Supplemental Digital Content (SDC) Table of Contents

Supplemental Digital Content 1. Panel selection & members.

Guideline leadership

Guideline leadership consisted of co-chairs (JJ, NB) and co-vice-chairs (MS, EH), supported by a clinician-methodologist (KH) appointed by the GUIDE group at McMaster University in Hamilton, Canada. Selection of the leadership for this guideline and all others is the responsibility of the Society of Critical Care Medicine (SCCM) and American College of Critical Care Medicine (ACCM) Board of Regents (BOR). The BOR follows the rules provided in the SCCM guidelines Standard Operating Procedures Manual (SOP) which is that the BOR identifies two chairs and two co-vice chair subject matter experts for each SCCM-approved guideline. There was a due consideration for diversity, equity and inclusion in the process and particular attention is paid to assuring that expertise is evaluated via submission of the Curriculum Vitae of each candidate. The BOR reviewed declared conflicts of interest (COI) for adjudication prior to appointment using the SCCM COI system.

Panel Selection

The guideline leadership selected an additional interdisciplinary panel of 15 professional members following the SOP requirements with attention to diversity, equity, and inclusion in the process of panel selection, followed by review by BOR. Panel members were selected based on clinical expertise in glycemic management in the ICU. The panel also included two patient/ family advisors who volunteered to participate when asked by a Co-Chair. Each member of the panel completed COI forms before they were officially appointed to the panel and at several additional time points throughout the guideline development process. Panelists served at the discretion of the BOR with ongoing monitoring of COI and performance.

Supplemental Digital Content 2. ACCM/SCCM Standard Operating Procedures for Conflict of Interest (COI) management.

SCCM maintains a commitment to trustworthy guidelines through a strict conflict of interest disclosure and management process. There were no disclosures directly related to the PICO questions within this guideline that required individual authors to abstain from voting on any recommendations. Disclosures are collected prior to voting by SCCM through a conflict of interest platform and voting is accomplished using Survey Monkey (http://www.surveymonkey.com).

Supplemental Digital Content 3. Population, Intervention, Comparator, Outcomes (PICO) Questions

1. Trigger blood glucose for insulin initiation

In **adult critically ill patients**, should we recommend initiating intravenous insulin therapy at a lower glucose threshold 6.1-10 mmol/L (110-180 mg/dL) or higher glucose threshold > 10 mmol/L (> 180 mg/dL)?

In **pediatric critically ill patients**, should we recommend initiating intravenous insulin therapy at a lower glucose threshold 6.1-10 mmol/L (110-180 mg/dL) or higher glucose threshold > 10 mmol/L (> 180 mg/dL)?

Population	**Intervention**	**Comparison**	**Outcomes**
Adult critically ill patients on insulin therapy	Initiate insulin infusion when BG 110 to 180	Initiate insulin infusion when BG > 180	SDC 4
Pediatric critically ill patients [defined as ≥ 42-week corrected GSA to 18 years] on insulin therapy	Initiate insulin infusion when BG 110 to 180	Initiate insulin infusion when BG > 180	SDC 4

2. Intensive versus conventional glucose targets

In **adult critically ill patients** on insulin therapy, should we recommend a lower blood glucose target (4.4-7.7 mmol/L or 80-139 mg/dL) **or** a higher glucose target (7.8-11.1 mmol/L or 140-200 mg/dL)?

In pediatric critically ill patients on insulin therapy, should we recommend a lower blood glucose target (4.4-7.7 mmol/L or 80-139 mg/dL) **or** a higher glucose target (7.8-11.1 mmol/L or 140-200 mg/dL)?

Population	**Intervention**	**Comparison**	**Outcomes**
Adult critically ill patients on insulin therapy	Lower BG target 80-139 mg/dL	Higher BG target 140-200 mg/dL	SDC 4
Pediatric critically ill patients [defined as ≥ 42-week corrected GSA to 18 years] on insulin therapy	Lower BG target 80-139 mg/dL	Higher BG target 140-200 mg/dL	SDC 4

3. Continuous IV infusion versus intermittent subcutaneous insulin

In the acute management of adult critically ill patients for whom insulin therapy is being initiated, should we recommend initiating continuous IV insulin infusion **or** intermittent subcutaneous insulin?

In the acute management of pediatric critically ill patients for whom insulin therapy is being initiated, should we recommend initiating continuous IV insulin infusion **or** intermittent subcutaneous insulin?

Population	**Intervention**	**Comparison**	**Outcomes**
Adult critically ill patients for whom insulin therapy is being initiated	Continuous intravenous insulin infusion	Intermittent subcutaneous insulin	SDC 4
Pediatric critically ill patients [defined as ≥ 42-week corrected GSA to 18 years] for whom insulin therapy is being initiated	Continuous intravenous insulin infusion	Intermittent subcutaneous insulin	SDC 4

4. Frequency of blood glucose monitoring

In adult critically ill patients on insulin infusion therapy, should we recommend monitoring of glucose at frequent intervals (≤ 1hour, continuous or near-continuous) **or** longer intervals (> 1 hour), during the period of glycemic instability?

In pediatric critically ill patients on insulin infusion therapy, should we recommend monitoring of glucose at frequent intervals (≤ 1hour, continuous or near-continuous) **or** longer intervals (> 1 hour), during the period of glycemic instability?

Population	**Intervention**	**Comparison**	**Outcomes**
Adult critically ill patients on insulin infusion therapy	Glucose check interval ≤ 1h (including continuous or near continuous)	Glucose check > 1h	SDC 4
Pediatric critically ill patients [defined as ≥ 42-week corrected GSA to 18 years] on insulin infusion therapy	Glucose check interval ≤ 1h (including continuous or near continuous)	Glucose check > 1h	SDC 4

5. Use of explicit clinical decision support tool versus standard care

In adult critically ill patients on insulin infusion therapy, should we recommend an explicit clinical decision support tool versus a protocol with no explicit clinical support tool for insulin titration?

In pediatric critically ill patients on insulin therapy, should we recommend an explicit clinical decision support tool versus a protocol with no explicit clinical support tool for insulin titration?

Population	**Intervention**	**Comparison**	**Outcomes**
Adult critically ill patients on insulin infusion therapy	Explicit clinical decision support tool [as defined below]	No explicit clinical decision support tool	SDC 4
Pediatric critically ill patients [defined as ≥ 42-week corrected GSA to 18 years] on insulin infusion therapy	Explicit clinical decision support tool [as defined below]	No explicit clinical decision support tool	SDC 4

Criteria for explicit clinical decision support tool ['the intervention']:

- Explicit recommendations (the bedside clinician knows exactly what to do each time) – *not* a range of options
- Reproducible actions (the same patient state will get treated the same way)
- Output incorporates > 1 patient-specific input variable (i.e., rate of change, hypoglycemia episodes, nutrition, etc.) and provides > 1 output variable (e.g., timing of next BG)
- Must be OPEN loop – allows for bedside clinician to agree with recommendation or disagree [clinician oversight]

Note: Such tools are usually computer-based, but do not have to be for inclusion.

Supplemental Digital Content 4. Outcome Prioritization

Hospital mortality	8.71
ICU mortality	8.53
Developmental Outcomes	8.41
Quality of life	8.06
Seizures	8
Long-term cognitive impairment	7.94
Acute kidney injury requiring dialysis	7.35
Return to work/ same work	7.35
Long-term psychological problems	7.12
ICU-acquired diabetes mellitus	6.94
ICU length of stay	6.82
Healthcare associated/ surgical site infections	6.82
Peripheral neurological complications	6.76
Bacteremia	6.65
Delirium	6.53
Hospital length of stay	6.47
Hypoglycemic events	6.41
Sleep disorders post-ICU	6.18
Sleep interruptions in ICU	5.47
Blood transfusions	5.29
Hyperglycemia episodes	4.94
Achieving/ maintaining desired glycemic control	4.59
Nursing workload	4.47
Personal protective equipment utilization	3.59

n = 19 panelists

Scores 7-9: Critical for decision making
Scores 4-6: Important, but not critical for decision making
Scores 1-3: Not important for decision making/ of lower importance to patients

Supplemental Digital Content 5. Literature search strategy

Search Strategy

Embase <1974 to 2021 February 03, search updated on 2023 January 05>, OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

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1 exp *Intensive Care Units/ use ppez
2 exp *Critical Care/ use ppez
3 *Critical Illness/ use ppez
4 *Critical Care Nursing/ use ppez
5 exp *Newborn intensive care/ or exp *Intensive care units, pediatric/ or exp *intensive care units, neonatal/
6 (((acute* or critical*) adj2 (ill* or injur* or wound*)) or trauma*).ti,kf,kw.
7 ((intensive* or critical* or neurointensive* or neuro-intensive* or neurocritical* or neuro-critical*) adj (care or therap* or treatment*)).ti,kf,kw.
8 (critical* or intensive* or trauma*).jn.
9 (ICU or MICU or CICU or CVICU or CCU or NICU or SICU or PICU or POCCU or ITU or HDU).ti.
10 (high dependency or coronary care unit*).ti.
11 exp *Intensive Care/ use oemezd
12 *Intensive Care Unit/ use oemezd
13 *Coronary Care Unit/ use oemezd
14 *Burn Unit/ use oemezd
15 *Stroke Unit/ use oemezd
16 or/1-15
17 exp animals/
18 exp animal experimentation/ or exp animal experiment/
19 exp models animal/
20 nonhuman/
21 exp vertebrate/ or exp vertebrates/
22 17 or 18 or 19 or 20 or 21
23 exp humans/
24 exp human experimentation/ or exp human experiment/
25 23 or 24
26 22 not 25
27 16 not 26
28 (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.
29 Randomized Controlled Trial/
30 exp Randomized Controlled Trials as Topic/
31 "Randomized Controlled Trial (topic)"/
32 Controlled Clinical Trial/
33 exp Controlled Clinical Trials as Topic/
34 "Controlled Clinical Trial (topic)"/
35 Randomization/
36 Random Allocation/
37 Double-Blind Method/
38 Double Blind Procedure/
39 Double-Blind Studies/

40 Single-Blind Method/
41 Single Blind Procedure/
42 Single-Blind Studies/
43 Placebos/
44 Placebo/
45 Control Groups/
46 Control Group/
47 (random* or sham or placebo*).ti,ab,hw,kf,kw.
48 ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
49 ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
50 (control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.
51 (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.
52 allocated.ti,ab,hw.
53 ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.
54 ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.
55 (pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.
56 ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.
57 ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.
58 (phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf,kw.
59 or/28-58
60 epidemiologic methods/
61 epidemiologic studies/
62 observational study/
63 observational studies as topic/
64 clinical studies as topic/
65 controlled before-after studies/
66 cross-sectional studies/
67 historically controlled study/
68 interrupted time series analysis/
69 exp seroepidemiologic studies/
70 national longitudinal study of adolescent health/
71 cohort studies/
72 cohort analysis/
73 longitudinal studies/
74 longitudinal study/
75 prospective studies/
76 prospective study/
77 follow-up studies/
78 follow up/
79 followup studies/
80 retrospective studies/
81 retrospective study/
82 case-control studies/
83 exp case control study/
84 cross-sectional study/
85 observational study/
86 quasi experimental methods/
87 quasi experimental study/
88 (observational study or validation studies or clinical study).pt.

89 (observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kf,kw.
90 cohort*.ti,ab,kf,kw.
91 (prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kf,kw.
92 ((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kf,kw.
93 ((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kf,kw.
94 (retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kf,kw.
95 ((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kf,kw.
96 (case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kf,kw.
97 (population adj3 (study or studies or analysis or analyses)).ti,ab,kf,kw.
98 (descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf,kw.
99 ((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf,kw.
100 (cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,kf,kw.
101 ((natural adj experiment) or (natural adj experiments)).ti,ab,kf,kw.
102 (quasi adj (experiment or experiments or experimental)).ti,ab,kf,kw.
103 ((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf,kw.
104 (prevalence adj3 (study or studies or analysis or analyses)).ti,ab,kf,kw.
105 case series.ti,ab,kf,kw.
106 case reports.pt.
107 case report/
108 case study/
109 (case adj3 (report or reports or study or studies or histories)).ti,ab,kf,kw.
110 organizational case studies/
111 or/60-110
112 59 or 111
113 *glucose blood level/ use oemezd or *blood glucose/ use ppez or ((blood or serum) adj2 (sugar or glucose)).ti,kf,kw.
114 (target or level or threshold or trigger or initiate or initiating or initiation or start or control).ti,kw,kf,ab.
115 *insulin treatment/ use oemezd or exp *Insulins/ use ppez or insulin*.ti,kf,kw.
116 (27 and 112 and 113 and 114) or (27 and 112 and 114 and 115)
117 116 use ppez
118 116 use oemezd
119 remove duplicates from 116
120 exp *intravenous drug administration/ use oemezd or exp *Administration, Intravenous/ use ppez or intravenous.ti,kf,kw.
121 27 and 112 and 115 and 120
122 *subcutaneous drug administration/ use oemezd or *Injections, subcutaneous/ use ppez or subcutaenous.ti,kf,kw.
123 27 and 112 and 115 and 122
124 121 or 123 (113)
125 124 use ppez
126 124 use oemezd
127 remove duplicates from 124
128 *blood glucose monitoring/ use oemezd or *Blood Glucose Self-Monitoring/ use ppez or ((sugar or glucose or glycemic) adj (monitor* or control)).ti,kw,kf.
129 (continuous or intermittent or frequent or continually or interval).ti,ab,kf,kw.

130 27 and 112 and 128 and 129
131 130 use ppez
132 130 use oemezd
133 remove duplicates from 130
134 exp *decision support system/ use oemezd or *Decision Support Systems, Clinical/ use ppez
135 exp *electronic health record/ use oemezd or exp *electronic health records/ use ppez
136 (glucose monitoring system or decision support or system).ti,kf,kw.
137 (Checks or star or sprint or glucocare or glucommander or glucostabilizer or endotool or grip).ti,kf,kw.
138 or/134-137
139 27 and 112 and 113 and 138
140 139 use ppez
141 139 use oemezd
142 remove duplicates from 139
143 (Accu-Chek Performa or glucometer or blood glucose monitor or blood glucose meter or blood glucose monitoring equipment or Breeze or CGMS or Contourplus elite or Contour Link or Dario or Dexcom or Enlite or Eotvia or Freestyle or G4 Platinum or Glucocard or GlucoDay or glucometer or GlucoWatch or GlucoWatch Biographer or GlucoWatch G2 Biographer or GlySure or iBGStar or iStat or Lhcer or Libre or Navigator or Noref or nova statstrip or OneTouch Ultra or OneTouch or OptiScanner or Optium Xceed or Performa or PGGM or STG-22 or STG-55 or SureStep).ti,ab.
144 exp *blood glucose meter/ use oemezd or *blood glucose self-monitoring/ use ppez or ((sugar or glucose or glycemic) adj (monitor* or control)).ti,kw,kf.
145 143 or 144
146 27 and 145
147 146 use ppez
148 146 use oemezd
149 127 or 133 or 142
150 remove duplicates from 149
151 150 or 146
152 or/116,124,130,139,146

Supplemental Digital Content 6. Systematic Review Methodology

1. Article Selection

We imported the results of the literature search into Covidence.org. A team of reviewers (Kimia Honarmand, Judith Jacobi, Michael Sirimaturos, Jennifer Chen, Ross Prager, Michelle Yee Suet Wong, Sophie Wax, Julia Bidonde, Stephanie A Ross, Janan Aldouhan), independently and in duplicate, screened all titles and abstracts to select potentially relevant articles. The same team of reviewers then performed full-text screening, again independently and in duplicate, to identify eligible articles. We included published articles and abstracts with any *controlled* study design (randomized, cluster-randomized, before-after, case-control, or cohort designs) that presented original data pertaining to each PICO question. We resolved conflicts through consensus or adjudication of a third reviewer as necessary.

2. Data Extraction

We extracted data into a pre-formatted data abstraction form on Microsoft Excel. For each included article, we recorded study methodological characteristics, data about the patient population and interventions, and outcome data. Where numerical outcomes were not reported, we summarized the findings as a statement summarizing the direction of the effect. A second reviewer (KH) then confirmed the accuracy and completeness of the data extraction.

3. Data Synthesis

The guideline methodologist synthesized the data and generated a GRADE Evidence Profile for each PICO question using the GDT software (www.GRADEPRO.com). All meta-analyses were performed using DataParty (DataParty Inc., Hamilton, Ontario, Canada. Available at https://dataparty.ca), a novel web-based meta-analysis platform, using a random-effects model to pool the estimate of effects across eligible studies. For binary outcomes, we reported risk ratio (RR) with accompanying 95% confidence interval (CI) and for continuous outcomes, we reported mean difference with 95% CI. We assessed statistical heterogeneity using Chi-squared and I-squared tests. Where reported data were insufficient for meta-analysis, we synthesized the evidence narratively.

Supplemental Digital Content 7. Grading of Recommendations Assessment, Development, and Evaluation Approach (GRADE) Methodology

1. Certainty in the Evidence

Using GRADE methodology, we determined the overall certainty in the evidence for each outcome using 5 domains:

1. **Risk of bias:** Describe the risk of bias based on the criteria used in the risk-of-bias table.
2. **Inconsistency:** Describe the degree of inconsistency by outcome using one or more indicators (e.g., I2 and P value), confidence interval overlap, difference in point estimate, between-study variance.
3. **Indirectness:** Describe if the majority of studies address the PICO – were they similar to the question posed?
4. **Imprecision:** Describe the number of events, and width of the confidence intervals.
5. **Other factors:** Publication bias, presence of a dose-response relationship, magnitude of the effect, assessment of the effect of plausible residual confounding or bias.

Randomized controlled trials were initially designated as 'high' certainty evidence, which could then be downgraded based on the assessment of the above 5 domains. Non-randomized studies were initially designated as 'low' certainty evidence, which could then be upgraded or further downgraded based on the assessment of the same 5 domains.

The GRADE approach then categorizes each outcome into four level of certainty:

- **High:** 'We are very confident that the true effect lies close to that of the estimate of the effect.'
- **Moderate:** 'We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of that effect, but there is a possibility that it is substantially different.'
- **Low:** 'Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.'
- **Very Low:** 'We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.'

2. GRADE Evidence-to-Decision Framework

For each PICO question, the panel held one or more web-based meetings, facilitated by Zoom video conferencing platform hosted by SCCM, to review the Evidence Profile and work through the GRADE Evidence-to-Decision (EtD) framework, and generate a recommendation. The EtD incorporates panel judgment across 12 domains:

1. Priority of the problem
2. Desirable effects of the intervention
3. Undesirable effects of the intervention
4. Certainty in the evidence
5. Value (i.e., how much people value the main outcomes)
6. Balance of desirable and undesirable effects
7. Resources required for the intervention
8. Certainty in the evidence of required resources, if available
9. Cost-effectiveness of the intervention

10. Impact of the intervention on health equity
11. Acceptability of the intervention to key stakeholders
12. Feasibility in implementing the intervention

3. Generating Recommendations

After reviewing the Evidence Profile and discussing each domain of the EtD, the panel generated a recommendation statement, either for or against the intervention, categorized either as strong or conditional. As per GRADE convention, strong recommendations are phrased as "We recommend…" and conditional recommendations as "We suggest…". The implications of each recommendation's strengths for patients, clinicians, and policy-makers are shown in **Table 1**.

