Raccomandazioni 14-15 della Linea Guida per la gestione integrata del trauma maggiore dalla scena dell'evento alla cura definitiva

Questo documento rappresenta la versione finale delle raccomandazioni cliniche che hanno completato l'intero processo previsto dal Manuale metodologico per la produzione di linee guida dell'Istituto Superiore di Sanità, inclusa la consultazione pubblica e la revisione esterna indipendente.

Il documento finale della presente Linea Guida sarà pubblicato quando il processo di elaborazione di tutte le raccomandazioni relative ai quesiti clinici sarà ultimato.

Febbraio 2021

SOMMARIO

Lista delle raccomandazioni formulate

Quesito 8: L'uso di agenti emostatici sistemici è clinicamente ed economicamente vantaggioso per migliorare gli esiti nei pazienti con emorragia confermata o sospetta a seguito di un trauma maggiore nel setting pre-ospedaliero?

Raccomandazione 14. Nel trauma maggiore con emorragia si raccomanda l'utilizzo di TXA rispetto al non utilizzo [raccomandazione forte, qualità delle prove bassa].
Nota: Il setting previsto per la raccomandazione è quello pre-ospedaliero. Tuttavia, se non eseguito in fase pre-ospedaliera se ne raccomanda l'uso nelle prime fasi del trattamento intraospedaliero.

Raccomandazione 15. Nel trauma cranico con GCS uguale o inferiore a 12 è preferibile l'utilizzo del TXA rispetto al non utilizzo [raccomandazione condizionata, qualità delle prove bassa].
Nota: Il setting previsto per la raccomandazione è quello pre-ospedaliero. Tuttavia, se non eseguito in fase pre-ospedaliera se ne raccomanda l'uso nelle prime fasi del trattamento intraospedaliero.

Il panel di esperti ha formulato le due raccomandazioni seguendo un processo metodologicamente rigoroso che, in conformità a quanto previsto dal Manuale metodologico dell'ISS, ha utilizzato il GRADE Evidence to Decision (EtD) framework per procedere in modo strutturato e trasparente dalle prove alla raccomandazione.

La valutazione degli interessi dichiarati dai membri del panel non ha rilevato nessun potenziale o rilevante conflitto di interesse rispetto alla tematica oggetto del quesito clinico.

Di seguito si riportano l'**EtD framework** e le seguenti appendici:

- Appendice A – Quesito clinico e Strategia di ricerca
- Appendice B – Caratteristiche degli studi inclusi ed elenco degli studi esclusi con motivazione
- Appendice C1 – Sintesi delle evidenze
- Appendice C2 – Sintesi delle evidenze – Supplemento: Sottogruppi di popolazione
- Appendice C3 – Supplemento: Sottogruppi per dose somministrata
- Appendice D – Valutazione della qualità metodologica degli studi inclusi
- Appendice E – Tabelle delle evidenze
- Appendice F – Bibliografia degli studi inclusi
- Appendice G – Risorse e costi.

Per i dettagli su: Gruppo di sviluppo della LG, Policy per la gestione del Conflitto di Interesse (CdI), Scope e Metodologia fare riferimento al documento **LGTM_Racc1_4_def** scaricabile dal link:
https://www.iss.it/documents/20126/8404212/LGTM_Racc1_4_def

EtD Framework - Quesito clinico n. 8

L'uso di agenti emostatici sistemici è clinicamente ed economicamente vantaggioso per migliorare gli esiti nei pazienti con emorragia confermata o sospetta a seguito di un trauma maggiore nel setting pre-ospedaliero?	
POPOLAZIONE:	Bambini, giovani e adulti affetti da TRAUMA in fase di rianimazione preospedaliera, in pronto soccorso e in sala operatoria per la fase rianimatoria.
INTERVENTO:	**Agenti emostatici** Fattore ricombinante VII (recombinant activated factor VII). Acido tranexamico. Concentrato di fibrinogeno. Concentrato di complesso protrombinico. Altri agenti antifibrinolitici.
CONFRONTO:	Nessuno. Un confronto con gli agenti emostatici sora menzionati. Una combinazione degli stessi. In aggiunta alla terapia usuale (intraospedaliero: componenti ematici (plasma, globuli rossi, piastrine), extraospedaliero (infusione cristalloidi).
ESITI PRINCIPALI:	**Critici** • Mortalità a 24 ore, 30 giorni/1 mese. • Qualità della vita. • Eventi avversi: eventi tromboembolici (MI/Stroke, malattia venosa tromboembolica), eventi correlati a trasfusioni eccessive, sepsi e/o insufficienza d'organo. • Utilizzo di prodotti ematici: globuli rossi, piastrine, plasma crioprecipitato. **Importanti** • Mortalità a 12 mesi. • Entità dell'emorragia. • Patient-reported outcomes (benessere psicologico).
SETTING:	Pre-ospedaliero (incluso il militare)
PROSPETTIVA:	Popolazione, SSN: • organizzazione ed erogazione de servizi per la gestione dei pazienti con trauma; • rete regionale per il trauma; • personale sanitario dei servizi di emergenza territoriale.
CONFLITTI DI INTERESSE	La policy ISS relativa alla dichiarazione e gestione del conflitto di interessi è stata applicata e non è stato identificato nessun interesse rilevante o potenzialmente rilevante. Tutti i membri del panel presenti alla riunione hanno votato, determinando la direzione e la forza della raccomandazione.

VALUTAZIONE

Problema

Il problema è una priorità?

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ No ○ Probabilmente no ○ Probabilmente si •Sì ○ Varia ○ Non so	Circa 3 milioni di persone all'anno muoiono in seguito a un trauma, molte dopo il ricovero in ospedale (Boffard, 2005; Kluger, 2007; Perel, 2012) con più di 1 milione di decessi a causa di incidenti stradali (CRASH-2 trial collaborators, 2010). Il trauma maggiore colpisce soprattutto soggetti tra i 15 ed i 40/44 anni di età (Boffard et al., 2005; Kluger et al., 2007) e l' emorragia incontrollata rappresenta una delle principali cause di morte, nei traumi civili e militari, condizionando circa il 40% della mortalità (Boffard et al., 2005). L'emorragia intracranica è una comune complicanza dei 60 milioni di traumi cranici che avvengono in un anno nel mondo. Questa condizione aumenta il rischio di morte e disabilità (CRASH-3 trial collaborators, 2019; Kluger et al., 2007) ed è causa rispettivamente di 1,5 milioni di decessi e 10 milioni di ospedalizzazioni (CRASH-2 Collaborators, Intracranial Bleeding Study, 2011; Perel et al., 2012). Il sanguinamento intracranico inoltre puo' rappresentare una condizione evolutiva per diverse ore a seguito della lesione (CRASH-3 trial collaborators, 2019). Il trattamento dell'emorragia da trauma è un problema clinico di rilievo (CRASH-2 trial collaborators et al., 2010; Kluger et al., 2007) visto che rappresenta una causa comune di morte in ospedale (Boffard et al., 2005; CRASH-2 trial collaborators et al., 2010; Roberts, 2013). Per gestire l'emorragia sono stati proposti gli agenti antifibrinolitici (CRASH-2 trial collaborators et al., 2010): tra cui l'**acido tranexamico (TXA)**, derivato sintetico dell'amminoacido lisina, e agenti coagulanti quali il fattore **ricombinante VIIa (rFVIIa)**. Il TXA, ampiamente utilizzato in chirurgia per ridurre la necessità di trasfusioni di emoderivati, ha effetti favorevoli nei pazienti emorragici riducendo il sanguinamento (Nishijima, 2019). Il rFVIIa è stato proposto nella gestione della coagulopatia traumatica, agendo come pro coagulante con una riduzione della perdita di sangue e la necessità di emoderivati (Hauser, 2010).	

Effetti desiderabili

Quanto considerevoli sono gli effetti desiderabili attesi?

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ Irrilevanti ○ Piccoli •Moderati ○ Grandi ○ Variano ○ Non so	È stata effettuata una revisione sistematica con ricerca della letteratura sulle banche dati Embase, Medline e Cochrane CENTRAL. Sono stati individuati 1518 record da cui sono state selezionate 8 referenze che soddisfano i criteri per rispondere al quesito clinico proposto, rispettivamente 5 studi primari e 3 revisioni sistematiche da cui sono stati ulteriormente estratti 3 studi. Inoltre, sono state interrogate clinicatrials.gov e le Linee guida NICE, aggiungendo all'inclusione altre 11 nuove pubblicazioni, 6 e 5 rispettivamente. In totale, sono state individuate 19 pubblicazioni afferenti 5 studi randomizzati e controllati: CRASH-2, CRASH-3, TXA trial, CONTROL trial e Boffard 2005. Gli studi inclusi sono controllati e randomizzati in cui il gruppo di controllo è rappresentato dal trattamento con placebo. In particolare: **CRASH-2**: è uno studio randomizzato e controllato, multicentrico, a doppio cieco in cui sono stati reclutati pazienti con evidente emorragia (SBP < 90 mm Hg e/o Heart Rate > 110 battiti al minuto), entro 8 ore dalla lesione, da 10 ospedali dell'India e della Colombia. Ai pazienti è stato	

somministrato casualmente o 1 g di TXA infuso in 10 minuti seguito da un'infusione endovenosa di 1 g nell'arco di 8 ore, o placebo (cloruro di sodio 0,9%) per dosi corrispondenti;

CRASH-3: è uno studio randomizzato e controllato, multicentrico, in cui sono stati reclutati pazienti adulti che hanno subito un trauma cranico (GCS ≤ 12), entro 3 ore dalla lesione, da 175 ospedali in 29 paesi (internazionale). Ai pazienti è stato somministrato casualmente o 1 g di TXA infuso in 10 minuti seguito da un'infusione endovenosa di 1 g nell'arco di 8 ore o placebo (cloruro di sodio 0,9%) per dosi corrispondenti;

TXA trial: è uno studio multicentrico randomizzato e controllato, a doppio cieco in cui sono stati inclusi i pazienti adulti (età ≥ 15 anni) con trauma cranico (pre-hospital GCS ≤ 12 e SBP ≥ 90), a cui sono stati assegnati casualmente 3 diversi trattamenti i) trattamento e mantenimento (1 g TXA nella fase pre-ospedaliera seguito da 1 g di mantenimento in infusione dall'arrivo in ospedale fino 8 ore) ii) solo trattamento (2 g di TXA nella fase pre-ospedaliera seguito da placebo di mantenimento in infusione dall'arrivo in ospedale fino 8 ore) iii) placebo;

Boffard 2005: sono stati condotti simultaneamente due studi clinici controllati e randomizzati a doppio cieco per valutare l'efficacia e la sicurezza del fattore ricombinante VIIa (rFVIIa) in pazienti con trauma maggiore con sanguinamento severo (richiedenti 6 U o più di GRC entro 4 h dall'ammissione in ED). Uno studio ha considerato i pazienti con trauma chiuso e l'altro pazienti con trauma penetrante; in entrambi gli studi, i pazienti sono stati randomizzati al trattamento con 3 iniezioni endovenose di rFVIIa (dopo la trasfusione di 8 unità di RBC 200 µg/kg, poi 100 µg/kg dopo 1 e 3 ore dalla prima dose) o al placebo;

CONTROL trial: è uno studio randomizzato e controllato, multicentrico, in cui sono stati reclutati pazienti con shock emorragico che hanno subito un trauma chiuso o penetrante a cui è stato somministrato casualmente rFVIIa (inizialmente 200 µg/kg, poi 100 µg/kg dopo 1 e 3 ore dalla prima dose) o placebo.

Sono stati inclusi tutti i 5 studi randomizzati controllati (RCT) per rispondere al quesito di efficacia dell'intervento sulla scena rispetto al non intervento (placebo), sia considerando l'agente emostatico **TXA** (CRASH-2, CRASH-3; TXA trial), che il **rFVIIa** (Boffard 2005, CONTROL trial).

i) Somministrazione pre-ospedaliera di TXA verso placebo:
  a) TXA 1 grammo in pre-ospedaliero + 1 grammo in infusione nelle 8 ore successive verso placebo (14 pubblicazioni afferenti a 3 studi randomizzati e controllati: CRASH-2 (11), CRASH-3 (2), TXA (1))
  b) TXA 2 grammi in pre-ospedaliero + placebo in infusione nelle ore successive verso placebo (una pubblicazione afferente ad uno studio randomizzato e controllato: TXA (1))

ii) Somministrazione pre-ospedaliera di rFVIIa verso placebo (5 pubblicazioni afferenti a 2 studi randomizzati e controllati: Boffard 2005 (2), CONTROL trial (3)).

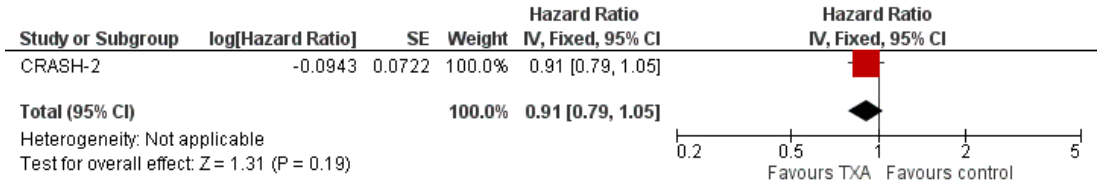
Nota sulla comparazione Fattore VII ricombinante vs placebo (CONTROL trial): studio interrotto precocemente per rischio di futilità all'interim analysis su primary endpoint (mortalità del campione incluso inferiore rispetto a quella attesa) (Hauser et al., 2010).

Gli effetti desiderabili sono indicati in:
- **Appendice C1** per le stime overall;
- **Appendice C2** per i sottogruppi di popolazione (trauma maggiore prevalentemente emorragico; trauma cranico);
- **Appendice C3** per il sottogruppo di dose.

1.1 Overall MORTALITY AT 24 – 48 h HOURS trauma maggiore con o senza trauma cranico (Dati di mortalità

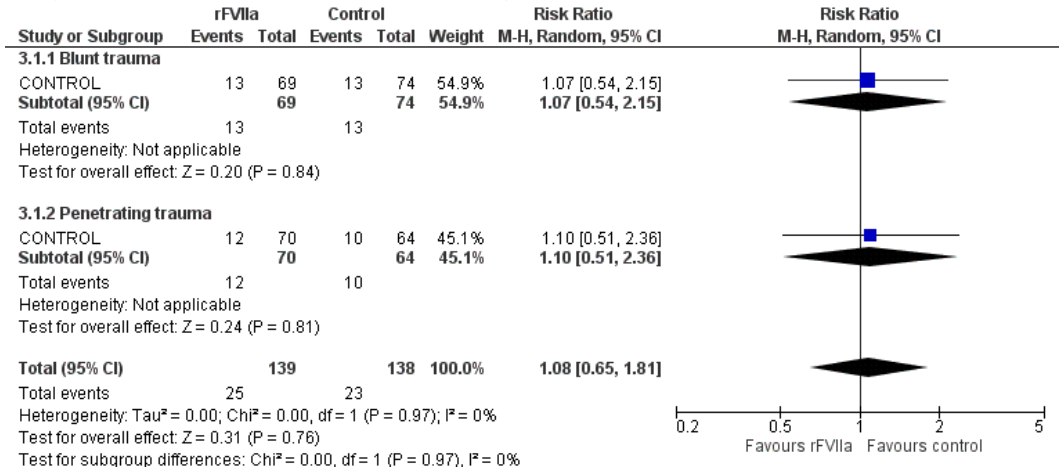
overall a 24-48 h disponibili solo per CRASH2 e CONTROL)

Comparazione 1. Acido Tranexamico vs placebo



Appendice C1, Figure 9. Hazard ratio for overall mortality (24 hours) of TXA versus placebo.

***Comparazione 2. Fattore VII ricombinante vs* placebo**



Appendice C1, Figure 12. Risk ratio for overall mortality (48 hours) of rFVIIa versus placebo, by considering (blunt or penetrating) trauma patients.

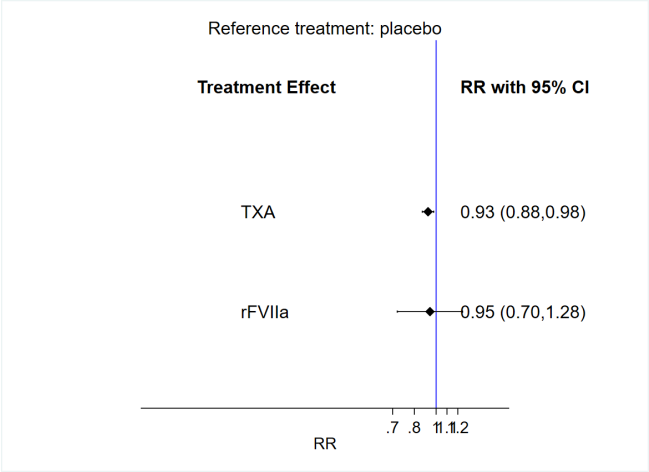
1.2 OVERALL MORTALITY trauma maggiore con o senza trauma cranico a 1 mese

Analisi di comparazione multipla di intervento: Network metanalisi

E' stata effettuata una network meta-analisi sull'outcome critico overall mortality. La network metanalisi permette di comparare in modo indiretto interventi per cui non esistono evidenze dirette di comparazione (es. acido tranexamico verso fattore ricombinante VIIa). Tutti gli studi inclusi comprendono soggetti con TBI ad eccezione del CRASH-2 con popolazione prevalentemente emorragica.

Le analisi mostrano i seguenti risultati inerenti la riduzione del rischio di mortalità a 1 mese per tutte le cause (overall mortality):

Appendice C1, Agenti emostatici verso placebo:



Appendice C1, tutti gli interventi vs tutti:

Overall mortality – General trauma	RR
TXA vs placebo	**0.93 (0.88,0.98)**
TXA vs rFVIIa	*0.98 (0.72,1.33)*
rFVIIa vs placebo	0.95 (0.70,1.28)

Di seguito le analisi per sottogruppo di popolazione (blunt o penetrating trauma population)

1. Blunt trauma popoulation

Overall mortality – blunt trauma	RR
TXA vs placebo	**0.92 (0.86,0.99)**
rFVIIa vs TXA	*1.00 (0.68,1.47)*
rFVIIa vs placebo	0.92 0.63,1.35)

2. Penetrating trauma population

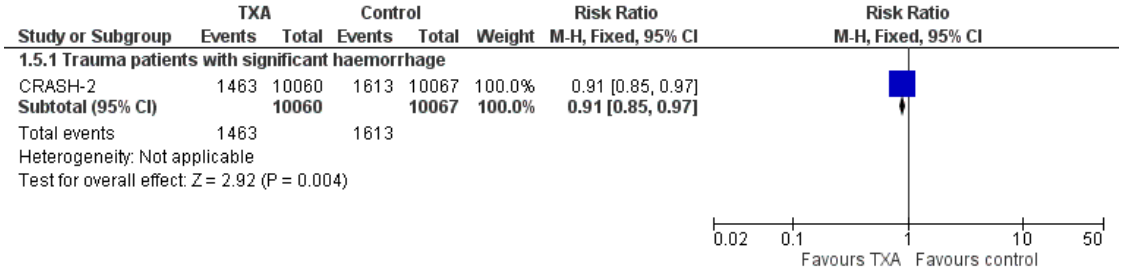
Overall mortality – blunt trauma	RR
TXA vs placebo	**0.86 (0.75,0.99)**
rFVIIa vs TXA	1.12 (0.67,1.88)
rFVIIa vs placebo	0.96 (0.59,1.59)

Nota: si segnala consistente eterogeneità nei criteri di inclusione oltre al trattamento negli studi considerati

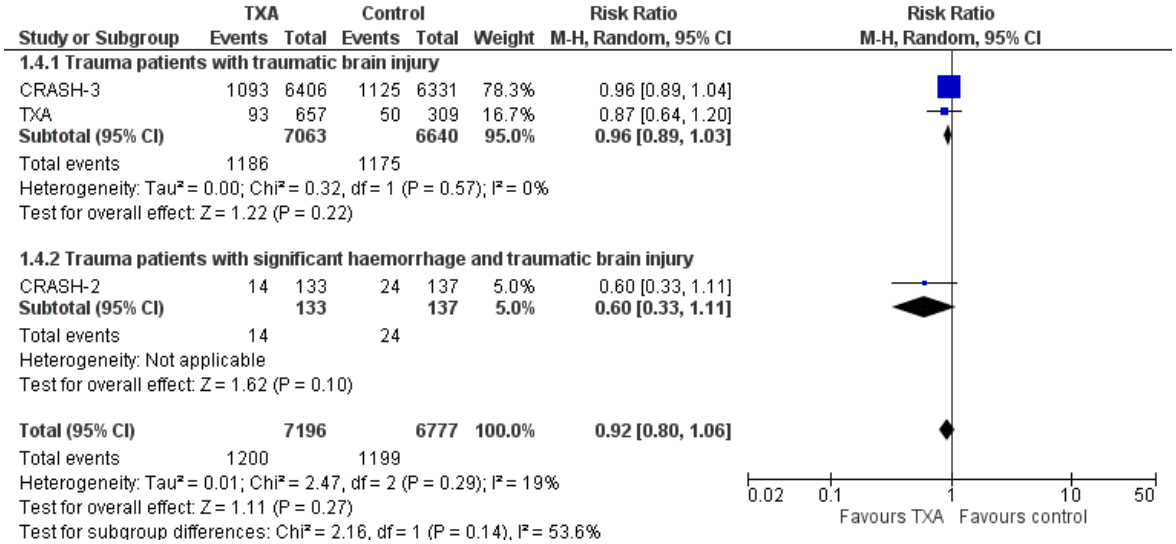
Analisi comparative a coppie di intervento/ pairwise per popolazione (Appendice C2)

Comparazione 1. Acido Tranexamico vs placebo (mortalità a 1 mese)

A. **Pazienti con significativa emorragia**: trauma patients with significant haemorrhage (CRASH-2)



B. **Pazienti con TBI:** trauma patients with TBI (CRASH-3, TXA); trauma patients with significant haemorrhage and TBI (CRASH-2: subgroup)

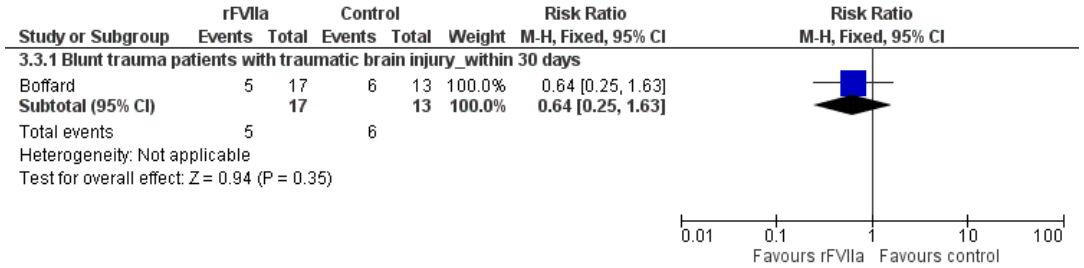


Appendice C2, Figure 1. Risk ratio for overall mortality (4 weeks) of TXA versus placebo by considering the population subgroups:

- trauma patients with significant haemorrhage and potentially suffering a TBI (CRASH-2),
- trauma patients with TBI (CRASH-3, TXA), trauma patients with TBI and significant haemorrhage (CRASH-2: subgroup).

Comparazione 2. Fattore VII ricombinante vs placebo

- **hemodynamically unstable blunt trauma patients with severe haemorrhage and TBI (Boffard 2005: subgroup)**



Appendice C2, Figure 3. Risk ratio for overall mortality (4 weeks) of rFVIIa versus placebo, by considering hemodynamically unstable blunt trauma patients with severe haemorrhage and TBI (Boffard 2005: subgroup).

1.3 MORTALITA' PER CAUSA-SPECIFICA (Appendice C1)
(tutta la popolazione [trauma cranico e/o trauma maggiore prevalentemente emorragico])

Le cause riportate negli RCT relative alla mortalità sono:

- **disfunzione multiorgano** per cui è stato possibile analizzare entrambe le comparazioni (TXA e rFVIIa vs placebo);
- **lesione cerebrale ed emorragia** per le quali è stato possibile analizzare solo la comparazione i.a) somministrazione pre-hospital di TXA 1 grammo in pre-ospedaliero + 1 grammo in infusione nelle 8 ore successive vs placebo;
- **embolia polmonare e sepsi** per le quali è stato possibile analizzare solo la comparazione ii) somministrazione pre-hospital di rFVIIa vs placebo.

1.3.1 Disfunzione multiorgano (Appendice C1)

Comparazione 1. Acido Tranexamico vs placebo

La mortalità a 4 settimane per disfunzione multiorgano non mostra una chiara indicazione dei benefici (CRASH-2 e CRASH-3).

Comparazione 2. Fattore VII ricombinante vs placebo

La mortalità per disfunzione multiorgano osservata da 48 ore dall'assunzione del fattore rFVIIa fino ai 30 giorni successivi, è stata riportata da 1 solo studio randomizzato e controllato (Boffard 2005) e non mostra una chiara indicazione dei benefici circa l'assunzione dell'agente emostatico rFVIIa.

1.3.2 Lesione cerebrale, Emorragia (Appendice C2)

Comparazione 1. Acido Tranexamico vs placebo

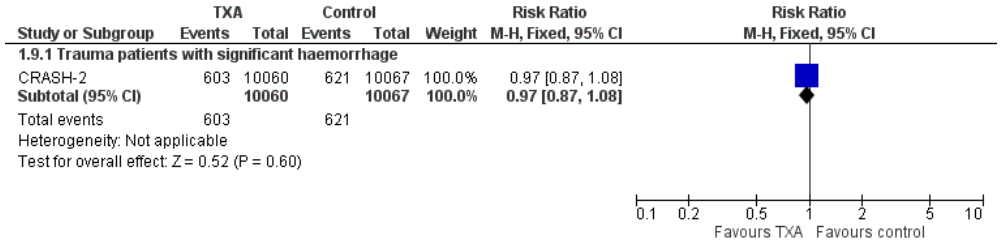
Mortality due to head injury (24 hours):

- **trauma patients with TBI (CRASH-3)**

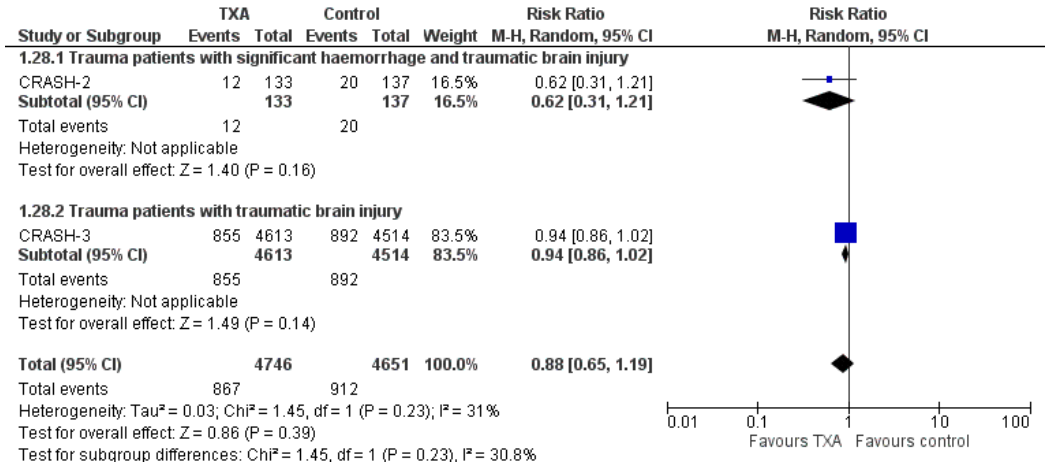
Appendice C2, Figure 5. Risk ratio for mortality due to head injury (24 hours) of TXA versus placebo by considering trauma patients with TBI (CRASH-3).

Mortality due to head injury (4 weeks), subgrouped for type of population:

A. **Pazienti con significativa emorragia:** trauma patients with significant haemorrhage (CRASH-2)



B. Pazienti con TBI: trauma patients with significant haemorrhage and TBI (CRASH-2: subgroup); trauma patients with TBI (CRASH-3)



Appendice C2, Figure 6. Risk ratio for mortality due to head injury (4 weeks) of TXA versus placebo by considering population subgroups:

- trauma patients with significant haemorrhage (CRASH-2),

- trauma patients with significant haemorrhage and TBI (CRASH-2: subgroup), trauma patients with TBI (CRASH-3).

1.3.3 Embolia polmonare, Sepsi

Comparazione 2. Fattore VII ricombinante vs placebo (Appendice C2)

Nella popolazione ristretta ai soli pazienti con trauma contusivo e lesione cerebrale traumatica, analizzata da un solo studio randomizzato e controllato (Boffard 2005) non si mostra una chiara indicazione dei benefici dovuti all'assunzione del fattore rFVIIa sulla mortalità, valutata da 48 ore dall'assunzione del trattamento fino ai 30 giorni successivi, sia in caso di decesso dovuto a embolia polmonare, che a sepsi.

2. HEALTH RELATED QUALITY OF LIFE

Appendice C1 riporta tutta la sintesi qualitativa. Di seguito la sintesi quantitativa:

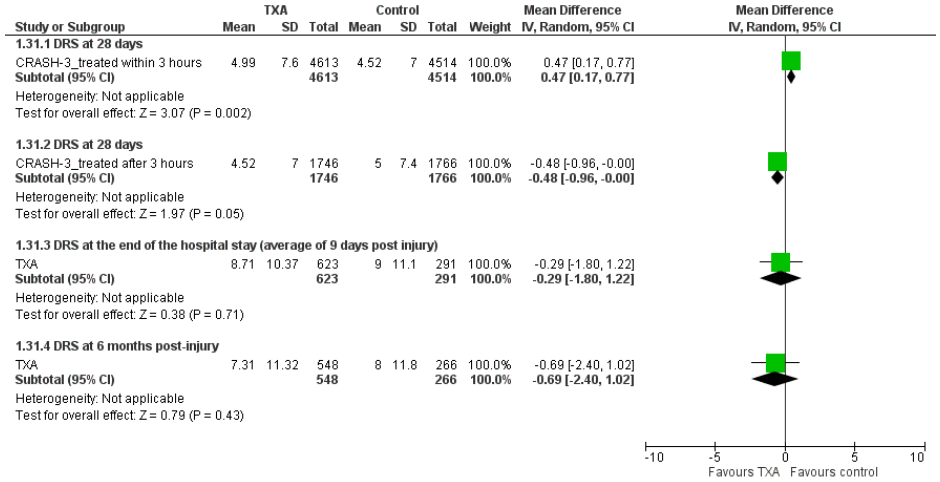


Figure 17. Mean difference for DRS (Disability Rating Scale) of TXA versus placebo, by considering trauma patients:

- treated within 3 hours and evaluation of DRS at 28 days,
- treated after 3 hours and evaluation of DRS at 28 days,
- DRS at the end of the hospital stay (average of 9 days post injury),
- DRS at 6 months post-injury.

3. USO DI EMOCOMPONENTI (Appendice C1):

Per la trasfusione di emocomponenti è stato possibile effettuare le seguenti comparazioni:

- PRBC (emazie concentrate) e trasfusione di sangue: sia per l'agente TXA che per il rFVIIa vs placebo;
- Platelets, Plasma cryoprecipitate e Fresh Frozen Plasma (FFP): solo per la comparazione riguardante la somministrazione del fattore rFVIIa vs placebo.

3.1 PRBCS, BLOOD PRODUCT TRANSFUSED, MASSIVE TRANSFUSION

	Comparazione 1. Acido Tranexamico vs placebo Per quanto riguarda la trasfusione di emocomponenti è stato rilevato quanto segue: PRBC: sia considerando le unità trasfuse che i soggetti che hanno subito trasfusioni di PRBC, non si rileva una riduzione significativa dalla somministrazione pre-ospedaliera dell'agente emostatico TXA (CRASH-2). ***Comparazione 2. Fattore VII ricombinante vs placebo*** Per quanto riguarda la trasfusione di emocomponenti è stato rilevato quanto segue: - PRBC non si fornisce una chiara indicazione riguardo al beneficio entro 48 ore dettato dalla somministrazione di rFVIIa (CONTROL trial). - trasfusione massiva a 24 ore (CONTROL trial) è stata rilevata una riduzione del rischio solamente nella popolazione con trauma penetrante, mentre a 48 ore (Boffard 2005) il beneficio dettato dalla somministrazione di rFVIIa riguarda sia l'intera popolazione, che i soggetti affetti da trauma chiuso (a differenza degli individui con trauma penetrante). **3.2 PLATELETS, PLASMA CRYOPRECIPITATE, FRESH FROZEN PLASMA (FFP)** ***Comparazione 2. Fattore VII ricombinante vs placebo*** Per quanto riguarda la trasfusione di emocomponenti è stato rilevato quanto segue: - Platelets e Cryoprecipitate: non forniscono una chiara indicazione riguardo al beneficio entro 48 ore dettato dalla somministrazione di rFVIIa (CONTROL trial). - FFP: un RCT (CONTROL trial) mostra una riduzione del rischio di trasfusione di FFP a seguito della somministrazione dell'agente emostatico rFVIIa a 48 ore, significativa nei pazienti con trauma chiuso (ma non nei pazienti con trauma penetrante) e nell'intera popolazione. **<u>IMPORTANTI:</u>** **1. MORTALITA' 12 MESI** Per entrambi i gli agenti emostatici non è mai stata riportata la mortalità a 12 mesi. **2. ENTITA' DELL'EMORRAGIA** ***Comparazione 1. Acido Tranexamico vs placebo (Appendice C2 per population)*** Considerando la somministrazione pre-ospedaliera dell'agente emostatico TXA, un solo RCT (CRASH-2) rileva una riduzione dell'entità dell'emorragia rilevata nelle 24-48 ore dal ricovero ospedaliero. **3. OUTCOMES RIPORTATI DAI PAZIENTI** Nessuno studio incluso ha riportato l'outcome d'interesse.	

Effetti indesiderabili

Quanto considerevoli sono gli effetti indesiderabili attesi?

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ Grandi ○ Moderati • Piccoli ○ Irrilevanti ○ Variano ○ Non so	È stata effettuata una revisione sistematica con ricerca della letteratura sulle banche dati Embase, Medline e Cochrane CENTRAL. Sono stati individuati 1518 record da cui sono state selezionate 8 referenze che soddisfano i criteri per rispondere al quesito clinico proposto, rispettivamente cinque studi primari e tre revisioni sistematiche da cui sono stati ulteriormente estratti tre studi. Altri 6 studi primari sono stati reclutati da clinicaltrial.gov e 5 dalle Linee Guida del NICE. In totale, sono state individuate 19 pubblicazioni afferenti a 5 studi randomizzati e controllati: CRASH-2, CRASH-3, TXA trial, CONTROL trial e Boffard 2005. Gli studi individuati permettono di rispondere alle seguenti comparazioni: *iii) Somministrazione pre-ospedaliera di TXA verso placebo:* *4. TXA 1 grammo in pre-ospedaliero + 1 grammo in infusione nelle 8 ore successive verso placebo (14 pubblicazioni afferenti a 3 studi randomizzati e controllati: CRASH-2 (11), CRASH-3 (2), TXA (1))* *5. TXA 2 grammi in pre-ospedaliero + placebo in infusione nelle ore successive verso placebo (una pubblicazione afferente ad uno studio randomizzato e controllato: TXA (1))* *iv) Somministrazione pre-ospedaliera di rFVIIa verso placebo (5 pubblicazioni afferenti a 2 studi randomizzati e controllati: Boffard 2005 (2), CONTROL trial (3).* Gli effetti indesiderabili (**Appendice C1**): **CRITICI:** **4.EVENTI AVVERSI *(Appendice C1 per overall, Appendice C2 per population)*** ***Nota sulla comparazione Fattore VII ricombinante vs placebo (CONTROL trial):*** "Sample size calculations were based on comparisons of mortality for the intent-to-treat (ITT) population using the one-sided X^2 test (significance level 2.5%). The aim was to detect a 16.7% mortality reduction with rFVIIa, assuming 30% mortality in placebo patients...The interim analysis of the mortality data from 447 blunt trauma patients showed lower than expected mortality rates. The power to demonstrate superiority of rFVIIa versus placebo was 11.2% (versus the predefined threshold of 50%). The trial was therefore stopped early (573 of 1502 patients) because of the high likelihood of futility in demonstrating the primary endpoint (mortality reduction) in the blunt trauma population" (Hauser et al., 2010). **4.1 SEPSI** ***Comparazione 1. Acido Tranexamico vs placebo*** L'evento avverso sepsi entro 4 settimane dall'assunzione del TXA è stato valutato da due trial randomizzati e controllati (CRASH-3 e TXA trial). Non ci sono evidenze di danni ottenuti dalla somministrazione pre-ospedaliera dell'agente emostatico TXA. ***Comparazione 2. Fattore VII ricombinante vs placebo*** L'evento avverso sepsi è stato valutato da un solo trial randomizzato e controllato (CONTROL), e rilevato entro 90 giorni dal trattamento sia nei pazienti con trauma contusivo che penetrante. Non emerge una chiara indicazione sul danno derivante dall'assunzione dell'agente rFVIIa.	Gli studi selezionati non sempre hanno pianificato adeguatamente la ricerca di trombosi venose profonde ed embolie polmonari subcliniche con reports eterogenei degli eventi. Pertanto, il panel ritiene che ancorché in termini quantitativi il rischio dell'utilizzo di questi farmaci non appaia eccessivo sulla base di questi studi esso vada comunque tenuto in considerazione.

4.2 EMBOLIA POLMONARE

Comparazione 1. Acido Tranexamico vs placebo

L'evento avverso embolia polmonare (valutato da 3 studi randomizzati e controllati, CRASH-2, CRASH-3, TXA) entro 4 settimane dall'assunzione del TXA, non ha mostrato una differenza statisticamente significativa rispetto alla somministrazione pre-ospedaliera dell'agente emostatico TXA, sia per la somministrazione di 1 grammo di TXA in fase pre-ospedaliera + 1 grammo entro 8 ore (CRASH-2, CRASH-3 e TXA) che di 2 grammi di TXA in fase pre-ospedaliera + placebo (TXA).

Comparazione 2. Fattore VII ricombinante vs placebo

Per l'embolia polmonare (valutata da un solo trial randomizzato e controllato CONTROL) non si mostra un significativo eccesso di rischio di insorgenza entro 4 settimane dall'assunzione dell'agente rFVIIa.

4.3 INFARTO MIOCARDICO, ICTUS

Comparazione 1. Acido Tranexamico vs placebo

Per gli eventi avversi di infarto al miocardio e ictus (valutati da 3 studi randomizzati controllati CRASH-2, CRASH-3, TXA), insorti entro 4 settimane dal trattamento, non si mostra una differenza significativa rispetto alla sicurezza da evento avverso sia per la somministrazione di 1 grammo di TXA in fase pre-ospedaliera + 1 grammo entro 8 ore (CRASH-2, CRASH-3 e TXA) che di 2 grammi + placebo (TXA).

Comparazione 2. Fattore VII ricombinante vs placebo

Per infarto al miocardio o ictus (valutati da un solo studio controllato e randomizzato, CONTROL), non si mostra una differenza significativa di eccesso rischio di insorgenza entro 4 settimane dall'assunzione dell'agente rFVIIa.

4.4 VASCOLARI:

Le cause riportate negli RCT relative agli eventi avversi prettamente vascolari sono:

- qualsiasi evento occlusivo vascolare per il quale è stato possibile analizzare solo le comparazioni i.a) somministrazione pre-hospital di TXA 1 grammo in pre-ospedaliero + 1 grammo in infusione nelle 8 ore successive vs placebo e i.b) TXA 2 grammi in pre-ospedaliero + placebo vs placebo;
- eventi avversi tromboembolici, trombotici arteriosi, trombotici venosi per i quali è stato possibile analizzare solo la comparazione ii) somministrazione pre-hospital di rFVIIa vs placebo;
- trombosi venosa profonda, coagulazione intravascolare disseminata per cui è stato possibile analizzare entrambe le comparazioni (TXA e rFVIIa vs placebo).

Comparazione 1. Acido Tranexamico vs placebo

Gli eventi avversi relativi a qualsiasi evento occlusivo vascolare, trombosi venosa profonda e coagulazione intravascolare disseminata (identificati da 3 studi controllati randomizzati, CRASH-2, CRASH-3 e TXA trial) insorti entro 4 settimane dall'assunzione del TXA, non hanno mostrato una differenza significativa rispetto alla somministrazione pre-ospedaliera dell'agente emostatico TXA, sia in caso di somministrazione dell'agente emostatico TXA per 1 grammo in fase pre-ospedaliera + 1 grammo entro 8 ore (CRASH-2, CRASH-3 e TXA), che per 2 grammi + placebo (TXA).

Comparazione 2. Fattore VII ricombinante vs placebo

In seguito all'assunzione dell'agente emostatico rFVIIa si sono valutati i seguenti outcomes:

- eventi avversi tromboembolici (dai trial Boffard 2005 a 48 ore e CONTROL a 90 giorni) per i quali non è stata riscontrata un eccesso di rischio sia nei soggetti con trauma contusivo che penetrante;
- eventi avversi trombotici arteriosi e venosi a 90 giorni (valutati da un solo studio controllato randomizzato, CONTROL) non si mostra un eccesso di rischio sia nei soggetti con trauma contusivo che penetrante;
- trombosi venosa profonda (dal trial CONTROL), per il quale non si mostra un rischio di insorgenza entro 4 settimane dall'assunzione dell'agente rFVIIa;

- coagulazione disseminata intravascolare a 90 giorni (dal trial CONTROL), per la quale non si mostra un eccesso di rischio di insorgenza a seguito della somministrazione pre-ospedaliera dell'agente emostatico rFVIIa, sia per la popolazione con trauma contusivo che penetrante.

4.5 ALTRI EVENTI AVVERSI: Sanguinamento gastrointestinale (TXA), Insufficienza renale (TXA), Danno renale acuto (TXA), Convulsioni (TXA), Sindrome da distress respiratorio acuto (rFVIIa), Disfunzione multiorgano (rFVIIa)

Le cause riportate negli RCT relative ad altri eventi avversi sono:

- sanguinamento gastrointestinale per il quale è stato possibile analizzare solo la comparazione i.a) somministrazione pre-hospital di TXA 1 grammo in pre-ospedaliero + 1 grammo in infusione nelle 8 ore successive vs placebo;
- insufficienza renale, danno renale acuto, convulsioni per i quali è stato possibile analizzare le comparazioni i.a) somministrazione pre-hospital di TXA 1 grammo in pre-ospedaliero + 1 grammo in infusione nelle 8 ore successive vs placebo e i.b) TXA 2 grammi in pre-ospedaliero + placebo vs placebo;
- sindrome da distress respiratorio acuto, disfunzione multiorgano per i quali è stato possibile analizzare solo la comparazione ii) somministrazione pre-hospital di rFVIIa vs placebo.

Comparazione 1. Acido Tranexamico vs placebo

Altri eventi avversi identificati da 3 trial (CRASH-2, CRASH-3, TXA) entro 4 settimane dall'assunzione del TXA, sono: emorragia gastrointestinale (valutata da 3 studi controllati randomizzati, CRASH-2, CRASH-3 e TXA trial), insufficienza renale (CRASH-3), danno renale acuto (TXA trial), convulsioni (CRASH-3 e TXA trial). In generale non si si mostra un eccesso di rischio dovuto alla somministrazione pre-ospedaliera dell'agente emostatico TXA.

Comparazione 2. Fattore VII ricombinante vs placebo

In seguito all'assunzione dell'agente emostatico rFVIIa sono stati valutati i seguenti eventi avversi:

- Sindrome da distress respiratorio acuto a 30 giorni (Boffard 2005) per il quale si mostra una riduzione significativa del rischio in coloro sottoposti al trattamento negli individui con trauma chiuso ma non negli individui con trauma penetrante. Inoltre, la sindrome da distress respiratorio acuto a 90 giorni (dal trial CONTROL) ha mostrato una significativa riduzione del rischio considerate entrambe le popolazioni trauma contusivo o penetrante.
- Disfunzione multiorgano (Boffard 2005 e CONTROL trial) per la quale si mostra una significativa riduzione del rischio con trattamento di insorgenza a 30 giorni dalla somministrazione dell'agente emostatico rFVIIa. Al contrario considerando l'outcome a 90 giorni (CONTROL trial) non vi è una significativa indicazione di sicurezza.

Qualità delle prove

Qual è la qualità complessiva delle prove di efficacia e sicurezza?

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ Molto bassa • Bassa ○ Moderata ○ Alta ○ Nessuno studio incluso	Considerando il giudizio più basso, la qualità complessiva delle prove di efficacia per comparazione *TXA verso placebo* è **bassa** mentre per la comparazione *Fattore VII ricombinante verso placebo* **molto bassa**.	

Overall quality assessment:	**TXA vs placebo**	**Fattore VII ricombinante vs placebo**
Critical:		
1. Mortality at 24 hours, 30 days/ 1 month	ALTA	MOLTO BASSA

2.	Health related quality of life	N.A.	N.A
3.	Adverse effects: venous thromboembolism thrombotic events (MI/Stroke, pulmonary embolism), over-transfusion related, morbidity, infections	DA BASSA AD ALTA	DA MOLTO BASSA A BASSA
4.	Blood product use: RBCs Platelets Plasma cryoprecipitate	DA MODERATA AD ALTA	DA MOLTO BASSA A BASSA
Important:			
5.	Mortality at 12 months	N.A.	N.A
6.	Entità dell'emorragia (growth)	ALTA	N.A
7.	Patient-reported outcomes (psychological wellbeing).	N.A	N.A

Nella comparazione *TXA verso placebo* la qualità delle prove è stata abbassata per: imprecisione della stima dell'effetto.

Nella comparazione *Fattore VII ricombinante* verso placebo la qualità delle prove è stata abbassata per: importanti limitazioni metodologiche (risk of bias), imprecisione della stima dell'effetto.

Si veda appendice E

Valori

C'è incertezza o variabilità nel valore attribuito agli esiti principali?

GIUDIZI	**RICERCA DELLE PROVE**	**CONSIDERAZIONI AGGIUNTIVE**
○ Importante incertezza o variabilità ○ Possibile importante incertezza o variabilità • Probabilmente nessuna incertezza o variabilità importante ○ Nessuna incertezza o variabilità importante	È stata effettuata una revisione sistematica con ricerca della letteratura sulle banche dati Embase, Medline. Non sono stati individuati record per valutare il seguente dominio.	Sottogruppi da considerare Testimoni di Geova attribuiscono maggiore importanza al risparmio di trasfusioni di GRC e altri emocomponenti. Individui con Disposizioni Anticipate di Trattamento (DAT).

Bilancio degli effetti

Il bilancio tra effetti desiderabili ed indesiderabili favorisce l'intervento o il confronto?

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ È in favore del confronto ○ Probabilmente è in favore del confronto ○ Non è in favore né dell'intervento né del confronto ○ Probabilmente è in favore dell'intervento • È in favore dell'intervento ○ Varia ○ Non lo so		Nel trauma cranico isolato l'effetto positivo è marginale e non significativo a 4 settimane (vedi mortalità tutte cause e per causa specifica).

Risorse necessarie

Qual è l'entità delle risorse necessarie (costi)?

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ Costi elevati ○ Costi moderati • Costi e risparmi irrilevanti ○ Risparmi moderati ○ Risparmi elevati ○ Varia ○ Non so	È stata effettuata una revisione sistematica con ricerca della letteratura sulle banche dati Embase, Medline. Sono stati individuati 28 record. Nessun record è stato considerato eleggibile per la valutazione del costo-efficacia della gestione delle emorragie nel setting pre-ospedaliero e ospedaliero con agenti emostatici. Perciò, si richiamano le prove che la linea guida NG39 sul trauma maggiore pubblicata dal NICE nel 2016 riporta in termini i costi e risorse necessarie. La linea guida NICE NG39 riporta le tabelle con unità di costo per gli interventi considerati dal quesito clinico. L'**Appendice G** riporta le tabelle di costi per intervento e costi per unità di emocomponenti come risorse necessarie correlate all'intervento. Per ulteriori dettagli si rimanda all'**Appendice G.**	Riferito ad ac. Tranexamico (intervento con dimostrata efficacia). Intervento già in parte adottato nella pratica clinica.

Tabella 3 – Appendice G: Costi di intervento

Intervention	Cost	Unit	Source
Factor 7 (recombinant activated factor VII)	£667		Blood products, band 1 (factor VIIa [recombinant]) (mean cost per episode of care where used). NHS reference cost 2012-1013. Health Resource Groups code XD05Z. (reference: NHS reference costs 2012-13)
Tranexamic acid	£1.55	500 mg	BNF (reference: British National Formulary)
Fibrinogen concentrate	£500	1-mg vial	GDG contact
Prothrombin complex concentrates	£600	1000 international units	Manufacturer website

La dose è dipendente da peso e gravità dell'emorragia, perciò i costi presentati sopra sono per unità e potrebbero non essere rappresentativi della dose totale di intervento necessaria per il trattamento del paziente. La dose viene inoltre rivalutata dopo il test di coagulazione. Il successo e l'efficacia degli agenti emostatici potrebbero essere misurati anche rispetto alla quantità di emocomponenti utilizzati. Una stima delle risorse necessarie in termini di emocomponenti è riportata sotto (le unità per paziente possono variare).

Tabella 4: Costi degli emocomponenti

Resource	Cost	Unit	Source
Packed RBCs	£122	1 pack 220-300 ml per pack	NHS Blood and transplant price list 2014/15 (reference: NHS Blood and Transplant)
FFP	£28	1 pack Mean: 271 ml per pack (240-280 is common)	NHS Blood and transplant price list 2014/15
Platelets	£197	1 adult therapeutic dose	NHS Blood and transplant price list 2014/15
Cryoprecipitate	£181	Pooled cryoprecipitate (5 pack) Mean: 199ml in pooled pack	NHS Blood and transplant price list 2014/15

Qualità delle prove relative alle risorse necessarie

Qual è la qualità delle prove relative alle risorse necessarie (costi)?

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ Molto bassa ○ Bassa • Moderata ○ Alta ○ Nessuno studio incluso	È stata effettuata una revisione sistematica con ricerca della letteratura sulle banche dati Embase, Medline. Sono stati individuati 28 record. Nessun record è stato considerato eleggibile per la valutazione del costo-efficacia della gestione delle emorragie nel setting pre-ospedaliero e ospedaliero con agenti emostatici. Perciò, si richiamano le prove che la linea guida NG39 sul trauma maggiore pubblicata dal NICE nel 2016 riporta in termini i costi e risorse necessarie. Le prove relative alle risorse necessarie sono contestualizzate in Inghilterra e nel contesto internazionale. Essendo il contesto inglese differente dal contesto italiano in termini di sistema sanitario nazionale, disponibilità di risorse economiche, la qualità delle prove risente di trasferibilità (indirectness), perciò con limitata applicabilità al contesto italiano. Inoltre, come la linea guida NICE afferma, la valutazione economica si è basata sui trial CRASH-2 per valutare il farmaco TXA (Roberts et al., 2013; Roberts, 2009) and il Boffard trial (Boffard et al., 2005) per il farmaco fattore VIIa ricombinante. Le valutazioni economiche risentiranno delle limitazioni metodologiche dei trials considerati. Inoltre, gli studi presi in esame per la valutazione del fattore VIIa ricombinante (Morris, 2007; Rossaint, 2007, 2005) presentano conflitti di interesse e non hanno considerato gli eventi avversi. Gli studi sono stati valutati come parzialmente applicabili (ad eccezione di Morris 2007, non direttamente applicabile) e con potenziali serie limitazioni (NICE, 2016).	Tuttavia, le prove relative al contesto italiano non ci consentono di dire quanto l'uso di TXA sia già diffuso, pertanto la stima dei costi aggiuntivi non può essere del tutto affidabile

Costo-efficacia

L'analisi di costo efficacia favorisce l'intervento o il confronto?

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ È in favore del confronto ○ Probabilmente è in favore del confronto ○ Non è in favore né del confronto né dell'intervento ○ Probabilmente è in favore dell'intervento • È in favore dell'intervento ○ Varia ○ Nessuno studio incluso	È stata effettuata una revisione sistematica con ricerca della letteratura sulle banche dati Embase, Medline. Sono stati individuati 28 record. Nessun record è stato considerato eleggibile per la valutazione del costo-efficacia della gestione delle emorragie nel setting pre-ospedaliero e ospedaliero con agenti emostatici. Perciò, si richiamano le prove che la linea guida NG39 sul trauma maggiore pubblicata dal NICE nel 2016 riporta in termini i costi e risorse necessarie. La linea guida NICE riporta: • una valutazione economica che compara acido tranexemico verso placebo (Roberts et al., 2013, 2009) • tre valutazioni economiche che comparano fattore ricombinante VIIa con placebo (Morris et al., 2007; Pohar, 2009; Rossaint et al., 2007, 2005); Per il farmaco acido tranexamico, l'outcome dello studio valutava il costo per anni di vita guadagnati: l'acido tranexamico ha un costo per anni di vita guadagnati pari a £ 42 comparato a placebo nei pazienti emorragici. Tuttavia, l'outcome non è stato espresso in costo per QALY e quindi non può essere valutata utilizzando la soglia di decisione di £20.000 per QALY. Questa valutazione economica è stata considerata parzialmente applicabile con potenziali serie limitazioni. La valutazione economica da tre studi del fattore VIIa ricombinante ha evidenziato che il rapporto costo efficacia è incerto: due studi hanno identificato che, comparando il fattore VIIa ricombinate con placebo, le analisi di costo utilità hanno trovato i seguenti risultati:	

1. Il fattore VIIa ricombinante comparato a placebo è costo efficace alla soglia di £20,000 (ICER - Il rapporto incrementale di costo-efficacia di £18,825 per QALY) nei pazienti emorragici. Questo studio è stato valutato come direttamente applicabile con potenziali serie limitazioni (Morris et al., 2007).
2. Il fattore VIIa ricombinante non è costo efficace comparato a placebo alla soglia di £20,000 (ICER di £21,613 per QALY) nei pazienti emorragici. Questo studio è stato valutato come parzialmente applicabile con potenziali serie limitazioni (Rossaint et al., 2007, 2005).
3. Il fattore VIIa ricombinante è più costoso rispetto a placebo alla soglia di £20,000 (£20,342 in più per paziente con incremento di QALYs calcolato ma non riportato. Questo studio è stato valutato come parzialmente applicabile con potenziali serie limitazioni (Pohar et al., 2009).

Tabella 1 (Appendice G): Economic evidence profile: Acido tranexamico verso placebo

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Roberts 2013 (UK)	Partially applicable	Potentially serious limitations[b]	Markov model estimating the gain in life years of a cohort of trauma patients with haemorrhage who receive tranexamic acid (TXA) compared with placebo. Mortality data from CRASH-2 trial.	£31	0.755 life years	£42 per life year gained	80% probability of being costeffectiveness at a threshold of £65 per life year gained.

Tabella 2 (Appendice G): Economic evidence profile: Fattore VIIa ricombinate verso placebo

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Morris 2007 (UK)	Directly applicable	Potentially serious limitations	Lifetime model based on patient level data from two randomised placebo-controlled phase II trials (Boffard et al., 2005). Data was supplemented with additional UK data to estimate costs and benefits (mortality following the trial duration, and QoL).	£13,243	0.70 QALYs	£18,825 per QALY	52% (61%) probability of being cost effective at a threshold of £20,000 (£30,000).
Rossaint 2007 (Germany)	Partially applicable	Potentially serious limitations	Lifetime model based on patient level data from two randomised placebo-controlled phase II trials (Boffard et al., 2005). Data was supplemented with	£14,831	0.69	£21,613 per QALY	48% (60%) probability of being cost effective at a threshold of £20,000 (£30,000)

				additional German data to estimate costs and benefits (mortality following the trial duration, and QoL).				
	Pohar 2009 (Canada)	Partially applicable	Potentially serious limitations	Decision tree model based on patient level data from two randomised placebo-controlled phase II trials (Boffard et al., 2005), supplemented by further sources for costing, utilities and in extrapolation technique to estimate long-term survival estimates.	£20,342	1.68 QALYs	£12,108 per QALY	36% (52%) probability of being cost effective at a threshold of £20,000 (£30,000)

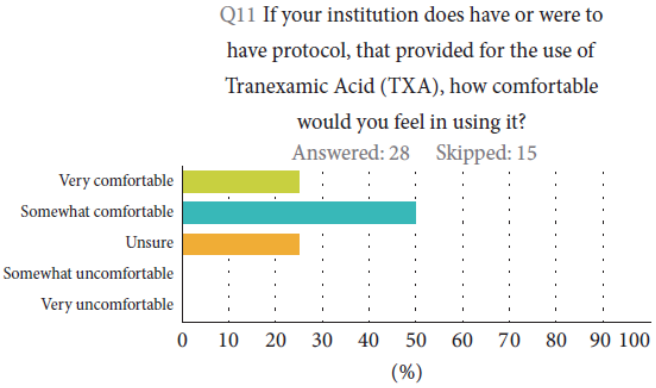
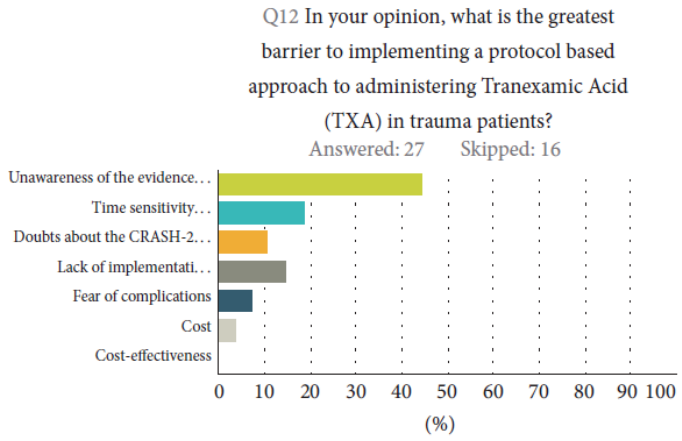
Equità

Quale sarebbe l'impatto in termini di equità?

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ Riduce l'equità ○ Probabilmente riduce l'equità ○ Probabilmente nessun impatto ○ Probabilmente migliora l'equità • Migliora l'equità ○ Varia ○ Non so	Non sono stati identificati studi relativi al contesto internazionale e italiano.	Anche le sottopopolazioni che per motivi religiosi o DAT rifiutano trattamenti con sangue ed emoderivati traggono beneficio dall'intervento (TXA).

Accettabilità

L'intervento è accettabile per i principali stakeholders?

