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Efficacy of antithrombin administration for patients with sepsis: A systematic review, meta-analysis, and meta-regression

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Abstract

Aims: There have been inconsistent reports regarding the effect of antithrombin on sepsis; furthermore, there are limited reports on how dosage affects therapeutic efficacy. Thus, we aimed to perform a systematic review and meta-analysis of the use of antithrombin for sepsis and a meta-regression analysis of antithrombin dosage.

Methods: We included randomized controlled trials (RCTs) and observational studies of adult patients with sepsis who received antithrombin. Outcomes included all-cause mortality and serious bleeding complications. Statistical analyses and data synthesis were performed using a random-effects model; further, meta-regression and funnel plots were used to explore heterogeneity and biases.

Results: Seven RCTs and six observational studies were included. Most patients in the RCTs and observational studies had severe sepsis and septic-disseminated intravascular coagulation (DIC), respectively. A meta-analysis using RCTs showed no significant differences in mortality between the antithrombin and control groups. However, the meta-analysis of observational studies indicated a trend of decreasing mortality rates with antithrombin administration (odds ratio [OR], 0.79; 95% confidence interval [CI], 0.68–0.92; $p = 0.002$). Bleeding complications were significantly higher in the antithrombin group than in the control group in both study types (OR, 1.90; 95% CI, 1.52–2.37; $p < 0.01$). The meta-regression analysis showed no correlation between antithrombin dosage and mortality.

Conclusion: A meta-analysis of RCTs confirmed no survival benefit of antithrombin, whereas that of observational studies, which mostly focused on septic DIC, showed a significant beneficial effect on improving outcomes. Indications of antithrombin should be considered based on its beneficial and harmful effects.

KEYWORDS
antithrombin, bleeding complications, disseminated intravascular coagulation, meta-analysis, sepsis

INTRODUCTION

Sepsis is a common acute illness that is responsible for one in five deaths worldwide and is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] Coagulation disorder is among the major organ dysfunctions related to sepsis and can cause further organ dysfunction, leading to multiple organ dysfunction syndrome and poor outcomes.[2] A large European database study reported that patients with sepsis and multiple organ failure, including coagulopathy, had poorer outcomes than those of patients without coagulopathy.[3] Accordingly, given the importance of treating coagulopathy in patients with sepsis, there have been numerous randomized controlled trials (RCTs) on the efficacy of anticoagulants, including antithrombin.

However, none of these studies found that anticoagulant therapy improved mortality in patients with sepsis.[4] Currently, the Surviving Sepsis Campaign Guidelines for the Management of Sepsis and Septic Shock (SSCG) 2021 do not mention coagulopathy.[5] However, as management strategies continue to evolve to improve sepsis outcomes, adjunctive anticoagulation treatment should be included in subsequent international guidelines.[6]

From the perspective of thrombosis and hemostasis, sepsis-related blood coagulation disorders are considered an important pathological concept. Disseminated intravascular coagulation (DIC) presents not only as coagulation activation but also as an impairment of anticoagulation and fibrinolytic suppression, which result in organ dysfunction due to microvascular thrombosis.[7] Large observational studies from Japan have indicated that the development of DIC is a poor prognostic factor in patients with sepsis, who present greater than twice the mortality rate of those without DIC.[8] Furthermore, the Japanese Association for Acute Medicine conducted an RCT on the effects of moderate antithrombin doses in patients with septic DIC. This study revealed that antithrombin treatment significantly decreased DIC scores and improved the rate of recovery from DIC. However, it did not show survival benefits, which could be attributed to the small sample size.[9] Contrastingly, a subgroup analysis of the KyberSept trial, which failed to identify a survival benefit of high-dose antithrombin, demonstrated the efficacy of antithrombin in patients with septic DIC who were treated without concomitant heparin.[10] Furthermore, Wiedermann et al. published a systematic review that revealed that antithrombin administration improves patient outcomes by targeting septic DIC.[11] Taken together, there have been inconsistent reports regarding the effects of antithrombin on sepsis pathology; further, its effectiveness remains unclear. Furthermore, there are limited studies on the appropriate dose of antithrombin for patients with sepsis[12,13]; accordingly, the appropriate antithrombin dosage should be properly evaluated.

Since there have been recently no new RCTs in this area, this study aimed to conduct a meta-analysis, which also included observational studies, in order to reconfirm the results; further, we aimed to evaluate dosage through meta-regression analysis. Taken together, this systematic review and meta-analysis aimed to investigate the efficacy of antithrombin administration in patients with sepsis and the differences in efficacy among different antithrombin doses.

