Title:

Is low dose Tranexamic acid less effective than a standard dose at reducing blood loss and inhibiting hyperfibrinolysis in hemorrhagic caesarean section?

Multicenter double–blind placebo-controlled dose-ranging (TRACES) trial.

Short title: Tranexamic acid antifibrinolytic dose-effect.

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**Key messages**: In hemorrhagic cesarean section,

* Hyperfibrinolysis occurs early and is marked by an increase in D-dimers, Plasmin-antiplasmin complexes and plasmin generation potential.
* Low Dose Tranexamic acid (0.5g) is less effective than the standard 1g dose to reduce additional blood loss and to inhibit fibrinolytic activation.

**Tweet**: Low Dose Tranexamic Acid (0.5g) is less effective than the standard 1gram dose to reduce additional blood loss and inhibit hyperfibrinolysis in hemorrhagic caesarean section.

**Key words**: fibrinolysis, tranexamic acid, postpartum hemorrhage, D-dimers, transfusion.

**Funding and registrations**: TRACES trial, funded by French Ministry of Health: PHRC 14-0032 and French Drug Safety Agency: ANSM 015. NCT 02797119.

**Abstract**

**Objective**: To study the effect of a low (0.5g) or a standard (1g) tranexamic acid (TA) dose compared to placebo on clinical and biological endpoints in women experiencing postpartum hemorrhage (PPH)

**Design**: TRACES trial is a double-blind, randomized, placebo-controlled, dose-ranging study

**Setting**: 8 women hospitals in France.

**Population**: Women experiencing PPH > 800 mL during caesarean section.

**Method**: After informed consent, patients were randomized to receive either TA 0.5g (n=57), TA 1g (n=58), or a placebo (n=60). Data were collected at 8 time-points.

**Main outcome measures**: Efficacy: additional blood loss after study drug, maternal morbidity, safety, biology: D-dimers, plasmin-antiplasmin complexes (PAP), simultaneous-generation-thrombin-plasmin-potential.

**Results**: Compared to 1g dose, 0.5g TA was less effective to reduce additional blood loss (300 mL [95% confidence interval (95%CI) 68 to 630] vs 134 mL [95%CI50 to 419] (p=0.042)). Compared to placebo, 1g TA, but not 0.5g, inhibited hyperfibrinolysis as shown by plasmin generation potential, % increase in D-dimers from injection to 120 minutes (93% [95%CI 68 to 118] vs 58% [ 95%CI 32 to 84] (p=0.06) vs 38% [95%CI 13 to 63] (p=0.003) and % increase in PAP from injection to 30 minutes (56% [95%CI 25 to 87] vs 13% [ 95%CI 18 to 43] (p=0,051) vs -2% [95%CI -32 to 28] (p=0.009)).

**Conclusions**: In this study, fibrinolysis inhibition was more sustained after the administration of 1g TA compared to 0.5g TA or a placebo. Further pharmacokinetic-pharmacodynamic modelling will be needed to determine the optimal TA dose to be administered in PPH.

