Introduction

From the late 1990s through the early 2000s, three mega-scale phase III clinical trials were performed to examine the efficacy of naturally occurring anticoagulants for severe sepsis. Recombinant human activated protein C (rhAPC) became the first drug approved by the Food and Drug Administration (FDA), after the success of PROWESS in November 2001. In contrast, KyberSept and OPTIMIST failed to demonstrate survival benefits of antithrombin and recombinant tissue factor pathway inhibitor (rTFPI), respectively. However, several post hoc analyses reported the potential benefits of antithrombin. In addition, from additional analysis, important hints were obtained regarding the potential usefulness of anticoagulant therapies. Extensive research has been continuously conducted on rhAPC, and the appropriate target and timing of therapy have been determined. Since each of the trials enrolled more than hundreds of subjects and was well performed, it is useful to summarize the findings thus far obtained as they impact current treatment strategy and future trials for severe sepsis.

1) rhAPC is effective in treating severe sepsis

The efficacy of rhAPC was first confirmed in PROWESS in 2001, and reconfirmed by another large-scale clinical trial, ENHANCE. ENHANCE was a single-arm, open-label trial of rhAPC treatment in patients with severe sepsis. Surprisingly, the mortality in ENHANCE was 25.3%, and very close to the rate observed for patients in PROWESS (24.7%). Furthermore, as shown by the Kaplan-Meier curves of Fig. 1, the pattern of survival was essentially identical for ENHANCE patients and rhAPC-treated patients in PROWESS. Both curves were higher than that for placebo in PROWESS. Since more than 2300 subjects were enrolled in ENHANCE and the efficacy of rhAPC was reconfirmed in it, we believe that the clinical advantages of rhAPC for severe sepsis have been clearly demonstrated.

With regard to rTFPI, the efficacy is still controversial. Although OPTIMIST failed to reveal...
改善は生存率に20%の相対的減少、28日の原因不明の死亡率の20%の相対的減少が観察されました。治療群とプラセボ群の間で比較したII期試験6)。肺器機能障害スコアと重症心臓・循環・凝固スコアの改善が観察されました。抗凝固酵素の使用により、DICが誘起される①-④。第2段階の研究では、DICの予後因子としての低抗凝固酵素レベルが示唆される11)-12)。第3段階の研究では、DICと敗血症の患者に対して、DICの持続時間を短縮する効果が確認された13)-14)。現在では、DICに対して抗凝固酵素の使用を推奨している。

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risk of death. They also performed an analysis of clinical trials and showed that these agents when used in sepsis trials were also significantly more efficacious in septic patients with higher risk of death and were harmful to those with low risk of death.

In the post hoc analysis of PROWESS, since a beneficial effect on survival had not been observed in less severe cases (i.e. Acute Physiology and Chronic Health Evaluation (APACHE II) score <25), the Food and Drug Administration (FDA) required an additional study to evaluate the efficacy of rhAPC for patients who had severe sepsis and a low risk of death. ADDRESS²⁴ was a double-blind, placebo-controlled, multicenter trial in which adult patients with severe sepsis and a low risk of death (APACHE II < 25 or single organ failure) were randomly assigned to receive intravenous infusion of placebo or rhAPC. The prospectively defined primary endpoint was 28-day mortality after the start of infusion in this study. In-hospital mortality within 90 days after the start of infusion was also measured. Enrollment in the trial was terminated early because of a low likelihood of meeting the prospectively defined objective of demonstrating a significant reduction in 28-day mortality rate with rhAPC. The study enrolled 2640 patients, and in it no significant differences were observed between the placebo group and the rhAPC-treated group in 28-day mortality (17.0% in the placebo group vs. 18.5% in the rhAPC group; \( p = 0.34 \),

