Raccomandazioni 28-29-30 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.

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Raccomandazione 28. Nei pazienti con TM si raccomanda di accertare l'esistenza di un trattamento anticoagulante/antiaggregante in corso [Raccomandazione forte a favore, qualità delle prove molto bassa].

Raccomandazione 29. Nei pazienti con TM che non hanno un sanguinamento attivo si suggerisce di non effettuare un reversal della terapia anticoagulante/antiaggregante [Raccomandazione condizionata contro, qualità delle prove molto bassa].

Raccomandazione 30. Nei pazienti con TM con emorragia in atto in sedi non comprimibili ed in trattamento con antagonisti della vitamina K si raccomanda l'impiego immediato di concentrati di complesso protrombinico [Raccomandazione forte a favore, qualità delle prove molto bassa].

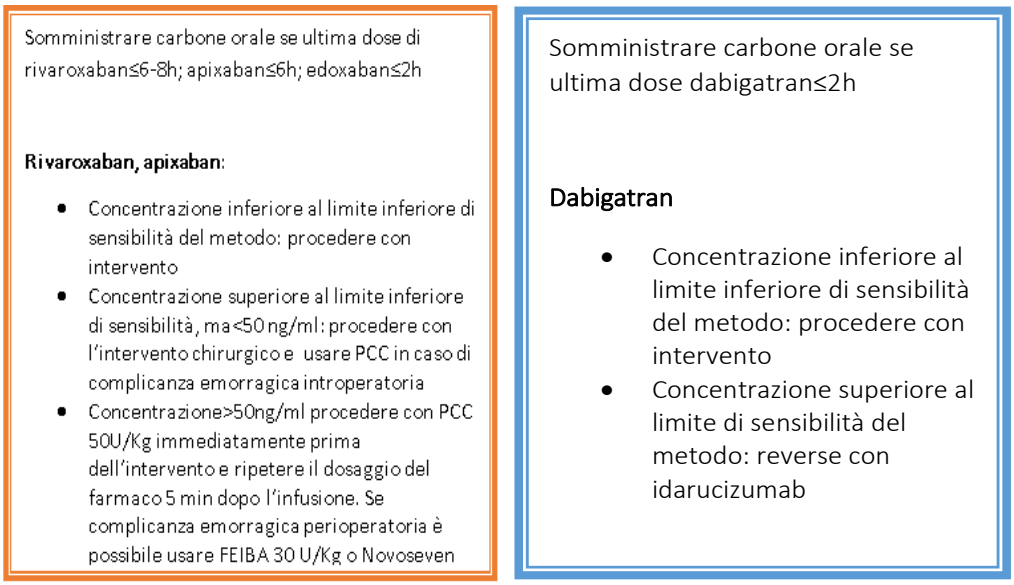
Considerazioni relative ai sottogruppi

Diversi pazienti assumono cronicamente anticoagulanti orali di recente introduzione (NAO) appartenenti a due categorie farmacologiche: inibitori diretti del fattore X (rivaroxaban, apixaban, edoxaban) e inibitori diretti della trombina (dabigatran). In caso di evento traumatico con sanguinamento attivo in sedi critiche con impossibilità all'emostasi meccanica immediata è necessario attivare un protocollo di reversal che preveda:

- Stop assunzione anticoagulante
- Valutazione funzionalità renale
- Richiesta dosaggio dell'anticoagulante (se disponibile)
- Richiesta supporto trasfusionale

Se ultima assunzione <12 ore per inibitori fattore X somministrare PCC 25-50U/Kg, per inibitori trombina IDARUCIZUMAB 2 boli da 2.5 g.

