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Sex-Based Differences in Transfusion Need After Severe Injury: Findings of the PROPPR Study

Marta McCrum, MD, MPH,

University of Utah

Brian Leroux, PhD,

University of Washington

Tingzhi Fang, BS,

University of Washington

Eileen Bulger, MD,

University of Washington

Sam Arbabi, MD, MPH,

University of Washington

Charles E. Wade, PhD,

University of Texas Health Science Center at Houston

Erin Fox, PhD,

University of Texas Health Science Center at Houston

John B. Holcomb, MD,

University of Texas Health Science Center at Houston

Bryce Robinson, MD, MS, and

University of Washington

The PROPPR Study Group

Abstract

Background: Females are underrepresented in trauma research, and aggregated results of clinical trials may mask effects that differ by sex. It is unclear if females respond differently to severe hemorrhage compared to males. We sought to evaluate sex-based differences in outcomes after severe trauma with hemorrhage.

Methods: Secondary analysis of the Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial. Trauma patients predicted to require massive transfusion were randomized to

Contact Information: 30N 1900E, Division of General Surgery, University of Utah, Salt Lake City, UT 84132, marta.mccrum@hsc.utah.edu, (w): 801-585-7280, (H): 617-981-3056.

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1:1:1 vs 1:1:2 plasma:platelet:RBC transfusion ratio. Analysis was performed according to sex, controlling for clinical characteristics and transfusion arm.

Results: 134 females and 546 males were analyzed. In multivariable analysis, there was no difference in mortality at 24-hours (HR for female 0.64, 95% CI 0.34 – 1.23, $p=0.18$) or in time to hemostasis (HR 1.10, 95% CI 0.84 – 1.42, $p=0.49$) by sex. There was no difference between sexes in volume of blood products transfused during active hemorrhage. However, after anatomic hemostasis, females received lower volumes of all products, with a 38% reduction in FFP (Mean Ratio 0.62 (95% CI 0.43 – 0.89, $p=0.01$), 49% reduction in platelets (MR 0.51, 95% CI 0.33 – 0.79, $p<0.01$) and 49% reduction in volume of RBCs (MR 0.51, 95% CI 0.33 – 0.79, $p<0.01$).

Conclusions: Mortality and time to hemostasis of trauma patients with hemorrhage did not differ by sex. While there was no difference in transfusion requirement during active hemorrhage, once hemostasis was achieved, females received fewer units of all blood products than males. Further research is required to determine if females exhibit differences in coagulation during and after severe traumatic hemorrhage.

INTRODUCTION

Traumatic injury is the leading cause of death among persons under age 45 in the United States, accounting for an estimated 200,000 deaths per year and \$214 billion in associated costs.¹ As uncontrolled hemorrhage is the primary cause of early death after injury, efforts to improve resuscitation and techniques for hemorrhage control remain at the forefront of research. The past decade has seen a transition from traditional transfusion practices toward “damage control resuscitation” (DCR), which prioritizes early administration of blood products over initial delivery of crystalloid and is designed to address acute coagulopathy while limiting ongoing blood loss^{2–4}. Most recently, research has focused on optimal ratios of initial blood products, with high transfusion ratios of plasma to platelets to red blood cells (RBCs) associated with decreased early mortality and deaths from exsanguination.^{5–8}

Females have been shown to be underrepresented in surgical clinical research, with lower enrollment in clinical trials, and infrequent analysis and reporting of results by sex.^{9–13} Such disproportionate inclusion is particularly pronounced in trauma, with its predominantly young, male population^{14–16}. Consequently, even robust, multi-institutional trials only contain a small minority of female patients^{5,17,18}. For example, women comprised only 16% of the landmark CRASH-2 trial, which remains the largest trial of patients following traumatic injury.¹⁹ This has important implications for the development of therapies and management strategies following severe injury, which may be specific to only one sex.

Numerous studies have investigated sex-based differences in clinical outcomes after trauma, with most claiming a protective effect of female sex.^{20–27} The reasons underlying this sex dimorphism have not been fully elucidated; however, one suggestion is that relative hypercoagulability of females in the first 24 hours after injury may result in improved hemostasis after traumatic hemorrhage.^{28,29} Such studies have been limited by their predominantly observational design and considerable variation in resuscitation practices, with little information on sex-based differences in the current era of damage-control resuscitation. Specifically, it remains unclear if females continue to exhibit favorable

outcomes compared to males when managed with “one-size fits all” ratio-based blood product resuscitation.