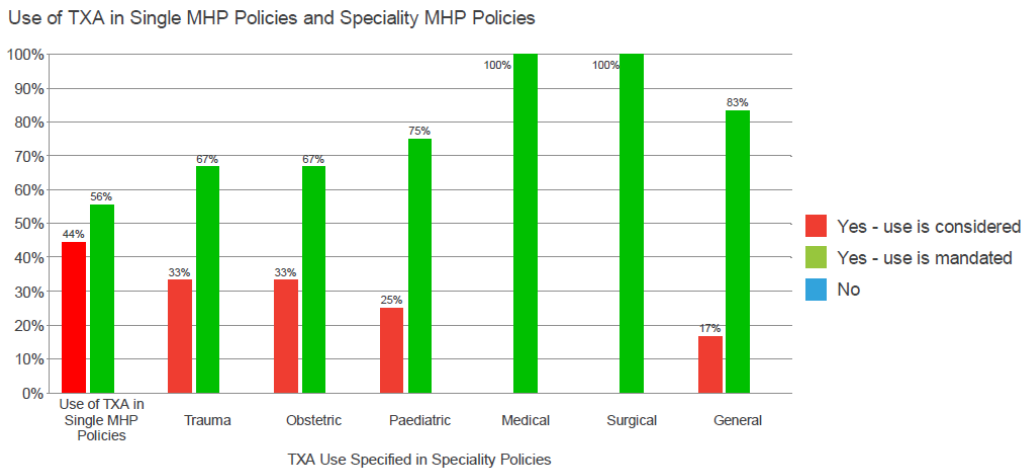
GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ No ○ Probabilmente no • Probabilmente sì ○ Si ○ Varia ○ Non so	È stata condotta una revisione sistematica su Medline ed Embase che ha portato a individuare 319 record relativi all'accettabilità/fattibilità della gestione dell'emorragia pre-ospedaliera con agenti emostatici. Sono stati inclusi 10 record e la LG NICE (NICE, 2016). L'accettabilità da parte degli operatori sanitari interessati all'introduzione degli agenti emostatici appare **variabile**. L'eterogeneità tra i centri è significativa per quanto riguarda i protocolli clinici e i pazienti traumatizzati e per quanto riguarda le risorse disponibili a livello locale. Le deviazioni dalle linee guida sono frequenti, differiscono da stato a stato e dipendono dalla formazione specialistica. Sono necessari ulteriori sforzi per fornire linee guida di consenso e per migliorare la loro attuazione nei paesi europei ed extra europei. Un sondaggio negli Stati Uniti è stato distribuito a 60 chirurghi traumatologici e 54 medici di emergenza (conferenza annuale del Maryland ACEP 2015, tasso di risposta: 38%) per indagare la conoscenza della letteratura, le barriere all'uso di TXA e suggerimenti su come implementare il TXA nei protocolli di trauma; La metà ha riferito di essere a conoscenza del TXA come parte del protocollo trasfusionale massivo del proprio istituto, la maggioranza dei partecipanti ha ritenuto che il TXA avrebbe avuto un impatto positivo significativo sulla sopravvivenza dei pazienti traumatizzati, inoltre la maggioranza ha ritenuto che l'uso di TXA sarebbe aumentato se la sua amministrazione fosse stata responsabilità sia dei chirurghi traumatologici che dei medici di emergenza. **La mancanza di consapevolezza dei dati clinici che supportano il suo utilizzo è uno dei principali ostacoli**. Tuttavia, la maggior parte dei fornitori di traumi e dei medici di emergenza hanno una **visione favorevole di TXA** e supportano la sua integrazione nei protocolli di trasfusione massiva. (Alburaih, 2017)  FIGURE 2: How comfortable would you feel to use TXA in exsanguinating trauma patients if TXA were incorporated in your institution massive transfusion protocols.  FIGURE 3: Greatest barrier to implementing TXA in trauma patients. In un altro sondaggio statunitense (191 chirurghi - 125 istituti di centri di livello I e II composti rispettivamente dal 70 e dal 18% dei siti che hanno risposto) gli autori hanno dichiarato **grandi variazioni nei modelli di pratica** e hanno concluso che esiste una confusione significativa nella definizione della migliore pratica nella trasfusione massiva. 123 istituzioni hanno un protocollo trasfusionale massivo (MTP); Il 54% dichiara di avere un MTP da meno di 5 anni. Il numero di refrigeratori e unità di globuli rossi, plasma e piastrine è molto variabile. L'acido tranexamico fa	Anche le sottopopolazioni che per motivi religiosi o DAT rifiutano trattamenti con sangue ed emoderivati traggono beneficio dall'intervento (TXA).

	parte dell'MTP nel 64% dei centri; Il 26% continua ad utilizzare il Fattore VII attivato ricombinante. L'attivazione MTP si verifica più di cinque volte al mese nel 32% dei centri. (Etchill, 2016) Tuttavia, uno studio retrospettivo ha esaminato la compliance della somministrazione di TXA presso un centro traumatologico di livello uno a Hamilton, Ontario, Canada: 134 pazienti hanno ricevuto TXA, che rappresenta **compliance del 27%**. Il tempo medio dall'arrivo alla somministrazione TXA è stato di 47 minuti. La compliance è aumentata per coloro che hanno richiesto trasfusioni massicce e con l'aumento del numero di criteri per la somministrazione di TXA. In conclusione la compliance con la somministrazione di TXA a pazienti traumatizzati con sospetta emorragia maggiore è bassa (Ghawnni, 2018). Anche un altro studio retrospettivo ha rilevato un basso tasso di compliance: 26 pazienti su 58 (44,8%) avevano soddisfatto i criteri di inclusione e avrebbero dovuto ricevere TXA secondo le linee guida ospedaliere ma solo 8 (30,7%) hanno ricevuto TXA come parte della loro rianimazione iniziale (Almansoor, 2018). Un sondaggio sottoposto ai delegati del congresso europeo dei traumi e della chirurgia d'urgenza (ESTES) e al 2 ° Congresso mondiale sui traumi tenutosi a Francoforte in maggio 2014(tasso di risposta: 29%), la maggior parte dei centri traumatologici (69%) ha implementato protocolli locali basati su linee guida internazionali e nazionali utilizzando prodotti sanguigni convenzionali, ad es. concentrati di globuli rossi (93,3%), concentrati di plasma fresco congelato (93,3%) e concentrati piastrinici (83%) e antifibrinolitici (100%). L'89% ha considerato l'assunzione continua di anticoagulanti, inclusi "nuovi anticoagulanti orali" e inibitori piastrinici, una minaccia crescente per i pazienti con trauma sanguinante. (Schäfer, 2015). Tuttavia, in Inghilterra e Galles vi è una bassa percentuale di pazienti trattati con TXA nell'intervallo di gravità della lesione e nell'intervallo di indicatori fisiologici di gravità del sanguinamento. Tra 228.250 pazienti, la percentuale di pazienti traumatizzati trattati con TXA è aumentata da quasi zero nel 2010 al 10% (4593) nel 2016. Nel 2016, la maggior parte dei pazienti (82%) che hanno ricevuto TXA lo ha fatto entro 3 ore dal trauma, tuttavia, solo il 30% dei pazienti ha ricevuto TXA entro un'ora dall'infortunio. Alla maggior parte (80%) dei pazienti che avevano subito una trasfusione di sangue precoce è stato somministrato TXA. I pazienti trattati con TXA da un paramedico di ambulanza hanno ricevuto un trattamento mediano di 49 min (IQR 33-72) rispetto a 111 min (IQR 77-162) per i pazienti trattati in ospedale. (Coats, 2019) Una valutazione della compliance alle linee guida europee sui traumi nello studio ETRAUSS ha mostrato con un sondaggio che solo 160 intervistati (66%) hanno dichiarato di utilizzare l'acido tranexamico sempre o spesso. (Hamada, 2015) **Popolazione di bambini** Lo studio CRASH-2 è stato condotto su adulti, ma il gruppo di sviluppo delle linee guida del NICE NG39 ha ritenuto che i risultati potessero essere estrapolati ai bambini. L'acido tranexamico è stato utilizzato in popolazioni pediatriche non traumatiche con una bassa incidenza di eventi avversi. (NICE, 2016)	

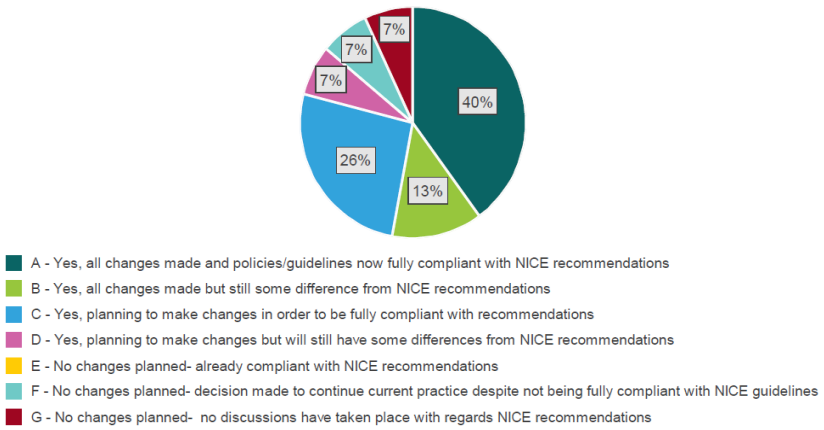
Fattibilità

È fattibile l'implementazione dell'intervento?

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ No ○ Probabilmente no ○ Probabilmente si • Sì ○ Varia	È stata condotta una revisione sistematica su Medline ed Embase che ha portato a individuare 319 record relativi all'accettabilità/fattibilità della gestione dell'agente emostatico nel setting pre-ospedaliero. Sono stati inclusi 3 record e la LG NICE. Per fattibilità si intende quanto l'intervento sia implementabile in termini di esiti e di compliance. Uno studio retrospettivo 'before and after' ha misurato gli esiti ospedalieri di pazienti adulti con grave emorragia da trauma nel Centro	NB Libretto illustrativo TXA (farmaco off-label) https://farmaci.agenziafarmaco.gov.it/aifa/servlet/PdfDownloadServlet?pdfFileN

○ Non so	traumatologico di Médecins Sans Frontières Tabarre a Port-au-Prince, Haiti, prima e dopo l'implementazione di un protocollo per l'emorragia massiva. l'implementazione di questo protocollo, inclusa la somministrazione precoce di TXA, è stato associato alla ridotta mortalità e degenza ospedaliera di pazienti adulti con gravi traumi chiusi e penetranti in un contesto con scarse risorse e disponibilità limitata di emoderivati (70% in meno di possibilità di morte durante il ricovero rispetto al gruppo "prima" (odds ratio aggiustato 0,3; 95%CI 0,1–0,8). Hanno anche avuto una degenza ospedaliera significativamente più breve (p = 0,02)). (Jachetti, 2019) Inoltre, uno studio ambientato in Sud Africa ha esaminato l'adeguatezza dell'uso di TXA (secondo le indicazioni dell'OMS e del CRASH2 - somministrato entro 3 ore) in un singolo distretto, utilizzando le linee guida provinciali come standard di riferimento. Lo studio era un'analisi retrospettiva di un database esistente: la conformità complessiva alla linea guida TXA era del 58% (172/295). Dei 115 pazienti che avevano una o una combinazione di indicazioni, 21 (18%) hanno ricevuto una prima dose di TXA. Dei 21 pazienti che hanno ricevuto una prima dose corretta di TXA, nessuno ha ricevuto l'infusione di proseguimento. Dei 180 pazienti che non avevano un'indicazione, 172 (96%) non hanno ricevuto TXA. L'acido tranexamico non è stato somministrato in modo appropriato a un numero significativo di pazienti che potevano avere indicazioni per l'uso. Ciò era principalmente dovuto al fatto che TXA non veniva fornito per le indicazioni delineate nelle linee guida cliniche locali. Dove è stata somministrato, è stata data solo la prima dose, ma nessuna infusione di proseguimento. I risultati suggeriscono che il TXA non era disponibile per l'uso, i pazienti impiegavano troppo tempo per raggiungere l'ospedale, i medici erano riluttanti a usarlo o i medici l'hanno usato, ma semplicemente non sono riusciti a documentarlo. (Jacobus, 2018) Le principali raccomandazioni delle Linee guida del (NICE) del novembre 2015 (NG24) incoraggiano i medici a prescrivere l'acido tranexamico (TXA) per i pazienti sottoposti a intervento chirurgico in cui è prevista una perdita di sangue> 500 ml. La logica è ridurre la perdita di sangue e quindi la necessità di trasfusioni. Il NICE raccomanda anche di prendere in considerazione il TXA e il "salvataggio cellulare "per i pazienti che dovrebbero perdere un volume molto elevato di sangue (ad esempio, trauma) (NICE, 2015). Per verificare l'uso appropriato di TXA come raccomandato nelle linee guida NICE 2015, è stato condotto un sondaggio in tutti gli ospedali NHS e indipendenti nella regione del West Midlands (Regno Unito). (Sherwood, 2018) Tutte le politiche MHP specificano l'uso di TXA anche se la formulazione della raccomandazione varia. È interessante notare che, nonostante la forte base di evidenze scientifiche nel trauma, 2/3 non impongono l'uso di TXA in questo contesto.  Inoltre, quando viene chiesto se le policy locali sono compliant con le LG NICE rispetto alla gestione dell'emorragia, queste sono le risposte: Have you changed, or are you planning to change, any of your policies (with regards use of TXA) based on the publication of the NG24 NICE	ame=footer_000550_022019_FI.pdf&retry=0&sys=m0b1l3 L'uso off-label del TXA in questo contesto andrebbe rivisto alla luce delle evidenze e delle raccomandazioni relative prodotte.

guidelines.



Di coloro che non sono e non intendono essere completamente conformi alle linee guida NICE, il motivo più comune è stata la mancanza di prove a supporto delle linee guida. Sherwood (Sherwood et al., 2018) Comunque è da segnalare che al momento della pubblicazione delle LG NICE (febbraio 2016), l'acido tranexamico non disponeva di un'autorizzazione all'immissione in commercio nel Regno Unito per questa indicazione. Il medico prescrittore in questo caso doveva seguire la guida professionale pertinente, assumendosi la piena responsabilità della decisione e raccogliere il consenso informato.

RIASSUNTO DEI GIUDIZI

	GIUDIZI						
PROBLEMA	No	Probabilmente no	Probabilmente si	**Sì**		Varia	Non so
EFFETTI DESIDERABILI	Irrilevanti	Piccoli	**Moderati**	Grandi		Varia	Non so
EFFETTI INDESIDERABILI	Grandi	Moderati	**Piccoli**	Irrilevanti		Varia	Non so
QUALITA' DELLE PROVE	Molto bassa	**Bassa**	Moderata	Alta			Nessuno studio incluso
VALORI	Importante incertezza o variabilità	Probabilmente importante incertezza o variabilità	**Probabilmente nessuna importante incertezza o variabilità**	Nessuna importante incertezza o variabilità			
BILANCIO DEGLI EFFETTI	A favore del confronto	Probabilmente a favore del confronto	Non è favorevole né al confronto né all'intervento	Probabilmente a favore dell'intervento	**A favore dell'intervento**	Varia	Non so
RISORSE NECESSARIE	Costi elevati	Costi moderati	**Costi e risparmi irrilevanti**	Risparmi moderati	Grandi risparmi	Varia	Non so
QUALITA' DELLE PROVE RELATIVE ALLE RISORSE NECESSARIE	Molto bassa	Bassa	**Moderata**	Alta			Nessuno studio incluso
COSTO EFFICACIA	A favore del confronto	Probabilmente a favore del confronto	Non è favorevole né al confronto né all'intervento	Probabilmente a favore dell'intervento	**A favore dell'intervento**	Varia	Nessuno studio incluso
EQUITA'	Riduce l'equità	Probabilmente riduce l'equità	Probabilmente nessun impatto sull'equità	Probabilmente aumenta l'equità	**Aumenta l'equità**	Varia	Non so
ACCETTABILITÀ	No	Probabilmente no	**Probabilmente si**	Si		Varia	Non so
FATTIBILITÀ	No	Probabilmente no	Probabilmente si	**Sì**		Varia	Non so

TIPO DI RACCOMANDAZIONE

N. 14 (TRAUMA MAGGIORE)

Raccomandazione forte contro l'intervento	Raccomandazione condizionata contro l'intervento	Raccomandazione condizionata per l'intervento o per il confronto	Raccomandazione condizionata a favore dell'intervento	**Raccomandazione forte a favore dell'intervento**
○	○	○	○	●

N. 15 (TRAUMA CRANICO)

Raccomandazione forte contro l'intervento	Raccomandazione condizionata contro l'intervento	Raccomandazione condizionata per l'intervento o per il confronto	**Raccomandazione condizionata a favore dell'intervento**	Raccomandazione forte a favore dell'intervento
○	○	○	●	○

CONCLUSIONI

Raccomandazione

N 14. Nel trauma maggiore con emorragia si raccomanda l'utilizzo di TXA rispetto al non utilizzo [raccomandazione forte, qualità delle prove bassa]
Nota: Il setting previsto per la raccomandazione è quello pre-ospedaliero. Tuttavia, se non eseguito in fase pre-ospedaliera se ne raccomanda l'uso nelle prime fasi del trattamento intraospedaliero.

N 15. Nel trauma cranico con GCS uguale o inferiore a 12 è preferibile l'utilizzo del TXA al non utilizzo [raccomandazione condizionata, qualità delle prove bassa].
Nota: Il setting previsto per la raccomandazione è quello pre-ospedaliero. Tuttavia, se non eseguito in fase pre-ospedaliera se ne raccomanda l'uso nelle prime fasi del trattamento intraospedaliero.

Giustificazione

Il vantaggio in termini di mortalità a breve e medio termine nel trauma maggiore con emorragia e l'assenza di eventi avversi significativi giustificano la raccomandazione forte a favore; nel trauma cranico con GCS uguale od inferiore a 12, il vantaggio marginale in termini di riduzione della mortalità a 4 settimane ed il rischio di possibili disabilità gravi legate alla severità del trauma cranico all'esordio (ancorché trattato con temporaneo successo con TXA) induce ad una maggiore cautela nel suo utilizzo.

Considerazioni relative ai sottogruppi

Nessuna.

Considerazioni per l'implementazione

Il farmaco va somministrato secondo lo schema previsto nei trials dove è stato dimostrato il successo (TXA 1 gr bolo ½ h + 1 gr in 8 h infusione).

Monitoraggio e valutazione

Priorità della ricerca

Nessuna.

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Appendice A - Quesito clinico e strategia di ricerca

CQ8. Gestione dell'emorragia nel pre-ospedaliero: agenti emostatici.

CQ8 Review question: Is the use of systemic haemostatic agents clinically and cost effective in improving outcomes in patients with confirmed or suspected haemorrhage in major trauma?

Objective: Which haemostatic agents administered systemically improve outcomes in patients with confirmed or suspected haemorrhage in major trauma?	
Population	Children, young people and adults who have a suspected haemorrhage following a traumatic incident. Setting: pre-hospital scene (including military setting)
Intervention	Factor 7 (recombinant activated factor vii) Tranexamic acid Fibrinogen concentrate Prothrombin complex concentrates Other anti-fibrinolytic agents
Comparison	Nothing A comparison of the above In combination In addition to standard care (Blood components (plasma, RBCs, platelets)/ cristalloyds)
Outcomes	Critical: 1. Mortality at 24 hours, 30 days/ 1 month 2. Adverse effects: venous thromboembolism thrombotic events (MI/Stroke, pulmonary embolism), over-transfusion related, morbidity, infections 3. Blood product use: RBCs Platelets Plasma cryoprecipitate Important: 1. Mortality at 12 months 2. Haemorrhage growth 3. Patient-reported outcomes (psychological wellbeing).
Exclusion	People with a major trauma resulting from burns
Search strategy	Databases: Medline, Embase, the Cochrane Library Date: All years Language: Restrict to English, Italian, Spanish, French, German Study designs: RCTs or Systematic reviews of RCTs; cohorts
The review strategy	Appraisal of methodological quality: The methodological quality of each study will be assessed the Newcastle-Ottawa Scale for observational studies, the Cochrane risk of bias tool for RCTs and GRADE.
Analysis	Stratify by age: children (0-17 years), adults (18 and over) Within-study confounders (if cohorts used) Age Injury severity Depth of shock Degree of head injury

SEARCH STRATEGIES _CLINICAL QUESTION CQ8

Limitation of language: English, Spanish, Italian, French, German
No altri filtri

POPULATION

F.2.1 Standard major trauma population

For the searches on information and support (question F.4.27), in Medline and Embase lines 1,2,5,6 and 7 were searched by title (ti) only and in Cochrane lines 2,3,10,11 and 12 were searched by title (ti) only.

Medline search terms

1.	(trauma* or polytrauma*).ti,ab.
2.	((serious* or severe* or major or life threaten*) adj3 (accident* or injur* or fall*)).ti,ab.
3.	multiple trauma/
4.	wounds, gunshot/ or wounds, stab/ or accidents, traffic/ or accidental falls/ or blast injuries/ or accidents, aviation/
5.	((motor* or motorbike* or vehicle* or road or traffic or car or cars or cycling or bicycle* or automobile* or bike* or head on or pile up) adj3 (accident* or crash* or collision* or smash*)).ti,ab.
6.	(mvas or mva or rtas or rta).ti,ab.
7.	(stabbed or stabbing or stab or gunshot* or gun or gunfire or firearm* or bullet* or knife* or knives or dagger).ti,ab.
8.	or/1-7

Embase search terms

1.	(trauma* or polytrauma*).ti,ab.
2.	((serious* or severe* or major or life threaten*) adj3 (accident* or injur* or fall*)).ti,ab.
3.	multiple trauma/
4.	gunshot injury/ or stab wound/ or traffic accident/ or falling/ or blast injury/ or aircraft accident/
5.	((motor* or motorbike* or vehicle* or road or traffic or car or cars or cycling or bicycle* or automobile* or bike* or head on or pile up) adj3 (accident* or crash* or collision* or smash*)).ti,ab.
6.	(mvas or mva or rtas or rta).ti,ab.
7.	(stabbed or stabbing or stab or gunshot* or gun or gunfire or firearm* or bullet* or knife* or knives or dagger).ti,ab.
8.	or/1-7

Cochrane search terms

#1.	MeSH descriptor: [multiple trauma] this term only
#2.	(trauma* or polytrauma*):ti,ab
#3.	((serious* or severe* or major) near/3 (accident* or injur* or fall*)):ti,ab
#4.	MeSH descriptor: [wounds, gunshot] this term only
#5.	MeSH descriptor: [wounds, stab] this term only
#6.	MeSH descriptor: [accidents, traffic] this term only
#7.	MeSH descriptor: [accidental falls] this term only
#8.	MeSH descriptor: [blast injuries] this term only
#9.	MeSH descriptor: [accidents, aviation] this term only
#10.	((motor* or motorbike* or vehicle* or road or traffic or car or cars or cycling or bicycle* or automobile* or bike*) near/3 (accident* or crash* or collision* or smash*)):ti,ab
#11.	(mvas or mva or rtas or rta):ti,ab
#12.	(stabbed or stabbing or stab or gunshot or gun or gunfire or firearm* or bullet or knife* or knives or dagger or shot):ti,ab
#13.	{or #1-#12}

F 2.2. Haemorrage population

Medline search terms

1.	hemorrhage/ or exsanguination/ or shock/ or shock, hemorrhagic/ or shock, traumatic/ or Hypovolemia/
2.	(hypovol?em* or shock or exsanguin* or olig?em* or h?emorrhag* or hypoperfus*).ti,ab.
3.	(coagulopath* or (abnormal* adj2 coagulation) or hyperfibrinolysis).ti,ab.
4.	(bleed* or bloodloss*).ti,ab.
5.	(blood* adj3 loss*).ti,ab.
6.	or/1-5

Embase search terms

1.	exp *hypovolemia/ or *hemorrhagic shock/ or *traumatic shock/ or exp *bleeding/ or *exsanguination/
2.	(haemorrhag* or hemorrhag* or hypovol?em* or shock or exsanguin* or olig?em* or h?emorrhag* or hypoperfus*).ti,ab.
3.	(coagulopath* or (abnormal* adj2 coagulation) or hyperfibrinolysis).ti,ab.
4.	(bleed* or bloodloss*).ti,ab.
5.	(blood adj2 loss*).ti,ab.
6.	or/1-6

Cochrane search term

#1.	MeSH descriptor: [hemorrhage] this term only
#2.	MeSH descriptor: [exsanguination] this term only
#3.	MeSH descriptor: [shock] this term only
#4.	MeSH descriptor: [shock, traumatic] this term only
#5.	MeSH descriptor: [shock, hemorrhagic] this term only
#6.	MeSH descriptor: [hypovolemia] this term only
#7.	(haemorrhag* or hemorrhag* or hypovolem* or hypovolaem* or shock or exsanguin* or oligem* or oligaem* or hypoperfus*):ti,ab
#8.	(coagulopath* or (abnormal* near/2 coagulation) or hyperfibrinolysis):ti,ab
#9.	(bleed* or bloodloss*):ti,ab
#10.	blood* near/3 loss*:ti,ab
#11.	{or #1-#10}

INTERVENTION

Medline search terms

1.	blood coagulation factors/
2.	factor vii/
3.	factor viia/
4.	(factor vii* or factor 7 or novo 7 or novoseven or aryoseven or fvii* or rfvii*).ti,ab.
5.	tranexamic acid/
6.	(tranexamic acid* or TXA).ti,ab.
7.	(cyklokapron or transamin or cyclo-f or femstrual).ti,ab.
8.	(transcam or traxyl or espercil or kapron).ti,ab.
9.	fibrinogen/
10.	(fibrinogen or riastap).ti,ab.
11.	prothrombin/
12.	(prothrombin adj2 (complex* or concentrate*)).ti,ab.
13.	PCC.ti,ab.
14.	(beriplex or octaplex or kcentra or cofact).ti,ab.
15.	antifibrinolytic agents/ or aminocaproic acid/ or alpha-2-antiplasmin/
16.	(antifibrinolytic* or anti-fibrinolytic*).ti,ab.
17.	ethamsylate/
18.	(dicynene or dicynone or etamsylate or ethamsylate).ti,ab.

19.	(aminocaproic acid or amicar or aminohexanoic acid).ti,ab.
20.	(haemostatic* adj2 agent*).ti,ab.
21.	(anti-h?emorrhagic* or antih?emorrhagic*).ti,ab.
22.	hemostatics/
23.	or/1-22

Embase search terms

1.	*blood clotting factor 7/ or *blood clotting factor 7a/
2.	(factor vii* or factor 7 or novo 7 or novoseven or aryoseven or FVII* or rFVII*).ti,ab.
3.	(cyklokapron or transamin or cyclo-f or femstrual).ti,ab.
4.	(transcam or traxyl or espercil or kapron).ti,ab.
5.	*fibrinogen/
6.	(fibrinogen or riastap).ti,ab.
7.	*prothrombin/
8.	(prothrombin adj2 (complex* or concentrate*)).ti,ab.
9.	PCC.ti,ab.
10.	(beriplex or octaplex or kcentra or cofact).ti,ab.
11.	exp *antifibrinolytic agent/
12.	aprotinin.ti,ab.
13.	*aprotinin/
14.	*4 aminomethylbenzoic acid/
15.	aminomethylbenzoic acid.ti,ab.
16.	*tranexamic acid/
17.	(tranexamic acid* or TXA).ti,ab.
18.	*aminocaproic acid/
19.	(aminocaproic acid or amicar or aminohexanoic acid).ti,ab.
20.	(antifibrinolytic* or anti-fibrinolytic*).ti,ab.
21.	*thrombin activatable fibrinolysis inhibitor/
22.	(thrombin activable fibrinolysis inhibitor or thrombin activatable fibrinolysis inhibitor).ti,ab.
23.	*alpha 2 antiplasmin/
24.	((alpha-2 or alpha2) adj2 (inhibitor* or antiplasmin or plasmin)).ti,ab.
25.	trasylol.ti,ab.
26.	(PAMBA or aminobenzoic acid).ti,ab.
27.	(carboxypeptidase u or procarboxypeptidase u or TAFI).ti,ab.
28.	*ethamsylate/

29.	(dicynene or dicynone or etamsylate or ethamsylate).ti,ab.
30.	(haemostatic* adj2 agent*).ti,ab.
31.	(anti-h?emorrhagic* or antih?emorrhagic*).ti,ab.
32.	*hemostatic agent/
33.	or/1-32

Cochrane search terms

#1.	MeSH descriptor: [blood coagulation factors] this term only
#2.	MeSH descriptor: [factor vii] explode all trees
#3.	(factor next vii* or factor next 7 or novo next 7 or novoseven or aryoseven or FVII* or rFVII*):ti,ab
#4.	MeSH descriptor: [tranexamic acid] this term only
#5.	tranexamic next acid*:ti,ab
#6.	TXA.ti,ab
#7.	(cyklokapron or transamin or cyclo next f or femstrual):ti,ab
#8.	(transcam or traxyl or espercil or kapron):ti,ab
#9.	MeSH descriptor: [fibrinogen] this term only
#10.	(fibrinogen or riastap):ti,ab
#11.	MeSH descriptor: [prothrombin] this term only
#12.	(prothrombin near/2 (complex or concentrate)):ti,ab
#13.	PCC:ti,ab
#14.	(beriplex or octaplex or kcentra or cofact):ti,ab
#15.	MeSH descriptor: [antifibrinolytic agents] this term only
#16.	MeSH descriptor: [alpha-2-antiplasmin] this term only
#17.	MeSH descriptor: [aminocaproic acid] this term only
#18.	(antifibrinolytic* or anti next fibrinolytic*):ti,ab
#19.	MeSH descriptor: [ethamsylate] this term only
#20.	(dicynene or dicynone or etamsylate or ethamsylate):ti,ab
#21.	(aminocaproic next acid or amicar or aminohexanoic next acid):ti,ab
#22.	(haemostatic* near/2 agent*):ti,ab
#23.	anti next h?emorrhagic*:ti,ab
#24.	antih?emorrhagic*.ti,ab
#25.	MeSH descriptor: [hemostatics] this term only
#26.	{or #1-#25}

Study designs and publication types

Systematic review (SR) search terms

Medline search terms

1.	meta-analysis/
2.	meta-analysis as topic/
3.	(meta analy* or metanaly* or metaanaly*).ti,ab.
4.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
5.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7.	(search* adj4 literature).ab.
8.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9.	cochrane.jw.
10.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
11.	or/1-10

Embase search terms

1.	systematic review/
2.	meta-analysis/
3.	(meta analy* or metanaly* or metaanaly*).ti,ab.
4.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
5.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7.	(search* adj4 literature).ab.
8.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9.	((pool* or combined) adj2 (data or trials or studies or results)).ab.
10.	cochrane.jw.
11.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
12.	or/1-11

Randomised controlled trials (RCTs) search terms

Medline search terms

1.	randomized controlled trial.pt.
2.	controlled clinical trial.pt.

3.	randomi#ed.ab.
4.	placebo.ab.
5.	randomly.ab.
6.	clinical trials as topic.sh.
7.	trial.ti.
8.	or/1-7

Embase search terms

1.	random*.ti,ab.
2.	factorial*.ti,ab.
3.	(crossover* or cross over*).ti,ab.
4.	((doubl* or singl*) adj blind*).ti,ab.
5.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
6.	crossover procedure/
7.	double blind procedure/
8.	single blind procedure/
9.	randomized controlled trial/
10.	or/1-9

Observational studies (OBS) search terms

Medline search terms

1.	epidemiologic studies/
2.	exp case control studies/
3.	exp cohort studies/
4.	cross-sectional studies/
5.	case control.ti,ab.
6.	(cohort adj (study or studies or analys*)).ti,ab.
7.	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
8.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or
	review or analys* or cohort*)).ti,ab.
9.	or/1-8

Embase search terms

1.	clinical study/
2.	exp case control study/
3.	family study/

4.	longitudinal study/
5.	retrospective study/
6.	prospective study/
7.	cross-sectional study/
8.	cohort analysis/
9.	follow-up/
10.	cohort*.ti,ab.
11.	9 and 10
12.	case control.ti,ab.
13.	(cohort adj (study or studies or analys*)).ti,ab.
14.	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
15.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
16.	or/1-8,11-15

The following study designs and publication types were removed from retrieved results using **the NOT** operator.
Aggiungere alla search con operatore NOT i seguenti search terms:

Medline search terms

1.	letter/
2.	editorial/
3.	news/
4.	exp historical article/
5.	anecdotes as topic/
6.	comment/
7.	case report/
8.	(letter or comment*).ti.
9	animals/ not humans/
10.	exp animals, laboratory/
11	exp animal experimentation/
12	exp models, animal/
13	exp rodentia/
14	(rat or rats or mouse or mice).ti.
15	or/1-14

Embase search terms

1.	letter.pt. or letter/
2.	note.pt.
3.	editorial.pt.
4.	case report/ or case study/
5.	(letter or comment*).ti.
6.	animal/ not human/
7.	nonhuman/
8.	exp animal experiment/
9.	exp experimental animal/
10.	animal model/
11.	exp rodent/
12.	(rat or rats or mouse or mice).ti.
13.	or/1-12

Appendice B - Caratteristiche degli studi inclusi ed elenco degli studi esclusi con motivazione.

CQ8. Gestione dell'emorragia nel pre-ospedaliero: agenti emostatici

Tabelle delle caratteristiche degli studi inclusi

Study	**CRASH-2**
Study type	Randomised Placebo-controlled Study
Number of studies/ number of participants	N=20211
Countries and Settings	Conducted in 274 hospitals in 40 countries
Funding	The project was funded by the Bupa Foundation, the J P Moulton Charitable Foundation, Pfizer and the NIHR Health Technology Assessment programme. The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author (IR) had full access to all the data in the study and had final responsibility for the decision to submit for publication.
Duration of study	The trial protocol was peer-reviewed and published on The Lancet website in 2005. The first patient was enrolled in May 2005 and the last one in January 2010.
Age, gender, ethnicity	Age [mean (SD)]: group 1: 34.6 (14.1), Group 2: 34.5 (14.4). Gender (% M): group 1: 83.6%, group 2: 84% Ethnicity: not reported
Patient characteristics	Adult trauma patients with significant haemorrhage (systolic blood pressure < 90 mmHg, heart rate > 110 beats per minute or both) or were considered to be at risk of significant haemorrhage and who were within 8 hours of injury, were eligible for the trial
Intervention	Group 1 (n=10 060): loading dose 1 g over 10 minutes of **tranexamic acid** (TXA) followed by infusion of 1 g over 8 hours Group 2 (n=10 067): placebo.
Outcomes	The primary outcome was death in hospital within 4 weeks of injury, with cause of death described with the following categories: bleeding, vascular occlusion (myocardial infarction, stroke, and pulmonary embolism), multiorgan failure, head injury, and other. The effect of the trial treatment on death due to bleeding was examined subdividing by four baseline characteristics: (1) time from injury to treatment (≤1, >1–3, >3 h); (2) severity of haemorrhage as assessed by systolic blood pressure (≤75, 76–89, >89 mm Hg); (3) Glasgow coma score (severe 3–8, moderate 9–12, mild 13–15); and (4) type of injury (penetrating only, blunt plus blunt and penetrating). Secondary outcomes were vascular occlusive events (myocardial infarction, stroke, pulmonary embolism, and deep vein thrombosis), surgical intervention (neurosurgery, thoracic, abdominal, and pelvic surgery), receipt

	of blood transfusion, and units of blood products transfused.

Study	**CRASH-3**
Study type	Randomised Placebo-controlled Study
Number of studies/ number of participants	N=12737
Countries and Settings	Conducted in 175 hospitals in 29 countries
Funding	National Institute for Health Research Health Technology Assessment, JP Moulton Charitable Trust, Department of Health and Social Care, Department for International Development, Global Challenges Research Fund, Medical Research Council, and Wellcome Trust (Joint Global Health Trials scheme). The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.
Duration of study	Between 20 July 2012 and 31 January 2019
Age, gender, ethnicity	Age [mean (SD)]: group 1: 41.7 (19.0), Group 2: 41.9 (19.0). Gender (% M): group 1: 80%, group 2: 80% Ethnicity: not reported
Patient characteristics	Adults with traumatic brain injury who were within 3 h of injury, had a Glasgow Coma Scale (GCS) score of 12 or lower or any intracranial bleeding on CT scan, and no major extracranial bleeding were eligible. The time window for eligibility was originally 8 hours but in 2016 the protocol was changed to limit recruitment to patients within 3 hours of injury.
Intervention	Group 1 (n=6406): loading dose 1 g over 10 minutes of **tranexamic acid** (TXA) followed by infusion of 1 g over 8 hours Group 2 (n=6331): placebo.
Outcomes	The primary outcome was head injury-related death in hospital within 28 days of injury in patients treated within 3 h of injury. Secondary outcomes were early head injury-related death (within 24 h after injury), all-cause and cause-specific mortality, disability, vascular occlusive events (myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism), seizures, complications, neuro-surgery, days in intensive care unit, and adverse events within 28 days of randomisation. A diagnosis of deep vein thrombosis or pulmonary embolism was recorded only if a positive result was found on imaging (eg, ultrasound) or at a post-mortem examination.

Study	**TXA**
Study type	Multi-center double-blind randomized controlled study
Number of studies/ number of participants	N=966
Countries and Settings	Participants were enrolled by 39 emergency management service (EMS) agencies and transported to 20 trauma centers within 12 regional sites in North America. Pre-hospital setting
Funding	This study protocol will be conducted as part of the Resuscitation Outcomes Consortium (ROC) at trauma centers in the United States and Canada. ROC is funded by the National Heart Lung and Blood Institute (NHLBI) in partnership with the US Army Medical Research and Materiel Command (USAMRMC), Canadian Institutes of Health Research, the Heart & Stroke Foundation of Canada, the American Heart Association (AHA), and the Defense Research and Development Canada.
Duration of study	Between May 2015 and March 2017 for primary outcomes
Age, gender, ethnicity	Age [mean (IQR)]: group 1: 39 (26-57), group 2: 38 (25-56), group 3: 36 (25-55) Gender (% M): group 1: 72.8%, group 2: 73.9%, group 3: 75.4% Ethnicity: group 1: 4.2% Asian, 16% Black or African American, 64.7% White group 2: 2.9% Asian, 15.4% Black or African American, 65.8% White group 3: 2.3% Asian, 14.9% Black or African American, 68.9% White
Patient characteristics	Patients with blunt or penetrating traumatic mechanism consistent with traumatic brain injury, prehospital Glasgow Coma Score (GCS) score ≤ 12 at any time prior to randomization and administration of sedative and/or paralytic agents,p Prehospital systolic blood pressure (SBP) ≥ 90 mmHg prior to randomization, prehospital intravenous (IV) or intraosseous (IO) access, age ≥ 15 (or estimated weight > 50 kg if age is unknown) and Emergency Medicine System (EMS) transport to a participating trauma center
Intervention	Group 1 (n= 312): Bolus/maintenance: 1 gr IV **TXA** bolus in the prehospital setting followed by a 1 gr IV maintenance infusion initiated on hospital arrival and infused over 8 hours. Group 2 (n= 345): Bolus only: 2 grams IV TXA in the prehospital setting followed by a placebo maintenance infusion initiated on hospital arrival and infused over 8 hours. Group 3 (n= 309): Placebo in the prehospital setting followed by a placebo maintenance infusion initiated on hospital arrival and infused over 8 hours.
Outcomes	Clinical outcomes: 28-day survival, frequency of neurosurgical interventions, and ventilator-free, ICU-free, and hospital-free days. Safety outcomes: Development of seizures, cerebral ischemic events, myocardial infarction, deep venous thrombosis, and pulmonary thromboembolism.

Study	**Boffard 2005**
Study type	Two parallel randomized, placebo-controlled, double blind trials, one in blunt trauma and one in penetrating trauma, were conducted simultaneously
Number of studies/ number of participants	N=291 (148 blunt trauma; 143 penetrating trauma)
Countries and Settings	Patients were enrolled by 32 hospitals throughout Australia, Canada, France, Germany, Israel, Singapore, South Africa, and the United Kingdom
Funding	Sponsor: Novo Nordisk A/S, Bagsvaerd, Denmark. Statistician: Tine Soerensen, MSc, Novo Nordisk, Bagsvaerd, Denmark.
Duration of study	Between March 2002 and September 2003
Age, gender, ethnicity	Blunt trauma: Age: group 1 (n=69): 33 ± 13; group 2 (n=74): 35 ± 13 Gender (% m): group 1: 70%, group 2: 70% Ethnicity: not reported Penetrating trauma: Age: group 1 (n=70): 29 ± 10, group 2: 32 ± 10 Gender (% m): group 1: 94%, group 2: 94% Ethnicity: not reported
Patient characteristics	Patients of age between 16 and 65 years with severe blunt and/or penetrating trauma
Intervention	Patients were equally randomized to receive three intravenous injections of **rFVIIa** of 200, 100, and 100 μg/kg dose (group 1) or three placebo injections (group 2). The first dose of trial product was to be administered immediately after transfusion of the eighth unit of RBCs, given that the patient—in the opinion of the managing physician—would require additional transfusions. The second and third doses followed 1 and 3 hours after the first dose, respectively.
Outcomes	Patients were monitored closely during the 48-hour period after the first dose of trial product. This included recording transfusion and infusion requirements, adverse events, and surgical procedures. Mortality, time on the ventilator, time in the intensive care unit (ICU), and serious adverse events including predefined critical complications (MOF and acute respiratory distress syndrome [ARDS]) as reported by the trial sites were recorded until day 30.

Study	**CONTROL**
Study type	Prospective, randomized, double-blinded, multicenter placebo-controlled study
Number of studies/ number of participants	N=554 (468 Blunt trauma; 86 penetrating trauma)
Countries and Settings	Patients were enrolled by 150 hospitals in 26 countries
Funding	Supported by Novo Nordisk A/S, Bagsvaerd, Denmark (sponsor). The sponsor was responsible for providing clinical trial supplies, preparing the study protocol, data management, statistical analysis, and preparing the clinical trial report. Anders Rosholm, PhD, is an employee of Novo Nordisk and assisted with the statistical analyses. Jen Faleska, PhD, and Charlotte Yap, MSc, are employees of Novo Nordisk and provided editorial assistance.
Duration of study	August 2005 to September 2008
Age, gender, ethnicity	Blunt trauma: Age: group 1 (n=221): 39.2 ± 14.3, group 2 (n=247): 39.9 ± 14.2 Gender (% m): group 1: 73.3%, group 2: 73.7% Ethnicity: group 1: 82.4% Caucasian, 4.1 % black or African American, 9.5% Asian, 4.1% other group 2: 85.4% Caucasian, 2.0 % black or African American, 9.7% Asian, 2.8% other Penetrating trauma: Age: group 1 (n=46): 33.8 ± 11.9, group 2 (n=40): 29.4 ± 10.3 Gender (% m): group 1: 93.5%, group 2: 92.5% Ethnicity: group 1: 63.0 % Caucasian, 28.3 % black or African American, 4.3 % Asian, 4.3% other group 2: 37.5 % Caucasian, 42.5 % black or African American, 12.5 % Asian, 7.5 % other
Patient characteristics	Blunt and/or penetrating trauma patients aged 18 years to 70 years were eligible if they had continuing torso and/or proximal lower extremity bleeding after receiving 4 units of RBCs despite standard haemostatic interventions
Intervention	Patients were randomized 1:1 to receive three doses of **rFVIIa** (group 1): 200 µg/kg at 0 hour, 100 µg/kg at 1 hour and 3 hours, or placebo (group 2).
Outcomes	The firsttier endpoint was superiority in all-cause 30-day mortality in blunt trauma. Predefined secondary endpoints included transfused units of RBC, fresh frozen plasma (FFP), platelets, cryoprecipitate, fibrinogen concentrate, and all allogeneic blood products at 24 hours and 48 hours after dosing and number of patients requiring massive RBC transfusions (defined as ≥ 10 units of RBC) at 24 hours. Other endpoints were number of patients with multiple organ failure (MOF) or single organ failure (SOF) and days alive and free from MOF, SOF, intensive care unit (ICU), hospital or ventilator, and/or renal replacement therapy, through day 30.

Tabella degli studi esclusi con motivi di esclusione

1	Innerhofer P, Fries D, Mittermayr M, et al. Reversal of trauma-induced coagulopathy using first-line coagulation factor concentrates or fresh frozen plasma (RETIC): a single-centre, parallel-group, open-label, randomised trial [published correction appears in Lancet Haematol. 2017 Jun;4(6):e257]. Lancet Haematol. 2017;4(6):e258-e271. doi:10.1016/S2352-3026(17)30077-7	HOSPITAL SETTING
2	Jokar A, Ahmadi K, Salehi T, Sharif-Alhoseini M, Rahimi-Movaghar V. The effect of tranexamic acid in traumatic brain injury: A randomized controlled trial. Chin J Traumatol. 2017;20(1):49-51. doi:10.1016/j.cjtee.2016.02.005	HOSPITAL SETTING
3	Hanley DF, Lane K, McBee N, et al. Thrombolytic removal of intraventricular haemorrhage in treatment of severe stroke: results of the randomised, multicentre, multiregion, placebo-controlled CLEAR III trial. Lancet. 2017;389(10069):603-611. doi:10.1016/S0140-6736(16)32410-2	HOSPITAL SETTING
4	Nascimento B, Callum J, Tien H, et al. Fibrinogen in the initial resuscitation of severe trauma (FiiRST): a randomized feasibility trial. Br J Anaesth. 2016;117(6):775-782. doi:10.1093/bja/aew343	HOSPITAL SETTING
5	McCaul, M, Kredo, T. Antifibrinolytic drugs for acute traumatic injury. SAMJ: South African Medical Journal. 2016;106(8): 777-778. https://dx.doi.org/10.7196/samj.2016.v106i8.11042	HOSPITAL SETTING
6	Bellam BL, Dhibar DP, Suri V, et al. Efficacy of tranexamic acid in haemoptysis: A randomized, controlled pilot study. Pulm Pharmacol Ther. 2016;40:80-83. doi:10.1016/j.pupt.2016.07.006	HOSPITAL SETTING
7	Arumugam A, A Rahman NA, Theophilus SC, Shariffudin A, Abdullah JM. Tranexamic Acid as Antifibrinolytic Agent in Non Traumatic Intracerebral Hemorrhages. Malays J Med Sci. 2015;22(Spec Issue):62-71.	POPULATION
8	Majeed A, Hwang HG, Eikelboom JW, et al. Effectiveness and outcome of management strategies for dabigatran- or warfarin-related major bleeding events. Thromb Res. 2016;140:81-88. doi:10.1016/j.thromres.2016.02.005	HOSPITAL SETTING
9	Gonzalez E, Moore EE, Moore HB, et al. Goal-directed Hemostatic Resuscitation of Trauma-induced Coagulopathy: A Pragmatic Randomized Clinical Trial Comparing a Viscoelastic Assay to Conventional Coagulation Assays. Ann Surg. 2016;263(6):1051-1059. doi:10.1097/SLA.0000000000001608	HOSPITAL SETTING
10	Ausset S, Glassberg E, Nadler R, et al. Tranexamic acid as part of remote damage-control resuscitation in the prehospital setting: A critical appraisal of the medical literature and available alternatives. J Trauma Acute Care Surg. 2015;78(6 Suppl 1):S70-S75. doi:10.1097/TA.0000000000000640	HOSPITAL SETTING
11	Curry N, Rourke C, Davenport R, et al. Early cryoprecipitate for major haemorrhage in trauma: a randomised controlled feasibility trial. Br J Anaesth. 2015;115(1):76-83. doi:10.1093/bja/aev134	HOSPITAL SETTING
12	Chapman MP, Moore EE, Chin TL, et al. Combat: Initial Experience with a Randomized Clinical Trial of Plasma-Based Resuscitation in the Field for Traumatic Hemorrhagic Shock. Shock. 2015;44 Suppl 1(0 1):63-70. doi:10.1097/SHK.0000000000000376	HOSPITAL SETTING

13	Galvagno SM Jr, Fox EE, Appana SN, et al. Outcomes after concomitant traumatic brain injury and hemorrhagic shock: A secondary analysis from the Pragmatic, Randomized Optimal Platelets and Plasma Ratios trial. J Trauma Acute Care Surg. 2017;83(4):668-674. doi:10.1097/TA.0000000000001584	HOSPITAL SETTING
14	Cornelius B. Air Medical Administration of Tranexamic Acid. J Trauma Nurs. 2017;24(1):30-33. doi:10.1097/JTN.0000000000000259	STUDY DESIGN
15	HALT-IT Trial Collaborators. Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): an international randomised, double-blind, placebo-controlled trial. Lancet. 2020;395(10241):1927-1936. doi:10.1016/S0140-6736(20)30848-5	HOSPITAL SETTING
16	Leal-Noval SR, Fernández Pacheco J, Casado Méndez M, Cuenca-Apolo D, Múñoz-Gómez M. Current perspective on fibrinogen concentrate in critical bleeding [published online ahead of print, 2020 Jun 1]. Expert Rev Clin Pharmacol. 2020;10.1080/17512433.2020.1776608. doi:10.1080/17512433.2020.1776608	HOSPITAL SETTING
17	Sperry JL, Guyette FX, Brown JB, et al. Prehospital Plasma during Air Medical Transport in Trauma Patients at Risk for Hemorrhagic Shock. N Engl J Med. 2018;379(4):315-326. doi:10.1056/NEJMoa1802345	WRONG INTERVENTION
18	Curry N, Foley C, Wong H, et al. The application of a haemorrhage assessment tool in evaluating control of bleeding in a pilot trauma haemorrhage trial. Transfus Med. 2019;29(6):454-459. doi:10.1111/tme.12644	HOSPITAL SETTING
19	Brenner A, Afolabi A, Ahmad SM, et al. Tranexamic acid for acute gastrointestinal bleeding (the HALT-IT trial): statistical analysis plan for an international, randomised, double-blind, placebo-controlled trial. Trials. 2019;20(1):467. Published 2019 Jul 30. doi:10.1186/s13063-019-3561-7	HOSPITAL SETTING
20	Monsef Kasmaei V, Javadi A, Naseri Alavi SA. Effects of tranexamic acid on reducing blood loss in pelvic trauma: A randomised double-blind placebo controlled study. J Clin Orthop Trauma. 2019;10(2):286-289. doi:10.1016/j.jcot.2018.04.011	HOSPITAL SETTING
21	Roberts I, Belli A, Brenner A, et al. Tranexamic acid for significant traumatic brain injury (The CRASH-3 trial): Statistical analysis plan for an international, randomised, double-blind, placebo-controlled trial. Wellcome Open Res. 2018;3:86. Published 2018 Sep 26. doi:10.12688/wellcomeopenres.14700.2	STUDY PROTOCOL
22	Khan M, Jehan F, Bulger EM, et al. Severely injured trauma patients with admission hyperfibrinolysis: Is there a role of tranexamic acid? Findings from the PROPPR trial. J Trauma Acute Care Surg. 2018;85(5):851-857. doi:10.1097/TA.0000000000002022	HOSPITAL SETTING
23	Sprigg N, Flaherty K, Appleton JP, et al. Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial. Lancet. 2018;391(10135):2107-2115. doi:10.1016/S0140-6736(18)31033-X	OUT OF SCOPE
24	Fakharian E, Abedzadeh-Kalahroudi M, Atoof F. Effect of Tranexamic Acid on Prevention of Hemorrhagic Mass Growth in Patients with Traumatic Brain Injury. World Neurosurg. 2018;109:e748-e753.	HOSPITAL SETTING

	doi:10.1016/j.wneu.2017.10.075	
25	McQuilten ZK, Crighton G, Brunskill S, et al. Optimal Dose, Timing and Ratio of Blood Products in Massive Transfusion: Results from a Systematic Review. Transfus Med Rev. 2018;32(1):6-15. doi:10.1016/j.tmrv.2017.06.003	WRONG INTERVENTION
26	Alhelaly, M. M., Soliman, A. M., Khaled, A., Ellotf, H., Attia, M. M., & Elmaraezy, A. (2019). Efficacy of tranexamic acid in traumatic brain injury: Updated systematic review and meta-analysis. Trauma, 21(3), 167–175. https://doi.org/10.1177/1460408619842736	HOSPITAL SETTING
27	Curry N, Foley C, Wong H, et al. Early fibrinogen concentrate therapy for major haemorrhage in trauma (E-FIT 1): results from a UK multi-centre, randomised, double blind, placebo-controlled pilot trial. Crit Care. 2018;22(1):164. Published 2018 Jun 18. doi:10.1186/s13054-018-2086-x	HOSPITAL SETTING
28	Tavakoli N, Mokhtare M, Agah S, et al. Comparison of the efficacy of intravenous tranexamic acid with and without topical administration versus placebo in urgent endoscopy rate for acute gastrointestinal bleeding: A double-blind randomized controlled trial. United European Gastroenterol J. 2018;6(1):46-54. doi:10.1177/2050640617714940	OUT OF SCOPE
29	Flaherty K, Bath PM, Dineen R, et al. Statistical analysis plan for the 'Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage' (TICH-2) trial. Trials. 2017;18(1):607. Published 2017 Dec 20. doi:10.1186/s13063-017-2341-5	OUT OF SCOPE
30	Sprigg N, Flaherty K, Appleton JP, et al. Tranexamic acid to improve functional status in adults with spontaneous intracerebral haemorrhage: the TICH-2 RCT. Health Technol Assess. 2019;23(35):1-48. doi:10.3310/hta23350	OUT OF SCOPE
31	Cornelius B, Moody K, Hopper K, et al. A Retrospective Study of Transfusion Requirements in Trauma Patients Receiving Tranexamic Acid. J Trauma Nurs. 2019;26(3):128-133. doi:10.1097/JTN.0000000000000437	STUDY DESIGN
32	Brown JB, Neal MD, Guyette FX, et al. Design of the Study of Tranexamic Acid during Air Medical Prehospital Transport (STAAMP) Trial: Addressing the Knowledge Gaps. Prehosp Emerg Care. 2015;19(1):79-86.	STUDY PROTOCOL
33	A nested mechanistic sub-study into the effect of tranexamic acid versus placebo on intracranial haemorrhage and cerebral ischaemia in isolated traumatic brain injury: study protocol for a randomised controlled trial (CRASH-3 Trial Intracranial Bleeding Mechanistic Sub-Study [CRASH-3 IBMS]).	STUDY PROTOCOL
34	Akbari E, Safari S, Hatamabadi H. The effect of fibrinogen concentrate and fresh frozen plasma on the outcome of patients with acute traumatic coagulopathy: A quasi-experimental study. Am J Emerg Med. 2018;36(11):1947-1950. doi:10.1016/j.ajem.2018.02.018	HOSPITAL SETTING

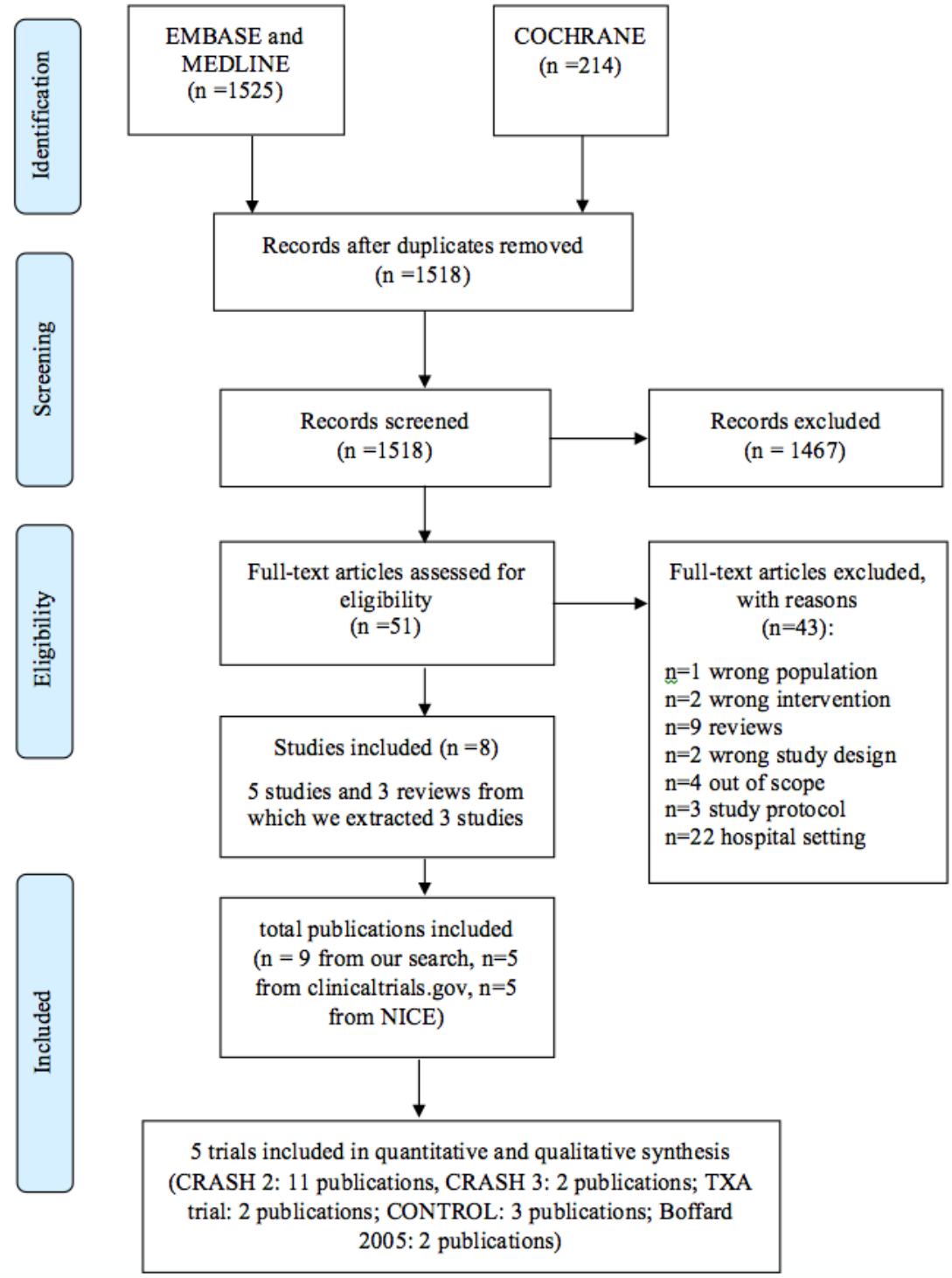
Appendice C1 - Sintesi delle evidenze

CQ8. Gestione dell'emorragia nel setting pre-ospedaliero: agenti emostatici

Indice

SELEZIONE DEGLI STUDI

Figure 1. Flow Chart of study selection



È stata effettuata una revisione sistematica con ricerca della letteratura sulle banche dati Embase, Medline e Cochrane CENTRAL aggiornata al 29 giugno 2020. Sono stati individuati 1518 records da cui sono state selezionate 8 referenze che soddisfano i criteri per rispondere al quesito clinico proposto, rispettivamente 5 studi primari e 3 revisioni sistematiche da cui sono stati ulteriormente estratti 3 studi. Inoltre, sono state interrogate clinicatrials.gov e le Linee guida NICE, aggiungendo all'inclusione altre 11 nuove pubblicazioni, 6 e 5 rispettivamente. In totale, sono state individuate 19 pubblicazioni afferenti 5 studi randomizzati e controllati: CRASH-2, CRASH-3, TXA trial, CONTROL trial e Boffard 2005. In data 9 settembre 2020 è stata rilanciata per aggiornamento la search strategy, da cui è stata aggiunta una pubblicazione inerente uno studio incluso (TXA trial).

Gli studi inclusi sono controllati e randomizzati in cui il gruppo di controllo è rappresentato dal trattamento con placebo. In particolare:

- **CRASH-2:** è uno studio randomizzato e controllato, multicentrico, a doppio cieco, in cui sono stati inclusi pazienti con evidente emorragia (SBP < 90 mm Hg e/o Heart Rate > 110 battiti al minuto), trattati entro 8 ore dalla lesione, reclutati da 10 ospedali dell'India e della Colombia. Ai pazienti è stato somministrato casualmente o 1 g di **TXA** infuso in 10 minuti seguito da un infusione endovenosa di 1 g nell'arco di 8 ore, o placebo (cloruro di sodio 0,9%) per dosi corrispondenti; questo studio comprende un sottogruppo di popolazione con trauma cerebrale -traumatic brain injury (TBI).
- **CRASH-3**: è uno studio randomizzato e controllato, multicentrico, in cui sono stati reclutati pazienti adulti che hanno subito un trauma cerebrale TBI (GCS ≤ 12), trattati entro 3 ore dalla lesione, reclutati da 175 ospedali in 29 paesi (internazionale). Ai pazienti è stato somministrato casualmente o 1 g di **TXA** infuso in 10 minuti seguito da un infusione endovenosa di 1 g nell'arco di 8 ore o placebo (cloruro di sodio 0,9%) per dosi corrispondenti;
- **TXA:** è uno studio multicentrico randomizzato e controllato (nord America, US and Canada), a doppio cieco, in cui sono stati inclusi pazienti adulti (età ≥ 15 anni) che hanno subito un trauma cerebrale TBI contusivo o penetrante (pre-hospital GCS ≤ 12 e SBP ≥ 90), a cui sono stati assegnati casualmente 3 diversi trattamenti i) trattamento e mantenimento (1 g **TXA** nella fase pre-ospedaliera seguito da 1 g di mantenimento in infusione dall'arrivo in ospedale fino 8 ore) ii) solo trattamento (2 g di TXA nella fase pre-ospedaliera seguito da placebo di mantenimento in infusione dall'arrivo in ospedale fino 8 ore) iii) placebo;
- **Boffard 2005:** sono stati condotti simultaneamente due studi clinici controllati e randomizzati a doppio cieco (internazionale, 32 ospedali) per valutare l'efficacia e la sicurezza del fattore ricombinante VIIa (**rFVIIa**). Uno studio ha considerato i pazienti emodinamicamente instabili con severa emorragia da trauma contusivo e l'altro pazienti con trauma penetrante; in entrambi gli studi, i pazienti sono stati randomizzati al trattamento con 3 iniezioni endovenose di rFVIIa (dopo la trasfusione di 8 unità di RBC 200 μg/kg, poi 100 μg/kg rispettivamente dopo 1 e 3 ore dalla prima dose) o al placebo; questo studio comprende un sottogruppo di popolazione con trauma cerebrale TBI.
- **CONTROL:** è uno studio randomizzato e controllato, multicentro (internazionale, 26 paesi, 150 ospedali), in cui sono stati reclutati pazienti in shock emorragico che hanno

subito un trauma contusivo o penetrante a cui è stato somministrato casualmente **rFVIIa** (inizialmente 200 μg/kg, poi 100 μg/kg rispettivamente dopo 1 e 3 ore dalla prima dose) o placebo.

Gli studi individuati permettono di rispondere alle seguenti comparazioni:

i) ***Somministrazione pre-ospedaliera di TXA verso placebo:***

ii) ***Somministrazione pre-ospedaliera di rFVIIa verso placebo*** *(5 pubblicazioni afferenti a 2 studi randomizzati e controllati: Boffard 2005 (2), CONTROL (3))*

iii) ***Somministrazione pre-ospedaliera di TXA verso rFVIIa*** *(evidenza indiretta tramite network meta-analisi)*

Table 1. Characteristics of patients.

