linked more to the size of the study than to a certain category of patients.

The NICE-SUGAR trial did not show differences in treatment effects on specific subgroups, except for perhaps trauma patients and patients treated with corticosteroids. A potential benefit of TGC in these patients was not excluded. Van den Bergh showed benefit in a surgical ICU populated mainly by post cardiac surgery patients [2]. It was suggested, that especially patients with a LOS of >5 days and septic patients profited. This was not confirmed by the NICE-SUGAR trial [24] or by subgroup analysis of the pooled data of this study and the study in the medical ICU that showed TGC resulted in a decrease in mortality in all diagnostic subgroups, except for patients with diabetes mellitus [26]. In the NICE-SUGAR trial and another paper better glycaemic control in the subgroup of patients with diabetes was not shown to be related to the lowering of mortality [27,24].

Mortality benefit was noted in all diagnostic subgroups in a large mixed ICU-population [21], but was most striking in patients with septic shock and in neurological and surgical patients.

No benefit was seen in a subgroup analysis of 48 patients with acute neurological injury in patients randomized to TGC or a control group, but this might be obscured by not achieving a lowering of median BG by TGC [15].

In the second Leuven study in a medical ICU, TGC did not result in a better mortality in the intention-to-treat group in contrast with patients with an ICU stay of at least three days [6]. This might suggest that short-stayers might be harmed by TGC. However, analysis of the subgroup with LOS of <3 days showed no difference in mortality or morbidity between the intention-to-treat group and the control group [26].

In summary, no clear differentiation in the effects of glycaemic control was apparent, in patients with different LOS or diagnoses, though this cannot be excluded.

The downside of glycaemic control

The possible benefits of glycaemic control must be weighed against its expense and potential risks.

Many ICU professionals are concerned about an increase in iatrogenic hypoglycaemia. A Dutch survey revealed that this concern may hamper the implementation of TGC [32]. Potential adverse effects of hypoglycaemia might diminish the overall benefits of glycaemic control, although glycaemic control still decreases mortality in a large study despite an increase in the occurrence of hypoglycaemia (OR 0.67; 95% CI 0.56-0.80; p<.0001) [33]. A 6-fold increase in the number of patients experiencing hypoglycaemia <2.2 mmol/l has been reported [2,6], and was reason to stop two large multicentre trials before their endpoints were met [7,8]. The incidence of glycaemic control-associated hypoglycaemia shows a broad range, ranging from 0.34% to 32% of patients. The fact that one study reports a decrease in the rate of hypoglycaemia after starting a formal glycaemic control protocol, suggests that protocol quality is an important factor in limiting the number of hypoglycaemic episodes [20]. Apart from the definition of hypoglycaemia, assays and blood compound used for BG testing, this disparity in hypoglycaemia rate might be the result of several other factors such as differing BG target ranges and insulin protocols, frequency of measurement of BG, category of patients, prevalence of diabetes mellitus, variations in nutrition or carbohydrate administration, sepsis, renal failure or renal replacement therapy, inotropic therapy, mechanical ventilation [33,34]. Other drugs (quinolones), severity of disease, sepsis, hepatic, renal or heart failure, glucocorticoid deficiency may all be causes of hypoglycaemia in ICU patients, as well as exogenous insulin administration [35]. Of course, in a complex environment occasional human error may always be a factor. It is conceivable that physiological defences
against hypoglycaemia – decrements in insulin, and increments in glucagon and epinephrine – are compromised in the critically ill patients. Glucagon and epinephrine responses to falling glucose levels may be reduced due to prior hypoglycaemic episodes, and due to sedation [35].

