

# Antithrombin III in critically ill patients: systematic review with meta-analysis and trial sequential analysis

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**EDITORIAL** by Torossian and colleagues

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## ABSTRACT

**Objective** To evaluate the benefits and harms of antithrombin III in critically ill patients.

**Design** Systematic review and meta-analysis of randomised trials.

**Data sources** CENTRAL, Medline, Embase, International Web of Science, LILACS, the Chinese Biomedical Literature Database, and CINHAL (to November 2006); hand search of reference lists, contact with authors and experts, and search of registers of ongoing trials.

**Review methods** Two reviewers independently selected parallel group randomised clinical trials comparing antithrombin with placebo or no intervention and extracted data related to study methods, interventions, outcomes, bias risk, and adverse events. Disagreements were resolved by discussion. Trials in any type of critically ill patients in intensive care were eligible. All trials, irrespective of blinding or language status, that compared any antithrombin III regimen with no intervention or placebo were included. Trials were considered to be at low risk of bias if they had adequate randomisation procedure, blinding, and used intention to treat analysis. Risk ratios with 95% confidence intervals were estimated with fixed and random effects models according to heterogeneity.

**Main outcome measures** Mortality, length of stay in intensive care or hospital, quality of life, severity of sepsis, respiratory failure, duration of mechanical ventilation, incidence of surgical intervention, intervention effect among various populations and adverse events (such as bleeding).

**Results** 20 trials randomly assigning 3458 patients met inclusion criteria. Eight trials had low risk of bias. Compared with placebo or no intervention, antithrombin III did not reduce overall mortality (relative risk 0.96, 95% confidence interval 0.89 to 1.03). No subgroup analyses on risk of bias, populations of patients, or with and without adjuvant heparin yielded significant results. Antithrombin III increased the risk of bleeding events (1.52, 1.30 to 1.78). Heterogeneity was observed in only a few analyses.

**Conclusion** Antithrombin III cannot be recommended for critically ill patients based on the available evidence.

## INTRODUCTION

Antithrombin III is a potent anticoagulant with anti-inflammatory properties. It is thought to have an inhibitory effect on the proinflammatory and procoagulant processes.<sup>1,2</sup> The blood concentration of antithrombin III falls by 20-40% in critically ill (septic) patients and correlates with severity of disease.<sup>1,3</sup> Hence, theoretically replenishing concentrations

might benefit critically ill patients. Furthermore, its interaction with heparin, which is a standard treatment for patients with disseminated intravascular coagulation, seems important.<sup>w1</sup>

Four small meta-analyses assessed the use of antithrombin III in critically ill patients.<sup>4,5w2 w3</sup> A Cochrane systematic review with two randomised controlled trials assessed use of antithrombin III for respiratory distress syndrome in preterm infants.<sup>5</sup> These meta-analyses had selected populations. All found non-significant effects on mortality, with wide confidence intervals (that is, “absence of evidence”).

Information from the Danish Medicinal Agency suggests that the extrapolated annual costs of antithrombin III in the US and the European Union are around £70m (€100m, \$145m). The clinical benefit of supplementation in critically ill patients, however, is still controversial and its efficacy debated.

## METHODS

### Study selection

We searched the Cochrane central register of controlled trials (CENTRAL), Medline (1950 to November 2006), Embase (1980 to November 2006), International Web of Science (1945 to November 2006), LILACS (1984 to March 2005), the Chinese Biomedical Literature Database (to March 2005), and CINHAL (1982 to March 2005). We used the search terms: antithrombin, antithrombin-3, sepsis, and critically ill. We searched for ongoing clinical trials and unpublished trials on <http://controlled-trials.com>, <http://clinicaltrials.gov>, and <http://centerwatch.com> up to March 2005. See [bmj.com](http://bmj.com) for full details.

Trials were included only if they were clearly randomised trials, reported in a full paper article, and provided data on mortality. The included patients were loosely defined as being critically ill—that is, sepsis, septic shock, disseminated intravascular coagulation, and other critical illnesses. There was no restriction of dose and duration of treatment. We excluded trials assessing administration of antithrombin III in invasive treatment of acute myocardial infarction.

