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# Impact of Tranexamic Acid on Postpartum Hemorrhage in Type 1 von Willebrand Disease Treated with Recombinant VWF

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**Abstract:**
Postpartum hemorrhage (PPH) affects up to 44% of women with von Willebrand disease (VWD) despite recombinant VWF (rVWF) treatment. As tranexamic acid (TXA) reduced PPH-related deaths in the WOMAN trial, we assessed whether TXA combined with rVWF versus rVWF alone prevents PPH in VWD. VWD-Woman, a phase 3, open-label, randomized pilot trial, enrolled pregnant women ≥18 years with VWD (VWF:RCo <0.50 IU/mL, bleeding history). Participants received intravenous rVWF 80 IU/kg at delivery and postpartum days 1 and 2, with or without TXA (1g within 3 hours of delivery). The primary outcome was quantitative blood loss (QBL) at delivery. Secondary outcomes included 21-day pictorial blood assessment chart (PBAC) scores, hemoglobin changes, transfusions, hysterectomy, and safety. (NCT04344860) Of 103 screened, 40 were eligible, and 20 were enrolled (10 per group), 100% of whom were iron deficient. Mean QBL was similar (TXA + rVWF: 727·0 mL [95% CI: 434·5, 1019·5] vs. rVWF: 539·7 mL [95% CI: 132·8, 946·6]; p=0·41), as were rates of PPH (30% in both groups). No significant differences were observed in hemoglobin change (-1·90 g/dL vs. -1·42 g/dL, p=0·49) or 21-day cumulative PBAC score (467·1 vs. 344·8, p=0·32). Stratified analyses showed no significant differences by age, BMI, VWF activity, or delivery type. No serious adverse events or thrombosis occurred. TXA plus rVWF is feasible and safe in type 1 VWD, but in this small pilot study, was not associated with a reduction in PPH compared to rVWF alone. Iron deficiency is prevalent but underrecognized. Further studies are needed to improve PPH prevention in VWD.

**Conflict of interest:** COI declared - see note

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**Agreement to Share Publication-Related Data and Data Sharing Statement:** Deidentified individual participant data that underlie the results reported in this article, along with the study protocol, will be made available upon reasonable request from the corresponding author. Data will be shared with researchers whose proposed use aligns with the aims of this study and is approved by the institutional review board or relevant oversight committee. Data will be available for 7 years following publication. Requests for access should be directed to machinnc2@upmc.edu.

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**Title:** Impact of Tranexamic Acid on Postpartum Hemorrhage in Type 1 von Willebrand Disease Treated with Recombinant VWF

**Running Title:** VWD-Woman Pilot Trial

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**Figures:** 2 **Tables:** 4 **References:** 41

**Data sharing**

Deidentified individual participant data that underlie the results reported in this article, along with the study protocol, will be made available upon reasonable request from the corresponding author. Data will be shared with researchers whose proposed use aligns with the aims of this study and is approved by the institutional review board or relevant oversight committee. Data will be available for 7 years following publication. Requests for access should be directed to machinnc2@upmc.edu.

**Key Points:**

-Postpartum TXA with rVWF was safe and feasible but did not reduce bleeding versus rVWF alone in type 1 VWD.

-Iron deficiency was present in all participants, underscoring the need for routine screening in pregnant women with VWD.

**Abstract**

Postpartum hemorrhage (PPH) affects up to 44% of women with von Willebrand disease (VWD) despite recombinant VWF (rVWF) treatment. As tranexamic acid (TXA) reduced PPH-related deaths in the WOMAN trial, we assessed whether TXA combined with rVWF versus rVWF alone prevents PPH in VWD. VWD-Woman, a phase 3, open-label, randomized pilot trial, enrolled pregnant women ≥18 years with VWD (VWF:RCo <0.50 IU/mL, bleeding history). Participants received intravenous rVWF 80 IU/kg at delivery and postpartum days 1 and 2, with or without TXA (1g within 3 hours of delivery). The primary outcome was quantitative blood loss (QBL) at delivery. Secondary outcomes included 21-day pictorial blood assessment chart (PBAC) scores, hemoglobin changes, transfusions, hysterectomy, and safety. (NCT04344860) Of 103 screened, 40 were eligible, and 20 were enrolled (10 per group), 100% of whom were iron deficient. Mean QBL was similar (TXA + rVWF: 727·0 mL [95% CI: 434·5, 1019·5] vs. rVWF: 539·7 mL [95% CI: 132·8, 946·6]; p=0·41), as were rates of PPH (30% in both groups). No significant differences were observed in hemoglobin change (-1·90 g/dL vs. -1·42 g/dL, p=0·49) or 21-day cumulative PBAC score (467·1 vs. 344·8, p=0·32). Stratified analyses showed no significant differences by age, BMI, VWF activity, or delivery type. No serious adverse events or thrombosis occurred. TXA plus rVWF is feasible and safe in type 1 VWD, but in this small pilot study, was not associated with a reduction in PPH compared to rVWF alone. Iron deficiency is prevalent but underrecognized. Further studies are needed to improve PPH prevention in VWD.

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**Introduction**

Von Willebrand disease (VWD) is the most common inherited bleeding disorder, caused by quantitative or qualitative deficiency of von Willebrand factor (VWF) and affecting approximately 1% of the general population[1]. Individuals with VWD experience primarily mucocutaneous bleeding including epistaxis and heavy menstrual bleeding and have an increased risk of bleeding during surgery and childbirth[2, 3]. Pregnant individuals with VWD are particularly vulnerable to both primary and secondary postpartum hemorrhage (PPH), with rates up to 44%, significantly higher than in the general obstetric population[4-8].

PPH remains a major cause of maternal morbidity and mortality worldwide, with consequences extending well beyond acute blood loss in the immediate postpartum period[9, 10]. Primary PPH is defined as >1000mL or hemodynamic instability due to bleeding which occurs within 24 hours of delivery and secondary PPH is bleeding from 24hrs to six weeks postpartum[11, 12]. Women with VWD who experience excess bleeding at delivery have a higher risk of prolonged hospitalization, iron deficiency anemia, impaired lactation, and postpartum depression[13, 14]. These maternal outcomes underscore the importance of achieving optimal hemostatic control at delivery to prevent immediate and long-term complications.