# INTRODUCTION

Postpartum hemorrhage (PPH) remains the leading cause of maternal death worldwide.1 Tranexamic acid (TA), an antifibrinolytic drug, has been shown to reduce bleeding and transfusion needs in major surgery and trauma-associated massive bleeding.2 In the context of PPH following vaginal delivery, a high dose (4g) of TA was shown to decrease the volume and duration of blood loss, as well as transfusion needs and maternal morbidity, in addition to early inhibition of fibrinolysis.3-4 In the large international World Maternal Antifibrinolytic (WOMAN) Trial, an uniform single 1g dose of TA reduced mortality due to hemorrhage when TA was administered within the first 3 hours after onset of PPH.5 TA appeared safe as only minor side effects were reported and no increased in the incidence of thromboembolism or seizure were described.5 The prophylactic use of 1g TA before vaginal delivery or caesarean sectionhas also been studied.6-7 In a pharmacokinetics model, Amzadia et al. recommended a dose of 600 mg to prevent PPH before elective non-hemorrhagic CS.8 The TRACES trial was a double-blind, randomized, placebo-controlled, dose-ranging study in patients experiencing PPH during cesarean section.9-10 The primary objective was to assess the efficacy of two dose-regimes of tranexamic acid either a standard dose of 1g or a low dose of 0.5g in comparison to placebo, in reducing blood loss and inhibit hyperfibrinolysis within 6 hours after administration.11 The secondary objectives were to determine the impact of TA dosage on maternal morbidity (anemia, transfusion requirement, rescue laparoscopy or invasive procedures, organ failure, intensive care hospitalization), mother to child interactions and death as well as the safety endpoints (i.e., nausea and vomiting, thrombosis, seizures, and acute kidney injury).9 The *in-vivo* biomarkers of hyperfibrinolysis and their TA-dependent inhibition were assessed by repeated measurements of D-dimers, Plasmin-antiplasmin (PAP) complexes and *ex-vivo* simultaneous thrombin (TG)-plasmin (PG) generation potential over a period of 6 hours.10

**Material and methods**

TRACES is a multicenter, randomized, double-blind, placebo-controlled and dose-ranging trial. The study protocol for the main and the ancillary TRACES studies have been previously published**.** 9-10 The study was conducted in 8 centers in France selected because of their strict adherence to French guidelines for the management of PPH between March 2016 and December 2019.11 TRACES trial was funded by public resources from the French ministry of Health (PHRC 14-0032) and the French agency for drug safety (ANSM 15-003). External peer review for scientific quality was conducted from the trial conception to the data analysis, and the funding agencies didn’t get involve in conducting the research, data analysis, nor writing the paper.

**Study protocol**

All patients received complete information, gave their written consent before non-emergent CS and were covered by social security. The inclusion criteria were patient experiencing a bleeding volume ≥ 800 mL due to surgery or to uterine atony after an elective caesarean section delivery. An amendment expanded the recruitment to patients experiencing an unexpected bleeding during an emergent CS, allowing for a better matching to PPH occurrence. Exclusion criteria were as follows: known hypersensitivity to TA, previous or ongoing arterial or venous thrombosis, renal failure, history of seizure, HELLP syndrome, administration of TA before inclusion, congenital haemorrhagic disorder, anticoagulant treatment within 24 hours before inclusion, previous inclusion in an interventional trial within 2 months, and patient unable to consent.

The randomization was centralized and stratified by center. The 1:1:1 assignment sequence (based on blocks of six and the use of a computer random-number generator) was produced by the sponsor. Numerated Boxes containing syringes ready for use were prepared and numerated following the clinical research guidelines by an accredited pharmacist and distributed to the centers.9 Syringes were prepared for every center according to their randomization list.9 Unblinding envelops were available in cases of emergency. The local investigator administered the product box following an increasing numeration in a blinded way for the group allocated. The blind injection of a 10 mL-vial consisting of either normal saline, 0.5g or 1g of TA was performed intravenously over one minute. Rescue administration of a second dose of 1g TA was allowed if PPH exceeded 1500 mL.

**Data collection and clinical outcomes.**

As recommended by the PPH core outcome set 12, the parameters described below were collected before inclusion (T0), at the end of the one-minute injection (T1), after 30 (T30), 60 (T60), 120 (T120), and 360 (T360) minutes, at day 2 (D2, +/- 12 h) and day 42 (D42, +/- 14 days) postpartum. Primary criterion was theestimated blood loss (EBL) between the end of the administration of the study drug and 6 hours after inclusion (T360). Bleeding was measured in the surgical or cell saver suction reservoirs, in the under-the-buttocks delivery bag, and by weighting drapes and pads. Antiseptic and amniotic fluids were strictly separated, collected in a separate aspiration bag, counted, and subtracted. Maternal morbidity criteria (total blood loss, postpartum anaemia, incidence of RBC transfusion and procoagulant therapy, rescue laparoscopy, invasive procedures, hysterectomy, postpartum organ failure and death);wellbeing criteria (skin to skin and breastfeeding rate, fatigue and posttraumatic stress disorders at D42) were collected as secondary endpoints.12 Safety endpoints included nausea and vomiting, blurred vision seizures, myocardial ischemia, stroke, deep venous or arterial thrombosis, oliguria, renal failure or any organ failure.12