Supplemental Digital Content 8. Voting outcomes

18 panel members completed a web-based poll to indicate their agreement with each recommendation from three response choices: ‘Agree’, ‘Disagree’, or ‘Abstain’. Each panel member was encouraged to provide comments to explain their response choice. As per SCCM requirements, consensus was defined as 80% agreement among at least 75% of panel members, excluding those who abstained.

PICO	Agree (%)	Disagree (%)	Abstain (%)	Comments
Adult Population				
PICO 1	100	0	0	
PICO 2	88.89	5.56	5.56	
PICO 3	100	0	0	
PICO 4	100	0	0	
PICO 5	100	0	0	
Pediatric Population				
PICO 1	83.3	0	16.7	Some members abstained due to lack of expertise in the care of pediatric patients.
PICO 2	88.9	0	11.1	
PICO 3	88.9	0	11.1	
PICO 4	88.9	0	.1	
PICO 5	94.4	0	5.6	

Supplemental Digital Content 9. Evidence Profiles & Evidence-to-Decision Framework for Critically Ill *Adults*

Glycemic Control in Critically Ill Adults

SDC 9-2. Intensive versus conventional glucose targets in critically ill *adults*

Question. Should insulin therapy be titrated to achieve intensive glucose levels (INT) (glucose 4.4-7.7 mmol/L or 80-139 mg/dL) or conventional glucose levels (CONV) (7.8-11.1 mmol/L or 140-200 mg/dL) critically ill *adults*?

SDC 9-2A. Evidence Profile. Intensive versus conventional glucose targets in critically ill *adults*

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intensive glucose control	conventional glucose control	Relative (95% CI)	Absolute (95% CI)		
Hospital mortality												
23	randomised trials	not serious	serious	not serious	not serious	none	1298/4989 (26.0%)	1387/4994 (27.8%)	**RR 0.91** (0.81 to 1.02)	**25 fewer per 1,000** (from 53 fewer to 6 more)	⨁⨁⨁◯ Moderate	CRITICAL
ICU mortality												
18	randomised trials	not serious	not serious	not serious	not serious	none	1341/5069 (26.5%)	1343/4978 (27.0%)	**RR 0.97** (0.91 to 1.03)	**8 fewer per 1,000** (from 24 fewer to 8 more)	⨁⨁⨁⨁ High	CRITICAL
Unfavorable neurological outcome - Neuro-ICU subgroup												
6	randomised trials	serious	not serious	not serious	not serious	none	296/635 (46.6%)	326/622 (52.4%)	**RR 0.89** (0.80 to 0.99)	**58 fewer per 1,000** (from 105 fewer to 5 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Any infection												
24	randomised trials	not serious	serious	not serious	not serious	none	1134/7822 (14.5%)	1280/7778 (16.5%)	**RR 0.79** (0.68 to 0.91)	**35 fewer per 1,000** (from 53 fewer to 15 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Surgical site infections												
4	randomised trials	not serious	not serious	not serious	not serious	none	20/518 (3.9%)	34/529 (6.4%)	**RR 0.61** (0.35 to 1.09)	**25 fewer per 1,000** (from 42 fewer to 6 more)	⨁⨁⨁⨁ High	CRITICAL
Severe hypoglycemia												
29	randomised trials	not serious	serious	not serious	not serious	strong association	1119/8574 (13.1%)	356/8604 (4.1%)	**RR 3.75** (2.38 to 5.90)	**114 more per 1,000** (from 57 more to 203 more)	⨁⨁⨁◯ Moderate	CRITICAL
ICU length of stay												
25	randomised trials	serious	serious	not serious	not serious	none	6475	6534	-	MD **0.48 days lower** (0.82 lower to 0.14 lower)	⨁⨁◯◯ Low	CRITICAL

SDC 9-2B. Forest Plots. Intensive versus conventional glucose targets in critically ill *adults*

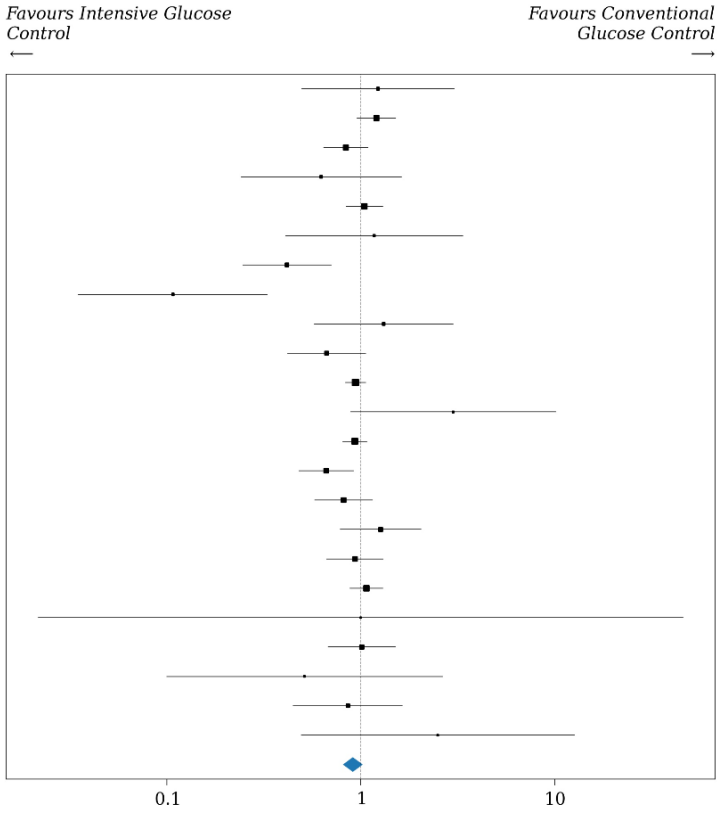
Hospital Mortality - all groups

Study	Intensive Glucose Control	(%)	Conventional Glucose Control	(%)	Weight	RR [95% CI]
LOGIC Trial 2007 #1850	6/11	(55%)	4/9	(44%)	1.5%	1.23 [0.49, 3.04]
GLUCONTROL 2009 #1338	125/536	(23%)	105/542	(19%)	8.2%	1.2 [0.96, 1.52]
Arabi 2008 #3670	72/266	(27%)	83/257	(32%)	7.4%	0.84 [0.64, 1.09]
Cappi 2012 #3875	5/28	(18%)	10/35	(29%)	1.4%	0.62 [0.24, 1.62]
De La Rosa 2008 #3266	102/254	(40%)	96/250	(38%)	8.5%	1.05 [0.84, 1.3]
Farah 2007 #3051	6/41	(15%)	6/48	(12%)	1.1%	1.17 [0.41, 3.35]
Grey 2004 #2816	11/34	(32%)	21/27	(78%)	3.5%	0.42 [0.25, 0.7]
Gupta 2020 #2778	3/50	(6%)	28/50	(56%)	1.0%	0.11 [0.03, 0.33]
Hamimy 2016 #2747	10/55	(18%)	9/65	(14%)	1.7%	1.31 [0.57, 3.0]
Hsu 2012 #2903	18/55	(33%)	28/57	(49%)	4.2%	0.67 [0.42, 1.06]
CGAO-REA 2014 #2452	376/1,336	(28%)	393/1,312	(30%)	10.6%	0.94 [0.83, 1.06]
Mitchell 2006 #1815	9/35	(26%)	3/35	(9%)	0.9%	3.0 [0.89, 10.16]
Van den Berghe 2006 #248	222/595	(37%)	242/605	(40%)	10.1%	0.93 [0.81, 1.08]
Van den Berghe 2001 #246	55/765	(7%)	85/783	(11%)	6.3%	0.66 [0.48, 0.92]
Mackenzie 2008 #4098	39/121	(32%)	47/119	(39%)	6.0%	0.82 [0.58, 1.15]
Taslimi 2009 #4102	26/67	(39%)	19/62	(31%)	4.0%	1.27 [0.78, 2.05]
Arabi 2011 #3667	42/120	(35%)	45/120	(38%)	6.0%	0.93 [0.67, 1.31]
COIITSS 2010 #4103	117/255	(46%)	109/254	(43%)	9.0%	1.07 [0.88, 1.3]
Hoedemaekers 2005 #2620	0/10	(0%)	0/10	(0%)	0.1%	1.0 [0.02, 46.06]
Yang 2009 #368	35/121	(29%)	34/119	(29%)	5.0%	1.01 [0.68, 1.51]
Coester 2010 #4088	2/39	(5%)	4/40	(10%)	0.5%	0.51 [0.1, 2.64]
Wang 2017 #4097	12/44	(27%)	14/44	(32%)	2.6%	0.86 [0.45, 1.64]
Umpierrez 2015 #4104	5/151	(3%)	2/151	(1%)	0.5%	2.5 [0.49, 12.69]
Pooled Estimate	1,298/4,989	(26%)	1,387/4,994	(28%)	I^2: 54%	0.91 [0.81, 1.02]

Mantel-Haenszel, DerSimonian-Laird Random Effects

p=0.12, z=1.57
τ^2=0.03

RR: Risk Ratio
CI: Confidence Interval



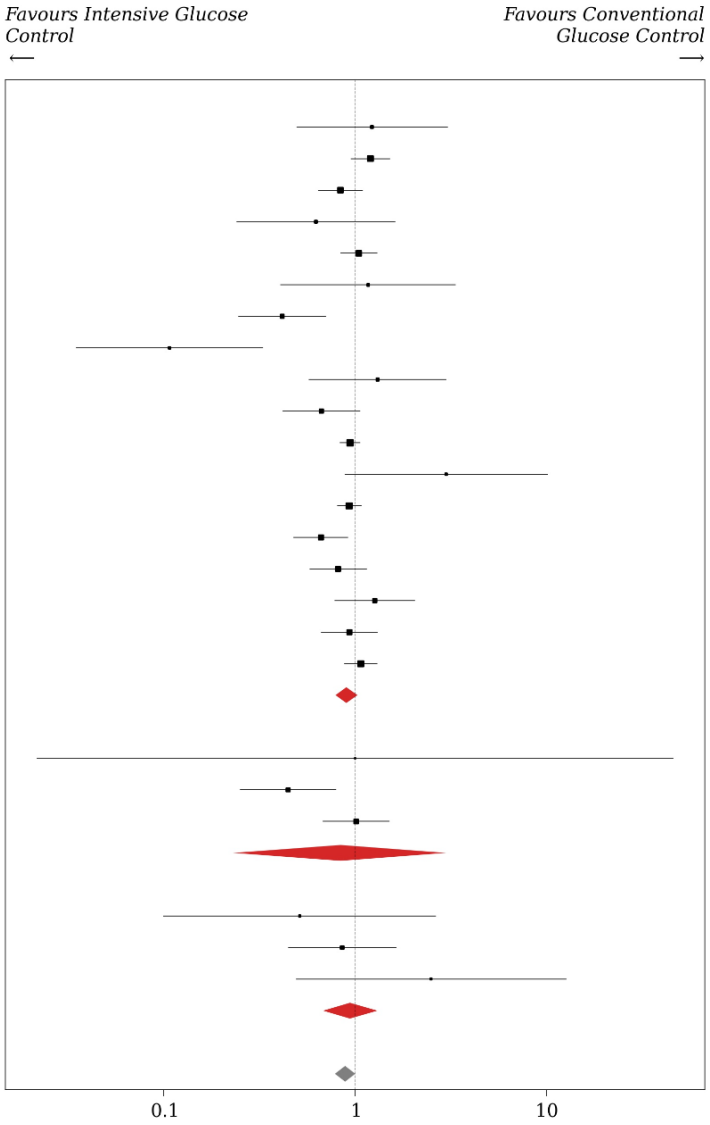
Hospital Mortality - by subgroup

Study	Intensive Glucose Control	(%)	Conventional Glucose Control	(%)	Weight	RR [95% CI]
mixed ICU						
LOGIC Trial 2007 #1850	6/11	(55%)	4/9	(44%)	1.6%	1.23 [0.49, 3.04]
GLUCONTROL 2009 #1338	125/536	(23%)	105/542	(19%)	7.7%	1.2 [0.96, 1.52]
Arabi 2008 #3670	72/266	(27%)	83/257	(32%)	7.1%	0.84 [0.64, 1.09]
Cappi 2012 #3875	5/28	(18%)	10/35	(29%)	1.4%	0.62 [0.24, 1.62]
De La Rosa 2008 #3266	102/254	(40%)	96/250	(38%)	8.0%	1.05 [0.84, 1.3]
Farah 2007 #3051	6/41	(15%)	6/48	(12%)	1.2%	1.17 [0.41, 3.35]
Grey 2004 #2816	11/34	(32%)	21/27	(78%)	3.6%	0.42 [0.25, 0.7]
Gupta 2020 #2778	3/50	(6%)	28/50	(56%)	1.1%	0.11 [0.03, 0.33]
Hamimy 2016 #2747	10/55	(18%)	9/65	(14%)	1.8%	1.31 [0.57, 3.0]
Hsu 2012 #2903	18/55	(33%)	28/57	(49%)	4.2%	0.67 [0.42, 1.06]
CGAO-REA 2014 #2452	376/1,336	(28%)	393/1,312	(30%)	9.7%	0.94 [0.83, 1.06]
Mitchell 2006 #1815	9/35	(26%)	3/35	(9%)	0.9%	3.0 [0.89, 10.16]
Van den Berghe 2006 #248	222/595	(37%)	242/605	(40%)	9.3%	0.93 [0.81, 1.08]
Van den Berghe 2001 #246	55/765	(7%)	85/783	(11%)	6.1%	0.66 [0.48, 0.92]
Mackenzie 2008 #4098	39/121	(32%)	47/119	(39%)	5.8%	0.82 [0.58, 1.15]
Taslimi 2009 #4102	26/67	(39%)	19/62	(31%)	4.0%	1.27 [0.78, 2.05]
Arabi 2011 #3667	42/120	(35%)	45/120	(38%)	5.9%	0.93 [0.67, 1.31]
COIITSS 2010 #4103	117/255	(46%)	109/254	(43%)	8.4%	1.07 [0.88, 1.3]
Subgroup Estimate	1,244/4,624	(27%)	1,333/4,630	(29%)	I^2: 63%	0.9 [0.79, 1.03]
cardiac surgery only						
Hoedemaekers 2005 #2620	0/10	(0%)	0/10	(0%)	0.1%	1.0 [0.02, 46.06]
Ingels 2006 #2866	16/477	(3%)	37/493	(8%)	3.2%	0.45 [0.25, 0.79]
Umpierrez 2015 #4104	5/151	(3%)	2/151	(1%)	5.0%	2.5 [0.49, 12.69]
Subgroup Estimate	21/638	(3%)	39/654	(6%)	I^2: 49%	0.84 [0.23, 2.99]
neuro-ICU only						
Yang 2009 #368	35/121	(29%)	34/119	(29%)	0.5%	1.01 [0.68, 1.51]
Coester 2010 #4088	2/39	(5%)	4/40	(10%)	2.7%	0.51 [0.1, 2.64]
Wang 2017 #4097	12/44	(27%)	14/44	(32%)	0.5%	0.86 [0.45, 1.64]
Subgroup Estimate	49/204	(24%)	52/203	(26%)	I^2: 0%	0.94 [0.68, 1.31]
Pooled Estimate					I^2: 58%	0.89 [0.78, 1.0]

Mantel-Haenszel, DerSimonian-Laird Random Effects Subgroup Effect

p=0.05, z=1.92
τ^2=0.04
χ^2=0.08, p=0.96, I^2=0.0%

RR: Risk Ratio
CI: Confidence Interval



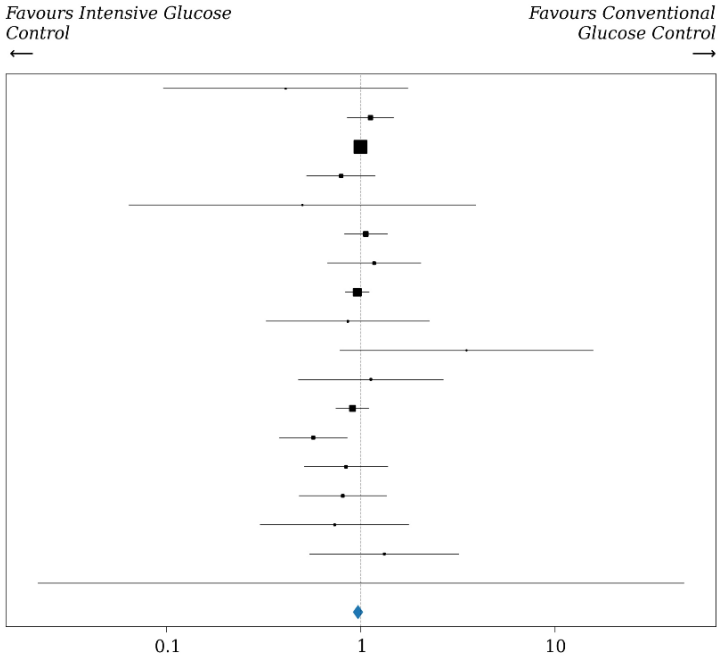
ICU Mortality - all groups

Study	Intensive Glucose Control	(%)	Conventional Glucose Control	(%)	Weight	RR [95% CI]
LOGIC Trial 2007 #1850	2/11	(18%)	4/9	(44%)	0.2%	0.41 [0.1, 1.75]
GLUCONTROL 2009 #1338	92/536	(17%)	83/542	(15%)	5.0%	1.12 [0.85, 1.47]
NICE SUGAR 2009 #3008	546/829	(66%)	498/751	(66%)	51.4%	0.99 [0.93, 1.07]
Arabi 2008 #3670	36/266	(14%)	44/257	(17%)	2.3%	0.79 [0.53, 1.19]
Bland 2005 #4001	1/5	(20%)	2/5	(40%)	0.1%	0.5 [0.06, 3.91]
De La Rosa 2008 #3266	84/254	(33%)	78/250	(31%)	5.7%	1.06 [0.82, 1.37]
Farah 2007 #3051	16/41	(39%)	16/48	(33%)	1.2%	1.17 [0.67, 2.04]
CGAO-REA 2014 #2452	302/1336	(23%)	310/1312	(24%)	17.4%	0.96 [0.83, 1.1]
Mahmoodpoor 2011 #1989	6/30	(20%)	7/30	(23%)	0.4%	0.86 [0.33, 2.25]
Mitchell 2006 #1815	7/35	(20%)	2/35	(6%)	0.2%	3.5 [0.78, 15.69]
Savioli 2009 #836	9/45	(20%)	8/45	(18%)	0.5%	1.12 [0.48, 2.65]
Van den Berghe 2006 #248	144/595	(24%)	162/605	(27%)	9.5%	0.9 [0.74, 1.1]
Van den Berghe 2001 #246	35/765	(5%)	63/783	(8%)	2.3%	0.57 [0.38, 0.85]
Mackenzie 2008 #4098	23/121	(19%)	27/119	(23%)	1.5%	0.84 [0.51, 1.37]
Arabi 2011 #3667	21/120	(18%)	26/120	(22%)	1.4%	0.81 [0.48, 1.35]
Azevedo 2007 #3282	8/31	(26%)	6/17	(35%)	0.5%	0.73 [0.3, 1.76]
Coester 2010 #4088	9/39	(23%)	7/40	(18%)	0.5%	1.32 [0.54, 3.19]
Hoedemaekers 2005 #2620	0/10	(0%)	0/10	(0%)	0.0%	1.0 [0.02, 46.06]
Pooled Estimate	1341/5069	(26%)	1343/4978	(27%)	I^2: 3%	0.97 [0.91, 1.03]

