

A systematic review and meta-analysis on targeting lower perioperative glucose levels to reduce surgical site infections.

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Author contributions

F.E.E. de Vries performed the literature search, data collection, data analysis and data interpretation and wrote the manuscript.

S.L. Gans was involved in the design of the study, performed the literature search and contributed to the writing of the manuscript.

B. Allegranzi is leading the the development of the Global Guidelines for prevention of surgical site infections commissioned by World Health Organisation (WHO) in Geneva and was involved in data interpretation and writing the manuscript.

J.S. Solomkin, E.P. Dellinger and M.A. Boermeester are members of the Guideline Development Group and were involved in the study design, data interpretation and writing the manuscript.

M. Egger is involved as a methodologist and GRADE expert for the development of the Global Guidelines for prevention of surgical site infections and was involved with data-analysis and reviewing the manuscript text.

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Abstract (248 words)

Background: There is a clear association between hyperglycaemia and surgical site infection (SSI). Nonetheless, there is concern that intensive glucose control risks hypoglycaemia, in turn resulting in potentially severe complications. Studies comparing intensive glucose control protocols with conventional protocols in relation to reduction of SSI and other outcomes including hypoglycaemia, mortality, and stroke were systematically reviewed.

Methods: Pubmed, Embase, CENTRAL, CINAHL, and WHO databases from 01-01-1990 to 01-08-2015 were searched. Inclusion criteria were randomized controlled trials (RCTs) comparing intensive glucose control protocols with conventional protocols, and reporting on the incidence of SSI. Meta-analyses were performed with a random effects model and meta-regression subsequently done. Targeted blood glucose levels, achieved blood glucose levels, and important adverse events were summarized.

Results: Fifteen RCTs were included. Summary estimate showed a significant benefit of an intensive protocol over a conventional protocol in reducing SSI, OR 0.43 (95% CI 0.29-0.64) $p < 0.001$. A significantly higher risk of hypoglycaemic events was found for the intensive group as compared to the conventional group (OR 5.55 (95% CI 2.58-11.96), without an increased risk of mortality or strokes (OR 0.74 (95% CI 0.45-1.23) and OR 1.37 (95% CI 0.26-7.20, respectively)). These results were consistent both in patients with and without diabetes and both in studies with moderate strict and very strict glucose control.

Conclusion: Targeting stricter and lower blood glucose levels (<150 mg/dL) using an intensive protocol in the perioperative period reduces SSI with an inherent risk of hypoglycaemic events but without a significant increase in serious adverse events.

Introduction

Surgical site infections (SSI) cause considerable morbidity, mortality, and increased health care costs worldwide.¹ An important factor resulting in an increased risk of SSI is hyperglycaemia (see Table 1 for definitions used). Multiple mechanisms contribute to hyperglycaemia seen with major surgery. The stress response to operative trauma results in a release of catabolic hormones and inhibition of insulin function. Surgical stress influences pancreatic β -cell function resulting in lower plasma insulin levels. Altogether, this relative hypo-insulinaemia, insulin resistance, and excessive catabolism from the action of counter regulatory hormones commonly lead to hyperglycaemia.²⁻⁴

Several observational studies showed an association between hyperglycaemia and SSI both in patients with and without diabetes, and in different procedures.⁵⁻⁸ The first large randomized controlled trial (RCT) addressing this topic⁹, showed a significant reduction in mortality in intensive care unit (ICU) patients when using tight glucose controls, but conflicting reports have been published since then. In recent years, several systematic reviews and meta-analysis¹⁰⁻¹³ addressing this subject have not all found a clear benefit of an intensive protocol over a conventional protocol using mortality as an endpoint. Moreover, the authors expressed concerns for the risk of hypoglycaemia and the resulting adverse effects.

Recently, additional trials assessing the effect of intensive glucose control have been reported. Present aim was to evaluate the impact of intensive (with stricter and lower blood glucose target levels) vs. conventional (with more liberal and higher blood glucose target levels) glucose control protocols on the risk of SSI, through a systematic literature review.

Present review also aimed to define optimal perioperative blood glucose target levels in diabetic and non-diabetic surgical patients to prevent SSI. Because of concerns regarding the risk of hypoglycaemia and the potential consequences of hypoglycaemic events, mortality, and strokes were included as outcomes in this systematic review and meta-analysis.

Methods

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed.¹⁴

Search strategy and selection criteria

PubMed, EMBASE (Ovid), the Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, and World Health Organization (WHO) global and regional databases were searched for articles published from January 1990 to August 2015 by use of the terms referring to SSI, glucose control, and surgical procedures. We have chosen not to include studies before 1990 as there have been continuous changes in other health care practices and older studies would confound conclusions. Language was restricted to English, Spanish, and French. The complete search is included in appendix A. Two authors (FdV and SG) independently screened all titles and abstracts. RCTs comparing a perioperative intensive glucose protocol (with stricter and lower blood glucose target levels) with a conventional glucose protocol (with more liberal and higher blood glucose target levels) in adult patients were included. The primary outcome was SSI (or wound infections). Secondary outcomes were hypoglycaemic events (both laboratory results or clinically relevant), stroke, and mortality. Studies comparing different protocols or a different route of administration with comparable blood glucose target levels were excluded. References of the included studies were screened for other relevant studies.

Data extraction

Study characteristics including year of publication, number of patients, types of surgical procedures, protocols for glucose control used, and outcomes were retrieved from the text

and summarized in the evidence table (Table 2). Protocols, target levels, and definitions of hypoglycaemia are summarized in Appendix B. Blood glucose target levels, achieved blood glucose levels, and adverse effects for both the intensive and the conventional group are summarized in appendix D. Glucose levels are presented throughout the text as mg/dL / mmol/L.

Quality assessment

Quality of the included studies was assessed with the Cochrane Collaboration's tool for assessing risk of bias.¹⁵ The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology (GRADE Pro software¹⁶) was used to assess the quality of the body of retrieved evidence.

Data synthesis and analysis

Meta-analyses were performed with Review Manager 5.3 with a random effect model.

Studies were divided in studies with an upper limit target level < 110 mg/dL (6.1 mmol/L) in the intensive group (very strict glucose control) and studies with an upper limit target level 110-150 mg/dL (6.1-8.3 mmol/L) (moderate strict glucose control) in the intensive group for meta-analyses. Meta-regression was performed with SPSS Statistics 22.0.

Results

Of the 1839 articles identified by the search, 27 articles were assessed for full review.

