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Correction of Trauma-induced Coagulopathy by Goal-directed Therapy: A Secondary Analysis of the ITACTIC Trial

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Goal-directed treatment to treat trauma-induced coagulopathy is used to optimize treatment as the mortality rate is high; however, the optimal algorithm for bleeding management is unknown
- The authors evaluated trauma-induced coagulopathy management strategies guided by conventional coagulation tests and viscoelastic hemostatic assays to determine whether one improved trauma-induced coagulopathy management as defined by coagulopathy correction by the 12th unit of erythrocyte transfusion

What This Article Tells Us That Is New

- The study evaluated 133 patients; 71% were coagulopathic on admission, whereas 16% developed coagulopathy during resuscitation
- The viscoelastic group received goal-directed therapy more often than conventional (76% *vs.* 47%), and only 20% corrected their coagulopathy (*vs.* 0% with empiric treatment alone) with time to first goal-directed treatment of 68 (53 to 88) min for the viscoelastic group and 110 (77 to 123) min for the conventional group
- Many bleeding trauma patients did not receive indicated goal-directed treatment, and interventions arrived late during resuscitation and were only partially effective at correcting coagulopathy

ABSTRACT

Background: Trauma hemorrhage induces a coagulopathy with a high associated mortality rate. The Implementing Treatment Algorithms for the Correction of Trauma Induced Coagulopathy (ITACTIC) randomized trial tested two goal-directed treatment algorithms for coagulation management: one guided by conventional coagulation tests and one by viscoelastic hemostatic assays (viscoelastic). The lack of a difference in 28-day mortality led the authors to hypothesize that coagulopathic patients received insufficient treatment to correct coagulopathy.

Methods: During ITACTIC, two sites were coenrolling patients into an ongoing prospective observational study, which included serial blood sampling at the same intervals as in ITACTIC. The subgroup in both studies had conventional and viscoelastic test results for each patient available for analysis. A goal-directed treatment was defined as one triggered by an ITACTIC algorithm. Coagulopathy was defined as rotational thromboelastometry EXTEM A5 less than 40 mm. The primary outcome was correction of coagulopathy by the 12th unit of erythrocyte transfusion during resuscitation.

Results: Full viscoelastic and conventional coagulation test results were available for 133 patients. Of these patients, 71% were coagulopathic on admission, and 16% developed a coagulopathy during resuscitation. ITACTIC viscoelastic hemostatic assay group patients were more likely to receive goal-directed treatment than the standard group (76% *vs.* 47%; odds ratio, 3.73; 95% CI, 1.64 to 8.49; $P = 0.002$). However, only 54% of patients received goal-directed treatment, and only 20% corrected their coagulopathy (*vs.* 0% with empiric treatment alone; not significant). Median time to first goal-directed treatment was 68 (53 to 88) min for viscoelastic and 110 (77 to 123) min for standard ($P = 0.005$).

Conclusions: In ITACTIC, many bleeding trauma patients did not receive an indicated goal-directed treatment. Interventions arrived late during resuscitation and were only partially effective at correcting coagulopathy.

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This article is featured in "This Month in ANESTHESIOLOGY," page A1. This article is accompanied by an editorial on p. 832. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has a video abstract. This article has an audio podcast. This article has a visual abstract available in the online version. Part of the work presented in this article has been presented as "Correction of Coagulopathy in Trauma Hemorrhage—Still Room for Improvement: A Secondary Analysis of the ITACTIC Trial" at the International Society on Thrombosis and Haemostasis Congress, in London, United Kingdom, July 10, 2022.

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One third of bleeding trauma patients will die, rising to around one half of those who require massive transfusion.[1–3] Trauma-induced coagulopathy develops rapidly after injury and is strongly associated with mortality.[4] Around 40% of trauma patients with severe bleeding are coagulopathic on arrival in the emergency department, increasing to around 70% with ongoing bleeding and transfusions.[5] Changes in resuscitation practice have been introduced to address this coagulopathy, including earlier diagnosis and targeted therapies.[1] However, when diagnostic aspects of these strategies were tested in the recent Implementing Treatment Algorithms for the Correction of Trauma Induced Coagulopathy (ITACTIC) randomized controlled trial, no overall reduction in mortality was observed.[6]

The ITACTIC randomized controlled trial compared standard empiric transfusion packs (based on 1:1:1 ratios of red blood cells, plasma, and platelets) augmented with targeted therapies guided by either conventional coagulation tests or viscoelastic hemostatic assays. These point-of-care tests of functional coagulation appear intrinsically attractive as diagnostic tools to guide coagulation management. Although patients in the viscoelastic hemostatic assay arm of ITACTIC received more targeted treatments earlier in their clinical course, this did not translate into improved mortality.[6] Possible explanations for this unexpected finding include that coagulopathy was not corrected sufficiently or within a critical timeframe or that coagulopathy was sufficiently corrected in both trial groups but that this does not affect survival. These are key questions for trauma resuscitation that could not be addressed within the ITACTIC trial protocol because different coagulation tests were performed between the two arms of the trial.