			Gender		Age	ISS	Systolic blood pressure					
RCT	**INTERVENTION**	**N**	**M**	**F**	**MEDIAN (IQR)**	**MEDIAN (IQR)**	**MEAN (SD)**	**< 90**	**90-119**	**≥ 120**		**unknown**
TXA	TXA: 1 gram pre-hospital + 1 gram within 8 hours	312	227	85	39 (26 to 57)	17 (8 to 27)	-	-	-	-	-	-
	TXA: 2 grams pre-hospital + placebo	345	255	90	40 (26 to 56)	17 (8 to 27)	-	-	-	-	-	-
	PLACEBO	309*	233	76	36 (25 to 55)	17 (9 to 27)	-	-	-	-	-	-
CRASH-2					**MEAN (SD)**	**MEAN (SD)**						
	TXA	10093	8439 (83,6%)	1654 (16,4%)	34,6 (14,1)	-	-	1566 (15,5%)	1615 (16%)	6901 (68,4%)		11 (0,11%)
	Subgroup: patients who also had TBI	133	111 (84%)	22 (16%)	36 (14)	-	116,4 (31,2)	9 (7%)	63 (47%)	61 (46%)		-
	PLACEBO	10114	8496 (84%)	1617 (16%)	34,5 (14,4)	-	-	1608 (15,9%)	1697 (16,8%)	6791 (67,1%)		18 (0,18%)
	Subgroup: patients who also had TBI	137	117 (85%)	20 (15%)	37 (14)	-	113,5 (29,4)	10 (7%)	69 (50%)	58 (43%)		-
CRASH-3										**120-139**	**≥ 140**	**unknown**
	TXA	4649	3742 (80%)	906 (19%)	41,7 (19)	-	-	89 (2%)	1508 (32%)	1461 (31%)	1576 (34%)	15 (<1%)
	PLACEBO	4553	3660 (80%)	893 (20%)	41,9 (19)	-	-	85 (2%)	1490 (33%)	1504 (33%)	1466 (32%)	8 (<1%)
CONTROL	**Population: Blunt trauma**											
	rFVIIa	221	162 (73,3%)	59 (26,7%)	39,2 (14,3)	32,8±11,3	100,9 (27,17)	-	-	-	-	-
	PLACEBO	247	182 (73,7%)	65 (26,3%)	39,9 (14,2)	32,8±11,5	96,6 (26,29)	-	-	-	-	-
	Population: Penetrating trauma											
	rFVIIa	46	43 (93,5)	3 (6,5%)	33,8 (11,9)	20,5±10,1	105,6 (26,95)	-	-	-	-	-
	PLACEBO	40	37 (92,5)	3 (7,5%)	29,4 (10,3)	22±8,9	107,1 (24,13)	-	-	-	-	-
Boffard 2005	**Population: Blunt trauma**											
	rFVIIa	69	48 (70%)	21 (30%)	33 (13)	33±13	102 (24)	-	-	-	-	-
	Subgroup: patients with a TBI component	17	10 (59%)	7 (41%)	33,5 (13,7)	38,7±13,7	-	-	-	-	-	-
	PLACEBO	74	52 (70%)	22 (30%)	35 (13)	32±12	111 (27)	-	-	-	-	-
	Subgroup: patients with a TBI component	13	8 (62%)	5 (38%)	32,6 (16,8)	36,8±12,8	-	-	-	-	-	-
	Population: Penetrating trauma											
	rFVIIa	70	66 (94%)	4 (6%)	29 (10)	26±15	111 (24)	-	-	-	-	-

	PLACEBO	64	60 (94%)	4 (6%)	32 (10)	26±11	114 (25)	-	-	-	-	-

		Heart Rate						Glasgow Coma Scale				
RCT	**INTERVENTION**	**MEAN (SD)**	**< 77**	**77-91**	**92-107**	**> 107**	**unknown**	**MEAN (SD)**	**Severe (3-8)**	**Moderate (9-12)**	**Mild (13-15)**	**unknown**
TXA	TXA: 1 gram pre-hospital + 1 gram within 8 hours	-	-	-	-	-	-	-	169	129	14	-
	TXA: 2 grams pre-hospital + placebo	-	-	-	-	-	-	-	177	159	9	-
	PLACEBO	-	-	-	-	-	-	-	186	115	8	-
CRASH-2	TXA	-	875 (8,7%)	1727 (17,1%)	2556 (25,3%)	4872 (48,3%)	63 (0,62%)	-	1799 (17,8%)	1353 (13,4%)	6934 (68,7%)	7 (0,07%)
	Subgroup: patients who also had TBI	100,7 (25,7)	-	-	-	-	-	10,5 (3,6)	45 (34%)	25 (19%)	63 (47%)	-
	PLACEBO	-	871 (8,6%)	1770 (17,5%)	2546 (25,2%)	4853 (48%)	74 (0,73%)	-	1839 (18,2%)	1351 (13,4%)	6908 (68,3%)	16 (0,16%)
	Subgroup: patients who also had TBI	101,6 (23,5)	-	-	-	-	-	10,5 (3,6)	45 (33%)	34 (25%)	58 (42%)	-
CRASH-3	TXA	-	-	-	-	-	-	-	1757 (40%)	1557 (33%)	1307 (27%)	28 (1%)
	PLACEBO	-	-	-	-	-	-	-	1732 (38%)	1524 (33%)	1262 (28%)	35 (1%)
CONTROL	**Population: Blunt trauma**											
	rFVIIa	-	-	-	-	-	-	13,0 (3,0)	-	-	-	-
	PLACEBO	-	-	-	-	-	-	13,2 (2,9)	-	-	-	-
	Population: penetrating trauma											
	rFVIIa	-	-	-	-	-	-	13,6 (2,8)	-	-	-	-
	PLACEBO	-	-	-	-	-	-	14,5 (1,0)	-	-	-	-
Boffard 2005	**Population: Blunt trauma**											
	rFVIIa	-	-	-	-	-	-	-	11 (16%)	11 (16%)	47 (68%)	-
	Subgroup: patients with a TBI component	-	-	-	-	-	-	-	-	-	-	-
	PLACEBO	-	-	-	-	-	-	-	8 (11%)	18 (24%)	48 (65%)	-
	Subgroup: patients with a TBI component	-	-	-	-	-	-	-	-	-	-	-
	Population: penetrating trauma											
	rFVIIa	-	-	-	-	-	-	-	4 (6%)	6 (9%)	60 (86%)	-
	PLACEBO	-	-	-	-	-	-	-	5 (8%)	8 (13%)	51 (80%)	-

		Type of injury		Respiratory rate				Capillary refill time				
RCT	**INTERVENTION**	**BLUNT**	**PENETRATING**	**< 10**	**10-29**	**> 29**	**unknown**	**MEAN (SD)**	**≤ 2**	**3-4**	**> 4**	**unknown**
TXA	TXA: 1 gram pre-hospital + 1 gram within 8 hours	16	12	-	-	-	-	-	-	-	-	-
	TXA: 2 grams pre-hospital + placebo	340	5	-	-	-	-	-	-	-	-	-
	PLACEBO	293	300	-	-	-	-	-	-	-	-	-
CRASH-2	TXA	6812 (67,5%)*	3281 (32,5%)	160 (1,6%)	8355 (82,8%)	1491 (14,8%)	87 (0,86%)	-	3432 (34%)	4665 (46,2%)	1699 (16,8%)	297 (2,9%)
	Subgroup: patients who also had TBI	132 (99,2%)	1 (0,8%)	-	-	-	-	3,4 (1,0)	-	-	-	-
	PLACEBO	6843 (67,7%)*	3271 (32,3%)	149 (1,5%)	8436 (83,4%)	1492 (14,1%)	100 (0,99%)	-	3406 (33,7%)	4722 (46,7%)	1672 (16,5%)	314(3,1%)
	Subgroup: patients who also had TBI	136 (99,3%)	1 (0,7%)	-	-	-	-	3,5 (1,1)	-	-	-	-
CRASH-3	TXA	-	-	-	-	-	-	-	-	-	-	-
	PLACEBO	-	-	-	-	-	-	-	-	-	-	-
CONTROL	**Population: Blunt trauma**											
	rFVIIa	221	-	-	-	-	-	-	-	-	-	-
	PLACEBO	247	-	-	-	-	-	-	-	-	-	-
	Population: Penetrating trauma											
	rFVIIa	-	46	-	-	-	-	-	-	-	-	-
	PLACEBO	-	40	-	-	-	-	-	-	-	-	-
Boffard 2005	**Population: Blunt trauma**											
	rFVIIa	69	-	-	-	-	-	-	-	-	-	-
	Subgroup: patients with a TBI component	17	-	-	-	-	-	-	-	-	-	-
	PLACEBO	74	-	-	-	-	-	-	-	-	-	-
	Subgroup: patients with a TBI component	13	-	-	-	-	-	-	-	-	-	-
	Population: Penetrating trauma											
	rFVIIa	-	70	-	-	-	-	-	-	-	-	-
	PLACEBO	-	64	-	-	-	-	-	-	-	-	-

		Time from injury to first dose (h)				
RCT	**INTERVENTION**	**MEAN (SD)**	**≤1**	**1-3**	**> 3**	**unknown**
TXA	TXA: 1 gram pre-hospital + 1 gram within 8 hours	-	-	-	-	-
	TXA: 2 grams pre-hospital + placebo	-	-	-	-	-
	PLACEBO	-	-	-	-	-
CRASH-2	TXA	2,8 (2,2)	3756 (37,2%)	3045 (30,2%)	3287 (32,6%)	5 (0,05%)
	Subgroup: patients who also had TBI	4,4 (1,8)	-	-	-	-
	PLACEBO	2,9 (2,6)	3722 (36,8%)	3006 (29,7%)	3380 (33,4%)	6 (0,06%)
	Subgroup: patients who also had TBI	4,2 (1,7)	-	-	-	-
CRASH-3	TXA		**≤1**	**1-2**	**2-3**	
		1,9 (0,7)	877 (19%)	2003 (43%)	1769 (38%)	-
	PLACEBO	1,9 (0,7)	869 (19%)	1889 (41%)	1795 (39%)	-
CONTROL	**Population: Blunt trauma**					
	rFVIIa	5,1 (2,6)	-	-	-	-
	PLACEBO	5,4 (3,1)	-	-	-	-
	Population: Penetrating trauma					
	rFVIIa	4,2 (2,5)	-	-	-	-
	PLACEBO	5,2 (3,1)	-	-	-	-
Boffard 2005	**Population: Blunt trauma**					
	rFVIIa	-	-	-	-	-
	Subgroup: patients with a TBI component	-	-	-	-	-
	PLACEBO	-	-	-	-	-
	Subgroup: patients with a TBI component	-	-	-	-	-
	Population: Penetrating trauma					
	rFVIIa	-	-	-	-	-
	PLACEBO	-	-	-	-	-

*Includes patients with both blunt and penetrating and only blunt injuries

COMPARAZIONE MULTIPLA DI INTERVENTI (Network Meta-analisi)

La Network meta-analisi (NMA), conosciuta come meta-analisi "a rete", è nata per soddisfare le richieste del processo di decision-making quando esistono tre o più trattamenti destinati alla medesima indicazione clinica. Una meta-analisi tradizionale si limita al confronto di due trattamenti perciò i risultati potrebbero non essere direttamente applicabili alla pratica clinica. La NMA è la comparazione simultanea di tre o più trattamenti in un unico modello statistico: l'analisi permette di comparare in modo "diretto" due trattamenti che sono stati oggetto di uno specifico trial comparativo (es. A vs C e B vs C) e in modo "indiretto" i trattamenti per cui sarebbe interessante valutare il confronto ma di cui non esiste uno specifico trial (es. A vs B). Attraverso la NMA è anche possibile calcolare la probabilità che un trattamento sia più specifico per un outcome oltre a classificare i trattamenti dal migliore al peggiore per ogni specifico outcome.

I risultati verranno presentati con i seguenti elementi:

- ***Network graph***: figura del network di interventi. Il grafico rappresenta la comparazione multipla tra gli interventi. Lo spessore della linea nera è direttamente proporzionale al numero di studi che valutano la comparazione in esame, mentre la larghezza del nodo blu è direttamente proporzionale al numero di pazienti randomizzati al trattamento in esame.

- ***Interval plot***: il grafico interval plot mostra gli effetti (riduzione in rischio relativo) degli interventi in esame (acido tranexamico e fattore VIIa ricombinante) rispetto a un reference standard (placebo), tenendo conto delle evidenze dirette e indirette che concorrono a modificare gli effetti.

- ***Netleague table***: la netleague table mostra gli effetti delle comparazioni tra tutti gli interventi. In questa tabella è possibile visualizzare gli effetti degli interventi per cui non esistono evidenze dirette (es. acido tranexamico verso fattore VIIa ricombinante). La tabella si legge nel modo seguente: l'intervento in colonna è comparato con l'intervento in riga.

- ***SUCRA probabilities***: la network meta-analisi permette di identificare la probabilità di quale intervento sia il migliore rispetto al network di interventi nell'outcome specifico di interesse.

OUTCOME CRITICI

MORTALITÀ

OUTCOME: Overall Mortality
Population: All trauma population
Table 2. Outcome data for overall mortality – all trauma population. Studies: 5 Trials.

studyid	author	trt	neventi	nTot
1	CRASH-2	TXA	1463	10060
1	CRASH-2	placebo	1613	10067
2	TXA study	TXA	93	657
2	TXA study	placebo	50	309
3	Boffard 2005	rFVIIa	34	139
3	Boffard 2005	placebo	40	138
4	CONTROL	rFVIIa	32	270
4	CONTROL	placebo	31	290
5	CRASH-3	TXA	1093	6406
5	CRASH-3	placebo	1124	6331

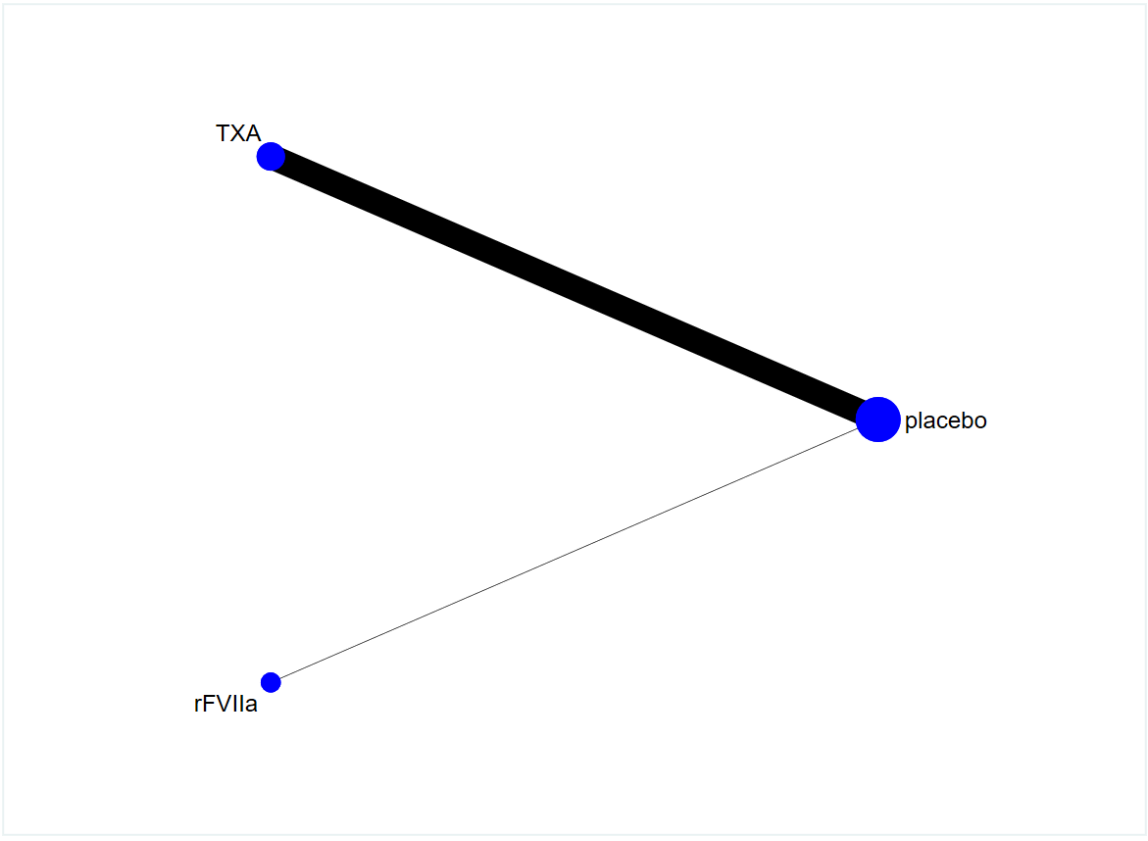


Figure 2. Network graph – overall mortality at 4 week. All trauma population.

Table 3. Interval plot – overall mortality at 4 weeks. All trauma population.
Reference treatment: placebo.

Comparison	_Effect_Size	_Standard_Error	_LCI	_UCI	_LPrI	_UPrI
TXA	-.0741357	.0264547	-.125986	-.0222855	-.125986	-.0222855
rFVIIa	-.0564072	.1531772	-.356629	.2438146	-.356629	.2438146

* Results are in log risk ratio.

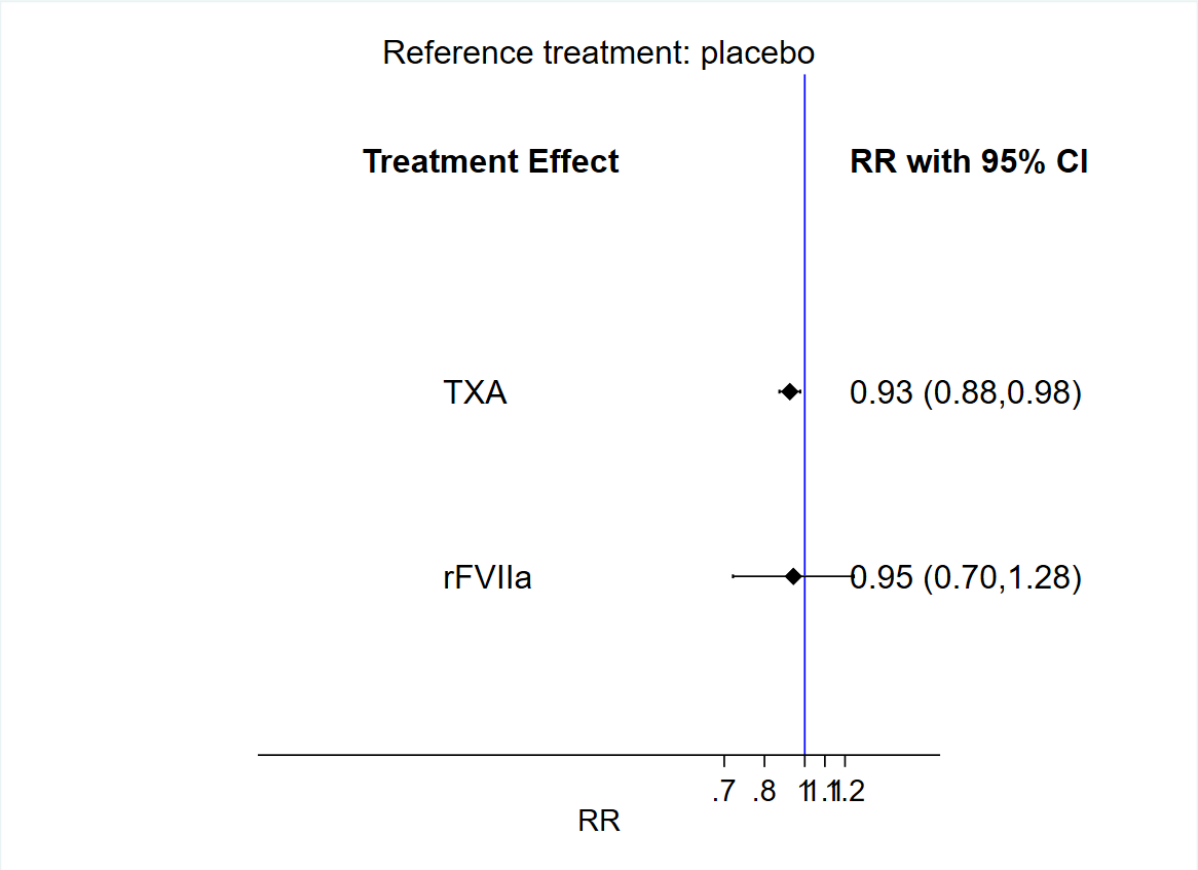


Figure 3. Interval plot network meta-analysis for overall mortality at 4 weeks. All trauma population.
* The treatment effect is displayed as risk ratio.

Table 4. Network rank (probability to be the best)

Treatment	**SUCRA**	**PrBest**
TXA	77.2	54.6
rFVIIa	54.8	45.3
placebo	18.0	0.1

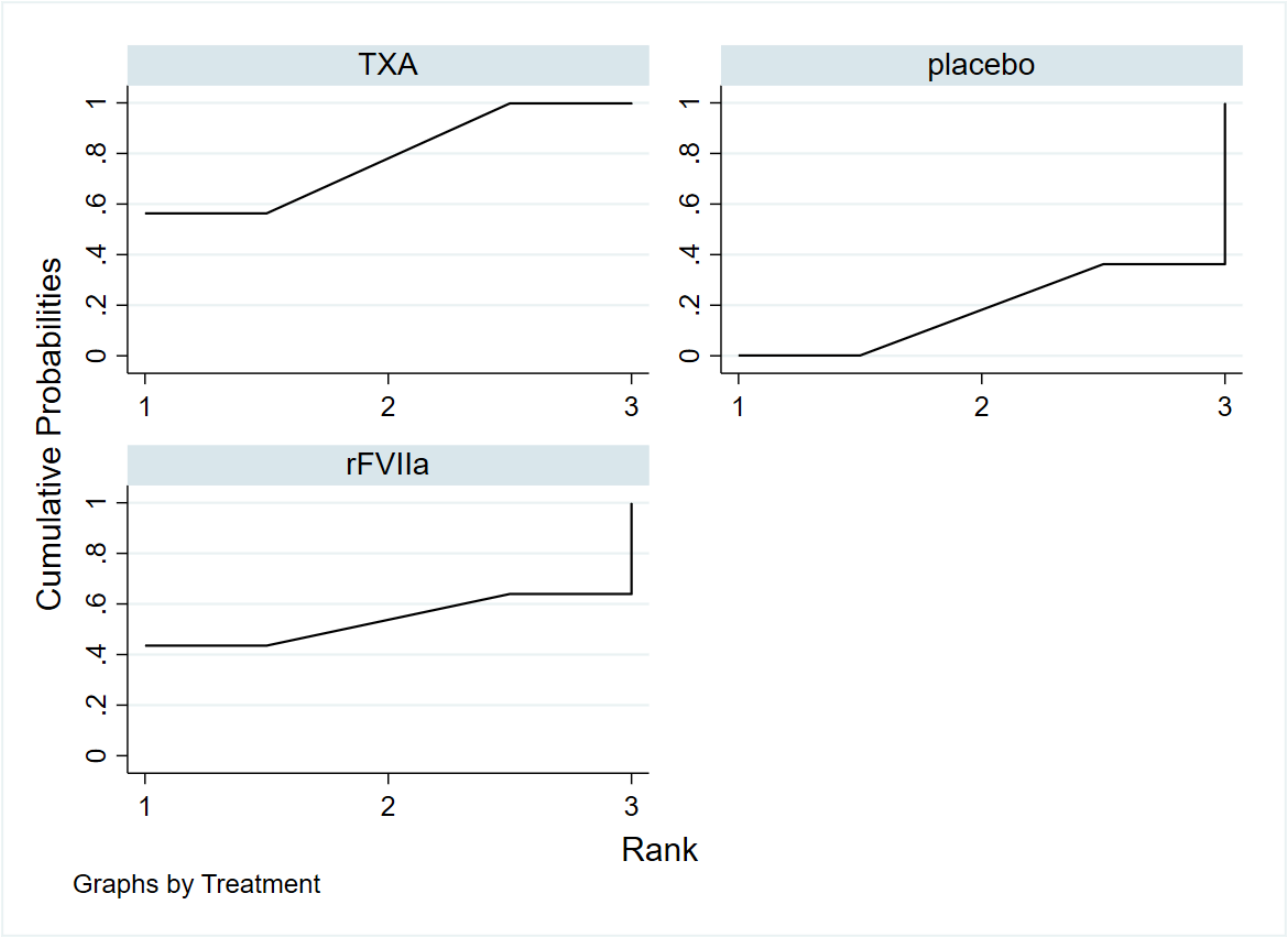


Figure 4. Cumulative Probabilities to be the best. SUCRA. Outcome: overall mortality. Population: all trauma.

Table 5. Netleague table for overall mortality, all trauma population.

placebo	0.95 (0.70,1.28)	0.93 (0.88,0.98)
	rFVIIa	0.98 (0.72,1.33)
		TXA

* The treatment effect is displayed as risk ratio.

OUTCOME CRITICI

MORTALITÀ- SUBGROUP ANALYSIS

1. **Population**: Blunt population

Table 6. Outcome data for overall mortality – blunt trauma population. Studies: 3 Trials.

studyid	author	trt	neventi	nTot
1	CRASH-2	TXA	1134	6788
1	CRASH-2	placebo	1233	6817
2	Boffard 2005	rFVIIa	17	69
2	Boffard 2005	placebo	22	74
3	CONTROL	rFVIIa	24	218
3	CONTROL	placebo	26	242

Table 7. Interval plot – overall mortality at 4 weeks. Blunt trauma population.
Reference treatment: placebo. * Results are in log risk ratio.

_Comparison	_Effect_Size	_Standard_Error	_LCI	_UCI	_LPrI	_UPrI
TXA	-.0794359	.0374012	-.152741	-.0061308	-.152741	-.0061308
rFVIIa	-.0782403	.192042	-.4546357	.298155	-.4546357	.298155

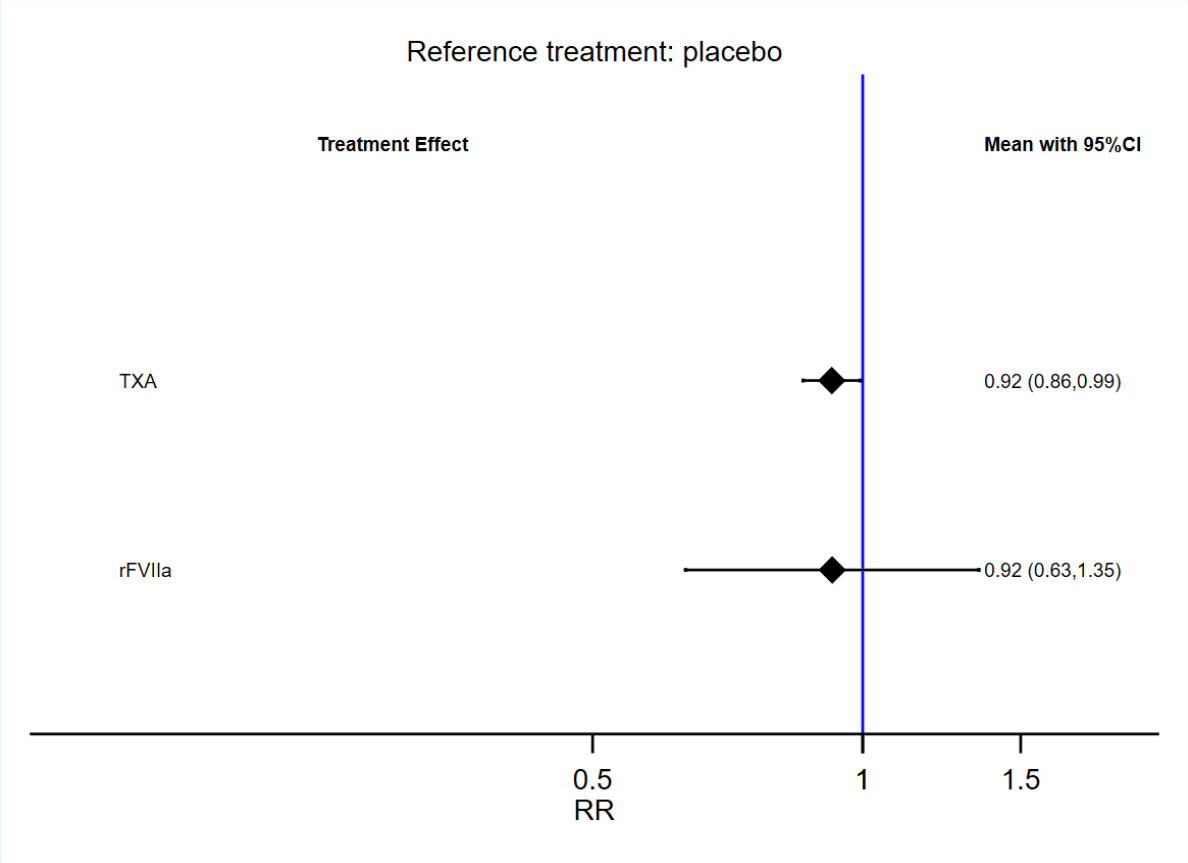


Figure 5. Interval plot network meta-analysis for overall mortality at 4 weeks. Blunt trauma population.
* The treatment effect is displayed as risk ratio.

Table 8. Network rank (probability to be the best). Overall mortality – blunt trauma population.

Treatment	SUCRA	PrBest
TXA	74.4	49.8
rFVIIa	58.0	49.6
Placebo	17.6	0.6

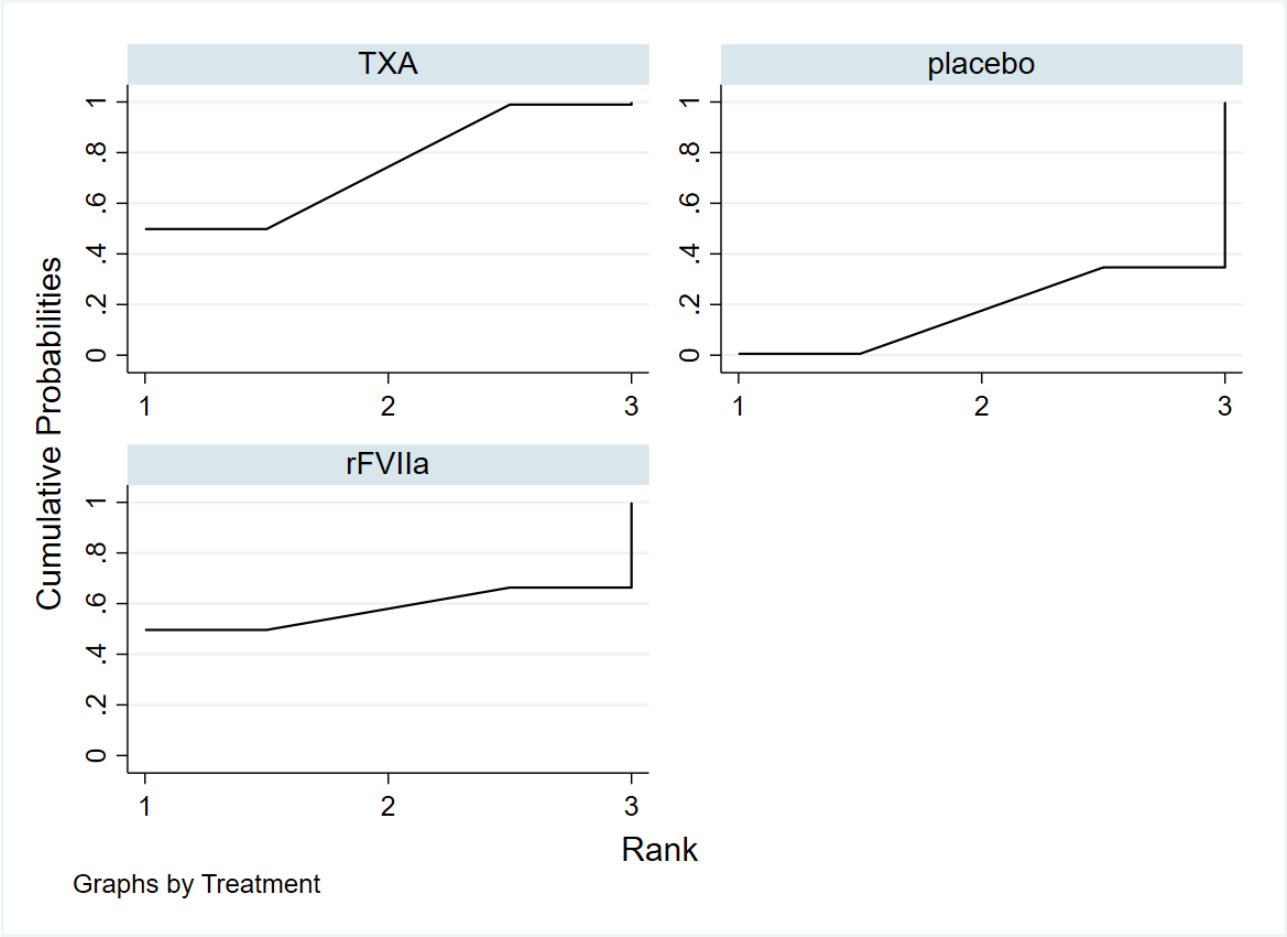


Figure 6. Cumulative Probabilities to be the best. SUCRA. Outcome: overall mortality. Population: blunt trauma.

Table 9. Netleague table for overall mortality, blunt trauma population.

placebo	0.92 (0.86,0.99)	0.92 (0.63,1.35)
1.08 (1.01,1.17)	**TXA**	1.00 (0.68,1.47)
1.08 (0.74,1.58)	1.00 (0.68,1.47)	**rFVIIa**

* The treatment effect is displayed as risk ratio.

2. Population: Penetrating population

Table 10. Outcome data for overall mortality – penetrating trauma population. Studies: 3 Trials.

studyid	author	trt	neventi	nTot
1	CRASH-2	TXA	329	3272
1	CRASH-2	placebo	380	3250
2	Boffard 2005	rFVIIa	17	70
2	Boffard 2005	placebo	18	64
3	CONTROL	rFVIIa	8	44
3	CONTROL	placebo	5	38

Table 11. Interval plot – overall mortality at 4 weeks. Penetrating trauma population. Reference treatment: placebo. * Results are in log risk ratio.

_Comparison	_Effect_Size	_Standard_Error	_LCI	_UCI	_LPrI	_UPrI
TXA	-.1508599	.071118	-.2902487	-.0114711	-.2902487	-.0114711
rFVIIa	-.0365825	.254308	-.5350171	.461852	-.5350171	.461852

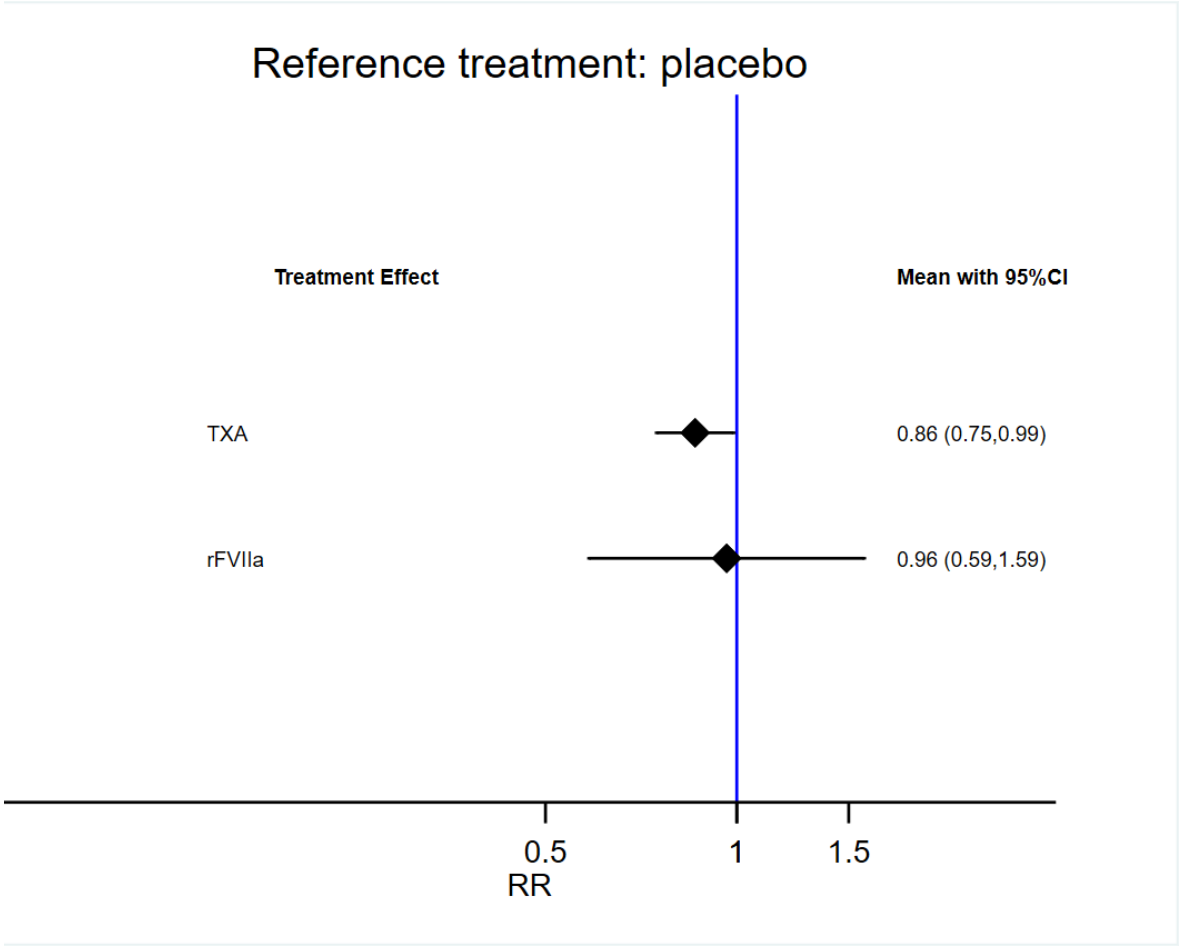


Figure 7. Interval plot network meta-analysis for overall mortality at 4 weeks. Penetrating trauma population. * The treatment effect is displayed as risk ratio.

Table 12. Network rank (probability to be the best). Overall mortality – penetrating trauma population.

Treatment	SUCRA	PrBest
TXA	82.1	65.2
rFVIIa	45.4	34
Placebo	22.5	0.7

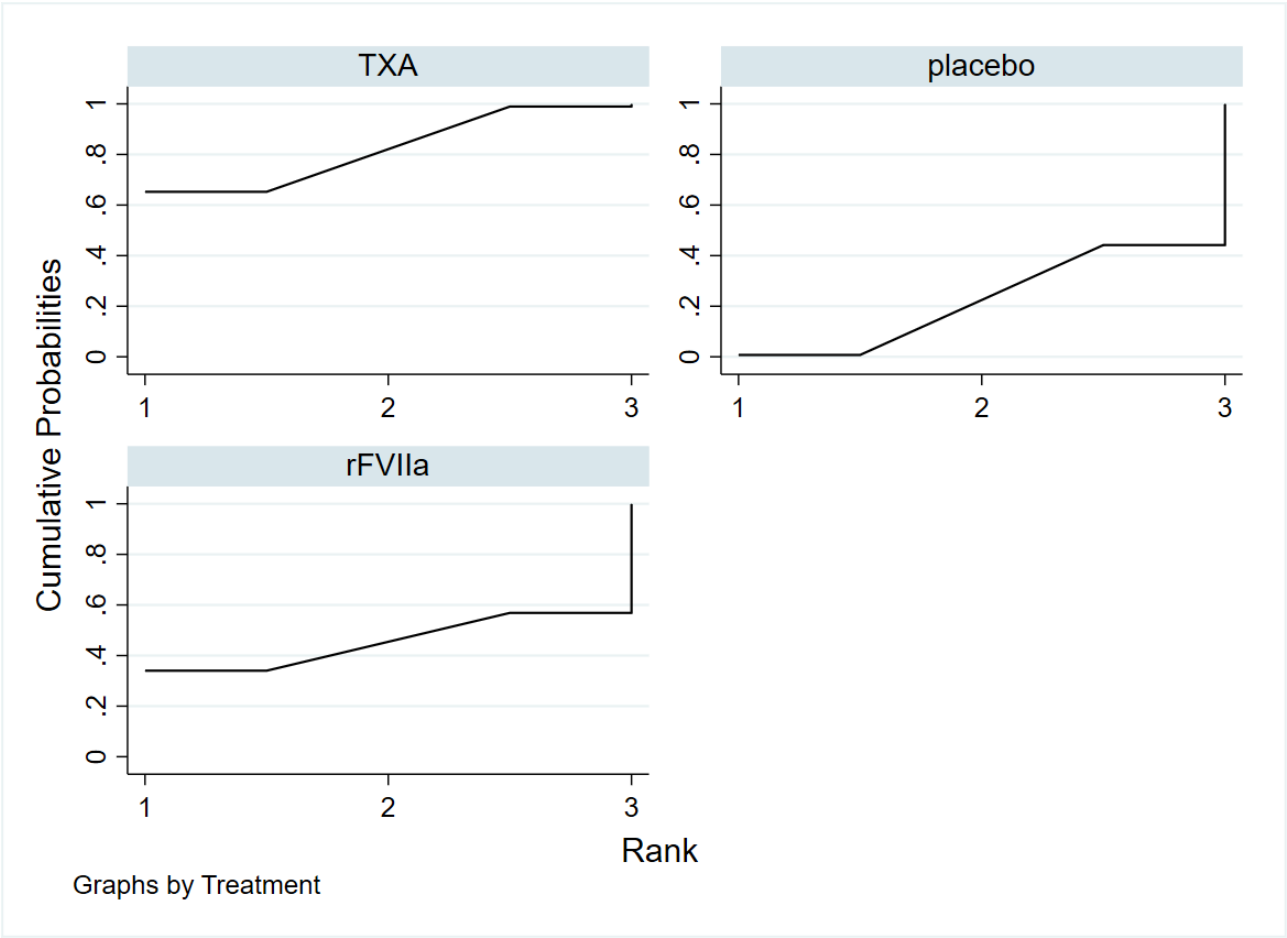


Figure 8. Cumulative Probabilities to be the best. SUCRA. Outcome: overall mortality. Population: penetrating trauma.

Table 13. Netleague table for overall mortality, penetrating trauma population.

placebo	0.86 (0.75,0.99)	0.96 (0.59,1.59)
1.16 (1.01,1.34)	**TXA**	1.12 (0.67,1.88)
1.04 (0.63,1.71)	0.89 (0.53,1.50)	**rFVIIa**

* The treatment effect is displayed as risk ratio.

COMPARAZIONE DI INTERVENTI A COPPIE (Pair-wise meta-analisi)

Trial	Population
CRASH-2	Blunt or penetrating trauma patients with significant haemorrhage and potentially suffering a TBI
CRASH-3	Trauma patients with TBI
TXA	Trauma patients with TBI
CONTROL	Blunt or penetrating trauma patients with haemorrhagic shock
Boffard 2005	Blunt or penetrating hemodynamically unstable trauma patients with severe haemorrhage and potentially suffering a TBI

Table 14. Clinical trial study population.

OUTCOME CRITICI

1. MORTALITÀ

1.1 OVERALL MORTALITY

Sono stati inclusi tutti i 5 studi randomizzati controllati (RCT) per rispondere al quesito di efficacia dell'intervento sulla scena rispetto al non intervento (placebo), sia considerando l'agente emostatico TXA (CRASH-2, CRASH-3; TXA), che il rFVIIa (Boffard 2005, CONTROL). Per entrambi gli agenti non è mai stata riportata la mortalità a 12 mesi.

Comparazione 1. Acido Tranexamico vs placebo

Si riportano, in Tabella 2, i dati relativi al tasso di mortalità rilevati alla somministrazione pre-ospedaliera dell'agente emostatico TXA o di placebo.

- Non si mostra una riduzione nella mortalità a 24 ore (CRASH-2);
- Si mostra una riduzione nella mortalità a 28 giorni (CRASH-2, CRASH-3 e TXA), anche stratificando la popolazione in soggetti con trauma contusivo o penetrante (CRASH-2).

Table 15. Outcome data for the comparisons of mortality: TXA versus placebo.

Overall Mortality						
RCT studies: pre-hospital use of TXA versus placebo						
	TXA		**Placebo**		**time point**	**Measure of association**
	n	**tot**	**n**	**tot**		
CRASH-2	na	10060	na	10067	24 hours	HR 0.91 (0.79-1.05)
CRASH-2	1463	10060	1613	10067	4 weeks	
- blunt trauma	1134	6788	1233	6817	4 weeks	
- penetrating trauma	329	3272	380	3250	4 weeks	
CRASH-3	1093	6406	1125	6331	28 days	
TXA	93	657	50	309	28 days	

Overall mortality (24 hours):

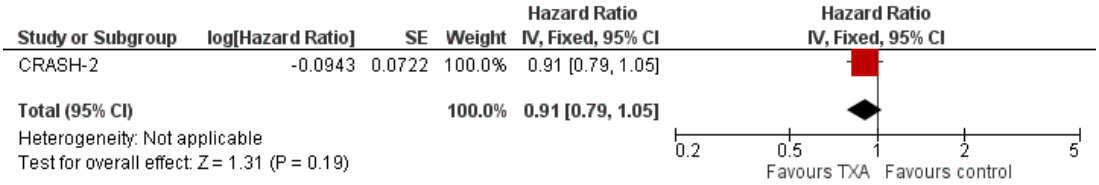


Figure 9. Hazard ratio for overall mortality (24 hours) of TXA versus placebo.

Overall mortality (4 weeks):

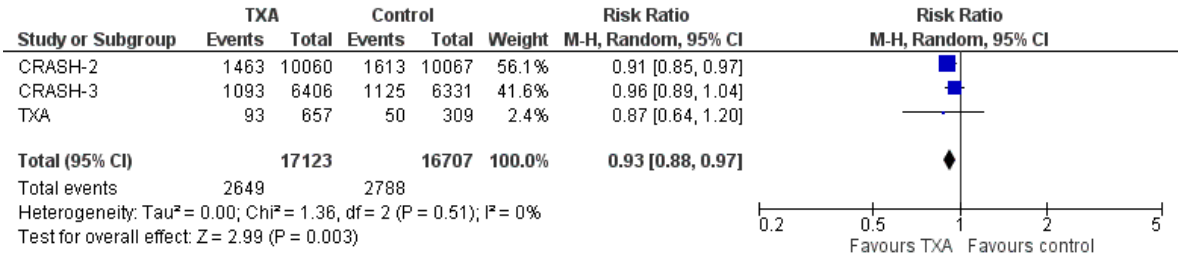


Figure 10. Risk ratio for overall mortality (4 weeks) of TXA versus placebo.

Overall mortality (4 weeks) among blunt or penetrating trauma patients:

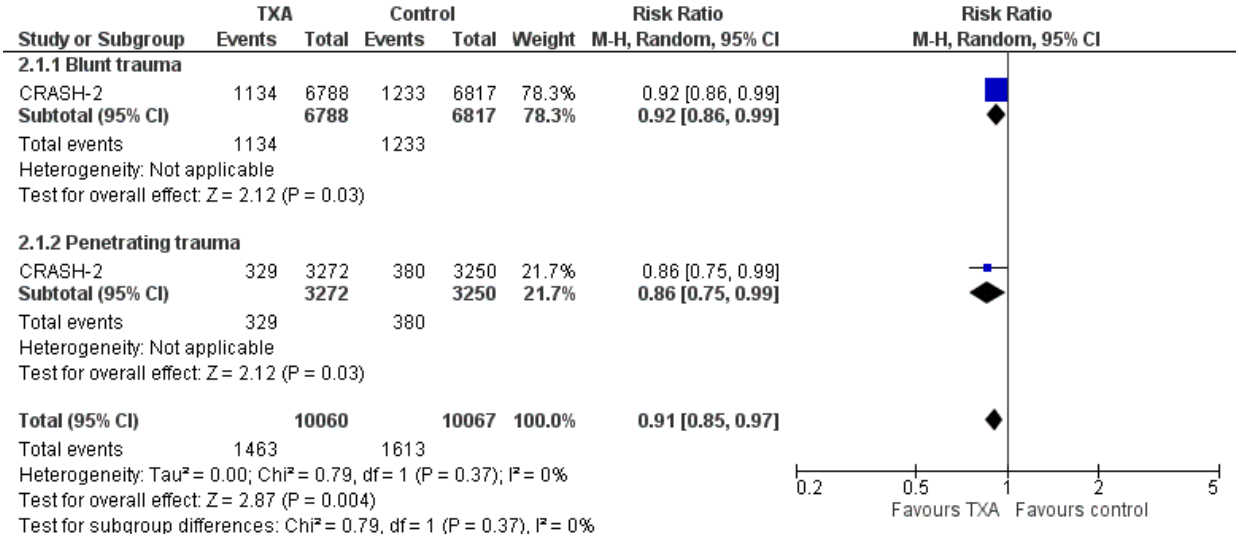


Figure 11. Risk ratio for overall mortality (4 weeks) of TXA versus placebo, by considering (blunt or penetrating) trauma patients.

***Comparazione 2. Fattore VII ricombinante vs* placebo**

In Tabella 3 sono riportati i dati degli studi randomizzati e controllati che valutano il tasso di mortalità in seguito alla somministrazione pre-ospedaliera dell'agente emostatico rFVIIa.
Sia per i soggetti con trauma contusivo che penetrante, non risulta una riduzione della mortalità a 48 ore e a 4 settimane.

Table 16. Outcome data for the comparisons of mortality: rFVIIa versus placebo.

Overall Mortality					
RCT studies focused on blunt and penetrating trauma patients: pre-hospital use of rFVIIa versus placebo					
	rFVIIa		**Placebo**		**time point**
	n	**tot**	**n**	**tot**	
CONTROL					
Blunt trauma	13	69	13	74	48 hours
Penetrating trauma	12	70	10	64	48 hours
Boffard 2005					
Blunt trauma	17	69	22	74	30 days
Penetrating trauma	17	70	18	64	30 days
CONTROL					
Blunt trauma	24	218	26	242	30 days
Penetrating trauma	8	44	5	38	30 days

Overall mortality (48 hours) among blunt or penetrating trauma patients:

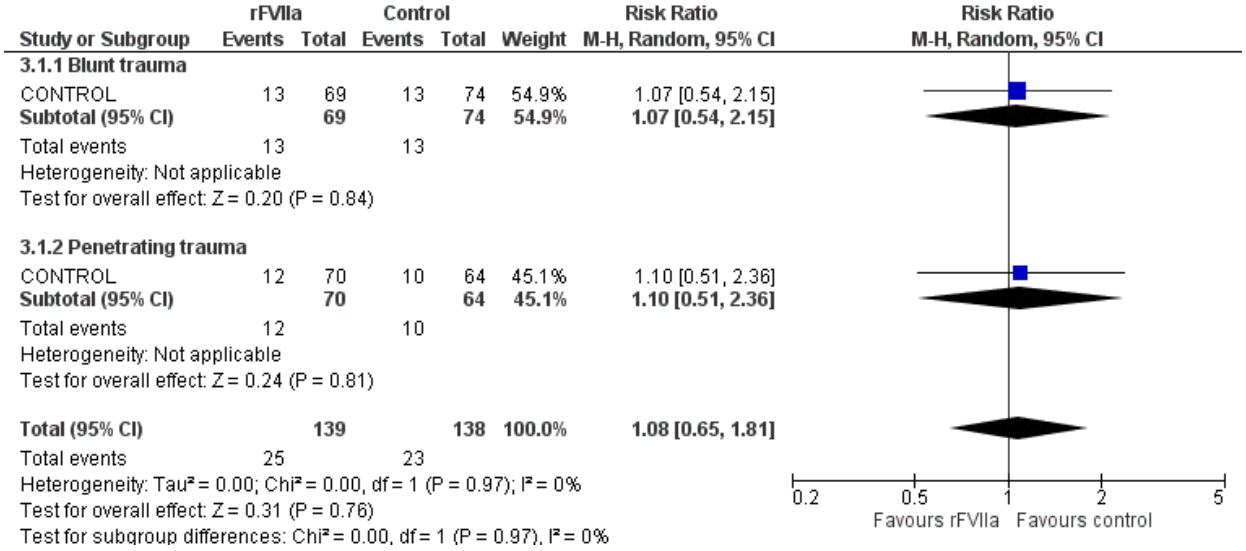


Figure 12. Risk ratio for overall mortality (48 hours) of rFVIIa versus placebo, by considering (blunt or penetrating) trauma patients.

Overall mortality (4 weeks) among blunt or penetrating trauma patients:

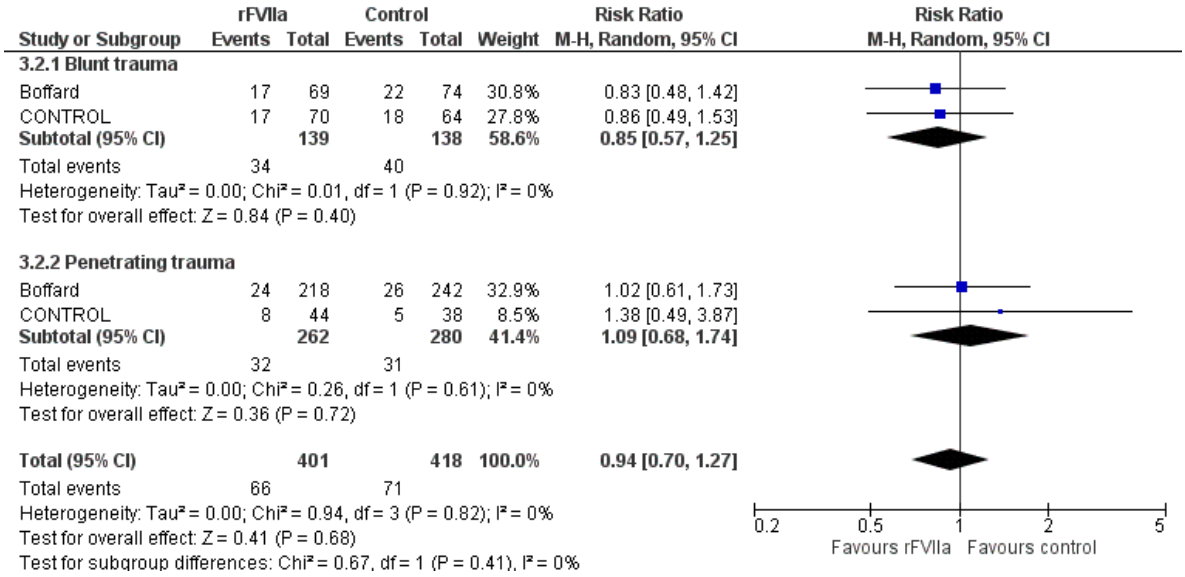


Figure 13. Risk ratio for overall mortality (4 weeks) of rFVIIa versus placebo, by considering (blunt or penetrating) trauma patients.

1.2 Mortalità per Causa-Specifica

Le cause riportate negli RCT relative alla mortalità sono:

- *disfunzione multiorgano* per cui è stato possibile analizzare entrambe le comparazioni (TXA e rFVIIa vs placebo);
- *lesione cerebrale ed emorragia* per le quali è stato possibile analizzare solo la comparazione somministrazione pre-hospital di TXA vs placebo;
- *embolia polmonare e sepsi* per le quali è stato possibile analizzare solo la comparazione somministrazione pre-hospital di rFVIIa vs placebo.

1.2.1 Mortalità per Disfunzione Multiorgano

Comparazione 1. Acido Tranexamico vs placebo

La mortalità a 4 settimane per disfunzione multiorgano non mostra una riduzione statisticamente significativa degli eventi a favore del farmaco emostatico nei confronti del placebo (CRASH-2 e CRASH-3).

Table 17. Outcome data for the comparisons of death due to multiorgan failure: TXA versus placebo.

Mortality due to multiorgan failure					
RCT studies: pre-hospital use of TXA versus placebo					
	TXA		**Placebo**		**time point**
	n	**tot**	**n**	**tot**	
CRASH-2	209	10060	233	10067	4 weeks
CRASH-3	27	6359	24	6280	28 days

Mortality due to multiorgan failure (4 weeks):

Figure 14. Risk ratio for death due to multiorgan failure (4 weeks) of TXA versus placebo.

Comparazione 2. Fattore VII ricombinante vs placebo

La mortalità per disfunzione multiorgano osservata da 48 ore dall'assunzione del fattore rFVIIa fino ai 30 giorni successivi, è stata riportata da 1 solo studio randomizzato e controllato (Boffard 2005) tra i soggetti con trauma cranico contusivo.

- *Per la mortalità dovuta a disfunzione multiorgano nelle 48 ore (Boffard 2005), si prega di prendere visione dell'Appendice C supplementare – Sottogruppi di Popolazione.*

1.2.2 Mortalità per Lesione Cerebrale, Emorragia

Comparazione 1. Acido Tranexamico vs placebo

In seguito alla somministrazione pre-ospedaliera dell'agente emostatico TXA:

- per la mortalità dovuta a lesione cerebrale **non** risulta una riduzione del rischio di decesso a 28 giorni (CRASH-2, CRASH-3);
- per la mortalità dovuta ad emorragia si mostra una riduzione significativa del rischio di decesso a 4 settimane, più marcata nei pazienti che hanno subito un trauma penetrante rispetto agli individui con trauma contusivo (CRASH-2).

- *Per la mortalità dovuta a lesione cerebrale a 24 ore (CRASH-3), si prega di prendere visione dell'Appendice C supplementare – Sottogruppi di Popolazione.*

Table 18. Outcome data for the comparisons of death due to head injury or bleeding: TXA versus placebo.

Mortality due to head injury					
RCT studies: pre-hospital use of TXA versus placebo					
	TXA		**Placebo**		**time point**
	n	**tot**	**n**	**tot**	
CRASH-2	603	10060	621	10067	4 weeks
CRASH-3	855	4613	892	4514	28 days
Bleeding death					
RCT studies: pre-hospital use of TXA versus placebo					
	TXA		**Placebo**		**time point**
	n	**tot**	**n**	**tot**	
CRASH-2	489	10060	574	10067	4 weeks
- blunt trauma	308	6788	347	6817	4 weeks
- penetrating trauma	181	3272	227	3250	4 weeks
CRASH-3	9	6359	7	6280	28 days

Mortality due to head injury (4 weeks) or bleeding death (4 weeks):

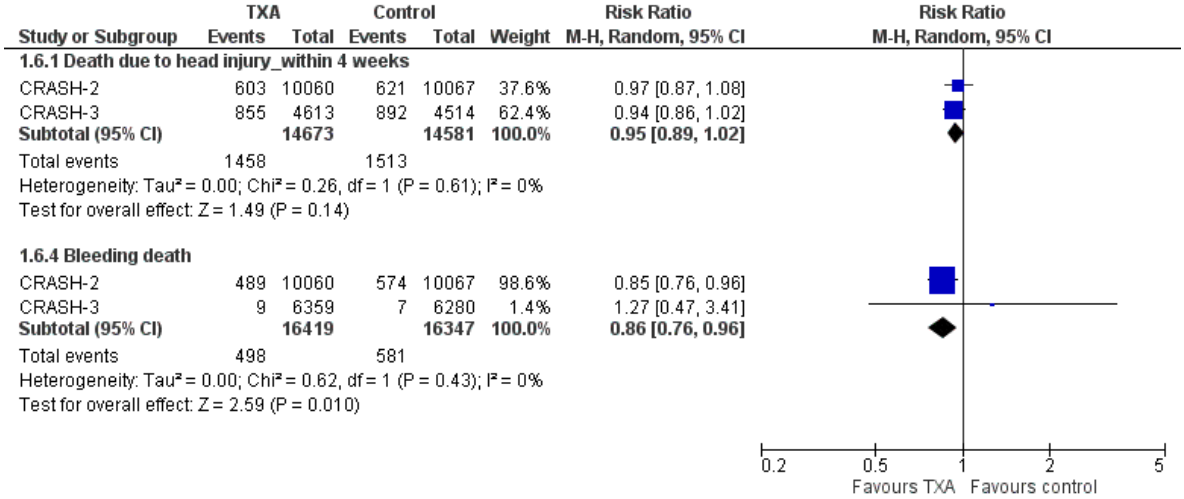


Figure 15. Risk ratio for mortality due to head injury or bleeding death (4 weeks) of TXA versus placebo.

Bleeding death (4 weeks) among blunt or penetrating trauma patients:

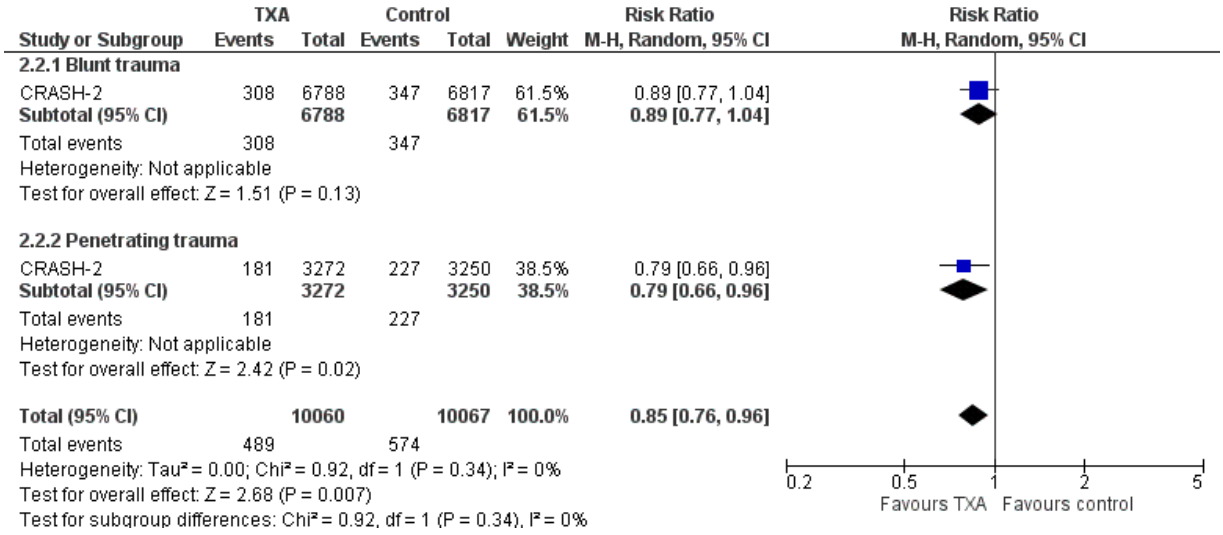


Figure 16. Risk ratio for bleeding death (4 weeks) of TXA versus placebo, by considering (blunt or penetrating) trauma patients.

