S2-file: MEDLINE database search, flow diagram illustrating the literature selection process, and evidence assessment for the first query and results from the PROPPR trial.

Query # 2: *"Does a fixed blood-plasma transfusion ratio reduce mortality in trauma?"*

PubMed search details: search date December 14 2014

((((("blood transfusion"[MeSH Terms] OR ("blood"[All Fields] AND "transfusion"[All Fields]) OR "blood transfusion"[All Fields] OR "transfusion"[All Fields]) AND ("policy"[MeSH Terms] OR "policy"[All Fields])) OR (("blood transfusion"[MeSH Terms] OR ("blood"[All Fields] AND "transfusion"[All Fields]) OR "blood transfusion"[All Fields] OR "transfusion"[All Fields]) AND strategy[All Fields]) OR (("blood transfusion"[MeSH Terms] OR ("blood"[All Fields] AND "transfusion"[All Fields]) OR "blood transfusion"[All Fields] OR "transfusion"[All Fields]) AND ("Ratio (Oxf)"[Journal] OR "ratio"[All Fields])) OR (massive[All Fields] AND ("blood transfusion"[MeSH Terms] OR ("blood"[All Fields] AND "transfusion"[All Fields]) OR "blood transfusion"[All Fields] OR "transfusion"[All Fields])))) AND (("injuries"[Subheading] OR "injuries"[All Fields] OR "trauma"[All Fields] OR "wounds and injuries"[MeSH Terms] OR ("wounds"[All Fields] AND "injuries"[All Fields]) OR "wounds and injuries"[All Fields]) OR (traumatic[All Fields] AND ("haemorrhage"[All Fields] OR "hemorrhage"[MeSH Terms] OR "hemorrhage"[All Fields])) OR ("shock, traumatic"[MeSH Terms] OR ("shock"[All Fields] AND "traumatic"[All Fields]) OR "traumatic shock"[All Fields] OR ("traumatic"[All Fields] AND "shock"[All Fields])))) AND ("2000"[PDAT] : "3000"[PDAT])

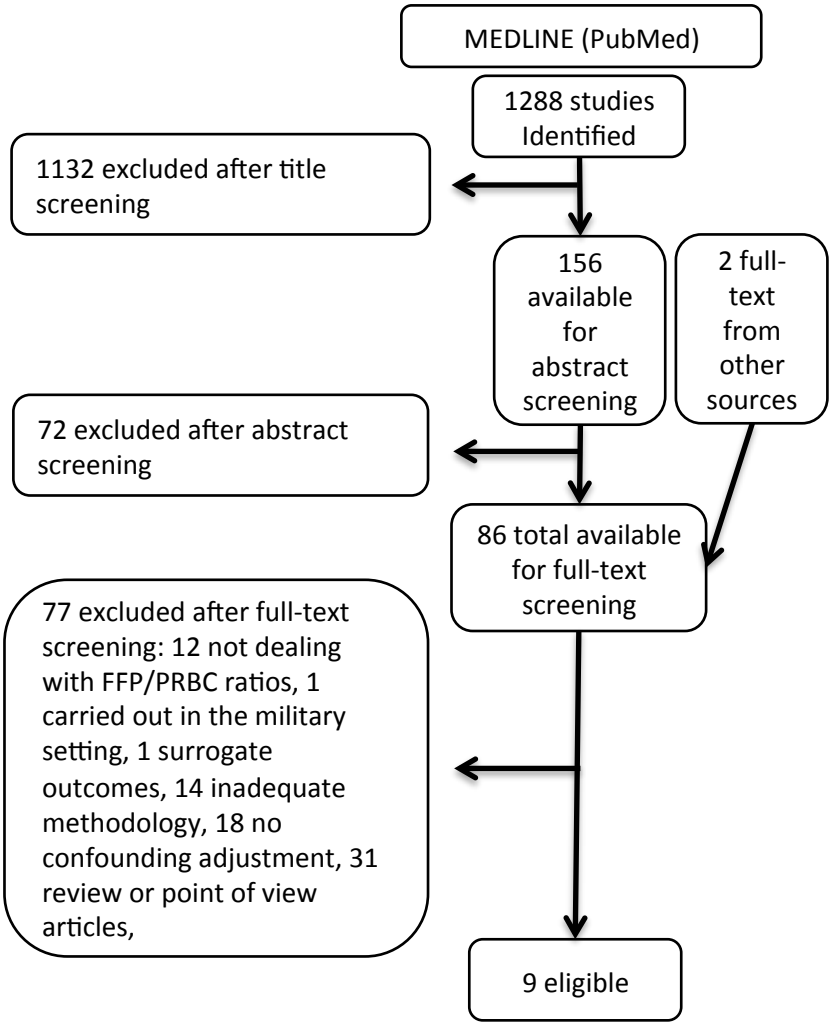
MEDLINE (PubMed)
1288 studies Identified
1132 excluded after title screening
156 available for abstract screening
2 full-text from other sources
72 excluded after abstract screening
86 total available for full-text screening
77 excluded after full-text screening: 12 not dealing with FFP/PRBC ratios, 1 carried out in the military setting, 1 surrogate outcomes, 14 inadequate methodology, 18 no confounding adjustment, 31 review or point of view articles,
9 eligible

