Postpartum haemorrhage related early increase in D-dimers is inhibited by tranexamic acid: haemostasis parameters of a randomized controlled open labelled trial

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Abstract

Background: Beneficial effects of tranexamic acid (TA) have been established in surgery and trauma. In ongoing postpartum haemorrhage (PPH), a moderate reduction of blood loss was observed in a previously published randomized controlled trial. Analysis of haemostasis parameters obtained from samples collected as part of this study are presented.

Methods: Women with PPH >800 ml after vaginal delivery were assigned to receive either TA (4 g over 1 h, then 1 g per h over six h) (TA) or not (H). A non-haemorrhagic group (NH), <800 ml blood loss, was included as postpartum reference. At four time-points (enrolment, +30 min, +2 h, +6 h), haemostasis was assessed. Haemostasis assays were performed blinded to group allocation. Data were expressed as median [interquartiles] and compared with non-parametric tests.

Results: In H compared with NH group, D-dimers increase (3730 ng ml\(^{-1}\) [2468–8493] vs 2649 [2667–4375]; \(P=0.0001\)) and fibrinogen and factor II decrease were observed at enrolment and became maximal 2 h later. When comparing TA to H patients, the increase in Plasmin-Antiplasmin-complexes at +30 min (486 ng ml\(^{-1}\) [340–1116] vs 674 [548–1640]; \(P=0.03\)) and D-dimers at +2 h (3888 ng ml\(^{-1}\) [2688–6172] vs 7495 [4400–15772]; \(P=0.0001\)) was blunted. TA had no effect on fibrinogen decrease.

Conclusions: This study provides biological evidence of an early increase in D-dimers and plasmin-antiplasmin complexes associated with active post-partum haemorrhage and its attenuation by the early use of a clinically effective high dose of TA, opening the perspective of dose ranging studies to determinate the optimal dose and timing in this setting.

Clinical trial registration: ISRCTN09968140.

Key words: fibrinogen; fibrinolysis; postpartum haemorrhage; tranexamic acid

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Editor's key points

- These results provide evidence that postpartum haemorrhage onset is associated with an early hyperfibrinolysis.
- It also provides evidence that an early and high dose of tranexamic acid inhibited this early fibrinolytic activity.

Post-partum haemorrhage (PPH) remains the leading cause of maternal mortality and morbidity worldwide. While most deaths occur in low-resource countries, the incidence of PPH is increasing in developed countries. Among early markers of severity predicting the poor outcome of PPH, is the existence of coagulopathy, and notably, low fibrinogen concentrations.

Tranexamic acid (TA) is a synthetic lysine analog that competitively binds to the lysine binding sites of plasmin(ogen). TA reduces blood loss and transfusion requirements in major surgery and decreases mortality in trauma patients. The prophylactic use of TA in elective Caesarean section reduces operative blood loss.

In ongoing postpartum haemorrhage (PPH) after vaginal delivery, TA significantly reduced blood loss, duration of bleeding and transfusion requirements in a randomized controlled trial. In this original study reporting 144 women (fi rst to third quartiles, 59–377) than in controls (221 ml; fi rst to third quartiles 105–564) (P=0.041). Bleeding duration was shorter (P=0.03); there were less severe PPH (P=0.028) and less RBC transfusions (P<0.001) in TA than in controls. PPH ceased after only uterotonic in 93% of women in the TA group vs 79% of controls (P=0.016).

While in trauma patients and patients undergoing hepatic and cardiac surgery, the pharmacological effect of TA has been assessed by a decrease in D-dimers, a breakdown product of cross-linked fibrin, no such study has ever been performed in PPH. Furthermore, the recent pregnancy disseminated intravascular coagulation (DIC) score adapted from the International Society on Thrombosis and Haemostasis (ISTH) DIC-score, does not integrate the fibrinolytic dimension of PPH-related coagulopathy because of the lack of contributive data.

Therefore, our aim was to describe the detailed haemostasis parameters blindly generated from the analysis of samples obtained as part of a randomized-controlled trial of TA in ongoing PPH, after vaginal delivery.