The overall objective of this study was to analyze the performance of goal-directed treatment algorithms to correct coagulopathy in the ITACTIC trial. Our first aim was to determine the incidence of admission coagulopathy as measured by individual coagulation parameters and to determine their associated mortality. The second aim was to analyze how these parameters responded to goal-directed interventions during hemorrhage. Finally, we wished to understand whether any differences in response to coagulopathy were related to the timings of goal-directed interventions delivered within the trial.

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Materials and Methods

ITACTIC Randomized Controlled Trial Overview

In the ITACTIC study, adult trauma patients were enrolled if they presented with clinical signs of bleeding activating the local major hemorrhage protocol and if erythrocyte transfusion had been initiated. Participants had to be randomized within 3 h of injury and a maximum of 1 h after admission to the emergency department. There were no additional exclusion criteria. All patients were treated with the local center's empiric major hemorrhage protocol care consisting of tranexamic acid, and blood products were administered in a 1:1 ratio of erythrocytes and plasma, with some empiric administration of platelet concentrates, cryoprecipitate, or fibrinogen concentrate. In addition, patients were randomized to receive additional goal-directed hemostatic therapy guided by either conventional coagulation test - or viscoelastic hemostatic assayVHA-driven algorithms.[7] In both arms, blood samples were taken at baseline and after every 4 units of erythrocyte transfusions until hemostasis. Subjects in the conventional coagulation test arm had only laboratory tests performed. In the viscoelastic hemostatic assay arm, viscoelastic and laboratory tests were performed, but only the viscoelastic results were used to guide study interventions. Test results were reviewed as soon as possible after they were available and used to guide administration of additional blood products and tranexamic acid.

ITACTIC Thresholds and Goal-directed Hemostatic Treatments

Thresholds for intervention were from the previously developed TACTIC algorithms.[7] Abnormal values triggered administration of goal-directed therapy as follows: 4 g of equivalent fibrinogen as two pools of cryoprecipitate (United Kingdom) or 4 g of fibrinogen concentrate (Norway) was indicated for a laboratory (Clauss) fibrinogen less than 2 g/l or rotational thromboelastometry (ROTEM) FIBTEM A5 less than 10 mm; one additional pool of platelet concentrate for a platelet count less than 100×10^9 or PLTTEM A5 (EXTEM A5 – FIBTEM A5) less than 30 mm; and four additional units of plasma were given with a prothrombin time ratio greater than 1.2 or an EXTEM clot time greater than 80 s with normal fibrinogen thresholds. For the viscoelastic hemostatic assay algorithm, an additional 1 g of tranexamic acid was given if EXTEM lysis index at 30 min was less than 85%.[7]

ACIT Prospective Observational Cohort Study

In the ITACTIC trial, a full panel of conventional and viscoelastic coagulation tests was not available for all participants. Patients in the conventional coagulation test arm did not have viscoelastic tests performed, but those in the viscoelastic hemostatic assay arm had both viscoelastic and laboratory tests. A parallel study, Activation of Coagulation and Inflammation in Trauma (ACIT) was active at some of the ITACTIC sites. ACIT is a prospective observational cohort study in which trauma patients are enrolled on arrival to a major trauma center and was already running at the London and Oslo ITACTIC study sites. As part of the ACIT study, blood samples for conventional coagulation tests and viscoelastic tests were taken at baseline and after 4, 8, and 12 units of erythrocyte transfusions.[8] These are the same sampling intervals used to guide goal-directed interventions in the ITACTIC trial. ITACTIC patients who were coenrolled into ACIT therefore had full coagulation profiles available for analysis.

The specifics of the ACIT study have been reported previously.[7] In brief, trauma patients arriving in the emergency department within 2 h of injury are eligible for inclusion. Patients were excluded if they had burns covering greater than 5% of the body surface area, were taking anticoagulant medications other than aspirin, received greater than 2,000 ml of IV fluids before arrival in the hospital, had a known bleeding disorder, or had moderate to severe liver disease.[8] At all times, the ITACTIC clinical teams were blinded to the viscoelastic hemostatic assay results performed in the ACIT study. For this study, only ACIT tests that matched those in the ITACTIC viscoelastic hemostatic assay algorithms were analyzed, specifically EXTEM A5, clot time, and lysis index at 30 min (LI30) and FIBTEM A5. Detailed methods for ROTEM have been described previously.[9,10]

Definitions

To define trauma-induced coagulopathy, we used the standard viscoelastic definition of ROTEM EXTEM A5 of less than 40 mm and a prolonged prothrombin time ratio (greater than 1.2) for conventional laboratory tests.[4,7,10,11] Goal-directed treatment was defined as administration of hemostatic therapy in response to an abnormal test value in accordance with TACTIC treatment algorithms. Time to intervention was defined as the time from the baseline blood sample to administration of the first targeted treatment for a specific abnormality as defined above.

