

OPEN The Effect of Early Goal-Directed Therapy on Outcome in Adult Severe Sepsis and Septic Shock Patients: A Meta-Analysis of Randomized Clinical Trials

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BACKGROUND: Whether early goal-directed therapy (EGDT) improves outcome in severe sepsis and septic shock remains unclear. We performed a meta-analysis of existing clinical trials to examine whether EGDT improved outcome in the resuscitation of adult sepsis patients compared with control care.

METHODS: We searched for eligible studies using MEDLINE, Elsevier, Cochrane Central Register of Controlled Trials, and Web of Science databases. Studies were eligible if they compared the effects of EGDT versus control care on mortality in adult patients with severe sepsis and septic shock. Two reviewers extracted data independently. Data including mortality, sample size of the patients with severe sepsis and septic shock, and resuscitation end points were extracted. Data were analyzed using methods recommended by the Cochrane Collaboration Review Manager 4.2 software. Random errors were evaluated by trial sequential analysis (TSA).

RESULTS: Nine studies compared EGDT with control care, and 5202 severe sepsis and septic shock patients were included. A nonsignificant trend toward reduction in the longest all-cause mortality was observed in the EGDT group compared with control care (relative risk, 0.89; 99% confidence interval, 0.74–1.07; $P = 0.10$). However, EGDT significantly reduced intensive care unit mortality in severe sepsis and septic shock patients (relative risk, 0.72; 99% confidence interval, 0.57–0.90; $P = 0.0002$). TSA indicated lack of firm evidence for a beneficial effect.

CONCLUSIONS: In this meta-analysis, a nonsignificant trend toward reduction in the longest all-cause mortality in patients resuscitated with EGDT was noted. However, EGDT significantly reduced intensive care unit mortality in severe sepsis and septic shock patients. TSA indicated a lack of firm evidence for the results. More powered, randomized controlled trials are needed to determine the effects. (*Anesth Analg* 2016;123:371–81)

Severe sepsis and septic shock are major causes of death in critically ill patients,¹ with a mortality rate of 14% to 40%.² Increased compliance with sepsis performance bundles is associated with a reduction in mortality.^{3,4} As fundamental principles for sepsis management, early recognition, control of infection, early and appropriate administration of antibiotics, and resuscitation with IV fluids and vasoactive drugs are widely accepted by intensivists.⁵ Early adequate hemodynamic resuscitation is emphasized, as the key elements should be focused on saving lives.

A proof-of-concept trial⁶ found that, when compared with a control protocol, early hemodynamic resuscitation with a specific protocol termed early goal-directed therapy (EGDT) improved outcomes in patients with severe sepsis. Several additional studies using a similar protocol involving central venous pressure, mean arterial pressure, and central venous oxygen saturation (Scvo₂) to guide hemodynamic resuscitation also found a survival benefit with EGDT.^{7–9} As a result, EGDT principles are subsequently incorporated into the early hemodynamic resuscitation bundle of the Surviving Sepsis Campaign guidelines.⁵ However, in 3 multicenter randomized trials^{10–12} (Protocolized Care for Early Septic Shock [ProCESS] study, the Australasian Resuscitation in Sepsis Evaluation [ARISE] study, and Protocolized Management in Sepsis [ProMISe] trial) published recently, EGDT did not decrease mortality in severe sepsis and septic shock when compared with control care.

The controversial question of whether EGDT improves outcome of severe sepsis and septic shock thus remains relevant. Moreover, whether specific patient characteristics are associated with a potential benefit of EGDT is also unclear. Finally, whether all elements of the protocol are necessary in the hemodynamic resuscitation of severe sepsis and septic shock is unknown. Our goal was to perform a meta-analysis to examine whether EGDT improved outcome when employed in the resuscitation of adult patients with severe sepsis and septic shock compared with control therapy.

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METHODS

Approval

Our IRB does not require ethics approval for systematic reviews, including network meta-analyses, because there are no data being collected from patients. We evaluated and synthesized only data in published trials.

Search Strategy for Identification of Relevant Studies

We searched the following databases: Medline, Elsevier, Cochrane Central Register of Controlled Trials, and Web of Science databases. The following keywords were used as searching terms: “goal-directed” or “goal-directed resuscitation” or “early goal-directed therapy” or “EGDT” or “bundle” or “sepsis bundle” and “sepsis” or “severe sepsis” or “septic shock” or “shock” or “critical ill” or “critical illness” or “intensive care units” or “intensive care” or “critical care” or “ICU.” No language restrictions were placed on the search. All databases were searched for articles published from inception until March 17, 2015. Additional files and supplementary appendices of the relevant articles were also reviewed. Detailed search strategies are shown in Supplemental Digital Content 1 (<http://links.lww.com/AA/B409>).

Study Selection

One reviewer screened the search results, and the full-text manuscripts of all potentially eligible studies were acquired. All the articles were then reviewed by 2 reviewers independently in accordance with the inclusion and exclusion criteria. Twelve disagreements between the 2 reviewers were resolved by consensus and discussion including a third reviewer. Any inconsistency in study inclusion and exclusion and their reason lead to the discussion. Details of the consensus are shown in Supplemental Digital Content 2 (<http://links.lww.com/AA/B410>).

Inclusion and Exclusion Criteria

We included trials with the following features:

1. Type of trials: randomized controlled clinical trials.
2. Population: trials including adult population with severe sepsis and septic shock. Severe sepsis was defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion.⁵
3. Intervention: patients submitted to EGDT, which used the protocol involving central venous pressure, mean arterial pressure, and ScvO₂ to guide hemodynamic resuscitation.
4. Comparison: control care, including usual care, protocol-based therapy, etc.
5. Outcome: the primary outcome was all-cause mortality, including 28-day mortality, 90-day mortality, or mortality at other time points.

Trials were excluded because of following reason:

1. If they were not published in English or Chinese.
2. If they were not published as original articles.
3. If they did not enroll adult patients.
4. If they did not compare EGDT with control care.

5. If they included no data on mortality in patients with severe sepsis and septic shock.
6. If full-text articles were not available.