Methods

Study design

This study is a post-hoc sub-study of haemostasis parameters in blood samples from a multicentre randomized controlled trial of conducted between 2005 and 2008, in eight French obstetric centres. The trial protocol was approved by the ethics committee of the Lille University Hospital in June 2005 (CP05-07, CCPP nord-ouest 4, France) for all study sites, in compliance with French law and research practice guidelines. Data concealment was validated by the French Commission Nationale Informatique et Libertés (CNIL-MRO1). A secondary amendment was submitted to and approved by both the Lille University Hospital ethics committee and French Ministry of Health research program directory committee, to allow the post-hoc assessment of haemostasis in study samples and reference samples from non-bleeding parturients.

All pregnant women were informed of the study during the mandatory preanaesthetic consultation at the third trimester of pregnancy. Bleeding parturients received full information on the study and the blood sample collection at the first stage of PPH upon first-line uterotonic use. If bleeding stopped, the parturient was not included. If bleeding persisted, reaching 800 ml, and written consent on study participation and blood collection was provided, the parturient was enrolled and randomized. All included women provided written consent before entering the study in accordance with the Declaration of Helsinki.

The academic multi-centre, randomized, controlled, open-label trial, evaluated the efficacy of TA in women with ongoing PPH after vaginal delivery. Patients with measured postpartum bleeding over 800 ml were included and managed according to French guidelines for uterotonic use, fluid loading and packed red blood cell transfusion and interventional procedures such as embolization, or arterial ligation. Immediately after enrolment, parturients were randomized to receive either TA (tranexamic acid group, ‘TA’) or no anti-fibrinolytic agent (haemorrhagic group, ‘H’). In both groups, no other prohaemostatic treatments were allowed (frozen plasma, fibrinogen, factors concentrates, recombinant activated factor VII). In the TA group (n=72), 4 g of TA diluted in 50 ml of normal saline was administered intravenously over a one-h period. After this loading dose, a maintenance i.v. infusion of 1 g per h was administered for six h. This high dose of TA had been chosen as the best clinically effective dose from data in high-risk cardiac surgery patients because, at the beginning of the study, this was the only data available about active dose in ongoing massive bleeding. Minor side-effects (nausea and vomiting and visual disturbance) were associated with this high dose but no major side-effects such as seizures and acute kidney injury were noted.

An additional group of non-bleeding parturients (non-haemorrhagic group, ‘NH’) was investigated as a reference group to measure natural post-delivery haemostasis. Blood samples were collected 30–60 min after delivery and at two h after delivery (‘enrolment’ and ‘enrolment+2 h’ time-points). These non-haemorrhagic parturients were recruited during the same period as the patients included in the RCT. Their enrolment criteria were: normal vaginal delivery after a normal uneventful pregnancy, bleeding after delivery less than 800 ml.

Blood loss was assessed visually precisely in each patient. For every parturient in the trial centers, uterine blood loss after vaginal delivery was routinely strictly recorded. If bleeding exceeded 500 ml, the PPH management protocol was initiated including: immediate uterine removal of the placenta, administration of oxytocin, and placement of a second peripheral vein catheter. Protocol information was provided to the parturient. If bleeding continued and reached 800 ml, written consent was obtained, randomization was performed and the drug was administered to patients in the TA group, blinded to the obstetricians and midwives assessing the bleeding. Specific delivery bags were used and changed at each visit, allowing precise blood loss assessment at each time point. Delivery bags and surgical drapes were weighed upon successful control of bleeding to confirm assessment of total blood loss.

Blood sample collection and haemostasis assessment

In the trial design, timed blood samples were collected for each parturient at each visit and the results were recorded in the patient’s hospital records. All haemostasis assays were performed blinded to group allocation. The haemostasis parameters assessment added in the first amendment to the protocol used these results. At the four time points (enrolment, enrolment+30 min [+30 min], enrolment+two h [+2 h] and enrolment+six h [+6 h]),
Tranexamic acid inhibits PPH associated increase in D-dimers

Translating this...