Outcomes

Our primary outcome was correction of coagulopathy during resuscitation (up to the 12th erythrocyte unit after baseline). Correction of coagulopathy was defined as normalization (to above the algorithm treatment threshold) of the coagulation parameter (*e.g.*, EXTEM A5 or prothrombin time ratio), from the baseline sample to the final sample available for each patient. Secondary outcomes of interest were blood component requirements at 24 h and 28-day mortality.

Consent and Ethics

Both ITACTIC and ACIT studies received ethical approval from local ethical review boards. Initial consent for enrollment in ACIT and ITACTIC was sought from a professional legal representative, usually an independent clinician involved in the patient's care. Subsequent consent was obtained from personal legal representatives as soon as possible after enrollment when it was possible to identify one and later by the participant if they regained capacity.

Statistical Analysis

The data were analyzed using R version 4.0.3. The data were assumed to be missing at random, and participants with missing data for a given test were excluded from any analysis of that test. The descriptive statistics are presented as median and interquartile range or as number and percentage. The three main comparison groups for this study were 28-day mortality (alive *vs.* dead), ITACTIC trial arm (conventional coagulation test *vs.* viscoelastic hemostatic assay), and goal-directed therapy (yes *vs.* no). For each comparison group, we analyzed the proportion who corrected coagulopathy (EXTEM A5) and the patterns of changes in coagulation test results over time. Differences in proportions of patients who corrected coagulopathy were analyzed using chi-square or Fisher's exact test. Differences in changes in coagulation parameters over time between the three main group comparisons were analyzed with two-way ANOVA. Additionally, mortality differences between ITACTIC arms by type of admission coagulopathy are presented as odds ratios and 95% CI, and differences were analyzed using chi-square or Fisher's exact test. Differences in times to administration of goal-directed treatments were analyzed with the Wilcoxon rank sum test. *P* values less than 0.05 were considered statistically significant. Statistical tests of $P = 0.05$ or above are reported as not significant. Where no *P* value is reported, statistical comparison of differences was not performed.

Results

Of the 236 ITACTIC patients recruited in London and Oslo, 133 patients were coenrolled into the ACIT study (representing 34% of the whole ITACTIC trial cohort). Patients had a median age of 36 yr, and 83% were male. Median injury severity score was 27, and 39% had sustained a penetrating injury (table 1). In ITACTIC, 58 of these had been enrolled into the conventional coagulation test arm

Table 1. Demographics, Injury, and Admission Characteristics for Patient Cohort

Characteristic	All Patients	Empiric Transfusion*	Goal-directed Therapy*
n	133	61	72
Demographics			
Age, yr	36 (26, 54)	38 (29, 54)	34 (22, 52)
Female	20 (17%)	8 (14%)	12 (19%)
Injury characteristics			
Penetrating	47 (39%)	22 (39%)	25 (40%)
ISS	27 (17, 43)	29 (18, 41)	26 (17, 43)
TBI (AIS head 4+)	25 (22%)	14 (25%)	11 (18%)
Admission physiology			
Heart rate	116 (97, 129)	110 (82, 123)	121 (104, 132)
Systolic blood pressure	87 (71, 114)	88 (74, 112)	83 (70, 123)
GCS	14 (6, 15)	13 (3, 14)	14 (8, 15)
Lactate	4.4 (3.0, 8.1)	5.0 (3.5, 8.4)	4.3 (2.5, 6.1)
Base deficit	10 (5, 15)	9 (5, 15)	10 (5, 14)
Admission coagulation			
EXTEM A5	35 (29, 41)	36 (28, 42)	35 (29, 41)
FIBTEM A5	8.0 (5.2, 11.0)	8 (6, 11)	8 (5, 11)
PLTTEM	27 (22, 31)	27 (23, 31)	26 (22, 30)
EXTEM lysis index at 30 min	100 (100, 100)	100 (100, 100)	100 (100, 100)
PTr	1.20 (1.10, 1.30)	1.10 (1.10, 1.20)	1.20 (1.10, 1.30)
Fibrinogen	1.72 (1.19, 2.10)	1.86 (1.38, 2.18)	1.49 (1.14, 2.00)
Platelet count	188 (148, 240)	209 (161, 256)	179 (133, 232)
Transfusion requirements			
Erythrocyte units	6 (4, 10)	4 (3, 7)	7 (5, 12)
Fresh frozen plasma/octaplasma	6 (4, 10)	4 (3, 6)	8 (5, 12)
Fibrinogen, g	4 (0, 8)	0 (0, 1)	7 (4, 8)
Platelet, pools	1 (0, 2)	0 (0, 1)	2 (1, 3)
Tranexamic acid	113 (85%)	49 (80%)	64 (89%)

*n; median (interquartile range); n (%).

