10.4.a. Optimal glucose control: Insulin therapy May 2015

2015 Recommendation: *Based on 26 level 2 studies, we recommend that hyperglycemia (blood sugars > 10 mmol/L) be avoided in all critically ill patients and we recommend a blood glucose target of around 8.0 mmol/L (or 7-9 mmol/L), rather than a more stringent target range (4.4 to 6.1 mmol/L) or a more liberal target range (10 to 11.1 mmol/L). There are insufficient data to recommend the administration of insulin via subcutaneous over IV.*

2015 Discussion: There were no new trials of intensive insulin therapy. However, the committee noted one new small study that compared subcutaneous insulin to intravenous administration of insulin as a more feasible way of achieving a target blood sugar range of 4.4- 6.1 mmol/L in non diabetic trauma patients (Aron 2013). SC administration of insulin was associated with a significantly lower incidence of hypoglycemia compared to IV insulin ($p<0.002$) but there were no differences with respect to ICU or hospital LOS, ventilation, mortality or infectious complications. The committee questioned the range of the target glucose levels as being lower than established guidelines and noted the gross underfeeding in both groups (4.5 ± 7.1 to 7.8 ± 7.9 kcals/kg/day) which limits the generalizability of the results to other ICUs. Despite the favourable cost and feasible considerations, the committee agreed that based on this study, a recommendation to support the administration of SC insulin over IV insulin could not be made. The discussions pertaining to intensive insulin therapy remain the same as 2013.

2013 Recommendation: *Based on 26 level 2 studies, we recommend that hyperglycemia (blood sugars > 10 mmol/L) be avoided in all critically ill patients and we recommend a blood glucose target of around 8.0 mmol/L (or 7-9 mmol/L), rather than a more stringent target range (4.4 to 6.1 mmol/L) or a more liberal target range (10 to 11.1 mmol/L).*

2013 Discussion The committee noted that with addition of 4 trials (Yu 2005, Savioli 2009, Annane 2009 and Arabi 2011) since the meta-analysis by Griesdale et al[1] and the removal of studies not felt to be in critically ill patients (stroke ICU, Bruno 2008), there was no changes in the treatment effect for mortality infections and the rating of the other values remained the same. Given the persistent signal that intensive insulin therapy is associated with a significant increase in the incidence of hypoglycemia, the committee agreed to recommend a range that avoided both high and low blood sugars.

2009 Recommendation: *We recommend that hyperglycemia (blood sugars > 10 mmol/L) be avoided in all critically ill patients. Based on the NICE-SUGAR study and a recent meta-analysis, we recommend a blood glucose target of around 8.0 mmol/L (or 7-9 mmol/L), rather than a more stringent target range (4.4 to 6.1 mmol/L) or a more liberal target range (10 to 11.1 mmol/L).*

2009 Discussion: The committee noted the results of the recently published meta-analysis [1] and the results of the largest multicentre trial, the NICE-SUGAR study[2]. Whilst the meta-analysis noted a possible treatment benefit with tight glycemic control in surgical patients, this was not supported

by the subgroup analysis in the NICE-SUGAR study which showed a significant increase in mortality in surgical patients. Furthermore, the NICE-SUGAR trial is more likely to be generalizable to Canada or other settings that use a predominantly enteral-based feeding approach. It was also noted that the positive signal in surgical patients in the CMAJ meta-analysis was primarily driven by two studies, the reproducibility of these results was considered questionable given the nature of the accompanying nutritional strategy used in one study[3] and the single centre nature of the other study[4]. Given this the committee reversed its prior recommendation and agreed that tight glycemic control (4.4 to 6.1 mmol/L) is no longer recommended for surgical patients. Instead the committee recommended that the target range be the resultant blood glucose range in the NICE SUGAR study i.e. 8.0 mmol/L (7.0-9.0 mmol/L). This range avoids hyperglycemia, while minimizing the risk of both iatrogenic hypoglycemia and other harms associated with a lower blood glucose target. The committee noted that insulin protocols (either paper or computerized) were used to achieve glycemic control in the reviewed studies but did not make a recommendation as to how best to achieve good glycemic control.

(1) Griesdale DE, de Souza RJ, van Dam RM, Heyland DK, Cook DJ, Malhotra A, Dhaliwal R, Henderson WR, Chittock DR, Finfer S, Talmor D. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ. 2009 Apr 14;180(8):821-7

(2) Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hébert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ for the NICE-SUGAR Study Investigators,. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009 Mar 26;360(13):1283-97

(3) Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in the critically ill patients. N Engl J Med. 2001 Nov 8;345(19):1359-67

(4) He W, Zhang TY, Zhou H, Li T, Zhao JY, Zhao D, Liu XH, Hou J, Wang C, Xu Y. [Impact of intensive insulin therapy on surgical critically ill patients] [Article in Chinese] Chinese Journal of Surgery [Zhonghua Wai Ke Za Zhi. 2007 Aug 1;45(15):1052-4.

Semi Quantitative Scoring

Value	Definition	2013 Score (0,1,2,3)	2015 Score (0.1,2.3) for SC vs IV insulin
Effect size	Magnitude of the absolute risk reduction attributable to the intervention listed--a higher score indicates a larger effect size	0 (mortality) 1 (infection)	0 (mortality) 0 (infection)
Confidence interval	95% confidence interval around the point estimate of the absolute risk reduction, or the pooled estimate (if more than one trial)--a higher score indicates a smaller confidence interval	1	0
Validity	Refers to internal validity of the study (or studies) as measured by the presence of concealed randomization, blinded outcome adjudication, an intention to treat analysis, and an explicit definition of VAP--a higher score indicates presence of more of these features in the trials appraised	2	3
Homogeneity or Reproducibility	Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	1	0
Adequacy of control group	Extent to which the control group represented standard of care (large dissimilarities = 1, minor dissimilarities=2, usual care=3)	2	3
Biological plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies =1, minimal inconsistencies =2, very consistent =3)	2	2
Generalizability	Likelihood of trial findings being replicated in other settings (low likelihood i.e. single centre =1, moderate likelihood i.e. multicentre with limited patient population or practice setting =2, high likelihood i.e. multicentre, heterogenous patients, diverse practice settings =3.	3	1
Low cost	Estimated cost of implementing the intervention listed--a higher score indicates a lower cost to implement the intervention in an average ICU	3	3
Feasible	Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	2	3
Safe	Estimated probability of avoiding any significant harm that may be associated with the intervention listed--a higher score indicates a lower probability of harm	1	2

10.4.a. Optimal glucose control: Insulin therapy

Question: Does tight blood sugar control result in better outcomes in the critically ill adult patient?

Summary of evidence: There was a recent meta-analysis of 26 randomized controlled trials (Greisdale 2009) that was reviewed. Subsequent to the publication of the meta-analysis, the data from two of the included trials (Bilotta 2007 and 2008) were replaced by the data from a more recent trial (Bilotta 2009) and 3 new studies were reviewed (Savioli 2009, Annane 2010, Arabi 2011). All 26 trials included were level 2 studies. Of the 26 trials, four of these were in surgical patients (Van den Berghe 2001, Grey 2004, He 2007 and Bilotta 2009), 14 were in mixed ICUs, and 10 were in medical patients. The target ranges of blood sugars in the intervention group varied from 4.0–6.0 to 4.4-8.3 mmol/L. In the Annane 2010 study, all patients were on steroids (compared to only 50% this population receives steriods), hence a sensitivity analysis was done without this study. One study compared intensive insulin therapy plus a carbohydrate restricted to maintain diet blood sugars < 10 mmol/L plus to intensive insulin therapy to maintain blood sugars < 8 mmol/L (de Azevedo 2010) and this study is summarized in the section 10.4 b Optimal glucose control: Carbohydrate restricted formula plus insulin therapy. A recent study (Aron 2013) compared intensive IV insulin therapy vs intensive subcutaneous insulin therapy and because both groups aimed at achieving tight glucose control of 4.4-6.1 mmol/L, the data from the study was not combined with other studies.