### Data abstraction

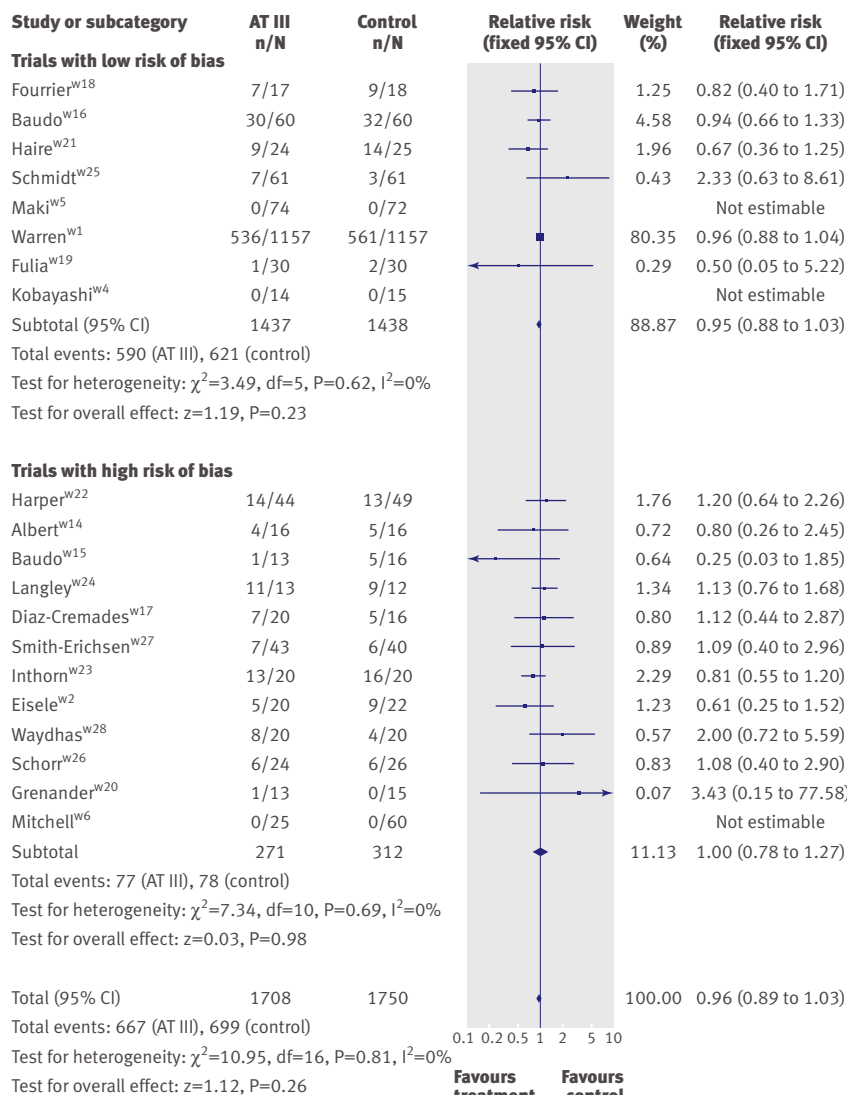
Two investigators independently screened the titles and abstracts for relevant articles, and abstracted trial data based on a predefined form. Disagreements were resolved by discussion. Authors of the included trials were approached for relevant additional information.

We evaluated the validity and design characteristics of each trial and major potential sources of bias (such as adequate random sequence generation, adequate

allocation concealment, adequate blinding, and use of intention to treat analysis). Trials were defined as low risk of bias if they fulfilled all of the above criteria. Our primary outcome was mortality, using the longest follow-up data from each trial. Secondary outcomes included length of stay in intensive care or hospital, severity of sepsis, respiratory failure (mechanically assisted ventilation), duration of mechanical ventilation, need for surgical intervention, and adverse events (such as bleeding).

### Statistical analysis

We used random and fixed effect models for all meta-analyses. In the case of heterogeneity, we reported results from the random effects model. We analysed data by intention to treat and included all patients. Heterogeneity was explored by Cochrane's  $Q^2$  test and  $I^2$ .  $I^2 > 75\%$  is considered as a heterogeneous meta-analysis.