AIS, Abbreviated Injury Scale; GCS, Glasgow Coma Scale; ISS, Injury Severity Scale; PTr, prothrombin time ratio; TBI, traumatic brain injury.

and 75 into the viscoelastic hemostatic assay arm (fig. 1). Demographics, injury characteristics and admission physiology were similar between the two arms and were representative of the whole ITACTIC cohort (supplemental table 1, https://links.lww.com/ALN/D651). Across both ITACTIC study arms, 54% (72 of 133) of patients received an algorithm-directed intervention, and 46% (61 of 133) received only empiric treatments as directed in the institution's major hemorrhage protocol (fig. 1).

On admission, 71% (93 of 131) presented with viscoelastic or laboratory identified coagulopathy (68% with EXTEM A5 less than 40mm, 33% with prothrombin time ratio greater than 1.2; table 1; supplemental table S1, https://links.lww.com/ALN/D651). Of those patients not coagulopathic on admission, 16% became coagulopathic by EXTEM A5, and 7% developed a prolonged prothrombin time ratio during resuscitation. Hypofibrinogenemia (fibrinogen less than 2 g/l) was present on admission in 66% (75 of 114) of patients and in 65% as measured by FIBTEM less than 10 mm. During bleeding and resuscitation, a further 8 and 12% subsequently developed hypofibrinogenemia as measured by laboratory (Clauss) fibrinogen and FIBTEM A5, respectively. A low admission platelet count was present in 7% (9 of 128) of patients on admission and only developed later during hemorrhage in 3% of those with a normal admission platelet count. In contrast, low platelet function (PLTTEM A5) was present in 70% of patients on admission and developed during bleeding in a further 25% of the patients who were initially normal. Only 8% of patients met the thresholds for additional plasma and 3% for additional tranexamic acid at baseline. Subsequent triggers for plasma were rare with only a single patient meeting the criteria. No patient developed ROTEM-detected hyperfibrinolysis during transfusion. In total, 111 patients (83%) had a coagulation test result that could have triggered an algorithm-guided intervention.

Overall, 28-day mortality in this cohort of patients was 29% (38 of 133; 28% viscoelastic hemostatic assay *vs.* 29% conventional coagulation test, 0.938; 95% CI, 0.41 to 2.16). The numbers in some subgroups of admission coagulopathy types were very small, but for all types of admission coagulopathy, 28-day mortality was generally lower in the viscoelastic hemostatic assay arm than in the conventional coagulation test arm (supplemental table 2, https://links.lww.com/ALN/D651). Odds ratios for mortality in the viscoelastic hemostatic assay arm compared to the conventional coagulation test arm varied depending on the baseline coagulation derangement, ranging from 0.68 (95% CI, 0.29 to 1.6) for those with EXTEM A5 less than 40 mm at baseline to 0.87 (95% CI, 0.35 to 2.17) for those with