Table S2

Observational study	1		
Year	2008		
Journal	AS		
First Author	Scalea		
Statistical method	Logistic regression		
Inclusion criteria	Patients admitted to the ICU for trauma occured within 24 hours		
Treatment	PRBC:FFP ratio as a continuous variable or 1:1		
		Outcome	
		NA	
Centres	1	**Variable: OR (95%-CI)**	
N° patients/centre/year	NA	PRBC:FFP ratio 1:1: 0.57 (0.19-1.66)	
Study duration (days)	882	PRBC:FFP ratio (continuous variable): 1.23 (0.81-1.87)	
Total (included in the model)	NA		
	GRADE CRITERIA		
	Statistical reporting	Partial	
	Statistical quality	Low	
Downgrading	Appropriate eligibility criteria		Yes
	Measurement of exposure		Yes
	Measurement of outcome		Yes
	Adequate control for confounding		No
	Bias		very serious
	GRADE overall		
Up-grading	Size of effect	Not relevant	
	Residual confounding	Does not indicate upgrading	
	Dose /response	Yes	
	DETAILS		
Downgrading	Adequate control for confounding: Important predictors were not included in the mortality model. Statistical reporting : Logistic regression. No Statistical support reported. Checking for conformity with linear gradient for continuos variables not reported. Test for interaction not reported. Goodness-of-fit assessment not reported. Collinearity assessment not reported. Statistical tests for models not reported. Reporting of variable coding method not indicated. Comments: 365 patients received PRBC, and of these 250 also FFP (thus, entering the logistic regression models). Statistical quality: Bivariate analysis for variable selection is an inappropriate method, especially when dealing with small samples. Automatic procedures such as the stepwise procedure used in the study are also not the best choice.The model was overfitted since it included 8 variables (not more than 51 deaths occured). The ICU length of stay was included in the model introducing a bias. The study did not account for survival bias. No propensity score was developed.		
Up-grading			
External validity	Single center study. Number of patients used for logistic regression not clearly reported		
Conclusive evaluation	GRADE rating up/down	Downgraded study	
	GRADE rating	Very low evidence	
	Statistical reporting	Partial	
	Statistical quality	Low	
	External validity issues	Yes	
	Final grading	Downgraded study	
	Final level of evidence	Very low evidence	

Table S2 (continued from the previous page)