**Fig 1** Forest plot of mortality (subgroup analyses on risk of bias). Weight is relative contribution of each study to overall estimate of treatment effect on log scale assuming random effects model

We carried out subgroup analyses in different populations (for example, trauma, newborns, etc), in patients with and without adjuvant heparin, in trials with short (less than one week) and long duration of treatment, in trials with short (less than the median follow-up) and long follow-up, and in trials with high and low risk of bias. If any results were significant, we estimated the difference between the estimates of the subgroups according to tests of interaction.

We created funnel plots for mortality to assess publication bias and other types of bias. We also carried out trial sequential analysis, which provides the necessary sample size for our meta-analysis and boundaries that determine whether the evidence in our meta-analysis is reliable and conclusive.<sup>6</sup> See [bmj.com](http://bmj.com) for further details.

## RESULTS

### Study search results

We identified 8778 references through electronic and hand searches. After exclusions, 20 trials fulfilled our inclusion criteria (see [bmj.com](http://bmj.com)). We received additional data for six trials through correspondence with authors.

### Characteristics of included trials and assessment of risk of bias

The trials included 3458 patients, and the sample sizes varied from 25 to 2314. Patients had sepsis ( $n=13$ ) or were from paediatric ( $n=3$ ), obstetric ( $n=2$ ), and trauma ( $n=2$ ) specialties. The dose regimen of antithrombin III varied from a single bolus to 14 days of administration, aiming for above normal antithrombin III activity. Follow-up ranged from 7 to 90 days.

Nine trials reported adequate allocation sequence generation; 12 adequate allocation concealment; 10 adequate double blinding; 14 performed intention to treat analysis, or provided sufficient data to allow us to do so, and the remaining trials excluded drop outs from the final analyses. Only eight trials reported adequate generation of allocation sequence, allocation concealment, blinding, and intention to treat analyses. These were classified as trials with low risk of bias.

### Effects of antithrombin III

Combination of data from all 20 trials showed no significant effect of antithrombin III on mortality, with 667 (39.1%) deaths in the intervention group compared with 699 (39.9%) in the control group (pooled relative risk 0.96, 95% confidence interval 0.89 to 1.03). There was no heterogeneity between trials ( $I^2=0\%$ ) (fig 1).

Compared with no intervention or placebo, antithrombin III did not significantly influence the incidence of respiratory failure (0.93, 0.76 to 1.14), duration of mechanical ventilation (weighted mean difference 2.2 days,  $-1.2$  days to 5.6 days), need for surgical intervention (relative risk 1.04, 0.85 to 1.27), and length of stay in hospital (weighted mean difference  $-1.9$  days,  $-11.4$  days to 7.7 days) or in intensive care unit (0.0 days,  $-1.8$  days to 1.8 days). One

trial found no significant effect of antithrombin III on quality of life, and most scores used to assess severity of sepsis were also non-significant.<sup>6</sup> Antithrombin III significantly increased the risk of bleeding events (1.52, 1.30 to 1.78,  $I^2=0\%$ ) (fig 2).

There was no significant effect on mortality or other outcome measures ( $P>0.05$ ) in all analyses of different subgroup populations. Additionally, subgroup analyses of trials with short and long duration of treatment, short or long follow-up, and high or low risk of bias showed no significant effect on the examined outcome measures. In the subgroup of patients who received antithrombin III without adjuvant heparin, antithrombin III was associated with a significant effect (0.87, 0.75 to 0.99) but with heterogeneity ( $I^2=1.1$ ,  $P=0.41$ ). When we used a random effects model because of the observed heterogeneity, the significant effect was no longer present (0.87, 0.77 to 1.02). Antithrombin III showed no significant effect in patients with adjuvant heparin (0.99, 0.90 to 1.09). The funnel plot analysis showed no evidence of bias ( $P=0.37$ ).

**Trial sequential analysis**

Trial sequential analysis showed that a relative risk reduction of 10% or more on mortality is unlikely and that we would need a sample of 14 294 (with 80% power and  $\alpha$  0.05) to detect a plausible treatment effect for antithrombin III on mortality, corresponding to a relative risk reduction of 5%. Currently 3458 patients have been randomised and no boundaries have been

crossed, indicating that the cumulative evidence is inconclusive for a 5% relative risk reduction (see [bmj.com](http://bmj.com)).