1.2.3 Mortalita' per Embolia Polmonare, Sepsi

Comparazione 2. Fattore VII ricombinante vs placebo

La mortalità dovuta a embolia polmonare o sepsi, valutata da 48 ore dall'assunzione del trattamento fino ai 30 giorni successivi, è stata riportata solo per la popolazione ristretta ai pazienti con trauma contusivo e lesione cerebrale traumatica (Boffard 2005).

- *Per la mortalità dovuta a embolia polmonare o sepsi (Boffard 2005), si prega di prendere visione dell'Appendice C supplementare – Sottogruppi di Popolazione.*

2. HEALTH RELATED QUALITY OF LIFE

CRASH 3

The CRASH-3 Trial Collaborators, 2019

We assessed the effect of tranexamic acid on disability in survivors by comparing the mean Disability Rating Scale (DRS) score (lower score means less disabled) between the tranexamic acid and placebo groups. The mean scores were similar between groups for patients treated within 3 h of injury (4.99 [SD 7.6] in the tranexamic acid group vs 5.03 [7.6] in the placebo group) and for those treated after 3 h (4.52 [7.0] in the tranexamic acid group vs 5.00 [7.4] in the placebo group).

TXA

- DRS: is designed to classify patients based on their degree of function after brain injury. The DRS consists of 8 items that fall into 4 categories: (a) arousability, awareness and responsivity, (b) cognitive ability for self-care activities, (c) dependence on others, and (d) psychosocial adaptability. The score ranges from 0 (no disability) to 30 (death). Outcome were classified as number of patients within the four categories (Rowell 2020) as well as the mean and sd of the scores (clinicaltrials.gov).

Rowell, 2020

- DRS: at discharge

Table 2. Hospital Course and Outcomes[a] in a Study of the Effect of Tranexamic Acid vs Placebo on Neurologic Outcomes in Patients With Traumatic Brain Injury

Outcome	Treatment group, No. (%)		
	Bolus maintenance (n = 312)	Bolus only (n = 345)	Placebo (n = 309)
Disability Rating Scale[f]	(n = 294)	(n = 329)	(n = 291)
0-1 (none to mild disability)	84 (29)	89 (27)	90 (31)
2-6 (partial to moderate)	92 (31)	122 (37)	92 (32)
7-11 (moderately severe)	37 (13)	41 (12)	33 (11)
12-21 (severe to extremely severe)	23 (8)	26 (8)	17 (6)
>21 (vegetative to death)	58 (20)	51 (16)	59 (20)

- DRS: at 6 Months post-injury

Table 2. Hospital Course and Outcomes[a] in a Study of the Effect of Tranexamic Acid vs Placebo on Neurologic Outcomes in Patients With Traumatic Brain Injury (continued)

Outcome	Treatment group, No. (%)		
	Bolus maintenance (n = 312)	Bolus only (n = 345)	Placebo (n = 309)
Disability Rating Scale score[f]	(n = 261)	(n = 287)	(n = 266)
0-1 (none to mild disability)	123 (47)	143 (50)	134 (50)
2-6 (partial to moderate disability)	64 (25)	79 (28)	53 (20)
7-11 (moderately severe disability)	12 (5)	10 (3)	12 (5)
12-21 (severe to extremely severe disability)	6 (2)	6 (2)	11 (4)
>21 (vegetative to death)	56 (21)	49 (17)	56 (21)

[f] The Disability Rating Scale is designed to classify patients based on their degree of function after brain injury, consisting of 8 components: eye opening, communication, motor response, feeding, toileting, grooming, dependence/level of functioning, and psychosocial adaptability/employability. The overall score ranges from 0 (complete recovery) to 30 (death).

Clinicaltrials.gov

- DRS: At the end of the hospital stay (average of 9 days post injury)

Arm/Group Title	Placebo	Bolus-Maintenance	Bolus Only
Arm/Group Description:	Placebo IV bolus in the prehospital setting followed by a placebo maintenance infusion initiated on hospital arrival and infused over 8 hours.	1 gram IV TXA bolus in the prehospital setting followed by a 1 gram IV maintenance infusion initiated on hospital arrival and infused over 8 hours.	2 grams IV TXA bolus in the prehospital setting followed by a placebo maintenance infusion initiated on hospital arrival and infused over 8 hours.
Overall Number of Participants Analyzed	291	294	329
Mean (Standard Deviation) Unit of Measure: score on a scale			
	9.0 (11.1)	9.4 (11.0)	8.1 (9.8)

- DRS: at 6 Months post-injury

Arm/Group Title	Placebo	Bolus-Maintenance	Bolus Only
Arm/Group Description:	Placebo IV bolus in the prehospital setting followed by a placebo maintenance infusion initiated on hospital arrival and infused over 8 hours.	1 gram IV TXA bolus in the prehospital setting followed by a 1 gram IV maintenance infusion initiated on hospital arrival and infused over 8 hours.	2 grams IV TXA bolus in the prehospital setting followed by a placebo maintenance infusion initiated on hospital arrival and infused over 8 hours.
Overall Number of Participants Analyzed	266	261	287
Mean (Standard Deviation) Unit of Measure: score on a scale			
	8.0 (11.8)	8.1 (11.9)	6.6 (10.8)

Disability rating scale:

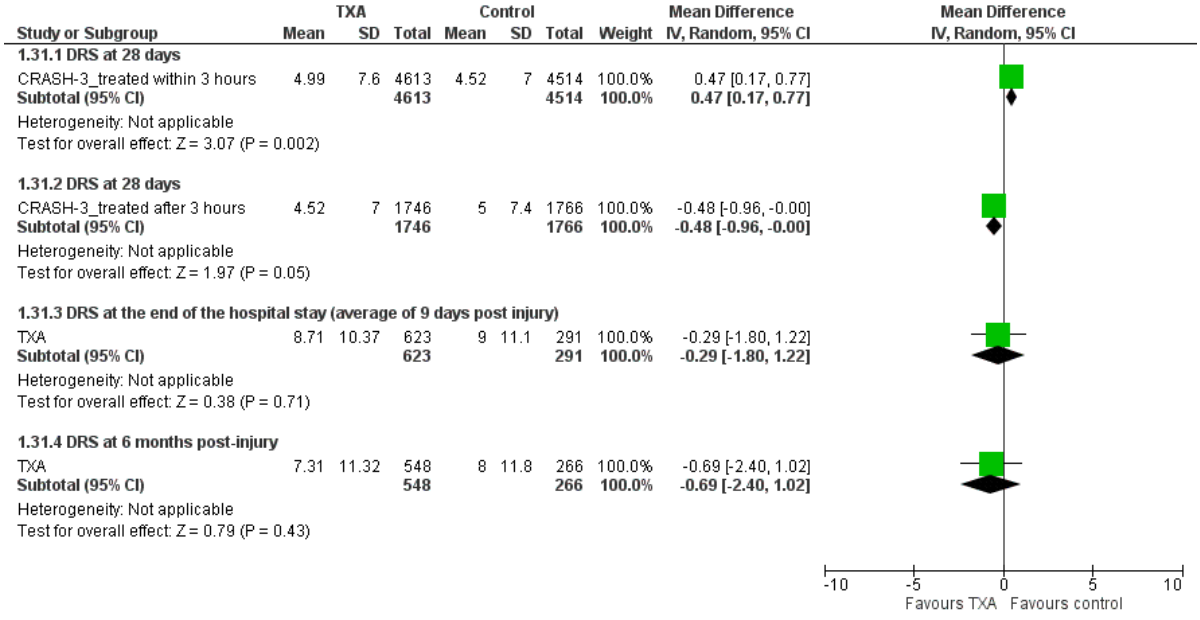


Figure 17. Mean difference for DRS of TXA versus placebo, by considering trauma patients:
- treated within 3 hours and evaluation of DRS at 28 days,
- treated after 3 hours and evaluation of DRS at 28 days,
- DRS at the end of the hospital stay (average of 9 days post injury),
- DRS at 6 months post-injury.

Glasgow Outcome Scale-Extended (GOS-E): subdivides the categories of severe and moderate disability and good recovery using a scale of 1 to 8 where 1 = death, 2 = vegetative state, 3 = lower severe disability, 4 = upper severe disability, 5 = lower moderate disability, 6 = upper moderate disability, 7 = lower good recovery, and 8 = upper good recovery. Structured telephone interviews have been developed and validated for the GOS-E and these questions were incorporated into the follow-up survey. GOS-E was dichotomized into unfavorable (1 to 4) and favorable (5 to 8) outcomes.

Rowell, 2020

GOSE score: at discharge

Table 2. Hospital Course and Outcomes[a] in a Study of the Effect of Tranexamic Acid vs Placebo on Neurologic Outcomes in Patients With Traumatic Brain Injury

Outcome	Treatment group, No. (%)		
	Bolus maintenance (n = 312)	Bolus only (n = 345)	Placebo (n = 309)
Hospital discharge outcomes	**(n = 294)**	**(n = 329)**	**(n = 292)**
Glasgow Outcome Scale-Extended score >4[e]	101 (34)	101 (31)	96 (33)

GOS-E: at 6 months post-injury

Table 2. Hospital Course and Outcomes[a] in a Study of the Effect of Tranexamic Acid vs Placebo on Neurologic Outcomes in Patients With Traumatic Brain Injury (continued)

Outcome	Treatment group, No. (%)		
	Bolus maintenance (n = 312)	Bolus only (n = 345)	Placebo (n = 309)
6-mo outcomes[m]			
Glasgow Outcome Scale-Extended score >4[e]	153 (58) (n = 262)	178 (62) (n = 289)	163 (60) (n = 272)

[m] There were 9 participants for whom the Glasgow Outcome Scale-Extended was taken at 6 months but not the Disability Rating Scale score (1 in the bolus maintenance group, 2 in the bolus only group, and 6 in the placebo group).

[e] The Glasgow Outcome Scale-Extended subdivides the categories of severe and moderate disability and good recovery using a scale of 1 to 8, where 1 indicates death; 2, vegetative state; 3, lower severe disability; 4, upper severe disability; 5, lower moderate disability; 6, upper moderate disability; 7, lower good recovery; and 8, upper good recovery. Structured telephone interviews have been developed and validated for the measure and these questions were incorporated into the follow-up survey. The measure was dichotomized into unfavorable (1-4) and favorable (5-8) outcomes for this trial.

Clinicaltrials.gov

GOSE score: at the end of the hospital stay (average of 9 days post injury)

Arm/Group Title	Placebo		Bolus-Maintenance		Bolus Only	
Arm/Group Description:	Placebo IV bolus in the prehospital setting followed by a placebo maintenance infusion initiated on hospital arrival and infused over 8 hours.		1 gram IV TXA bolus in the prehospital setting followed by a 1 gram IV maintenance infusion initiated on hospital arrival and infused over 8 hours.		2 grams IV TXA bolus in the prehospital setting followed by a placebo maintenance infusion initiated on hospital arrival and infused over 8 hours.	
Overall Number of Participants Analyzed	292		294		329	
Measure Type: Count of Participants Unit of Measure: Participants						
	196	67.1%	193	65.6%	228	69.3%

GOS-E: at 6 months post-injury

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	0.87
	Estimation Comments	Odds ratio for unfavorable GOS-E (<=4) for the Combined TXA Arms (numerator) vs. Placebo (denominator)

CRASH-2
Nishijiama, 2019

- Modified Oxford Handicap Scale, which measured the functional status, is an ordinal scale with the following functional categories (best to worst): no symptoms, minor symptoms, some restriction, dependent (not requiring constant attention), fully dependent, and dead. We converted the ordinal modified Oxford Handicap Scale score to a utility-weighted score. This conversion was based on previous measurements of health-related quality of- life in patients with different functional outcome scores after acute neurologic injuries

The modified Oxford Handicap Scale scores stratified by intervention are reported in Table 3. The mean utility weighted score was 0.66 (SD 0.33) for patients randomized to tranexamic acid compared with a mean of 0.64 (SD 0.34) for those randomized to placebo (mean difference 0.02; 95% CI 0.01 to 0.03; P=.001). Adjusted analysis demonstrated that tranexamic acid use was significantly associated with higher utility-weighted modified Oxford Handicap Scale scores (coefficient 0.02; 95% CI 0.01 to 0.03).

Table 3. Modified Oxford Handicap Scale score by intervention (n=13,432).

	Intervention, No. (%)	
Category	**TXA, n=6,753**	**Placebo, n=6,679**
No symptoms	1,052 (15.6)	941 (13.9)
Minor symptoms	2,190 (32.4)	2,140 (32.0)
Some restrictions	1,311 (19.4)	1,324 (19.8)
Dependent	807 (11.9)	779 (11.7)
Fully dependent	421 (6.2)	396 (5.9)
Dead	972 (14.4)	1,109 (16.6)

3. EVENTI AVVERSI

3.1 Sepsi

<u>Comparazione 1. Acido Tranexamico vs placebo</u>

L'evento avverso *sepsi* entro 4 settimane dall'assunzione del TXA è stato valutato da due trial randomizzati e controllati (CRASH-3 e TXA).

- *Per l'evento avverso "sepsi" nelle 4 settimane (CRASH-3, TXA), si prega di prendere visione dell'Appendice C supplementare – Sottogruppi di Popolazione.*

<u>Comparazione 2. Fattore VII ricombinante vs placebo</u>

L'evento avverso *sepsi,* rilevato entro 90 giorni dal trattamento sia nei pazienti con trauma contusivo che penetrante, è stato valutato in seguito alla somministrazione pre-ospedaliera dell'agente rFVIIa da un solo trial randomizzato e controllato (CONTROL), da cui non emerge una riduzione del rischio statisticamente significativa.

Table 19. Outcome data for sepsis: rFVIIa versus placebo.

Sepsis					
RCT studies focused on blunt and penetrating trauma patients: pre-hospital use of rFVIIa versus placebo					
	rFVIIa		**Placebo**		**time point**
CONTROL	**n**	**tot**	**n**	**tot**	
Blunt trauma	33	224	42	250	90 days
Penetrating trauma	4	46	2	40	90 days

Sepsis (90 days) among blunt or penetrating trauma patients:

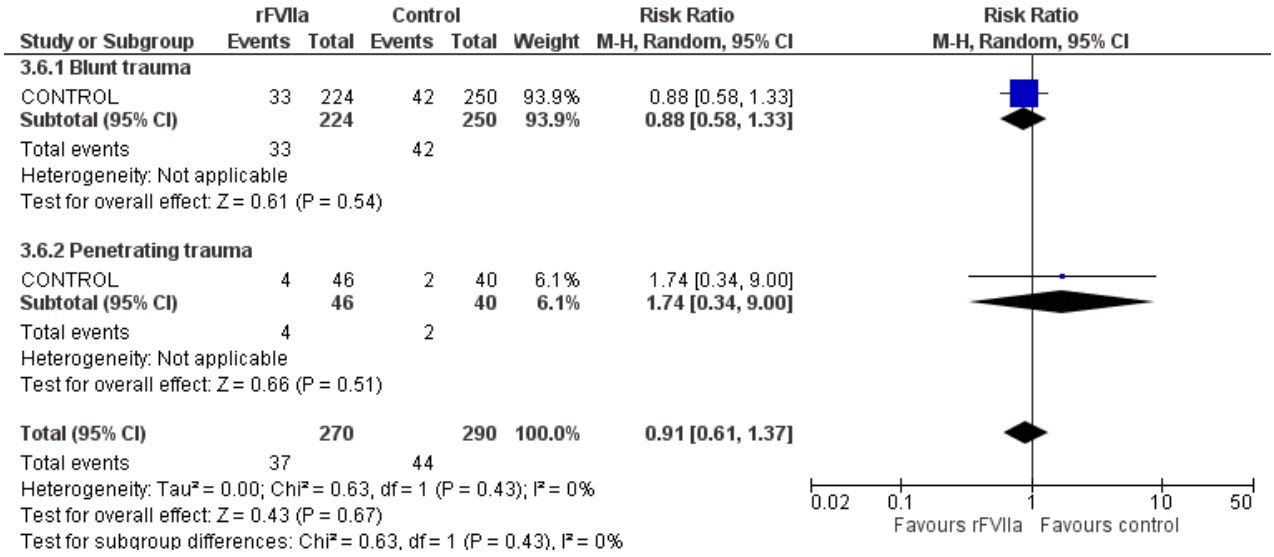


Figure 18. Risk ratio for sepsis (90 days) of rFVIIa versus placebo, by considering (blunt or penetrating) trauma patients.

3.2 Embolia Polmonare

Comparazione 1. Acido Tranexamico vs placebo

Per l'evento avverso *embolia polmonare,* valutato entro 4 settimane dall'assunzione del TXA, analizzato da 3 studi randomizzati e controllati (CRASH-2, CRASH-3, TXA), non è stata dimostrata una differenza significativa nella somministrazione dell'agente emostatico.

Table 20. Outcome data for the comparisons of pulmonary embolism: TXA versus placebo.

Pulmonary embolism					
RCT studies: pre-hospital use of TXA versus placebo					
	TXA		**Placebo**		**time point**
	n	**tot**	**n**	**tot**	
CRASH-2	72	10060	71	10067	within 28 days
CRASH-3	24	6359	32	6280	within 28 days
TXA	9	657	5	309	within 28 days

Pulmonary embolism (28 days):

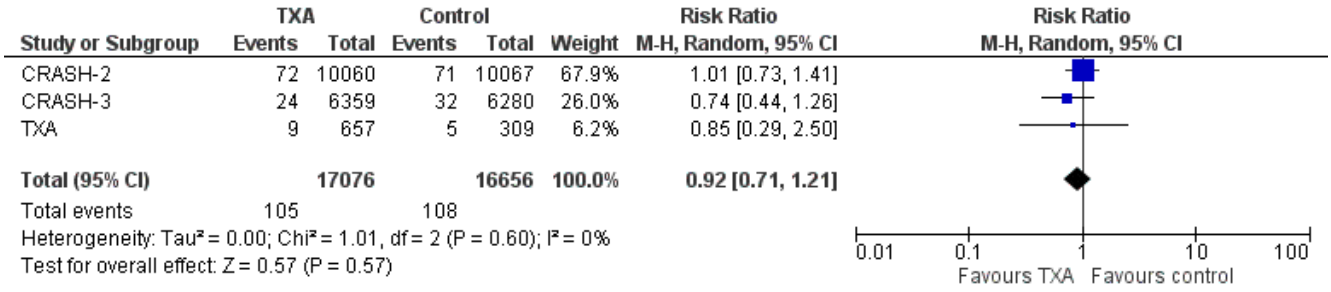


Figure 19. Risk ratio for pulmonary embolism (28 days) of TXA versus placebo by considering trauma patients.

Comparazione 2. Fattore VII ricombinante vs placebo

Per l'evento avverso *embolia polmonare*, valutato da un solo trial randomizzato e controllato (CONTROL) non si mostra una differenza statisticamente significativa, entro 4 settimane, dall'assunzione dell'agente rFVIIa.

Table 21. Outcome data for the comparisons of pulmonary embolism: rFVIIa versus placebo.

Pulmonary embolism					
RCT studies: pre-hospital use of rFVIIa versus placebo					
	rFVIIa		**Placebo**		**time point**
	n	**tot**	**n**	**tot**	
CONTROL	9	270	8	290	within 28 days

Pulmonary embolism (28 days) among blunt or penetrating trauma patients:

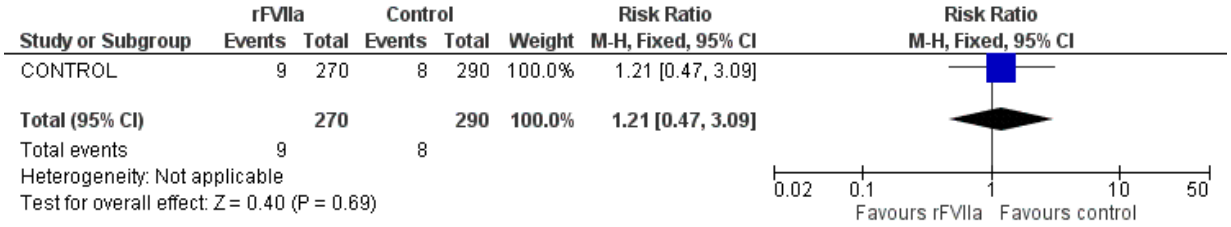


Figure 20. Risk ratio for pulmonary embolism (28 days) of rFVIIa versus placebo by considering (blunt or penetrating) trauma patients.

3.3 Infarto Miocardico, Ictus

Comparazione 1. Acido Tranexamico vs placebo

Per gli eventi avversi di *infarto al miocardio e ictus*, valutati da 3 studi randomizzati controllati (CRASH-2, CRASH-3, TXA), insorti entro 4 settimane dal trattamento, anche se in presenza di un trend spostato a favore del farmaco Acido Tranexamico, non si mostra una differenza statisticamente significativa.

Table 22. Outcome data for the comparisons of MI or stroke: TXA versus placebo.

MI					
RCT studies: pre-hospital use of TXA versus placebo					
	TXA		**Placebo**		**time point**
	n	**tot**	**n**	**tot**	
CRASH-2	35	10060	55	10067	within 28 days
CRASH-3	18	6359	20	6331	within 28 days
TXA	5	657	1	309	within 28 days
Stroke					
RCT studies: pre-hospital use of TXA versus placebo					
	TXA		**Placebo**		**time point**
	n	**tot**	**n**	**tot**	
CRASH-2	57	10060	66	10067	within 28 days
CRASH-3	46	6359	42	6280	within 28 days
TXA	16	657	10	309	within 28 days

MI (28 days):

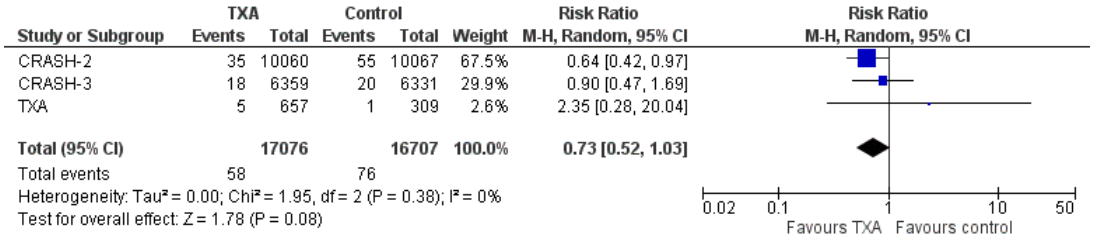


Figure 21. Risk ratio for MI (28 days) of TXA versus placebo by considering trauma patients.

Stroke (28 days):

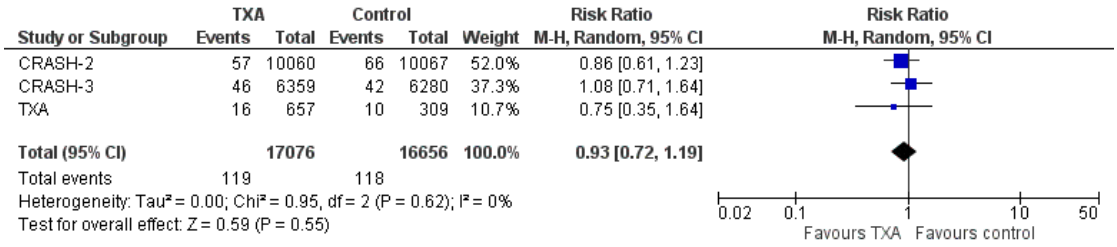


Figure 22. Risk ratio for stroke (28 days) of TXA versus placebo by considering trauma patients.

<u>Comparazione 2. Fattore VII ricombinante vs placebo</u>

Per gli eventi avversi di *infarto al miocardio o ictus*, valutati da un solo studio controllato e randomizzato, (CONTROL), non si mostra una differenza statisticamente significativa del rischio di insorgenza entro 4 settimane dall'assunzione dell'agente rFVIIa.

Table 23. Outcome data for the comparisons of MI or stroke: rFVIIa versus placebo.

MI or stroke					
RCT studies: pre-hospital use of rFVIIa versus placebo					
	rFVIIa		**Placebo**		**time point**
	n	**tot**	**n**	**tot**	
CONTROL	5	270	5	290	within 28 days

MI or Stroke (28 days) among blunt or penetrating trauma patients:

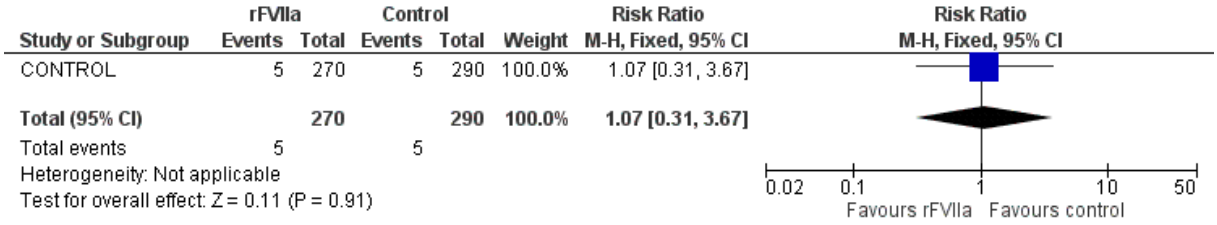


Figure 23. Risk ratio for MI or stroke (28 days) of rFVIIa versus placebo by considering (blunt or penetrating) trauma patients.

3.4 Vascolari: qualsiasi evento occlusivo vascolare (TXA), eventi avversi tromboembolici (rFVIIA), trombotici arteriosi (rFVIIA), trombotici venosi (rFVIIA), trombosi venosa profonda, coagulazione intravascolare disseminata

Le cause riportate negli RCT relative agli eventi avversi prettamente vascolari sono:

- *qualsiasi evento occlusivo vascolare* per il quale è stato possibile analizzare solo le comparazioni TXA in pre-ospedaliero vs placebo;
- *eventi avversi tromboembolici, trombotici arteriosi, trombotici venosi* per i quali è stato possibile analizzare solo la comparazione ii) somministrazione pre-hospital di rFVIIa vs placebo;
- *trombosi venosa profonda, coagulazione intravascolare disseminata* per cui è stato possibile analizzare entrambe le comparazioni (TXA e rFVIIa vs placebo).

➢ *Per l'outcome di coagulazione intravascolare disseminata nelle 4 settimane (TXA), si prega di prendere visione dell'Appendice C supplementare – Sottogruppi di Popolazione.*

<u>Comparazione 1. Acido Tranexamico vs placebo</u>

Non è stata rilevata una diminuzione significativa nel rischio di sviluppare gli eventi avversi relativi a *qualsiasi evento occlusivo vascolare, trombosi venosa profonda* (identificati da 3 studi controllati randomizzati, CRASH-2, CRASH-3 e TXA) insorti entro 4 settimane dall'assunzione del TXA, ed ottenuti dalla somministrazione pre-ospedaliera dell'agente emostatico TXA.

Table 24. Outcome data for the comparisons of any vascular occlusive event: TXA versus placebo.

Any vascular occlusive event					
RCT studies: pre-hospital use of TXA versus placebo					
	TXA		**Placebo**		**time point**
	n	**tot**	**n**	**tot**	
CRASH-2	168	10060	201	10067	within 28 days
CRASH-3	101	6359	102	6280	within 28 days
TXA	44	657	30	309	within 28 days

Any vascular occlusive event (28 days):

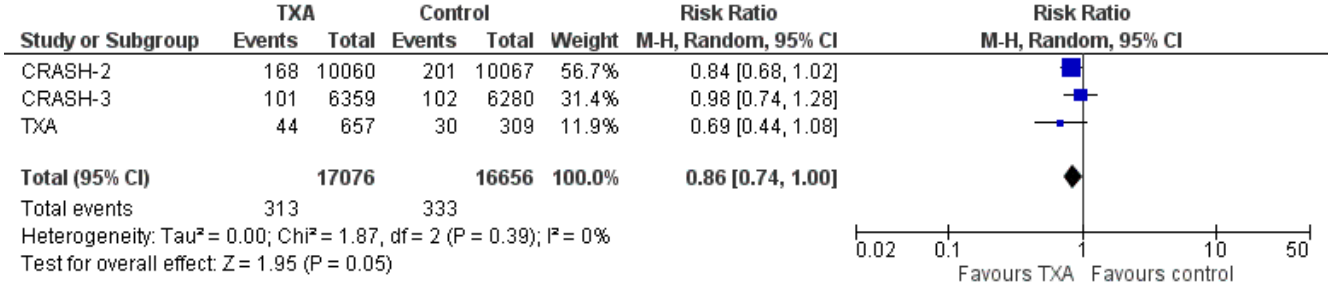


Figure 24. Risk ratio for any vascular occlusive event (28 days) of TXA versus placebo by considering trauma patients.

Table 25. Outcome data for the comparisons of deep vein thrombosis: TXA versus placebo.

Deep vein thrombosis					
RCT studies: pre-hospital use of TXA versus placebo					
	TXA		**Placebo**		**time point**
	n	**tot**	**n**	**tot**	
CRASH-2	40	10060	41	10067	within 28 days
CRASH-3	19	6359	16	6280	within 28 days
TXA	13	657	9	309	within 28 days

Deep vein thrombosis (28 days):

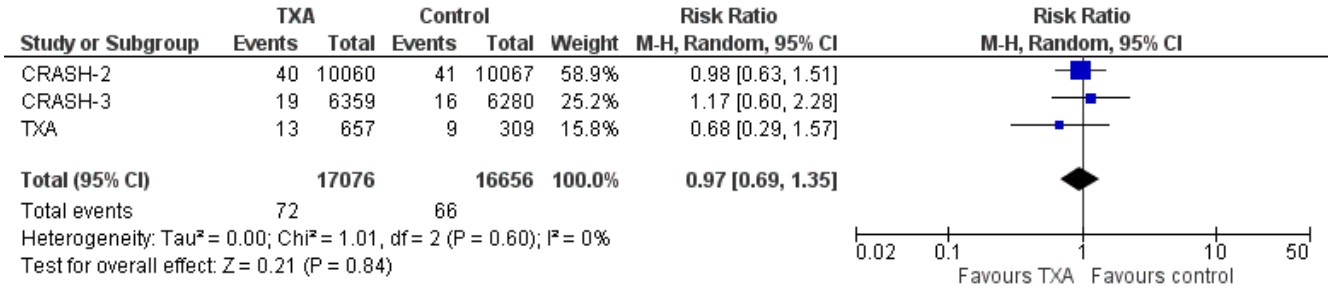


Figure 25. Risk ratio for deep vein thrombosis (28 days) of TXA versus placebo by considering trauma patients.

Comparazione 2. Fattore VII ricombinante vs placebo

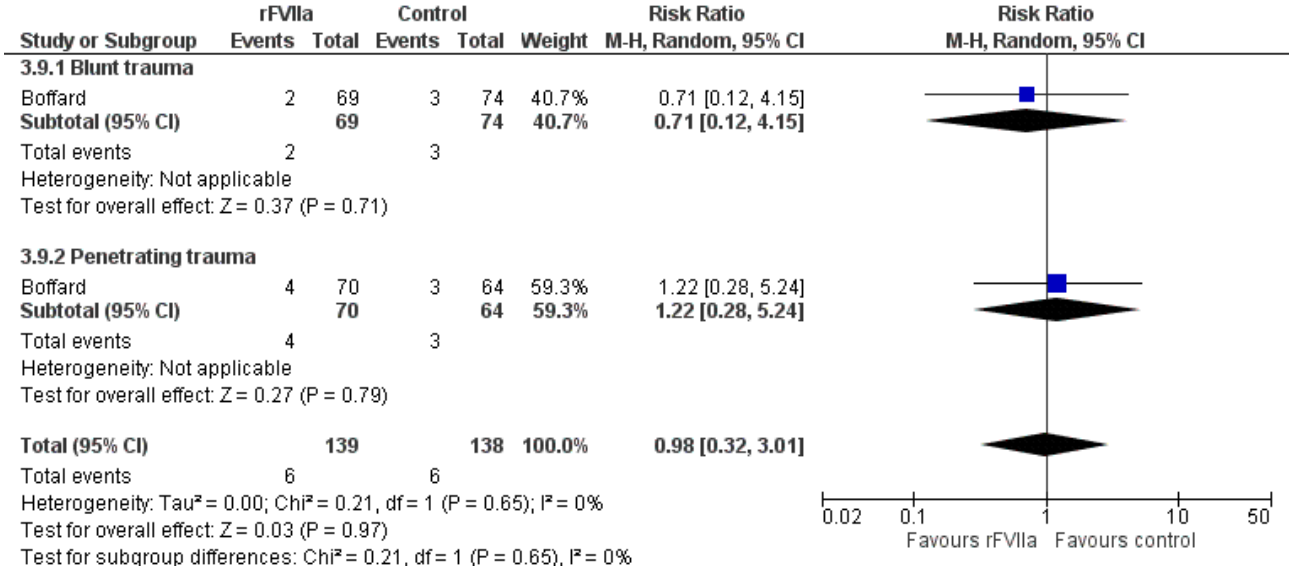
In seguito all'assunzione dell'agente emostatico rFVIIa si sono valutati i seguenti outcomes:

- *eventi avversi tromboembolici* a 48 ore (Boffard 2005) e a 90 giorni (CONTROL) per i quali non è stata riscontrata una riduzione del rischio sia nei soggetti con trauma contusivo che penetrante;
- *eventi avversi trombotici arteriosi* e *venosi* a 90 giorni, valutati da un solo studio controllato randomizzato (CONTROL) per i quali non si mostra una riduzione del rischio sia nei soggetti con trauma contusivo che penetrante;
- *trombosi venosa profonda* (dal trial CONTROL), per la quale non è mostrata una chiara riduzione del rischio di insorgenza entro 4 settimane dall'assunzione dell'agente rFVIIa;
- *coagulazione disseminata intravascolare* a 90 giorni (dal trial CONTROL), per la quale non si rileva una diminuzione significativa a seguito della somministrazione pre-ospedaliera dell'agente emostatico rFVIIa, sia per la popolazione con trauma contusivo che penetrante.

Table 26. Outcome data for thromboembolic adverse events: rFVIIa versus placebo.

Thromboembolic adverse events					
RCT studies focused on blunt and penetrating trauma patients: pre-hospital use of rFVIIa versus placebo					
	rFVIIa		**Placebo**		**time point**
Boffard 2005 Blunt trauma	**n**	**tot**	**n**	**tot**	
	2	69	3	74	48 hours
Penetrating trauma	**n**	**tot**	**n**	**tot**	
	4	70	3	64	48 hours
	rFVIIa		**Placebo**		**time point**
CONTROL Blunt trauma	**n**	**tot**	**n**	**tot**	
	36	224	33	250	90 days
Penetrating trauma	**n**	**tot**	**n**	**tot**	
	2	46	4	40	90 days

A) Thromboembolic adverse events (48 hours) among blunt or penetrating trauma patients:



B) Thromboembolic adverse events (90 days) among blunt or penetrating trauma patients:

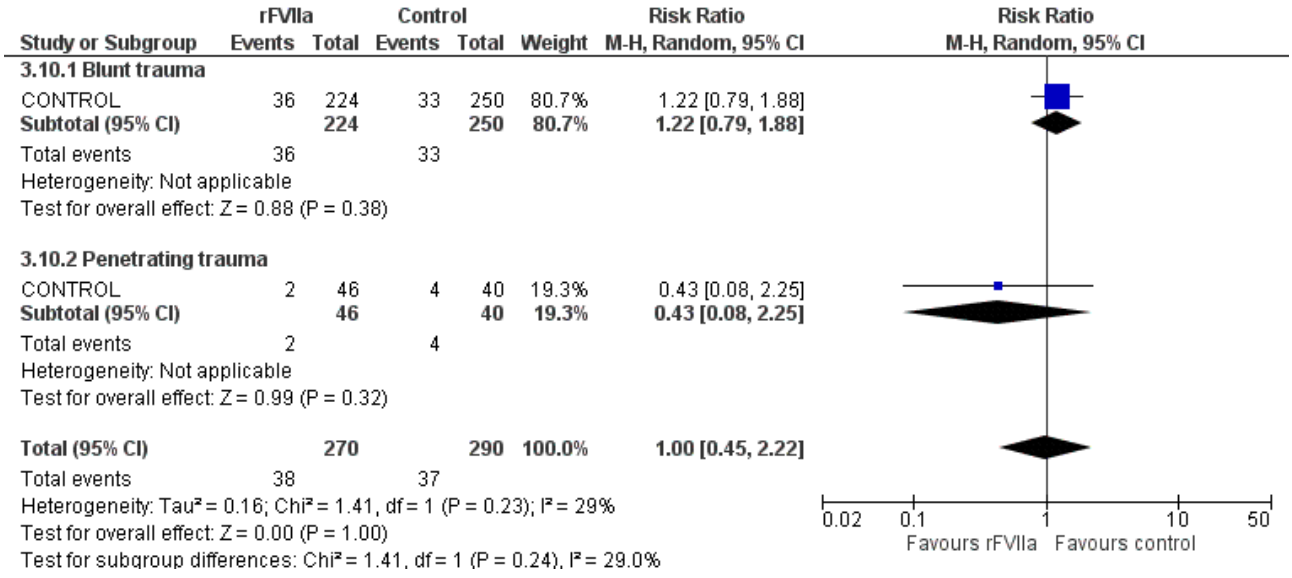


Figure 26. Risk ratio for thromboembolic adverse events of rFVIIa versus placebo at A) 48 hours B) 90 days by considering (blunt or penetrating) trauma patients.

- *Per gli eventi avversi tromboembolici entro 4 settimane (Boffard 2005), si prega di prendere visione dell'Appendice C supplementare – Sottogruppi di Popolazione.*

Table 27. Outcome data for the comparisons of arterial thrombotic adverse events: rFVIIa versus placebo.

Arterial thrombotic adverse events					
RCT studies focused on blunt and penetrating trauma patients: pre-hospital use of rFVIIa versus placebo					
	rFVIIa		**Placebo**		**time point**
CONTROL Blunt trauma	**n**	**tot**	**n**	**tot**	
	16	224	11	250	90 days
Penetrating trauma	**n**	**tot**	**n**	**tot**	
	2	46	1	40	90 days

Arterial thrombotic adverse events (90 days) among blunt or penetrating trauma patients:

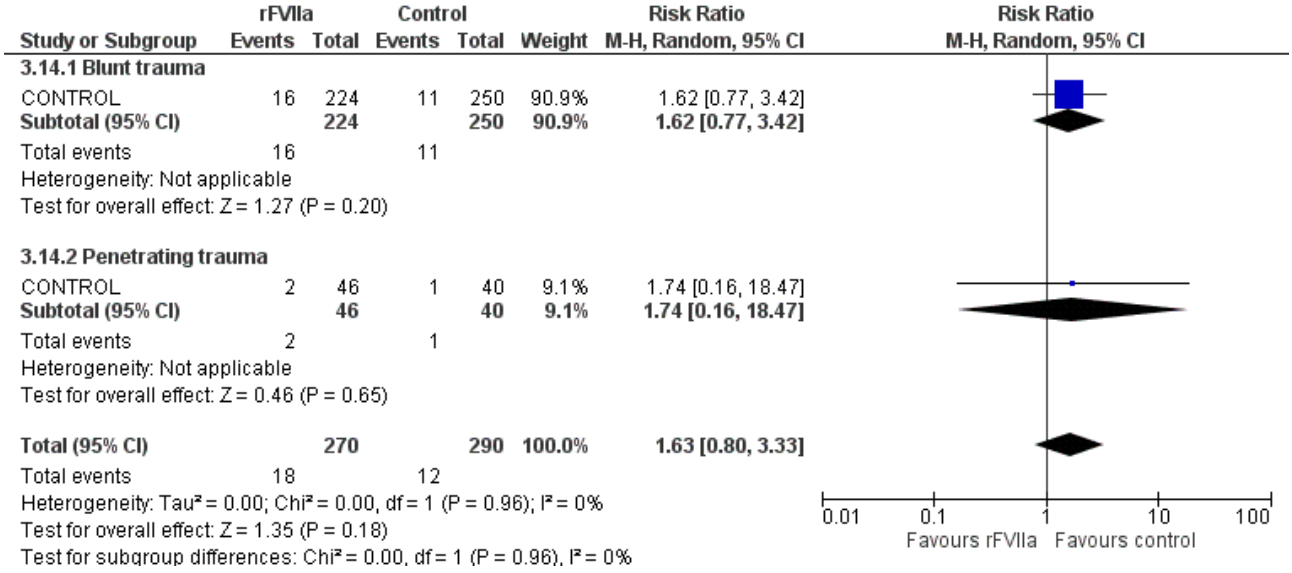


Figure 27. Risk ratio for arterial thrombotic adverse events (90 days) of rFVIIa versus placebo, by considering (blunt or penetrating) trauma patients.

Table 28. Outcome data for venous thromboembolic adverse events (90 days): rFVIIa versus placebo.

Venous thromboembolic adverse events					
RCT studies focused on blunt and penetrating trauma patients: pre-hospital use of rFVIIa versus placebo					
	rFVIIa		**Placebo**		**time point**
CONTROL Blunt trauma	**n**	**tot**	**n**	**tot**	
	29	224	24	250	90 days
Penetrating trauma	**n**	**tot**	**n**	**tot**	
	0	46	4	40	90 days

Venous thromboembolic adverse events (90 days) among blunt or penetrating trauma patients:

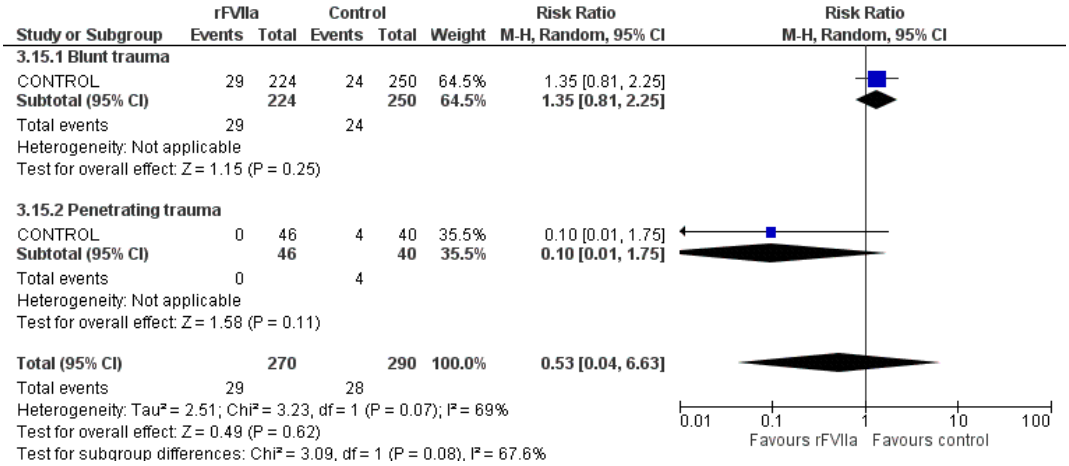


Figure 28. Risk ratio for venous thromboembolic adverse events (90 days) of rFVIIa versus placebo, by considering (blunt or penetrating) trauma patients.

Table 29. Outcome data for the comparisons of deep vein thrombosis: rFVIIa versus placebo.

Deep-vein thrombosis					
RCT studies: pre-hospital use of rFVIIa versus placebo					
	rFVIIa		**Placebo**		**time point**
	n	**tot**	**n**	**tot**	
CONTROL	14	270	16	290	within 28 days

Deep vein thrombosis (28 days) among blunt or penetrating trauma patients:

Figure 29. Risk ratio for deep vein thrombosis (28 days) of rFVIIa versus placebo, by considering (blunt or penetrating) trauma patients.

Table 30. Outcome data for the comparisons of disseminated intravascular coagulation: rFVIIa versus placebo.

Disseminated intravascular coagulation					
RCT studies focused on blunt and penetrating trauma patients: pre-hospital use of rFVIIa versus placebo					
	rFVIIa		**Placebo**		**time point**
	n	**tot**	**n**	**tot**	
CONTROL					
Blunt trauma	6	224	10	250	90 days
	n	**tot**	**n**	**tot**	
Penetrating trauma	1	46	1	40	90 days

Disseminated intravascular coagulation (90 days) among blunt or penetrating trauma patients:

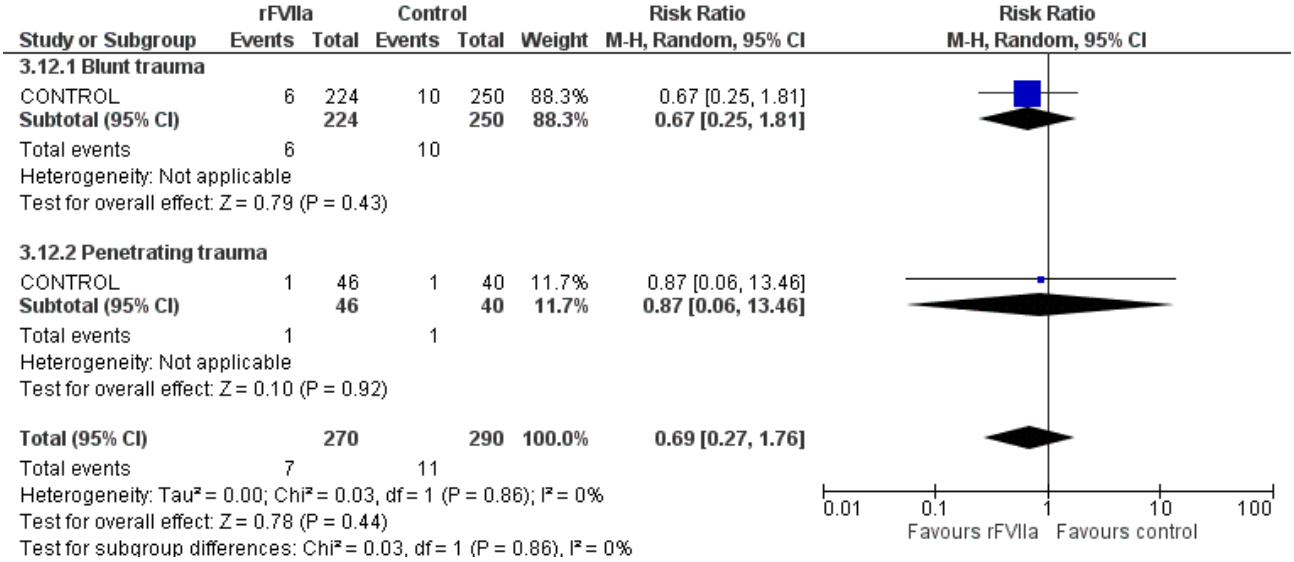


Figure 30. Risk ratio for disseminated intravascular coagulation (90 days) of rFVIIa versus placebo, by considering (blunt or penetrating) trauma patients.

3.5. Altri Eventi Avversi: Sanguinamento gastrointestinale (TXA), Insufficienza renale (TXA), Danno renale acuto (TXA), Convulsioni (TXA), Sindrome da distress respiratorio acuto (rFVIIa), Disfunzione multiorgano (rFVIIa)

Le cause riportate negli RCT relative ad altri eventi avversi sono:
- *sanguinamento gastrointestinale* per il quale è stato possibile analizzare solo la comparazione somministrazione pre-hospital di TXA vs placebo;
- *insufficienza renale, danno renale acuto, convulsioni* per i quali è stato possibile analizzare le comparazioni somministrazione pre-hospital di TXA vs placebo;
- *sindrome da distress respiratorio acuto, disfunzione multiorgano* per i quali è stato possibile analizzare solo la comparazione somministrazione pre-hospital di rFVIIa vs placebo.

Comparazione 1. Acido Tranexamico vs placebo

- *Per l'outcome di emorragia gastrointestinale (CRASH-3), insufficienza renale (CRASH-3, TXA), danno renale acuto (TXA), convulsioni (CRASH-3, TXA) nelle 4 settimane, si prega di prendere visione dell'Appendice C supplementare – Sottogruppi di Popolazione.*

Comparazione 2. Fattore VII ricombinante vs placebo

In seguito all'assunzione dell'agente emostatico rFVIIa sono stati valutati i seguenti eventi avversi:

- *Sindrome da distress respiratorio acuto* a 30 giorni (Boffard 2005) per il quale si mostra una riduzione del rischio negli individui con trauma contusivo ma non negli individui con trauma penetrante. Inoltre, la *sindrome da distress respiratorio acuto* a 90 giorni (dal trial CONTROL) ha mostrato una diminuzione significativa a seguito dell'assunzione dell'agente rFVIIa per l'intera popolazione rispetto ai soggetti con trauma contusivo o penetrante.
- *Disfunzione multiorgano* (Boffard 2005 e CONTROL) per la quale non si mostra una riduzione del rischio di insorgenza a 30 giorni dalla somministrazione dell'agente emostatico rFVIIa e così tra i soggetti con trauma contusivo o penetrante. Al contrario considerando l'outcome a 90 giorni (CONTROL) non vi è una riduzione significativa, sia per i soggetti che presentavano trauma contusivo che penetrante.

Table 31. Outcome data for the comparisons of acute respiratory distress syndrome: rFVIIa versus placebo.

Acute respiratory distress syndrome					
RCT studies focused on blunt and penetrating trauma patients: pre-hospital use of rFVIIa versus placebo					
	rFVIIa		**Placebo**		**time point**
Boffard 2005 Blunt trauma	**n**	**tot**	**n**	**tot**	
	3	69	12	74	30 days
Penetrating trauma	**n**	**tot**	**n**	**tot**	
	4	70	5	64	30 days
CONTROL					90 days

Blunt trauma	**n**	**tot**	**n**	**tot**	
	8	224	18	250	
Penetrating trauma	**n**	**tot**	**n**	**tot**	
	0	46	3	40	90 days

Acute respiratory distress syndrome (30 days) among blunt or penetrating trauma patients:

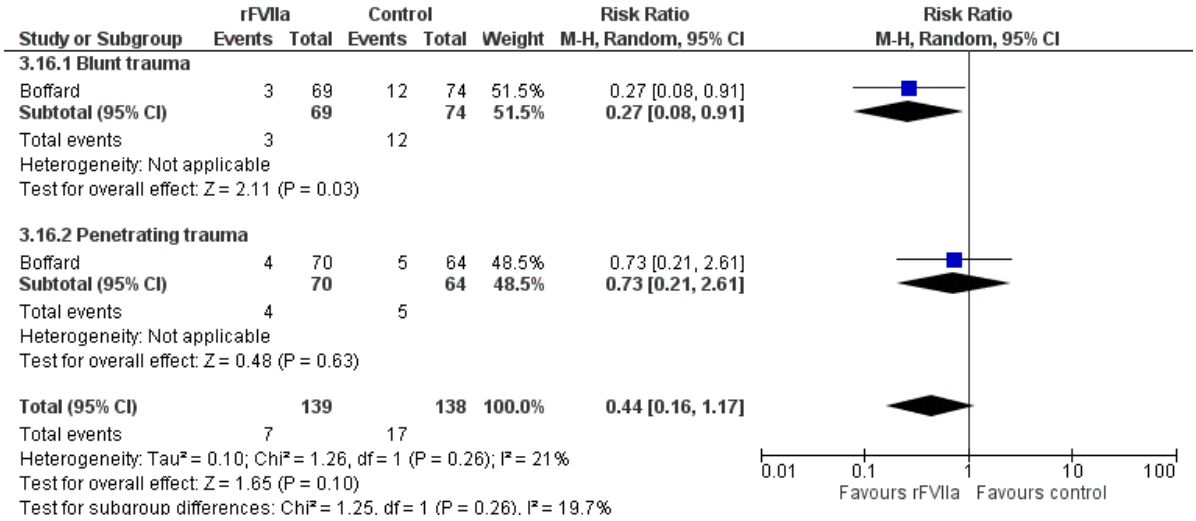


Figure 31. Risk ratio for acute respiratory distress syndrome (30 days) of rFVIIa versus placebo, by considering (blunt or penetrating) trauma patients.

Acute respiratory distress syndrome (90 days) among blunt or penetrating trauma patients:

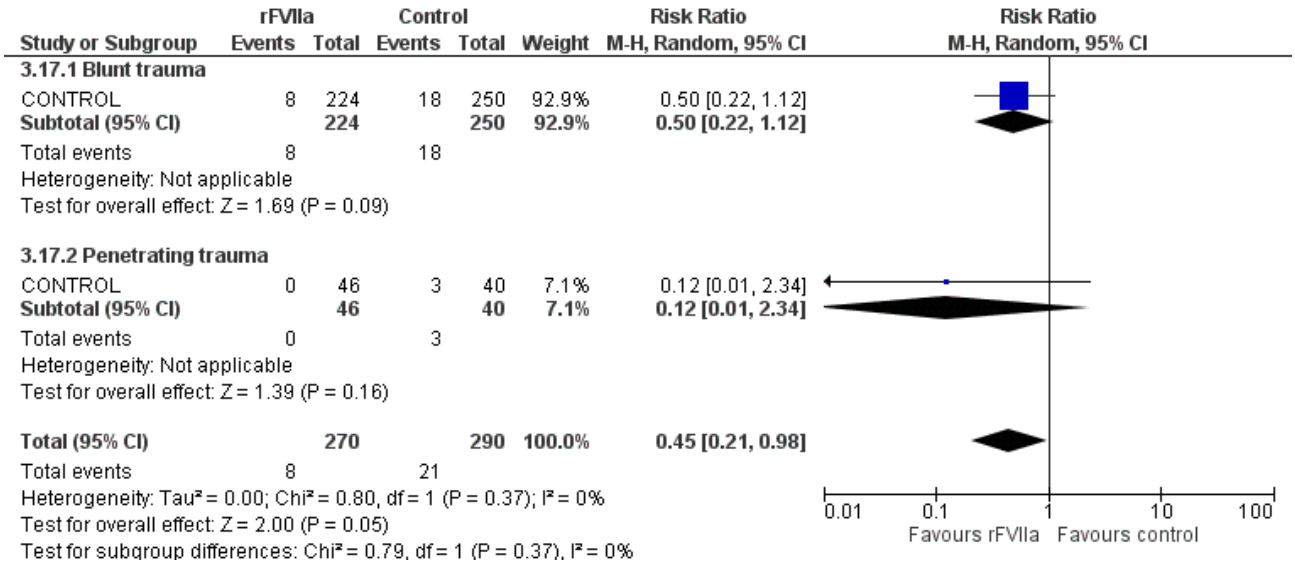


Figure 32. Risk ratio for acute respiratory distress syndrome (90 days) of rFVIIa versus placebo, by considering (blunt or penetrating) trauma patients.

Table 32. Outcome data for the multiple organ failure: rFVIIa versus placebo.

Multiple organ failure					
RCT studies focused on blunt and penetrating trauma patients: pre-hospital use of rFVIIa versus placebo					
	rFVIIa		**Placebo**		**time point**
	n	**tot**	**n**	**tot**	
Boffard 2005					
Blunt trauma	5	69	9	74	30 days
	n	**tot**	**n**	**tot**	
Penetrating trauma	2	70	7	64	30 days
	n	**tot**	**n**	**tot**	
CONTROL					
Blunt trauma	98	218	129	242	30 days
	10	224	17	250	90 days
	n	**tot**	**n**	**tot**	
Penetrating trauma	10	44	9	38	30 days
	1	46	1	40	90 days

Multiple organ failure (30 days) among blunt or penetrating trauma patients:

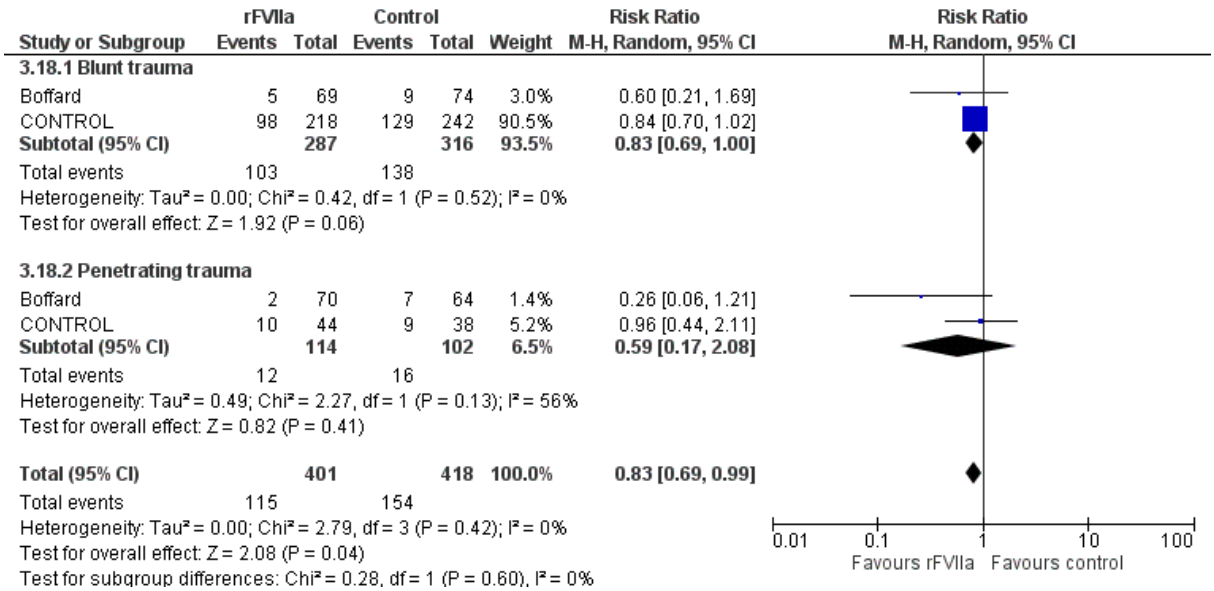


Figure 33. Risk ratio for multiple organ failure (30 days) of rFVIIa versus placebo, by considering (blunt or penetrating) trauma patients.

Multiple organ failure (90 days) among blunt or penetrating trauma patients:

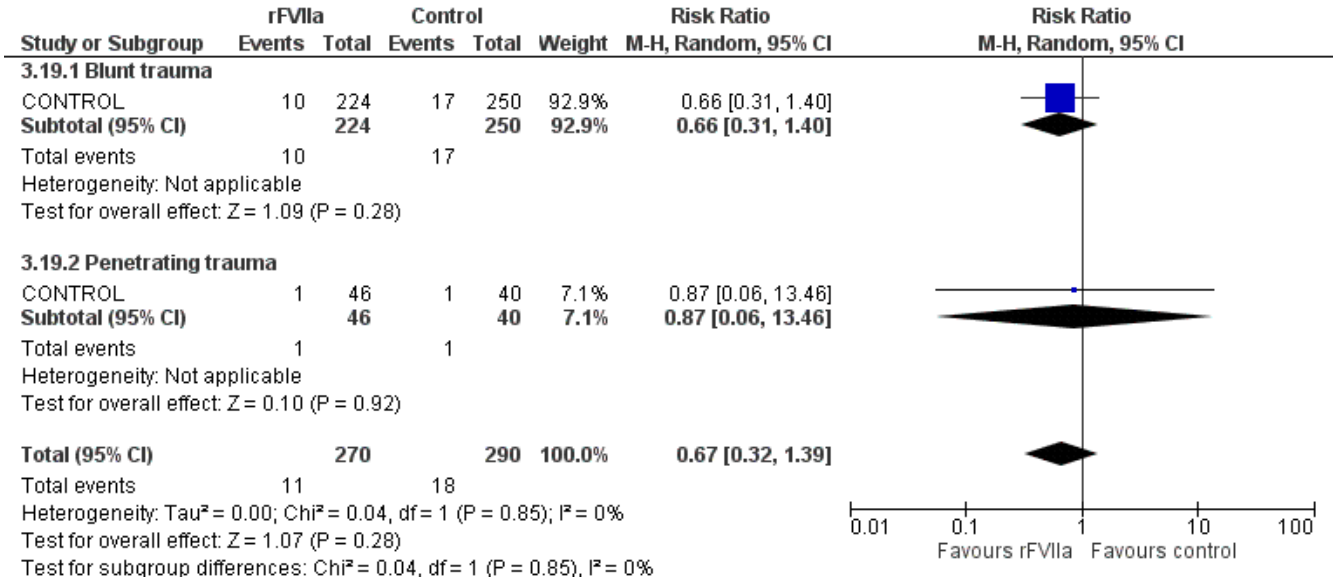


Figure 34. Risk ratio for multiple organ failure (90 days) of rFVIIa versus placebo, by considering (blunt or penetrating) trauma patients.