**Biological data.**

Blood and urines samples were collected. Coagulation, blood cells and renal tests were measured at each time-point. Hemostasis parameters: fibrinogen (g/L), factor II (IU/mL), factor V (IU/mL), antithrombin (IU/mL) D-dimers (ng/ml, Stago) and fibrin monomers (μg/L, Stago) were performed on STAR automated coagulation analyser (Diagnostica Stago, Asnières, France), according to standard procedures; thrombin-antithrombin complexes (TAT, μg/L, Siemens) and plasmin-antiplasmin complexes (PAP, ng/ml, Technoclone, Vienna, Austria) concentrations were measured by ELISA.9-10 The general population reference values of these hemostasis laboratory parameters are as follows: fibrinogen (2–4 g/L), factor II and factor V (60–120 IU/ml), D-dimers (<500 ng/ml) and fibrin monomers (<6 ng/ml), thrombin-antithrombin complexes (TAT <4 ng/L) and plasmin-antiplasmin complexes (0–514 ng/ml). Hyperfibrinolytic profile was defined by D-dimers > 1500 ng/mL.4

The innovative test of simultaneous-generation-thrombin (TG)-plasmin (PG)-assay (SGTPA) was developed as previously published and the postpartum reference values were established.9-10,13-14 To describe the proteolytic activity of both thrombin and plasmin, several variables were defined and automatically calculated using an Excel® macro. For TG, four variables were determined: TG lag time (min), *i.e.* the time between reaction initiation and the start of TG; thrombin time to peak (min), *i.e.* the time at which the TG peak occurred; thrombin peak (nM), *i.e.* maximal velocity of thrombin production; TG area under the curve (AUC, nM.min) for TG, *i.e.* the total thrombin generated; For PG, four other variables were defined: the fibrin lysis time (FLT) (min), *i.e.* the interval time between the start of PG and its peak; the plasmin peak (nM) *i.e.* the PG when the curve shifted from a convex shape to a linear shape, representing lysis of the clot by plasmin; plasmin time to peak (min), *i.e.* the time when PG reached its greatest velocity; PG area under the curve (AUC, nM.min) for PG, between fibrinolysis onset and the plasmin peak. The interaction between TG and PG was probed with the time interval between the TG and PG peaks.

The TA concentration analysis was performed using liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) on EDTA plasma (venous and uterine bleeding) and 2 timed urinary samples.9-10

***Statistical method***

Data management was organized as described below. The coordinating team included the coordinator, the promotor and the major investigators of each of the centers. Data and consents collection was monitored by the promotor. An independent safety monitoring committee observed blindly safety issues.

*Sample size*

The sample size computation was based on the expected 15% reduction of the estimated blood loss between the placebo group and the 0.5g dose. According to the results of the EXADELI trial with a type I error of 5%, a power of 80% and a maximum 10% drop outs or missing data, 114 subjects per group needed to be included for a total of 342 patients.3,9 To demonstrate a difference in D-dimer levels between T30 and T120, the number of patients to be included in the pharmaco-biological sub-study was estimated at 48 patients per group.4,10 Because of a competing research program7, recruitment for clinical primary objective was slower than expected in some of the centers and didn’t reach the target despite the addition of 3 new centers. Based on the protocol and safety monitoring committee recommendations, the trial was ended when the pharmacobiological substudy recruitment was achieved.9-10

