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REVIEW

Perioperative hemodynamic goal-directed therapy and mortality: a systematic review and meta-analysis with meta-regression

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ABSTRACT

INTRODUCTION: Recent data found that perioperative goal directed therapy (GDT) was effective only in higher control mortality rates (>20%) with a relatively high heterogeneity that limited the strength of evidence. The aim of the present meta-analysis was to clearly understand which high risk patients may benefit of GDT.

EVIDENCE ACQUISITION: Systematic review of randomized controlled trials with meta-analyses, including a meta-regression technique. MEDLINE, EMBASE, and The Cochrane Library databases were searched (1980-January 2015). Trials enrolling adult surgical patients and comparing the effects of GDT versus standard hemodynamic therapy were considered. The primary outcome measure was mortality. Data synthesis was obtained by using Odds Ratio (OR) with 95% confidence interval (CI) by random-effects model.

EVIDENCE SYNTHESIS: Fifty eight studies met the inclusion criteria (8171 participants). Pooled OR for mortality was 0.70 (95% CI 0.56-0.88, P=0.002, no statistical heterogeneity). GDT significantly reduced mortality when it is >10% in control group (OR 0.43, 95% CI 0.30-0.61, P<0.00001). The meta-regression model showed that the cut off of 10% of mortality rate in control group significantly differentiates 43 studies from the other 15, with a regression coefficient b of -0.033 and a P value of 0.0001. The significant effect of GDT was driven by high risk of bias studies (OR 0.48, 95% CI 0.34-0.67, P<0.0001).

CONCLUSIONS: The present meta-analysis, adopting the meta-regression technique, suggests that GDT significantly reduces mortality even when the event control rate is >10%.

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Key words: Perioperative care - Mortality - Therapy.

Introduction

The strategy of hemodynamic goal-directed therapy (GDT) refers to monitoring and manipulation of physiological hemodynamic parameters by means of therapeutic interventions,[1] based mainly on fluids, red blood cells and inotropic drugs. This regimen was originally applied in surgical patients with the aim to reach normal or supranormal values of cardiac output and oxygen delivery [2] and later applied to critically ill patients. A first meta-analysis [3] including surgical and critically ill patients did not demonstrate any significant overall benefit. Some years later, a lower mortality was observed only in very severe surgical, trauma and medical patients in whom optimization treatment was performed before organ failure occurrence.[4] A

Comment in p. 1135.

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subsequent meta-analytic study,[5] differentiating surgical patients from patients with sepsis and organ failure, showed that in septic patients no benefit was observed, although the matter is still under debate,[6] while mortality was improved in perioperative subgroup, although the presence of statistical heterogeneity and inconsistency reduced the strength of evidence. The benefit was recently confirmed only in very high risk patients (control group mortality >20%) on the basis of a priori subgroup division.[7, 8] In these papers, however, no clear explanation was provided about how this cut-off was obtained and a relatively high heterogeneity was still observed in all the analyses,[7, 8] thus reducing the strength of evidence.

We therefore conducted a meta-analysis with meta-regression to clearly evaluate which high risk patient can benefit from perioperative GDT.

Evidence acquisition

Eligibility criteria

RCTs were selected according to the following inclusion criteria:[9]

— types of participants. Adult patients (ages 18 years and older) undergoing major surgery were considered. Studies involving mixed populations of critically ill, nonsurgical patients, or postoperative patients with sepsis or organ failure were excluded;

— types of interventions. GDT was defined as monitoring and manipulation of hemodynamic parameters to reach normal or supranormal values by fluid infusion alone or in combination with inotropic therapy in the perioperative period within eight hours after surgery. Studies including late hemodynamic optimization treatment were excluded;

— types of comparisons. Trials comparing the beneficial and harmful effects of GDT versus standard hemodynamic therapy were considered. RCTs with no description or no difference in optimization strategies between groups, as well as RCTs in which therapy was titrated to the same goal in both groups or was not titrated to predefined end points were excluded;

— types of outcome measures. The primary outcome measure was mortality. For those RCTs providing more data on mortality (*i.e.* in-hospital, 30-day, 90-day), the in-hospital mortality was considered. Sensitivity analysis was planned including only low risk of bias trials (see below). Moreover, another sub-group analysis was planned on the basis of the result of the meta-regression model (see below). A third subgroup analysis was planned combining the results of the previous two analyses (*i.e.* high mortality/high risk of bias, high mortality/low risk of bias, low mortality/high risk of bias, low mortality/low risk of bias);

— types of studies. RCTs on perioperative GDT in surgical patients were included. No language, publication date, or publication status restrictions were imposed.

Information sources

Different search strategies (last update January 2015) were performed to retrieve relevant randomized controlled trials (RCTs) by using MEDLINE, The Cochrane Library and EMBASE databases. No date restriction was applied for MEDLINE and The Cochrane Library databases, while the search was limited to 2008-2014 for EMBASE database.[10] Additional RCTs were searched in The Cochrane Library and the Database of Abstracts of Reviews of Effects (DARE) databases and in the reference lists of previously published reviews and retrieved articles. Other data sources were hand-searched in the annual proceedings (2008-2014) of the Society of Critical Care Medicine, the European Society of Intensive Care Medicine, the Society of Cardiovascular Anesthesiologists, the Royal College of Anesthetists, the American Society of Anesthesiologists. In order to reduce publication bias, abstracts were searched.[11] Publication language was not a search criterion.

Search terms

Trials selection was performed by using the following search terms: randomized con-

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trolled trial, controlled clinical trial, surgery, goal directed, goal oriented, goal target, cardiac output, cardiac index, DO_2, oxygen consumption, cardiac volume, stroke volume, fluid therapy, fluid loading, fluid administration, optimization, supranormal. The search strategies used for the MEDLINE, The Cochrane Library and EMBASE databases are reported in the Supplementary Appendix I, online content only.

Study selection

Two investigators (FM, NB) examined at first each title and abstract to exclude clearly irrelevant studies and to identify potentially relevant articles. Other two investigators (LD, MG) independently determined eligibility of full-text articles retrieved. The names of the author, institution, journal of publication and results were unknown to the two investigators at this time.

Data abstraction and study characteristics

Data were independently collected by two investigators (MG, NB), with any discrepancy resolved by re-inspection of the original article. To avoid transcription errors, the data were input into statistical software and rechecked by different investigators (LD, FM).

RCT data gathered

Data abstraction included surgical risk (defined by the authors on the basis of POSSUM score,[12] ASA physical status classification, age >60 years, pre-operative morbidity, as previously adopted),[13] mortality of control group, type of surgery (*i.e.*, elective or emergent, abdominal, thoracic, vascular, etc.), anesthesiological management, hemodynamic goal-directed therapy (end-points, therapeutic intervention and monitoring tools).

Risk of bias in individual studies

A domain-based evaluation, as proposed by the Cochrane Collaboration, was used to evaluate the methodological quality of RCTs.[14] This is a two-part tool, addressing seven specific domains (namely, sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting) that are strongly associated with bias reduction.[15, 16] Each domain in the tool includes one or more specific entries in a "Risk of bias" table. Within each entry, the first part of the tool describes what was reported to have happened in the study, in sufficient detail to support a judgement about the risk of bias. The second part of the tool assigns a judgement relating to the risk of bias for that entry. This is achieved by assigning a judgement of "Low risk", "High risk", or "Unclear risk" of bias. After each domain was completed, a "Risk of bias summary" figure presenting all of the judgements in a cross-tabulation of study by entry are generated. The green plus indicates low risk of bias, the red minus indicates high risk of bias, the white color indicates unclear risk of bias. For each study the number of green plus obtained for every domain was calculated: RCTs with 5 or 6 green plus were considered as having an overall low risk of bias.

Summary measures and planned method of analysis

Meta-analytic techniques (analysis software RevMan, version 5.3.5, Cochrane Collaboration, Oxford, England, UK) were used to combine studies using odds ratios (ORs) and 95% confidence intervals (CIs). A statistical difference between groups was considered to occur if the pooled 95% CI did not include 1 for the OR. An OR less than 1 favored GDT when compared with control group. Two-sided P values were calculated. A random-effects model was chosen for all analyses. Statistical heterogeneity and inconsistency were assessed by using the Q and I^2 tests, respectively.[17, 18] When the P value of the Q-Test was <0.10 [17] and/or the I^2 was >25%, heterogeneity and inconsistency were considered significant.[19]

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Meta-regression. Assessing the impact of the slope

In the present meta-analysis the chosen covariates were the mortality rate in control group, the risk of bias evaluation (considering how many green plus the study obtained) and the year of publication. The meta-regression model [20-22] was applied to all the included studies. The software used was Comprehensive Meta Analysis Version 3.0

Evidence synthesis

Study selection

The search strategies identified 3244 (MEDLINE), 9948 (Cochrane Library) and 3054 (EMBASE) articles. Thirteen articles were identified through other sources (congress abstracts, reference lists). After initial screening and subsequent selection, a pool of 98 potentially relevant RCTs was identified. The subsequent eligibility process (Figure 1) excluded 40 articles and, therefore, 58 articles [23-80] with a total sample of 8171 patients, were considered for the analysis.