Mantel-Haenszel, DerSimonian-Laird Random Effects

p=0.27, z=1.09
τ^2=0.00

RR: Risk Ratio
CI: Confidence Interval



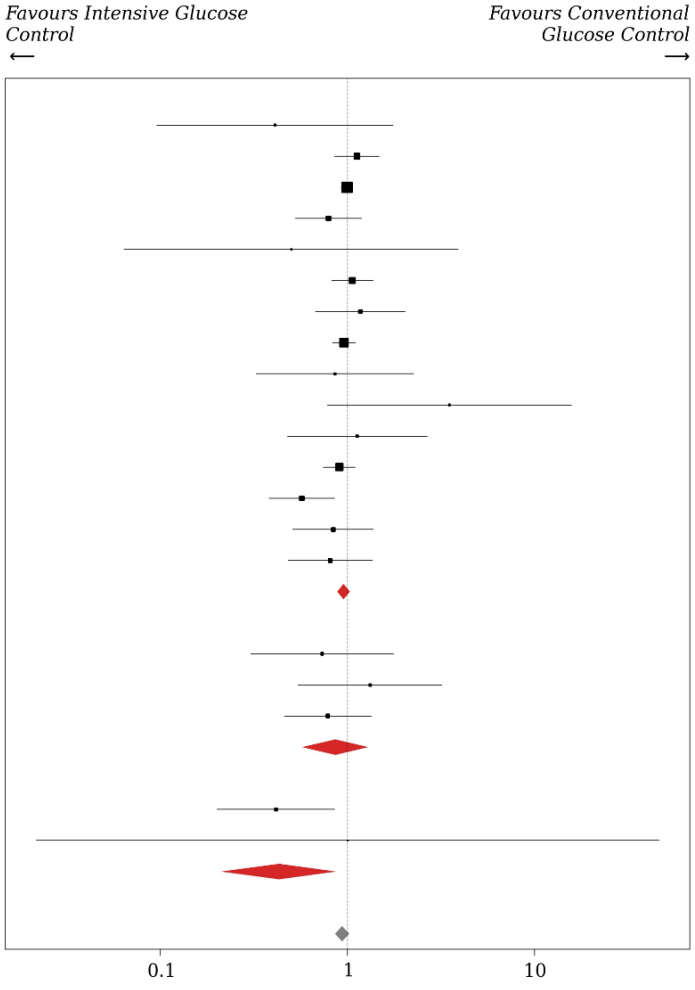
ICU Mortality - by subgroup

Study	Intensive Glucose Control	(%)	Conventional Glucose Control	(%)	Weight	RR [95% CI]
mixed ICU						
LOGIC Trial 2007 #1850	2/11	(18%)	4/9	(44%)	0.4%	0.41 [0.1, 1.75]
GLUCONTROL 2009 #1338	92/536	(17%)	83/542	(15%)	7.9%	1.12 [0.85, 1.47]
NICE SUGAR 2009 #3008	546/829	(66%)	498/751	(66%)	28.0%	0.99 [0.93, 1.07]
Arabi 2008 #3670	36/266	(14%)	44/257	(17%)	4.1%	0.79 [0.53, 1.19]
Bland 2005 #4001	1/5	(20%)	2/5	(40%)	0.2%	0.5 [0.06, 3.91]
De La Rosa 2008 #3266	84/254	(33%)	78/250	(31%)	8.7%	1.06 [0.82, 1.37]
Farah 2007 #3051	16/41	(39%)	16/48	(33%)	2.3%	1.17 [0.67, 2.04]
CGAO-REA 2014 #2452	302/1336	(23%)	310/1312	(24%)	18.3%	0.96 [0.83, 1.1]
Mahmoodpoor 2011 #1989	6/30	(20%)	7/30	(23%)	0.8%	0.86 [0.33, 2.25]
Mitchell 2006 #1815	7/35	(20%)	2/35	(6%)	0.3%	3.5 [0.78, 15.69]
Savioli 2009 #836	9/45	(20%)	8/45	(18%)	1.0%	1.12 [0.48, 2.65]
Van den Berghe 2006 #248	144/595	(24%)	162/605	(27%)	12.7%	0.9 [0.74, 1.1]
Van den Berghe 2001 #246	35/765	(5%)	63/783	(8%)	4.1%	0.57 [0.38, 0.85]
Mackenzie 2008 #4098	23/121	(19%)	27/119	(23%)	2.8%	0.84 [0.51, 1.37]
Arabi 2011 #3667	21/120	(18%)	26/120	(22%)	2.6%	0.81 [0.48, 1.35]
Subgroup Estimate	1324/4989	(27%)	1330/4911	(27%)	I^2: 16%	0.95 [0.88, 1.03]
neuro-ICU only						
Azevedo 2007 #3282	8/31	(26%)	6/17	(35%)	1.0%	0.73 [0.3, 1.76]
Coester 2010 #4088	9/39	(23%)	7/40	(18%)	0.9%	1.32 [0.54, 3.19]
NICE SUGAR-TBI 2015 #3009	22/203	(11%)	26/188	(14%)	2.5%	0.78 [0.46, 1.33]
Subgroup Estimate	39/273	(14%)	39/245	(16%)	I^2: 0%	0.86 [0.57, 1.29]
cardiac surgery only						
Ingels 2006 #2866	10/477	(2%)	25/493	(5%)	1.4%	0.41 [0.2, 0.85]
Hoedemaekers 2005 #2620	0/10	(0%)	0/10	(0%)	0.1%	1.0 [0.02, 46.06]
Subgroup Estimate	10/487	(2%)	25/503	(5%)	I^2: 0%	0.43 [0.21, 0.87]
Pooled Estimate					I^2: 20%	0.93 [0.86, 1.02]

Mantel-Haenszel, DerSimonian-Laird Random Effects Subgroup Effect

p=0.13, z=1.52
τ^2=0.01
χ^2=5.09, p=0.08, I^2=60.7%

RR: Risk Ratio
CI: Confidence Interval



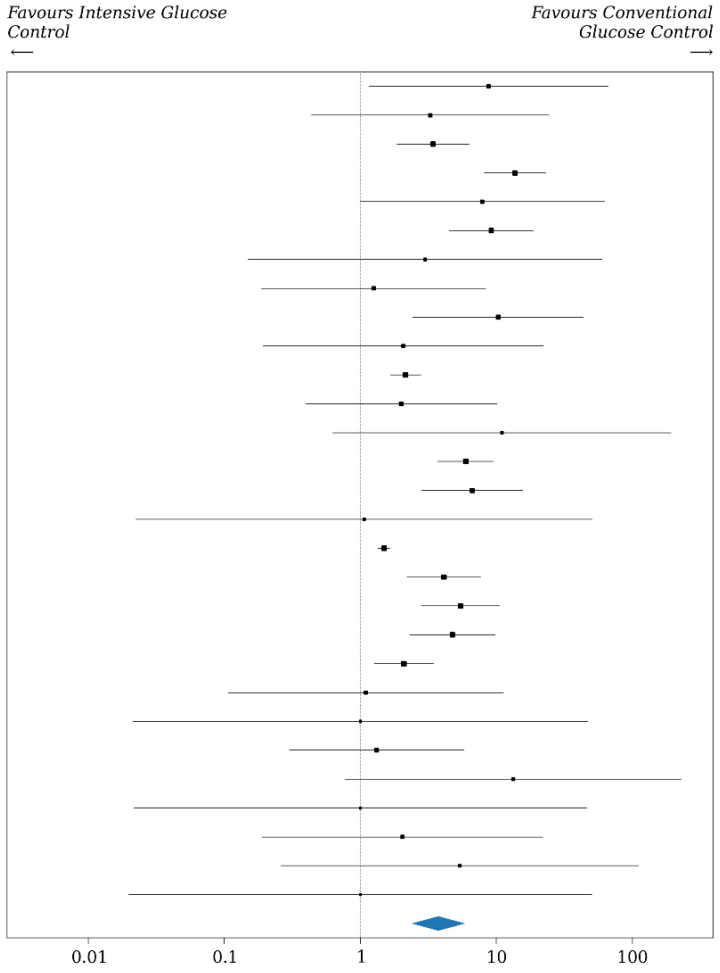
Severe Hypoglycemia [< 2.2 mmol/L or < 40 mg/dL] - all groups

Study	Intensive Glucose Control	(%)	Conventional Glucose Control	(%)	Weight	RR [95% CI]
SUGAR Trial 2009 #2680	8/32	(25%)	1/35	(3%)	2.7%	8.75 [1.16, 66.15]
LOGIC Trial 2007 #1850	4/11	(36%)	1/9	(11%)	2.8%	3.27 [0.44, 24.34]
GLUCONTROL 2009 #1338	44/536	(8%)	13/542	(2%)	5.4%	3.42 [1.87, 6.28]
NICE SUGAR 2009 #3008	206/3,016	(7%)	15/3,014	(0%)	5.5%	13.72 [8.15, 23.12]
Cao 2011 #3879	8/125	(6%)	1/123	(1%)	2.7%	7.87 [1.0, 62.01]
Arabi 2008 #3670	76/266	(29%)	8/257	(3%)	5.2%	9.18 [4.52, 18.63]
Bland 2005 #4001	1/5	(20%)	0/5	(0%)	1.7%	3.0 [0.15, 59.89]
Cappi 2012 #3875	2/28	(7%)	2/35	(6%)	2.9%	1.25 [0.19, 8.32]
De La Rosa 2008 #3266	21/254	(8%)	2/250	(1%)	3.7%	10.33 [2.45, 43.61]
Hsu 2012 #2903	2/55	(4%)	1/57	(2%)	2.3%	2.07 [0.19, 22.21]
CGAO-REA 2014 #2452	174/1,317	(13%)	79/1,284	(6%)	5.9%	2.15 [1.66, 2.77]
Mahmoodpoor 2011 #1989	4/30	(13%)	2/30	(7%)	3.4%	2.0 [0.4, 10.11]
Mitchell 2006 #1815	5/35	(14%)	0/35	(0%)	1.8%	11.0 [0.63, 191.7]
Van den Berghe 2006 #248	111/595	(19%)	19/605	(3%)	5.6%	5.94 [3.7, 9.54]
Van den Berghe 2001 #246	39/765	(5%)	6/783	(1%)	4.9%	6.65 [2.83, 15.62]
Zuran 2009 #5	0/14	(0%)	0/15	(0%)	1.1%	1.07 [0.02, 50.44]
Bilotta 2009 #4085	226/241	(94%)	152/242	(63%)	5.9%	1.49 [1.35, 1.65]
VISEP 2008 #4087	42/247	(17%)	12/290	(4%)	5.4%	4.11 [2.21, 7.63]
Mackenzie 2008 #4098	50/121	(41%)	9/119	(8%)	5.3%	5.46 [2.82, 10.6]
Arabi 2011 #3667	38/120	(32%)	8/120	(7%)	5.2%	4.75 [2.31, 9.75]
COIITSS 2010 #4103	42/255	(16%)	20/254	(8%)	5.6%	2.09 [1.26, 3.46]
Azevedo 2007 #3282	2/31	(6%)	1/17	(6%)	2.3%	1.1 [0.11, 11.23]
Mousavi 2014 #1761	0/13	(0%)	0/13	(0%)	1.1%	1.0 [0.02, 46.96]
Yang 2009 #368	4/117	(3%)	3/116	(3%)	3.7%	1.32 [0.3, 5.78]
Coester 2010 #4088	6/39	(15%)	0/40	(0%)	1.8%	13.32 [0.78, 228.83]
Hoedemaekers 2005 #2620	0/10	(0%)	0/10	(0%)	1.1%	1.0 [0.02, 46.06]
Chan 2009 #4092	2/54	(4%)	1/55	(2%)	2.3%	2.04 [0.19, 21.81]
Desai 2012 #4089	2/91	(2%)	0/98	(0%)	1.6%	5.38 [0.26, 110.6]
Umpierrez 2015 #4104	0/151	(0%)	0/151	(0%)	1.1%	1.0 [0.02, 50.08]
Pooled Estimate	1,119/8,574	(13%)	356/8,604	(4%)	I^2: 90%	3.75 [2.38, 5.9]

Mantel-Haenszel, DerSimonian-Laird Random Effects

p=0.00, z=5.70
τ^2=0.90

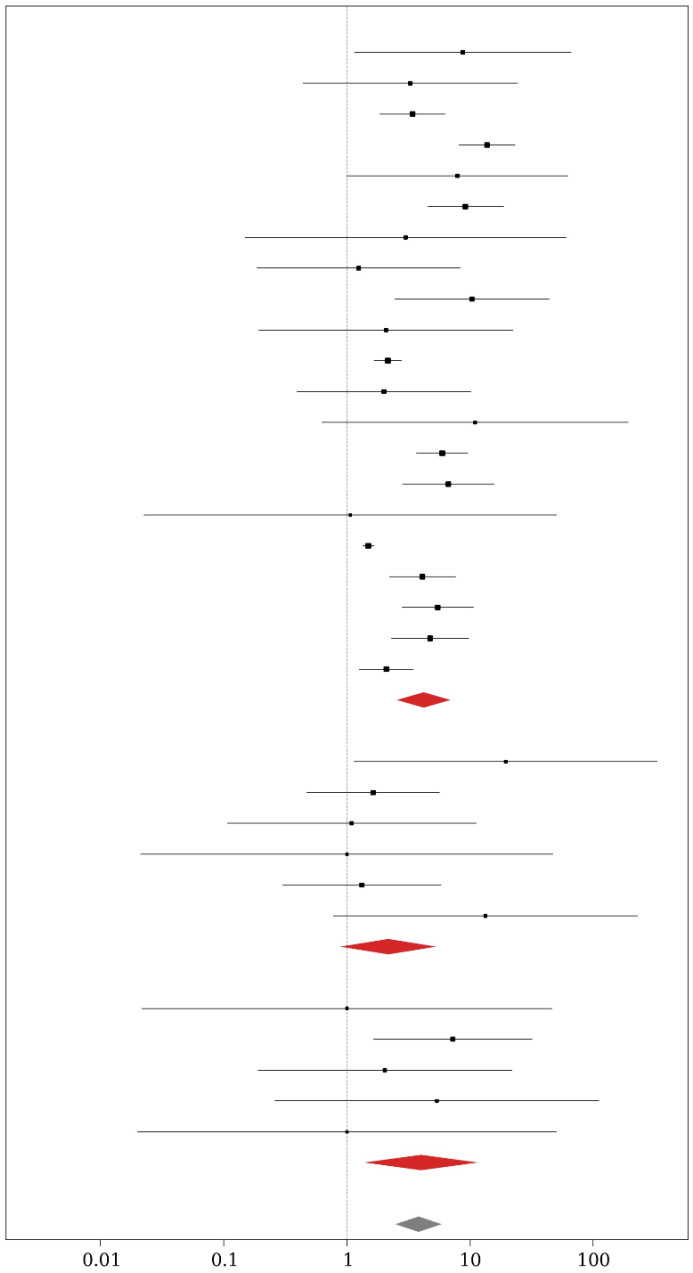
RR: Risk Ratio
CI: Confidence Interval



Severe Hypoglycemia [< 2.2 mmol/L or < 40 mg/dL] - by subgroup

Study	Intensive Glucose Control	(%)	Conventional Glucose Control	(%)	Weight	RR [95% CI]
mixed ICU						
SUGAR Trial 2009 #2680	8/32	(25%)	1/35	(3%)	2.5%	8.75 [1.16, 66.15]
LOGIC Trial 2007 #1850	4/11	(36%)	1/9	(11%)	2.5%	3.27 [0.44, 24.34]
GLUCONTROL 2009 #1338	44/536	(8%)	13/542	(2%)	4.9%	3.42 [1.87, 6.28]
NICE SUGAR 2009 #3008	206/3,016	(7%)	15/3,014	(0%)	5.0%	13.72 [8.15, 23.12]
Cao 2011 #3879	8/125	(6%)	1/123	(1%)	2.4%	7.87 [1.0, 62.01]
Arabi 2008 #3670	76/266	(29%)	8/257	(3%)	4.8%	9.18 [4.52, 18.63]
Bland 2005 #4001	1/5	(20%)	0/5	(0%)	1.5%	3.0 [0.15, 59.89]
Cappi 2012 #3875	2/28	(7%)	2/35	(6%)	2.7%	1.25 [0.19, 8.32]
De La Rosa 2008 #3266	21/254	(8%)	2/250	(1%)	3.4%	10.33 [2.45, 43.61]
Hsu 2012 #2903	2/55	(4%)	1/57	(2%)	2.1%	2.07 [0.19, 22.21]
CGAO-REA 2014 #2452	174/1,317	(13%)	79/1,284	(6%)	5.3%	2.15 [1.66, 2.77]
Mahmoodpoor 2011 #1989	4/30	(13%)	2/30	(7%)	3.1%	2.0 [0.4, 10.11]
Mitchell 2006 #1815	5/35	(14%)	0/35	(0%)	1.6%	11.0 [0.63, 191.7]
Van den Berghe 2006 #248	111/595	(19%)	19/605	(3%)	5.1%	5.94 [3.7, 9.54]
Van den Berghe 2001 #246	39/765	(5%)	6/783	(1%)	4.5%	6.65 [2.83, 15.62]
Zuran 2009 #5	0/14	(0%)	0/15	(0%)	1.0%	1.07 [0.02, 50.44]
Bilotta 2009 #4085	226/241	(94%)	152/242	(63%)	5.4%	1.49 [1.35, 1.65]
VISEP 2008 #4087	42/247	(17%)	12/290	(4%)	4.9%	4.11 [2.21, 7.63]
Mackenzie 2008 #4098	50/121	(41%)	9/119	(8%)	4.8%	5.46 [2.82, 10.6]
Arabi 2011 #3667	38/120	(32%)	8/120	(7%)	4.7%	4.75 [2.31, 9.75]
COIITSS 2010 #4103	42/255	(16%)	20/254	(8%)	5.1%	2.09 [1.26, 3.46]
Subgroup Estimate	1,103/8,068	(14%)	351/8,104	(4%)	I^2: 93%	4.2 [2.54, 6.94]
neuro-ICU only						
NICE SUGAR-TBI 2015 #3009	10/203	(5%)	0/188	(0%)	1.6%	19.46 [1.15, 329.75]
CGAO-REA-TBI 2014 #3416	6/90	(7%)	4/98	(4%)	3.8%	1.63 [0.48, 5.6]
Azevedo 2007 #3282	2/31	(6%)	1/17	(6%)	2.1%	1.1 [0.11, 11.23]
Mousavi 2014 #1761	0/13	(0%)	0/13	(0%)	1.0%	1.0 [0.02, 46.96]
Yang 2009 #368	4/117	(3%)	3/116	(3%)	3.3%	1.32 [0.3, 5.78]
Coester 2010 #4088	6/39	(15%)	0/40	(0%)	1.6%	13.32 [0.78, 228.83]
Subgroup Estimate	28/493	(6%)	8/472	(2%)	I^2: 15%	2.17 [0.88, 5.32]
cardiac surgery only						
Hoedemaekers 2005 #2620	0/10	(0%)	0/10	(0%)	1.0%	1.0 [0.02, 46.06]
Ingels 2006 #2866	14/477	(3%)	2/493	(0%)	3.3%	7.23 [1.65, 31.66]
Chan 2009 #4092	2/54	(4%)	1/55	(2%)	2.1%	2.04 [0.19, 21.81]
Desai 2012 #4089	2/91	(2%)	0/98	(0%)	1.5%	5.38 [0.26, 110.6]
Umpierrez 2015 #4104	0/151	(0%)	0/151	(0%)	1.0%	1.0 [0.02, 50.08]
Subgroup Estimate	18/783	(2%)	3/807	(0%)	I^2: 0%	4.0 [1.38, 11.61]
Pooled Estimate					I^2: 89%	3.81 [2.47, 5.89]