*Statistical analysis:*

Analyses were performed in the intention-to-treat population. Primary efficacy analysis was conducted using constrained longitudinal data analysis (cLDA) model proposed by Liang and Zeger *et al.* including center as random effect.153-16 If normality of model residuals was not satisfied (even after a logarithmic transformation), absolute changes between baseline and 6 hours were compared between the 2 treatments groups and placebo using non-parametric analysis of covariance (ANCOVA) adjusted for baseline values.17-18 An exploratory analysis comparing TA 1 g versus TA 0.5g was performed using the cLDA model if appropriate or non-parametric ANCOVA otherwise. As there is no correction for multiple tests, all secondary and supplementary analyses were considered exploratory and presented with the effect size without p-values as recommended by the New England journal of medicine.19 Since the effect size (between-group mean differences) was computed after logarithmic or rank transformation of original variable in case of non-normal residuals, which would not be easy to interpret, effect size measure was also reported by Cohen’s d for each variable.20 Secondary binary outcomes were compared using a mixed logistic regression model including the treatment as fixed effect and centers as random effect; adjusted odds ratios were calculated as the treatments’ effect sizes. For the secondary clinical and biological quantitative longitudinal outcomes, the variation between the baseline and the different times were compared between the two treatment groups and placebo using the same methodology as the primary endpoint.20 The other secondary quantitative outcomes were analyzed using a mixed linear regression model to consider the center effect. If normality of model residuals was not satisfied (even after a logarithmic transformation), non-parametric analysis was used. Data were censored at T360. Data were analyzed using the SAS software (Version 9.4. SAS Institute Inc, Cary, NC, USA).

**Results**

One hundred seventy-five patients were included among 8 centers between 2016 to 2019: 60 were included into the placebo group, 57 into the low dose group and 58 into the standard dose group out of which 52, 50 and 48 had collected biological samples (Figure 1). Protocol deviations were noted in 4 patients. Table 1 summarizes baseline demographic, obstetrical, surgical, anesthetic data balanced between groups. In the placebo, low and standard dose groups respectively, one or several supplementary doses were given in 7 (11%), 5 (9%), and 8 (14%) patients due to PPH >1500mL.

A statistical difference in additional blood loss at 6 hour was found between the low dose and the standard dose regimens in favor of the 1g dose (300mL [95% CI 68 to 630] versus 134mL [95% CI 50 to 419] (p=0.042)). In the placebo group, additional bleeding (208mL [95% CI 55 to 539]) did not differ significantly from either standard (p=0.35) or low dose groups (p=0.28) (Figure 2A). No difference was identified between the placebo group, low and standard dose groups for total blood loss at 6 hours and bleeding duration; PPH life-threatening evolution rate >2500mL; hemoglobin drop and anemia, transfusion or procoagulant treatment need, invasive procedures rate, ICU admission rate and organ failure rate (Table S1).

**Inhibition of fibrinolysis.**

Complete time-points repeated biological data were obtained in 33 patients in placebo group, 33 patients in the low-dose group and 31 patients in the standard-dose group.

In the standard dose vs placebo group respectively, median [interquartile] D-dimers level differed at 120 minutes (4340 ng/mL [3240 to 5960] vs 8930 ng/mL [3820 to 17940] (Figure 2B) (Table S2). Compared to placebo increase (4470 ng/mL [95% CI 1610 to 8360] (93% [95%CI 68 to 118])), D-dimers increase from T0 to 120 minutes (median difference [95%CI] and % of difference from baseline) was significantly inhibited in the standard dose group (630 ng/mL [95% CI 240 to 2000] (38% [95%CI 13 to 63]) (p=0.003)) with a strong size-effect (d-Cohen : 0.51) but not in the low dose group (1260 ng/mL (95%CI 150 to 5915] (58% [ 95%CI 32 to 84]) (p=0.058)) (Figure2C) (Table S3-S4).

In the standard dose vs placebo group, median [interquartile] PAP complexes level differed at 30 minutes: 347 ng/mL [261 to 485] vs 639 ng/mL [455 to 199] and 60 minutes: 499 ng/mL [379 o 1107] vs 1158 ng/mL [717 to 2532] (Figure 2D) (Table S2 ). PAP increase (% of difference from baseline to 30 minutes) observed in placebo group (56% [95%CI 25 to 87]) was significantly inhibited in the standard-dose group (-2% [95%CI -32 to 28 ] (p=0.009)) but not in the low dose group (13% [ 95%CI -18 to 43] (p=0,051)) (Figure 2D) (Table S4).

