

10.4a 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 steroids), 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 \pm 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 \pm 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 \pm 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 # (%)‡	
				Intensive Insulin	Conventional Insulin	Intensive Insulin	Conventional Insulin
1) Van Den Bergh 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 Bergh 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 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	
	Intensive Insulin ICU Hospital	Conventional Insulin ICU Hospital	Intensive Insulin	Conventional Insulin	Intensive Insulin Hypoglycemia	Conventional Insulin Hypoglycemia
1) Van Den Berghe 2001	7 ± 11* 23 ± 32 *	9 ± 15* 23 ± 28 *	5 ± 11*	7 ± 15*	39/765 (5)	6/783 (<1)
2) Grey 2004	33.4 ± 68.3	24.5 ± 19.4	NR	NR	11/34 (32)	20/27 (74)
3) Bland 2005	NR	NR	NR	NR	Intensive Insulin Severe hypoglycemia 1/5 (20) Moderate hypoglycemia 4/5 (80) Total hypoglycemia 5/5 (100)	Conventional Insulin Severe hypoglycemia 1/5 (20) Moderate hypoglycemia 3/5 (60) Total hypoglycemia 4/5 (80)
4) Henderson 2005	7.42 (5.12-12.72) 22 (13-40.5)	11.5 (7.39-20.95) 33 (21-66)	Intensive Insulin (hours) 132.2 (90-28)	Conventional Insulin (hours) 228.2 (140-459)	Intensive Insulin Hypoglycemic events 8/32 (24)	Conventional Insulin Hypoglycemic events 1/35 (3)
5) Yu 2005***	NR	NR	Intensive Insulin 10 (9)	Conventional Insulin 17 (10)	Intensive Insulin Hypoglycemia 3/28 (11)	Conventional Insulin Hypoglycemia 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 Hypoglycemia 6/58 (10)	Conventional Insulin Hypoglycemia 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 Hypoglycemia More often in the intensive group	Conventional Insulin Hypoglycemia

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 Severe hypoglycemia 5/35 (14)	Conventional Insulin 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 Glasgow Outcome Scale Extended 9 (53) Convulsions 1 (3)	Conventional Insulin 5 (56) 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 Hypoglycemia 80/550 (15)	Conventional Insulin 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 Hypoglycemic events 23/41 (56)	Conventional Insulin 23/48 (48)
12) He 2007***	NR	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 Severe hypoglycemia 4/11 (36)	Conventional Insulin 1/9 (11)
14) Oksanen 2007	NR	NR	NR	NR	Intensive Insulin % bl. gl measurements in targeted range 71 (62-79)	Conventional Insulin 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 Hypoglycemia 76/266 (29)	Conventional Insulin 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 Hypoglycemia 42/247 (17)	Conventional Insulin Hypoglycemia 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 Hypoglycemia 21/254 (8.3)	Conventional Insulin Hypoglycemia 20/250 (0.8)
18) He 2008***	NR	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 Severe hypoglycemia 8/36 (22)	Conventional Insulin Severe hypoglycemia 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 Incidence of hypoglycemia Morning laboratory 8/121 (7)	Conventional Insulin Incidence of hypoglycemia Morning laboratory 1/119 (1)
					Bedside 50/121 (41)	Bedside 9/119 (8)
					Total 58/121 (48)	Total 10/119 (8)
21) Zhang 2008***	NR	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 Patients ≥ 1 hypoglycemic episodes 226/242 (93)	Conventional Insulin Patients ≥ 1 hypoglycemic episodes 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 Severe hypoglycemia 206/3016 (7)	Conventional Insulin Severe hypoglycemia 15/3014 (1)
24) Savioli 2009	NR	NR	NR	NR	Intensive Insulin Hypoglycemic episodes 45/45 (100)	Conventional Insulin Hypoglycemic episodes 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 Hypoglycemia 72 (43-100)	Conventional Insulin Hypoglycemia 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
ITT: intent to treat; NA: not available
LOS: length of stay

‡ refers to the # of patients with infections unless specified
** RR= relative risk, CI= Confidence intervals

(-): median (range)
() : mean ± Standard deviation (number)

ICU: intensive care unit
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. Aron 2013

Study	Population	Methods (score)	Intervention	Mortality # (%)		Infections # (%)‡	
				IV Insulin Hospital	SC Insulin Hospital	IV Insulin Total infections	SC Insulin Total 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).	3/29 (10.3)	1/29 (10.3)	0.5 ± 1.3 (p=0.7) Pneumonia 4/29 (13.8)	0.4 ± 0.7 Pneumonia 7/29 (24.1)

Table 2. Aron 2013 (continued)

