




REVIEW ARTICLE

Fibrinolytic therapy for refractory COVID-19 acute respiratory distress syndrome: Scientific rationale and review

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic has caused respiratory failure and associated mortality in numbers that have overwhelmed global health systems. Thrombotic coagulopathy is present in nearly three quarters of patients with COVID-19 admitted to the intensive care unit, and both the clinical picture and pathologic findings are consistent with microvascular occlusive phenomena being a major contributor to their unique form of respiratory failure. Numerous studies are ongoing focusing on anticytokine therapies, antibiotics, and antiviral agents, but none to date have focused on treating the underlying thrombotic coagulopathy in an effort to improve respiratory failure in COVID-19. There are animal data and a previous human trial demonstrating a survival advantage with fibrinolytic therapy to treat acute respiratory distress syndrome. Here, we review the extant and emerging literature on the relationship between thrombotic coagulopathy and pulmonary failure in the context of COVID-19 and present the scientific rationale for consideration of targeting the coagulation and fibrinolytic systems to improve pulmonary function in these patients.

Christopher D. Barrett and Hunter B. Moore are co-first authors.

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KEY WORDS

acute respiratory distress syndrome, COVID-19, fibrinolysis, pulmonary failure, tissue plasminogen activator

Essentials

- Coronavirus disease 2019 (COVID-19) has caused thrombotic coagulopathy and respiratory failure in unprecedented numbers.
- Pulmonary microvascular thrombosis is particularly prominent in COVID-19 respiratory failure.
- Animal and limited human data support a role for fibrinolytic therapy in respiratory failure.
- Urgent study of fibrinolytic therapy is needed. A phase 2a trial is pending (NCT 04357730).

1 | INTRODUCTION

As the coronavirus disease 2019 (COVID-19) pandemic accelerates, cases have grown exponentially around the world. Other countries' experience suggests that 5%-16% of in-patients with COVID-19 will undergo prolonged intensive care,¹⁻³ with 50%-70% needing mechanical ventilation (MV),³⁻⁵ threatening to overwhelm hospital capacity.⁶

While COVID-19 overall mortality likely ranges from 1% to 5%, this is much higher in patients with COVID-19-induced acute respiratory distress syndrome (ARDS) (22%-64%).^{3,4,7} There are currently few proven ARDS therapies other than low-tidal-volume⁸ and prone-positioning⁹ MV. Most current trials on clinicaltrials.gov for COVID-19-induced ARDS aim at modulating the inflammatory response. Sarilumab and tocilizumab, which block interleukin-6 effects, are being tested in randomized controlled trials for patients hospitalized with severe COVID-19 (NCT04317092⁹). The World Health Organization international trial SOLIDARITY will test remdesivir, chloroquine plus hydroxychloroquine, lopinavir plus ritonavir, and lopinavir plus ritonavir and interferon- β . However, studies targeting the coagulation system, which is intrinsically intertwined with the inflammatory response, are lacking.¹⁰⁻¹⁴

2 | FIBRINOLYSIS, ARDS, AND THE POSSIBLE ROLE OF FIBRINOLYTIC THERAPY IN COVID-19

Our group has shown that low fibrinolysis is associated with ARDS,¹⁵⁻¹⁹ and patients with COVID-19 in the intensive care unit (ICU) have now been shown on thromboelastography to universally have lower levels of fibrinolysis than the reference population.²⁰ Over the past decades, studies have demonstrated the systemic and local effects of dysfunctional coagulation, specifically related to fibrin, in ARDS.^{11,13,14,21,22} ARDS, regardless of cause, is associated with fibrin deposition in air spaces and fibrin-platelet microthrombi in the pulmonary vasculature,²³⁻²⁵ which is also consistently observed in the lung microvasculature of patients with COVID-19.²⁶⁻²⁸ This pathologic fibrin deposition reflects a dysfunctional clotting system, with enhanced clot formation and propagation as well as fibrinolysis