### Table 1 Summary of phase II trials using antithrombin in cases of severe sepsis

<table>
<thead>
<tr>
<th>Author</th>
<th>Basal disease</th>
<th>AT No</th>
<th>Control No</th>
<th>Mortality in AT group</th>
<th>Mortality in Control</th>
<th>Treatment in AT group</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinazzer H²⁶</td>
<td>Shock and DIC</td>
<td>84</td>
<td>49</td>
<td>14%</td>
<td>30%</td>
<td>Loading: 1000 IU maintenance: 500 IU after 24 and 48 hours</td>
<td>Decrease in mortality in AT group (( p = 0.04 ))</td>
</tr>
<tr>
<td>Dzinic L²⁷</td>
<td>Severe diseases and trauma</td>
<td>20</td>
<td>12</td>
<td>45%</td>
<td>66.7%</td>
<td>-</td>
<td>Trend of improvement in DIC in AT group</td>
</tr>
<tr>
<td>Albert</td>
<td>Surgery trauma, infection</td>
<td>16</td>
<td>16</td>
<td>25%</td>
<td>31.3%</td>
<td>(100-AT concentration (%)) ( \times ) body weight (kg)</td>
<td>Rapid normalization in PT, CRP in AT group</td>
</tr>
<tr>
<td>Fourrier F²⁰</td>
<td>Septic shock with DIC</td>
<td>17</td>
<td>18</td>
<td>28%</td>
<td>50%</td>
<td>Loading: 90 to 120 IU/kg maintenance: 90 to 120 IU/kg/day ( \times ) 4 days</td>
<td>Shortening of DIC length in AT group, 44% reduction in 28-day mortality (NS)</td>
</tr>
<tr>
<td>Waydhas C²⁰</td>
<td>Severe injury</td>
<td>20</td>
<td>20</td>
<td>15%</td>
<td>5%</td>
<td>Total 20000 IU over 4 days</td>
<td>Shortening the duration of organ failure in AT group, survival benefit: NS</td>
</tr>
<tr>
<td>Baudo F²²</td>
<td>Sepsis and/or postsurgical complications</td>
<td>60</td>
<td>60</td>
<td>50%</td>
<td>54%</td>
<td>Total 24000 IU over 5 days</td>
<td>30 days mortality in total: NS, 30% reduction in shock patients (( p &lt; 0.05 ))</td>
</tr>
<tr>
<td>Eisele B²²</td>
<td>Severe sepsis</td>
<td>20</td>
<td>22</td>
<td>25%</td>
<td>41%</td>
<td>Loading: 3000 IU maintenance: 3000 IU/day ( \times ) 5 days</td>
<td>39% reduction in mortality in AT group (NS)</td>
</tr>
<tr>
<td>Hoffmann JN²⁴</td>
<td>Severe sepsis</td>
<td>20</td>
<td>20</td>
<td>30%</td>
<td>25%</td>
<td>AT substitution aimed at a plasma AT activity &gt;1200% ( \times ) 14 days</td>
<td>Increased PT (( p &lt; 0.01 )) and fibrinogen level (( p &lt; 0.01 )) in AT group</td>
</tr>
</tbody>
</table>
risk ratio (RR): 1.08, 95% confidence interval (CI): 0.92–1.28 (Fig. 2) or 90-day mortality. Since ADDRESS confirmed the findings of post hoc analysis in PROWESS, it can be concluded that rhAPC has survival benefit only for patients with high risk of death.

In the case of antithrombin, although beneficial effects were not recognized in KyberSept analysis (total 2314 cases, mortality rate 38.9% in antithrombin-treated group vs. 38.7% in placebo group), subgroup analysis revealed a trend toward efficacy in patients with very high risk of death\(^2\). Wiedermann et al.\(^{25}\) studied 1,008 patients (43.6% of the overall intention-to-treat population of KyberSept) with a predicted mortality rate of 30–60% at study entry as determined by Simplified Acute Physiology Score II. In Kaplan-Meier analysis, survival rate when followed up for 90 days after admission was increased in the high-dose antithrombin group compared with the placebo group (p = 0.04) (Fig. 3, left). If heparin was avoided during the 4-day treatment phase with high-dose antithrombin (n = 140) or placebo (n = 162), treatment effect appeared to be even more pronounced, with 28-day mortality rates of 35.7% vs. 44.4% (RR: 0.804, 95% CI: 0.607–1.064) and 90-day mortality rates of 42.8%...
vs. 55.1% (RR: 0.776, 95% CI: 0.614–0.986) (Fig. 3, right). These findings suggest that antithrombin may be beneficial if severity of sepsis is within a certain range.