MATERIALS AND METHODS

Protocol and registration

Before conducting the review, we developed a protocol that was registered with the University Hospital Medical Information Network (registration number: UMIN000049492).

Search strategy

The databases used in the literature search included MEDLINE (source, PubMed, 1966 to January 2023), the Cochrane Central Register of Controlled Trials (through January 2023), Scopus (1788 to January 2023), and the ICHUSHI Web (1983 to January 2023). ICHUSHI is the Japanese database for medical journals published by the Japan Medical Abstract Society. It is the largest database for medical articles in Japan, with a collection of ≈7800 journals and >15 million references. Therefore, non-English articles were included in the analysis. Table S1 provides details of the search formula.

Study selection and inclusion criteria

Three independent reviewers (T.T., Y.M., and T.W.) screened the abstracts and titles of the studies and subsequently reviewed the full-text articles for inclusion. The inclusion criteria for the trials were as follows:

Study types: RCTs and observational studies
Population/patients: Adult patients (age ≥18 years) with sepsis
Intervention: Intravenous antithrombin administration
Control: Placebo or no intervention
Outcomes: At least one of the following outcome measures: 28-day, 30-day, or 90-day all-cause mortality; intensive care unit stay; or in-hospital mortality.

Risk of bias in individual studies

Two independent reviewers (T.T. and T.W.) assessed the risk of bias in individual studies to determine the methodological quality of the articles, with disagreements being resolved through discussion and consensus. Uniform criteria were applied to evaluate the risk of bias associated with individual RCTs based on the revised Cochrane risk of bias tool for randomized trials (RoB2). We also applied the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool to assess the risk of bias in observational studies.

Data extraction

Three independent reviewers (T.T., Y.M., and T.W.) extracted study data using a standardized data extraction sheet, with disagreements being resolved through discussion and consensus. If multiple publications by the same investigator were found, the studies were reviewed carefully, or the investigator was contacted to ensure that no data were analyzed in duplicate. We identified the primary author's name, year of publication, inclusion and exclusion criteria, patient

population, antithrombin dose and duration, and follow-up duration. Only observational studies that included results obtained after adjusting for potential confounding factors were considered eligible.

The primary outcome measure was all-cause mortality; the secondary outcome was serious bleeding complications, which is a critical outcome for patients. Bleeding complications were defined as intracranial hemorrhage or the need for therapeutic intervention, including blood transfusions.[9,14-16]

Statistical analysis and data synthesis

We reviewed the data from all eligible studies and, if possible, synthesized and analyzed the data using a random-effects model given the expected among-study differences in the participants and antithrombin doses. For the primary outcome, we identified the number of participants in each trial arm and the number of events, when appropriate. Moreover, we expressed the odds ratios (OR) with 95% confidence intervals (CI) for the risk measures of the antithrombin group compared with those of the control group. We separately synthesized the findings of RCTs and observational studies and used the I^2 statistic to measure the among-study heterogeneity in each analysis. Substantial heterogeneity was defined as an I^2 value of >50%.

The effect estimates (OR) were plotted according to the antithrombin dose in each study to analyze the relationship between antithrombin dose and mortality. The influence of the daily or total antithrombin dose on the treatment period was evaluated. If a specific dose was not reported, including the dose per kg body weight, we estimated the average dose based on the standard body weight. Moreover, we generated funnel plots to explore possible small-study biases for the primary outcomes. We also evaluated the reporting bias by checking the study protocols when they were identifiable from the search trial registries. All statistical analyses were performed using Review Manager Version 5.3. and R version 4.2.3. Differences with p-values <0.05 were considered statistically significant.

RESULTS

Literature search

A PRISMA flowchart of study selection for the systematic review is shown in Figure 1. We identified 13 articles (seven RCTs and six observational studies) in our systematic review.[9,14,16-26] Table 1 summarizes the characteristics of the included studies. Among the included studies, five were conducted in Japan, and their antithrombin doses ranged from 1500 to 3000 units/day, which was low compared with those reported in other studies. Except in one study,[14] antithrombin was administered for 3–5 days. The control group consisted of patients treated without antithrombin; in some RCTs,[14,18-20] the control patients received a placebo at the same volume as that of antithrombin.

