Supplemental Files for

Guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients.

Tight Glycemic Control versus Routine Glycemic Control

Description of the condition

Hyperglycemia is a common condition in patients admitted to ICUs

Description of the intervention

Insulin infusion (with or without SQ insulin) targeted to reduce BG below 150 mg/dL using conventional control or to keep it in the range of 80-110 mg/dL (tight control)

How the intervention might work

Reduction of BG is the intermediate pharmacological effect. Precise mechanism is not yet known.

Why it is important to do this review

Several studies have suggested reduction in mortality associated with better BG control.

Objectives

Methods

Criteria for considering studies for this review

Types of studies

RCT and observational

Types of participants

All ICU patients

Types of interventions

Insulin infusion (with or without SQ insulin)

Types of outcome measures

Survival, clinical events

Primary outcomes

Mortality (Hospital or 30 day)

Secondary outcomes

ICU Mortality, severe hypoglycemia (<40 mg/dL), renal replacement therapy, transfusion, ICU length of stay.

Proposed but inadequate number of studies reporting: moderate hypoglycemia (40-60 mg/dL), critical illness polyneuropathy

Search methods for identification of studies

Electronic and manual

Electronic searches

PubMed, Ovid, Google Scholar

Searching other resources

Manual

Data collection and analysis

Selection of studies

Data extraction and management

Manual

Assessment of risk of bias in included studies

Measures of treatment effect

Mortality

Definitions of Study Quality

High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Part 1: Overview of Findings

Outcome	Hospital or 28 Day Mortality	ICU Mortality	Severe Hypoglycemia	Renal Replacement Therapy	Blood Transfusion	Bacteremia	ICU Length of Stay
Comparisons	**Number of participants (Number of studies)**						
Tight glycemic control vs. conventional glycemic control in all ICU patients	35334 (14)	21438 (8)	27530 (10)	9468 (7)	8616 (4)	9427 (6)	12491 (9)

Summary of all studies for trial design characteristics, limitations, quality and relationship to the desired outcome: impact on mortality

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Tight glycemic control**	**conventional glycemic control**	**Relative (95% CI)**	**Absolute**		
Hospital or 28 Day Mortality												
14	observational study	serious[1]	serious[2]	serious[3]	serious[4]	strong association[5] dose response gradient[6]	3161/22268 (14.2%)	2414/13066 (20.2%)	OR 0.82 (0.68 to 0.98)	31 fewer per 1,000	⊕OOO VERY LOW	CRITICAL
ICU Mortality												
8	observational study	serious[7]	serious[8]	serious[9]	serious[10]	dose response gradient[11]	1776/13575 (13.1%)	1158/7863 (16.8%)	OR 0.99 (0.86 to 1.15)	1 fewer per 1,000	⊕OOO VERY LOW	CRITICAL
Severe Hypoglycemia												
10	observational study	serious[12]	no serious inconsistency	serious[13]	no serious imprecision	strong association[14] dose response gradient[15]	775/16622 (4.7%)	144/10908 (2%)	OR 5.18 (2.91 to 9.22)	75 more per 1,000	⊕⊕OO LOW	CRITICAL
Renal Replacement Therapy												
7	observational study	serious[16]	serious[17]	serious[18]	serious[19]	none	641/4713 (13.6%)	653/4755 (13.2%)	OR 0.89 (0.69 to 1.15)	13 fewer per 1,000	⊕OOO VERY LOW	IMPORTANT
Blood Transfusion												
4	randomised trial	serious[20]	serious[21]	serious[22]	serious[23]	none	1777/4279 (41.5%)	1777/4337 (38.9%)	OR 1.07 (0.89 to 1.28)	20 more per 1,000	⊕OOO VERY LOW	IMPORTANT
Bacteremia												
6	randomized	serious[24]	serious[25]	serious[26]	serious[27]	strong	483/4703	515/4724	OR 0.75	23 fewer	⊕OOO	CRITICAL

	trial					association[28]	(10.3%)	(10.1%)	(0.53 to 1.06)	per 1,000	VERY LOW	
ICU Length of Stay (range of scores: -; Better indicated by less)												
9	observational study	serious[29]	serious[30]	serious[31]	serious[32]	none	6261	6230	-	SMD -0.04 (-0.13 to 0.05)	⊕OOO VERY LOW	IMPORTANT

CI: Confidence interval; OR: Odds ratio; SMD: Standardized mean difference

[1] No study was blinded. Single site studies for this outcome: Van den Berghe 2001, Grey 2004, Furnary 2006, Toft 2006, Krinsley 2006, Van den Berghe 2006, Scalea 2007, Farah 2007, Treggiari 2008, De La Rosa 2008, and Arabi 2008. Hyperglycemic BG targets (in mg/dL) in the control groups were 140-180 (Glucontrol, 2009), 140-200 (Farah 2007), 180-200 (Van den Berghe 2001, 2006, VISEP 2008, De La Rosa 2008, Arabi 2008), and 180-220 (Grey, 2004).
[2] Four positive studies, 10 negative studies. Van den Berghe 2006 sub-group analysis inconsistent.
[3] Van den Berghe 2001 included only intubated surgical patients, Furnary 2006 included only diabetics, Van den Berghe 2006 included only MICU patients, Scalea 2007 included only trauma patients, VISEP included only patients with severe sepsis.
[4] Negative studies (observed power, %): Grey 2004 (20.00), Toft 2006 (10.43), Van den Berghe 2006 (15.87), Farah 2007(10.81), VISEP 2008 (5.94), Treggiari 2008 (23), De La Rosa 2008 (6.29), Arabi 2008 (25.61), NICE-SUGAR (negative at 28 days, 29.15), Glucontrol (34.43).
[5] Furnary 2006 relative risk = 2.52.
[6] Treggiari 2008; Krinsley, 2006; Furnary, 2006.
[7] No study was blinded. Single site studies for this outcome: Van den Berghe 2001, Van den Berghe 2006, Farah 2007, Treggiari 2008, De La Rosa 2008, and Arabi 2008. Hyperglycemic BG targets (in mg/dL) in the control groups for this outcome were 140-180 (Glucontrol, 2009), 140-200 (Farah 2007), 180-200 (Van den Berghe 2001, 2006, De La Rosa 2008, Arabi 2008).
[8] One positive study, 7 negative studies.
[9] Van den Berghe 2001 included only intubated surgical patients, Van den Berghe 2006 included only MICU patients.
[10] Negative studies (observed power, %): Van den Berghe 2006 (17.71), Farah 2007 (11.11), Treggiari 2008 (31), De La Rosa 2008 (7.23), Arabi 2008 (20.54), NICE-SUGAR (37.72), Glucontrol (13.35).
[11] Treggiari 2008.
[12] No study was blinded. Single site studies for this outcome: Van den Berghe 2001, Toft 2006, Krinsley 2006, Van den Berghe 2006, Treggiari 2008, De La Rosa 2008, and Arabi 2008. Hyperglycemic BG targets for this outcome (in mg/dL) in the control groups were 140-180 (Glucontrol, 2009), and 180-200 (Van den Berghe 2001, 2006, VISEP 2008, De La Rosa 2008, Arabi 2008).
[13] Van den Berghe 2001 included only intubated surgical patients, Van den Berghe 2006 included only MICU patients, VISEP included only patients with severe sepsis.
[14] , Overall Relative Risk 4.67, Odds Ratio 5.18.
[15] Treggiari 2008; Krinsley, 2006.
[16] No study was blinded. Single site studies for this outcome: Van den Berghe 2001, Grey 2004, Toft 2006, De La Rosa 2008, and Arabi 2008. Hyperglycemic BG targets (in mg/dL) in the control groups for this outcome were 180-200 (Van den Berghe 2001, VISEP 2008, De La Rosa 2008, Arabi 2008), and 180-220 (Grey, 2004).
[17] One positive study, 6 negative studies.
[18] Van den Berghe 2001 included only intubated surgical patients, VISEP included only patients with severe sepsis.
[19] Negative studies (observed power): Grey 2004 (19.94), Toft 2006 (19.94), VISEP 2008 (26.37), De La Rosa 2008 (11.56), Arabi 2008 (5.10), NICE-SUGAR (16.34),
[20] No study was blinded. Single site studies for this outcome: Van den Berghe 2001, De La Rosa 2008. Hyperglycemic BG targets (in mg/dL) in the control groups for this outcome were 180-200 (Van den Berghe 2001, VISEP 2008, De La Rosa 2008).
[21] One study favoring the control group, 3 negative studies.
[22] Van den Berghe 2001 included only intubated surgical patients, VISEP included only patients with severe sepsis.
[23] Negative studies (observed power, %): Van den Berghe 2001 (17.67), De La Rosa 2008 (10.43), NICE-SUGAR (9.45).
[24] No study was blinded. Single site studies for this outcome: Van den Berghe 2001, Grey 2004, Van den Berghe 2006, Farah 2007, De La Rosa 2008. Hyperglycemic BG targets (in mg/dL) in the control groups for this outcome were 140-200 (Farah 2007), 180-200 (Van den Berghe 2001, 2006, De La Rosa 2008, and 180-220 (Grey, 2004),
[25] Two positive studies, 4 negative studies.
[26] Van den Berghe 2001 included only intubated surgical patients, Van den Berghe 2006 included only MICU patients.
[27] Four negative studies: Van den Berghe 2006 (9.95), Farah 2007(13.07), De La Rosa 2008 (5.42), NICE-SUGAR (7.38).
[28] Grey relative risk = 0.353
[29] No study was blinded. Single site studies for this outcome: Van den Berghe 2001, Grey 2004, Scalea 2007, Farah 2007, De La Rosa 2008, and Arabi 2008. Hyperglycemic BG targets (in mg/dL) in the control groups for this outcome were 140-200 (Farah 2007), 180-200 (Van den Berghe 2001, VISEP 2008, De La Rosa 2008, Arabi 2008), and 180-220 (Grey, 2004).

