ANESTHESIOLOGY

Exposure–Response Relationship of Tranexamic Acid in Cardiac Surgery

A Model-based Meta-analysis

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ABSTRACT

Background: It is unclear whether high-dose regimens of tranexamic acid in cardiac surgery (total dose, 80 to 100 mg/kg) confer a clinical advantage over low-dose regimens (total dose, approximately 20 mg/kg), particularly as tranexamic acid–associated seizure may be dose-related. The authors' aim was to characterize the exposure–response relationship of this drug.

Methods: Databases were searched for randomized controlled trials of intravenous tranexamic acid in adult patients undergoing cardiopulmonary bypass surgery. Observational studies were added for seizure assessment. Tranexamic acid concentrations were predicted in each arm of each study using a population pharmacokinetic model. The exposure–response relationship was evaluated by performing a model-based meta-analysis using nonlinear mixed-effect models.

Results: Sixty-four randomized controlled trials and 18 observational studies (49,817 patients) were included. Seventy-three different regimens of tranexamic acid were identified, with the total dose administered ranging from 5.5 mg/kg to 20 g. The maximum effect of tranexamic acid for postoperative blood loss reduction was 40% (95% credible interval, 34 to 47%), and the EC_{50} was 5.6 mg/l (95% credible interval, 0.7 to 11 mg/l). Exposure values with low-dose regimens approached the 80% effective concentration, whereas with high-dose regimens, they exceeded the 90% effective concentration. The predicted cumulative blood loss up to 48 h postsurgery differed by 58 ml between the two regimens, and the absolute difference in erythrocyte transfusion rate was 2%. Compared to no tranexamic acid, low-dose and high-dose regimens increased the risk of seizure by 1.2-fold and 2-fold, respectively. However, the absolute risk increase was only clinically meaningful in the context of prolonged open-chamber surgery.

Conclusions: In cardiopulmonary bypass surgery, low-dose tranexamic acid seems to be an appropriate regimen for reducing bleeding outcomes. This meta-analysis has to be interpreted with caution because the results are observational and dependent on the lack of bias of the predicted tranexamic acid exposures and the quality of the included studies.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Tranexamic acid is an antifibrinolytic agent that reduces postoperative blood loss and rates of erythrocyte transfusion and rethoracotomy in cardiopulmonary bypass surgery
- There appears to be a dose–response relationship between tranexamic acid and the risk of postoperative seizure
- Model-based meta-analysis is an extension of traditional meta-analysis that includes parametric models to describe the effect of dose

What This Article Tells Us That Is New

- This model-based meta-analysis found that low-dose tranexamic acid (total dose, approximately 20 mg/kg) was sufficient to reduce postoperative blood loss and erythrocyte transfusion in cardiopulmonary bypass surgery
- Although higher tranexamic acid doses were found to achieve a marginal gain in effectiveness, they increased the risk of postoperative seizure, particularly in procedures involving a high risk of bleeding

Tranexamic acid is an antifibrinolytic agent that reduces postoperative blood loss and rates of erythrocyte transfusion and rethoracotomy in cardiopulmonary bypass surgery.[1] Guidelines on patient blood management recommend the routine use of tranexamic acid for adult cardiac surgery.[2] However, there is no consensus on the dosing regimen of tranexamic acid to be administered. One dose–response study reported that low-dose tranexamic acid (10 mg/kg followed by 1 mg · kg^{-1} · h^{-1} over 12 h) was sufficient to reduce blood loss and that there was no evidence to support the use of higher doses.[3]

Yet on the basis of pharmacokinetic models,[4,5] some authors have proposed regimens targeting tranexamic acid plasma levels that were shown to fully inhibit fibrinolysis in *in vitro* studies.[6] These regimens involve the administration of high doses of tranexamic acid (*e.g.*, 30 mg/kg followed by 16 mg · kg^{-1} · h^{-1} during surgery with 2 mg/kg added to the pump prime, or a preoperative bolus of 100 mg/

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kg). Although the relationship between *in vivo* blood concentrations of tranexamic acid, fibrinolytic inhibition, and blood loss reduction has never been validated, several trials have shown a greater reduction in blood loss with these high doses compared to lower doses.[1,7,8] Unfortunately, tranexamic acid administration increases the risk of postoperative seizure,[1] a risk that appears to be dose-related.[9] The optimal tranexamic acid regimen for cardiopulmonary bypass surgery, in terms of both effectiveness and safety, therefore remains uncertain.

Model-based meta-analysis is an extension of traditional meta-analysis including parametric models to describe the effect of dose.[10,11] It also allows the impact of covariates such as surgical or demographic characteristics on the dose–response relationship to be taken into account. Using this meta-analytic technique, we aimed to quantify the effect of tranexamic acid exposure on postoperative bleeding events and seizure with the ultimate objective of clarifying the optimal dosing regimen of this agent in cardiopulmonary bypass surgery.

Materials and Methods

This systematic review and meta-analysis is reported in accordance with the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[12] The protocol was submitted to International Prospective Register of Systematic Reviews (PROSPERO) for registration in March 2019 and was registered in April 2020 (registration No. CRD42020132076).

Eligibility Criteria

We searched for trials that included adult patients (aged 18 yr or older) undergoing cardiopulmonary bypass (CPB) for cardiac or thoracic aortic surgery. To assess the exposure–response relationship of tranexamic acid with regard to effectiveness, we restricted our search to randomized controlled trials that compared an intravenous dose of tranexamic acid to another intravenous tranexamic acid dose or to no treatment (including placebo). Trial arms that administered topical tranexamic acid, oral tranexamic acid, or another antifibrinolytic were excluded. The efficacy outcomes selected were postoperative blood loss, allogeneic erythrocyte transfusion, and rethoracotomy for any reason. Postoperative blood loss, the primary outcome, was recorded as the volume of chest tube drainage. All measurements up to drain removal were collected. For the other efficacy outcomes, there was no restriction on the timing of measurements of the events concerned. To assess the exposure–response relationship with respect to safety, the endpoint of interest was postoperative seizure. As this event is rare and its occurrence in relation to the use of tranexamic acid has been reported only since 2008 in cardiac surgery,[13] we extended our search to observational studies and also included arms of randomized controlled trials of intravenous tranexamic acid that had an ineligible comparator for the effectiveness analysis. These latter trial arms were considered as observational studies in this review. There was no restriction as to the type or cause of seizure. Seizures occurring after intensive care (*i.e.*, 24 to 48 h after the end of surgery) were not taken into consideration.

Search Strategy and Study Selection

Relevant trials were identified by a computerized search in Medical Literature Analysis and Retrieval System Online (MEDLINE, PubMed) and the Cochrane Central Registry of Controlled Trials (Central) from the inception of these databases up to June 2019. The systematic search strategy used for both databases is shown in the Supplemental Digital Content 1 (http://links.lww.com/ALN/C513). In addition, we checked the reference lists of the trials selected and those of relevant systematic reviews. To identify eligible trials in progress or unpublished, we searched the International Clinical Trials Registry Platform and ClinicalTrials.gov. No language, publication date, or publication status restrictions were imposed. Foreign papers were translated. Three of the authors (B.G., B.V., and P.J.Z.) developed and independently conducted the search. Studies were first screened on the basis of title and/or abstract. The full texts of potentially eligible trials were then retrieved and evaluated for inclusion. Any disagreements were resolved by consensus.