Quality Assessment

The quality of each article was assessed by 2 reviewers independently. Disagreement that occurred once was resolved by consulting a third reviewer. The 5-point Jadad scale¹³ was calculated to assess the quality of the trial. This scale includes the method of randomization, blinding, and loss to follow-up. In addition, sequences generation, allocation concealment, incomplete outcome data, selective reporting, and other bias were also inspected to assess the risk of bias. The latter was reported as low risk, unclear risk, or high risk for each trial. Low risk was defined as low risk of bias in all domains. Unclear risk was defined as unclear risk of bias in at least 1 domain with no high risk of bias domains. High risk was defined as high risk of bias in 1 or more domains.

Data Extraction and Management

Using a data extraction table, 2 reviewers independently extracted data. Disagreements that occurred twice were resolved by discussion with another reviewer until a consensus was achieved. Then, data were proofread by another reviewer.

Mortality data were recorded as primary predefined outcome parameters during the data extraction. When >1 value for mortality was provided by the article, the mortality for the longest complete follow-up was preferentially used in the meta-analysis. If no 28-day or 90-day mortality values were presented, intensive care unit (ICU) or hospital mortality, or mortality at other time points, was recorded. Ninety-day mortality was reported by the ProCESS study,¹⁰ the ARISE study,¹¹ and the ProMISE study.¹² Sixty-day mortality was reported by the study of Rivers et al.⁶ Twenty-eight-day mortality was reported by the study of Yan et al.¹⁴ Fourteen-day mortality was reported by the study of Wang et al.¹⁵ In-hospital mortality was reported by the study of Rivers et al.,⁶ the ProCESS study,¹⁰ the ARISE study,¹¹ the ProMISE study,¹² the study of Jones et al.,¹⁶ and the study of Lu et al.¹⁷ ICU mortality was reported by the ARISE study,¹¹ the study of Yan et al.,¹⁴ the study of Wang et al.,¹⁵ and the study of Chen et al.¹⁸

Other data, including ICU length of stay, study characteristics, inclusion and exclusion criteria, sample size of the trial, resuscitation end points, and detailed information, were extracted as secondary predefined outcome parameters. If there was insufficient information in the publications, the authors were contacted to obtain missing information.

The effects of EGDT on all-cause mortality, hospital mortality, ICU mortality, and ICU length of stay in severe sepsis and septic shock patients were observed in the meta-analysis. Then effects of EGDT on mortality in severe sepsis and septic shock patients with different severity of illness and with/without venous oxygen saturation were evaluated.

Statistical Analysis

Data were analyzed by Review Manager 4.2 (The Nordic Cochrane Center, Rigshospitalet, Copenhagen, Denmark). The relative risk for dichotomous data and mean differences for continuous data with 99% confidence intervals (CIs) were calculated. The statistical heterogeneity of the data

was explored and quantified using the I^2 test. Heterogeneity was predefined as $P < 0.05$. I^2 value of 0% to 24.9%, 25% to 49.9%, 50% to 74.9%, and 75% to 100% were considered as none, low, moderate, and high thresholds, respectively.^{19,20} The randomized-effects model was used if heterogeneity was observed²¹; otherwise, the fixed-effects model was used. To explore the significant heterogeneity, sensitivity analyses were performed. Results were considered statistically significant at 2-sided $P < 0.01$.

Most continuous data were displayed by mean \pm SD. However, the ICU length of stay was reported by median and interquartile ranges in ARISE¹¹ and ProMISe trial,¹² with large sample sizes. As a result, we used median instead of mean, and SD calculated by interquartile range divided by 1.35.

Predefined subgroup analysis was conducted comparing EGDT protocols with and without ScvO₂. In addition, we performed post hoc analyses according to setting (emergency department versus ICU), timing (within 6 hours versus unclear), and fluids (fluid resuscitation volume in 6 hours >4 L versus fluid volume in 6 hours <4 L).

With the type I errors resulting from an increased risk of error and repeated significance testing, trial sequential analysis (TSA; TSA software version 0.9 Beta; Copenhagen Trial Unit, Copenhagen, Denmark) was performed to combine information size estimation with an adjusted threshold for statistical significance in the cumulative meta-analysis. Information size was calculated as diversity-adjusted information size, suggested by the relative risk reduction of the intervention in the included studies.

RESULTS

Study Location and Selection

A total of 1135 records were identified through the initial search, and 149 were removed as duplicates. The remainder of the 986 records was screened. After assessment of the titles and abstracts, 943 articles were excluded as irrelevant; 2 full-text articles were unavailable. The flow diagram is presented in Figure 1. In total, 41 potentially eligible studies were identified and 32 of these were excluded, leaving 9 studies^{6,10-12,14-18} that met inclusion criteria and compared EGDT with control

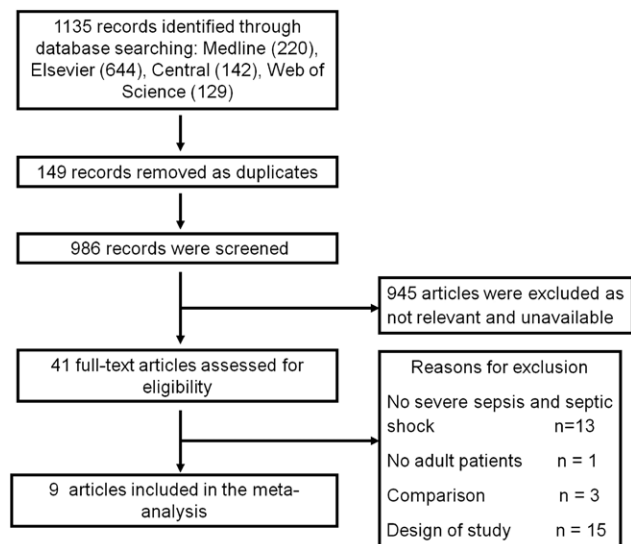


Figure 1. Flow diagram of the search process and study selection.

care. Detailed excluded articles are listed in Supplemental Digital Content 2 (<http://links.lww.com/AA/B410>).

Study Characteristics

The characteristics of the included studies are shown in Supplemental Digital Content 3 (<http://links.lww.com/AA/B411>). The meta-analysis included 5202 severe sepsis and septic shock patients, 2382 in the EGDT group and 2820 in the control group. Among the 9 trials, 5^{10-12,14,16} were multiple-center studies, and the remaining 4^{6,15,17,18} were single-center studies. Four trials^{14,15,17,18} were conducted in the ICU, and the remaining 5^{6,10-12,16} were conducted in the emergency department. Seven trials^{6,10-12,14,17,18} enrolled and resuscitated patients within 6 hours, and 2 trials^{15,16} reported unclear timing of enrollment. The severity of disease was reported in each study by the acute physiology and chronic health evaluation II score (APACHE II score), and data were presented as mean \pm SD or medians (interquartile ranges). The distinction between higher severity of disease and less severity was differentiated by us according to the means of APACHE II scores in each article. The APACHE II scores of the included patients in 5 trials^{6,10,14,15,17} were >20; 3^{11,12,18} of the remaining were <20 or unclear. The fluid volume for resuscitation of the included patients in 2 trials^{6,15} was >4 L, in 5 trials^{10-12,16,17} was <4 L, and in the other 2 trials^{14,18} was unclear.