Risk of bias within studies

The risk of bias assessment of the RCTs using RoB2 is shown in Figure 2A. Due to unblinded intervention, only one trial was judged to be at a high risk of bias on D2. All domains were determined to have some concerns of bias; however, the others were judged to have a low risk of bias, yielding a judgment of low overall risk of bias.

The risk of bias assessment of the observational studies that were conducted using ROBINS-I is shown in Figure 2B. Due to confounding factors, three studies that appeared to involve insufficient adjustment were assessed as having a high risk of bias. For selection bias, the risk was classified as moderate or high, except in one study considered unaffected by participant limitations. Due to subtle differences in patients in each group or differences in antithrombin dosage, not all studies were free from bias due to deviations from the intended intervention; accordingly, they were judged to have greater than moderate bias.

Mortality

The results of the analysis of the seven RCTs (2647 patients) are shown in Figure 3A. The mortality rates did not significantly differ between the antithrombin and control groups (OR, 0.88; 95% CI, 0.67–1.16; $p = 0.36$). Heterogeneity was not observed ($I^2 = 6\%$); additionally, there was no evidence of publication bias based on visual assessments of funnel plots (Table S1).

Moreover, we evaluated the effects of antithrombin administration on mortality using a meta-analysis of the observational studies. Five of the six observational studies described the number of events in the adjusted analysis of the original study,[16,17,23-25] while the remaining one described only the hazard ratios.[26] Therefore, the results of Ebina et al., which were expressed as hazard ratios (Figure S2), could not be included in the meta-analysis since there were no other studies that could be integrated; accordingly, this study was only included in the systematic review. An analysis of observational studies revealed a trend toward decreased mortality in the antithrombin group (OR, 0.79; 95% CI, 0.68–0.92; $p = 0.002$) (Figure 3B). The observational studies revealed no heterogeneity ($I^2 = 28\%$) (Figure 3B); additionally, no obvious heterogeneity was observed on the funnel plot (Figure S1).

Bleeding

Studies that described the number of bleeding complications in the adjusted patient groups were used to analyze bleeding complications. Consequently, three RCTs were included in this analysis.[9,14,18] Only one observational study specified