[30] One positive study, 8 negative studies
[31] Van den Berghe 2001 included only intubated surgical patients, Furnary 2006 included only diabetics, Scalea 2007 included only trauma patients, VISEP included only patients with severe sepsis.
[32] Negative studies (observed power, %): Van den Berghe 2001 (5.0), Grey 2004 (9.9), Farah 2007(15.8), VISEP 2008 (34.6), De La Rosa 2008 (5.0), Arabi 2008 (27.9), NICE-SUGAR (5.0), Glucontrol (5.0).

Tight glycemic control compared to conventional glycemic control for ICU patients

Patient or population: ICU patients
Settings: Intensive care units
Intervention: Tight glycemic control
Comparison: conventional glycemic control
Summary of studies for selected outcome and overall quality of evidence relative to that outcome.

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk conventional glycemic control	Corresponding risk Tight glycemic control				
Hospital or 28 Day Mortality	**Medium risk population**		**OR 0.82** (0.68 to 0.98)	35334 (14)	⊕OOO **very low**[1,2,3,4,5,6]	
	202 per 1000	**172 per 1000** (147 to 199)				
ICU Mortality	**Medium risk population**		**OR 0.99** (0.86 to 1.15)	21438 (8)	⊕OOO **very low**[7,8,9,10,11]	
	168 per 1000	**167 per 1000** (148 to 188)				
Severe Hypoglycemia	**Medium risk population**		**OR 5.18** (2.91 to 9.22)	27530 (10)	⊕⊕OO **low**[12,13,14,15]	
	20 per 1000	**96 per 1000** (56 to 158)				
Renal Replacement Therapy	**Medium risk population**		**OR 0.89** (0.69 to 1.15)	9468 (7)	⊕OOO **very low**[16,17,18,19]	
	132 per 1000	**119 per 1000** (95 to 149)				
Blood Transfusion	**Medium risk population**		**OR 1.07** (0.89 to 1.28)	8616 (4)	⊕OOO **very low**[20,21,22,23]	
	389 per 1000	**405 per 1000** (362 to 449)				
Bacteremia	**Medium risk population**		**OR 0.75** (0.53 to 1.06)	9427 (6)	⊕OOO **very low**[24,25,26,27,28]	
	101 per 1000	**78 per 1000** (56 to 106)				
ICU Length of Stay	See comment	See comment		12491 (9)	[29,30,31,32]	SMD -0.04 (-0.13 to 0.05)

CI: Confidence interval; OR: Odds ratio; SMD: Standardized mean difference

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

Footnotes

[1] No study was blinded. Single site studies for this outcome: Van den Berghe 2001, Grey 2004, Furnary 2006, Toft 2006, Krinsley 2006, Van den Berghe 2006, Scalea 2007, Farah 2007, Treggiari 2008, De La Rosa 2008, and Arabi 2008. Hyperglycemic BG targets (in mg/dL) in the control groups were 140-180 (Glucontrol, 2009), 140-200 (Farah 2007), 180-200 (Van den Berghe 2001, 2006, VISEP 2008, De La Rosa 2008, Arabi 2008), and 180-220 (Grey, 2004).
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[5] Furnary 2006 relative risk = 2.52.
[6] Treggiari 2008; Krinsley, 2006; Furnary, 2006.
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[26] Van den Berghe 2001 included only intubated surgical patients, Van den Berghe 2006 included only MICU patients.
[27] Four negative studies: Van den Berghe 2006 (9.95), Farah 2007(13.07), De La Rosa 2008 (5.42), NICE-SUGAR (7.38).
[28] Grey relative risk = 0.353
[29] No study was blinded. Single site studies for this outcome: Van den Berghe 2001, Grey 2004, Scalea 2007, Farah 2007, De La Rosa 2008, and Arabi 2008. Hyperglycemic BG targets (in mg/dL) in the control groups for this outcome were 140-200 (Farah 2007), 180-200 (Van den Berghe 2001, VISEP 2008, De La Rosa 2008, Arabi 2008), and 180-220 (Grey, 2004).
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[32] Negative studies (observed power, %): Van den Berghe 2001 (5.0), Grey 2004 (9.9), Farah 2007(15.8), VISEP 2008 (34.6), De La Rosa 2008 (5.0), Arabi 2008 (27.9), NICE-SUGAR (5.0), Glucontrol (5.0).

