11.1 Optimal glucose control: Insulin therapy

There are no new randomized controlled trials since the 2015 updates and hence there are no changes to the following summary of evidence.

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 may be associated with a reduction in overall mortality.
2) Intensive insulin therapy has no effect on infections.
3) Intensive insulin therapy is associated with a 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 an 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=1078 of 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** NR	**Conventional Insulin** NR
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** NR	**Conventional Insulin** NR
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* **	NR	NR	NR	NR	NR
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* **	NR	NR	NR	NR	NR
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* **	NR	NR	NR	NR	NR
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)	Not applicable

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

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. Aron 2013

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)

Table 2. Aron 2013 (continued)

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)	

IV: intravenous SC: subcutaneous

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: Tau² = 0.02; Chi² = 40.37, df = 24 (P = 0.02); I² = 41%
Test for overall effect: Z = 1.65 (P = 0.10)

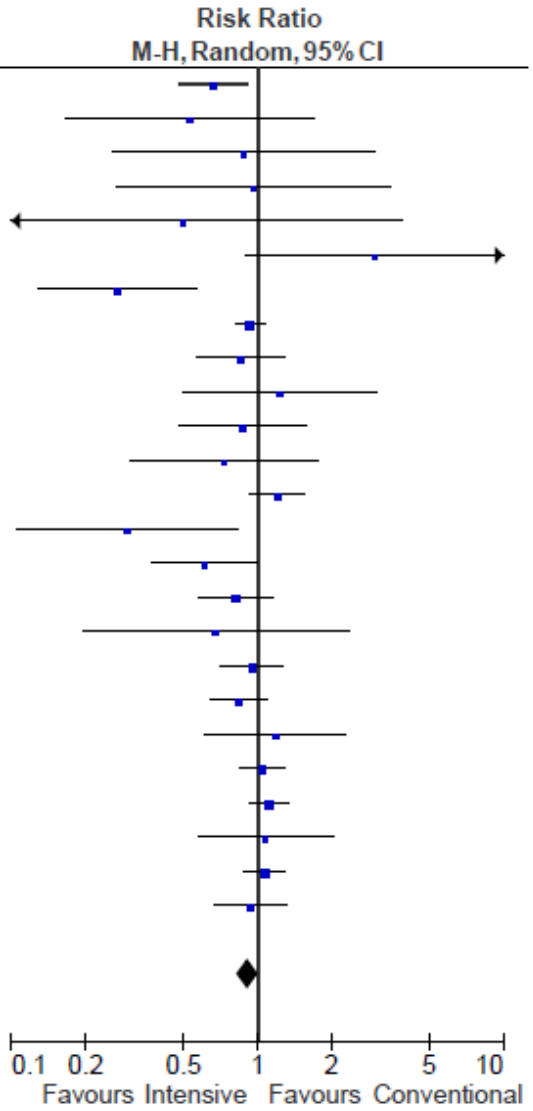


Figure 1b. Overall mortality (excluding Annane 2010)

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)