Study characteristics

All included articles evaluated the effects of hemodynamic optimization on mortality as primary or secondary outcome and had a population sample of adult surgical patients, undergoing both elective or emergent procedures (Supplementary Table I, online content only).[23-80] The studies were performed in Australia, United States, Europe, Canada, Brazil, China, Israel and India from 1991 to 2014 (Supplementary Table I) and were all published in English.

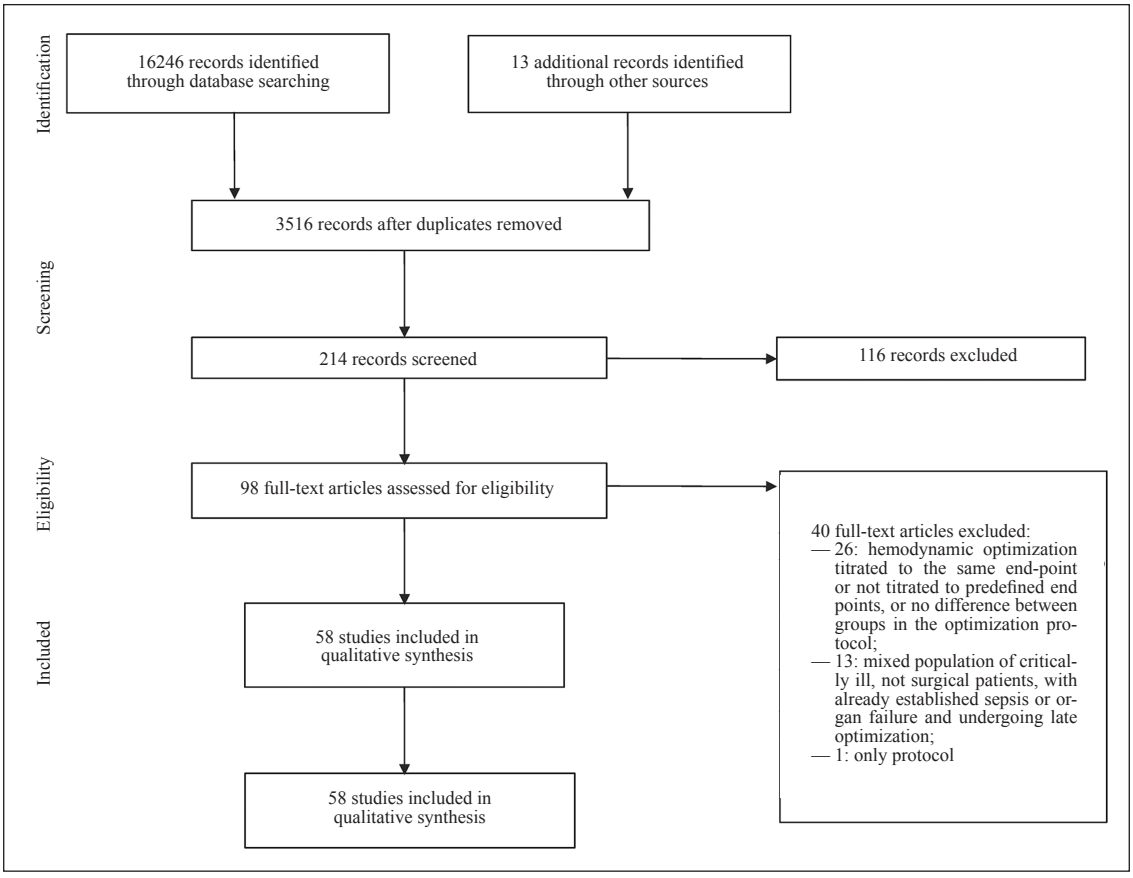

Figure 1.—Flow chart summarizing the studies selection procedure for the meta-analysis.

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Data concerning RCTs morbidity/mortality risk definition, population and type of surgery are presented in Supplementary Table I. The risk of bias assessment for each trial is showed (in Supplementary Table II online content only).

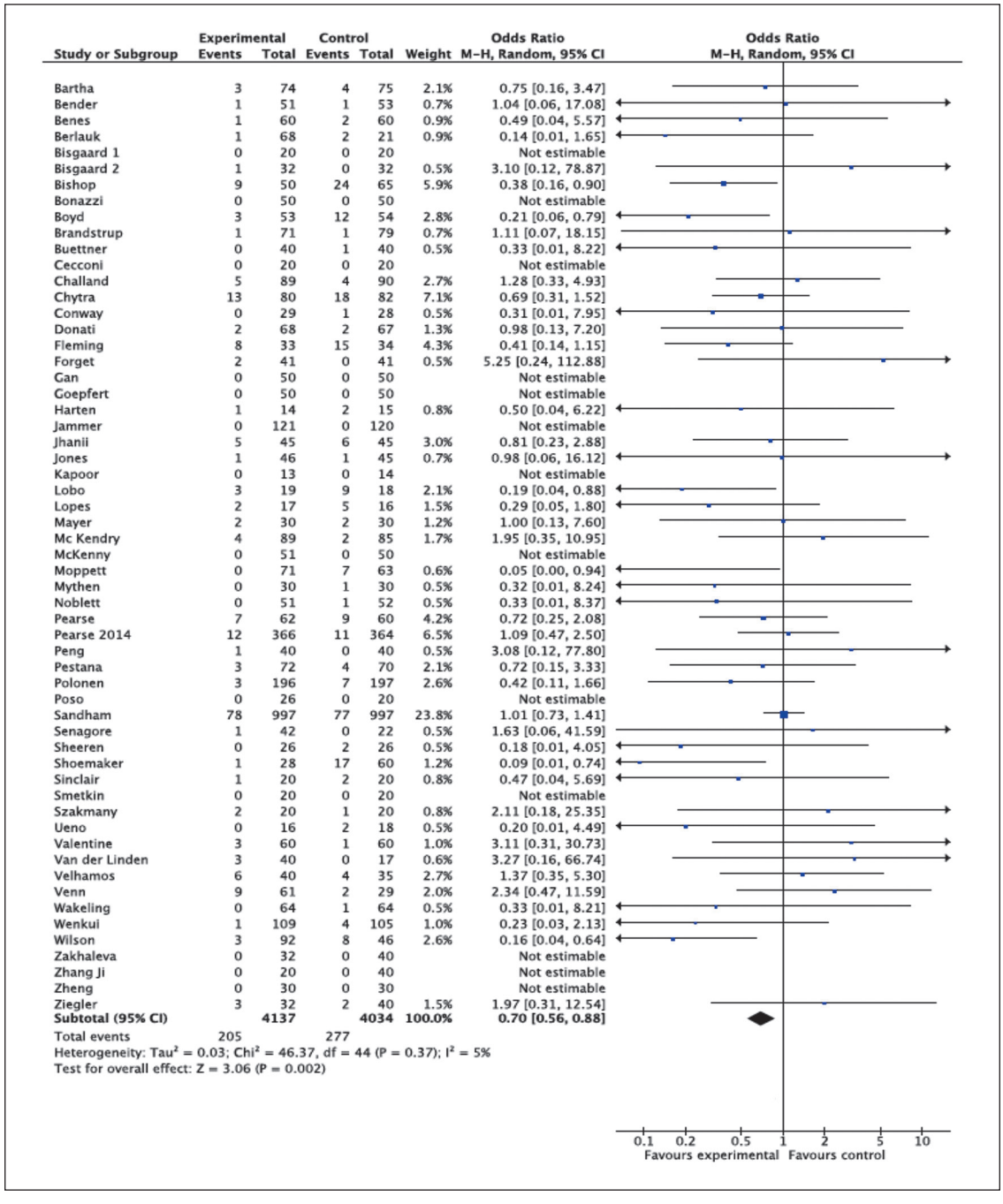

Figure 2.—Rates of mortality for each of the studies with Odds Ratios (ORs) and 95% Confidence Intervals (CI). The pooled OR and 95% CI are shown as the total. The size of the box at the point estimate of the OR gives a visual representation of the "weighting" of the study. The diamond represents the point estimate of the pooled OR and the length of the diamond is proportional to the CI.

