# Venous and arterial thromboembolism in severe sepsis

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**Summary**

The burden of thromboembolism (TE) in severe sepsis is largely unknown. We assessed the prevalence of venous and arterial TE in patients with severe sepsis over a four-week period. We performed a retrospective analysis of a pooled database of three randomized, placebo-controlled trials of two novel pharmacological agents for the treatment of severe sepsis, drotrecogin alfa (activated) (DrotAA)and secretory phospholipase $A_2$ inhibitor ($sPLA_2I$). The study was conducted at intensive care units of the participating institutions. A total of 2,649 patients with known or suspected infection and sepsis-associated acute organ dysfunction were enrolled in the three trials and were assigned to treatment groups (DrotAA=850; $sPLA_2I$ =578; placebo=1221). The database was queried for venous and arterial TE, using investigator reports of serious adverse events. Eighty-four of 2,649 patients (3.2%; 95% confidence interval, 2.5% to 3.9%) developed at least one thromboembolic event over 28 days. Nearly three-quarters of episodes were atheroembolic (n=62); 25% involved the deep venous system (n=25). Ischemic stroke (n=30) and venous thromboembolism (n=25) each occurred in about 1% of patients. Ischemic stroke and acute coronary syndrome had a higher peak incidence during the first five days compared to venous TE onset, which was more constant over the 28-day period. Subgroup analysis by pooled treatment groups yielded TE rates of 2.0% (DrotAA), 3.5% (placebo), and 4.0% ($sPLA_2I$), respectively. Clinically manifest TE occurred in about 3% of severe sepsis patients treated in the intensive care unit over a 28-day period. Arterial TE may be more common than previously recognized. More accurate estimates of TE prevalence and relationship to sepsis await future studies.

**Keywords**

Sepsis, thromboembolism, stroke, venous thrombosis, pulmonary embolism, drotrecogin alfa (activated)

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## Introduction

Venous thromboembolic disease and arterial thromboses are well-recognized causes of in-hospital death, particularly among postoperative and immobilized medical patients (1–4). However, there are far fewer data on the burden of venous and arterial thromboembolism (TE) in critical illness, particularly in the context of severe sepsis. Severe sepsis patients may be at risk for venous TE, as they harbor many of the traditional risk factors including mechanical ventilation, endovascular catheters, along with disease-specific factors such as the host inflammatory response, activation of haemostasis (e.g. platelet, endothelial cell, coagulation), and reduced fibrinolysis (5–14). Sepsis-related systemic hypotension, septic shock, tissue hypoxemia, and need for vasopressor support may also predispose to acute venous and arterial TE (15–20).

Several studies have documented the prevalence of venous TE in the general intensive care unit (ICU) population, with estimates of venous TE prevalence in critical illness ranging from 10% to 30%, in the absence of thromboprophylaxis (21–22). Unfortunately, none of these studies specifically examined venous TE in severe sepsis. Similarly, while previous studies documented rates of cardiomyonecrosis of 5–25% and ischemic stroke of <1% in the general ICU population (23–28), none reported on the rate of arterial TE in patients with severe sepsis.

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The recent completion of randomized placebo-controlled trials on the effectiveness and safety of novel pharmacological agents for the treatment of severe sepsis provided an opportunity to assemble a severe sepsis-specific clinical trial database of the 2,649 patients enrolled in these studies. Clinical trial databases offer a number of advantages including a prospectively defined patient cohort with uniform diagnostic criteria, natural history data provided by a placebo-controlled group, and source-verified data. These pooled experimental data provide a venue for exploratory analyses aimed at a better understanding of complications associated with severe sepsis. Using this database, we conducted a retrospective analysis of venous and arterial thromboembolic complications in the intensive care population of severe sepsis patients.