Data Collection and Risk of Bias Assessment

Data were extracted using a data extraction sheet specifically designed for this review in Excel (Microsoft, USA). One of the authors conducting the literature search (P.J.Z.) extracted the data from the studies selected. The two others (B.G. and B.V.) checked the extracted data. In the event of disagreement with regard to data extraction, the decision of a fourth author (E.O.) was final. The authors of the selected trials were contacted to supply any missing information or clarifications required in June 2019. A reminder was sent in July 2019 if necessary. Data were extracted from each trial included with respect to (1) the characteristics of the trial participants (including age, weight, and type and duration of surgery); (2) the tranexamic acid regimen used; (3) risk factors for postoperative bleeding,[14] erythrocyte transfusion,[15] and seizure;[9,16] (4) outcome data; and (5) the number of patients randomized and the number of patients available for the analyses. A full description of the extracted data is provided in the Supplemental Digital Content 1 (http://links.lww.com/ALN/C513). The risk of bias for each randomized control trial was assessed (by P.J.Z.) using the Cochrane risk of bias tool. Trials were considered to be at low summary risk of bias if allocation concealment, blinding of participants, and study personnel, and blinding of outcome assessment were all judged to be adequate. The risk of bias for each observational study was assessed (by B.V.) using the Newcastle–Ottawa quality scale.[17]

Data Synthesis and Analysis

Summary Measures. For each postoperative blood loss observation, the timing of the measurement relative to the

end of surgery and the mean and corresponding SD were collected. When the median and range (or minimum–maximum range) were reported rather than the mean and SD, approximation methods were used to estimate these latter values.[18] Normally distributed postoperative blood loss values were then converted to the logarithmic scale.[19]

The proportions of patients requiring erythrocyte transfusion and rethoracotomy, respectively, and the proportion experiencing seizure were calculated. In the case of zero events, a continuity correction of 0.5 was applied.

Tranexamic acid exposure in each treatment arm was evaluated by simulation. The mean tranexamic acid kinetic was simulated on the basis of the characteristics of each arm (dosing regimen, mean patient body weight) and the pharmacokinetic model developed by Grassin-Delyle *et al.*[5] In the event of missing information on mean body weight, CPB duration, or surgery duration, a multivariate imputation was performed using the multivariate imputation by chained equations, mice package in R software (R core team, Austria).[20] The mean tranexamic acid concentration from the start of surgery up to 12 h ($[TXA]^{0-12h}$) was calculated for each arm of each study.

Synthesis of Results. The relationship between tranexamic acid exposure and outcome data was evaluated by performing a model-based meta-analysis using nonlinear mixed-effect models.[10] For each outcome, the analysis provided an estimation of maximum-effect and EC_{50} parameters corresponding respectively to the maximum effect of tranexamic acid and the value of $[TXA]^{0-12h}$ required to achieve 50% of this maximum effect. For postoperative blood loss, we also modeled tranexamic acid exposure as a time-varying covariate to identify the period when tranexamic acid exposure contributed the most to blood loss reduction.

We first performed a longitudinal model-based meta-analysis to describe the time course of blood loss and the relationship between $[TXA]^{0-12h}$ and postoperative blood loss.[11] The following model was used:

$$LBL_{ijk} = \log\left(\frac{BL_{MAXi}\times\tau_{ijk}}{\tau_{50}+\tau_{ijk}}\times\left(1-\frac{E_{MAXi}\times[TXA]_{ij}^{0-12h}}{EC_{50}+[TXA]_{ij}^{0-12h}}\right)\right)+\hat{\sigma}_{ijk}\times\varepsilon_{ijk}$$

where LBL_{ijk} and τ_{ijk} correspond to the observed postoperative blood loss (on a logarithmic scale) and to the sampling time in the j[th] arm of the i[th] study at the k[th] sampling point, respectively. The parameters τ_{50} and EC_{50} correspond, respectively, to the time to attainment of 50% of the maximum blood loss and to the mean tranexamic acid concentration achieving 50% of the maximum effect. The parameters BL_{MAXi} and E_{MAXi} correspond, respectively, to the study-specific maximum blood loss and to the maximum effect. These parameters were assumed to conform to a log-normal and a logit-normal distribution, respectively:

$$\log(BL_{MAXi}) = \mu_{BL_{MAX}} + u_i \text{ with } u_i \sim N\left(0,\ \sigma^2_{BL_{MAX}}\right)$$

$$\text{logit}(E_{MAXi}) = \mu_{E_{MAX}} + v_i \text{ with } v_i \sim N\left(0,\ \sigma^2_{E_{MAX}}\right)$$

where u_i and v_i are the random effects representing interstudy variability. Unexplained intrastudy variability was accounted for using a residual error term that was assumed to be normally distributed ($\varepsilon_{ijk} \sim N(0, \sigma^2_e)$) and scaled according to the standard error of each observation ($\hat{\sigma}_{ijk}$)

To explore tranexamic acid as a time-varying covariate during the first 48 h after the start of the surgery, the data were fitted to a second model:

$$LBL_{ijk} = \log\left(\frac{BL_{MAXi}\times\tau_{ijk}}{\tau_{50}+\tau_{ijk}}\times\left(1-\int_0^{48}\pi(\delta,\gamma,t)\times\frac{E_{MAXi}\times C_{ij}(t)}{EC_{50}+C_{ij}(t)}dt\right)\right)+\hat{\sigma}_{ijk}\times\varepsilon_{ijk}$$

where $C_{ij}(t)$ is the simulated mean tranexamic acid concentration in the j[th] arm of the i[th] study. The function $\pi(\delta,\gamma,t)$ is a weighting function. The periods associated with high values of $\pi(\delta,\gamma,t)$ correspond to those contributing the most to the overall effect of tranexamic acid. The weighting function is based on a reparametrized gamma distribution:

$$\pi(\delta,\gamma,t) = G(t;\alpha,\beta)$$
$$\alpha = 1+\delta\times\beta$$
$$\beta = \frac{\delta+\sqrt{\delta^2+4\times\gamma^2}}{2\times\gamma^2}$$

with $G(t;\alpha,\beta)$ representing the density of a gamma distribution with a shape parameter α and a rate parameter β. The parameter δ corresponds to the mode of the distribution (*i.e.*, to the time at which the weighting is maximal and consequently to the time at which tranexamic acid exposure contributes the most to the overall effect of the drug) and γ to the SD of the distribution.

The relationship between $[TXA]^{0-12h}$ and erythrocyte transfusion to compensate for blood loss was assessed using the following model:

$$\text{logit}(Trans_{ij}) = \text{logit}\left(Trans_{0i}\times\left(1-\frac{E_{MAXi}\times[TXA]_{ij}^{0-12h}}{EC_{50}+[TXA]_{ij}^{0-12h}}\right)\right)+\hat{\sigma}_{ij}\times\varepsilon_{ij}$$

where $Trans_{ij}$ corresponds to the proportion of patients who received erythrocyte transfusion to compensate for blood loss in the j[th] arm of the i[th] study. The parameter $Trans_{0i}$ corresponds to the study-specific transfusion rate in the absence of tranexamic acid exposure. It is assumed to follow a logit-normal distribution:

$$\text{logit}(Trans_{0i}) = \mu_{Trans_0} + w_i \text{ with } w_i \sim N\left(0, \sigma^2_{Trans_0}\right)$$

The relationship between $[TXA]^{0-12h}$ and seizure was assessed using the following logit-linear model:

$$\text{logit}\left(Conv_{ij}\right) = \beta_0 + \beta_{\text{TXA}} \times \left[TXA\right]_{ij}^{0-12h} + \omega_i + \hat{\sigma}_{ij} \times \varepsilon_{ij}$$

where $Conv_{ij}$ corresponds to the proportion of patients experiencing seizure in the j[th] arm of the i[th] study. Parameter ω_i corresponds to the random intercept and is assumed to be normally distributed ($\omega_i \sim N\left(0, \sigma_\omega^2\right)$).