In the PPH group (H), D-dimers increased (*P* < 0.0001) at PPH onset compared to H-group levels. The differences were not significant between TA and H groups (Table 1). Fibrinogen and factor II concentrations significantly decreased at enrolment (*P* < 0.0001 and *P* < 0.0001 respectively) to the lowest values at +2 h. Plasma-antiplasmin complexes remained as low as at the enrolment level (3888 ng ml⁻¹) vs 6172 ng ml⁻¹, respectively (Fig. 2a) and D-dimers remained as low as at the enrolment level (3888 ng ml⁻¹) vs 6172 ng ml⁻¹, respectively (Table 1). All persons performing biological tests were blinded to group allocation and outcome.

Sample size calculation

Sample size of the clinical trial had been calculated on the primary outcome of blood loss reduction. To demonstrate a decrease of 20% in the volume of PPH in the TA group, the number of patients required was 184 for a type I error of 5% and a power of 90%. The post-hoc study of haemostasis parameters presented here was performed on samples from these 144 parturients. The sample size of the non-haemorrhagic (NH) reference group was calculated by taking into account the Hayashi and colleagues' variations and sd of the haemostasis parameters involved in PPH.

Statistical analysis

Anonymous data were managed by an independent operator (Altizem, Nanterre, France). For continuous variables, the normality of distributions was tested using the Shapiro-Wilk test. As the distribution of numerous variables was not normal, all continuous variables were expressed as median and [interquartiles]. Categorical variables were expressed as frequencies and percentages. Sequential comparisons were performed between H and NH groups, then between H and TA groups (a) to provide a reference for values of D-dimers in non-haemorrhagic parturients and (b) to avoid the bias of interpreting significant results in favour of TA group because of the addition of a NH group. The comparisons of patient characteristics and biological parameters between the TA and H groups were performed using the Mann-Whitney U-test. The intra-group evolution of haemostasis parameters was analysed by using an ANOVA for repeated measures after rank transformation as recommended by Conover. Mixed-model COANOVA was adjusted on centers and baseline blood loss. When the analysis was performed on a single group, post hoc analyses concerning the time effect was performed using a paired Wilcoxon test and a Bonferroni correction. When the evolution was compared between two groups, post hoc analyses concerning the group effect was performed using the Mann-Whitney U-test and a Bonferroni correction. All statistical analyses were performed using SAS software (SAS Institute, Cary, NC, USA). A P value <0.05 was considered statistically significant.

Results

The trial was conducted between 2005 and 2008 in eight French obstetric centres, included, after informed consent, 144 women in the haemorrhagic groups (72 in the H group and 72 in the TA group), and demonstrated a significant reduction of blood loss volume and duration and transfusion requirements as previously described. Twenty three additional parturients consented to participate in the haemostasis study in the non-haemorrhagic (NH) group.

Anthropomorphic, obstetric and anaesthetic characteristics were not significantly different between TA and H groups, and PPH management for uterotonic drug, transfusion therapy or vascular loading and interventional procedures, with no site-specific differences between the centres regarding clinical outcome, fibrinogen (P = 0.65) or haemoglobin concentrations (P = 0.66) at PPH onset.

Active PPH was associated with an early increase of D-dimers

In the untreated haemorrhagic group (H) compared with non haemorrhagic group (NH),

<table>
<thead>
<tr>
<th>Variable</th>
<th>H (n=72)</th>
<th>NH (n=72)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-dimers at enrolment</td>
<td>6172 ng/ml</td>
<td>4400 ng/ml</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>D-dimers at +2 h</td>
<td>548 ng/ml</td>
<td>3645 ng/ml</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Comparing +2 h to enrolment values in the haemorrhagic group (H), D-dimers increased (*P* < 0.0001) and became maximal at +2 h (P < 0.0001), simultaneously to PAP complex increase (Table 2) whereas fibrinogen and factor II decreased (P = 0.0001 and P = 0.0001 respectively) to the lowest values at +2 h (Table 2).