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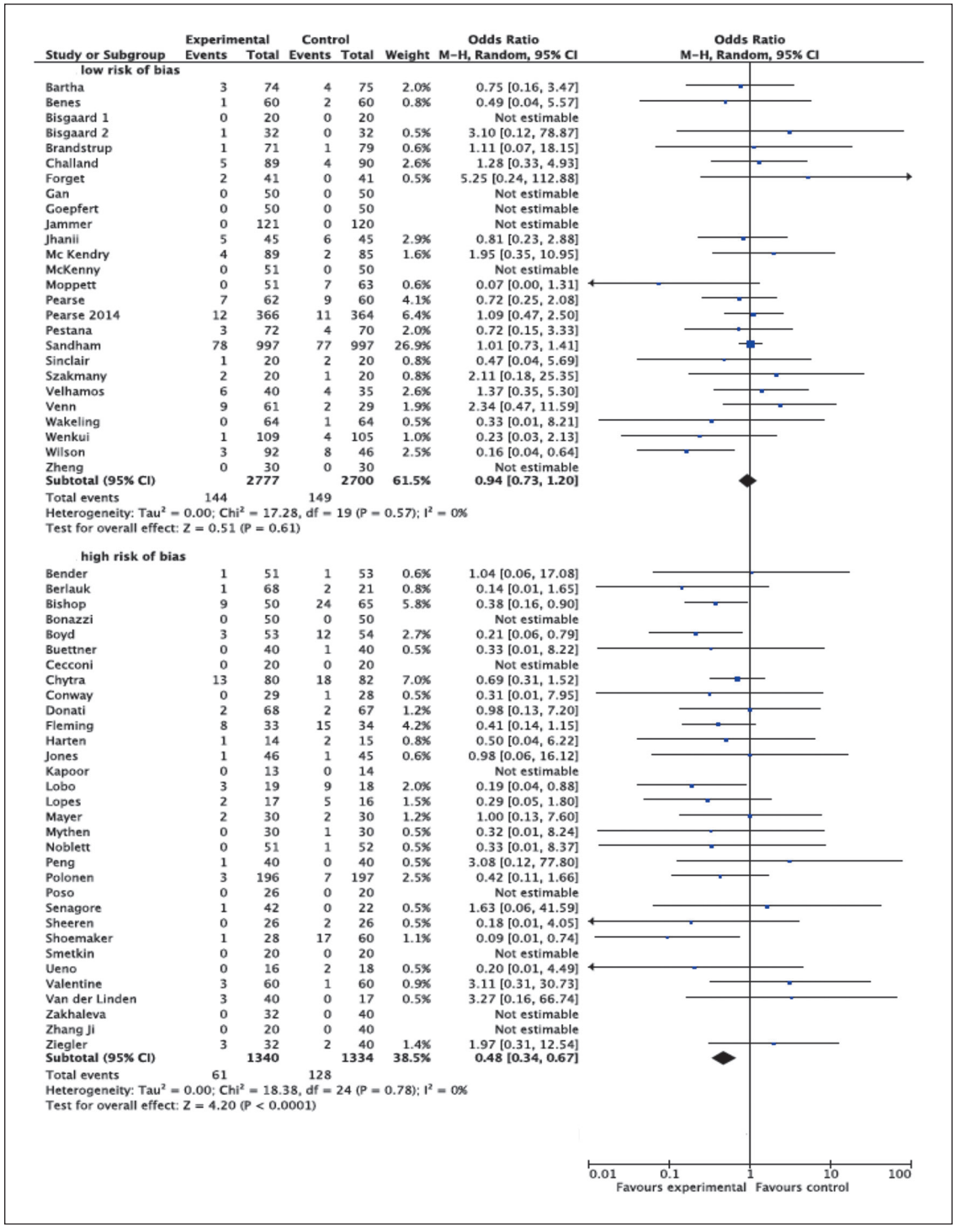

Figure 3.—Rates of mortality with Odds Ratios (ORs) and 95% Confidence Intervals (CI) in subgroup according to risk of bias. Studies were divided in high risk of bias and low risk of bias according to the Cochrane domain-based evaluation (see text for details). The pooled OR and 95% CI are shown as the total. The size of the box at the point estimate of the OR gives a visual representation of the "weighting" of the study. The diamond represents the point estimate of the pooled OR and the length of the diamond is proportional to the CI.

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Quantitative data synthesis

In 58 RCTs, 482 patients died: 205 out of 4137 (5%) were randomized to perioperative goal-directed therapy, and 277 out of 4034 (7%) were randomized to control. Pooled OR for mortality was 0.70 and 95% CI was 0.56-0.88. No statistical heterogeneity and inconsistency were detected (Figure 2). Excluding the largest study,[61] the result was confirmed: OR was 0.62 with 95% CI 0.48-0.80 (P=0.0002, 6177 pts), and no significant statistical heterogeneity (Q statistic P=0.56; I^2=0%) was observed.

The sensitivity analysis showed that the significant effect of GDT on mortality was driven by high risk of bias RCTs (OR 0.48, 95% CI 0.34-0.67, P<0.0001, Q statistic P=0.78; I^2=0%, 32 RCTs), while no effect was demonstrated in low risk of bias trials (OR 0.94, 95% CI 0.73- 1.20, P=0.61, Q statistic P=0.57; I^2=%, 26 RCTs) (Figure 3).

Meta-regression

Figure 4 showed the plot of log odds ratio on control group mortality: the meta-regression model identified, by inspection to the plot, a point (cut-off) on the upper confidence interval of the regression line that separates positive log odds ratios to negative log odds ratios: this cut-off coincides with the mortality rate in control group of 10%. In other words, the meta-regression model, applied to all 58 RCTs, showed that the cut off of 10% of mortality rate in control group significantly differentiated 43 studies from the other 15, with a regression coefficient b of -0.033 and a P value of 0.0001 (see Figure 4). Supplementary Table III (online content only), showed the results for meta-regression using control group mortality to predict the log odds ratio.

The subgroup analysis including only studies in which the mortality rate in the control group was lower than 10% showed no significant results (OR 0.99, 95% CI 0.78-1.27, P=0.95, Q statistic P=0.97 I^2=0%, 43 RCTs), while a statistical significant effect was observed in those RCTs with a mortality rate in control group >10% (OR 0.43, 95% CI 0.30-0.61, P<0.00001, Q statistic P=0.41; I^2=3%, 15 RCTs, (Figure 5).

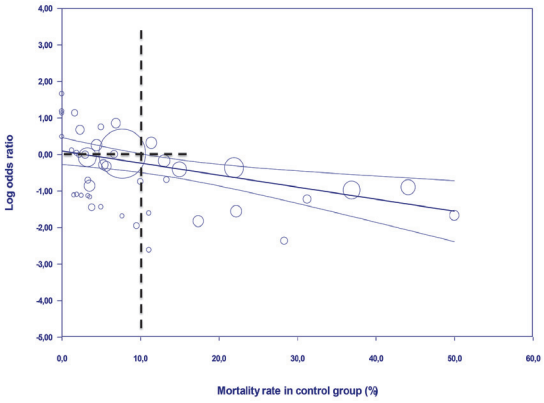

Figure 4.—Regression model applied to all 58 studies, basing on mortality rate in control group. The cut off of 10% of mortality rate in control group significantly differentiates 43 studies on the right side of the graph from 15 on the left side. The regression coefficient b=-0.033 with a P-value of 0.0001 confirms the analysis (see text for details).

Figure 6 showed the plot of log odds ratio on risk of bias evaluation. The meta-regression model was applied to all 58 RCTs. The inspection to the plot showed that only studies with high risk of bias (<5 green plus obtained with the Cochrane domain-based evaluation for risk of bias) had a significant reduction in mortality rate, with a regression coefficient b of 0.225 and a P value<0.00001 (Figure 6), while no significant reduction was observed in low risk of bias RCTs. Supplementary Table IV (online content only) showed the results for meta-regression using risk of bias evaluation to predict the log odds ratio. Figure 7 showed the results of the combined 4 subgroups (*i.e.* mortality <10%/high risk of bias, mortality <10%/low risk of bias, mortality >10%/high risk of bias, mortality >10%/low risk of bias): only the group with mortality rate >10% and high risk of bias reached statistical significance (OR 0.38, 95% CI 0.25-0.57, P<0.00001, Q statistic P=0.66; I^2=0%, 9 RCTs). The group with mortality rate >10% and low risk of bias did not show any statistical significance (OR 0.53, 95% CI 0.25-1.13, P=0.10, Q statistic P=0.19; I^2=33%, 6 RCTs).