Part 2: Characteristics of studies

Characteristics of included studies (see publication for reference citations)

Arabi 2008

Methods	Randomized clinical trial
Participants	523 participants (266 intervention, 257 control) medical-surgical ICU patients
Interventions	intensive insulin therapy (target 80-110 mg/dl) versus conventional control (180-200 mg/dl)
Outcomes	Hospital Mortality, ICU mortality, severe hypoglycemia, renal replacement therapy, transfusion, ICU acquired infections
Notes	Negative study, observed power 33.74%

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Yes	Block randomization, stratified for postoperative and nonoperative
Allocation concealment?	Yes	
Blinding?	No	Blinding of bedside care takers not possible
Free of selective reporting?	Yes	
Free of other bias?	No	Control group target range 180-200 mg/dl
Multicenter	No	

De La Rosa 2008

Methods	Randomized clinical trial
Participants	504 participants (253 intervention, 250 control) medical-surgical ICU patients
Interventions	intensive insulin therapy (target 80-110 mg/dl) versus conventional control (180-200 mg/dl)
Outcomes	Hospital Mortality, ICU mortality, severe hypoglycemia, renal replacement therapy, transfusion,
Notes	Negative study, observed power 24.46%

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Yes	Block randomization, stratified for diagnosis of diabetes
Allocation concealment?	Yes	Randomization done by Pharmacy

Blinding?	No	Blinding of bedside care takers not possible
Free of selective reporting?	Yes	
Free of other bias?	No	Control group target range 180-200 mg/dL
Multicenter	No	

Farah 2007

Methods	Randomized clinical trial
Participants	89 participants (41 intervention, 48 control)
Interventions	Intensive therapy (target 110-140 mg/dL) versus conventional (target 140-200 mg/dL)
Outcomes	28 day mortality, ICU mortality, bacteremia, ICULOS
Notes	Negative trial, observed power 8.50%

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported
Blinding?	No	
Free of selective reporting?	No	< 3 day ICU LOS patients were excluded.
Free of other bias?	No	single site
Multicenter	No	

Furnary 2006

Methods	Observational Study
Participants	5534 participants (4469 intervention, 1065 control)
Interventions	Historical controls with SQ Insulin as compared to Continuous Insulin Infusion
Outcomes	Hospital mortality
Notes	Strong effect size RR = 5.21/2.1 = 2.52

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	No	not randomized
Allocation concealment?	No	not randomized
Blinding?	No	Blinding of bedside care takers not possible
Free of selective reporting?	Yes	
Free of other bias?	No	Extended time frame of study may have led to reduced mortality alone
Multicenter	No	

Glucontrol 2009

Methods	Randomized clinical trial
Participants	1,101 participants (542 control, 536 intensive insulin therapy
Interventions	intensive insulin therapy target 79 - 110 mg/dL
Outcomes	Primary: ICU Mortality. Secondary: Hospital and 28-day mortality, ICU and hospital LOS,
Notes	Trial stopped early for unintended protocol violations, i.e., neither group achieved a large percentage of patients in their respective target ranges.

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Yes	Block randomization
Allocation concealment?	Yes	
Blinding?	No	
Free of selective reporting?	Yes	
Free of other bias?	No	Control target 140 180 mg/dL
Multicenter	Yes	21 ICUs

Grey 2004

Methods	Randomized clinical trial
Participants	61 patients (34 intervention, 27 control), surgical ICU patients
Interventions	strict insulin therapy (target 80-120 mg/dL) versus standard insulin therapy (target 180-220 mg/dL)
Outcomes	Hospital mortality, renal replacement therapy, moderate hypoglycemia, septicemia, ICU LOS
Notes	

Risk of bias table

Item	**Judgment**	**Description**
Adequate sequence generation?	Yes	Coin toss
Allocation concealment?	Yes	
Blinding?	No	
Free of selective reporting?	Yes	
Free of other bias?	No	Control group target range 180-220 mg/dL
Multicenter	No	

Krinsley 2006

Methods	Observational
Participants	5365 participants (2699 intervention, 2666 control) medical-surgical ICU patients
Interventions	Routine glycemic control (80-140 mg/dl) versus tight glycemic control (80-125 mg/dl)
Outcomes	Hospital mortality
Notes	

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	No	not randomized
Allocation concealment?	No	not randomized
Blinding?	No	Blinding of bedside care takers not possible
Free of selective reporting?	Yes	
Free of other bias?	No	historical controls
Multicenter	No	

NICE-SUGAR

Methods	Randomized clinical trial
Participants	6104 participants (3054 intensive control and 3050 conventional control)
Interventions	Tight glycemic control (81-108 mg/dL) versus routine glycemic control (<180 mg/mL)
Outcomes	90 day mortality, 28 day mortality, ICU mortality, severe hypoglycemia, renal replacement therapy, bacteremia, transfusion, ICU LOS
Notes	Only those with an expected LOS > 3 days were randomized.

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding?	No	Blinding of bedside care takers not possible
Free of selective reporting?	Yes	
Free of other bias?	No	Control group target range <180 mg/dL
Multicenter	Yes	

Scalea 2007

Methods	Observational study
Participants	2129 participants (1108 intervention, 1021 control) trauma ICU patients
Interventions	Tight glycemic control (100-150 mg/dl) versus routine glycemic control (control range not specified)
Outcomes	Hospital mortality, ICU LOS
Notes	

Risk of bias table

Item	**Judgment**	**Description**
Adequate sequence generation?	No	not randomized
Allocation concealment?	No	not randomized
Blinding?	No	Blinding of bedside care takers not possible
Free of selective reporting?	Yes	
Free of other bias?	No	historical controls
Multicenter	No	

Toft 2006

Methods	Observational study
Participants	271 participants (136 tight glycemic control, 135 routine glycemic control) medical- surgical ICU patients
Interventions	Tight glycemic control (79-110 mg/dL) versus routine glycemic control (<216 mg/dL)
Outcomes	Hospital Mortality, severe hypoglycemia, renal replacement therapy, transfusion
Notes	Negative study, observed power 0.84%

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	No	Not randomized
Allocation concealment?	No	Not randomized
Blinding?	No	Blinding of bedside care takers not possible
Free of selective reporting?	Yes	
Free of other bias?	No	Historical controls
Multicenter	No	

Treggiari 2008

Methods	Observational study
Participants	10,456 participants (Phase 1: 2,366; Phase II: 3,322; Phase III: 4,786)
Interventions	Phase I target 120-180 mg/dl, Phase II target 80-130 mg/dl, Phase III target 80-110 mg/dl
Outcomes	Hospital mortality, ICU mortality, severe hypoglycemia
Notes	Negative study, trend favors routine control, observed power 23%

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	No	Not randomized
Allocation concealment?	No	Not randomized
Blinding?	No	Blinding of bedside care takers not possible
Free of selective reporting?	Yes	
Free of other bias?	No	Historical controls
Multicenter	No	

Van den Berghe 2001

Methods	Randomized Controlled Trial
Participants	1548 participants (765 intervention, 783 control) mechanically ventilated surgical ICU patients
Interventions	intensive insulin therapy (target 80-110 mg/dl) versus conventional control (180-200 mg/dl)
Outcomes	Hospital Mortality, ICU mortality, severe hypoglycemia, renal replacement therapy, septicemia, transfusion
Notes	

Risk of bias table

Item	**Judgment**	**Description**
Adequate sequence generation?	Yes	Block randomization in permuted blocks of 10
Allocation concealment?	Yes	Sealed envelope
Blinding?	No	Blinding of bedside caretakers not possible
Free of selective reporting?	Yes	
Free of other bias?	No	Control target range 180-200 mg/dl
Multicenter	No	