Se necessità di interventi chirurgici o di radiologia interventistica o endoscopici provvedere come di seguito indicato:



Per i pazienti in duplice terapia anti-piastrinica (DAPT) in caso di evento traumatico con sanguinamento attivo in sedi critiche senza possibilità di emostasi meccanica immediata è indispensabile un trattamento di neutralizzazione nei seguenti casi:

- Sanguinamento attivo in sedi critiche senza possibilità di emostasi meccanica immediata
- Trauma cranico con necessità di intervento neurochirurgico
- Trauma cranico senza necessità di intervento ma con lesione cerebrale emorragica (ematomi, emorragia subaracnoidea).

Nelle altre situazioni la neutralizzazione sistematica della DAPT non è indispensabile e va valutato ogni singolo caso.

In caso di necessità di neutralizzazione della DAPT si suggerisce il seguente protocollo:

- Aspirina: trasfusione di PLT $0.5\text{-}0.7 \times 10^{11}$/ 10 kg di peso (dose standard)
- Clopidogrel: 2 dosi standard di PLT (efficacia ridotta se assunzione clopidogrel <6 ore)
- Prasugrel: 2 dosi standard di PLT (efficacia ridotta se assunzione prasugrel <6 ore)
- Ticagrelor:
  - ultima assunzione <24 ore: PLT inefficaci, considerare rFVIIa (nessuna evidenza)
  - ultima assunzione >24 ore: dose standard di PLT ripetuta (neutralizzazione parziale).

Il panel di esperti ha formulato le 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 appendici per le raccomandazioni 28, 29 e 30:

- Appendice A – Quesito clinico e strategia di ricerca
- Appendice B – Caratteristiche degli studi inclusi ed elenco degli studi esclusi con motivazione
- Appendici C – Sintesi delle evidenze
- Appendice D – Valutazione della qualità metodologica degli studi inclusi
- Appendice E – Tabelle delle evidenze
- Appendice F – Bibliografia degli studi inclusi
- Appendice G – Costi e costo-efficacia

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.15: reversal della terapia anticoagulante

Qual è il regime più efficace dal punto di vista clinico e dei costi per il reversal della terapia anticoagulante pre-esistente (effetto documentabile in laboratorio) nel trauma maggiore?	
POPOLAZIONE:	Bambini, giovani e adulti che hanno subito un trauma e sono in terapia anticoagulante terapeutica pre-esistente. Classi anticoagulanti considerate: • Coumarins and phenindione • Inibitori diretti della trombina o inibitori diretti del fattore X • Agenti anti-piastrinici • Eparina a basso peso molecolare Esclusi: Persone con un trauma maggiore derivante da ustioni. Pazienti sotto shock, non per trauma.
INTERVENTO:	Reversal agents: • Fibrinogen concentrate • Cryoprecipitate • Platelets • Vitamin K (Phytonadione) • Fresh frozen plasma • Prothrombin complex concentrates (PCCs) • Fattore ricombinante VIIa
CONFRONTO:	Confronto di quanto sopra esposto
ESITI PRINCIPALI:	**Critici** Mortalità a 24 ore, 30 giorni/1 mese, a 12 mesi Qualità della vita correlata alla salute Eventi avversi: Stroke, MI, Thromboembolism (PA and venous) Grado di rianimazione (unità di sangue trasfuso) Esito neurologico (pazienti con lesioni cerebrali) Progressione emorragia intracranica. **Importanti** Esiti riferiti dal paziente (dolore/disagio, ritorno alle normali attività, benessere psicologico). Reversal di anti-coagulanti misurata mediante valutazione di laboratorio (riduzione dell'INR) o evidenza clinica di miglioramento della coagulazione Necessità di craniotomia
SETTING:	Pre-ospedaliero e intra ospedalieri (pronto soccorso)
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 ● Si ○ Varia ○ Non so	I farmaci anticoagulanti o antiaggreganti sono comunemente prescritti per le persone che sono a rischio elevato di sviluppare patologia tromboatica venosa o arteriosa, e agiscono per prevenirla. Le persone che subiscono una lesione traumatica e assumono queste terapie corrono un rischio maggiore di sanguinamento, per effetto di una condizione in cui la capacità del sangue di coagulare è compromessa. A seguito di un rischio di emorragia esacerbato dal farmaco aumenta la probabilità di morte. Di conseguenza, la mortalità può essere ridotta invertendo gli effetti di qualsiasi farmaco anticoagulante o antiaggregante assunto in precedenza. Esistono vari meccanismi con cui agiscono gli anticoagulanti/antiaggreganti ed ogni classe di farmaci richiede il proprio regime di reversal. Il warfarin, l'anticoagulante più prescritto, appartiene alla classe della coumarins and phenindione. L'utilizzo di anticoagulanti diretti fattore II o X configura un rischio che richiede un approccio differenziato, sulla base della disponibilità di antidoti specifici. Va considerato che oltre il 40% della popolazione più anziana di 65 anni assume costantemente o saltuariamente una terapia antiaggregante o anticoagulante.	