4. USO DI EMOCOMPONENTI

Per la trasfusione di emocomponenti è stato possibile effettuare le seguenti comparazioni:
- PRBC e trasfusione di sangue: sia per l'agente TXA che per il rFVIIa vs placebo;
- Platelets, Plasma cryoprecipitate e Fresh Frozen Plasma (FFP): solo per la comparazione riguardante la somministrazione del fattore rFVIIa vs placebo.

4.1 PRBCS, Blood Product Transfused, Massive Transfusion

Comparazione 1. Acido Tranexamico vs placebo

Per quanto riguarda la trasfusione di emocomponenti è stato rilevato quanto segue:
PRBC: sia considerando le unità trasfuse che i soggetti che hanno subito trasfusioni di PRBC, non si rileva una riduzione significativa indotta dalla somministrazione pre-ospedaliera dell'agente emostatico TXA (CRASH-2).

Table 33. Outcome data for the comparisons of blood product use: TXA versus placebo.

PRBC transfusion					
RCT studies: pre-hospital use of TXA versus placebo					
	TXA		**Placebo**		**time point**
	N = 10060		**N= 10067**		
CRASH-2	**mean**	**sd**	**mean**	**sd**	
	6.06	9.98	6.29	10.31	within 28 days
Blood product transfused					
RCT studies: pre-hospital use of TXA versus placebo					
	TXA		**Placebo**		**time point**
CRASH-2	**n**	**tot**	**n**	**tot**	
	5067	10060	5160	10067	within 4 weeks

Blood product use (28 days):

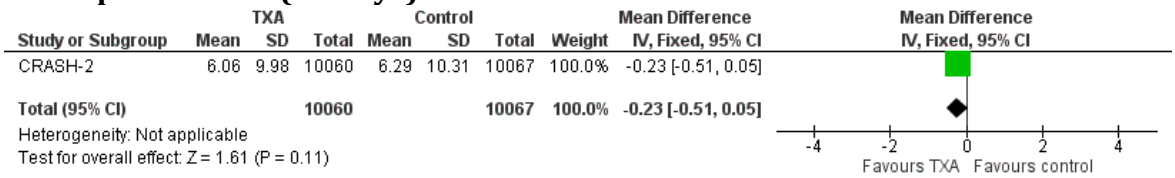


Figure 35. Mean difference for blood product use (28 days) of TXA versus placebo, by considering trauma patients.

Blood product transfused (4 weeks):

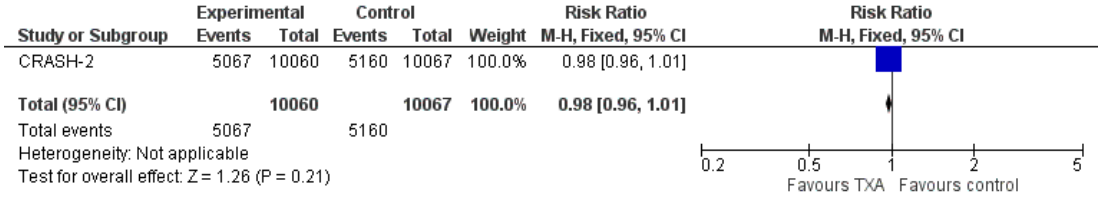


Figure 36. Risk ratio for blood product transfused (4 weeks) of TXA versus placebo, by considering trauma patients.

Comparazione 2. Fattore VII ricombinante vs placebo

Per quanto riguarda la trasfusione di emocomponenti è stato rilevato quanto segue:

- *PRBC* non si fornisce una chiara indicazione riguardo al beneficio entro 48 ore dettato dalla somministrazione di rFVIIa (CONTROL).
- *trasfusione massiva* a 24 ore (CONTROL) è stata rilevata una riduzione del rischio solamente nella popolazione con trauma penetrante, mentre a 48 ore (Boffard 2005) il beneficio dettato dalla somministrazione di rFVIIa riguarda sia l'intera popolazione, che i soggetti affetti da trauma contusivo (a differenza degli individui con trauma penetrante).

Table 34. Outcome data for the comparisons of blood product use: rFVIIa versus placebo.

PRBC transfusion					
RCT studies focused on blunt and penetrating trauma patients: pre-hospital use of rFVIIa versus placebo					
CONTROL	**rFVIIa**		**Placebo**		**time point**
	N = 221		**N= 247**		
Blunt trauma	**mean**	**sd**	**mean**	**sd**	
	7.8	10.6	9.1	11.3	within 48 hours
	N = 46		**N= 40**		
Penetrating trauma	**mean**	**sd**	**mean**	**sd**	
	5	7.4	6.8	6.9	within 48 hours
Massive transfusion					
RCT studies focused on blunt and penetrating trauma patients: pre-hospital use of rFVIIa versus placebo					
CONTROL (10 units of RBC from injury to 24-h postdose)					
	n	**tot**	**n**	**tot**	
Blunt trauma	111	221	134	247	within 24 hours
Penetrating trauma	**n**	**tot**	**n**	**tot**	
	14	46	21	40	within 24 hours
	rFVIIa		**Placebo**		**time point**
Boffard 2005 (patients alive at 48 hours receiving more than 12 units of RBCs within 48 hours of the first dose)					
	n	**tot**	**n**	**tot**	
Blunt trauma	8	56	20	61	within 48 hours
Penetrating trauma	**n**	**tot**	**n**	**tot**	
	4	58	10	54	within 48 hours

Blood product use (48 hours) among blunt or penetrating trauma patients:

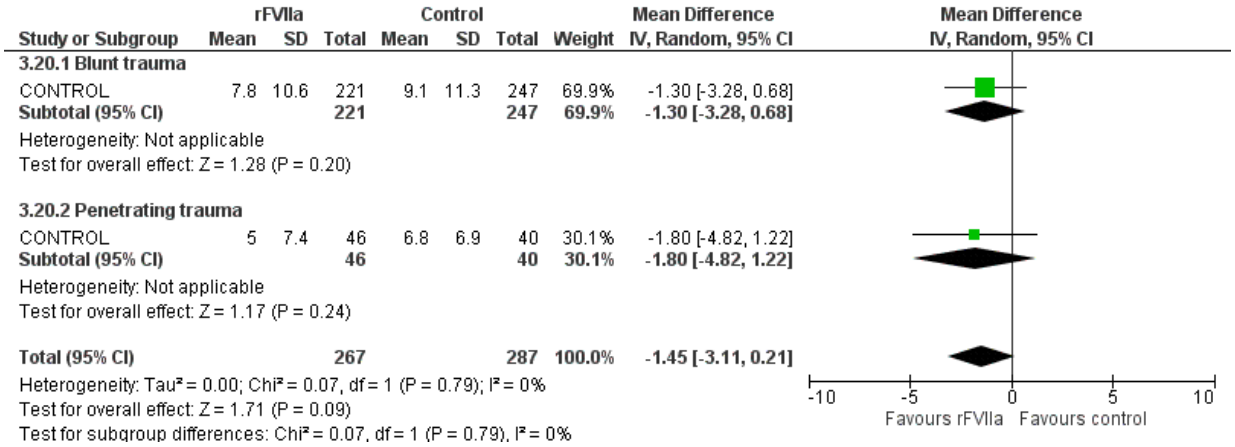


Figure 37. Mean difference for blood product use (48 hours) of rFVIIa versus placebo, by considering (blunt or penetrating) trauma patients.

Massive blood transfusion (24 hours) among blunt or penetrating trauma patients:

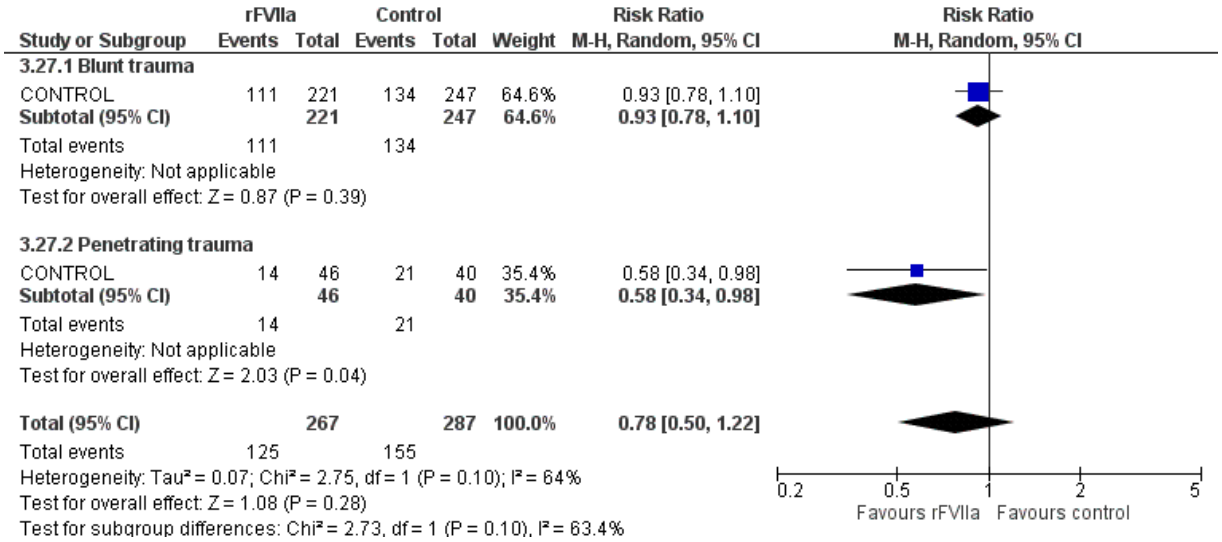


Figure 38. Risk ratio for massive blood transfusion (24 hours) of rFVIIa versus placebo, by considering (blunt or penetrating) trauma patients.

Massive blood transfusion (48 hours) among blunt or penetrating trauma patients:

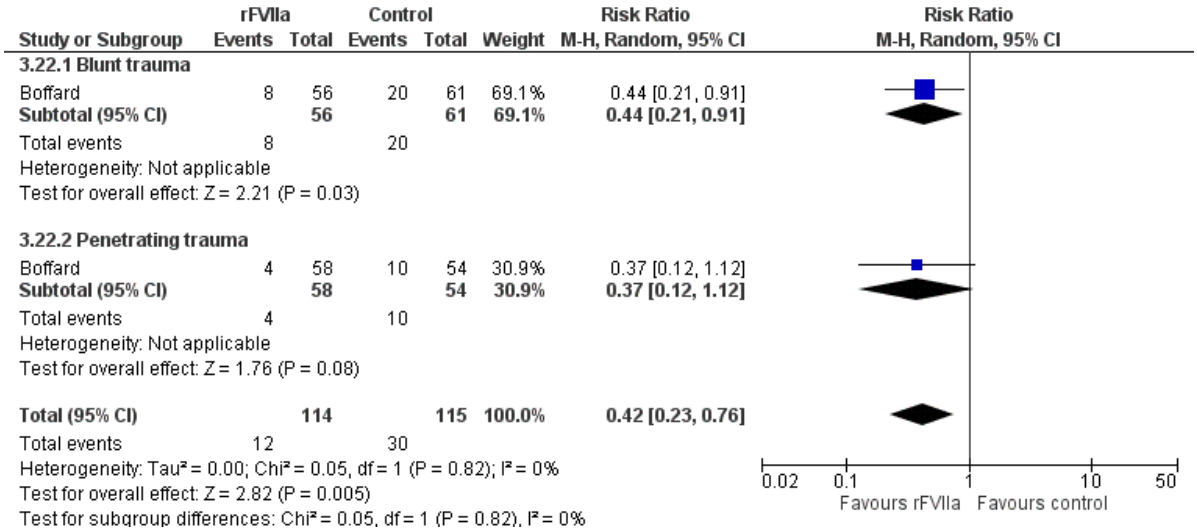


Figure 39. Risk ratio for massive blood transfusion (48 hours) of rFVIIa versus placebo, by considering (blunt or penetrating) trauma patients.

4.2 Platelets, Plasma Cryoprecipitate, Fresh Frozen Plasma (Ffp)

Comparazione 2. Fattore VII ricombinante vs placebo

Per quanto riguarda la trasfusione di emocomponenti è stato rilevato quanto segue:

- *Platelets e Cryoprecipitate*: non forniscono una chiara indicazione riguardo al beneficio entro 48 ore dettato dalla somministrazione di rFVIIa (CONTROL).
- *FFP*: un RCT (CONTROL) mostra una riduzione del rischio di trasfusione di FFP a seguito della somministrazione dell'agente emostatico rFVIIa a 48 ore, significativa nei pazienti con trauma contusivo (ma non nei pazienti con trauma penetrante) e nell'intera popolazione.

Table 35. Outcome data for the comparisons of Platelets, Cryoprecipitate, FFP use: rFVIIa versus placebo.

Platelets transfusion					
RCT studies focused on blunt and penetrating trauma patients: pre-hospital use of rFVIIa versus placebo					
CONTROL	**rFVIIa**		**Placebo**		**time point**
	N = 221		**N= 247**		
Blunt trauma	**mean**	**sd**	**mean**	**sd**	
	3.7	8.6	3.9	7.8	within 48 hours
	N = 46		**N= 40**		
Penetrating trauma	**mean**	**sd**	**mean**	**sd**	
	1.9	3.9	2.7	4.1	within 48 hours
Cryoprecipitate transfusion					
RCT studies focused on blunt and penetrating trauma patients: pre-hospital use of rFVIIa versus placebo					
	rFVIIa		**Placebo**		**time point**
	N = 221		**N= 247**		
CONTROL Blunt trauma	**mean**	**sd**	**mean**	**sd**	
	0.9	3.3	1.4	4.5	within 48 hours
	N = 46		**N= 40**		
Penetrating trauma	**mean**	**sd**	**mean**	**sd**	
	1.6	4.1	2	4.8	within 48 hours
Fresh Frozen Plasma transfusion					
RCT studies focused on blunt and penetrating trauma patients: pre-hospital use of rFVIIa versus placebo					
	rFVIIa		**Placebo**		**time point**
	N = 221		**N= 247**		
CONTROL Blunt trauma	**mean**	**sd**	**mean**	**sd**	
	5.3	6.7	8	10.1	within 48 hours
Penetrating trauma	**N = 46**		**N= 40**		within 48 hours

	mean	sd	mean	Sd
	4	6.2	6.5	7.6

Platelets transfusion (48 hours) among blunt or penetrating trauma patients:

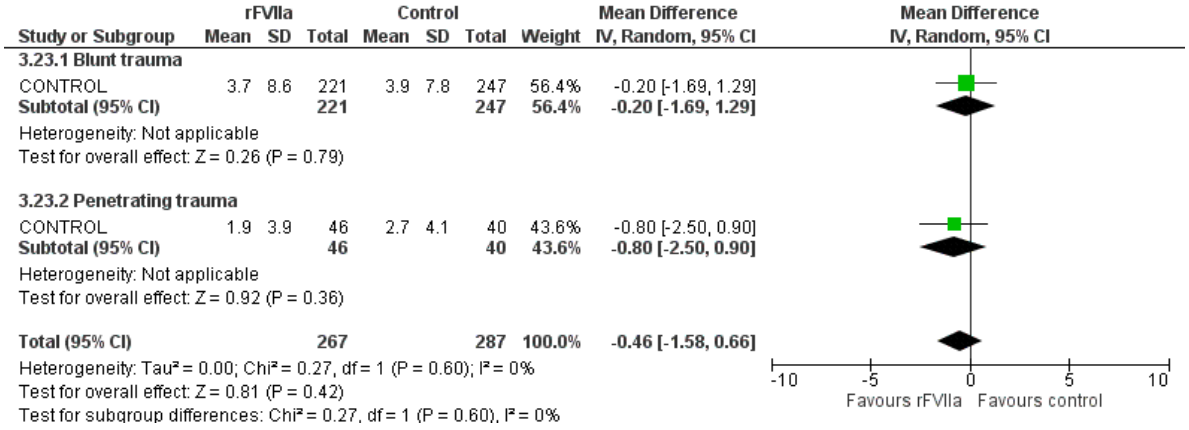


Figure 40. Mean difference for platelets transfusion (48 hours) of rFVIIa versus placebo, by considering (blunt or penetrating) trauma patients.

Cryoprecipitate transfusion (48 hours) among blunt or penetrating trauma patients:

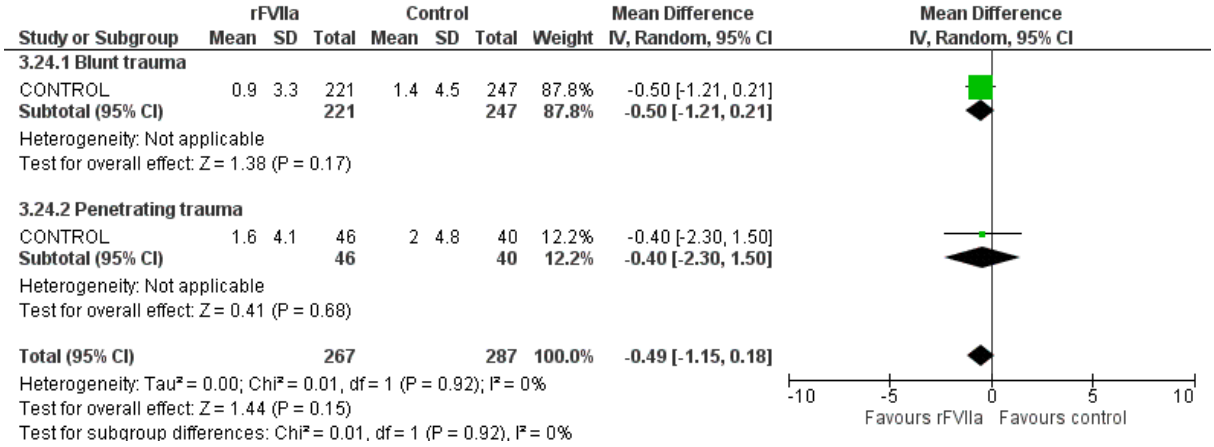


Figure 41. Mean difference for cryoprecipitate transfusion (48 hours) of rFVIIa versus placebo, by considering (blunt or penetrating) trauma patients.

Fresh frozen plasma transfusion (48 hours) among blunt or penetrating trauma patients:

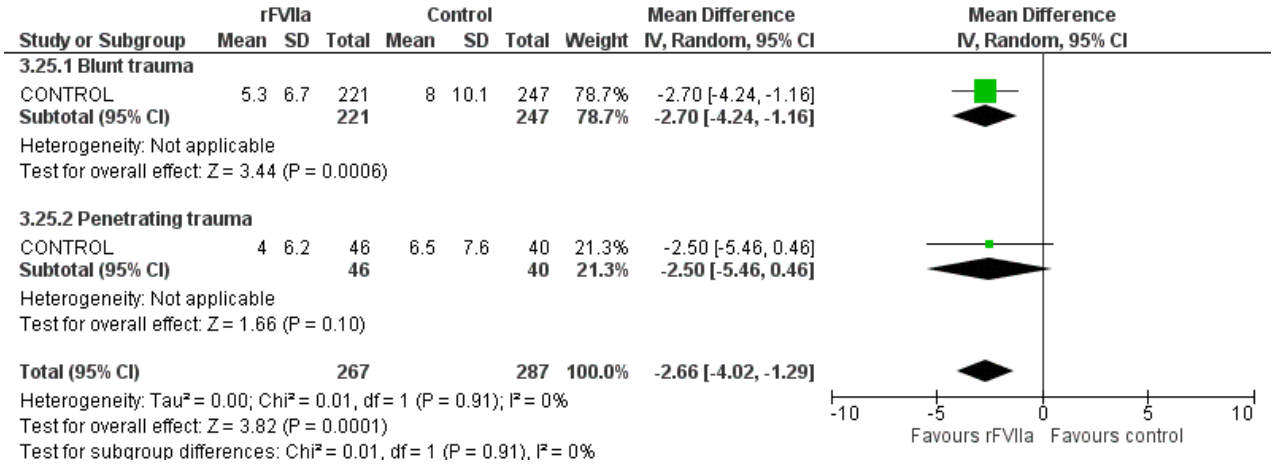


Figure 42. Mean difference for fresh frozen plasma transfusion (48 hours) of rFVIIa versus placebo, by considering (blunt or penetrating) trauma patients.

OUTCOME IMPORTANTI

1. MORTALITÀ A 12 MESI

Nessuno studio incluso ha riportato l'outcome d'interesse.

2. ENTITÀ DELL'EMORRAGIA

Comparazione 1. Acido Tranexamico vs placebo

Considerando la somministrazione pre-ospedaliera dell'agente emostatico TXA, un solo RCT (CRASH-2) rileva l'aumento dell'emorragia nelle 24-48 ore dal ricovero ospedaliero, tra soggetti con trauma cranico e importante perdita ematica.

- *Per il tempo definitivo di controllo dell'emorragia nelle 24-48 ore (CRASH-2), si prega di prendere visione dell'Appendice C supplementare – Sottogruppi di Popolazione.*

3. OUTCOMES RIPORTATI DAI PAZIENTI

Nessuno studio incluso ha riportato l'outcome d'interesse.

ALTRI OUTCOME NON IMPORTANTI

Oltre agli outcome indicati dal PICO, si riportano le analisi di altri outcome rilevati negli articoli inclusi.
Le cause riportate negli RCT relative ad altri eventi avversi sono:
- *necessità di intervento neurochirurgico* per il quale è stato possibile analizzare solo la comparazione somministrazione pre-hospital di TXA vs placebo;
- *giorni liberi da ricovero ospedaliero, da ventilazione, da ricovero in terapia intensiva* per i quali è stato possibile analizzare le comparazioni per i due agenti emostatici (TXA, rFVIIa).

➢ *Per i giorni liberi da ricovero ospedaliero (TXA), da ventilazione (TXA), da ricovero in terapia intensiva (TXA), si prega di prendere visione dell'Appendice C supplementare – Sottogruppi di Popolazione.*

1. NECESSITÀ DI INTERVENTO NEUROCHIRURGICO

<u>Comparazione 1. Acido Tranexamico vs placebo</u>

Il rischio di dover essere sottoposti ad intervento neurochirurgico entro 28 giorni è stato riportato da 2 RCT (CRASH-2, TXA), che non mostrano un chiaro beneficio a seguito della somministrazione pre-ospedaliera dell'agente emostatico TXA.

Table 36. Outcome data for neurosurgical intervention: TXA versus placebo.

Neurosurgical intervention					
RCT studies: pre-hospital use of TXA versus placebo					
	TXA		**Placebo**		**time point**
	n	**tot**	**n**	**tot**	
CRASH-2	1040	10060	1059	10067	within 28 days
TXA	137	657	54	309	within 28 days

Neurosurgical intervention (within 28 days):

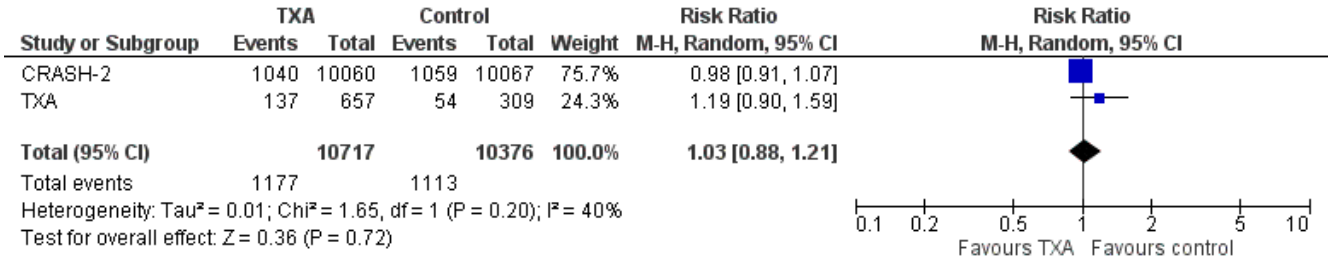


Figure 43. Risk ratio for neurosurgical intervention (28 days) of TXA versus placebo by considering trauma patients.

2. *GIORNI LIBERI DA RICOVERO OSPEDALIERO*

Comparazione 2. Fattore VII ricombinante vs placebo

Per i giorni liberi dal ricovero a 30 giorni non si mostra una chiara indicazione dei benefici a seguito dell'assunzione pre-ospedaliera dell'agente emostatico rFVIIa (CONTROL) sia per la popolazione affetta da trauma contusivo che penetrante.

Table 37. Outcome data for the comparisons of hospital-free days: rFVIIa versus placebo.

Hospital-free days					
RCT studies focused on blunt and penetrating trauma patients: pre-hospital use of rFVIIa versus placebo					
	rFVIIa		**Placebo**		**time point**
CONTROL	**N = 218**		**N= 242**		
	mean	**sd**	**mean**	**sd**	
Blunt trauma	4	6.9	3.5	6.4	30 days
	rFVIIa		**Placebo**		**time point**
	N = 44		**N= 38**		
Penetrating trauma	**mean**	**sd**	**mean**	**sd**	
	13.2	10.4	11.3	9.1	30 days

Hospital-free days (30 days) among blunt or penetrating trauma patients:

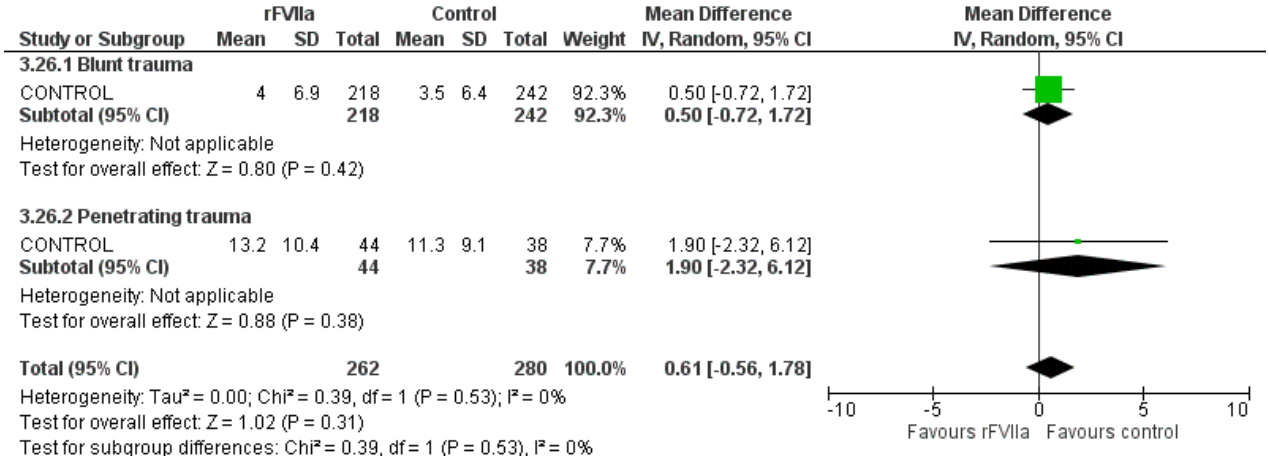


Figure 44. Mean difference for hospital-free days (30 days) of rFVIIa versus placebo, by considering (blunt or penetrating) trauma patients.

3. *GIORNI LIBERI DA VENTILAZIONE*

Comparazione 2. Fattore VII ricombinante vs placebo

Per i giorni liberi da ventilazione a 30 giorni non si mostra una chiara indicazione dei benefici a seguito dell'assunzione pre-ospedaliera dell'agente emostatico rFVIIa (CONTROL) sia per la popolazione che presentava trauma contusivo che penetrante. Inoltre, lo studio di Boffard 2005 mostra solo valori mediani.

Table 38. Outcome data for the comparisons of ventilator free-days: rFVIIa versus placebo.

Ventilator free days					
RCT studies focused on blunt and penetrating trauma patients: pre-hospital use of rFVIIa versus placebo					
	rFVIIa		**Placebo**		**time point**
CONTROL	**N = 218**		**N= 242**		
	mean	**sd**	**mean**	**sd**	
Blunt trauma	17.2	10.3	16.4	10.3	30 days
	N = 44		**N= 38**		
	mean	**sd**	**mean**	**sd**	
Penetrating trauma	21.2	11.1	21.9	10	30 days
	N = 69		**N= 74**		
Boffard 2005 Blunt trauma	**median**	**IQR**	**median**	**IQR**	
	17	(0-29)	13	(0-29)	30 days
	N = 70		**N= 64**		
Penetrating trauma	**median**	**IQR**	**median**	**IQR**	
	25	(0-29)	20	(0-29)	30 days

Ventilator-free days (30 days) among blunt or penetrating trauma patients:

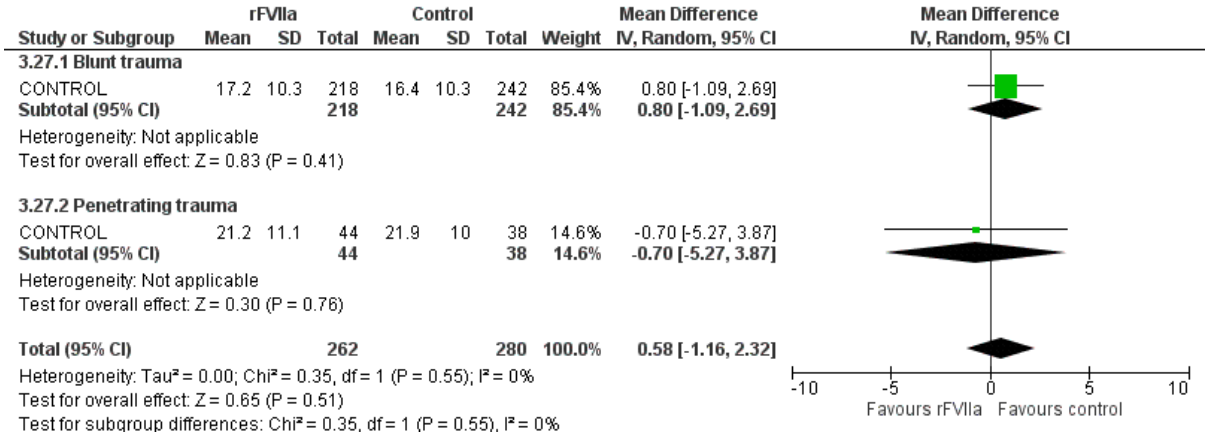


Figure 45. Mean difference for ventilator-free days (30 days) of rFVIIa versus placebo, by considering (blunt or penetrating) trauma patients.

4. GIORNI LIBERI DA RICOVERO IN TERAPIA INTENSIVA

Comparazione 2. Fattore VII ricombinante vs placebo

Per i giorni liberi dal ricovero in terapia intensiva a 30 giorni non si mostra una chiara indicazione dei benefici a seguito dell'assunzione pre-ospedaliera dell'agente emostatico rFVIIa (CONTROL) sia per la popolazione che presentava trauma contusivo, che penetrante. Inoltre, lo studio di Boffard 2005 mostra solo valori mediani.

Table 39. Outcome data for the comparisons of ICU-free days: rFVIIa versus placebo.

ICU free days					
RCT studies focused on blunt and penetrating trauma patients: pre-hospital use of rFVIIa versus placebo					
CONTROL	**rFVIIa**		**Placebo**		**time point**
	N = 218		**N= 242**		
Blunt trauma	**mean**	**sd**	**mean**	**sd**	
	13.7	10.4	12.9	9.9	30 days
	N = 44		**N= 38**		
Penetrating trauma	**mean**	**sd**	**mean**	**sd**	
	18.7	11.2	19.5	10.6	30 days
	N = 69		**N= 74**		
Boffard 2005 Blunt trauma	**median**	**IQR**	**median**	**IQR**	
	12	(0-29)	8	(0-29)	30 days
	N = 70		**N= 64**		
Penetrating trauma	**median**	**IQR**	**median**	**IQR**	
	23	(0-29)	18	(0-29)	30 days

ICU-free days (30 days) among blunt or penetrating trauma patients:

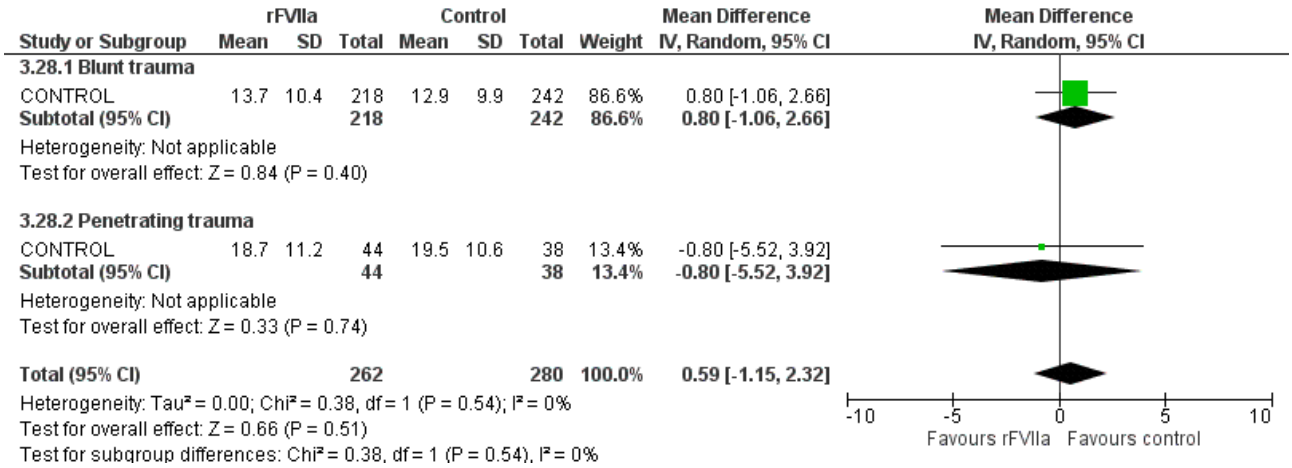


Figure 46. Mean difference for ICU-free days (30 days) of rFVIIa versus placebo, by considering (blunt or penetrating) trauma patients.

TABELLA RIASSUNTIVA – EVIDENZE DI EFFICACIA

Table 40. Summary table of clinical outcomes regarding the pre-hospital administration of TXA or rFVIIa versus placebo.

OUTCOME	TXA vs placebo	rFVIIa vs placebo
OUTCOME CRITICI:		
1) MORTALITÀ		
1.1) Overall		
24 ore	HR 0.91 (0.79 to 1.05)	-
48 ore	-	RR 1.08 (0.65 to 1.81)
4 settimane	RR 0.93 (0.88 to 0.97)	RR 0.94 (0.70 to 1.27)
1.2) Causa-specifica		
Disfunzione multiorgano 4 settimane	RR 0.92 (0.77 to 1.09)	*Supplementary: Population*
Lesione cerebrale		
24 ore	*Supplementary: Population*	-
4 settimane	RR 0.95 (0.89 to 1.02)	-
Emorragia 4 settimane	RR 0.86 (0.76 to 0.96)	-
Embolia polmonare 4 settimane	-	*Supplementary: Population*
Sepsi 4 settimane	-	*Supplementary: Population*
2) HEALTH RELATED QUALITY OF LIFE	v. sezioni precedenti	-
3) EVENTI AVVERSI		
3.1) Sepsi		
4 settimane	*Supplementary: Population*	-
90 giorni	-	RR 0.91 (0.61 to 1.37)
3.2) Embolia polmonare		
4 settimane	RR 0.92 (0.71 to 1.21)	RR 1.21 (0.47 to 3.09)
3.3) MI/Ictus		
Infarto miocardico 4 settimane	RR 0.73 (0.52 to 1.03)	-
Ictus 4 settimane	RR 0.93 (0.72 to 1.19)	-
MI o ictus 4 settimane	-	RR 1.07 (0.31 to 3.67)
3.4) Vascolari		
Qualsiasi evento occlusivo vascolare 4 settimane	RR 0.86 (0.74 to 1.00)	-

Eventi avversi tromboembolici		
48 ore	-	RR 0.98 (0.32 to 3.01)
90 giorni	-	RR 1.00 (0.45 to 2.22)
4 settimane	-	*Supplementary: Population*
Trombotici arteriosi 90 giorni	-	RR 1.63 (0.80 to 3.33)
Trombotici venosi 90 giorni	-	RR 0.53 (0.04 to 6.63)
Trombosi venosa profonda 4 settimane	RR 0.97 (0.69 to 1.35)	RR 0.94 (0.47 to 1.89)
Coagulazione intravascolare disseminata		
4 settimane	*Supplementary: Population*	-
90 giorni	-	RR 0.69 (0.27 to 1.76)
3.5) Altri eventi avversi		
Sanguinamento gastrointestinale 4 settimane	*Supplementary: Population*	-
Insufficienza renale 4 settimane	*Supplementary: Population*	-
Danno renale acuto 4 settimane	*Supplementary: Population*	-
Convulsioni 4 settimane	*Supplementary: Population*	-
Sindrome da distress respiratorio acuto		
4 settimane	-	RR 0.44 (0.16 to 1.17)
90 giorni	-	RR 0.45 (0.21 to 0.98)
Disfunzione multiorgano		
4 settimane	-	RR 0.83 (0.69 to 0.99)
90 giorni	-	RR 0.67 (0.32 to 1.39)
4) USO DI EMOCOMPONENTI		
PRBC		
48 ore	-	MD -1.45 (-3.11 to 0.21)
4 settimane	MD -0.23 (-0.51 to 0.05)	-
Trasfusione di sangue 4 settimane	RR 0.98 (0.96 to 1.01)	-
Trasfusione massiva		
24 ore	-	RR 0.78 (0.50 to 1.22)
48 ore	-	RR 0.42 (0.23 to 0.76)
Piastrine 48 ore	-	MD -0.46 (-1.58 to 0.66)
Plasma crioprecipitato 48 ore	-	MD -0.49 (-1.15 to 0.18)
Plasma fresco congelato 48 ore	-	MD -2.66 (-4.02 to -1.29)
OUTCOME IMPORTANTI:		
1) TEMPO DI CONTROLLO DEFINITIVO DELL'EMORRAGIA		
Totale crescita dell'emorragia 24-48 ore	*Supplementary: Population*	-

ALTRI OUTCOME NON IMPORTANTI:		
1) NECESSITÀ DI INTERVENTO NEUROCHIRURGICO 4 settimane	RR 1.03 (0.88 to 1.21)	-
2) GIORNI LIBERI DA RICOVERO OSPEDALIERO 4 settimane	*Supplementary: Population*	MD 0.61 (-0.56 to 1.78)
3) GIORNI LIBERI DA VENTILAZIONE 4 settimane	*Supplementary: Population*	MD 0.58 (-1.16 to 2.32)
4) GIORNI LIBERI DA RICOVERO IN TERAPIA INTENSIVA 4 settimane	*Supplementary: Population*	MD 0.59 (-1.15 to 2.32)

ANALISI AGGIUNTIVE - DESCRITTIVE MORTALITÀ

Mortalità stratificata per tempo di somministrazione del trattamento

Diverse pubblicazioni afferenti al trial CRASH-2 (CRASH-2 Collaborators, Intracranial Bleeding Study, 2011; Roberts et al., 2013; Roberts et al., 2014) e al CRASH-3 (CRASH-3 Trial Collaborators, 2019) hanno riportato l'associazione tra la mortalità e il tempo di somministrazione del trattamento (entro 1 ora, da 1 a 3 ore o oltre 3 ore).
In particolare, viene mostrata l'associazione tra il tempo al trattamento con TXA dalla lesione e la mortalità, intesa come overall, rispettivamente causata o no da emorragia (CRASH-2 Collaborators, Intracranial Bleeding Study, 2011). Di seguito i risultati.

	N	All causes of death	Bleeding death	Non-bleeding death
Overall	20 127	0·91 (0·85–0·97); p=0·0035	0·85 (0·76–0·96); p=0·0077	0·94 (0·86–1·02); p=0·13
Time to treatment (h)				
≤1	7451	0·87 (0·76–0·97)	0·68 (0·57–0·82)	1·04 (0·89–1·21)
>1–3	6033	0·87 (0·77–0·97)	0·79 (0·64–0·97)	0·91 (0·78–1·05)
>3	6634	1·00 (0·90–1·13)	1·44 (1·12–1·84)	0·89 (0·78–1·02)
χ^2 test of homogeneity	..	4·411 (p=0·11)	23·516 (p=0·0000)	2·537 (p=0·28)

Table 1: Relative risk (95% CI) of death with tranexamic acid, overall and by time to treatment

Inoltre, in Roberts et al., 2013 viene riportata un'associazione significativa tra la riduzione della mortalità dovuta ad emorragia e la somministrazione precoce (immediatamente dopo la lesione) dell'agente emostatico TXA (OR: 0,61; 95% CI: 0,50 to 0,74). Per ogni ora che passa dalla lesione al trattamento, è stato stimato che l'associazione (OR) si moltiplichi di 1,15 (95% CI: 1,08 to 1,23).
Infine, in CRASH-3 Trial Collaborators, 2019 viene riportato un RR per la mortalità dovuta a lesioni cerebrali pari a 0,96 (95% CI: 0,79 – 1,17) in seguito alla somministrazione dell'agente emostatico TXA entro la prima ora dalla lesione. Nei pazienti casualmente assegnati al trattamento tra la prima e la terza ora dalla lesione di 0,93 (95% CI: 0,85 – 1,02) o dopo la terza ora pari a 0,94 (95% CI: 0,81 – 1,09). Tuttavia, i pazienti trattati immediatamente dopo la lesione presentavano spesso una lesione cerebrale più severa, pertanto, i risultati potrebbero risentire del confondimento dato dalla gravità della lesione stessa.

Mortalità stratificata per giorni al decesso dalla lesione

Oltre che per la tempestività per trattamento, viene riportata la mortalità, intesa come overall, rispettivamente causata o no da emorragia, anche considerando i giorni dalla lesione (Roberts et al., 2014).

Table 1 Hazard ratios (95% CI) of the effect of tranexamic acid on all-cause mortality, bleeding and non-bleeding deaths by day since injury

Days since injury	All-cause	Bleeding	Non-bleeding
0	0.83 (0.73, 0.93)	0.80 (0.68, 0.94)	0.87 (0.71, 1.06)
1	0.91 (0.79, 1.04)	0.89 (0.72, 1.11)	0.92 (0.76, 1.11)
2	0.96 (0.77, 1.19)	1.17 (0.74, 1.86)	0.91 (0.71, 1.16)
3	1.01 (0.76, 1.34)	0.66 (0.32, 1.37)	1.09 (0.80, 1.48)
4	0.96 (0.70, 1.36)	0.77 (0.29, 2.06)	1.01 (0.71, 1.43)

Per un'analisi ancora più dettagliata, si riportano le stime della mortalità (overall e rispettivamente causata o meno da emorragia) calcolate stratificando ulteriormente per tempestività del trattamento (entro o dopo 3 ore dalla lesione) e considerando i giorni dal verificarsi del trauma (Roberts et al., 2014).

Table 2 Hazard ratios (95% CI) of the effect of tranexamic acid on all-cause mortality, bleeding and non-bleeding deaths by day since injury and time from injury to treatment

Days since injury	Time to treatment ≤3 h			Time to treatment >3 h		
	All-cause	Bleeding	Non- bleeding	All-cause	Bleeding	Non- bleeding
0	0.78 (0.68, 0.90)	0.72 (0.60, 0.86)	0.89 (0.71, 1.11)	1.02 (0.76, 1.36)	1.28 (0.85, 1.93)	0.79 (0.51, 1.22)
1	0.86 (0.72, 1.02)	0.72 (0.55, 0.94)	0.98 (0.78, 1.23)	1.02 (0.80, 1.31)	1.47 (0.97, 2.21)	0.81 (0.59, 1.13)
2	0.86 (0.65, 1.13)	1.01 (0.58, 1.77)	0.82 (0.59, 1.12)	1.16 (0.81, 1.66)	1.61 (0.70, 3.70)	1.08 (0.72, 1.60)
3	0.95 (0.66, 1.37)	0.26 (0.09, 0.78)	1.20 (0.80, 1.81)	1.11 (0.73, 1.71)	2.76 (0.73, 10.39)	0.98 (0.62, 1.55)
4	0.94 (0.61, 1.45)	0.64 (0.18, 2.28)	0.99 (0.63, 1.57)	1.04 (0.62, 1.75)	1.04 (0.21, 5.13)	1.04 (0.60, 1.80)

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Appendice C2 – Sintesi delle evidenze – Supplemento: Sottogruppi di popolazione

CQ8. Gestione dell'emorragia nel setting pre-ospedaliero: agenti emostatici.

Indice

È stata effettuata una revisione sistematica con ricerca della letteratura sulle banche dati Embase, Medline e Cochrane CENTRAL aggiornata al 29 giugno 2020. Sono stati individuati 1518 records da cui sono state selezionate 8 referenze che soddisfano i criteri per rispondere al quesito clinico proposto, rispettivamente 5 studi primari e 3 revisioni sistematiche da cui sono stati ulteriormente estratti 3 studi. Inoltre, sono state interrogate clinicatrials.gov e le Linee guida NICE, aggiungendo all'inclusione altre 11 nuove pubblicazioni, 6 e 5 rispettivamente. In totale, sono state individuate 19 pubblicazioni afferenti 5 studi randomizzati e controllati: CRASH-2, CRASH-3, TXA trial, CONTROL trial e Boffard 2005. In data 9 settembre 2020 è stata rilanciata per aggiornamento la search strategy, da cui è stata aggiunta una pubblicazione inerente uno studio incluso (TXA trial).

Gli studi inclusi sono controllati e randomizzati in cui il gruppo di controllo è rappresentato dal trattamento con placebo.
Questa appendice riporta le analisi per 2 tipi di popolazione:

- popolazione con trauma emorragico
- popolazione con trauma cranico

Si esplicitano le seguenti comparazioni:

iv) ***Somministrazione pre-ospedaliera di TXA verso placebo:***
   a. *Pazienti con significativa emorragia (CRASH-2) **
   b. *Pazienti con TBI:*
      -significativa emorragia e trauma cranico (CRASH-2: sottogruppo derivante dalla pubblicazione NESTED)
      -Pazienti con trauma cranico (CRASH-3, TXA)

   **10% dei soggetti potenzialmente ha TBI*

v) ***Somministrazione pre-ospedaliera di rFVIIa verso placebo:***
   Pazienti emodinamicamente instabili con trama cranico contusivo e severa emorragia (Boffard 2005: sottogruppo derivante da una pubblicazione successiva)

Table 1. Characteristics of patients.

			Gender		Age	ISS	Systolic blood pressure					
RCT	**INTERVENTION**	**N**	**M**	**F**	**MEDIAN (IQR)**	**MEDIAN (IQR)**	**MEAN (SD)**	**< 90**	**90-119**	**≥ 120**		**unknown**
TXA	TXA: 1 gram pre-hospital + 1 gram within 8 hours	312	227	85	39 (26 to 57)	17 (8 to 27)	-	-	-	-	-	-
	TXA: 2 grams pre-hospital + placebo	345	255	90	40 (26 to 56)	17 (8 to 27)	-	-	-	-	-	-
	PLACEBO	309*	233	76	36 (25 to 55)	17 (9 to 27)	-	-	-	-	-	-
CRASH-2					**MEAN (SD)**	**MEAN (SD)**						
	TXA	10093	8439 (83,6%)	1654 (16,4%)	34,6 (14,1)	-	-	1566 (15,5%)	1615 (16%)	6901 (68,4%)		11 (0,11%)
	Subgroup: patients who also had TBI	133	111 (84%)	22 (16%)	36 (14)	-	116,4 (31,2)	9 (7%)	63 (47%)	61 (46%)		-
	PLACEBO	10114	8496 (84%)	1617 (16%)	34,5 (14,4)	-	-	1608 (15,9%)	1697 (16,8%)	6791 (67,1%)		18 (0,18%)
	Subgroup: patients who also had TBI	137	117 (85%)	20 (15%)	37 (14)	-	113,5 (29,4)	10 (7%)	69 (50%)	58 (43%)		-
CRASH-3										**120-139**	**≥ 140**	**unknown**
	TXA	4649	3742 (80%)	906 (19%)	41,7 (19)	-	-	89 (2%)	1508 (32%)	1461 (31%)	1576 (34%)	15 (<1%)
	PLACEBO	4553	3660 (80%)	893 (20%)	41,9 (19)	-	-	85 (2%)	1490 (33%)	1504 (33%)	1466 (32%)	8 (<1%)
Boffard 2005	**Population: Blunt trauma**											
	rFVIIa											
	Subgroup: patients with a TBI component	17	10 (59%)	7 (41%)	33,5 (13,7)	38,7±13,7	-	-	-	-	-	-
	PLACEBO											
	Subgroup: patients with a TBI component	13	8 (62%)	5 (38%)	32,6 (16,8)	36,8±12,8	-	-	-	-	-	-

		Heart Rate						Glasgow Coma Scale				
RCT	**INTERVENTION**	**MEAN (SD)**	**< 77**	**77-91**	**92-107**	**> 107**	**unknown**	**MEAN (SD)**	**Severe (3-8)**	**Moderate (9-12)**	**Mild (13-15)**	**unknown**
TXA	TXA: 1 gram pre-hospital + 1 gram within 8 hours	-	-	-	-	-	-	-	169	129	14	-
	TXA: 2 grams pre-hospital + placebo	-	-	-	-	-	-	-	177	159	9	-
	PLACEBO	-	-	-	-	-	-	-	186	115	8	-
CRASH-2	TXA	-	875 (8,7%)	1727 (17,1%)	2556 (25,3%)	4872 (48,3%)	63 (0,62%)	-	1799 (17,8%)	1353 (13,4%)	6934 (68,7%)	7 (0,07%)
	Subgroup: patients who also had TBI	100,7 (25,7)	-	-	-	-	-	10,5 (3,6)	45 (34%)	25 (19%)	63 (47%)	-
	PLACEBO	-	871 (8,6%)	1770 (17,5%)	2546 (25,2%)	4853 (48%)	74 (0,73%)	-	1839 (18,2%)	1351 (13,4%)	6908 (68,3%)	16 (0,16%)
	Subgroup: patients who also had TBI	101,6 (23,5)	-	-	-	-	-	10,5 (3,6)	45 (33%)	34 (25%)	58 (42%)	-
CRASH-3	TXA	-	-	-	-	-	-	-	1757 (40%)	1557 (33%)	1307 (27%)	28 (1%)
	PLACEBO	-	-	-	-	-	-	-	1732 (38%)	1524 (33%)	1262 (28%)	35 (1%)
Boffard 2005	**Population: Blunt trauma**											
	rFVIIa											
	Subgroup: patients with a TBI component	-	-	-	-	-	-	-	-	-	-	-
	PLACEBO											
	Subgroup: patients with a TBI component	-	-	-	-	-	-	-	-	-	-	-

		Type of injury		Respiratory rate				Capillary refill time				
RCT	**INTERVENTION**	**BLUNT**	**PENETRATING**	**< 10**	**10-29**	**> 29**	**unknown**	**MEAN (SD)**	**≤ 2**	**3-4**	**> 4**	**unknown**
TXA	TXA: 1 gram pre-hospital + 1 gram within 8 hours	16	12	-	-	-	-	-	-	-	-	-
	TXA: 2 grams pre-hospital + placebo	340	5	-	-	-	-	-	-	-	-	-
	PLACEBO	293	300	-	-	-	-	-	-	-	-	-
CRASH-2	TXA	6812 (67,5%)*	3281 (32,5%)	160 (1,6%)	8355 (82,8%)	1491 (14,8%)	87 (0,86%)	-	3432 (34%)	4665 (46,2%)	1699 (16,8%)	297 (2,9%)
	Subgroup: patients who also had TBI	132 (99,2%)	1 (0,8%)	-	-	-	-	3,4 (1,0)	-	-	-	-
	PLACEBO	6843 (67,7%)*	3271 (32,3%)	149 (1,5%)	8436 (83,4%)	1492 (14,1%)	100 (0,99%)	-	3406 (33,7%)	4722 (46,7%)	1672 (16,5%)	314(3,1%)
	Subgroup: patients who also had TBI	136 (99,3%)	1 (0,7%)	-	-	-	-	3,5 (1,1)	-	-	-	-
CRASH-3	TXA	-	-	-	-	-	-	-	-	-	-	-
	PLACEBO	-	-	-	-	-	-	-	-	-	-	-
Boffard 2005	**Population: Blunt trauma**											
	rFVIIa											
	Subgroup: patients with a TBI component	17	-	-	-	-	-	-	-	-	-	-
	PLACEBO											
	Subgroup: patients with a TBI component	13	-	-	-	-	-	-	-	-	-	-

		Time from injury to first dose (h)				
RCT	**INTERVENTION**	**MEAN (SD)**	**≤1**	**1-3**	**> 3**	**unknown**
TXA	TXA: 1 gram pre-hospital + 1 gram within 8 hours	-	-	-	-	-
	TXA: 2 grams pre-hospital + placebo	-	-	-	-	-
	PLACEBO	-	-	-	-	-
CRASH-2	TXA	2,8 (2,2)	3756 (37,2%)	3045 (30,2%)	3287 (32,6%)	5 (0,05%)
	Subgroup: patients who also had TBI	4,4 (1,8)	-	-	-	-
	PLACEBO	2,9 (2,6)	3722 (36,8%)	3006 (29,7%)	3380 (33,4%)	6 (0,06%)
	Subgroup: patients who also had TBI	4,2 (1,7)	-	-	-	-
CRASH-3	TXA		**≤1**	**1-2**	**2-3**	
		1,9 (0,7)	877 (19%)	2003 (43%)	1769 (38%)	-
	PLACEBO	1,9 (0,7)	869 (19%)	1889 (41%)	1795 (39%)	-
Boffard 2005	**Population: Blunt trauma**					
	rFVIIa					
	Subgroup: patients with a TBI component	-	-	-	-	-
	PLACEBO					
	Subgroup: patients with a TBI component	-	-	-	-	-

*Includes patients with both blunt and penetrating and only blunt injuries

COMPARAZIONE DI INTERVENTI A COPPIE (Pair-wise meta-analisi)

OUTCOME CRITICI

1 MORTALITÀ

1.1 OVERALL MORTALITY

Comparazione 1. Acido Tranexamico vs placebo

Si riportano, in Tabella 2, i dati relativi al tasso di mortalità rilevati alla somministrazione pre-ospedaliera dell'agente emostatico TXA o di placebo.

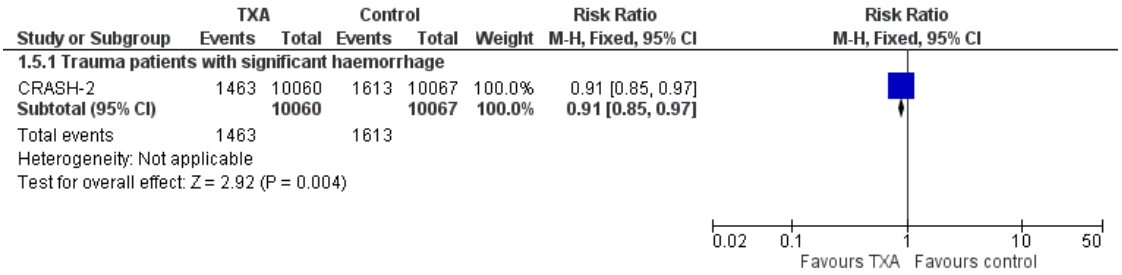
Per la mortalità a 28 giorni (CRASH-2, CRASH-3 e TXA), considerando la tipologia di popolazione, non risulta una riduzione significativa nei pazienti con forte emorragia (CRASH-2), tra i soggetti con i) trauma cranico (CRASH-3, TXA) e con ii) trauma cranico e forte emorragia (CRASH-2: sottogruppo).

Table 2. Outcome data for the comparisons of mortality: TXA versus placebo.

Overall Mortality					
RCT studies: pre-hospital use of TXA versus placebo					
	TXA		**Placebo**		**time point**
	n	**tot**	**n**	**tot**	
CRASH-2	1463	10060	1613	10067	4 weeks
with TBI	14	133	24	137	28 days
CRASH-3	1093	6406	1125	6331	28 days
TXA	93	657	50	309	28 days

Overall mortality (4 weeks), subgrouped for type of population:

C. **Pazienti con significativa emorragia**: trauma patients with significant haemorrhage (CRASH-2)



D. **Pazienti con TBI:** trauma patients with TBI (CRASH-3, TXA); trauma patients with significant haemorrhage and TBI (CRASH-2: subgroup)

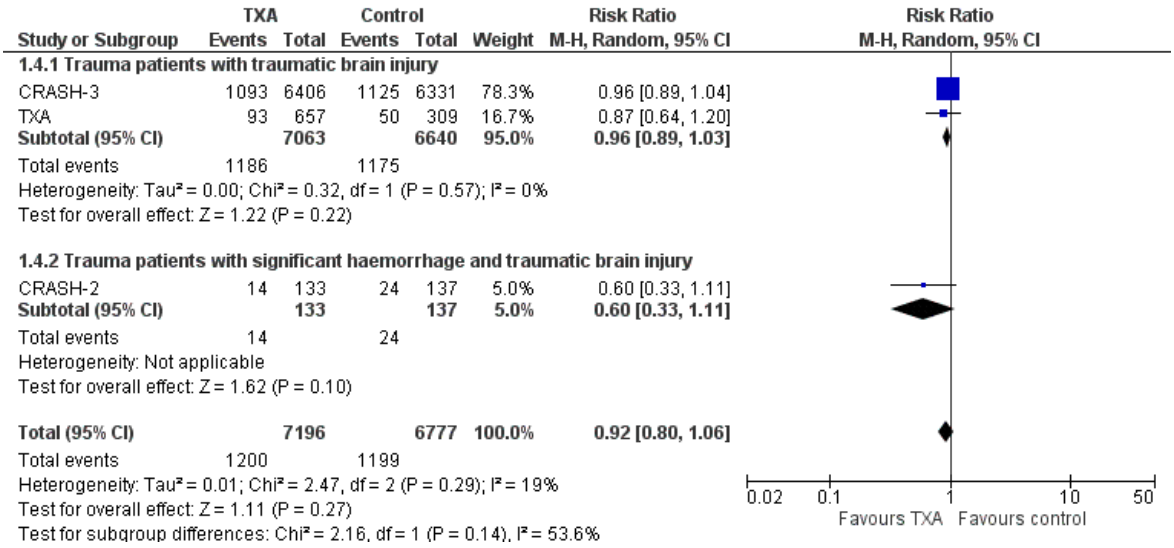


Figure 1. Risk ratio for overall mortality (4 weeks) of TXA versus placebo by considering the population subgroups:

- trauma patients with significant haemorrhage and potentially suffering a TBI (CRASH-2),
- trauma patients with TBI (CRASH-3, TXA), trauma patients with TBI and significant haemorrhage (CRASH-2: subgroup).

***Comparazione 2. Fattore VII ricombinante vs* placebo**

In tabella 3 sono riportati i dati degli studi randomizzati e controllati che valutano il tasso di mortalità in seguito alla somministrazione pre-ospedaliera dell'agente emostatico rFVIIa. Nei pazienti con trauma cranico contusivo non risulta una riduzione significativa della mortalità sia a 48 ore che a 4 settimane (Boffard 2005: sottogruppo).

Table 3. Outcome data for the comparisons of mortality: rFVIIa versus placebo.

Overall Mortality					
RCT studies focused on blunt and penetrating trauma patients: pre-hospital use of rFVIIa versus placebo					
	rFVIIa		**Placebo**		**time point**
	n	**tot**	**n**	**tot**	
Boffard 2005					
Blunt trauma with TBI	2	17	3	13	48 hours
Boffard 2005					
Blunt trauma with TBI	5	17	6	13	30 days

Overall mortality (48 hours), subgrouped for TBI:

- **hemodynamically unstable blunt trauma patients with severe haemorrhage and TBI (Boffard 2005: subgroup)**

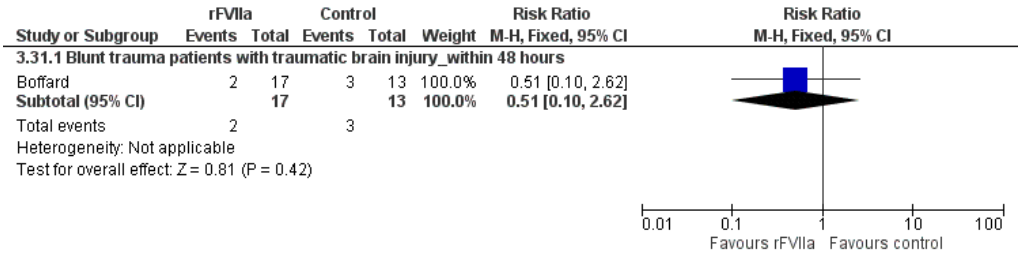


Figure 2. Risk ratio for overall mortality (48 hours) of rFVIIa versus placebo, by considering hemodynamically unstable blunt trauma patients with severe haemorrhage and TBI (Boffard 2005: subgroup).