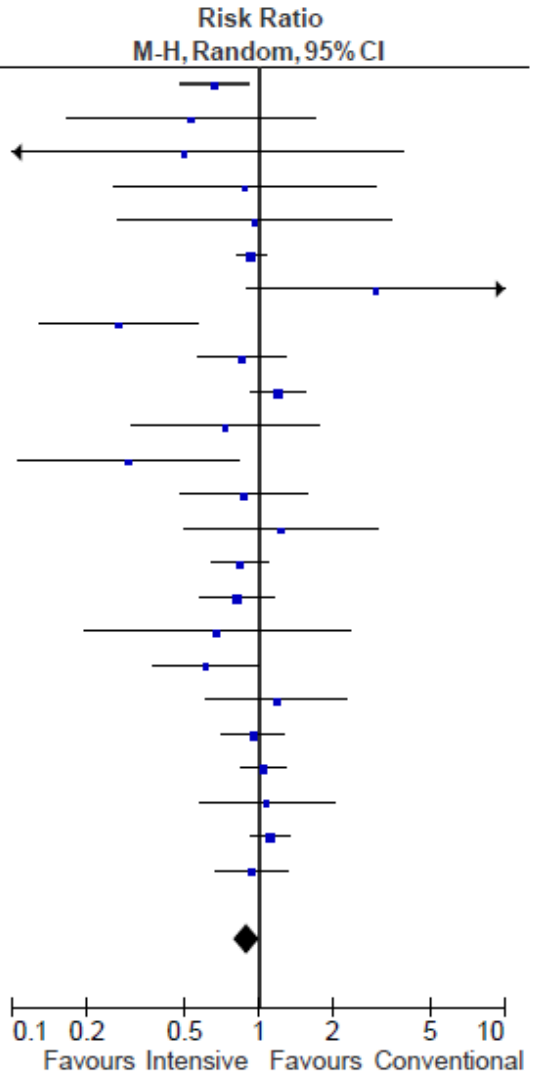


Figure 2a. Infections

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)

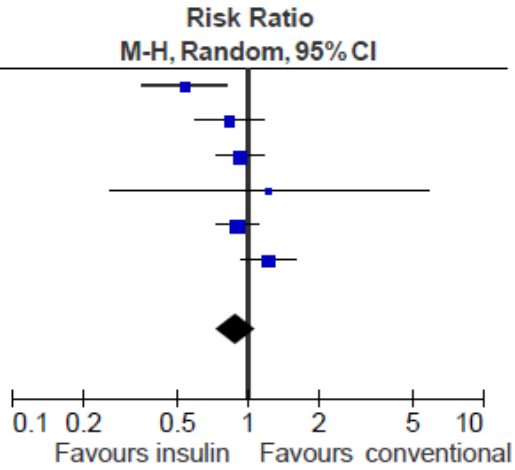


Figure 2b. Infections (excluding Van den Berghe 2001)

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)