In order to look to the effect of time as a covariate, another meta-regression was per-

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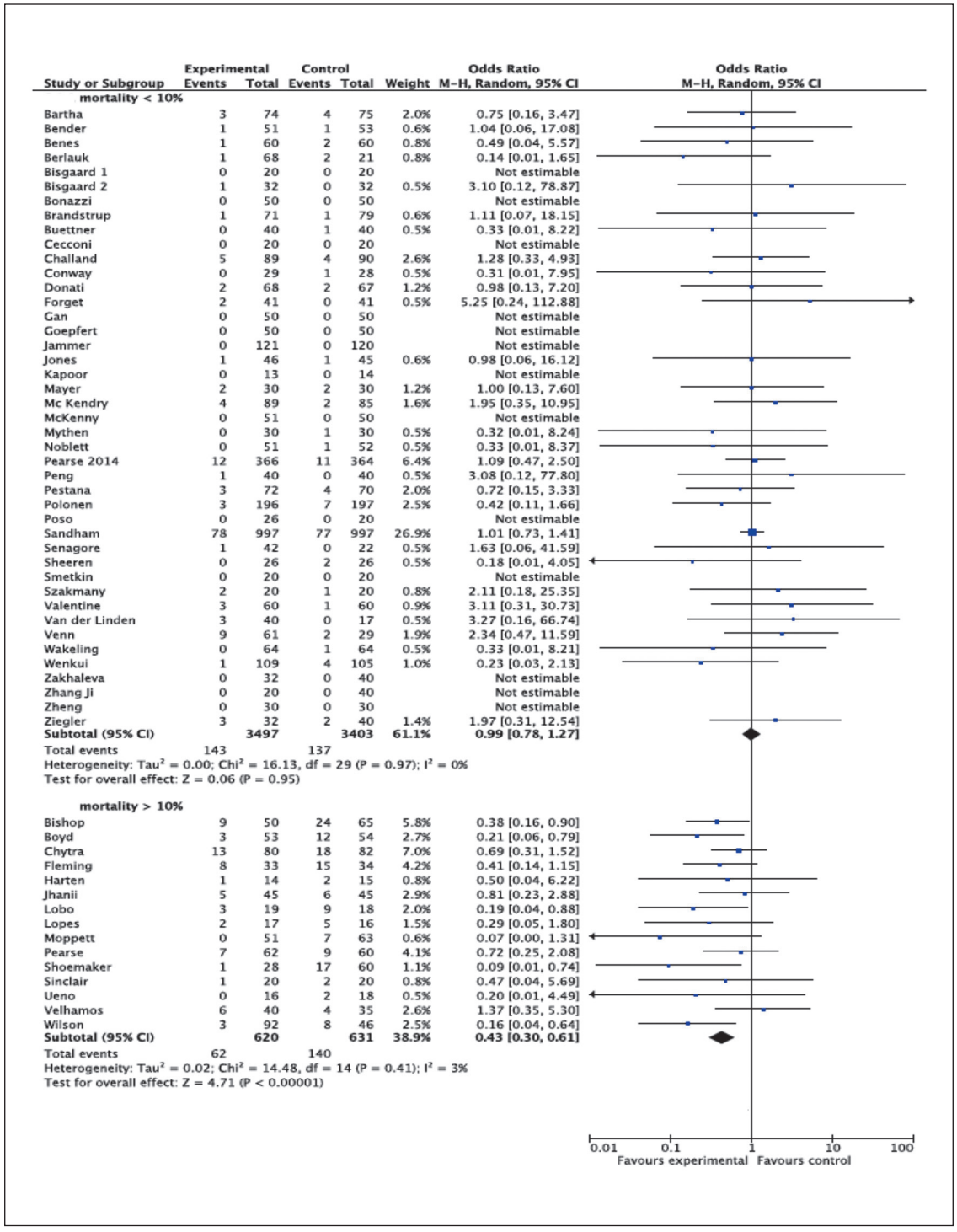

Figure 5.—Rates of mortality with Odds Ratios (ORs) and 95% Confidence Intervals (CI) in subgroups defined according to the mortality rate in control group. RCTs were divided in studies with a control mortality rate < of 10% or > of 10%. The pooled OR and 95% CI are shown as the total. The size of the box at the point estimate of the OR gives a visual representation of the "weighting" of the study. The diamonds represent the point estimate of the pooled ORs and the length of the diamonds is proportional to the CI.

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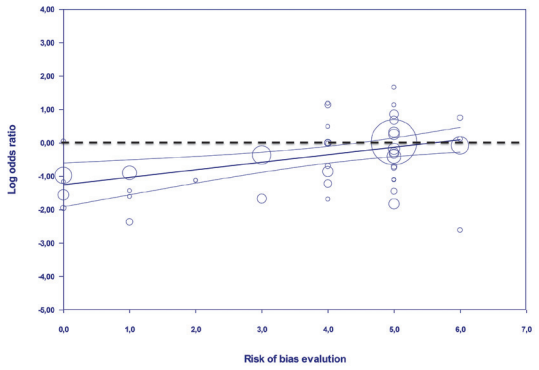

Figure 6.—Regression model applied to all 58 studies, basing on risk of bias evaluation (number of green plus obtained by each RCT according to the domain-based risk of bias evaluation, as proposed by the Cochrane Collaboration). The regression coefficient b=0.225 with a P-value of 0.0001 confirms the result of the sensitive analysis: the global effect of GDT on mortality was driven by high risk of bias studies, while the higher quality studies did not demonstrate any benefit in mortality reduction. (see text for details).

formed, adopting the publication year as a covariate: this analysis (Figure 8) showed that there is no statistical dependence between the effect on mortality and the year of publication (regression coefficent 0.045).

Discussion

This systematic review and meta-analysis confirmed that perioperative GDT reduced mortality after surgery. This significant effect was maintained when the mortality rate in control group was >10% and when high risk of bias RCTs were considered. No significant effect was observed in low risk of bias trials.

GDT has been originally applied in surgical patients in order to face the perioperative increase in oxygen demand and to prevent organ failure. When performed in patients with already established organ failure, no outcome improvement was found.[5] These different results may rely on the basis that only in the early stage of systemic inflammatory response syndrome (*i.e.* in the early preoperative period) it is possible to prevent the deleterious effects of hypoperfusion and decreased oxygen delivery, while, when oxygen debt is no longer reversible, increasing oxygen transport is no more effective.

Expected mortality appears to be a very striking factor affecting effectiveness of GDT. Shoemaker *et al.*[2] found that GDT was effective only when optimization treatment was performed in high risk medical, surgical and trauma patients (control group mortality >20%) before organ failure occurrence. Recent data [7, 8] have confirmed GDT benefits only in surgical patients, but have again limited its effectiveness only in patients with very high control mortality (*i.e.*, >20%). This reported cut-off, however, may result from a priori classification and may not reflect the "real life" of every day practice.[81, 82] The present meta-analysis, adopting the meta-regression technique, demonstrated that preoperative hemodynamic optimization significantly reduced mortality even when the event control rate is >10%. It should be underscored, however, that, in this meta-regression model, the relationship between effect estimates and the control group risk is complicated by a technical phenomenon known as regression to the mean. This arises because the control group risk forms an integral part of the effect estimate. A high risk in a control group, observed entirely by chance, will on average give rise to a higher than expected effect estimate, and vice versa. This phenomenon results in a false correlation between effect estimates and control group risks. This is the reason why we decided to perform also a subgroup analysis that is another way to investigate heterogeneous results or to answer specific questions about particular patient groups. The subgroup adopting the cut-off of mortality rate in control group >10% reinforced the meta-regression result. Moreover, despite the existence of methodological heterogeneity among studies dealing with GDT, such as timing, monitoring and protocols, a strong statistical homogeneity and consistency (even using conservative cut-off values) was still observed in the main as well as in the sensitive analyses, whereas moderate to high heterogeneity and inconsistency has limited precedent results.[7] A reason for this discrepancy is that the present meta-analysis did not include two [83, 84] of the 32 studies of previous papers, because in these two papers dopex-