While VWF levels physiologically increase during pregnancy, this rise is often inadequate in women with VWD. International guidelines recommend maintaining VWF and factor VIII:C (FVIII:C) levels above 50% to permit safe epidural analgesia and minimize the risk of postpartum hemorrhage[15-18]. However, this target may not sufficiently mimic the physiological hemostatic changes observed in women without VWD, who experience up to a 300% elevation in VWF levels at term[19, 20]. Such levels are seldom achieved in women with VWD, even with VWF replacement therapy[21, 22]. Consequently, there is increasing debate surrounding optimal VWF dosing targets at delivery, with some evidence suggesting that higher replacement levels may improve outcomes[23]. A recent single-institution cohort study reported that targeting higher VWF and FVIII:C levels at delivery (≥100IU/dL) led to improved hemostatic outcomes in women with VWD, including reduced estimated blood loss, fewer transfusions, and a lower incidence of postpartum hemorrhage[24].

Tranexamic acid (TXA), an antifibrinolytic agent that inhibits the breakdown of fibrin clots and thereby stabilizes blood clots and reduces excessive bleeding, has been recognized for its efficacy in managing postpartum hemorrhage in the general population[25-27].The landmark WOMAN trial demonstrated a significant reduction in PPH-associated mortality when TXA was administered within three hours of delivery, solidifying its role as a standard adjunct in PPH management[28]. TXA has also been shown to effectively manage heavy menstrual bleeding in women including those with VWD[29, 30]. While often used in clinical practice, there is limited randomized trial data regarding the efficacy and safety of the combination of TXA with VWF concentrate to optimize hemostasis in women with VWD at delivery.

In this pilot study, we aimed to evaluate the safety and feasibility of administering TXA in combination with recombinant von Willebrand factor (rVWF) compared to rVWF alone for the prevention of postpartum hemorrhage in women with VWD. We aimed to inform future strategies for optimizing hemostatic management in this high-risk population by addressing this critical gap in the evidence base.

## Methods

### Study Design and Participants

VWD-Woman was an investigator-initiated, industry-sponsored, phase 3, open-label, randomized single-center pilot trial. Participants were screened and enrolled during routine clinic visits at the Hemophilia Center of Western Pennsylvania, with delivery planned at UPMC Magee-Womens Hospital in Pittsburgh, Pennsylvania. The study was approved by the University of Pittsburgh Biomedical Institutional Review Board April 28, 2021, and between June 4, 2021 and May 17, 2024, 20 patients were enrolled.

The study enrolled pregnant females aged 18 years or older with confirmed von Willebrand disease (VWD), defined by a historical von Willebrand factor ristocetin cofactor (VWF:RCo) level <0·50 IU/mL and a documented bleeding history, who planned delivery at UPMC Magee-Womens Hospital. Bleeding history was assessed using ISTH Bleeding Assessment Tool (ISTH-BAT) scores previously completed as part of standard clinical care and documented in the medical record, along with records of prior treatment for mucocutaneous or procedural bleeding episodes. Although individuals with all VWD subtypes were eligible, all enrolled participants had type 1 VWD. Participants were required to consent to blood draws, comply with random assignment, maintain a 21-day postpartum pictorial blood assessment chart (PBAC) diary, document hemostatic agent use, and attend study visits. The 21-day postpartum period was selected to capture secondary outcomes, including delayed or prolonged bleeding, hemoglobin recovery, transfusion requirements, and adverse events. Obstetric data collected included mode of delivery, gestational age, induction of labor, preeclampsia, prior cesarean, and other risk factors for obstetric hemorrhage.

Exclusion criteria included having a bleeding disorder other than VWD or known thrombophilia; prior identification of the D1472H sequence variant on genetic testing; a history of thrombosis, cardiac disease, untreated hypertension, renal disease, or cerebrovascular accident; a platelet count below 100,000/µL; or a past allergic reaction to von Willebrand factor concentrates or tranexamic acid. Participants were also excluded if they had undergone surgery within eight weeks of enrollment; used antiplatelet drugs (excluding low-dose aspirin), anticoagulants, or NSAIDs; or received treatment with desmopressin (DDAVP), cryoprecipitate, whole blood, plasma, or plasma derivatives containing substantial quantities of VWF within five days of enrollment. All participants provided written informed consent prior to enrollment.

Participants were not screened for the D1472H polymorphism as part of the study protocol; however, individuals with a known D1472H variant were excluded during screening. Additional clinical testing relevant to VWD classification is described in the Results.

**Randomization**

Following confirmation of eligibility, participants were randomly assigned 1:1, to receive rVWF at delivery and on postpartum days 1 and 2, with TA within 3 hours of delivery, or rVWF alone. Randomization was performed using a permuted block design with random block sizes of four to six. The allocation sequence was generated by an unmasked statistician prior to the enrollment of any participant and securely stored to ensure allocation concealment. Once eligibility was confirmed, clinical coordinators enrolled participants within 72 hours of screening and assigned them to their randomized study group via a secure electronic web portal. Blinding or masking was not implemented; all drugs were administered in an open-label manner.

**Procedures**

Following randomization, all 20 participants received rVWF (Vonvendi, Takeda Pharmaceuticals USA Lexington, MA, USA) 80 IU/kg using pre-pregnancy weight by standard intravenous technique over 5-10 minutes prior to neuraxial anesthesia or during active labor and again 24 and 48 hours postpartum. All participants received rVWF at delivery and postpartum days 1 and 2 per study protocol, regardless of third-trimester VWF levels. A dose of 80 IU/kg was selected based on concerns regarding increased plasma volume during pregnancy and the observation that VWF activity levels in unaffected women typically rise significantly at delivery. This higher dose was intended to approximate physiologic third-trimester VWF activity levels and optimize hemostatic protection.