Another 12 articles were excluded for the following reasons: five studies did not report on SSI or wound infections as a separate outcome^{9,17-20}; two studies^{9,17} included medical, as well as surgical patients; five studies compared a different protocol or route of administration but with comparable blood glucose target levels²¹⁻²⁵; one study involved trauma patients but no surgical procedure²⁶; and one more study was not a randomized trial.²⁷ Finally, 15 RCTs were included for analysis. The flowchart of the search is depicted in Figure 1.

Study characteristics

Fifteen RCTs²⁸⁻⁴² compared an intensive protocol (targeting stricter/lower blood glucose target levels) with a conventional protocol (targeting more liberal/higher) blood glucose target levels. All studies in the intensive group used intravenous insulin administration whereas three studies in the conventional group employed subcutaneous administration.^{35,38,41} Some of the studies used continuous insulin administration whereas others used intermittent. One study used a fixed high dose with dextrose 20% separately (“insulin clamp”).²⁹ All protocols used are summarized in Appendix B.

An important variable was the duration of glucose control. Two studies^{28,29} compared only intraoperative glucose control. Eight studies^{30,33,35,36,38-40,42} investigated intraoperative and postoperative glucose control and there were five studies^{31,32,34,37,41} examining postoperative glucose control. The definition of ‘postoperative’ varied from 18 hours, “until enteral nutrition” to a maximum of 14 days. Five studies^{31,35,38,39,41} were in patients with

diabetes, eight studies^{28-30,33,34,36,37,40} both in patients with and without diabetes, and two studies^{32,42} in patients without diabetes. Nine studies^{28,29,33-36,38,39,42} were performed in patients undergoing cardiac surgery and four studies^{31,32,40,41} in patients undergoing abdominal surgery, one study³⁷ in critical ill surgical patients, and one other study³⁰ in patients undergoing emergency cerebral aneurysm clipping. Most of these studies were performed in an ICU setting.

None of the studies had SSI or wound infections as their primary outcome, but SSI rates were reported. Most studies had a combined outcome of post-operative complications. The definition of SSI/wound infection also differed between studies. Four studies^{28,34,36,42} only mentioned deep/organ space wound infections, one study²⁹ only reported superficial wound infections and the other studies either reported on both, or did not clearly describe their definitional criteria. The risk of bias in the included studies was serious as many variables were scored as unclear or even high. The risk of bias scoring is provided in Table 3. The evidence table with baseline characteristics and outcome is summarized in Table 2.

Intensive protocol versus conventional protocol

Fifteen RCTs compared an intensive protocol with a conventional protocol. The meta-analysis, which had 1442 patients in the intensive group and 1394 in the control group, showed a significant benefit of an intensive protocol over a conventional protocol in reducing surgical site infections, OR 0.43 (95% CI 0.29-0.64) $p < 0.001$ (Figure 2). Meta-analysis of eight studies^{28,29,31,32,36,40-42} with an upper limit target level < 110 mg/dL (6.1 mmol/L) in the intensive group showed a significant benefit of an intensive protocol pooled OR 0.50 (95% CI 0.35 – 0.73) and seven studies^{30,33-35,37-39} with an upper limit target level 110-150

mg/dL (6.1-8.3 mmol/L) showed similar effects with a pooled OR 0.27 (95% CI 0.09-0.78) (Figure 2). In meta-regression analyses, there was no evidence that the effect of intensive blood glucose control differed between studies including patients with or without diabetes (P=0.590). There was some evidence that the effect was smaller in studies that used intensive blood glucose control intra-operatively only (OR 0.88; 95% CI 0.45-1.74) compared to studies that used intensive blood glucose controls post-operatively or both intra- and post-operatively (OR 0.37; 95% CI 0.25-0.55, P=0.049 for difference between these ORs). This comparison was similar in studies with very strict and moderate strict glucose control (P=0.328).

Adverse events

Meta-analysis of adverse events showed a higher risk of hypoglycaemic events in intensive protocols vs conventional protocols (OR 5.55 (95% CI 2.58-11.96). These results were similar for studies with very strict (upper limit target level < 110 mg/dl) and moderate strict (upper limit target level 110-150 mg/dl) glucose control (OR 4.18 (95% CI 1.79-9.79) and OR 9.87 (95% CI 1.41-69.20), respectively). However, four^{29,35,38,40} of the 12 studies included in meta-analysis had no hypoglycaemic events and only five studies^{28,32,34,39,41} found significantly more asymptomatic hypoglycaemic events when using an intensive protocol while three other studies did not find a significant difference.^{31,36,42} For three studies the number of patients with a hypoglycaemic events were not reported and these studies were not included in meta-analysis. Meta-analyses of postoperative deaths^{28-34,36-39,41,42} and strokes^{28,29,36,38,39,41} showed no significant differences (OR 0.74 (95% 0.45-1.23) and OR 1.37 (95%; CI 0.26-7.20) respectively) between intensive vs. conventional protocols. These meta-analyses are included in appendix C. Meta-regression showed no evidence for a difference in

risk of adverse events between studies with very strict and those with moderate strict protocols of intensive glucose control. The risk was similar for hypoglycaemia (P=0.413), mortality (P=0.484), and stroke (P=0.511). All hypoglycaemic events are summarized in appendix D.

Achieved blood glucose level

Figure 3 shows targeted blood glucose levels, mean achieved blood glucose levels, and surgical site infections. In appendix D there is an overview of the different blood glucose target levels, achieved mean blood glucose level and adverse events. The achieved blood glucose levels in the intensive group were lower than the conventional group for all studies. Four studies did not report their mean achieved blood glucose level but reported on the percentage of measurements within the target level, on minimum/maximum blood glucose levels or mentioned the fact that achieved blood glucose levels were significantly different between both groups.

GRADE

Overall evidence was qualified using GRADE. Overall, low quality of evidence shows that an intensive protocol has significant benefit in reducing SSI when compared to a conventional protocol. The level of evidence was downgraded due to serious risk of bias and indirectness. The GRADE table is included in table 4.

Discussion

Present systematic review and meta-analysis demonstrates that intensive protocols with stricter and lower blood glucose target levels are associated with a reduction in the number of surgical site infections, with an increased risk of hypoglycaemic events but without increased risks of stroke or mortality. This systematic review also compares achieved target levels in terms of surgical site infections and adverse events.

Meta-regression analysis showed, that the benefit of an intensive protocol over a conventional protocol was consistent both in patients with and without diabetes and begun both intra- and postoperative. A benefit of an intensive protocol in reducing surgical site infections was found both in studies with very strict glucose control (upper limit glucose level < 110 mg/dL (6.1 mmol/L)) and studies with moderate strict glucose control (upper limit between 110 and 150 mg/dL (6.1-8.3 mmol/L)). Moreover, the risk of severe adverse events (hypoglycaemia, mortality and stroke) was comparable between studies with very strict or moderate strict glucose control in the intensive group.