Favours Intensive Glucose Control ⟵ ⟶ *Favours Conventional Glucose Control*



Mantel-Haenszel, DerSimonian-Laird Random Effects Subgroup Effect

p=0.00, z=6.05
τ^2=0.90
χ^2=1.62, p=0.45, I^2=0.0%

RR: Risk Ratio
CI: Confidence Interval

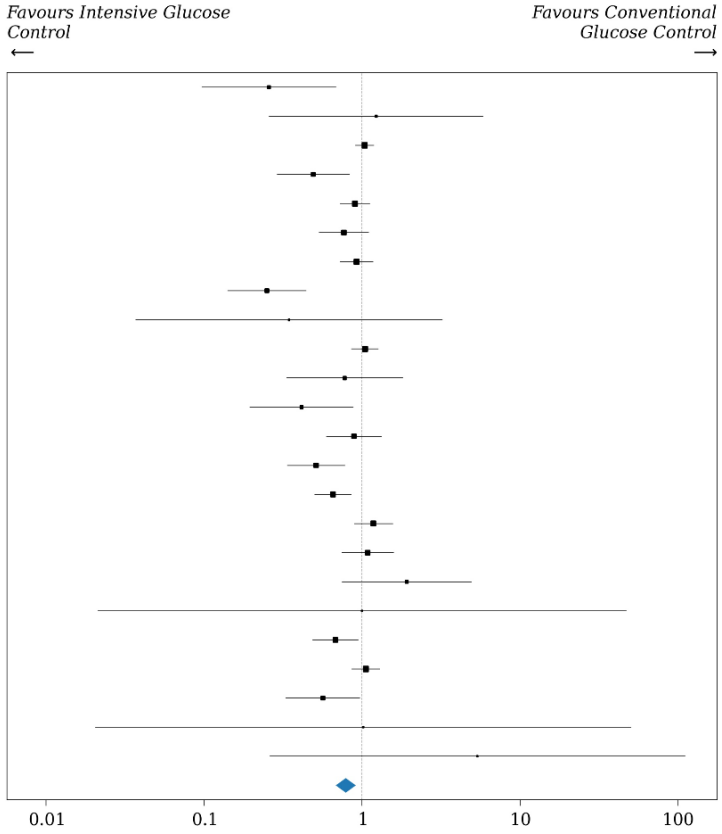
Any infections [No. of patients] - all groups

Study	Intensive Glucose Control	(%)	Conventional Glucose Control	(%)	Weight	RR [95% CI]
SUGAR Trial 2009 #2680	4/32	(12%)	17/35	(49%)	1.8%	0.26 [0.1, 0.68]
LOGIC Trial 2007 #1850	3/11	(27%)	2/9	(22%)	0.8%	1.23 [0.26, 5.82]
NICE SUGAR 2009 #3008	387/3014	(13%)	372/3011	(12%)	8.0%	1.04 [0.91, 1.19]
Cao 2011 #3879	17/125	(14%)	34/123	(28%)	4.1%	0.49 [0.29, 0.83]
Arabi 2008 #3670	98/266	(37%)	105/257	(41%)	7.3%	0.9 [0.73, 1.12]
De La Rosa 2008 #3266	43/254	(17%)	55/250	(22%)	5.7%	0.77 [0.54, 1.1]
Farah 2007 #3051	30/41	(73%)	38/48	(79%)	7.0%	0.92 [0.73, 1.17]
Gupta 2020 #2778	10/50	(20%)	40/50	(80%)	3.7%	0.25 [0.14, 0.44]
Hsu 2012 #2903	1/55	(2%)	3/57	(5%)	0.4%	0.35 [0.04, 3.22]
CGAO-REA 2014 #2452	183/1335	(14%)	172/1311	(13%)	7.5%	1.04 [0.86, 1.27]
Mahmoodpoor 2011 #1989	7/30	(23%)	9/30	(30%)	2.2%	0.78 [0.33, 1.82]
Okabayashi 2014 #1121	9/222	(4%)	22/225	(10%)	2.6%	0.41 [0.2, 0.88]
Van den Berghe 2006 #248	42/595	(7%)	48/605	(8%)	5.3%	0.89 [0.6, 1.33]
Van den Berghe 2001 #246	32/783	(4%)	61/765	(8%)	5.1%	0.51 [0.34, 0.78]
Bilotta 2009 #4085	62/241	(26%)	95/242	(39%)	6.7%	0.66 [0.5, 0.85]
Arabi 2011 #3667	59/120	(49%)	50/120	(42%)	6.6%	1.18 [0.89, 1.56]
COIITSS 2010 #4103	47/255	(18%)	43/254	(17%)	5.5%	1.09 [0.75, 1.58]
Azevedo 2007 #3282	14/31	(45%)	4/17	(24%)	1.9%	1.92 [0.75, 4.92]
Mousavi 2014 #1761	0/13	(0%)	0/13	(0%)	0.1%	1.0 [0.02, 46.96]
Yang 2009 #368	38/121	(31%)	55/119	(46%)	6.0%	0.68 [0.49, 0.94]
Coester 2010 #4088	33/39	(85%)	32/40	(80%)	7.4%	1.06 [0.86, 1.3]
Wang 2017 #4097	13/44	(30%)	23/44	(52%)	4.0%	0.57 [0.33, 0.97]
Chan 2009 #4092	0/54	(0%)	0/55	(0%)	0.1%	1.02 [0.02, 50.42]
Desai 2012 #4089	2/91	(2%)	0/98	(0%)	0.2%	5.38 [0.26, 110.6]
Pooled Estimate	1134/7822	(14%)	1280/7778	(16%)	I^2: 68%	0.79 [0.68, 0.91]

Mantel-Haenszel, DerSimonian-Laird Random Effects

p=0.00, z=3.16
τ^2=0.06

RR: Risk Ratio
CI: Confidence Interval



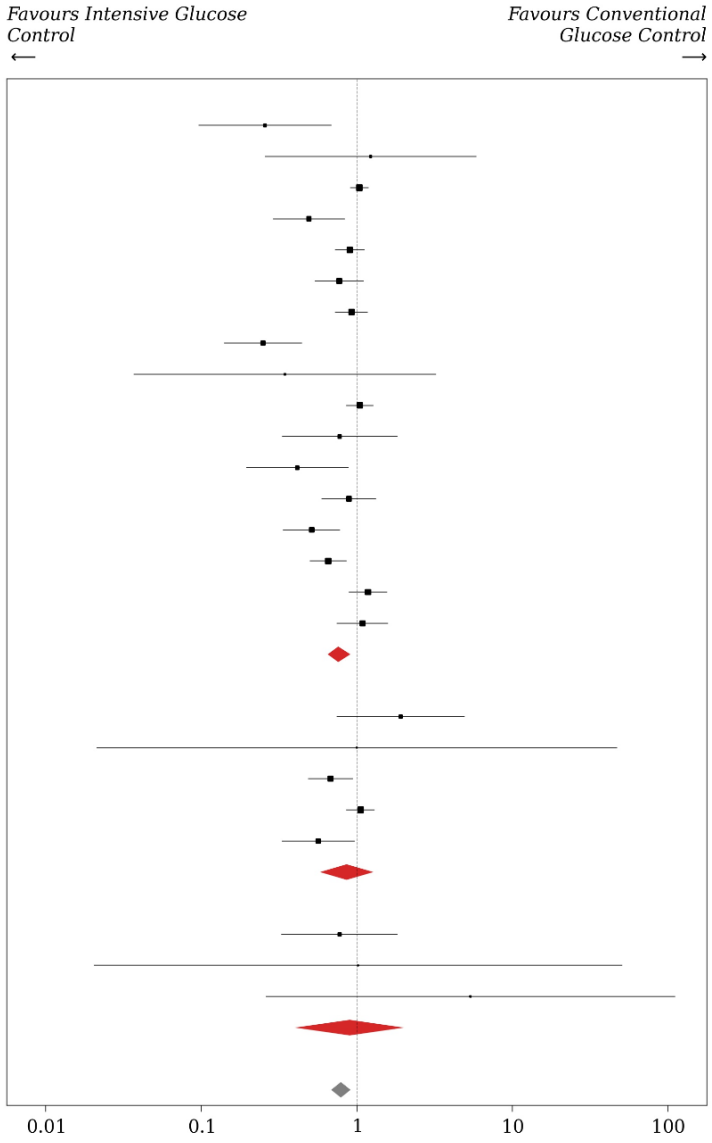
Any infections [No. of patients] - by subgroup

Study	Intensive Glucose Control	(%)	Conventional Glucose Control	(%)	Weight	RR [95% CI]
mixed ICU						
SUGAR Trial 2009 #2680	4/32	(12%)	17/35	(49%)	1.7%	0.26 [0.1, 0.68]
LOGIC Trial 2007 #1850	3/11	(27%)	2/9	(22%)	0.8%	1.23 [0.26, 5.82]
NICE SUGAR 2009 #3008	387/3014	(13%)	372/3011	(12%)	7.9%	1.04 [0.91, 1.19]
Cao 2011 #3879	17/125	(14%)	34/123	(28%)	4.0%	0.49 [0.29, 0.83]
Arabi 2008 #3670	98/266	(37%)	105/257	(41%)	7.1%	0.9 [0.73, 1.12]
De La Rosa 2008 #3266	43/254	(17%)	55/250	(22%)	5.6%	0.77 [0.54, 1.1]
Farah 2007 #3051	30/41	(73%)	38/48	(79%)	6.9%	0.92 [0.73, 1.17]
Gupta 2020 #2778	10/50	(20%)	40/50	(80%)	3.6%	0.25 [0.14, 0.44]
Hsu 2012 #2903	1/55	(2%)	3/57	(5%)	0.4%	0.35 [0.04, 3.22]
CGAO-REA 2014 #2452	183/1335	(14%)	172/1311	(13%)	7.4%	1.04 [0.86, 1.27]
Mahmoodpoor 2011 #1989	7/30	(23%)	9/30	(30%)	2.1%	0.78 [0.33, 1.82]
Okabayashi 2014 #1121	9/222	(4%)	22/225	(10%)	2.5%	0.41 [0.2, 0.88]
Van den Berghe 2006 #248	42/595	(7%)	48/605	(8%)	5.1%	0.89 [0.6, 1.33]
Van den Berghe 2001 #246	32/783	(4%)	61/765	(8%)	5.0%	0.51 [0.34, 0.78]
Bilotta 2009 #4085	62/241	(26%)	95/242	(39%)	6.6%	0.66 [0.5, 0.85]
Arabi 2011 #3667	59/120	(49%)	50/120	(42%)	6.4%	1.18 [0.89, 1.56]
COIITSS 2010 #4103	47/255	(18%)	43/254	(17%)	5.4%	1.09 [0.75, 1.58]
Subgroup Estimate	1034/7429	(14%)	1166/7392	(16%)	I^2: 74%	0.76 [0.65, 0.91]
neuro-ICU only						
Azevedo 2007 #3282	14/31	(45%)	4/17	(24%)	1.8%	1.92 [0.75, 4.92]
Mousavi 2014 #1761	0/13	(0%)	0/13	(0%)	0.1%	1.0 [0.02, 46.96]
Yang 2009 #368	38/121	(31%)	55/119	(46%)	5.9%	0.68 [0.49, 0.94]
Coester 2010 #4088	33/39	(85%)	32/40	(80%)	7.2%	1.06 [0.86, 1.3]
Wang 2017 #4097	13/44	(30%)	23/44	(52%)	3.9%	0.57 [0.33, 0.97]
Subgroup Estimate	98/248	(40%)	114/233	(49%)	I^2: 68%	0.86 [0.58, 1.28]
cardiac surgery only						
Ingels 2006 #2866	9/477	(2%)	12/493	(2%)	2.1%	0.78 [0.33, 1.82]
Chan 2009 #4092	0/54	(0%)	0/55	(0%)	0.1%	1.02 [0.02, 50.42]
Desai 2012 #4089	2/91	(2%)	0/98	(0%)	0.2%	5.38 [0.26, 110.6]
Subgroup Estimate	11/622	(2%)	12/646	(2%)	I^2: 0%	0.9 [0.4, 2.01]
Pooled Estimate					I^2: 67%	0.79 [0.68, 0.91]

Mantel-Haenszel, DerSimonian-Laird Random Effects Subgroup Effect

p=0.00, z=3.22
τ^2=0.06
χ^2=0.43, p=0.81, I^2=0.0%

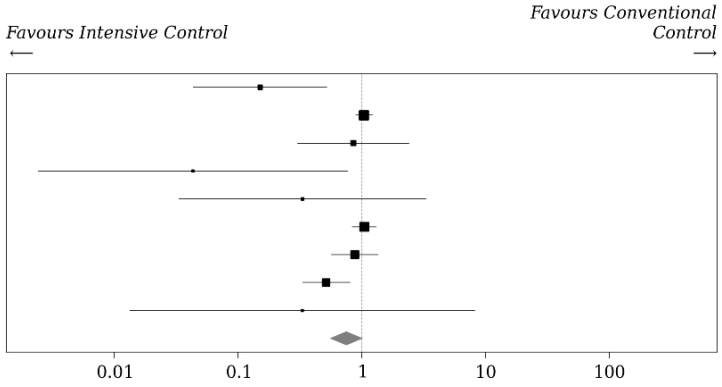
RR: Risk Ratio
CI: Confidence Interval



Bacteremia - All groups

Study	Intensive Control	(%)	Conventional Control	(%)	Weight	OR [95% CI]
SUGAR Trial 2009 #2680	4/32	(12%)	17/35	(49%)	5.1%	0.15 [0.04, 0.52]
NICE SUGAR 2009 #3008	387/3,014	(13%)	372/3,011	(12%)	25.4%	1.05 [0.9, 1.22]
De La Rosa 2008 #3266	7/254	(3%)	8/250	(3%)	6.8%	0.86 [0.31, 2.4]
Gupta 2020 #2778	0/50	(0%)	9/50	(18%)	1.1%	0.04 [0.0, 0.77]
Hsu 2012 #2903	1/55	(2%)	3/57	(5%)	1.7%	0.33 [0.03, 3.31]
CGAO-REA 2014 #2452	183/1,335	(14%)	172/1,311	(13%)	23.7%	1.05 [0.84, 1.32]
Van den Berghe 2006 #248	42/595	(7%)	48/605	(8%)	17.8%	0.88 [0.57, 1.36]
Van den Berghe 2001 #246	32/765	(4%)	61/783	(8%)	17.5%	0.52 [0.33, 0.8]
Umpierrez 2015 #4104	0/151	(0%)	1/151	(1%)	0.9%	0.33 [0.01, 8.19]
Pooled Estimate	656/6,251	(10%)	691/6,253	(11%)	I^2: 67%	0.75 [0.55, 1.03]

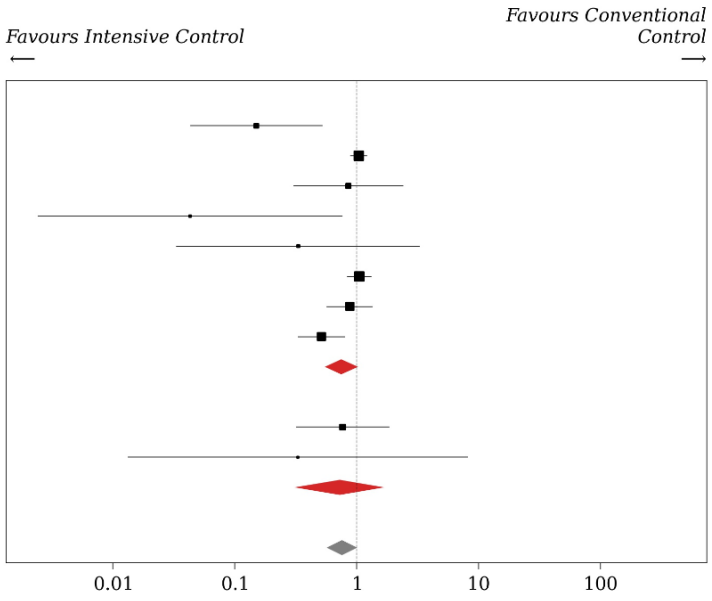
Mantel-Haenszel, DerSimonian-Laird Random Effects
p=0.07, z=1.80
τ^2=0.09
OR: Odds Ratio
CI: Confidence Interval



Bacteremia

Study	Intensive Control	(%)	Conventional Control	(%)	Weight	OR [95% CI]
mixed ICU						
SUGAR Trial 2009 #2680	4/32	(12%)	17/35	(49%)	4.5%	0.15 [0.04, 0.52]
NICE SUGAR 2009 #3008	387/3,014	(13%)	372/3,011	(12%)	24.0%	1.05 [0.9, 1.22]
De La Rosa 2008 #3266	7/254	(3%)	8/250	(3%)	6.0%	0.86 [0.31, 2.4]
Gupta 2020 #2778	0/50	(0%)	9/50	(18%)	1.0%	0.04 [0.0, 0.77]
Hsu 2012 #2903	1/55	(2%)	3/57	(5%)	1.5%	0.33 [0.03, 3.31]
CGAO-REA 2014 #2452	183/1,335	(14%)	172/1,311	(13%)	22.2%	1.05 [0.84, 1.32]
Van den Berghe 2006 #248	42/595	(7%)	48/605	(8%)	16.3%	0.88 [0.57, 1.36]
Van den Berghe 2001 #246	32/765	(4%)	61/783	(8%)	16.1%	0.52 [0.33, 0.8]
Subgroup Estimate	656/6,100	(11%)	690/6,102	(11%)	I^2: 70%	0.75 [0.55, 1.03]
cardiac surgery only						
Ingels 2006 #2866	9/477	(2%)	12/493	(2%)	7.7%	0.77 [0.32, 1.85]
Umpierrez 2015 #4104	0/151	(0%)	1/151	(1%)	0.8%	0.33 [0.01, 8.19]
Subgroup Estimate	9/628	(1%)	13/644	(2%)	I^2: 0%	0.73 [0.31, 1.69]
Pooled Estimate					I^2: 63%	0.76 [0.57, 1.01]