Effetti desiderabili

Quanto considerevoli sono gli effetti desiderabili attesi?

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ Irrilevanti ○ Piccoli ○ Moderati ● Variano ○ Non so	Si provvede ad aggiornare la linea guida NICE NG39(1). È stata effettuata una revisione sistematica con ricerca della letteratura sulle banche dati Embase, Medline e Cochrane Library che ha identificato 18 studi, di cui 2 revisioni sistematiche e 16 studi osservazionali che permettono di rispondere alle seguenti comparazioni: Effetti desiderabili righe verdi, effetti indesiderabili righe arancioni. Si rimanda **all'Appendice C** per la sintesi dell'evidenza per le singole comparazioni. **A- Anticoagulanti versus no-reversal:** • PLT vs no-reversal (2 review (con 14 studi osservazionali) + 2 studi osservazionali [1 con dati aggiustati e 1 senza dati aggiustati]) • PCC vs no-reversal (1 studio osservazionale con dati aggiustati*) • FFP vs no reversal (1 studio osservazionale con dati aggiustati *)	È stata effettuata una ricerca specifica sulle possibilità di reversal degli inibitori diretti della trombina o del fattore X e degli anti-aggreganti.

- DDVAP vs no reversal (1 studio osservazionale con dati aggiustati)

*stesso studio con 3 braccia di intervento (Lumas 2020): PCC versus FFP+vitamin K versus vitamin K

Comparisons Vs NO REVERSAL				
Outcome	**A1. PLT**	**A2. PCC**	**A3. FFP**	**A4.DDVAP**
Mortality at 24 hours, 30days/1month, and 12 months	MOLTO BASSA (adjusted data)	MOLTO BASSA (adjusted data)	MOLTO BASSA	MOLTO BASSA
Health related quality of life				
Adverse effects (Stroke, MI, Thromboembolism (PA and venous) /comlications	MOLTO BASSA			MOLTO BASSA
Reversal of anti-coagulation as measured by laboratory assessment (degree of reversal (reduction of INR))		MOLTO BASSA		
Degree of resuscitation (units of blood transfused)	BASSA			
Neurological outcome (brain injured patients)	MOLTO BASSA			MOLTO BASSA
Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing).	MOLTO BASSA	MOLTO BASSA	MOLTO BASSA	MOLTO BASSA
ICH progression	MOLTO BASSA (adjusted data)	MOLTO BASSA	MOLTO BASSA	MOLTO BASSA
Need for neurosurgical surgery (craniotomy)	MOLTO BASSA (adjusted data)	MOLTO BASSA (adjusted data)	MOLTO BASSA	

B- Prothrombin complex concentrate (PCC) versus altro:

- aPCC versus FFP (1 studio osservazionale senza dati aggiustati)
- aPCC+FFP + vitamin K versus FFP+vitamin K (1 studio osservazionale senza dati aggiustati)
- PCC + vitamin K versus vitamin K (1 studio osservazionale con dati non aggiustati)
- PCC vs FFP * (1 studio osservazionale con dati aggiustati), in tutti bracci pazienti assumono Vitamina K