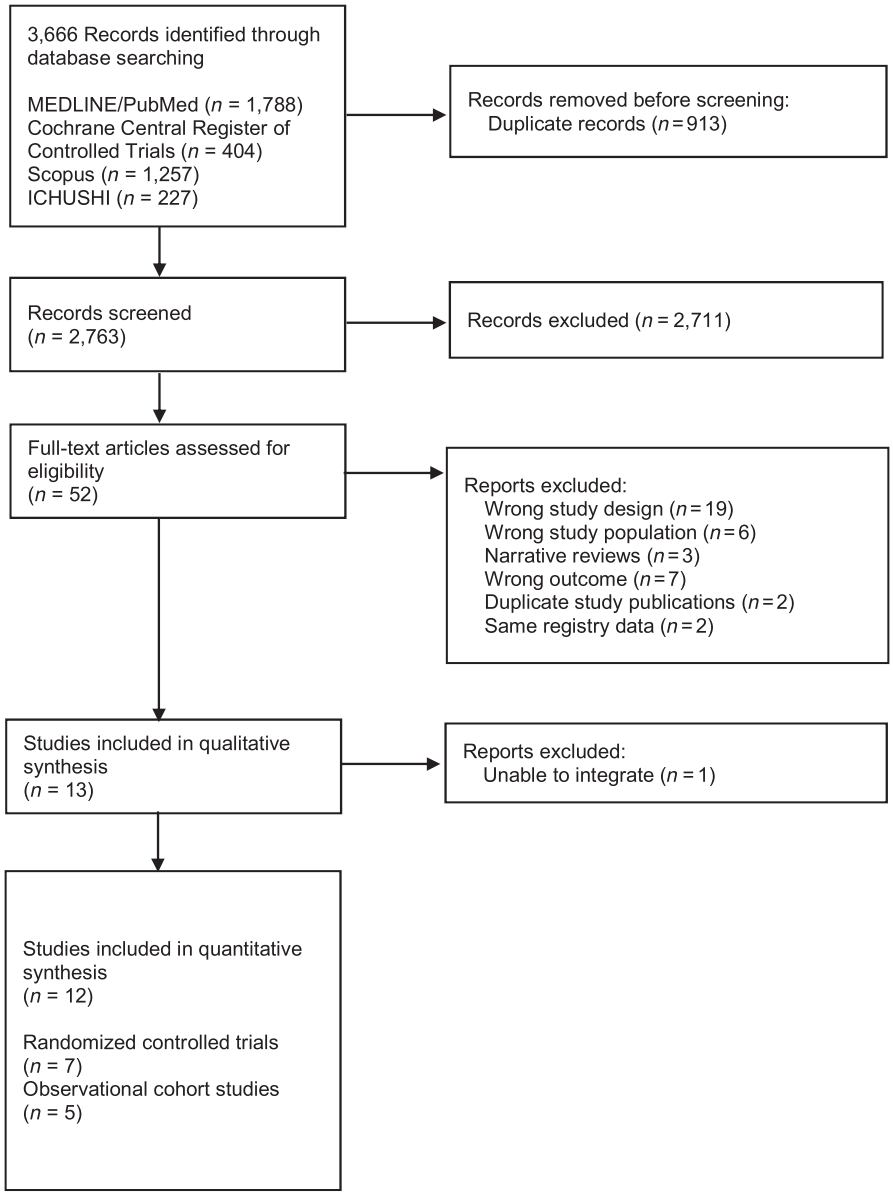

FIGURE 1 PRISMA chart. Identification and selection of studies for inclusion.

hemorrhagic complications[16]; accordingly, we could not perform a meta-analysis of observational studies with respect to hemorrhagic complications. There were significantly more hemorrhagic complications in the antithrombin group than in the control group (OR, 1.90; 95% CI, 1.52–2.37; $p < 0.01$) (Figure 4).

Effect of antithrombin dosage on mortality

The impact of the daily dose of antithrombin or the total antithrombin dose for the treatment period on the effect of antithrombin on mortality was evaluated using a meta-regression analysis for each RCT and observational study (Figure 5). Consistent with this observation, the meta-regression analysis for RCTs revealed no correlation of the daily or total antithrombin dose with mortality (p-values 0.22 and 0.06, respectively) (Figure 5A,C). Furthermore, in observational studies, there was no correlation between daily antithrombin dose and mortality ($p = 0.43$) (Figure 5B,D).

DISCUSSION

In the present systematic review, a meta-analysis was performed on seven RCTs and five observational studies that evaluated the efficacy of antithrombin in patients with sepsis. Most patients in the RCTs and observational studies had severe sepsis and septic DIC, respectively. Although the RCTs did not reveal survival benefits of antithrombin, the results from observational studies revealed a trend toward improved survival in the antithrombin group. Bleeding complications were more prevalent in the antithrombin group than in the control group; additionally, meta-regression analysis of the

TABLE 1 Characteristics of included studies.

Source	Study venue	Population	Sample size, *n*			Mean age (yrs)	Intervention		Control	Mortality measures
			Total	AT	Control		AT			
							Loading	Maintain		
Randomized controlled trials										
Gando S 2013[5]	Japan	Septic DIC	60	30	30	70		30 IU/kg/day	Without AT	28 days
Warren BL 2001[13]	Multinational	Severe sepsis	2314	1157	1157	58	6000 U	6000 IU/day	Placebo	28 days
Fourrier F 1993[17]	France	Septic DIC	32	14	18	52	90–120 IU/kg	90–120 IU/Kg/day	Placebo	28 days
Baudo F 1998[18]	Italy	Sepsis	120	60	60	60	4000 IU	2000 IU/12 h	Placebo	30 days
Eisele B 1998[19]	Multinational	Severe sepsis	42	20	22	58	3000 IU	3000 IU/day	Placebo	30 days
Inthorn D 1997[20]	Germany	Severe sepsis	29	14	15	62	NA	Body weight (kg)* (120-AT(%))*1.25 IU/day	Without AT	90 days
Schorr M 2000[21]	Germany	Peritonitis	50	24	26	60	Body weight (kg)* (140-AT(%)) IU	200–800 IU/h	Without AT	90 days
Observational studies										
Hayakawa M 2016[15]	Japan	Septic DIC	922	461	461	70	NA	1500 IU/day	Without AT	Overall
Tagami T 2014[16]	Japan	DIC due to severe pneumonia	4388	2194	2194	74	NA	1500 IU/day	Without AT	28 days
Moubarak P 2008[22]	Germany	Severe sepsis				NA	NA	Body weight (kg)* (120-AT(%))* 1.25 IU/12 h	Without AT	28 days
Kim Y 2019[23]	Korea	Septic DIC	68	34	34	NA	30 IU/kg	3000 IU/day	Without AT	28 days
Tagami T 2015[24]	Japan	Septic DIC due to peritonitis	1036	518	518	NA	NA	1500–3000 IU/day	Without AT	28 days
Ebina M 2019[25]	Japan	Sepsis with thrombocytopenia	214	51	163	73	NA	1500 IU/day	Without AT	28 days

Abbreviations: AT, antithrombin; DIC, disseminated intravascular coagulation; IU, international unit.