## Materials and methods

Two experimental pharmacologic agents developed at Lilly Research Laboratories (Eli Lilly and Company, Indianapolis, IN, USA) were evaluated in three company-sponsored trials. The three index trials consisted of the phase 3 study of drotrecogin alfa (activated) (DrotAA), a recombinant form of human activated protein C, (29) and two phase 2 studies of a potent and selective inhibitor of group IIA, secretory phospholipase $A_2$ ($sPLA_2$) (30, 31). About two-thirds of the 2,649 patients originated from the phase 3 DrotAA study (N=1,690), followed by the $sPLA_2$ Study-1 (N = 586), and the $sPLA_2$ Study-2 (N = 373). Trial execution and analyses conformed to the International Conference on Harmonization for experimental agents, including approval by an Institutional Review Board at each participating site, and obtaining written informed consent from each study participant or designated representative prior to enrollment.

Severe sepsis was defined uniformly across the three trials as proven or suspected infection, accompanied by sepsis-induced acute organ dysfunction (29–31). There were few differences in entry criteria among studies, the most salient being:1) inclusion of ≥2 sepsis-induced organ dysfunctions in $sPLA_2$ Study-2 versus ≤1 for the DrotAA and $sPLA_2$ Study-1 trials; 2) exclusion of patients with serious hemorrhage or high risk for bleeding in the DrotAA study.

The trial database was interrogated for onset of both venous and arterial TE during the time period from study enrollment (i.e. treatment assignment) through 28 days. Specific thromboembolic events surveyed were: 1) deep vein thrombosis (DVT) of lower extremity or other central deep vein (subclavian, internal jugular, superior vena cava, portal vein); 2) pulmonary embolism; 3) acute coronary syndrome; 4) ischemic stroke; 5) peripheral arterial occlusion.

**Table 1: Distribution of baseline characteristics among trials and between treatment groups.**

| | DrotAA (PROWESS) | | $sPLA_2$I (EZZF) | | $sPLA_2$I (EZZI) | |
|---|---|---|---|---|---|---|
| | DrotAA N = 850 | Placebo N = 840 | $sPLA_2$I N=390 | Placebo N = 196 | $sPLA_2$I N=188 | Placebo N = 185 |
| Mean age, years ± SD | 60.5 ± 17.2 | 60.6 ± 16.5 | 57.5 ± 16.3 | 57.3 ± 16.5 | 60.9 ± 15.9 | 60.8 ± 17.0 |
| Male gender, % | 56.1 | 58.0 | 54.4 | 59.2 | 54.3 | 51.9 |
| Mean APACHE II ± SD | 24.6 ± 7.6 | 25.0 ± 7.8 | 23.9 ± 7.6 | 23.6 ± 7.8 | 25.2 ± 8.0 | 25.6 ± 7.8 |
| Surgery within 30 days, % | 28.8 | 30.6 | 36.2 | 34.7 | 48.1 | 42.7 |
| Presumed or known site of infection, % | | | | | | |
| Abdominal | 20.0 | 19.9 | 25.2 | 20.5 | 27.7 | 18.4 |
| Lung | 53.7 | 53.6 | 45.5 | 51.3 | 36.7 | 40.0 |
| Urinary tract | 10.0 | 10.2 | 9.5 | 8.7 | 9.0 | 13.0 |
| Other | 16.4 | 16.3 | 19.8 | 19.5 | 26.6 | 28.7 |
| Type of organism, % | | | | | | |
| Gram-positive | 24.6 | 25.8 | 31.0 | 33.2 | 26.6 | 23.2 |
| Gram-negative | 22.4 | 25.2 | 20.3 | 17.4 | 15.4 | 15.7 |
| Mixed | 10.8 | 11.4 | 16.9 | 17.9 | 5.9 | 6.0 |
| Other | 42.2 | 37.5 | 31.8 | 31.2 | 52.1 | 55.1 |
| ≤1 organ dysfunction | 25.4 | 24.2 | 23.3 | 21.5 | 0.5 | 0.5 |
| 2 organ dysfunctions, % | 31.8 | 32.5 | 32.8 | 38.0 | 39.4 | 36.8 |
| ≥3 organ dysfunctions, % | 42.8 | 43.3 | 43.9 | 40.5 | 60.1 | 62.7 |
| Septic shock, % | 11.3 | 10.4 | 5.6 | 6.1 | 8.5 | 11.9 |
| Mechanical ventilation, % | 73.3 | 77.6 | 82.6 | 81.6 | 73.9 | 80.0 |
| Thrombocytopenia, % | 16.2 | 15.5 | 31.8 | 28.1 | 27.7 | 28.7 |
| Receiving prophylactic heparin, % | 60.4 | 64.3 | 43.1 | 43.9 | 32.5 | 28.1 |