Further research is needed to better understand the clinical response of injured females to current resuscitation practices and determine if this population should be managed differently than males. We therefore sought to evaluate sex-based differences in clinical outcomes after severe trauma with hemorrhage in patients who received ratio-based damage-control resuscitation. We hypothesized that female sex would confer a protective effect due to early hypercoagulability, resulting in decreased mortality and time to hemostasis, as well as lower overall transfusion requirement.

METHODS

Study Design and Population

We performed a secondary analysis of the Pragmatic Randomized Optimal Platelet and Plasma Ratio (PROPPR) trial, which was performed from August 3, 2012 to December 2, 2013 under Exception from Informed Consent (EFIC) guidelines and approved by all institutional review boards at participating hospitals.⁶ Detailed methods of the trial have been published previously.³⁰ Severely injured patients with ongoing hemorrhage who were predicted to receive a massive transfusion and admitted to one of 12 level I North American trauma centers were prospectively randomized to either a 1:1:1 or 1:1:2 ratio of plasma: platelets: RBCs. Eligibility criteria included transfusion of at least 1 unit of blood component during prehospital transport or the first hour of arrival, but not more than 2 units prior to randomization. All transfusions during active hemorrhage were per ratio-based protocol. After hemostasis was achieved, further transfusions were guided per normal institutional practices, including laboratory values and clinical judgement.

Outcomes

Our primary outcome was 24-hour mortality. Secondary outcomes included 30-day mortality, time to hemostasis, as well as number and type of transfused blood products in the time from randomization until hemostasis was achieved (pre-hemostasis period) and the number and type of blood products used after hemostasis was achieved up to 24-hours post-admission (post-hemostasis period). Anatomic hemostasis was defined as control of surgical bleeding in the operating room or resolution of contrast blush in the interventional radiology suite per the attending surgeon and confirmed by no further transfusions in the following two hours. Massive transfusion was defined as requiring 10 or more units of blood within 24 hours, while the Critical Administration Threshold (CAT) required the receipt of at least three units of blood within the first hour of admission.³¹ Descriptive statistics were used to analyze additional outcomes including death due to exsanguination at 24 hours and 30 days as well as adverse events.

Statistical analysis

Baseline demographic, physiologic and biochemical information, Injury Severity Score (ISS), Abbreviated Injury Score (AIS), time of death, time to hemostasis, and units of plasma, platelets and red blood cells given in the pre-randomization, pre-hemostasis and

post-hemostasis periods was obtained. Descriptive statistics were expressed as frequencies and percentages for categorical variables and as medians and interquartile ranges for quantitative variables.

We used Cox regression to evaluate the sex-based differences in mortality and time to hemostasis and presented results as hazard ratios with 95% confidence intervals. Poisson regression with robust standard errors was used to evaluate differences in blood products transfused with results presented as mean ratios and 95% confidence intervals. For all multivariable models, covariates were selected *a priori* based on clinical relevance. All analyses included age, sex, race, weight, height, mechanism of injury, base deficit, INR, AIS head, chest, abdomen, extremities, external, face and neck, transfusion arm (1:1:1 vs 1:1:2) and study center. For model covariates with missing data (height, weight, INR, and base deficit) multiple imputation (MI) was performed using the multivariable imputation by chained equations (MICE) with 20 imputed data sets from predictive mean matching using the same covariates as in the fitted models.³²

Several sensitivity analyses were performed to assess robustness of results to model assumptions. These included comparisons of MI analyses to available-case analyses that ignored missing data, comparisons of models with random effects versus fixed effects for sites, and comparison of analyses with versus without adjustment for covariates. Results of all sensitivity analyses were similar to those presented. To assess for effect modification by sex, we performed additional analyses separately to assess interaction terms for sex with treatment arm, and interactions between sex with age>50 (a surrogate for post-menopausal status) for all primary outcomes as well as all blood product variables. Results were presented with estimates and 95% confidence intervals from adjusted analyses and statistical significance was assessed using 2-sided tests at significance level $p = 0.05$ for all analyses. Statistical analyses were performed using R v3.3.2 (R, Vienna, Austria) including the packages ‘metaphor’, ‘survival’, ‘mice’, ‘sandwich’, and ‘lmtest’.³³