* studio con 3 braccia di intervento (Lumas 2020) PCC versus FFP+vitamin K versus vitamin K

Prothrombin complex concentrate (PCC) versus altro				
Outcome	B1. aPCC versus FFP	B2. aPCC+FFP + vitamin K versus FFP+vitamin K	B3. PCC + vitamin K versus vitamin K	B4. PCC vs FFP
Mortality at 24 hours, 30days/1month, and 12 months	MOLTO BASSA	MOLTO BASSA		MOLTO BASSA (adjusted data)
Health related quality of life				
Adverse effects (Stroke, MI, Thromboembolism (PA and venous)	MOLTO BASSA		MOLTO BASSA	
Reversal of anti-coagulation as	MOLTO BASSA	MOLTO BASSA		MOLTO BASSA

measured by laboratory assessment (degree of reversal (reduction of INR))				
Degree of resuscitation (units of blood transfused)	MOLTO BASSA			
Neurological outcome (brain injured patients)				
Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing).	MOLTO BASSA			MOLTO BASSA
ICH progression			MOLTO BASSA	MOLTO BASSA (adjusted data)
Need for neurosurgical surgey (craniotomy)	MOLTO BASSA	MOLTO BASSA		MOLTO BASSA (adjusted data)

C- 4FPCC versus altro

- 4FPCC versus 3FPCC+rFVIIa (1 studio osservazionale senza dati aggiustati)
- 4FPCC versus 3FPCC (2 studi osservazionali con dati aggiustati)
- 4FPCC versus Factor IX complex + vitamin K with or without FFP (1 studio osservazionale senza dati aggiustati)

4FPCC versus altro			
Outcome	C1. 4FPCC versus 3FPCC+rFVIIa	C2. 4FPCC versus 3FPCC	C3. 4FPCC versus Factor IX complex + vitamin K with or without FFP
Mortality at 24 hours, 30days/1month, and 12 months	MOLTO BASSA	MOLTO BASSA	
Health related quality of life			
Adverse effects (Stroke, MI, Thromboembolism (PA and venous)	MOLTO BASSA	MOLTO BASSA (adjusted data)	MOLTO BASSA
Reversal of anti-coagulation as measured by laboratory assessment (degree of reversal (reduction of INR))	MOLTO BASSA	MOLTO BASSA (adjusted data)	MOLTO BASSA
Degree of resuscitation (units of blood transfused)		BASSA	
Neurological outcome (brain injured patients)			
Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing).			
ICH progression			
Need for neurosurgical surgey (craniotomy)	MOLTO BASSA		

D- Dosi diverse 4FPCC a confronto

	• 4FPCC 1500 versus 4FPCC 1000 (2 studi osservazionali di cui 1 con dati aggiustati) ***Outcome*** — **D1.** 4FPCC 1500 versus 4FPCC 1000 Mortality at 24 hours, 30days/1month, and 12 months — MOLTO BASSA Health related quality of life — Adverse effects (Stroke, MI, Thromboembolism (PA and venous) — MOLTO BASSA Reversal of anti-coagulation as measured by laboratory assessment (degree of reversal (reduction of INR)) — MOLTO BASSA Degree of resuscitation (units of blood transfused) — Neurological outcome (brain injured patients) — Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing) — ICH progression — Need for neurosurgical surgey (craniotomy) —	

Effetti indesiderabili

Quanto considerevoli sono gli effetti indesiderabili attesi?