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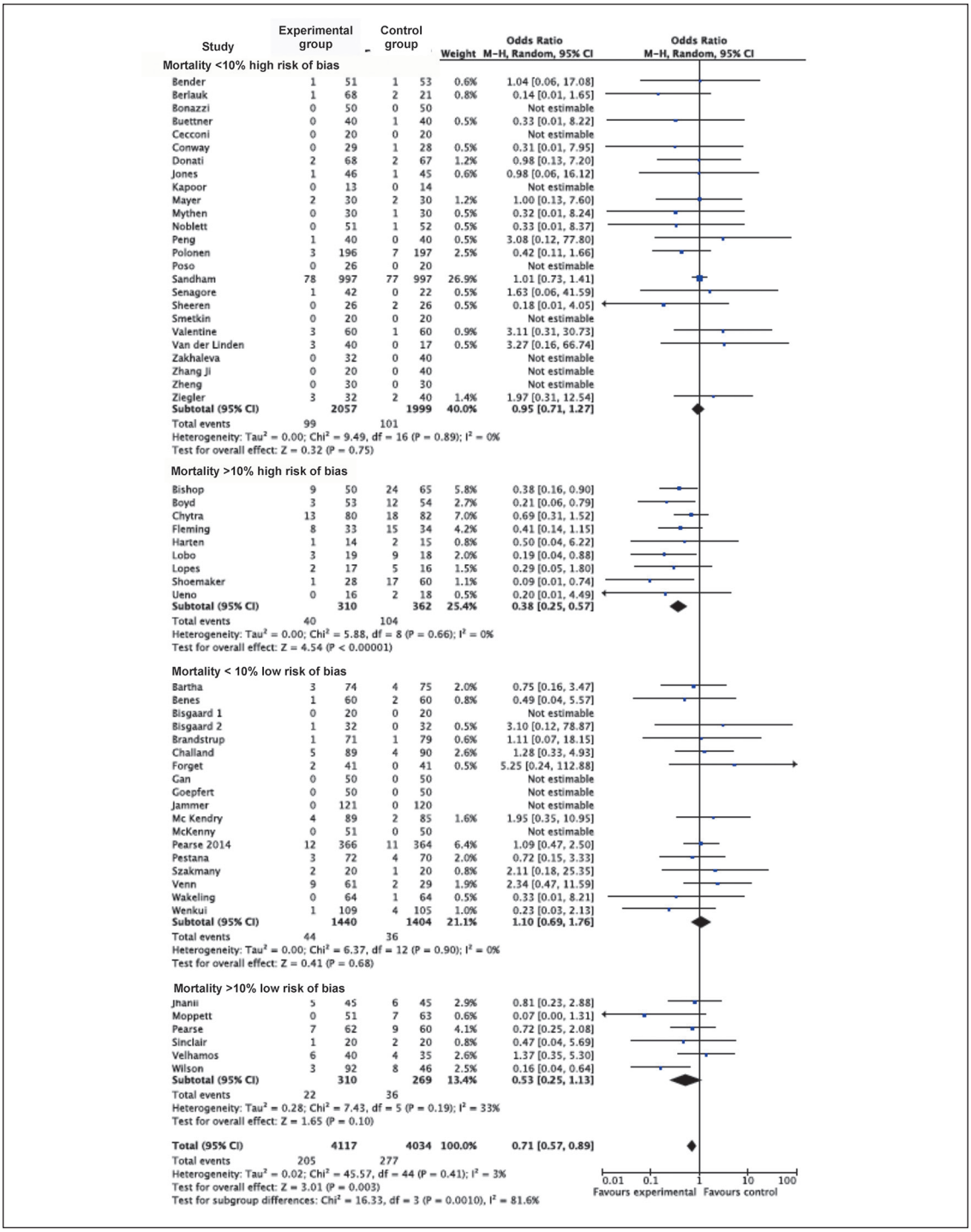

Figure 7.—Rates of mortality with Odds Ratios (ORs) and 95% Confidence Intervals (CI) in subgroup according to the combination of mortality > or <10% and risk of bias. Four subgroup were obtained: mortality <10%/high risk of bias, mortality <10%/low risk of bias, mortality >10%/high risk of bias, mortality >10%/low risk of bias (see text for details). The pooled OR and 95% CI are shown as the total. The size of the box at the point estimate of the OR gives a visual representation of the "weighting" of the study. The diamond represents the point estimate of the pooled OR and the length of the diamond is proportional to the CI.

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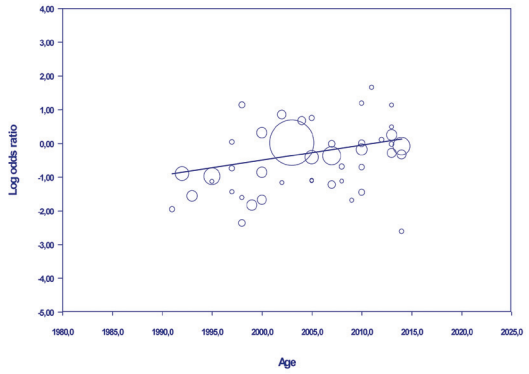

Figure 8.—Regression model applied to all 58 studies, basing on the publication year as a covariate: this analysis shows that there is no statistical dependence between the effect on mortality and the year of publication (regression coefficient 0.045).

amine was used without predefined hemodynamic end points. Another paper [8] reviewed the use of GDT to reduce mortality, and again arbitrarily adopted a 20% cut-off of mortality rate in control group. Once again, heterogeneity reduced the strength of the evidence. One included paper [85] was not included in the present meta-analysis for methodological reason (both the control and the GDT group were treated with the same protocol). Moreover, the present meta-analysis was updated with new 19 studies published from 2010 to 2014. All these reasons may have reduced the variability in the outcome observed.

The ineffectiveness of GDT in reducing mortality in the low control mortality subgroups could be due to a low statistical power needing much larger numbers of patients to show statistical significance. However, this subgroup analysis including 6900 patients was enough powered to exclude the latter hypothesis. An alternative hypothesis is that patients that are not very ill may not respond as clearly to increased hemodynamic.

The quality analysis showed that the global effect of GDT on mortality was driven by high risk of bias studies, while higher quality studies did not demonstrate any benefit in mortality reduction. The meta-regression analysis further confirmed this figure. The risk of bias for each study was evaluated and studies were classified as low and high risk of bias according to the domain-based evaluation, as that proposed by the Cochrane Collaboration. Out of 58 studies, 26 reached a low risk of bias evaluation. Many studies presented some important limitations since were conducted in single centers with limited patient samples, and only few RCTs were adequately randomized and double-blinded. The overall low quality of individual studies on GDT has been previously called into question,[3] although the trial quality seemed to influence the outcome in the studies including perioperative patients less than in the subset of patients with established sepsis and multiple organ failure.[5, 7] However, it is well established that studies with high risk of bias often overestimate the true effect, reducing the clinical significance of any result,[13] and this could explain the results of the present study. Interestingly, most of the studies with low risk of bias are also low mortality studies: we therefore tried to combine the two subgroup analyses making high mortality/low bias, high mortality/high bias, low mortality/low bias and low mortality/high bias groups. This analysis confirmed that no effect was seen in mortality rate <10%, both in low and in high risk of bias, while the benefit on mortality was driven by high risk of bias trials (9 RCTs), while the subgroup including mortality >10% and low risk of bias (6 RCTs) did not reach statistical significance.

It has been proposed that the year of publication could affect the risk of bias, since older paper are more prone to high risk of bias, while newer ones are less affected by risk of bias. The meta-regression adopting the publication year as a covariate showed that there is no statistical dependence between the effect on mortality and the year of publication, suggesting that also older RCTs, if well planned and conducted, could be considered as low risk of bias, while recent ones, if not adequately designed, could be affected by high risk of bias. Therefore, another possible interpretation of the present meta-analysis could be that, when dealing with the effect of perioperative hemodynamic optimization on mortality, one should consider not only the "risk of bias" *per se*, but

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also the design of the study, and, maybe more important, the type of population enrolled, including co-morbidities, ASA class and mortality risk.

This study had a number of limitations. No attempt was made to correct for the type or quantity of fluids or inotropes given, because they are inconsistently reported in the literature and have a demonstrable wide variability in their dosing across studies. Moreover, the studies included varied in terms of hemodynamic monitoring, the goals proposed and achieved, the timing of intervention: this could have introduced a relatively high clinical heterogeneity, although the results remained consistent across a number of subgroups and sensitivity analyses. However, the high heterogeneity among the tools and goals used to define GDT is still a major clinical problem. It is hard to believe that GDT by means of a Masimo pulse oxymeter can in anyway be equal to GDT conducted by a pulmonary artery catheter which is the goal standard to measure cardiac output.