Van den Berghe MICU 2006

Methods	Randomized clinical trial
Participants	1200 participants (595 intervention, 605 control)
Interventions	Tight glycemic control (80-110 mg/dl) versus routine glycemic control (180-200 mg/dl)
Outcomes	Hospital mortality, ICU mortality, severe hypoglycemia, renal replacement therapy, septicemia
Notes	Negative study, observed power 15.87%

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding?	No	Blinding of bedside care takers not possible
Free of selective reporting?	Yes	
Free of other bias?	No	Control target range 180-200 mg/dL
Multicenter	No	

VISEP 2008

Methods	Randomized clinical trial
Participants	537 participants (247 intervention, 290 control)
Interventions	Tight glycemic control (80-110 mg/dL) versus routine glycemic control (180-200 mg/dL)
Outcomes	28 day mortality, severe hypoglycemia, renal replacement therapy, transfusion, ICU LOS
Notes	Negative study, observed power 2.25%

Risk of bias table

Item	Judgment	Description
Adequate sequence generation?	Unclear	not reported
Allocation concealment?	Unclear	not reported
Blinding?	No	Blinding of bedside care takers not possible
Free of selective reporting?	Yes	
Free of other bias?	No	Control target range 180-200 mg/dl
Multicenter	Yes	

Characteristics of excluded studies

Furnary 2003

Reason for exclusion	Data duplicated in other resports

Krinsley 2004

Reason for exclusion	Data duplicated in other reports

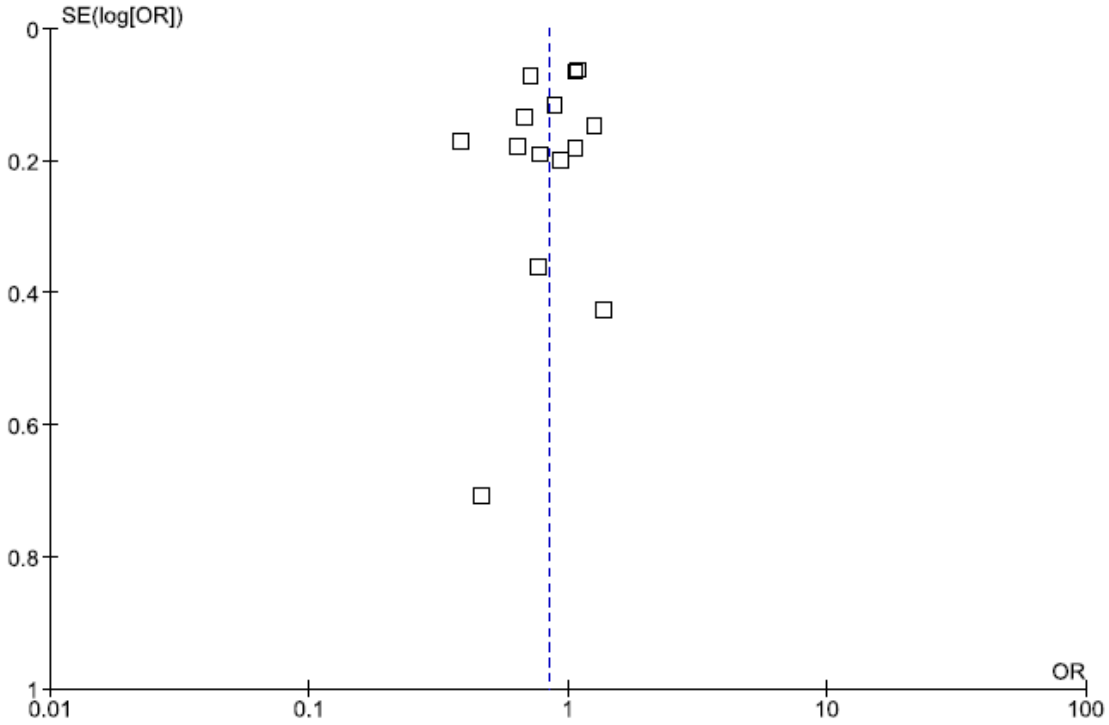
Guide to Figures

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Hospital or 28 Day Mortality (see paper Figure 1A, Supplemental Figure 1A)	14	35334	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.68, 0.98]
1.2 ICU Mortality (see paper Figure 1B, see Supplemental Figure 1B)	8	21438	Odds Ratio (M-H, Random, 95% CI)	0.99 [0.86, 1.15]
1.3 Subset Hospital Mortality RCT vs. Observational Trials (see Supplemental Figure 1A,B)				
1.4 ICU Length of Stay (see Supplemental Figure 2A,B)	9	12491	Std. Mean Difference (IV, Random, 95% CI)	-0.04 [-0.13, 0.05]
1.5 Severe Hypoglycemia (see paper Figure 3, Supplemental Figure 4)	10	27530	Odds Ratio (M-H, Random, 95% CI)	5.18 [2.91, 9.22]
1.6 Renal Replacement Therapy (see Supplemental Figure 5A,B)	7	9468	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.69, 1.15]
1.7 Blood Transfusion (see Supplemental Figure 6A,B)	4	8616	Odds Ratio (M-H, Random, 95% CI)	1.07 [0.89, 1.28]
1.8 Bacteremia (see Supplemental Figure 7A,B)	6	9427	Odds Ratio (M-H, Random, 95% CI)	0.75 [0.53, 1.06]
1.9 Mortality Neurologic Patients (see paper Figure 2, see Supplemental Figure 8A,B)				

CI: Confidence interval; OR: Odds ratio; M-H: Mantel-Haenszel, I-V: Inverse variance.