For the seven participants who underwent cesarean section rVWF was administered prior to neuraxial anesthesia preoperatively. All thirteen participants who had vaginal deliveries elected for epidural anesthesia and received rVWF prior to catheter placement. The time from epidural placement to delivery was less than 12hrs for all but one participant who required an additional dose of rVWF 24hrs after initial dosing due to prolonged labor. Participants randomized to the rVWF plus TXA group received intravenous tranexamic acid (TXA; Cyclokapron, Pfizer Pharmaceuticals, San Diego, CA, USA), 1 g (100 mg/mL) infused over 10 minutes at a rate of 1 mL per minute, administered within three hours of delivery. All participants in this group received the TXA dose within 1 hour postpartum (median 35 minutes, range 9–59 minutes). An additional 1 g rescue dose of TXA was available for ongoing bleeding persisting beyond 30 minutes, at the discretion of the obstetric team.

There were no planned interim analyses. Assigned study drug was prepared for each participant, with rVWF stored at the Hemophilia Center of Western of Pennsylvania at 2-8◦C and delivered to the Investigational Pharmacy at Magee-Womens Hospital for each participant prior to delivery. TXA was prepared and provided by the same Investigational Pharmacy.

Participants completed an initial screening visit and additional study visits on admission for delivery, postpartum days 1 and 2, and a final visit at 21 days postpartum. Laboratory assessments at each visit included hemoglobin, platelets, ferritin, D-dimer, fibrinogen, VWF:Ag, and VWF:RCo. Concomitant medications and narrative descriptions of postpartum management by the obstetrical team were collected. Quantitative Blood Loss (QBL) was determined by clinical staff as the sum of the blood volume collected in suction canisters (after subtracting irrigation fluids) and the weight of blood-soaked materials (subtracting standardized dry weight), and was recorded continuously from the time of delivery through at least 4 hours postpartum, in accordance with institutional protocols[31]. Postpartum lochial bleeding was quantified by each participant, using a 21-day diary and Pictorial Bleeding Assessment Chart (PBAC)[32]. To standardize measurement of lochial blood loss, all participants received a 21-day supply of Kotex super-plus sanitary pads (Kimberly-Clark, Irving, TX, USA) for exclusive use during the trial.

Protocol amendments included expansion of inclusion criteria to include participants on low dose aspirin therapy for obstetrical indication, i.e. preeclampsia risk, and patient screening and enrollment beyond 32 weeks gestation. All participants receiving low dose aspirin had this medication discontinued by their treated obstetrician between 35-37 weeks gestation and none delivered on active aspirin therapy. Stopping rules that, if reached, would halt the trial included thrombosis or grade 2–5 allergic reactions. Safety was assessed by lochial blood loss assessed by each participant by pictorial blood assessment chart (PBAC), blood product transfusion, thromboembolic event, allergic reaction, and hysterectomy within 21 days of delivery. Adverse events were graded by Common Terminology Criteria for Adverse Event (CTCAE), National Cancer Institute) grading, version 6.

Coagulation testing followed manufacturer protocols using a BCS-XP automated coagulation analyzer (Siemens). D-dimer was assessed via immunoturbidimetric assay (INNOVANCE D-Dimer kit, Siemens Healthineers, Malvern, PA, USA), measuring change in optical density against calibration curves and reported in mg/L Fibrinogen Equivalent Units (FEU). Fibrinogen activity was measured by the modified Clauss method (Multifibren U, Siemens Healthineers, Malvern, PA, USA), in which the clotting time was compared to a fibrinogen standard and reported in mg/dL. VWF:Ag and VWF:RCo were evaluated by agglutination assays (STA-Liatest VWF, BC von Willebrand Reagent, Siemens Healthcare Diagnostics, Marburg, Germany), with results expressed in U/mL. Activated partial thromboplastin time (aPTT) and FVIII activity were determined by clotting assays, using Pathromtin SL reagent (Siemens Healthineers, Malvern, PA, USA) and FVIII-deficient plasma, calibrated by standard plasma curve.

**Outcomes:**

The primary endpoint was QBL at delivery, calculated by a labor suite nurse using standardized methods[33]. Secondary endpoints included safety assessments, such as lochial blood loss quantified by PBAC, blood product usage, transfusion requirement, and hysterectomy within 21 days postpartum. Additionally, mechanisms of PPH reduction were explored by analysis of VWF:Ag, VWF:RCo, fibrinogen levels, and D-dimer values.

**Statistical Analysis**

The statistical analysis for this pilot study, designed to assess the safety and feasibility of rVWF in combination with TXA at delivery in women with von VWD, was exploratory and not powered for statistical significance. QBL, the primary endpoint, was analyzed using descriptive statistics and compared between treatment arms with a Mann-Whitney U test for non-normal data. Secondary endpoints included 21-day lochial blood loss (PBAC) and safety outcomes (hemoglobin change, blood product usage, hysterectomy), analyzed using descriptive statistics and appropriate parametric or non-parametric tests. Stratified analyses assessed QBL by age, BMI at delivery, baseline VWF activity, and delivery type. Analyses were performed in STATA (Version 16, StataCorp, College Station, TX, USA), with results focused on trends.

**Role of the funding source**

The funding source did not have a role in the study design, execution, data collection, analysis, or interpretation of the data. However, the funding source reviewed and provided comments on the manuscript. The authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

## Results

### Enrollment and Study Completion

Between June 4, 2021, and May 17, 2024, 103 women were screened, 40 met eligibility criteria, and 20 were randomized: 10 to receive recombinant von Willebrand factor (rVWF) with tranexamic acid (TXA) and 10 to receive rVWF alone (Figure 1). All participants completed the study protocol and attended all study visits. The most common reasons for screen failure included delivery at an outside facility and inability to verify a von Willebrand disease diagnosis from historical laboratory results. Of the 40 eligible women, 20 declined participation, most often due to concerns about added demands during pregnancy. This was more commonly expressed by women in their first pregnancy, based on consent discussions. Full screening outcomes are shown in Figure 1.