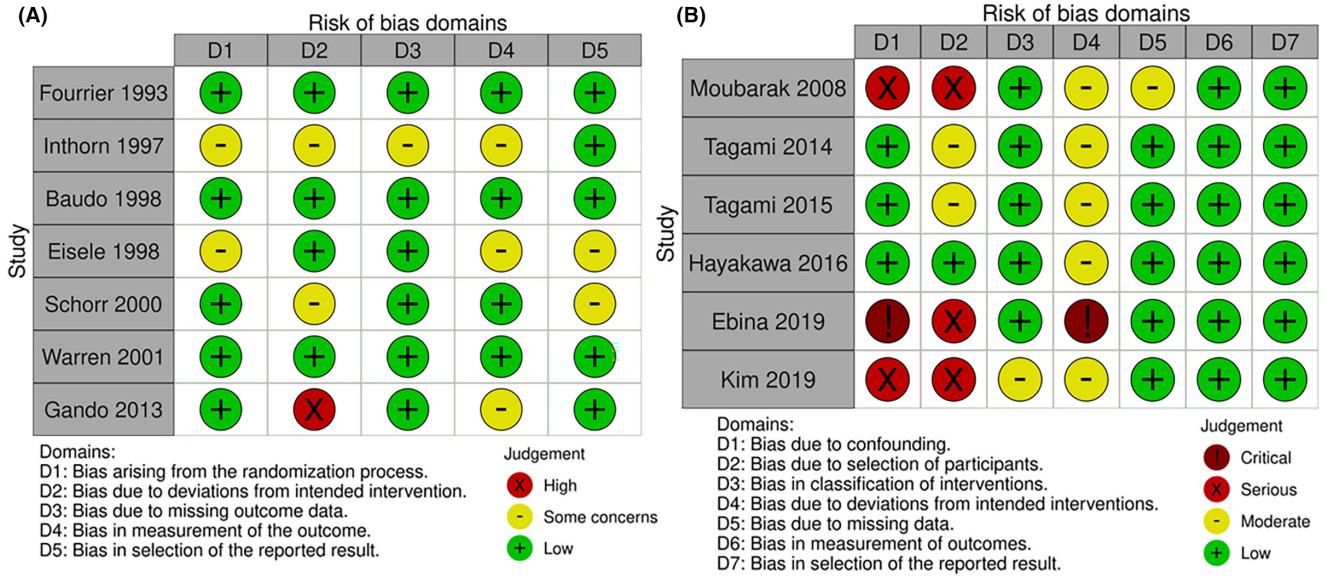

FIGURE 2 Risk of bias summary. A review of the authors' judgment about the risk of bias for each included study, based on the criteria recommended by the Cochrane risk-of-bias tool (RoB2) for randomized controlled trials (A) and risk of bias tool to assess nonrandomized studies of interventions (ROBINS-I) for observational studies (B).