Additional well-designed randomized controlled studies are necessary to clarify these discrepancies and to determine whether mortality can be reduced through the maintenance of perioperative tissue perfusion in high-risk surgical patient. Moreover, several issues need to be clarified, such as timing, monitoring tools and protocols adopted, as well as the targets adopted, as recently underscored.[86]

Conclusions

This meta-analysis, within the limitations of existing data, the high heterogeneity among adopted protocols, and the analytic approaches used, suggested that preoperative GDT significantly reduced mortality when the event control rate is >10%. In well conducted non-biased studies no mortality benefit was observed but the effect may be limited due to inclusion of small number of high mortality trials. Additional well-designed randomized controlled studies are still necessary to clarify several discrepancies among monitoring tools, goals and timing.

Key messages

— The present meta-analysis, adopting the meta-regression technique, suggested that preoperative hemodynamic optimization significantly reduced mortality even when the event control rate is >10%.

— The global effect of GDT on mortality was driven by high risk of bias studies, while higher quality studies did not demonstrate any benefit in mortality reduction.

— When dealing with the effect of perioperative hemodynamic optimization on mortality, one should consider not only the "risk of bias" *per se*, but also the design of the study, and, maybe more important, the type of population enrolled, including co-morbidities, ASA class and mortality risk.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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SUPPLEMENTARY MATERIALS

Supplementary Appendix I.—Search strategies.

For the MEDLINE database, the Cochrane highly sensitive search strategy was used:
1 randomized controlled trial [pt]
2 controlled clinical trial[pt]
3 randomized[tiab]
4 placebo[tiab]
5 clinical trial as topic[mesh:noexp]
6 randomly[tiab]
7 trial[ti]
8 # 1 OR #2 OR #3 OR #4 OR # 5 OR #6 OR #7
9 animals[mh] not (humans[mh] and animals[mh])
10 # 8 NOT #9
11 surgery[mh]
12 surgery[tiab]
13 surgery[sh]
14 surgery[mh] OR surgery[tiab] OR surgery[sh]
15 goal directed[tiab] OR goal directed[sh] OR goal directed[mh]
16 goal oriented[tiab] OR goal oriented[sh] OR goal oriented[mh]
17 goal target[tiab] OR goal target[sh] OR goal target[mh]
18 cardiac output[tiab] OR cardiac output[mh] OR cardiac output[sh]
19 cardiac index[tiab] OR cardiac index[mh] OR cardiac index[sh]
20 oxygen delivery[tiab] OR oxygen delivery[mh] OR oxygen delivery[sh]
21 oxygen consumption[tiab] OR oxygen consumption[mh]
22 cardiac volume[tiab] OR cardiac volume[mh]
23 stroke volume[tiab] OR stroke volume[mh] OR stroke volume[sh]
24 fluid therapy[tiab] OR fluid therapy[mh]
25 fluid loading[tiab] OR fluid loading[mh] OR fluid loading[sh]
26 fluid administration[tiab] OR fluid administration[mh] OR fluid administration[sh]
27 optimization[tiab] OR optimization[mh] OR optimization[sh]
28 optimisation[tiab] OR optimisation[mh] OR optimisation[sh]
29 pulse pressure variation[tiab] OR pulse pressure variation[mh] OR pulse pressure variation[sh]
30 pleth index variability[tiab] OR pleth index variability[mh] OR pleth index variability[sh]
31 stroke volume variation[tiab] OR stroke volume variation[mh] OR stroke volume variation[sh]
32 systolic pressure variation[tiab] OR systolic pressure variation[mh] OR systolic pressure variation[sh]
33 # 15 OR # 16 OR #17 OR # 18 OR # 19 OR # 20 OR #21 OR # 22 OR # 23 OR # 24 OR # 25 OR # 26 OR # 27 OR #28 OR # 29 OR #30 OR #31 OR #32
34 # 10 AND # 14 AND # 33.

For Embase, the following search strategy was used, limiting the search to the years 2010-2013:
1 random$
2 randomized controlled trial/exp
3 cross-over procedures/exp
4 double blind procedures/exp
5 single blind procedures/exp
6 factoral$
7 crossover$
8 cross over$
9 cross-over$
10 placebo$
11 assign$
12 allocat$
13 volunteer$
14 # 1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
15 surgery
16 ('surgery'/exp/mj OR 'surgery')
17 'surgery'/syn

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18 #15 OR #16 OR #17
19 ('heart'/exp/mj OR 'heart') AND output
20 ('heart output'/exp/mj OR 'heart output')
21 "goal directed"
22 "goal oriented"
23 "goal target"
24 'heart index'/exp/mj OR 'heart index'
25 ('heart stroke volume'/exp/mj OR 'heart stroke volume')
26 ('oxygen consumption'/exp/mj OR 'oxygen consumption')
27 "oxygen delivery"
28 "fluid therapy"/exp
29 "fluid loading"/exp
30 "fluid administration"/exp
31 "pulse pressure variation"
32 "stroke volume variation"
33 "pleth index variability"
34 "systolic pressure variation"
35 "optimization"
36 # 19 OR # 20 OR #21 OR # 22 OR # 23 OR # 24 OR # 25 OR #26 OR # 27 OR #28 OR # 29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35
37 #14 AND #18 AND #36.

For the Cochrane Library database, the following search strategy was used:
#1 MeSh descriptor Surgery explode all trees
2 MeSh descriptor Specialities, Surgery explode all trees
3 surgical*
4 surgery*
5 # 1 OR #2 OR #3 OR # 4
6 MeSh descriptor Cardiac Output explode all trees
7 Cardiac near output*
8 Cardiac near index*
9 Cardiac near volume*
10 MeSh descriptor Oxygen Delivery explode all trees
11 Oxygen near delivery*
12 MeSh descriptor Oxygen Consumption explode all trees
13 Oxygen near consumption*
14 Pleth near index near variability*
15 Pulse near pressure near variation*
16 Stroke near volume near variation*
17 Systolic near pressure near variation*
18 MeSh descriptor Stroke Volume explode all trees
19 Stroke near volume*
20 MeSh descriptor Fluid Therapy explode all trees
21 Fluid near therapy*
22 Fluid near administration*
23 Fluid near loading*
24 MeSh descriptor Goal Directed explode all trees
25 Goal near directed*
26 Goal near oriented*
27 Goal near targeted*
28 # 6OR # 7 OR # 8 OR # 9 OR # 10 OR #11 OR # 12 OR # 13 OR # 14 OR # 15 OR # 16 OR #17 OR # 18 OR # 19 OR # 20 OR #21 OR # 22 OR # 23 OR # 24 OR # 25 OR # 26 OR # 27
29 # 5 AND # 28.

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SUPPLEMENTARY TABLE I.—*Characteristics of included studies.*