TA reduces PPH-induced increase of D-dimers

In the treated haemorrhagic group (TA) group compared with the untreated haemorrhagic group (H),

<table>
<thead>
<tr>
<th>Variable</th>
<th>TA (n=72)</th>
<th>H (n=72)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-dimers at enrolment</td>
<td>6172 ng/ml</td>
<td>6172 ng/ml</td>
<td>0.717</td>
</tr>
<tr>
<td>D-dimers at +2 h</td>
<td>3645 ng/ml</td>
<td>3645 ng/ml</td>
<td>0.001</td>
</tr>
</tbody>
</table>

(ii) PAP complexes were significantly reduced at +30 min (486 µg ml⁻¹ [340–1116] vs 674 µg ml⁻¹ [548–1640]; P = 0.03) (Fig. 2a) and fibrinogen and factor II decreased (P = 0.0001 and P = 0.0001 respectively) to the lowest values at +2 h (Table 2).

Discussion

These results provide biological evidence that D-dimers and plasmin-antiplasmin complexes increase from active postpartum haemorrhage onset when compared with non haemorrhagic postpartum. It also provides evidence that an early 4 g dose of tranexamic acid, inhibits these early D-dimers and PAP complexes increases.
The data concerning the specific changes in haemostasis parameters occurring immediately after childbirth are rare. Pregnancy-induced changes in haemostasis and fibrinolysis are marked by an increase in coagulation factors and a parallel decrease in fibrinolytic potential as a result of endothelial secretion of plasminogen activator inhibitor 1 (PAI-1) and placental secretion of plasminogen activator inhibitor 2 (PAI-2).\textsuperscript{18–21} Reference values of D-dimers identified a progressive increase during normal pregnancy, discriminating pregnant from non-pregnant stage.\textsuperscript{22} In this longitudinal study, the reference median values observed at day two after delivery were decreased compared with third trimester. However the dispersion of the postpartum values seems significantly larger than during pregnancy.\textsuperscript{22} Thirty min after delivery and spontaneous placental removal, a sudden decrease in PAI-2 and a large increase in plasminogen activators are observed, leading to natural adapted moderate fibrinolysis.\textsuperscript{18} This can be observed in our study, in the non haemorrhagic reference group. Of interest is the gap between our haemorrhagic and non-haemorrhagic groups’ D-dimers concentrations at the onset of PPH and 2 h later (Table 1). There is a cut-off between higher quartile in NH group and lower quartile in H group at +2 h. Although direct comparison is not easy because of the difference in biological measurement methods, Karlsson and colleagues\textsuperscript{23} observed a significant D-dimers increase by 100% in the 55 parturients with massive obstetric haemorrhage group, compared with 49 control non-haemorrhagic parturients with no difference between severe and non-severe haemorrhage. Wang and colleagues\textsuperscript{21} observed a similar increase in fibrin–fibrinogen degradation products and D-dimers compared with reference literature values, in a large comparative series of 1343 healthy pregnant women and 1042 uncomplicated postpartum women. In order to explore the activation of fibrinolysis and explain, at least in part, the increase of the D-dimers in the haemorrhagic group, plasmin-antiplasmin complexes were used. Reference values for plasmin-antiplasmin concentration after non-haemorrhagic delivery can be extrapolated from Hayashi and colleagues\textsuperscript{16} dosages in 21 normal pregnant women before and after Caesarean section compared with 20 normal healthy cycling women. The PAP concentrations observed in our series after haemorrhagic untreated vaginal delivery were increased and reached the postoperative values described by Hayashi and colleagues.\textsuperscript{16} Coagulopathy has been identified and explored as a marker of severity and tissue injury in massive haemorrhage as a result of trauma.\textsuperscript{24–31} D-dimers have been used as a marker of fibrinolytic activity in trauma coagulopathy and in cardiac surgery.\textsuperscript{12–25} A fibrinolytic profile established by a lower fibrinogen, and higher D-dimers and fibrin/fibrinogen degradation products, at the early stage of trauma, has been described as an independent predictor of death.\textsuperscript{25–27} Moreover, in this setting, occult or overt hyperfibrinolysis has been demonstrated as an additional important contributor to the coagulopathic process.\textsuperscript{25–27} Hyperfibrinolysis in trauma becomes predominant when shock and tissular lesion are present.\textsuperscript{28–31} In postpartum severe haemorrhage, the major component of induced coagulopathy yet described is hypofibrinogenemia.\textsuperscript{3} Despite the growing importance of a better analysis of the fibrinolytic phenotype in massive bleeding induced DIC,
Table 1 Comparison of haemostasis parameters between haemorrhagic control group H compared with non haemorrhagic NH group at baseline and +2 h. Biological parameters collected at baseline and 2 h later. Comparison with reference non haemorrhagic women. *P values for repeated measures at PPH onset and 2 h later. †P values for haemorrhagic vs non haemorrhagic group