suppression,²⁹⁻³¹ largely due to tissue factor produced by alveolar epithelial cells and macrophages,³² and high levels of plasminogen activator inhibitor-1 (PAI-1) produced by endothelial cells or activated platelets.^{33,34} Consistent with this, prothrombin time prolongation, elevated D-dimer and fibrin degradation products, and uniquely elevated fibrinogen levels have been reported in severely ill patients with COVID-19, particularly in nonsurvivors.^{3,4,20,35-38} Similar findings have been observed in sepsis,^{29,39} endotoxemia,⁴⁰ and extensive tissue disruption,¹⁸ in which early activation of coagulation and fibrinolysis is followed by late fibrinolytic shutdown and endothelial dysfunction. It is also consistent with an initial viral infection of airway epithelial cells, with later spread to endothelial cells, which has now been shown to occur in COVID-19,⁴¹ both of which express the receptor protein for the virus, angiotensin-converting-enzyme-2 (ACE2).⁴² Furthermore, it has now also been shown that critically ill patients with COVID-19 universally demonstrate hypercoagulable findings on viscoelastic assays relative to the reference population, with shortened reaction time, increased α -angle, increased maximal amplitude, and in virtually all cases a reduced level of fibrinolysis on thromboelastography.²⁰

Targeting the coagulation and fibrinolytic systems to improve ARDS and associated pulmonary clot formation syndromes has been described^{34,43-47} and tested in animal models,⁴⁸⁻⁵¹ and in light of the mounting findings in COVID-19, as described above, may also have a role in the management of COVID-19 respiratory failure. In 2001, Hardaway and colleagues described a small, noncontrolled human trial in severe ARDS, showing that uro/streptokinase led to remarkable improvement in oxygen requirements without bleeding events.⁵² Tissue-type plasminogen activator (t-PA) is a more modern fibrinolytic approach with higher clot lysis efficacy without increased bleeding risk. A meta-analysis of acute lung injury in animals showed that, compared to controls, t-PA improved survival, arterial pO₂ and pCO₂ better than either urokinase plasminogen activator or plasmin, although none of the studies included viral-induced ARDS.⁵⁰ In other studies, intra-airway delivered t-PA improved survival and morbidity associated with acute plastic bronchitis crisis, in which intra-airway clotting occurs.^{46,53-60} Both nebulized and direct instillation of t-PA into the airways via bronchoscopy have been used off-label to treat fibrin airway casts.⁶¹ In a lethal animal model of both severe pulmonary microvascular thrombi and severe bronchial

fibrin casts, treatment with airway t-PA resulted in improved survival, dissolved airway casts, and normalized pO_2 and pCO_2 .^{62,63} However, the mounting evidence specific to COVID-19 that shows pulmonary microvascular thrombosis as a predominant finding²⁶⁻²⁸ combined with normal lung compliance and high alveolar-arterial oxygen gradients⁶⁴ suggests intravascular delivery may be the more appropriate delivery route, with concern that intra-airway delivery via intratracheal instillation or nebulized solutions may increase the risk to health care workers by exposing them to infectious airway secretions.

Taken together, the extant data on fibrinolytic therapy in ARDS combined with the thrombotic coagulopathy and clinical findings consistent with pulmonary vascular thrombo-occlusive disease in COVID-19 suggest that manipulation of the fibrinolytic system through administration of t-PA may have a role in the therapy of severe, medically refractory COVID-19-induced ARDS. Importantly, such an approach is nonexclusive and could be used in patients who have been treated with other experimental agents, including anti-interleukin-6 receptor blockers and other immune modulators, antibiotics, and antiviral agents.

3 | RISK CONSIDERATIONS FOR FIBRINOLYTIC THERAPY IN COVID-19 ARDS

The main risk if fibrinolytic therapy were considered for treatment of severe, medically refractory hypoxemia in COVID-19 respiratory failure is bleeding. The bleeding risk can be estimated from its use in myocardial infarction (MI) and submassive pulmonary embolism. In the largest available prospectively collected data set of intravenous alteplase for non-stroke indication (GUSTO [Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries] trial; MI), the risk of hemorrhagic stroke was 0.7% and severe/life-threatening bleeding was 0.4% in the group that received 50 mg of alteplase over 90 minutes followed immediately by a 5000 U bolus of intravenous unfractionated heparin and a therapeutic heparin drip (n = 10 396 patients).⁶⁵ In a trial of high-dose alteplase (100 mg over 2 hours) given concomitant with therapeutic systemic heparinization for submassive pulmonary embolism, the rate of major bleeding was 0.8%, and none of the 118 patients in the alteplase arm of the trial developed a hemorrhagic stroke.⁶⁶ These 2 patient groups are expected to be relatively similar to those with severe COVID-19 illness regarding comorbidities and the absence of active stroke, which increases the risk of hemorrhagic conversion. There are multiple studies that quote higher risks of "major bleeding," with a commonly referenced meta-analysis by Chatterjee et al⁶⁷ quoting a major bleeding risk with t-PA in pulmonary embolism as being 9.24% relative to 3.42% for anticoagulation alone. The majority of the patients in this meta-analysis came from a single study (the PEITHO [Pulmonary Embolism International Thrombolysis] study) that used tenecteplase,⁶⁸ which is resistant to PAI-1 inhibition.⁶⁹ Additionally, many of the included studies had no prespecified definition of a major bleeding event, several included studies considered