Levels of brief hypoglycaemia due to TGC protocols in the ICU can be very low, but evidence of severe consequences is limited. Iatrogenic hypoglycaemia due to a glycaemic control protocol must be differentiated from spontaneous hypoglycaemia (without the administration of insulin), as these might be the result of different disease entities [36]. Though the overall occurrence of hypoglycaemia is associated with increased mortality [6, 7, 33], spontaneous hypoglycaemia is associated with a 1.7-fold higher mortality than hypoglycaemia with insulin administration [26]. This might suggest hypoglycaemia indicates a high risk of death instead of being the cause of it. Cognitive damage due to hypoglycaemia is feared, but no new neurological problems in surviving patients having suffered hypoglycaemia were detected [26]. According to a recent review, the evidence in the literature of severe adverse effects of hypoglycaemia induced by TGC in ICU patients that might offset the benefits of TGC, was very limited [37]. On the other hand, long-term adverse effects of hypoglycaemia on cognitive function of ICU patients are hard rule out, as these are not routinely recorded and complications of hypoglycaemia might be underreported in publications. The lack of benefit of TGC versus moderate control in the largest multicentre trial, together with the increase in hypoglycaemia associated with TGC in most studies, do not rule out hypoglycaemia as a factor limiting positive effects of TGC. It is clear; all measures should be taken in order to limit the number of hypoglycaemic episodes and extent of hypoglycaemia. Most glycaemic control algorithms recommend if necessary frequent hourly BG measurement in the low range or until stabilization. Recognition of patients most at risk of hypoglycaemia (a prior diagnosis of diabetes mellitus, septic shock, renal failure or possibly bicarbonate-based continuous venovenous haemofiltration, mechanical ventilation, high severity of illness, insulin use, inotropic support and decrease of nutrition without adjustment of insulin) is important. Regulation of BG can be improved by using a good quality, nurse-driven, computer-aided dynamic scale protocol, with continuous insulin infusion and close blood glucose monitoring [38,39].

Conclusions
There is not enough evidence to support lowering of blood glucose to very strictly regulated levels. We suggest moderate glycaemic control, while limiting the amount and extent of hypoglycaemic episodes and the variability of BG. In individual ICUs, practical considerations on the work floor must be taken into account while choosing a target range that can be safely and effectively achieved.

As short-stay patients with less benefit of glycaemic control cannot be identified for sure beforehand, it is not practical to exclude them from glycaemic control.

It is hard to identify unambiguous differentiation in treatment effects for certain diagnostic subgroups up to date.

**ABBREVIATIONS**

- Blood glucose (BG)
- 95% confidence interval (95 CI)
- Continuous venovenous haemofiltration (CVVH)
- Critical illness polyneuropathy (CIPNP)
- Length of stay (LOS), in days
- Mechanical ventilation (MV)
- Out-of-hospital arrest (OHCA)
- Odds ratio (OR)
- Patients (pts)
- Randomized controlled trial (RCT)
- Renal replacement therapy (RRT)
- Risk ratio (RR)
- Tight glycaemic control (TGC)
- Ventricular fibrillation (VF)

Values expressed in mean/standard deviation (±) or median (interquartile range) as appropriate.
### Table of the reviewed studies

