

## [ 01RC2

### Recent evidence for interventions in anaesthesia and critical care; a practical way to apply evidence-based medicine

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It is almost impossible to cover all of the recent advances in the fields of anaesthesia and critical care because the number of publications within the last year alone exceeds 50,000. This fact emphasises the need for an overview, a so-called 'umbrella review', of evidence-based knowledge. This overview should provide the best clinical evaluation and approach to generate firm evidence about health-care interventions for specific patient care. This is achieved through systematic reviews, which are prepared using a systematic approach to minimise bias and random errors in clinical trials. Systematic reviews, usually employing meta-analyses, allow for a more precise appraisal of the evidence than traditional narrative reviews and, as such, may help resolve uncertainty when original research results disagree. Systematic reviews are also important in identifying when the available evidence is insufficient and where new, adequately sized trials are required [1, 2].

Meta-analyses are a snapshot summary of the actual information gathered. As such the actual information size may be scarce and merely an interim-analysis of data required over a longer period. Therefore, it seems important to evaluate the information presented in meta-analyses and adjust that for potential multiple testing performed when new trial results appear as well as the fraction of the required information size it provides. This is achieved by applying *trial sequential analysis* (TSA) [1, 2] which has the potential to provide both the required information size, which may reveal the gap between the actual and the required information size, and the adjustment for multiple testing in cumulative meta-analysis. It seems especially important to perform TSA on meta-analyses with claims of a statistically significant intervention effect in the light of how many tests could potentially have been conducted as well as how much information has actually been provided relative to the required information. We will try to provide an example based on recently published evidence-based reviews. We will illustrate how statistically significant findings in various meta-analyses are no longer reproducible when the results of recent randomised controlled trials (RCTs) are incorporated into some of them. However, we wish to emphasise that our review is not a systematic update of the included reviews.

Let us consider a 65 yr-old male patient admitted with acute abdominal pain and fever. He is diagnosed with perforated colon due to cancer and is septic despite fluid resuscitation and relevant antibiotics. He is transferred to the operating theatre. What is the level of evidence for the following interventions during this patient's peri- and postoperative care:

- Peri-operative beta-blockers
- Remifentanyl
- Bispectral index monitoring
- Oesophageal Doppler for fluid replacement
- Hydrocortisone for septic shock
- Tight glycaemic control for septic shock
- Anti-thrombin III for sepsis

### Should we use peri-operative $\beta$ -blockers?

A recent systematic review with a meta-analysis [3] of 33 trials of peri-operative beta-blockade for non-cardiac surgery involving 11,815 patients concluded that although  $\beta$ -blockers were associated with a decreased risk of non-fatal myocardial infarction (odds ratio (OR) 0.65, 95% confidence interval (CI) 0.54 to 0.79; Figure 1) and myocardial ischaemia (OR 0.36, 95% CI 0.26 to 0.50), they were associated with an increased risk of non-fatal stroke (OR 2.01, 95% CI 1.27 to 3.68; Figure 2), and, in trials with low risk of bias, possibly an increased all-cause mortality (OR 1.27, 95% CI 1.01 to 1.61; Figure 3) [3]. The beneficial effects were driven mainly by trials with high risk of bias. TSA for non-fatal myocardial infarction (Figure 4) and non-fatal stroke supported this. However, more certainty is warranted for all-cause mortality (Figure 5).  $\beta$  blockers were associated with a high risk of peri-operative bradycardia requiring treatment, with numbers needed to harm (NNH) of 22, and peri-operative hypotension requiring treatment with NNH of 17. No increased risk of bronchospasm was recorded. There is no evidence to support the use of  $\beta$ -blocker therapy for the prevention of peri-operative clinical outcomes in patients having non-cardiac surgery.

### Should we choose remifentanyl instead of another short-acting opioid?

Komatsu et al addressed this issue in their systematic review of adult patients ( $\geq 18$  yr) receiving general anaesthesia (GA) with tracheal intubation or laryngeal mask airway, rigid bronchoscopy or laryngoscopy without intubation [4]. They included 85 trials (involving 13,057 patients); 6621 patients received remifentanyl and of the remaining 6436 patients, 17% received alfentanil, 80% received fentanyl and 3% received sufentanil. Remifentanyl was associated with adequate anaesthesia and deep intra-operative analgesia (relative risk (RR) 0.65; 95% CI 0.48 to 0.87,  $p < 0.001$ ), hypotension (RR 1.68; 95% CI 1.36 to 2.07,  $p < 0.006$ ), increased vasopressor requirement (RR 1.40; 95% CI 1.13 to 1.72,  $p < 0.03$ ) (Table 1), faster recovery, extubation and return to spontaneous ventilation (weighted mean difference (WMD) -0.94; 95% CI -1.80 to -0.08,  $p < 0.001$ ) but a more frequent need for postoperative analgesia (RR 1.36; 95% CI 1.21 to 1.53,  $p < 0.005$ ) (Table 2). There was no difference in the incidence of postoperative nausea and vomiting (PONV), shivering, respiratory depression, naloxone requirement, recall of intra-operative awareness (Figure 6) or muscle rigidity. Remifentanyl does not appear to offer any advantage for lengthy, major interventions. (Tables 1 and 2)

**Table 1**

Number of participants and relative risks various intra-operative outcomes

Postoperative outcomes	Studies included	No. of participants (n/N remifentanyl n/N other opioids)	RR (95% CI)	P value for statistical significance	P value for heterogeneity
Inadequate anaesthesia: responses during entire anaesthesia period	9	253/530 382/530	0.65 (0.48 to 0.87)	0.004	< 0.001
Hypertension, entire anaesthesia period	20	187/778 314/801	0.60 (0.46 to 0.78)	0.0002	0.007
Hypotension, entire anaesthesia period	27	458/2177 237/2162	1.68 (1.36 to 2.07)	< 0.001	0.006
Bradycardia	22	95/791 61/812	1.46 (1.04 to 2.05)	0.030	0.290
Vasopressor requirement	19	728/3015 489/3063	1.40 (1.13 to 1.72)	0.002	0.030

**Table 2**

Number of participants and the relative risk (RR) of experiencing postoperative outcomes, § total number of patients and weighted mean differences (remifentanyl/other opioids) are given for times (min); CI= confidence interval

Postoperative outcomes	Studies included	No. of participants (n/N remifentanyl n/N other opioids)	RR or WMD§ (95% CI)	p value for statistical significance	p value for heterogeneity
Postoperative analgesic	30	609/1085 364/992	1.36 (1.21 to 1.53)	< 0.001	0.005
Rigidity	16	26/774 22/683	1.07 (0.65 to 1.75)	0.80	0.87
Nausea	32	1384/4821 1329/4724	1.03 (0.97 to 1.09)	0.340	0.69
Vomiting	29	618/4784 579/4691	1.06 (0.96 to 1.17)	0.27	0.71
Shivering	14	232/2784 104/2800	2.15 (1.73 to 2.69)	< 0.001	0.59
Respiratory depression	15	6/1899 26/1807	0.32 (0.09 to 1.16)	0.08	0.10
Naloxone requirement	14	10/570 79/484	0.25 (0.14 to 0.47)	< 0.001	0.42
Time to extubation (min)	21	563/587§	-2.03§ (- 2.92 to -1.14)	< 0.001	< 0.001
Time to spontaneous ventilation (min)	15	509/528§	0.94§ (- 1.80 to -0.08)	0.030	< 0.001

### Does Bispectral index reduce the risk of anaesthesia awareness and reduce the amount of hypnotics administered?

Punjasawadwong et al addressed this issue in their Cochrane systematic review [5]. In terms of requirements for hypnotics, the combined results from seven studies (n = 578) demonstrated the significant effect of Bispectral index (BIS) monitoring in reducing propofol consumption (-1.30 mg.kg.hr; 95% CI -1.97 to -0.62). Additionally, there was a significant effect of BIS monitoring on reducing the use of volatile anaesthetics (11 studies, n = 689, -0.17 mean alveolar concentration (MAC) equivalents; 95% CI -0.27 to -0.07). Awareness was reported in only two studies (involving 2493 surgical patients with high risk of awareness), with two reported cases of awareness in the BIS group and 13 in the control group. There was a significant reduction in the incidence of awareness in the BIS group (0.21 RR; 95% CI 0.05 to 0.79).

Avidan et al recently randomly assigned 1941 patients to BIS-guided anaesthesia (target BIS, 40 to 60) or end-tidal anaesthetic gas (ETAG) guided anaesthesia [6]. Patients were then assessed for anaesthesia awareness at three intervals: 0 to 24 hr; 24 to 72 hr; and 30 days after extubation. They assessed 967 patients in the BIS group and 974 in the ETAG group. Two cases of definite awareness occurred in each group (an overall incidence of 0.21%). Five additional patients (four in the BIS group and one in the control group) had possible awareness. In the majority of cases BIS values were persistently < 60 during the period when awareness occurred. There was no difference in the amount of inhaled volatile gases between the two groups. By adding the data from Avidan's study to the existing meta-analysis [5], there is no longer any statistical benefit in the use of BIS to reduce the risk of awareness (RR 0.57, 95% CI 0.10 to 3.26, I<sup>2</sup> = 63.4%; Figure 7). This issue still remains controversial due to the small event rate and the substantial heterogeneity present. The required information size to resolve this controversy reliably (heterogeneity adjusted [1, 2]) may be greater than 40,000 participants, leaving us presently with only 12% of the required information size.