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

IV: intravenous

SC: subcutaneous

Figure 1a. Overall mortality

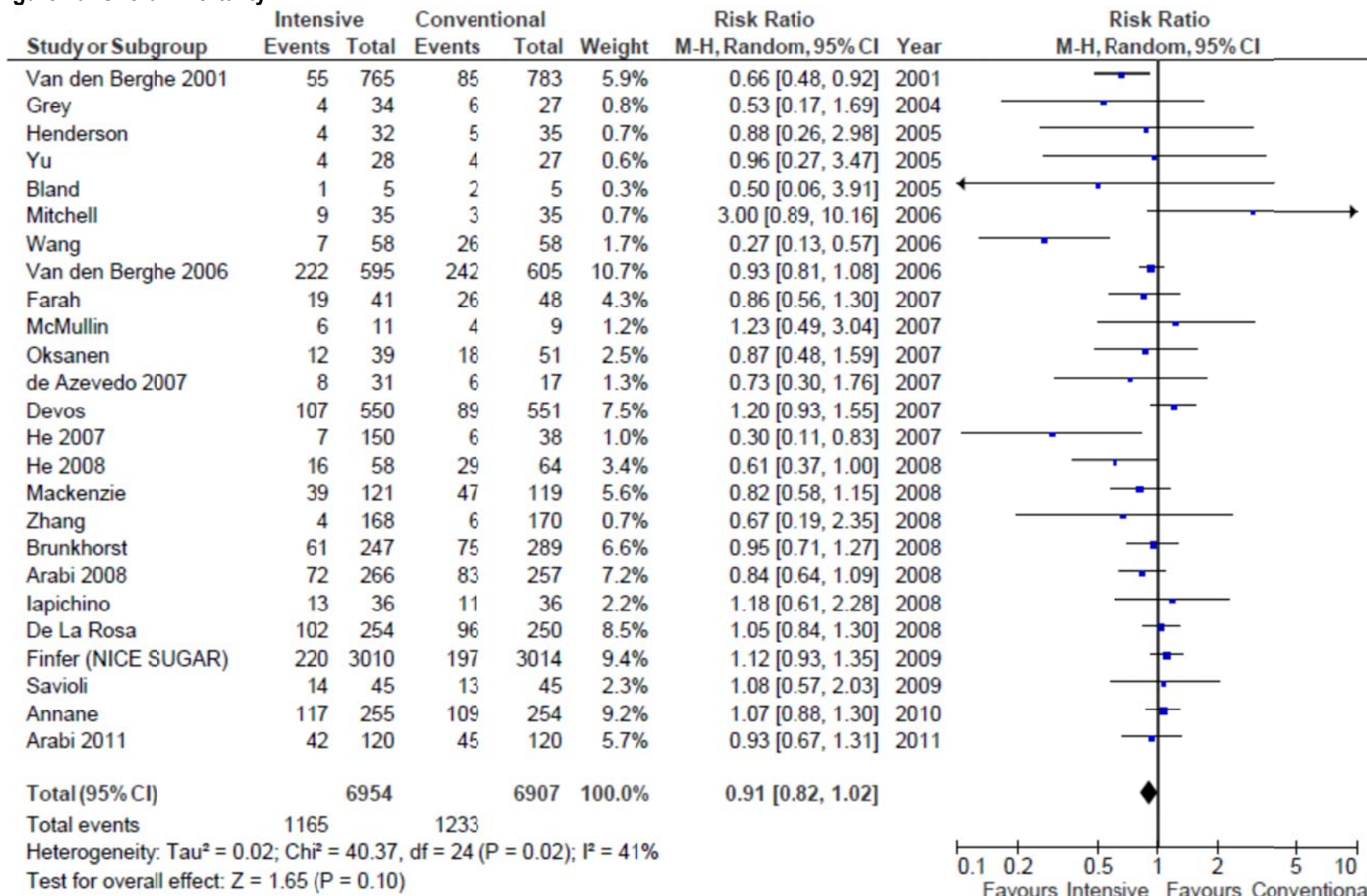


Figure 1b. Overall mortality (excluding Annane 2010)