RESULTS

680 patients were analyzed, of which there were 546 males (80%) and 134 females (20%). Demographics, baseline physiologic and coagulation (thromboelastography [TEG]) data are presented in Table 1. Compared to males, females were older, with an overall higher ISS (F: 29 [21–41] vs M: 26 [16–38]), higher proportion of severe head injury with AIS 3 (F: 44 (33%) vs M: 109 (20%)) and lower initial hemoglobin (F: 10.4 [8.4 – 12.1], M: 12.1 [10.6 – 13.5]). Expected differences included greater height and weight for males compared to females. Of the subset of patients with TEG measures, there were no significant differences in initial TEG R-Time, K-Time, Alpha Angle or maximum amplitude between males and females.

There was no difference in mortality at 24-hours or 30-days, or in time to hemostasis by sex (Table 2). The proportion of deaths due to exsanguination at 24-hours were the same in the overall male and female cohorts (M: 12% vs F: 12%). Similar proportions of males and females required massive transfusion or met the Critical Administration Threshold. Similarly, total volumes of blood products in the pre-randomization, pre-hemostasis and

post-hemostasis periods did not differ by sex. We also examined pre-specified thrombosis-related complications, including deep vein thrombosis, symptomatic and asymptomatic pulmonary embolism and stroke, and found no differences between sexes.

When transfused blood volumes were analyzed by sex and transfusion arm in unadjusted analysis, there were no significant differences between male and females in the pre-hemostasis period. However, in the post-hemostasis period- after anatomic hemostasis was achieved and patients were not transfused per study protocol - males in the 1:1:2 transfusion arm received significantly higher volumes of platelets and PRBCs compared to females in the 1:1:2 arm (Figure 1). Males in the 1:1:2 group also received significantly more platelets in the post-hemostasis period than males in the 1:1:1 group (mean 3.95 Units, standard deviation 7.7 vs 2.01 Units, std dev 4.9, $p<0.001$) whereas there was no difference post-hemostasis platelet volume across treatment groups for females (1:1:2 mean 2.38 units, std dev 4.0 vs 1:1:1 2.12, units, std dev 3.4, $p=0.71$). This suggests that while males in low-transfusion ratio group required more platelets after anatomic hemostasis had been achieved compared to males in the high-transfusion ratio group, females did not demonstrate this difference in need across transfusion arms. However, this result must be interpreted with caution due to the fact that the interactions between sex and treatment arm were not statistically significant.

In multivariable analysis, sex was not significantly associated with 24-hour (HR 0.64, 95% CI 0.34 – 1.19, $p=0.16$) or 30-day mortality (HR 0.75, 95% CI 0.47 – 1.20, $p=0.23$), or time to hemostasis (HR 1.10, 95% CI 0.84 – 1.42, $p=0.49$) after adjusting for treatment arm and relevant patient and injury characteristics (Figure 2a). Sex was similarly not associated with volume of blood products transfused in the pre-randomization or pre-hemostasis periods in adjusted analysis. However, in the post-hemostasis period, female sex was independently associated with a 38% reduction in FFP (Mean Ratio 0.62 (95% CI 0.43 – 0.89, $p=0.01$), 49% reduction in platelets (Mean Ratio 0.51, 95% CI 0.34 – 0.76, $p<0.01$) and 49% reduction in volume of RBCs (Mean Ratio 0.51, 95% CI 0.33 – 0.79, $p<0.01$) transfused (Figure 2b). There was no significant interaction effect between sex and treatment arm or sex and age >50 years for any outcome investigated. Full model results available as Supplementary Tables (S1–S6).

Finally, we examined coagulation profiles for separate TEG measures (r-time, k-time, alpha angle, maximum amplitude and LY-30) throughout the study period and found similar values for females and males across multiple time points.

DISCUSSION

In this analysis of severely injured patients with hemorrhage who received ratio-based damage control resuscitation, we found no difference between females and males in mortality or time to hemostasis after accounting for patient characteristics and transfusion ratio. Blood product requirement also did not differ between sexes during the period of on-protocol resuscitation. However, once anatomic hemostasis had been achieved, females received significantly fewer units of all blood products than males. These results suggest that while females and males did not react differently during time of acute hemorrhage, there

may still be physiologic differences between sexes that become clinically relevant after initial hemostasis is achieved.