Since several cohort studies, in patients with and without diabetes, have shown that hyperglycaemia is associated with poorer postoperative outcome, most guidelines⁴³⁻⁴⁶ implemented blood glucose target levels between 140-200 mg/dl (7.8-11.1 mmol/L).

Concern for the risk of hypoglycaemia has led to concerns for targeting lower levels. This is primarily based on results of the NICE-SUGAR¹⁷ study, which showed increased mortality in the intensive protocol group. Present analyses supports the notion that concerns driven by the results of the NICE-SUGAR trial (not including surgical patients) should not delay implementation of a more intensive protocol with stricter and lower blood glucose target levels. The NICE-SUGAR trial was performed in an ICU setting with critically ill patients who

are at higher risk for mortality, and 21.6% of the patients were already septic at the time of randomization. Secondly, blood glucose target levels in the intensive group of the NICE-SUGAR trial are along the lowest of studies performed on this topic (81-108 mg/dl / 4.5-6.0 mmol/L). Umpierrez et al.²⁴ showed in the RABBIT-2 trial, which studied a basal-bolus insulin protocol versus a sliding scale insulin protocol targeting blood glucose levels between 100-140 mg/dL / 5.6 - 7.8 mmol/L in a general surgical population with diabetes type 2, that a basal-bolus insulin protocol reduces postoperative complications including wound infection, pneumonia, bacteremia, and respiratory and acute renal failure (OR 3.39 (95% CI 1.50–7.65); $p = 0.003$). Their difference in wound infections was borderline significant ($p=0.050$). They found no difference in mortality and even a decrease in length of ICU stay. This study showed that targeting blood glucose levels between 100-140 mg/dL can be performed safely. Another observational study of Furnary et al.⁴⁷ on cardiac surgery patients revealed that targeting blood glucose levels < 150 mg/dL (8.3 mmol/L) reduced SSIs by 66% ($p<0.001$) and reduced mortality.

In 2009 Kao et al.¹¹ has performed a systematic review and meta-analysis investigating perioperative glycaemic control for the prevention of SSI. This study group has concluded that there was insufficient evidence to support intensive glucose control compared with conventional glucose control for the prevention of SSI. This conclusion is in conflict with the conclusion from the present systematic review, which can be explained by different inclusion criteria. The 2009 review has included studies with the same target levels in both groups and studies not reporting on SSI exclusively. Moreover, several new RCTs have been published since the 2009 review which are included in the present systematic review. Other systematic

reviews and meta-analyses^{10,12,13} on perioperative glucose control focused on specific patient groups or had different endpoints.

In present meta-analyses of adverse events, the study of Gandhi et al.³⁶ is the only study showing a significant higher number of strokes and deaths in the intensive group compared with the control group. When looking more in detail at the achieved blood glucose target levels in both groups it was found that achieved blood glucose levels were comparable after a 24-hour ICU stay (103 mg/dL / 5.7 mmol/L versus 104 mg/dL / 5.8 mmol/L, $p=0.720$) although they were significantly lower in the intensive protocol group during the operation and at baseline in the ICU ($p<0.001$). In addition, these achieved blood glucose levels are among the lowest in the included studies as we show in figure 3. This might clarify the relatively higher number of adverse events in this study. Other studies, including Ata et al.⁴⁸ and Jeon et al.⁴⁹, found a clear dose-response relation between blood glucose levels and surgical site infections in favour of lower blood glucose levels.

Five studies reported significantly more hypoglycaemic measurements in the intensive group as compared to the control group. Although these events were asymptomatic (none of the studies reported clinical consequences), it remains unknown to what extent these hypoglycaemic episodes harm patients on the long term. And, even more important, if this potential harm outweighs the reduced risk of SSI. A higher odds ratio was found for hypoglycaemic events for moderate strict glucose control (OR 9.87 (95% CI 1.41-69.20) compared to very strict glucose control (OR 4.18 (95% CI 1.79-9.79)). This is probably due to the fact that only two studies were included in the meta-analysis of moderate strict groups compared to six studies in the meta-analysis of very strict group. This uncertainty is also reflected in the very wide confidence interval in the former mentioned.

Summarizing the aforementioned and considering the risk of hypoglycaemia, the evidence points out that both targeting lower stricter and lower blood glucose levels with an intensive protocol can be performed safely without the risk of a significant increase of serious adverse events. Blood glucose target levels as low as used for the NICE-SUGAR trial or Leuven-trial (80-110 mg/dL / 4.5-6.0 mmol/L) should probably be avoided as the consequences of hypoglycaemic events remain unclear.

Several limitations should be addressed. Most of the studies used in this meta-analysis were performed in patients undergoing major cardiac or gastrointestinal surgery with a substantial part of the study population having a postoperative ICU stay. The question remains if present meta-analysis results can be extrapolated to a more general population, although observational studies outside the ICU in non-cardiac surgical patients show the same effect^{7,50,51,52,53} and the association of SSI and hyperglycaemia in a general surgical population is widely accepted. Moreover, the infrastructure to carry out safe intensive glucose control outside the ICU is a major concern as intensive glucose control demands skilled staff and brings higher workload and increased health care costs. However, intensive glucose control during the surgical procedure seems achievable in most settings. Probably results are primarily influenced by target or achieved blood glucose levels rather than differences in protocols or route of administration. Some studies²¹⁻²³ (excluded from present review) comparing subcutaneous with intravenous administration with comparable blood glucose target levels did not show any difference in SSI, while studies^{35,38, 41} (included in present review) comparing subcutaneous and intravenous administration did find a significant difference. Therefore, using subcutaneous insulin administration outside the operation room or ICU might also reduce the number of SSI.

There is substantial clinical heterogeneity between studies. Although all studies compared stricter and lower blood glucose target levels in the intensive group compared with more liberal and higher levels in the conventional group, there was a wide variety in protocols used, blood glucose target levels and achieved target levels. Moreover, in most studies there was a lack of information on baseline use of medication (for example antibiotics or anticoagulation) and intra-operative details such as blood loss. These factors might have influenced baseline risk of SSI and outcome.

Targeting stricter and lower blood glucose levels with an intensive perioperative glucose control protocol reduces surgical site infections without increased risks of mortality and stroke. Although the optimal target level cannot be derived from published data, the summary data of present systematic review and meta-analysis indicates that targeting glucose levels <150 mg/dL (<8.3 mmol/L) in the perioperative period can be performed safely with a minimal risk of asymptomatic hypoglycaemic events but without a significant increase in serious adverse events. Since studies with very strict and moderate strict glucose control are comparable effective in reducing SSI, and considering the risk of hypoglycaemia, targeting moderate strict glucose levels (110-150 mg/dL / 6.1-8.3 mmol/L) is preferred.