Details of intervention used in included studies are shown in Table 1. Intervention goals of the EGDT group included CVP \geq 8 to 12 mm Hg, MAP \geq 65 mm Hg, and ScvO₂ \geq 70% in all included studies. Four trials^{6,14,16,18} used the protocol, including identical goal of CVP and MAP but without ScvO₂ as control care, the other 5 trials^{10-12,15,17} used control care with different protocols.

Quality assessment of the included studies is shown in Table 2. Three trials^{6,10,16} were judged to be at low risk of bias or unclear risk of bias, and the remaining 6 trials^{11,12,14,15,17,18} were judged to be at high risk of bias. None of the 9 studies was double-blinded because of the extreme difficulty in blinding required to evaluate the complex intervention such as EGDT. However, we judged that mortality and ICU length of stay were not likely to be influenced by lack of blinding.

The Effects of EGDT on Mortality in Severe Sepsis and Septic Shock Patients

The effects of EGDT on mortality in patients with severe sepsis were estimated from 9 trials (Figure 2), and the heterogeneity was observed ($P = 0.04$, $I^2 = 51.6\%$). The longest complete follow-up mortality rates of all the trials were evaluated in the analysis of all-cause mortality. The overall mortality in the EGDT and control group was 636 of 2382 (26.7%) and 831 of 2820 (29.5%), respectively. No significantly reduced all-cause mortality was observed in EGDT group compared with control care (relative risk [RR], 0.89; 99% CI, 0.74–1.07; $P = 0.10$).

The Effects of EGDT on Hospital Mortality in Severe Sepsis and Septic Shock Patients

Six trials^{6,10-12,16,17} reported hospital mortality in patients with severe sepsis and septic shock. Hospital mortality was not significantly different between EGDT and control care (RR, 0.98; 99% CI, 0.78–1.24; $P = 0.86$).

Table 1. Details of Interventions Used in Included Studies

Study Year	Fluids in 6 h (mL)		Vasopressors in 6 h		Packed Red Cell in 6 h		Dobutamine in 6 h		Intervention Goal		Mechanical Ventilation in 6 h	
	EGDT	Control	EGDT	Control	EGDT	Control	EGDT	Control	EGDT	Control	EGDT	Control
Rivers et al (2010) ⁶	4981 ± 2984	3499 ± 2438	36 (27.4)	40 (30.3)	83 (64.1)	25 (18.5)	18 (13.7)	1 (0.8)	CVP ≥ 8–12 mm Hg; MAP ≥ 65 mm Hg; ScvO ₂ ≥ 70%; MAP ≥ 65 mm Hg; CVP ≥ 8–12 mm Hg; ScvO ₂ > 70%;	CVP 8–12 mm Hg; MAP ≥ 65 mm Hg; UO ≥ 0.5 mL/kg/h	69 (53.0)	72 (53.8)
Wang et al (2006) ¹⁵	4895 ± 210	2340 ± 95	N/A	N/A	N/A	N/A	N/A	N/A	MAP ≥ 65 mm Hg; ScvO ₂ ≥ 70%; UO ≥ 0.5 mL/min	Decisions made by treating clinical team according to blood pressure and UO	4 (25.0)	5 (29.4)
Chen et al (2007) ¹⁸	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	CVP ≥ 8–12 mm Hg; MAP ≥ 65 mm Hg; ScvO ₂ ≥ 70%	CVP 8–12 mm Hg; MAP ≥ 65 mm Hg; UO ≥ 0.5 mL/kg/h	N/A	N/A
Jones et al (2010) ¹⁶	4300 ± 2210	4500 ± 2360	113 (75.3)	108 (72.0)	5 (3.3)	11 (7.3)	8 (5.3)	5 (3.3)	CVP ≥ 8 mm Hg; MAP ≥ 65 mm Hg; ScvO ₂ ≥ 70%	CVP ≥ 8 mm Hg; MAP ≥ 65 mm Hg; lactate clearance ≥ 10%	39 (26.0)	40 (26.7)
Yan et al (2010) ¹⁴	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	MAP ≥ 65 mm Hg; ScvO ₂ ≥ 70%; CVP ≥ 8–12 mm Hg; MAP ≥ 65 mm Hg; SBP > 90 mm Hg; ScvO ₂ ≥ 70%; UO ≥ 0.5 mL/kg/h	CVP 8–12 mm Hg; MAP ≥ 65 mm Hg; SBP > 90 mm Hg; UO ≥ 0.5 mL/kg/h	N/A	N/A
The ProCESS trial investigators (2014) ¹⁰	2805 ± 1957	3285 ± 1743 (standard); 2279 ± 1881 (usual)	241 (54.9)	233 (52.2); 201 (44.1)	63 (14.4)	37 (8.3); 34 (7.5)	35 (8.0)	5 (1.1); 4 (0.9)	UO ≥ 0.5 mL/kg/h; CVP ≥ 8–12 mm Hg; MAP ≥ 65 mm Hg; ScvO ₂ ≥ 70%	Standard care: SBP ≥ 100 mm Hg or shock index < 0.8; usual care: care directed by treating clinical team	116 (26.4)	110 (24.7); 99 (21.7)
Lu et al (2014) ¹⁷	2809 ± 795	3608 ± 715	N/A	N/A	N/A	N/A	N/A	N/A	CVP ≥ 8–12 mm Hg; MAP ≥ 65 mm Hg; ScvO ₂ ≥ 70%; UO ≥ 0.5 mL/kg/h	ITBVI 800–1000 mL/m ² ; MAP ≥ 65 mm Hg	N/A	N/A
The ARISE trial investigators (2014) ¹¹	1964 ± 1415	1713 ± 1401	528 (66.6)	461 (57.8)	108 (13.6)	56 (7.0)	122 (15.4)	21 (2.6)	CVP ≥ 8–12 mm Hg; MAP ≥ 65 mm Hg; ScvO ₂ ≥ 70%	Decisions made by treating clinical team. No ScvO ₂ measurement	276 (34.8)	263 (32.9)
The ProMISE trial investigators (2015) ¹²	2226 ± 1443	2022 ± 1271	332 (53.3%)	291 (46.6)	55 (8.8)	24 (3.8)	113 (18.1)	24 (3.8)	CVP ≥ 8–12 mm Hg; MAP > 65 mm Hg; SBP > 90 mm Hg; ScvO ₂ ≥ 70%	Treatment determined by the treating clinicians	N/A	N/A

Data presented as mean ± SD or medians (interquartile ranges) or n (%).