DrotAA = drotrecogin alfa (activated); APACHE = Acute Physiology and Chronic Health Evaluation.

**Table 2: Thromboembolic events*.**

| | DrotAA | | $sPLA_2I$ (EZZF) | | $sPLA_2I$ (EZZI) | | All |
|---|---|---|---|---|---|---|---|
| | DrotAA N = 850 | Placebo N = 840 | $sPLA_2I$ N = 390 | Placebo N = 196 | $sPLA_2I$ N = 188 | Placebo N=185 | N =2649 |
| Thromboembolic events (%) | | | | | | | |
| Ischemic stroke | 5 (0.6) | 10 (1.2) | 7 (1.8) | 2 (1.0) | 1 (0.5) | 5 (2.7) | 30 (1.1) |
| Pulmonary embolism | 3 (0.3) | 5 (0.6) | 2 (0.5) | 0 | 1 (0.5) | 1 (0.5) | 12 (0.5) |
| Deep vein thrombosis | 1 (0.1) | 2 (0.2) | 3 (0.7) | 1 (0.5) | 3 (1.6) | 3 (1.6) | 13 (0.5) |
| Arterial thromboembolism | 1 (0.1) | 0 | 0 | 0 | 0 | 0 | 1 (0.04) |
| Peripheral arterial occlusion | 0 | 1 (0.1) | 0 | 1 (0.5) | 4 (2.1) | 0 | 6 (0.2) |
| Acute coronary syndrome | 8 (0.9) | 10 (1.2) | 2 (0.5) | 3 (1.5) | 1 (0.5) | 1 (0.5) | 25 (0.9) |
| All** | 18 (2.1) | 27 (3.2) | 14 (3.6) | 7 (3.6) | 9 (4.9) | 9 (4.9) | 84 (3.2) |

DrotAA = drotrecogin alfa (activated), $sPLA_2I$ = Secretory phospholipase A2 inhibitor. Unless otherwise stated, data are shown as N (%).** Based on total number of patients.

Thromboembolic events were not *a priori* defined endpoints in any of the trials; hence the database query relied on the investigator reports for serious adverse events. The definition and reporting of serious adverse events were uniform among studies, and in accordance to internationally accepted criteria.

A dedicated research assistant reviewed all cases identified by the database query in order to ensure the specificity of serious adverse reports for TE. Cases were reviewed in a blinded fashion (i.e. without knowledge of experimental agent or individual patient treatment assignment), using pre-defined diagnostic criteria. Only cases meeting the secondary review criteria were retained in the analyses.

Cases of deep vein thrombosis, central vein thrombosis or pulmonary embolism required confirmation by objective testing with one or more of the following: compression ultrasound, venography, impedance plethysmography, pulmonary angiography (i.e. digital, spiral computed tomography [CT] or conventional angiography), or post-mortem. Acute coronary syndrome consisted of any of the following: 1) ST-elevation acute myocardial infarction (ischemic chest pain, ST elevation on EKG, with or without increased enzymes), 2) non-ST-elevation myocardial infarction (ischemic chest pain with evidence of elevated cardiac enzymes but no ST elevation), or 3) the need for coronary artery bypass graft or percutaneous vascular intervention for ischemic cardiac pain. Peripheral arterial occlusion consisted of objectively confirmed lower or upper extremity embolism or *in situ* TE. Ischemic stroke required clinical diagnosis and absence of intracranial haemorrhage or non-vascular causes by brain imaging with non-contrast CT scanning.