Two protocol deviations occurred: one participant in the rVWF + TXA group received an additional 1 g dose of intravenous (IV) TXA during epidural placement, in addition to the study dose administered within 3 hours of delivery. Another participant in the rVWF-alone group received a rescue dose of 80 IU/kg rVWF following over 24 hours of labor. These participants were included in the analysis.

Quantitative blood loss (QBL) data were available for all participants (20/20, 100%), and 21-day pictorial bleeding assessment chart (PBAC) data were available for 19 of 20 participants (95%). Out of 200 scheduled laboratory draws across 20 participants, only four values (2%) were missing.

### Baseline Characteristics

Baseline demographic and clinical characteristics were comparable between the two treatment groups (Table 1). The mean age of participants was 29·0 years (SD 5·23), with no significant difference between the rVWF + TXA group (29·1 years, SD 5·2) and the rVWF-alone group (28·8 years, SD 5·7). Most participants (90%) were White, and all participants had type 1 von Willebrand disease (VWD).

Ferritin levels obtained in the third trimester indicated universal iron deficiency among participants, with a mean ferritin level of 15·8 ng/mL (SD 9·1). Although all participants reported taking a daily prenatal vitamin, only two were on formulations containing iron. None had undergone ferritin assessment in the previous year, were prescribed iron supplementation, or received recommendations for iron replacement before enrollment. Ferritin levels were <50 ng/mL in all 20 participants; of these, 19 (95%) received intravenous iron before during the third trimester prior to delivery. One participant declined intravenous iron and was treated with oral ferrous sulfate instead.

The mean pre-pregnancy BMI was 30·9 (SD 8·4), increasing to 36·1 (SD 8·1) by delivery, with no significant difference between groups. Third-trimester hemoglobin levels were also comparable (12·1 g/dL [SD 0·9] in the rVWF + TXA group vs. 11·8 g/dL [SD 1·0] in the rVWF-alone group).

Among the 20 participants enrolled, 11 had prior clinical next-generation sequencing (NGS) confirming absence of the D1472H variant. An additional 3 participants, while lacking NGS data, had VWF:GP1bM activity <0.5 IU/mL outside of pregnancy, reducing concern for misclassification due to this polymorphism. Thus, 14 of 20 participants had available clinical data supporting accurate VWD classification (Table 2).

### Delivery Outcomes

Quantitative blood loss (QBL) at delivery was numerically higher in the rVWF + TXA group compared to the rVWF-alone group, with a median QBL of 802·5 mL (350·0, 1027·5) versus 355·0 mL (255·0, 499·3), respectively ($p = 0·41$); this difference was not statistically significant. Postpartum hemorrhage (PPH), defined as QBL >1000 mL, occurred in 3 participants (30%) in the rVWF + TXA group and 1 participant (10%) in the rVWF-alone group ($p = 0·25$).

Obstetricians initiated additional interventions for bleeding in 6 participants, with 3 participants (30%) in each group (Table 2). All received uterotonics, including misoprostol and oxytocin. Intrauterine tamponade balloon placement was required in two participants. In the rVWF + TXA group, one participant received a rescue dose of TXA for PPH within 24 hours after delivery. In the rVWF-alone group, three participants received 1 g of IV TXA within 3 hours of delivery due to clinical concern for primary PPH, per standard hospital protocol; all were included in the final analysis. No participant required additional doses of rVWF outside of the study protocol.

Cesarean delivery was significantly more common in the rVWF + TXA group (60%) compared to the rVWF-alone group (10%; p = 0·027), with vaginal deliveries accounting for the remaining 40% and 90% of births, respectively. Stratification of QBL by delivery type revealed higher mean QBL among participants undergoing cesarean section (903·0 mL, SD 285·0) compared to those with vaginal delivery (462·5 mL, SD 459·0; p = 0·13). Stratified analyses of QBL by delivery type, BMI, and age revealed no significant subgroup differences.

**Secondary Outcomes**

**Hemoglobin and Bleeding Outcomes**

Hemoglobin levels declined by a mean of 1·9 g/dL (SD 1·5) in the rVWF + TXA group and 1·4 g/dL (SD 1·6) in the rVWF-alone group; this difference was not statistically significant ($p$ = 0·49). The proportion of participants experiencing a >2 g/dL hemoglobin decrease was slightly higher in the rVWF + TXA group (40%) compared to the rVWF-alone group (30%; $p$ = 0·32). The median cumulative 21-day pictorial bleeding assessment chart (PBAC) score was 442·0 (224·0, 724.0) in the rVWF + TXA group and 344·8 (185·0, 512.5) in the rVWF-alone group ($p$ = 0·32). The duration of lochial bleeding was similar between groups: 19·1 days (SD 3·1) in the rVWF + TXA group and 19·0 days (SD 5·4; $p$ = 0·96). The mean PBAC scores over time were comparable between groups (Figure 2). On day 21, eight women had ongoing lochial bleeding: three in the rVWF + TXA group and five in the rVWF-alone group. One participant in the rVWF + TXA group did not complete the PBAC diary and was excluded from this analysis.

**Coagulation Markers**

Laboratory markers of coagulation, including VWF:Ag, VWF:RCo, FVIII, fibrinogen, and D-dimer, did not differ significantly between groups across study visits (Table 4).

Participants were divided into those clinically managed for PPH (6) and those who were not (14) to explore potential differences in characteristics and coagulation testing. The group treated for PPH by the obstetrician included all four participants with QBLs over 1000 mL, while the other two participants had QBLs of 800 mL and 300 mL. Within the group managed for PPH three patients' delivery by cesarian sections and three vaginally. The age (26·6, SD 5·2 vs 30·0 SD 5·1; p=0·15) and BMI (37·9, SD 12·0 vs 35·3 SD 6·3; p = 0·63) of the participants with and without PPH were similar. There was no difference in third trimester VWF:Ag, VWF:RCo, VIII, d-dimer or fibrinogen levels between participants who were and were not managed clinically for PPH. Evaluation VWF:Ag over study times points did demonstrate lower VWF:Ag (1·39, SD 0·40) on admission for delivery for participants with PPH compared to those who did not (2·45, SD 1·07), p= 0·006. There was no difference between groups for fibrinogen, d-dimer, VWF:RCo, VIII or VWF:Ag at across other study timepoints.