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ Grandi ● Moderati ○ Piccoli ○ Irrilevanti ○ Variano ○ Non so	Si provvede ad aggiornare la linea guida NICE NG39(1). È stata effettuata una revisione sistematica con ricerca della letteratura sulle banche dati Embase, Medline e Cochrane Library che ha identificato 18 studi, di cui 2 revisioni sistematiche e 16 studi osservazionali (**Appendice F**) che permettono di rispondere alle varie comparazioni: Si rimanda al dominio effetti desiderabili, in cui le tabelle presentato gli effetti desiderabili con le righe verdi, e gli effetti indesiderabili con le righe arancioni. Inoltre, si rimanda **all'Appendice C** per la sintesi dell'evidenza.	Le prove del presente EtD sono limitate all'utilizzo del concentrato di fattore protrombinico. Per quanto concerne gli inibiltori diretti di trombina o fattore 10 o antipiastrinici si rimanda alla valutazione specifica successiva.

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	Il rischio di bias degli studi valutati è in **Appendice D** (in generale moderata-alta qualità). La **qualità dell'evidenza** è riportata in **Appendice E:** la qualità delle prove complessivamente MOLTO BASSA a causa di studi prevalentemente osservazioni con dati non aggiustati, a volte con outcome non reporting bias e piccoli campioni.	

○ Nessuno studio incluso		

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 che ha identificato 6 records. Nessuno studio incluso.	

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	Le prove sono limitate.	

Risorse necessarie

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

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ Costi elevati ○ Costi moderati ○ Costi e risparmi irrilevanti	È stata condotta una revisione sistematica su Medline ed Embase. La strategia di ricerca ha identificato 6 records ma nessuno rilevante in contesto italiano. Inoltre sono state considerate altre fonti (NICE, strategia di ricerca quesito outcome efficacia CQ15, prontuario AIFA). In totale sono stati inclusi 4 studi, di cui **2 inerenti i costi + la fonte del prontuario AIFA**.	

○ Risparmi moderati ○ Risparmi elevati ● Varia ○ Non so	Si riportano qui di seguito solo i dati italiani del prontuario AIFA per i costi unitari dei regimi di reversal attualmente utilizzati in Italia, con la relativa fascia di rimborso (Tabella 1). I costi unitari delle varie formulazioni sono molto eterogenei. Per tutte fonti incluse si rimanda all' **Appendice G**. Tabella 1. Costi unitari delle varie formulazioni reversal. **REVERSAL** — **CLASSE** — **prezzo ex factory** IDARUCIZUMAB — H — 2.493,75 € COMPLESSO PROTROMBINICO CONCENTRATO 4 FATTORI — C — 208,13 € PLASMA FRESCO CONGELATO — H — 20,00-40,00€ COMPLESSO PROTROMBINICO ATTIVATO (Feiba) — H — 1.224,31 € PROTAMINA CLORIDRATO — H — 4,38 € COMPLESSO PROTROMBINICO CONCENTRATO 3 FATTORI per unità — H — 460,00 € FATTORE VII RICOMBINANTE — H — 466,72 € ANDEXANET ALFA — C — 23.407,34 €	

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	La valutazione della qualità delle evidenze di costo-efficacia è stata condotta a due livelli: ➔ la checklist CHEERS - Consolidated Health Economics Evaluations Reporting Standards- (Husereau 2013) per una valutazione della qualità metodologica degli studi. ➔ checklist per la valutazione della generalizzabilità (Drummond, 2005; Ruggeri, 2015) dei risultati ottenuti. Non sono presenti informazioni in merito tali da permettere una valutazione con entrambe le checklist (**Appendice G).**	

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 stata condotta una revisione sistematica su Medline ed Embase. La strategia di ricerca ha identificato 6 records ma nessuno rilevante in contesto italiano. Inoltre sono state considerate altre fonti (NICE, strategia di ricerca quesito outcome efficacia CQ15, prontuario AIFA). In totale sono stati inclusi 4 studi, di cui **2 inerenti la costo-efficacia**. Per dettagli si rimanda all' **Appendice G.** • La linea guida NICE aggiornata al 2016 (1) aveva trovato un solo studio rispondente al quesito di costo-efficacia (2). L'articolo è relativo alla valutazione costo efficacia del plasma fresco congelato versus protrombina. Il lavoro mostra come l'utilizzo della	The GDG stated that in patients with haemorrhage, effective and immediate reversal of anticoagulant medication is essential. Delays in reversal are associated with an increase in poor outcomes. As such, the GDG agreed it was imperative that anticoagulant