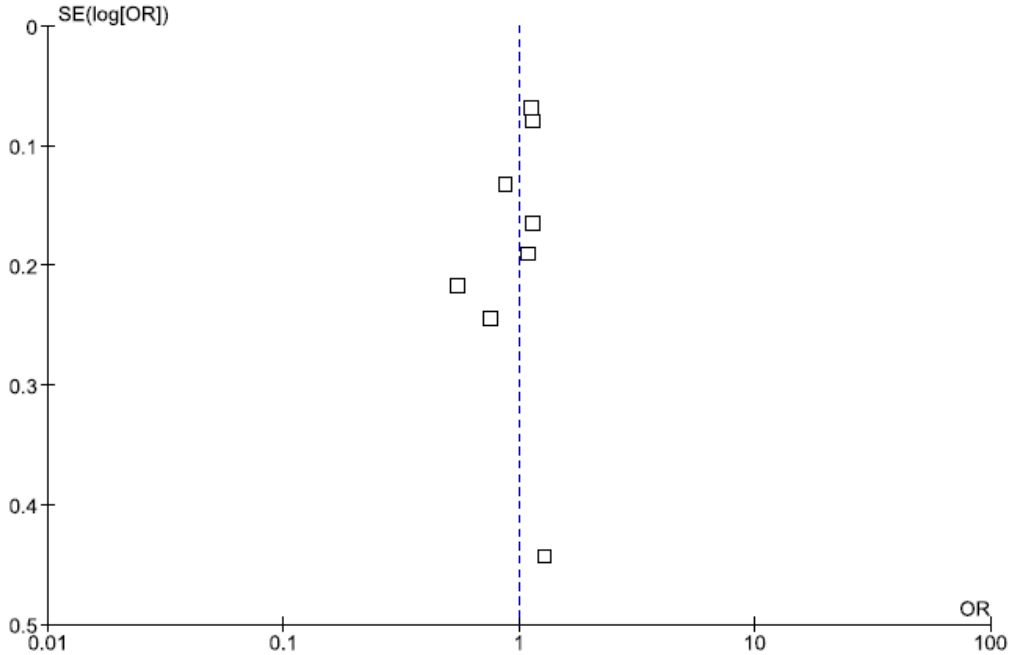
Supplemental Figures

Figure 1A: Hospital Mortality



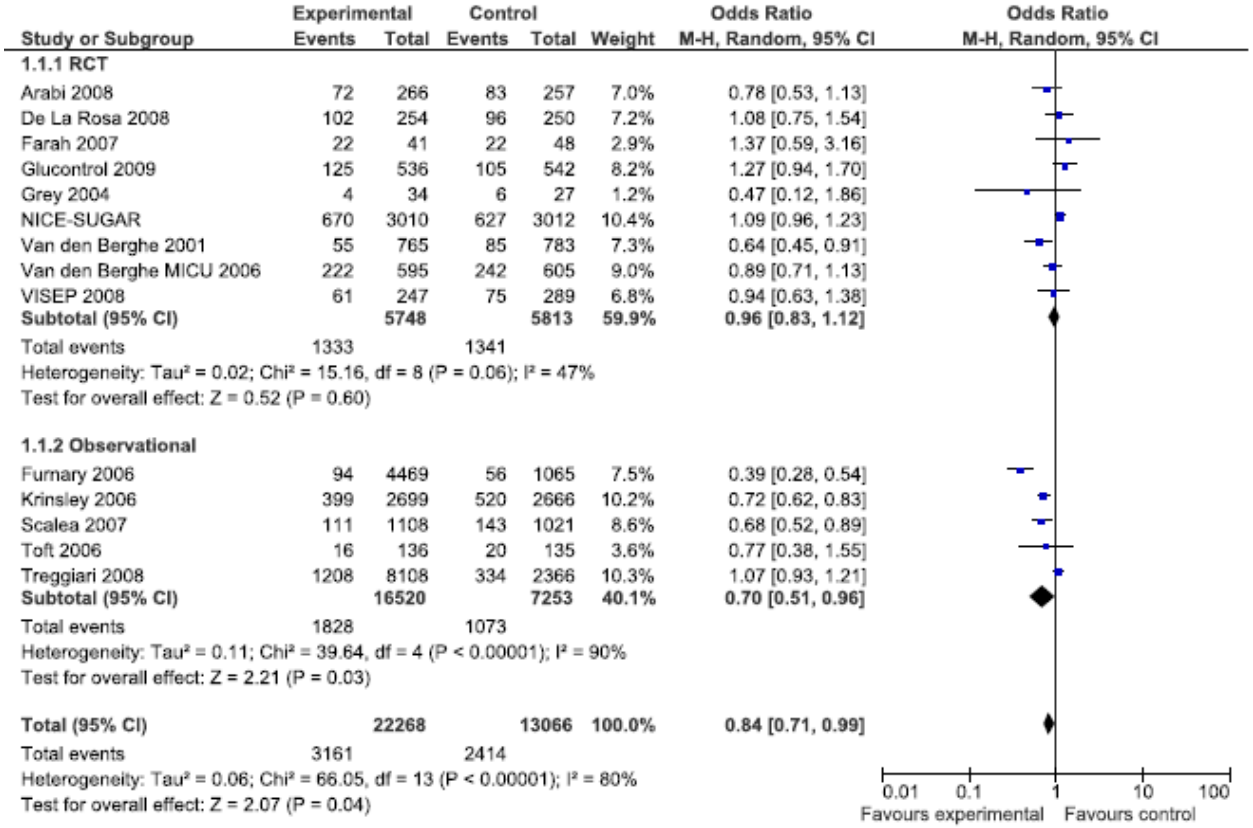
Funnel plot of comparison: 1 Glycemic Control, outcome: 1.1 Hospital Mortality.

Figure 1B: ICU Mortality



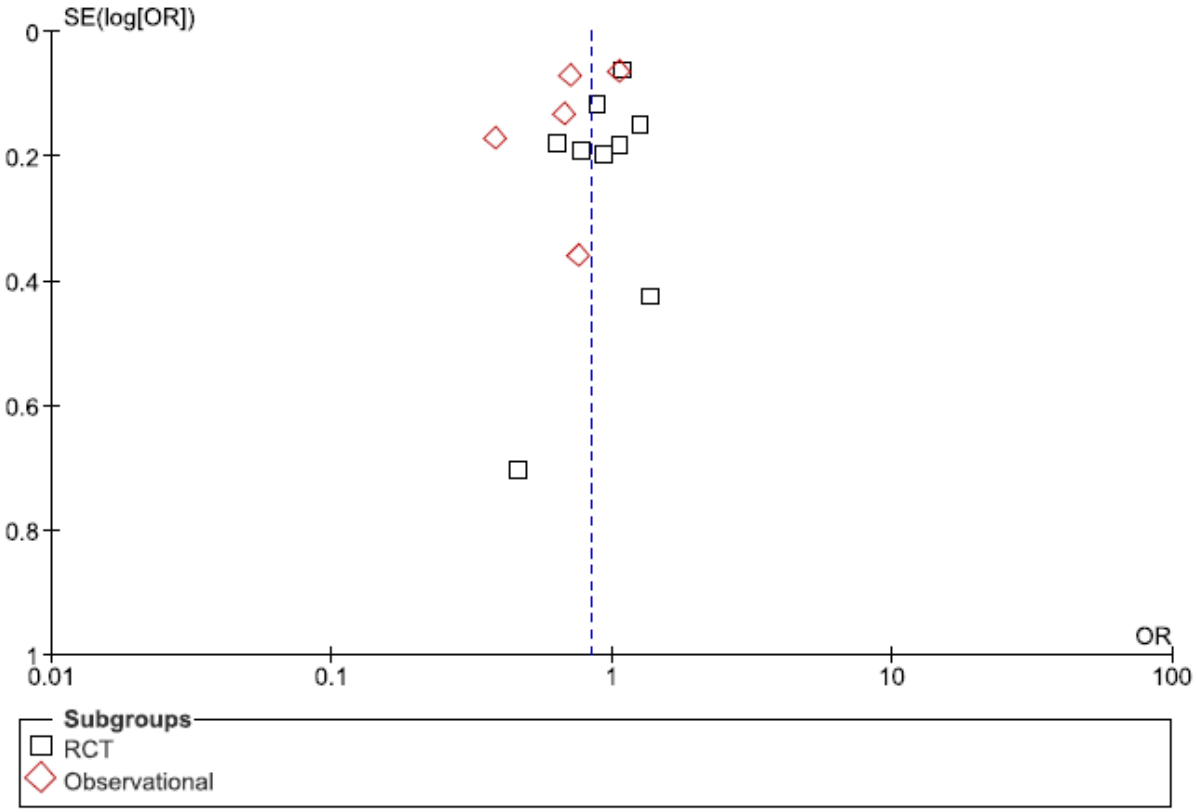
Funnel plot of comparison: 1 Glycemic Control, outcome: 1.2 Hospital Mortality.