With regard to rTFPI, the results obtained were confusing. Despite the accumulation of preclinical data, there have been only two clinical sepsis trials published with use of this agent, leaving the relationship between the effect of rTFPI and risk of death unclear. However, among the limited data available, phase II data indicate that higher baseline international normalized ratios (INR) is associated with more beneficial effects of rTFPI. In contrast, data from the OPTIMIST study suggest the reverse trend.

III) Early initiation of rhAPC therapy is more effective

In ENHANCE, patients 0-24 hrs from first sepsis-induced organ dysfunction had a lower observed mortality rate than those treated after 24 hrs (22.9% vs. 27.4%, \( p = 0.01 \)) (Fig. 4). This suggests that earlier treatment with rhAPC is associated with increased survival, so that early initiation of treatment should be recommended. In ENHANCE, the inclusion criteria were modified from those used as criteria for severe sepsis, i.e. three inclusion criteria were required: a) known or suspected infection; b) the meeting of at least three of the four criteria defining systemic inflammatory response syndrome (SIRS); and c) existence of one or more sepsis-induced organ dysfunction (cardiovascular, respiratory, renal, hematologic, metabolic acidosis). The patients were included if they met the entry criteria, and infusion was begun within 48 hrs of entry. Based on the results of ENHANCE, initiation of rhAPC therapy within 24 hrs of the time a patient has met the above criteria can be recommended.

No such analysis was performed in phase II or III trials with respect to antithrombin. However, the timing of initiation of treatment was carefully regulated in KyberSept, and subjects received either placebo or antithrombin within 24 hrs (plus another 2 hrs to obtain informed consent, etc.) once they had met the inclusion criteria.

It is generally accepted that patients treated earlier have less severe sepsis than those treated later. However, late stage does not always indicate severe sepsis. When we consider the application of the treatment, both the effect of time to treatment and the severity to treatment effect must be considered. That means we must identify the appropriate patients who will complicate very severe sepsis but still in the very early stage. Since anticoagulant therapy has significant adverse effects, it is important to determine those patients who can benefit from the treatment and perform it early. Early treatment of patients with high risk of death is of key importance, though
it must be noted that patients treated within the first 24 hrs exhibited a lower mortality rate than those treated after the first 24 hrs regardless of disease severity in ENHANCE.

With respect to bleeding events and timing of treatment, it was found in ENHANCE that even though disease severity and mortality were greater in patients treated later, no differences of the bleeding incidence were observed between patients treated early or late.

**IV) rhAPC and antithrombin are more efficacious for patients with DIC**

The effect of rhAPC was clearer in the group with DIC. An FDA clinical review\textsuperscript{27} reported that rhAPC appeared to have a treatment effect in patients with DIC and no effect in those without DIC. However, since the diagnostic criteria in PROWESS were not standard, Dhainaut et al.\textsuperscript{28} evaluated the effects of rhAPC using the diagnostic criteria proposed by the International Society on Thrombosis and Haemostasis (ISTH). rhAPC-treated patients with DIC tended to have greater reduction in relative risk of mortality than patients not treated with rhAPC (29\% vs. 18\%, \(p = 0.261\)), while rates of serious bleeding during rhAPC infusion were slightly increased (\(p = 0.498\)) compared with placebo.

Proof of reduced mortality from DIC with administration of antithrombin in prospective controlled clinical studies has not yet been reported. However, Kienast et al.\textsuperscript{29} analyzed the data of KyberSept and reported a treatment effect of high-dose antithrombin without concomitant heparin. Fig. 5 shows all-cause mortality of patients with severe sepsis and DIC. In DIC patients, Kaplan-Meier survival functions until day 90 showed better survival with high-dose antithrombin treatment compared to placebo, while no effect of antithrombin on survival was seen in patients without DIC.