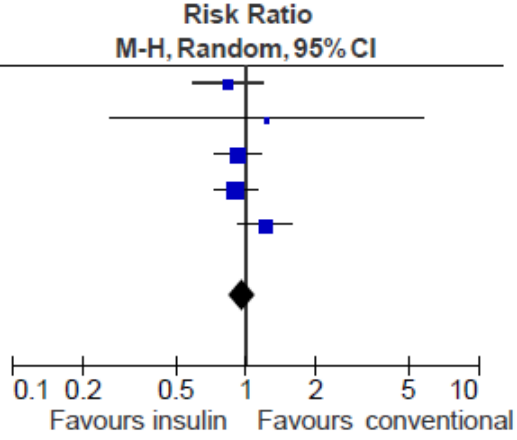


Figure 3a. ICU LOS

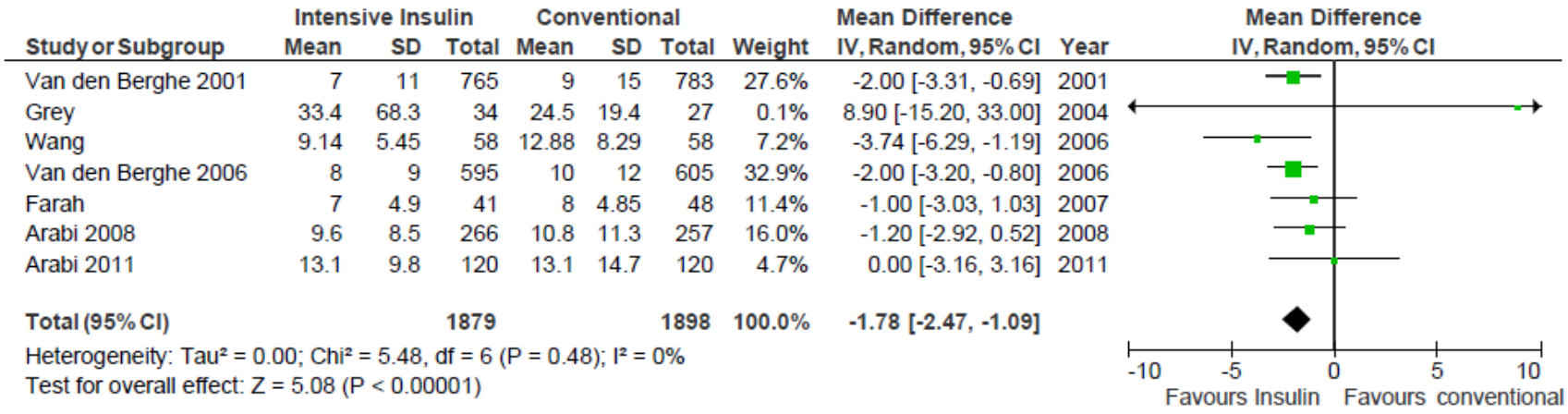


Figure 3b. ICU LOS (excluding Van den Berghe 2001, 2006)

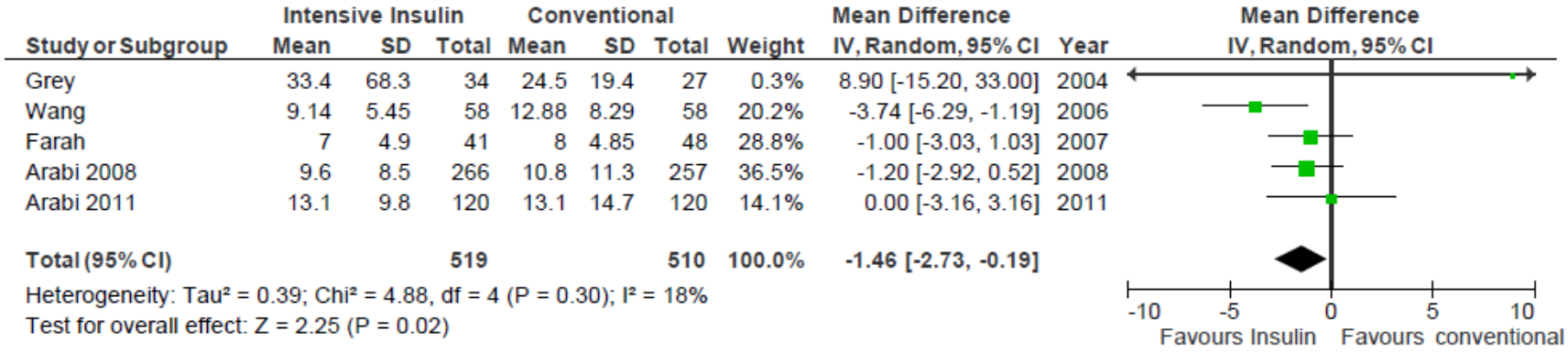


Figure 4a. Hospital LOS

Study or Subgroup	Insulin Mean	Insulin SD	Insulin Total	Conventional Mean	Conventional SD	Conventional Total	Weight	Mean Difference 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)

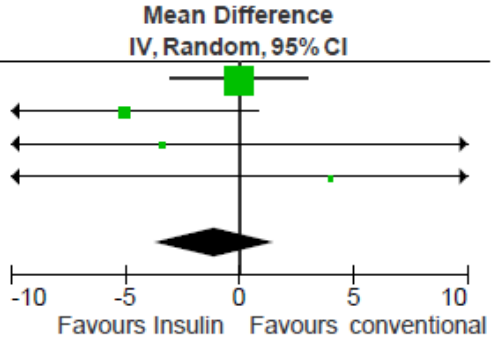


Figure 4b. Hospital LOS (excluding Van den Berghe 2001, 2006)

Study or Subgroup	Insulin Mean	Insulin SD	Insulin Total	Conventional Mean	Conventional SD	Conventional Total	Weight	Mean Difference 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)