To explore the heterogeneity between studies, we evaluated the impact of covariates on the exposure–response relationships. We evaluated risk factors for postoperative bleeding, erythrocyte transfusion, and seizure (described in Supplemental Digital Content 1, http://links.lww.com/ALN/C513) and also the risk of bias within studies. Each of these covariates were included in the previous models to assess their impact on BL_{MAXi}, E_{MAXi}, $Trans_{0i}$, and $Conv_{ij}$.

For example, the effect of the mean patient body weight (BW_i) within each study on the study-specific transfusion rate was implemented as follows:

$$\text{logit}(Trans_{0i}) = \mu_{Trans_0} + \theta_{BW} \times (BW_i - 76) + w_i \; with \; w_i \sim N\left(0, \sigma^2_{Trans_0}\right)$$

where θ_{BW} corresponds to the effect of mean patient body weight on the study-specific transfusion rate.

For seizure, the effect of the proportion of patients undergoing open-chamber surgery within each study (OC_i) on the study-specific probability of seizure was implemented as follows:

$$\text{logit}\left(Conv_{ij}\right) = \beta_0 + \beta_{\text{TXA}} \times \left[TXA\right]_{ij}^{0-12h} + \theta_{OC} \times OC_i + \omega_i + \hat{\sigma}_{ij} \times \varepsilon_{ij}$$

where θ_{OC} corresponds to the effect of the percentage of open chamber surgery on the study-specific seizure probability.

Parameter Estimation. Data analysis was performed using R software.[21] The meta-analysis model was estimated by a Bayesian approach using the rstan package in R. As no previous information on exposure response parameters was available, noninformative previous distributions were assumed for all the parameters ($\mathcal{U}\left(-\infty;+\infty\right)$ for mean parameters and $\mathcal{U}\left(0;+\infty\right)$ for SD)) except EC_{50}, for which a weakly informative uniform previously was assumed ($\mathcal{U}\left(0;100\right)$). During the modeling process, the robustness of the results to the choice of previous distribution was explored. The models for covariate selection were compared by leave-one-out cross-validation using the loo package in R.[22] The final model was assessed in terms of basic goodness-of-fit plots using a visual predictive check. All graphics were generated using the ggplot2 package in R.[23]

Sensitivity Analyses. Two sensitivity analyses were performed to assess the impact of the uncertainty of the pharmacokinetic predictions on the exposure–response relationships. We first limited our analysis to studies for which no imputation had been used for estimating tranexamic acid exposure. The second analysis considered uncertainty in the predictions of tranexamic acid exposure. We generated 500 data sets. In each data set, tranexamic acid exposures ($\left[TXA\right]^{0-12h}$) were simulated using the standard errors of the tranexamic acid pharmacokinetic parameters reported by Grassin-Delyle *et al.*[5] Posterior mean of the parameters of the model-based meta-analyses were calculated for each data set. The distributions of the obtained values were presented as histograms.

Simulations of the Effect of Different Dosing Regimens. We simulated the outcomes in two hypothetical trials to examine the effect of different tranexamic acid dosing regimens on postoperative bleeding events and seizure. The first trial included patients undergoing coronary artery bypass graft (CABG) surgery (closed-chamber procedure) with a mean duration of surgery and CPB of 3 h and 1.5 h, respectively. The second trial included patients undergoing complex open-chamber surgery with a mean duration of surgery and CPB of 4 h and 2.5 h, respectively. In both cases, the body weight value used for simulation was the mean weight observed in the meta-analysis. The dosing regimens were chosen on the basis of the total dose administered (high- *vs.* low-dose) and the duration of tranexamic acid administration (single bolus *vs.* bolus plus infusion). For high-dose tranexamic acid, we chose administration of a single preoperative bolus as proposed by Karski *et al.* (100 mg/kg)[7] and a second regimen corresponding to that used in the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) study (30 mg/kg followed by 16 mg · kg^{-1} · h^{-1} during surgery, with a further 2 mg/kg being added to the pump prime).[24] For low-dose tranexamic acid, we chose a single preoperative bolus of 20 mg/kg as proposed by Lambert *et al.*,[25] and finally the regimen proposed by Horrow *et al.* (10 mg/kg followed by 1 mg · kg^{-1} · h^{-1} for 12 h).[3]

Results

Study Selection

A total of 82 clinical trials (49,817 patients) were selected, comprising 64 randomized controlled studies (12,378 patients) for the effectiveness analysis and 18 additional observational studies (37,439 patients) for the analysis of seizure. The flow chart of the study selection process is presented in figure 1. Altogether, 61 authors reporting 73 trials were contacted, of whom 34 replied, with 19 providing supplementary information for 20 trials (see Acknowledgments).

Study Characteristics

In total, 36 (44%) studies included CABG surgery, and 55 (66%) studies included open-chamber surgery. The mean duration of CPB was 1 h 48 min (range, 1 h 2 min to 5 h 28 min), and the mean duration of surgery was 4 h 7 min (range, 2 h 19 min to 7 h 45 min). Women comprised 31% of the patients. The mean age was 62 yr (range, 36 to 77 yr), and the mean weight was 74 kg (range, 49 to 89 kg). Altogether, 73 different intravenous tranexamic acid regimens were identified, with the total dose of tranexamic