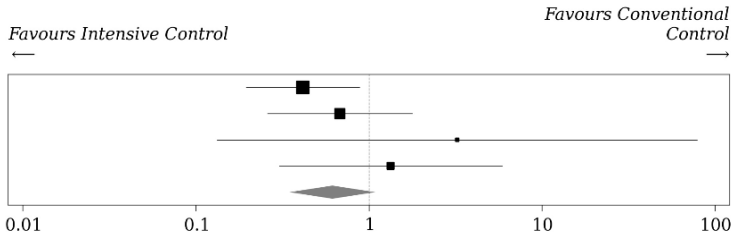
Mantel-Haenszel, DerSimonian-Laird Random Effects Subgroup Effect
p=0.06, z=1.86
τ^2=0.08
χ^2=0.01, p=0.94, I^2=0.0%
OR: Odds Ratio
CI: Confidence Interval



Surgical site infection [No. of patients] - all groups

Study	Intensive Control	(%)	Conventional Control	(%)	Weight	RR [95% CI]
Okabayashi 2014 #1121	9/222	(4%)	22/225	(10%)	50.1%	0.41 [0.2, 0.88]
Chan 2009 #4092	6/54	(11%)	9/55	(16%)	32.3%	0.68 [0.26, 1.78]
Desai 2012 #4089	1/91	(1%)	0/98	(0%)	3.2%	3.23 [0.13, 78.26]
Umpierrez 2015 #4104	4/151	(3%)	3/151	(2%)	14.4%	1.33 [0.3, 5.86]
Pooled Estimate	20/518	(4%)	34/529	(6%)	I^2: 6%	0.61 [0.35, 1.09]

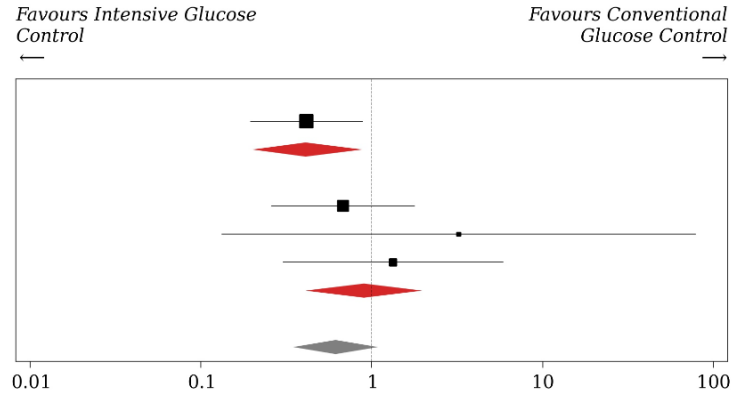
Mantel-Haenszel, DerSimonian-Laird Random Effects; *p=0.09, z=1.67*; *τ^2=0.02*; *RR: Risk Ratio*; *CI: Confidence Interval*



Surgical site infection [No. of patients]

Study	Intensive Glucose Control	(%)	Conventional Glucose Control	(%)	Weight	RR [95% CI]
mixed ICU						
Okabayashi 2014 #1121	9/222	(4%)	22/225	(10%)	50.1%	0.41 [0.2, 0.88]
Subgroup Estimate	9/222	(4%)	22/225	(10%)	I^2: 0%	0.41 [0.2, 0.88]
cardiac surgery only						
Chan 2009 #4092	6/54	(11%)	9/55	(16%)	32.3%	0.68 [0.26, 1.78]
Desai 2012 #4089	1/91	(1%)	0/98	(0%)	3.2%	3.23 [0.13, 78.26]
Umpierrez 2015 #4104	4/151	(3%)	3/151	(2%)	14.4%	1.33 [0.3, 5.86]
Subgroup Estimate	11/296	(4%)	12/304	(4%)	I^2: 0%	0.9 [0.41, 1.97]
Pooled Estimate					I^2: 6%	0.61 [0.35, 1.09]

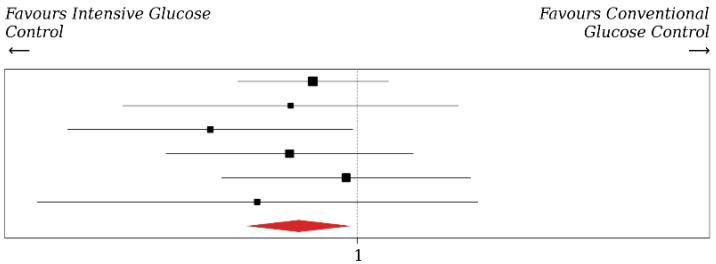
Mantel-Haenszel, DerSimonian-Laird Random Effects Subgroup Effect; *p=0.09, z=1.67*; *τ^2=0.02*; *χ^2=1.96, p=0.16, I^2=49.0%*; *RR: Risk Ratio*; *CI: Confidence Interval*



Unfavorable neurological outcome [based on the GOS/ GOSE]

Study	Intensive Glucose Control	(%)	Conventional Glucose Control	(%)	Weight	RR [95% CI]
Yang 2009 #368 - 6 mos fup	83/117	(71%)	90/116	(78%)	27.5%	0.91 [0.79, 1.06]
Coester 2010 #4088 - 6 mos fup	23/39	(59%)	27/40	(68%)	8.1%	0.87 [0.62, 1.23]
Wang 2017 #4097 - 6 mos fup	26/44	(59%)	35/44	(80%)	10.6%	0.74 [0.56, 0.99]
NICE SUGAR-TBI 2015 #3009 - 2 yr fup	68/166	(41%)	70/149	(47%)	22.4%	0.87 [0.68, 1.12]
Bilotta 2009 #4085 - 6 mos fup	72/179	(40%)	72/175	(41%)	22.1%	0.98 [0.76, 1.26]
Cinotti 2014 #3416* - 90d fup	24/90	(27%)	32/98	(33%)	9.3%	0.82 [0.52, 1.27]
Pooled Estimate	296/635	(47%)	326/622	(52%)	I^2: 0%	0.89 [0.8, 0.99]

Mantel-Haenszel Fixed Effects; *p=0.03, z=2.18*; *RR: Risk Ratio*; *CI: Confidence Interval*



Note: Unfavorable neurological outcomes were less frequent in those with intensive glucose control.

critical illness polyneuropathy [based on EMG]

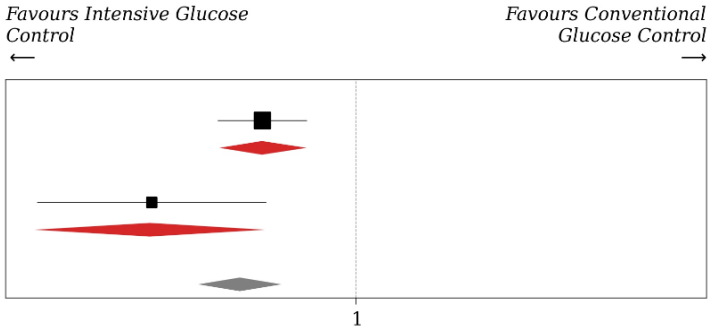
Study	Intensive Glucose Control	(%)	Conventional Glucose Control	(%)	Weight	RR [95% CI]
mixed ICU patients						
Van den Berghe 2001 #246	45/157	(29%)	107/206	(52%)	73.5%	0.55 [0.42, 0.73]
Subgroup Estimate	45/157	(29%)	107/206	(52%)	I^2: 0%	0.55 [0.42, 0.73]
cardiac surgery						
Ingels 2006 #2866	9/477	(2%)	34/493	(7%)	26.5%	0.27 [0.13, 0.56]
Subgroup Estimate	9/477	(2%)	34/493	(7%)	I^2: 0%	0.27 [0.13, 0.56]
Pooled Estimate					I^2: 70%	0.48 [0.37, 0.62]

Mantel-Haenszel Fixed Effects Subgroup Effect

p=0.00, z=5.48

χ^2=6.05, p=0.01, I^2=83.5%

RR: Risk Ratio
CI: Confidence Interval



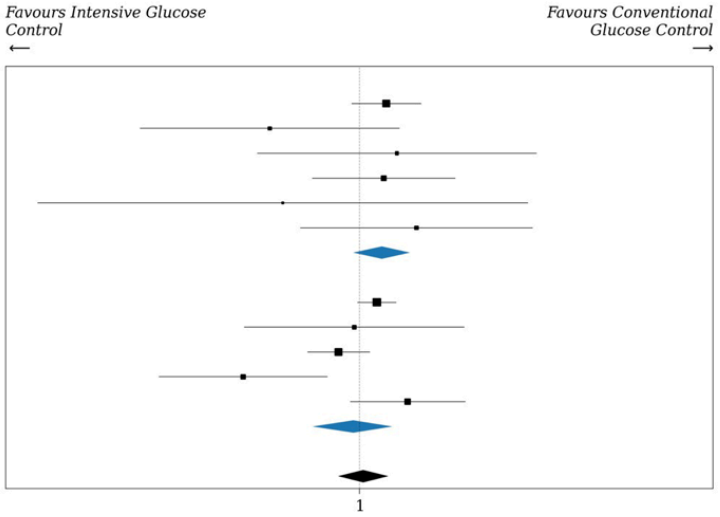
mortality - DM subgroup analysis - core studies

Study	Intensive Glucose Control	(%)	Conventional Glucose Control	(%)	Weight	RR [95% CI]
diabetic subgroup						
NICE SUGAR 2009 #3008 - 90d mortality	195/615	(32%)	165/596	(28%)	17.4%	1.15 [0.96, 1.36]
Arabi 2008 #3670 - ICU mortality	11/85	(13%)	25/123	(20%)	3.3%	0.64 [0.33, 1.22]
De La Rosa 2008 #3266 - hospital mortality	12/32	(38%)	9/29	(31%)	2.9%	1.21 [0.6, 2.44]
Van den Berghe 2006 #248 - hospital mortality	42/106	(40%)	34/97	(35%)	8.4%	1.13 [0.79, 1.62]
Van den Berghe 2001 #246 - ICU mortality	4/101	(4%)	6/103	(6%)	1.0%	0.68 [0.2, 2.34]
Glucontrol [Preiser 2009 #1338] - ICU mortality	18/78	(23%)	18/104	(17%)	4.0%	1.33 [0.74, 2.39]
Subgroup Estimate	282/1017	(28%)	257/1052	(24%)	I^2: 0%	1.12 [0.97, 1.29]
non-diabetic subgroup						
NICE SUGAR 2009 #3008 - 90d mortality	634/2394	(26%)	586/2416	(24%)	22.4%	1.09 [0.99, 1.2]
Arabi 2008 #3670 - ICU mortality	25/181	(14%)	19/134	(14%)	4.4%	0.97 [0.56, 1.69]
Van den Berghe 2006 #248 - hospital mortality	180/489	(37%)	208/509	(41%)	18.6%	0.9 [0.77, 1.05]
Van den Berghe 2001 #246 - ICU mortality	31/664	(5%)	57/680	(8%)	6.6%	0.56 [0.36, 0.85]
Glucontrol [Preiser 2009 #1338] - ICU mortality	86/375	(23%)	64/356	(18%)	11.0%	1.28 [0.96, 1.7]
Subgroup Estimate	956/4103	(23%)	934/4095	(23%)	I^2: 72%	0.97 [0.79, 1.18]
Pooled Estimate					I^2: 48%	1.02 [0.9, 1.16]

Mantel-Haenszel, DerSimonian-Laird Random Effects Subgroup Effect

p=0.77, z=0.30
τ^2=0.02
χ^2=1.33, p=0.25, I^2=24.8%

RR: Risk Ratio
CI: Confidence Interval



Hypoglycemia - diabetes subgroup analysis

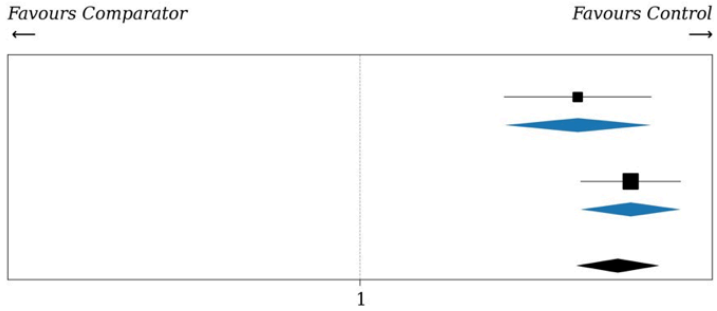
Study	Comparator	(%)	Control	(%)	Weight	RR [95% CI]
diabetic subgroup						
Glucontrol [Preiser 2009 #1338]	56/78	(72%)	25/104	(24%)	26.8%	2.99 [2.07, 4.32]
Subgroup Estimate	56/78	(72%)	25/104	(24%)	I^2: 0%	2.99 [2.07, 4.32]
non-diabetic subgroup						
Glucontrol [Preiser 2009 #1338]	234/375	(62%)	57/356	(16%)	73.2%	3.9 [3.03, 5.01]
Subgroup Estimate	234/375	(62%)	57/356	(16%)	I^2: 0%	3.9 [3.03, 5.01]
Pooled Estimate					I^2: 29%	3.65 [2.96, 4.5]

Mantel-Haenszel Fixed Effects Subgroup Effect

p=0.00, z=12.12

χ^2=0.56, p=0.46, I^2=0.0%

RR: Risk Ratio
CI: Confidence Interval



SDC 9-2C. Summary of Judgments. Intensive versus conventional glucose targets in critically ill *adults*

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	**Large**	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

SDC 9-3. Continuous intravenous insulin infusion versus intermittent subcutaneous insulin in critically ill *adults*

Question. In the acute management of hyperglycemia in *adult* critically ill patients for whom insulin therapy is being initiated, should continuous intravenous insulin infusions or intermittent subcutaneous insulin be initiated?

SDC 9-3A. Evidence Profile. Continuous intravenous insulin infusion versus intermittent subcutaneous insulin in *adults*

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	continuous IV insulin infusion	intermittent subcutaneous insulin	Relative (95% CI)	Absolute (95% CI)		
Hospital mortality												
1	randomised trials	not serious	not serious	not serious	very serious [a,b]	none	3/29 (10.3%)	1/29 (3.4%)	**OR 3.23** (0.32 to 33.10)	**69 more per 1,000** (from 23 fewer to 507 more)	⨁⨁◯◯ LOW	CRITICAL
Mortality												
2	observational studies	very serious [c]	not serious	not serious	not serious	none	Two observational studies found **no difference** in mortality between those who received continuous IV insulin infusion and those who received intermittent subcutaneous insulin (pooled findings: 21 of 193 deaths in the intervention group; 19 of 149 deaths in the comparison group).				⨁◯◯◯ VERY LOW	CRITICAL
ICU length of stay												
2	randomised trials	not serious	not serious	not serious	very serious [a]	none	Two RCTs with modest sample sizes (54 and 111 respectively) found **no difference** in ICU length of stay. In one trial (Aron 2013), mean ICU length of stays were 2 days in the continuous IV insulin group and 3 days in the intermittent subcutanous insulin group (effect size -1.3, 95% CI -5.9, 3.4). In the other trial (Calvalcanti 2009), mean ICU length of stays were 7 days in both groups (no variability metric was reported).				⨁⨁◯◯ LOW	CRITICAL
Hospital length of stay												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	26	28	-	effect size **3 days lower** (8 lower to 2 higher)	⨁⨁◯◯ LOW	IMPORTANT
Achievement of target glycemic range: Percentage of blood glucose measurements between target range [60 - 140 mg/dL]												
1	randomised trials	not serious	not serious	not serious	serious	none	58 (67.9 +/- 20.8%)	53 (47.1 +/- 30.2%)	-	MD **20.8 % higher** (11.07 higher to 30.53 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Achievement of target glycemic control												
3	observational studies	very serious [c]	serious [d]	not serious	not serious	none	Three observational studies reported percentage of proportion of time with BG within target range. Two retrospective observational studies (Tran 2019; Huntt 2021) reported a **higher "percentage of time"** BG was controlled within target range in the continuous IV insulin cohort than the intermittent subcutaneous insulin cohort. Conversely, one prospective observational study (De Block 2006) reported **no significant difference** in the proportion of time BG within the target range between the IV insulin cohort and the subcutaneous insulin cohort.				⨁◯◯◯ VERY LOW	IMPORTANT

Hyperglycemia index: measured by HGI 140 (mg/dL per hour)

1	randomised trials	not serious	not serious	not serious	serious	none	58 (mean 10.5, SD 13.5) Calculated based on reported medians, IQRs	53 (mean 22.8, SD 28.7) Calculated based on reported medians, IQRs	-	MD **12.3 mg/dL per hour lower** (20.62 lower to 3.98 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT

Hyperglycemia

3	observational studies	very serious [c]	not serious	not serious	not serious	none	Three observational studies found less hyperglycemia in the continuous IV insulin cohort. One study (De Block 2006) reported that the percentage time in glycemia > 110 mg/dL was **lower** in the IV insulin cohort (55 +/- 22%) compared to the subcutaneous insulin cohort (71 +/- 24%; p = 0.02). The same study reported no significant difference in percentage of time in glycemia > 140 or > 200 mg/dL. Another study (Tran 2019) reported that the proportion of BG measurements > 180 mg/dL was **lower** in the IV insulin cohort (35.8%) than the subcutaneous insulin cohort (52.2%, p < 0.01). Another study (Huntt 2021) also reported that the percentage of time with BG > 180 mg/dL was **lower** in the IV insulin cohort (36%) compared to the subcutaneous insulin cohort (63%). **Given their observational design and high risk of bias due to significant baseline differences between the groups which likely influenced the choice of route of insulin therapy in one of the studies, the certainty in the evidence is very low.**			⨁◯◯◯ VERY LOW	IMPORTANT

Hypoglycemia episodes

2	randomised trials	not serious	not serious	not serious	serious [e]	none	Two RCTs with modest sample sizes (54 and 111 respectively) found higher incidence of hypoglycemic events in the intervention group. Once RCT (Aron 2013) defined hypoglycemia as a blood glucose < 3.9 mmol/L (or 70 mg/dL) and reported a total of 23 hypoglycemic episodes among 12 patients in the intervention group, compared with 3 events in an unspecified number of patients in the control group. Another RCT (Cavalcanti 2009) defined hypoglycemia as blood glucose < 40 mg/dL and reported 24 episodes of hypoglycemia in the intervention group (Leuven protocol), compared with 2 events in the control group.			⨁⨁⨁◯ MODERATE	IMPORTANT