Figure legends

Figure 1. PRISMA flow chart of the systematic review

Figure 2. Meta-analysis target glucose levels vs. SSI

Figure 3. Target and achieved blood glucose levels and SSI

Declarations of interest

F.E.E. de Vries, S.L. Gans, J.S. Solomkin, B. Allegranzi and M. Egger declare no conflict of interest.

E.P. Dellinger reports personal fees from Merck, personal fees from Ortho-McNeil, personal fees from Targanta, personal fees from Schering-Plough, personal fees from Astellas, personal fees from Allergan, personal fees from Care Fusion, personal fees from Durata, personal fees from Pfizer, personal fees from Applied Medical, personal fees from Rib-X, personal fees from Affinium, personal fees from Tetrphase, personal fees from Televancin, personal fees from R-Pharm, personal fees from Cubist, personal fees from Melinta, personal fees from 3M, grants from Motif, outside the submitted work.

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Figure 1. PRISMA flow chart of the systematic review

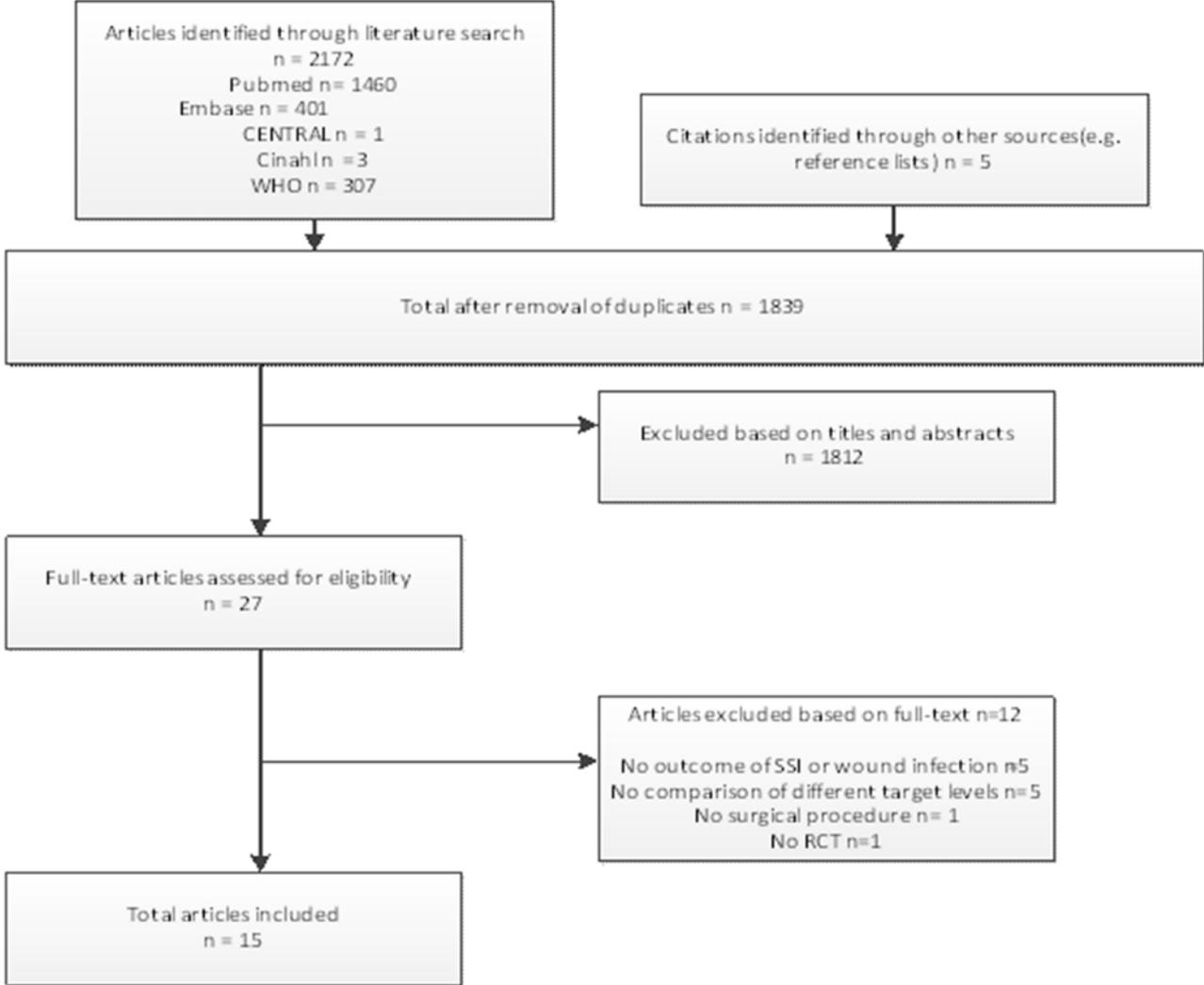


Figure 2. Meta-analysis target glucose levels vs. SSI

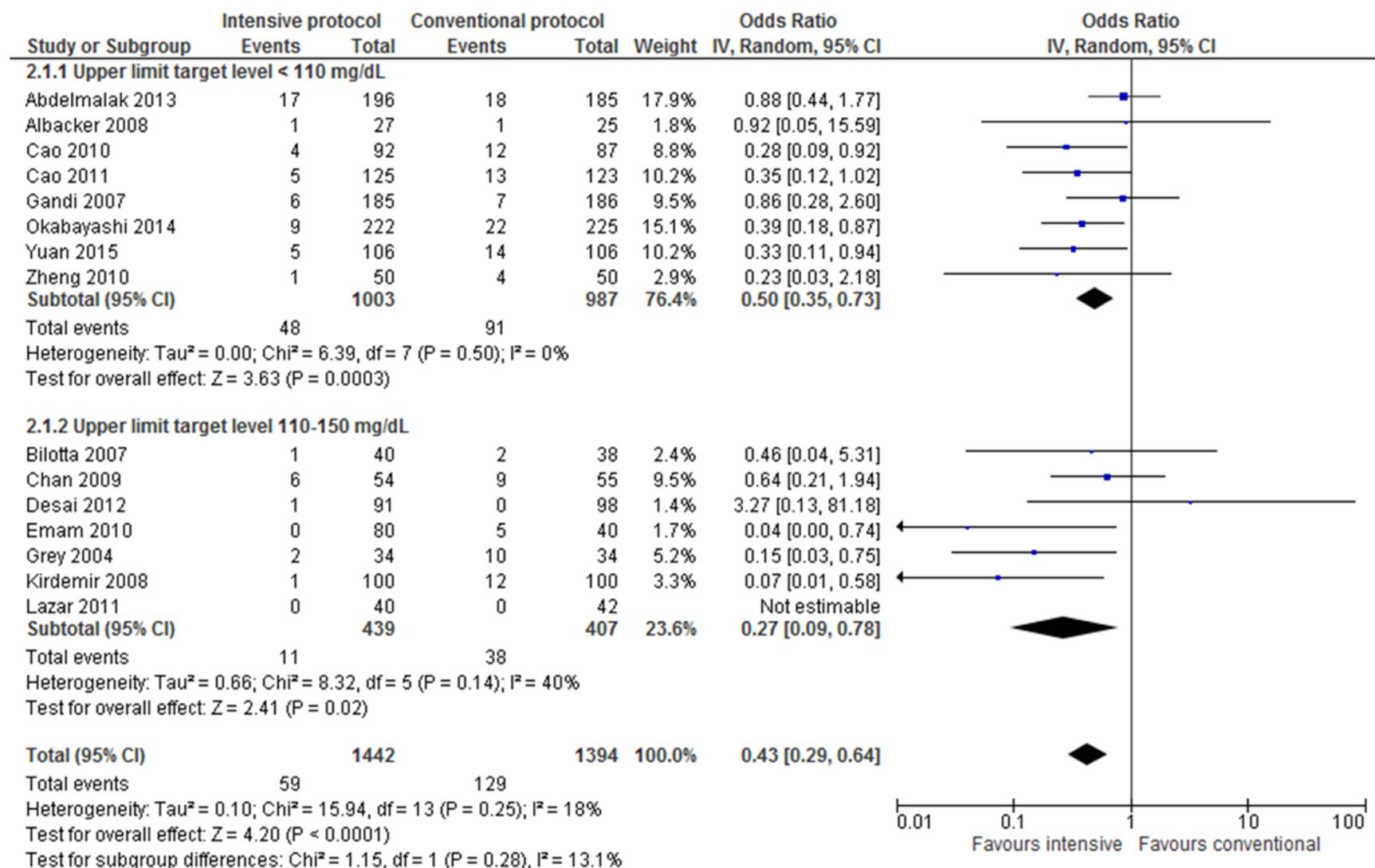


Figure 3. Target and achieved blood glucose levels and SSI

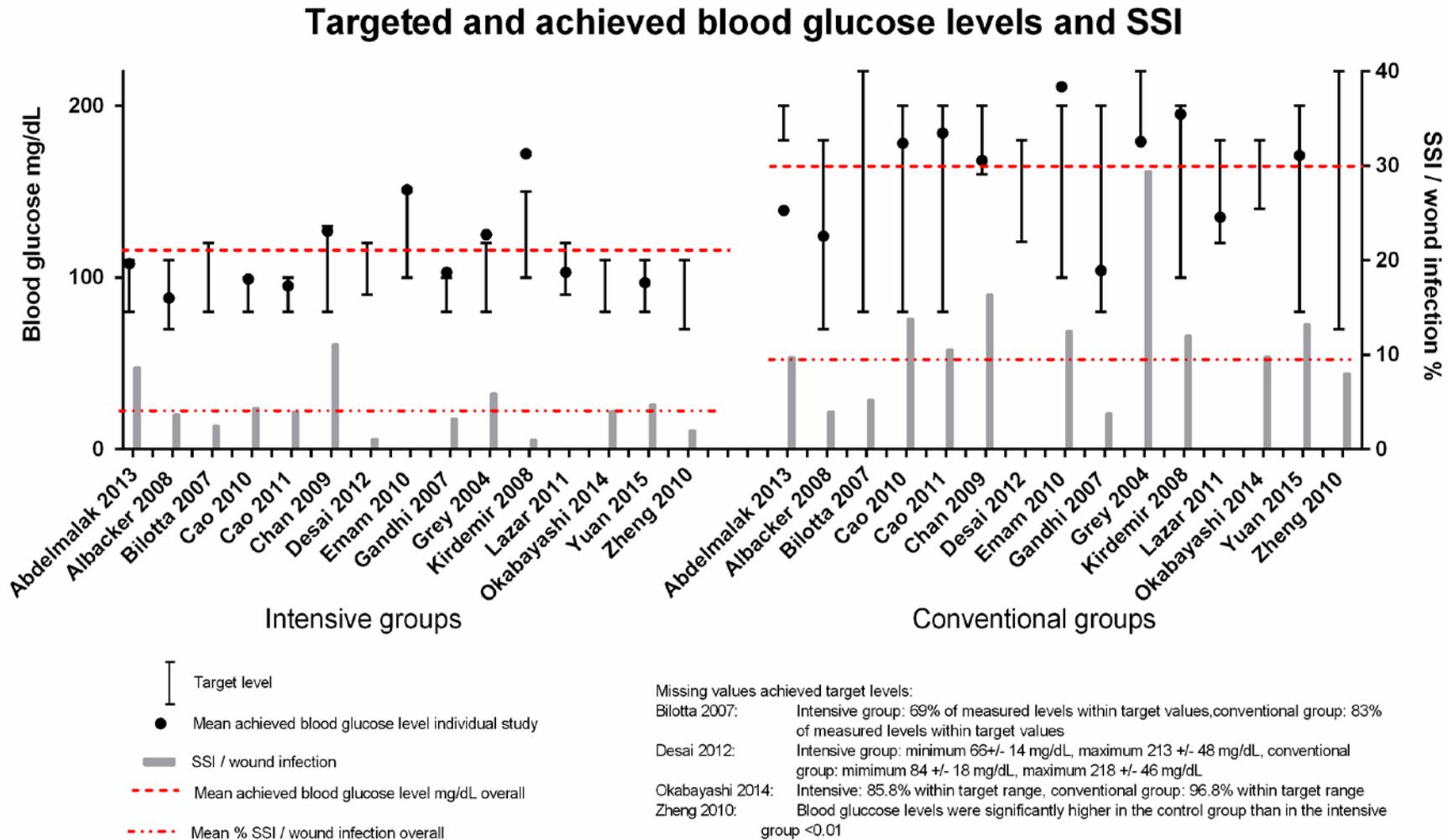


Table 1. Explanatory table of definitions used

Hyperglycaemia	High blood glucose, definitions varying from > 180 mg/dl / 10.0 mmol/L to > 220 mg/dl / 12.2 mmol/L
Hypoglycaemia	Low blood glucose, definitions varying from <40 mg/dl / 2.2 mmol/L to <80 mg/dl / 4.4 mmol/L
Intensive protocol	Stricter and lower blood glucose target levels, generally \leq 150 mg/dl / 8.3 mmol/L
Conventional protocol	More liberal and higher blood glucose target levels, generally \leq 220 mg/dl / 12.2 mmol/L