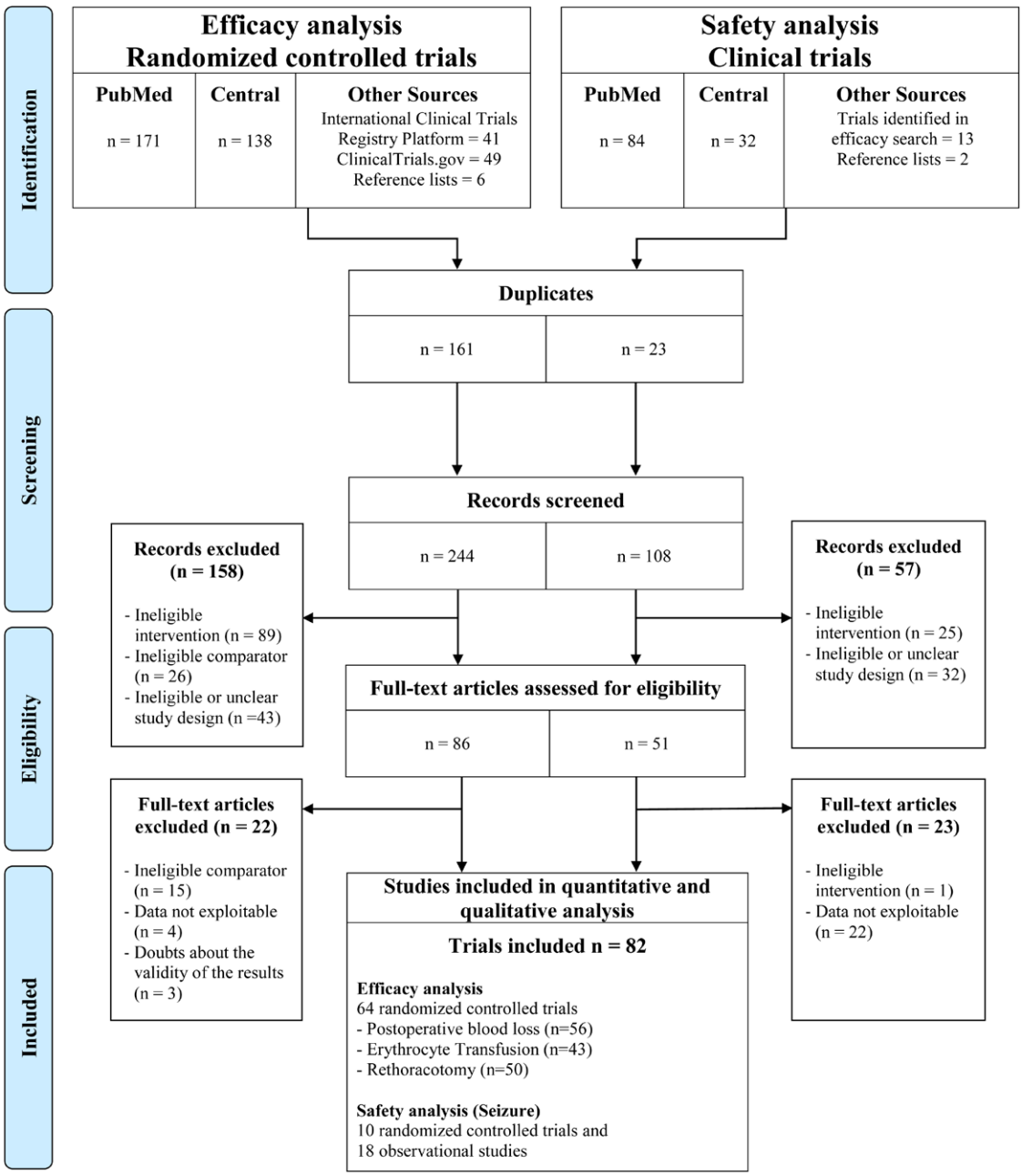

Fig. 1. Flow chart of the study selection process. The selection of studies included in the effectiveness analysis is illustrated on the *left* and that of studies included in the analysis of tranexamic acid-associated seizure on the *right*. Central, Cochrane Central Registry of Controlled Trials.

acid administered ranging from 5.5 mg/kg to 20 g. Patient weights and durations of CPB and surgery were imputed to estimate plasma tranexamic acid exposure in 19, 1, and 18 trials, respectively. Population pharmacokinetic estimations of the mean tranexamic acid concentration from the start of surgery up to 12 h ($[TXA]^{0-12h}$) ranged from 6.2 to 281 mg/l (mean, 69 mg/l). The characteristics of each trial selected are summarized in the Supplemental Digital Content 1 (http://links.lww.com/ALN/C513) and 2 (http://links.lww.com/ALN/C514).

Risk of Bias within Studies

In all, 49 randomized, controlled trials were double-blind, of which 18 had adequate allocation concealment. The

individual components of the risk of bias across studies, using the Cochrane Collaboration's tools, are presented in figure 2. All the observational studies had a score of five or above on the Newcastle–Ottawa scale. The Supplemental Digital Content 1 (http://links.lww.com/ALN/C513) presents the risk of bias in individual studies.

Outcomes

Postoperative Blood Loss. A total of 56 randomized controlled trials reported postoperative blood loss, including 158 observations with tranexamic acid and 100 without tranexamic acid (fig. 3).

A nonlinear mixed-effects maximum-effect model was used to describe bleeding over time. We included a trial-specific random effect on the maximum postoperative blood loss parameter (BL_{MAX}) to account for the variability between trials in terms of postoperative blood loss observations. The time to reach 50% of $BL_{MAX,}$ τ_{50} was 13.0 h (95% credible interval, 11.6 to 14.5 h).

To quantify the effect of tranexamic acid on blood loss, we first performed an analysis in which the tranexamic acid exposure marker was the non–time-varying covariate ($[TXA]^{0-12h}$). The maximum effect of tranexamic acid on blood loss reduction was 40% (95% credible interval, 34 to 47%). The EC_{50}, the value of $[TXA]^{0-12h}$ needed to achieve 50% of the maximum effect, was 5.6 mg/l (95% credible interval, 0.7 to 11.1 mg/l). This EC_{50} corresponds to an 80% effective concentration of 22.4 mg/l. The exposure–response relationship of tranexamic acid for postoperative blood loss is presented in figure 4.

Covariate analysis indicated that the risk of bias within studies did not significantly affect the maximum-effect parameter of tranexamic acid. Furthermore, none of the risk factors for postoperative blood loss was found to have a statistically significant impact on BL_{MAX}.

The parameter estimates and 95% credible intervals for this first model are shown in the Supplemental Digital Content 1 (http://links.lww.com/ALN/C513). The visual predictive check indicated that this model was suitable for predicting the observed data on postoperative drain blood loss (fig. 3).

A second model was used to quantify postoperative blood loss in which exposure to tranexamic acid from the start of surgery up to 48 h was modeled as a time-varying covariate. A weighting function was added to estimate the contribution of tranexamic acid concentrations over time to the overall effect. The estimated values of the parameters BL_{MAX}, τ_{50}, tranexamic acid maximum effect, and EC_{50} were similar to those estimated in the first model (Supplemental Digital Content 1, http://links.lww.com/ALN/C513). The shape of the weighting function indicated that the impact of tranexamic acid was not constant over time (fig. 5) but instead increased during the surgical intervention, reaching a maximum value 3.8 h (95% credible interval, 2.1 to 6.1 h) after the start of surgery. The impact of tranexamic acid then decreased, with virtually no further impact of tranexamic acid plasma concentrations 8 h after the start of surgery.

Erythrocyte Transfusion to Compensate for Blood Loss. A total of 43 randomized controlled trials reported erythrocyte transfusion, including 109 observations with tranexamic acid and 39 without tranexamic acid (fig. 3). Seventeen of these observations were not clearly defined as erythrocyte transfusion outcomes and may have included patients receiving transfusions of other blood constituents.