Author, year, country	Risk definiton	Surgery	Goal-Directed Therapy (Tools and goals)	Modality of optimization	Mortality rate in control group (%)
Bartha *et al.* [23], 2013, Europe	high risk	Orthopedic	Lidco; SV<10%, DO_2>600 L·min^{-1}·m^{-2}	Fluids and inotropes	5.3
Bender *et al.*[24], 1997, USA		Elective aortic and vascular	PAC; CI≥2.8 L min^{-1}·m^{-2}, 8≤Pcwp≤14 mmHg, SVR≤1100 dyne·sec·cm^{-5}	Fluids and inotropes	1.9
Benes *et al.* [25], 2010, Europe	high risk	Elective abdominal	FloTrac/Vigileo; CI ≥2.5 L·min^{-1}·m^{-2}	Fluids and inotropes	3.3
Berlauk *et al.* [26], 1991, USA		Elective peripheral vascular	PAC; CI≥2.8 L min^{-1}·m^{-2}, 8≤Pcwp≤14 mmHg, SVR≤1100 dyne·sec·cm^{-5}	Fluids and inotropes	9.5
Bisgaard *et al.* [27], 2013, Europe	high risk	Elective peripheral vascular	Lidco; SV<10%, DO_2>600 L·min^{-1}·m^{-2}	Fluids and inotropes	0.0
Bisgaard *et al.* [28], 2013, Europe	high risk	Abdominal aortic	Lidco; SV<10%, DO_2>600 L·min^{-1}·m^{-2}		0.0
Bishop *et al.* [29], 1995, USA	high risk	Emergent trauma	PAC; CI≥4.5 L min^{-1}·m^{-2}, DO_2≥670 L·min^{-1}·m^{-2} VO_2≥166 mL·min^{-1}·m^{-2}	Fluids and inotropes	36.9
Bonazzi *et al.* [30], 2002, Europe		Elective vascular	PAC; CI≥3 L min^{-1}·m^{-2}, DO_2>600 L·min^{-1}·m^{-2} SVR≤1450 dyne·sec·cm^{-5}	Fluids and inotropes	0.0
Boyd *et al.* [31], 1993, Europe	high risk	Emergent or elective major abdominal or vascular	PAC; DO_2>600 L·min^{-1}·m^{-2}	Fluids and inotropes	22.2
Brandstrup *et al.* [32], 2012, Europe	high risk	Elective abdominal	Esophageal Doppler SV increase>10%	Fluids	1.3
Buettner *et al.* [33], 2008, Europe		Major abdominal	PiCCO plus system; SPV<10%	Fluids	2.5
Cecconi *et al.* [34], 2011, Europe		Orthopedic	FloTrac/Vigileo; SV<10%, DO_2>600 L·min^{-1}·m^{-2}	Fluids and inotropes	0.0
Challand *et al.* [35], 2013, Europe	high risk	Major abdominal	Esophageal Doppler SV increase of 10%	Fluids	4.4
Chytra *et al.* [36], 2007, Europe	high risk	Emergent trauma	Esophageal Doppler SV optimization with FTc>0.35 sec	Fluids (noradrenaline intraoperatively)	22.0
Conway *et al.* [37], 2002, Europe		Elective major bowel resection	Esophageal Doppler SV optimization with FTc>0.35 sec	Fluids	3.6
Donati *et al.* [38], 2007, Europe	high risk	Elective major abdominal or aortic	CVC; O_2ERe (SaO_2 - $ScvO_2$ /SaO_2) <27%	Fluids and inotropes	3.0
Fleming *et al.* [39], 1992, USA	high risk	Emergent trauma	PAC; CI≥4.5 L min^{-1}·m^{-2}, DO_2≥670 L·min^{-1}·m^{-2} VO_2≥166 mL·min^{-1}·m^{-}	Fluids and inotropes	44.1
Forget *et al.* [40], 2011, Europe		Major abdominal	Masimo set pulse oxymeter; PVI<13%	Fluids	0.0
Gan *et al.* [41], 2002, USA		Elective general, urologic, gynecologic	Esophageal Doppler; SV optimization with FTc between 0.35 sec-0.4 sec	Fluids	0.0
Goepfert *et al.* [42], 2013, Europe	high risk	Elective cardiac (on-pump)	PiCCO plus system; SVV<10%, DO_2>600 L·min^{-1}·m^{-2}	Fluids and inotropes	0.0
Harten *et al.* [43], 2008, Europe	high risk	Emergent abdominal	Lidco; PPV<10%	Fluids	13.3
Jammer *et al.* [44], 2010, Europe		Colo-rectal surgery	CVC $ScVO_2$>75%	Fluids	0.0

(*To be continued*)

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SUPPLEMENTARY TABLE I.—*Characteristics of included studies.*

Author, year, country	Risk definiton	Surgery	Goal-Directed Therapy (Tools and goals)	Modality of optimization	Mortality rate in control group (%)
Jhanii *et al.* [45], 2010, Europe		Eelective gastro-intestinal	Not stated rise of SV>10%	Fluids and inotropes	13.0
Jones *et al.* [46], 2013, Europe		Hepatic resection	Lidco; rise of SV >10%, CI>3 L $min^{-1}\cdot m^{-2}$	Fluids	2.2
Kapoor *et al.* [47], 2008, India		Elective cardiac (on-pump)	FloTrac/Vigileo; SVV<10%, CI>2.5 and <4.2 L/ $L\cdot min^{-1}$, $ScvO_2$>70%, DO_2>450 and <600 $mL\cdot min^{-1}\cdot m^{-2}$	Fluids and inotropes	0.0
Lobo *et al.* [48], 2000, Brazil	high risk	Elective major abdominal or vascular	PAC; DO_2>600 $mL\cdot min^{-1}\cdot m^{-2}$	Fluids and inotropes	50.0
Lopes *et al.* [49], 2007, Brazil	high risk	Elective abdominal	Radial artery line; ΔPP≤10%	Fluids	31.3
Mayer *et al.* [50], 2010, Europe	high risk	Major abdominal	FloTrac/Vigileo; CI≥2.5 $L\cdot min^{-1}\cdot m^{-2}$	Fluids and inotropes	6.7
McKendry *et al.* [51], 2004, Europe		Elective cardiac	Esophageal Doppler; SI>35 mL/m^2	Fluids	2.4
McKenny *et al.* [52], 2013, Europe		Elective gynecologic	Esophageal Doppler; SV <10%	Fluids	0.0
Moppett *et al.* [53], 2014, Europe	high risk	Emergent orthopedic	LiDCO; SV increase <10%	Fluids	11.1
Mythen *et al.* [54], 1995, Europe	high risk	Elective cardiac	Esophageal Doppler; SV optimization and rise in CVP<3 mmHg	Fluids	3.3
Noblett *et al.* [55], 2005, Europe		Major abdominal	Esophageal Doppler; SV optimization	Fluids	1.9
Pearse *et al.* [56], 2005, Europe	high risk	Elective or emergent major general	LiDCO; DO_2>600 $mL\cdot min^{-1}\cdot m^{-2}$, SV >10%	Fluids and inotropes	15.0
Pearse *et al.* [57], 2014, Europe	high risk	Major general	LiDCO; SV increase <10%	Fluids and inotropes	3.3
Peng *et al.* [58], 2014, China		Orthopedic	FloTrac/Vigileo; SVV<10% supine or <14% prone	Fluids	0.0
Pestana *et al.* [59], 2014, multicentric		Major abdominal	NICOM; CI≥2.5 $L\cdot min^{-1}\cdot m^{-2}$	Fluids and inotropes	5.7
Polonen *et al.* [60], 2000, Europe		Elective cardiac (on-pump)	PAC; SvO_2>70%, Lactate ≤2.0 mmol/L	Fluids and inotropes	3.6
Poso *et al.* [61], 2014,Sweden		Laparoscopic bariatric surgery	FloTrac/Vigileo; SVV<12% supine	Fluid and inotropes	0.0
Sandham *et al.* [62], 2003, Canada	high risk	Elective or emergent major abdominal, thoracic, vascular, or orthopedic	PAC; CI>3.5and <4.5 L $min^{-1}\cdot m^{-2}$, 550<DO_2<600 $mL\cdot min^{-1}\cdot m^{-2}$, MAP>70 mmHg, Pcwp<18 mmHg	Fluids and inotropes	7.7
Schereen *et al.* [63], 2013, Europe	high risk	Major abdominal and urologic	FloTrac/Vigileo; SVV<10%	Fluids	0.0
Senagore *et al.* [64], 2009, USA		Major abdominal	Esophageal Doppler increase of SV >10%	Fluids	7.7
Shoemaker *et al.* [65], 1998, USA	high risk	Emergent or elective major abdominal (general or vascular)	PAC; CI>4.5 $L\cdot min^{-1}\cdot m^{-2}$, DO_2>600 $mL\cdot min^{-1}\cdot m^2$, VO_2>170 $mL\cdot min^{-1}\cdot m^{-2}$	Fluids and inotropes	28.3
Sinclair *et al.* [66], 1997, Europe	high risk	Orthopedic	Esophageal Doppler SV optimization with FTc between 0.35 sec-0.4 sec	Fluids	10.0
Smetkin *et al.* [67], 2009, Europe		Elective cardiac (off-pump)	PiCCO plus system ITBI 850-1000 mL m^{-1}, $ScvO_2$>60%	Fluids and inotropes	0.0
Szakmany *et al.* [68], 2005, Europe	high risk	Major abdominal and hepatic resection	PiCCO plus system ITBI 850-950 mL m^{-1}	Fluids	5.0

(*To be continued*)

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SUPPLEMENTARY TABLE I.—*Characteristics of included studies.*