Hypoglycemia: Percentage of blood glucose measurements below threshold for hypoglycemia

4	observational studies	very serious [c]	serious [f]	not serious	not serious	none	Two observational studies (Tran 2019; Rabinovich 2020) reported reduced proportion of blood glucose measurements < 70 mg/dL. However, in the study by Tran (2019), the proportion of severe hypoglycemia (BG ≤ 40 mg/dL) was similar between the two groups (0.12% and 0.13%, respectively; p = 0.86). Conversely, two observational studies (De Block 2006; Huntt 2021) found no difference percentage of time at in the hypoglycemic range.			⨁◯◯◯ VERY LOW	IMPORTANT

Blood transfusions

1	randomised trials	not serious	not serious	not serious	very serious [e]	none	29	29	-	effect size **0.13 number of packed RBC units transfused higher** (0.39 lower to 0.64 higher)	⨁⨁◯◯ LOW	IMPORTANT

Need for renal replacement therapy (assessed with: new hemodialysis)

1	randomised trials	not serious	not serious	not serious	very serious [a]	none	2/29 (6.9%)	1/29 (3.4%)	**OR 2.1** (0.2 to 25.0)	**35 more per 1,000** (from 27 fewer to 437 more)	⨁⨁◯◯ LOW [g]	IMPORTANT

Need for renal replacement therapy (assessed with: CVVH or HD)

1	observational studies	very serious [c]	not serious	not serious	serious [e]	none	One prospective observational study (De Block 2006) found higher rate of renal replacement therapy in the continuous IV insulin cohort (9 of 22) compared with the intermittent subcutaneous cohort (2 of 28). However, this observational study had high risk of bias due to significant baseline differences between the two groups and the finding was associated with a wide confidence interval, which may account for the difference found. As such, there is very low certainty in the evidence that IV insulin infusion therapy does not influence the need for renal replacement therapy.				⨁◯◯◯ VERY LOW	IMPORTANT

Total infections

1	randomised trials	not serious	not serious	not serious	very serious [a]	none	29	29	-	effect size **0.1 infections higher** (0.4 lower to 0.6 higher)	⨁⨁◯◯ LOW [h]	IMPORTANT

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

Explanations

a. Downgraded for imprecision due to wide confidence interval.
b. Downgraded for imprecision due to small sample size, not meeting the Optimal Information Size (OIS) criterion.
c. Downgraded for risk of bias due to significant baseline imbalance between groups in illness severity (De Block et al., 2006) and medical vs. surgical patient populations (Tran 2019).
d. Downgraded for inconsistency due to high variability in target glycemic range.
e. Downgraded due to small sample size/ event rates.
f. Downgraded for inconsistency in reported findings.
g. The same study (Aron 2013) also reported no difference in rates of acute kidney injury (4 in the intervention group, 3 in the control group).
h. The same study (Aron 2013) also reported similar rates of bacteremia, line sepsis, wound infections, urinary tract infections, pneumonia, and intra-abdominal infections, although event rates were relatively small for these outcomes (ranging from 0 to 7).

SDC 9-3B. Summary of Judgments. Continuous intravenous insulin infusion versus intermittent subcutaneous insulin *adults*

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

SDC 9-4. Frequency of blood glucose monitoring in critically ill *adults*

Question. In *adult* critically ill patients on insulin infusion therapy, should blood glucose be monitored frequently (interval ≤ 1 hour, continuous or near-continuous) or less frequently (> 1 hour) during periods of glycemic instability?

SDC 9-4A. Evidence Profile. Frequency of blood glucose monitoring in *adults*

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	continuous glucose monitoring	intermittent glucose monitoring	Relative (95% CI)	Absolute (95% CI)		
Hospital or 28-day mortality												
4	randomised trials	not serious	not serious	not serious	very serious[a]	none	68/231 (29.4%)	59/228 (25.9%)	**RR 1.14** (0.83 to 1.57)	**36 more per 1,000** (from 44 fewer to 148 more)	⊕⊕◯◯ Low	CRITICAL
ICU mortality												
4	randomised trials	not serious	serious[b]	not serious	very serious[a]	none	47/254 (18.5%)	50/247 (20.2%)	**RR 1.0** (0.54 to 1.85)	**0 fewer per 1,000** (from 93 fewer to 172 more)	⊕◯◯◯ Very low	CRITICAL
Renal replacement therapy												
2	randomised trials	not serious	not serious	not serious	very serious[c]	none	9/90 (10.0%)	18/89 (20.2%)	**RR 0.50** (0.24 to 1.05)	**82 fewer per 1,000** (from 125 fewer to 8 more)	⊕⊕◯◯ Low	CRITICAL
ICU length of stay												
4	randomised trials	serious	serious[b]	not serious	not serious	none	231	228	-	MD **1.59 days higher** (0.3 higher to 2.87 higher)	⊕⊕◯◯ Low	CRITICAL
Hospital length of stay												
2	randomised trials	not serious	not serious	not serious	serious[c]	none	90	89	-	MD **1.53 days lower** (3.17 lower to 6.23 higher)	⊕⊕⊕◯ Moderate	IMPORTANT
New infections in ICU												
2	randomised trials	not serious	serious[b]	not serious	not serious	none	Two RCTs (total N = 194) found no difference in the number of new infections in ICU patients (Lu 2018) or surgical site infections in cardiac surgery patients (Punke 2012).				⊕⊕⊕◯ Moderate	CRITICAL
Frequency of hypoglycemia [number of patients]												
5	randomised trials	not serious	not serious	serious[d]	not serious	none	16/270 (5.9%)	35/266 (15.0%)	**RR 0.50** (0.29 to 0.85)	**61 fewer per 1,000** (from 89 fewer to 17 fewer)	⊕⊕⊕◯ Moderate	IMPORTANT

Time within target glucose range [%]

6	randomised trials	not serious	serious[e]	serious[f]	not serious	none	295	291	-	MD **5.40 % higher** (1.15 lower to 11.95 higher)	⊕⊕◯◯ Low	IMPORTANT

Glycemic variability (assessed with: Coefficient of variation [%])

3	randomised trials	not serious	not serious	not serious	serious[c]	none	129	127	-	MD **1.69 % lower** (3.39 lower to 0.01 higher)	⊕⊕⊕◯ Moderate	IMPORTANT

Hyperglycemia [time in hyperglycemic range]

3	randomised trials	not serious	serious[b]	serious[g]	not serious	none	168	167	-	MD **5.95 % lower** (11.3 lower to 0.61 lower)	⊕⊕◯◯ Low	IMPORTANT

Blood transfusions

2	randomised trials	not serious	not serious	not serious	very serious[a]	none	52/90 (57.8%)	55/89 (61.8%)	**RR 0.93** (0.74 to 1.17)	**43 fewer per 1,000** (from 161 fewer to 105 more)	⊕⊕◯◯ Low	IMPORTANT

Nursing workload

1	randomised trials	serious	not serious	not serious	not serious	none	One trial (Boom 2014) found reduced nursing workload with continuous glucose monitoring (total N = 156). The mean reduction in total nursing workload was 19 minutes per 24 hours or 53% in favour of the intervention group.				⊕⊕⊕◯ Moderate	IMPORTANT

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

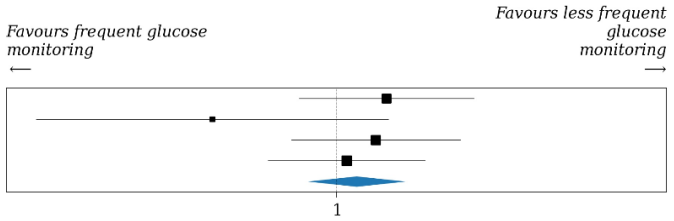
a. Rated down by two levels due to very wide confidence interval that crosses no effect.
b. Rated down for inconsistency due to high heterogeneity across studies.
c. Rated down for imprecision due to wide confidence interval that crosses no effect.
d. Rated down for indirectness due to variability in definition of hypoglycemia across studies.
e. Rated down for inconsistency due to high variability in target glycemic range.
f. Rated down for indirectness due to variability in target glucose range across studies.
g. Rated down for indirectness due to variability in definition of hyperglycemia.

SDC 9-4B. Forest Plots. Frequency of blood glucose monitoring in *adults*

mortality [hospital or 28-day]

Study	frequent glucose monitoring	(%)	less frequent glucose monitoring	(%)	Weight	RR [95% CI]
#1302 Lu 2018	22/74	(30%)	15/70	(21%)	28.2%	1.39 [0.79, 2.45]
#2314 DeBlock 2015 [REGIMEN]	3/16	(19%)	8/19	(42%)	7.5%	0.45 [0.14, 1.4]
#2125 Boom 2014 [RESCUE II]	22/78	(28%)	17/78	(22%)	30.1%	1.29 [0.75, 2.24]
#1648 Holzinger 2010	21/63	(33%)	19/61	(31%)	34.2%	1.07 [0.64, 1.78]
Pooled Estimate	68/231	(29%)	59/228	(26%)	I^2: 9%	1.14 [0.83, 1.57]

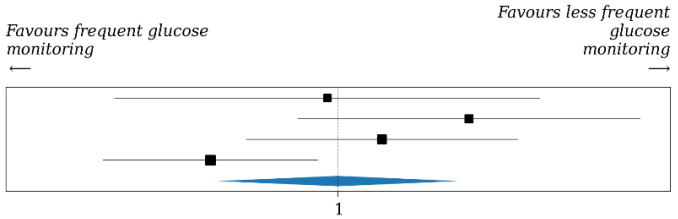
Mantel-Haenszel, DerSimonian-Laird Random Effects — *p=0.42, z=0.81, τ²=0.01* — *RR: Risk Ratio, CI: Confidence Interval*



mortality [ICU]

Study	frequent glucose monitoring	(%)	less frequent glucose monitoring	(%)	Weight	RR [95% CI]
#1302 Lu 2018	6/74	(8%)	6/70	(9%)	18.3%	0.95 [0.32, 2.79]
#499 Preiser 2018	12/39	(31%)	6/38	(16%)	22.8%	1.95 [0.81, 4.66]
#2125 Boom 2014 [RESCUE II]	15/78	(19%)	12/78	(15%)	27.4%	1.25 [0.63, 2.5]
#1648 Holzinger 2010	14/63	(22%)	26/61	(43%)	31.5%	0.52 [0.3, 0.9]
Pooled Estimate	47/254	(19%)	50/247	(20%)	I^2: 61%	1.0 [0.54, 1.85]

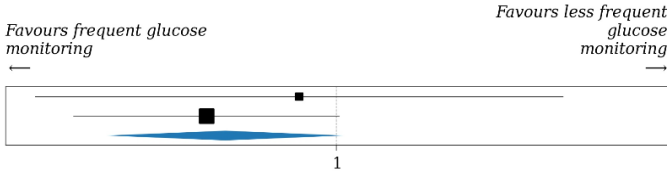
Mantel-Haenszel, DerSimonian-Laird Random Effects — *p=0.99, z=0.01, τ²=0.24* — *RR: Risk Ratio, CI: Confidence Interval*



renal replacement therapy

Study	frequent glucose monitoring	(%)	less frequent glucose monitoring	(%)	Weight	RR [95% CI]
#2314 DeBlock 2015 [REGIMEN]	2/16	(12%)	3/19	(16%)	20.2%	0.79 [0.15, 4.17]
#1302 Lu 2018	7/74	(9%)	15/70	(21%)	79.8%	0.44 [0.19, 1.02]
Pooled Estimate	9/90	(10%)	18/89	(20%)	I^2: 0%	0.5 [0.24, 1.05]

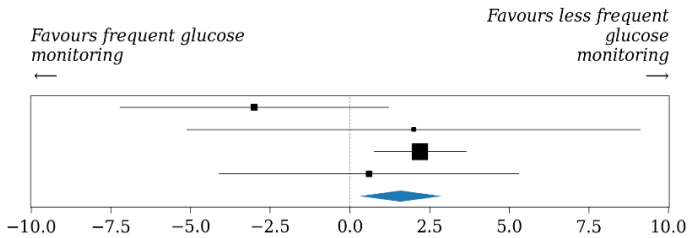
Mantel-Haenszel, DerSimonian-Laird Random Effects — *p=0.07, z=1.84, τ²=0.00* — *RR: Risk Ratio, CI: Confidence Interval*



ICU length of stay

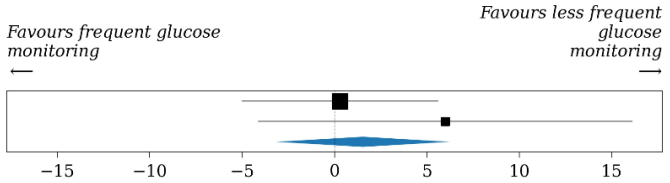
Study	frequent glucose monitoring	(N)	less frequent glucose monitoring	(N)	Weight	MD [95% CI]
#1302 Lu 2018	17.0 ± 12.1	(74)	20.0 ± 13.6	(70)	9.4%	-3.0 [-7.21, 1.21]
#2314 DeBlock 2015 [REGIMEN]	18.0 ± 13.0	(16)	16.0 ± 7.0	(19)	3.3%	2.0 [-5.11, 9.11]
#2125 Boom 2014 [RESCUE II]	6.4 ± 5.6	(78)	4.2 ± 3.3	(78)	79.8%	2.2 [0.76, 3.64]
#1648 Holzinger 2010	17.4 ± 14.4	(63)	16.8 ± 12.2	(61)	7.5%	0.6 [-4.09, 5.29]
Pooled Estimate					I^2: 45%	1.59 [0.3, 2.87]

Inverse Variance Fixed Effects — *p=0.02, z=2.41* — *MD: Mean Difference, CI: Confidence Interval*



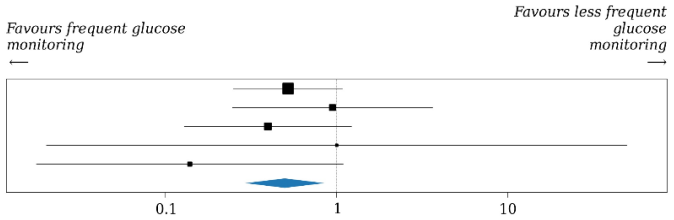
hospital length of stay

Study	frequent glucose monitoring	(N)	less frequent glucose monitoring	(N)	Weight	MD [95% CI]
#1302 Lu 2018	25 ± 16.6	(74)	24.7 ± 15.9	(70)	78.4%	0.3 [-5.01, 5.61]
#2314 DeBlock 2015 [REGIMEN]	31 ± 18.0	(16)	25.0 ± 11.0	(19)	21.6%	6.0 [-4.11, 16.11]
Pooled Estimate					I^2: 0%	1.53 [-3.17, 6.23]
Inverse Variance Fixed Effects	*p=0.52, z=0.64*					*MD: Mean Difference CI: Confidence Interval*



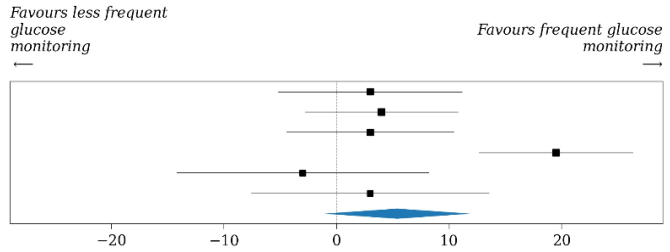
incidence of hypoglycemia [no. of patients]

Study	frequent glucose monitoring	(%)	less frequent glucose monitoring	(%)	Weight	RR [95% CI]
#499 Preiser 2018 [< 70 mg/ dL]	8/39	(21%)	15/38	(39%)	53.2%	0.52 [0.25, 1.08]
#1302 Lu 2018 [< 40 mg/ dL]	4/74	(5%)	4/70	(6%)	15.7%	0.95 [0.25, 3.64]
#2314 DeBlock 2015 [REGIMEN] [< 60 mg/ dL]	3/16	(19%)	9/19	(47%)	22.6%	0.4 [0.13, 1.22]
#2125 Boom 2014 [RESCUE II] [< 40 mg/ dL]	0/78	(0%)	0/78	(0%)	1.9%	1.0 [0.02, 49.78]
#1648 Holzinger 2010 [< 40 mg/ dL]	1/63	(2%)	7/61	(11%)	6.7%	0.14 [0.02, 1.09]
Pooled Estimate	16/270	(6%)	35/266	(13%)	I^2: 0%	0.5 [0.29, 0.85]
Mantel-Haenszel, DerSimonian-Laird Random Effects	*p=0.01, z=2.56 τ²=0.00*					*RR: Risk Ratio CI: Confidence Interval*



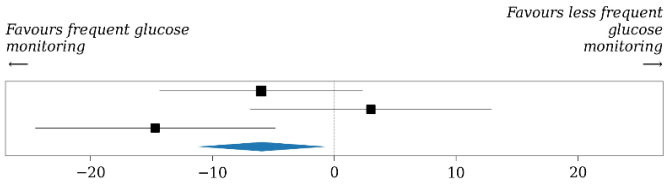
time in target glycemia range

Study	frequent glucose monitoring	(N)	less frequent glucose monitoring	(N)	Weight	MD [95% CI]
#2125 Boom 2014 [RESCUE II] [90-160 mg/ dL]	69.0 ± 26.0	(78)	66.0 ± 26.0	(78)	17.0%	3.0 [-5.16, 11.16]
#1648 Holzinger 2010 [< 110 mg/ dL]	59.0 ± 20.4	(63)	55.0 ± 18.0	(61)	18.5%	4.0 [-2.77, 10.77]
#2314 DeBlock 2015 [REGIMEN] [80-110 mg/ dL]	37.0 ± 12.0	(16)	34.0 ± 10.0	(19)	17.8%	3.0 [-4.4, 10.4]
#1302 Lu 2018 [145-180 mg/ dL]	49.6 ± 27.8	(74)	30.1 ± 11.2	(70)	18.4%	19.5 [12.64, 26.36]
#499 Preiser 2018 [90-150 mg/ dL]	70.0 ± 27.0	(39)	73.0 ± 23.0	(38)	13.8%	-3.0 [-14.19, 8.19]
#485 Punke 2012 [80-150 mg/ dL]	75.0 ± 19.0	(25)	72.0 ± 19.0	(25)	14.5%	3.0 [-7.53, 13.53]
Pooled Estimate					I^2: 74%	5.4 [-1.15, 11.95]
Inverse Variance, DerSimonian-Laird Random Effects	*p=0.11, z=1.62 τ²=48.34*					*MD: Mean Difference CI: Confidence Interval*