Abbreviations: CVP, central venous pressure; EGDT, early goal directed therapy; ITBVI, intrathoracic blood volume index; MAP, mean arterial pressure; N/A, not applicable; SBP, systolic blood pressure; ScvO₂, central venous oxygen saturation; UO, urinary output.

Table 2. Quality Assessment of the Included Studies

Authors	Sequences Generation	Allocation Concealment	Blinding of Participants and Researchers	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias	Overall Risk of Bias
Rivers et al (2001) ⁶	Low	Low	Low	Low	Low	Low	Low	Low
Wang et al (2006) ¹⁵	Unclear	Unclear	High	High	Low	Unclear	Low	High
Chen et al (2007) ¹⁸	Unclear	Unclear	High	High	Unclear	Unclear	Low	High
Jones et al (2010) ¹⁶	Low	Low	Low	Low	Low	Unclear	Low	Unclear
Yan et al (2010) ¹⁴	Low	Unclear	High	High	Low	Unclear	Low	High
The ProCESS study investigators (2014) ¹⁰	Low	Low	Low	Low	Low	Low	Low	Low
Lu et al (2014) ¹⁷	Low	Unclear	High	High	Low	Unclear	Low	High
The ARISE study investigators (2014) ¹¹	Low	Low	High	High	Low	Low	Low	High
The ProMISe study investigators (2015) ¹²	Low	Low	High	High	Low	Low	Low	High

Sequence generation: Rivers et al⁶ used computer-generated blocks of 2 to 8 for randomization. Random numbers was used by the study of Yan et al¹⁴ and of Lu et al.¹⁷ No detailed sequence generation was reported by the study of Wang et al¹⁵ and Chen et al.¹⁸ The group assignment sequence was generated by an independent statistician using a parallel design, balanced randomization schedule in the study of Jones et al.¹⁶ Randomization was performed with the use of a centralized Web-based program in variable block sizes of 3, 6, or 9 by the ProCESS study.¹⁰ Randomization was stratified according to study center with the use of a permuted block method and was performed by means of a centralized telephone interactive voice-response system that was accessible 24 hours a day by the ARISE study.¹¹ Study-group assignment was performed by means of randomized permuted blocks, with variable block lengths of 4, 6, and 8, and stratified according to site by the ProMISe study.¹²

Allocation concealment: No detailed allocation concealment was reported by Wang et al.¹⁵ Chen et al.,¹⁸ Yan et al.,¹⁴ and Lu et al.¹⁷ Rivers et al⁶ and Jones et al¹⁶ used sealed, opaque, randomly assorted envelopes. Stratification according to site and race with the use of a centralized Web-based program was used by the ProCESS study.¹⁰ Randomization was stratified according to study center with the use of a permuted block method and was performed by means of a centralized telephone interactive voice-response system that was accessible 24 hours a day by the ARISE study.¹¹ Study-group assignment was performed by means of randomized permuted blocks, with variable block lengths of 4, 6, and 8, and stratified according to site by the ProMISe study.¹²

Blinding: Clinicians who subsequently assumed the care of the patients were blinded to the treatment assignment in the study of Rivers et al.⁶ Blinding was not reported by the study of Wang et al.,¹⁵ Chen et al.,¹⁸ Jones et al.,¹⁶ Yan et al.,¹⁴ and Lu et al.¹⁷ The clinical coordinating team and investigators at the participating sites remained unaware of the study-group outcomes until the data were locked by the ProCESS study.¹⁰ No blinding to study-group assignment was reported by the ARISE study¹¹ and the ProMISe study.¹²

Incomplete outcome data: All trials described the follow-up.

Selective reporting: The study protocols of the ProCESS study,¹⁰ the ARISE study,¹¹ and the ProMISe study¹² were obtained.

Other bias: No evidence of other sources of bias.

The Effects of EGDT on ICU Mortality in Severe Sepsis and Septic Shock Patients

Four trials^{11,14,15,18} reported ICU mortality in patients with severe sepsis and septic shock. EGDT significantly reduced ICU mortality in severe sepsis and septic shock patients (RR, 0.72; 99% CI, 0.57–0.90; $P = 0.0002$).

The Effects of EGDT on Mortality in Severe Sepsis and Septic Shock Patients With Different Severity of Illness

For patients with a higher severity of disease (APACHE II score ≥ 20), mortality benefit trended toward EGDT (RR, 0.87; 99% CI, 0.74–1.03; $P = 0.03$) when compared with control care (Figure 3).

The Effects of Goal-Directed Therapy on Mortality in Severe Sepsis and Septic Shock Patients With and Without Central Venous Oxygen Saturation

Predefined subgroup analysis according to protocol with versus without ScvO₂ suggested no significant difference of mortality between the 2 protocols; however, mortality benefit trended toward ScvO₂ monitoring (RR, 0.88; 99% CI, 0.73–1.06; $P = 0.07$) when compared with protocol including identical remaining intervention goals (Figure 4).

Post Hoc Subgroup Analyses for Overall Mortality

Post hoc subgroup analyses (Table 3) according to the setting of EGDT for resuscitation suggested that mortality

benefit was only seen in the subgroup when EGDT was conducted in the ICU (RR, 0.67; 99% CI, 0.51–0.88; $P = 0.0002$) but not in the subgroup conducted in the emergency department. Moreover, although there was a lack of statistical significance, more trending toward reduced mortality was found when EGDT was performed within 6 hours than when timing of EGDT was unclear (RR, 0.87; 99% CI, 0.72–1.05; $P = 0.05$) or when there was EGDT with more fluid volume in patients with severe sepsis and septic shock (RR, 0.77; 99% CI, 0.55–1.06; $P = 0.04$). Sensitivity analyses for the effects of EGDT on mortality in severe sepsis and septic shock patients with higher severity of illness and timing were performed (Table 4).