Observational study	2	
Year	2010	
Journal	JACS	
First Author	Inaba	
Statistical method	Propensity score matching	
Inclusion criteria	Trauma admitted to surgical ICU receiving < 10 PRBC units within 12 hours from admssion (excluding deaths occured within 24 hours)	
Treatment	Receiving FFP	
		Outcome
		Hospital mortality: 89 (15.7%)
Centres	1	**Variable: OR (95%-CI)**
N° patients/centre/year	95	FFP: 1.27 (0.81-2.0)
Study duration (days)	2191	
Total (included in the model)	568	
Hospital mortality	89 (15.7%)	
	GRADE CRITERIA	
	Statistical reporting	Partial
	Statistical quality	Low
Downgrading	Appropriate eligibility criteria	Yes
	Measurement of exposure	Yes
	Measurement of outcome	Yes
	Adequate control for confounding	No
	Bias	very serious
	GRADE overall	
Up-grading	Size of effect	Not relevant
	Residual confounding	Does not indicate upgrading
	Dose /response	Not applicable
	DETAILS	
Downgrading	Adequate control for confounding: Important predictors were not included in the propensity score. Cut-offs for variable dichotomization were arbitrarily defined. Statistical reporting: The propensity score development process was not reported and was not available for quality assessment. Statistical quality: Insufficient statistical reporting. All continuous variables were dichotomized according to arbitrary cut-offs. Although the study was well designed from a statistical point of view, the lack of reporting of the propensity score limits its evaluability. The study did not account for survival bias.	
Up-grading		
External validity	Single center study	
Conclusive evaluation	GRADE rating up/down	Downgraded study
	GRADE rating	Very low evidence
	Statistical reporting	Partial
	Statistical quality	Low
	External validity issues	Yes
	Final grading	Downgraded study
	Final level of evidence	Very low evidence

Table S2 (continued from the previous page)

Observational	3	
Year	2011	
Journal	JT	
First Author	Wafaisade	
Statistical method	Logistic regression	
Inclusion criteria	Patients receiving more than 3 and less than 10 PRBC units from arrival to the ER and admission to the ICU (excluding those dying within one hour from hospital admission)	
Treatment	FFP:PRBC ratio > 1:1	
		Outcome
		Hospital mortality: 321 (23.6%)
Centres	116	**Variable: OR (95%-CI)**
N° patients/centre/year	3	FFP:PRBC ratio <1:1: Ref = 1
Study duration (days)	1460	FFP:PRBC ratio =1:1: 0.8 (0.54-1.18)
Total (included in the model)	1362	FFP:PRBC ratio >1:1: 0.52 (0.31-0.87)
	GRADE CRITERIA	
	Statistical reporting	Partial
	Statistical quality	Low
Downgrading	Appropriate eligibility criteria	0
	Measurement of exposure	No
	Measurement of outcome	No
	Adequate control for confounding	No
	Bias	Not assessable
	GRADE overall	Not assessable
Up-grading	Size of effect	Not relevant
	Residual confounding	Does not indicate upgrading
	Dose /response	Yes
	DETAILS	
Downgrading	Adequate control for confounding: Only 3 variables remained in the model an insufficient number for explanatory purposes. Statistical reporting: Logistic regression. No Statistical support reported. Checking for conformity with linear gradient for continuos variables not reported. Test for interaction not reported. Goodness-of-fit assessment not reported. Collinearity assessment not reported. Statistical tests for models not reported. Variable selection method: Stepwise forward selection. Reporting of variable coding method not performed.. Statistical quality: Insufficient statistical reporting. Bivariate analysis was performed to select variables to enter the stepwise forward selection process, using a low p value cut-off (0.05). Total-body CT scan surprisingly turned out to be protective, the study did not account for survival bias. No propensity score was developed though a treatment was investigated.	
Up-grading	Dose /response: Progressive Odds Ratios reduction with increasing PRBC:FFP ratios generated , however, by a potentially biased model. Upgrading not indicated.	
External validity	Only 3 patients/centre/year were recruited on average questioning the representativeness of the sample.	
Conclusive evaluation	GRADE rating up/down	Downgraded study
	GRADE rating	Very low evidence
	Statistical reporting	Partial
	Statistical quality	Low
	External validity issues	Yes
	Final grading	Downgraded study
	Final level of evidence	Very low evidence

Table S2 (continued from the previous page)