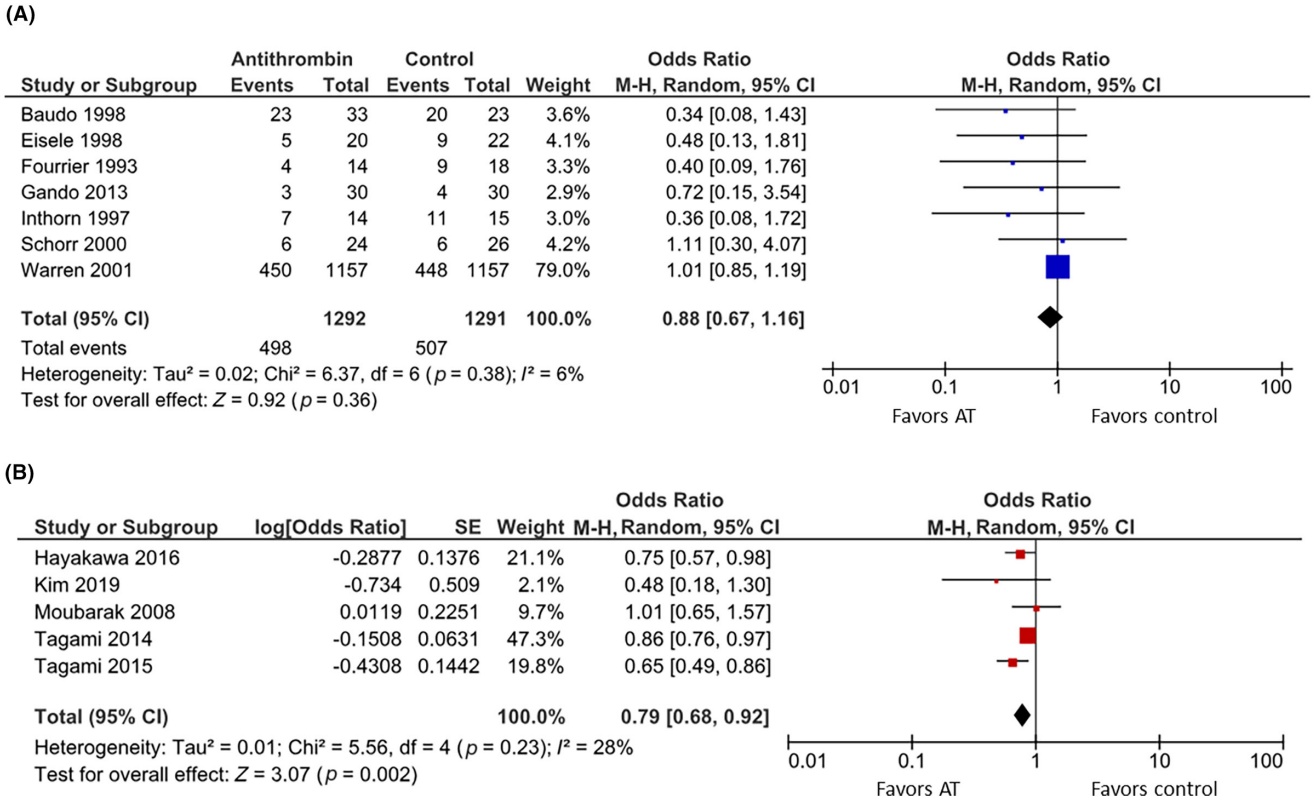

FIGURE 3 Forest plots comparing all-cause mortality in antithrombin versus no antithrombin patient populations. (A) Randomized controlled trials; (B) observational studies. AT, antithrombin; CI, confidence interval; M–H, Mantel–Haenszel; SE, standard error.

relationship between antithrombin dosage and mortality revealed no significant correlations.

While a large RCT found no benefit of antithrombin administration in patients with sepsis,[14] a secondary analysis of this RCT that focused on septic DIC confirmed the efficacy of antithrombin.[10] A meta-analysis found that anticoagulation therapy, including antithrombin, is more effective in patients with septic DIC than in the overall population of patients with sepsis.[27] Based on this evidence, the DIC working group of the Japanese Clinical Practice Guidelines

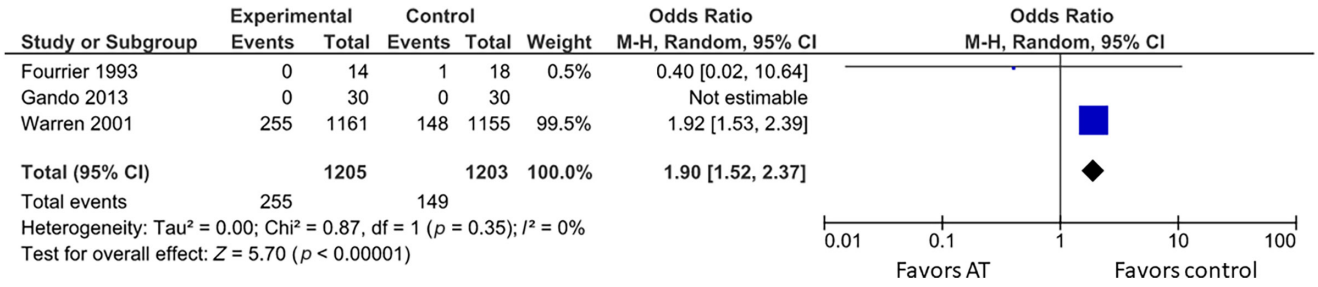

FIGURE 4 Forest plot of the comparison of bleeding in antithrombin versus no antithrombin patient populations. AT, antithrombin; CI, confidence interval; M–H, Mantel–Haenszel.