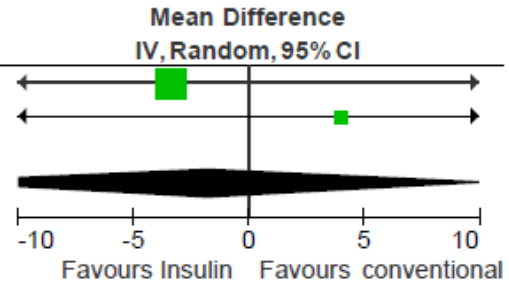


Figure 5a. Ventilator days

Study or Subgroup	Insulin Mean	Insulin SD	Insulin Total	Conventional Mean	Conventional SD	Conventional Total	Weight	Mean Difference 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)

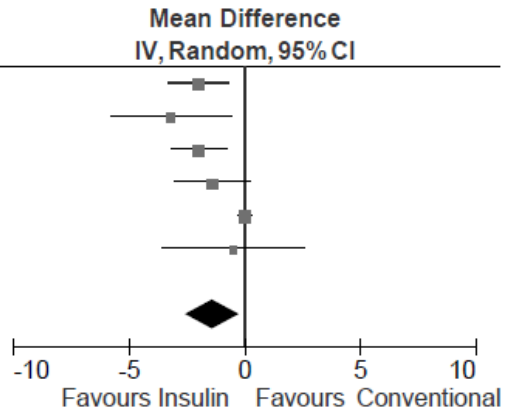


Figure 5b. Ventilator days (excluding Van den Berghe 2001, 2006)

Study or Subgroup	Insulin Mean	Insulin SD	Insulin Total	Conventional Mean	Conventional SD	Conventional Total	Weight	Mean Difference 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)

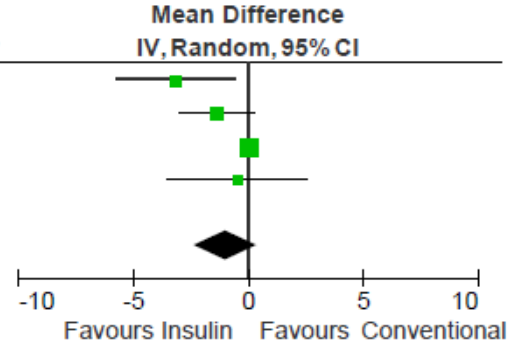


Figure 6a. Hypoglycemia

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)

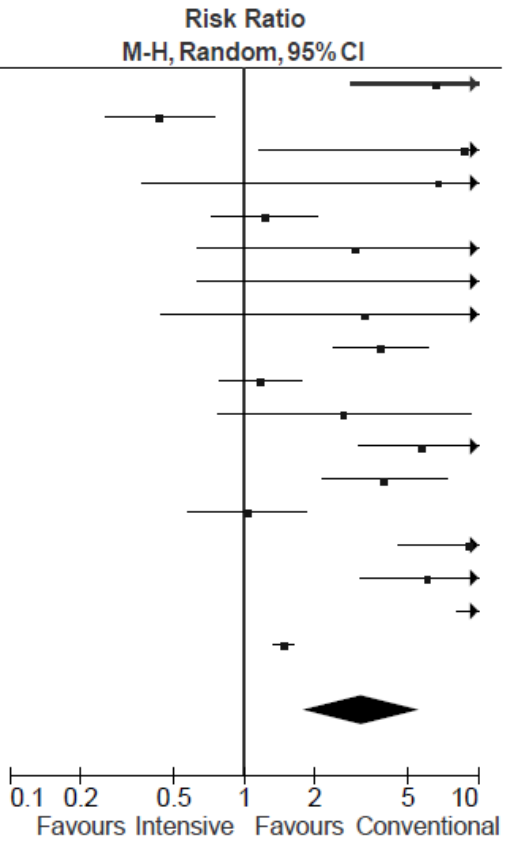
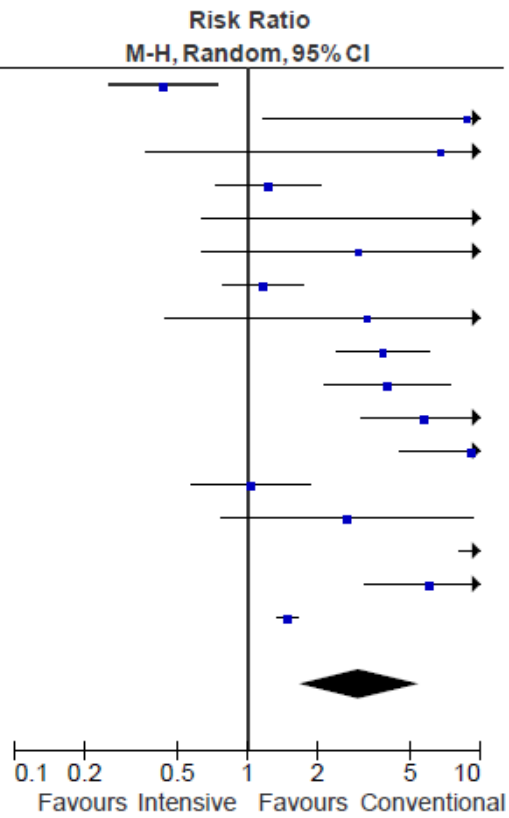