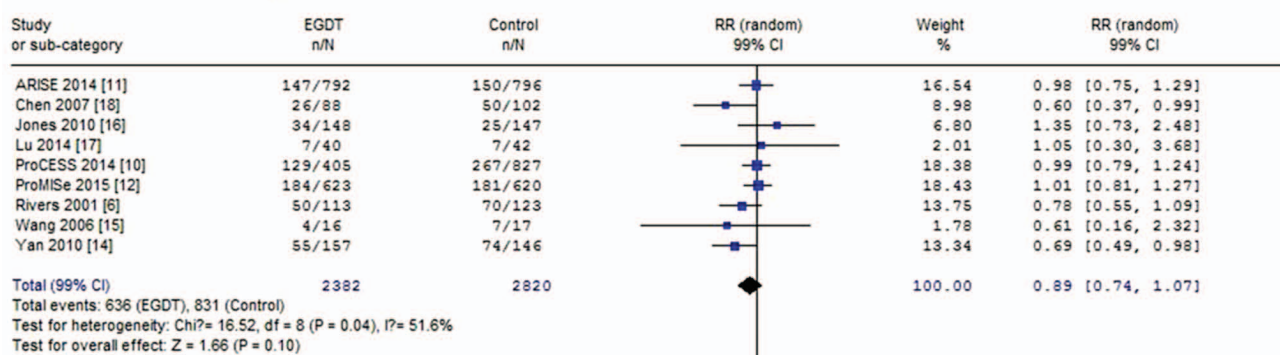
The Effects of EGDT on ICU Length of Stay in Severe Sepsis and Septic Shock Patients

The ICU length of stay was also evaluated (Figure 5). Five studies^{10,14–17} reported ICU length of stay by mean \pm SD. However, the ICU length of stay was reported by median and interquartile ranges in the ARISE¹¹ and the ProMISe trial¹² with a large sample size. As a result, we used median instead of mean, and SD was calculated by interquartile range divided by 1.35. Compared with control care, EGDT displayed no beneficial effect on ICU length of stay in severe sepsis and septic shock patients.

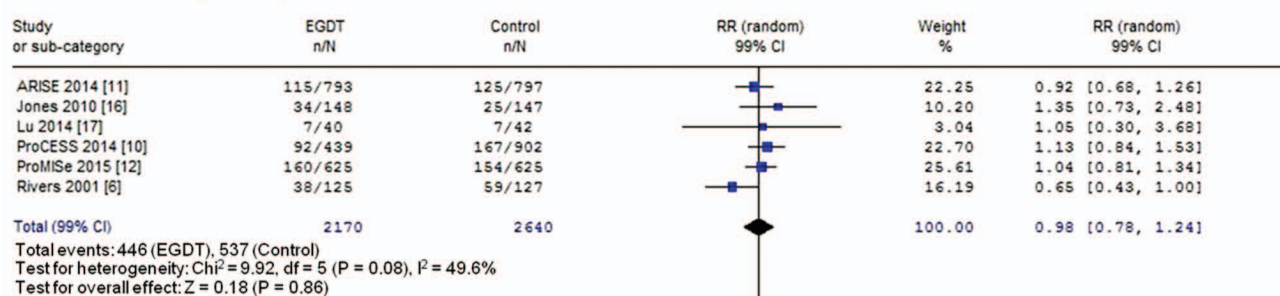
Random Errors

To correct for random error and repetitive testing of sparse data, TSA was calculated with $\alpha = 0.05$ and $\beta = 0.20$ (power 80%). The required diversity-adjusted information

Outcome: 01 All-cause mortality



Outcome: 02 In-hospital mortality



Outcome: 03 ICU mortality

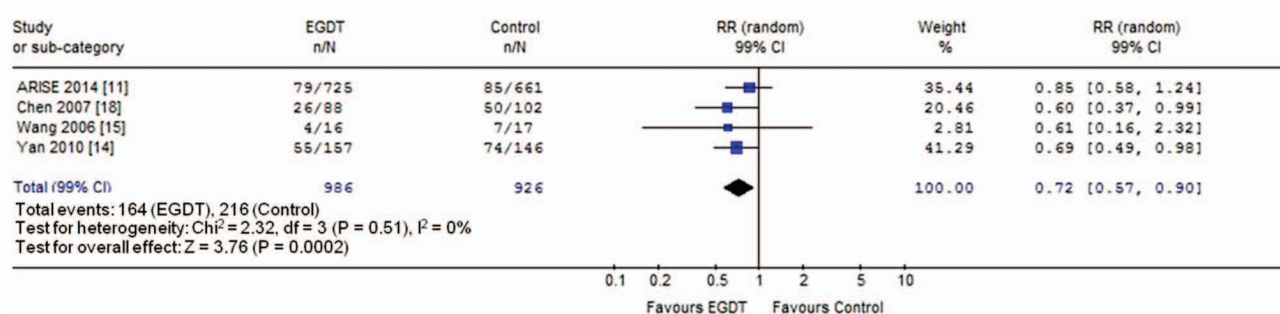


Figure 2. The effects of early goal-directed therapy (EGDT) on mortality in patients with severe sepsis and septic shock. Mortality data were recorded during the data extraction. When there is >1 value about mortality published in the article, the longest complete follow-up was preferentially used for evaluation of all-cause mortality. However, when 28-day or 90-day mortality values were not presented, intensive care unit (ICU) or hospital mortality or mortality at other time points were recorded. Ninety-day mortality was reported by the ARISE study,¹¹ the ProCESS study,¹⁰ and the ProMiSe study.¹² Sixty-day mortality was reported by the study of Rivers et al.⁶ Twenty-eight-day mortality was reported by the Yan study.¹⁴ Fourteen-day mortality was reported by the study of Wang et al.¹⁵ In-hospital mortality was reported by the study of Rivers et al.,⁶ the study of Jones et al.,¹⁶ Lu study,¹⁷ ARISE study,¹¹ ProCESS study,¹⁰ and ProMiSe study.¹² ICU mortality was reported by the study of Chen et al.,¹⁸ the study of Wang,¹⁵ Yan study,¹⁴ and ARISE study.¹² CI indicates confidence interval; RR, relative risk.

size based on the intervention effect was suggested by the included trials using a random-effects model (with the relative risk reduction of 9.5% regarding mortality and 21,342 patients). TSA indicated lack of reliable and conclusive evidence for a beneficial effect of EGDT for the longest complete follow-up mortality in severe sepsis and septic shock patients (Figure 6) because the monitoring boundary was not surpassed and the required information size was not reached.