○ È in favore dell'intervento ○ Varia ○ Nessuno studio incluso	protrombina abbia un profilo di costo efficacia molto favorevole rispetto al plasma fresco congelato, con un rapporto costo efficacia incrementale ampiamente al di sotto delle soglie critiche di accettabilità (£ 35.000/QALY) in tutti gli scenari considerati. Nell'analisi di sensibilità probabilistica, venivano inoltre effettuate 1.000 simulazioni delle quali il 100% restituiva un ICER inferiore ai £ 16.000/QALY. **Certainty of Evidence**: la valutazione economica è difficilmente applicabili a pazienti con trauma, dato che la popolazione oggetto di studio era soggetta ad emorragie non da trauma, di tipo gastrointestinale, intracranico e retroperitoneale. ➔ **PCC è cost-effective nella comparazione PCC vs FFP per reversal del warfarin.** **Table 58: Economic evidence profile: PCC versus FFP** **Study** | **Applicability** | **Limitations** | **Other comments** | **Incremental cost** | **Incremental effects** | **Cost effectiveness** | **Uncertainty** Guest 2010[57,57] (UK) | Partially applicable[a] | Potentially/ very serious limitations[b] | Probabilistic decision tree with a lifetime horizon comparing PCCs with FFP for three different types of haemorrhage: intracranial, gastrointestinal and retroperitoneal in patients receiving anti-coagulant therapy using warfarin.[c] | Intracranial £3,246 Gastrointestinal £401 Retroperitoneal £534 | Intracranial 2.1 QALYs Gastrointestinal 0.14 QALYs Retroperitoneal 0.71 QALYs | Intracranial £1,600 per QALY Gastrointestinal £2,900 per QALY Retroperitoneal £800 per QALY | PSA with 10,000 iterations was performed, with variation in probabilities, utilities, unit costs and resource use in the model. The probability of PCC being cost-effective was ≥ 90% at a threshold of £10,000 per QALY for all types of haemorrhage. Deterministic sensitivity analyses were also performed. All sensitivities for all types of haemorrhage resulted in a cost per QALY of ≤ £16,000 for treatment with PCC. fonte: Linea guida NICE NG39 (1) • Il secondo lavoro (Mangram et al., 2016) è stato identificato con metodi alternativi alla stringa di ricerca. Questo lavoro ha l'obiettivo di valutare l'efficacia, la sicurezza e la costo efficacia del 4F-PCC contro il 3F-CC. Per quanto riguarda l'analisi economica, il lavoro dimostra che, sebbene il 4F-PCC sia più costoso del 3F-PCC, il costo per reversal ottenuto si dimostra favorevole ($ 5.382 vs $ 3.797).	reversal is prioritised in actively bleeding patients without necessarily waiting for laboratory results. To ensure this is standard practice in hospitals receiving trauma patients, the GDG considered it important that all hospitals have a policy for the rapid identification and reversal of oral anticoagulant agents. The GDG recommended PCC because in their opinion it provides rapid effective specific reversal of a vitamin K antagonist compared with other reversal therapies. It is better than plasma because it is comprised of pooled plasma products that have higher levels of coagulation factors and therefore leads to the much more rapid normalisation of INR. PCCs also have the advantage that, in contrast to plasma, they may be held in emergency departments; their volume of infusion is small and not associated with volume-associated sequelae from fluid overload. Furthermore, faster normalisation of INR is possible with PCCs as due to faster preparation (no thawing required) and faster infusion of the product.

Equità

Quale sarebbe l'impatto in termini di equità?

GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ Riduce l'equità ○ Probabilmente riduce l'equità ○ Probabilmente nessun	Non sono stati identificati studi relativi al contesto internazionale e italiano.	

impatto ● Probabilmente migliora l'equità ○ Migliora l'equità ○ Varia ○ Non so		
Accettabilità L'intervento è accettabile per i principali stakeholders?		
GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ No ○ Probabilmente no ● Probabilmente si ○ Si ○ Varia ○ Non so	È stata condotta una revisione sistematica su Medline ed Embase che ha portato a individuare 83 records relativi all'accettabilità/fattibilità. Nessuno studio risponde al quesito.	Sottogruppi di pz con convinzioni religiose, filosofiche o morali potrebbero non condividere i trattamenti con plasma e piastrine.
Fattibilità È fattibile l'implementazione dell'intervento?		
GIUDIZI	RICERCA DELLE PROVE	CONSIDERAZIONI AGGIUNTIVE
○ No ○ Probabilmente no ● Probabilmente si ○ Si ○ Varia ○ Non so	È stata condotta una revisione sistematica su Medline ed Embase che ha portato a individuare 83 records relativi all'accettabilità/fattibilità e 2 studi rispondono al quesito evidenziando l'implementazione di un protocollo e la disponibilità di sanitari per l'erogazione dell'intervento. **Implementazione di specifici protocolli aumenta l'efficienza del processo di cura** Uno studio condotto nella community-based American College of Surgeons-verified Level I trauma center in the Denver metropolitan area (3) che eroga più di 13,000 trattamenti per trauma maggiore all'anno ha partecipato alla implementazione di un protocollo di Nurse-Driven Rapid Reversal. "one hundred seventy-eight patients were included in the study; 90 (50.6%) were admitted before and 88 (49.4%) after implementation. After implementation, there were improvements in activation rates (34.4% vs. 65.9%; $p < .001$), the frequency of head CT scans (55.6% vs. 83.0%; $p < .001$), time to INR (24.0 min vs. 15.0 min; $p < .05$), and, for patients with ICH with an INR 1.5 or more, decreased time to FFP (157.0 vs. 90.5; $p < .05$). In conclusion, our protocol led to a more efficient process of care for patients with TBI on warfarin." **Disponibilità di un professionista 24h su 24 che possa erogare l'intervento riduce la gestione dei tempi di intervento impattando sul processo di cura** Uno studio retrospettivo (4) svolto in un Level I trauma center ha valutato la fattibilità dell'erogazione dell'intervento usufruendo della presenza di un farmacista 24ore su 24 (h24) per la somministrazione di 4F-PCC (four-factor prothrombin concentrate complex). Lo studio confronta presenza di un farmacista (RPh) h24 verso la non presenza h24 di un farmacista (RPh) in pronto soccorso. "This study demonstrates the positive impact of a 24/7 pharmacist in the ED on time from order and arrival to administration of 4F-PCC. The mean time from order entry to administration of 4F-PCC in the post-RPh group, 35.2 minutes, was significantly shorter than the pre-RPh group, 71.2 minutes ($p<0.001$, 95% CI [27.0 – 45.0]). Additionally, the median time from	

arrival to the ED to administration of 4F-PCC in the post-RPh group was significantly shorter than the post-RPh group (p=0.033). Hospital LOS and ICU admission were greater in the post-RPh group. dmission mortality occurred at similar rates between groups".

Through the involvement of 24/7 pharmacists in the ED, time to a potentially life-saving therapy has been reduced. The pre-RPh group had a delayed administration compared with the post-RPh group".