Mortality: When the data from the studies were aggregated, intensive insulin therapy was associated with a trend towards a reduction in overall mortality (RR 0.91, 95% CI 0.82, 1.02, p=0.10, heterogeneity I^2=41%; figure 1a). When a sensitivity analysis was done excluding the Annane 2010 study, this trend towards a reduction in overall mortality remained. (RR 0.90, 95% CI 0.80, 1.01, p=0.06, heterogeneity I^2=41%; figure 1b). The Bilotta 2009 study was not included in the analyses since it only reported mortality at 6-months.

Infections: Only 6 studies reported the total number of infections per group and when the data from these studies were aggregated, intensive insulin therapy had no effect on the number of infections (RR 0.89, 95% CI 0.73, 1.09, p=0.26, heterogeneity I^2=55%; figure 2a); the result was the same when the Van den Berghe 2001 study that provided high IV glucose was excluded from the analysis (RR 0.96, 95% CI 0.84, 1.10, p=0.59, heterogeneity I^2=9%; figure 2b).

Length of stay: When the data from the 7 studies that reported ICU length of stay as a mean ± standard deviation were aggregated, intensive insulin therapy was associated with a significant reduction in ICU length of stay (WMD -1.78, 95% CI -2.47, -1.09, p<0.00001, heterogeneity I^2=0%; figure 3a); the result was the same when both Van den Berghe studies were excluded from the analysis (WMD -1.46, 95% CI -2.73, -0.19, p=0.02, heterogeneity I^2=18%; figure 3b). When the data from the 4 studies that reported hospital length of stay as a mean ± standard deviation were aggregated, intensive insulin therapy had no effect on hospital length of stay (WMD -1.07, 95% CI -3.68, 1.54, p=0.42, heterogeneity I^2=0%; figure 4a); the result remained the same when the two Van den Berghe studies were excluded from the analysis (WMD -1.71, 95% CI -13.85, 10.43, p=0.78, heterogeneity I^2=0%; figure 4b).

Duration of ventilation When the data from the 6 studies that reported duration of ventilation as a mean ± standard deviation were aggregated, intensive insulin therapy was associated with a significant reduction in the number of ventilation days (WMD -1.41, 95% CI -2.58, -0.23, p=0.02, heterogeneity I^2=79%; figure 5a); however when the two Van den Berghe studies were excluded from the analysis, intensive insulin therapy was associated with a trend towards a reduction in the number of ventilation days (WMD -0.99, 95% CI -2.36, 0.39, p=0.16, heterogeneity I^2=63%; figure 5b).

Hypoglycemia: When the data from the 18 studies that reported hypoglycemic events were aggregated, intensive insulin therapy was associated with a significant increase in incidence of hypoglycemia (RR 3.19, 95% CI 1.81, 5.60, p<0.0001, severe heterogeneity, I^2=94%; figure 6a); the result was the same when the Van den Berghe 2001 study was excluded from the analysis (RR 3.03, 95% CI 1.71, 5.40, p=0.0002, severe heterogeneity, I^2=94%; figure 6b).

Conclusions:

1) Intensive insulin therapy is associated with a trend towards a reduction in overall mortality.
2) Intensive insulin therapy has no effect on infections.
3) Intensive insulin therapy may be associated with a significant reduction in ICU length of stay and duration of ventilation.
4) Intensive insulin therapy has no effect on hospital length of stay.
5) Intensive insulin therapy is associated with a significant increase in hypoglycemia.

Table 1. Randomized studies evaluating intensive insulin therapy in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)		Infections # (%)‡	
1) Van Den Berghe 2001	ICU ventilated (mainly surgical) N=1548	C.Random: yes ITT: yes Blinding: no (11)	Intensive insulin therapy (bl. glucose range between 4.4 –6.1 mmol/L) vs. Conventional (bl. glucose range between 10-11.1 mmol/L)	Intensive Insulin ICU 35/765 (5) Hospital 55/765 (7)	Conventional Insulin ICU 63/783 (8) Hospital 85/783 (11)	Intensive Insulin 32/765 (4)	Conventional Insulin 61/783 (8)
2) Grey 2004	Surgical ICU needing treatment for hyperglycemia N=61	C.Random: no ITT: no Blinding: no (4)	Strict insulin therapy (bl. glucose range between 4.4 to 6.6 mmol/L) vs. conventional (blood sugar range between 10-12 mmol/L) in patients requiring treatment for hyperglycemia (bl. glucose > 7.7 mmol/L)	Intensive Insulin Hospital 4/34 (11)	Conventional Insulin Hospital 6/27 (27)	Intensive Insulin 21/34 (26)	Conventional Insulin 20/27 (38)
3) Bland 2005	Medical ICU patients N=10	C.Random: no ITT: no Blinding: no (5)	Intensive insulin therapy (bl. glucose range between 4.4 to 6.1 mmol/L) vs. conventional (bl. glucose range between 10-11.1 mmol/L) and insulin given if bs > 11.1 mmol/L	Intensive Insulin 28 day 1/5 (20)	Conventional Insulin 28 day 2/5 (40)	Intensive Insulin NR	Conventional Insulin NR
4) Henderson 2005	Mixed ICU patients N=67	C.Random: yes ITT: yes Blinding: no (9)	Intensive insulin therapy (bl. glucose range 5-7mmol/L) vs conventional insulin therapy (bl. glucose range 9-11mmol/L)	Intensive Insulin 28 day 4/32 (13)	Conventional Insulin 28 day 5/35 (14)	Intensive Insulin NR	Conventional Insulin NR
5) Yu 2005***	Patients with sepsis/ organ failures N=55	C.Random: no ITT: yes Blinding: no (6)	Intensive insulin therapy (bl. glucose range between 4.4 to 6.1 mmol/L) vs. conventional (bl. glucose range between 10-11.1 mmol/L) and insulin given if bs > 11.9 mmol/L	Intensive insulin ICU 3/28 (11) Hospital 4/28 (14)	Conventional Insulin ICU 4/27 (15) Hospital 4/27 (15)	Intensive Insulin Antibiotic days 10 Patients with bacteria in blood 8/28 (29)	Conventional Insulin Antibiotic days 17 Patients with bacteria in blood 13/27 (48)
6) Mitchell 2006	Mixed ICU patients N=70	C.Random: yes ITT: yes Blinding: no (9)	Intensive insulin therapy (bl. glucose range 4.4-6.1 mmol/L) vs conventional (bl. glucose range 10- 11.1 mmol/L)	Intensive insulin ICU 7/35 (20) Hospital 9/35 (26)	Conventional Insulin ICU 2/35 (6) Hospital 3/35 (9)	Intensive insulin NR	Conventional Insulin NR