Figure 6b. Hypoglycemia (excluding Van den Berghe 2001)

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)



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Excluded Articles

#	Reason excluded	Citation
1	Diabetic patients	Davies RR, Newton RW, McNeill GP, Fisher BM, Kesson CM, Pearson D. Metabolic control in diabetic subjects following myocardial infarction: difficulties in improving blood glucose levels by intravenous insulin infusion.Scott Med J. 1991 Jun;36(3):74-6.
2	Not ICU patients, not mechanically ventilated	Stefanidis A, Melidonis A, Tournis S, Zairis M, Handanis S, Olympios C, Asimacopoulos P, Foussas S. Intensive insulin treatment reduces transient ischaemic episodes during acute coronary events in diabetic patients. Acta Cardiol. 2002 Oct;57(5):357-64.
3	Same study as NEJM 2001	Van den Berghe G, Wouters PJ, Bouillon R, Weekers F, Verwaest C, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P. Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control. Crit Care Med. 2003 Feb;31(2):359-66
4	No clinical outcomes	Holzinger U, Zauner A, Nimmerrichter P, Schiefermeier M, Ratheiser K, Zauner C. Metabolic inefficacy of a short-term low-dose insulin regimen in critically ill patients: a randomized, placebo-controlled trial. Wien Klin Wochenschr. 2004 Sep 30;116(17-18):603-7
5	Elective surgery patients	Lazar HL, Chipkin SR et al. Tight glycemic control in diabetic coronary artery bypass graft patients improves perioperative outcomes and decreases recurrent ischemic events. Circulation 2004;109:1497-1502.
6	Elective surgery patients	Hoedemaekers CW, Pickkers P, Netea MG, van Deuren M, Van der Hoeven JG. Intensive insulin therapy does not alter the inflammatory response in patients undergoing coronary artery bypass grafting: a randomized controlled trial [ISRCTN95608630]. Crit Care. 2005;9(6):R790-7
7	Insulin withdrawn within 6 hrs after admission to ICU	Koskenkari JK, Kaukoranta PK et al. Metabolic and hemodynamic effects of high-dose insulin treatment in aortic valve and coronary surgery. Ann Thorac Surg 2005;80:511-7
8	Not ICU patients	Mehta SR, Yusuf S, Díaz R, Zhu J, Pais P, Xavier D, Paolasso E, Ahmed R, Xie C, Kazmi K, Tai J, Orlandini A, Pogue J, Liu L; CREATE-ECLA Trial Group Investigators. Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: the CREATE-ECLA randomized controlled trial. JAMA. 2005 Jan 26;293(4):437-46.
9	Subset of earlier van Den Berg NEJM 2001 paper	Siroen MP, van Leeuwen PA, Nijveldt RJ, Teerlink T, Wouters PJ, Van den Berghe G. Modulation of asymmetric dimethylarginine in critically ill patients receiving intensive insulin treatment: a possible explanation of reduced morbidity and mortality? Crit Care Med. 2005 Mar;33(3):504-10