any blood transfusion as a major bleed, and none used hemodynamic parameters or massive transfusion protocol activation as criteria. With respect to COVID-19 ICU patients on mechanical ventilation where death is as likely as survival, life-threatening hemorrhage is the most relevant for consideration, which again suggests the GUSTO study of over 40 000 patients including over 10 000 patients in the alteplase bolus plus heparin group is likely the most relevant for risk considerations for fibrinolytic therapy in severe, medically refractory hypoxemic respiratory failure in COVID-19.⁶⁵ Furthermore, given the profound hypercoagulable/thrombotic coagulopathy in the majority of critically ill COVID-19 patients^{20,35,38,70,71} where bleeding is quite rare and thrombosis predominates, the risk of systemic fibrinolysis therapy may be even lower. Similarly, while we posit that intravascular delivery of t-PA would likely be more effective, if intra-airway t-PA were to be pursued and effective, the available case reports of t-PA airway delivery have thus far showed no bleeding events.^{46,61}

In addition to bleeding events, there is also risk specific to the COVID-19 betacoronavirus itself. Cell entry by this virus requires cleavage of a trimeric spike (S) glycoprotein that protrudes from the viral envelope, generating 2 subunits (S1 and S2), followed by additional cleavage within S2.⁷² The S1 subunit provides the receptor binding domain, which binds to ACE2 on the cell surface.^{73,74} The S2 subunit then drives fusion between the virus and the cell membranes, resulting in viral entry. S protein cleavage at the S1-S2 junction and within S2 occurs through host cell proteases, primarily transmembrane serine protease 2 (TMPRSS2), at specific arginine-serine sequences.⁷² Plasmin, like TMPRSS2, also favors cleavage between arginine-serine sequences⁷⁵; thus, t-PA administration with plasmin generation could conceivably enhance viral infectivity. However, patients in COVID-19 terminal stages are likely already massively infected with high viral loads, where the profound hypoxemic respiratory failure resulting from pulmonary microvascular thrombosis and the host inflammatory response to the virus is the imminent threat to life rather than the virus itself. As such, we posit that plasmin activation effects on viral entry or decreased clearance would be minor compared with salvage of pulmonary gas exchange and correction of profound hypoxemic respiratory failure to prevent imminent death by restoring pulmonary microvascular patency.

4 | PRACTICAL CONSIDERATIONS IF FIBRINOLYTIC THERAPY WERE CONSIDERED IN COVID-19 ARDS

In the absence of effective therapies for medically refractory COVID-19 hypoxemic respiratory failure where critical care physicians have exhausted all available treatment options in a dying patient, patients with prothrombotic presentations, normal lung compliance on the ventilator, and high alveolar-arterial oxygen gradients could potentially be considered for fibrinolytic therapy; as such, a clinical presentation is suggestive of vascular occlusive disease as a primary cause of hypoxemia. It should be noted that in a disease entity only several