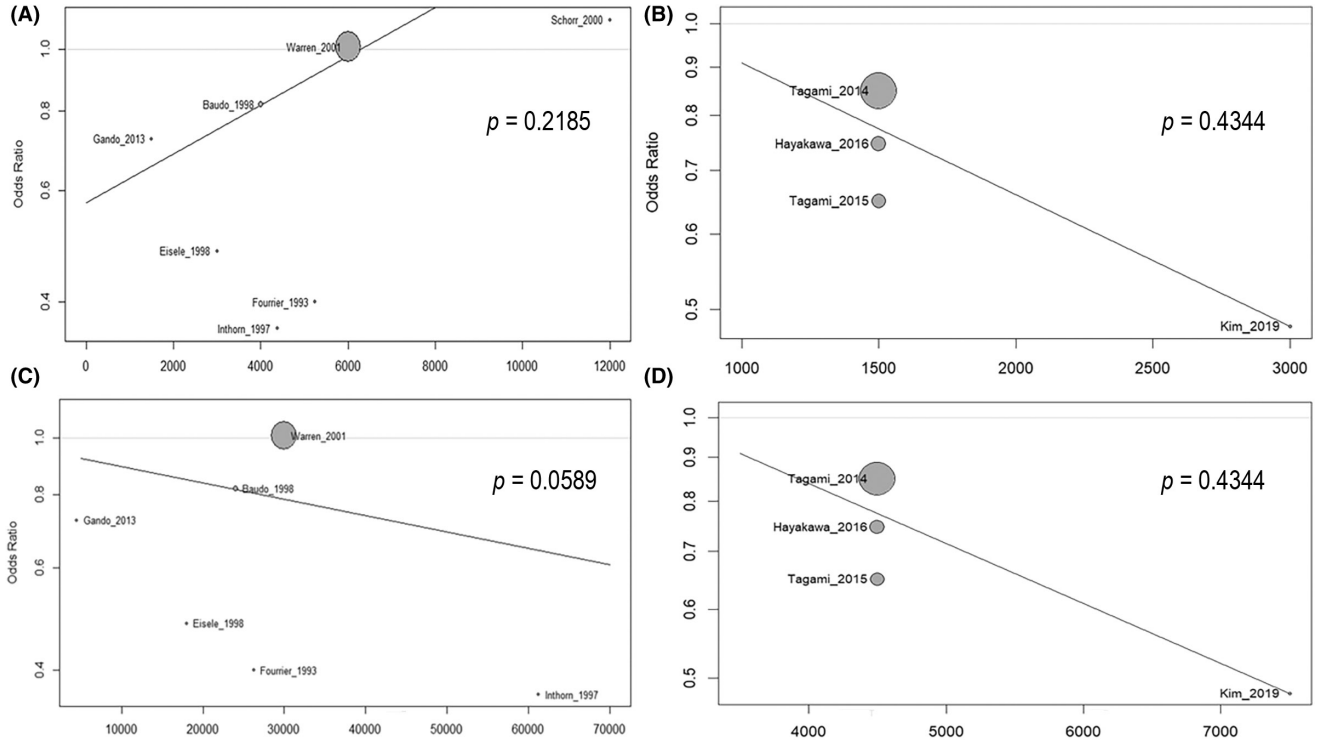

FIGURE 5 Results of a meta-regression analysis on antithrombin dosage. (A) Randomized controlled trials (daily dosage); (B) observational studies (daily dosage); (C) randomized controlled trials (total dosage for treatment period); (D) observational studies (total dosage for treatment period).

for Management of Sepsis and Septic Shock 2020 (J-SSCG 2020) conducted meta-analyses on RCTs that included patients with sepsis and DIC. The J-SSCG 2020 results suggested that antithrombin administration provides a viable therapeutic intervention.[28] Most observational studies in the present meta-analysis originated in Japan and mainly included patients with septic DIC as the target patient population (Table 1). However, the included RCTs rarely included patients with septic DIC. Overall, our findings, in which the effect of antithrombin on mortality was observed only in observational studies, are consistent with the findings of previous studies.