### Should we apply oesophageal Doppler monitoring for fluid replacement during surgery?

The role of oesophageal Doppler monitoring in major abdominal surgery was examined by Abbas and Hill [7]. They included five RCTs with 428 patients randomly allocated to either Doppler-guided fluid administration or using conventional parameters. The combined results of all five studies did not show any difference in mortality (0.63 RR, 95% CI 0.17 to 2.37; Figure 8). However, the total number of events is two in the intervention group and four in the control group, making its efficiency somewhat dubious. In addition, there were fewer admissions to the ICU (OR 0.20; 95% CI 0.07 to 0.57); reduced hospital stay (WMD (fixed) -1.60; 95% CI -2.58 to -0.62); and fewer complications in the intervention group (OR 0.28; 95% CI 0.17 to 0.46) (Tables 3 and 4); the difference in mean arterial pressure, central venous pressure (CVP) and cardiac output did not reach statistical significance (Table 4).

Table 3

Oesophageal Doppler monitoring for peri-operative fluid management - various outcomes

Postoperative outcomes	Studies included	No. of participants (n/N Doppler n/N control)	Odds ratio (95% CI)	P value for statistical significance	I <sup>2</sup> (heterogeneity)
Overall rate of complication	4	47/194 91/194	0.28 (0.17 to 0.46)	< 0.00001	9.0%
ICU admissions	3	4/130 20/130	0.20 (0.07 to 0.57)	0.002	4.0%

Table 4

Oesophageal Doppler monitoring for peri-operative fluid management - various outcomes WMD = weighted mean differences, CI = confidence interval

Postoperative outcomes	Studies included	No. of participants (Doppler/control)	WMD (fixed) (95% CI)	p value for statistical significance	I <sup>2</sup> (heterogeneity)
Hospital stay	4	194/194	-1.60 (-2.58 to -0.62)	0.001	10.4%
Return of bowel function	4	194/194	-1.66 (-1.85 to -1.47)	<0.00001	26.5%
Mean arterial pressure	3	122/121	-2.59 (-6.21 to 1.03)	0.16	0%
Cardiac output	5	214/214	-0.97 (-1.31 to -0.63)	<0.00001	0%

### Should we use hydrocortisone therapy for septic shock?

The use of hydrocortisone in sepsis remains controversial [8]. The logic behind this therapy is based on the assumption that sepsis is complicated by impaired corticosteroid production and a reduced response to corticotropin. Interestingly, Annane found a reduction of 28-day overall mortality with long course of low dose corticosteroid (five trials, n = 465, RR; 0.80, 95% CI 0.67 to 0.95) which has since been the rationale for corticosteroid therapy in sepsis. Sprung et al added to this controversy via their multi-centre RCT, (CORTICUS) [8]. The patients were randomised to either intravenous hydrocortisone 50 mg or placebo every six hours for five days and then tapered during a six-day period. They found no difference in 28-day mortality between the two study groups who did not respond to corticotropin stimulation hydrocortisone group, (39.2%; 95% CI 30.5 to 47.9) vs placebo group, (36.1%; 95% CI 26.9 to 45.3, p = 0.69); or between those who were responders to corticotropin stimulation hydrocortisone group 28.8% (95% CI 20.6 to 37.0) vs placebo group 28.7% (95% CI 21.1 to 36.3, p = 1.0). Overall 28 day mortality was 34.3% (95% CI 28.3 to 40.2) in the hydrocortisone group and 31.5% (95% CI 25.6 to 37.3; p = 0.51) in placebo group. Death during hospitalisation was more common in the intervention group (40.6%) vs placebo group (40.8%) but did not reach statistical significance. Additionally, there were more episodes of superinfection, including new episodes of sepsis and septic shock. The CORTICUS trial was stopped prematurely due to slow recruitment and expiry of the supply of study drug; along with the finding that mortality was lower amongst the control group. This resulted in a study power of less than 35% to detect a 20% reduction in relative risk of death.

Adding the data published in the CORTICUS trial to three of the most important meta-analyses of Annane's systematic review: 'all cause mortality at 28 days, during hospitalisation and among trials with long courses of low dose corticosteroids', no longer provides any evidence of beneficial effect of corticosteroids in patients with severe sepsis or septic shock (Figures 9-11). The required sample size to resolve this controversy reliably may be more than 25,000 participants in order to detect or reject an intervention effect of 5% relative risk reduction (RRR) with a Type I error risk of 5% and a Type II error risk of 20%. Currently, approximately 10% of the required information size has been studied in randomised controlled trials.

### Should this patient receive tight glycaemic control?

In 2004 the *Surviving Sepsis Campaign* incorporated into its guidelines the need for tight glycaemic control amongst critically ill patients based on the publication by Van Den Berghe et al [11, 12]. This study, conducted in a surgical ICU setting, reduced the risk of in-hospital mortality by one-third. It has since been endorsed by various professional societies and persists in the 2008 update of *Surviving Sepsis Campaign* [13]. In their recent systematic review, Wiener et al identified 29 RCTs totalling 8432 patients who were randomly assigned to receive either tight or standard glucose control [14]. Wiener et al found no overall difference in hospital mortality between tight glycaemic control and usual care (27 trials, n = 8315, mortality 21.6% vs 23.3%; RR, 0.93; 95% CI 0.85 to 1.03; Figure 12). They conducted subgroup analyses based on glucose goal defined as very tight ( $\leq 6$  mmol/l) or moderately tight ( $<8.3$  mmol/l) and based on the ICU setting (surgical, medical or medical-surgical). They found no difference in mortality when stratified by glucose goal (very tight: 23% vs 25.2%, RR 0.90, 95% CI, 0.77 to 1.04; moderately tight: 17.3% vs 18.0%; RR 0.99; 95% CI, 0.83 to 1.18). Furthermore, there was no difference in mortality based on the ICU setting (Figures 13-15); and no reduction in need for dialysis (nine trials, n = 3629, 11.2% vs 12.1%; RR, 0.96; 95% CI, 0.76 to 1.20). The authors found that the risk of hypoglycaemia increased almost 5-fold regardless of the ICU setting and was more commonly observed amongst patients receiving very tight glycaemic control (glucose  $\leq 2.2$  mmol/l; 15 trials, n = 6613, 13.7% vs 2.5%; RR, 5.13; 95% CI, 4.09 to 6.43). Tight glycaemic control was found to decrease the risk of septicaemia compared with usual care (nine trials, n = 3916, 10.9% vs 13.4%; RR, 0.76; 95% CI, 0.59 to 0.97). However, the latter was limited to surgical ICU patients and was not observed in medical or medical-surgical ICU patients.

Arabi et al recently published a RCT of critically ill patients in a medical-surgical ICU (n = 523) assigned to insulin therapy with either target blood glucose of 4.4-6 mmol/l or 10-11 mmol/l [15]. There was no significant difference in ICU mortality (13.5% vs 17.1%, p=0.30) or in hospital mortality (27.1% vs 32.3%, p=0.19). Hypoglycaemia occurred more frequently with intensive insulin therapy (28.6% vs 3.1% of patients; p < 0.0001). There was no significant difference in any of the other secondary outcome measures. Adding the data from Arabi's RCT to the meta-analyses of Wiener et al (Figures 16 and 17) does not appear to have any impact on the primary and secondary outcomes. More light will be shed on this controversy when the results of the NICE SUGAR multi-centre RCT are published in 2009.

### Should we use Anti-thrombin III for disseminated intravascular coagulation?

We examined this issue in our recent systematic review [16]. Anti-thrombin III (AT III) is an anticoagulant with anti-inflammatory properties. We included 20 RCTs with a total of 3458 participants. Thirteen of these trials had high risk of bias. AT III did not reduce overall mortality compared with the control group (RR 0.96, 95% CI 0.89 to 1.03; Figure 18) and as the actual size exceeded that required information size to detect a 10% relative risk reduction, we were able to exclude an intervention effect of this magnitude.

However, AT III did increase bleeding events (Figure 19). A total of 32 subgroup and sensitivity analyses were carried out but gave insignificant differences (including examination of adjuvant heparin). As it currently stands, AT III cannot be recommended for critically ill patients based on the available evidence and there is a need for a RCT without adjuvant heparin since the required sample size, to detect a 5% relative risk reduction (numbers need to treat (NNT) = 20), based on our current best estimate of a possible intervention effect is 14,294.

## Discussion

The above mentioned publications illustrate the need for applying evidence-based practice to the treatment of critically ill patients within anaesthesia and intensive care. It is a daunting task trying to convert anaesthesiologists and intensivists away from their conventional practices, but the future appears bright since ever more journals, international scientific organisations and societies appear to be embracing systematic reviews as the highest standard of evidence when dealing with interventions and treatment of patients.

It is important to remember that guidelines and treatment recommendations based on small trials or meta-analyses of small numbers of trials can be misleading due to random error, study design and bias [2, 17, 18]. As illustrated above, we need to focus on more than just a p value < 0.05 or a confidence interval which both may have to be corrected by sequential methods in cumulative meta-analysis when conducting systematic reviews or when focusing on guidelines and recommendations based on few RCT's.

Often, when larger and methodologically sound trials appear, the evidence for beneficial effects becomes less convincing and subsequently disappears or even turns around to become evidence for a harmful effect. This certainly emphasises the need for careful estimation of the amount of low-bias information we need before we consider implementing interventions. We should view any gathered information as a mere step in the right direction urging us to evaluate its significance in the light of results from sequential methods. Unfortunately, very few of our treatment regimens in critical care are founded on the basis of solid evidence. Hence, there is a need for a critical open mind rather than blind adherence to guidelines, which optimally should take on the form of updated evidence rather than expertise-based recommendations [3]. When confronted with various decisions in our daily practice, we should constantly ask ourselves whether the patients will benefit from our practices when they are not evidence-based. Even intensivists appear more focused on applying evidence-based practices [19].

Levy et al's recent controversial publication indicates a greater mortality for patients managed by critical care physicians than those who are not [20]. This study has various shortcomings in terms of design, bias, and admission to open unit ICU's (primarily found in the USA). Nonetheless, it does raise the question of what benefit our patients have from our actions and interventions when they are not evidence-based.