Observational study	4	
Year	2013	
Journal	JAMA surg	
First Author	Holcomb	
Statistical method	Cox proportional hazards	
Inclusion criteria	Patients requiring the highest level of trauma activation receiving and at least one PRBC unit within 6 hours from admission	
Treatment	FFP:PRBC ratio >= 1:1 received between 30 minutes and 6 hours from admission	
		Outcome #VALUE!
Centres	10	**Variable: OR (95%-CI)**
N° patients/centre/year	79	FFP:PRBC ratio ≥ 1:1: HR 0.23 (95%-CI NA)
Study duration (days)	406	FFP:PRBC ratio: ≥ 1:2-<1:1: HR 0.42 (95%-CI NA)
Total (included in the model)	876	FFP:PRBC ratio < 1:2: HR ref=1 (95%-CI NA)
		FFP:PRBC (continuous): HR 0.31 (0.16-0.58)
	GRADE CRITERIA	
	Statistical reporting	Sufficient for quality assessment
	Statistical quality	High
Downgrading	GRADE overall	0
	Indirectness	No
	Imprecision	No
	Other	No
	Publication bias	Not assessable
	Inconsistency with other studies	Not assessable
Up-grading	Size of effect	Large
	Residual confounding	Does not indicate upgrading
	Dose /response	Yes
	DETAILS	
Downgrading	Adequate control for confounding: Insufficient number of variables for an explanatory model. Statistical reporting: Multi-level time-dependent Cox proportional hazards regression. Dichotomization of continuos variables. Goodness-of-fit assessment not reported. Collinearity assessment not reported. Statistical tests for models not reported. Variable selection method: Purposeful variables selection strategy. Reporting of variable coding method not performed. Statistical quality: Sophisticated analysis accounting for survival bias. However, propensity score for different FFP-PRBC ratio approaches would have been indicated but was not performed, potentially generating a selection bias.	
Up-grading	Size of effect: Large protective effect generated, however, by a potentially biased model. No upgrading indicated. Dose /response: FFP:PRBC ratio significant as a continuous variable generated, however, by a probably biased model. Upgrading not indicated.	
External validity	Multicenter study, with an adequate number of patients per center	
Conclusive evaluation	GRADE rating up/down	No grading modification
	GRADE rating	Low evidence
	Statistical reporting	Sufficient for quality assessment
	Statistical quality	High
	External validity issues	No
	Final grading	No grading modification
	Final level of evidence	Low evidence

Table S2 (continued from the previous page)

Observational study	5	
Year	2009	
Journal	JT	
First Author	Teixeira	
Statistical method	Logistic regression	
Inclusion criteria	Trauma patients receiving 10 or more PRBC units within the first 24 hours	
Treatment	FFP:PRBC ratio (continuous variable)	
Centres	1	**Outcome** Hospital mortality: 161 (42%) **Variable: OR (95%-CI)**
N° patients/centre/year	64	FFP:PRBC ratio: 0.02 (0.01-0.07)
Study duration (days)	2191	
Total (included in the model)	383	
	GRADE CRITERIA	
	Statistical reporting	Partial
	Statistical quality	Low
Downgrading	GRADE overall	0
	Indirectness	No
	Imprecision	No
	Other	No
	Publication bias	Not assessable
	Inconsistency with other studies	Not assessable
Up-grading	Size of effect	Very large
	Residual confounding	Does not indicate upgrading
	Dose /response	Yes
	DETAILS	
Downgrading	Adequate control for confounding: Important predictors were not included in the propensity score. Cut-offs for variable dichotomization were arbitrarily defined. Statistical reporting: Logistic regression. No Statistical support reported. Checking for conformity with linear gradient for continuos variables not reported. Test for interaction not reported. Goodness-of-fit assessment not reported. Collinearity assessment not reported. Variable selection method: Stepwise bidirectional elimination after bivariate selection. Reporting of variable coding method not performed. Statistical quality: Insufficient statistical reporting. All continuous variables were arbitrarily dichotomized with the exception of the FFP:PRBC Bivariate variables selection before automatic procedure (stepwise bidirectional elimination). The study did not account for survival bias. No propensity score was developed.	
Up-grading	Size of effect: Very large protective effect generated, however, by a potentially biased model. No upgrading indicated. Dose /response: FFP:PRBC ratio significant as a continuous variable generated, however, by a probably biased model. Upgrading not indicated.	
External validity	Single center study.	
Conclusive evaluation	GRADE rating up/down	Downgraded study
	GRADE rating	Very low evidence
	Statistical reporting	Partial
	Statistical quality	Low
	External validity issues	Yes
	Final grading	Downgraded study
	Final level of evidence	Very low evidence