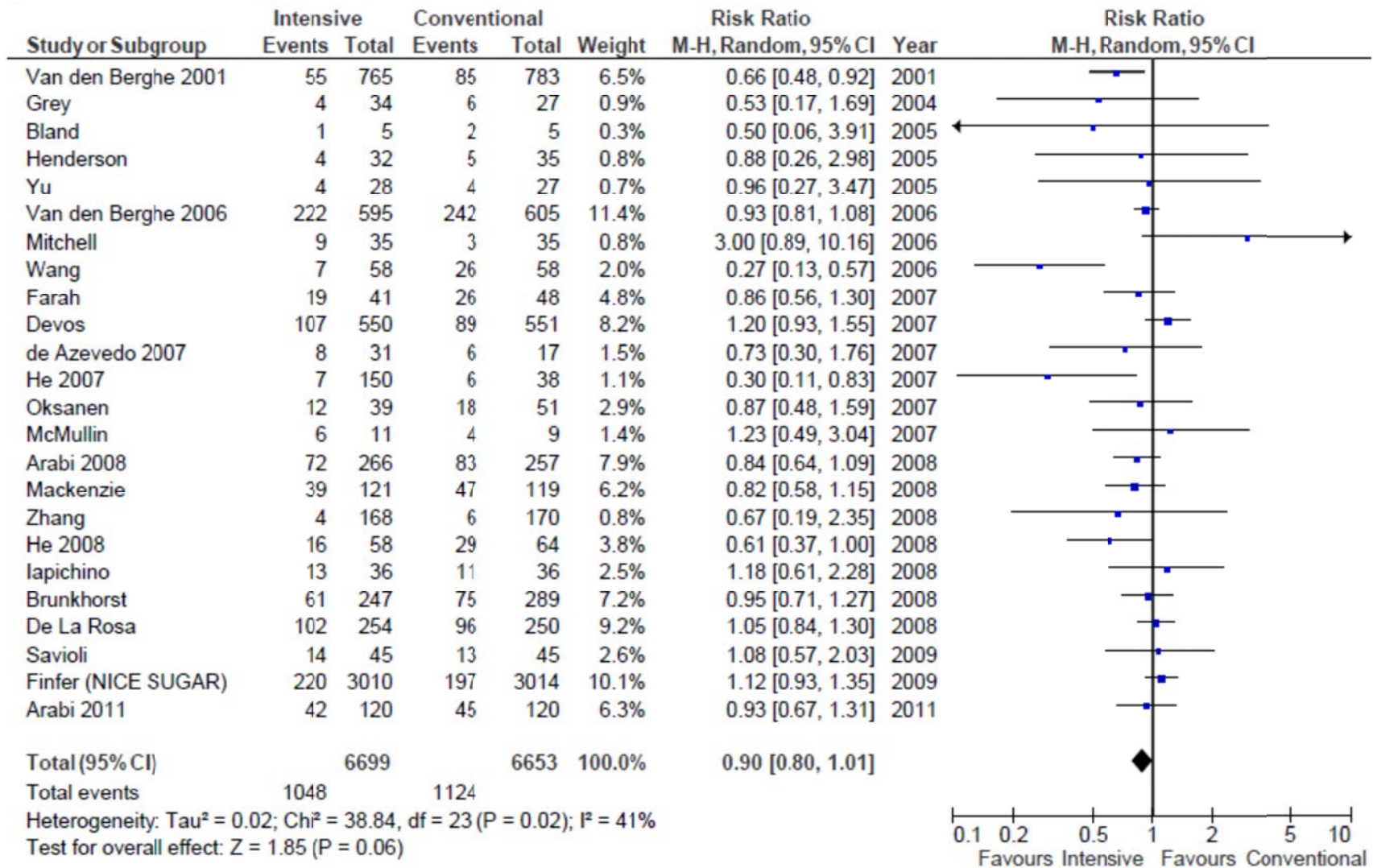


Figure 2a. Infections

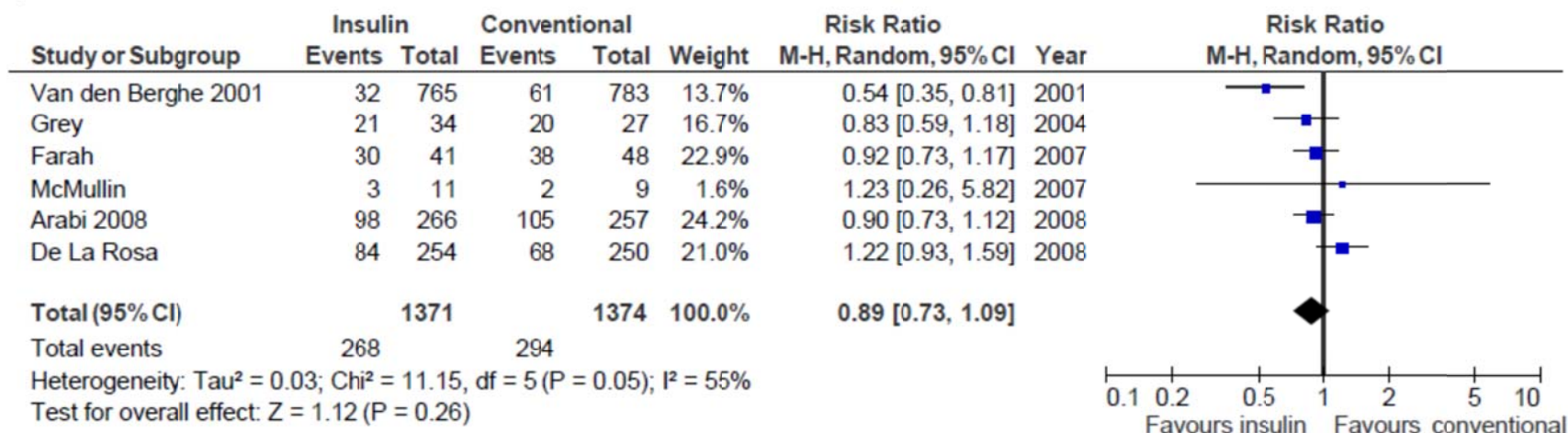


Figure 2b. Infections (excluding Van den Berghe 2001)