2A: RCT vs. Observational Trials



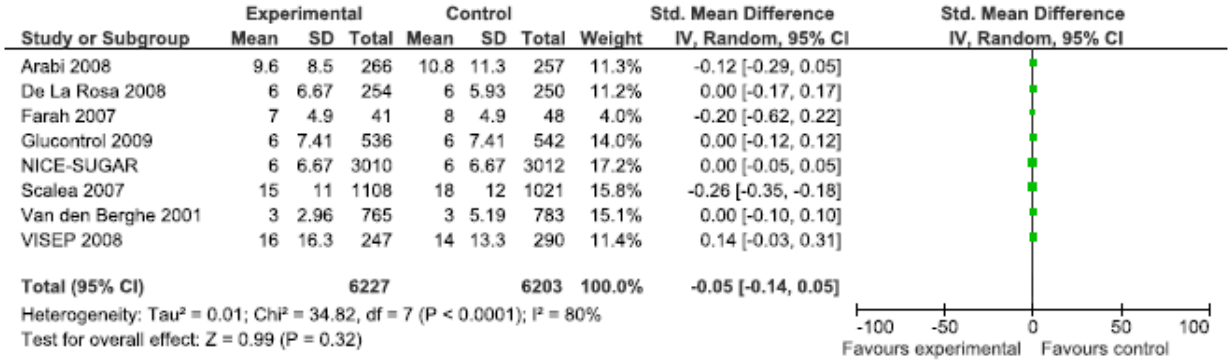
Forest plot of comparison: 1 Glycemic Control, outcome: 1.3 Randomized Controlled Trial vs. Observational Trial

Figure 2B: RCT vs. Observational Trials



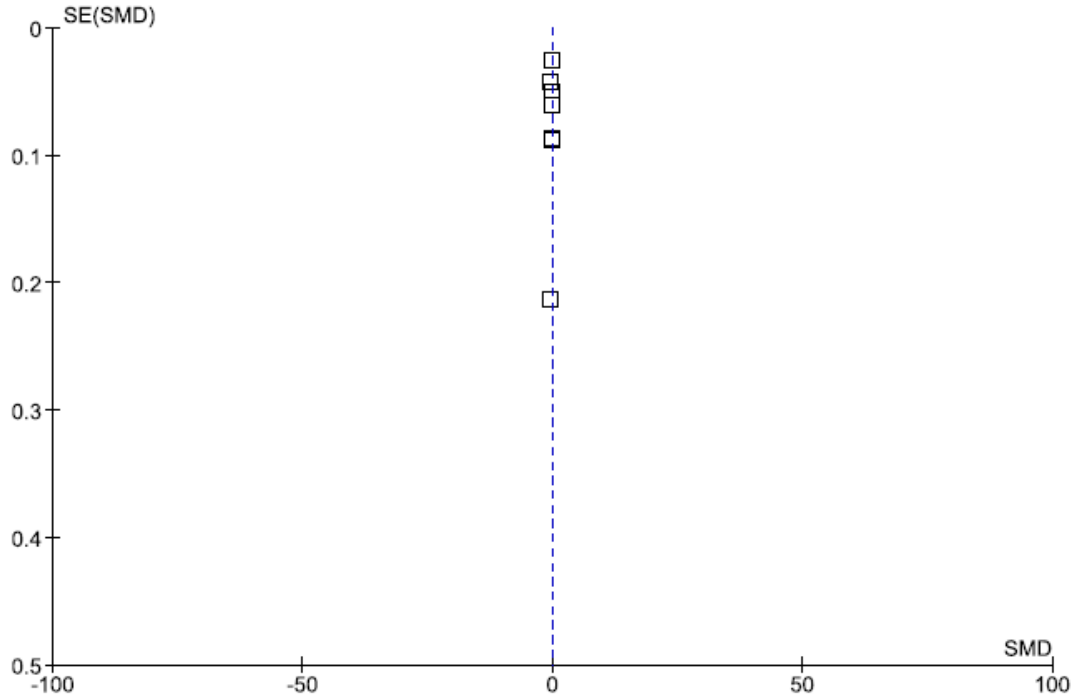
Funnel plot of comparison: 1 Glycemic Control, outcome: 1.3 Randomized Controlled Trial vs. Observational Trial

Figure 3A: ICU Length of Stay



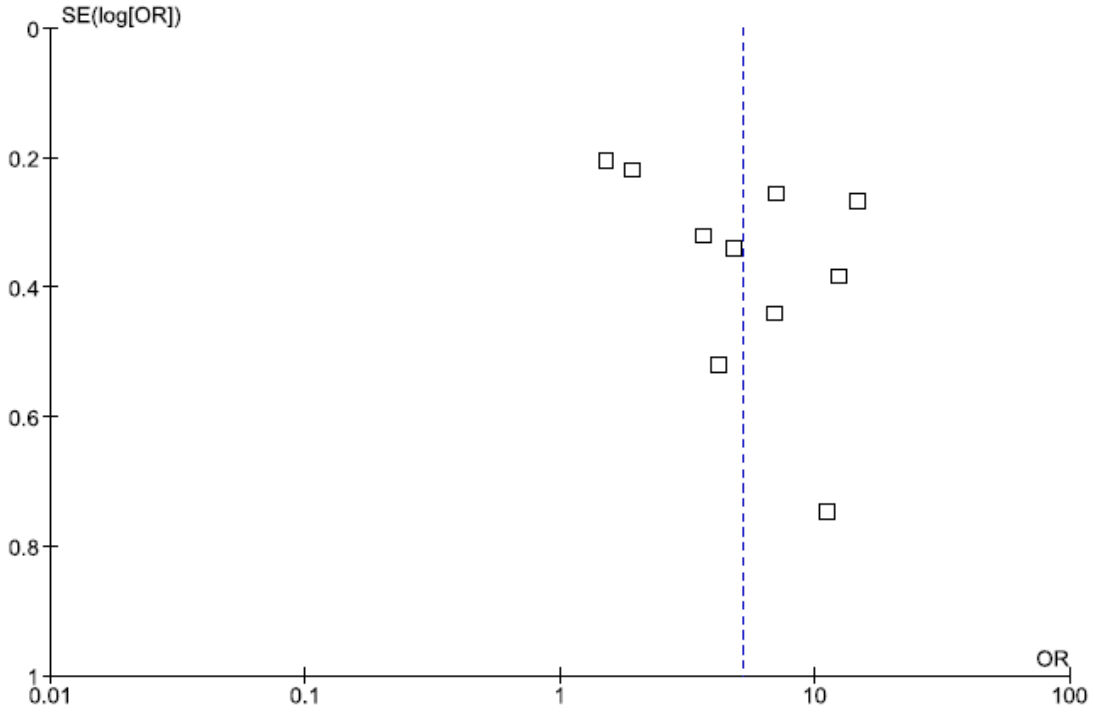
Forest plot of comparison: 1 Glycemic Control, outcome: 1.4 Hospital Length of Stay