Table S2 (continued from the previous page)

Observational	6	
Year	2011	
Journal	JT	
First Author	Sambavisan	
Statistical method	Cox proportional hazards including propensity score	
Inclusion criteria	Patients receiving at least one but less than 10 PRBC units within 24 hours from admission (excluding deaths occured within 2 hours)	
Treatment	FFP:PRBC ratio ≥1	
		Outcome
		Hospital mortality: 173 (14.6%)
Centres	23	**Variable: OR (95%-CI)**
N° patients/centre/year	22	FFP:PRBC ratio ≥1: HR 0.87 (0.55-1.38)
Study duration (days)	851	
Total (included in the model)	1181	
	GRADE CRITERIA	
	Statistical reporting	Partial
	Statistical quality	Low
Downgrading	GRADE overall	0
	Indirectness	No
	Imprecision	No
	Other	No
	Publication bias	Not assessable
	Inconsistency with other studies	Not assessable
Up-grading	Size of effect	Not relevant
	Residual confounding	Does not indicate upgrading
	Dose /response	Not applicable
	DETAILS	
Downgrading	Adequate control for confounding: Only five variables remained in the final model, insufficient number for explanatory purposes. Few variables were also included in the propensity score. Statistical reporting: Proportional hazards including propensity score. Checking for conformity with linear gradient for continuos variables not reported. Test for interaction not reported. Goodness-of-fit assessment not reported. Collinearity assessment not reported. Statistical tests for models not reported. Variable selection method: Stepwise forward selection. Reporting of variable coding method not indicated. Statistical quality: Insufficient statistical reporting. Hazard proportional assumption not checked. Few variables entered the mortality model and important covariates were not considered. Low statistical quality. The study did not account for survival bias.	
Up-grading		
External validity	Multicenter study, with an acceptable number of patients treated per center.	
Conclusive evaluation	GRADE rating up/down	Downgraded study
	GRADE rating	Very low evidence
	Statistical reporting	Partial
	Statistical quality	Low
	External validity issues	Yes
	Final grading	Downgraded study
	Final level of evidence	Very low evidence

Table S2 (continued from the previous page)

Observational	7		
Year	2011		
Journal	JT		
First Author	Holcomb		
Statistical method	Cox proportional hazards including propensity score		
Inclusion criteria	Trauma patients receiving 10 or more PRBC units within 24 hours from admission		
Treatment	FFP:PRBC ratio (continuous variable)		
Centres	22	**Outcome** 30-day mortality: 181 (28.1%) **Variable: OR (95%-CI)**	
N° patients/centre/year	29	FFP:PRBC ratio: HR 0.49 (0.28-0.86)	
Study duration (days)	364		
Total (included in the model)	643		
	GRADE CRITERIA		
	Statistical reporting	Partial	
	Statistical quality	Low	
Downgrading	GRADE overall	0	
	Indirectness	No	
	Imprecision	No	
	Other	No	
	Publication bias	Not assessable	
	Inconsistency with other studies	Not assessable	
Up-grading	Size of effect	Large	
	Residual confounding	Does not indicate upgrading	
	Dose /response	Yes	
	DETAILS		
Downgrading	Adequate control for confounding: Few variables included in the final model, insufficient for explanatory purposes. Statistical reporting: Statistical model: Cox proportional hazards. No Statistical support reported. Checking for conformity with linear gradient for continuos variables not reported. Test for interaction not reported. Goodness-of-fit assessment not reported. Collinearity assessment not reported. Statistical tests for models not reported. Variable selection method: Not Reported. Reporting of variable coding method not performed. Statistical quality: Insufficient statistical reporting. Important covariates (e.g. age) were not included in the mortality model (underfitting). No propensity score for FFP:PRBC ratio was developed. The study did not account for survival bias.		
Up-grading	Size of effect: Large protective effect generated, however, by a potentially biased model. No upgrading indicated. Dose /response: FFP:PRBC ratio significant as a continuous variable generated, however, by a probably biased model. Upgrading not indicated.		
External validity	Multicenter study, with an acceptable number of patients treated per center.		
Conclusive evaluation	GRADE rating up/down	Downgraded study	
	GRADE rating	Very low evidence	
	Statistical reporting	Partial	
	Statistical quality	Low	
	External validity issues	No	
	Final grading	Downgraded study	
	Final level of evidence	Very low evidence	