7) Van den Berghe 2006	Medical ICU patients expected to stay in ICU ≥ 3 days N=1200	C.Random: yes ITT: yes Blinding: no (12)	Intensive insulin therapy (bl. glucose range 4.4-6.1 mmol/L) vs conventional (blood sugar range 10-11mmol/L and insulin given if bl. glucose >12 mmol/L)	Intensive Insulin ICU 144/595 (24) Hospital 222/595 (37) 28 day 178/595 (30)	Conventional Insulin ICU 162/605 (27) Hospital 242/605 (40) 28 day 182/605 (30)	Intensive insulin NR No effect on bacteremia (reduction was 7-8% in intensive insulin group)	Conventional Insulin NR
8) Wang 2006***	Mixed ICU patients N=116	C.Random: not sure ITT: yes Blinding: no (5)	Intensive insulin therapy (bl. glucose range 4.4-6.1 mmol/L) vs conventional (bl. glucose range 10- 11.1 mmol/L) and insulin given if bs > 11.9 mmol/L	Intensive insulin Hospital 7/58 (12)	Conventional Insulin Hospital 26/58 (45)	Intensive Insulin NR	Conventional Insulin NR
9) de Azevedo 2007	Patients with neurological injury N=206	C.Random: no ITT: yes Blinding: no (6)	Intensive insulin therapy continuous IV to maintain bl. glucose range 80-120 mg/dL vs conventional (patients received insulin if bl. glucose was higher than 180 mg/dL)	Intensive Insulin ICU 8/31 (26)	Conventional Insulin ICU 6/17 (35)	Intensive Insulin Pneumonia 9/31 (30) UTI 3/31 (10)	Conventional Insulin Pneumonia 3/17 (18) UTI 1/17 (6)
10) Devos 2007	Patients from 21 mixed ICUs N=1101	C.Random: yes ITT: yes Blinding: no (9)	Intensive insulin therapy (bl. glucose range 4.4-6.1 mmol/L) vs conventional (bl. glucose range 7.8 to 10 mmol/L)	Intensive Insulin ICU 92/550 (17) Hospital 107/550 (20)	Conventional Insulin ICU 84/551 (15) Hospital 89/551(16)	Intensive Insulin Antibiotic days 3.9 ± 7.0	Conventional Insulin Antibiotic days 3.7 ± 6.7
11) Farah 2007	Mixed ICU patients N=89	C.Random: not sure ITT: no Blinding: no (3)	Intensive insulin therapy** (bl. glucose range 6.1-7.8 mmol/L) vs conventional (insulin given to keep bl. glucose range 7.8 to 11.1 mmol/L)	Intensive Insulin ICU 16/41 (39) 28 day 19/41 (46)	Conventional Insulin ICU 16/48 (31) 28 day 26/48 (54)	Intensive Insulin All 30/41 (73) Pneumonia 24/41 (59)	Conventional Insulin All 38/48 (79) Pneumonia 28/48 (58)
12) He 2007	Surgical ICU N=188	Pending translation	Intensive insulin therapy (BG 4.44-6.11 mmol/L) vs medium (BG 6.7-8.3 mmol/L) vs high (BG 10.0 – 11.1 mmol/L)	Intensive Insulin 7/150 (5)	Conventional Insulin 6/38 (16)	Intensive Insulin TBD	Conventional Insulin TBD
13) McMullin 2007	Medical ICU patients N=20	C.Random: yes ITT: yes Blinding: no (9)	Intensive insulin therapy (bl. glucose range 5-7 mmol/L) vs conventional (bl. glucose range 8-10mmol/L)	Intensive Insulin ICU 2/11 (18) Hospital 6/11 (55)	Conventional Insulin ICU 4/9 (44) Hospital 4/9 (44)	Intensive insulin 3/11 (27)	Conventional Insulin 2/9 (22)

14) Oksanen 2007	Medical ICU N=90	C.Random: no ITT: no Blinding: no (12)	Strict glucose control (4-6 mmol/L) vs. moderate glucose control (6-8 mmol/L)	Intensive Insulin 30 day 12/39 (33)	Conventional Insulin 30 day 18/51 (35)	Intensive Insulin NR	Conventional Insulin NR
15) Arabi 2008	Mixed ICU patients with blood sugars > 6.1 mmol/L N=523	C.Random: yes ITT: yes Blinding: no (9)	Intensive insulin therapy (bl. glucose range 4.4-6.1 mmol/L) vs conventional (bl. glucose range 10- 11.1 mmol/L)	Intensive Insulin ICU 36/266 (14) Hospital 72/266 (27)	Conventional Insulin ICU 44/257 (17) Hospital 83/257 (32)	Intensive Insulin % sepsis 98/266 (37) New infections per 1000 days 56	Conventional Insulin % sepsis 105/257 (41) New infections per 1000 days 59
16) Brunkhorst 2008	Septic shock patients from 18 ICUs N=537	C.Random: not sure ITT: yes Blinding: no (10)	Intensive insulin therapy** (bl. glucose range 4.0-6.1 mmol/L) vs conventional (blood sugar range 10-11.1 mmol/L and insulin given if bl. glucose >11.1 mmol/L)	Intensive Insulin 28 day 61/247 (25) 90 day 98/247 (38)	Conventional Insulin 28 day 75/289 (26) 90 day 102/288 (35)	Intensive Insulin NR	Conventional Insulin NR
17) De La Rosa 2008	Mixed ICU Patients N=504	C.Random: yes ITT: yes Blinding: no (11)	Intensive insulin therapy (bl glucose range 4.4-6.1 mmol/L) vs conventional (bl glucose range 10- 11.1 mmol/L)	Intensive Insulin ICU 84/254 (33) Hospital 102/254 (40) 28 day 93/254 (37)	Conventional Insulin ICU 78/250 (31) Hospital 96/250 (38) 28 day 81/250 (38)	Intensive Insulin All 84/254 (33) Pneumonia 43/254 (16.9)	Conventional Insulin All 68/250 (27) Pneumonia 55/250 (22)
18) He 2008	Mixed ICU N=122	C.Random: no ITT: no Blinding: no (4)	Intensive insulin therapy (BG 4.4-6.1 mmol/L) vs high (BG 10.0-11.1 mmol/L)	Intensive Insulin 16/58 (28)	Conventional Insulin 29/64 (45)	Intensive Insulin TBD	Conventional Insulin TBD
19) Iapichino 2008	Septic patients from 3 ICUs N=90	C.Random: no ITT: no Blinding: no (8)	Intensive insulin therapy (bl glucose range 4.4-6.1 mmol/L) vs conventional (bl glucose range 10-12 mmol/L)	Intensive Insulin ICU 8/36 (22) 90 day 13/36 (36)	Conventional Insulin ICU 6/36 (17) 90 day 11/36 (31)	Intensive Insulin NR	Conventional Insulin NR
20) Mackenzie 2008	Mixed ICU patients from 2 ICUs N=240	C.Random: no ITT: yes Blinding: no (8)	Tight bl. glucose (range 4-6 mmol/L, threshold > 6 mmol/L) vs conventional glycaemic control (range 10-11 mmol/L, threshold >11mmol/L)	Intensive Insulin ICU 23/121 (19) Hospital 39/121 (32)	Conventional Insulin ICU 27/119 (23) Hospital 47/119 (39)	Intensive Insulin Days of septic shock 0 (0,0)	Conventional Insulin Days of septic shock 1 (0, 3)

21) Zhang 2008***	Mixed ICU N=338	C.Random: no ITT: yes Blinding: no (5)	Intensive insulin therapy (BG 4.44-6.11 mmol/L) vs conventional (BG 7.2-8.3 mmol/L)	Intensive Insulin 4/168 (2)	Conventional Insulin 6/170 (3)	Intensive Insulin TBD	Conventional Insulin TBD
22) Bilotta 2009	Neurosurgical ICU undergoing elective or emergency surgery N=483	C.Random: no ITT: yes Blinding: no (11)	Intensive insulin therapy (BG 4.44-6.11 mmol/L) vs conventional (BG < 11.94) for 14 days or until discharge	Intensive Insulin 6 months 63/242 (26)	Conventional Insulin 6 months 68/241 (28)	Intensive Insulin # pts **≤ 1 infection** 62/242 (26)	Conventional Insulin # pts **≤ 1 infection** 95/241 (40)
23) Finfer (NICE SUGAR) 2009	Mixed ICU N=6022	C.Random: yes ITT: no Blinding: no (9)	Intensive insulin therapy (BG range 4.5-6.0 mmol/L) vs conventional insulin therapy (BG range < 10 mmol/L)	Intensive Insulin ICU 546/3010 (18) Hospital 220/3010 (7) 28 day 829/3010 (28) 90 day 670/3010 (22)	Conventional Insulin ICU 498/73012 (17) Hospital 197/3012 (7) 28 day 751/3012 (25) 90 day 627/3012 (21)	Blood culture + for pathogens 387/3014 (13)	Blood culture + for pathogens 372/3011 (15)
24) Savioli 2009	Patients with severe sepsis and septic shock N=90	C.Random: no ITT: yes Blinding: no (6)	Strict glucose control (BG 4.4-6.1 mmol/L) vs conventional (BG 10-11.1 mmol/L)	Intensive Insulin ICU 9/45 (20) 90-day 14/45 (31)	Conventional Insulin ICU 8/45 (18) 90-day 13/45 (29)	Intensive Insulin NR	Conventional Insulin NR
25) Annane 2010	Severe sepsis, multiple organ dysfunction, on vasopressors and hydrocortisone N=509	C.Random: yes ITT: yes Blinding: no (11)	Intensive insulin therapy (bl. glucose range 4.4-6.1 mmol/L) vs conventional (blood sugar range 10-11mmol/L and insulin given if bl. glucose >12 mmol/L)	Intensive Insulin Hospital 117/255 (46) Hydrocort + Fludro Hospital 105/245 (43)	Conventional Insulin Hospital 109/254 (43) Hydrocort + Fludro Hospital 121/264 (46)	Intensive Insulin NR	Conventional Insulin NR
26) Arabi 2011	Mixed ICU; one-third with brain trauma and 40% with type-2 diabetes N=240	C. Random: yes ITT: yes Blinding: no (9)	Intensive insulin therapy (4.4–6.1 mmol/L) vs conventional insulin therapy (10–11.1 mmol/L)	Intensive Insulin ICU 21/120 (18) Hospital 42/120 (35) 28-day 23/120 (19) 180-day 45/118 (38)	Conventional Insulin ICU 26/120 (22) Hospital 45/120 (38) 28-day 27/120 (23) 180-day 45/115 (39)	Intensive Insulin VAP /1000 vent days 14.8 All inf 1000 ICU days 56.4 All sepsis 59/120 (49)	Conventional Insulin VAP /1000 vent days 8.9 All inf /1000 ICU days 51.7 All sepsis 50/120 (42)

