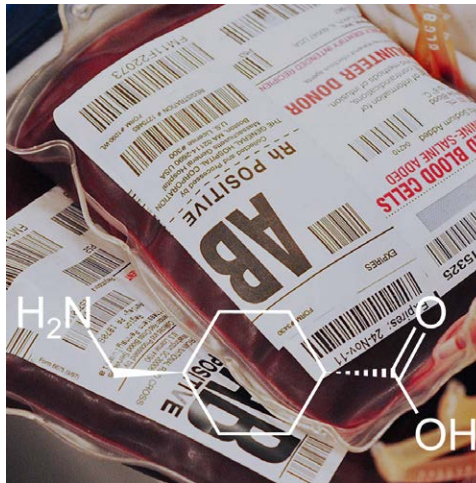


# Optimal Tranexamic Acid Dosing Regimen in Cardiac Surgery: What Are the Missing Pieces?

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Multiple randomized clinical trials evaluating prophylactic tranexamic acid administration consistently demonstrate a reduction of bleeding and allogeneic blood product transfusion requirements.<sup>1,2</sup> International guidelines recommend prophylactic administration of antifibrinolytic agents in patients undergoing high-risk cardiac surgical procedures.<sup>3,4</sup> In the most recent large trial, patients scheduled to undergo coronary artery bypass surgery and at risk for perioperative complications were randomized to receive either tranexamic acid (50 to 100 mg/kg of actual body weight) or placebo.<sup>5</sup> Tranexamic acid was associated with a lower risk of bleeding than placebo without increase in mortality or thrombotic complications within 30 days of surgery. However, tranexamic acid was also associated with a higher risk of postoperative seizures (0.1% *vs.* 0.7%,  $P = 0.002$ ). In a 1-yr follow-up study, there was no difference in death or severe disability between patients exposed to tranexamic acid or the placebo.<sup>6</sup> Despite the favorable safety profile of tranexamic acid, several questions remain unanswered (fig. 1), and the optimal dose needed to reduce bleeding without increasing the risk of side effects, especially seizures, is still not established.

In this issue of *ANESTHESIOLOGY*, Zufferey *et al.* performed a model-based meta-analysis to describe the effect of different tranexamic acid doses on postoperative bleeding and clinical seizures.<sup>7</sup> Their meta-analysis objectives were to estimate the dose-response relationship and identify the optimal dosing regimen to be used in adults undergoing



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cardiac surgery with cardiopulmonary bypass. The authors included 64 randomized controlled trials and 18 observational studies of intravenous tranexamic acid administration in adult cardiac surgical patients. They found that the plasma concentration required to achieve 50% of maximum effect was 5.6 mg/l (95% credible interval, 0.7 to 11.1 mg/l) or 22.4 mg/l to achieve 80% inhibition of fibrinolytic activation. The authors also reported an increased risk of postoperative clinical seizure incidence of 1.07 (95% credible interval, 1.06 to 1.09) per 10 mg/l increase in tranexamic acid plasma concentration. Compared to no exposure to tranexamic acid, a plasma concentration of 100 mg/l doubled the risk of clinical seizures (2.1; 95% credible interval, 1.9 to 2.4). Among other risk factors, open-chamber procedures and prolonged cardiopulmonary bypass duration both significantly increased the risk of clinical seizures. Using their model-based meta-analysis, the authors conclude that low-dose tranexamic acid (total dose of 20 mg/kg of actual body weight) provides the best balance between reduction in postoperative blood loss and red blood cell transfusion and the risk of clinical seizure. The use of higher doses would only marginally improve the clinical effect at the cost of an increased risk of seizure.

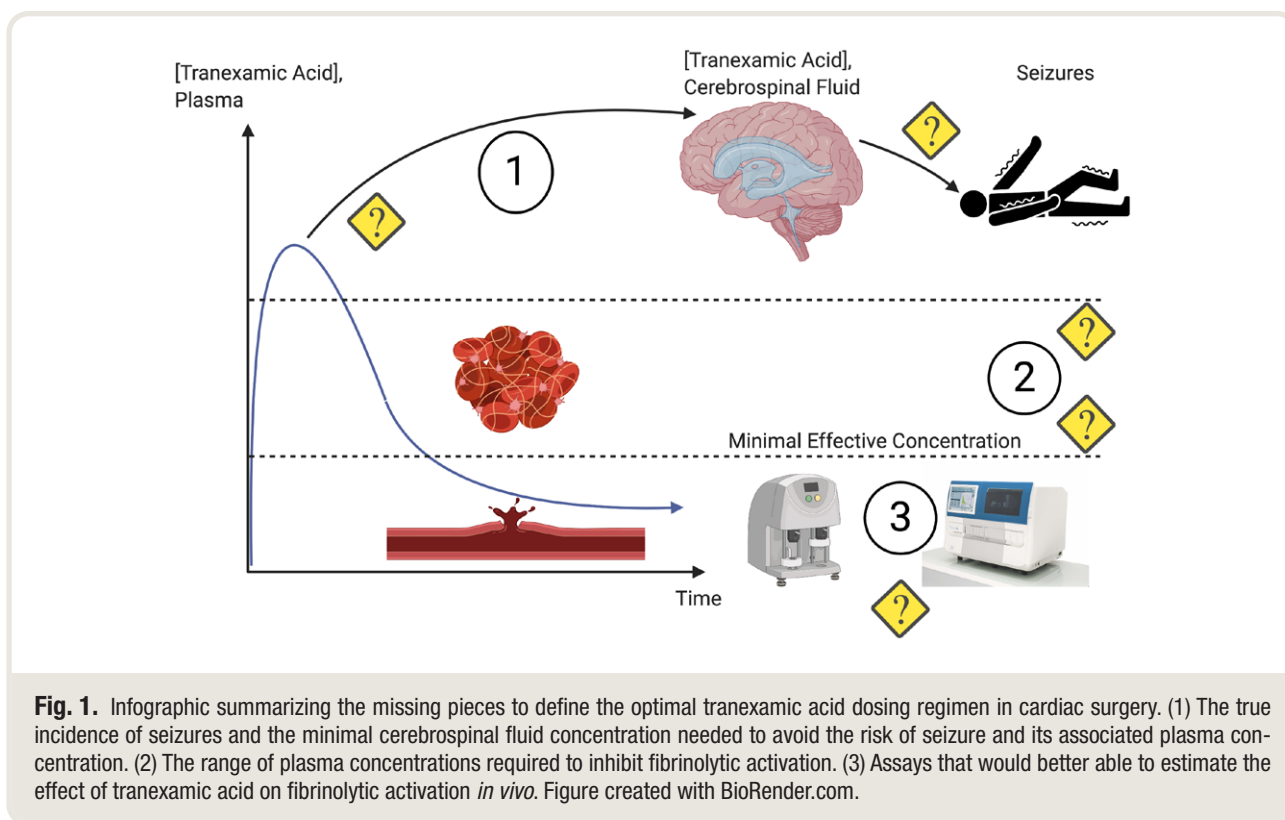
The results reported in this model-based meta-analysis are relevant and an important step toward defining the optimal tranexamic acid dosing regimen in adult cardiac surgical patients. This analysis first integrates the results obtained from large clinical trials with our knowledge of