Table 2. Evidence table (blood glucose = mg/dL / mmol/L)

Study	Type of surgery	Population	SSI definition	Intervention	Control	Timing	Outcome (SSI/wound infections) (Hypoglycaemia)
Abdelmalak 2013 ²⁸	Major non-cardiac surgery, \geq 40 years, ASA \leq 4	Diabetic and non-diabetic patients	Deep and organ space surgical site infections	Intensive: dynamic intravenous infusion with blood glucose concentrations were targeted 80-110 / 4.4-6.1	Conventional group: dynamic intravenous infusion with blood glucose concentrations were targeted 180-200 / 10.0-11.1	Intra-operative + 2 hours post-operatively (is intraoperative in analysis)	Intensive group: 17/196, Conventional group 18/185 (OR 0.88, 95% CI 0.24 – 3.20, p=0.72) 29/196 of intensive group and 4/185 of conventional group had at least one episode of moderate hypoglycemia (<72.7 / 4.0). No episodes of severe hypoglycemia (< 40/ 2.2).
Albacker 2008 ²⁹	Cardiac surgery (CABG)	Diabetic and non-diabetic patients	Superficial wound infection	Intensive group: fixed high dose intravenous insulin infusion with dextrose 20% separately to maintain glucose level between 70 - 110 / 3.9-6.1 ("insulin clamp").	Conventional group: Intravenous insulin infusion (sliding scale method) to maintain blood glucose < 180 / 10.0	Intra-operative	Fixed high-dose insulin group 1/27 Conventional group 1/25 (p=0.99) No patients developed hypoglycemia

Bilotta 2007 ³⁰	Emergency cerebral aneurysma clipping	Diabetic and non-diabetic patients	Wound infections as defined by National Nosocomial Infection Surveillance System (NNIS).	Intensive group: continuous intravenous infusion maintain glucose levels 80 – 120 / 4.4-6.7	Conventional group: continuous intravenous insulin infusion to maintain glucose levels 80- 220/ 4.4-12.2	Intra- and postoperative (until discharge from ICU or day 14)	Intensive group 1/40 Conventional group 2/38 Hypoglycaemia (<80 / 4.4) occurred more in the strict group compared with the conventional group, RR 3.0 (95% CI 2.07 to 4.35)
Cao 2010 ³¹	Gastrectomy	Diabetic patients (type 2) receiving parenteral nutrition	Wound infection (SSI, CDC)	Intensive group: continuous intravenous insulin infusion target BG 80-100 / 4.4-6.7	Conventional group: continuous intravenous insulin infusion with target BG < 200 / 11.1	Post-operative until oral intake	Intensive group 4/92 Conventional group 12/87 Severe hypoglycemia (<40 / 2.2) 6/92 strict group and 1/87 conventional group
Cao 2011 ³²	Gastrectomy	Non-diabetic patients receiving parenteral nutrition	Wound infection (SSI, CDC)	Intensive group: continuous intravenous insulin infusion target BG 80-100 / 4.4-6.7	Conventional group: continuous intravenous insulin infusion with target BG < 200 / 11.1	Postoperative until oral intake	Intensive group 5/125 Conventional group 13/123 Severe hypoglycemia (<40 / 2.2) occurred in 8/125 in strict group and 1/123 conventional group.
Chan 2009 ³³	Cardiac surgery	Patients with and without diabetes	Wound infection (no specific definition)	Intensive group: targeted glucose level 80-130 / 4.4 - 7.2 , continuous intravenous insulin infusion was initiated when glucose levels exceeded 130 / 7.2	Conventional: targeted glucose level 160-200 / 8.9-11.1 , continuous intravenous insulin infusion was initiated only if blood glucose levels exceeded 200/ 11.1	Intra-operative and 36-hours after surgery	Intensive group 6/54 Control group 9/55 (p = 0.09, 95% CI 0.3-1.2) Hypoglycemia (<50 / 2.8) was not significantly different in both groups p=0.67
Desai 2012 ³⁴	Cardiac surgery	Patients with and without diabetes	Deep sternal wound infection	Intensive group: target blood glucose level 90-120 / 5.0-6.7	Conventional group: target blood glucose level 121-180 / 6.7 – 10.0	Post-operative for a minimum 72 hours	Intensive: 1/91 Conventional: 0/98 (treatment difference -0.01 95% CI -0.03 to 0.01) Hypoglycemia (<60 / 3.3): I 30/91, C 11/98

Emam 2010 ³⁵	Cardiac surgery	All type 2 diabetic patients	Wound infection (superficial, deep)	Intensive group: intravenous insulin infusion (Braithwaite protocol) on the evening before surgery or sooner if BG $\geq 150 / 8.3$ Target level of BG was 100-150 / 5.6-8.3 .	Conventional group: Subcutaneous insulin per sliding scale. Target BG < 200 / 11.1 .	Intra-operative and 48 hours post-operatively	Intensive group 0/80 Conventional group: 5/40 No patient in either group suffered a hypoglycaemic episode, either clinically or biochemically (less than 50 / 2.8 .
Gandhi 2007 ³⁶	Cardiac surgery	Diabetic and non-diabetic patients	Deep sternal infections (definition of Society of Thoracic Surgeons)	Intensive group: continuous insulin infusion to maintain intraoperative glucose levels between 80-100 / 4.4 – 5.6	Conventional group: Not given insulin during surgery unless glucose levels were greater than >200 / 11.1 , then intravenous insulin infusion	Intra- and postoperative (not specified)	Intensive group 6/185. Conventional group 7/186. (RR 0.9 (95% CI 0.3-2.5, p = 0.79)). No significant difference when stratified by diabetic status. One patient in every group experienced intra-operative hypoglycemia (< 60 / 3.3) RR 1.01 (95% CI 0.06-15.95), 8 in strict group and 14 conventional group had hypoglycemic episode during first 24 hours in ICU.
Grey 2004 ³⁷	Critical ill surgical patients	RCT, all hyperglycemic ($\geq 140 / 7.8$) adult surgical ICU patients with and without diabetes	SSI	Intensive group: intravenous infusion to maintain blood glucose between 80-120 / 4.4-6.7	Conventional group: intravenous infusion to maintain blood glucose between 180 – 220/ 10.0-12.2	Postoperative throughout their ICU stay	Intensive group 2/34 Conventional group 10/34. Hypoglycemic events (<60 / 3.3) occurred in 32% of the patients in strict protocol and 7.4% of the patients in conventional protocol (p<0.001)
Kirdemir 2008 ³⁸	Cardiac surgery	All diabetic patients	Sternal wound infection	Intensive group: continuous insulin infusion, target glucose 100-150 / 5.6-8.3	Conventional group: subcutaneous insulin, target glucose level <200 / 11.1 (sliding scale)	Intra-operative and until third post-operative day	Intensive group: 1/100 Conventional group: 12/100, p=0.003 No hypoglycemic episodes
Lazar 2011 ³⁹	Cardiac surgery	All diabetic patients	Sternal infection (any infection reaching or directly involving the sternum)	Intensive group: continuous intravenous infusion with blood glucose target level 90-120/ 5.0-6.7	Conventional group: continuous intravenous infusion with blood glucose target level 120-180/ 6.7-10.0	Intra- and 18h postoperative	Intensive 0/40 Conventional 0/42 Hypoglycemic episodes (< 80/ 4.4) intensive 30/40, conventional 4/42