Let us help our patients by addressing the fundamental question of quality standards and start basing our practice on solid and robust evidence. In summary, let us conduct and base our recommendations for interventions on large high quality RCTs as well as systematic reviews with meta-analyses of such RCTs rather than reinforcing implementation of interventions with dubious evidence. We should dedicate ourselves to help close the information gap.

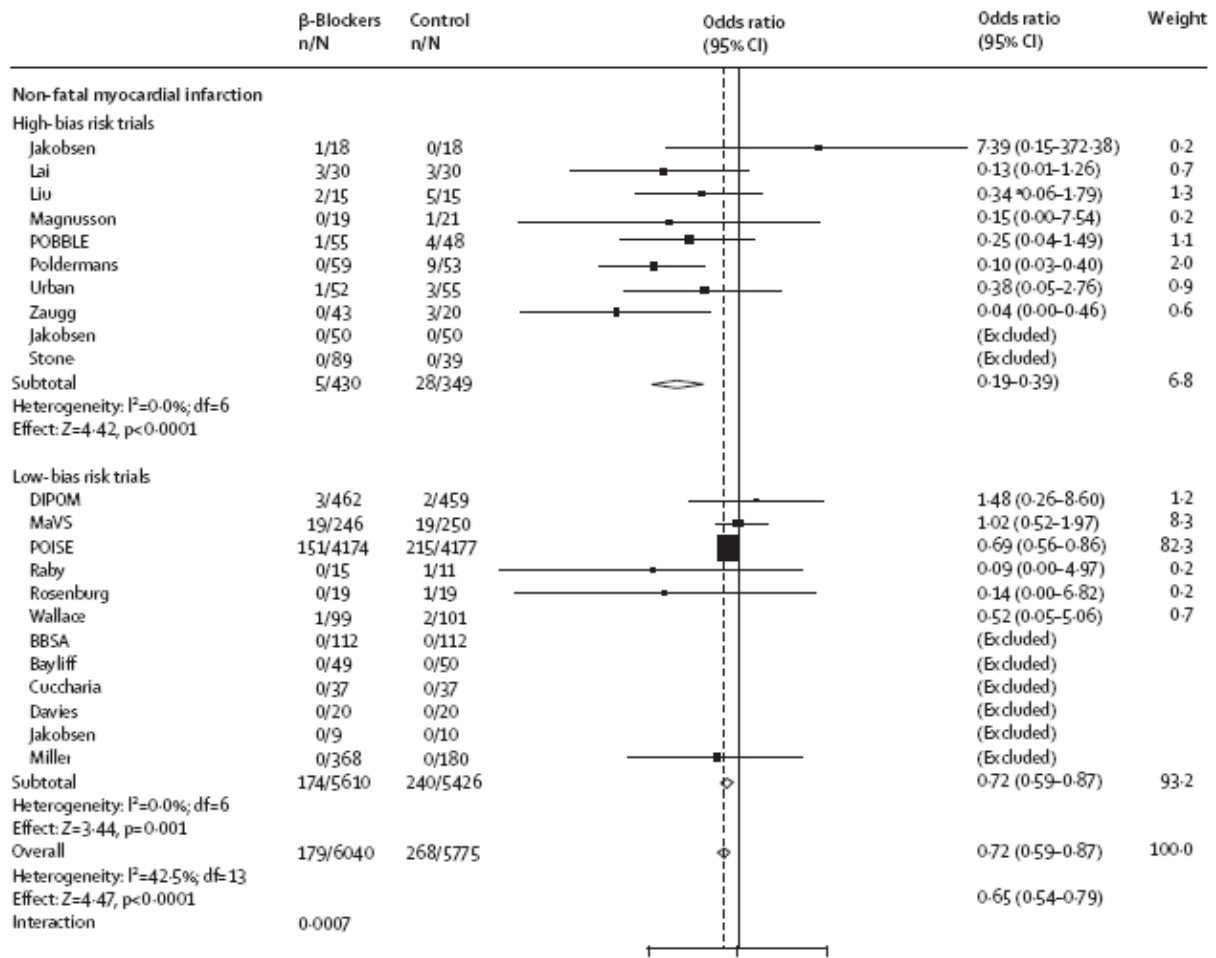
## Key Learning Points

- Systematic reviews allow for a more precise appraisal of the evidence and may help resolve uncertainty when original research results disagree.
- Systematic reviews and meta-analysis should avoid systematic errors by focusing on trials with a low risk of bias to produce realistic estimates of intervention effects.
- Systematic reviews and meta-analysis should avoid random error by including an adequate number of participants and events.
- Systematic reviews and meta-analysis should avoid design errors by focusing on important clinical patient outcomes and not surrogates.
- Let us base our recommendations and clinical practice on large, high quality RCTs as well as systematic reviews and meta-analyses of such RCTs.

## References

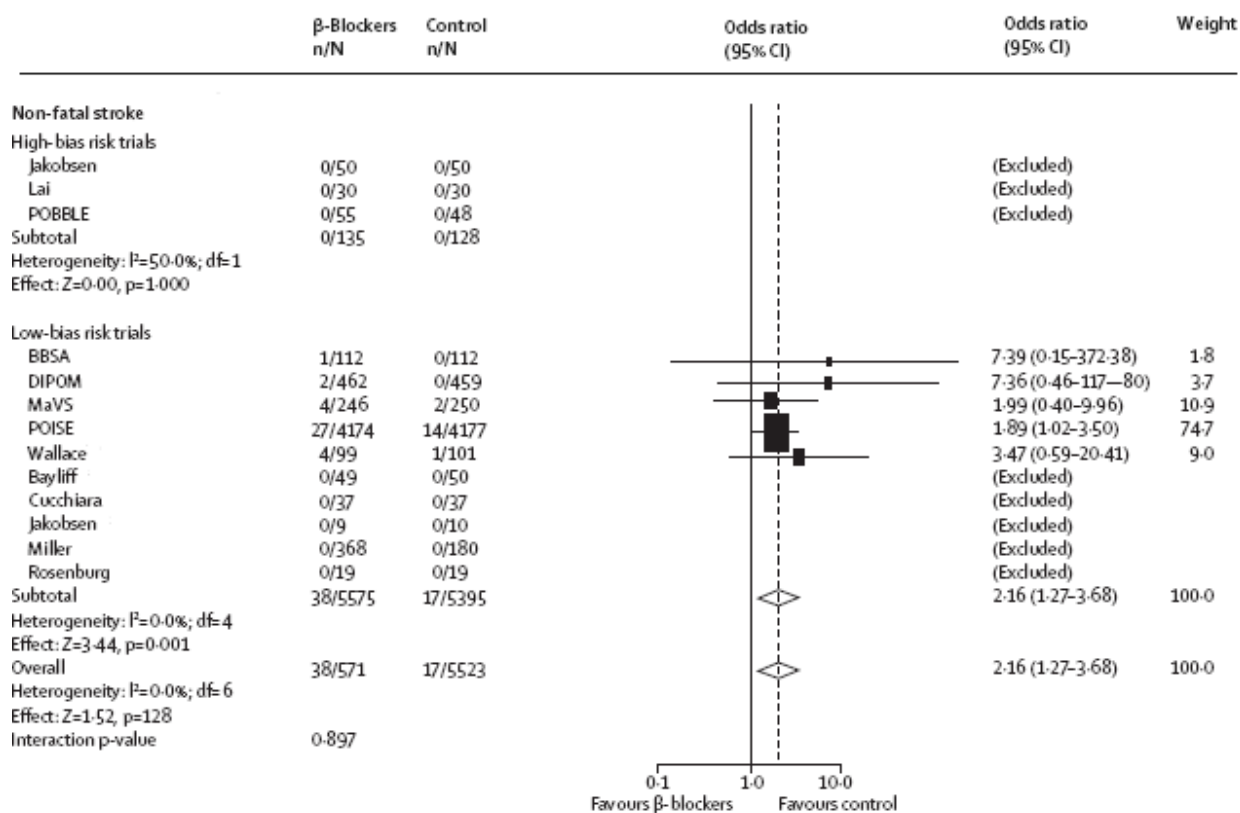
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Figure 1