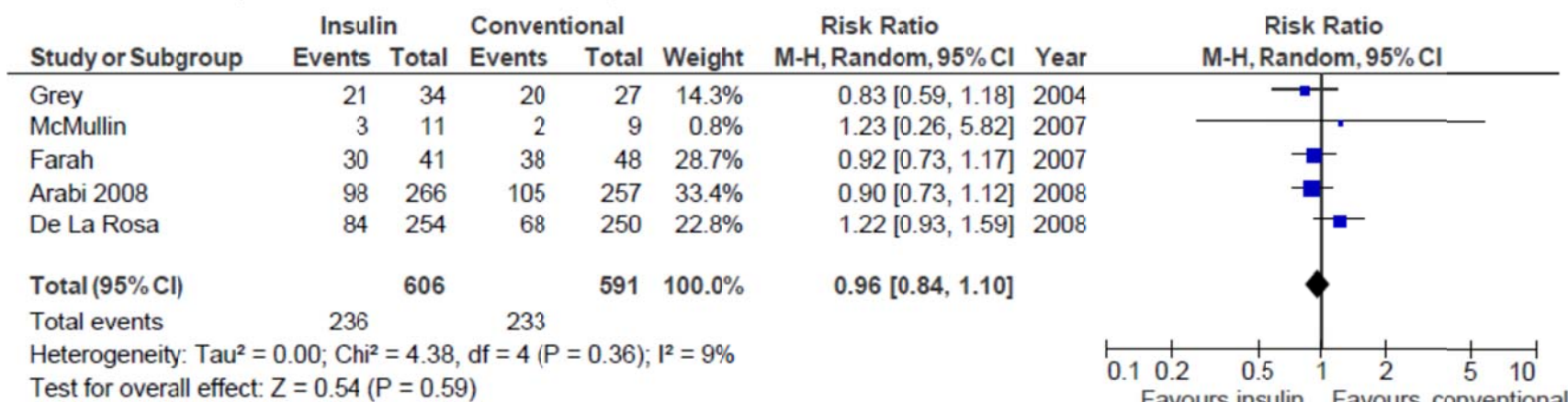


Figure 3a. ICU LOS

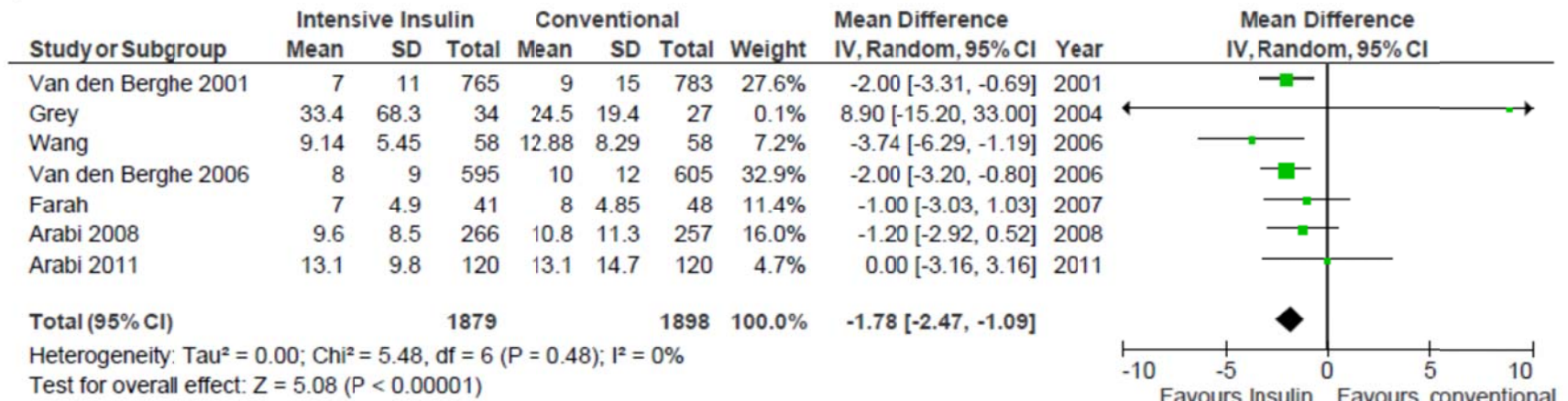


Figure 3b. ICU LOS (excluding Van den Berghe 2001, 2006)