<table>
<thead>
<tr>
<th>STUDY</th>
<th>DESIGN</th>
<th>BG TARGET RANGE, MMOL/L</th>
<th>NO AND CATEGORY OF PTS</th>
<th>BG RESULTS, MMOL/L</th>
<th>OUTCOME</th>
<th>MORBIDITY</th>
<th>HYPOGLYCAEMIA, DEFINITION (MMOL/L) AND INCIDENCE</th>
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<tbody>
<tr>
<td>[24]</td>
<td>Prospective RCT multcentre</td>
<td>4.5-6.0</td>
<td>6104 mixed</td>
<td>6.4 ±1.0</td>
<td>90day 27.5% OR 1.14 (95CI 1.02-1.28) absolute risk increase 2.6%</td>
<td>No difference in hosp/ ICU LOS, new organ failure, duration MV/ RRT, positive blood cultures, transfusion</td>
<td>BG&lt;2.2 6.6% pts (no sequels)</td>
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<td></td>
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<td>8.0-10.0</td>
<td>8.0 ±1.3</td>
<td>24.9%</td>
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<td>[2]</td>
<td>Prospective RCT 1 centre</td>
<td>4.4-6.1</td>
<td>1548 Surgical primary cardiac</td>
<td>Morning 5.7 ±1.1</td>
<td>ICU 4.6% (p&lt;0.04), apparent risk reduction 42% (95CI 22-62%), hospital mort 7.2% (p&lt;0.01), mostly with LOS&gt;5days</td>
<td>Less MV&gt;14 days Less RRT Fewer septic episodes Less CIPNP Less RBC transfused</td>
<td>BG&lt;2.2 5.1% pts</td>
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<td>10.0-11.1</td>
<td>8.5 ±1.8</td>
<td>ICU 7.8% Hospital 10.9%</td>
<td>0.8%</td>
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<td>[6]</td>
<td>Prospective RCT 1 centre predefined subgroup analysis LOS≥3</td>
<td>4.4-6.1</td>
<td>1200 medical</td>
<td>Morning 6.2 ±1.6</td>
<td>Hospital 37% (NS) LOS≥3: 43% (p&lt;.01)</td>
<td>New renal failure 5.9% (p=.04) Shorter duration of MV (hazard ratio 1.21[95CI 1.02-1.44])</td>
<td>BG&lt;2.2 18.7% pts</td>
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<td>10.0-11.1</td>
<td>8.5 ±1.7</td>
<td>40% LOS≥3: 53%</td>
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<td>[22]</td>
<td>RCT 1 centre</td>
<td>4.4-6.1</td>
<td>70 mixed, predefined LOS &gt;48h ICU</td>
<td>Median 5.4 (5.1-5.7)</td>
<td>Hospital 26% NS RIR 3.0 (95CI 0.78-15.7)</td>
<td>New renal failure 8.9%</td>
<td>BG&lt;2.2 14.3% pts (no sequels)</td>
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<td>10-11.1</td>
<td>7.9 (7.2-9.0)</td>
<td>9%</td>
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<td>[7]</td>
<td>RCT, 2-by-2 factorial trial, Multicentre Suspended</td>
<td>4.4-6.1</td>
<td>537 severe sepsis</td>
<td>Morning 6.2 (p&lt;.001)</td>
<td>No difference: 28day mortality 24.7% (p=.74) 90day 39.7% (p=0.31) ; Cox regression hazard ratio for death 0.95 (95CI 0.70-1.28; p=.72)</td>
<td>No difference in SOFA, acute renal failure, need for renal replacement therapy, vasopression, ventilator-free days, LOS IC; serious adverse events (including hypog) 10.9% (p=.01) – no severe adverse event resulted directly in death</td>
<td>BG&lt;2.2 17.0% pts (p&lt;.001)</td>
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<td>10-11.1</td>
<td>8.4</td>
<td>28day 26% (NS) 90day 35.4% (NS)</td>
<td>Severe adverse events 5.2%</td>
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<td>[23]</td>
<td>RCT 2 centre</td>
<td>4-6 during 1st 48h ICU stay</td>
<td>90 resuscitated from OHCA with VF as initial rhythm</td>
<td>Med BG 5.0 (4.5-5.8) (71% of BG in range)</td>
<td>6.4 (5.5-7.4) (41% in range; largely below target)</td>
<td>30day mortality NS: 33% (p=0.846)</td>
<td>No difference in S-neuron specific endease</td>
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<td>6-8</td>
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**Table notes:**
- **STUDY:** Reference to the study.
- **DESIGN:** Design of the study.
- **BG TARGET RANGE, MMOL/L:** Target blood glucose range.
- **NO AND CATEGORY OF PTS:** Number of participants and category of patients.
- **BG RESULTS, MMOL/L:** Blood glucose results.
- **OUTCOME:** Outcomes of the study.
- **HYPOGLYCAEMIA, DEFINITION (MMOL/L) AND INCIDENCE:** Hypoglycaemia definition and incidence.