Numerous efforts have been made to assess the effect of sex on clinical outcomes after traumatic injury, with most suggesting favorable outcomes for females. In one of the largest studies of patients with severe trauma with hypotension, Haider and colleagues found lower mortality in hormonally active women age 13–64 compared to men and post-menopausal women.²¹ Similarly, Trentzsch and colleagues in their analysis of 3,887 matched pairs of severely injured trauma patients found females to have both lower mortality as well as lower rate of multiple organ failure and sepsis.²⁷ Other retrospective studies found no difference in mortality, but lower rates or less severe morbidity in females compared to males.^{23,26,34} Though few studies considered transfusion requirement, Deitch and colleagues in their analysis of 4106 major trauma patients found premenopausal females to receive less blood than male patients.²⁵ While these studies benefit from large sample sizes, they represent heterogeneous patient populations with respect to injury severity, and have limited information on transfusion and resuscitation strategy – notably, nearly all analyzed data from prior to the advent of DCR.

In recent years, attention has turned to evaluating sex-based differences in coagulopathy after trauma. Early studies using thromboelastography to evaluate baseline differences in coagulopathy found female sex to be associated with increased measures of whole blood coagulability.^{35,36} Female trauma patients have since been shown to be more hypercoagulable than males within the first 24 hours after trauma, but without an apparent difference in transfusion requirements.^{28,29} Brown and colleagues specifically examined coagulopathic trauma patients with an admission INR of ≥ 1.5 and found females to have a twofold higher risk of mortality with similar risk of multiple-organ failure as male patients, suggesting that any protective effect of female sex is negated when acute traumatic coagulopathy is present.³⁷ Finally, Rowell and colleagues examined sex-based differences in response to high (1:1) and low (1:2) transfusion ratios in massively transfused trauma patients, and found no mortality benefit in females receiving high transfusion ratios, in contrast to males who exhibited improved survival in the high-ratio group.³⁸ These authors questioned if females may not experience the same benefit from high-ratio resuscitation as males due to underlying differences in coagulation profile.

Our study builds on this body of literature by specifically considering patients with severe hemorrhage who were managed with modern damage-control resuscitation strategy and protocolized ratio-based blood product transfusion. Due to the design of the PROPPR trial, we were able to independently assess blood product use during the time of active hemorrhage and the hours following hemostasis, in addition to standard clinical outcome measures such as mortality and major morbidity. In contrast to studies from the pre-DCR era, we found no differences between sexes with regards to rate of mortality or major morbidity. Similarly, there was no difference between females and males in transfusion requirement for any blood component during the intervention phase of the study, prior to hemostasis. One potential explanation for these findings is that severe, active hemorrhage might negate any mild or moderate protective effect of early hypercoagulability in females. Alternatively, DCR strategy with its early administration of plasma and platelets, might

compensate for the differences in coagulopathy between males and females, resulting in comparable outcomes between the sexes during acute hemorrhage.

Given these results, we were surprised to find a significant difference in transfusion volume of all three blood components in the post-hemostasis period, with females receiving nearly 50% less product than males. Approximately 75% of patients achieved hemostasis within the first three hours after admission; consequently, the post-hemostasis period still predominantly took place during the first 24-hours post-admission, when previous studies have shown females to be more hypercoagulable after trauma. Our analysis suggests that the period immediately following initial hemostasis may be distinct from that of ongoing severe hemorrhage. Nevertheless, due to overall small sample size, and significant missing TEG data at multiple time points throughout the study (e.g. approximately 20% of patients were missing baseline TEG data), we were unable to demonstrate the differences in coagulopathy between males and females that have been consistently demonstrated elsewhere in the literature. Specifically, we were unable to directly evaluate differences in TEG values between males and females in the post-hemostasis period.