The estimated probability of transfusion in the absence of tranexamic acid exposure ($Trans_0$) was 62% (95% credible interval, 53 to 72%). Tranexamic acid reduced the rate of transfusion with a maximum effect of 0.33 (95% credible interval, 0.25 to 0.42). The EC_{50} was 3.1 mg/l (95% credible interval, 0.1 to 6.3 mg/l), corresponding to an 80% effective concentration of 12.5 mg/l (fig. 4). As in the case of postoperative blood loss, the risk of bias within studies was not found to be statistically significant for inclusion

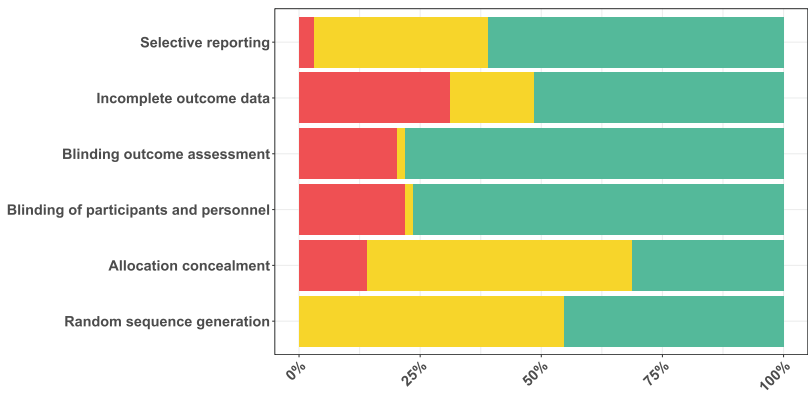

Fig. 2. Summary of the risk of bias across studies. The percentage of studies judged to be at low (*green*), unclear (*yellow*), or high risk (*red*) of bias is presented for each risk of bias domain.

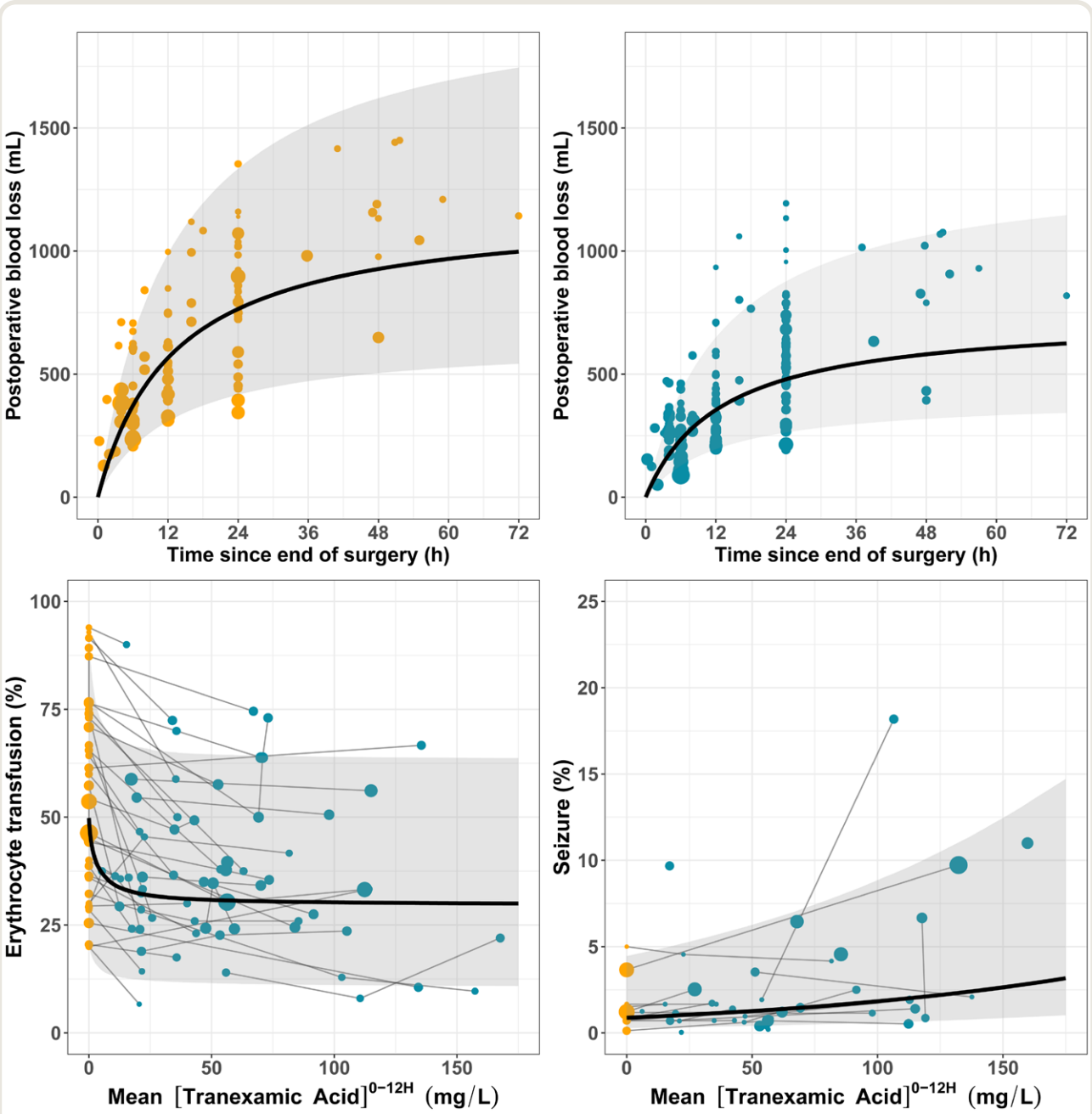

Fig. 3. Visual predictive checks. *Top*, The time course of postoperative blood loss without tranexamic acid (*left*) and with tranexamic acid (*right*). *Bottom*, Representation, as a function of the mean tranexamic acid concentration from the start of surgery up to 12 h, the percentage of patients with erythrocyte transfusion (*left*) and with seizure (*right*). The *solid lines* indicate model-based predictions of outcomes, the *shaded areas* showing the respective 90% Bayesian credible intervals. *Circles* represent observed values without tranexamic acid (*yellow*) and with tranexamic acid (*blue*). *Bottom*, Observations from the same trial are connected by a *solid line*.

in the model. Total body weight was the only covariate found to affect the $Trans_0$ parameter to a statistically significant extent. We could not estimate a model in which the tranexamic acid exposure marker was a time-varying covariate. The parameter estimates and 95% credible intervals are presented in the Supplemental Digital Content 1 (http://links.lww.com/ALN/C513). The visual predictive check indicated that the model was suitable for predicting the observed erythrocyte transfusion rates (fig. 3).

Reoperation. Rethoracotomy was reported in 50 trials selected for the effectiveness analysis. The median rate was 4.4% (interquartile range, 2.8 to 8.5%) in the placebo or