Ninety-five percent confidence intervals (CI) for event rate estimates were derived using SAS version 8.2 software (SAS Institute, Inc., Cary, NC, USA). Direct comparisons between event rates across clinical trials were not performed. All analyses were exploratory.

## Results

Table 1 displays the distribution of important baseline characteristics among the trials and treatment groups. Overall, these were similar among studies. However, a notable exception (by study design) was the greater prevalence of two or more organ dysfunctions in patients enrolled in the $sPLA_2I$ EZZI study (100%) compared to either the DrotAA (75%) or the $sPLA_2I$ EZZF (77%) study (29–31). Heparin prophylaxis was administered to 60.4% and 64.3% of the PROWESS study and control patients, respectively, and approximately 40%, and 30% of the patients enrolled in the EZZF and EZZI trials, respectively. In PROWESS, one patient with a TE received enoxaparin prophylaxis, three received therapeutic enoxaparin after the TE. In the sPLA2 studies, six patients received prophylactic enoxaparin, one prophylactic dalteparin, four therapeutic enoxaparin.

A total of 87 thromboembolic events occurred in 84 patients (incidence rate: 3.2%; 95% confidence interval [CI], 2.5%-3.9%) throughout the 28-day follow-up period (Table 2). Ischemic stroke was the most common event (30 of 87 events), accounting for about one-third of all episodes, followed by venous TE (25 of 87 events), acute coronary syndrome (25 of 87 events), and peripheral arterial occlusion (7 of 87 events). As shown in Table 2, thromboembolic events occurred in all trials and the observed TE rates were similar across the studies.

Figure 1 displays the occurrence of thromboembolic events over time in the entire patient cohort. In general, each type of thromboembolic event exhibited a gradual decline in its cumulative rate of incidence during the 28-day period. The temporal profile of thromboembolic events suggests an earlier peak onset for acute coronary syndrome and ischemic stroke, whereas the onset of venous TE was more constant during the follow-up period. A similar temporal profile was obtained after adjusting for mortality (data not shown). Figure 2 displays onset of thromboembolic events over time by treatment groups. Cumulative rates were 2.0% in the drotrecogin alfa (activated) group, 3.5% in the pooled placebo group, and 4.0% in the pooled $sPLA_2I$ group, respectively.

As indexed in Table 3, patients with TE were slightly older, had more prior hypertension (54% vs. 41%), had more instances of pulmonary infection as primary infection site (56% vs. 50%), had ≥3 sepsis-induced acute organ dysfunctions (54% vs. 45%), and had a higher mean Acute Physiology and Chronic Health Evaluation (APACHE) II score (26.8 vs. 24.6) (34), compared to those without TE. However, patients with and without TE were