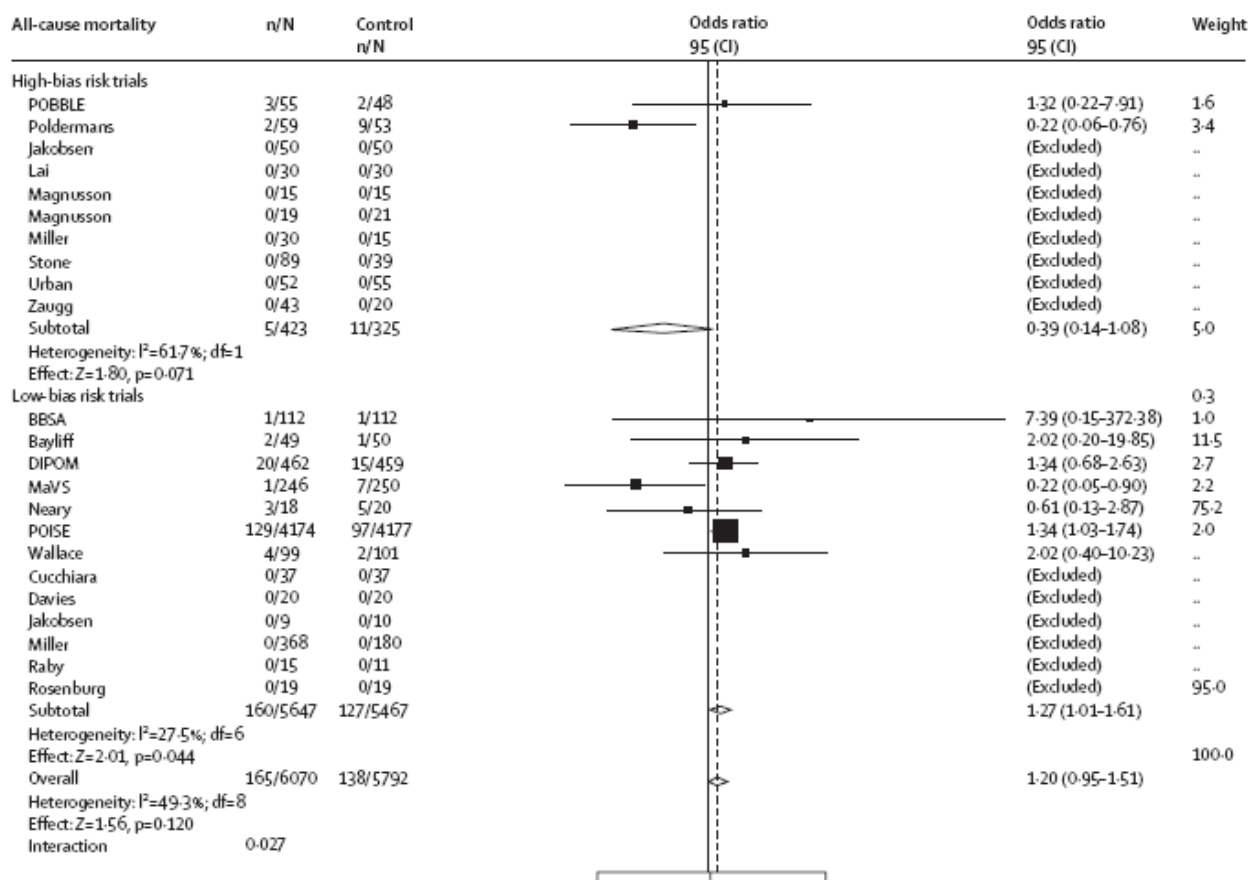
Odds ratios for 30 day non-fatal myocardial infarction associated with peri-operative treatment with  $\beta$ -blockers (data from Bangalore et al [3]).

Figure 2



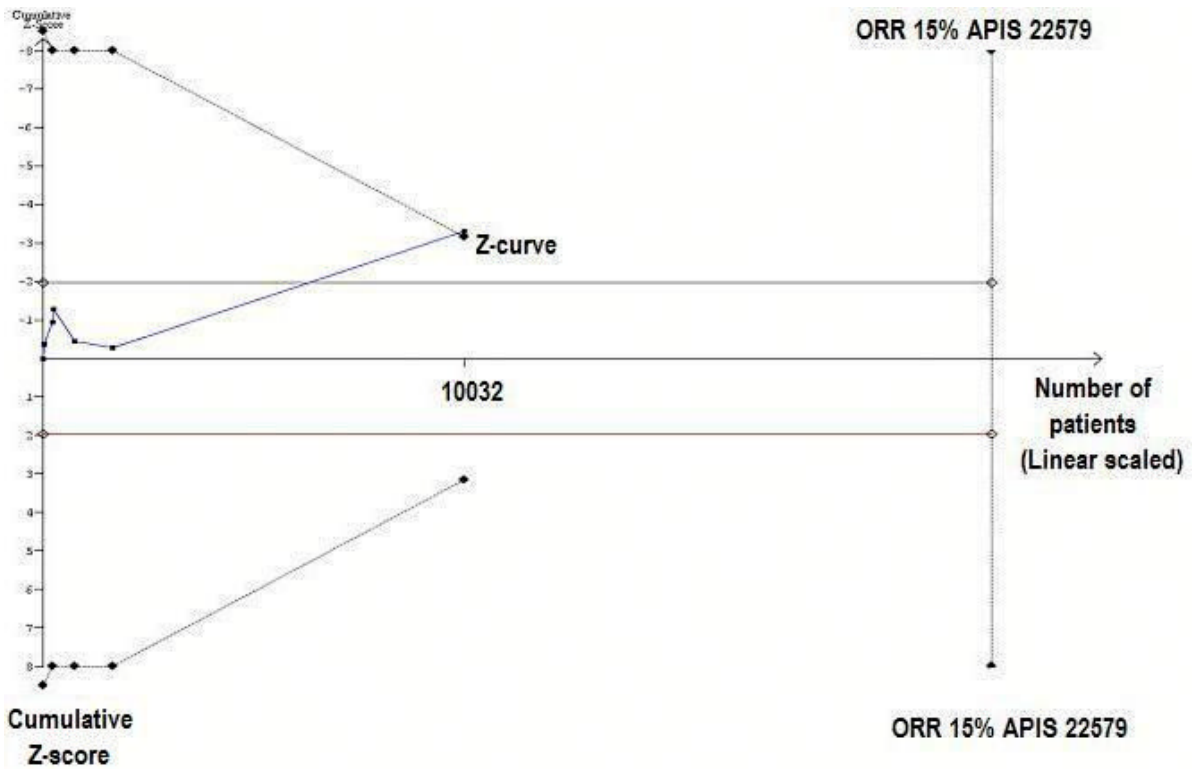
Odds ratios for 30 day non-fatal stroke associated with peri-operative treatment with  $\beta$ -blockers (data from Bangalore et al [3]).

Figure 3



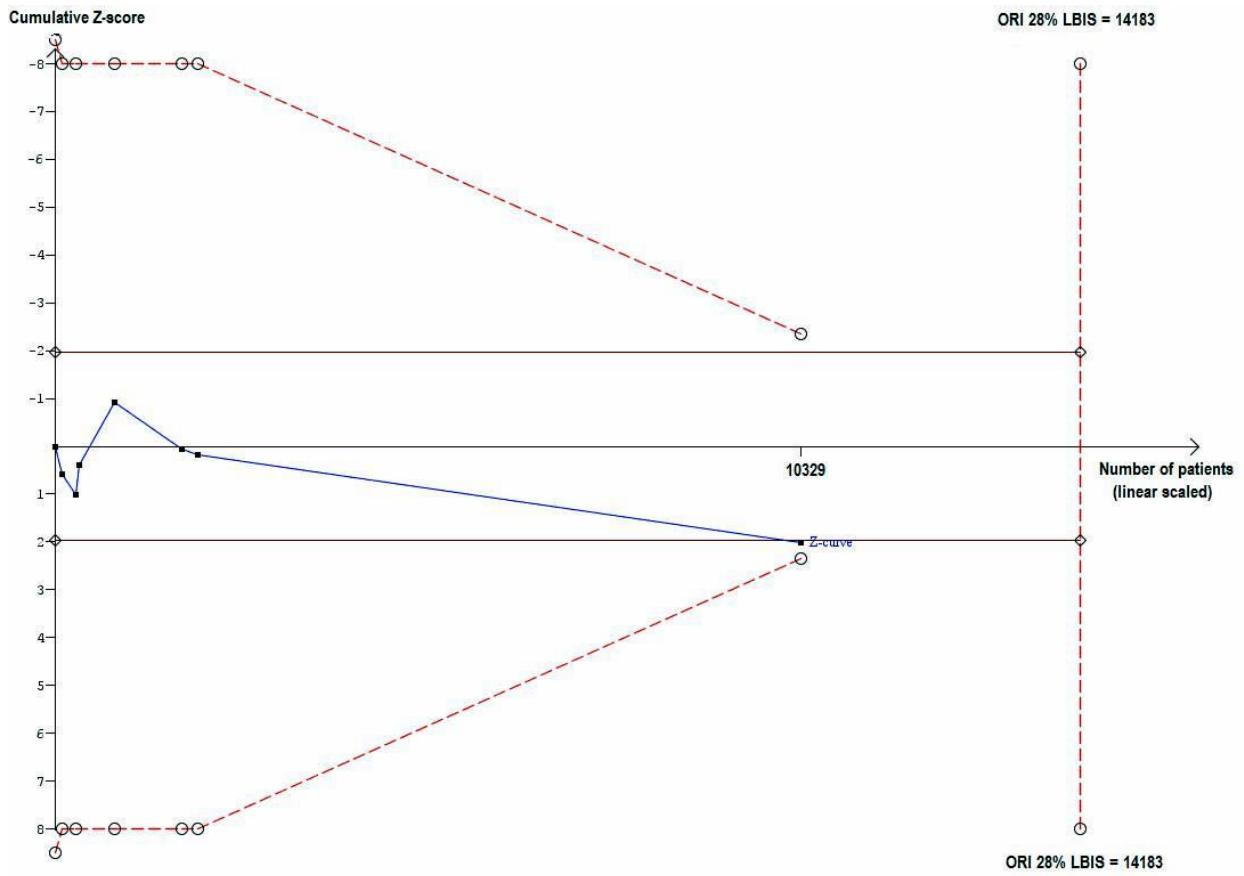
Odds ratios for all-cause mortality associated with peri-operative treatment with  $\beta$ -blockers (data from Bangalore et al [3]).