Plasmin generation peak was lower in both treated groups compared to placebo group (Figure 2E) (Table S5). Plasmin time to peak and the interval between Tg and PG peaks decreased significantly in the standard-dose group compared to placebo whereas the low-dose didn’t show any impact on these parameters (Figure 2F-2G) (Table S5). There was no impact of the 2 TA dose-regimens compared to placebo on fibrinogen, fibrin-monomers, factor II and factor V, antithrombin, thrombin-antithrombin complexes and the thrombin generation potential (Table S3, S6). TA concentrations are presented in Table 2.

**Safety endpoints**

Compared to placebo, minor adverse side-effects i.e., nausea and vomiting, were more frequent in the standard-dose regimen but not in the low-dose group (Table S1). There was no thrombotic event, no renal failure and 2 transient high creatininemia in the placebo group.

**Discussion**

***Main findings***

The TRACES study demonstrated that a low 0.5g dose of TA was less effective than a standard 1g dose to reduce blood loss and inhibit fibrinolytic activation in hemorrhagic cesarean section

***Dose-ranging effect on blood loss reduction***

In our previous EXADELI study, a high dose of 4g TA was found to reduce additional blood loss, the duration of bleeding and the morbidity when given at the onset of PPH.3 The dose of 4g over one hour followed by 1 g-continuous infusion over 6 hours had been chosen as the only effective dose published in cardiac surgery at the time of this trial.21 However, the administration of such a high dose of TA has been questioned since, due to the reported risk of seizure after cardiac surgery and the suspicion of kidney injury in preeclamptic patients.22-23

In the WOMAN trial, the authors randomized 10,051 to receive a single 1g dose of TA and 10,009 patients to receive a placebo in a pragmatic study of women suffering from PPH.5 The reduction of maternal death related to bleeding was only significant when TA was given within the first 3 hours after delivery women died in the TA vs placebo group (89 (1.2%) vs 127 (1.7%), [RR 0.69, 95%CI 0·52–0.91] (p=0.008)).5 During the 3 hours after bleeding onset, a reduction in the rescue laparotomy rate was observed in the treated group vs placebo.5

In the TRACES trial, we found that a single low dose of TA (0.5g) was less effective compared to the standard 1g dose to reduce persistent bleeding. No difference was observed in either of the treated groups versus placebo on total blood loss, anemia, transfusion need for maternal morbidity and wellbeing but the number of patients included was too small to draw conclusions. Indeed, The WOMAN trial needed 5,000 extra-patients and 20,060 patients in low resource countries to demonstrate the clinical impact.5

***An optimal time-interval for TA administration***

Moreover, the WOMAN trial showed that, during the first hour after PPH onset, TA was ineffective and after the third hour after PPH onset, TA worsen the clinical outcome.5 The international guidelines recommended TA administration before the third hour after bleeding onset.5,24 Kolev *et al.* explained this optimal time-interval by the paradoxical effect of TA on late plasminogen activation by urokinase-plasminogen activator (on which TA is ineffective) and the competitive mechanism of action of TA and alpha2-antiplasmin.25 This competitive mechanism could be explain the lack of effectiveness for the low dose TA observed in our trial.

***Is a part of the dose lost in the hemorrhagic flow?***

The lack of clinical impact of TA during the first hour could be explained by the elimination of the drug in hemorrhagic blood loss.5-26 A preliminary model was established from 53 points in 9 hemorrhagic patients of the TRACES pilot study,10,26 The better model to predict TA plasmatic concentrations was a bicompartimental model with a double (urinary and non-urinary) first order elimination.24 This model was different from Li *et al.* model established in 30 non-hemorrhagic patients receiving 5, 10 or 15 mg/kg of TA.27 They found that the better model was bicompartimental with a single first order urinary elimination.25 The leakage in the blood flow is thus suggested like in trauma, not-observed in a non-hemorrhagic context.28 The low-dose impact may disappear in cases of high flow PPH.