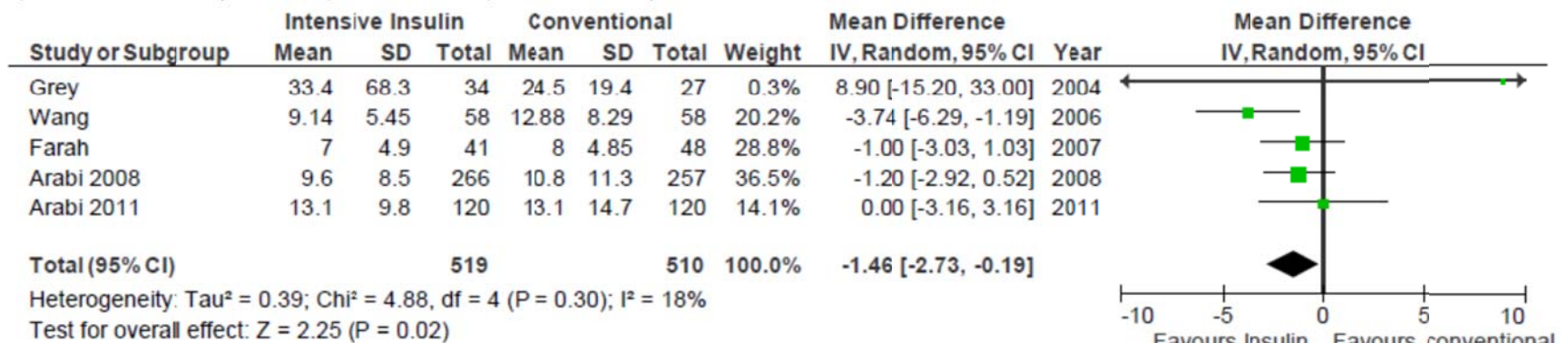


Figure 4a. Hospital LOS

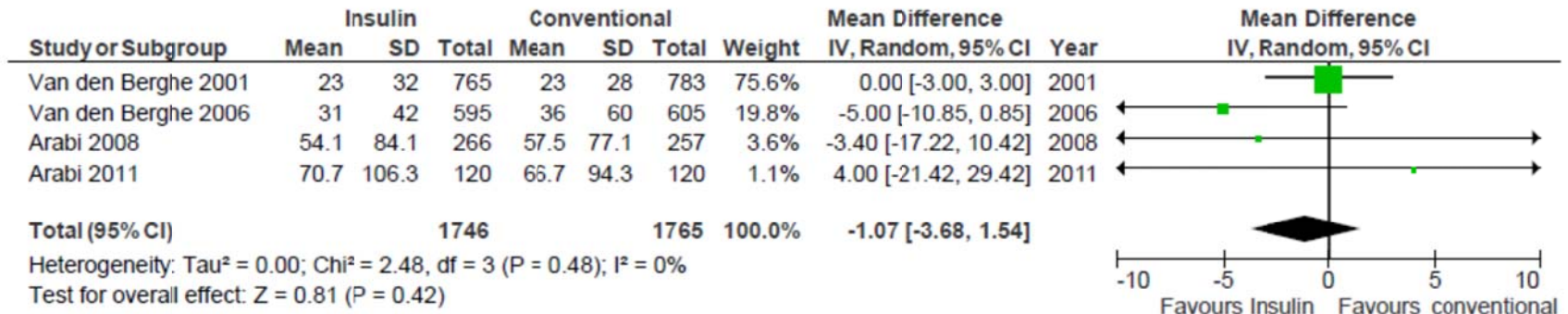


Figure 4b. Hospital LOS (excluding Van den Berghe 2001, 2006)

