Reply to 'The role of tranexamic acid in trauma — a life-saving drug with proven benefit'

Ernest E. Moore, Hunter B. Moore and Angela Sauaia

We thank Ian Roberts and Francois-Xavier Ageron for their interest in our Primer (Moore, E. E. et al. Trauma-induced coagulopathy. *Nat. Rev. Dis. Primers* **7**, 30 (2021))[1], which raised some important points (Roberts, I. & Ageron, F.-X. The role of tranexamic acid in trauma — a life-saving drug with proven benefit. *Nat. Rev. Dis. Primers* https://doi.org/10.1038/s41572-022-00367-5 (2022))[2]. We were surprised by the statement that we proposed guidelines for the use of tranexamic acid (TXA) post-injury. In actuality, the Primer (a narrative review, not a guideline) described the current TXA-related practices in Europe versus those in the USA and provided a critical appraisal of the evidence (as in Box 1 of the Primer) behind both approaches.

Based on the survival benefit demonstrated in the CRASH ($n > 20{,}000$) randomized controlled trials (RCTs) and elective surgery studies, Roberts and Ageron promote pre-emptive TXA in the pre-hospital and hospital phases of post-injury care. We disagree that elective surgery results should be generalized as evidence for TXA's efficacy and safety in trauma. We also question the generalizability of the CRASH findings, conducted primarily in austere, resource-poor environments with prolonged pre-hospital transport and limited access to blood products, to well-resourced emergency and trauma systems.

In their letter, the authors mentioned the 'smaller US randomized trials', namely the STAAMP[3] ($n = 903$) and Prehospital TXA for moderate to severe traumatic brain injury[4] ($n = 966$), which were adequately powered to detect clinically meaningful differences in their primary outcomes. Pondering on the different populations and settings these studies addressed may illuminate the reason for disparate results and help define the individuals and/or settings most likely to benefit from TXA. Furthermore, pooling results of the CRASH trials with the STAAMP and Prehospital TXA for moderate to severe traumatic brain injury studies, which addressed rather heterogeneous settings (that is, high clinical heterogeneity) and with a strong dominance of the large CRASH trials, as in Fig. 1 of the letter, is not recommended[5].

While the beneficial effects of TXA for hyperfibrinolysis are unquestioned, it remains unclear how this medication affects patients with physiological or shutdown fibrinolysis, which represent most trauma patients presenting to trauma centres. Our Primer[1] reviewed our group's work on the association of thrombotic complications and mortality with TXA in injured patients without hyperfibrinolysis.

The correspondence quotes a recent study showing that early empirical TXA did not increase late mortality regardless of fibrinolysis patterns[6]. However, it neglected to mention that this study also detected a significantly higher incidence of micro-thrombotic complications in TXA recipients with admission hypofibrinolysis who evolved with persistent hypofibrinolysis. Indeed, our independent analysis of CRASH-2 data indicated that, among patients requiring blood transfusions as well as among those with hypotension upon hospital arrival, TXA decreased the odds of death among those with low tissue injury-to-shock ratio, but it increased the odds of death in patients with a high tissue injury-to-shock ratio (H.B.M., E.E.M. and A.S., unpublished data).

The correspondence also contended that there is no definitive evidence that TXA provokes thromboembolic events (TEs). However, systematic reviews[7–9] observed a significant effect of TXA in increasing TEs in neurological and other conditions, as did the HALT-IT trial and an RCT in severe traumatic haemorrhage[10]. Of course, there are also several RCTs that did not detect TE increase with TXA. The controversy demonstrates the lack of definitive answers regarding the effect of TXA on TEs, especially in neurological conditions and in settings with rapid transport to well-equipped trauma centres.

Convinced that delivering TXA to the right patient at the right time in the right environment will optimize outcomes, we developed modified viscoelastic haemostatic assays to rapidly identify the correct patient[11]. We call the trauma community to focus on the pressing need to develop cost-effective methods to efficiently identify patients most likely to benefit from TXA. Ultimately, we all have the same goal to optimize the use of TXA across the globe.

Ernest E. Moore[1,2]✉, *Hunter B. Moore*[2] *and Angela Sauaia*[2,3]

[1]*Ernest E Moore Shock Trauma Center at Denver Health, Denver, CO, USA.*

[2]*Department of Surgery, University of Colorado Denver, Aurora, CO, USA.*

[3]*Colorado School of Public Health, University of Colorado Denver, Aurora, CO, USA.*

✉*e-mail: Ernest.Moore@dhha.org*

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Competing interests

E.E.M. currently receives research support from Haemonetics, Instrumentation Laboratory, Stago, Hemosonics, Diapharma, Prytime, Humacyte and Genentech; he is a co-founder of ThromboTherapeutics; he is listed as inventor on the following patents relating to blood coagulation or fibrinolysis (including assays): WO-2016073668-A1 (assignee: The Regents Of The University Of Colorado; status: published); US-9354243-B2 (assignee: Haemonetics Corporation, The Regents Of The University Of Colorado, A Body Corporate; status: granted); WO-2019014595-A1 (assignee: Thrombo Therapeutics, Inc.; status: published); EP-3215634-A1 (assignee: The Regents of the University of Colorado; status: published); EP-3303943-A1 (assignee: The Regents of The University of Colorado, A Body Corporate; status: published); WO-2021158799-A1 (assignee: The Regents Of The University Of Colorado, A Body Corporate; status: published); and US-2020208194-A1 (assignee: Massachusetts Institute Of Technology, University Of Colorado; status: published). H.B.M. receives research support from Haemonetics and Instrumentation Laboratory; he is a co-founder of ThromboTherapeutics; he is listed as inventor on the following patents relating to blood coagulation or fibrinolysis (including assays): WO-2016073668-A1 (assignee: The Regents Of The University Of Colorado; status: published); WO-2019014595-A1 (assignee: Thrombo Therapeutics, Inc.; status: published); EP-3215634-A1 (assignee: The Regents of the University of Colorado; status: published); and US-2020208194-A1 (assignee: Massachusetts Institute Of Technology, University Of Colorado; status: published). A.S. declares no competing interests.

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