**DISCUSSION**

Treatment of critically ill patients with antithrombin III does not significantly affect mortality and length of stay in hospital or in intensive care but is associated with a significantly increased risk of bleeding events. In patients who do not receive heparin there might be a benefit, though this should be explored in further randomised trials. In the overall mortality analysis, one low bias risk trial<sup>w1</sup> dominates the analysis, contributing 80% of the available information.

**Strength and limitations**

We carried out a comprehensive search to identify randomised controlled trials. Two investigators independently obtained data from all corresponding authors. This reduces the risk of publication, ascertainment, and information bias. We incorporated mortality data from 20 randomised controlled trials in our meta-analysis (adding 11 trials more than previously reported).

Furthermore, we evaluated the strength of the available evidence through trial sequential analysis.<sup>6</sup> This analysis supports our findings and shows that if antithrombin III has any effect on mortality, it is small.

The weaknesses of our conclusions are closely linked with the weaknesses in the individual trials. Only eight of the 20 included trials reported adequate randomisation, double blinding, and intention to treat analysis. We found no significant association between risk of bias and trial estimates of intervention effects in subgroup analyses. Furthermore, the funnel plot did not indicate publication bias and other bias. These findings, combined with the absence of heterogeneity observed in most meta-analyses, support the robustness of our results but do not exclude the possibility of bias.

Although there was minimal heterogeneity among trial results on mortality, we are aware that we pooled heterogeneous trials regarding patients, setting, and treatment regimen. However, all included conditions were associated with low concentrations of antithrombin III, can result in disseminated intravascular coagulation, and have similar inflammatory pathways. Further, a broad meta-analysis increases power, reduces the risk of erroneous conclusions, and facilitates exploratory analyses, which can generate hypotheses for future research (such as adjuvant heparin).

**Effects of antithrombin III in subgroups**

All subgroup analyses but one had non-significant results, analogous to the overall analyses on mortality. In one subgroup that did not receive adjuvant heparin, antithrombin III seemed to reduce mortality significantly with a fixed effect model. When we used a random effects model, the effect was no longer

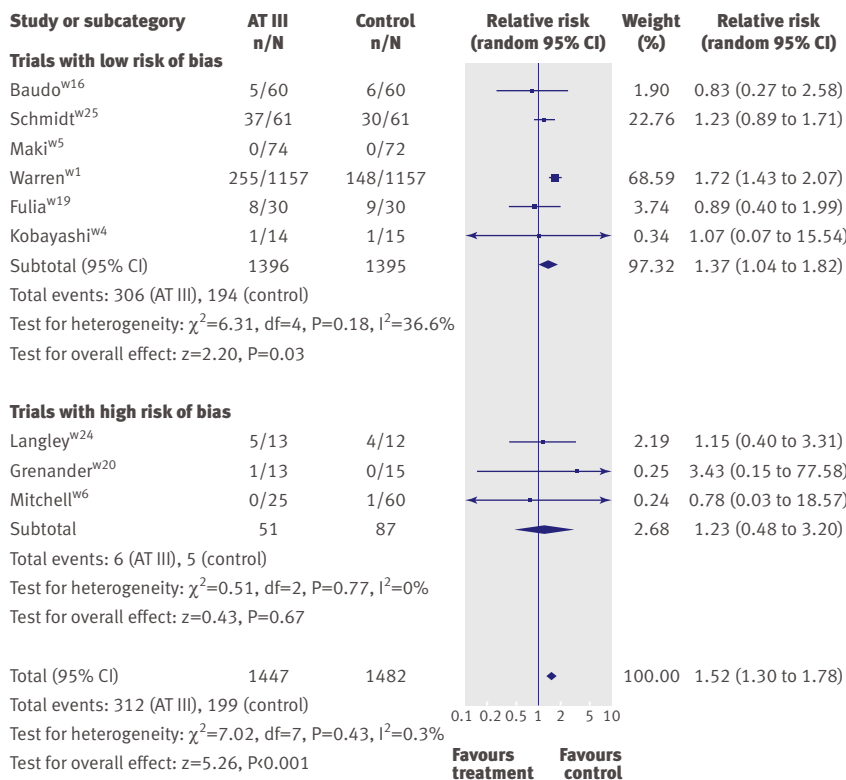


Fig 2 | Forest plot for bleeding events

**WHAT IS ALREADY KNOWN ON THIS TOPIC**

Antithrombin III is a costly intervention that is widely used for critically ill patients