**Fig. 5  Effects of high-dose antithrombin on survival in patients with severe sepsis with or without DIC**

The subgroup analysis of KyberSept demonstrated the efficacy of high-dose antithrombin in decreasing mortality in patients with DIC. The Kaplan-Meier survival curve until day 90 showed better survival with high-dose antithrombin treatment compared to placebo, while no effect of antithrombin on survival was seen in patients without DIC.
Although the efficacy of rTFPI has not been compared in patients with and without DIC, it appears to differ between patients with low and those with high INR. In OPTIMIST, overall 28-day all-cause placebo mortality was 22.9%, compared with 12.0% for patients receiving rTFPI ($p = 0.051$) among those with INR $< 1.2$. While the beneficial trend was not observed in patients with INR is more than 1.2. This finding is curious since the effect of rTFPI is considered to be demonstrated through the suppression of activated coagulation system. It was reported in the same study that rTFPI treatment was associated with improvement of coagulation markers, such as lower prothrombin fragment 1.2 and thrombin antithrombin complex levels at 24 and 96 hrs after initiation of treatment ($p < 0.001$).

V) Concomitant use of heparin abolish the effects of antithrombin and rTFPI

The anticoagulative properties of antithrombin have been investigated exhaustively, and this agent is known to inhibit serine proteases. Since the late 1980s, additional results from several laboratories have shown that antithrombin also has strong anti-inflammatory effects that are independent of its anticoagulative effects. These effects were first postulated by Taylor and coworkers $^{30,31}$ based on their experiments on DIC in a baboon model. Infusions of antithrombin significantly reduced mortality in baboons previously treated intravenously with lethal doses of Escherichia coli. The therapeutic effects on systemic blood pressure and organ failure, however, could not be explained on the basis of its direct effect on thrombin.

Recent studies have suggested that antithrombin directly affects inflammatory cell function by ligating antithrombin-binding glycosaminoglycans (GAGs), including members of the syndecan family of heparin sulfate proteoglycans (HSPGs). Syndecans are surface molecules in a variety of types of cells including leukocytes and endothelial cells that mediate homotypic cell-cell adhesion and are involved in proliferation, migration, and differentiation. Heparins are known to prevent antithrombin from binding to syndecans $^{32}$. If the heparin binding capacity of circulating antithrombin is not blocked or exhausted by soluble heparin or by HSPG detached from the endothelium, deposition of antithrombin on surface heparins of the endothelium can antagonize the activated thrombin also deposited at the same sites of the endothelium at sites of vascular injury $^{33}$. There is evidence that syndecan-4 mediates these direct effects of antithrombin, as one of the antithrombin receptors on endothelial cells $^{34-36}$.

In the setting of clinical trials, concomitant prophylactic use (for purposes of venous thromboembolism prophylaxis) of low-dose unfractionated or low-molecular-weight heparin was allowed in PROWESS, KyberSept, and OPTIMIST. In the latter two trials, even low-dose heparin appeared to affect results. The favorable tendency in the group without concomitant heparin in the clinical trials disappeared once heparin was administered. The 28-day mortality in the subjects receiving high-dose antithrombin without concomitant heparin was 37.8%, while that in subjects receiving placebo without concomitant heparin was 43.6% (RR : 0.86, 95% CI : 0.73–1.02). In contrast, the mortalities in subjects receiving antithrombin or placebo together with concomitant heparin were 39.4% and 36.6%, respectively (RR : 1.08, 95% CI: 0.96–1.22). Wiedermann et al. $^{25}$ analyzed the interaction between antithrombin and low-dose heparin in a subgroup with high risk of death. In this subgroup, 140 patients in the antithrombin-
treated group and 162 patients in the placebo group did not receive concomitant heparin. The treatment effect favoring the antithrombin group was stronger in this subgroup (Fig. 3).