Despite the differences in post-hemostasis transfusion requirement, we cannot conclude based on this analysis that females should be managed with a different transfusion strategy than males in the setting of trauma-related hemorrhage. A greater proportion of the 1:1:1 group in both female and male cohorts attained hemostasis, compared to the 1:1:2 arm. Interestingly, while there were fewer deaths from exsanguination at 24-hours with 1:1:1 transfusion in males, there was no appreciable difference between transfusion arms in females. Due to the low number of events in the female cohort, we cannot definitively conclude that the two transfusion strategies are equivalent in females, however this does lend support to Rowell and colleagues' hypothesis that females may not benefit from a high transfusion ratio in the same manner as males.³⁸ Similar to the main PROPPR trial, we found no increase in thrombotic complications in females managed with a high-ratio transfusion strategy, suggesting a high-ratio resuscitation protocol is also safe for females. Given the lower blood products transfused during the post-hemostasis period, it may be reasonable to consider sex-specific monitoring and resuscitation protocols during this time frame.

This study must be interpreted in the context of its limitations. This is a secondary analysis of a randomized controlled trial that was not designed to address the specific questions investigated here. Females comprised only 20% of the study population, with just 54 individuals over age 50, which limited our power to detect differences between sexes, transfusion arms, and preand post-menopausal women. Nevertheless, this population size is in line with other contemporary studies of ratio-based resuscitation.³⁸ We acknowledge that inherent differences between females and males – particularly body mass and blood volume – may contribute to differences in response to resuscitation with similar volume of blood product. We attempted to control for these differences by including height and weight in the model, which has been found to perform similarly to other models of body surface area.³⁹ Females and males tend to have different patterns of injuries and different treatment needs, which we also attempted to account for by including mechanism and all body region AIS scores in our model. Specifically, females had a higher proportion of severe head injury, and

therefore head AIS was used to control for this. Nevertheless, unmeasured confounders may still remain. As this was a pragmatic trial, transfusion during the post-hemostasis period was not protocolized, and driven by usual institutional practices, which introduces room for provider bias during this time frame.

Finally, there was considerable variation in timing of TEG measurements, with a substantial number of patients missing TEG values prior to randomization. This limited our ability to reliably assess sex-based differences in coagulation profile, particularly during ongoing hemorrhage, and may account for our inability to detect the early hypercoagulability of females identified in other studies.

Despite these issues, our study benefits from using data from a well-designed, multicenter randomized control trial, specifically considering critically ill trauma patients with ongoing hemorrhage. There was a high degree of compliance with protocol in the original study, and complete follow-up in all but four patients at 30 days. Due to the design of the trial, we were also able to separate transfusion requirements during ongoing hemorrhage from that after hemostasis was achieved. Commonly-used large datasets, such as the National Trauma Database typically do not contain this level of detail regarding timing of hemostasis and product transfusion, making the PROPPR trial one of the best datasets currently available to answer this question.

The physiologic mechanisms underlying response to injury are complex, and further sex-specific research is required to more fully understand sex-based differences in outcomes after severe trauma, particularly in the setting of modern resuscitation practice.⁴⁰ Such efforts will require rigorous methodology, including consideration of the effect of sex hormones and X-linked genetic polymorphisms on measures of coagulation. Our study suggests that while sex-based differences may not be clinically apparent during times of massive hemorrhage, females may exhibit important differences in coagulation during the period immediately following hemostasis, and that consideration should be given to identifying optimal management strategies for female trauma patients receiving massive transfusion. Prospective, multicenter studies will be required to accrue enough female patients to achieve this goal.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Mean units of blood products by sex and treatment arm for the post-hemostasis period

Figure 2a). Hazard Ratio for clinical outcomes: female sex

Model adjusted for age, sex, race, weight, height, mechanism of injury, base deficit, INR, AIS head, chest, abdomen, extremities, external, face and neck, and transfusion arm (1:1:1 vs 1:1:2)

Figure 2b). Mean Ratios for post-hemostasis period blood transfusion volume: female sex
Model adjusted for age, sex, race, weight, height, mechanism of injury, base deficit, INR, AIS head, chest, abdomen, extremities, external, face and neck, and transfusion arm (1:1:1 vs 1:1:2)

Table 1.

Baseline characteristics of patients enrolled in the PROPPR trial by gender and randomized treatment arm (N=680).