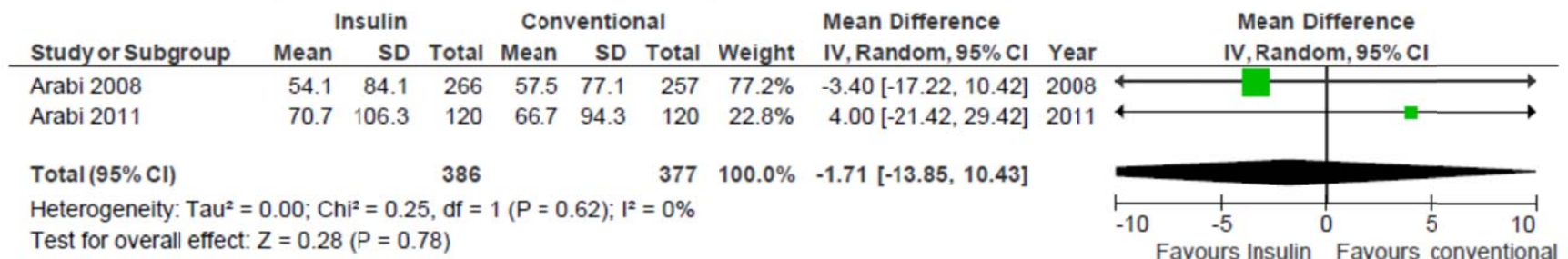


Figure 5a. Ventilator days

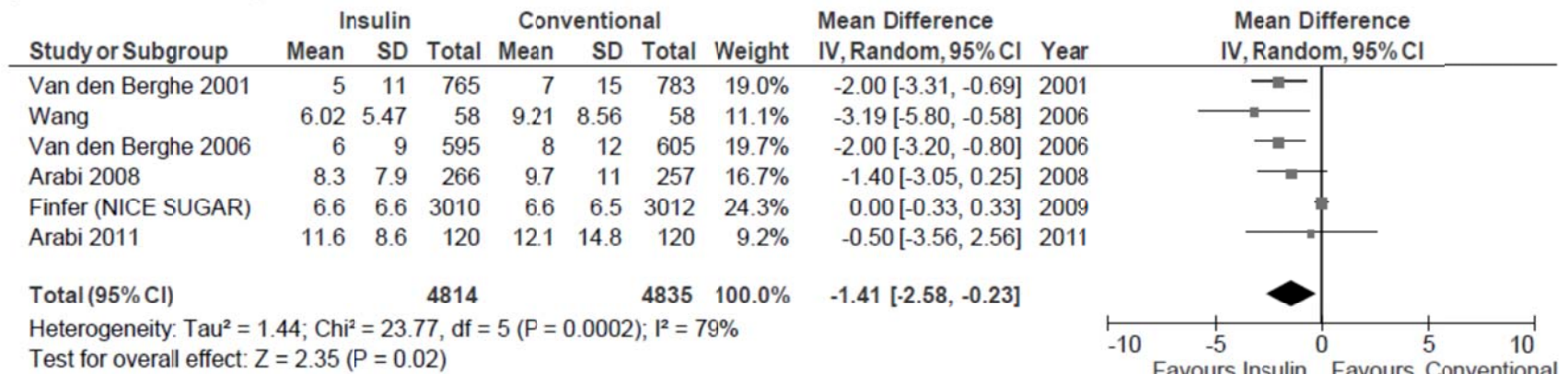


Figure 5b. Ventilator days (excluding Van den Berghe 2001, 2006)