Table 1. Randomized studies evaluating intensive insulin therapy in critically ill patients (continued)

Study	LOS days		Ventilator days		Other
1) Van Den Berghe 2001	Intensive Insulin ICU 7 ± 11* Hospital 23 ± 32 *	Conventional Insulin ICU 9 ± 15* Hospital 23 ± 28 *	Intensive Insulin 5 ± 11*	Conventional Insulin 7 ± 15*	Intensive insulin Conventional Insulin Hypoglycemia 39/765 (5) 6/783 (<1)
2) Grey 2004	Intensive Insulin ICU 33.4 ± 68.3	Conventional Insulin ICU 24.5 ± 19.4	Intensive Insulin NR	Conventional Insulin NR	Intensive Insulin Conventional Insulin Hypoglycemia 11/34 (32) 20/27 (74)
3) Bland 2005	Intensive Insulin NR	Conventional Insulin NR	Intensive Insulin NR	Conventional Insulin NR	Intensive Insulin Conventional Insulin Severe hypoglycemia 1/5 (20) 1/5 (20) Moderate hypoglycemia 4/5 (80) 3/5 (60) Total hypoglycemia 5/5 (100) 4/5 (80)
4) Henderson 2005	Intensive Insulin ICU 7.42 (5.12-12.72) Hospital 22 (13-40.5)	Conventional Insulin ICU 11.5 (7.39-20.95) Hospital 33 (21-66)	Intensive Insulin (hours) 132.2 (90-28)	Conventional Insulin (hours) 228.2 (140-459)	Intensive Insulin Conventional Insulin Hypoglycemic events 8/32 (24) 1/35 (3)
5) Yu 2005***	Intensive Insulin NR	Conventional Insulin NR	Intensive Insulin 10 (9)	Conventional Insulin 17 (10)	Intensive Insulin Conventional Insulin Hypoglycemia 3/28 (11) 0/27 (0)
6) Mitchell 2006	Intensive Insulin ICU 5 (3-8)	Conventional Insulin ICU 4 (3-9)	Intensive Insulin 15 (7.5-28.5)	Conventional Insulin 18 (11-31.5)	Intensive Insulin Conventional Insulin Hypoglycemia 6/58 (10) 2/58 (3)
7) Van den Berghe 2006	Intensive Insulin ICU 8 ± 9* Hospital 31 ± 42*	Conventional Insulin ICU 10 ± 12* Hospital 36 ± 60*	Intensive Insulin 6 ± 9*	Conventional Insulin 8 ± 12*	Intensive Insulin Conventional Insulin Hypoglycemia More often in the intensive group

8) Wang 2006***	Intensive Insulin ICU 9.14 ± 5.45 (58)	Conventional Insulin ICU 12.88 ± 8.29 (58)	Intensive Insulin 6.02 ± 5.47 (58)	Conventional Insulin 9.21 ± 8.56 (58)	Intensive Insulin Conventional Insulin Severe hypoglycemia 5/35 (14) 0/35 (0)
9) de Azevedo 2007	Intensive Insulin ICU 9 (4-22) Hospital 19.5 (7.7-39.2)	Conventional Insulin ICU 9 (4-15.5) Hospital 15.5 (4.2-21.7)	Intensive Insulin NR	Conventional Insulin NR	Intensive Insulin Conventional Insulin Glascow Outcome Scale Extended 9 (53) 5 (56) Convulsions 1 (3) 0 (0)
10) Devos 2007	Intensive Insulin ICU 6 (3-13) Hospital 16 (11-30)	Conventional Insulin ICU 6 (3-13) Hospital 16 (11-29)	Intensive Insulin Patient days 2532	Conventional Insulin Patient days 2572	Intensive Insulin Conventional Insulin Hypoglycemia 80/550 (15) 21/551 (4)
11) Farah 2007	Intensive Insulin ICU 7 ± 4.9 (41)	Conventional Insulin ICU 8 ± 4.85 (48)	Intensive Insulin NR	Conventional Insulin NR	Intensive insulin Conventional Insulin Hypoglycemic events 23/41 (56) 23/48 (48)
12) He 2007***	TBD	TBD	TBD	TBD	TBD
13) McMullin 2007	Intensive Insulin ICU 15 (6-25) Hospital 21 (17-40)	Conventional Insulin ICU 6 (4-20) Hospital 16 (10-23)	Intensive Insulin NR	Conventional Insulin NR	Intensive Insulin Conventional Insulin Severe hypoglycemia 4/11 (36) 1/9 (11)
14) Oksanen 2007	NR	NR	NR	NR	Intensive Insulin Conventional Insulin % bl. gl measurements in targeted range 71 (62-79) 47 (29-64)
15) Arabi 2008	Intensive Insulin ICU 9.6 ± 8.5 (266) Hospital 54.1 ± 84.1 (266)	Conventional Insulin ICU 10.8 ± 11.3 (257) Hospital 57.5 ± 77.1 (257)	Intensive Insulin 8.3 ± 7.9 (266)	Conventional Insulin 9.7 ± 11.0 (257)	Intensive Insulin Conventional Insulin Hypoglycemia 76/266 (29) 8/257 (3)