Figure 3B: ICU Length of Stay



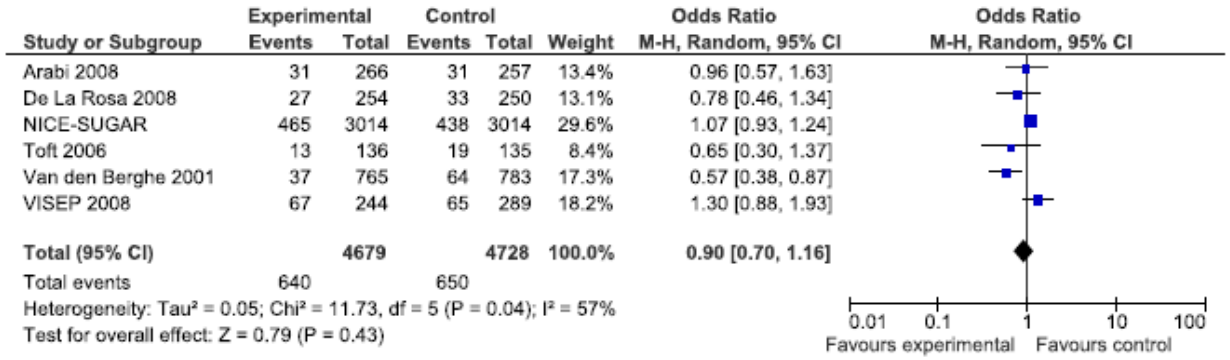
Funnel plot of comparison: 1 Glycemic Control, outcome: 1.4 Hospital Length of Stay

Figure 4: Severe Hypoglycemia



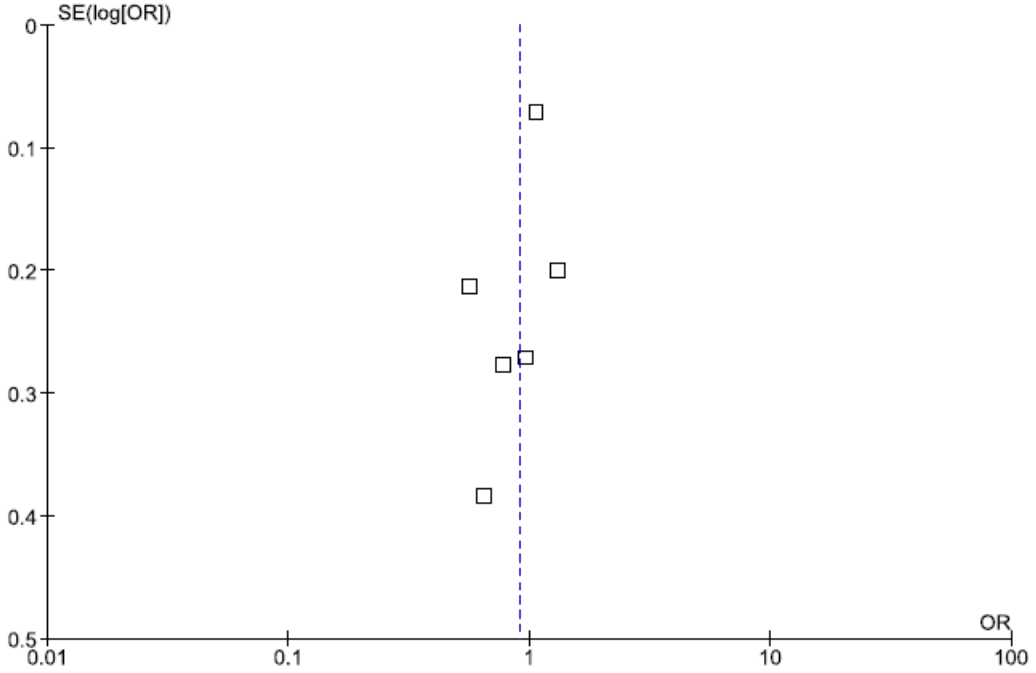
Funnel plot of comparison: 1 Glycemic Control, outcome: 1.5 Severe Hypoglycemia.

Figure 5A: Renal Replacement Therapy



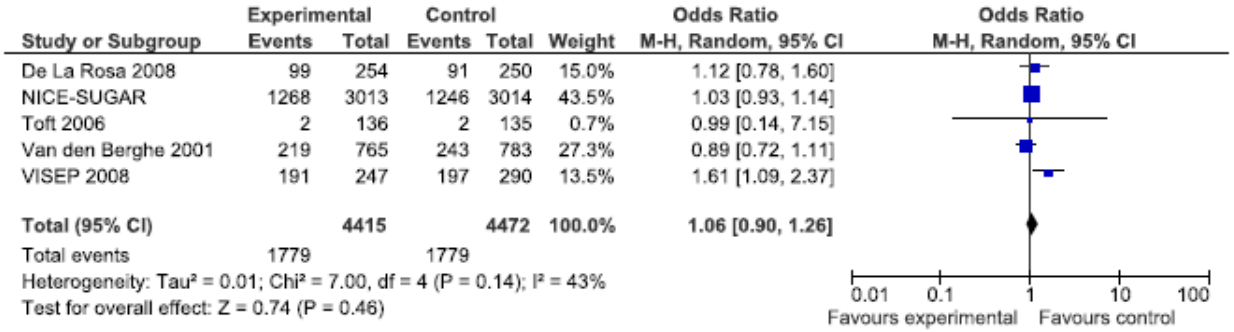
Forest plot of comparison: 1 Glycemic Control, outcome: 1.6 Renal Replacement Therapy.

Figure 5B: Renal Replacement Therapy



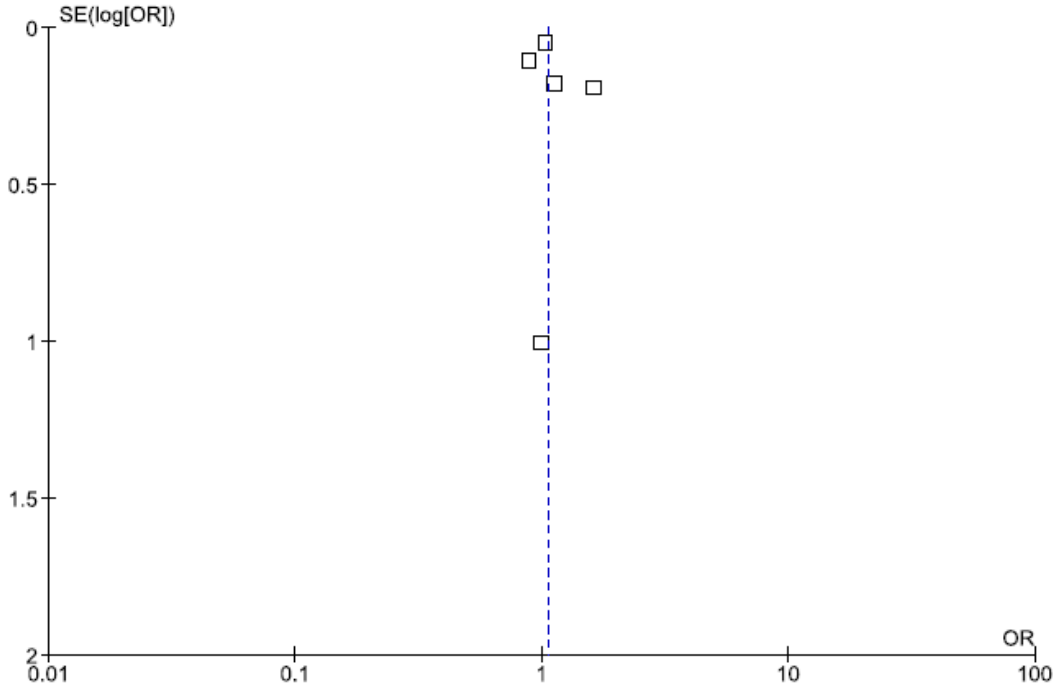
Funnel plot of comparison: 1 Glycemic Control, outcome: 1.6 Renal Replacement Therapy.