10	Subgroup analyses of earlier included Van den Berghe trials	Van den Berghe G, Schoonheydt K, Becx P, Bruyninckx F, Wouters PJ. Insulin therapy protects the central and peripheral nervous system of intensive care patients. Neurology. 2005 Apr 26;64(8):1348-53.
11	Not ICU patients, used glucose-insulin-potassium (GIK) treatment	Koskenkari JK, Kaukoranta PK, Rimpiläinen J, Vainionpää V, Ohtonen PP, Surcel HM, Juvonen T, Ala-Kokko TI. Anti-inflammatory effect of high-dose insulin treatment after urgent coronary revascularization surgery. Acta Anaesthesiol Scand. 2006 Sep;50(8):962-9.
12	Elective surgery patients	Plank J, Blaha J, Cordingley J, Wilinska ME, Chassin LJ, Morgan C, Squire S, Haluzik M, Kremen J, Svacina S, Toller W, Plasnik A, Ellmerer M, Hovorka R, Pieber TR. Multicentric, randomized, controlled trial to evaluate blood glucose control by the model predictive control algorithm versus routine glucose management protocols in intensive care unit patients. Diabetes Care. 2006 Feb;29(2):271-6.
13	Elective surgery patients	Svanfeldt M, Thorell A, Nygren J, Ljungqvist O. Postoperative parenteral nutrition while proactively minimizing insulin resistance. Nutrition. 2006 May;22(5):457-64. Epub 2006 Feb 13.
14	Elective surgery patients	van Wezel HB, Zuurbier CJ, de Jonge E, van Dam EW, van Dijk J, Endert E, de Mol BA, Fliers E. Differential effects of a perioperative hyperinsulinemic normoglycemic clamp on the neurohumoral stress response during coronary artery surgery. J Clin Endocrinol Metab. 2006 Oct;91(10):4144-53
15	Not critically ill patients	Walters MR, Weir CJ, Lees KR. A randomised, controlled pilot study to investigate the potential benefit of intervention with insulin in hyperglycaemic acute ischaemic stroke patients. Cerebrovasc Dis. 2006;22(2-3):116-22
16	Included as Bilotta 2009	Bilotta F, Spinelli A, Giovannini F, Doronzio A, Delfini R, Rosa G. The effect of intensive insulin therapy on infection rate, vasospasm, neurologic outcome, and mortality in neurointensive care unit after intracranial aneurysm clipping in patients with acute subarachnoid hemorrhage: a randomized prospective pilot trial. J Neurosurg Anesthesiol. 2007 Jul;19(3):156-60.
17	Note : Earlier version of Preiser 2009	Devos P, Preiser J, Mélot C. Impact of tight glucose control by intensive insulin therapy on ICU mortality and the rate of hypoglycaemia: final results of the glucontrol study [abstract]. Intensive Care Med 2007;33:S189
18	Elective surgery patients	Ghandi GY et al. Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery. Ann Intern Med. 2007;146:233-243
19	Not intensive insulin therapy	Gray CS, Hildreth AJ, Sandercock PA, O'Connell JE, Johnston DE, Cartlidge NE, Bamford JM, James OF, Alberti KG; GIST Trialists Collaboration. Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: the UK Glucose Insulin in Stroke Trial (GIST-UK). Lancet Neurol. 2007 May;6(5):397-406.
20	Included as Bilotta 2009	Bilotta F, Caramia R, Cernak I, Paoloni FP, Doronzio A, Cuzzone V, Santoro A, Rosa G. Intensive insulin therapy after severe traumatic brain injury: a randomized clinical trial. Neurocrit Care. 2008;9(2):159-66.
21	Elective surgery patients	Biolo G, De Cicco M, Lorenzon S, Dal Mas V, Fantin D, Paroni R, Barazzoni R, Zanetti M, Iapichino G, Guarnieri G. Treating hyperglycemia improves skeletal muscle protein metabolism in cancer patients after major surgery. Crit Care Med. 2008 Jun;36(6):1768-75.
22	Subcutaneous vs. IV insulin	Bodur HA, Saygili E, Saygili S, Doganay LH, Yesil S. Continuous infusion of subcutaneous compared to intravenous insulin for tight glycaemic control in medical intensive care unit patients. Anaesth Intensive Care. 2008 Jul;36(4):520-7.
23	Not ICU patients	Bruno A, Kent TA, Coull BM, Shankar RR, Saha C, Becker KJ, Kissela BM, Williams LS. Treatment of hyperglycemia in ischemic stroke (THIS): a randomized pilot trial. Stroke. 2008 Feb;39(2):384-9