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**Study details:**
- **[24]** Prospective RCT multcentre, 6104 mixed, BG 6.4 ±1.0, 90day 27.5% OR 1.14 (95CI 1.02-1.28) absolute risk increase 2.6%.
- **[2]** Prospective RCT 1 centre, 1548 Surgical primary cardiac, Morning 5.7 ±1.1, ICU 4.6% (p<0.04), apparent risk reduction 42% (95CI 22-62%), hospital mort 7.2% (p<0.01), mostly with LOS>5days.
- **[6]** Prospective RCT 1 centre predefined subgroup analysis LOS≥3, 1200 medical, Morning 6.2 ±1.6, Hospital 37% (NS) LOS≥3: 43% (p<.01).
- **[22]** RCT 1 centre, 70 mixed, predefined LOS >48h ICU, Median 5.4 (5.1-5.7), Hospital 26% NS RIR 3.0 (95CI 0.78-15.7).
- **[7]** RCT, 2-by-2 factorial trial, Multicentre Suspended, 537 severe sepsis, Morning 6.2 (p<.001), No difference: 28day mortality 24.7% (p=.74).
- **[23]** RCT 2 centre, 90 resuscitated from OHCA with VF as initial rhythm, Med BG 5.0 (4.5-5.8) (71% of BG in range), 6.4 (5.5-7.4) (41% in range; largely below target).
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<tr>
<td>[4]</td>
<td>Prospective RCT 1 centre</td>
<td>4.4-6.7</td>
<td>61 surgical</td>
<td>6.9 ±2</td>
<td>Hospital 32% (p=.50)</td>
<td>Fewer nosocomial infections: BG=3.3 32% (p&lt;.001)</td>
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<td></td>
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<td>10-12.2</td>
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<td>9.9 ±3.4</td>
<td>78%</td>
<td>3.5-fold increase in intravascular device sepsis and surgical site infections (p&lt;.05)</td>
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<td>[17]</td>
<td>Pilot, Prospective RCT</td>
<td>4.4-6.7</td>
<td>78 subarachnoidal haemorrhage pts in ICU</td>
<td>? (in range 69%)</td>
<td>No difference in 6 months mortality: 15% (p=.90)</td>
<td>Infection rate up to 14th postop day 27% (p&lt;.001); vasospasm, no difference in 6-month neurological outcome</td>
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<td>4.4-12.2</td>
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<td>(in range 83%)</td>
<td>18%</td>
<td>42%</td>
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<td>[19]</td>
<td>RCT 1 centre</td>
<td>6.1-7.8</td>
<td>89 mixed, LOS &gt;24 h ICU</td>
<td>Mean 7.9 (±0.8)</td>
<td>No difference in hospital-, ICU- or 28day mortality; 28day 46.4% NS</td>
<td>No difference in infection rate up to 14th postop day 27% (p&lt;.001); vasospasm, no difference in 6-month neurological outcome</td>
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<td>7.8-11.1</td>
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<td>9.7 (±1.1)</td>
<td>54.2%</td>
<td>39.6%</td>
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<td>[25]</td>
<td>Prospective before-after cohort 1 centre</td>
<td>4.4-6.1</td>
<td>271 mixed, non cardiac surgery LOS ≥2</td>
<td>6.1 (5.8-6.5)</td>
<td>No difference: 11.8% (RRR 20% NS)</td>
<td>Secondary infections NS: 21.5%; no difference in pts receiving RBC; No difference in: MV, inotropy, CVVH</td>
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<td>&lt;12</td>
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<td>7.4 (6.7-8.3)</td>
<td>14.8%</td>
<td>Secondary infections 16.0%</td>
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<td>[20]</td>
<td>Retro-prospective before-after cohort 1 centre</td>
<td>4.5-6.1</td>
<td>100 mixed</td>
<td>?</td>
<td>ICU 36%</td>
<td>BG=2.2 4% of pts</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&quot;physicians discretion&quot;</td>
<td></td>
<td></td>
<td>ICU 56%</td>
<td>16% of pts</td>
<td></td>
</tr>
<tr>
<td>[21]</td>
<td>Before-after cohort 1 centre</td>
<td>&lt;7.8</td>
<td>1600 mixed</td>
<td>7.3 ±3.1 (p&lt;.001)</td>
<td>Hospital 15% (decrease 29%, p=.002) Mostly septic shock, neurological or surgical pts</td>
<td>New renal failure 3% (decrease 75%, p=.03) Pts RBC 21% (decrease 19%, p=.04) LOS ICU median 1.6 (decrease 11%, p=.01)</td>
<td>BG=2.2 0.34% pts (NS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>None</td>
<td></td>
<td>8.4 ±5.2</td>
<td>21%</td>
<td>New renal 12% Pts RBC 25% LOS ICU median 1.9</td>
<td></td>
</tr>
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<td>Before-after cohort 1 centre</td>
<td>&lt;7.8</td>
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</tr>
<tr>
<td>[18]</td>
<td>Retro-prospective before-after cohort 1 centre</td>
<td>5-8 nomogram</td>
<td>86 mixed</td>
<td>Morning 7.1 ±1.8</td>
<td>No difference: ICU 32% (p=.29)</td>
<td>No difference in vasopression, antibiotic use or ICU LOS</td>
<td>BG=2.2 no difference; 0.2% of BG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B-10 ad hoc</td>
<td></td>
<td>9.8 ±2.8</td>
<td>45%</td>
<td>0.4%</td>
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</tbody>
</table>