months old, such an approach has no pre-existing controlled trial data and must be considered with extreme caution, although there are now a handful of case reports that so far have demonstrated temporal associations with alteplase administration and improvement of the respiratory status of critically ill patients with COVID-19 (emphasis: a causal relationship in uncontrolled case reports cannot be inferred)⁷⁶ (Poor et al, in review; Barrett et al, in review). The large experience using intravenous t-PA for strokes, myocardial infarctions, and pulmonary emboli^{66,77,78} may provide a useful guide for its use in COVID-19 respiratory failure in the absence of prior controlled trial data. Our suggestion in such a situation is to consider an initial intravenous bolus dose of 50 or 100 mg of alteplase over 2 hours, concomitant with, or immediately followed by, systemic anticoagulation with heparin. Multiple sites across the United States have already taken this approach (fibrinolytic therapy) in severe, medically refractory COVID-19 hypoxemic respiratory failure, and the specifics around the use of heparin vary from fully therapeutic heparin drips (partial thromboplastin time goal 60-80 seconds) while t-PA is infusing, to 500 U/h heparin while t-PA is infusing, followed by full anticoagulation after tPA is finished, to starting therapeutic heparin right after t-PA finishes infusing with no heparin during the actual tPA administration period. As a rationale for dosing with respect to t-PA (alteplase), we performed pharmacokinetic simulations on 2 test subjects (75 and 60 kg), and found that the 50- and 100-mg bolus dose regimens would quickly achieve t-PA plasma concentrations above median PAI-1 levels in injured patients (200 ng/mL, 4.7 nmol/L) (Moore et al, unpublished; Cardenas et al⁷⁹) (Figure 1). Importantly, this pharmacokinetic model also supports a redosing

strategy at 12 hours or later in transient responders (eg, those that may have rethrombosed due to inadequate anticoagulation, as suspected in the case series observations by Wang et al⁷⁶), since by this time the plasma levels of t-PA from the first bolus have fallen below the level of circulating t-PA in normal patients.⁸⁰ A phase II clinical trial will be required to confirm these estimates and is now planned (discussed below). While we believe that intravascular delivery of t-PA is likely a more appropriate route of administration in COVID-19 respiratory failure if fibrinolytic therapy were considered, if intra-airway t-PA delivery were to be pursued, we suggest 50 mg (or 0.7 mg/kg) of t-PA instilled into the airways, preferentially by bronchoscopy, followed by repeat dosing every 4-8 hours as needed for sustained improvement of oxygen requirements. This regimen is based on empiric guidelines for treatment of plastic bronchitis patients at the Children's Hospital of Colorado, as well as multiple case reports and animal studies.^{51,54,56,61} The same exclusion criteria for MI treatment with tPA should apply, with patients maintained on a heparin infusion after t-PA treatment completion to prevent reaccumulation of fibrin clot in the lung microvasculature. A possible algorithm for consideration of fibrinolytic therapy in severe, medically refractory COVID-19 respiratory failure is shown in Figure 2, with the key points being: (1) that in the absence of controlled trial data such an approach should be considered only in patients with persistent, refractory hypoxemic respiratory failure despite maximal management strategies; (2) have evidence of a hypercoagulable state; and (3) have normal lung compliance with high alveolar-arterial oxygen gradients that suggest the patient's hypoxemia likely has a vascular occlusive component. While this scenario of a hypercoagulable