24	Intervention is oral	Mojtahedzadeh M et al. Advantage of adjunct metformin and insulin therapy in the management of glycemia in critically ill patients. Evidence for nonoccurrence of lactic acidosis and needing to parenteral metformin. Arch Med Sci. 2008;4(2):174-181
25	Two different protocols & no clinical outcomes	Pachler C, Plank J, Weinhandl H, Chassin LJ, Wilinska ME, Kulnik R, Kaufmann P, Smolle KH, Pilger E, Pieber TR, Ellmerer M, Hovorka R. Tight glycaemic control by an automated algorithm with time-variant sampling in medical ICU patients. Intensive Care Med. 2008 Jul;34(7):1224-30.
26	Meta-analysis	Schetz M, Vanhorebeek I, Wouters PJ, Wilmer A, Van den Berghe G. Tight blood glucose control is renoprotective in critically ill patients. J Am Soc Nephrol. 2008 Mar;19(3):571-8.
27	Meta-analysis	Soylemez-Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis JAMA. 2008;300(8):933-44.
28	No clinical outcomes	Blaha J, Kopecky P, Matias M, Hovorka R, Kunstyr J, Kotulak T, Lips M, Rubes D, Stritesky M, Lindner J, Semrad M, Haluzik M. Comparison of three protocols for tight glycemic control in cardiac surgery patients. Diabetes Care. 2009 May;32(5):757-61.
29	2 different protocols	Cavalcanti AB, Silva E, Pereira AJ, Caldeira-Filho M, Almeida FP, Westphal GA, Beims R, Fernandes CC, Correa TD, Gouvea MR, Eluf-Neto J. A randomized controlled trial comparing a computer-assisted insulin infusion protocol with a strict and a conventional protocol for glucose control in critically ill patients. J Crit Care. 2009 Sep;24(3):371-8.
30	2 methods, not ICU patients	Long H, Lin ZC, Wang YN, Lu HP, Situ DR. [Effect of different ways of insulin infusion in parenteral nutrition patients on activation and concentration of insulin and blood glucose control:a prospective randomized comparison study]. Zhonghua Wai Ke Za Zhi. 2009 Feb 15;47(4):286-8. Chinese.
31	Meta analysis	Subramaniam B, Panzica PJ, Novack V, Mahmood F, Matyal R, Mitchell JD, Sundar E, Bose R, Pomposelli F, Kersten JR, Talmor DS. Continuous perioperative insulin infusion decreases major cardiovascular events in patients undergoing vascular surgery: a prospective, randomized trial. Anesthesiology. 2009 May;110(5):970-7.
32	No clinical outcomes	Zuran I, Poredos P, Skale R, Voga G, Gabrscek L, Pareznik R. Intensive insulin treatment improves forearm blood flow in critically ill patients: a randomized parallel design clinical trial. Crit Care. 2009;13(6):R198.
33	Elective surgery patients (esophagectomy)	Egi M, Toda Y, Katayama H, Yokoyama M, Morita K, Arai H, Yamatsuji T, Bailey M, Naomoto Y. Safer glycemic control using isomaltulose-based enteral formula: a pilot randomized crossover trial. J Crit Care. 2010 Mar;25(1):90-6. Epub 2009 Sep 24.
34	Not ICU patients	Kruyt ND, Biessels GJ, Vriesendorp TM, Devries JH, Hoekstra JB, Elbers PW, Kappelle LJ, Portegies P, Vermeulen M, Roos YB. Subjecting acute ischemic stroke patients to continuous tube feeding and an intensive computerized protocol establishes tight glycemic control. Neurocrit Care. 2010 Feb;12(1):62-8. Epub 2009 May 27.
35	2 methods	Schnipper JL, Liang CL, Ndumele CD, Pendergrass ML. Effects of a computerized order set on the inpatient management of hyperglycemia: a cluster-randomized controlled trial. Endocr Pract. 2010 Mar-Apr;16(2):209-18.
36	No clinical outcomes	Mousavi SN, Norouzy A, Nematy M, Safarian M, Samini F, Birjandinejad A, Purafzlifiruzabadi SJ. Intensive insulin therapy reduces infections in patients on parenteral nutrition- A randomized clinical trial. 2012;1(1):2-7.
37	Secondary analysis of Brunkhorst 2008	Elke G, Kuhnt E, Ragaller M, Schädler D, Frerichs I, Brunkhorst FM, Löffler M, Reinhart K, Weiler N; German Competence Network Sepsis (SepNet). Enteral nutrition is associated with improved outcome in patients with severe sepsis. A secondary analysis of the VISEP trial. Med Klin Intensivmed Notfmed. 2013 Apr;108(3):223-33.