Author, year, country	Risk definiton	Surgery	Goal-Directed Therapy (Tools and goals)	Modality of optimization	Mortality rate in control group (%)
Ueno *et al.* [69], 1998, China		Hepatic resection	PAC; CI>4.5 L·min^{-1}·m^{-2}, DO_2>600 mL·min^{-1}·m^2, VO_2>170 mL·min^{-1}·m^{-2}	Fluids and inotropes	11.1
Valentine *et al.* [70], 1998, USA		Elective aortic	PAC; CI≥2.8 L·min^{-1}·m^{-2} 8≤Pcwp≤15 mmHg, SVR≤1100 dyne·sec·cm^{-5}	Fluids and inotropes	1.7
Van der Linden *et al.* [71], 2010, Europe		Elective peripheral vascular	FloTrac/Vigileo; CI>2.5 L min^{-1}·m^{-2}	Fluids and inotropes	0.0
Velhamos *et al.* [72], 2000, USA	high risk	Emergent trauma	Thoracic bioimpedance; CI>4.5 L·min^{-1}·m^{-2}	Fluids and inotropes	11.4
Venn *et al.* [73], 2002, Europe	high risk	Orthopedic	Esophageal Doppler SV optimization with FTc>0. 4 sec	Fluids	6.9
Wakeling *et al.* [74], 2005, Europe		Elective major bowel	Esophageal Doppler; SV optimization and rise in CVP<3 mmHg	Fluids	1.6
Wenkui *et al.* [75], 2010, China	high risk	Major abdominal	Lactate blood levels Lactate <1.6 mmoL/L	Fluids	3.8
Wilson *et al.* [76], 1999, Europe	high risk	Elective major (abdominal, vascular, urologic)	PAC; DO_2>600 mL·min^{-1}·m^{-2}	Fluids and inotropes	17.4
Zakhaleva *et al.* [77], 2013, Europe		Bowel resection	Esophageal Doppler SV optimization with FTc between 0.35 sec-0.4 sec	Fluids	0.0
Zhang *et al.* [78], 2013, China		Thorascopic lobectomy	FloTrac/Vigileo; SVV< 10%, CI>2.5 L min^{-1}·m^{-2}	Fluids and inotropes	0.0
Zheng *et al.* [79], 2013, China	high risk	Elective abdominal	FloTrac/Vigileo; SVI>35 mL/m^2, CI≥2.5 L min^{-1}·m^{-2}	Fluids and inotropes	0.0
Ziegler *et al.* [80], 1997, USA		Elective vascular (aortic and limb salvage)	PAC; SvO_2≥65%, Hb≥10 g/dL, Pcwp≥12 mmHg	Fluids and inotropes	5.0

PPV: Pulse Pressure Variation; PVI: Pleth Variability Index; SVV: Stroke Volume Variation; SPV: Systolic Pressure Variation; SV: stroke volume; CI: Cardiac Index; MAP: Mean Arterial Pressure; CVP: Central Venous Pressure; SVI: Stroke Volume Index; SVRI: Systemic Vascular Resistance Index; $ScvO_2$: Central Venous Oxygen Saturation; SvO_2: Mixed Venous Oxygen Saturation; DO_2: Oxygen Delivery; EVLWI: Extravascula Lung Water Index; Pcwp: pulmonary capillary wedge pressure; PAC: pulmonary artery catheter; FTc: flow-time-corrected; O_2ERe: estimated oxygen extraction ratio; SVR: systemic vascular resistance; VO_2: oxygen consumption; ITBI: intra-thoracic blood volume index; LiDCO: lithium diluition cardiac output monitoring; NICOM: noninvasive cardiac output monitoring obtained via bioreactance; PiCCO: pulse indicator cardiac output monitoring.

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SUPPLEMENTARY TABLE II.—*The risk of bias assessment for each trial, according to the Cochrane domain-based evaluation. This is a two-part tool, addressing seven specific domains (namely sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and 'other issues') that are strongly associated with bias reduction. The green plus indicates low risk of bias, the red minus indicates high risk of bias, the white color indicates unclear risk of bias. (see text for details).*

Author, year, country	Blinding of participants and personel (performance bias)	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Outcome assessment (detection bias	Incomple outcome data (attrition bias)	Selective reporting (reportig bias)
Bartha *et al.* [23], 2013, Europe		+	+	+	+	+
Bender *et al.* [24], 1997, USA	-	-	-		-	
Benes *et al.* [25], 2010, Europe		+	+	+	+	+
Berlauk *et al.* [26], 1991, USA	-	-	-	-	-	
Bisgaard *et al.* [27], 2013, Europe	+	+		+	+	+
Bisgaard *et al.* [28], 2013, Europe	+	+		+	+	+
Bishop *et al.* [29], 1995, USA	-	-	-	-		+
Bonazzi *et al.* [30], 2002, Europe		+		-	-	-
Boyd *et al.* [31], 1993, Europe	-	-	-			
Brandstrup *et al.* [32], 2012, Europe	+	+	+	+	+	+
Buettner *et al.* [33], 2008, Europe			+	+		
Cecconi *et al.* [34], 2011, Europe			+	+	+	+
Challand *et al.* [35], 2013, Europe	+	+	+	+		+
Chytra *et al.* [36], 2007, Europe	-	-		+	+	+
Conway *et al.* [37], 2002, Europe		-	-			
Donati *et al.* [38], 2007, Europe		+		+	+	+
Fleming *et al.* [39], 1992, USA	-	-	-	-	+	
Forget *et al.* [40], 2011, Europe		+	+	+	+	+
Gan *et al.* [41], 2002, USA		+	+	+	+	+
Goepfert *et al.* [42], 2013, Europe	+	+	+		+	+
Harten *et al.* [43], 2008, Europe			+	+	+	+
Jammer *et al.* [44], 2010, Europe		+	+	+	+	+
Jhanii *et al.* [45], 2010, Europe		+	+	+	+	+
Jones *et al.* [46], 2013, Europe	+	+	+			+
Kapoor *et al.* [47], 2008, India			+	+		+
Lobo *et al.* [48], 2000, Brazil		+			+	+
Lopes *et al.* [49], 2007, Brazil		-	+	+	+	+
Mayer *et al.* [50], 2010, Europe			+	+	+	+
McKendry *et al.* [51], 2004, Europe		+	+	+	+	+
McKenny *et al.* [52], 2013, Europe		+	+	+	+	+
Moppett *et al.* [53], 2014, Europe	+	+	+	+	+	+
Mythen *et al.* [54], 1995, Europe		+	-	+	-	-
Noblett *et al.* [55], 2005, Europe	+	-	+	+	+	+
Pearse *et al.* [56], 2005, Europe		+	+	+	+	+
Pearse *et al.* [57], 2014, Europe	+	+	+	+	+	+
Peng *et al.* [58], 2014, China		+		+	+	
Pestana *et al.* [59], 2014, multicentric	+	+	+	+	+	
Polonen *et al.* [60], 2000, Europe			+	+	+	+
Poso *et al.* [61], 2014,Sweden		-	-	+	+	+
Sandham *et al.* [62], 2003, Canada	+	+	+	+		+
Schereen *et al.* [63], 2013, Europe			+	+	+	+
Senagore *et al.* [64], 2009, USA			+	+	+	+
Shoemaker *et al.* [65], 1998, USA		-	-	-	-	+
Sinclair *et al.* [66]1997, Europe	+		+	+	+	+
Smetkin *et al.* [67], 2009, Europe	-	-	-	-	+	+
Szakmany *et al.* [68] 2005, Europe	+	+	+	+	+	+
Ueno *et al.* [69], 1998, China	-	+	-			
Valentine *et al.* [70], 1998, USA			+	+	+	+
Van der Linden *et al.* [71], 2010, Europe	+	+		+		+
Velhamos *et al.* [72], 2000, USA		+	+	+	+	+
Venn *et al.* [73], 2002, Europe		+	+	+	+	+
Wakeling *et al.* [74], 2005, Europe		+	+	+	+	+
Wenkui *et al.* [75], 2010, China		+	+	+	+	+
Wilson *et al.* [76], 1999, Europe	+	+	+	+	+	
Zakhaleva *et al.* [77], 2013, Europe		+	+		+	+
Zhang *et al.* [78], 2013, China		+	+		+	+
Zheng *et al.* [79], 2013, China	+	+	+	+	+	+
Ziegler *et al.* [80], 1997, USA		-	-	+		

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SUPPLEMENTARY TABLE III.—*Main results for meta-regression, using control group mortality to predict the log odds ratio.*

Covariate	Coefficient	Standard error	95% Lower	95% Upper	Z value	2-sided P value
Intercept	0.1264	0.161	0.1892	0.4419	0.78	0.4325
Mortality rate in control group%	-0.0337	0.0089	0.0512	-0.062	-3.77	0.0002
Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero Q=14.19, df=1, P=0.0002						
Proportion of total between-study variance R^2 analog=1.00						

SUPPLEMENTARY TABLE IV.—*Main results for meta-regression, using risk of bias evaluation to predict the log odds ratio.*

Covariate	Coefficient	Standard error	95% Lower	95% Upper	Z value	2-sided P value
Intercept	-1.2361	0.2576	-1.741	0.7313	-4.8	0
Risk of bias evaluation	0.2259	0.0582	0.1118	0.3401	3.88	0.0001
Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero Q=15.06, df=1, P=0.0001						
Proportion of total between-study variance R^2 analog=1.00						

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