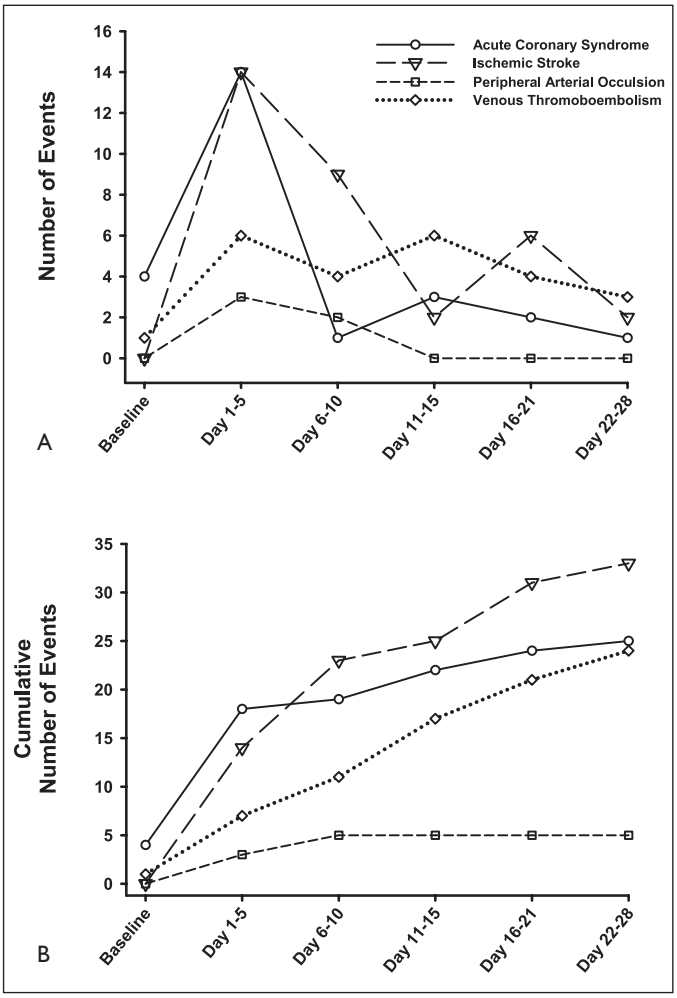


**Figure 1: Thromboembolic events through day 28 for all patients.** Venous thromboembolism included pulmonary embolism and deep vein thrombosis. Data expressed as number of events per time interval in A and cumulative number of events at each time interval in B.

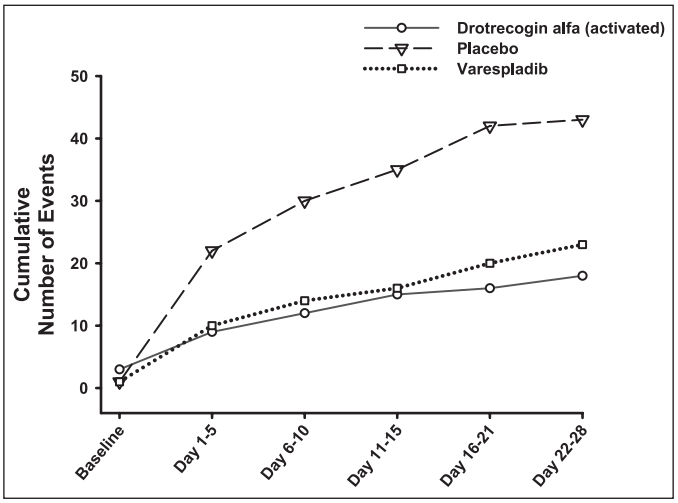


**Figure 2: Thromboembolic events through day 28 by random treatment assignment.** Incidence of thromboembolic events was subdivided into groups of patients receiving drotrecogin alfa (activated), n=850; $sPLA_2I$, n=578; and placebo treatment, n=1,221. Data expressed as cumulative number of events at each time interval.

remarkably similar in terms of prophylactic heparin usage (50% vs. 54%), pathogen type, and need for mechanical ventilation (79% vs. 77%) when assessed either as a combined population, or within each individual trial (data not shown).

## Discussion

The incidence of thrombotic events in the ICU population remains incompletely defined. Even less information is available for thromboembolic events in the severe sepsis population. Therefore, inferences about these complications in severe sepsis patients have been derived from studies of the general ICU population. Several small studies exploring the occurrence of venous TE in critically ill patients have been conducted. Cook et al. described a 5.4% incidence of DVT in medical-surgical ICU patients (35), while Samama et al. reported a rate of 14.9% for venographically confirmed DVT in the placebo-arm of a study of acutely ill medical patients (4). Other studies in medical and surgical ICU populations describe DVT rates ranging from 11.7% to 33% (21, 35, 36). From the standpoint of arterial TE, Bleck et al. described a stroke rate of 2.7% among 1,758 critically ill patients (27), while Wijdicks et al. observed 19 strokes (0.7%), half of them haemorrhagic, among 2,555 medical ICU patients (28). None of these studies specifically examined these complications in severe sepsis patients.