16) Brunkhorst 2008	Intensive Insulin ICU 16 (8-30)	Conventional Insulin ICU 14 (7-25)	Intensive Insulin Ventilator-free days 3 (1-7)	Conventional Insulin Ventilator-free days 3 (1-6)	Intensive Insulin Conventional Insulin Hypoglycemia 42/247 (17) 12/280 (4)
17) De La Rosa 2008	Intensive Insulin ICU 6 (3-12)	Conventional Insulin ICU 6 (3-11)	Intensive Insulin 6 (2-10)	Conventional Insulin 5 (2-9)	Intensive Insulin Conventional Insulin Hypoglycemia 21/254 (8.3) 20/250 (0.8)
18) He 2008***	TBD	TBD	TBD	TBD	TBD
19) Iapichino 2008	Intensive Insulin ICU 16 (8.1-28.5)	Conventional Insulin ICU 13 (6.5-23.5)	Intensive Insulin NR	Conventional Insulin NR	Intensive Insulin Conventional Insulin Severe hypoglycemia 8/36 (22) 3/36 (8)
20) Mackenzie 2008	Intensive Insulin ICU (hours) 160 (66-461) Hospital (days) 29 (15-58)	Conventional Insulin ICU (hours) 167 (81-409) Hospital (days) 27 (12-58)	Intensive Insulin (hours) 111 (24, 341)	Conventional Insulin (hours) 120 (35, 330)	Intensive Insulin Conventional Insulin Incidence of hypoglycemia Morning laboratory 8/121 (7) 1/119 (1) Bedside 50/121 (41) 9/119 (8) Total 58/121 (48) 10/119 (8)
21) Zhang 2008***	NA	NA	NA	NA	NA
22) Bilotta 2009	Intensive Insulin ICU 6 (median)	Conventional Insulin ICU 8 (median)	Intensive Insulin 4.2 (median)	Conventional Insulin 6.1 (median)	Intensive Insulin Conventional Insulin Patients **≥ 1 hypoglycemic episodes** 226/242 (93) 152/241 (63)
23) Finfer (NICE SUGAR) 2009	Intensive Insulin ICU 6 (2-11) Hospital 17 (8-35)	Conventional Insulin ICU 6 (2-11) Hospital 17 (8-35)	Intensive Insulin 6.6 ± 6.6 (3010)	Conventional Insulin 6.6 ± 6.5 (3012)	Intensive Insulin Conventional Insulin Severe hypoglycemia 206/3016 (7) 15/3014 (1)
24) Savioli 2009	NR	NR	NR	NR	Intensive Insulin Conventional Insulin Hypoglycemic episodes 45/45 (100) 7/45 (16)

25) Annane 2010	Intensive Insulin ICU 9 (4-14) Hospital 16 (6-34)	Conventional Insulin ICU 9 (4-15) Hospital 15 (7-30)	Intensive Insulin Ventilator-free days 10 (2-22)	Conventional Insulin Ventilator-free days 13 (2-23)	Intensive Insulin Conventional Insulin Hypoglycemia 72 (43-100) 44 (32-56)
26) Arabi 2011	Intensive Insulin ICU 13.1 ± 9.8 Hospital 70.7 ± 106.3	Conventional Insulin ICU 13.1 ± 14.7 Hospital 66.7 ± 94.3	Intensive Insulin 11.6 ± 8.6 (120)	Conventional Insulin 12.1 ± 14.8 (120)	?

C.Random: concealed randomization ‡ refers to the # of patients with infections unless specified TNA: Total Nutrient Admixtures (-): median (range)
ITT: intent to treat; NA: not available ** RR= relative risk, CI= Confidence intervals ( ) : mean ± Standard deviation (number) NR: not reported

To convert values of glucose to mg/dL, multiply mmol/L X 18.01; to convert to mmol/L, multiply mg/dL x 0.05551
** data on group receiving pentastarch not shown
*** translated from Chinese

Table 2.

Study	Population	Methods (score)	Intervention	Mortality # (%)		Infections # (%)‡	
1. Aron 2013	Trauma ICU pts without diabetes N=58	C. Random: no ITT: yes Blinding: no (11)	Intensive IV insulin therapy (blood glucose range 4.4-6.1) during ICU stay vs subcutaneous insulin (blood glucose range 4.4-6.1).	IV Insulin Hospital 3/29 (10.3)	SC Insulin Hospital 1/29 (10.3)	IV Insulin Total infections 0.5 ± 1.3 (p=0.7) Pneumonia 4/29 (13.8)	SC Insulin Total infections 0.4 ± 0.7 Pneumonia 7/29 (24.1)

Study	LOS days		Ventilator days		Other
1. Aron 2013	IV Insulin ICU LOS 2 (1-4) Hospital LOS 6 (3-9)	SC Insulin ICU LOS 3 (2-10) (p=0.084) Hospital LOS 8 (5-16) (p=0.09)	IV Insulin 3 (2-9)	SC Insulin 6 (1-9)	IV insulin SC Insulin Hypoglycemia 0.9 ± 1.3 0.1 ± 0.4 (p=0.002) Kcal/kg/d 4.5 ± 7.1 7.8 ± 7.9 (p=0.14)

Figure 1a. Overall mortality

Study or Subgroup	Intensive Events	Intensive Total	Conventional Events	Conventional Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Van den Berghe 2001	55	765	85	783	5.9%	0.66 [0.48, 0.92]	2001
Grey	4	34	6	27	0.8%	0.53 [0.17, 1.69]	2004
Henderson	4	32	5	35	0.7%	0.88 [0.26, 2.98]	2005
Yu	4	28	4	27	0.6%	0.96 [0.27, 3.47]	2005
Bland	1	5	2	5	0.3%	0.50 [0.06, 3.91]	2005
Mitchell	9	35	3	35	0.7%	3.00 [0.89, 10.16]	2006
Wang	7	58	26	58	1.7%	0.27 [0.13, 0.57]	2006
Van den Berghe 2006	222	595	242	605	10.7%	0.93 [0.81, 1.08]	2006
Farah	19	41	26	48	4.3%	0.86 [0.56, 1.30]	2007
McMullin	6	11	4	9	1.2%	1.23 [0.49, 3.04]	2007
Oksanen	12	39	18	51	2.5%	0.87 [0.48, 1.59]	2007
de Azevedo 2007	8	31	6	17	1.3%	0.73 [0.30, 1.76]	2007
Devos	107	550	89	551	7.5%	1.20 [0.93, 1.55]	2007
He 2007	7	150	6	38	1.0%	0.30 [0.11, 0.83]	2007
He 2008	16	58	29	64	3.4%	0.61 [0.37, 1.00]	2008
Mackenzie	39	121	47	119	5.6%	0.82 [0.58, 1.15]	2008
Zhang	4	168	6	170	0.7%	0.67 [0.19, 2.35]	2008
Brunkhorst	61	247	75	289	6.6%	0.95 [0.71, 1.27]	2008
Arabi 2008	72	266	83	257	7.2%	0.84 [0.64, 1.09]	2008
Iapichino	13	36	11	36	2.2%	1.18 [0.61, 2.28]	2008
De La Rosa	102	254	96	250	8.5%	1.05 [0.84, 1.30]	2008
Finfer (NICE SUGAR)	220	3010	197	3014	9.4%	1.12 [0.93, 1.35]	2009
Savioli	14	45	13	45	2.3%	1.08 [0.57, 2.03]	2009
Annane	117	255	109	254	9.2%	1.07 [0.88, 1.30]	2010
Arabi 2011	42	120	45	120	5.7%	0.93 [0.67, 1.31]	2011
Total (95% CI)		**6954**		**6907**	**100.0%**	**0.91 [0.82, 1.02]**	
Total events	1165		1233				

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 40.37$, df = 24 (P = 0.02); $I^2 = 41\%$

Test for overall effect: Z = 1.65 (P = 0.10)

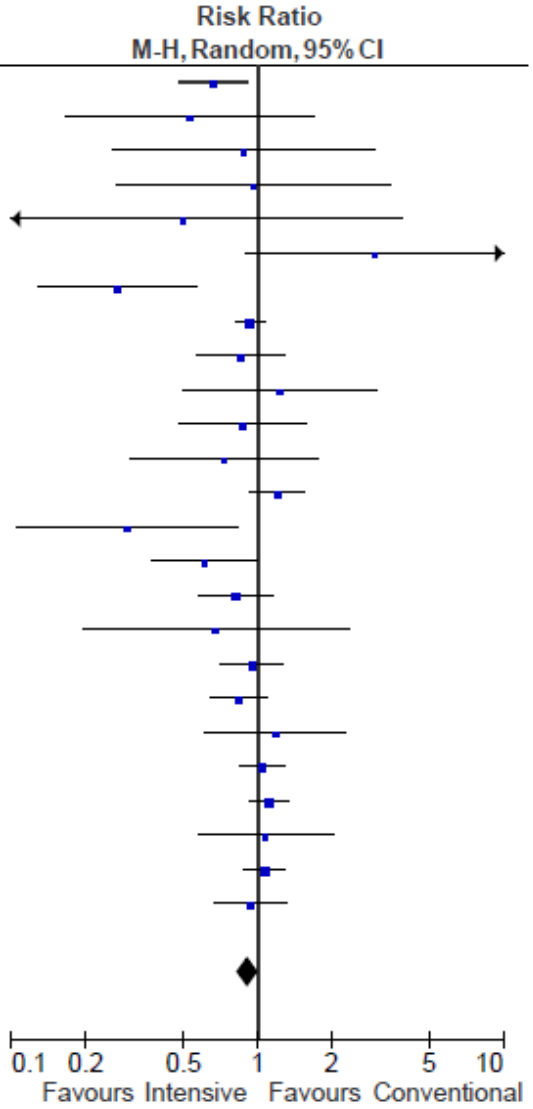

Figure 1b. Overall mortality (excluding Annane 2010)