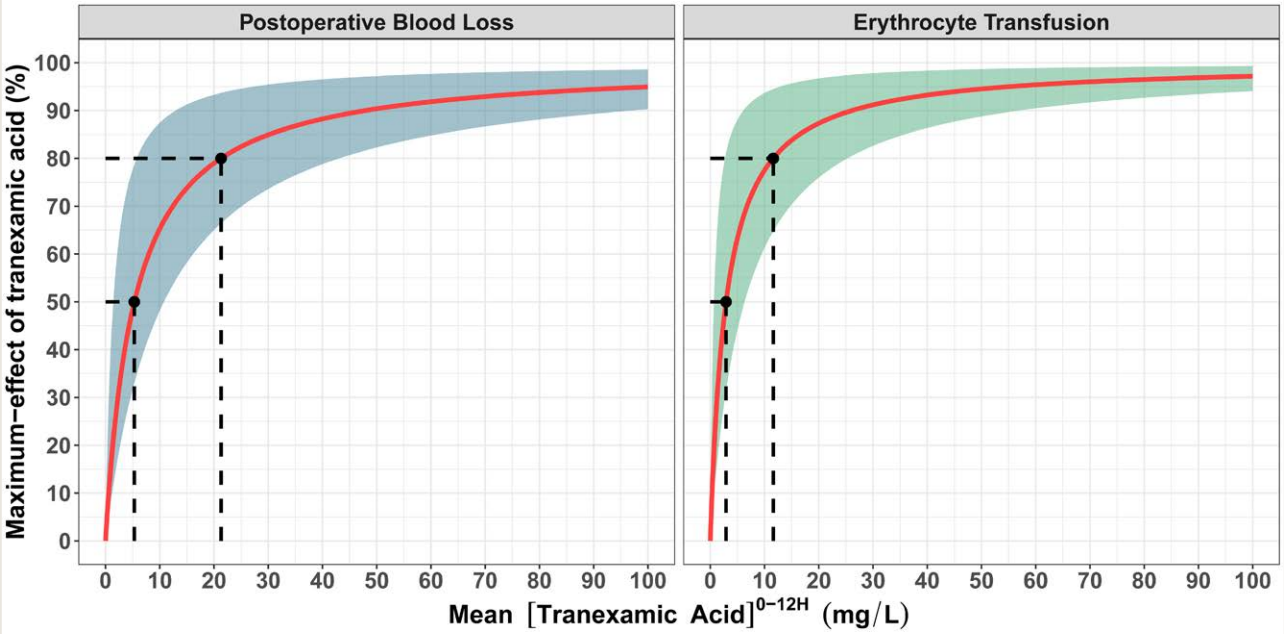

Fig. 4. Exposure–response curve for tranexamic acid and bleeding events. Exposure to tranexamic acid is the mean tranexamic acid concentration from the start of surgery up to 12 h; the *dashed lines* represent the EC_{50} and the 80% effective concentration.

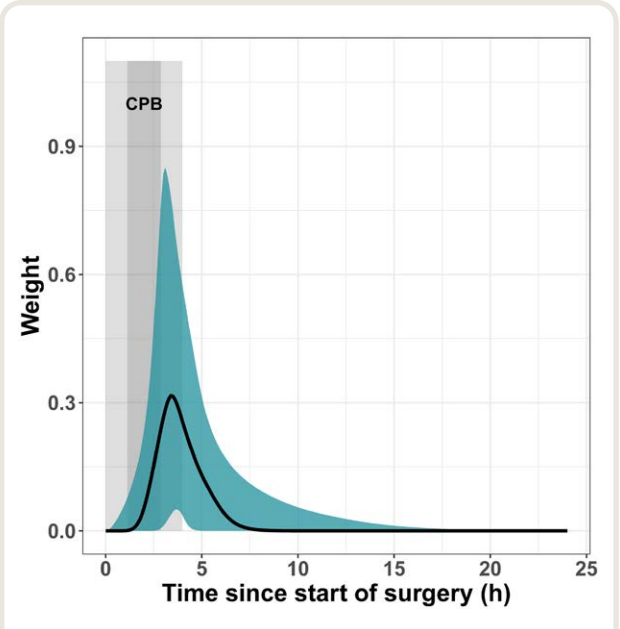

Fig. 5. Effect of tranexamic acid over time. The *solid line*, with its *shaded* 90% credible interval, is a parametric weight function indicating the period when tranexamic acid contributes the most to postoperative blood loss reduction. The *dark gray column* represents the mean duration of cardiopulmonary bypass (CPB) in the meta-analysis.

no-treatment arms and 2.6% (interquartile range, 1.4 to 4.6%) in the tranexamic acid treatment arms. No concentration–response relationship for tranexamic acid could be estimated for this outcome, probably owing to the low rate of events.

Seizure. A total of 56 seizure observations were extracted from 10 randomized controlled trials and 18 observational studies, all published from 2008 onward. The concentration–response relationship for tranexamic acid with regard to seizure was modeled using a linear model after logit transformation. Tranexamic acid increased the risk of postoperative seizure by 1.07 (95% credible interval, 1.06 to 1.09) per 10 mg/l increase in $[TXA]^{0-12h}$. Compared to no exposure to tranexamic acid, a $[TXA]^{0-12h}$ of 100 mg/l doubled the risk of seizure (2.1; 95% credible interval, 1.9 to 2.4). Covariate analysis did not reveal any statistically significant effect of the type of study reported (randomized controlled trials *vs.* observational studies). In contrast, the type of surgery and the duration of CPB both affected the risk of seizure. Open-chamber surgery resulted in a 5.5-fold increase in the risk of seizure compared to closed-chamber procedures (95% credible interval, 3.2 to 10). Each additional hour of CPB doubled the risk of seizure (2.0; 95% credible interval, 1.2 to 3.2). The parameter estimates and 95% credible intervals are shown in the Supplemental Digital Content 1 (http://links.lww.com/ALN/C513). The visual predictive check indicated that the model was suitable for predicting the observed seizure rates (fig. 3).

Sensitivity Analyses

Two sensitivity analyses were performed to assess the impact of imputing data for pharmacokinetic predictions and the uncertainty in the parameter estimates of the pharmacokinetic model used for predictions. Both analyses showed results similar to the primary analysis. Exclusion of studies in which imputation was performed increased the credible interval of the EC_{50} parameters. The results are shown in the Supplemental Digital Content 1 (http://links.lww.com/ALN/C513).

Simulations

We simulated the outcomes in two hypothetical trials to examine the effect of different tranexamic acid dosing regimens on postoperative bleeding events and seizure.

The first trial included patients undergoing CABG surgery (closed-chamber procedure) with a mean duration of surgery and CPB of 3 h and 1.5 h, respectively. The concentration-time courses of tranexamic acid for the different dosing regimens are presented in figure 6. With low-dose tranexamic acid, the mean exposure values were 21 mg/l, close to the 80% effective concentration for postoperative blood loss. With high-dose tranexamic acid, the mean exposure values were above the 90% effective concentration. The estimated cumulative blood loss up to 48 h after the end of surgery without tranexamic acid was 909 ml (95% credible interval, 815 to 1,016 ml). Low-dose tranexamic acid, given either as a single preoperative bolus or as a preoperative bolus followed by an intraoperative infusion, reduced postoperative blood loss by 32% (95% credible interval, 27 to 37%; fig. 6 and Supplemental Digital Content 1, http://links.lww.com/ALN/C513). Compared to low-dose tranexamic acid, high-dose tranexamic acid reduced cumulative postoperative blood loss up to 48 h postsurgery by a further 58 ml (95% credible interval, 54 to 65 ml). The probability of erythrocyte transfusion as a function of tranexamic acid exposure ($[TXA]^{0-12h}$) is illustrated in figure 6. Exposure values for all tranexamic acid regimens were above the 80% effective concentration for erythrocyte transfusion. Without tranexamic acid, the probability of transfusion was 66% (95% credible interval, 57 to 74%), with low-dose tranexamic acid it was 46% (95% credible interval, 38 to 54%), and with high-dose tranexamic acid it was 44% (95% credible interval, 36 to 52%; fig. 6). The absolute rate difference in erythrocyte transfusion between low- and high-dose tranexamic acid was 2% (95% credible interval, 0.4 to 4.3%). In this first case scenario, the probability of postoperative seizure remained low, less than 1%, regardless of the tranexamic acid regimen (fig. 6).