In contrast to DVT and stroke, more studies have examined cardiac complications in severe sepsis, although reported rates vary across studies and may be heavily dependant on how events were defined. In a study of 209 ICU patients, 32 (15%) demonstrated elevated troponin I, one-third of whom (5% of the total) developed clinically manifest myocardial infarction (25). Arlati et al. found that more then half of the severe sepsis/septic shock patients and all of the hypovolemic shock patients under investigation had biochemical evidence of myocardial damage; five of these 31 patients developed ECG findings of non-Q wave infarction (26). Finally, in a study by Turner et al., 12 of 15 patients in septic shock had serum cardiac troponin I concentrations diagnostic of acute myocardial infarction (37).

Our study differs from those noted above in several important ways. First, to our knowledge, this is the first study examining TE rates within the specific context of severe sepsis in patients requiring intensive care support; the studies above focused on more general populations of ICU patients. Incidence rates of venous and arterial TE were determined in a well-defined cohort of patients with severe sepsis over a uniform follow-up period of 28-days. Patients with TE were generally older, had a greater incidence of prior hypertension, and had higher APACHE II scores at baseline. This is consistent with previous studies that related the incidence of TE to age (38, 39) and multiple organ dysfunction (40). TE rates were remarkably uniform, averaging 3.2% among the three independent trials and within treatment groups, except for the lower rate observed in the DrotAA treatment group compared to its placebo group. This may be due to

**Table 3: Summary of aggregate baseline characteristics.**

| Characteristic | Thromboembolism (N=84) | No thromboembolism (N=2565) | All patients (N=2649) |
|---|---|---|---|
| Age ± SD | 63.1 ± 14.7 | 59.8 ± 16.8 | 59.9 ± 16.7 |
| Age ≥75 years, % | 22.6 | 21.2 | 21.3 |
| Male gender, % | 59.5 | 56.1 | 56.3 |
| Caucasian, % | 78.6 | 77.5 | 77.6 |
| APACHE II Score ≥25, % | 60.7 | 47.3 | 47.8 |
| Mean pre-infusion APACHE II ± SD | 26.8 ± 7.0 | 24.6 ± 7.8 | 24.6 ± 7.7 |
| Receiving prophylactic heparin, % | 50.0 | 53.7 | 53.6 |
| Meningococcal or pneumococcal infection**, % | 14.3 | 14.7 | 14.6 |
| Medical history, % | | | |
| Hypertension | 53.6 | 41.1 | 41.5 |
| Myocardial infarction | 19.0 | 13.0 | 13.2 |
| Diabetes | 29.8 | 23.9 | 24.1 |
| Pancreatitis | 6.0 | 4.1 | 4.1 |
| COPD | 29.8 | 22.6 | 22.8 |
| Malignancy | 16.7 | 15.7 | 15.7 |
| Surgery within 30 days | 36.9 | 33.1 | 33.2 |
| Thrombocytopenia,% | 22.6 | 20.8 | 20.8 |
| Septic Shock, % | 14.3 | 9.5 | 9.6 |
| Mechanical ventilation, % | 78.6 | 77.1 | 77.2 |
| Overt DIC* | 17.8 | 27.1 | 26.9 |
| Organ dysfunction(s), % | | | |
| 1 | 14.3 | 21.1 | 20.9 |
| 2 | 32.1 | 33.6 | 33.5 |
| ≥3 | 53.6 | 45.3 | 45.6 |
| Site of infection, % | | | |
| Intra-abdominal | 11.9 | 21.5 | 21.2 |
| Lung | 56.0 | 49.9 | 50.1 |
| Urinary tract | 11.9 | 10.0 | 10.1 |
| Other | 20.2 | 18.6 | 18.6 |
| Culture status, % | | | |
| Pure Gram-positive | 32.1 | 26.4 | 26.6 |
| Pure Gram-negative | 27.4 | 21.4 | 21.6 |
| Mixed Gram | 4.8 | 12.0 | 11.7 |
| Other | 35.7 | 40.2 | 40.1 |

APACHE = Acute Physiology and Chronic Health Evaluation, DIC = disseminated intravascular coagulation. *Overt DIC definition was based on the International Society of Thrombosis and Hemostasis definition (32, 33) and was only measured in PROWESS. This analysis included 45 patients with and 1645 patients without serious thrombosis.