**Safety Outcomes**

No serious adverse events, thrombotic events, or allergic reactions were observed. No hysterectomies occurred within the 21-day postpartum period. Of the 19 participants who received intravenous iron there were no infusions reactions or complications.

**Discussion**

Despite current prophylactic approaches, women with VWD remain at high risk for bleeding at delivery. In this pilot randomized trial, we evaluated the feasibility and impact of combining TXA with recombinant VWF (rVWF) at delivery. Substantial blood loss persisted in both treatment groups, with a median QBL exceeding 700 mL in the combination arm and one-third of all participants requiring additional clinical intervention for bleeding. These findings highlight the limitations of current therapies in fully preventing postpartum bleeding in VWD. As this study enrolled only women with type 1 VWD, the applicability of these findings to more severe subtypes remains uncertain.

The high proportion of these VWD participants with iron deficiency in the third trimester of pregnancy was notable and aligns with growing awareness of iron deficiency among pregnant women[34]. However, the absence of guidelines by the USPHS and controversy over standardization of screening and management appears to contribute to the lack of iron screening and repletion as women with VWD approach delivery[35]. Until guidelines are available, routine screening should be implemented during the second and third trimester with repletion as necessary, given the poor quality of life and morbidity associated with iron deficiency and growing evidence of impact on fetal outcomes[36].

There are several limitations of this study. First, the small sample size and pilot nature of this study restrict the generalizability of the findings. Subgroup and stratified analyses were underpowered and should be interpreted as exploratory. Larger, multicenter studies will be necessary to validate these results. Further, as findings in type 1 VWD may not predict those with more severe disease, future studies should include pregnant females with type 2 and 3 VWD. The high rate of cesarean deliveries in the TXA group may have influenced the quantitative blood loss (QBL) results, introducing a potential confounder that should also be addressed in larger future trials. Participants receiving VWF alone who subsequently developed PPH were managed with TXA, which could influence coagulation assay testing and PBAC scores postpartum. Moreover, the lack of understanding of the mechanism of PPH in VWD and the lack of objective predictors of PPH highlight the complexity of designing a trial to optimize PPH management in women with VWD. Despite VWF and TXA co-administration, the PPH rate remains high, 20%, suggesting a need for better therapies, better dosing strategies, and better pharmacologic and procedural approaches to prevent PPH in VWD.

Consistent with current clinical guidelines and prior studies, all participants in our trial were treated with a regimen designed to achieve VWF and FVIII levels >50% to permit safe neuraxial anesthesia and provide hemostatic protection[15, 16]. While our study was not designed to compare different factor level targets, the persistent rate of PPH despite achieving this threshold suggests that a target of >50% may be insufficient for some individuals with VWD. Recent studies have proposed aiming for higher factor levels to mimic physiologic third-trimester hemostasis better, though the optimal target remains uncertain[24, 37]. Emerging data from European cohorts and the recently reported PRIDES study suggest that more intensive or repeated postpartum VWF replacement may better reflect physiologic hemostatic changes and could reduce PPH risk[38]. These evolving practices support the rationale for our protocol's repeated rVWF dosing

Recent data suggest that the antifibrinolytic efficacy of TXA may be reduced in states of low hematocrit, due to decreased reinforcement of clot structure by red blood cells. In our cohort, while hemoglobin levels were modestly reduced, 100% of participants were iron deficient, which may have influenced TXA response. Future studies should explore whether hematocrit optimization or TXA dosing adjustments in iron-deficient individuals could improve bleeding outcomes[39].

Our protocol prioritized immediate postpartum bleeding risk, with TXA administered within hours of delivery to target peak fibrinolysis. However, a single inpatient dose is unlikely to influence bleeding patterns across the broader postpartum period. Future studies should evaluate extended TXA regimens to address delayed or secondary postpartum hemorrhage.

Despite these considerations, the study demonstrated the feasibility of conducting a randomized trial in pregnant patients with VWD, with full participant retention, high compliance with study protocol visits, labs, treatment, and safety with combined therapy interventions. The trial greatly benefited from its conduct in a women's hospital with a team of collaborative anesthesiologists, obstetricians, and pharmacists, suggesting this successful approach in future larger-scale studies.

A notable finding in this cohort was the 100% prevalence of iron deficiency, and the need, despite the absence of guidelines, vigilance is needed for screening and management in women with VWD, as it represents a low-cost, high-yield intervention to improve maternal outcome and reduce the burden and hasten recovery from associated bleeding-related complications[40, 41].

In conclusion, while the study provides encouraging data on the safety of conducting clinical trials in pregnant women with VWD, as well as the safety of combining rVWF and TXA in postpartum management in women with type 1 VWD, the limitations underscore the necessity for larger, more diverse studies including other VWD subtypes, as well as studies designed to evaluate hematologic modifiers of TXA efficacy such as hematocrit and red cell mass, and to explore optimized dosing, novel therapeutics, and iron deficiency management strategies to reduce the unacceptably high PPH risk.

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**Authors Contributors**

All authors contributed to the conceptualization, methodology, formal analysis, and interpretation of results.

Data Curation: Nicoletta C. Machin, DO, MS, Maria M. Brooks, PhD, and Margaret V. Ragni, MD, MPH directly accessed and verified the underlying data reported in the manuscript. All authors confirm that they had full access to all the data in the study and accept responsibility for submitting the manuscript for publication.

Data Collection & Management: Nicoletta C. Machin, DO, MS led data collection, statistical analysis, and manuscript drafting (*writing – original draft*). Deborah Vehec, MS, RN, Dana Ivanco, and Brandon Lawryk, BS contributed to data collection and management.

Statistical Methodology: Maria M. Brooks, PhD provided expertise in statistical methodology and data analysis (*formal analysis*).