The second trial included patients undergoing open-chamber surgery with a mean duration of surgery and CPB of 4 h and 2.5 h, respectively. Simulated bleeding events were similar to those in the first scenario, as our models for bleeding events did not include surgical covariates. However, the risk of seizure was increased in this second scenario as both open-chamber surgery and CPB duration were associated with a higher risk of this event. Without administration of tranexamic acid, the probability of seizure was 2.85% (95% credible interval, 1.82 to 4.63%). The probability was increased 1.2-fold with low-dose tranexamic acid and was doubled with high-dose tranexamic acid (fig. 6).

Discussion

With regard to effectiveness, our results indicated a reduction in postoperative blood loss and erythrocyte transfusion as exposure to tranexamic acid increased. We chose the commonly used maximum-effect model to describe the effect of tranexamic acid exposure. With this model, the increase in effectiveness progressively declined with increasing exposure. Once the concentration exceeds the 80% effective concentration, further changes in drug concentration appear to have little impact on drug effect.[26] The exposure value with the low-dose tranexamic acid regimen proposed by Horrow *et al.*[3] (10 mg/kg followed by 1 mg · kg^{-1} · h^{-1} over 12 h) was close to the 80% effective concentration for postoperative blood loss and above the 80% effective concentration for erythrocyte transfusion. Compared to this regimen, a fivefold increase in total dose (100 mg/kg) achieved only a 58 ml (95% credible interval, 54 to 65 ml) increment in the reduction of postoperative blood loss, up to 48 h postsurgery, with a decrease in erythrocyte transfusion rate from 46% to 44%. Our exposure–response relationship for erythrocyte transfusion corroborates the results of a previous meta-analysis in cardiac surgery showing in a subgroup analysis that tranexamic acid at doses less than 2 g and at doses of 2 to 10 g achieved similar reductions in erythrocyte transfusion rate.[27]

To examine when tranexamic acid should be initiated and for how long, we modeled tranexamic acid exposure as a time-varying covariate. The result (fig. 5) suggests that tranexamic acid administration should be initiated before CPB, as proposed by Brown *et al.*,[28] and should be designed to achieve effective concentrations approximately 4 h after the start of surgery (*i.e.*, toward the end of surgery) when tranexamic acid contributes the most to blood loss reduction. Concentrations close to 80% effective concentration can be achieved at the end of surgery with a low-dose regimen administered either as a preoperative bolus plus infusion (10 mg/kg followed by 1 mg · kg^{-1} · h^{-1})[5,29] or as a single preoperative loading dose of 20 mg/kg (fig. 6). Postoperative administration of tranexamic acid appears unnecessary because tranexamic acid concentrations will decrease but nevertheless remain sufficient (greater than or equal to EC_{50}) up to the end of the drug's contribution to blood loss reduction (8 h after the start of surgery). This supports the findings of Casati *et al.* showing that tranexamic acid administration after cardiac surgery was not advantageous.[30]

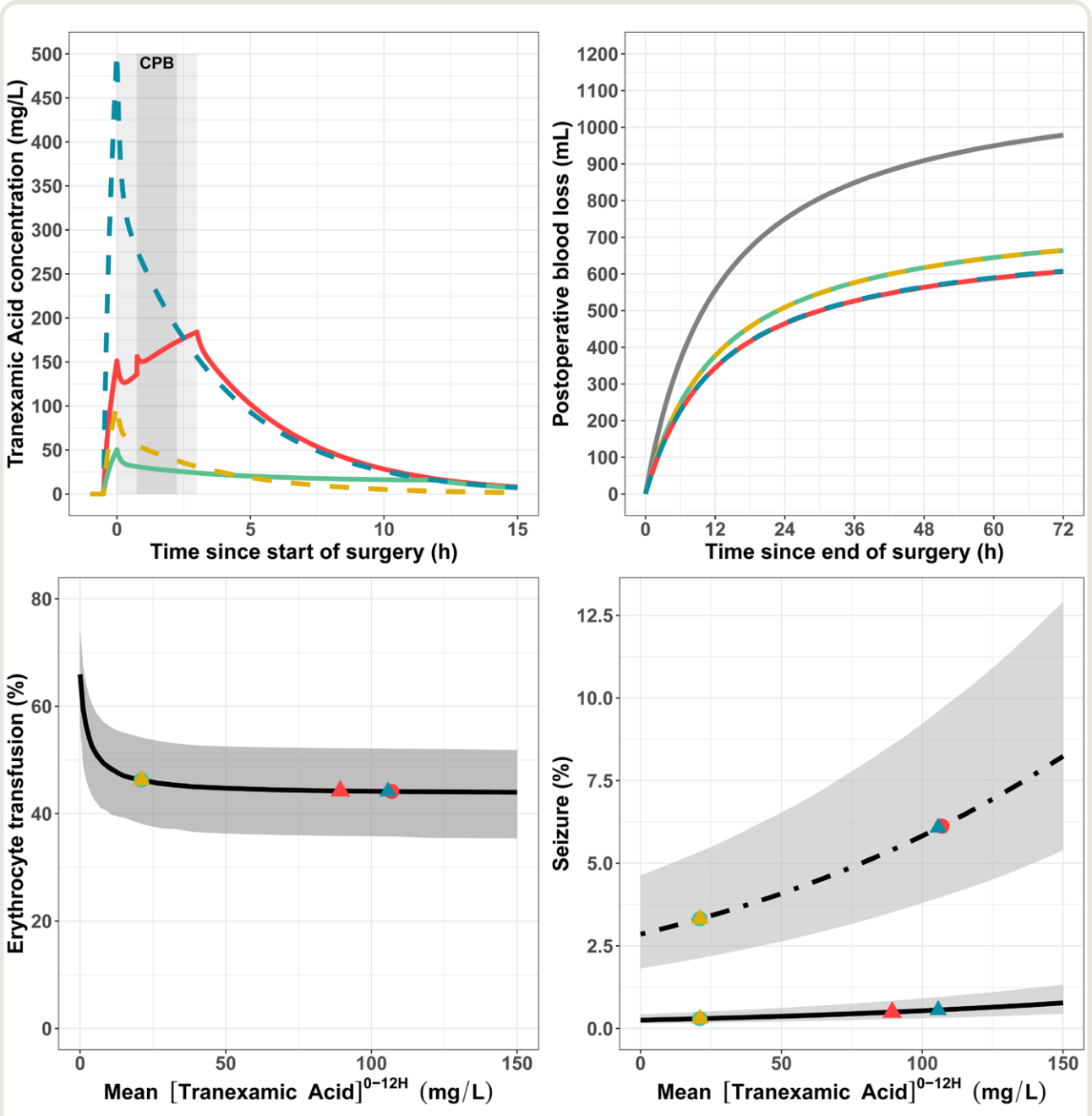

Fig. 6. Simulated bleeding and seizure events. The following tranexamic acid regimens were simulated: 100 mg/kg preoperative loading dose (*blue dashed line* and *blue triangle*); 30 mg/kg preoperative loading dose followed by 16 mg · kg^{-1} · h^{-1} during surgery with a further 2 mg/kg added to the cardiopulmonary bypass (CPB) pump prime (*red solid line* and *red triangle* for 3 h of surgery, *red circle* for 4 h of surgery); 10 mg/kg preoperative loading dose followed by 1 mg · kg^{-1} · h^{-1} for 12 h (*green solid line* and *green circle*); 20 mg/kg preoperative loading dose (*yellow dashed line* and *yellow triangle*). *Top left*, Predicted concentrations of tranexamic acid for various regimens indicated as described above, the *dark gray column* representing the mean duration of CPB in the meta-analysis. *Top right*, Predicted postoperative mediastinal blood loss without tranexamic acid (*gray solid line*) and for the different tranexamic acid regimens indicated as described above. *Bottom*, As a function of the mean tranexamic acid concentration from start of surgery up to 12 h, the probability of erythrocyte transfusion (*left*) and of seizure (*right*). *Bottom right*, The *black solid line* represents model-based study-level predictions of a hypothetical trial of patients undergoing coronary artery bypass grafting with a mean duration of surgery and CPB of 3 h and 1.5 h, respectively; the *black dot-dash line* represents model-based predictions at the study level of a hypothetical trial in patients undergoing open-chamber surgery with a mean duration of surgery and CPB of 4 h and 2.5 h, respectively; the average weight was 74 kg.