Table S2 (continued from the previous page)

Observational	8	
Year	2011	
Journal	VS	
First Author	Borgman	
Statistical method	Logistic regression	
Inclusion criteria	TASH score ≥ 15 excluding patients died within 1 hour from admission	
Treatment	FFP:PRBC ratio (continuous variable)	
Centres	100	**Outcome** Hospital mortality: NA (NA%) **Variable: OR (95%-CI)**
N° patients/centre/year	1	FFP:PRBC ratio: Survival OR 2.5 (1.56-4.00)
Study duration (days)	2190	
Total (included in the model)	557	
	GRADE CRITERIA	
	Statistical reporting	Partial
	Statistical quality	Low
Downgrading	GRADE overall	0
	Indirectness	No
	Imprecision	No
	Other	No
	Publication bias	Not assessable
	Inconsistency with other studies	Not assessable
Up-grading	Size of effect	Large
	Residual confounding	Does not indicate upgrading
	Dose /response	Yes
	DETAILS	
Downgrading	Adequate control for confounding: Only three variables remained in the final model, insufficient number for explanatory purposes. Few variables were also included in the propensity score. Statistical reporting: Statistical model: Logistic regression. No Statistical support reported. Checking for conformity with linear gradient for continuos variables not reported. Test for interaction not reported. Internal validity assessment not reported. Goodness-of-fit assessment not reported. Collinearity assessment not reported. Statistical tests for models not reported. Reporting of variable coding method not indicated. Statistical quality: Insufficient statistical reporting. No propensity score for treatment performed. Variable selection method: Bivariate analysis. Only three variables entered the model that was clearly underfitted. no propensity score for FFP:PRBC ratio was developed.	
Up-grading	Size of effect: Large protective effect generated, however, by a potentially biased model. No upgrading indicated. Dose /response: FFP:PRBC ratio significant as a continuous variable generated, however, by a probably biased model. Upgrading not indicated.	
External validity	Multicenter study, with 1 patients admitted per center on average. Probably several centers did not enroll patients. Inadequate reporting.	
Conclusive evaluation	GRADE rating up/down	Downgraded study
	GRADE rating	Very low evidence
	Statistical reporting	Partial
	Statistical quality	Low
	External validity issues	Yes
	Final grading	Downgraded study
	Final level of evidence	Very low evidence

Table S2 (continued from the previous page)