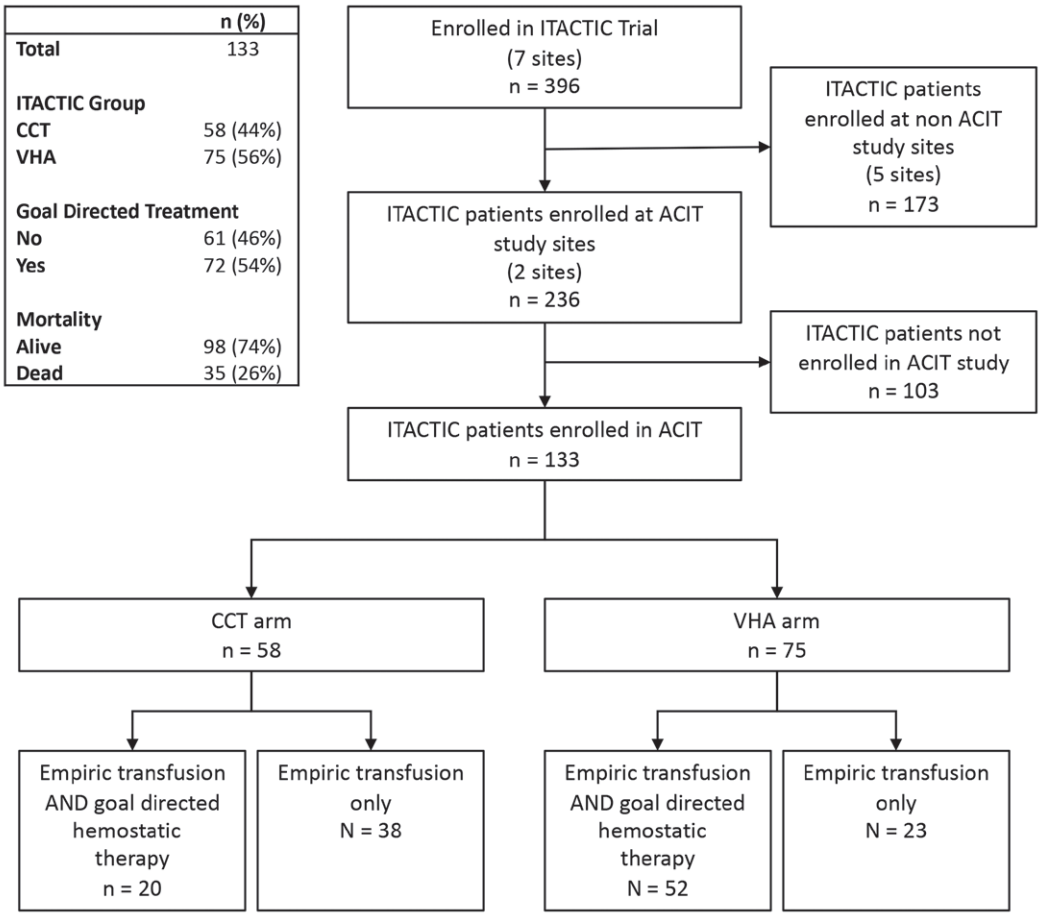

Fig. 1. Study flow chart. ACIT, Activation of Coagulation and Inflammation in Trauma; CCT, conventional coagulation test; ITACTIC, Implementing Treatment Algorithms for the Correction of Trauma Induced Coagulopathy; VHA, viscoelastic hemostatic assay.

fibrinogen less than 2 g/dl (supplemental table 2, https://links.lww.com/ALN/D651).

For patients who were coagulopathic at baseline, coagulation was corrected during resuscitation in a higher proportion of survivors than in those who died (25% *vs.* 9%; odds ratio, 3.33; 95% CI, 0.25 to 45.11; P = not significant; fig. 2A). There was no difference between the ITACTIC viscoelastic hemostatic assay and conventional coagulation test arms in the proportion of patients who corrected their EXTEM A5 (14% viscoelastic hemostatic assay *vs.* 17% conventional coagulation test; odds ratio, 0.94; 95% CI, 0.44 to 2.03; P = not significant; fig. 2B). Irrespective of ITACTIC study arm, only patients who received a goal-directed intervention improved their EXTEM A5 during hemorrhage (20% *vs.* 0%; odds ratio, ∞; P = not significant; fig. 2C). However, as shown in figure 2, the majority of patients did not correct coagulopathy during resuscitation.

The trajectories of coagulation abnormalities during hemorrhage are shown in figure 3 and supplemental figures S1 and S2 (https://links.lww.com/ALN/D651). Survivors had improved coagulation profiles compared to nonsurvivors across all cohorts with admission coagulation deficits (fig. 3; supplemental figs. S1 and S2, https://links.lww.com/ALN/D651). There was no significant difference in correction profiles between the viscoelastic hemostatic assay and conventional coagulation test arms of the ITACTIC trial. Of the 111 patients who triggered an ITACTIC algorithm, only 72 (65%) received a goal-directed intervention before receiving their 12th unit of erythrocyte transfusion. ITACTIC viscoelastic hemostatic assay group patients triggering the algorithm were more likely to receive a goal-directed therapy (52 of 68) than those in the conventional coagulation test group (20 of 43; 76% *vs.* 47% conventional coagulation test; odds ratio, 3.73; 95% CI, 1.64 to 8.49; $P = 0.002$). These goal-directed therapies resulted in statistically significant coagulation improvements from baseline for those who presented with low EXTEM A5 or prolonged prothrombin time ratio on admission (both $P < 0.001$; fig. 3), but