Tranexamic acid administration increases the risk of postoperative seizure,[1] a risk that appears to be dose-related.[9] Our meta-analysis indicated that intraoperative administration of high-dose tranexamic acid (total dose, 80 to 100 mg/kg) resulted in a twofold increase in postoperative seizures, whereas low-dose tranexamic acid (total dose, approximately 20 mg/kg) was associated with a less than 1.2-fold increase in seizure rate. However, the absolute increase in the incidence of postoperative seizures with tranexamic acid also depends on the coexistence of other risk factors for such seizures, such as the duration of CPB, open-heart procedures, older age, renal failure, or redux surgery.[9,16] Our covariate analysis suggested that open-chamber surgery and duration of CPB were associated with a higher rate of seizure independently of tranexamic acid exposure. The simulation suggested that during isolated CABG surgery, tranexamic acid had virtually no effect on postoperative seizure rate, but this was not true for complex open-heart procedures (fig. 6). Unfortunately, most of the risk factors for postoperative bleeding adverse events[14,15] are also risk factors for postoperative seizure in the context of cardiac surgery. The administration of high-dose tranexamic acid to patients at high risk of bleeding may expose patients to an increased risk of seizure for a minimal reduction in bleeding events. Based on a benefit–risk analysis, the use of high-dose tranexamic acid is questionable.

Our study has several limitations that need to be addressed. First, the exposure–response relationships are strongly dependent on the lack of bias of the predicted tranexamic acid exposures. Blood concentrations of tranexamic acid were simulated because real concentrations were not available. We chose the pharmacokinetic model developed by Grassin-Delyle *et al.*[5] over other models[4,31–33] as it included the largest number of patients, it covered a wide range of patients' characteristics, and it requires only one covariate, body weight, for pharmacokinetic simulation. The presence of variability and uncertainty in the parameter estimates of this pharmacokinetic model, the model extrapolations, and the imputation of body weight and surgical duration in some studies all contributed to a degree of uncertainty in the pharmacokinetic predictions. To account for this uncertainty, we performed sensitivity analyses that showed results similar to those obtained with the primary analysis.

Second, the exposure–response relationships are also dependent on the unbiased assessment of outcomes. For efficacy outcomes, our assessment of the risk of bias within studies was not found to be statistically significant for inclusion in the models. Yet for seizure, the risk of information bias was noticeable and probably resulted in an underestimation of the true incidence of events. None of the included studies was designed to assess this safety outcome. The detection or confirmation of seizure with an objective test (electroencephalogram or computed tomography scans) was not mandatory. Also, patients may have been deeply sedated when seizures would be expected. As in a previously reported meta-analysis,[34] we combined data from randomized and observational studies for the assessment of tranexamic acid–associated seizure to increase the power of the analysis and help offset the limitations of analyzing this rare outcome. Yet the risk of selection and confounding bias is nonnegligible in observational studies.[35] Because of this, great care should be taken when interpreting our covariate analysis for seizure that did not reveal any statistically significant effect of the type of study reported (randomized controlled trials *vs.* observational studies).

Finally, the exposure–response relationships are also dependent on the data analysis. Our analyses were limited by statistical power as model-based meta-analysis requires the estimation of multiple parameters compared to conventional meta-analyses. We could not estimate a dose–effect relationship for rethoracotomy, probably owing to the low rate of events. It is therefore not possible to conclude for this outcome an advantage of a dosage regimen over another. We could not estimate the time course of the effect of tranexamic acid on either erythrocyte transfusion or seizure. The dosing regimen proposals relative to the timing of surgery for postoperative blood loss reduction cannot be applied to erythrocyte transfusion and seizure. For these two outcomes, exposure to tranexamic acid was calculated as the mean tranexamic acid concentration from the start of surgery up to 12 h ($[TXA]^{0-12h}$). A 12-h range was chosen to account for postoperative exposure. Yet this exposure marker smooths out peak and trough effects (a 20 mg/kg bolus and a 10 mg/kg bolus plus 1 mg/kg for 12 h have similar $[TXA]^{0-12h}$; fig. 6). This is an important issue for the evaluation of seizure as the toxicity of tranexamic acid in the cortex and spinal cord is concentration-dependent.[36] Thus, as proposed by a reviewer, we also tested tranexamic acid blood peak concentrations. Both tranexamic acid blood peak concentrations and $[TXA]^{0-12h}$ showed a relationship with seizure. Unfortunately, these exposure markers are correlated with each other, and it is unknown how these markers reflect the concentration of tranexamic acid at the effect site, the cerebrospinal fluid.

Studies included in a meta-analysis vary in their study characteristics. We performed covariate analyses with the aim to explain part of the interstudy heterogeneity. These analyses used summary-level data (*e.g.*, average patient weight in a study) and have several pitfalls.[37] The relationships we described are observational associations across trials. There is risk of a false-positive conclusion as we tested multiple covariates (although they were prespecified) and because bias by confounding cannot be ruled out. An example of bias is the ecological fallacy when results based on summary-level data are extrapolated to individual patients. Our covariate analysis for seizure should be interpreted as follows: studies with the highest proportion of patients undergoing open-chamber surgery showed a greater risk of seizure, rather than patients undergoing open-chamber surgery necessarily being the actual patients who are more

likely to convulse. Thus, our models cannot be used for predictions in individuals. The use of mean values for continuous variables may also have limited our covariate analyses due to the limited difference in means between studies. In addition, the scope of covariate analyses was limited by the fact that certain variables were not reported in all the studies included. For example, we could not assess the effect of renal dysfunction, which increases exposure to tranexamic acid and is a risk factor for tranexamic acid–associated seizure.[9] Tranexamic acid doses should be lowered in patients with chronic renal dysfunction presenting for cardiac surgery.[33]

In conclusion, this model-based meta-analysis suggested that low-dose tranexamic acid (total dose, approximately 20 mg/kg) was sufficient for reducing postoperative blood loss and erythrocyte transfusion in CPB surgery. Higher doses achieved a marginal gain in effectiveness but increased the risk of postoperative seizure, particularly in procedures involving a high risk of bleeding. These results have to be interpreted with caution because they are observational. They are wholly dependent on the lack of bias of the predicted tranexamic acid exposures and of the quality of the included studies.

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Competing Interests

The authors declare no competing interests.

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