DrotAA's anaticoagulant effects though this was not addressed in this study.

This rate is lower then in the studies noted above which may be due to use of heparin in half of the patients studied, and detection of events using serious adverse event (SAE) reports rather then screening systematically for TE. While this is likely to capture clinically important events, the total event rate can be much lower then in studies in which systematic screening is employed. Owing to the limitations of this study, these findings must be interpreted with caution and warrant further investigation. However, in aggregate, these observations still suggest that thromboembolic complications are part of the burden of severe sepsis, occurring in approximately one out of every 32 severe sepsis patients.

Ischemic stroke, acute coronary syndrome, and venous TE were the three most commonly observed clinically manifest thromboembolic events in this study, while peripheral artery occlusion and arterial TE were far less common. Despite the lack of formal screening for neurological events, the incidence rate of ischemic stroke was in the range reported for the more general ICU population. These observations suggest that strokes and

acute myocardial infarctions may be more common in severe sepsis patients then previously reported. In contrast, the incidence of serious venous TE may be less common in severe sepsis patients requiring intensive care support than in the general ICU population, as clinically manifest venous TE was no more common than strokes or acute coronary syndromes. Conversely, the prominence of ischemic stroke and acute coronary syndrome may reflect the more dramatic clinical presentation of these complications, which are thus more likely to be detected and reported than other less symptomatic thromboembolic events.

There were several methodological limitations of this study. As a retrospective analysis, this was an exploratory study; these results are an attempt to define the problem, but need to be confirmed in prospective, more definitive studies. Use of SAE reports only accounted for serious thromboembolic events. Thromboembolic events were not specifically screened for as outcome events in the three core studies. Prospective ultrasound examinations and autopsies looking for TE were not conducted in the three trials under study. As a result, the overall incidence rates were lower for the current study than those reported in previous prospective studies. In addition, exclusion criteria in PROWESS, such as exclusion of patients at risk of haemorrhage or with a history of recent thrombotic events (29) may have resulted in the selection of a lower risk population for TE. Finally, the use of heparin in half the patient population also renders the determination of the rates of TE in this population less certain. In a real-world study, with venous TE prophylaxis usually administered in less than one third of patients requiring it (41), the risk may be much larger than that noted in this study. Supporting this supposition is the fact that the TE rate was slightly higher in the two sPLA2I studies; these patient populations, including the placebo groups, had lower rates of venous TE prophylaxis compared to the PROWESS trial. The recent publication of the XPRESS trial further supports this assumption in that heparin-treated patients had a lower incidence of ischemic stroke, though the venous TE rate was low and not statistically different between heparin- and placebo-treated patients (17). Finally, the interactions of heparin with potential treatments for sepsis may be clinically important (42, 43), though the role of heparin as a treatment for sepsis remains undefined (44).

However, the rates of TE across these three independent trials including large placebo groups that comprised the current study were remarkably uniform. While adverse event reporting is an accepted methodology that should have detected any thromboembolic event that would increase length of stay, morbidity or mortality this method is not without limitations, as adverse event assessment can vary among clinical trials (45). However, importantly, this approach appears to have provided uniform assessment of patients across the three trials. Therefore, while the true incidence of TE in sepsis may be higher then in the current study, we have defined a clinically significant burden of both venous and arterial thromboembolic disease in sepsis.

## Conclusions

Non-fatal thromboembolic events occurred among 3% of survivors during the first four weeks after the onset of severe sepsis. The incidence of arterial TE was at least as common as venous TE and ischemic stroke was the most frequent arterial thromboembolic event. Arterial TE occurred predominantly during the first week, while the onset of venous TE was more constant over time. Given the low sensitivity of clinical detection, the true prevalence of venous TE is probably higher than measured in this study. Globally, these findings support the hypotheses that the risk of macro-vascular DVT may be lower than initially anticipated and that a number of factors pertaining to severe sepsis may predispose to brain ischemia. Further research in these areas appears warranted.

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