DISCUSSION

Our meta-analysis showed no significantly reduced all-cause mortality in patients resuscitated with EGDT when

compared with control therapy. This meta-analysis differs considerably from those of recently published meta-analyses, but we obtained similar results.²²⁻²⁵

In our meta-analysis, TSA indicated lack of firm evidence for our results because of considerable heterogeneity between groups. Our results suggest that although 3 recent multicenter randomized controlled studies reported negative results, conclusive evidence regarding the benefit of EGDT is not possible, and more randomized controlled trials are needed.

Our results, however, suggest that some patient subgroups may benefit from EGDT. In our meta-analysis, for example, we found a trend toward the longest complete

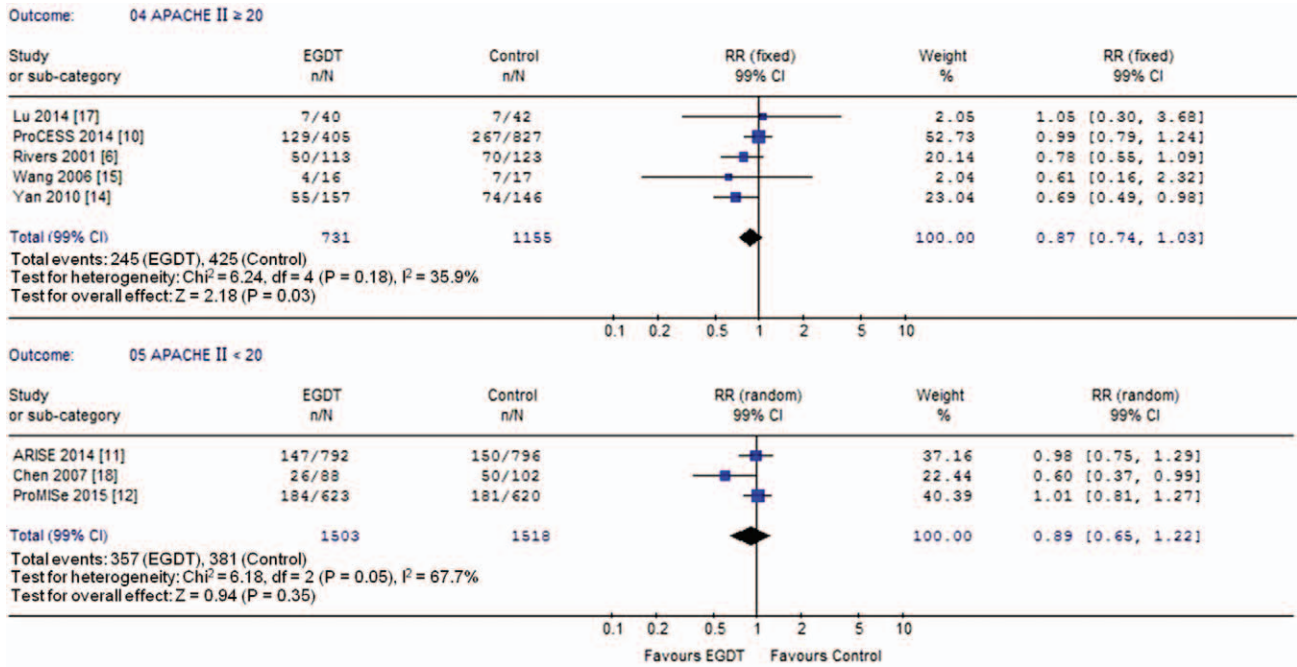


Figure 3. The effects of early goal-directed therapy (EGDT) on mortality in severe sepsis and septic shock patients with different severity of illness. The severity of illness was reported in each study by the acute physiology and chronic health evaluation II score (APACHE II score), and the data were presented as mean \pm SD or medians (interquartile ranges). The distinction between higher severity of illness and less severity was differentiated by us according to the means of APACHE II scores in each article. The APACHE II score of the included patients in 5 trials^{6,10,14,15,17} were >20 , the remaining 3^{11,12,18} were <20 or unclear. CI indicates confidence interval; RR, relative risk.