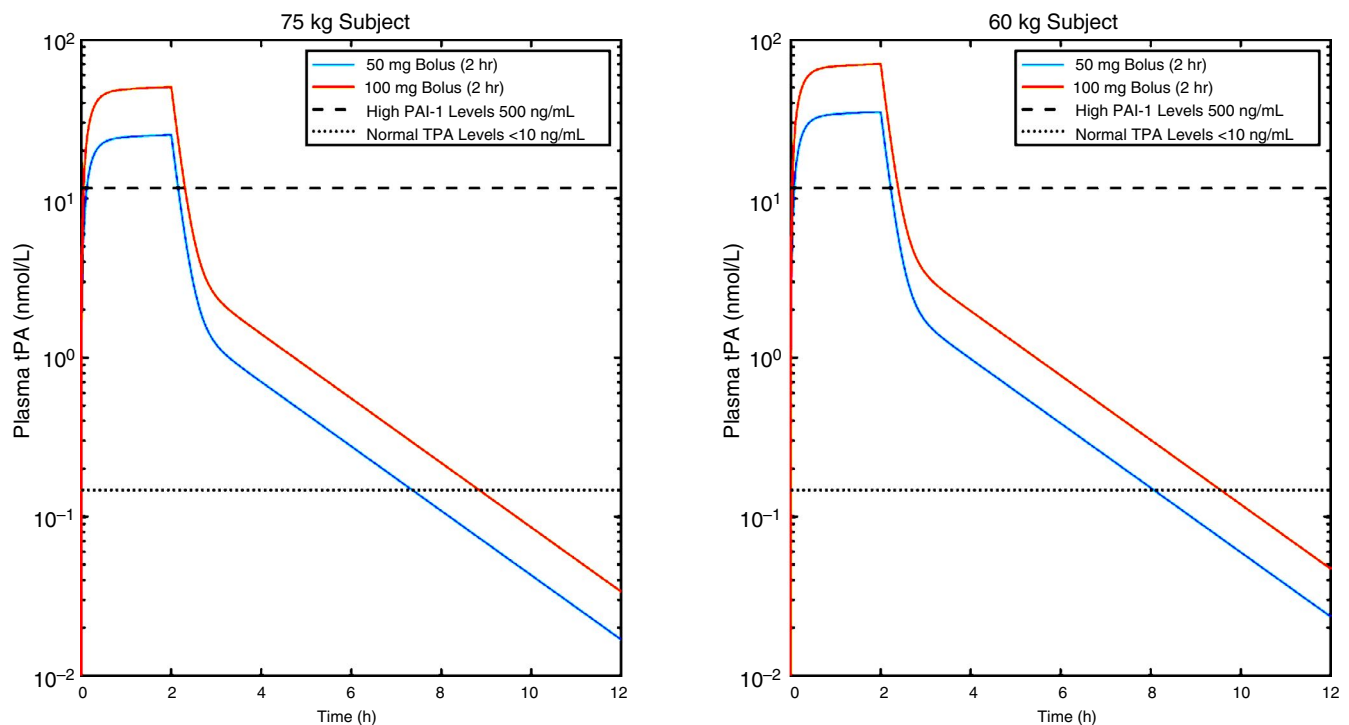


FIGURE 1 Pharmacokinetic simulations of t-PA levels over time relative to its native inhibitor (PAI-1) in patients with COVID-19 based on various body mass and bolus/maintenance doses of t-PA. The model assumes a plasma clearance of 8.3 min, and a terminal half-life of 88 min.⁸² PAI-1, plasminogen activator inhibitor-1; t-PA, tissue-type plasminogen activator