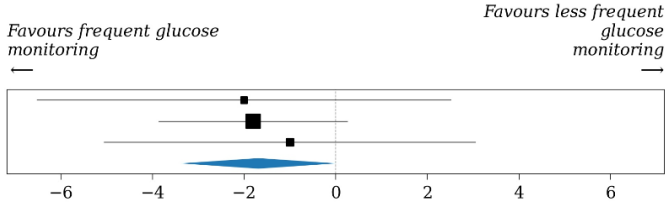
time in hyperglycemic range

Study	frequent glucose monitoring	(N)	less frequent glucose monitoring	(N)	Weight	MD [95% CI]
#2125 Boom 2014 [RESCUE II] [> 160 mg/ dL]	28.0 ± 26	(78)	34 ± 27	(78)	41.3%	-6.0 [-14.32, 2.32]
#2314 DeBlock 2015 [REGIMEN] [> 150 mg/ dL]	20.0 ± 18	(16)	17 ± 10	(19)	29.1%	3.0 [-6.9, 12.9]
#1302 Lu 2018 [> 180 mg/ dL]	33.3 ± 33	(74)	48 ± 27	(70)	29.6%	-14.7 [-24.53, -4.87]
Pooled Estimate					I^2: 68%	-5.95 [-11.3, -0.61]
Inverse Variance Fixed Effects	*p=0.03, z=2.18*					*MD: Mean Difference CI: Confidence Interval*



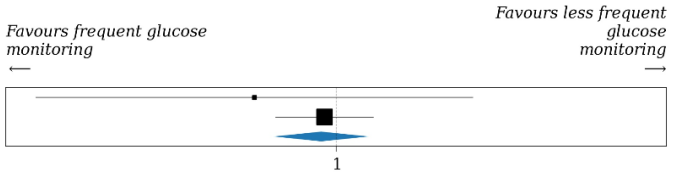
glycemic variability [coefficient of variation, %]

Study	frequent glucose monitoring	(N)	less frequent glucose monitoring	(N)	Weight	MD [95% CI]
#2314 DeBlock 2015 [REGIMEN]	25.0 ± 8.0	(16)	27.0 ± 5.0	(19)	14.1%	-2.0 [-6.52, 2.52]
#1302 Lu 2018	18.1 ± 7.2	(74)	19.9 ± 5.3	(70)	68.3%	-1.8 [-3.86, 0.26]
#499 Preiser 2018	17.0 ± 8.0	(39)	18.0 ± 10.0	(38)	17.6%	-1.0 [-5.05, 3.05]
Pooled Estimate					I^2: 0%	-1.69 [-3.39, 0.01]
Inverse Variance, DerSimonian-Laird Random Effects	*p=0.05, z=1.95 τ²=0.00*					*MD: Mean Difference CI: Confidence Interval*



blood transfusions

Study	frequent glucose monitoring	(%)	less frequent glucose monitoring	(%)	Weight	RR [95% CI]
#2314 DeBlock 2015 [REGIMEN]	4/16	(25%)	7/19	(37%)	4.8%	0.68 [0.24, 1.91]
#1302 Lu 2018	48/74	(65%)	48/70	(69%)	95.2%	0.95 [0.75, 1.19]
Pooled Estimate	52/90	(58%)	55/89	(62%)	I^2: 0%	0.93 [0.74, 1.17]
Mantel-Haenszel, DerSimonian-Laird Random Effects	*p=0.53, z=0.62 τ²=0.00*					*RR: Risk Ratio CI: Confidence Interval*



SDC 9-4C. Summary of Judgements. Frequency of blood glucose monitoring in *adults*

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	**Reduced**	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

SDC 9-5. Explicit clinical decision support tool versus conventional care in critically ill *adults*

Question. In *adult* critically ill patients on insulin infusion therapy, should an explicit decision support tool be used compared to conventional care for the management of hyperglycemia?

SDC 9-5A. Evidence Profile. Explicit clinical decision support tool versus conventional care in *adults*

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	explicit decision support tool	conventional care	Relative (95% CI)	Absolute (95% CI)		
Hospital mortality												
3	randomised trials	not serious	not serious[a]	not serious	serious[b]	none	91/976 (9.8%)	94/974 (10.2%)	**RR 1.16** (0.60 to 2.24)	**15 fewer per 1,000** (from 39 fewer to 120 more)	⊕⊕⊕◯ Moderate	CRITICAL
ICU Mortality												
2	randomised trials	not serious	not serious	not serious	very serious[c]	none	49/926 (5.3%)	51/924 (5.5%)	**RR 1.16** (0.80 to 1.66)	**9 more per 1,000** (from 11 fewer to 36 more)	⊕⊕◯◯ Low	CRITICAL
Quality of life (follow-up: 90 days; assessed with: EuroQoL 5D-3L/ EQ-5D index)												
1	randomised trials	serious[d]	not serious	not serious	serious[e]	none	777	773	-	MD **0** (0.015 fewer to 0.015 more)	⊕⊕◯◯ Low	CRITICAL
ICU length of stay												
2	randomised trials	not serious	not serious	not serious	serious[c]	none	926	924	-	MD **0 days** (0.28 lower to 0.28 higher)	⊕⊕⊕◯ Moderate	CRITICAL
Hospital length of stay												
2	randomised trials	not serious	serious[f]	not serious	serious[c]	none	926	924	-	MD **1.02 days more** (1.76 fewer to 3.81 more)	⊕⊕◯◯ Low	IMPORTANT
New infections (assessed with: number of patients)												
3	randomised trials	not serious	not serious	not serious	serious[b]	none	Three RCTs evaluated the rates of new infections in the ICU. Dubois et al. (2017) reported no difference in the incidence of new infections in the ICU between those who were managed using an explicit decision support tool (LOGIC-C: 104 of 777, or 13%) and those who were managed using conventional, nurse-directed (Nurse-C: 117 of 773, or 15.14%) among mixed medical-surgical ICU patients. Punke et al. (2012) reported no difference in the rates of surgical site infections between groups among 50 patients after cardiac surgery (numerical data not reported). Zeitoun et al. (2021) reported a slightly lower number of patients in a coronary care unit with infections the use of an explicit decision support tool (6 of 50, or 12%) compared to those without its use (13/50, or 26%; p > 0.05). **Use of an explicit decision support tool to manage glycemia in the ICU does not affect rates of new infections.**				⊕⊕⊕◯ Moderate	IMPORTANT
Time to achieve target glycemic control												
5	randomised trials	not serious	serious[f]	not serious	serious[e]	none	1083	1101	-	MD **1.3 hours lower** (2.29 lower to 0.30 lower)	⊕⊕◯◯ Low	IMPORTANT

Time within target glycemic range

10	randomised trials	not serious	serious[f]	not serious	not serious	none	1214	1230	-	MD **13.95 % higher** (8.85 higher to 19.06 higher)	⨁⨁⨁◯ Moderate	IMPORTANT

Time above target glycemic range

5	randomised trials	not serious	serious[f]	not serious	not serious	none	106	104	-	**MD 12.46% lower** (19.11 lower to 5.81 lower)	⨁⨁⨁◯ Moderate	IMPORTANT

Hyperglycemia index [HGI]

5	randomised trials	not serious	serious[f]	not serious	serious[e]	none	967	967	-	MD **2.65 lower** (5.17 lower to 0.13 lower)	⨁⨁◯◯ Low	IMPORTANT

HYPOglycemia [number of patients with BG < 60]

5	randomised trials	not serious	not serious	not serious	serious[c]	none	80/1024 (8.0%)	109/1020 (11.0%)	**RR 0.74** (0.57 to 0.98)	**28 fewer per 1,000** (from 46 fewer to 2 fewer)	⨁⨁⨁◯ Moderate	IMPORTANT

glycemic variability (assessed with various measures as described)

6	randomised trials	not serious	serious[f,g]	not serious	not serious	none	Six trials evaluated different measures of glycemic variability using various measures, including the standard deviation of the mean blood glucose (3 studies), the maximum glycemic variability (3 studies), and the glycemic penalty index (2 studies). Among the 6 trials, 4 studies (2,178 patients) reported lower glycemic variability in the intervention group, whereas 2 studies (94 patients), both reporting the standard deviation of the mean blood glucose, found no difference. **Use of an explicit clinical decision support tool may lead to lower glycemic variability (moderate certainty evidence).**				⨁⨁⨁◯ Moderate	IMPORTANT

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Although I2 was high, sensitivity analysis showed the overall certainty would not be different with removal of 2nd study.
b. Downgraded for imprecision due to small event rate, not meeting the Optimal Information Size (OIS) criterion.
c. Downgraded for imprecision due to wide confidence interval around the point of no effect.
d. Downgraded for risk of bias due to inconsistencies in reporting of missing outcome data.
e. Downgraded for imprecision due to the upper 95% CI suggesting minimal clinically important difference.
f. Downgraded for inconsistency due to high heterogeneity across studies.
g. Downgraded for inconsistency in reported findings.

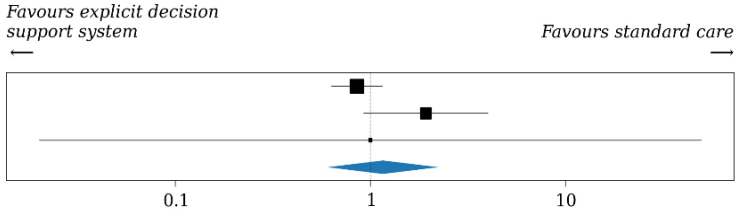
SDC 9-5B. Forest Plots. Explicit clinical decision support tool versus conventional care in *adults*

hospital mortality

Study	explicit decision support system	(%)	standard care	(%)	Weight	RR [95% CI]
Dubois 2017 [#1914]	72/777	(9%)	84/773	(11%)	60.2%	0.85 [0.63, 1.15]
Van Herpe 2013 [#171]	19/149	(13%)	10/151	(7%)	37.1%	1.93 [0.93, 4.0]
Zeitoun 2021 [#1090]	0/50	(0%)	0/50	(0%)	2.7%	1.0 [0.02, 49.44]
Pooled Estimate	91/976	(9%)	94/974	(10%)	I^2: 51%	1.16 [0.6, 2.24]

Mantel-Haenszel, DerSimonian-Laird Random Effects — *p=0.66, z=0.44, τ^2=0.16*

RR: Risk Ratio, CI: Confidence Interval

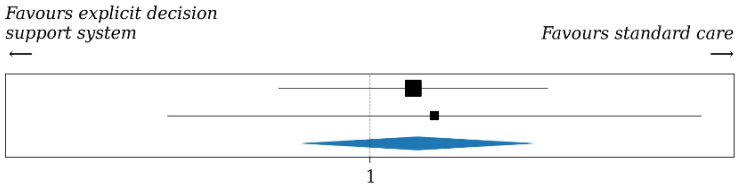


ICU mortality

Study	explicit decision support system	(%)	standard care	(%)	Weight	RR [95% CI]
Dubois 2017 [#1914]	47/777	(6%)	41/773	(5%)	79.8%	1.14 [0.76, 1.71]
VanHerpe 2013 [#171]	12/149	(8%)	10/151	(7%)	20.2%	1.22 [0.54, 2.73]
Pooled Estimate	59/926	(6%)	51/924	(6%)	I^2: 0%	1.16 [0.8, 1.66]

Mantel-Haenszel, DerSimonian-Laird Random Effects — *p=0.44, z=0.78, τ^2=0.00*

RR: Risk Ratio, CI: Confidence Interval

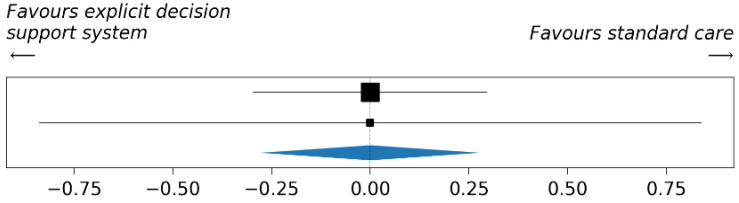


ICU length of stay

Study	explicit decision support system	(N)	standard care	(N)	Weight	MD [95% CI]
Dubois 2017 [#1914]	3.67 ± 2.97	(777)	3.67 ± 2.97	(773)	88.9%	0.0 [-0.3, 0.3]
VanHerpe 2013 [#171]	4.3 ± 3.7	(149)	4.3 ± 3.7	(151)	11.1%	0.0 [-0.84, 0.84]
Pooled Estimate					I^2: 0%	0.0 [-0.28, 0.28]

Inverse Variance, DerSimonian-Laird Random Effects — *p=1.00, z=0.00, τ^2=0.00*

MD: Mean Difference, CI: Confidence Interval

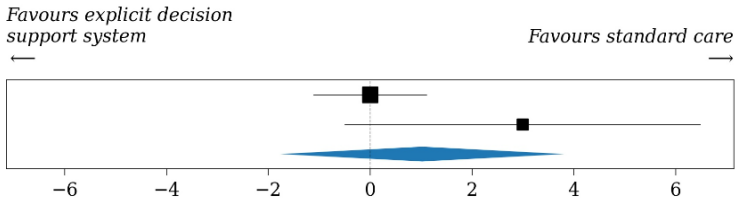


hospital length of stay

Study	explicit decision support system	(N)	standard care	(N)	Weight	MD [95% CI]
Dubois 2017 [#1914]	14.3 ± 11.1	(777)	14.3 ± 11.1	(773)	65.9%	0.0 [-1.11, 1.11]
VanHerpe 2013 [#171]	19.6 ± 17.2	(149)	16.6 ± 13.4	(151)	34.1%	3.0 [-0.49, 6.49]
Pooled Estimate					I^2: 61%	1.02 [-1.76, 3.81]

Inverse Variance, DerSimonian-Laird Random Effects — *p=0.47, z=0.72, τ^2=2.75*

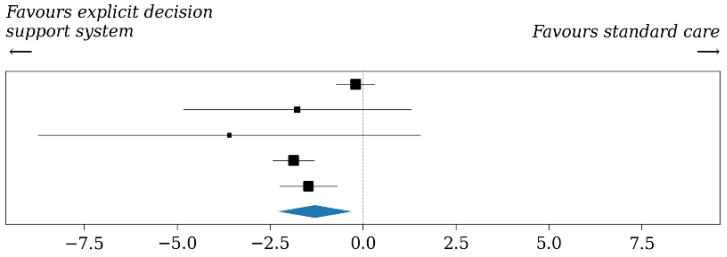
MD: Mean Difference, CI: Confidence Interval



time to achieve glycemic target

Study	explicit decision support system	(N)	standard care	(N)	Weight	MD [95% CI]
Dumont 2012 [#1913]	3.6 ± 2.3	(141)	3.8 ± 2.3	(159)	30.6%	-0.2 [-0.72, 0.32]
Cordingly 2009 [#2374] - cohort 1	5.98 ± 3.93	(10)	7.75 ± 3.0	(10)	8.0%	-1.77 [-4.83, 1.29]
Cordingly 2009 [#2374] - cohort 2	4.28 ± 1.6	(6)	7.88 ± 7.18	(8)	3.4%	-3.6 [-8.74, 1.54]
Dubois 2017 [#1914]	2.43 ± 3.79	(777)	4.3 ± 6.91	(773)	30.2%	-1.87 [-2.43, -1.31]
Van Herpe 2013 [#171]	1.9 ± 2.85	(149)	3.37 ± 3.89	(151)	27.8%	-1.47 [-2.24, -0.7]
Pooled Estimate					I^2: 81%	-1.3 [-2.29, -0.3]

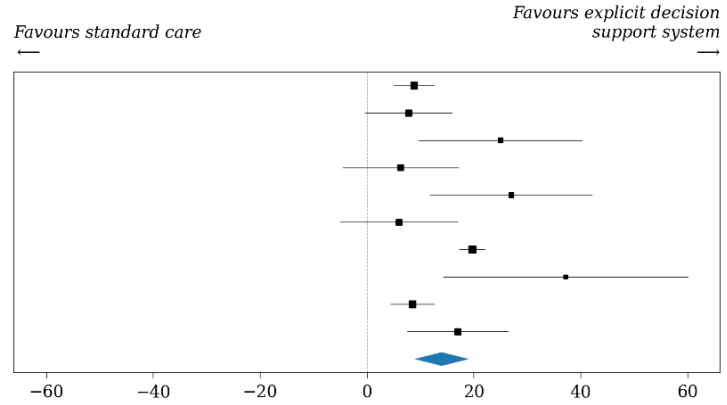
Inverse Variance, DerSimonian-Laird Random Effects — *p=0.01, z=2.56, τ^2=0.77* — *MD: Mean Difference, CI: Confidence Interval*



time within target range

Study	explicit decision support system	(N)	standard care	(N)	Weight	MD [95% CI]
#1913 - Dumont 2012	70.4 ± 15.2	(141)	61.6 ± 17.9	(159)	14.4%	8.8 [5.05, 12.55]
#2152 - Blaha 2009	46.0 ± 18.9	(40)	38.2 ± 18.3	(40)	11.1%	7.8 [-0.35, 15.95]
#485 - Punke 2012	75.0 ± 19.0	(25)	50.0 ± 34.0	(25)	6.5%	25.0 [9.73, 40.27]
#2374 - Cordingley 2009 - Cohort 1	67.6 ± 10.8	(10)	61.3 ± 13.7	(10)	9.2%	6.3 [-4.51, 17.11]
#2374 - Cordingley 2009 - Cohort 2	58.5 ± 10.0	(6)	31.5 ± 18.6	(8)	6.6%	27.0 [11.83, 42.17]
#1250 - Mann 2011	47.0 ± 17.0	(18)	41.0 ± 16.6	(18)	9.1%	6.0 [-4.98, 16.98]
#1914 - Dubois 2017	66.4 ± 20.8	(777)	46.7 ± 27.4	(773)	15.1%	19.7 [17.28, 22.12]
#1383 - Leelarathna 2013	57.0 ± 24.0	(12)	19.8 ± 32.6	(12)	3.8%	37.2 [14.3, 60.1]
#171 - VanHerpe 2013	68.6 ± 16.7	(149)	60.1 ± 18.8	(151)	14.2%	8.5 [4.48, 12.52]
#385 - Xu 2017	69.0 ± 15.0	(36)	52.0 ± 24.0	(34)	10.2%	17.0 [7.56, 26.44]
Pooled Estimate					I^2: 82%	13.95 [8.85, 19.06]

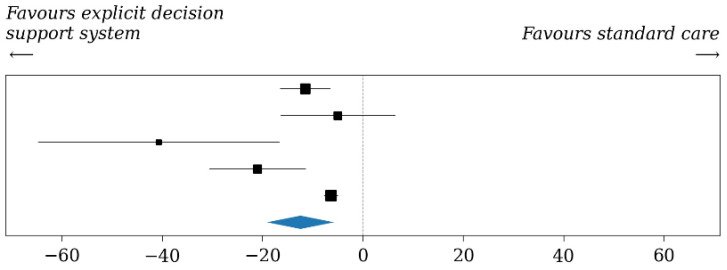
Inverse Variance, DerSimonian-Laird Random Effects — *p=0.00, z=5.36, τ^2=43.52* — *MD: Mean Difference, CI: Confidence Interval*



time above target glycemic range

Study	explicit decision support system	(N)	standard care	(N)	Weight	MD [95% CI]
#2152 - Blaha 2009	1.3 ± 7.6	(40)	12.8 ± 13.93	(40)	27.0%	-11.5 [-16.42, -6.58]
#1250 - Mann 2011	49.0 ± 17.8	(18)	54.0 ± 17.1	(18)	16.4%	-5.0 [-16.4, 6.4]
#1383 - Leelarathna 2013	37.9 ± 23.3	(12)	78.6 ± 35.4	(12)	6.2%	-40.7 [-64.68, -16.72]
#385 - Xu 2017	21.0 ± 14.0	(36)	42.0 ± 25.0	(34)	19.1%	-21.0 [-30.57, -11.43]
#1090 - Zeitoun 2021	7.16 ± 3.88	(50)	13.54 ± 3.0	(50)	31.3%	-6.38 [-7.74, -5.02]
Pooled Estimate					I^2: 80%	-12.46 [-19.11, -5.81]