Figure 4



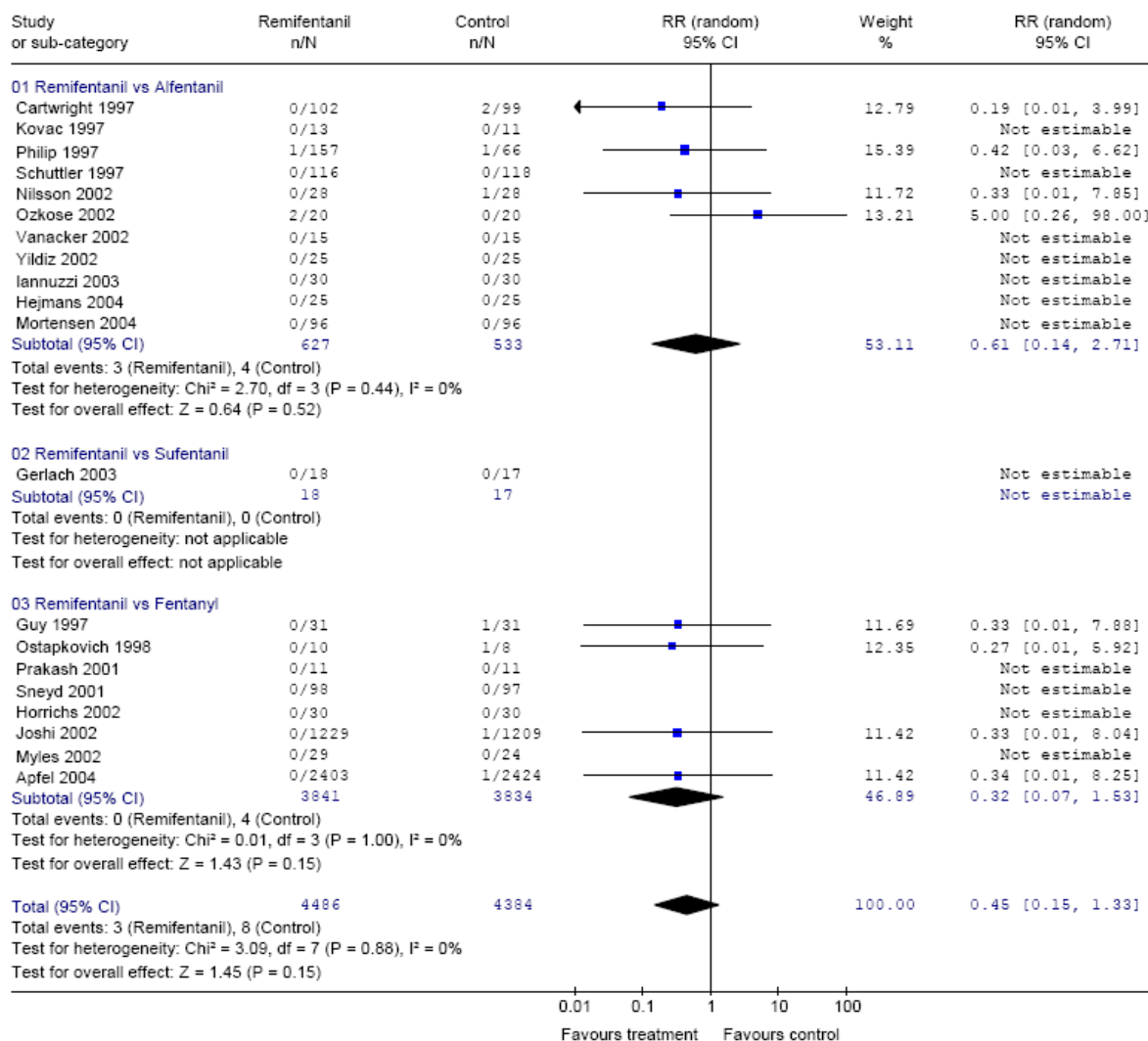
Trial sequential monitoring boundary for the outcome of non-fatal myocardial infarction. The traditional boundary ( $p=0.05$   $z=-1.965$ ) as well as the trial sequential monitoring boundary constructed for an a priori information size (APIS) of 22 579 patients corresponding to an odds ratio reduction (ORR) of 15% are crossed supporting the evidence that peri-operative  $\beta$ -blockade reduces the rate of non-fatal myocardial infarction among survivors with 15% (data from Bangalore et al [3]).

Figure 5



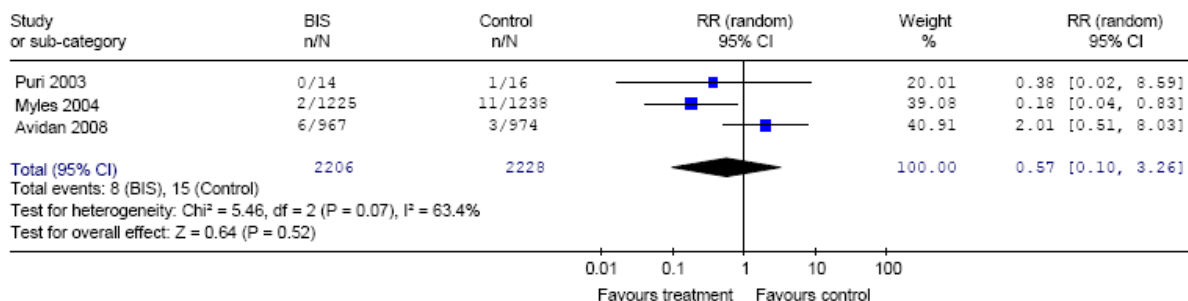
Trial sequential monitoring boundary for the outcome of all-cause mortality. The trial sequential monitoring boundary constructed for an intervention effect suggested by the low-bias trials with a required information size (LBIS) of 14 183 participants corresponding to an odds ratio increase (ORI) in mortality with peri-operative  $\beta$ -blockade of 28%  $\alpha=5\%$  and  $\beta=20\%$ . The cumulative z-curve crosses the traditional boundary ( $p=0.05$ ) but not the trial sequential monitoring boundary indicating that the crossing of the traditional monitoring boundary ( $z=1.96$ ) may be a random error due to repetitive testing on accumulating data (data from Bangalore et al [3]).

Figure 6



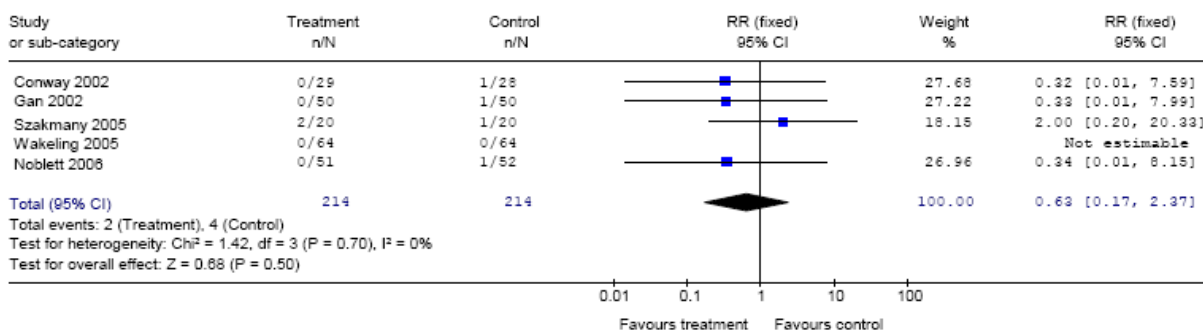
Intra-operative awareness in remifentanil-treated and control opioid-treated patients (data from Komatsu et al [4]).

Figure 7



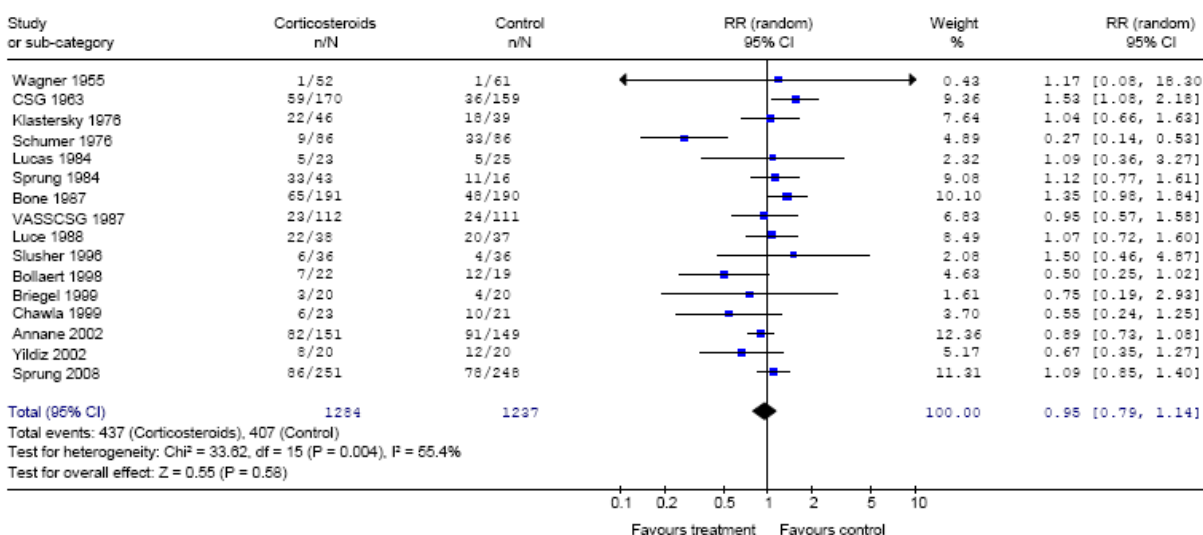
Awareness in surgical patients with high risk of awareness (data from Punjasawadwong et al [5] and Avidan et al [6]).