Clinical Oversight & Hematologic Interpretation: Craig D. Seaman, MD, MS and Fredrico Xavier, MD, MS provided clinical oversight, hematologic interpretation, and critical manuscript review (*writing – review & editing*).

Laboratory & Mechanistic Expertise: Sruti Shiva, PhD, and Angela Verdoni, PhD contributed expertise in laboratory and mechanistic aspects of the study in addition to critical manuscript review (*writing – review & editing*).

Supervision, Funding & Project Administration: Margaret V. Ragni, MD, MPH supervised the study (*supervision*), provided critical revisions (*writing – review & editing*), and secured funding acquisition.

All authors reviewed and approved the final manuscript.

**Conflict of Interest**

Nicoletta C. Machin, DO, MS has received research funding from Takeda Pharmaceuticals USA and has served on advisory boards for Sanofi and Star Therapeutics.

Margaret V. Ragni, MD, MPH has received research funding from Takeda Pharmaceuticals USA.

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Maria M. Brooks, PhD; Sruti Shiva, PhD; Angela Verdoni, PhD; Dana Ivanco; Deborah Vehec, MS, RN; and Brandon Lawryk, BS declare no competing interests.

**Declaration of generative AI and AI-assisted technologies in the writing process**

During the preparation of this work, the authors used ChatGPT for editing and text refinement. After using this tool, the author(s) reviewed and edited the content as needed and take full responsibility for the content of the publication.

*Figure 1:* Consort Diagram

*Figure 2:* Average PBAC score of lochial blood loss reported by patient diary over 21 days. One subject in the rVWF +TXA group did not complete a diary.



**Table 1: Baseline Demographics and Laboratory Studies Overall and by Assigned Treatment Group**

| | Total N=20 | Recombinant VWF and tranexamic acid N=10 | Recombinant VWF N=10 |
|---|---|---|---|

| | | | |
|---|---|---|---|
| **Age, years** | 29·0 (5·3) | 29·1 (5·2) | 28·8 (5·7) |
| **Race** | | | |
| **White** | 18 (90) | 9 (90) | 9 (90) |
| **Black** | 2 (10) | 1 (10) | 1 (10) |
| **Ethnicity** | | | |
| **Not Hispanic or Latino** | 20 (100) | 10 (100) | 10 (100) |
| **Height, cm** | 161·5 (8·3) | 161·5 (10·6) | 161·4 (5·5) |
| **Pre-pregnancy weight, kg** | 80·9 (23·7) | 78·6 (29·0) | 83·3 (18·1) |
| **Pre-pregnancy BMI, kg/m$^2$** | 30·9 (8·4) | 29·8 (9·8) | 32·0 (7·0) |
| **Delivery weight, kg** | 94·4 (24·0) | 93·5 (28·2) | 95·3 (20·5) |
| **Delivery BMI, kg/m$^2$** | 36·1 (8·1) | 35·6 (9·3) | 36·5 (7·3) |
| **Hemoglobin, g/d$^\wedge$** | 11·9 (0·9) | 12·1 (0·9) | 11·8 (1·0) |
| **Ferritin, ng/mL** | 15·8 (9·1) | 18 (11·1) | 13·5 (6·5) |
| **Low ferritin†** | 20 (100) | 10 (100) | 10 (100) |
| **VWD type** | | | |
| **Type 1** | 20 (100) | 10 (100) | 10 (100) |
| **VWF:Ag, IU/mL*** | 0·5 (0·3-1·9) | 0·7 (0·3-1·9) | 0·4 (0·3-0·7) |
| **VWF:RCo, IU/mL*** | 0·3 (0·1-0·5) | 0·4 (0·2-0·5) | 0·3 (0·1-0·4) |
| **VIII, IU/mL*** | 0·7 (0·3-1·1) | 0·6 (0·4-1·1) | 0·6 (0·3-1·1) |

*Table 1:* Data are mean (SD), (range) or n (%). *VWF ristocetin cofactor, VWF antigen, and factor VIII clotting activity are historic (pre-pregnancy). $^\wedge$Hemoglobin at third-trimester screening visit. †Abnormally low ferritin is defined as <50 µg/L in the context of pregnancy.

**Table 2: Genetic Testing and VWF:GP1bM Activity by Treatment Group**

| | Total N=20 | Recombinant VWF and tranexamic acid N=10 | Recombinant VWF N=10 |
|---|---|---|---|
| **Baseline VWF:GP1bM available** | 12 (60) | 8 (80) | 4 (40) |
| **VWF:GP1bM, IU/dL** | 0·45 (0·23-0·64) | 0·48 (0·23-0·64) | 0·39 (0·23-0·48) |
| **NGS: VWF available** | 11 (55) | 6 (60) | 5 (50) |
| **p.D1472H polymorphism**[#] | 1 | 1 | 0 |
| **Pathogenetic variant** | 2 | 2 | 0 |
| **Variant of unknown significance** | 4 | 2 | 2 |

*Table 2:* Available NGS results and lowest recorded VWF:GP1bM activity levels outside of pregnancy. These tests were not conducted as part of the study protocol but were obtained from clinical records. #One participant had a p.D1472H polymorphism in conjunction with a separate pathogenic VWF variant.

| Table 3: Delivery Outcomes | | | | |
|---|---|---|---|---|
| | **Total N=20** | **Recombinant VWF and tranexamic acid N=10** | **Recombinant VWF N=10** | **p-value for treatment difference** |
| **Vaginal delivery** | 13 (65) | 4 (40) | 9 (90) | -- |
| **Cesarean section delivery** | 7 (35) | 6 (60) | 1 (10) | 0·027 |
| **Neuraxial anesthesia** | 20 (100) | 10 (100) | 10 (100) | -- |
| **Quantitative blood loss at delivery, mL** | 633·4 (468·5) | 727·0 (802·5) | 539·7 (355·08) | 0·41 |
| **Quantitative blood loss >1000mL** | 4 (20) | 3 (30) | 1 (10) | 0·25 |
| **Obstetrician managed for bleeding#** | 6 (30) | 3 (30) | 3 (30) | -- |
| **Cumulative 21-day pictorial bleeding assessment tool*** | 402·7 (344·0) | 467·1 (442·0) | 344·8 (315·5) | 0·32 |