Overall mortality (4 weeks), subgrouped for TBI:

- **hemodynamically unstable blunt trauma patients with severe haemorrhage and TBI (Boffard 2005: subgroup)**

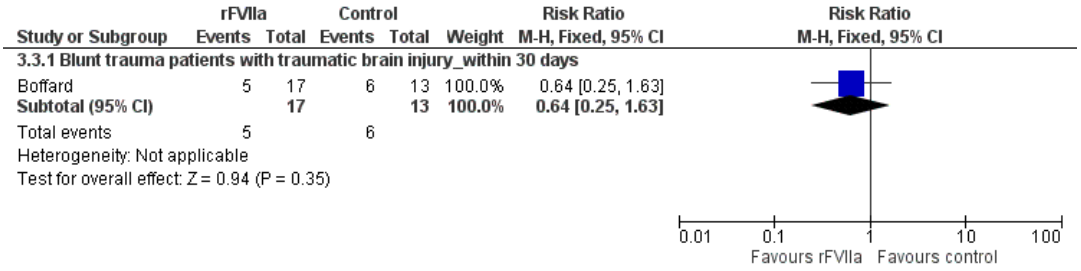


Figure 3. Risk ratio for overall mortality (4 weeks) of rFVIIa versus placebo, by considering hemodynamically unstable blunt trauma patients with severe haemorrhage and TBI (Boffard 2005: subgroup).

1.2 MORTALITÀ PER CAUSA-SPECIFICA

Nei pazienti con trauma cranico, le cause riportate negli RCT relative alla mortalità sono:

- *disfunzione multiorgano* per cui è stato possibile analizzare solo la comparazione rFVIIa vs placebo;
- *lesione cerebrale ed emorragia* per le quali è stato possibile analizzare solo la comparazione TXA vs placebo;
- *embolia polmonare e sepsi* per le quali è stato possibile analizzare solo la comparazione rFVIIa vs placebo.

1.2.1 MORTALITÀ PER DISFUNZIONE MULTIORGANO

Comparazione 2. Fattore VII ricombinante vs placebo

Tra i soggetti con trauma cranico contusivo la mortalità per disfunzione multiorgano, osservata da 48 ore dall'assunzione del fattore rFVIIa fino ai 30 giorni successivi, è stata riportata da 1 solo studio randomizzato e controllato (Boffard 2005: sottogruppo) in cui, a seguito dell'assunzione l'assunzione dell'agente emostatico rFVIIa, non si mostra una riduzione significativa.

Table 4. Outcome data for the comparisons of death due to multiorgan failure: rFVIIa versus placebo.

Mortality due to multiorgan failure					
RCT studies focused on blunt trauma with a TBI component: pre-hospital use of rFVIIa versus placebo					
	rFVIIa		**Placebo**		**time point**
Boffard 2005	**n**	**tot**	**n**	**tot**	
Blunt trauma with TBI	1	17	1	13	>48 hours to 30 days

Mortality due to multiorgan failure (>48 hours to 30 days), subgrouped for TBI:

- **hemodynamically unstable blunt trauma patients with severe haemorrhage and TBI (Boffard 2005: subgroup)**

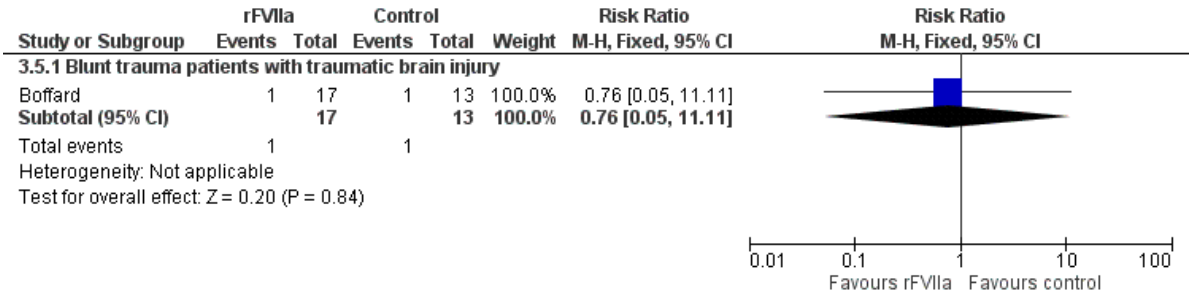


Figure 4. Risk ratio for mortality due to multiorgan failure (>48 hours to 30 days) of rFVIIa versus placebo, by considering hemodynamically unstable blunt trauma patients with severe haemorrhage and TBI (Boffard 2005: subgroup).

1.2.2 MORTALITÀ PER LESIONE CEREBRALE

Comparazione 1. Acido Tranexamico vs placebo

In seguito alla somministrazione pre-ospedaliera dell'agente emostatico TXA, tra i pazienti con trauma cranico risulta una riduzione significativa del rischio di decesso a 24 ore per la mortalità dovuta a lesione cerebrale (CRASH-3). Tuttavia, valutando la mortalità dovuta a lesione cerebrale a 28 giorni e considerando le diverse tipologie di popolazione, quali i soggetti con forte emorragia (CRASH-2), con i) trauma cranico e significativa emorragia (CRASH-2: sottogruppo) e ii) trauma cranico (CRASH-3) la riduzione non risulta più essere significativa.

Table 5. Outcome data for the comparisons of death due to head injury: TXA versus placebo.

Mortality due to head injury					
RCT studies: pre-hospital use of TXA versus placebo					
	TXA		**Placebo**		**time point**
	n	**tot**	**n**	**tot**	
CRASH-3	260	6406	317	6331	24 hours
CRASH-2	603	10060	621	10067	4 weeks
with TBI	12	133	20	137	28 days
CRASH-3	855	4613	892	4514	28 days

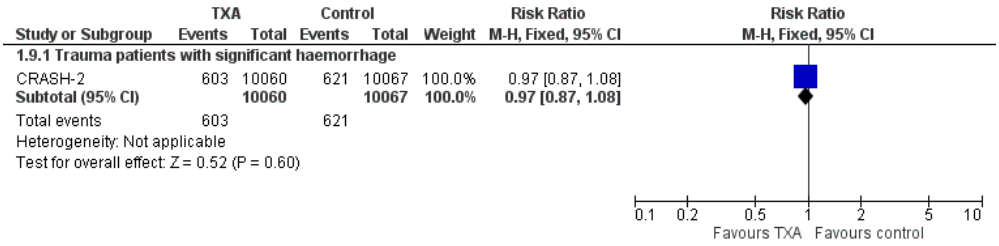
Mortality due to head injury (24 hours):

- **trauma patients with TBI (CRASH-3)**

Figure 5. Risk ratio for mortality due to head injury (24 hours) of TXA versus placebo by considering trauma patients with TBI (CRASH-3).

Mortality due to head injury (4 weeks), subgrouped for type of population:

C. **Pazienti con significativa emorragia:** trauma patients with significant haemorrhage (CRASH-2)



D. **Pazienti con TBI:** trauma patients with significant haemorrhage and TBI (CRASH-2: subgroup); trauma patients with TBI (CRASH-3)

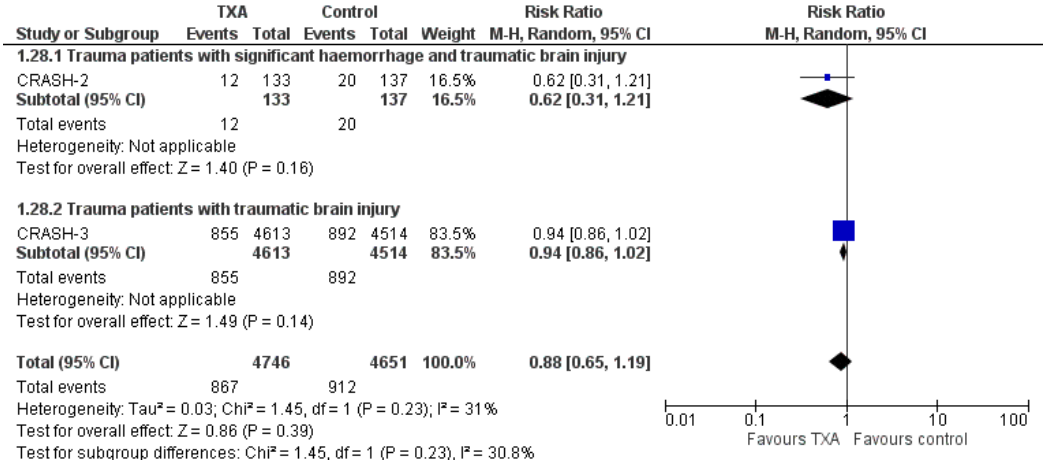


Figure 6. Risk ratio for mortality due to head injury (4 weeks) of TXA versus placebo by considering population subgroups:
- trauma patients with significant haemorrhage (CRASH-2),
- trauma patients with significant haemorrhage and TBI (CRASH-2: subgroup), trauma patients with TBI (CRASH-3).

1.2.3 MORTALITÀ PER EMBOLIA POLMONARE, SEPSI

Comparazione 2. Fattore VII ricombinante vs placebo

Nella popolazione ristretta ai soli pazienti con trauma contusivo e lesione cerebrale traumatica, analizzata da un solo studio randomizzato e controllato (Boffard 2005: sottogruppo), a seguito dell'assunzione del fattore rFVIIa non si mostra una riduzione significativa della mortalità dovuta ad embolia polmonare. Al contrario, si mostra un aumento, seppur non significativo, nel rischio di mortalità dovuta a sepsi.

Table 6. Outcome data for the comparisons of death due to pulmonary embolism or sepsis: rFVIIa versus placebo.

Mortality due to pulmonary embolism					
RCT studies focused on blunt trauma with a TBI component: pre-hospital use of rFVIIa versus placebo					
	rFVIIa		**Placebo**		**time point**
Boffard 2005	**n**	**tot**	**n**	**tot**	
Blunt trauma with TBI	0	17	1	13	>48 hours to 30 days
Mortality due to sepsis					
RCT studies focused on blunt trauma with a TBI component: pre-hospital use of rFVIIa versus placebo					
	rFVIIa		**Placebo**		**time point**
Boffard 2005	**n**	**tot**	**n**	**tot**	
Blunt trauma with TBI	1	17	0	13	>48 hours to 30 days

Mortality due to pulmonary embolism or sepsis (>48 hours to 30 days), subgrouped for TBI:

- hemodynamically unstable blunt trauma patients with severe haemorrhage and TBI (Boffard 2005: subgroup)

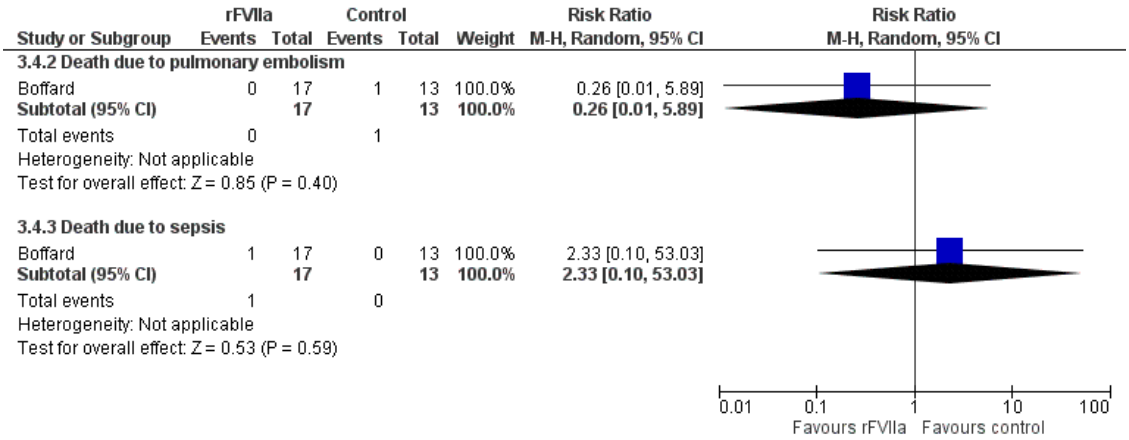


Figure 7. Risk ratio death due to pulmonary embolism or sepsis (>48 hours to 30 days) of rFVIIa versus placebo, by considering hemodynamically unstable blunt trauma patients with severe haemorrhage and TBI (Boffard 2005: subgroup).

2 EVENTI AVVERSI

2.1 SEPSI

Comparazione 1. Acido Tranexamico vs placebo

L'evento avverso *sepsi* entro 4 settimane dall'assunzione del TXA è stato valutato da due trial randomizzati e controllati (CRASH-3 e TXA). Non ci sono evidenze di sicurezza sulla somministrazione pre-ospedaliera dell'agente emostatico TXA.

Table 7. Outcome data for the comparisons of sepsis: TXA versus placebo.

Sepsis					
RCT studies: pre-hospital use of TXA versus placebo					
	TXA		**Placebo**		**time point**
	n	**tot**	**n**	**tot**	
CRASH-3	411	6359	412	6280	within 28 days
TXA	20	657	6	309	within 28 days

Sepsis (28 days), subgrouped for TBI:

Trauma patients with TBI (CRASH-3, TBI)

Figure 8. Risk ratio for sepsis (28 days) of TXA versus placebo by considering trauma patients with TBI (CRASH-3, TXA).

2.2 VASCOLARI: coagulazione intravascolare disseminata (TXA), eventi avversi tromboembolici (rFVIIA).

Comparazione 1. Acido Tranexamico vs placebo

Non è stata rilevata una diminuzione significativa nel rischio di sviluppare *coagulazione intravascolare disseminata* (TXA) insorti entro 4 settimane dall'assunzione del TXA, ed ottenuti dalla somministrazione pre-ospedaliera dell'agente emostatico TXA.

Table 8. Outcome data for the comparisons of disseminated intravascular coagulation: TXA versus placebo.

Disseminated intravascular coagulation					
RCT studies: pre-hospital use of TXA versus placebo					
	TXA		**Placebo**		**time point**
	n	**tot**	**n**	**tot**	
TXA	2	657	0	309	within 28 days

Disseminated intravascular coagulation (28 days), subgrouped for TBI:

Trauma patients with TBI (TXA)

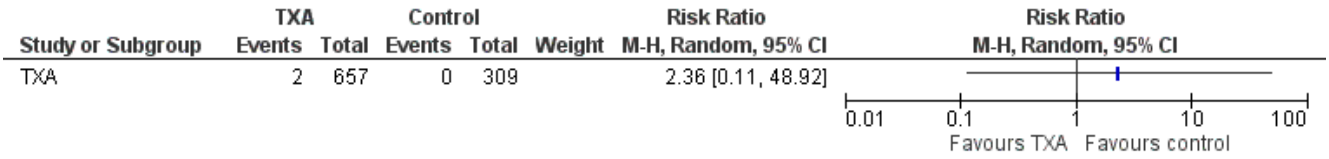


Figure 9. Risk ratio for disseminated intravascular coagulation (28 days) of TXA versus placebo by considering trauma patients with TBI (TXA).

Comparazione 2. Fattore VII ricombinante vs placebo

Considerando i soggetti con trauma cranico contusivo, in seguito all'assunzione dell'agente emostatico rFVIIa si sono valutati gli *eventi avversi tromboembolici*, per i quali non risulta una riduzione del rischio significativa a 30 giorni (Boffard 2005: sottogruppo).

Table 9. Outcome data for thromboembolic adverse events: rFVIIa versus placebo.

Thromboembolic adverse events					
RCT studies focused on blunt and penetrating trauma patients: pre-hospital use of rFVIIa versus placebo					
	rFVIIa		**Placebo**		**time point**
Boffard 2005					
Blunt trauma with TBI	0	17	2	13	30 days

Thromboembolic adverse events (30 days), subgrouped for TBI

- **hemodynamically unstable blunt trauma patients with severe haemorrhage and TBI (Boffard 2005: subgroup)**

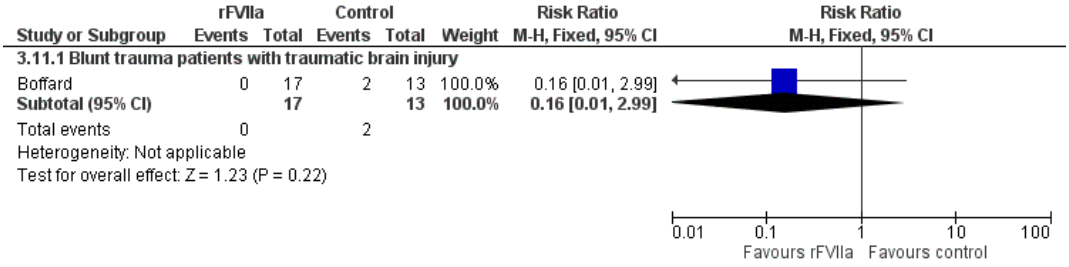


Figure 10. Risk ratio for thromboembolic adverse events of rFVIIa versus placebo at 30 days, by considering hemodynamically unstable blunt trauma patients with severe haemorrhage and TBI (Boffard 2005: subgroup).

2.3 ALTRI EVENTI AVVERSI: Sanguinamento gastrointestinale (TXA), Insufficienza renale (TXA), Danno renale acuto (TXA), Convulsioni (TXA), Sindrome da distress respiratorio acuto (rFVIIa), Disfunzione multiorgano (rFVIIa)

Comparazione 1. Acido Tranexamico vs placebo

In generale non si evidenzia una chiara indicazione rispetto alla sicurezza della somministrazione pre-ospedaliera dell'agente emostatico TXA per altri eventi avversi, quali *emorragia gastrointestinale* (CRASH-3), *insufficienza renale* (CRASH-3, TXA), *danno renale acuto* (TXA), e *convulsioni* (CRASH-3 e TXA), identificati da 3 trial (CRASH-2, CRASH-3, TXA) entro 4 settimane dall'assunzione del TXA.

Table 10. Outcome data for the comparisons of other adverse events: TXA versus placebo.

	TXA		Placebo		time point
	n	tot	n	tot	
Gastrointestinal bleeding					
RCT studies: pre-hospital use of TXA versus placebo					
CRASH-3	24	6359	35	6280	within 28 days
Renal failure					
RCT studies: pre-hospital use of TXA versus placebo					
CRASH-3	100	6359	84	6280	within 28 days
TXA	5	657	0	309	within 28 days
Acute kidney injury					
RCT studies: pre-hospital use of TXA versus placebo					
TXA:	33	657	13	309	within 28 days
Seizures					
RCT studies: pre-hospital use of TXA versus placebo					
CRASH-3	206	6359	186	6280	within 28 days
TXA	22	657	7	309	within 28 days

Gastrointestinal bleeding (28 days), subgrouped for TBI:

Trauma patients with TBI (CRASH-3)

Figure 11. Risk ratio for gastrointestinal bleeding (28 days) of TXA versus placebo, by considering trauma patients with TBI (CRASH-3).

Renal failure (28 days), subgrouped for TBI:

Trauma patients with TBI (CRASH-3, TXA)

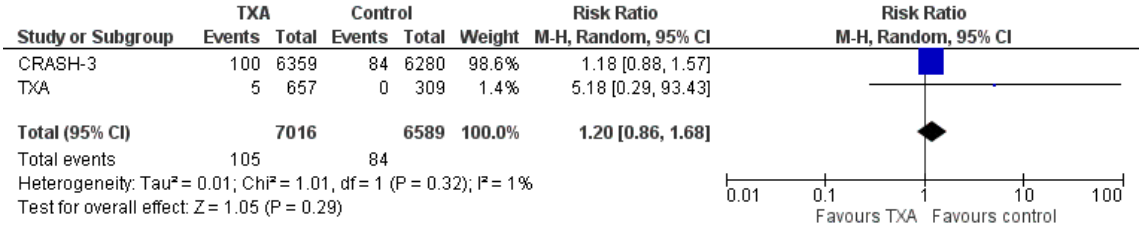


Figure 12. Risk ratio for renal failure (28 days) of TXA by considering trauma patients with TBI (CRASH-3, TXA).

Acute kidney injury (28 days), subgrouped for TBI:

Trauma patients with TBI (TXA)

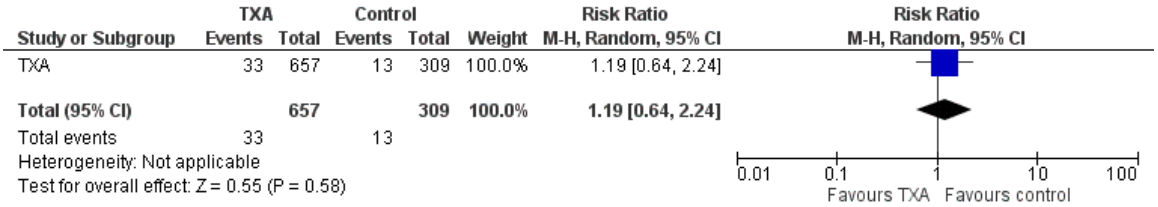


Figure 13. Risk ratio for acute kidney injury (28 days) of TXA versus placebo by considering trauma patients with TBI (TXA).

Seizures (28 days), subgrouped for TBI:

Trauma patients with TBI (CRASH-3, TXA)

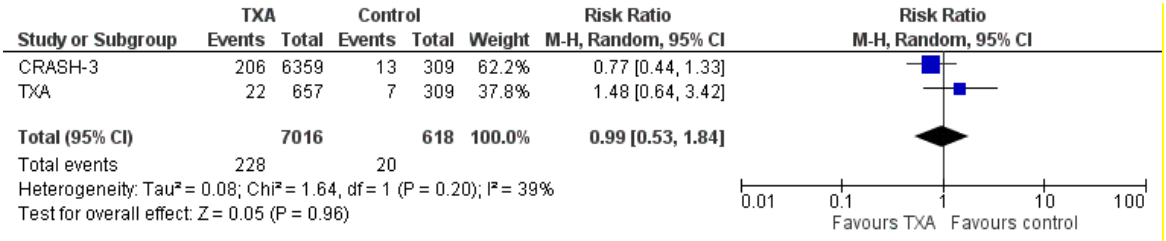


Figure 14. Risk ratio for seizures (28 days) of TXA versus placebo subgrouped for doses of TXA by considering trauma patients with TBI (CRASH-3, TXA).

Comparazione 2. Fattore VII ricombinante vs placebo

Tra i soggetti con trauma cranico contusivo (Boffard 2005: sottogruppo), in seguito all'assunzione dell'agente emostatico rFVIIa sono stati valutati gli eventi avversi a 30 giorni relativi a s*indrome da distress respiratorio acuto* e *disfunzione multiorgano* per i quali non risulta una riduzione significativa del rischio.

Table 11. Outcome data for the comparisons of acute respiratory distress syndrome: rFVIIa versus placebo.

Acute respiratory distress syndrome					
RCT studies focused on blunt and penetrating trauma patients: pre-hospital use of rFVIIa versus placebo					
	rFVIIa		**Placebo**		**time point**
Boffard 2005	**n**	**tot**	**n**	**tot**	
Blunt trauma with TBI	2	17	2	13	30 days

Acute respiratory distress syndrome (30 days), subgrouped for TBI:

- **hemodynamically unstable blunt trauma patients with severe haemorrhage and TBI (Boffard 2005: subgroup)**

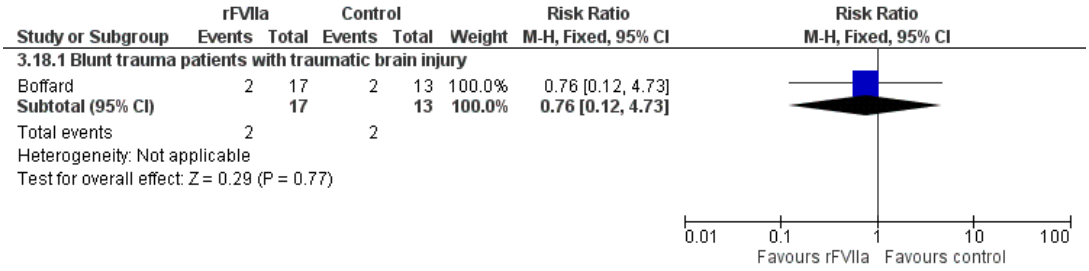


Figure 15. Risk ratio for acute respiratory distress syndrome (30 days) of rFVIIa versus placebo, by considering hemodynamically unstable blunt trauma patients with severe haemorrhage and TBI (Boffard 2005: subgroup).

Table 12. Outcome data for the multiple organ failure: rFVIIa versus placebo.

Multiple organ failure					
RCT studies focused on blunt and penetrating trauma patients: pre-hospital use of rFVIIa versus placebo					
	rFVIIa		**Placebo**		**time point**
Boffard 2005	**n**	**tot**	**n**	**tot**	
Blunt trauma with TBI	3	17	2	13	30 days

Multiple organ failure (30 days), subgrouped for TBI:

- **hemodynamically unstable blunt trauma patients with severe haemorrhage and TBI (Boffard 2005: subgroup)**

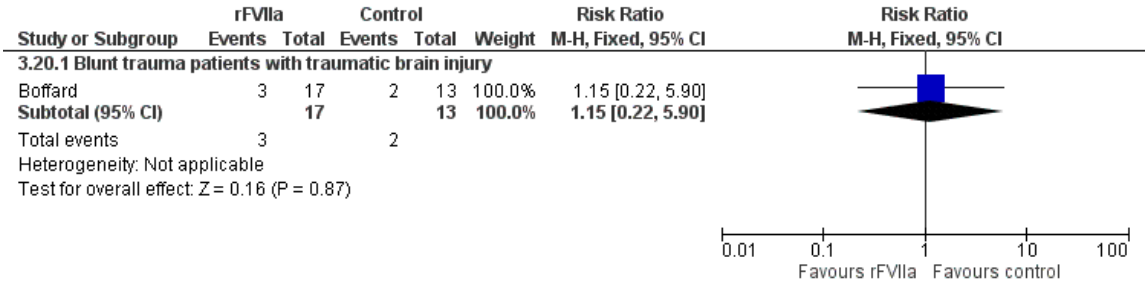


Figure 16. Risk ratio for multiple organ failure (30 days) of rFVIIa versus placebo, by considering hemodynamically unstable blunt trauma patients with severe haemorrhage and TBI (Boffard 2005: subgroup).

OUTCOME IMPORTANTI

1. ***ENTITÀ DELL'EMORRAGIA***

<u>Comparazione 1. Acido Tranexamico vs placebo</u>

Considerando la somministrazione pre-ospedaliera dell'agente emostatico TXA tra soggetti con trauma cranico e forte emorragia non si rileva una riduzione significativa della crescita dell'emorragia nelle 24-48 ore dal ricovero ospedaliero (CRASH-2: sottogruppo).

Table 13. Outcome data for total haemorrhage growth: TXA versus placebo.

Total haemorrhage growth					
RCT studies: pre-hospital use of TXA versus placebo					
	TXA		**Placebo**		**time point**
	mean	**sd**	**mean**	**sd**	
CRASH-2	**N = 133**		**N= 137**		between hospital admission and then 24–48 hours later
with TBI	5.9	26.8	8.1	29.2	

Total haemorrhage growth (hospital admission to 24/48 hours later), subgrouped for TBI:

- **trauma patients with significant haemorrhage and TBI (CRASH-2: subgroup)**

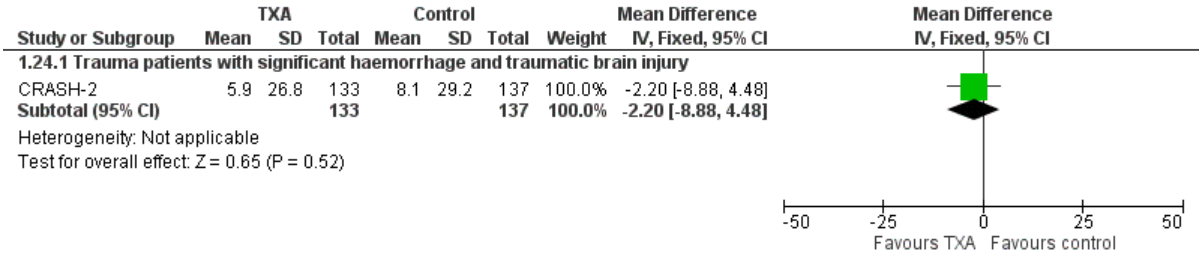


Figure 17. Mean difference for total haemorrhage growth (between hospital admission and then 24-48 hours later) of TXA versus placebo, by considering the trauma patients with significant haemorrhage and TBI (CRASH-2:subgroup).

ALTRI OUTCOME NON IMPORTANTI

Oltre agli outcome indicati dal PICO, si riportano le analisi di altri outcome rilevati negli articoli inclusi.

Le cause riportate negli RCT relative ad altri eventi avversi sono:

- *necessità di intervento neurochirurgico* per il quale è stato possibile analizzare solo la comparazione TXA vs placebo;
- *giorni liberi da ricovero ospedaliero, da ventilazione, da ricovero in terapia intensiva* per i quali è stato possibile analizzare le comparazioni per i due agenti emostatici (rFVIIa).

NECESSITÀ DI INTERVENTO NEUROCHIRURGICO

Comparazione 1. Acido Tranexamico vs placebo

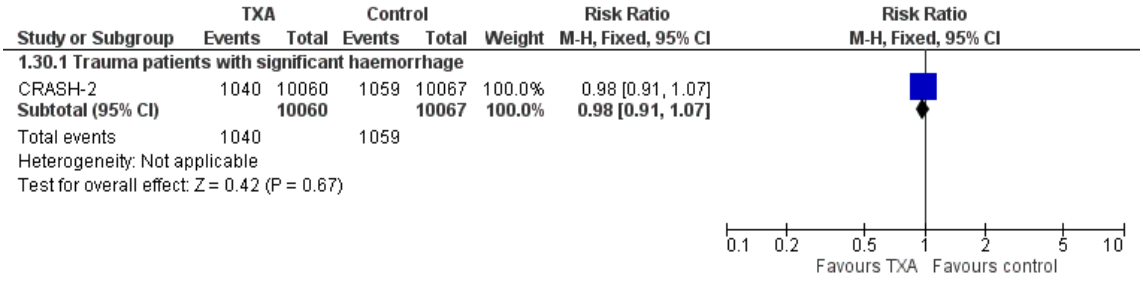
Considerando la tipologia di popolazione, nei soggetti con forte emorragia (CRASH-2) così come tra i soggetti con i) trauma cranico (TXA) e tra gli individui con ii) trauma cranico e forte emorragia (CRASH-2: sottogruppo) non risulta una chiara riduzione del rischio di essere sottoposti ad intervento neurochirurgico entro 28 giorni dalla lesione.

Table 14. Outcome data for neurosurgical intervention: TXA versus placebo.

Neurosurgical intervention					
RCT studies: pre-hospital use of TXA versus placebo					
	TXA		**Placebo**		**time point**
	n	**tot**	**n**	**tot**	
CRASH-2	1040	10060	1059	10067	within 28 days
with TBI	20	133	21	137	within 28 days
TXA	137	657	54	309	within 28 days

Neurosurgical intervention (within 28 days), subgrouped for type of population:

- **trauma patients with significant haemorrhage and potentially suffering a TBI (CRASH-2)**



- **trauma patients with TBI (TXA); trauma patients with significant haemorrhage and TBI (CRASH-2: subgroup)**

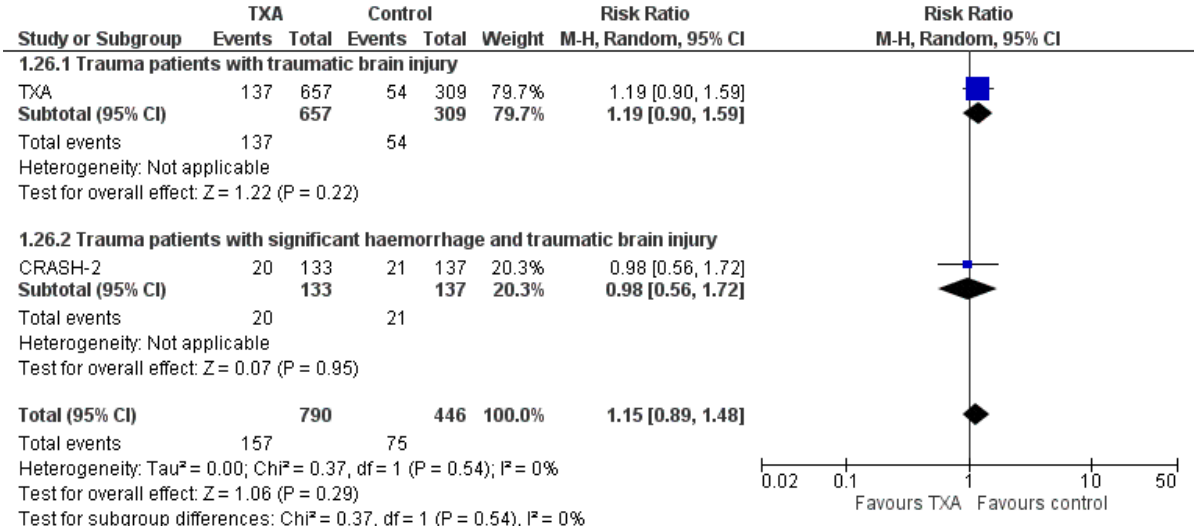


Figure 18. Risk ratio for neurosurgical intervention (28 days) of TXA versus placebo for population subgroups, by considering:
- trauma patients with significant haemorrhage and potentially suffering a TBI (CRASH-2)
- trauma patients with traumatic brain injury (TXA), trauma patients with significant haemorrhage and TBI (CRASH-2: subgroup).

2 GIORNI LIBERI DA RICOVERO OSPEDALIERO

<u>Comparazione 1. Acido Tranexamico vs placebo</u>

I giorni liberi da ricovero ospedaliero (trial TXA) non mostrano una chiara indicazione dei benefici a seguito dell'assunzione pre-ospedaliera dell'agente emostatico TXA.

Table 15. Outcome data for the comparisons of hospital-free days: TXA versus placebo.

Hospital-free days					
RCT studies: pre-hospital use of TXA versus placebo					
	TXA		**Placebo**		**time point**
	N = 623		**N= 295**		
TXA	**mean**	**sd**	**mean**	**sd**	
	13.9	10.5	13.6	10.7	28 days

Hospital-free days (28 days), subgrouped for TBI:

Trauma patient with TBI (TXA)

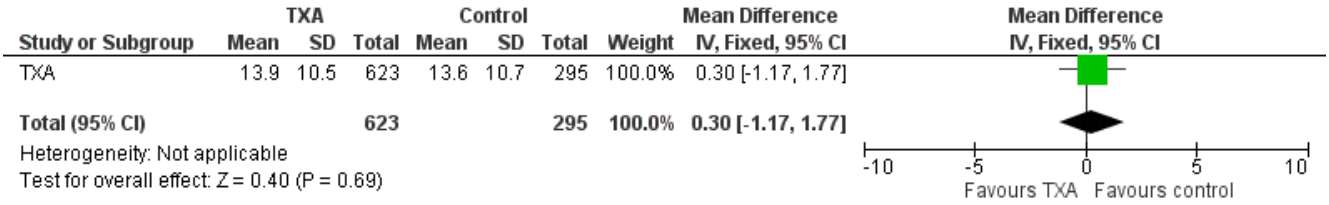


Figure 19. Mean difference for hospital-free days (28 days) of TXA versus placebo by considering trauma patients with TBI (TXA).

3 GIORNI LIBERI DA VENTILAZIONE

Comparazione 1. Acido Tranexamico vs placebo

Per i giorni liberi da ventilazione (trial TXA) non si mostra una chiara indicazione dei benefici a seguito dell'assunzione pre-ospedaliera dell'agente emostatico TXA verso placebo.

able 16. Outcome data for the comparisons of ventilator free-days: TXA versus placebo.

Ventilator free days					
RCT studies: pre-hospital use of TXA versus placebo					
	TXA		**Placebo**		**time point**
	N = 624		**N= 295**		
TXA	**mean**	**sd**	**mean**	**sd**	28 days
	15.1	15	20.2	10.5	

Ventilator-free days (28 days), subgrouped for TBI:

Trauma patients with TBI (TXA)

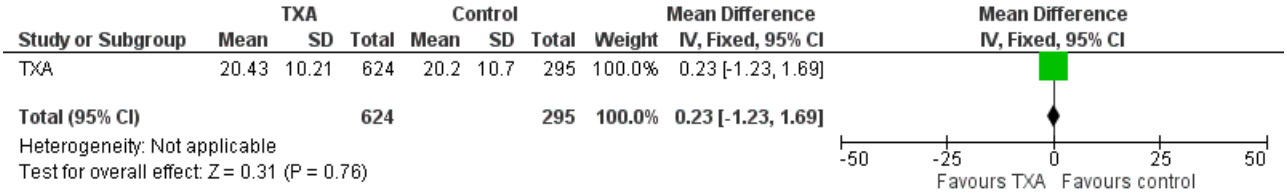


Figure 20. Mean difference for ventilator-free days (28 days) of TXA versus placebo by considering trauma patients with TBI (TXA).

Comparazione 2. Fattore VII ricombinante vs placebo

Per i giorni liberi da ventilazione a 30 giorni, lo studio di Boffard 2005 (sottogruppo) mostra solo valori mediani.

Table 17. Outcome data for the comparisons of ventilator free-days: rFVIIa versus placebo.

Ventilator free days					
RCT studies focused on blunt and penetrating trauma patients: pre-hospital use of rFVIIa versus placebo					
	rFVIIa		**Placebo**		**time point**
	median	**IQR**	**median**	**IQR**	
Boffard 2005	**N = 17**		**N= 13**		
Blunt trauma with TBI	3	(0-23)	0	(0-21)	30 days

4 GIORNI LIBERI DA RICOVERO IN TERAPIA INTENSIVA

Comparazione 1. Acido Tranexamico vs placebo

Per i giorni liberi da ricovero in terapia intensiva (trial TXA) non mostra una chiara indicazione dei benefici a seguito dell'assunzione pre-ospedaliera dell'agente emostatico.

Table 18. Outcome data for the comparisons of ICU-free days: TXA versus placebo.

ICU free days					
RCT studies: pre-hospital use of TXA versus placebo					
	TXA		**Placebo**		**time point**
	N = 624		**N= 295**		
TXA	**mean**	**sd**	**mean**	**sd**	
	18.6	10.2	18.5	10.6	28 days

ICU-free days (28 days), subgrouped for TBI:

Trauma patients with TBI (TXA)

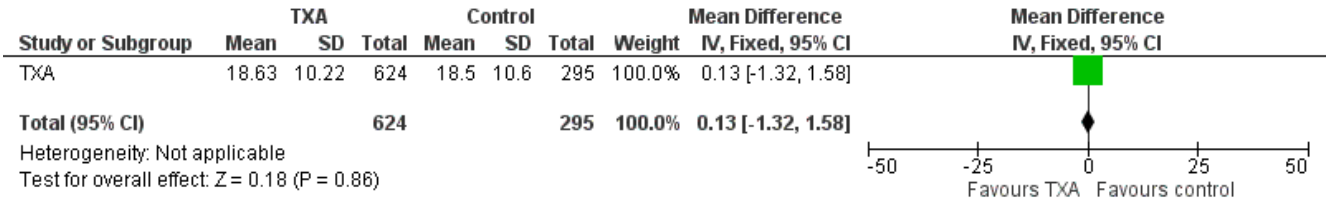


Figure 21. Mean difference for ICU-free days (28 days) of TXA versus placebo by considering trauma patients with TBI (TXA).

Comparazione 2. Fattore VII ricombinante vs placebo

Per i giorni liberi dal ricovero in terapia intensiva a 30 giorni, lo studio di Boffard 2005 (sottogruppo) mostra solo valori mediani.

Table 19. Outcome data for the comparisons of ICU-free days: rFVIIa versus placebo.

ICU free days					
RCT studies focused on blunt and penetrating trauma patients: pre-hospital use of rFVIIa versus placebo					
	rFVIIa		**Placebo**		**time point**
	median	**IQR**	**median**	**IQR**	
Boffard 2005	**N = 17**		**N= 13**		
Blunt trauma with TBI	10	(0-24)	0	(0-25)	30 days

TABELLA RIASSUNTIVA – EVIDENZE DI EFFICACIA

Table 20. Summary table of clinical outcomes regarding the pre-hospital administration of TXA or rFVIIa versus placebo.

OUTCOME	TXA vs placebo			rFVIIa vs placebo
	Trauma patients with significant haemorrhage and potentially suffering a TBI.	Trauma patients with TBI.	Trauma patients with significant haemorrhage and TBI.	Hemodynamically unstable blunt trauma patients with severe haemorrhage and TBI.
	CRASH-2	**CRASH-3, TXA**	**CRASH-2: subgroup**	**Boffard 2005: subgroup**
OUTCOME CRITICI:				
1) MORTALITÀ				
1.1) Overall				
48 ore	-	-	-	RR 0.51 (0.10 to 2.62)
4 settimane	RR 0.91 (0.85 to 0.97)	RR 0.96 (0.89 to 1.03)	RR 0.60 (0.33 to 1.11)	RR 0.64 (0.25 to 1.63)
1.2) Causa-specifica				
Disfunzione multiorgano 4 settimane	-	-	-	RR 0.76 (0.05 to 11.11)
Lesione cerebrale				
24 ore	-	RR 0.81 (0.69 to 0.95)*	-	-
4 settimane	RR 0.97 (0.87 to 1.08)	RR 0.94 (0.86 to 1.02)*	RR 0.62 (0.31 to 1.21)	-
Embolia polmonare 4 settimane	-	-	-	RR 0.26 (0.01 to 5.89)
Sepsi 4 settimane	-	-	-	RR 2.33 (0.10 to 53.03)
2) EVENTI AVVERSI				
2.1) Sepsi 4 settimane	-	RR 0.99 (0.87 to 1.13)	-	-
2.2) Vascolari				
Coagulazione intravascolare disseminata				
4 settimane	-	RR 2.36 (0.11 to 48.92)**	-	-
Eventi avversi tromboembolici				
4 settimane	-	-	-	RR 0.16 (0.01 to 2.99)

3.5) Altri eventi avversi				
Sanguinamento gastrointestinale 4	-	RR 0.68 (0.40 to 1.14)*	-	-
settimane	-	RR 1.20 (0.86 to 1.68)	-	-
Insufficienza renale 4 settimane	-	RR 1.19 (0.64 to 2.24)**	-	-
Danno renale acuto 4 settimane	-	RR 0.99 (0.53 to 1.84)	-	-
Convulsioni 4 settimane				
Sindrome da distress respiratorio acuto 4 settimane	-	-	-	RR 0.76 (0.12 to 4.73)
Disfunzione multiorgano 4 settimane	-	-	-	RR 1.15 (0.22 to 5.90)
OUTCOME IMPORTANTI:				
1) TEMPO DI CONTROLLO DEFINITIVO DELL'EMORRAGIA				
Totale crescita dell'emorragia 24-48 ore	-	-	MD -2.20 (-2.97 to -1.43)	-
ALTRI OUTCOME NON IMPORTANTI:				
1) NECESSITÀ DI INTERVENTO NEUROCHIRURGICO 4 settimane	RR 0.98 (0.91 to 1.07)	RR 1.19 (0.90 to 1.59)**	RR 0.98 (0.56 to 1.72)	-
2) GIORNI LIBERI DA RICOVERO OSPEDALIERO 4 settimane	-	MD 0.30 (-1.17 to 1.77)**	-	-
3) GIORNI LIBERI DA VENTILAZIONE 4 settimane	-	MD 0.23 (-1.23 to 1.69)**	-	Median values
4) GIORNI LIBERI DA RICOVERO IN TERAPIA INTENSIVA 4 settimane	-	MD 0.13 (-1.32 to 1.58)**	-	Median values

*only CRASH-3 trial
** only TXA trial

Appendice C3 – Supplemento: Sottogruppi per dose somministrata

CQ8. Gestione dell'emorragia nel setting pre-ospedaliero: agenti emostatici.

Indice

È stata effettuata una revisione sistematica con ricerca della letteratura sulle banche dati Embase, Medline e Cochrane CENTRAL aggiornata al 29 giugno 2020. Sono stati individuati 1518 records da cui sono state selezionate 8 referenze che soddisfano i criteri per rispondere al quesito clinico proposto, rispettivamente 5 studi primari e 3 revisioni sistematiche da cui sono stati ulteriormente estratti 3 studi. Inoltre, sono state interrogate clinicatrials.gov e le Linee guida NICE, aggiungendo all'inclusione altre 11 nuove pubblicazioni, 6 e 5 rispettivamente. In totale, sono state individuate 19 pubblicazioni afferenti 5 studi randomizzati e controllati: CRASH-2, CRASH-3, TXA trial, CONTROL trial e Boffard 2005. In data 9 settembre 2020 è stata rilanciata per aggiornamento la search strategy, da cui è stata aggiunta una pubblicazione inerente uno studio incluso (TXA trial).

Gli studi inclusi sono controllati e randomizzati in cui il gruppo di controllo è rappresentato dal trattamento con placebo.

Considerando la dose somministrata, gli studi individuati permettono di rispondere alle seguenti comparazioni:

vi) ***Somministrazione pre-ospedaliera di TXA verso placebo:***

a. *TXA 1 grammo in pre-ospedaliero + 1 grammo in infusione nelle 8 ore successive verso placebo*
   (CRASH-2 (11), CRASH-3 (2), TXA (1))
b. *TXA 2 grammi in pre-ospedaliero + placebo in infusione nelle ore successive verso placebo (una pubblicazione afferente ad uno studio randomizzato e controllato: TXA(1))*

Table 1. Characteristics of patients.

			Gender		Age	ISS	Systolic blood pressure					
RCT	**INTERVENTION**	**N**	**M**	**F**	**MEDIAN (IQR)**	**MEDIAN (IQR)**	**MEAN (SD)**	**< 90**	**90-119**	**≥ 120**		**unknown**
TXA	TXA: 1 gram pre-hospital + 1 gram within 8 hours	312	227	85	39 (26 to 57)	17 (8 to 27)	-	-	-	-	-	-
	TXA: 2 grams pre-hospital + placebo	345	255	90	40 (26 to 56)	17 (8 to 27)	-	-	-	-	-	-
	PLACEBO	309*	233	76	36 (25 to 55)	17 (9 to 27)	-	-	-	-	-	-
CRASH-2					**MEAN (SD)**	**MEAN (SD)**						
	TXA	10093	8439 (83,6%)	1654 (16,4%)	34,6 (14,1)	-	-	1566 (15,5%)	1615 (16%)	6901 (68,4%)		11 (0,11%)
	Subgroup: patients who also had TBI	133	111 (84%)	22 (16%)	36 (14)	-	116,4 (31,2)	9 (7%)	63 (47%)	61 (46%)		-
	PLACEBO	10114	8496 (84%)	1617 (16%)	34,5 (14,4)	-	-	1608 (15,9%)	1697 (16,8%)	6791 (67,1%)		18 (0,18%)
	Subgroup: patients who also had TBI	137	117 (85%)	20 (15%)	37 (14)	-	113,5 (29,4)	10 (7%)	69 (50%)	58 (43%)		-
CRASH-3										**120-139**	**≥ 140**	**unknown**
	TXA	4649	3742 (80%)	906 (19%)	41,7 (19)	-	-	89 (2%)	1508 (32%)	1461 (31%)	1576 (34%)	15 (<1%)
	PLACEBO	4553	3660 (80%)	893 (20%)	41,9 (19)	-	-	85 (2%)	1490 (33%)	1504 (33%)	1466 (32%)	8 (<1%)

		Heart Rate						Glasgow Coma Scale				
RCT	**INTERVENTION**	**MEAN (SD)**	**< 77**	**77-91**	**92-107**	**> 107**	**unknown**	**MEAN (SD)**	**Severe (3-8)**	**Moderate (9-12)**	**Mild (13-15)**	**unknown**
TXA	TXA: 1 gram pre-hospital + 1 gram within 8 hours	-	-	-	-	-	-	-	169	129	14	-
	TXA: 2 grams pre-hospital + placebo	-	-	-	-	-	-	-	177	159	9	-
	PLACEBO	-	-	-	-	-	-	-	186	115	8	-
CRASH-2	TXA	-	875 (8,7%)	1727 (17,1%)	2556 (25,3%)	4872 (48,3%)	63 (0,62%)	-	1799 (17,8%)	1353 (13,4%)	6934 (68,7%)	7 (0,07%)
	Subgroup: patients who also had TBI	100,7 (25,7)	-	-	-	-	-	10,5 (3,6)	45 (34%)	25 (19%)	63 (47%)	-
	PLACEBO	-	871 (8,6%)	1770 (17,5%)	2546 (25,2%)	4853 (48%)	74 (0,73%)	-	1839 (18,2%)	1351 (13,4%)	6908 (68,3%)	16 (0,16%)
	Subgroup: patients who also had TBI	101,6 (23,5)	-	-	-	-	-	10,5 (3,6)	45 (33%)	34 (25%)	58 (42%)	-
CRASH-3	TXA	-	-	-	-	-	-	-	1757 (40%)	1557 (33%)	1307 (27%)	28 (1%)
	PLACEBO	-	-	-	-	-	-	-	1732 (38%)	1524 (33%)	1262 (28%)	35 (1%)

		Type of injury		Respiratory rate				Capillary refill time				
RCT	**INTERVENTION**	**BLUNT**	**PENETRATING**	**< 10**	**10-29**	**> 29**	**unknown**	**MEAN (SD)**	**≤ 2**	**3-4**	**> 4**	**unknown**
TXA	TXA: 1 gram pre-hospital + 1 gram within 8 hours	16	12	-	-	-	-	-	-	-	-	-
	TXA: 2 grams pre-hospital + placebo	340	5	-	-	-	-	-	-	-	-	-
	PLACEBO	293	300	-	-	-	-	-	-	-	-	-
CRASH-2	TXA	6812 (67,5%)*	3281 (32,5%)	160 (1,6%)	8355 (82,8%)	1491 (14,8%)	87 (0,86%)	-	3432 (34%)	4665 (46,2%)	1699 (16,8%)	297 (2,9%)
	Subgroup: patients who also had TBI	132 (99,2%)	1 (0,8%)	-	-	-	-	3,4 (1,0)	-	-	-	-
	PLACEBO	6843 (67,7%)*	3271 (32,3%)	149 (1,5%)	8436 (83,4%)	1492 (14,1%)	100 (0,99%)	-	3406 (33,7%)	4722 (46,7%)	1672 (16,5%)	314(3,1%)
	Subgroup: patients who also had TBI	136 (99,3%)	1 (0,7%)	-	-	-	-	3,5 (1,1)	-	-	-	-
CRASH-3	TXA	-	-	-	-	-	-	-	-	-	-	-
	PLACEBO	-	-	-	-	-	-	-	-	-	-	-

		Time from injury to first dose (h)				
RCT	**INTERVENTION**	**MEAN (SD)**	**≤1**	**1-3**	**> 3**	**unknown**
TXA	TXA: 1 gram pre-hospital + 1 gram within 8 hours	-	-	-	-	-
	TXA: 2 grams pre-hospital + placebo	-	-	-	-	-
	PLACEBO	-	-	-	-	-
CRASH-2	TXA	2,8 (2,2)	3756 (37,2%)	3045 (30,2%)	3287 (32,6%)	5 (0,05%)
	Subgroup: patients who also had TBI	4,4 (1,8)	-	-	-	-
	PLACEBO	2,9 (2,6)	3722 (36,8%)	3006 (29,7%)	3380 (33,4%)	6 (0,06%)
	Subgroup: patients who also had TBI	4,2 (1,7)	-	-	-	-
CRASH-3	TXA		**≤1**	**1-2**	**2-3**	
		1,9 (0,7)	877 (19%)	2003 (43%)	1769 (38%)	-
	PLACEBO	1,9 (0,7)	869 (19%)	1889 (41%)	1795 (39%)	-

COMPARAZIONE DI INTERVENTI A COPPIE (Pair-wise meta-analisi)

Trial	Population
CRASH-2	Blunt or penetrating trauma patients with significant haemorrhage and potentially suffering a TBI
CRASH-3	Trauma patients with TBI
TXA	Trauma patients with TBI

Table 2. Clinical trial study population.

OUTCOME CRITICI

MORTALITÀ

1.2 OVERALL MORTALITY

Comparazione 1. Acido Tranexamico vs placebo

Si riportano, in Tabella 2, i dati relativi al tasso di mortalità a 4 settimane in seguito alla somministrazione pre-ospedaliera dell'agente emostatico TXA o di placebo.
Per la mortalità a 28 giorni, valutata da tre studi controllati randomizzati (CRASH-2, CRASH-3 e TXA), si mostra una riduzione solo per il confronto i.a) che prevede la somministrazione di 1 g di TXA in fase pre-ospedaliera, seguita dalla somministrazione di 1 g nelle 8 ore successive (CRASH-2, CRASH-3) ma non nel confronto i.b) in cui la somministrazione dell'agente emostatico TXA nella fase pre-ospedaliera è pari a 2 g + placebo (TXA).

Table 3. Outcome data for the comparisons of mortality: TXA versus placebo.

Overall Mortality					
RCT studies: pre-hospital use of TXA versus placebo					
	TXA		**Placebo**		**time point**
	n	**tot**	**n**	**tot**	
CRASH-2	1463	10060	1613	10067	4 weeks
CRASH-3	1093	6406	1125	6331	28 days
TXA:					
1 g pre-hospital + 1 g within 8 hours	53	312	25	154*	28 days
2 grams pre-hospital + placebo	40	345	25	154*	28 days

***** The placebo group (n=309) of the TXA trial has been splitted into two groups for the pooled analysis (Higgins JPT, Eldridge S, Li T (editors). Chapter 23: Including variants on randomized trials. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.)

Overall mortality (4 weeks), subgrouped for doses:

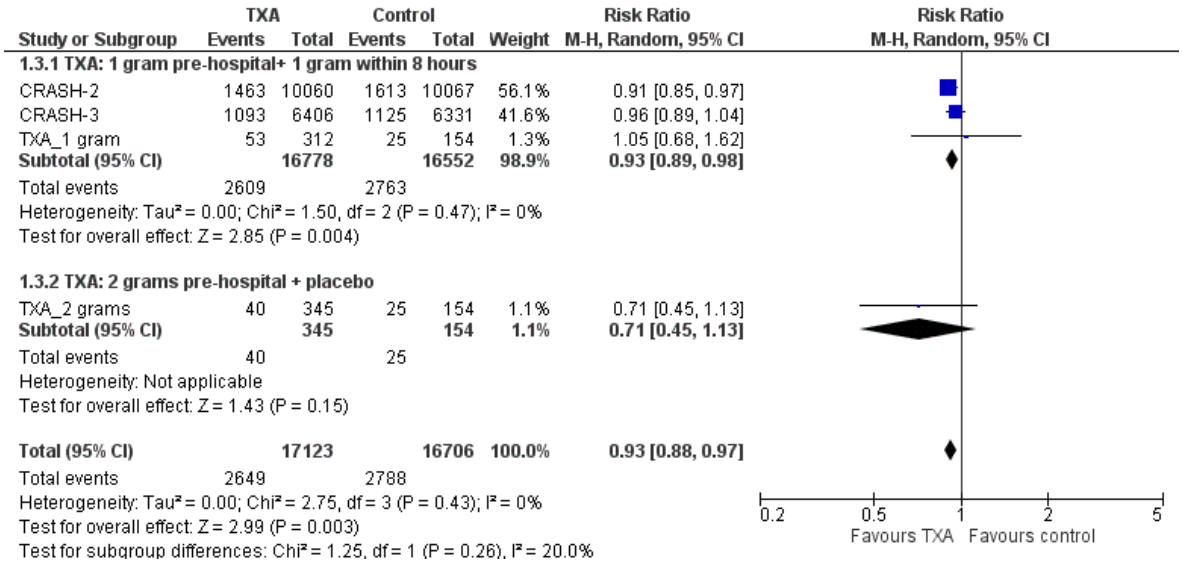


Figure 1. Risk ratio for overall mortality (4 weeks) of TXA versus placebo subgrouped for doses of TXA (1 g in pre-hospital + 1 g within 8 hours and 2 g in pre-hospital + placebo).

EVENTI AVVERSI

3.1 SEPSI

Comparazione 1. Acido Tranexamico vs placebo

L'evento avverso *sepsi* entro 4 settimane dall'assunzione del TXA è stato valutato da due trial randomizzati e controllati (CRASH-3 e TXA). Non ci sono evidenze di sicurezza sulla somministrazione pre-ospedaliera dell'agente emostatico TXA.

Table 4. Outcome data for the comparisons of sepsis: TXA versus placebo.

Sepsis					
RCT studies: pre-hospital use of TXA versus placebo					
	TXA		**Placebo**		**time point**
	n	**tot**	**n**	**tot**	
CRASH-3	411	6359	412	6280	within 28 days
TXA: 1 g pre-hospital + 1 g within 8 hours	11	312	3	154*	within 28 days
2 g pre-hospital + placebo	9	345	3	154*	within 28 days

*The placebo group (n=309) of the TXA trial has been splitted into two groups for the pooled analysis (Higgins JPT, Eldridge S, Li T (editors). Chapter 23: Including variants on randomized trials. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.)

Sepsis (28 days), subgrouped for doses:

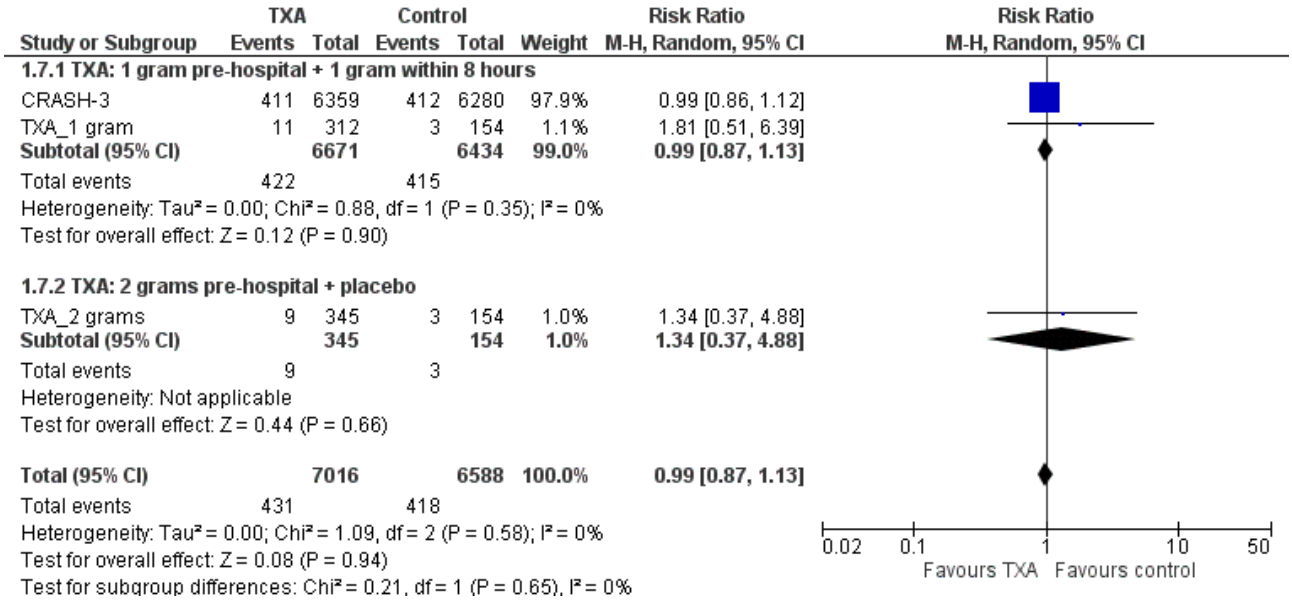


Figure 2. Risk ratio for sepsis (28 days) of TXA versus placebo subgrouped for doses of TXA (1 g in pre-hospital + 1 g within 8 hours and 2 g in pre-hospital + placebo), by considering trauma patients.

1.3 EMBOLIA POLMONARE

Comparazione 1. Acido Tranexamico vs placebo

Per l'evento avverso *embolia polmonare*, valutato da 3 studi randomizzati e controllati (CRASH-2, CRASH-3, TXA) entro 4 settimane dall'assunzione del TXA, non si mostra una differenza significativa nella sicurezza derivante dalla somministrazione, sia di 1 grammo di TXA in fase pre-ospedaliera + 1 grammo entro 8 ore (CRASH-2, CRASH-3 e TXA) che di 2 grammi di TXA in fase pre-ospedaliera + placebo (TXA).

Table 5. Outcome data for the comparisons of pulmonary embolism: TXA versus placebo.

Pulmonary embolism					
RCT studies: pre-hospital use of TXA versus placebo					
	TXA		**Placebo**		**time point**
	n	**tot**	**n**	**tot**	
CRASH-2	72	10060	71	10067	within 28 days
CRASH-3	24	6359	32	6280	within 28 days
TXA: 1 g pre-hospital + 1 g within 8 h	3	312	2*	154**	within 28 days
2 g pre-hospital + placebo	6	345	2*	154**	within 28 days

*five events in the placebo group.

*The placebo group (n=309) of the TXA trial has been splitted into two groups for the pooled analysis (Higgins JPT, Eldridge S, Li T (editors). Chapter 23: Including variants on randomized trials. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.)