TFPI is also known to interact with heparin. Its third Kunitz domain and C terminus bind heparin with low affinity. Thus, similar to antithrombin, heparin displaces TFPI from GAGs on the surface of endothelial cells. In OPTIMIST, the mortality of patients receiving rTFPI who did not receive heparin before or during administration was 34.6%, compared with 42.7% in the placebo group (p = 0.05). In contrast, the mortality of patients with high INR receiving rTFPI who received heparin under similar conditions was 34.0%, although the mortality rate in the placebo group was 29.8%.

VI) Anticoagulant therapy increases the incidence of bleeding

Even if they are naturally derived, the risk of hemorrhage was greater in patients treated with anticoagulants than in patients in the placebo control group. The magnitude of risk of bleeding was greatest in patients who received antithrombin, yet even the placebo in the antithrombin group appeared to have a significantly increased risk of hemorrhage.

Among adverse effects of treatment with rhAPC, ENHANCE patients experienced serious bleeding events compared with 2.4% and 1.0% in rhAPC- and placebo-treated patients, respectively, in PROWESS. Approximately 50% of serious bleeding events that occurred during the infusion period were considered procedure-related. During the postinfusion period, 3.2% of patients experienced a serious bleeding event, compared with 1.2% and 1.1% in rhAPC- and placebo treated patients, respectively, in PROWESS.

In ADDRESS, the rate of serious bleeding was greater in the rhAPC group than in the placebo group during both the infusion (2.4% vs. 1.2%, p = 0.02) and the 28-day study period (3.9% vs. 2.2%, p = 0.01). The absence of a beneficial treatment effect, coupled with the increased incidence of serious bleeding complications, indicates that rhAPC should not be used in patients with severe sepsis who are at low risk of death, such as those with single-organ failure or an APACHE II score less than 25.

In summary, treatment with anticoagulants is associated with a significant increase in rate of hemorrhagic adverse effects, making strict observance of contraindications and correct patient selection important.

VII) Concomitant use of heparin with antithrombin increases the risk of bleeding

Concomitant use of heparin increases the incidence of bleeding events with antithrombin but not with rhAPC or rTFPI. Concomitant heparin increased the rate of adverse events in KyberSept. In this trial, either unfractioned or low-molecular-weight heparin (≤10,000 IU/day) was permitted for prophylaxis of venous thrombosis, and the incidence of any bleeding in subjects enrolled in the treatment group increased from 17.8% without concomitant heparin to 23.8% with concomitant use of heparin, with major bleeding reported in 7.9% (RR: 1.71, 95%CI: 0.95–3.07) of antithrombin treated patients and an increase in incidence of major bleeding to 10.9% (RR: 1.77, 95%CI: 1.27–2.45) in patients treated with antithrombin with heparin. Thus, in addition to its potential abrogation of the anti-inflammatory effect of antithrombin, heparin might enhance bleeding tendency, and thereby diminish the beneficial effects of antithrombin.

In PROWESS, heparin was used to a maximum of 15,000 IU/day for prophylaxis. Among patients
who received rhAPC, the incidence of serious bleeding was similar for those who received rhAPC alone and those who also received heparin (3.7 percent and 3.5 percent).

The opposite trend was observed with rTFPI. The incidence of bleeding events in the treatment group was 23% with heparin and 28% without heparin in the high-risk group (INR ≥ 1.2). In addition, incidence of serious bleeding in high-risk patients was 6.0% with rTFPI vs. 7.0% with rTFPI with heparin.

VIII) The effectiveness of neither low-dose unfractioned heparin nor low-molecular-weight heparin has been confirmed

A number of smaller clinical studies have suggested that sepsis-related DIC is associated with high mortality, while attenuation of DIC may ameliorate organ dysfunction and possibly reduce mortality. Early studies used unfractioned heparin to prevent activation of coagulation and treatment of DIC, but did not reveal a significant benefit with regard to incidence of organ dysfunction or mortality.