Observational	9	
Year	2010	
Journal	Injury	
First Author	Mitra	
Statistical method	Logistic regression	
Inclusion criteria	Patients receiving more than 4 packed red blood cell units within 4 hours from admission	
Treatment	FFP:PRBC ratio measured at 4 hours from admission (continuous variable)	
Centres	1	**Outcome** 30-day mortality: 99 (29.9%) **Variable: OR (95%-CI)**
N° patients/centre/year	90	FFP:PRBC ratio: 0.15 (0.05-0.48)
Study duration (days)	1338	
Total (included in the model)	331	
	GRADE CRITERIA	
	Statistical reporting	Partial
	Statistical quality	Low
Downgrading	GRADE overall	0
	Indirectness	No
	Imprecision	No
	Other	No
	Publication bias	Not assessable
	Inconsistency with other studies	Not assessable
Up-grading	Size of effect	Very large
	Residual confounding	Does not indicate upgrading
	Dose /response	Yes
	DETAILS	
Downgrading	Adequate control for confounding: Only five variables remained in the final model, insufficient number for explanatory purposes. Few variables were also included in the propensity score. Statistical reporting: Logistic regression. Checking for conformity with linear gradient for continuos variables not reported. Test for interaction not reported. Internal validity assessment not reported. Goodness-of-fit assessment not reported. Collinearity assessment not reported. Statistical tests for models not reported. Variable selection method: Stepwise backward elimination. Reporting of variable coding method not indicated. Statistical quality: Insufficient statistical reporting. Possible underfitting of the model, no propensity score for FFP administraton was developed. The study did not account for survival bias.	
Up-grading	Size of effect: Large protective effect generated, however, by a potentially biased model. No upgrading indicated. Dose /response: FFP:PRBC ratio significant as a continuous variable generated, however, by a probably biased model. Upgrading not indicated.	
External validity	Single center study	
Conclusive evaluation	GRADE rating up/down	Downgraded study
	GRADE rating	Very low evidence
	Statistical reporting	Partial
	Statistical quality	Low
	External validity issues	Yes
	Final grading	Downgraded study
	Final level of evidence	Very low evidence

Table S2 (continued from the previous page)

RCT 1			
Year	2015	First Author	Holcomb
Journal	JAMA		
Sample	trauma patients for whom the highest level of activation was required		
Treatment	FFP/Platelets/PRBC ratio 1:1:1		
Control	FFP/Platelets/PRBC ratio 1:1:2		
Outcome	24-hour mortality		
		Outcome	
	n° pz	n	%
Treatment	335	43	12.8
Control	341	58	17.0
Total	676	101	14.9
Centres	12 Centres		
Power	0.332	TB 24 (95%-CI NNTB 10 to ∞ to NNTH 82)	
		GRADE CRITERIA	
Downgrading		Allocation concealment	Yes
		Intention to treat principle observed	Yes
		Blinding	No
		Completement of follow-up	Yes
		Early stopping	Yes
		Bias	No
		Indirectness	No
		Imprecision	No
		Publication bias	No
		Inconsistency with other trials	Not assessable
Up-grading		Size of effect	Not relevant
		Residual confounding	Not assessable
		Dose /response	Not relevant
		DETAILS	
Downgrading			
Up-grading			
Conclusive evaluation		GRADE rating up/down	No grading modification
		GRADE rating	High evidence
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	High
		External validity issues	Yes
		Final grading	No grading modification
		Final level of evidence	High evidence

Table S2 (continued from the previous page)

RCT 2			
Year	2015	First Author	Holcomb
Journal	JAMA		
Sample	trauma patients for whom the highest level of activation was required		
Treatment	FFP/Platelets/PRBC ratio 1:1:1		
Control	FFP/Platelets/PRBC ratio 1:1:2		
Outcome	30-day mortality		
		Outcome	
	n° pz	n	%
Treatment	335	75	22.4
Control	341	89	26.1
Total	676	164	24.3
Centres	Single Center		
Power	0.202	TB 27 (95%-CI NNTB 10 to ∞ to NNTH 36)	
		GRADE CRITERIA	
Downgrading		Allocation concealment	Yes
		Intention to treat principle observed	Yes
		Blinding	Yes
		Completement of follow-up	Yes
		Early stopping	No
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	High
		Indirectness	No
		Publication bias	No
		Inconsistency with other trials	Not assessable
Up-grading		Size of effect	Not relevant
		Residual confounding	Not assessable
		Dose /response	Not relevant
		DETAILS	
Downgrading			
Up-grading			
Conclusive evaluation		GRADE rating up/down	No grading modification
		GRADE rating	High evidence
		Statistical reporting	Sufficient for quality assessment
		Methodological and statistical quality	High
		External validity issues	No
		Final grading	No grading modification
		Final level of evidence	High evidence

Figure S2 : Forest plots illustrating absolute and relative risks for the PROPPR trial. The 24-hour and 30-day mortality outcomes are reported