Okabayashi 2014 ⁴⁰	Hepato-biliary-pancreatic surgery	Diabetic and non-diabetic patients	Surgical site infection	Intensive group: intravenous insulin infusion with blood glucose target level 80-110 / 4.4-6.1	Conventional group: intravenous insulin infusion with blood glucose target level 140-180 / 7.8-10.0	Intra-and postoperative	Intensive group 9/222 Conventional group 22/225 (p=0.028) No hypoglycemic (<80 / 4.4) events
Yuan 2015 ⁴¹	Gastrectomy	All diabetic (type 2) patients	Surgical site infection	Intensive group: continuous insulin infusion with target glucose 80-110 / 4.4-6.1	Conventional group: subcutaneous bolus insulin with target glucose target < 200 / 11.1	Post-operative	Intensive 5/106 Conventional 14/106 (p<0.03) Severe hypoglycemia (<40 /2.2): intensive group 8/106 , conventional 1/106, p=0.035
Zheng 2010 ⁴²	Cardiac surgery (valve replacement)	Non-diabetic patients	Nosocomial infections of deep sternal wounds	Intensive group: Continuous intravenous infusion to maintain BG 70-110 / 3.9-6.1 (Portland protocol)	N/S ("standard care", no control for blood glucose)	Intra- and postoperative	Intensive group: 1/50 Conventional group: 4/50 (NS) Hypoglycemic events: intensive group 3/50, conventional group 1/50 (NS)

Table 3. Risk of bias

RCT, Author, year	Sequence generation	Allocation concealment	Participants blinded	Care providers blinded	Outcome assessors blinded	Incomplete outcome data	Selective outcome reporting
Abdelmalak 2013	LOW	LOW	LOW	HIGH	LOW	UNCLEAR	LOW
Albacker 2008	LOW	LOW	HIGH	HIGH	HIGH	UNCLEAR	HIGH
Bilotta 2007	LOW	LOW	LOW	UNCLEAR	LOW	UNCLEAR	UNCLEAR
Cao 2010	UNCLEAR	LOW	HIGH	LOW	LOW	LOW	LOW
Cao 2011	LOW	LOW	UNCLEAR	UNCLEAR	UNCLEAR	HIGH	HIGH
Chan 2008	LOW	UNCLEAR	LOW	LOW	LOW	LOW	LOW
Desai 2012	UNCLEAR	UNCLEAR	LOW	HIGH	LOW	UNCLEAR	UNCLEAR
Emam 2010	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	HIGH	UNCLEAR	UNCLEAR
Gandi 2007	LOW	LOW	LOW	LOW	LOW	UNCLEAR	UNCLEAR
Grey 2004	LOW	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW
Kirdemir 2008	LOW	UNCLEAR	UNCLEAR	UNCLEAR	HIGH	UNCLEAR	LOW
Lazar 2011	LOW	LOW	UNCLEAR	HIGH	HIGH	LOW	LOW
Okabayashi 2014	LOW	LOW	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW
Yuan 2015	LOW	UNCLEAR	HIGH	LOW	HIGH	UNCLEAR	UNCLEAR
Zheng 2010	LOW	UNCLEAR	UNCLEAR	UNCLEAR	HIGH	UNCLEAR	UNCLEAR