	Males			Females		
Characteristic	Overall (N = 546)	1:1:1 Arm (N = 263)	1:1:2 Arm (N = 283)	Overall (N = 134)	1:1:1 Arm (N = 75)	1:1:2 Arm (N = 59)
Age, y, median (IQR)	33 (24–47)	33 (24–47)	34 (34–47)	41 (26–60)	46 (28–62)	34 (23–57)
Race, n (%)						
White	334 (61%)	155 (59%)	179 (63%)	100 (75%)	55 (73%)	45 (76%)
Black	167 (31%)	84 (32%)	83 (29%)	20 (15%)	10 (13%)	10 (17%)
Other	46 (8%)	25 (10%)	21 (7%)	14 (10%)	10 (13%)	4 (7%)
Hispanic Ethnicity, n (%)	91 (17%)	43 (16%)	48 (17%)	29 (22%)	18 (24%)	11 (19%)
Weight, kg, median (IQR) [N=605]	81.7 (72.7–95.3)	80 (72.6–95)	84 (73.9–98.5)	69.6 (60–81.7)	70 (59–82.2)	68.8 (61.1–81.7)
Height, m, median (IQR) [N=586]	1.78 (1.73–1.83)	1.78 (1.73–1.83)	1.78 (1.73–1.83)	1.65 (1.62–1.68)	1.63 (1.61–1.67)	1.65 (1.62–1.70)
Blunt mechanism, n (%)	256 (47%)	124 (47%)	132 (47%)	102 (76%)	61 (81%)	41 (69%)
ISS, median (IQR)	26 (16–38)	25 (16–38)	26 (17–38)	29 (21–41)	34 (22–45)	27 (20–34)
AIS Head 3, n (%)	109 (20%)	46 (17%)	63 (22%)	44 (33%)	25 (33%)	19 (32%)
AIS Chest 3, n (%)	329 (60%)	143 (54%)	186 (66%)	84 (63%)	46 (61%)	38 (64%)
AIS Abdomen 3, n (%)	274 (50%)	138 (52%)	136 (48%)	66 (49%)	43 (57%)	23 (39%)
AIS Extremities 3, n (%)	274 (50%)	138 (52%)	136 (48%)	66 (49%)	43 (57%)	23 (39%)
Systolic blood pressure 90, n (%) [N=658]	205 (39%)	98 (38%)	107 (39%)	50 (39%)	29 (40%)	21 (38%)
Pulse 120, n (%) [N=677]	242 (44%)	120 (46%)	122 (43%)	58 (44%)	28 (38%)	30 (51%)
Respiratory rate, /min, median (IQR) [N=621]	21 (18–26)	20 (17–27)	21 (18–26)	20 (16–24)	20 (18–25)	20 (16–24)
Hemoglobin, g/dL, median (IQR) [N=652]	12.1 (10.6–13.5)	12.1 (10.7–13.5)	12.1 (10.5–13.6)	10.4 (8.4–12.1)	10.3 (8.2–12)	10.4 (8.6–12.2)
INR, ratio, median (IQR) [N=436]	1.3 (1.18–1.52)	1.22 (1.15–1.51)	1.3 (1.2–1.52)	1.3 (1.17–1.62)	1.3 (1.17–1.6)	1.29 (1.17–1.72)
Platelets, median (IQR) [N=634]	211 (165–256)	212 (168–255)	209 (165–259)	222 (154–295)	215 (154–287)	235 (159–298)
Base excess, mmol/L, median (IQR) [N=619]	−8 (−12.3 to −4)	−7.9 (−12.2 to −3.7)	−8.4 (−12.8 to −4.4)	−8.9 (−14 to −5.2)	−8.9 (−14.7 to −4.9)	−8.8 (−12.8 to −5.9)
Base excess −4, n (%) [N=619]	380 (76%)	183 (74%)	197 (79%)	97 (80%)	55 (79%)	42 (82%)