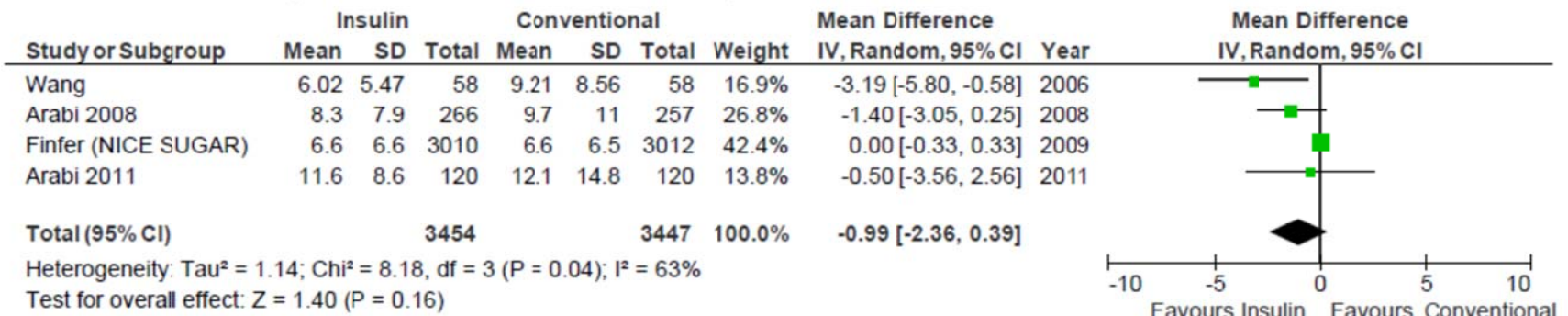


Figure 6a. Hypoglycemia

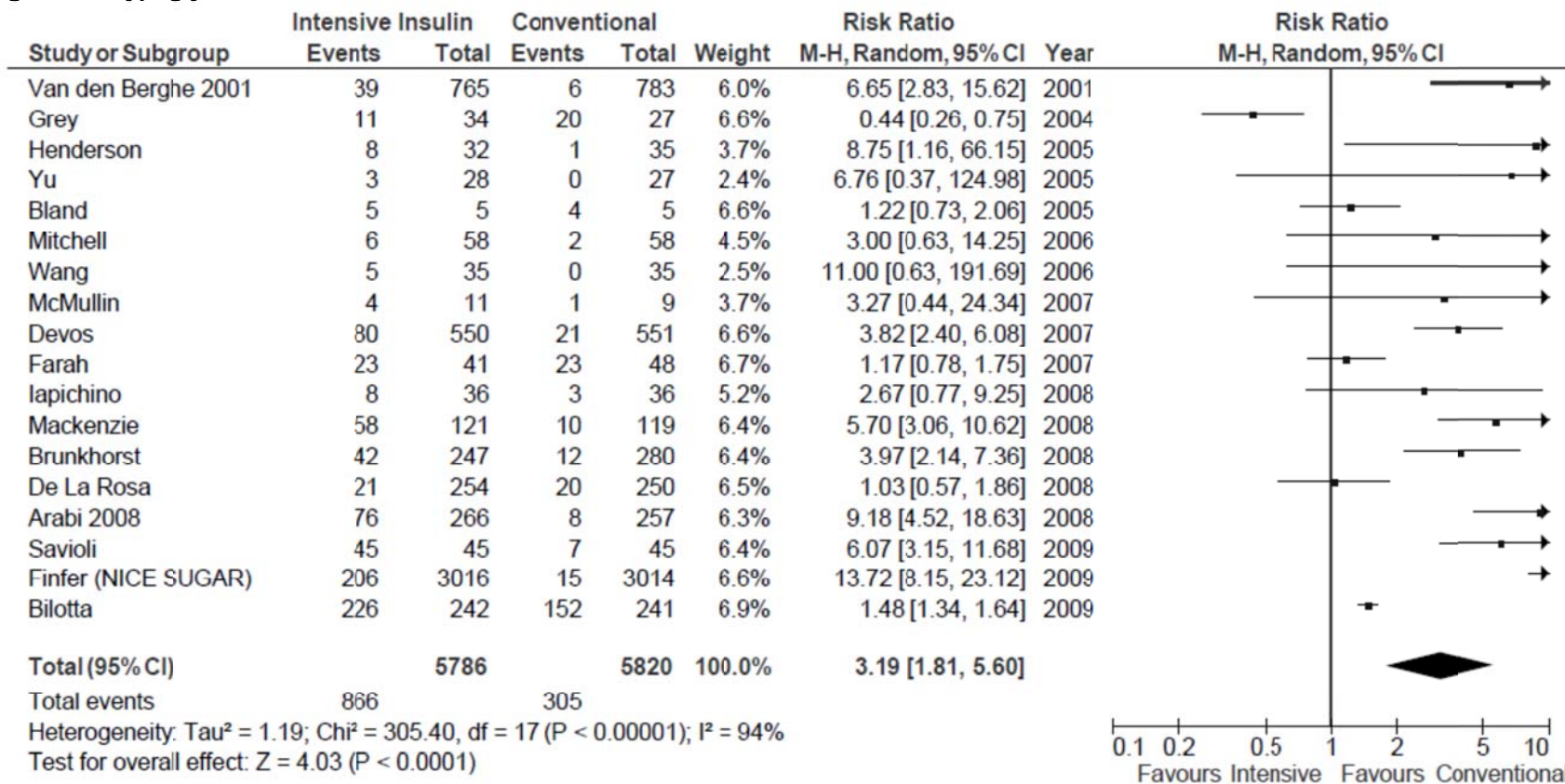


Figure 6b. Hypoglycemia (excluding Van den Berghe 2001)