Table 4. GRADE table

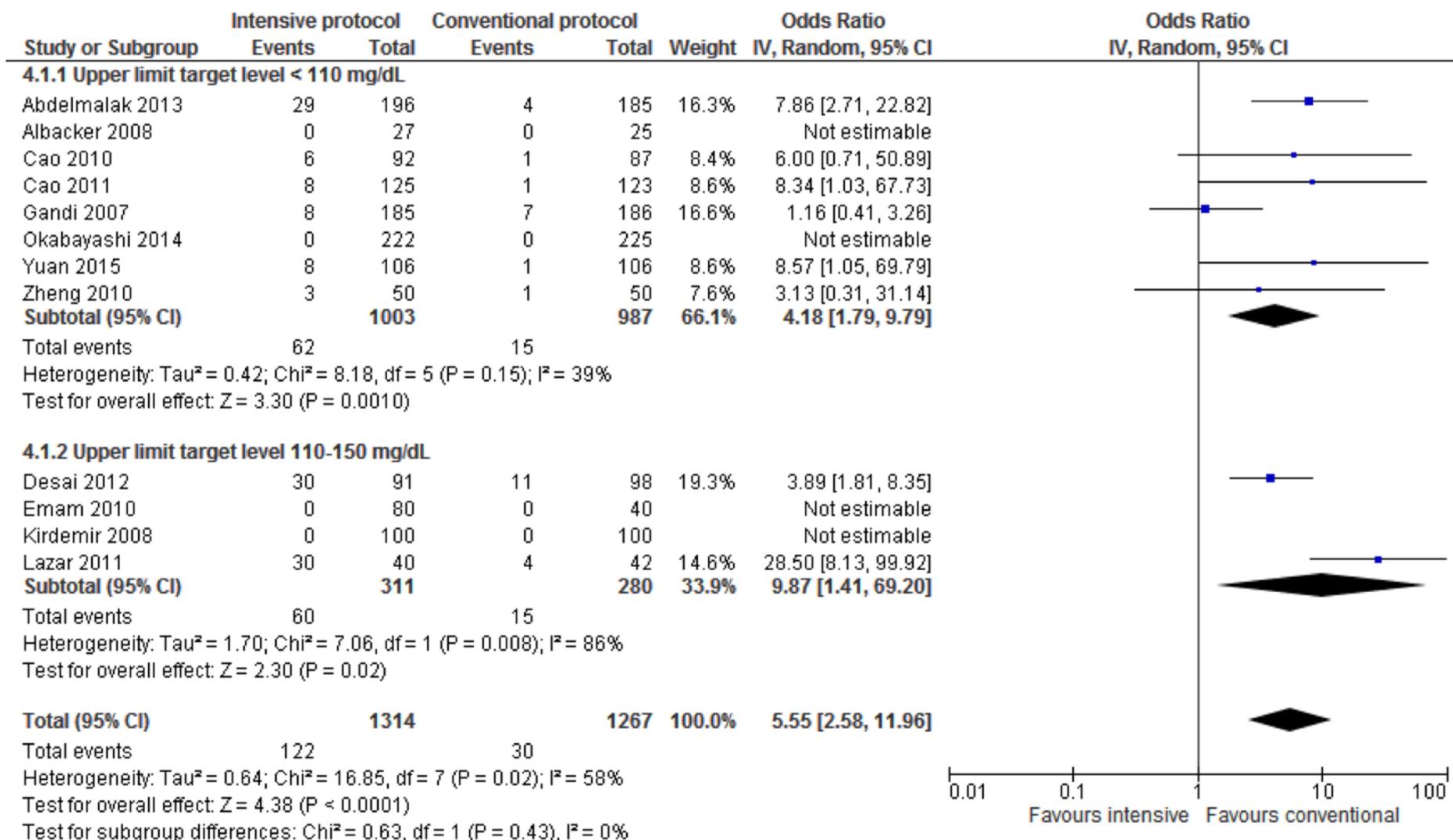
An intensive protocol with strict blood glucose target levels vs. a conventional protocol for perioperative glucose control to prevent surgical site infection											
Quality assessment							Summary of findings				
N_o of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With a conventional protocol	With an intensive protocol with strict blood glucose target levels		Risk with a conventional protocol	Risk difference with an intensive protocol with strict blood glucose target levels
Surgical site infections											
2836 (15 RCTs)	serious ¹	not serious	serious ²	not serious	none	⊕⊕○○ LOW ^{1 2}	129/1394 (9.3%)	59/1442 (4.1%)	OR 0.43 (0.29–0.64)	Study population	
										93 per 1000	51 fewer per 1000 (64 fewer to 31 fewer)
										Moderate	
									0 per 1000	0 fewer per 1000 (0 fewer to 0 fewer)	

1. Overall, there was a great deal of unclear to high risk in blinding (especially outcome assessors), allocation concealment and incomplete outcome data

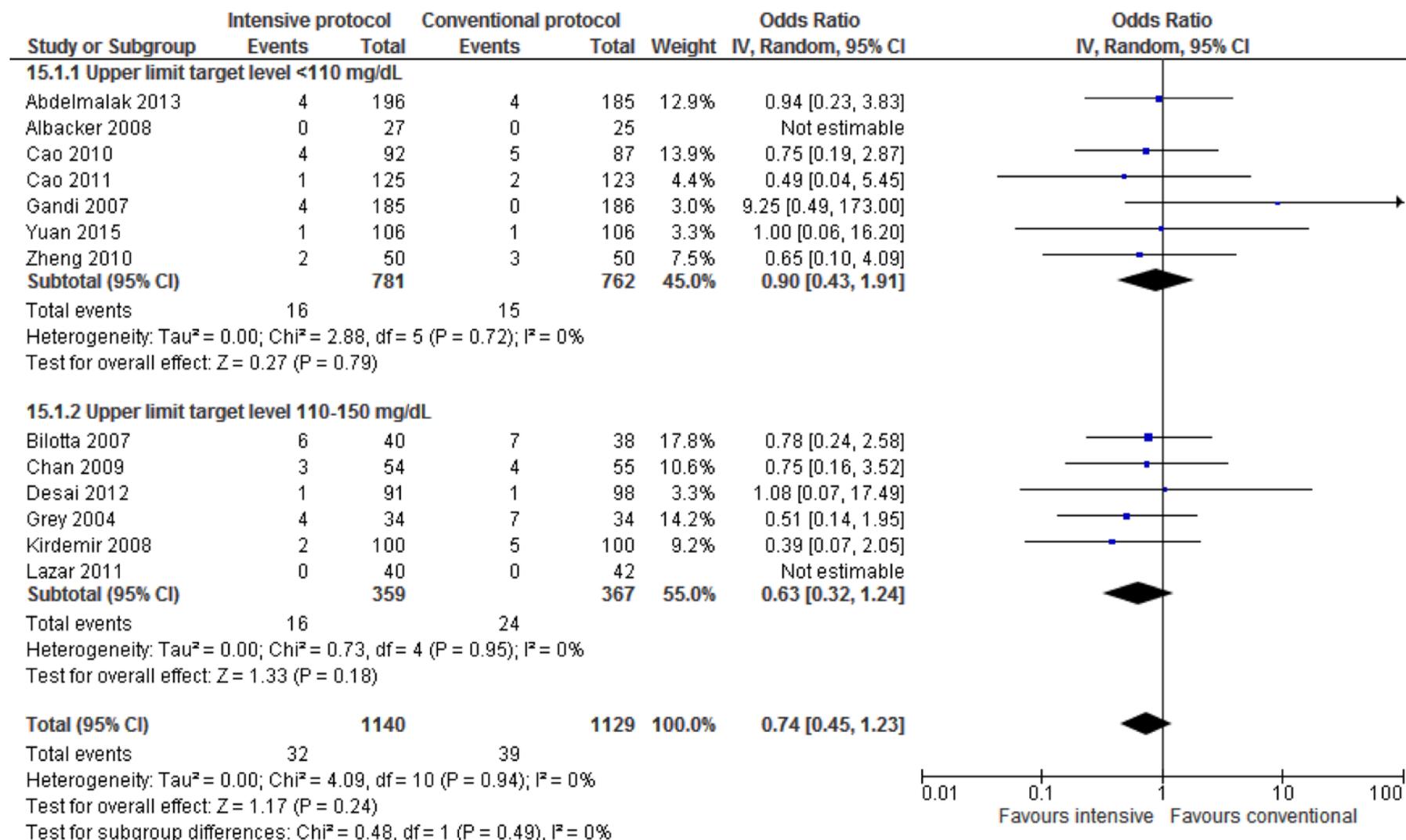
2. Most included studies investigated an intensive care population, which was mainly a cardiac population

CI: confidence interval; OR: odds ratio; RCT: randomized controlled trial

Appendix C1. Hypoglaecemic Events



Appendix C2. Postoperative deaths



Appendix C3. Postoperative strokes

