S4-file: MEDLINE database search, flow diagram illustrating the literature selection process, evidence assessment for the first query, and results from the CRASH2 trial.

Query # 4: *"Does tranexamic acid administration reduce mortality in trauma?"*

PubMed search details: search date December 13 2014

((("tranexamic acid"[MeSH Terms] OR ("tranexamic"[All Fields] AND "acid"[All Fields]) OR "tranexamic acid"[All Fields]) OR ("antifibrinolytic agents"[Pharmacological Action] OR "antifibrinolytic agents"[MeSH Terms] OR ("antifibrinolytic"[All Fields] AND "agents"[All Fields]) OR "antifibrinolytic agents"[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 ("2"[PDAT] : "3000"[PDAT])

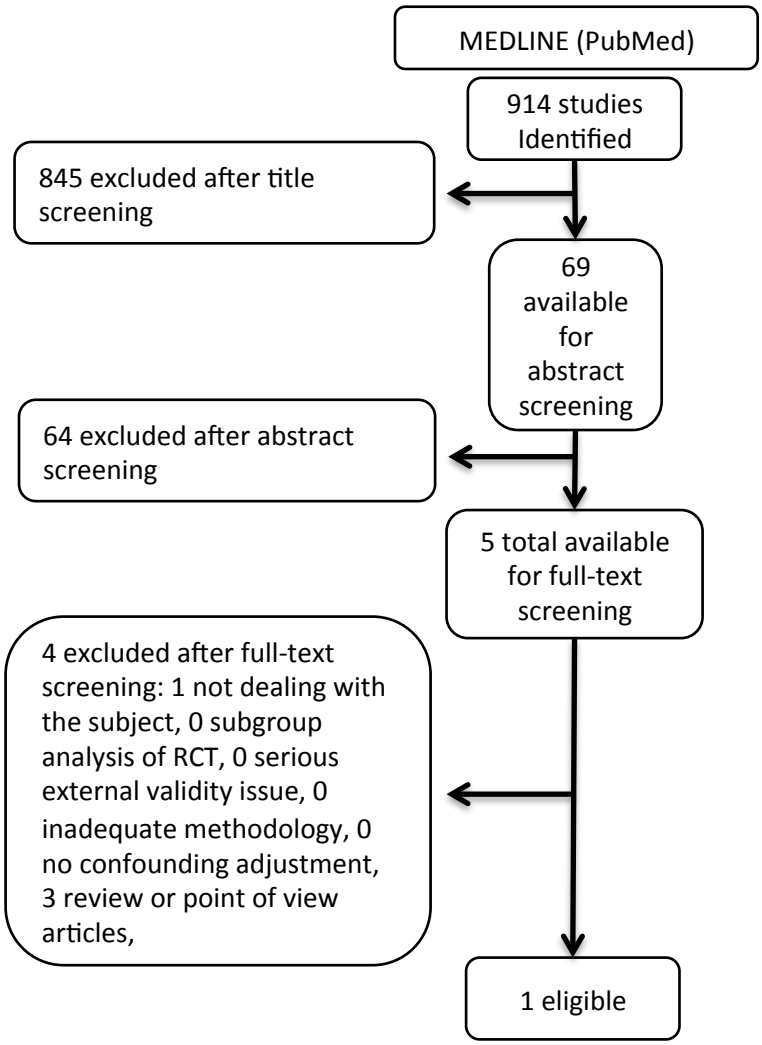
MEDLINE (PubMed)
914 studies Identified
845 excluded after title screening
69 available for abstract screening
64 excluded after abstract screening
5 total available for full-text screening
4 excluded after full-text screening: 1 not dealing with the subject, 0 subgroup analysis of RCT, 0 serious external validity issue, 0 inadequate methodology, 0 no confounding adjustment, 3 review or point of view articles,
1 eligible

Table S4

Observational study	1		
Year	2012		
Journal	JTH		
First Author	Rourke		
Statistical method	Logistic regression		
Inclusion criteria	Time fron injury to arrival within 120 minutes, SBP < 90 at admission, poor responsiveness to initial fluid administration		
Treatment	Fibrinogen administration within the first 12 hours		
Centres	2	**Outcome** NA **Variable: OR (95%-CI)**	
N° patients/centre/year	NA	Fibrinogen: 0.91 (0.81-1.01)	
Study duration (days)	1095		
Total (included in the model)	NR		
	GRADE CRITERIA		
	Statistical reporting	Partial	
	Statistical quality	Low	
Downgrading	Appropriate eligibility criteria		Yes
	Measurement of exposure		Yes
	Measurement of outcome		Yes
	Control for confounding		No
	Bias		very serious
	GRADE overall		
Up-grading	Size of effect	Very large	
	Residual confounding	Does not indicate upgrading	
	Dose /response	Yes	
	DETAILS		
Downgrading	Control for confounding: Important predictors were not included in the mortality model. Statistical reporting : Subgroup of coagulopathic patients from a sample of 517 patients. Not reported the number of patients and of deaths. 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. Variable selection method: Stepwise forward selection. Reporting of variable coding method not performed. Statistical quality: Insufficient statistical reporting. Important covariates are missing in the model (possible underfitting). No propensity score was developed. The analysis does not account for survival bias.		
Up-grading			
External validity	Only two centres participating to the 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	

Figure S4 : Forest plots illustrating absolute and relative risks for the CRASH2 trial