Figure 6A: Blood Transfusion



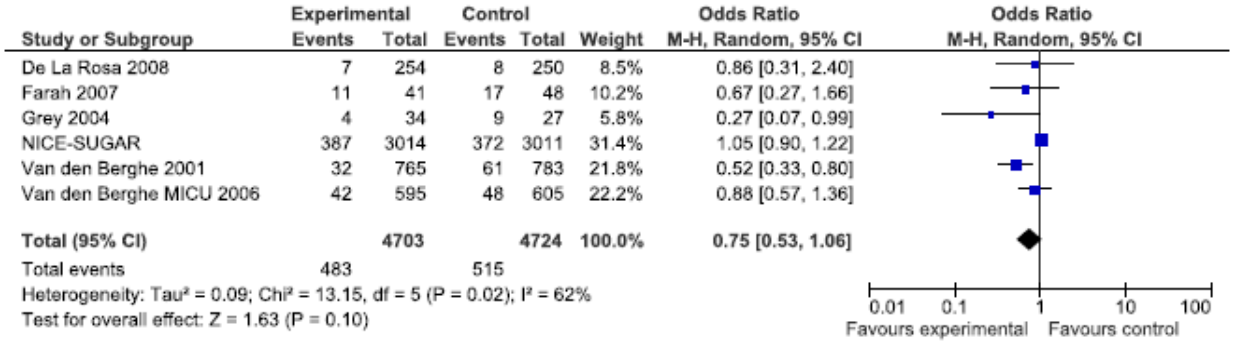
Forest plot of comparison: 1 Glycemic Control, outcome: 1.7 Blood Transfusion.

Figure 6B: Blood Transfusion



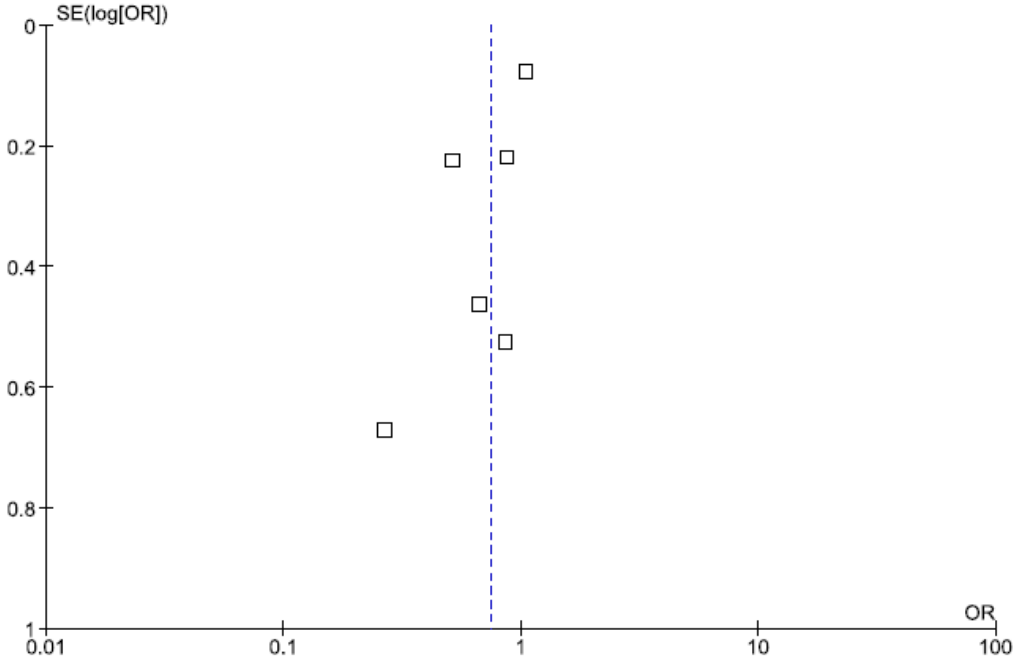
Funnel plot of comparison: 1 Glycemic Control, outcome: 1.7 Blood Transfusion.

Figure 7A: Bacteremia



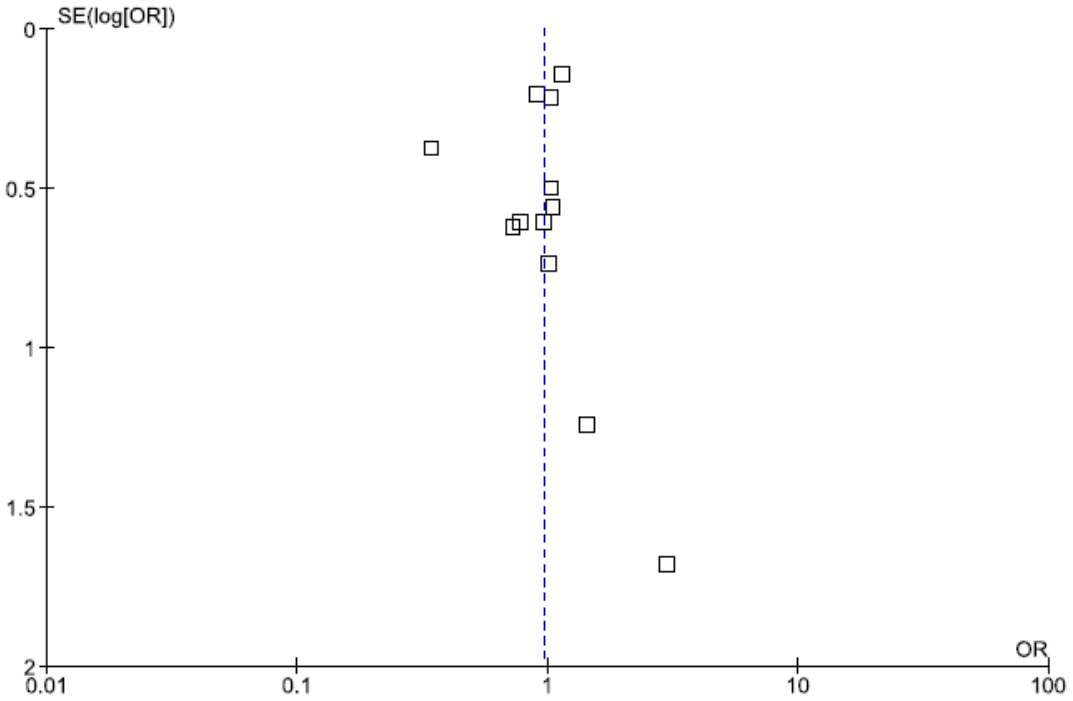
Forest plot of comparison: 1 Glycemic Control, outcome: 1.8 Bacteremia.

Figure 7B: Bacteremia



Funnel plot of comparison: 1 Glycemic Control, outcome: 1.8 Bacteremia.

Figure 8: Mortality in Neurologic Patients



Funnel plot of comparison: 1 Glycemic Control, outcome: 1.9 Neurologic Patient Mortality