Study or Subgroup	Intensive Events	Intensive Total	Conventional Events	Conventional Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Van den Berghe 2001	55	765	85	783	6.5%	0.66 [0.48, 0.92]	2001
Grey	4	34	6	27	0.9%	0.53 [0.17, 1.69]	2004
Bland	1	5	2	5	0.3%	0.50 [0.06, 3.91]	2005
Henderson	4	32	5	35	0.8%	0.88 [0.26, 2.98]	2005
Yu	4	28	4	27	0.7%	0.96 [0.27, 3.47]	2005
Van den Berghe 2006	222	595	242	605	11.4%	0.93 [0.81, 1.08]	2006
Mitchell	9	35	3	35	0.8%	3.00 [0.89, 10.16]	2006
Wang	7	58	26	58	2.0%	0.27 [0.13, 0.57]	2006
Farah	19	41	26	48	4.8%	0.86 [0.56, 1.30]	2007
Devos	107	550	89	551	8.2%	1.20 [0.93, 1.55]	2007
de Azevedo 2007	8	31	6	17	1.5%	0.73 [0.30, 1.76]	2007
He 2007	7	150	6	38	1.1%	0.30 [0.11, 0.83]	2007
Oksanen	12	39	18	51	2.9%	0.87 [0.48, 1.59]	2007
McMullin	6	11	4	9	1.4%	1.23 [0.49, 3.04]	2007
Arabi 2008	72	266	83	257	7.9%	0.84 [0.64, 1.09]	2008
Mackenzie	39	121	47	119	6.2%	0.82 [0.58, 1.15]	2008
Zhang	4	168	6	170	0.8%	0.67 [0.19, 2.35]	2008
He 2008	16	58	29	64	3.8%	0.61 [0.37, 1.00]	2008
Iapichino	13	36	11	36	2.5%	1.18 [0.61, 2.28]	2008
Brunkhorst	61	247	75	289	7.2%	0.95 [0.71, 1.27]	2008
De La Rosa	102	254	96	250	9.2%	1.05 [0.84, 1.30]	2008
Savioli	14	45	13	45	2.6%	1.08 [0.57, 2.03]	2009
Finfer (NICE SUGAR)	220	3010	197	3014	10.1%	1.12 [0.93, 1.35]	2009
Arabi 2011	42	120	45	120	6.3%	0.93 [0.67, 1.31]	2011
Total (95% CI)		6699		6653	100.0%	0.90 [0.80, 1.01]	
Total events	1048		1124				

Heterogeneity: Tau² = 0.02; Chi² = 38.84, df = 23 (P = 0.02); I² = 41%
Test for overall effect: Z = 1.85 (P = 0.06)

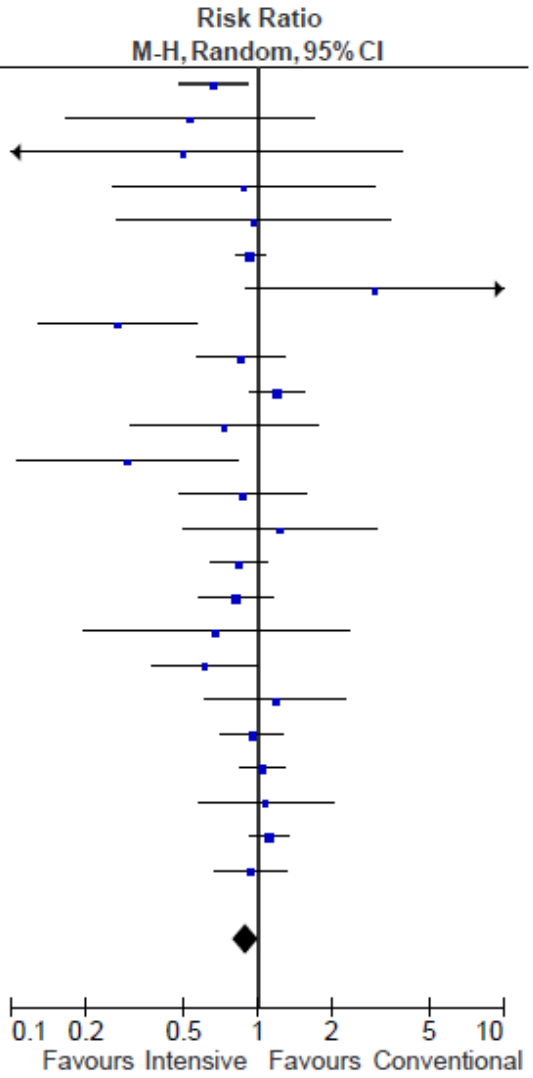

Figure 2a. Infections

Study or Subgroup	Insulin Events	Insulin Total	Conventional Events	Conventional Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Van den Berghe 2001	32	765	61	783	13.7%	0.54 [0.35, 0.81]	2001
Grey	21	34	20	27	16.7%	0.83 [0.59, 1.18]	2004
Farah	30	41	38	48	22.9%	0.92 [0.73, 1.17]	2007
McMullin	3	11	2	9	1.6%	1.23 [0.26, 5.82]	2007
Arabi 2008	98	266	105	257	24.2%	0.90 [0.73, 1.12]	2008
De La Rosa	84	254	68	250	21.0%	1.22 [0.93, 1.59]	2008
Total (95% CI)		**1371**		**1374**	**100.0%**	**0.89 [0.73, 1.09]**	
Total events	268		294				

Heterogeneity: Tau² = 0.03; Chi² = 11.15, df = 5 (P = 0.05); I² = 55%
Test for overall effect: Z = 1.12 (P = 0.26)

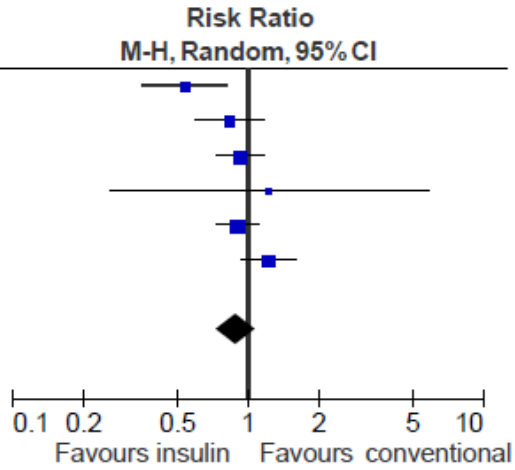

Figure 2b. Infections (excluding Van den Berghe 2001)

Study or Subgroup	Insulin Events	Insulin Total	Conventional Events	Conventional Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Grey	21	34	20	27	14.3%	0.83 [0.59, 1.18]	2004
McMullin	3	11	2	9	0.8%	1.23 [0.26, 5.82]	2007
Farah	30	41	38	48	28.7%	0.92 [0.73, 1.17]	2007
Arabi 2008	98	266	105	257	33.4%	0.90 [0.73, 1.12]	2008
De La Rosa	84	254	68	250	22.8%	1.22 [0.93, 1.59]	2008
Total (95% CI)		**606**		**591**	**100.0%**	**0.96 [0.84, 1.10]**	
Total events	236		233				

Heterogeneity: Tau² = 0.00; Chi² = 4.38, df = 4 (P = 0.36); I² = 9%
Test for overall effect: Z = 0.54 (P = 0.59)