<table>
<thead>
<tr>
<th>Non-haemorrhagic group (n=23)</th>
<th>Enrolment</th>
<th>+2 h</th>
<th>P*</th>
<th>Untreated haemorrhagic group (n=72)</th>
<th>Enrolment</th>
<th>+2 h</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-dimers (ng ml⁻¹)</td>
<td>1586 [1300-2006]</td>
<td>2649 [2267-4375]</td>
<td>0.0001</td>
<td>3730* [2468-8493]</td>
<td>7495* [4400-15772]</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen (g litre⁻¹)</td>
<td>5.1 [4.1-5.6]</td>
<td>4.65 [4-5.2]</td>
<td>0.024</td>
<td>3.95† [3.2-4.75]</td>
<td>3.34† [2.6-4]</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Factor II (U dl⁻¹)</td>
<td>118 [95-124]</td>
<td>104 [92-112]</td>
<td>0.0001</td>
<td>90† [83-106]</td>
<td>78† [68-88]</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Factor V (U dl⁻¹)</td>
<td>113 [89-124]</td>
<td>102 [84-109]</td>
<td>0.002</td>
<td>97 [78-116]</td>
<td>77† [66-90]</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Platelet (10⁹ litre⁻¹)</td>
<td>221 [166-290]</td>
<td>201 [160-275]</td>
<td>0.0001</td>
<td>180† [156-228]</td>
<td>172† [043-198]</td>
<td>0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 Serial haemostasis parameters. TA treated with control group comparison. Serial biological parameters. Comparison TA treated group with untreated haemorrhagic women. *P values for repeated time measures in each group (wilcoxon non parametric test). ††P values for TA treated vs untreated haemorrhagic patients (Mann-Whitney U-test non parametric test); T2 comparison: PAP P=0.03; T3 comparison: D Dimers P=0.0009; T4 comparison: D Dimers P=0.0001

<table>
<thead>
<tr>
<th>Group</th>
<th>Control untreated Haemorrhagic n=72</th>
<th>Enrolment</th>
<th>+30 min</th>
<th>+2 h</th>
<th>+6 h</th>
<th>P value</th>
<th>TA treated Haemorrhagic n=72</th>
<th>Enrolment</th>
<th>+30 min</th>
<th>+2 h</th>
<th>+6 h</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen (g litre⁻¹)</td>
<td>3.95 [3.2-4.75]</td>
<td>3.25 [2.8-4.2]</td>
<td>3.1 [2.6-4]</td>
<td>3.4 [3-4.15]</td>
<td>0.0001</td>
<td>4.1 [3.4-4.8]</td>
<td>3.2 [2.8-4.1]</td>
<td>3.1 [2.8-3.8]</td>
<td>3.4 [3-4]</td>
<td>0.0001</td>
<td></td>
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</tbody>
</table>

Tranexamic acid inhibits PPH associated increase in D-dimers.
postpartum-adapted DIC scores do not take into account fibrinolysis.13

The clinical efficacy of a high dose of 4 g TA given intravenously over one h followed by a 6 g infusion over 6 h has been demonstrated by the improvement of clinical outcomes, such as progression to severe PPH (P=0.028) and RBC transfusion (P<0.001).11 PPH stopped after only uterotonics in 93% of women in the TA group vs 79% of controls (P=0.016).11 In our biological sub study analysing the haemostasis parameters obtained from samples collected as part of the clinical study, the biological inhibition of D-dimers and plasmin-antiplasmin increase was observed in parallel to clinical efficacy.