Figure 8



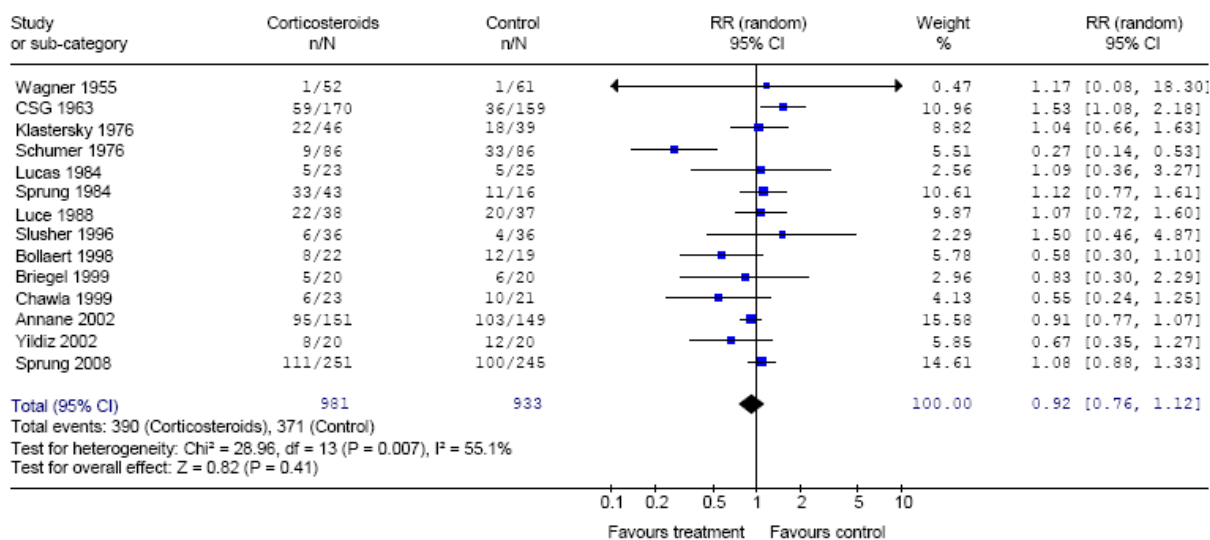
Mortality using oesophageal Doppler for peri-operative fluid management in major abdominal surgery (data from Abbas et al [7]).

Figure 9



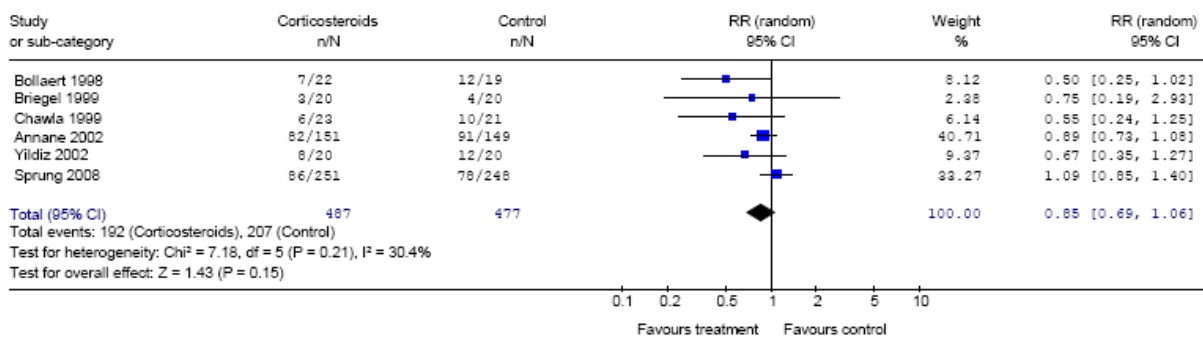
Effects of corticosteroids on overall mortality at 28 days in patients with severe sepsis and septic shock (data from Sprung et al [8] and Anname et al [9]).

Figure 10



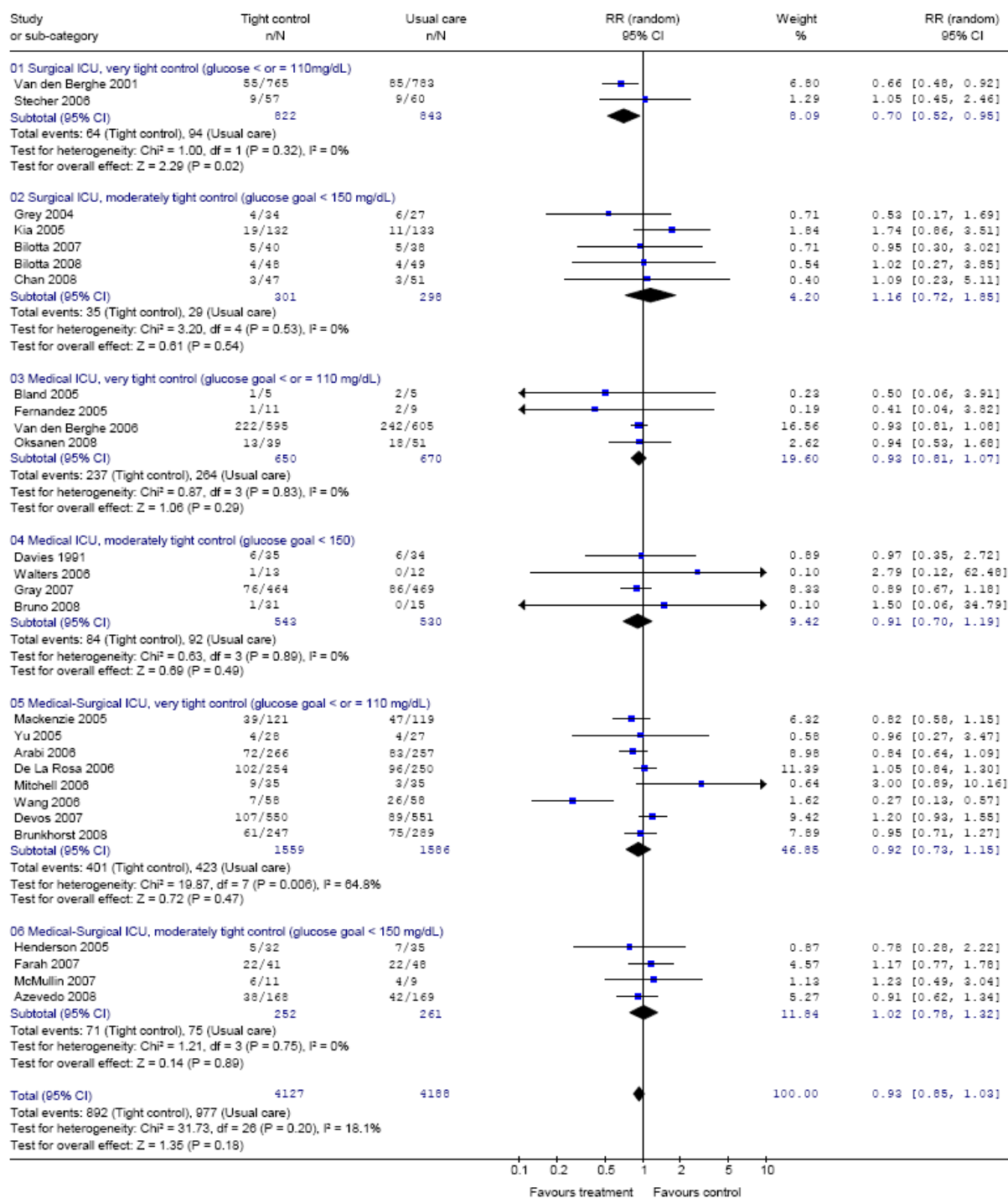
Effects of corticosteroids on overall mortality during hospitalization in patients with severe sepsis and septic shock (data from Sprung et al [8] and Annane et al [9]).

Figure 11



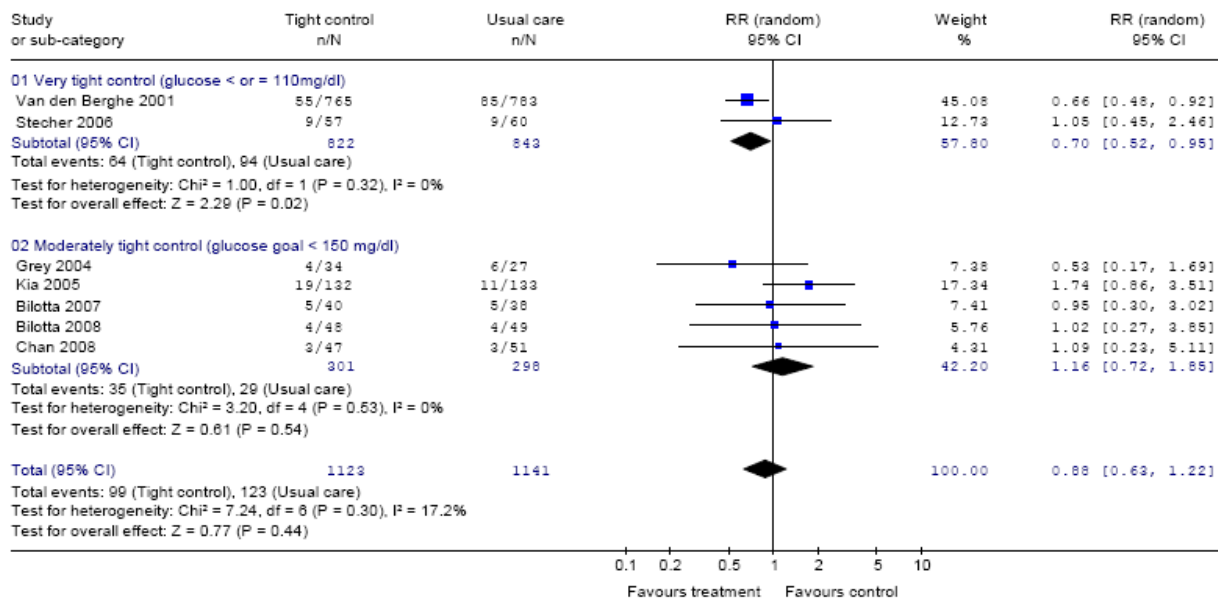
Effects of long courses of low dose corticosteroids on overall mortality at 28 days in patients with severe sepsis and septic shock (data from Sprung et al [8] and Annane et al [9]).