Heparin binds to antithrombin and activates its
antithrombotic activity, and thereby dramatically reduces thrombin generation and fibrin formation. In contrast to providing anticoagulant substances, heparin takes advantage of the one existing molecule in its natural environment to increase its activity a thousand-fold\(^4\). Furthermore, animal and human models have suggested that heparin, in addition to successfully inhibiting the coagulation cascade in sepsis, may also modulate a wide array of responses to infection\(^4\)-\(^6\).

The three mega-clinical trials of anticoagulants each permitted the use of prophylactic treatment for venous thrombosis with doses of heparin up to 10,000 or 15,000 units subcutaneously per day. Although administration of heparin was not randomly performed, when those who did receive heparin were compared to those who did not in the placebo arms of the clinical trials, all three studies revealed higher mortality in the subgroups that did not receive heparin (Table 2). This observation suggests that anticoagulation itself might have protective effects in severe sepsis. Nevertheless, these observations should be interpreted with caution, since patients were not randomized for heparin administration, and heparin might thus have been used more frequently in less severely ill patients. Eventually, patients in the placebo group who received heparin had a much lower rate of mortality than those who did not (36.6% and 43.6%, respectively, in KyberSept). Similarly, in OPTIMIST, the patients who received heparin were not as severely ill, as determined by APACHE II scores, INR value, and mean organ dysfunction score, as those who did not receive it. Furthermore, in ADDRESS, the rate of mortality of placebo patients was almost the same (16.9% with heparin vs. 17.3% without heparin, \(p = 0.91\)).

As noted in a recent editorial in JAMA\(^4\), heparin is the most widely available, least expensive, and most frequently used anticoagulant. Despite the common recommendation of continuous infusion of low doses (300–500 units/hour) in the treatment of DIC\(^4\)-\(^9\), its potential usefulness for the treatment of sepsis has not been rigorously tested in a randomized clinical trial. Currently, a clinical trial is being conducted using low-dose continuous infusion of unfractioned heparin (500 units/hour for 7 days) as complementary treatment for septic patients. The answer to the question whether heparin is efficacious awaits the results of this study.

IX) The improvement in DIC does not always lead to the survival benefit

As shown chapter IV, anticoagulant therapy is more efficacious if used for patients with DIC. However, the improvement obtained in DIC does not always improve survival. Taylor Jr. et al. demonstrated that inhibition of coagulation with active site-blocked factor Xa effectively blocked DIC but did not reduce mortality in a primate sepsis model\(^5\). In addition, numerous clinical findings suggest that imbalance in coagulation/fibrinolysis and microthrombus formation plays major roles in the development of organ failure and subsequent death during sepsis. Furthermore, extensive findings have been reported from postmortem examination in DIC patients\(^5\). The clinical importance of DIC in the progression of sepsis is thus indisputable, and some recent clinical trials have supported the use of antithrombin and APC supplementation in DIC associated with severe sepsis\(^1\)-\(^3\)-\(^6\). However, the significance of treating DIC is still controversial. Freeman et al.\(^5\) demonstrated that improvement in laboratory indicators of blood coagulation or score systems was not associated with significant improvement of survival. More recently, Hoffmann et al.\(^1\) demonstrated that co-administration of
antithrombin and heparin significantly reduced septic coagulopathy in severe sepsis. However, in their study, despite improvement of laboratory variables over time, the 14-day mortality was somewhat higher in the patients treated with antithrombin/heparin (five of 20 (25%) controls vs. six of 20 (30%) treated patients). These observations suggest that improvement of abnormalities in coagulation/fibrinolysis is necessary but the improvement of coagulopathy seems not to be sufficient for improving survival. Therefore, the primary goal of anticoagulant therapy should be set to the improvement of survival but not the improvement of DIC.

Summary

Much evidence had confirmed the efficacy of rhAPC for patients with severe sepsis with high risk of death. Use of rhAPC in the early stage, once patients have met the criteria, should be recommended. The effects of high-dose antithrombin in patients with severe sepsis are still controversial, but when it is administered, heparin should not be administered concomitantly. The use of antithrombin for septic DIC is a clinically reasonable choice. However, since anticoagulant therapy increases bleeding events, it should be carefully performed.

References