High doses of TA (50–100 mg kg⁻¹) have been shown to provide higher peak plasma concentrations than low doses (10 mg kg⁻¹) and maintain the concentration above a presumed therapeutic concentration, resulting in a longer therapeutic effect in the setting of cardiopulmonary bypass surgery.35 This evidence was considered important in our situations of ongoing active and major bleeding.41 5 This evidence was also the only data available concerning doses effective in reducing ongoing major bleeding when our study was designed and approved. Since then the CRASH-2 trial and the ongoing WOMAN trial studied a lower dose of 1 g+1 g of tranexamic acid in patients experiencing or at risk of significant haemorrhage.5 36 In the CRASH-2 trial, a large international randomized trial in more than 20 000 trauma patients, this lower dose of TA reduced global mortality and mortality as a result of haemorrhage, but not transfusion rates.5

Levy commented on the CRASH-2 results and underlined this gap between a significant reduction of mortality and the absence of blood product sparing.37 Furthermore, the mechanisms of TA-related effects were not biologically documented as in many older studies.37 Because a low dose of 2 g over eight h was not sufficient to inhibit plasminogen activation, Levy suggested plasmin inhibition within the clot, fibrinogenolysis, platelet activation and inhibition of proinflammatory pathways, to be the major mechanisms of TA beneficial effects.37 Our haemostasis data demonstrating an inhibition of D-dimers increase after 2 g of TA over 30 min are in line with these suggestions. Moreover obstetrical catastrophic emergencies, such as placental abruption or amniotic fluid embolism, had been previously treated with higher or repeated doses of TA, regarding the major activation of coagulation and fibrinolysis.38–40 On the other part, high doses of TA demonstrated a risk of seizures in cardiovascular surgery and was associated with a higher frequency of nausea and vomiting and visual disturbance in our series.11 15 Recently, pharmacokinetic studies have been developed in parallel with clinical assessment of the effects of TA in the setting of paediatrics cardiopulmonary bypass and surgery.41

Fig. 2 Haemostasis parameters in treated TA vs untreated haemorrhagic H groups. Haemostasis parameters collected at onset of PPH, 30 min, 2 and 6 h in treated tranexamic haemorrhagic group (open triangle ▵) compared with untreated H haemorrhagic group (open circle ○). Data expressed as median [interquartile range]. **P values for non-haemorrhagic group vs untreated haemorrhagic group by using Mann-Whitney U-test non parametric test. (A) D Dimers (ng ml⁻¹) (b): Plasmin antiplasmin PAP complexes (ng ml⁻¹) (c): Fibrinogen (g litre⁻¹) (d): Factor II (IU ml⁻¹).
Enrolment was performed shortly after PPH onset, allowing early and serial analyses of PPH biological data. The haemorrhagic group (H) was untreated: no prohaemostatic treatments were allowed (no plasma, nor fibrinogen concentrate, nor tranexamic acid, nor platelets, nor recombinant factor VIIa), allowing the study to provide the first data on the natural course of ongoing PPH induced coagulopathy. Similarly, the treated haemorrhage (TA) group did not receive any haemostatic treatment other than TA (no fresh frozen Plasma, nor fibrinogen concentrates, nor recombinant factor VIIa) allowing the study to provide data on the effects of TA alone.

The major weakness of the previously published randomized, controlled study is its open-label, unblinded design. However, the trial was partially blinded for obstetricians. Haematologists were not aware of the treatment group. Biological analysis was performed regardless of the group allocation. Therefore, the blinded biological results seem robust and validate the clinical effects demonstrated in the initial clinical study.

A second limitation is the limited number of patients in the non-haemorrhagic reference group. However, the reference values in our series were comparable with the literature normal values.16 19

Third, the limitation of the biological analysis to the routine haemostasis parameters limits the scope of determining the mechanisms involved in PPH induced coagulopathy. Although limited, these are the first sequential and timed data observed from the onset of PPH after vaginal delivery.

The present study provides the first demonstration that a rapid onset increase in D-dimers exists in PPH-related coagulopathy. These results also suggest that the favourable clinical impact of early TA administration was concomitant to an inhibition of this D-dimers increase.

Authors’ contributions
Study design/planning: A.S.D.-B., A.D., S.S.
Study conduct: A.S.D.-B., A.D., A.T., A.P.-D., E.J., G.D., E.P., the EXADELI study group
Data analysis: A.S.D.-B., A.D., S.S.
Revising paper: all authors

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Declaration of interest
None declared.

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