38	No clinical outcomes	Leelarathna L, English SW, Thabit H, Caldwell K, Allen JM, Kumareswaran K, Wilinska ME, Nodale M, Mangat J, Evans ML, Burnstein R, Hovorka R. Feasibility of fully automated closed-loop glucose control using continuous subcutaneous glucose measurements in critical illness: a randomized controlled trial. Crit Care. 2013 Jul 24;17(4):R159.
39	No clinical outcomes	Bilotta F, Badenes R, Lolli S, Belda FJ, Einav S, Rosa G. Insulin infusion therapy in critical care patients: Regular insulin vs short-acting insulin. A prospective, crossover, randomized, multicenter blind study. J Crit Care. 2015 Apr;30(2):437.e1-6.
40	Elective surgery pts	Oghazian MB, Javadi MR, Radfar M, Torkamandi H, Sadeghi M, Hayatshahi A, Gholami K. Effectiveness of regular versus glargine insulin in stable critical care patients receiving parenteral nutrition: a randomized controlled trial. Pharmacotherapy. 2015 Feb;35(2):148-57.
41	Follow up to NICE Sugar Study	NICE-SUGAR Study Investigators for the Australian and New Zealand Intensive Care Society Clinical Trials Group and the Canadian Critical Care Trials Group, Finfer S, Chittock D, Li Y, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Hebert P, Henderson W, Heyland D, Higgins A, McArthur C, Mitchell I, Myburgh J, Robinson B, Ronco J. Intensive versus conventional glucose control in critically ill patients with traumatic brain injury: long-term follow-up of a subgroup of patients from the NICE-SUGAR study. Intensive Care Med. 2015 Jun;41(6):1037-47.
42	Prospective, randomized within patient crossover study. No clinically significant outcomes	Wolahan SM, Prins ML, McArthur DL, Real CR, Hovda DA, Martin NA, Vespa PM, Glenn TC. Influence of Glycemic Control on Endogenous Circulating Ketone Concentrations in Adults Following Traumatic Brain Injury. Neurocrit Care. 2017 Apr;26(2):239-246.
43	No critically ill	Duncan AE, Sessler DI, Sato H, Sato T, Nakazawa K, Carvalho G, Hatzakorzian R, Codere-Maruyama T, Abd-Elsayed A, Bose S, Said T, Mendoza-Cuartas M, Chowdary H, Mascha EJ, Yang D, Gillinov AM, Schricker T. Hyperinsulinemic Normoglycemia during Cardiac Surgery Reduces a Composite of 30-day Mortality and Serious In-hospital Complications: A Randomized Clinical Trial. Anesthesiology. 2018 Jun;128(6):1125-1139. doi: 10.1097/ALN.0000000000002156. PMID: 29537981; PMCID: PMC6509049.