*Table 3:* Data are mean (median) or n (%). # Treating obstetrician-initiated management for increased bleeding clinical concern for PPH. *Patient reported cumulative 21-day PBAC for lochial blood loss post-delivery, Participant 10 in the rVWF +TA group did not complete a PBAC diary and was excluded.

| Table 4: Coagulation Studies by Study Visit | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Hemoglobin** g/dL (SD) | **Hematocrit** (%) | **Platelet count** x $10^3$/µL (SD) | **VWF:Ag** IU/mL (SD) | **VWF:RCo** IU/mL (SD) | **VIII** IU/mL (SD) | **Fibrinogen** mg/dL (SD) | **D-dimer** µg/mL (SD) |
| **Third trimester*** | | | | | | | | |
| Recombinant VWF and tranexamic acid | 12·1 (0·9) | 35·7 (2·9) | 217 (68·9) | 1·89 (1·1) | 1·0 (0·5) | 1·6 (0·5) | 521 (109·3) | 1·3 (0·9) |
| Recombinant VWF | 11·8 (1·0) | 34·9 (2·6) | 268 (61·7) | 1·41 (0·6) | 1·08 (0·7) | 1·5 (0·5) | 525·2 (122·3) | 0·9 (0·3) |
| **Admission for delivery** | | | | | | | | |
| Recombinant VWF and tranexamic acid | 12·6 (1·2) | 37.0 (3·6) | 202 (61·5) | 2·2 (1·1) | 0·97 (0·5) | 1·6 (0·6) | 512·4 (150·4) | 1·3 (0·8) |
| Recombinant VWF^ | 11·9 (1·0) | 35.3 (3·0) | 253 (83·2) | 2·0 (1·0) | 1·1 (0·6) | 1·8 (0·6) | 500·3 (108·8) | 1·2 (0·5) |
| **24 hours postpartum** | | | | | | | | |
| Recombinant VWF and tranexamic acid** | 11·7 (1·8) | 34.5 (4·8) | 207 (62·6) | 3·3 (0·9) | 1·9 (0·9) | 1·8 (0·5) | 489·5 (116·2) | 1·7 (1·1) |
| Recombinant VWF | 10·8 (1·8) | 32·6 (5.7) | 210 (70·5) | 3·4 (1·3) | 2·2 (0·9) | 1·8 (0·5) | 499·6 (116·8) | 4·7 (5·1) |
| **48 hours postpartum** | | | | | | | | |
| Recombinant VWF and tranexamic acid& | 11·0 (1·9) | 33·0 (4·8) | 239 (238·9) | 4·0 (1·2) | 2·3 (0·6) | 2·1 (0·4) | 562 (96·8) | 1·1 (0·5) |
| Recombinant VWF# | 10·5 (1·9) | 31·5 (5·7) | 207 (68·0) | 3·5 (0·9) | 2·1 (0·8) | 2·0 (0·4) | 497 (149·2) | 1·6 (1·1) |
| **21 days postpartum** | | | | | | | | |
| Recombinant VWF and tranexamic acid@ | 13·5 (1·8) | 40·7 (4·7) | 290 (88·4) | 0·9 (0·7) | 0·5 (0·2) | 2·1 (0·4) | 320·4 (107·1) | 0·6 (0·4) |
| Recombinant VWF | 12·9 (1·0) | 39·1 (3·2) | 361 (99·5) | 0·9 (0·3) | 0·5 (0·2) | 2·0 (0·4) | 293·7 (50·4) | 0·6 (0·5) |

*Table 4: Hemoglobin. platelet and coagulation studies over study visits*. *Third trimester laboratories were collected between 32-36 weeks gestation. Annotations are for missing laboratory values as follows ˆOne missed blood draw, **two missing platelet counts and one missing hemoglobin, &one subject missing all values, # one subject missing hemoglobin and platelets, @one subject did not have VWF:Ag, VWF:RCo, VIII, fibrinogen or D-dimer collected mean and standard deviation of the mean calculated for available laboratory data.