Regarding bleeding complications, the RCT and observational study results revealed a significant increase in bleeding complications in the antithrombin group (Figure 4), which is consistent with previous findings.[10] Contrastingly, a previous meta-analysis indicated that anticoagulant therapy, including antithrombin, had a relatively low risk of complications in patients with sepsis-induced DIC than in the overall population of patients with sepsis.[27] Given that the KyberSept trial, which contributed significantly to our findings, indicated an increase in the risk of bleeding complications with the combination of heparin and antithrombin, it is important to consider bias in individual studies when interpreting our results. Moreover, bleeding complications range in severity from minor to life-threatening bleeding. Consequently, the decision to initiate anticoagulation therapy in patients with sepsis depends on a balance between efficacy and safety. According to our analysis, anticoagulation was associated with a risk of hemorrhagic complications; however, a previous study revealed that the risk of severe bleeding associated with antithrombin administration in

patients with septic DIC was <2%, which was probably an acceptably low risk of bleeding.[13] The benefits of antithrombin outweigh the risks in some patient populations, including patients with severe diseases such as DIC.

The antithrombin doses administered to patients with sepsis varied widely among studies (Table 1), and several studies have been conducted to determine the optimal antithrombin dose.[11,12] These studies compared low-dose (1500 units/day) and high-dose (3000 units/day) antithrombin, which covers the range available for use under Japanese insurance. These studies revealed a higher DIC recovery rate in the high-dose group than in the low-dose group without an increased risk of bleeding. Notably, antithrombin activity in the high-dose group (3000 units/day) increased to >100% after 3 days of administration, while the low-dose group (1500 units/day) did not exhibit normal antithrombin activity (>80%) at any time point during the study period.[11] However, our meta-regression results revealed no significant relationship between antithrombin dose and survival (Figure 5). Thus, the optimal antithrombin dosage for patients with septic DIC eligible for antithrombin administration remains unclear; therefore, future studies are warranted. Currently, when administering antithrombin, the dose should be determined individually with reference to multiple factors, including the dose approved by health insurance and antithrombin activity before administration.

Limitations

This study has several limitations. First, since patients with sepsis in the included studies were diagnosed based on previous diagnostic criteria for sepsis (Sepsis-1 or Sepsis-2), our findings may not be fully applicable to patients diagnosed according to the current sepsis diagnostic criteria, Sepsis-3. Second, most of the observational studies included in this meta-analysis were conducted in Japan, and the results may not be generalizable to Western populations. Third, this meta-analysis did not evaluate detailed data on treatment (e.g., time from sepsis diagnosis to initiation of treatment) since many studies had insufficient data. Additionally, the antithrombin dosage was calculated based on the data in the original paper; however, this was not necessarily accurate because we could not obtain raw data on body weight and antithrombin activity levels. Fourth, cohort studies cannot adjust for confounding variables, and retrospective designs must be cautiously interpreted, with attention to cohort and exposure definitions. Indeed, many of the included observational studies had serious confounding and selection biases (Figure 2B).

CONCLUSION

A meta-analysis on RCTs targeting patients with sepsis showed no survival benefit of antithrombin, while that of observational studies, which mostly focused on septic DIC, demonstrated a significant beneficial effect on improving outcomes. Although antithrombin administration can increase the risk of hemorrhagic complications, its indications may need to be considered based on the relative value of the beneficial and harmful effects. Further, the optimal dosage could not be determined in the present study and remains unknown. To clarify the effect of antithrombin on sepsis pathology, it is desirable to conduct large-scale studies to verify the characteristics of the optimal patient population who benefit from this treatment as well as the optimal dosage, duration of administration, and target activity levels.

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CONFLICT OF INTEREST STATEMENT

T.W. received honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from Asahi Kasei Pharma and Japan Blood Products Organization. K.Y. reported receiving a research grant from Japan Blood Products Organization. T.I received a grant from JIMRO, a consulting fee from Japan Blood Products Organization, and honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from Asahi Kasei Pharma and Toray Medical. The other authors declare no conflict of interests for this article. T.I. is an Editorial Board member of AMS Journal and a co-author of this article. To minimize bias, they were excluded from all editorial decision-making related to the acceptance of this article for publication.

DATA AVAILABILITY STATEMENT

The corresponding authors will disclose additional data upon reasonable request.

ETHICS STATEMENT

Approval of the research protocol: Not applicable.
Informed consent: Not applicable.
Registry and the registration no. of the study/trial: Not applicable.
Animal studies: Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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