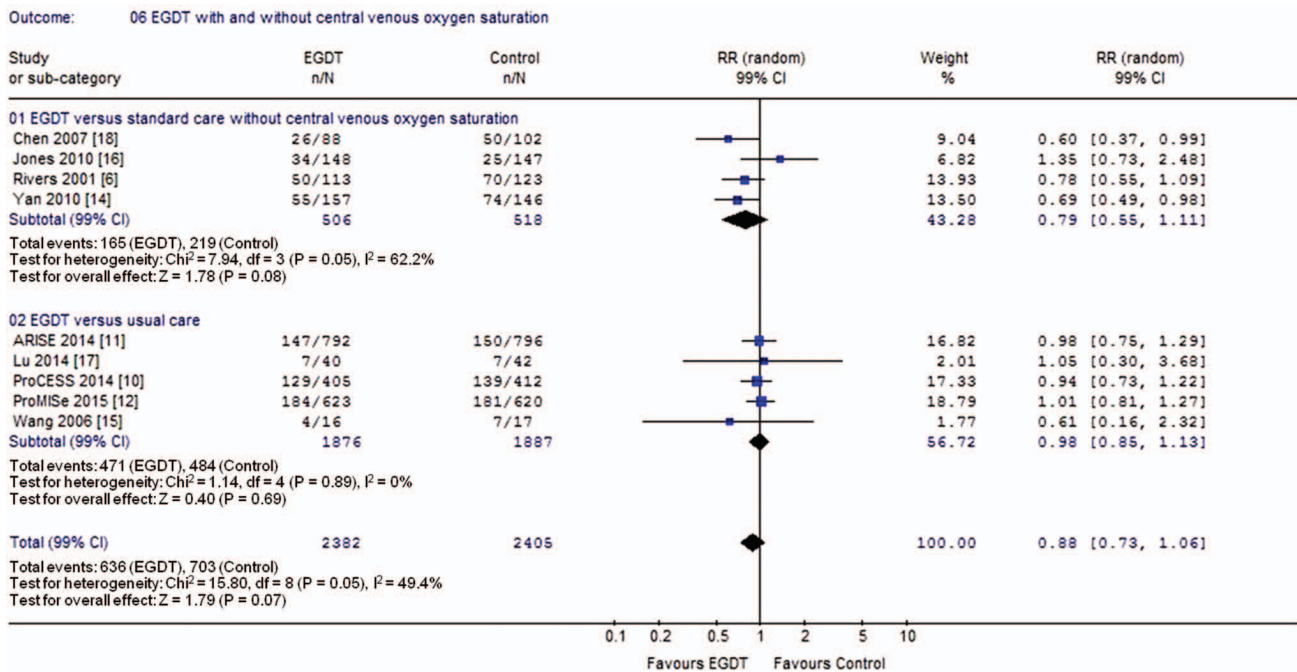


Figure 4. The effects of goal-directed therapy on mortality in severe sepsis and septic shock patients with and without central venous oxygen saturation. Mortality data were recorded during the data extraction. When there is >1 value about mortality published in the article, the longest complete follow-up was preferentially used for evaluation of all-cause mortality. However, when 28-day or 90-day mortality values were not presented, intensive care unit (ICU) or hospital mortality or mortality at other time points were recorded. Ninety-day mortality was reported by the ARISE study,¹¹ the ProCESS study,¹⁰ and the ProMISe study.¹² Sixty-day mortality was reported by the study of Rivers et al.⁶ Twenty-eight-day mortality was reported by Yan study.¹⁴ Fourteen-day mortality was reported by the study of Wang et al.¹⁵ In-hospital mortality was reported by the study of Rivers et al.,⁶ the study of Jones et al.,¹⁶ Lu study,¹⁷ ARISE study,¹¹ ProCESS study,¹⁰ and ProMISe study.¹² ICU mortality was reported by the study of Chen et al.,¹⁸ study of Wang et al.,¹⁵ Yan study,¹⁴ and ARISE study.¹² CI indicates confidence interval; RR, relative risk.

Table 3. Subgroup Analyses for Overall Mortality

Subgroups	No. of Studies	No. of Patients	RR (99% Confidence Interval)	P Value	I ² (%)
Setting					
Intensive care unit ^{14,15,17,18}	4	608	0.67 (0.51–0.88)	0.0002	0
Emergency department ^{6,10–12,16}	5	4594	0.97 (0.84–1.13)	0.64	21.8
Timing					
Within 6 h ^{6,10–12,14,17,18}	7	4874	0.87 (0.72–1.05)	0.05	54.1
Unclear ^{15,16}	2	328	1.04 (0.39–2.73)	0.92	48.9
Fluid volume					
More ^{6,15}	2	269	0.77 (0.55–1.06)	0.04	0
Less ^{10–12,16,17}	5	4440	1.01 (0.88–1.16)	0.84	0

Abbreviations: RR, relative risk.

Table 4. Sensitivity Analyses of the Studies

Study Attributes	No. of Studies	No. of Patients	RR (95% Confidence Interval)	P Value	I ² (%)
Sensitivity analyses for the effects of EGDT on mortality in severe sepsis and septic shock patients with higher severity of illness					
APACHE II > 20 ^{6,10,14,15,17}	5	1886	0.87 (0.74–1.03)	0.03	35.9
Rivers et al ⁶	4	1650	0.84 (0.60–1.18)	0.19	45.3
ProCESS ¹⁰	4	654	0.74 (0.58–0.94)	0.001	0
Yan et al ¹⁴	4	1583	0.91 (0.76–1.10)	0.20	0
Wang et al ¹⁵	4	1853	0.84 (0.64–1.09)	0.08	48.3
Lu et al ¹⁷	4	1804	0.82 (0.62–1.07)	0.05	50.5
Sensitivity analyses for timing of EGDT on mortality in severe sepsis and septic shock patients					
Within 6 h ^{6,10–12,14,17,18}	7	4874	0.87 (0.72–1.05)	0.05	54.1
Rivers et al ⁶	6	4638	0.88 (0.72–1.09)	0.13	56.7
ProCESS ¹⁰	6	3642	0.84 (0.66–1.05)	0.04	57.6
ARISE ¹¹	6	3286	0.84 (0.67–1.05)	0.05	59.1
ProMISe ¹²	6	3631	0.83 (0.67–1.04)	0.03	54.0
Yan et al ¹⁴	6	4571	0.91 (0.76–1.09)	0.17	42.2
Lu et al ¹⁷	6	4792	0.86 (0.71–1.05)	0.05	61.5
Chen et al ¹⁸	6	4684	0.91 (0.77–1.07)	0.13	40.6

Abbreviations: RR, relative risk.

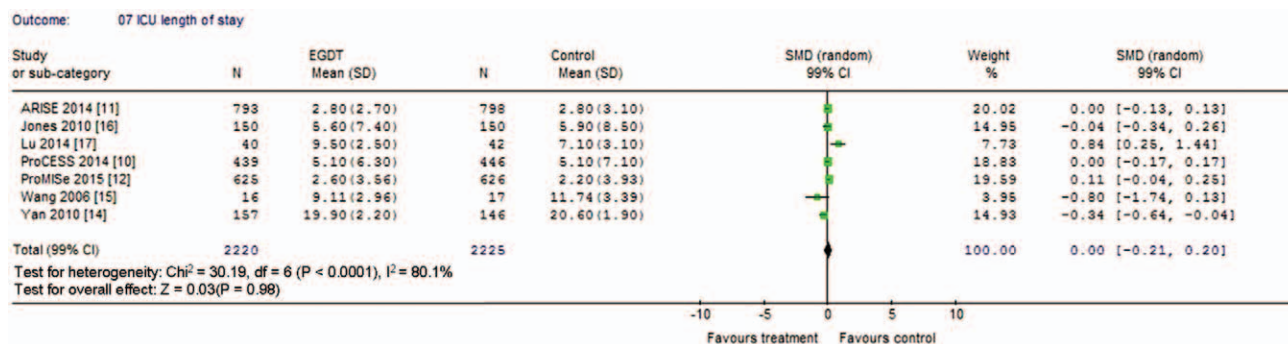


Figure 5. The effects of early goal-directed therapy (EGDT) on intensive care unit (ICU) length of stay in severe sepsis and septic shock patients. CI indicates confidence interval.

follow-up mortality benefit with EGDT in patients with a higher severity of disease (APACHE II score ≥ 20). In addition, EGDT was associated with decreased ICU mortality when compared with control care. These results suggest that EGDT may have some benefit in more critically ill patients.