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Figure 1

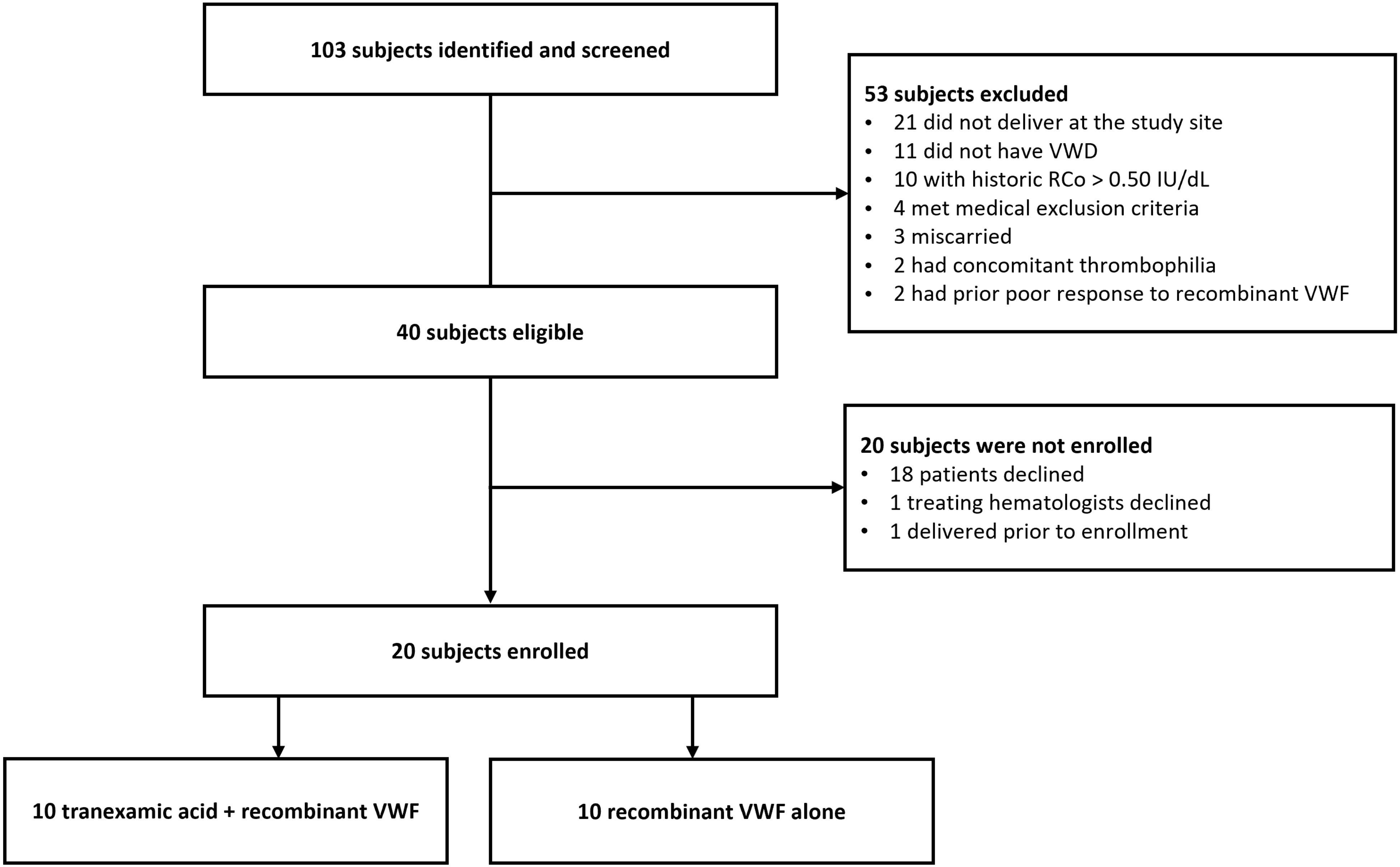
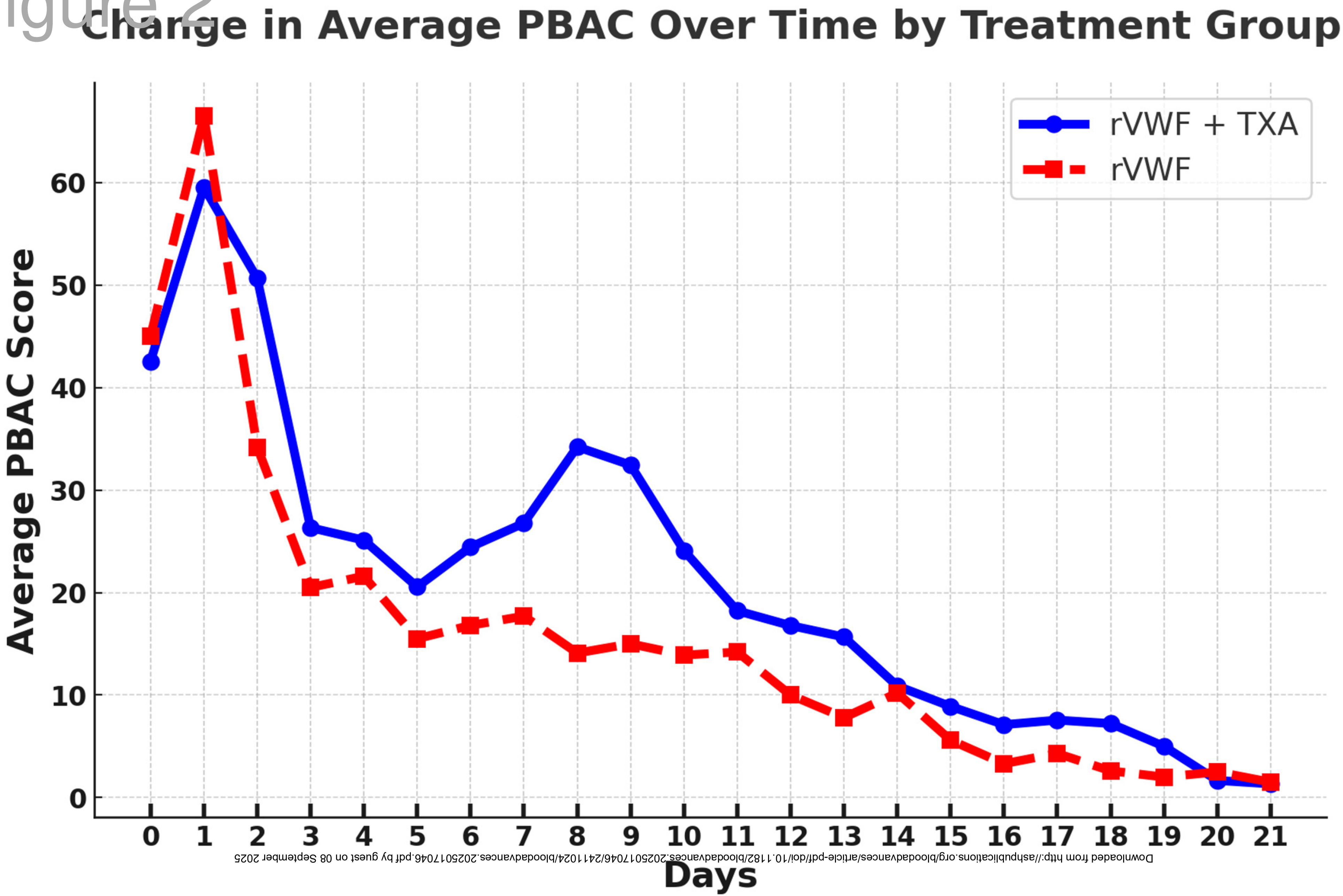



*Figure 1:* Consort diagram

Figure 2



Change in Average PBAC Over Time by Treatment Group
rVWF + TXA
rVWF
Average PBAC Score
0
10
20
30
40
50
60
Days
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21