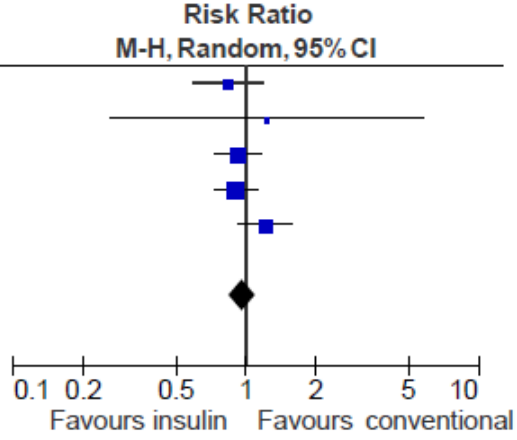

Figure 3a. ICU LOS

Study or Subgroup	Intensive Insulin Mean	SD	Total	Conventional Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Van den Berghe 2001	7	11	765	9	15	783	27.6%	-2.00 [-3.31, -0.69]	2001
Grey	33.4	68.3	34	24.5	19.4	27	0.1%	8.90 [-15.20, 33.00]	2004
Wang	9.14	5.45	58	12.88	8.29	58	7.2%	-3.74 [-6.29, -1.19]	2006
Van den Berghe 2006	8	9	595	10	12	605	32.9%	-2.00 [-3.20, -0.80]	2006
Farah	7	4.9	41	8	4.85	48	11.4%	-1.00 [-3.03, 1.03]	2007
Arabi 2008	9.6	8.5	266	10.8	11.3	257	16.0%	-1.20 [-2.92, 0.52]	2008
Arabi 2011	13.1	9.8	120	13.1	14.7	120	4.7%	0.00 [-3.16, 3.16]	2011
Total (95% CI)			**1879**			**1898**	**100.0%**	**-1.78 [-2.47, -1.09]**	

Heterogeneity: Tau² = 0.00; Chi² = 5.48, df = 6 (P = 0.48); I² = 0%
Test for overall effect: Z = 5.08 (P < 0.00001)

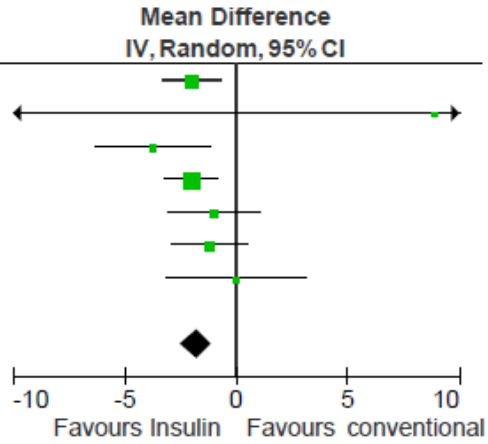

Figure 3b. ICU LOS (excluding Van den Berghe 2001, 2006)

Study or Subgroup	Intensive Insulin Mean	SD	Total	Conventional Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Grey	33.4	68.3	34	24.5	19.4	27	0.3%	8.90 [-15.20, 33.00]	2004
Wang	9.14	5.45	58	12.88	8.29	58	20.2%	-3.74 [-6.29, -1.19]	2006
Farah	7	4.9	41	8	4.85	48	28.8%	-1.00 [-3.03, 1.03]	2007
Arabi 2008	9.6	8.5	266	10.8	11.3	257	36.5%	-1.20 [-2.92, 0.52]	2008
Arabi 2011	13.1	9.8	120	13.1	14.7	120	14.1%	0.00 [-3.16, 3.16]	2011
Total (95% CI)			**519**			**510**	**100.0%**	**-1.46 [-2.73, -0.19]**	

Heterogeneity: Tau² = 0.39; Chi² = 4.88, df = 4 (P = 0.30); I² = 18%
Test for overall effect: Z = 2.25 (P = 0.02)

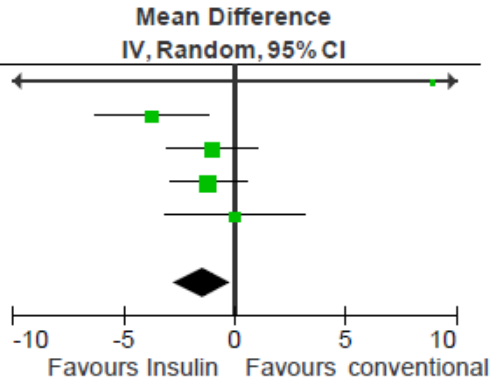

Figure 4a. Hospital LOS

	Insulin			Conventional				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Van den Berghe 2001	23	32	765	23	28	783	75.6%	0.00 [-3.00, 3.00]	2001
Van den Berghe 2006	31	42	595	36	60	605	19.8%	-5.00 [-10.85, 0.85]	2006
Arabi 2008	54.1	84.1	266	57.5	77.1	257	3.6%	-3.40 [-17.22, 10.42]	2008
Arabi 2011	70.7	106.3	120	66.7	94.3	120	1.1%	4.00 [-21.42, 29.42]	2011
Total (95% CI)			**1746**			**1765**	**100.0%**	**-1.07 [-3.68, 1.54]**	

Heterogeneity: Tau² = 0.00; Chi² = 2.48, df = 3 (P = 0.48); I² = 0%
Test for overall effect: Z = 0.81 (P = 0.42)

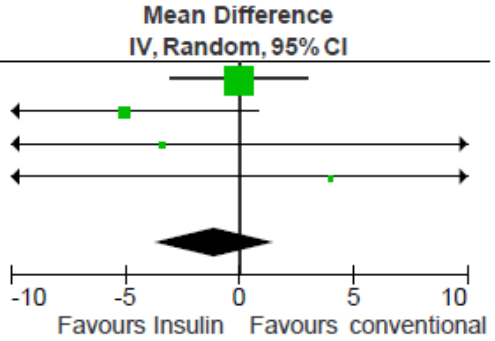

Figure 4b. Hospital LOS (excluding Van den Berghe 2001, 2006)

	Insulin			Conventional				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Arabi 2008	54.1	84.1	266	57.5	77.1	257	77.2%	-3.40 [-17.22, 10.42]	2008
Arabi 2011	70.7	106.3	120	66.7	94.3	120	22.8%	4.00 [-21.42, 29.42]	2011
Total (95% CI)			**386**			**377**	**100.0%**	**-1.71 [-13.85, 10.43]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.28 (P = 0.78)

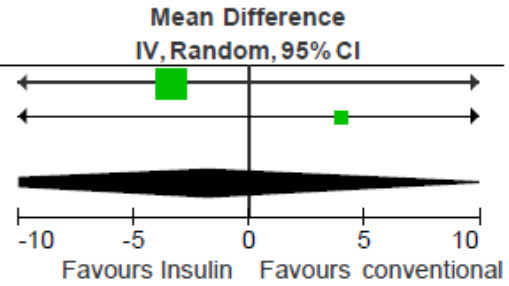

Figure 5a. Ventilator days

	Insulin			Conventional				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Van den Berghe 2001	5	11	765	7	15	783	19.0%	-2.00 [-3.31, -0.69]	2001
Wang	6.02	5.47	58	9.21	8.56	58	11.1%	-3.19 [-5.80, -0.58]	2006
Van den Berghe 2006	6	9	595	8	12	605	19.7%	-2.00 [-3.20, -0.80]	2006
Arabi 2008	8.3	7.9	266	9.7	11	257	16.7%	-1.40 [-3.05, 0.25]	2008
Finfer (NICE SUGAR)	6.6	6.6	3010	6.6	6.5	3012	24.3%	0.00 [-0.33, 0.33]	2009
Arabi 2011	11.6	8.6	120	12.1	14.8	120	9.2%	-0.50 [-3.56, 2.56]	2011
Total (95% CI)			**4814**			**4835**	**100.0%**	**-1.41 [-2.58, -0.23]**	