As the cornerstone for resuscitation in patients with severe sepsis and septic shock, EGDT has been recommended by the Surviving Sepsis Guidelines,⁵ and studies have suggested³ that every 10% increase in compliance is associated with a significant decrease in the odds ratio for

mortality. However, the role of EGDT in the treatment of sepsis remains controversial.

Different study time periods may influence the value of EGDT. Earlier trials supported EGDT for severe sepsis and septic shock patients; however, after 15 years, the most recent 3 trials all failed to show any benefit of EGDT. When comparing these studies with the original study of Rivers et al, there were concerns, including the amount of fluids before randomization and the lower overall mortality rate. These concerns could be explained by the broad implementation of, and compliance with, the Guidelines, suggesting

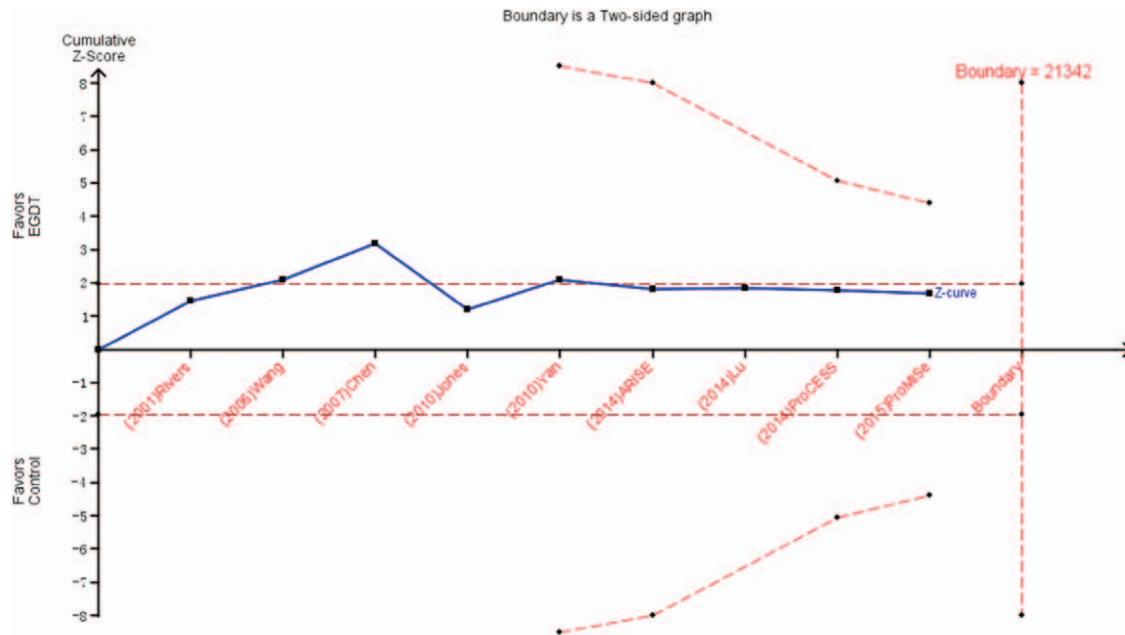


Figure 6. Trial sequential analysis for a relative risk reduction of all-cause mortality of 9.5% in control group in 9 trials. A required diversity-adjusted information size of 21,342 patients was calculated based on a control event proportion of 9.5%, early goal-directed therapy (EGDT) induced relative risk reduction of mortality of 9.5% suggested by all trials, $\alpha = 0.05$ two-sided, $\beta = 0.20$ (power = 80%). The cumulated Z-curve (blue) crosses the traditional boundary ($P = 0.05$) but not the trial sequential monitoring boundary, indicating lack of firm evidence for a beneficial effect of EGDT.

that patients with severe sepsis and septic shock need early attention and resuscitation. The earlier we treat sepsis, the better outcome is shown.

Three recent large multicenter trials^{10–12} with lower mortality (ProCESS: 21.0% vs 18.9% vs 18.2%; ARISE: 18.6% vs 18.8%; ProMISE: 29.5% vs 29.2%) compared with the study of Rivers et al (30.5% vs 46.5%) have found no difference in mortality between EGDT and control care, leading to lively discussions.^{26–29} Possible explanations for the difference between trial results include the study population, intervention methods, and goals. The timing and volume of fluids, for example, may play an important role.³⁰ As a result, the focus during the golden time of resuscitation for septic shock should be fluid administration. However, in the recent trials, the volume of fluid administration is less (ProCESS: 2805 ± 1957 vs 3285 ± 1743 vs 2279 ± 1881 mL; ARISE: 1964 ± 1415 vs 1713 ± 1401 mL; ProMISE: 2226 ± 1443 vs 2022 ± 1271 mL) than that in the study of Rivers et al (4981 ± 2984 vs 3499 ± 2438 mL).

Many EGDT protocols specify using CVP and ScvO₂ monitoring to guide management of fluids, vasopressors, packed red-blood-cell transfusions, and dobutamine. Some negative studies^{16,31} have challenged the role of ScvO₂ in EGDT protocols and have used lactate clearance instead. Another multicenter study³² reported that abnormal ScvO₂ values (90%–100%) observed in the emergency department were associated with increased mortality, indicating that an ScvO₂ target should be achieved in the resuscitation of sepsis.

Our analysis has several limitations. First, only 9 trials were included in our meta-analysis, and some were at high risk of bias. Second, the protocols of control care were different, which may have affected results. Third, different end points were used for mortality evaluation, which may

influence the overall results; and ICU length of stay might not be a reliable marker of success because criteria for discharge from the ICU are not uniform.

CONCLUSIONS

The results of this meta-analysis suggested a nonsignificant trend toward reduction in the longest all-cause mortality in patients resuscitated with EGDT. However, TSA indicated lack of firm evidence for the results. High powered, randomized controlled trials are needed to determine the effects. ■■

DISCLOSURES

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Contribution: This author performed the analysis and interpretation of data and participated in drafting, editing, and submitting the manuscript.

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Contribution: This author reviewed all the articles independently in accordance with the inclusion criteria.

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Contribution: This author contributed to study analysis and interpretation of data.

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Contribution: This author was responsible for revising the manuscript for important intellectual content.

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