Pulmonary embolism (28 days), subgrouped for doses:

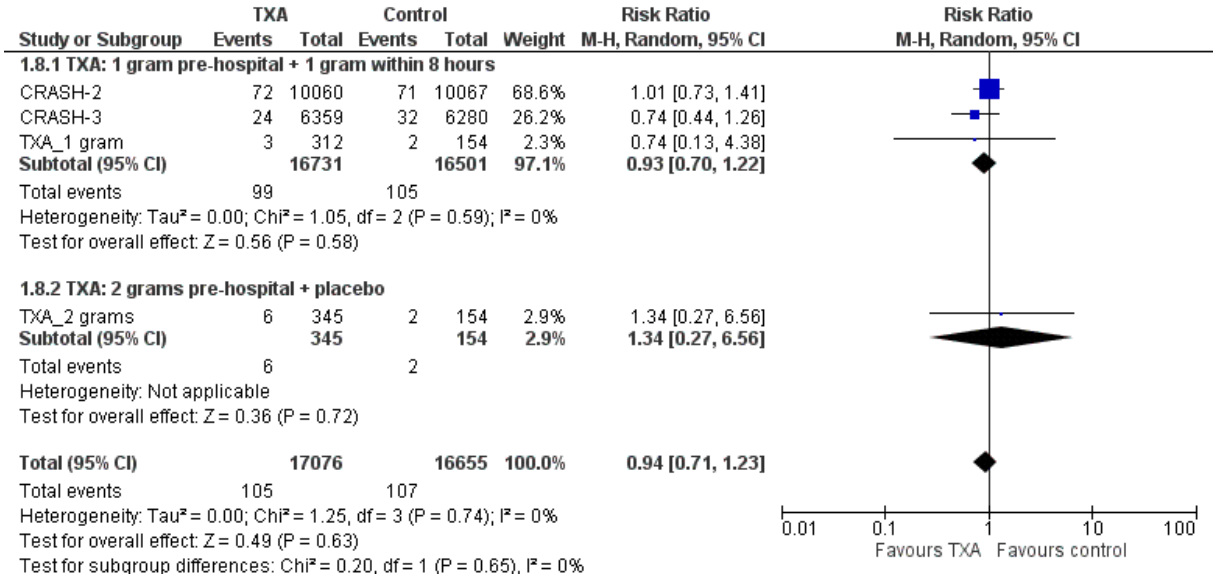


Figure 3. Risk ratio for pulmonary embolism (28 days) of TXA versus placebo subgrouped for doses of TXA (1 g in pre-hospital + 1 g within 8 hours and 2 g in pre-hospital + placebo), by considering trauma patients.

3.3 ICTUS

Comparazione 1. Acido Tranexamico vs placebo

Per l'evento avverso *ictus*, valutato da 3 studi randomizzati controllati (CRASH-2, CRASH-3, TXA) entro 4 settimane dal trattamento, anche se in presenza di un trend spostato a favore del farmaco Acido Tranexamico, non si mostra una differenza statisticamente significativa in termini di sicurezza per la somministrazione sia di 1 grammo di TXA in fase pre-ospedaliera + 1 grammo entro 8 ore (CRASH-2, CRASH-3 e TXA che di 2 grammi + placebo (TXA).

Table 6. Outcome data for the comparisons of stroke: TXA versus placebo.

Stroke					
RCT studies: pre-hospital use of TXA versus placebo					
	TXA		**Placebo**		**time point**
	n	**tot**	**n**	**tot**	
CRASH-2	57	10060	66	10067	within 28 days
CRASH-3	46	6359	42	6280	within 28 days
TXA: 1 g pre-hospital + 1 g within 8 h	3	312	5	154*	within 28 days
2 g pre-hospital + placebo	13	345	5	154*	within 28 days

*The placebo group (n=309) of the TXA trial has been splitted into two groups for the pooled analysis (Higgins JPT, Eldridge S, Li T (editors). Chapter 23: Including variants on randomized trials. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.)

Stroke (28 days), subgrouped for doses:

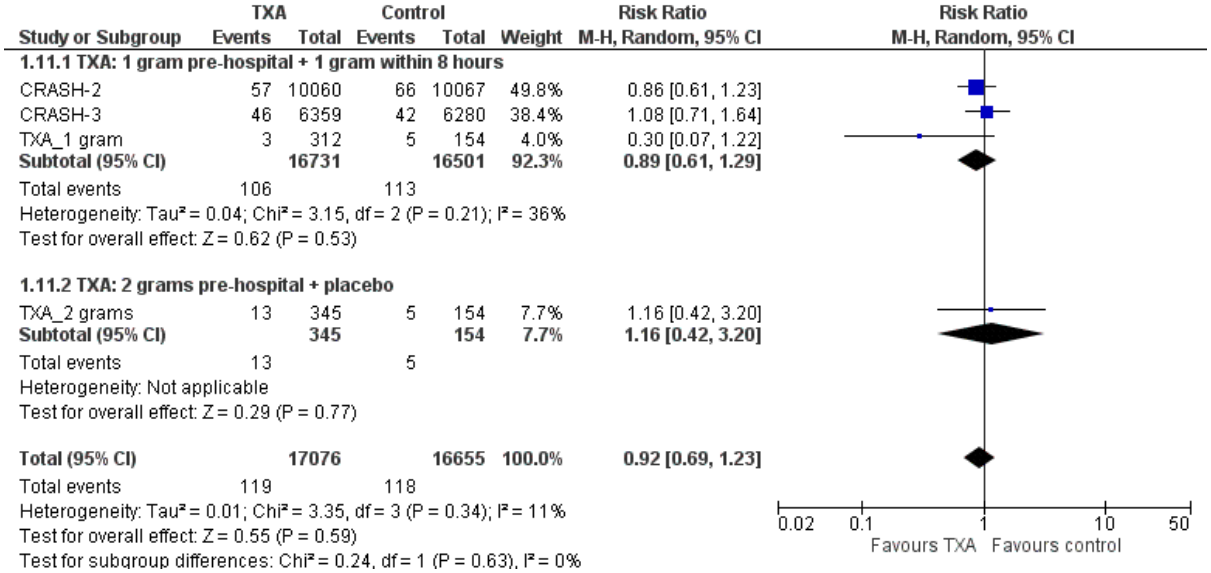


Figure 4. Risk ratio for stroke (28 days) of TXA versus placebo subgrouped for doses of TXA (1 g in pre-hospital + 1 g within 8 hours and 2 g in pre-hospital + placebo) by considering trauma patients.

3.4 VASCOLARI: qualsiasi evento occlusivo vascolare (TXA), trombosi venosa profonda, coagulazione intravascolare disseminata

Le cause riportate negli RCT relative agli eventi avversi prettamente vascolari quali *qualsiasi evento occlusivo vascolare, trombosi venosa profonda, coagulazione intravascolare disseminata* sono state analizzate per entrambe le comparazioni i.a) somministrazione pre-hospital di TXA 1 grammo in pre-ospedaliero + 1 grammo in infusione nelle 8 ore successive vs placebo e i.b) TXA 2 grammi in pre-ospedaliero + placebo vs placebo;

Comparazione 1. Acido Tranexamico vs placebo

Per gli eventi avversi relativi a *qualsiasi evento occlusivo vascolare, trombosi venosa profonda* e *coagulazione intravascolare disseminata*, identificati da 3 studi controllati randomizzati (CRASH-2, CRASH-3 e TXA), insorti entro 4 settimane dall'assunzione del TXA, non è stata rilevata una diminuzione significativa sia in caso di somministrazione dell'agente emostatico TXA per 1 grammo in fase pre-ospedaliera + 1 grammo entro 8 ore (CRASH-2, CRASH-3 e TXA), che per 2 grammi + placebo (TXA).

Table 7. Outcome data for the comparisons of any vascular occlusive event: TXA versus placebo.

Any vascular occlusive event					
RCT studies: pre-hospital use of TXA versus placebo					
	TXA		**Placebo**		**time point**
	n	**tot**	**n**	**tot**	
CRASH-2	168	10060	201	10067	within 28 days
CRASH-3	101	6359	102	6280	within 28 days
TXA: 1 g pre-hospital + 1 g within 8 hours (any thromboembolic event)	13	312	15	154*	within 28 days
2 g pre-hospital + placebo (any thromboembolic event)	31	345	15	154*	within 28 days

***** The placebo group (n=309) of the TXA trial has been splitted into two groups for the pooled analysis (Higgins JPT, Eldridge S, Li T (editors). Chapter 23: Including variants on randomized trials. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.)

Any vascular occlusive event (28 days), subgrouped for doses:

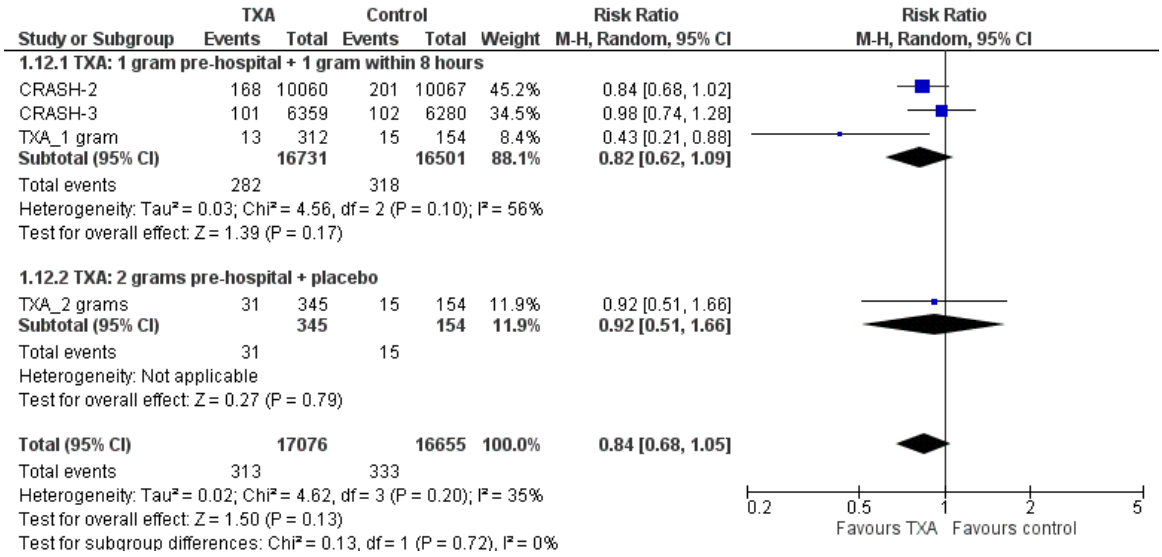


Figure 5. Risk ratio for any vascular occlusive event (28 days) of TXA versus placebo subgrouped for doses of TXA (1 g in pre-hospital + 1 g within 8 hours and 2 g in pre-hospital + placebo) by considering trauma patients.

Table 8. Outcome data for the comparisons of deep vein thrombosis: TXA versus placebo.

Deep vein thrombosis					
RCT studies: pre-hospital use of TXA versus placebo					
	TXA		**Placebo**		**time point**
	n	**tot**	**n**	**tot**	
CRASH-2	40	10060	41	10067	within 28 days
CRASH-3	19	6359	16	6280	within 28 days
TXA: 1 g pre-hospital + 1 g within 8 hours	3	312	4*	154**	within 28 days
2 g pre-hospital + placebo	10	345	4*	154**	within 28 days

* 9 events in the placebo group

***** The placebo group (n=309) of the TXA trial has been splitted into two groups for the pooled analysis (Higgins JPT, Eldridge S, Li T (editors). Chapter 23: Including variants on randomized trials. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.)

Deep vein thrombosis (28 days), subgrouped for doses:

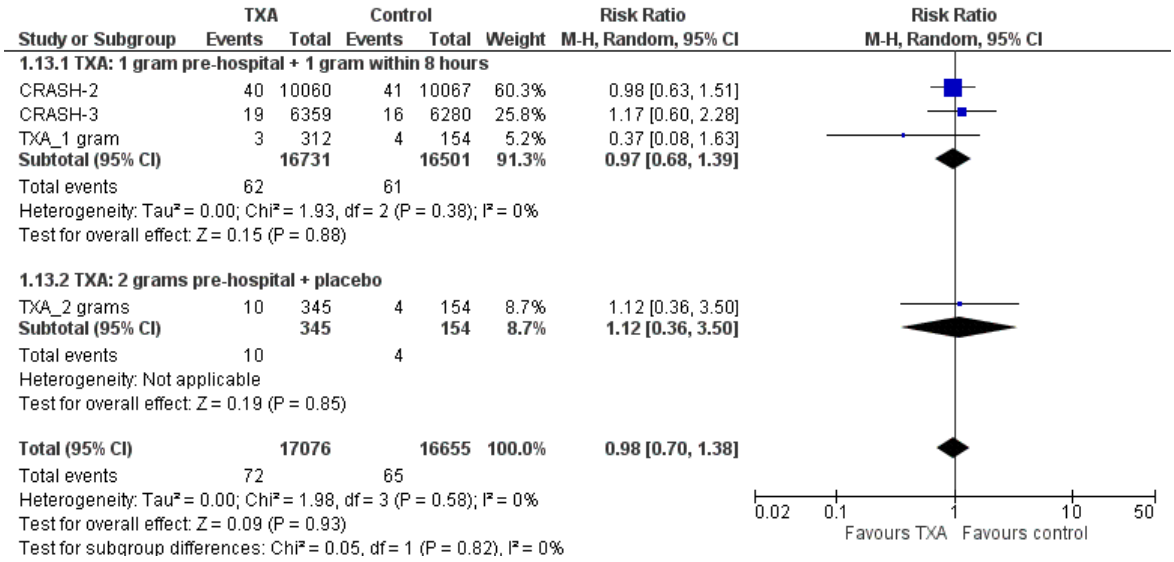


Figure 6. Risk ratio for deep vein thrombosis (28 days) of TXA versus placebo subgrouped for doses of TXA (1 g in pre-hospital + 1 g within 8 hours and 2 g in pre-hospital + placebo) by considering trauma patients.

Table 9. Outcome data for the comparisons of disseminated intravascular coagulation: TXA versus placebo.

Disseminated intravascular coagulation					
RCT studies: pre-hospital use of TXA versus placebo					
	TXA		**Placebo**		**time point**
	n	**tot**	**n**	**tot**	
TXA: 1 g pre-hospital + 1 g within 8 hours	1	312	0	154*	within 28 days
2 g pre-hospital + placebo	1	345	0	154*	within 28 days

***** The placebo group (n=309) of the TXA trial has been splitted into two groups for the pooled analysis (Higgins JPT, Eldridge S, Li T (editors). Chapter 23: Including variants on randomized trials. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.)

Disseminated intravascular coagulation (28 days), subgrouped for doses:

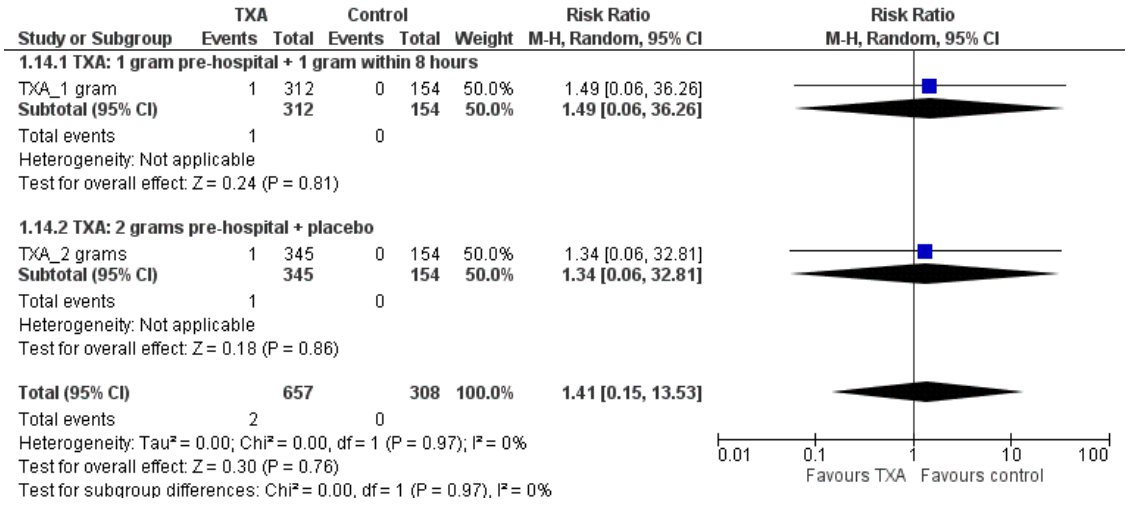


Figure 7. Risk ratio for disseminated intravascular coagulation (28 days) of TXA versus placebo subgrouped for doses of TXA (1 g in pre-hospital + 1 g within 8 hours and 2 g in pre-hospital + placebo) by considering trauma patients.

3.5 ALTRI EVENTI AVVERSI: Sanguinamento gastrointestinale (TXA), Insufficienza renale (TXA), Danno renale acuto (TXA), Convulsioni (TXA)

Le cause riportate negli RCT relative ad altri eventi avversi sono:
- *sanguinamento gastrointestinale* per il quale è stato possibile analizzare solo la comparazione i.a) somministrazione pre-hospital di TXA 1 grammo in pre-ospedaliero + 1 grammo in infusione nelle 8 ore successive vs placebo;
- *insufficienza renale, danno renale acuto, convulsioni* per le quali è stato possibile analizzare entrambe le comparazioni i.a) somministrazione pre-hospital di TXA 1 grammo in pre-ospedaliero + 1 grammo in infusione nelle 8 ore successive vs placebo e i.b) TXA 2 grammi in pre-ospedaliero + placebo vs placebo.

Comparazione 1. Acido Tranexamico vs placebo

Per gli altri eventi avversi identificati da 3 trial (CRASH-2, CRASH-3, TXA) rilevati entro 4 settimane dall'assunzione del TXA, quali *emorragia gastrointestinale* (CRASH-3), *insufficienza renale* (CRASH-3, TXA), *danno renale acuto* (TXA), e *convulsioni* (CRASH-3 e TXA), non si evidenzia una chiara indicazione rispetto alla sicurezza della somministrazione pre-ospedaliera dell'agente emostatico TXA.

Per l'emorragia gastrointestinale entro 28 giorni (CRASH-3), si prega di prendere visione dell'Appendice C supplementare – Sottogruppi di Popolazione.

Table 10. Outcome data for the comparisons of other adverse events: TXA versus placebo.

	TXA		Placebo		time point
	n	tot	n	tot	
Gastrointestinal bleeding					
RCT studies: pre-hospital use of TXA versus placebo					
CRASH-3	24	6359	35	6280	within 28 days
Renal failure					
RCT studies: pre-hospital use of TXA versus placebo					
CRASH-3	100	6359	84	6280	within 28 days
TXA:					
1 g pre-hospital + 1 g within 8 hours	0	312	0	154***	within 28 days
2 g pre-hospital + placebo	5	345	0	154***	within 28 days
Acute kidney injury					
RCT studies: pre-hospital use of TXA versus placebo					

	TXA		Placebo		time point
	n	tot	n	tot	
TXA: 1 g pre-hospital + 1 g within 8 hours	17	312	6*	154***	within 28 days
2 g pre-hospital + placebo	16	345	6*	154***	within 28 days
Seizures					
RCT studies: pre-hospital use of TXA versus placebo					
	TXA		**Placebo**		**time point**
	n	**tot**	**n**	**tot**	
CRASH-3	206	6359	186	6280	within 28 days
TXA: 1 g pre-hospital + 1 g within 8 hours	5	312	3**	154***	within 28 days
2 g pre-hospital + placebo	17	345	3**	154***	within 28 days

*with 13 events in the placebo group; ** with 7 events in the placebo group
*** The placebo group (n=309) of the TXA trial has been splitted into two groups for the pooled analysis (Higgins JPT, Eldridge S, Li T (editors). Chapter 23: Including variants on randomized trials. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.)

Renal failure (28 days), subgrouped for doses:

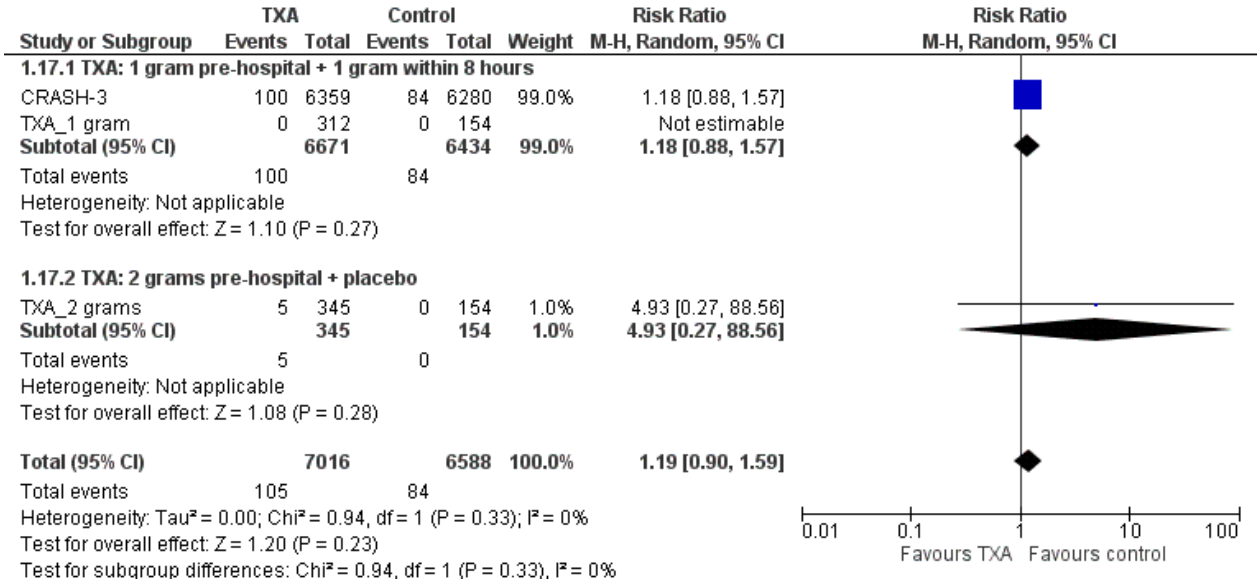


Figure 8. Risk ratio for renal failure (28 days) of TXA subgrouped for doses (1 g in pre-hospital + 1 g within 8 hours and 2 g in pre-hospital + placebo), by considering trauma patients.

Acute kidney injury (28 days), subgrouped for doses:

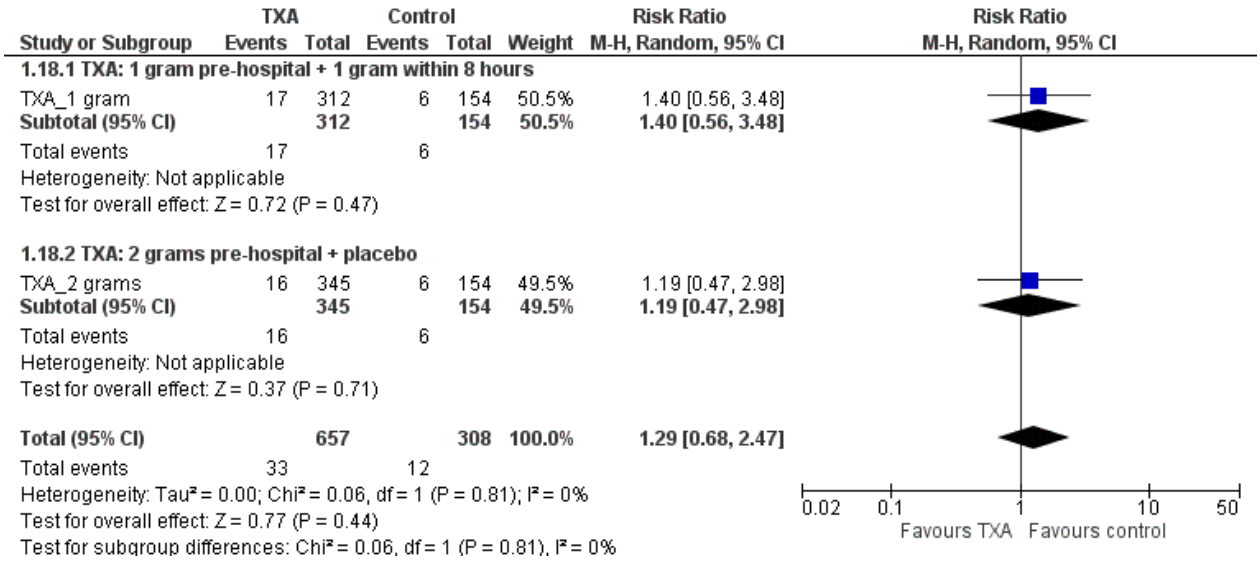


Figure 9. Risk ratio for acute kidney injury (28 days) of TXA versus placebo subgrouped for doses of TXA (1 g in pre-hospital + 1 g within 8 hours and 2 g in pre-hospital + placebo), by considering trauma patients.

Seizures (28 days), subgrouped for doses:

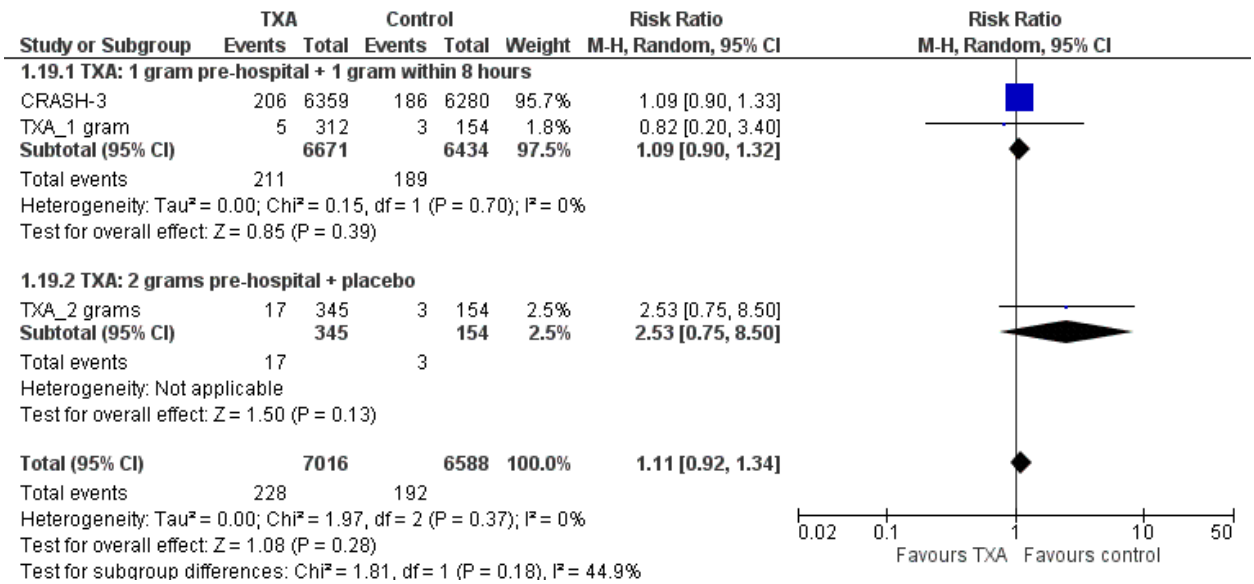


Figure 10. Risk ratio for seizures (28 days) of TXA versus placebo subgrouped for doses of TXA (1 g in pre-hospital + 1 g within 8 hours and 2 g in pre-hospital + placebo), by considering trauma patients.

ALTRI OUTCOME NON IMPORTANTI

Oltre agli outcome indicati dal PICO, si riportano le analisi di altri outcome rilevati negli articoli inclusi.
Le cause riportate negli RCT relative ad altri eventi avversi sono:

- *necessità di intervento neurochirurgico* per il quale è stato possibile analizzare solo la comparazione i.a) somministrazione pre-hospital di TXA 1 grammo in pre-ospedaliero + 1 grammo in infusione nelle 8 ore successive vs placebo;
- *giorni liberi da ricovero ospedaliero, da ventilazione, da ricovero in terapia intensiva* per i quali è stato possibile analizzare entrambe le comparazioni i.a) somministrazione pre-hospital di TXA 1 grammo in pre-ospedaliero + 1 grammo in infusione nelle 8 ore successive vs placebo e i.b) TXA 2 grammi in pre-ospedaliero + placebo vs placebo.

5 NECESSITÀ DI INTERVENTO NEUROCHIRURGICO

Comparazione 1. Acido Tranexamico vs placebo

Il rischio di essere sottoposti ad intervento neurochirurgico entro 28 giorni è stato riportato da due RCT (CRASH-2, TXA), che non mostrano un chiaro beneficio a seguito della somministrazione pre-ospedaliera dell'agente emostatico TXA, sia per somministrazioni dell'agente emostatico TXA per 1 grammo in fase pre-ospedaliera + 1 grammo entro 8 ore (trial CRASH-2 e TXA) che per 2 grammi + placebo (trial TXA).

Table 11. Outcome data for neurosurgical intervention: TXA versus placebo.

Neurosurgical intervention					
RCT studies: pre-hospital use of TXA versus placebo					
	TXA		**Placebo**		**time point**
	n	**tot**	**n**	**tot**	
CRASH-2	1040	10060	1059	10067	within 28 days
TXA 1 g pre-hospital + 1 g within 8 hours	62	312	27	154*	within 28 days
2 g pre-hospital + placebo	75	345	27	154*	within 28 days

***** The placebo group (n=309) of the TXA trial has been splitted into two groups for the pooled analysis (Higgins JPT, Eldridge S, Li T (editors). Chapter 23: Including variants on randomized trials. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.)

Neurosurgical intervention (within 28 days), subgrouped for doses:

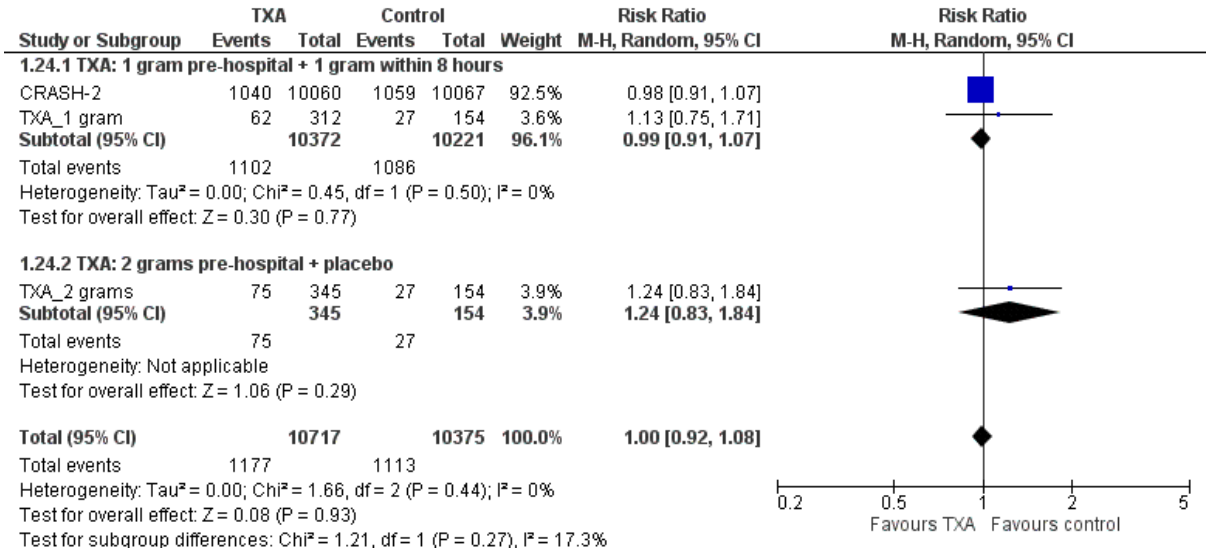


Figure 11. Risk ratio for neurosurgical intervention (28 days) of TXA versus placebo subgrouped for doses, by considering trauma patients.

6 GIORNI LIBERI DA RICOVERO OSPEDALIERO

Comparazione 1. Acido Tranexamico vs placebo

Per i giorni liberi da ricovero ospedaliero (trial TXA) non si mostra una chiara indicazione dei benefici a seguito dell'assunzione pre-ospedaliera dell'agente emostatico TXA, sia per somministrazioni dell'agente emostatico TXA per 1 grammo in fase pre-ospedaliera + 1 grammo entro 8 ore che per 2 grammi + placebo.

Table 12. Outcome data for the comparisons of hospital-free days: TXA versus placebo.

Hospital-free days					
RCT studies: pre-hospital use of TXA versus placebo					
	TXA		**Placebo**		**time point**
	mean	**sd**	**mean**	**sd**	
TXA:	**N = 292**		**N = 147***		
1 g pre-hospital + 1 g within 8 h	13.6	10.7	13.6	10.7	28 days
	N = 331		**N = 147***		
2 g pre-hospital + placebo	14.1	10.4	13.6	10.7	28 days

* The placebo group (n=295) of the TXA trial has been splitted into two groups for the pooled analysis; (Higgins JPT, Eldridge S, Li T (editors). Chapter 23: Including variants on randomized trials. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.)

Hospital-free days (28 days), subgrouped for doses:

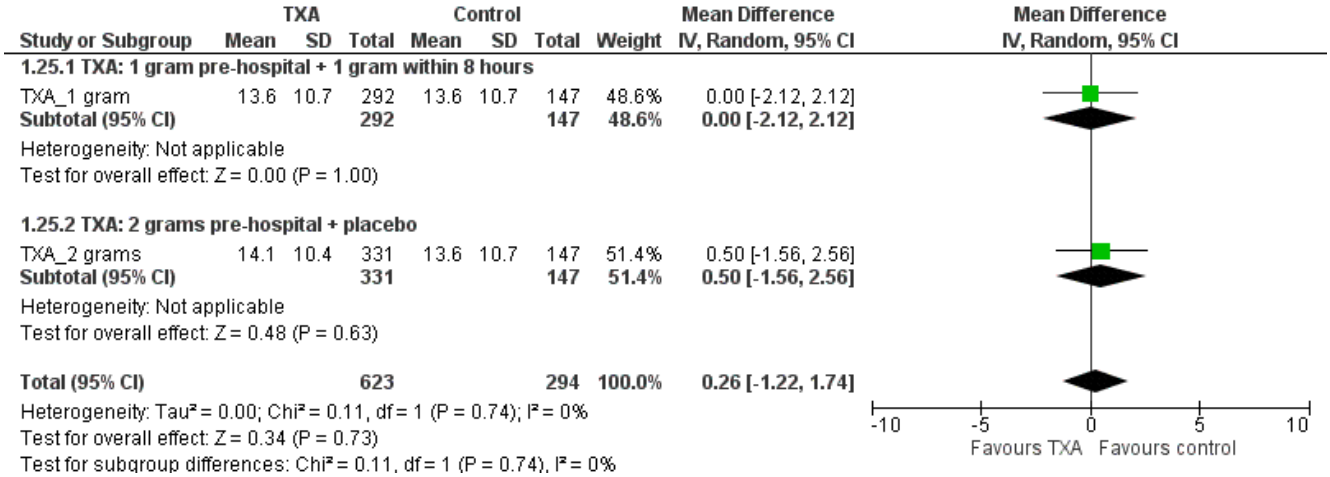


Figure 12. Mean difference for hospital-free days (28 days) of TXA versus placebo subgrouped for doses of TXA (1 g in pre-hospital + 1 g within 8 hours and 2 g in pre-hospital + placebo), by considering trauma patients.

7 GIORNI LIBERI DA VENTILAZIONE

Comparazione 1. Acido Tranexamico vs placebo

Per i giorni liberi da ventilazione (trial TXA) non si mostra una chiara indicazione dei benefici a seguito dell'assunzione pre-ospedaliera dell'agente emostatico TXA, sia per somministrazioni dell'agente emostatico TXA per 1 grammo in fase pre-ospedaliera + 1 grammo entro 8 ore che per 2 grammi + placebo.

Table 13. Outcome data for the comparisons of ventilator free-days: TXA versus placebo.

Ventilator free days					
RCT studies: pre-hospital use of TXA versus placebo					
	TXA		**Placebo**		**time point**
	mean	**sd**	**mean**	**sd**	
TXA: 1 g pre-hospital + 1 g within 8 h	**N = 293**		**N = 147***		
	19.9	10.8	20.2	10.5	28 days
	N = 331		**N = 147***		
2 g pre-hospital + placebo	**mean**	**sd**	**mean**	**sd**	
	20.9	9.7	20.2	10.5	28 days

* The placebo group (n=295) of the TXA trial has been splitted into two groups for the pooled analysis; (Higgins JPT, Eldridge S, Li T (editors). Chapter 23: Including variants on randomized trials. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.)

Ventilator-free days (28 days), subgrouped for doses:

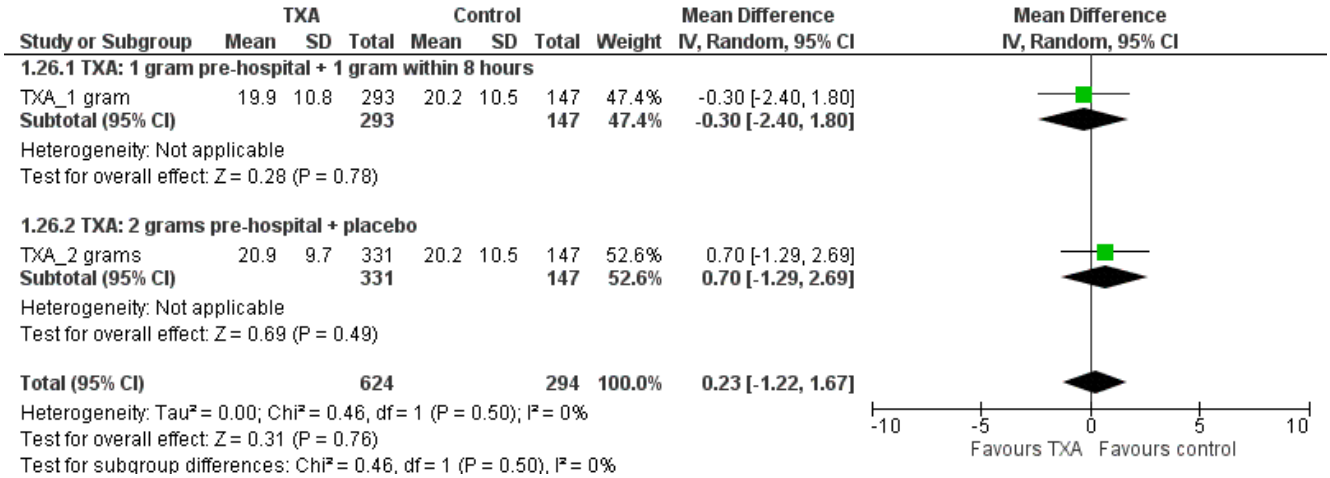


Figure 13. Mean difference for ventilator-free days (28 days) of TXA versus placebo subgrouped for doses of TXA (1 g in pre-hospital + 1 g within 8 hours and 2 g in pre-hospital + placebo), by considering trauma patients.

8 GIORNI LIBERI DA RICOVERO IN TERAPIA INTENSIVA

Comparazione 1. Acido Tranexamico vs placebo

Per i giorni liberi da ricovero in terapia intensiva (trial TXA) non si mostra una chiara indicazione dei benefici a seguito dell'assunzione pre-ospedaliera dell'agente emostatico TXA considerando la dose di 1 grammo + 1 grammo entro 8 ore o indistintamente l'assunzione del TXA. In egual modo non si rileva un aumento significativo dei giorni di ricovero in terapia intensiva, considerando la dose pre-ospedaliera pari a 2 grammi + placebo.

Table 14. Outcome data for the comparisons of ICU-free days: TXA versus placebo.

ICU free days					
RCT studies: pre-hospital use of TXA versus placebo					
	TXA		**Placebo**		**time point**
	mean	**sd**	**mean**	**sd**	
TXA:					
1 g pre-hospital + 1 g within 8 h	**N = 293**		**N = 147***		
	18.1	10.8	18.5	10.6	28 days
	N = 331		**N = 147***		
2 g pre-hospital + placebo	19.1	9.7	18.5	10.6	28 days

* The placebo group (n=295) of the TXA trial has been splitted into two groups for the pooled analysis; (Higgins JPT, Eldridge S, Li T (editors). Chapter 23: Including variants on randomized trials. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.)

ICU-free days (28 days), subgrouped for doses:

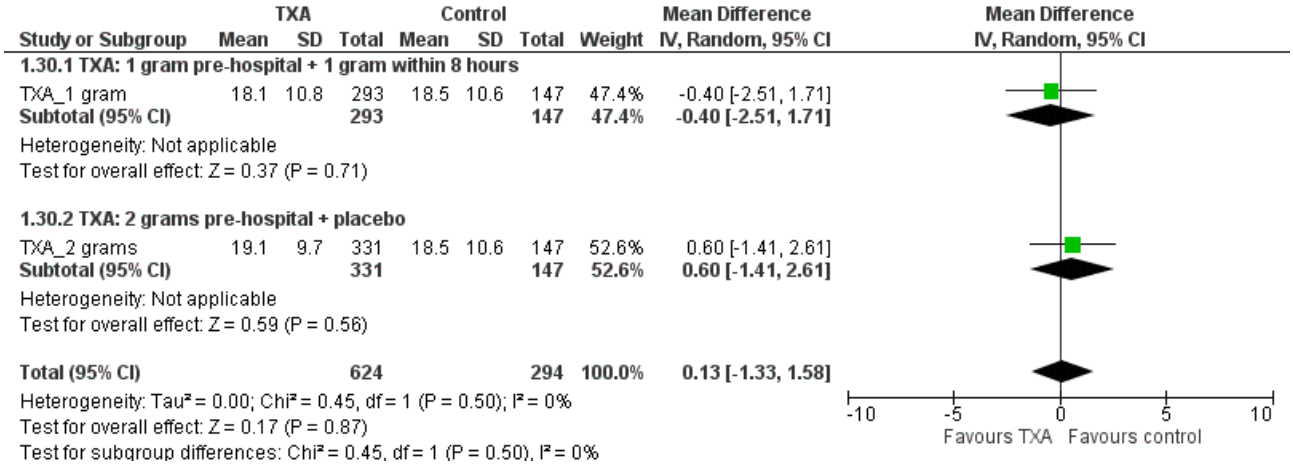


Figure 14. Mean difference for ICU-free days (28 days) of TXA versus placebo subgrouped for doses of TXA (1 g in pre-hospital + 1 g within 8 hours and 2 g in pre-hospital + placebo), by considering trauma patients.

TABELLA RIASSUNTIVA – EVIDENZE DI EFFICACIA

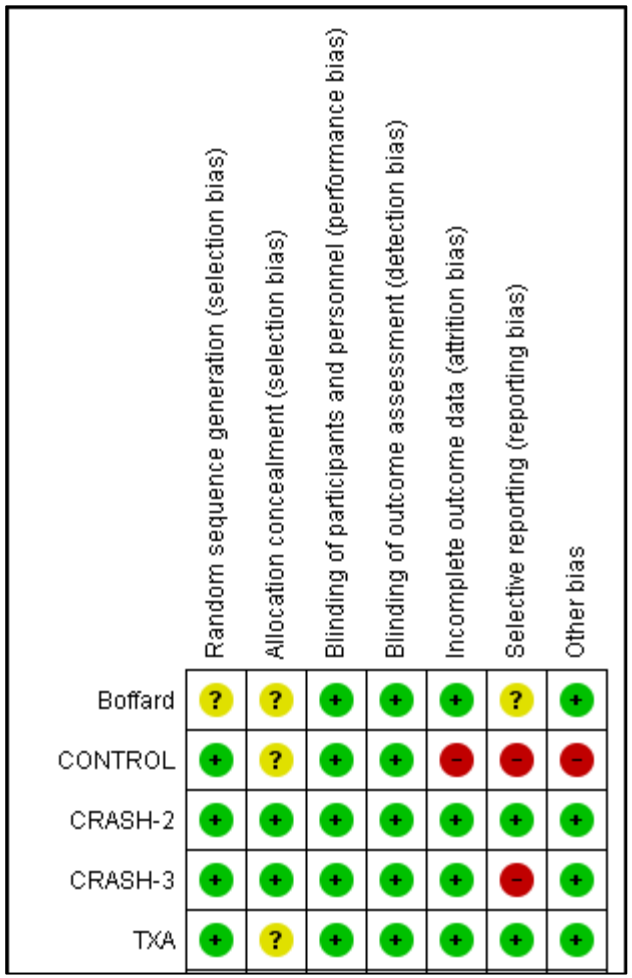
Table 15. Summary table of clinical outcomes regarding the pre-hospital administration of TXA versus placebo.

OUTCOME	TXA vs placebo 1 g pre-hospital + 1 g within 8 hours	TXA vs placebo 2 grams pre-hospital + placebo
OUTCOME CRITICI:		
1) MORTALITÀ		
1.1) Overall 4 settimane	RR 0.93 (0.89 to 0.98)	RR 0.71 (0.45 to 1.13)
3) EVENTI AVVERSI		
3.1) Sepsi 4 settimane	RR 0.99 (0.87 to 1.13)	RR 1.34 (0.37 to 4.88)
3.2) Embolia polmonare 4 settimane	RR 0.93 (0.70 to 1.22)	RR 1.34 (0.27 to 6.56)
3.3) Ictus 4 settimane	RR 0.89 (0.61 to 1.29)	RR 1.16 (0.42 to 3.20)
3.4) Vascolari		
Qualsiasi evento occlusivo vascolare 4 settimane	RR 0.82 (0.62 to 1.09)	RR 0.92 (0.51 to 1.66)
Trombosi venosa profonda 4 settimane	RR 0.97 (0.68 to 1.39)	RR 1.12 (0.36 to 3.50)
Coagulazione intravascolare disseminata 4 settimane	RR 1.49 (0.06 to 36.26)	RR 1.34 (0.06 to 32.81)
3.5) Altri eventi avversi		
Insufficienza renale 4 settimane	RR 1.18 (0.88 to 1.57)	RR 4.93 (0.27 to 88.56)
Danno renale acuto 4 settimane	RR 1.40 (0.56 to 3.48)	RR 1.19 (0.47 to 2.98)
Convulsioni 4 settimane	RR 1.09 (0.90 to 1.32)	RR 2.53 (0.75 to 8.50)

ALTRI OUTCOME NON IMPORTANTI:		
1) NECESSITÀ DI INTERVENTO NEUROCHIRURGICO 4 settimane	RR 0.99 (0.91 to 1.07)	RR 1.24 (0.83 to 1.84)
2) GIORNI LIBERI DA RICOVERO OSPEDALIERO 4 settimane	MD 0.00 (-2.12 to 2.12)	MD 0.50 (-1.56 to 2.56)
3) GIORNI LIBERI DA VENTILAZIONE 4 settimane	MD -0.30 (-2.40 to 1.80)	MD 0.70 (-1.29 to 2.69)
4) GIORNI LIBERI DA RICOVERO IN TERAPIA INTENSIVA 4 settimane	MD -0.40 (-2.51 to 1.71)	MD 0.61 (-1.41 to 2.61)

Appendice D - Valutazione della qualità metodologica degli studi inclusi

CQ8. Gestione dell'emorragia nel setting pre-ospedaliero: agenti emostatici



Studi randomizzati controllati: CRASH-2

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	LOW RISK	"Randomisation was balanced by centre, with an allocation sequence based on a block size of eight, generated with a computer random number generator. In hospitals in which telephone randomisation was not practicable we used a local pack system that selected the lowest numbered treatment pack from a box containing eight numbered packs. Apart from the pack number, the treatment packs were identical. The randomization service used a minimisation algorithm balancing for sex, age, time since injury, type of injury (blunt or penetrating), Glasgow Coma Score, systolic blood pressure, respiratory rate, central capillary refill time, and country, taking into account what packs were available at that hospital."
Allocation concealment (selection bias)	LOW RISK	"Randomisation was balanced by centre, with an allocation sequence based on a block size of eight, generated with a computer random number generator. In hospitals in which telephone randomisation was not practicable we used a local pack system that selected the lowest numbered treatment pack from a box containing eight numbered packs. Apart from the pack number, the treatment packs were identical. The randomization service used a minimisation algorithm balancing for sex, age, time since injury, type of injury (blunt or penetrating), Glasgow Coma Score, systolic blood pressure, respiratory rate, central capillary refill time, and country, taking into account what packs were available at that hospital."
Blinding of participants and personnel (performance bias)	LOW RISK	"Both participants and study staff (site investigators and trial coordinating centre staff) were masked to treatment allocation."
Blinding of outcome assessment (detection bias)	LOW RISK	Since outcomes are objective they cannot be influenced the effect. "Data were sent to the coordinating centre either electronically (by encrypted electronic data forms which could be sent by email or uploaded to a secure server) or by fax, and were entered onto a central database at the trial coordinating centre in London".
Incomplete outcome data (attrition bias)	LOW RISK	"All analyses were on an intention-to-treat basis and, because almost all randomised patients were followed up, there was no need to use imputation methods for missing data"
Selective reporting (reporting bias)	LOW RISK	"The trial protocol was peer-reviewed and published on The Lancet website in 2005. This study is registered as ISRCTN86750102, Clinicaltrials.gov NCT00375258, and South African Clinical Trial Register DOH-27-0607-1919."
Other bias	LOW RISK	Funding. "Funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The Writing Committee had full access to all data in the study and had final responsibility for the decision to submit for publication. The London School of Hygiene and Tropical Medicine supported the core trial coordinating staff during the first year of the trial set-up. Funding for the run-in stage was provided by J P Moulton Charitable Foundation and the BUPA Foundation. A grant-in-aid for purchasing the tranexamic acid and placebo

		was provided by Pfizer. The main phase of this trial was funded by the UK NIHR Health Technology Assessment programme and will be published in full in the Health Technology Assessment journal series". Similarity at baseline. "Treatment groups were balanced with respect to all baseline patient characteristics"

Studi randomizzati controllati: CRASH-3

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	LOW RISK	"An independent statistician from Sealed Envelope (London, UK) prepared the randomisation codes and gave them to the drug packers so that treatment packs could be prepared. We randomly allocated eligible patients to receive tranexamic acid or matching placebo (0·9% sodium chloride) by intravenous infusion. After baseline information was collected on the entry form, the lowest numbered treatment pack remaining was taken from a box of eight treatment packs. At this point, provided that the ampoules inside the treatment pack were intact, the patient was considered to be randomized"
Allocation concealment (selection bias)	LOW RISK	"An independent statistician from Sealed Envelope (London, UK) prepared the randomisation codes and gave them to the drug packers so that treatment packs could be prepared. We randomly allocated eligible patients to receive tranexamic acid or matching placebo (0·9% sodium chloride) by intravenous infusion. After baseline information was collected on the entry form, the lowest numbered treatment pack remaining was taken from a box of eight treatment packs. At this point, provided that the ampoules inside the treatment pack were intact, the patient was considered to be randomized"
Blinding of participants and personnel (performance bias)	LOW RISK	"Participants and study staff (site investigators and trial coordinating centre staff) were masked to allocation."
Blinding of outcome assessment (detection bias)	LOW RISK	"The primary outcome was head injury-related death as assessed by the responsible clinician. Although some misclassification of cause of death is inevitable, the assessment was made blind to the trial treatment". "The method of randomisation ensured that participating clinicians had no foreknowledge of the treatment allocation and the use of placebo control ensured that outcome assessments were blind to the intervention." .
Incomplete outcome data (attrition bias)	LOW RISK	"We enrolled 9202 (72.2%) patients within 3 h of injury. 40 patients withdrew consent after randomisation but 13 of these agreed to outcome data collection or had outcome

		data collected as part of adverse event reporting". As shown by Figure 1, there were 71 lost to follow-up. "All analyses were on an intention to-treat basis. We did a complete case analysis with no imputation for missing data"
Selective reporting (reporting bias)	HIGH RISK	Two outcomes were not reported in the Results section: Neuro-surgery; Days in intensive care unit. "This trial was registered with ISRCTN (ISRCTN15088122), ClinicalTrials.gov (NCT01402882), EudraCT (2011-003669-14), and the Pan African Clinical Trial Registry (PACTR20121000441277)."
Other bias	LOW RISK	Funding. "The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The run-in phase (the first 500 patients) was funded by The JP Moulton Charitable Trust. The main phase was funded jointly by the National Institute for Health Research Health Technology Assessment (NIHR HTA; 14/190/01), and Joint Global Health Trials, Medical Research Council, Department for International Development, Global Challenges Research Fund, and the Wellcome Trust (MRM0092111). Paul Atkinson, Saint John Regional Hospital, Canada received a $10 000 CAD grant from the New Brunswick Trauma Program to support the trial in Canada." Similarity at baseline. "Baseline characteristics were similar between treatment groups for patients treated within 3 h of injury and for those treated after 3 h. Baseline prognostic factors were well balanced and because almost all randomly assigned patients were followed up there was little potential for bias."

Studi randomizzati controllati: TXA

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)*	LOW RISK	in the protocol report: "Eligible patients will be randomly allocated in a proportion of 1:1:1 bolus/maintenance arm, bolus only arm, and placebo. Randomization assignments will be generated by the ROC (is a research network of North American Emergency Medical Systems and level one trauma centers (10 regional clinical centers and 7 satellite centers)) DCC (a single data coordinating center). To attempt balance by site, permuted blocks of varying concealed size will be used. Nevertheless, location of the episode and availability of providers determine which agency responds to the episode and the order

		in which the containers are used cannot be determined a priori. As a result, the randomization will represent a complete randomization rather than a permuted block randomization."
Allocation concealment (selection bias)*	UNCLEAR RISK	in the protocol report: "Eligible patients will be randomly allocated in a proportion of 1:1:1 bolus/maintenance arm, bolus only arm, and placebo. Randomization assignments will be generated by the ROC (is a research network of North American Emergency Medical Systems and level one trauma centers (10 regional clinical centers and 7 satellite centers)) DCC (a single data coordinating center). To attempt balance by site, permuted blocks of varying concealed size will be used. Nevertheless, location of the episode and availability of providers determine which agency responds to the episode and the order in which the containers are used cannot be determined a priori. As a result, the randomization will represent a complete randomization rather than a permuted block randomization."
Blinding of participants and personnel (performance bias)*	LOW RISK	in the protocol report: "All providers will be blinded to the intervention assignment in a double blind manner. At no point will EMS or hospital providers be able to distinguish the treatment group unless emergency unblinding is required. The blinding process will involve labeling the prehospital study kits with randomization numbers that will be used as the package identification and labeling the in-hospital dose vials with unique code identifiers that can be matched to the study kit randomization numbers."
Blinding of outcome assessment (detection bias)*	LOW RISK	https://clinicaltrials.gov/ct2/show/results/NCT01990768: "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)" In the protocol report: "All providers will be blinded to the intervention assignment in a double blind manner. At no point will EMS or hospital providers be able to distinguish the treatment group unless emergency unblinding is required as described in section 5.2.3. Adherence to the treatment protocol will be carefully monitored and protocol deviations will be identified through the data collected or reported to the ROC DCC by study coordinators. The blinding process will involve labeling the prehospital study kits with randomization numbers that will be used as the package identification and labeling the in-hospital dose vials with unique code identifiers that can be matched to the study kit randomization numbers." "Head CT scans will be reviewed centrally at OHSU under the direction of a

		neuroradiologist who will be blinded to the treatment group assignment"
Incomplete outcome data (attrition bias)	LOW RISK	in the protocol report: "The primary analysis will be a modified intention to treat analysis that will include all patients who were randomized and began treatment. Because of the double-blind design of the study, this analysis tests the primary study hypothesis, and with slightly higher power than an analysis of all randomized patients. The primary analysis of this endpoint will use multiple imputation methods to account for missing outcome data" As reported by the Results section in clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/results/NCT01990768), withdrawal by subjects, by considering 6 months of follow-up, corresponded to: 25, 25, 26 respectively in the placebo group, TXA 1 gram pre-hospital + 1 gram within 8 hours and TXA 2 grams pre-hospital + placebo.
Selective reporting (reporting bias)	LOW RISK	No reporting bias in the manuscript. This study protocol will be conducted as part of the Resuscitation Outcomes Consortium (ROC) at trauma centers in the United States and Canada. Study protocol registered on clinicaltrials.gov at number NCT01990768.
Other bias*	LOW RISK	in the protocol report: Funding. "The U.S. Department of Defense is providing grants funds for this study. This study is funded by grants received from the U.S. National Institutes of Health, US Army Medical Research and Materiel Command (USAMRMC), and other funding agencies. " "This study protocol will be conducted as part of the Resuscitation Outcomes Consortium (ROC) at trauma centers in the United States and Canada. ROC is funded by the National Heart Lung and Blood Institute (NHLBI) in partnership with the US Army Medical Research and Materiel Command (USAMRMC), Canadian Institutes of Health Research, the Heart & Stroke Foundation of Canada, the American Heart Association (AHA), and the Defense Research and Development Canada" Similarity at baseline. "The treatment and placebo groups were well matched. Baseline characteristics of the treatment and placebo groups appeared to be similar, as reported in the Results section of clinicaltrials.gov."

*For these specific domains we have examined the study protocol published in clinicaltrials.gov (https://clinicaltrials.gov/ProvidedDocs/68/NCT01990768/Prot_SAP_ICF_002.pdf) because of missing publications.

Studi randomizzati controllati: Boffard 2005

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	UNCLEAR RISK	Not enough information are present.
Allocation concealment (selection bias)	UNCLEAR RISK	Not enough information are present.
Blinding of participants and personnel (performance bias)	LOW RISK	Not enough information are present, however the control group was placebo. "We therefore conducted two large, randomized, placebo-controlled, double-blind clinical trials to evaluate the efficacy and safety of rFVIIa as adjunctive therapy for control of bleeding in patients with severe blunt or penetrating trauma."
Blinding of outcome assessment (detection bias)	LOW RISK	An independent data safety monitoring board was established to perform ongoing safety evaluation. Safety reporting on MOF and ARDS was based on prespecified definitions provided in the study protocol. "Bias in investigator assessments might have been introduced in cases where routine monitoring of prothrombin time could have potentially revealed whether a patient received rFVIIa or placebo. Because of the emergency medical nature of the trial population and the requirement of adherence to protocol-defined transfusion guidelines, we judge the effect of such bias on trial results to be small if not negligible." However, the outcome were objective and cannot be influenced the effect.
Incomplete outcome data (attrition bias)	LOW RISK	In the blunt trauma trial, 10 patients were withdrawn before receiving trial drug, and waived informed consent was not subsequently confirmed for 5 of the remaining 148 patients who received trial drug, leaving 143 patients eligible for analysis. In the penetrating trauma trial, 8 patients were withdrawn before receiving trial drug, and waived informed consent was not subsequently confirmed for 1 patient, leaving 134 patients eligible for analysis.
Selective reporting (reporting bias)	UNCLEAR RISK	No reporting bias is present in the manuscript. "The study protocol was approved by the ethics committee of each participating institution, and the trial was conducted according to Good Clinical Practice standards. However, no trial protocol was published." This study is registered as Clinicaltrials.gov NCT01563523.
Other bias	LOW RISK	Funding. "Supported by Novo Nordisk A/S, Bagsvaerd, Denmark." Similarity at baseline. "Treatment groups were well matched in terms of baseline characteristics within each of the trauma populations"

Studi randomizzati controllati: CONTROL

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	LOW RISK	"The trial drugs were provided by the Sponsor to the sites in patient-specific boxes that were provided with a unique identification box number. Randomization was conducted in random permuted blocks, with the allocation of every randomization block to a specific center. Eligible patients were randomized and assigned the lowest available randomization number. Randomization was confirmed through an interactive voice response system set up by the Sponsor who was accessible by telephone or the internet. The Sponsor was responsible for data management."
Allocation concealment (selection bias)	UNCLEAR RISK	Not enough information are present to define how the randomization was allocated. "The trial drugs were provided by the Sponsor to the sites in patient-specific boxes that were provided with a unique identification box number. Randomization was conducted in random permuted blocks, with the allocation of every randomization block to a specific center. Eligible patients were randomized and assigned the lowest available randomization number. Randomization was confirmed through an interactive voice response system set up by the Sponsor who was accessible by telephone or the internet. The Sponsor was responsible for data management."
Blinding of participants and personnel (performance bias)	LOW RISK	Not enough information are present, however the control group was placebo. "The CONTROL trial was a prospective, randomized, double-blinded, multicenter (150 hospitals in 26 countries), placebo-controlled trial conducted from August 2005 to September 2008."
Blinding of outcome assessment (detection bias)	LOW RISK	Outcomes are objective and they cannot be influenced the effect. "A Novo Nordisk safety committee periodically evaluated blinded safety data, and an Independent Data Monitoring Committee and an independent statistician (Novo Nordisk consultant but functioning independently and reporting data only to the Data Monitoring Committee) reviewed unblinded safety data at predefined intervals."
Incomplete outcome data (attrition bias)	HIGH RISK	"Ten patients (5 blunt and 5 penetrating injury patients) were randomized but withdrawn from the study before trial product was administered because they were found to be ineligible. Three patients (2 blunt and 1 penetrating injury patients) died before trial product could be administered. Six rFVIIa- dosed patients with blunt injury were randomized but excluded from the ITT set because of inadequate informed consent. Of the blunt injury patients, 461 of 474 dosed patients completed the trial to day 90 (including patients who survived or died but excluding patients who were withdrawn or lost to follow-up) (219 rFVIIa and 242 placebo). Of the penetrating injury patients, 80 of 86 completed to day 90 (42 rFVIIa and 38 placebo)." "The trial was therefore stopped early (573 of 1502 patients) because of the high

		likelihood of futility in demonstrating the primary endpoint in the blunt trauma population." "The CONTROL trial was terminated early. Thus, it was underpowered for its primary endpoints, and the results should be interpreted in that context."
Selective reporting (reporting bias)	HIGH RISK	"The sponsor was responsible for providing clinical trial supplies, preparing the study protocol, data management, statistical analysis, and preparing the clinical trial report". "The trial was conducted according to International Conference on Harmonization Good Clinical Practice standards. Protocols, amendments, and consents were approved by local Independent Ethics Committees/Institutional Review Boards. The CONTROL trial is registered at clinicaltrial.gov NCT00184548 and has been merged with the trial F7TRAUMA-1648 (NCT00323570). However, no trial protocol was published." The outcome of acute lung injury was not reported in the Results section.
Other bias	HIGH RISK	Funding. "Supported by Novo Nordisk A/S, Bagsvaerd, Denmark (sponsor). The sponsor was responsible for providing clinical trial supplies, preparing the study protocol, data management, statistical analysis, and preparing the clinical trial report." Similarity at baseline. "Baseline characteristics of the treatment groups were similar for blunt and penetrating traumas. There were no relevant differences in baseline ISS, GCS, blood pressure, hemoglobin, or markers of acidosis and coagulopathy between groups."