***Fibrinolysis activation and its TA-induced inhibition***

In conjunction to the unfavorable clinical bleeding reduction effect of the low versus the standard dose of TA, we observed a discriminant dose-effect on fibrinolytic inhibition in favor of the standard dose.

Fibrinolytic activation increases rapidly following a physiological delivery resulting in elevated D-dimer and PAP levels.4-29 TRACES simultaneous clinical and biologic data analysis demonstrated an early but variable D-dimers and PAP increase. This early onset of fibrinolytic activation was found by Roberts *et al*. in 23% of the 167 patients.30 In this monocentric sub-study of the WOMAN trial, 83 patients received a 1g dose of TA and 84 patients received a placebo.30 The mean (SD) D-dimer concentration was 7.1 (7.0) mg/L in TA-treated group and 9.6 (8.6) mg/L in placebo group (p=0.09). There was no difference between groups in maximal lysis measured by thromboelastometry (12.3% (18.4) and 10.7% (12.6), respectively; p=0.52).29 In the TRACES trial, the results demonstrated that the 1g dose was able to inhibit fibrinolytic activation defined *in vivo* as a reduction in D-dimers with a maximal effect at 120 minutes and a reduction in PAP at the 30th minute until 60th minute, whereas that reduction wasn’t observed with a 0.5 g dose.

Inhibition of hyperfibrinolysis can now be measured *ex vivo* as a reduction in the plasmin generation potential (PG peak and time to peak).13-14 Our results were concordant with Miszta *et al.* results demonstrating a reduction of PG peak and time-to-peak out of the plasma of 30 non-hemorrhagic patients receiving TA 5, 10 or 15 mg/kg with a maximum of 1,000 mg.14 In addition, the TRACES trial was supporting the supplementary information that TA had no impact on thrombin generation potential neither on fibrinogen, fibrin monomers, thrombin-antithrombin complexes and factor II. These data contribute to the safety message regarding the absence of increased thrombotic risk of TA.

Amzadia *et al*. targeted a TA plasmatic concentration of 10 mg/L and a maximal lysis reduction from 100% (after t-PA addition) to 17% (in the treated plasmas).8 This model carried some limitations: 1/ the *ex-vivo* definition of the antifibrinolytic impact of the treated plasmas does not consider the large variability of fibrinolytic activation in PPH ; 2/ the 10 mg/L TA plasmatic concentration has been targeted by an *in-vitro* model regardless to clinical or biological effect; 3/ despite a 40% obese patients’ recruitment, the model was not improved by weight as a covariable.8,27 They recommended a prophylactic dose of TA of 600 mg before elective caesarean section.8 TRACES brought the concordant clinical and biological evidence that a 500mg dose was not sufficient to stop hemorrhage and inhibit fibrinolytic activation.

***Strengths of the TRACES study:***

The TRACES trial added some major information and generates relevant questions on the optimal TA dose and time interval in PPH, using a robust randomized double blinded placebo-controlled methodology and statistical analysis. The results should be considered to adapt the optimal dose and timing of TA to hyperfibrinolysis intensity and duration.

***Limitations:***

Despite its prospective randomized nature, our study presents some limitations. First, the limited recruitment of 175 patients carried a risk of insufficient power to demonstrate the efficacy and safety of the two TA doses. The second limitation could be the choice of additional blood loss as primary objective of TRACES trial. This endpoint was recommended in PPH research programs.12 Blood loss measurement is assumed to be imprecise due to the contamination with other fluids but the strict conditions of measurement was applied in each center. Moreover, TRACES was a randomized and double-blind trial, the imprecision of this criterion was assumed to be identical in the three groups.9

**Conclusion 47 words**

In the TRACES study, a low 0.5g tranexamic acid appeared less effective than a standard 1g dose to reduce blood loss and inhibit fibrinolysis activation during postpartum hemorrhage. Pharmacokinetics-pharmacodynamic model will further help determine an optimal dose and timing of TA in this hemorrhagic context.