Heterogeneity: Tau² = 1.44; Chi² = 23.77, df = 5 (P = 0.0002); I² = 79%
Test for overall effect: Z = 2.35 (P = 0.02)

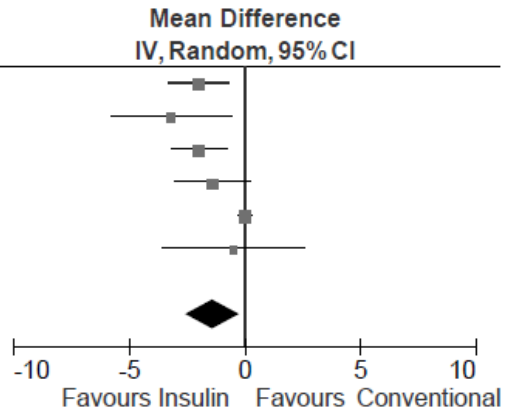

Figure 5b. Ventilator days (excluding Van den Berghe 2001, 2006)

	Insulin			Conventional				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Wang	6.02	5.47	58	9.21	8.56	58	16.9%	-3.19 [-5.80, -0.58]	2006
Arabi 2008	8.3	7.9	266	9.7	11	257	26.8%	-1.40 [-3.05, 0.25]	2008
Finfer (NICE SUGAR)	6.6	6.6	3010	6.6	6.5	3012	42.4%	0.00 [-0.33, 0.33]	2009
Arabi 2011	11.6	8.6	120	12.1	14.8	120	13.8%	-0.50 [-3.56, 2.56]	2011
Total (95% CI)			**3454**			**3447**	**100.0%**	**-0.99 [-2.36, 0.39]**	

Heterogeneity: Tau² = 1.14; Chi² = 8.18, df = 3 (P = 0.04); I² = 63%
Test for overall effect: Z = 1.40 (P = 0.16)

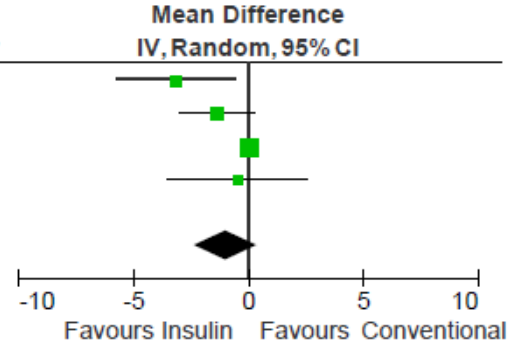

Figure 6a. Hypoglycemia

Study or Subgroup	Intensive Insulin Events	Total	Conventional Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Van den Berghe 2001	39	765	6	783	6.0%	6.65 [2.83, 15.62]	2001
Grey	11	34	20	27	6.6%	0.44 [0.26, 0.75]	2004
Henderson	8	32	1	35	3.7%	8.75 [1.16, 66.15]	2005
Yu	3	28	0	27	2.4%	6.76 [0.37, 124.98]	2005
Bland	5	5	4	5	6.6%	1.22 [0.73, 2.06]	2005
Mitchell	6	58	2	58	4.5%	3.00 [0.63, 14.25]	2006
Wang	5	35	0	35	2.5%	11.00 [0.63, 191.69]	2006
McMullin	4	11	1	9	3.7%	3.27 [0.44, 24.34]	2007
Devos	80	550	21	551	6.6%	3.82 [2.40, 6.08]	2007
Farah	23	41	23	48	6.7%	1.17 [0.78, 1.75]	2007
Iapichino	8	36	3	36	5.2%	2.67 [0.77, 9.25]	2008
Mackenzie	58	121	10	119	6.4%	5.70 [3.06, 10.62]	2008
Brunkhorst	42	247	12	280	6.4%	3.97 [2.14, 7.36]	2008
De La Rosa	21	254	20	250	6.5%	1.03 [0.57, 1.86]	2008
Arabi 2008	76	266	8	257	6.3%	9.18 [4.52, 18.63]	2008
Savioli	45	45	7	45	6.4%	6.07 [3.15, 11.68]	2009
Finfer (NICE SUGAR)	206	3016	15	3014	6.6%	13.72 [8.15, 23.12]	2009
Bilotta	226	242	152	241	6.9%	1.48 [1.34, 1.64]	2009
Total (95% CI)		**5786**		**5820**	**100.0%**	**3.19 [1.81, 5.60]**	
Total events	866		305				

Heterogeneity: Tau² = 1.19; Chi² = 305.40, df = 17 (P < 0.00001); I² = 94%
Test for overall effect: Z = 4.03 (P < 0.0001)

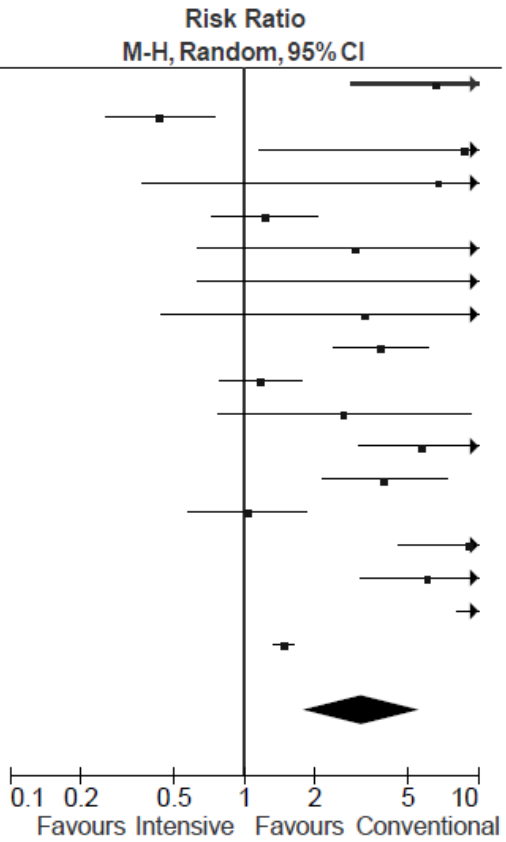

Figure 6b. Hypoglycemia (excluding Van den Berghe 2001)

Study or Subgroup	Intensive Insulin Events	Total	Conventional Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Grey	11	34	20	27	7.0%	0.44 [0.26, 0.75]	2004
Henderson	8	32	1	35	3.9%	8.75 [1.16, 66.15]	2005
Yu	3	28	0	27	2.6%	6.76 [0.37, 124.98]	2005
Bland	5	5	4	5	7.0%	1.22 [0.73, 2.06]	2005
Wang	5	35	0	35	2.6%	11.00 [0.63, 191.69]	2006
Mitchell	6	58	2	58	4.8%	3.00 [0.63, 14.25]	2006
Farah	23	41	23	48	7.2%	1.17 [0.78, 1.75]	2007
McMullin	4	11	1	9	3.9%	3.27 [0.44, 24.34]	2007
Devos	80	550	21	551	7.1%	3.82 [2.40, 6.08]	2007
Brunkhorst	42	247	12	280	6.8%	3.97 [2.14, 7.36]	2008
Mackenzie	58	121	10	119	6.8%	5.70 [3.06, 10.62]	2008
Arabi 2008	76	266	8	257	6.7%	9.18 [4.52, 18.63]	2008
De La Rosa	21	254	20	250	6.9%	1.03 [0.57, 1.86]	2008
Iapichino	8	36	3	36	5.5%	2.67 [0.77, 9.25]	2008
Finfer (NICE SUGAR)	206	3016	15	3014	7.0%	13.72 [8.15, 23.12]	2009
Savioli	45	45	7	45	6.8%	6.07 [3.15, 11.68]	2009
Bilotta	226	242	152	241	7.4%	1.48 [1.34, 1.64]	2009
Total (95% CI)		**5021**		**5037**	**100.0%**	**3.03 [1.71, 5.40]**	
Total events	827		299				

Heterogeneity: Tau² = 1.16; Chi² = 288.37, df = 16 (P < 0.00001); I² = 94%

Test for overall effect: Z = 3.78 (P = 0.0002)