Appendice E -Tabelle delle evidenze

CQ8. Gestione dell'emorragia nel pre-ospedaliero: agenti emostatici

Comparazione 1. Acido Tranexamico vs placebo

Certainty assessment							№ di pazienti		Effetto		Qualità complessiva	Importanza
№ degli studi	Disegno dello studio	Rischio di distorsione	Mancanza di riproducibilità dei risultati	Mancanza di generalizzabilità	Imprecisione	Ulteriori considerazioni	TXA	placebo	Relativo (95% CI)	Assoluto (95% CI)		
Mortality 24 hours_CRASH-2												
1	studi randomizzati	non importante	non importante	non importante	non importante	nessuno	-/10060	-/10067	**HR 0.91** (0.79 a 1.05)	**-- per 1.000** (da -- a --)	⨁⨁⨁⨁ ALTA	CRITICO
Mortality 4 weeks												
3	studi randomizzati	non importante	non importante	non importante	non importante	nessuno	2649/17123 (15.5%)	2788/16706 (16.7%)	**RR 0.93** (0.88 a 0.97)	**12 meno per 1.000** (da 20 meno a 5 meno)	⨁⨁⨁⨁ ALTA	CRITICO
Death due to multiorgan failure												
2	studi randomizzati	non importante	non importante	non importante	non importante	nessuno	236/16419 (1.4%)	257/16347 (1.6%)	**RR 0.92** (0.77 a 1.09)	**1 meno per 1.000** (da 4 meno a 1 più)	⨁⨁⨁⨁ ALTA	CRITICO
Mortality due to head injury_24 hours												
1	studi randomizzati	non importante	non importante	non importante	non importante	nessuno	260/6406 (4.1%)	317/6331 (5.0%)	**RR 0.81** (0.69 a 0.95)	**10 meno per 1.000** (da 16 meno a 3 meno)	⨁⨁⨁⨁ ALTA	CRITICO
Other causes of death - Death due to head injury_within 4 weeks												
2	studi randomizzati	non importante	non importante	non importante	non importante	nessuno	1458/14673 (9.9%)	1513/14581 (10.4%)	**RR 0.95** (0.89 a 1.02)	**5 meno per 1.000** (da 11 meno a 2 più)	⨁⨁⨁⨁ ALTA	CRITICO
Other causes of death - Bleeding death												
2	studi randomizzati	non importante	non importante	non importante	non importante	nessuno	498/16419 (3.0%)	581/16347 (3.6%)	**RR 0.86** (0.76 a 0.96)	**5 meno per 1.000** (da 9 meno a 1 meno)	⨁⨁⨁⨁ ALTA	CRITICO
Sepsis												
2	studi randomizzati	non importante	non importante	non importante	non importante	nessuno	431/7016 (6.1%)	418/6588 (6.3%)	**RR 0.99** (0.87 a 1.13)	**1 meno per 1.000** (da 8 meno a 8 più)	⨁⨁⨁⨁ ALTA	CRITICO
Pulmonary embolism												
3	studi randomizzati	non importante	non importante	non importante	serio [a,b]	nessuno	105/17076 (0.6%)	107/16655 (0.6%)	**RR 0.94** (0.71 a 1.23)	**0 meno per 1.000** (da 2 meno a 1 più)	⨁⨁⨁◯ MODERATA	CRITICO

Certainty assessment							№ di pazienti		Effetto		Qualità complessiva	Importanza
№ degli studi	Disegno dello studio	Rischio di distorsione	Mancanza di riproducibilità dei risultati	Mancanza di generalizzabilità	Imprecisione	Ulteriori considerazioni	TXA	placebo	Relativo (95% CI)	Assoluto (95% CI)		
MI												
3	studi randomizzati	non importante	non importante	non importante	serio [a,b]	nessuno	58/17076 (0.3%)	76/16707 (0.5%)	**RR 0.73** (0.52 a 1.03)	**1 meno per 1.000** (da 2 meno a 0 meno)	⨁⨁⨁◯ MODERATA	CRITICO
Stroke												
3	studi randomizzati	non importante	non importante	non importante	serio [a,b]	nessuno	119/17076 (0.7%)	118/16655 (0.7%)	**RR 0.92** (0.69 a 1.23)	**1 meno per 1.000** (da 2 meno a 2 più)	⨁⨁⨁◯ MODERATA	CRITICO
Any vascular occlusive event												
3	studi randomizzati	non importante	non importante	non importante	serio [a]	nessuno	313/17076 (1.8%)	333/16655 (2.0%)	**RR 0.84** (0.68 a 1.05)	**3 meno per 1.000** (da 6 meno a 1 più)	⨁⨁⨁◯ MODERATA	CRITICO
Deep-vein thrombosis												
3	studi randomizzati	non importante	non importante	non importante	molto serio [a,b]	nessuno	72/17076 (0.4%)	65/16655 (0.4%)	**RR 0.98** (0.70 a 1.38)	**0 meno per 1.000** (da 1 meno a 1 più)	⨁⨁◯◯ BASSA	CRITICO
Disseminated intravascular coagulation												
1	studi randomizzati	non importante	non importante	non importante	molto serio [a,b]	nessuno	2/657 (0.3%)	0/308 (0.0%)	**RR 1.41** (0.15 a 13.53)	**0 meno per 1.000** (da 0 meno a 0 meno)	⨁⨁◯◯ BASSA	CRITICO
Gastrointestinal bleeding												
1	studi randomizzati	non importante	non importante	non importante	serio [a,b]	nessuno	24/6359 (0.4%)	35/6280 (0.6%)	**RR 0.68** (0.40 a 1.14)	**2 meno per 1.000** (da 3 meno a 1 più)	⨁⨁⨁◯ MODERATA	CRITICO
Renal failure												
2	studi randomizzati	non importante	non importante	non importante	serio [a,b]	nessuno	105/7016 (1.5%)	84/6588 (1.3%)	**RR 1.19** (0.90 a 1.59)	**2 più per 1.000** (da 1 meno a 8 più)	⨁⨁⨁◯ MODERATA	CRITICO
Acute kidney injury												
1	studi randomizzati	non importante	non importante	non importante	molto serio [a,b]	nessuno	33/657 (5.0%)	12/308 (3.9%)	**RR 1.29** (0.68 a 2.47)	**11 più per 1.000** (da 12 meno a 57 più)	⨁⨁◯◯ BASSA	CRITICO
Seizures												
2	studi randomizzati	non importante	non importante	non importante	serio [a]	nessuno	228/7016 (3.2%)	192/6588 (2.9%)	**RR 1.11** (0.92 a 1.34)	**3 più per 1.000** (da 2 meno a 10 più)	⨁⨁⨁◯ MODERATA	CRITICO
Blood units												

Certainty assessment							№ di pazienti		Effetto		Qualità complessiva	Importanza
№ degli studi	Disegno dello studio	Rischio di distorsione	Mancanza di riproducibilità dei risultati	Mancanza di generalizzabilità	Imprecisione	Ulteriori considerazioni	TXA	placebo	Relativo (95% CI)	Assoluto (95% CI)		
1	studi randomizzati	non importante	non importante	non importante	serio [a]	nessuno	10060	10067	-	MD **0.23 inferiore** (0.51 inferiore a 0.05 maggiore)	⨁⨁⨁◯ MODERATA	CRITICO
Blood product transfused												
1	studi randomizzati	non importante	non importante	non importante	non importante	nessuno	5067/10060 (50.4%)	5160/10067 (51.3%)	**RR 0.98** (0.96 a 1.01)	**10 meno per 1.000** (da 21 meno a 5 più)	⨁⨁⨁⨁ ALTA	CRITICO
Total haemorrhage growth												
1	studi randomizzati	non importante	non importante	non importante	non importante	nessuno	10060	10067	-	MD **2.2 inferiore** (2.97 inferiore a 1.43 inferiore)	⨁⨁⨁⨁ ALTA	IMPORTANTE

CI: Confidence interval; **HR:** Hazard Ratio; **RR:** Risk ratio; **MD:** Mean difference

Spiegazioni

a. Outcomes were downgraded by one increment if the upper or lower 95% CI crossed the lower MID or the upper or lower 95% CI crossed the upper MID. Outcomes were downgraded by two increments if the upper CI simultaneously crossed the upper MID and the lower CI crossed the lower MID. Default MIDs were set at RRs of 0.75 and 1.25 for dichotomous variables, and at 0.5 of the control group weighted mean standard deviation either side of the null line for continuous variables.
b. events<300 rule of thumb

Comparazione 2. Fattore VII ricombinante vs placebo

Certainty assessment							№ di pazienti		Effetto		Qualità complessiva	Importanza
№ degli studi	Disegno dello studio	Rischio di distorsione	Mancanza di riproducibilità dei risultati	Mancanza di generalizzabilità	Imprecisione	Ulteriori considerazioni	Recombinant factor VIIa	placebo	Relativo (95% CI)	Assoluto (95% CI)		
All cause of death (within 48 hours)												
1	studi randomizzati	molto serio [a]	non importante	non importante	molto serio [b,c]	nessuno	25/139 (18.0%)	23/138 (16.7%)	**RR 1.08** (0.65 a 1.81)	**13 più per 1.000** (da 58 meno a 135 più)	⨁◯◯◯ MOLTO BASSA	CRITICO
Mortality 4 weeks												
2	studi randomizzati	molto serio [a]	non importante	non importante	molto serio [b,c]	nessuno	66/401 (16.5%)	71/418 (17.0%)	**RR 0.94** (0.70 a 1.27)	**10 meno per 1.000** (da 51 meno a 46 più)	⨁◯◯◯ MOLTO BASSA	CRITICO
Death due to multiorgan failure												
1	studi randomizzati	serio [a]	non importante	non importante	molto serio [b,c]	nessuno	1/17 (5.9%)	1/13 (7.7%)	**RR 0.76** (0.05 a 11.11)	**18 meno per 1.000** (da 73 meno a 778 più)	⨁◯◯◯ MOLTO BASSA	CRITICO
Blunt trauma with a TBI component_other causes of death - Death due to pulmonary embolism												
1	studi randomizzati	serio [a]	non importante	non importante	molto serio [b,c]	nessuno	0/17 (0.0%)	1/13 (7.7%)	**RR 0.26** (0.01 a 5.89)	**57 meno per 1.000** (da 76 meno a 376 più)	⨁◯◯◯ MOLTO BASSA	CRITICO
Blunt trauma with a TBI component_other causes of death - Death due to sepsis												
1	studi randomizzati	serio [a]	non importante	non importante	molto serio [b,c]	nessuno	1/17 (5.9%)	0/13 (0.0%)	**RR 2.33** (0.10 a 53.03)	**0 meno per 1.000** (da 0 meno a 0 meno)	⨁◯◯◯ MOLTO BASSA	CRITICO
Sepsis												
1	studi randomizzati	molto serio [a]	non importante	non importante	molto serio [b,c]	nessuno	37/270 (13.7%)	44/290 (15.2%)	**RR 0.91** (0.61 a 1.37)	**14 meno per 1.000** (da 59 meno a 56 più)	⨁◯◯◯ MOLTO BASSA	CRITICO
Pulmonary embolism												
1	studi randomizzati	molto serio [a]	non importante	non importante	molto serio [b,c]	nessuno	9/270 (3.3%)	8/290 (2.8%)	**RR 1.21** (0.47 a 3.09)	**6 più per 1.000** (da 15 meno a 58 più)	⨁◯◯◯ MOLTO BASSA	CRITICO
MI or stroke												

Certainty assessment							№ di pazienti		Effetto		Qualità complessiva	Importanza
№ degli studi	Disegno dello studio	Rischio di distorsione	Mancanza di riproducibilità dei risultati	Mancanza di generalizzabilità	Imprecisione	Ulteriori considerazioni	Recombinant factor VIIa	placebo	Relativo (95% CI)	Assoluto (95% CI)		
1	studi randomizzati	molto serio [a]	non importante	non importante	molto serio [b,c]	nessuno	5/270 (1.9%)	5/290 (1.7%)	**RR 1.07** (0.31 a 3.67)	**1 più per 1.000** (da 12 meno a 46 più)	⨁◯◯◯ MOLTO BASSA	CRITICO
Thromboembolic adverse events_48 hours												
1	studi randomizzati	serio [d]	non importante	non importante	molto serio [b,c]	nessuno	6/139 (4.3%)	6/138 (4.3%)	**RR 0.98** (0.32 a 3.01)	**1 meno per 1.000** (da 30 meno a 87 più)	⨁◯◯◯ MOLTO BASSA	CRITICO
Thromboembolic adverse events_90 days												
1	studi randomizzati	molto serio [a]	non importante	non importante	molto serio [b,c]	nessuno	38/270 (14.1%)	37/290 (12.8%)	**RR 1.00** (0.45 a 2.22)	**0 meno per 1.000** (da 70 meno a 156 più)	⨁◯◯◯ MOLTO BASSA	CRITICO
Arterial thrombotic adverse events												
1	studi randomizzati	molto serio [a]	non importante	non importante	molto serio [b,c]	nessuno	18/270 (6.7%)	12/290 (4.1%)	**RR 1.63** (0.80 a 3.33)	**26 più per 1.000** (da 8 meno a 96 più)	⨁◯◯◯ MOLTO BASSA	CRITICO
Venous thromboembolic adverse events												
1	studi randomizzati	molto serio [a]	non importante	non importante	molto serio [b,c]	nessuno	29/270 (10.7%)	28/290 (9.7%)	**RR 0.53** (0.04 a 6.63)	**45 meno per 1.000** (da 93 meno a 544 più)	⨁◯◯◯ MOLTO BASSA	CRITICO
Deep vein thrombosis												
1	studi randomizzati	molto serio [a]	non importante	non importante	molto serio [b,c]	nessuno	14/270 (5.2%)	16/290 (5.5%)	**RR 0.94** (0.47 a 1.89)	**3 meno per 1.000** (da 29 meno a 49 più)	⨁◯◯◯ MOLTO BASSA	CRITICO
Dissaminated intravascular coagulation												
1	studi randomizzati	molto serio [a]	non importante	non importante	molto serio [b,c]	nessuno	7/270 (2.6%)	11/290 (3.8%)	**RR 0.69** (0.27 a 1.76)	**12 meno per 1.000** (da 28 meno a 29 più)	⨁◯◯◯ MOLTO BASSA	CRITICO
Acute respiratory distress syndrome_30 days												
1	studi randomizzati	serio [a]	non importante	non importante	molto serio [b,c]	nessuno	7/139 (5.0%)	17/138 (12.3%)	**RR 0.44** (0.16 a 1.17)	**69 meno per 1.000** (da 103 meno a 21 più)	⨁◯◯◯ MOLTO BASSA	CRITICO
Acute respiratory distress syndrome_90 days												

Certainty assessment							№ di pazienti		Effetto		Qualità complessiva	Importanza
№ degli studi	Disegno dello studio	Rischio di distorsione	Mancanza di riproducibilità dei risultati	Mancanza di generalizzabilità	Imprecisione	Ulteriori considerazioni	Recombinant factor VIIa	placebo	Relativo (95% CI)	Assoluto (95% CI)		
1	studi randomizzati	molto serio [a]	non importante	non importante	serio [c]	nessuno	8/270 (3.0%)	21/290 (7.2%)	**RR 0.45** (0.21 a 0.98)	**40 meno per 1.000** (da 57 meno a 1 meno)	⨁◯◯◯ MOLTO BASSA	CRITICO
Multiple organ failure_30 gg												
2	studi randomizzati	molto serio [a,d]	non importante	non importante	serio [c]	nessuno	115/401 (28.7%)	154/418 (36.8%)	**RR 0.83** (0.69 a 0.99)	**63 meno per 1.000** (da 114 meno a 4 meno)	⨁◯◯◯ MOLTO BASSA	CRITICO
Multiple organ failure_90 gg												
1	studi randomizzati	molto serio [a]	non importante	non importante	molto serio [b,c]	nessuno	11/270 (4.1%)	18/290 (6.2%)	**RR 0.67** (0.32 a 1.39)	**20 meno per 1.000** (da 42 meno a 24 più)	⨁◯◯◯ MOLTO BASSA	CRITICO
Blood units												
1	studi randomizzati	molto serio [a]	non importante	non importante	serio [b]	nessuno	267	287	-	MD **1.45 inferiore** (3.11 inferiore a 0.21 maggiore)	⨁◯◯◯ MOLTO BASSA	CRITICO
Need for massive transfusion_24 hours												
1	studi randomizzati	molto serio [a]	non importante	non importante	molto serio [b,c]	nessuno	125/267 (46.8%)	155/287 (54.0%)	**RR 0.78** (0.50 a 1.22)	**119 meno per 1.000** (da 270 meno a 119 più)	⨁◯◯◯ MOLTO BASSA	CRITICO
Need for massive transfusion_48 hours												
1	studi randomizzati	serio [a]	non importante	non importante	serio [c]	nessuno	12/114 (10.5%)	30/115 (26.1%)	**RR 0.42** (0.23 a 0.76)	**151 meno per 1.000** (da 201 meno a 63 meno)	⨁⨁◯◯ BASSA	CRITICO
Platelets												
1	studi randomizzati	molto serio [a]	non importante	non importante	serio [b]	nessuno	267	287	-	MD **0.46 inferiore** (1.58 inferiore a 0.66 maggiore)	⨁◯◯◯ MOLTO BASSA	CRITICO
Cryoprecipitate												

Certainty assessment							№ di pazienti		Effetto		Qualità complessiva	Importanza
№ degli studi	Disegno dello studio	Rischio di distorsione	Mancanza di riproducibilità dei risultati	Mancanza di generalizzabilità	Imprecisione	Ulteriori considerazioni	Recombinant factor VIIa	placebo	Relativo (95% CI)	Assoluto (95% CI)		
1	studi randomizzati	molto serio [a]	non importante	non importante	serio [b]	nessuno	267	287	-	MD **0.49 inferiore** (1.15 inferiore a 0.18 maggiore)	⨁◯◯◯ MOLTO BASSA	CRITICO
Fresh frozen plasma												
1	studi randomizzati	molto serio [a]	non importante	non importante	non importante	nessuno	267	287	-	MD **2.66 inferiore** (4.02 inferiore a 1.29 inferiore)	⨁⨁◯◯ BASSA	CRITICO

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Spiegazioni

a. For the CONTROL trial: high risk of bias for incomplete outcome data, selective reporting and funding, and unclear risk of bias for blinding of outcome assessment; For the Boffard 2005 trial: unclear risk of bias for random sequence generation, allocation concealment, blinding of outcome assessment and selective reporting.

b. Outcomes were downgraded by one increment if the upper or lower 95% CI crossed the lower MID or the upper or lower 95% CI crossed the upper MID. Outcomes were downgraded by two increments if the upper CI simultaneously crossed the upper MID and the lower CI crossed the lower MID. Default MIDs were set at RRs of 0.75 and 1.25 for dichotomous variables, and at 0.5 of the control group weighted mean standard deviation either side of the null line for continuous variables.

c. events<300 rule of thumb

Overall quality assessment

Overall quality assessment:	*TXA*	*Fattore VII ricombinante*
Critical:		
1. Mortality at 24 hours, 30 days/ 1 month	ALTA	MOLTO BASSA
2. Health related quality of life	N.A.	N.A
3. Adverse effects: venous thromboembolism thrombotic events (MI/Stroke, pulmonary embolism), over-transfusion related, morbidity, infections	DA BASSA AD ALTA	DA MOLTO BASSA A BASSA
4. Blood product use: RBCs Platelets Plasma cryoprecipitate	DA MODERATA AD ALTA	DA MOLTO BASSA A BASSA
Important:		
5. Mortality at 12 months	N.A.	N.A
6. Entità dell'emorragia (growth)	ALTA	N.A
7. Patient-reported outcomes (psychological wellbeing).	N.A	N.A

Appendice F - Bibliografia degli studi inclusi

CQ8. Gestione dell'emorragia nel pre-ospedaliero: agenti emostatici

TXA

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CRASH-2

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CRASH-3

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Appendice G – Risorse e costi

CQ8. Gestione dell'emorragia nel pre-ospedaliero: agenti emostatici.

E' stata effettuata una revisione sistematica con ricerca della letteratura sulle banche dati Embase, Medline. Sono stati individuati 28 records. Perciò, si richiamano le prove che la linea guida NG39 sul trauma maggiore pubblicata dal NICE nel 2016 riporta in termini i costi e risorse necessarie.
La linea guida NICE NG39 riporta le valutazioni economiche comprendenti unità di costo e valutazioni di costo/efficacia per gli interventi considerati dal quesito clinico da 4 studi di analisi economica (Roberts 2009-2013; Morris 2007; Rossaint 2005-2007; Pohar 2009). La linea guida NICE riporta:

- Una valutazione economica che compara acido tranexemico verso placebo (Roberts 2009-2013)
- Tre valutazioni economiche che comparano fattore ricombinante VIIa con placebo (Morris 2007; Rossaint 2005-2007; Pohar 2009).

Per il farmaco acido tranexamico, l'outcome dello studio valutava il costo per anni di vita guadagnati: l'acido tranexamico ha un costo per anni di vita guadagnati pari a £ 42 comparato a placebo nei pazienti emorragici. Tuttavia, l'outcome non è stato espresso in costo per QALY e quindi non può essere valutata utilizzando la soglia di decisione di £20.000 per QALY. Questa valutazione economica è stato considerata parzialmente applicabile con potenziali serie limitazioni.

La valutazione economica da tre studi del fattore VIIa ricombinante ha evidenziato che la costo efficacia è incerta: due studi hanno identificato che, comparando il fattore VIIa ricombinate con placebo, le analisi di costo utilità hanno trovato i seguenti risultati:

1. Il fattore VIIa ricombinante comparato a placebo è costo efficace alla soglia di £20,000 (ICER - Il rapporto incrementale di costo-efficacia di £18,825 per QALY) nei pazienti emorragici. Questo studio è stato valutato come direttamente applicabile con potenziali serie limitazioni (Morris 2007).
2. Il fattore VIIa ricombinante non è costo efficace comparato a placebo alla soglia di £20,000 (ICER di £21,613 per QALY) nei pazienti emorragici. Questo studio è stato valutato come parzialmente applicabile con potenziali serie limitazioni (Rossaint 2005-2007).
3. Il fattore VIIa ricombinante è più costoso rispetto a placebo alla soglia di £20,000 (£20,342 in più per paziente con incremento di QALYs calcolato ma non riportato. Questo studio è stato valutato come parzialmente applicabile con potenziali serie limitazioni (Pohar 2009).

L'acideo tranexamico ha costi sostanzialmente più bassi rispetto al fattore VIIa ricombinante.
Di seguito si riportano le analisi:

- ***Economic evidence profile***
  - Comparazione 1 : Tranexamic acid versus placebo (Tabella 1)
  - Comparazione 2: Factor VIIa versus placebo (Tabella 2)
- ***Unità di costo***
  - Costi per unità di intervento (Tabella 3)
  - Costi per unità di trasfusione/emocomponenti (Tabella 4)
- ***Tabelle/Economic evidence per singolo studio***
  - Roberts 2013 (Tabella 5)
  - Morris 2007 (Tabella 6)
  - Rossaint 2007 (Tabella 7)
  - Pohar 2009 (Tabella 8).

Tabella 1: Economic evidence profile: Tranexamic acid versus placebo

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Roberts 2013 (UK)	Partially applicable[a]	Potentially serious limitations[b]	Markov model estimating the gain in life years of a cohort of trauma patients with haemorrhage who receive tranexamic acid (TXA) compared with placebo. Mortality data from CRASH-2 trial.	£31	0.755 life years	£42 per life year gained	80% probability of being costeffectiveness at a threshold of £65 per life year gained.[c]

(a) Appropriate population and treatment comparison in a UK NHS setting with discounting of life years (costs not discounted they are incurred in the first year only). However, the main health outcome is life years gained rather than QALYs.

(b) The model does not consider any adverse events of the intervention. Additionally, the only costs included were those of the intervention and non-ICU stay days. Does not use QALYs. Does not include long-term costs, therefore, does not take into account potential future health savings as CRASH-2 trial showed that a higher proportion of patients in TXA group reported no symptoms, therefore, TXA group potentially more likely to survive without disability.

Study only looked at cost effectiveness from a willingness to pay threshold of £0 to £163 per life year gained

Tabella 2: Economic evidence profile: Factor VIIa versus placebo

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Morris 2007 (UK)	Directly applicable[a]	Potentially serious limitations[b]	Lifetime model based on patient level data from two randomised placebo-controlled phase II trials[16,16]. Data was supplemented with additional UK data to estimate costs and benefits (mortality following the trial duration, and QoL).	£13,243	0.70 QALYs	£18,825 per QALY	52% (61%) probability of being cost effective at a threshold of £20,000 (£30,000).
Rossaint 2007 **(Germany)**	Partially applicable[c]	Potentially serious limitations [d]	Lifetime model based on patient level data from two randomised placebo-controlled phase II trials[16,16]. Data was supplemented with additional German data to estimate costs and benefits (mortality following the trial duration, and QoL).	£14,831	0.69	£21,613 per QALY	48% (60%) probability of being cost effective at a threshold of £20,000 (£30,000)[h]
Pohar 2009 (Canada)	Partially applicable[e]	Potentially serious limitations[f]	Decision tree model based on patient level data from two randomised placebo-controlled phase II trials[16,16]., supplemented by further sources for costing, utilities and in extrapolation technique to estimate long-term survival estimates.	£20,342[g]	1.68 QALYs[g]	£12,108 per QALY[g]	36% (52%) probability of being cost effective at a threshold of £20,000 (£30,000)[h]

Abbreviations: NR, not reported; QoL, quality of life; QALYs, quality-adjusted life years

(a) Appropriate population (blunt severe trauma who are bleeding or at risk of bleeding), intervention and comparison, in a UK setting with costs and benefits discounted at 3.5%.

(b) Adverse events not included (from the interventions and consequences of blood transfusions). The trial that the economic evaluation is based on is stated to be underpowered to detect mortality and comprised of a sample of 143 patients. Potential conflict of interest from the authors and funders (study funded by drug manufacturer). First two authors have received fees from the company and third and fourth authors are employees of the company. No information given on the structure of the model. Extrapolation methods used to predict probability of survival post 30 days are not explained enough to identify whether there may be any issues such as the previous stage in the 3 stage process are having an impact on the probability derived for later stages. Also the populations compared within the TARN database are stated to be older and less severely injured than the patients in the Boffard trial.

(c) *Appropriate population (blunt severe trauma who are bleeding or at risk of bleeding), intervention and comparison. Costs from a German third party payer perspective (social insurance). Costs and effects discounted at 5%.*

(d) *Adverse events not included (from the interventions and consequences of blood transfusions). The trial that the economic evaluation is based on is stated to be underpowered to detect mortality and comprised of a sample of 143 patients. Potential conflict of interest from the authors and funders (original trial funded by drug manufacturer and most of the authors have received fees from Novo Nordisk). Limitations in trial data used to estimate of mortality in first 30 days may carry through in limiting the estimation of longer term mortality, thus limiting the lifetime horizon estimates*

(e) *Appropriate population (blunt severe trauma who are bleeding or at risk of bleeding), intervention and comparison. Costs from the Canadian perspective. Does not report the discounted QALYs or ICER despite reporting that discounted values were calculated. Benefits discounted at 5%, costs not discounted as only include first year costs.*

(f) *No adverse events considered. Costs beyond one year were not considered. Not possible to work out a discounted ICER as mean discounted QALYs not reported. So ICER estimated in table above using the undiscounted QALYs reported. The trial that the economic evaluation is based on is stated to be underpowered to detect mortality and comprised of a sample of 143 patients. Estimation of mortality post 30 days used data from the Rossaint paper (please see limitations described in footnote (d) above).*

(g) *Only undiscounted values reported. Mean discounted QALY not reported, however, confidence interval for discounted incremental QALY reported to be -1.50 to 2.95 ICER presented was calculated by NCGC using undiscounted mean values.*

(h) *From inspection of cost-effectiveness acceptability curve*

The Pohar study does not report discounted QALYs, and therefore, the ICER reported in the table has been estimated based on the undiscounted QALYs reported which further limits the applicability of the findings. The incomplete reporting may also be seen as a limitation, as it is uncertain where the mean incremental discounted QALY may lie within the reported confidence interval of -1.50 to 2.95. The benefit of this paper in terms of usefulness for decision making is that it is funded by the Canadian Government (as it is a Canadian Health Technology Assessment) and is, therefore, likely to be more impartial compared with the Morris and Rossaint papers whose authors have conflicts of interest.

UNITA' DI COSTO

Tabella 3: Costi di intervento

Intervention	Cost	Unit	Source
Factor 7 (recombinant activated factor VII)	£667		Blood products, band 1 (factor VIIa [recombinant]) (mean cost per episode of care where used). NHS reference cost 2012-1013. Health Resource Groups code XD05Z (reference: NHS reference costs 2012-13)
Tranexamic acid	£1.55	500 mg	BNF (reference: British National Formulary)
Fibrinogen concentrate	£500	1-mg vial	GDG contact
Prothrombin complex concentrates	£600	1000 international units	Manufacturer website

La dose è dipendente da peso e gravità dell'emorragia

CQ8. Gestione dell'emorragia nel pre-ospedaliero: agenti emostatici.

Appendice A. Quesito clinico e strategia di ricerca.

CQ8 Review question: Is the use of systemic haemostatic agents clinically and cost effective in improving outcomes in patients with confirmed or suspected haemorrhage in major trauma?

Objective: Which haemostatic agents administered systemically improve outcomes in patients with confirmed or suspected haemorrhage in major trauma?	
Population	Children, young people and adults who have a suspected haemorrhage following traumatic incident. Setting: pre-hospital scene (including military setting)
Intervention	Factor 7 (recombinant activated factor vii) Tranexamic acid Fibrinogen concentrate Prothrombin complex concentrates Other anti-fibrinolytic agents
Comparison	Nothing A comparison of the above In combination In addition to standard care (Blood components (plasma, RBCs, platelets)) La somministrazione di emoderivati nel pre-ospedaliero non e' uno standard di c ma un protocollo di studio in alcuni sistemi pre-ospedalieri. Lo standard attuale e somministrazione di cristalloidi con un target pressorio limitato (ipotensione permissiva) variabile in funzione della tipologia di trauma. Ce ne occuperemo qu parliamo delle infusion nel pre-ospedaliero
Outcomes	Critical: 1. Mortality at 24 hours, 30 days/ 1 month 2. Adverse effects: venous thromboembolism thrombotic events (MI/Strol pulmonary embolism), over-transfusion related, morbidity, infections 3. Blood product use: RBCs Platelets Plasma cryoprecipitate Important: 1. Mortality at 12 months 2. Time to definitive control of haemorrhage 3. Patient-reported outcomes (psychological wellbeing).
Exclusion	People with a major trauma resulting from burns
Search strategy	Databases: Medline, Embase, the Cochrane Library Date: All years Language: Restrict to English, Italian, Spanish, French, German Study designs: RCTs or Systematic reviews of RCTs; cohorts
The review strategy	Appraisal of methodological quality: The methodological quality of each study wi assessed the Newcastle-Ottawa Scale for observational studies, the Cochrane ris bias tool for RCTs and GRADE.
Analysis	Stratify by age: children (0-17 years), adults (18 and over) Within-study confounders (if cohorts used) Age Injury severity Depth of shock Degree of head injury

perciò i costi presentati sopra sono per unità e potrebbero non essere rappresentativi della dose totale di intervento necessaria per il trattamento del paziente. La dose viene inoltre rivalutata dopo il test di coagulazione. Il successo/efficacia degli agenti emostatici potrebbero

essere misurati anche rispetto alla quantità di emocomponenti utilizzati. Una stima delle risorse necessarie in termini di emocomponenti è riportata sotto (le unità per paziente possono variare).

Tabella 4: Costi degli emocomponenti

Resource	Cost	Unit	Source
Packed RBCs	£122	1 pack 220-300 ml per pack	NHS Blood and transplant price list 2014/15 (reference: NHS Blood and transplant)
FFP	£28	1 pack Mean: 271 ml per pack (240-280 is common)	NHS Blood and transplant price list 2014/15
Platelets	£197	1 adult therapeutic dose	NHS Blood and transplant price list 2014/15
Cryoprecipitate	£181	Pooled cryoprecipitate (5 pack) Mean: 199ml in pooled pack	NHS Blood and transplant price list 2014/15

Note: Unit information sourced from GDG contact and internet.

La linea guida NICE pone la specifica per la popolazione dei bambini: i costi degli emocomponenti FFP e cryoprecipitati sono sostanzialmente più alti a causa delle raccomandazioni del Department of Health (NHS): infatti per coloro nati dopo il 1.1.1996 dovrebbe essere usato un particolare tipo di FFP and cryoprecipitate che sono stati sottoposti a una procedura addizionale per la riduzione del rischio da infezioni virali.

Tabelle per singolo studio – Economic Evidence Table

Tabella 5. Roberts 2013

Roberts I, Shakur H, Coats T, Hunt B, Balogun E, Barnetson L et al. The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. Health Technology Assessment. 2013; 17(10):1-79. (Guideline Ref ID ROBERTS2013)				
Study details	**Population and interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CEA (health outcome: Life years gained) **Study design:** Probabilistic decision analytic model. **Approach to analysis:** Markov model estimating the gain in life years of a cohort of trauma patients with haemorrhage who receive tranexamic acid (TXA) compared with placebo. Mortality data from within CRASH-2 trial. Cycle lengths of 1 year,	**Population:** Trauma patients with significant haemorrhage or at risk of significant haemorrhage and who were within 8 hours of injury.[(a)] **Cohort settings:** Start age: 18, 22, 30, 42 and 75 years Male: NR **Intervention 1:** Placebo (0.9% saline), same dose and timing **Intervention 2:** TXA, loading dose 1g over	**Total costs (mean per patient):** Intervention 1: £2,127 Intervention 2: £2,158 Incremental (2-1): £31 (95% CI NR; p=NR) **Currency and cost year:** 2009 US dollars (presented here as 2009 UK pounds[(b)]) **Cost components incorporated:** TXA Saline and IV infusion Nurse time (cost per hour for preparing and administering TXA)	**Life years (mean per patient):** Intervention 1: 23.407 Intervention 2: 24.162 Incremental (2-1): 0.755 (95% CI NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £42 per life year gained (da) 95% CI: NR Probability Intervention 2 cost-effective (WTP threshold of £65 ($100) per LY gained/Max WTP threshold of £163 per LY gained): 80%/100%[(d)] **Analysis of uncertainty:** One-way sensitivity analysis was undertaken on the: • **Relative risk of death with tranexamic acid** Increasing the relative risk of death for TXA to 0.95 resulted in an incremental cost per life year gained of £110. Reducing the relative risk to 0.81 resulted in an ICER of £28 per life year gained. • **Cost of tranexamic acid** If the cost of TXA was as low as £2, the incremental

patients are either alive or dead. **Perspective:** UK NHS **Time horizon/Followup:** Lifetime **Treatment effect duration:** 12 months **Discounting:** Costs: None[c] ; Outcomes: 3.5%	10 minutes then infusion of 1g over 8 hours	□ Non-ICU stay cost per day		cost per life year gained would be £17. If the cost of TXA was as high as £30, the cost per life year gained would be £56. • **Cost of additional non-ICU stay and cost per non-ICU day** If the cost of non-ICU stay is reduced to £59, the ICER reduces to £30 per life year gained. With a nonICU stay cost of £512, the ICER increases to £54 per life year gained. • **Increase in non-ICU hospital stay following TXA** When the additional ICU stay from TXA is increased to 0.08 days, the cost per life year gained rises to £56. • **Effect of using different parametric survival functions.** Using a log-normal parametric function reduced the cost per life year to £25. A probabilistic sensitivity analysis was performed with 1000 simulations. The net benefit was calculated using a threshold of £163($250) per life year to produce a CEAC.
Data sources				
Health outcomes: The CRASH-2 trial recorded data up to 28 days or death, a parametric survival function was fitted to extrapolate mortality over 12 months following injury. In the statistical analysis three covariates were explored (age, sex and GDP). The cumulative hazard rate implied that after trauma the hazard rate decreases over time, the probability of dying increases with age, and GDP coefficients were found to be highly significant, but sex was not found to be influential for the hazard rate. (The hazard rate decreases to almost zero in the first 40 days after hospital admission and remains constant for the rest of the year). Risk of death during the first year following trauma in the tranexamic group was estimated by multiplying the cumulative hazard for the placebo group by the relative risk reduction in all-cause mortality estimated by the CRASH-2 trial (RR=0.87 (95% CI 0.81 to 0.95). Beyond 12 months, the risk of death is assumed to be equal whether or not the patient received TXA, and is equal to the risk of death for the relevant age-sex group in the general population.				

Quality-of-life weights: n/a **Cost sources:** Cost per day in non-ICU facility ($429) from NHS reference costs 2008-2009. Tranexamic acid cost ($5.70/g) and IV infusion and saline bag prices (IV administration set $4.35) from BNF 2009. Cost per hour of nursing ($38) from Unit costs of Health and Social Care. Cost of syringe (syringes and needles $0.23) from Dziekan et al.
Comments
Source of funding: UK National Institute for Health Research Health Technology Assessment programme, Pfizer, the Bupa Foundation and the J P Moulton Charitable Foundation. **Limitations:** The model only takes into account the effect on mortality and does not consider adverse events, which could impact cost effectiveness (for example the clinical review found that there is a reduction in the number of MI's/strokes for tranexamic acid which would impact resource use, however this is just within the boundary of not being clinically important (0.76 RR). Does not use QALYs. Analysis does not allow for future health service savings, as CRASH-2 trial showed that after 28 days the proportion of patients reporting no symptoms at discharge was significantly higher in TXA group than in placebo group. Therefore, if TXA arm are patients more likely to survive without disability then the study undervalues the potential cost saving arising from the administration of TXA as healthier people will use future health care services less. Only includes costs which the CRASH-2 trial found evidence of a difference for (between the two arms); TXA cost and non-ICU stay cost.
Overall applicability: Partially applicable **Overall quality:** Potentially serious limitations

Abbreviations: BNF: British National Formulary; CEA: cost-effectiveness analysis; CEAC: cost-effectiveness acceptability curve; 95% CI: 95% confidence interval; da: deterministic analysis; ICER: incremental cost-effectiveness ratio; ICU: intensive care unit; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years; TXA: tranexamic acid; WTP = Willingness to Pay (a) Significant haemorrhage indicated by systolic blood pressure (BP) < 90mmHg, heart rate > 110 beats per minute or both.

- *a) Converted using 2009 purchasing power parities[70]. This study assessed three different settings (UK, India and Tanzania) so all costs were converted to US dollars in the study using purchasing power parities (OECD and Penn World Table, accessed 2010). Where necessary, the US Consumer Price Index was used to inflate prices (US Department of Labor, accessed 30th January 2009).*
- *b) Costs were not discounted as the costs associated with giving tranexamic acid occur within the year following trauma (for example reduction on number of strokes may result in long term cost savings compared with placebo).*
- *c) The threshold presented in the analysis was $100 per life year. The CEAC showed values the probability for thresholds up to $250 per life year. The thresholds presented were converted to 2009 UK pounds.*

Tabella 6. Morris 2007 [63]

Morris S, Ridley S, Munro V, Christensen MC. Cost effectiveness of recombinant activated factor VII for the control of bleeding in patients with severe blunt trauma injuries in the United Kingdom. Anaesthesia. United Kingdom 2007; 62(1):43-52. (Guideline Ref ID MORRIS2007)				
Study details	**Population and interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA **Study design:** Model	**Population:** 16 to 64 years of age with blunt trauma, who received 6 units of RBC	**Total costs (mean per patient):** Intervention 1: £57,639 Intervention 2: £70,882	**Total QALYs (mean per patient):** Intervention 1: 9.88 Intervention 2: 10.59	**ICER (Intervention 2 versus Intervention 1):** £18,825 per QALY (da) 95% CI: NR

based on patient level data **Approach to analysis:** Model based on patient level data from two randomised placebo-controlled phase II trials. Data was supplemented with additional UK data to estimate costs and benefits (mortality and QoL). **Perspective:** UK NHS **Time horizon/Followup:** Lifetime **Treatment effect duration:** 30 days **Discounting:** Costs: 3.5% ; Outcomes: 3.5%	within 4 hours of admission. **Cohort settings:** N: 143 Mean age: 34 Male: 70% **Intervention 1:** Placebo **Intervention 2:** Recombinant activated factor VII, 3 injections (200, 100 and 100 micrograms/kg). Second and third injections given 1 hour and 3 hours after the initial dose.	Incremental (2–1): £13,243 (95% CI £1973 – £24,516; p=0.02) **Currency and cost year:** 2004 UK pounds **Cost components incorporated:** drug acquisition costs RBC fresh frozen plasma platelets cryoprecipitate surgical procedures undertaken (including fixed costs covering overheads and consumables and a variable cost) ICU days and regular inpatient days Long-term costs of annual health expenditure per capita, and rehabilitation costs	Incremental (2-1): 0.70 (95% CI -1.5 – 2.9; p=0.54) **Life years (mean per patient):** Intervention 1: 14.75 Intervention 2: 15.80 Incremental (2-1): 1.05 (95% CI -2.3 – 4.4; p=0.54)	£12,613 per life year gained Probability Intervention 2 cost-effective (£20k/£30k threshold): 52%/61% **Analysis of uncertainty:** **Difference in mortality risk** Baseline = 5% 10%: £8,990 per QALY. 6%: £14,983 per QALY. 4%: £22,474 per QALY. 3%: £29,966 per QALY. 1%: £89,897 per QALY. **Cost per surgical procedure** Baseline = £6.40 per minute plus £788 Costs halved: £18,692 per QALY. Costs doubles: £19,091 per QALY. **Long-term trauma-related costs** Baseline = £1654 per year with an additional £10,000 in first year. £1,654 in first year only with no additional cost: £15,754 per QALY. £1,654 per year with an additional £20,000 in first year: £19,545 per QALY. **Life expectancy** Baseline = no adjustment from residual general population life expectancy. 90% of general population residual life expectancy: £20,614 per QALY **Health state utilities** Baseline = 0.67 each year following trauma

				0.67 in first year followed by UK age- and genderspecific norms: £15,406 per QALY **Multivariate analysis** Two multivariate sensitivity analysis were performed with the following parameter values: Utility of 0.67 in first year with UK population norms for remaining years of life. 90% of general population residual life expectancy. Long-term trauma-related costs per patient: **Analysis 1** - £1654 in first year and £0 in subsequent years; **Analysis 2** - £20,000 + £1,654 in first year and £1654 in subsequent years. **Analysis 1:** £12,893 per QALY **Analysis 2:** £21,412 per QALY
Data sources				
Health outcomes: Mortality data and resource use data within the first 30 days was taken from Boffard et al[10]. Survival after 30 days was estimated using a three stage approach: Stage 1 – Data from TARN was used to model survival up to the time of hospital discharge (max time to hospital discharge among TARN cohort was 90 days) or death in hospital; survivors in the trial at 30 days were assigned a survival probability based on the probability of survival for a matched cohort of patients in TARN. Stage 2 – Data was used from a cohort of 166 trauma patients admitted to the intensive care unit of the Western Infirmary, Glasgow between 1985-92, alive at 90 days post trauma. This cohort was followed until 1997 giving a follow-up period of 5 years, thus the probability of survival at 5 years was modelled using logistic regression (survival at 5 years was the binary variable and regressed against gender, age, and whether or not the patient was still in the intensive care unit 30 days post trauma). Stage 3 – UK life tables were used (for 2002-4) to generate age and gender specific residual life expectancy for each patient alive at 5 years post trauma. Same life expectancy was assumed at 5 years as for the general population. **Quality-of-life weights:** A utility of 0.67 was applied to all survivors. This was taken from a published study using a cross sectional survey design (Seguin et al[81]) **Cost sources:** For the first 30 days resources from the Boffard trial were costed up, for post 30 days length of hospital stay data was taken from TARN. Source of the cost of the intervention is unclear (£462.88/mg). Blood product costs from the National Blood Service (UK) (RBC = £131.80/unit, FFP = £0.13/ml, platelets = £0.99/ml, cryoprecipitate = £0.91/ml). Surgical and inpatient costs also from UK sources; (NHS reference costs 2004) (cost of ICU day = £1328, cost of inpatient day = £176), fixed theatre cost from Guidance to the Methods of Technology Appraisal; NICE, 2004 (variable theatre cost of £6.40 per minute and fixed cost of £788). Long term healthcare costs (from 90 days till death) were estimated using the mean annual health expenditure per capita in the UK of £1,654 (OHE Compendium of Health Statistic; OHE, 2006). Baseline estimates also included £10,000 in the first year for rehabilitation costs.				
Comments				
Source of funding: Original trial and cost effectiveness study funded by Novo Nordisk (manufacturers of intervention).				

Limitations: Adverse events not included (of the intervention and consequences from blood transfusions). Original trial the data is taken from is stated to be underpowered to detect mortality and study sample comprised of 143 patients. Potential conflict of interest from the authors and funders (First two authors have received fees from the company, and third and fourth authors are employees of the company). **Other:** Extrapolation methods to predict probability of survival post 30 days are not explained enough to identify whether there may be any issues such as the previous stages in the 3 stage process are affecting the probability derived for the later stages. Also the populations compared within TARN and Scottish data have been stated as being older and less severely injured than the patients in the trial. How applicable is this study to a low risk population? Are the confounders used in the regression analysis appropriate?; "these were chosen because they were collected by Boffard and also included in the Scottish data". Large uncertainty around cost effectiveness. No information given on structure of the model.
Overall applicability: Directly applicable Overall quality: Potentially serious limitations

Abbreviations: BNF, British National Formulary; CUA, cost-utility analysis; CEAC, cost-effectiveness acceptability curve; 95% CI, 95% confidence interval; da, deterministic analysis; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit, NR, not reported; pa, probabilistic analysis; QALYs, quality-adjusted life years; RBC, red blood cells, FFP, fresh frozen plasma

Tabella 7. Rossaint 2007

Rossaint R, Christensen M, Choong P, Boffard K, Riou B, Rizoli S et al. Cost-Effectiveness of Recombinant Activated Factor VII as Adjunctive Therapy for Bleeding Control in Severely Injured Trauma Patients in Germany. Eur J Trauma Emerg Surg.: Urban & Vogel. 2007; 33(5):528-538. (Guideline Ref ID ROSSAINT2007)				
Study details	**Population and interventions[a]**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome = QALY) **Study design:** Model based on patient level data **Approach to analysis:** Model based on patient level data from two randomised placebo-controlled phase II trials. Data was supplemented with additional German data to	**Population:** 16 to 64 years of age with blunt trauma, who received 6 units of RBC within 4 hours of admission. **Cohort settings:** N: 143 Mean age: 34 Male: 70% **Intervention 1:** Placebo **Intervention 2:** Recombinant activated factor VII, 3 injections (200, 100 and	**Total costs (mean per patient):** Intervention 1: £48,344 Intervention 2: £63,175 Incremental (2–1): £14,831 (95% CI: £5,492 - £24,171; p<0.01) **Currency and cost year:** 2005 Euro (presented here as 2005 UK pounds) [(b)] **Cost components incorporated:** • drug acquisition costs • RBC	**QALYs (mean per patient):** Intervention 1: 8.94 Intervention 2: 9.63 Incremental (2-1): 0.69 (95% CI: -1.27 – 2.64; p=0.49) **Life years (mean per patient):** Intervention 1: 11 Intervention 2: 11.85 Incremental (2-1): 0.85 (95% CI: -1.52 – 3.21; p=0.48)	**ICER (Intervention 2 versus Intervention 1):** £21,613 per QALY (da) 95% CI: NRs Probability Intervention 2 cost-effective (£20k/£30k threshold): 48%/60% [(c)] **Analysis of uncertainty:** An estimate of the uncertainty around the ICER was generated using bootstrapping with replacement. *One way sensitivity analyses:* The incremental cost per QALY is most sensitive to the difference in mortality risk between the intervention and placebo at 30 days, and the discount rate.

estimate costs and benefits (mortality and QoL). **Perspective:** Third party payer perspective **Time horizon/Followup:** Lifetime **Treatment effect duration:** 30 days **Discounting:** Costs = 5%; Outcomes = 5%	100 micrograms/kg). Second and third injections given 1 hour and 3 hours after the initial dose.	• fresh frozen plasma • platelets • cryoprecipitate • surgical procedures undertaken (including fixed costs covering overheads and consumables and a variable cost) • ICU days and regular inpatient days • Long-term costs of annual health expenditure per capita, and rehabilitation costs		**Difference in mortality risk at 30 days** Baseline = 5% 4% = £29,201 3% = £38,935 2% = £58,402 1% = £116,804 **Discount rate** Baseline = 5% 0% = £9,831 3% = £16,497 10% = £34,805 **Long-term trauma-related costs** Baseline = £2,128 per year. €0 in the first year and all subsequent years: £18,681 per QALY. £2,128 (€2,900) per year with an additional £7,339 (€10,000) in first year: £22,031 per QALY. **Life expectancy** Baseline = Assumed trauma patients have 90% of the age and gender specific residual life expectancy of the general population. 80% of general population residual life expectancy: £24,319 per QALY 100% of general population residual life expectancy: £19,449 per QALY **Health state utilities** Baseline = 0.67 in the first year after trauma, and assumed equal to the age and gender specific population norms for the German population for the remaining years of life.

				□ 0.67 for remaining years of life: £26,061 per QALY

Data sources

Health outcomes: Differences in mortality and resource use for the first 30 days were taken from Boffard et al[10]. Secondary data sources were used to estimate survival post 30 days. The life years for all 30 day survivors were calculated using the following two stage approach: Stage 1 – Patients from the German Trauma Registry (a cohort of 358) were identified based on the inclusion and exclusion criteria from Boffard, and patients from the trial who were alive at 30 days were assigned an individual survival probability for the period until hospital discharge or death based on a set of patient characteristics developed from the patient level data in the trauma registry. Markers with the greatest explanatory power to predict mortality that were included in the model were; multiple organ failure, ISS ≥16, and in the ICU at day 30. Stage 2 – for the period after discharge, German life table data for the general population (http://www.mortality.org) were used to generate age and gender specific residual life expectancy for each individual patient assumed to be discharged alive from the hospital after day 30 (it was assumed trauma patients have 90% of the age and gender specific residual life expectancy of the general population for the remaining years of their life).

Quality-of-life weights: For the first year post injury it was assumed patients have a utility of 0.67 (Seguin et al[81]). For the remaining years of life the utility was assumed equal to the age and gender specific norms for the population (reference states this data is from Novo Nordisk – the manufacturer)

Cost sources: For the first 30 days, resource use from the Boffard trial was costed up. Blood product costs are from the German Red Cross (through oral communication, May 2005). Surgical costs are from a study on costs (Pape 2003). ICU costs were from the same paper which calculated ICU costs based on a scoring system comprising 28 measures of medical treatment received when on ICU. Applying this model to patients in the 30 day trial provided a cost of €35 per point on the 28 point score.

For the 30 days post trauma until hospital discharge home or death, cost data from the German Trauma Registry was used. Included were regular inpatient ward costs, ICU costs (including time spent on a ventilator) and inpatient rehab costs. Patient groups used to predict treatment costs for patients surviving to discharge were (with corresponding treatment costs from day 30 to discharge); 'patients on regular inpatient ward at day 30 + no severe extremity injury' = €7,872, 'patients on regular inpatient ward day at day 30 + severe extremities injury' = €12,079, 'patients in ICU at day 30 + no multiple organ failure' = €22,135, 'patients in ICU at day 30 + multiple organ failure' = €32,261.

Long term healthcare costs were estimated for the period of hospital discharge until death. These costs were approximated using the mean annual healthcare expenditure per capita in Germany of €2,900 (from the Federal Statistics office Germany).

Comments

Source of funding: Trial funded by Novo Nordisk, the manufacturer of the product.

Limitations: Does not include adverse events, focus is on mortality. Original trial the data is taken from is stated to be underpowered to detect mortality and study sample comprised of 143 patients. Potential conflict of interest from the authors and funders (Most of the authors have received funds from Novo Nordisk).

Other: Large uncertainty around cost effectiveness. Not clear as to the source of utility data for the years following the first year. Are the confounders appropriate? Is it possible that the staging process of identifying the mortality post 30 days has limitations such as the previous stages in the staging process are affecting the probability derived for the later stages?

Overall applicability: Directly applicable **Overall quality: Potentially serious limitations**

Abbreviations: CUA, cost-utility analysis; CEAC, cost-effectiveness acceptability curve; 95% CI, 95% confidence interval; da, deterministic analysis; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; NR, not reported; pa, probabilistic analysis; QALYs, quality-adjusted life years; RBC, red blood cells

(a) Population and interventions data not explained in the published paper. Detail in this column taken from Morris 2007 which used the same RCT to estimate effect.

(b) Not all the cost sources state the dates, therefore 2005 was chosen as it is stated this is when communication occurred with the German Red Cross who provided the costs on blood products. Converted using 2005 purchasing power parities[70].

(c) These probabilities of being cost effective were read off from the cost effectiveness acceptability curve, with around €27,200 being equal to £20,000, and €40,900 being equal to £30,000.

Tabella 8. Pohar 2009

S. L. Pohar, E. Tsakonas, G. Murphy, D. Anderson, D. Carney, C. Moltzan, and R. Banks. Recombinant activated Factor VII in treatment of hemorrhage unrelated to hemophilia: a systematic review and economic evaluation. Anonymous. Anonymous. Canada: Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH). 2009. (Guideline Ref ID POHAR2009)				
Study details	**Population and interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome = QALY) **Study design:** Model based on patient level data **Approach to analysis:** Decision tree model based on patient level data from two randomised placebocontrolled phase II trials. Data was supplemented with additional data to estimate costs and benefits (mortality and QoL). **Perspective:**	**Population:** 16 to 64 years of age with blunt trauma, who received 6 units of RBC within 4 hours of admission. **Cohort settings:** N: 143 Mean age: 34 Male: 70% **Intervention 1:** Placebo **Intervention 2:** Recombinant activated factor VII, 3 injections (200, 100 and 100 micrograms/kg). Second and third injections given 1 hour and 3 hours after the initial dose.	**Total costs (mean per patient):** ***Undiscounted (only 1 year costs):*** Intervention 1: £41,075 Intervention 2: £61,416 Incremental (2−1): £20,342 (95% CI: NR; p=NR) **Currency and cost year:** 2008 Canadian Dollars (presented here as 2008 UK pounds) [a] **Cost components incorporated:** Drug acquisition costs RBC hospital costs inpatient physician	**QALYs (mean per patient):** **Undiscounted:** Intervention 1: 23.30 Intervention 2: 24.98 Incremental (2-1): 1.68 (95% CI: NR; p=NR) **Discounted:** Intervention 1: NR Intervention 2: NR Incremental (2-1): NR (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** Not reported in study (da or pa) 95% CI: NR Calculated using undiscounted costs and QALYS: £12,108 per QALY Probability Intervention 2 cost-effective (£20k/£30k threshold): 36%/52% [b] **Analysis of uncertainty:** *One way sensitivity analyses:* As the ICER was not reported, the sensitivity analysis results are reported as the percentage change impact on the non-reported ICER. Analyses were conducting on the following: Discount rate Mortality risk difference at 30 days Mortality rate form 30 days to discharge

Canadian publicly funded healthcare system **Time horizon/Followup:** Lifetime **Treatment effect duration:** 30 days **Discounting:** Costs = 0%; Outcomes = 5%		consultations • long term care • inpatient rehab • post-acute care physician consultation • physiotherapy and occupation therapy		(changed both for same group and also varied for the two groups). Patient weight Difference in RBC transfusion units between the two groups Drug cost Hospital costs In patient physician costs Reduced LoS in factor 7 patients Long term care costs Utility Residual life expectancy at discharge Two way analyses on utility and residual life expectancy The parameter with the largest impact on the ICER is the mortality risk difference at 30 days. With only a 1% difference in risk then the ICER increases by 354%. With a 10% difference in risk the ICER decreases by 42%. (Baseline is 5%).
Data sources				
Health outcomes: Treatment outcome probabilities (mortality at 30 days) were based on Boffard et al. Estimates of patient outcomes after 30 days were taken from other sources; death in hospital after 30 days was taken from another economic evaluation (Rossaint 2007). The probabilities of being discharged to different locations (long term care facility, in patient rehab, home care) were taken from Boffard and the Canadian Institute for Health Information (Ottawa, Canada. Discharge Abstract Database 2006-7). Estimates of the proportion of patients who live in the community and use physiotherapy and occupational therapy were taken from a published source (Gabbe et al). It was assumed that the survivors of a major trauma had 90% of the age and gender specific life expectancy of the general population. Median number of RBC units by treatment group that was reported by Boffard did not permit the estimation of differences so average RBC units were used for these patients estimated from the data in the Rossaint study. Hospital length of stay was based on durations reported in Boffard and those estimated by Rossaint after 30 days. Average 6 month length of stay assumed in a long term care facility. Inpatient rehabilitation length of stay from Canadian Institute for Health Information (CIHI) (Inpatient rehabilitation in Canada, 2006-2007). One in hospital physician visit per patient per day was assumed. Post acutely, an average of 15 physician consults was estimated for each patient. One weekly physiotherapy and occupational therapy session in six months was			

assumed.

Quality-of-life weights: A utility of 0.67 was identified from the literature (Seguin et al). It is stated the mean ISS in the group of patients from this study was 22 whereas the mean ISS in Boffard was 32, however because the mean ISS in Boffard included 27% of all patients who died who likely had higher ISS, then 0.67 was felt to be a reasonable reflection of QoL for patients who survived discharge from hospital. Data from a Canadian study (Brenneman et al) suggested an improvement in QoL (using the SF-36) of around 25% in the first year after injury. Thus it was assumed patients would experience a 25% improvement in utility in the first year after injury increasing the utility score to 0.84. A final assumption was made that a 5% improvement in quality of life would be experienced in the second year post injury resulting in a utility value of 0.88. Utility values were left at 95% of the population norm for the remainder of life expectancy.

Cost sources: Cost of factor 7 from the Canadian Pharmacists Association (C$1,100.27/mg). Per day hospital costs were estimated using resource intensity weights that were obtained from tabulations provided by the Canadian Institute for Health Information Discharge Abstract Database (2006-7) and using the average cost per weighted hospital case in Canadian hospitals (C$1,191/day). The cost of a physician consultation was based on the average fees charged by general surgeons and general physicians for non-emergency consultations in Quebec and Ontario (C$60/visit). The cost of blood transfusions was from a published study; Amin (2004) (C$308.26/transfusion). Cost per day for long term care was from a published study; Wodchis (2007) (C$315/day). Cost of an inpatient rehab stay estimated from published cost data for a Canadian setting (Mahomed 2008) (C$306/day). Home care cost per patient estimated using data on total public sector expenditures for home care and the estimated number of publicly funded home care per 1000 population in Canada (Canadian Institute for Health Information (CIHI). Public-sector expenditures and utilization of home care services in Canada: exploring the data) (C$4,863/per episode of service).
Post acutely: cost of a physician consultation estimated from the average rates charged by GP's in Ontario and Quebec (C$51.55). Cost of physiotherapy and occupational therapy based on sources estimated from across Canada (C$65/session).
All costs obtained from sources that were dated before 2008 were inflated to 2008 Canadian Dollars using the Canadian Consumer Price Index.

Comments

Source of funding: Not stated, however it is a Canadian Health Technology Assessment thus publicly funded.

Limitations: No adverse events considered ("thromboembolic events ad their potential impact on cost effectiveness were not considered"). Costs beyond one year were not considered. Not possible to work out the ICER as average discounted QALYs for both groups or incremental QALYs were not reported. Original trial the data is taken from is stated to be underpowered to detect mortality and study sample comprised of 143 patients. Some of the limitations which apply to Rossaint study may also apply here as data was used from the Rossaint paper.

Other: Cost effectiveness uncertain (although actual ICER not reported).

Overall applicability: Partially applicable **Overall quality: Very serious limitations**

Abbreviations: CUA, cost-utility analysis; CEAC, cost-effectiveness acceptability curve; 95% CI, 95% confidence interval; da, deterministic analysis; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; NR, not reported; pa, probabilistic analysis; QALYs, quality-adjusted life years; QoL, quality of life; RBC, red blood cells

(a) Converted using 2008 purchasing power parities[70].

(b) These probabilities of being cost effective were read off from the cost effectiveness acceptability curve, with around C$37,600 being equal to £20,000, and C$56,300 being equal to £30,000.

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