Inverse Variance, DerSimonian-Laird Random Effects — *p=0.00, z=3.67, τ^2=36.40* — *MD: Mean Difference, CI: Confidence Interval*



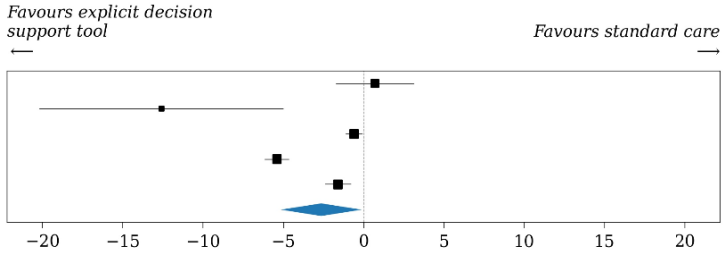
Hyperglycemia Index [HGI]

Study	explicit decision support tool	(N)	standard care	(N)	Weight	MD [95% CI]
Cordingly 2009 [#2374] - Cohort 1	5.6 ± 2.9	(10)	4.9 ± 2.6	(10)	20.0%	0.7 [-1.71, 3.11]
Cordingly 2009 [#2374] - Cohort 2	9.0 ± 5.4	(6)	21.6 ± 9.0	(8)	7.6%	-12.6 [-20.19, -5.01]
Pachler 2008 [#1053]	1.1 ± 0.8	(25)	1.7 ± 1.0	(25)	24.3%	-0.6 [-1.1, -0.1]
Dubois 2017 [#1914]	3.9 ± 4.1	(777)	9.3 ± 9.5	(773)	24.1%	-5.4 [-6.13, -4.67]
VanHerpe 2013 [#171]	2.7 ± 2.4	(149)	4.3 ± 4.4	(151)	24.0%	-1.6 [-2.4, -0.8]
Pooled Estimate					I^2: 97%	-2.65 [-5.17, -0.13]

Inverse Variance, DerSimonian-Laird Random Effects

p=0.04, z=2.06
τ^2=6.74

MD: Mean Difference
CI: Confidence Interval



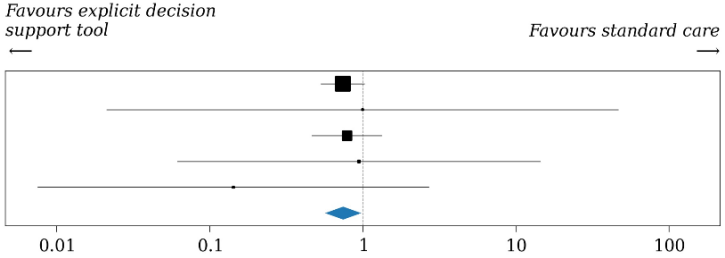
no. of patients with episodes of hypoglycemia [< 60 mg/dL or 3.3 mmol/L]

Study	explicit decision support tool	(%)	standard care	(%)	Weight	RR [95% CI]
Dubois 2017 [#1914]	58/777	(7%)	78/773	(10%)	70.5%	0.74 [0.53, 1.02]
Leelarathna 2013 [#1383]	0/12	(0%)	0/12	(0%)	0.5%	1.0 [0.02, 46.71]
VanHerpe 2013 [#171]	21/149	(14%)	27/151	(18%)	27.2%	0.79 [0.47, 1.33]
Xu 2017 [#385]	1/36	(3%)	1/34	(3%)	1.0%	0.94 [0.06, 14.51]
Zeitoun 2021 [#1090]	0/50	(0%)	3/50	(6%)	0.9%	0.14 [0.01, 2.7]
Pooled Estimate	80/1,024	(8%)	109/1,020	(11%)	I^2: 0%	0.74 [0.57, 0.98]

Mantel-Haenszel, DerSimonian-Laird Random Effects

p=0.03, z=2.12
τ^2=0.00

RR: Risk Ratio
CI: Confidence Interval



SDC 9-5C. Summary of Judgements. Explicit clinical decision support tool versus conventional care in *adults*

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

Supplemental Digital Content 10. Evidence Profiles & Evidence-to-Decision Framework for Critically Ill *Children*

Glycemic Control in Critically Ill Children

SDC 10-2. Intensive versus conventional glucose targets in critically ill *children*

Question. Should insulin therapy be titrated to achieve intensive glucose levels (INT) (glucose 4.4-7.7 mmol/L or 80-139 mg/dL) or conventional glucose levels (CONV) (7.8-11.1 mmol/L or 140-200 mg/dL) critically ill *children*?

SDC 10-2A. Evidence Profile. Intensive versus conventional glucose targets in critically ill *children*

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intensive glucose control	conventional glucose control	Relative (95% CI)	Absolute (95% CI)		
Mortality - Pediatric Medical/ Surgical												
2	randomised trials	not serious	serious[a]	not serious	serious[a]	none	49/398 (12.3%)	47/486 (9.7%)	**RR 0.88** (0.24 to 3.27)	**12 fewer per 1,000** (from 73 fewer to 220 more)	⊕⊕◯◯ Low	CRITICAL
ICU length of stay - Pediatric Medical/ Surgical												
2	randomised trials	not serious	not serious	not serious	not serious	none	273	259	-	MD **1.1 lower** (2.09 lower to 0.1 lower)	⊕⊕⊕⊕ High	CRITICAL
Any infection - Pediatric Medical/ Surgical												
2	randomised trials	not serious	serious[b]	not serious	serious[a]	none	16/398 (4.0%)	35/486 (7.2%)	**RR 1.02** (0.13 to 8.16)	**1 more per 1,000** (from 63 fewer to 516 more)	⊕⊕◯◯ Low	CRITICAL
Neurocognitive outcomes - Pediatric Medical/ Surgical												
2	randomised trials	not serious	not serious	not serious	not serious	none	The HALF-PINT trial (Agus et al., 2017; Biagas et al., 2020) reported greater improvement in the higher glucose target group on psychosocial health at one year follow-up, but no difference in other measures of psychosocial and behavior. The CHiP trial (Macrae et al., 2014) reported more favorable scores on a measure of emotional health and behavior in the higher glucose target group at follow-up.				⊕⊕⊕⊕ High	CRITICAL
Severe hypoglycemia - Pediatric Medical/ Surgical												
3	randomised trials	not serious	not serious	not serious	not serious	none	59/671 (8.8%)	27/745 (3.6%)	**RR 2.99** (1.91 to 4.67)	**72 more per 1,000** (from 33 more to 133 more)	⊕⊕⊕⊕ High	IMPORTANT

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

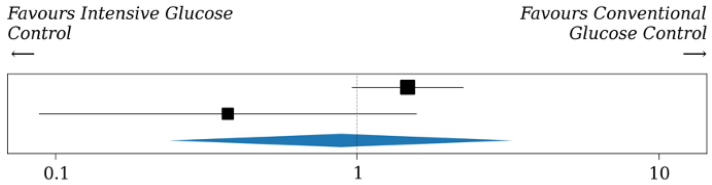
Explanations

a. Downgraded for imprecision due to wide confidence interval.
b. Rated down for inconsistency due to high heterogeneity across studies.

SDC 10-2B. Forest Plots. Intensive versus conventional glucose targets in critically ill *children*

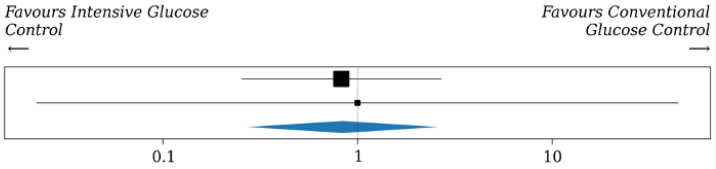
Mortality - Pediatric Medical/Surgical

Study	Intensive Glucose Control	(%)	Conventional Glucose Control	(%)	Weight	RR [95% CI]
HALF-PINT Agus 2017 #3757	47/349	(13%)	32/349	(9%)	62.9%	1.47 [0.96, 2.24]
Jeschke 2010 #4106	2/49	(4%)	15/137	(11%)	37.1%	0.37 [0.09, 1.57]
Pooled Estimate	49/398	(12%)	47/486	(10%)	I^2: 69%	0.88 [0.24, 3.27]
Mantel-Haenszel, DerSimonian-Laird Random Effects	*p=0.85, z=0.19 τ²=0.66*					*RR: Risk Ratio CI: Confidence Interval*



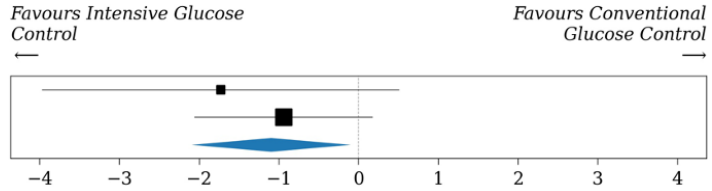
Mortality - Pediatric Cardiac Surgery

Study	Intensive Glucose Control	(%)	Conventional Glucose Control	(%)	Weight	RR [95% CI]
SPECS Agus 2012 #3763 - 30d mortality	5/488	(1%)	6/484	(1%)	91.2%	0.83 [0.25, 2.69]
Vlasselaers 2010 #160	0/7	(0%)	0/7	(0%)	8.8%	1.0 [0.02, 44.5]
Pooled Estimate	5/495	(1%)	6/491	(1%)	I^2: 0%	0.84 [0.27, 2.59]
Mantel-Haenszel, DerSimonian-Laird Random Effects	*p=0.76, z=0.30 τ²=0.00*					*RR: Risk Ratio CI: Confidence Interval*



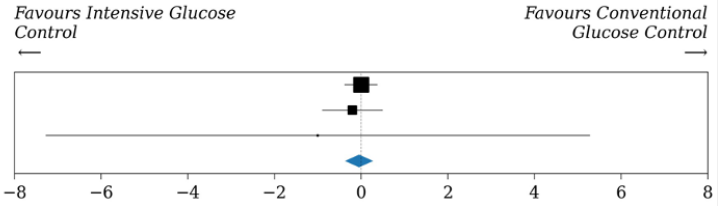
ICU length of stay - Pediatric Medical/Surgical

Study	Intensive Glucose Control	(N)	Conventional Glucose Control	(N)	Weight	MD [95% CI]
HALF-PINT Agus 2017 #3757	15.07 ± 17.27	(349)	16.8 ± 12.51	(349)	19.9%	-1.73 [-3.97, 0.51]
CHiP Macrae 2014 #2009/2011	7.74 ± 6.25	(273)	8.68 ± 6.83	(259)	80.1%	-0.94 [-2.05, 0.17]
Pooled Estimate					I^2: 0%	-1.1 [-2.09, -0.1]
Inverse Variance, DerSimonian-Laird Random Effects	*p=0.03, z=2.16 τ²=0.00*					*MD: Mean Difference CI: Confidence Interval*



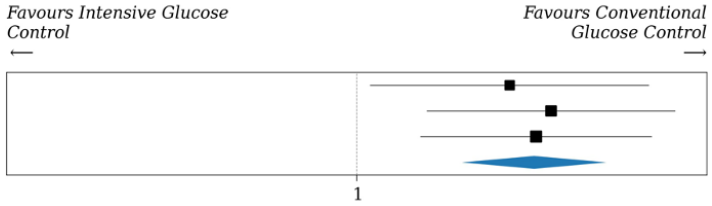
ICU length of stay - Pediatric Cardiac Surgery

Study	Intensive Glucose Control	(N)	Conventional Glucose Control	(N)	Weight	MD [95% CI]
SPECS Trial 2012 #3763	3.67 ± 2.97	(490)	3.67 ± 2.97	(490)	77.3%	0.0 [-0.37, 0.37]
CHiP Trial Macrae 2014 #2009/2011	5.69 ± 4.79	(421)	5.89 ± 5.37	(416)	22.5%	-0.2 [-0.89, 0.49]
Vlasselaers D 2010 #160	7.66 ± 5.51	(7)	8.66 ± 6.43	(7)	0.3%	-1.0 [-7.27, 5.27]
Pooled Estimate					I^2: 0%	-0.05 [-0.37, 0.28]
Inverse Variance, DerSimonian-Laird Random Effects	*p=0.78, z=0.29 τ²=0.00*					*MD: Mean Difference CI: Confidence Interval*



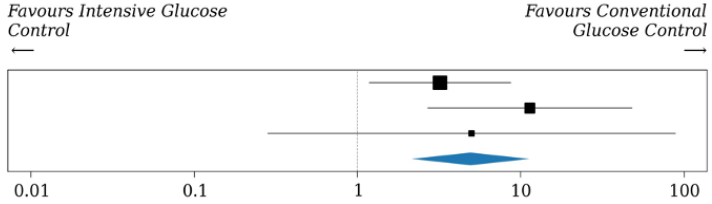
Severe hypoglycemia - Pediatric Medical/Surgical

Study	Intensive Glucose Control	(%)	Conventional Glucose Control	(%)	Weight	RR [95% CI]
HALF-PINT Agus 2017 #3757	18/349	(5%)	7/349	(2%)	26.9%	2.57 [1.09, 6.08]
CHiP Macrae 2014 #2009/2011	28/273	(10%)	8/259	(3%)	33.9%	3.32 [1.54, 7.15]
Jeschke 2010 #4106	13/49	(27%)	12/137	(9%)	39.2%	3.03 [1.48, 6.18]
Pooled Estimate	59/671	(9%)	27/745	(4%)	I^2: 0%	2.99 [1.91, 4.67]
Mantel-Haenszel, DerSimonian-Laird Random Effects	*p=0.00, z=4.81 τ^2=0.00*					*RR: Risk Ratio CI: Confidence Interval*



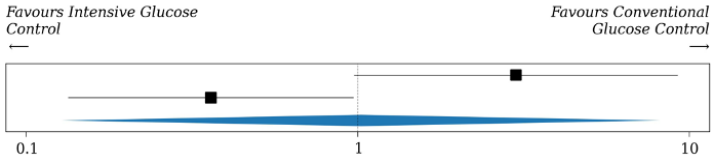
Severe hypoglycemia - Pediatric Cardiac Surgery

Study	Intensive Glucose Control	(%)	Conventional Glucose Control	(%)	Weight	RR [95% CI]
SPEC Trial 2012 #3763	16/490	(3%)	5/490	(1%)	60.7%	3.2 [1.18, 8.67]
CHiP Macrae 2014 #2009/2011	23/421	(5%)	2/416	(0%)	31.1%	11.36 [2.7, 47.89]
Vlasselaers 2010 #160	2/7	(29%)	0/7	(0%)	8.2%	5.0 [0.28, 88.53]
Pooled Estimate	41/918	(4%)	7/913	(1%)	I^2: 6%	4.93 [2.15, 11.3]
Mantel-Haenszel, DerSimonian-Laird Random Effects	*p=0.00, z=3.76 τ^2=0.04*					*RR: Risk Ratio CI: Confidence Interval*



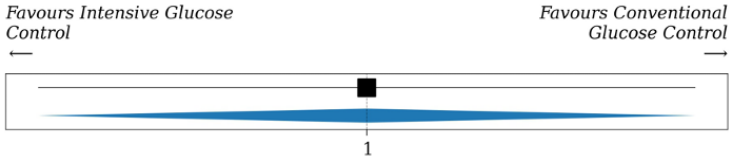
Any new infections - Pediatric Medical/ Surgical

Study	Intensive Glucose Control	(%)	Conventional Glucose Control	(%)	Weight	RR [95% CI]
HALF-PINT Agus 2017 #3757 [any new infection]	12/349	(3%)	4/349	(1%)	49.2%	3.0 [0.98, 9.21]
Jeschke 2010 #4106 [sepsis]	4/49	(8%)	31/137	(23%)	50.8%	0.36 [0.13, 0.97]
Pooled Estimate	16/398	(4%)	35/486	(7%)	I^2: 87%	1.02 [0.13, 8.16]
Mantel-Haenszel, DerSimonian-Laird Random Effects	*p=0.98, z=0.02 τ^2=1.95*					*RR: Risk Ratio CI: Confidence Interval*



Infection - Pediatric Cardiac Surgery

Study	Intensive Glucose Control	(%)	Conventional Glucose Control	(%)	Weight	RR [95% CI]
SPECS Trial 2012 #3763	24/490	(5%)	24/490	(5%)	100%	1.0 [0.58, 1.74]
Pooled Estimate	24/490	(5%)	24/490	(5%)	I^2: 0%	1.0 [0.58, 1.74]
Mantel-Haenszel, DerSimonian-Laird Random Effects	*p=1.00, z=0.00 τ^2=0.00*					*RR: Risk Ratio CI: Confidence Interval*



SDC 10-2C. Summary of Judgments. Intensive versus conventional glucose targets in critically ill *children*

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	**Favors the comparison**	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
●	○	○	○	○

SDC 10-5. Explicit clinical decision support tool versus conventional care in critically ill *children*

Question. In *pediatric* critically ill patients on insulin infusion therapy, should an explicit decision support tool be used compared to conventional care for the management of hyperglycemia?

SDC 10-5A. Evidence Profile. Explicit clinical decision support tool versus conventional care in critically ill *children*

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	an explicit decision support tool for management of glycemia	conventional care	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	observational studies	not serious	not serious	not serious	serious[a]	none	0/12 (0.0%)	9/42 (21.4%)	**RR 0.17** (0.01 to 2.79)	**178 fewer per 1,000** (from 212 fewer to 384 more)	⨁◯◯◯ Very low	CRITICAL
Severe hypoglycemia (number of patients)												
1	observational studies	not serious	not serious	serious[b]	not serious	none	3/12 (25.0%)	4/42 (9.5%)	**RR 2.62** (0.68 to 10.15)	**154 more per 1,000** (from 30 fewer to 871 more)	⨁◯◯◯ Very low	CRITICAL
Glucose variability index (GVI)												
1	observational studies	not serious	serious[b]	not serious	not serious	none	14.4	18.7	-	MD **4.3 lower** (9.37 lower to 0.77 higher)	⨁◯◯◯ Very low	IMPORTANT
Achievement of target glycemic range (assessed with: % of BG measures in range)												
1	observational studies	not serious	serious[b]	not serious	not serious	none	One retrospective observational study (Faraon-Pogaceanu et al., 2010) reported higher time in target glucose range in the e-Protocol group (41%) compared with the paper protocol group (33%).				⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Downgraded for imprecision due to wide confidence interval.
b. Downgraded for inconsistency due to high variability in target glycemic range.

SDC 10-5B. Summary of Judgments. Explicit clinical decision support tool versus conventional care in critically ill *children*

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○