HISTORICALLY CONTROLLED COHORT

<table>
<thead>
<tr>
<th>STUDY</th>
<th>DESIGN</th>
<th>BG TARGET RANGE, MMOL/L</th>
<th>NO AND CATEGORY OF PTS</th>
<th>BG RESULTS, MMOL/L</th>
<th>OUTCOME</th>
<th>MORBIDITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>[25]</td>
<td>Prospective before-after cohort 1 centre</td>
<td>4.4-6.1</td>
<td>271 mixed, non cardiac surgery LOS ≥2</td>
<td>6.1 (5.8-6.5)</td>
<td>No difference: 11.8% (RRR 20% NS)</td>
<td>Secondary infections NS: 21.5%; no difference in pts receiving RBC; No difference in: MV, inotropy, CVVH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;12</td>
<td></td>
<td>7.4 (6.7-8.3)</td>
<td>14.8%</td>
<td>Secondary infections 16.0%</td>
</tr>
<tr>
<td>[20]</td>
<td>Retro-prospective before-after cohort 1 centre</td>
<td>4.5-6.1</td>
<td>100 mixed</td>
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SUBANALYSES OF RANDOMIZED CONTROLLED TRIALS

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<th>BG TARGET RANGE, MMOL/L</th>
<th>NO AND CATEGORY OF PTS</th>
<th>BG RESULTS, MMOL/L</th>
<th>OUTCOME</th>
<th>MORBIDITY</th>
<th>HYPOGLYCAEMIA, DEFINITION (MMOL/L) AND INCIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>[26]</td>
<td>Subanalysis pooled data VdBerghe 2001(2) + 2006(8)</td>
<td>Posthoc analysis</td>
<td>Strata: mean BG&lt;6.1 6.1-8.3; &gt;8.3</td>
<td>Hospital mortality lower with decreasing mean BG (OR 1.38 95CI 1.10-1.75) with BG=8.3 vs 6.1-8.3; OR 0.77 (0.61-0.96) with BG=6.1 vs 6.1-8.3] - subgroup diabetes: no benefit of TGC; all other diagnostic groups did not reaching vs vs after initial correction of BG</td>
<td>MORTALITY</td>
<td>MORBIDITY</td>
<td>- new renal failure: OR 0.56 (95CI 0.41-0.78); new CIPNP: OR 0.49 (0.37-0.65); both most effective with BG=6.1 - subgroup diabetes: morbidity benefit</td>
</tr>
</tbody>
</table>

| [27]  | Retrospective observational 4 centres | General goal BG 6-10 No specific protocol | 7049 mixed | Mean 8.0 ± 2.0 SD 1.7 ± 1.3 | ICU 23.3% | Variability of BG sign= indep predicted ICU+hospital mortality, stronger predictor than mean BG; Lower ICU+hospital mortality with lower SD BG (p<.01) and with lower mean BG (>8.9, 7.9-8.9, 6.8-7.9; p<.01; except <6.8 vs 6.8-7.9) Diabetes: no relation BG control indices and ICU/hospital mortality |

| [28]  | Prospective observational 1 centre | 5.0-8.0 | 523 cardiothoracic surgical + medical; Proportion of time spent in BG<4.4; 4.4-6.1; 6.1-8.0; 8.0-10; 10-11.1; >11.1 | ICU 5.2% | Hospital 5.7%; OR's for time in glycaemic strata NS; tendency of lower mortality with increasing time in lower BG strata |

OBSERVATIONAL STUDIES

- [29] Prospective cohort 1 centre pts reaching vs not reaching target mean BG<7, after initial correction of BG

References

6. Van den Bergh, G., Wilmer, A., Hermans, G., Meersseman, W., Wouters, P. J., Mi-