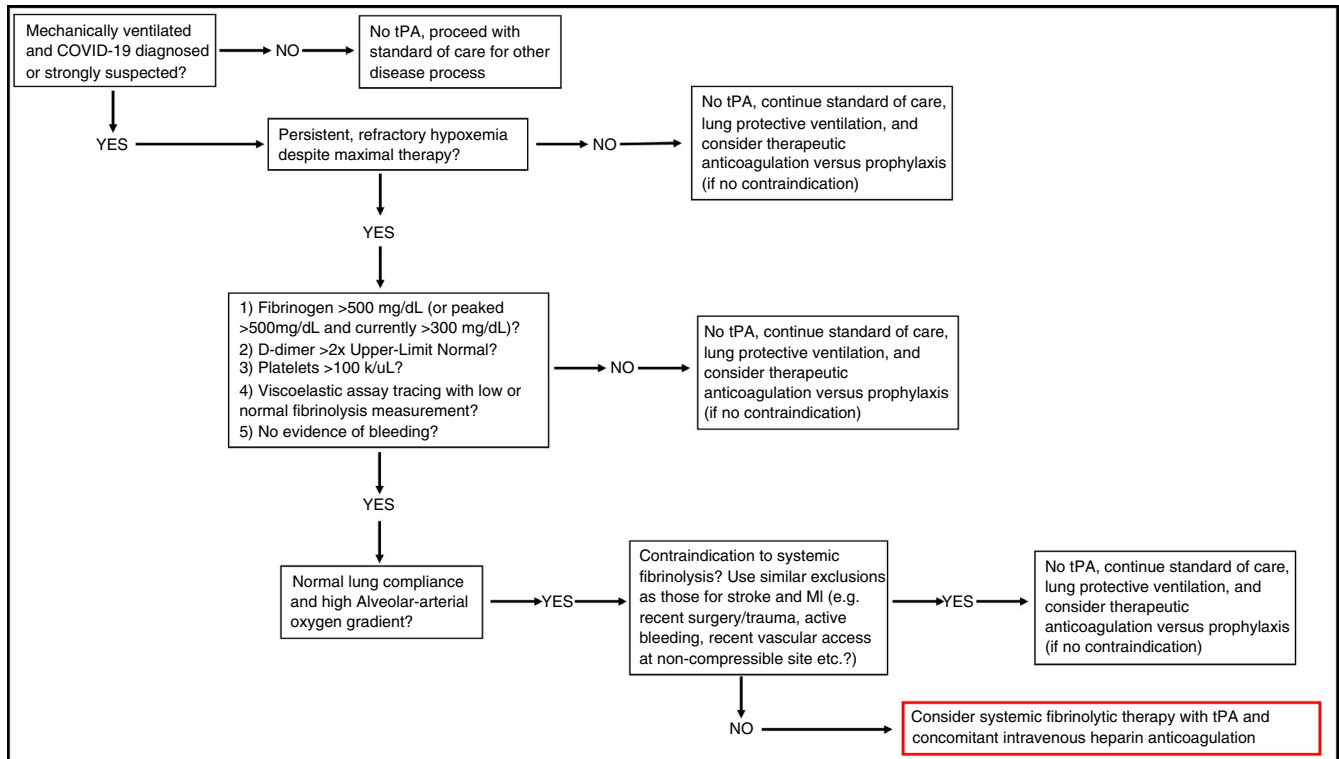


FIGURE 2 Possible algorithm for consideration of fibrinolytic therapy in severe, medically refractory COVID-19 respiratory failure. COVID-19, coronavirus disease 2019; MI, myocardial infarction; t-PA, tissue-type plasminogen activator inhibitor-1

state, normal lung compliance, and high alveolar-arterial oxygen gradients is seen in the majority of patients with COVID-19 respiratory failure and microvascular thrombosis is present in the majority of autopsies, the possibility of macrovascular pulmonary embolism is not insignificant^{71,81} and similarly may improve after fibrinolytic therapy. As discussed above, such an approach involves risk, but such risk in carefully selected patients is likely outweighed by certainty of death in the proposed population and justifies consideration of salvage t-PA therapy when all other therapeutic options are exhausted. We would encourage all those who are inclined to treat critically ill patients with COVID-19 with t-PA for refractory respiratory failure to track the success or failure of this approach and report their clinical outcomes.

5 | SUMMARY AND CONCLUSIONS

In the present COVID-19 crisis, facing a disease entity that has existed only for several months, physicians (particularly critical care physicians) are faced with large numbers of patients in profound, medically refractory hypoxemic respiratory failure with multiple clinical clues and autopsy reports that suggest a significant pulmonary microvascular thrombotic component. Level 1 evidence from randomized controlled trials for managing COVID-19 and its associated severe, refractory hypoxemic respiratory failure is months, if not years, away. As such, clinicians facing life-and-death situations in critically ill patients with COVID-19 must treat them using

clinical reasoning based on observation of the patient's physiology, as the standard protocols and best practice "pathways" that modern medicine has become dependent on simply do not exist yet in this emerging and lethal disease. If t-PA fibrinolytic therapy were used in decompensating patients with no options for escalation of care, and shown to be effective with a greater risk of benefit than harm, such an approach could be rapidly broadened globally due to t-PA's availability at most medical centers. While we cannot specifically advocate for its use in a systematic way at this time, and caution against broad implementation of this approach in the absence of controlled trial data, such an approach should at least be known to clinicians treating critically ill patients with COVID-19 in the event that they have an imminently dying patient meeting the criteria outlined above and in Figure 2, and have exhausted all other options. Formal study of this potential therapy is urgently needed. A phase IIa multicenter randomized controlled trial of alteplase therapy in severe, medically refractory hypoxemic respiratory failure in COVID-19 is now underway (ClinicalTrials.gov, NCT 04357730).

RELATIONSHIP DISCLOSURE

CDB, HBM, EEM, and MBY have patents pending related to both coagulation/fibrinolysis diagnostics and therapeutic fibrinolytics, and are passive cofounders and hold stock options in Thrombo Therapeutics, Inc. HBM and EEM have received grant support from Haemonetics and Instrumentation Laboratories. EEM holds a grant from Genentech. MBY has previously received a gift of alteplase (t-PA) from Genentech and owns stock options as a cofounder of

Merrimack Pharmaceuticals. JB and JA are cofounders of Applied BioMath and own stock. FH owns stock in Applied BioMath. LAV has received grant support from Genentech. PCM, PKM, AS, DL, RM, and DST report nothing to disclose.

AUTHOR CONTRIBUTION

CDB, HBM, EEM, AS, LAV, and MBY prepared the manuscript with critical input and revisions from DST and DRL. Pharmacokinetics models were generated by JB, FH, and JA.

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