**Declarations sections**

***Ethical Approval and Consent to participate***

TRACES trial obtained approval from the competent national authorities (ANSM 201500249926) and the Ethics Committee (CPP 15/50 020216) before beginning the study, in accordance with article L1121-4 of the Public Healthcare Code. This trial has been declared on the clinical trials registration on June 13, 2016 under the number CT 02797119. Registration will be performed in accordance with decree dated November 14, 2006 about gathering data in the national register of individuals participating in biomedical research.

***Consent for publication***

Authors and sponsors have given their consent and defined the publication rules.

***Availability of supporting data***

Supporting data are available

***Competing interests***

The authors declare no competing interest.

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***Authors' contributions***

AS Ducloy-Bouthors contributed to the study conception and design, preliminary studies for production, and biological specific tests, data management concept as well as data acquisition, management, analysis and interpretation, and drafting and revising the final version of the present manuscript submitted for publication. S Gilliot contributed to preliminary studies for dose ranging preliminary model, data analysis and interpretation, pharmacokinetics pharmacodynamics ongoing study and drafting and revising the present manuscript. Maeva Kyheng contributed to the data analysis and revision of the manuscript. D.Faraoni contributed to the manuscript draft and final version revision. A Turbelin, H Keita-Meyer, A Rigouzzo, G Moyatidou, B Constant, F Broisin, A Le Gouez, R Favier, E Peynaud and L Ghesquiere, contributed to data acquisition and management and revision of the manuscript. G Lebuffe contributed to the data analysis and interpretation, and revision of the final version of the present manuscript submitted for publication A Duhamel contributed to study conception and design as well as to data management, analysis and interpretation, and drafting and revising the manuscript. D Allorge and S Susen elaborated contributed to the study conception and design, preliminary studies for simultaneous thrombin plasmin generation assay as well as data acquisition, management, analysis and interpretation, and drafting and revising the final version of the present manuscript submitted for publication. B Hennart contributed to the study conception and design, elaborated the biological measurement method for tranexamic acid concentration, performed the pharmaceutical validation of the study drug production and performed the preliminary studies for dose ranging variations analysis as well as data acquisition, management, analysis and interpretation, and drafting and revising the final version of the present manuscript submitted for publication. E Jeanpierre contributed to the study conception and design, preliminary studies for simultaneous thrombin plasmin generation assay as well as data acquisition, management, analysis and interpretation, and drafting and revising the final version of the present manuscript submitted for publication. P Odou contributed to preliminary studies for dose ranging preliminary model, data analysis and interpretation, pharmacokinetics pharmacodynamics ongoing study and drafting and revising the present manuscript.