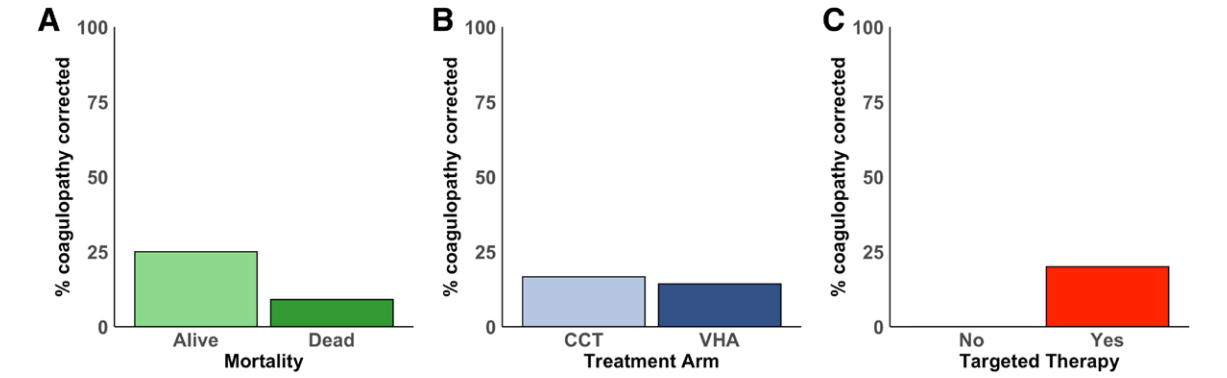

Fig. 2. Correction of coagulopathy (EXTEM A5 less than 40 mm) by mortality, treatment arm, and goal-directed therapy. Shown are the percentages of patients with admission coagulopathy (EXTEM A5 less than or equal to 40 mm) in whom coagulopathy has resolved by the final sample available for each patient. (*A*) Survivors *versus* nonsurvivors. (*B*) Conventional coagulation test (CCT) *versus* viscoelastic hemostatic assay (VHA) arm. (*C*) Goal-directed therapy *versus* empiric transfusion protocol (all *P* = not significant).

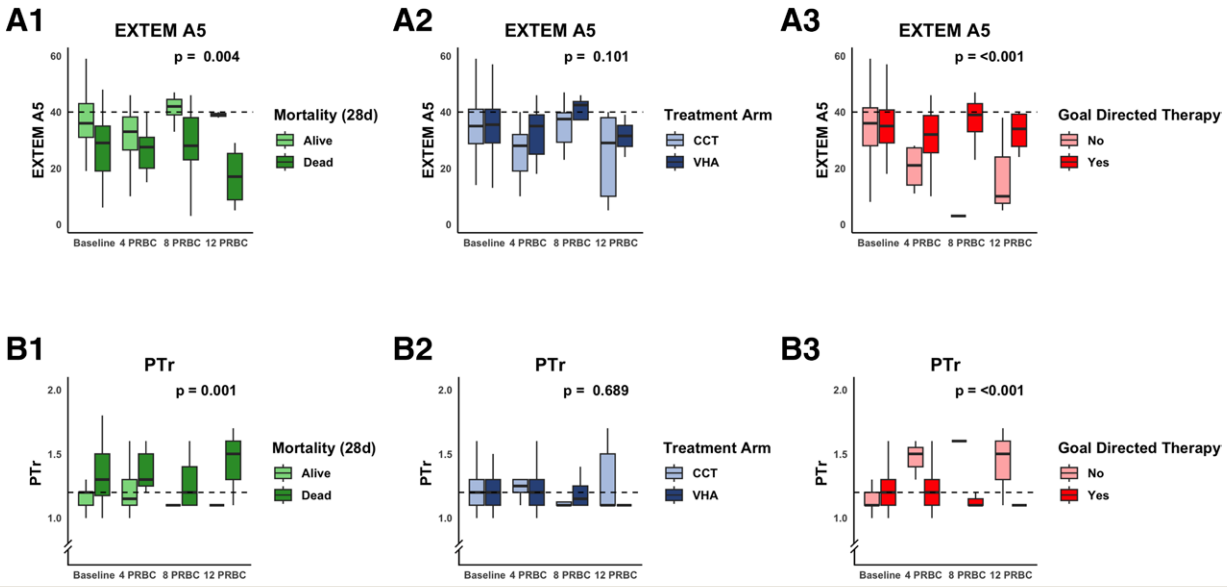

Fig. 3. Trauma-induced coagulopathy during resuscitation. The box plots show changes in EXTEM A5 (A1–3) and prothrombin time ratio (PTr, B1–3) during hemorrhage and resuscitation. The sampling points are at baseline and after 4, 8, and 12 units of packed erythrocytes (PRBC). *Green*, survivors *versus* nonsurvivors; *blue*, conventional coagulation test (CCT) *versus* viscoelastic hemostatic assay (VHA) arms; *red*, targeted treatment *versus* no targeted treatment. The *dotted lines* represent the ROTEM and PTr thresholds for trauma-induced coagulopathy (EXTEM A5 less than 40 mm and PTr greater than 1.2). Differences in coagulation parameters between groups during transfusion were analyzed with two-way ANOVA.

not for other laboratory or viscoelastic parameters (supplemental figs. S1 and S2, https://links.lww.com/ALN/D651).