Image: J. P. Rathmell.

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the tranexamic acid pharmacokinetic profile in adult cardiac surgical patients. By pooling the effects reported in each of the included studies on bleeding, transfusion, and clinical seizures, and by modeling the association between dose regimen and outcomes, the authors were able to confirm that the use of low doses of tranexamic acid (e.g., 20 mg/kg of actual body weight) would suffice to reduce bleeding without increasing the risk of seizures. However, a few important limitations need to be taken into account when interpreting the authors' conclusions for their meta-analysis.

As for any meta-analysis, the quality of the results obtained by pooling data is highly influenced by the quality of the studies included. While all studies included bleeding and transfusion as their primary endpoints, important heterogeneity on the definition of bleeding and transfusion practices can be expected among the studies. Although clinical seizures are an important safety endpoint in trials studying the clinical effect and safety of tranexamic acid, the incidence is relatively low and has been shown to be influenced by preexisting conditions as well as the type of surgical procedure performed. As reported in an experimental model,<sup>8</sup> the peak of tranexamic acid concentration observed in the cerebrospinal fluid was approximately 10% of the peak observed in the plasma and was delayed by 3 to 5 h after peak plasma concentration occurred. Due to the complex nature of the relationship between the kinetics of the distribution of tranexamic acid from the plasma to the

cerebrospinal fluid and the lack of knowledge about cerebrospinal fluid tranexamic acid concentrations associated with seizures, it is currently impossible to define a dosing regimen that would be predicted to optimize therapeutic plasma tranexamic acid concentrations while maintaining cerebrospinal fluid concentrations below the seizure threshold. In addition, because cardiac surgical patients are sedated when peak concentrations occur in the cerebrospinal fluid, the true incidence of clinical seizures may not be known. Further, current clinical trials were not designed or powered to correlate plasma tranexamic acid levels with the incidence of clinical seizure. The results of the meta-analysis should be interpreted knowing those limitations.

Although the pharmacokinetics of tranexamic acid in adult cardiac surgical patients is known, the dose regimen simulations published based on the pharmacokinetics are targeting plasma concentrations that have never been shown to adequately inhibit fibrinolytic activation *in vivo*.<sup>1</sup> On the basis of the initial investigations from the 1970s, two basic target concentrations have been advocated: a lower concentration of approximately 10 to 20 mg/l, which is thought to inhibit approximately 80% of fibrinolysis, and a high concentration of approximately 100 mg/l, which should completely inhibit fibrinolysis.<sup>9</sup> To date, the minimal effective concentration required to inhibit fibrinolysis was only studied *ex vivo* by addition of high-dose tissue-type plasminogen activator, and the degree of

fibrinolysis was measured with viscoelastic testing, either thromboelastography or thromboelastometry.<sup>10,11</sup> From those studies, the tranexamic acid concentration to effectively inhibit fibrinolysis was in the range of 6 to 15 mg/l. Two important limitations need to be noted. Experiments were performed *ex vivo* in the absence of endothelium and other plasma components that could influence fibrinolytic activation. Further, viscoelastic hemostatic tests have poor sensitivity to detect fibrinolytic activation.<sup>12</sup> Plasmin generation assays have recently been used to measure the impact of intravenous tranexamic acid administration on plasmin generation and fibrinolytic activation. In a cohort of healthy women undergoing cesarean delivery, the ability of the plasmin generation assay to detect the effect of tranexamic acid on fibrinolytic activation was found superior to what could be detected using thromboelastometry.<sup>13</sup> Although such an assay could be seen as a promising tool to estimate the effect of tranexamic acid on fibrinolytic activation in cardiac surgical patients, further *in vivo* clinical studies are needed before the minimal effective concentration of tranexamic acid can be used to define the optimal dosing scheme.

In summary, the model-based meta-analysis published by Zufferey *et al.* in this issue of *ANESTHESIOLOGY* confirms the safety and the clinical effect of low-dose tranexamic acid in adult cardiac surgical patients. In order to further refine the optimal dosing scheme, more studies will be needed to complete the missing information required to determine the minimal effective concentration of tranexamic acid to be targeted to inhibit fibrinolytic activation and reduce bleeding, while minimizing the risk of seizures.

### Competing Interests

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