Figure 12



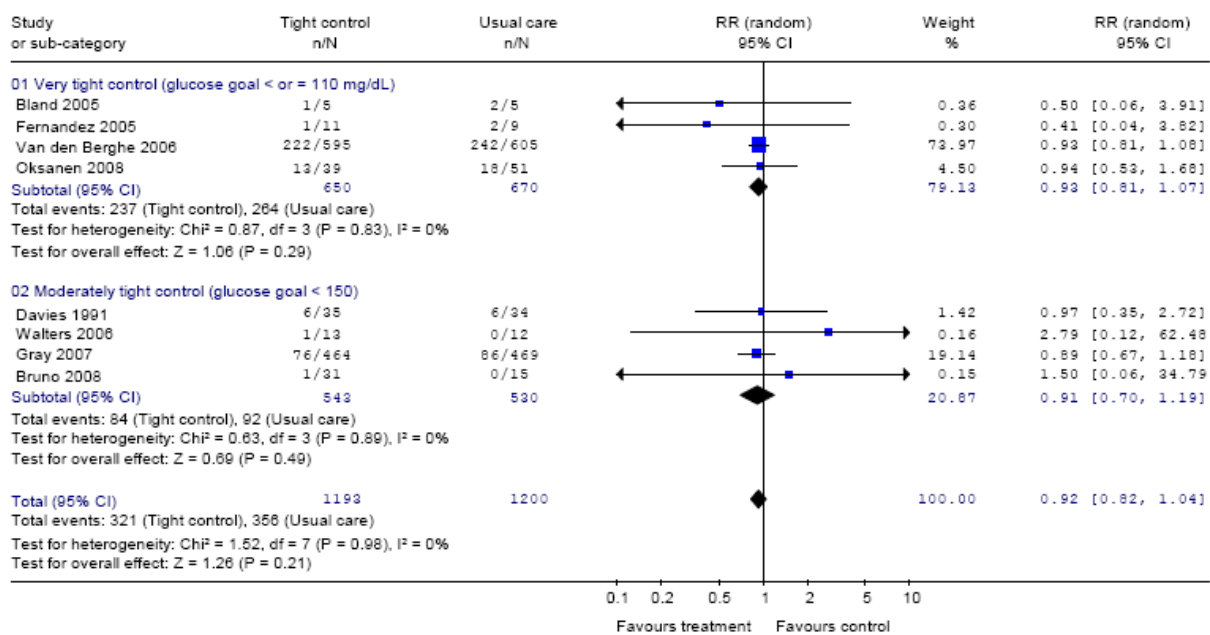
Association of tight glucose control vs usual care with hospital mortality, all critically ill patients (data from Wiener et al [14]).

Figure 13



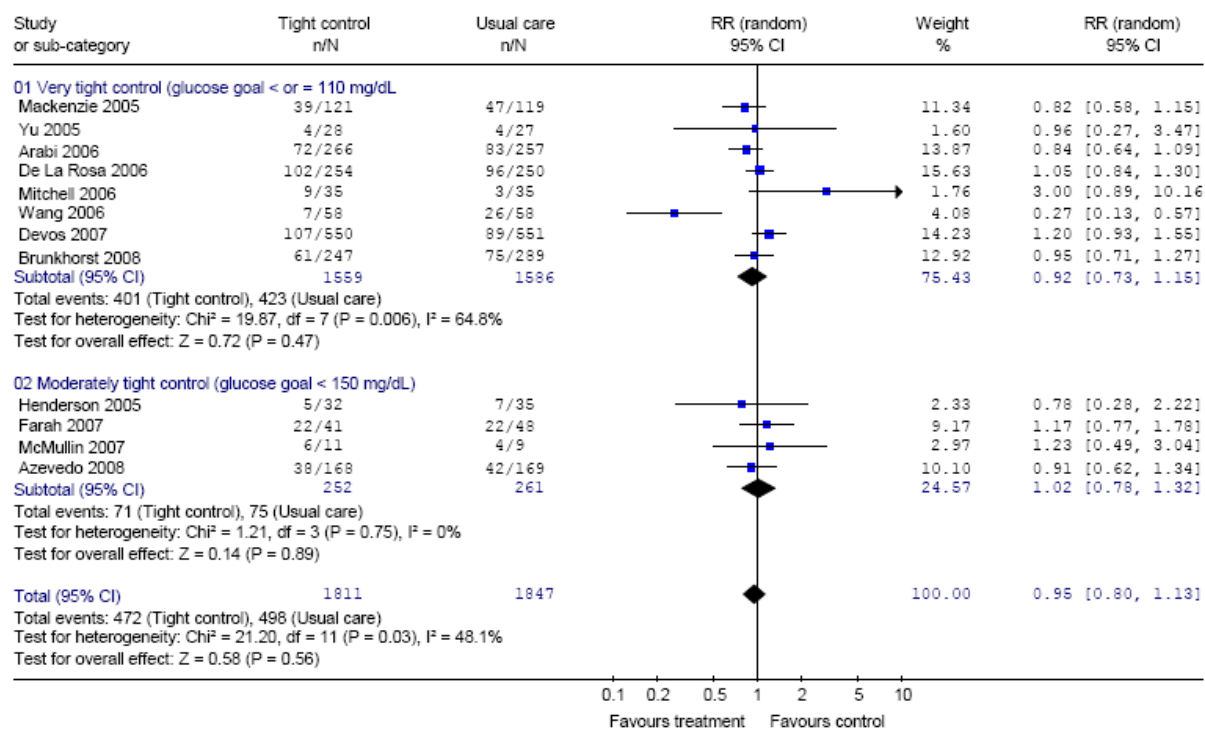
Association of tight glucose control vs usual care with hospital mortality, surgical ICU (data from Wiener et al [14]).

Figure 14



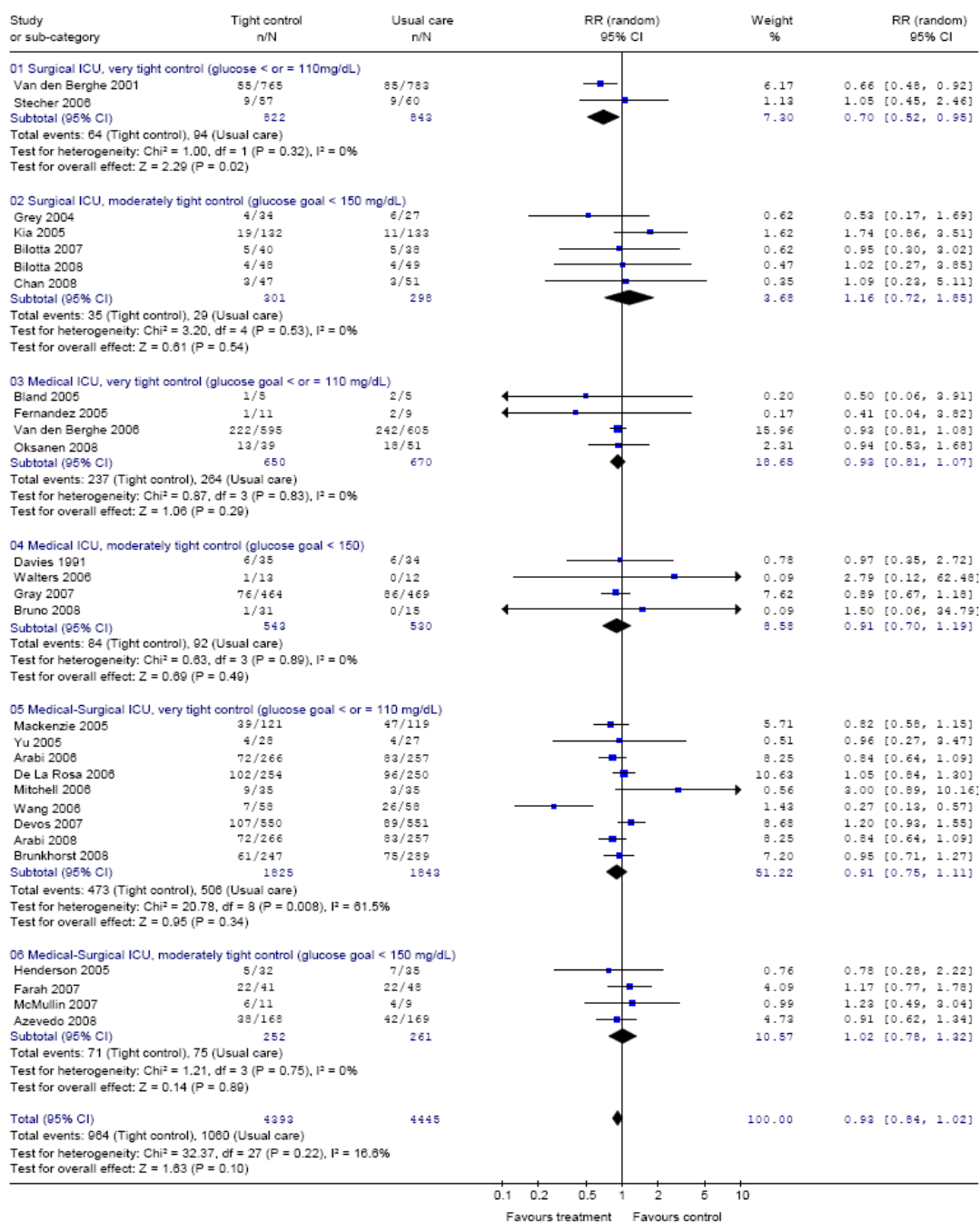
Association of tight glucose control vs usual care with hospital mortality, medical ICU (data from Wiener et al [14]).