We examined the time delay between coagulopathy detection and administration of the therapeutic intervention (fig. 4). Median time to diagnosis was 14 (8 to 25) min in the viscoelastic hemostatic assay arm and 64 (55 to 73) min in the conventional coagulation test arm. The benefit of early diagnosis in the viscoelastic hemostatic assay arm was overshadowed by the length of time to deliver the goal-directed intervention. Overall, the median time from diagnosis on baseline sample to the first goal-directed intervention was a further 76 (59 to 102) min. Patients in the viscoelastic hemostatic assay arm were more likely to receive a goal-directed intervention (viscoelastic hemostatic assay *vs.* conventional

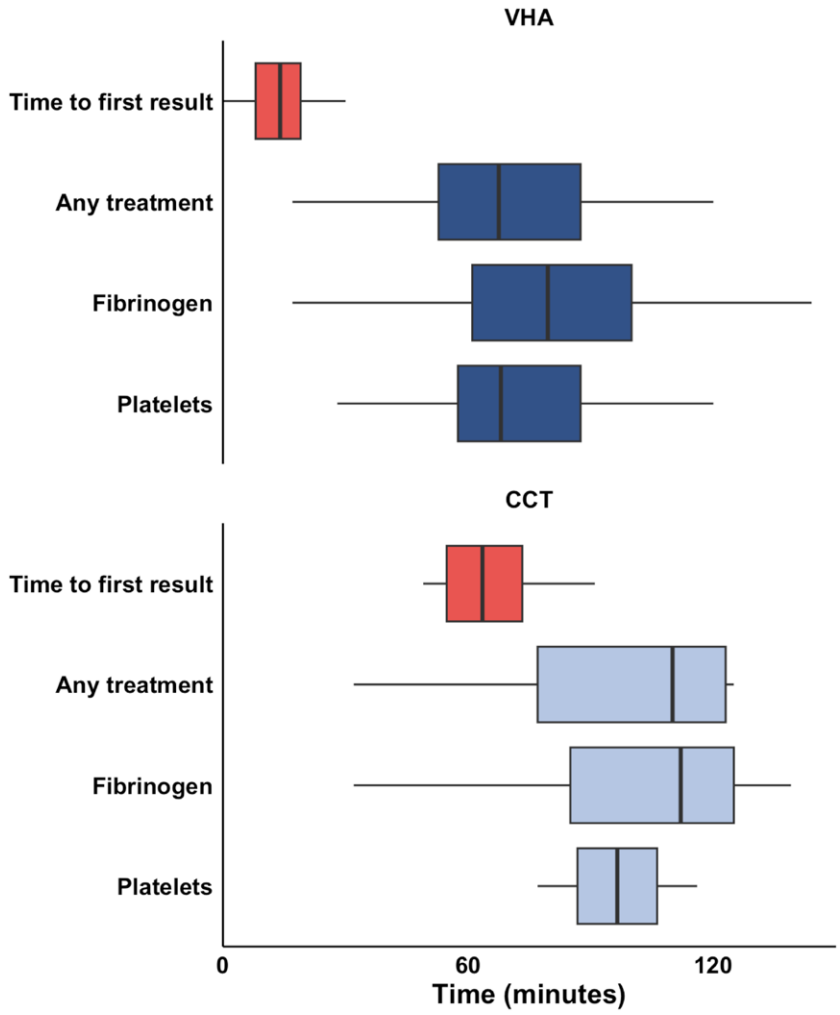

Fig. 4. Timing of diagnostic test result availability and administration of goal-directed interventions. The box plots show the time to first actionable result (*red boxes*) for each test and the time to transfusion of the first targeted treatments for patients with a baseline abnormality in the viscoelastic hemostatic assay (VHA, *dark blue*) and conventional coagulation test (CCT, *light blue*) arms. For VHA, any treatment n = 36, fibrinogen n = 28, platelets n = 32; and for CCT, any treatment n = 13; fibrinogen n = 17, platelets n = 2.

coagulation test, 31% *vs.* 19%; odds ratio, 3.48; 1.33 to 9.51; $P = 0.005$), and the viscoelastic hemostatic assay-guided algorithm delivered the first goal-directed intervention to coagulopathic patients a median of 42 min faster than the conventional coagulation test algorithm. This was still over an hour after the baseline sample was taken and approached 2 h in the conventional coagulation test arm (viscoelastic hemostatic assay *vs.* conventional coagulation test, 68 [53 to 88] *vs.* 110 [77 to 123] min; $P = 0.005$; fig. 4).

Discussion

This secondary analysis of the ITACTIC trial provides a detailed description of the effect of contemporary approaches to hemostatic resuscitation on trauma-induced coagulopathy. The cohort and subgroup sizes were small, and the results should be interpreted in this context. There are consistent results that suggest goal-directed treatments improved coagulation profiles more than empiric care alone, across the spectrum of coagulation deficits. However, goal-directed interventions were delivered to only around two thirds of patients who needed them. They took over an hour to deliver regardless of diagnostic approach and did not restore coagulation to normal during bleeding and resuscitation. The over-riding picture is that any improvements in diagnosis provided by point of care viscoelastic testing were negated by a failure of delivery or efficacy of the therapeutic interventions.