	Males			Females		
Characteristic	Overall (N = 546)	1:1:1 Arm (N = 263)	1:1:2 Arm (N = 283)	Overall (N = 134)	1:1:1 Arm (N = 75)	1:1:2 Arm (N = 59)
TEG R-Time, min, median (IQR) [N=555]	3.8 (2.9–4.7)	3.8 (2.9–4.7)	3.7 (2.8–4.7)	3.9 (2.8–4.7)	3.8 (2.8–4.4)	4.1 (2.8–4.9)
TEG K-Time, min, median (IQR) [N=529]	1.5 (1.2–2)	1.4 (1.2–1.9)	1.6 (1.2–2.1)	1.3 (1–1.8)	1.2 (1–1.8)	1.6 (1.2–2)
TEG Alpha Angle, %, median (IQR) [N=548]	70.1 (63.6–74.3)	71.2 (65.6–74.6)	69.3 (62.9–73.5)	70.3 (65.7–74.8)	71.7 (67.4–75.5)	68.5 (64.4–72.4)
TEG Maximum Amplitude, mm, median (IQR) [N=549]	60.4 (54.3–64.8)	61.5 (55.8–65.1)	59.5 (52.1–64.3)	61.1 (51.7–67.6)	61.9 (53.5–68.8)	59.2 (47.7–66.8)
TEG LY-30, %, median (IQR) [N=547]	0.3 (0–2.1)	0.3 (0–1.9)	0.5 (0–2.3)	0.3 (0–3.0)	0.2 (0–4.1)	0.5 (0–1.9)

ISS, Injury Severity Score; AIS, Abbreviated injury scale; INR, international normalized ratio; IQR, interquartile range; TEG, Thromboelastography. Sample sizes for each variable are equal to 680 unless noted in square brackets [N].

Table 2.

Outcomes by sex and randomized treatment arm for patients enrolled in the PROPPR trial (N=680).

	Males			Females		
Characteristic	Overall (N = 546)	1:1:1 Arm (N = 263)	1:1:2 Arm (N = 283)	Overall (N = 134)	1:1:1 Arm (N = 75)	1:1:2 Arm (N = 59)
24-hour mortality, n (%)	77 (14%)	30 (11%)	47 (17%)	23 (17%)	12 (16%)	11 (19%)
30-day mortality, n (%)	124 (23%)	51 (20%)	73 (26%)	40 (30%)	24 (32%)	16 (27%)
24-hour exsanguination, n (%)	65 (12%)	22 (8.4%)	43 (15%)	16 (12%)	9 (12%)	7 (12%)
30-day exsanguination, n (%)	68 (13%)	25 (9.6%)	43 (15%)	18 (13%)	11 (15%)	7 (12%)
Achieved Hemostasis, n (%)	447 (82%)	227 (86%)	220 (78%)	110 (82%)	64 (85%)	46 (78%)
Time to Hemostasis, min, median (IQR)	136 (93–208.5)	143 (95–206.5)	128.5 (90–209.2)	146.5 (94–244.8)	153 (102–247.5)	137.5 (89–227.8)
Massive transfusion, n (%)	216 (40%)	98 (37%)	118 (42%)	53 (40%)	35 (47%)	18 (31%)
Critical administration threshold, n (%) [N=678]	481 (88%)	219 (84%)	262 (93%)	114 (85%)	62 (83%)	52 (88%)
Pre-Randomization Plasma, median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
Pre-Randomization Platelets, median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
Pre-Randomization RBC, median (IQR)	2 (1–2)	2 (1–2)	2 (1–2)	2 (1–3)	2 (2–3)	2 (1–2)
Pre-Hemostasis Plasma, median (IQR)	3 (2–8)	5 (2–9)	3 (1–6.5)	3.5 (2–7)	5 (2–14)	3 (1–5)
Pre-Hemostasis Platelets, median (IQR)	6 (0–12)	6 (6–12)	6 (0–6)	6 (6–12)	6 (6–18)	6 (0–6)
Pre-Hemostasis RBC, median (IQR)	6 (3–12)	5 (2–10)	6 (4–13.5)	6 (3–11)	6 (3–13.5)	6 (3–9.5)
Post-Hemostasis Plasma, median (IQR)	0 (0–2)	0 (0–2)	1 (0–3)	0 (0–2)	0 (0–2)	0 (0–4)
Post-Hemostasis Platelets, median (IQR)	0 (0–6)	0 (0–0)	0 (0–6)	0 (0–6)	0 (0–6)	0 (0–6)
Post-Hemostasis RBC, median (IQR)	0 (0–2)	0 (0–2)	0 (0–2)	0 (0–2)	0 (0–2)	0 (0–2)

RBC, Red Blood Cell. Samples sizes are equal to 680 for 24-hour mortality and hemostasis, 676 for 30-day mortality and 30-day exsanguination, 621 for post-hemostasis blood product variables, and 557 for time to hemostasis.