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**Figure legend:**

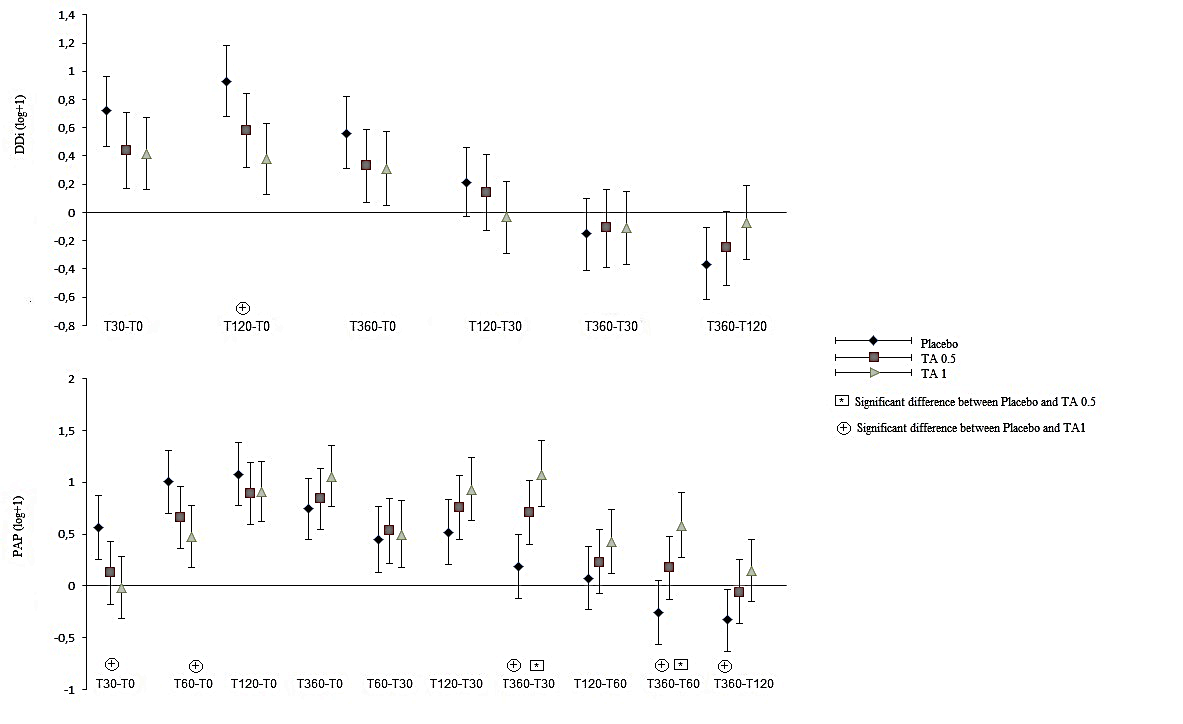
**Figure 1**: Flow chart

**Figure 2**: Additional blood loss and hyperfibrinolysis inhibition in placebo (TA0), low-dose (TA0.5) and standard-dose (TA 1) groups

**Figure 2A**: Additional blood loss (mL) observed 6 hours after 0, 0.5 or 1 gram infusion in placebo (column 0), low-dose (column 0.5) and standard-dose (column 1) groups. Median – interquartile box-plots. Comparison by a linear mixed model.

**Figure 2B**: D-dimers increase reduction (ng/mL) between T0 and 2 hours after study drug administration in standard-dose groups compared to placebo. Comparative analysis by a mixed linear model of covariance of low-dose (column 0.5) and standard-dose (column 1) versus placebo (column 0).

**Figure 2C to 2G legend:**



**Figure 2C**: Significant reduction of D-dimers increase from T0 to T120 in the standard-dose group compared to placebo. D-dimers increase percentage (ng/mL) from baseline and each time-points T0-T30, T0-T120, T0-T360 in placebo (column 0), low-dose (column 0.5) and standard-dose (column 1) groups. Comparative analysis by a mixed linear model of covariance.

**Figure 2D**: Significant reduction of plasmin-antiplasmin complexes (PAP) increase from T0 to T30 and from T0 to T60 in the standard-dose group compared to placebo. D-dimers increase percentage (ng/mL) from baseline to each time-points T0-T30, T0-T60, T0-T120, T0-T360 in placebo (column 0), low-dose (column 0.5) and standard-dose (column 1) groups. Comparative analysis by a mixed linear model of covariance.

**Figure 2E**: Significant reduction of plasmin (PLA) peak in both treated groups versus placebo from T0 to each time-points T0-T30, T0-T60, T0-T120, T0-T360. Plasmin peak decrease percentage from baseline to each time-points. Comparative analysis by a linear mixte model of covariance in placebo (column 0), low-dose (column 0.5) and standard-dose (column 1) groups.

**Figure 2F**: Significant reduction of plasmin (PLA) time to peak in standard-dose group versus placebo. Percentage of decrease from baseline to each time-points T0-T30, T0-T60, T0-T120, T0-T360. Comparative analysis by a mixed linear model of covariance in placebo (column 0), low-dose (column 0.5) and standard-dose (column 1) groups.

**Figure 2G**: Significant reduction of time-interval between thrombin and plasmin generation time to peak interval in standard-dose group versus placebo. Percentage of decrease from baseline to each time-points T0-T30, T0-T60, T0-T120, T0-T360. Comparative analysis by a mixed linear model of covariance in placebo (column 0), low-dose (column 0.5) and standard-dose (column 1) groups.

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