Hemostatic resuscitation was introduced to directly target trauma-induced coagulopathy.[12] Major hemorrhage

transfusion algorithms attempt to prevent coagulopathy developing or worsening, principally through the empiric administration of whole blood or balanced blood component transfusions.[13] Before the introduction of these empiric algorithms, coagulation factor levels would fall precipitously during hemorrhage, leading to severe and irreversible bleeding.[14,15] Transfusion with balanced erythrocyte, plasma, and platelet transfusions has been shown to slow the development of coagulation factor deficits. However, the empiric administration of concentrated coagulation therapeutics has not been shown to improve outcomes.[16,17] In ITACTIC patients, the progression of coagulopathy in patients receiving empiric therapy alone (without receiving targeted treatments), was indistinguishable from that described in studies from a decade ago.[5]

Goal-directed treatment algorithms aim to identify established coagulation deficits and correct these using concentrated products.[7] Traditionally, these have been guided using laboratory-based conventional coagulation tests, which have repeatedly been shown to have long turnaround times inappropriate for rapidly bleeding patients.[10,18] The viscoelastic hemostatic assays such as ROTEM and thromboelastogram have moved diagnosis to point of care, providing rapid results and more information on specific coagulation factor defects.[7,10] Our results show that both conventional coagulation test and viscoelastic hemostatic assay-guided approaches produce improved coagulation profiles compared to empiric therapy alone. There were general trends to improved responses with viscoelastic hemostatic assay-guided algorithms and associated nonsignificant trends to lower mortality, but these were not to the extent that was expected, and neither approach led to correction of trauma-induced coagulopathy during hemorrhage.

These findings call into question both the delivery and efficacy of these interventions. The dose of product administered in ITACTIC may have been insufficient, or it may be that the coagulopathy is not correctable by the chosen therapeutic. Most therapeutics administered by the ITACTIC algorithms were blood components, which had to be specifically requested from the transfusion laboratory, often thawed, picked up, delivered to the treating team, and then administered in a queue of other transfusion therapies. Patients who received goal-directed therapy received more erythrocyte transfusions than the empiric group, possibly reflecting the length of time it takes to deliver such an intervention. Although the viscoelastic hemostatic assay-guided arm of the trial delivered diagnostic results faster than the conventional coagulation test arm and patients were more likely to receive an intervention, it appears this was not enough to offset the long delay to delivering and administering the required blood products across the whole trial population.

This study has several limitations. Not all sites were able to recruit to both ITACTIC and ACIT in parallel, and we were only able to analyze just over a quarter of the ITACTIC study cohort. Additionally, there was a large degree of heterogeneity in the patients, leading to wide variation on coagulation responses. Our findings are therefore underpowered in many of the analyses. A second important limitation is that we were unable to track the triggering of an algorithm to the administration of a specific treatment and then the subsequent response of the coagulation system to that intervention. Analysis at this level of granularity was impossible due to the speed of resuscitation, the variable time between ordering an intervention and the patient receiving it, and multiple nearly simultaneous product administrations. This process and human factors analysis is an important area for future research.

In conclusion, major hemorrhage protocols that include goal-directed hemostatic therapy improve coagulation profiles compared to empiric protocols alone. Patients who correct their coagulopathy had a lower mortality, and viscoelastic assays increase the proportion of patients who receive goal-directed treatment. However, the overall benefits of earlier diagnosis appear to be heavily offset by delayed administration of interventions, which are only partially effective. Future progress in correcting trauma-induced coagulopathy and improving clinical outcome will require focus on the rapid delivery and administration of more effective coagulation therapeutics.

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Competing Interests

Dr. Curry has received research grants from CSL Behring (King of Prussia, Pennsylvania) and Sobi (Stockholm, Sweden) and has served on advisory boards for LFB Biomedicaments (Les Ulis, France), Octapharma (Lachen, Switzerland), and Sobi. Dr. Maegele has received honoraria for lectures and speakers' bureaus, congress travel support, and financial support for research projects from Astra Zeneca (Cambridge, United Kingdom), Bayer (Leverkusen, Germany), CSL Behring, Werfen (Barcelona, Spain), LFB Biomedicaments, Octapharma, and Portola Inc. (South San Francisco, California). Dr. Johansson has received unrestricted research grants from Haemonetics Corp. (Boston, Massachusetts) and Octapharma. Dr. Gaarder has received honoraria for lectures from Octapharma, has received research grant support from Haemonetics (Boston, Massachusetts) and Werfen in the form of device and reagent support, and also has previously

served on the advisory board for Nycomed (Zurich, Switzerland). Dr. Brohi and Dr. Davenport have received research grant support from Werfen and Haemosonics (Boston, Massachusetts) in the form of device and reagent support and have served on external advisory panels for Octapharma, Astra Zeneca, and Werfen. Dr. Brohi has previously served on external advisory panels for Haemonetics Corp, Werfen, CSL Behring, Bayer, and Astra Zeneca. The other authors declare no competing interests.

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Supplemental Digital Content

Interventions in ITACTIC – supplemental tables and figures, https://links.lww.com/ALN/D651

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