Four minor meta-analyses of randomised and non-randomised trials in selected populations have previously shown inconclusive evidence on mortality

**WHAT THIS STUDY ADDS**

Trial sequential analysis showed that there is evidence of absence of beneficial effects (10% mortality reduction or more) of antithrombin III in critically ill patients

Antithrombin III increases the risk of bleeding

significant. This might or might not support the previously generated hypothesis that antithrombin III is beneficial in patients who do not receive adjuvant heparin.<sup>w1</sup> In this subgroup analysis, however, we split one trial<sup>w1</sup> into two “separate trials” with and without concomitant use of heparin. If this trial was not split, the subgroup without adjuvant heparin becomes insignificant. These results could suggest that antithrombin III cannot be recommended for patients without adjuvant heparin, but it might be relevant to explore this further in future trials. The negative interaction between antithrombin III and heparin has been recognised on a molecular level.<sup>3</sup>

Nevertheless, if antithrombin III is used in clinical practice adjuvant heparin should be avoided as the potentially harmful interactions are unclear.<sup>7,8</sup>

**Conclusion**

We have shown that antithrombin III seems ineffective in any population of critically ill patients regarding

mortality and it even increases the risk of bleeding events. Its use in critically ill patients cannot be recommended based on the available evidence, but it may be relevant to explore this further in future trials.

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- 1 Opal SM, Kessler CM, Roemisch J, Knaub S. Antithrombin, heparin, and heparan sulfate. *Crit Care Med* 2002;30(5 suppl):S325-31.
- 2 Rublee D, Opal SM, Schramm W, Keinecke HO, Knaub S. Quality of life effects of antithrombin III in sepsis survivors: results from the KyberSept trial. *Crit Care* 2002;6:349-56.
- 3 Wiedermann CJ, Römisch J. The anti-inflammatory actions of antithrombin—a review. *Acta Med Austriaca* 2002;29:89-92.
- 4 Freeman BD, Zehnbauer BA, Buchman TG. A meta-analysis of controlled trials of anticoagulant therapies in patients with sepsis. *Shock* 2003;20:5-9.
- 5 Bassler D, Millar D, Schmidt B. Antithrombin for respiratory distress syndrome in preterm infants. *Cochrane Database Syst Rev* 2006;(4):CD005383.
- 6 Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analyses may establish when firm evidence is reached in cumulative meta-analyses. *J Clin Epidemiol* doi: 10.1016/j.jclinepi.2007.03.013.
- 7 Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001;29:1303-10.
- 8 Levi M, de Jonge E, van der Poll T. New treatment strategies for disseminated intravascular coagulation based on current understanding of the pathophysiology. *Ann Med* 2004;36:41-9.

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## Hemiarthroplasty or internal fixation for intracapsular displaced femoral neck fractures: randomised controlled trial

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**EDITORIAL** by Parker

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**ABSTRACT**

**Objective** To compare the functional results after displaced fractures of the femoral neck treated with internal fixation or hemiarthroplasty.

**Design** Randomised trial with blinding of assessments of functional results.

**Setting** University hospital.

**Participants** 222 patients; 165 (74%) women, mean age 83 years. Inclusion criteria were age above 60, ability to walk before the fracture, and no major hip pathology, regardless of cognitive function.

**Interventions** Closed reduction and two parallel screws (112 patients) and bipolar cemented hemiarthroplasty (110 patients). Follow-up at 4, 12, and 24 months.

**Main outcome measures** Hip function (Harris hip score), health related quality of life (Eq-5d), activities of daily living (Barthel index). In all cases high scores indicate better function.

**Results** Mean Harris hip score in the hemiarthroplasty group was 8.2 points higher (95% confidence interval 2.8 to 13.5 points,  $P=0.003$ ) at four months and 6.7 points (1.5 to 11.9 points,  $P=0.01$ ) higher at 12 months. Mean Eq-5d index score at 24 months was 0.13 higher in the hemiarthroplasty group (0.01 to 0.25,  $P=0.03$ ). The Eq-5d visual analogue scale was 8.7 points higher in the hemiarthroplasty group after 4 months (1.9 to 15.6,  $P=0.01$ ). After 12 and 24 months the percentage scoring 95 or 100 on the Barthel index was higher in the hemiarthroplasty group (relative risk 0.67, 0.47 to 0.95,