Figure 15



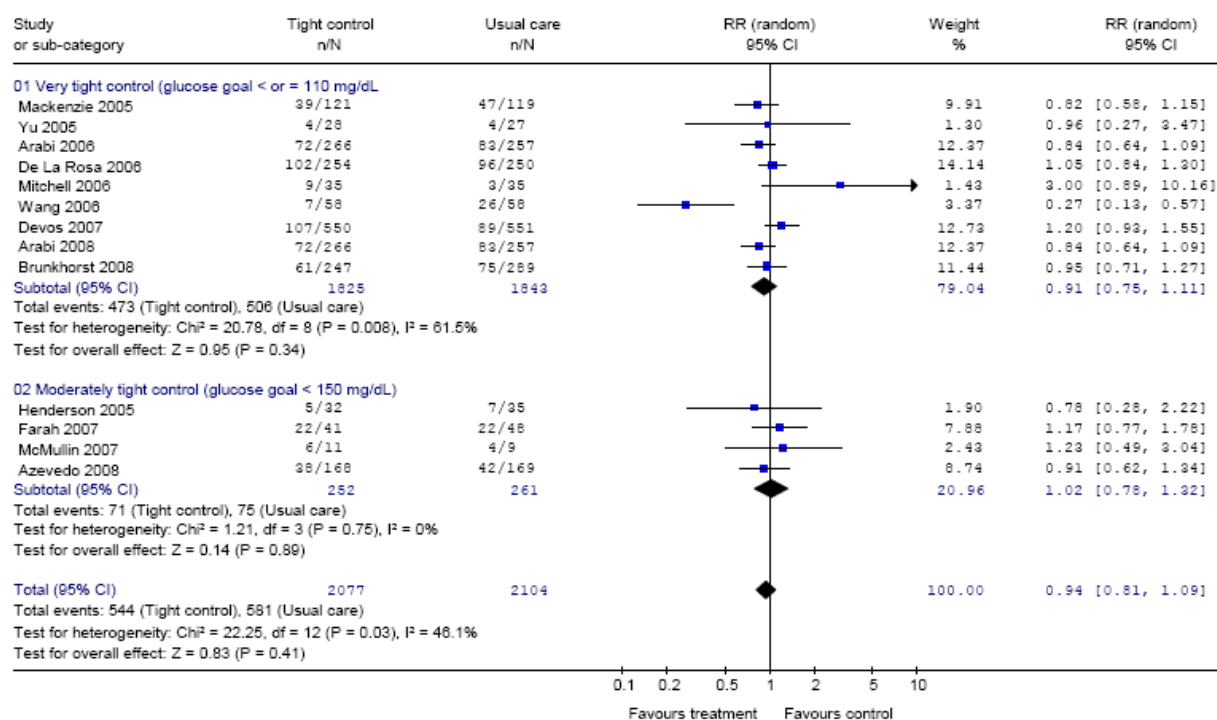
Association of tight glucose control vs usual care with hospital mortality, medical-surgical ICU (data from Weiner et al [14]).

Figure 16



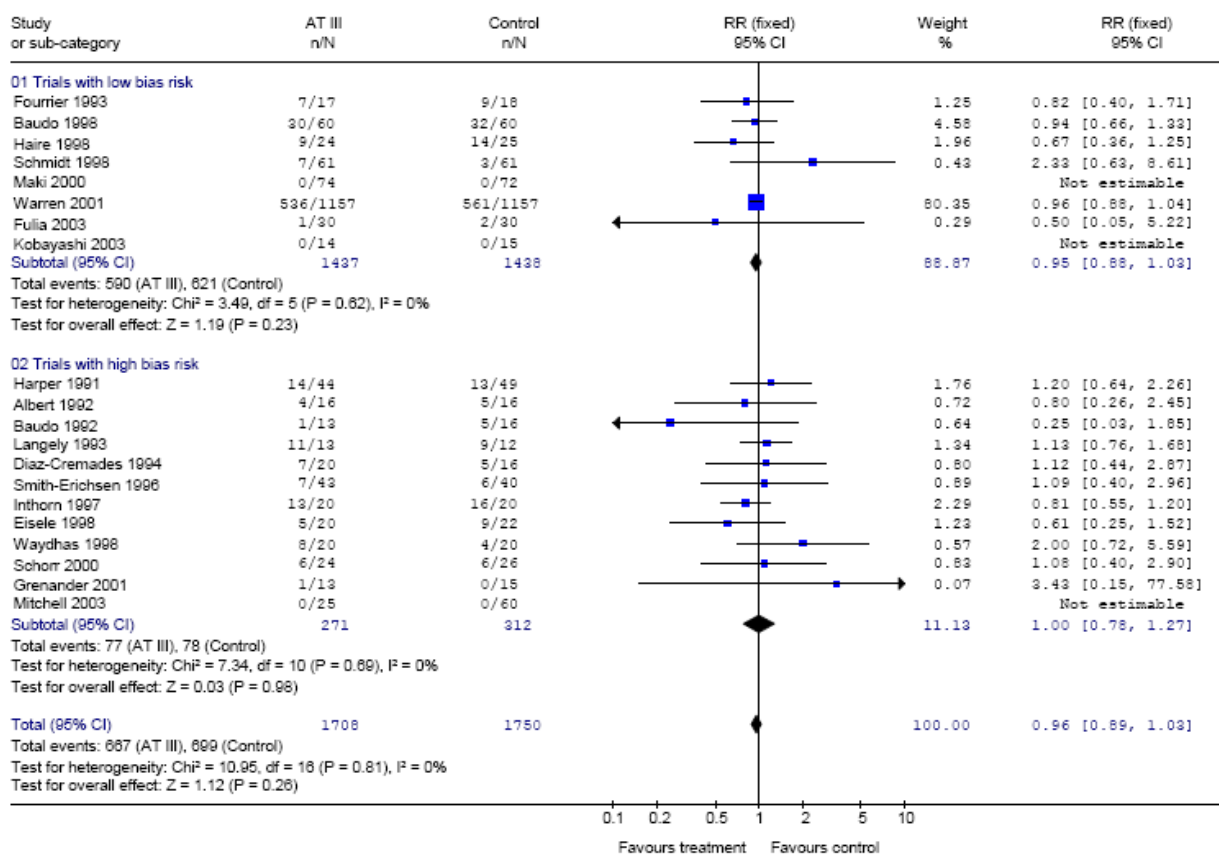
Association of tight glucose control vs usual care with hospital mortality, all critically ill patients (data from Wiener et al [14] and Arabi et al [15]).

Figure 17



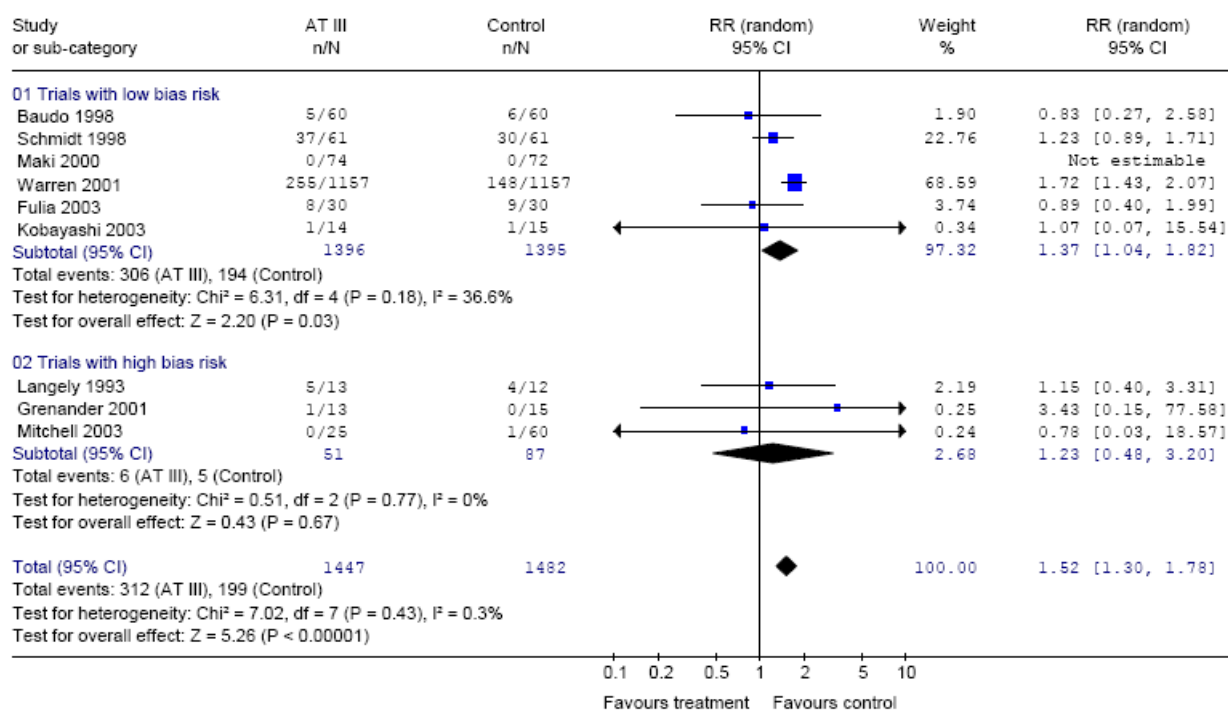
Association of tight glucose control vs usual care with hospital mortality, medical-surgical ICU (data from Wiener et al [14] and Arabi et al [15]).

Figure 18



Mortality in Antithrombin III versus standard care (subgroup analysis on risk of bias) (data from Afshari et al [16]).

Figure 19



Bleeding events associated with AT III versus standard care (data from Afshari et al [16]).