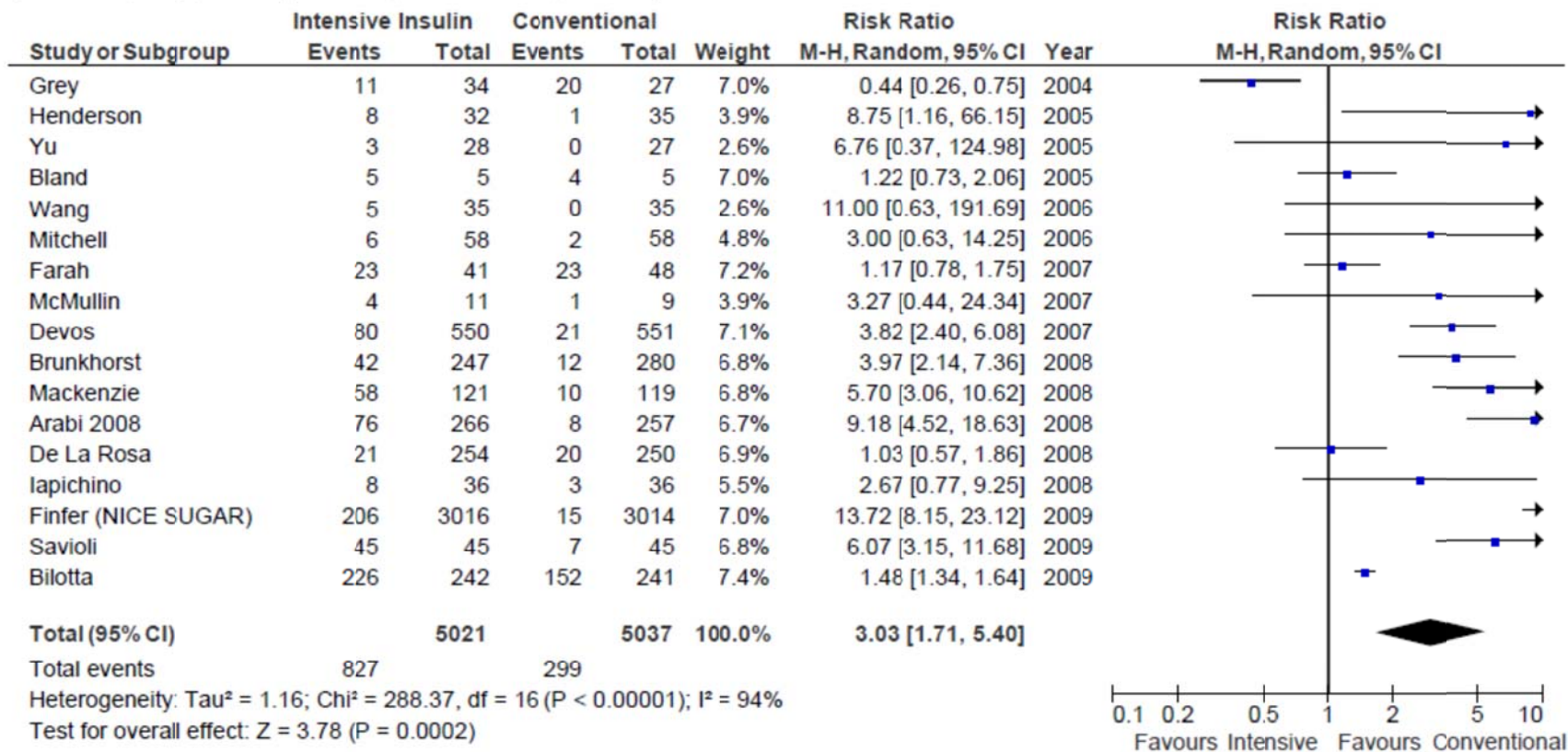


Table 3. Excluded Articles

#	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. <i>Scott Med J.</i> 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. <i>Acta Cardiol.</i> 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. <i>Crit Care Med.</i> 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. <i>Wien Klin Wochenschr.</i> 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. <i>Circulation</i> 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]. <i>Crit Care.</i> 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. <i>Ann Thorac Surg</i> 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. <i>JAMA.</i> 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? <i>Crit Care Med.</i> 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. <i>Neurology.</i> 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. <i>Acta Anaesthesiol Scand.</i> 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. <i>Diabetes Care.</i> 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. <i>Nutrition</i> . 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, Ender E, de Mol BA, Fliers E. Differential effects of a perioperative hyperinsulinemic normoglycemic clamp on the neurohumoral stress response during coronary artery surgery. <i>J Clin Endocrinol Metab</i> . 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. <i>Cerebrovasc Dis</i> . 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. <i>J Neurosurg Anesthesiol</i> . 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]. <i>Intensive Care Med</i> 2007;33:S189
18	Elective surgery patients	Ghandi GY et al. Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery. <i>Ann Intern Med</i> . 2007;146:233-243
19	Not intensive insulin therapy	Gray CS, Hildreth AJ, Sandercock PA, O'Connell JE, Johnston DE, Cartledge 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). <i>Lancet Neurol</i> . 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. <i>Neurocrit Care</i> . 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. <i>Crit Care Med</i> . 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. <i>Anaesth Intensive Care</i> . 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. <i>Stroke</i> . 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. <i>Arch Med Sci</i> . 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. <i>Intensive Care Med</i> . 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. <i>J Am Soc Nephrol</i> . 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 <i>JAMA</i> . 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 glycaemic control in cardiac surgery patients. <i>Diabetes Care</i> . 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. <i>J Crit Care.</i> 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]. <i>Zhonghua Wai Ke Za Zhi.</i> 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. <i>Anesthesiology.</i> 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. <i>Crit Care.</i> 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. <i>J Crit Care.</i> 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. <i>Neurocrit Care.</i> 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. <i>Endocr Pract.</i> 2010 Mar-Apr;16(2):209-18.
36	No clinical outcomes	Mousavi SN, Norouzy A, Nematy M, Safarian M, Samini F, Birjandinejad A, Purafzifiruzabadi 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. <i>Med Klin Intensivmed Notfmed.</i> 2013 Apr;108(3):223-33.
38	No clinical outcomes	Leelarathna L, English SW, Thabit H, Caldwell K, Allen JM, Kumareswaran K, Wilińska 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. <i>Crit Care.</i> 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. <i>J Crit Care.</i> 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. <i>Pharmacotherapy.</i> 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. <i>Intensive Care Med.</i> 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.
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