Table 2. Study End Points and Subgroup Analyses

	Pre-RPh n=33	Post-RPh n=67	*p*-Value	95% CI
Time (min) from order to administration of 4F-PCC, mean ± SD	71.2 ± 31.0	35.2 ± 14.4	< 0.001	27.0 – 45.0
Time (min) from arrival to administration of 4F-PCC, median (IQR)	153 (89-205)	106 (66-142)	0.033	
Hospital LOS (days), median (IQR)	4.1 (2.8-5.8)	6.9 (3.6-9.8)	0.017	
ICU admissions, n (%)	10 (30.3)	43 (64.2)	0.003	
ICU LOS (days), median (IQR)	1.6 (0.83-3.4)	2.2 (0.79-2.9)	0.745	
Admission mortality, n (%)	4 (12.1)	10 (14.9)	1.000	
FFP within 24 hours of 4F-PCC dose, n (%)	6 (18.2)	5 (7.5)	0.171	
Plt within 24 hours of 4F-PCC dose, n (%)	7 (21.2)	2 (3.0)	0.005	
PRBC within 24 hours of 4F-PCC dose, n (%)	5 (15.2)	21 (31.3)	0.095	
Intracranial hemorrhage	**Pre-RPh n=23**	**Post-RPh n=35**		
Time (min) from order to administration of 4F-PCC, mean ± SD	71.6 ± 32.6	33.2 ± 13.9	< 0.001	26.0 – 50.8
Time (min) from arrival to administration of 4F-PCC, median (IQR)	124 (73-185)	80 (54-124)	0.021	

RIASSUNTO DEI GIUDIZI

	GIUDIZI						
PROBLEMA	No	Probabilmente no	Probabilmente si	**Si**		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**	Si		Varia	Non so

TIPO DI RACCOMANDAZIONE

N° 28

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° 29

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° 30

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. 28 Nei pz con trauma maggiore si raccomanda di accertare l'esistenza di un trattamento anticoagulante/antiaggregante in corso (Raccomandazione forte a favore, qualità delle prove molto bassa)

N. 29 Nei pz con trauma maggiore che non hanno un sanguinamento attivo si suggerisce di non effettuare un *reversal* della terapia anticoagulante/antiaggregante (Raccomandazione condizionata contro, qualità delle prove molto bassa)

N. 30 Nei pz con trauma maggiore con emorragia in atto in sedi non comprimibili ed in trattamento con antagonisti della vitamina K si raccomanda l'impiego immediato di concentrati di complesso protrombinico (Raccomandazione forte a favore, qualità delle prove molto bassa)

Giustificazione

Il panel ritiene essenziale la verifica di un trattamento anticoagulante/antiaggregante in corso per approntare con tempestività ed efficacia tutti i provvedimenti diagnostico/terapeutici per contrastare un'evoluzione sfavorevole dell'emorragia in specie nei pz con trauma cranico.
Il panel non ritiene necessario un utilizzo profilattico del reversal nei pz con TM senza evidenza di emorragia in atto mancando studi specifici che ne dimostrino l'efficacia.

Considerazioni relative ai sottogruppi

Diversi pazienti assumono cronicamente anticoagulanti orali di recente introduzione (NAO) appartenenti a due categorie farmacologiche: inibitori diretti del fattore X (rivaroxaban, apixaban, edoxaban) e inibitori diretti della trombina (dabigatran). In caso di evento traumatico con sanguinamento attivo in sedi critiche con impossibilità all'emostasi meccanica immediata è necessario attivare un protocollo di reversal che preveda:

1- Stop assunzione anticoagulante
2- Valutazione funzionalità renale
3- Richiesta dosaggio dell'anticoagulante (se disponibile)
4- Richiesta supporto trasfusionale

Se ultima assunzione <12 ore per inibitori fattore X somministrare PCC 25-50U/Kg, per inibitori trombina IDARUCIZUMAB 2 boli da 2.5 g.
Se necessità di interventi chirurgici o di radiologia interventistica o endoscopici provvedere come di seguito indicato:

Somministrare carbone orale se ultima dose di rivaroxaban≤6-8h; apixaban≤6h; edoxaban≤2h

Rivaroxaban, apixaban:

- Concentrazione inferiore al limite inferiore di sensibilità del metodo: procedere con intervento
- Concentrazione superiore al limite inferiore di sensibilità, ma<50 ng/ml: procedere con l'intervento chirurgico e usare PCC in caso di complicanza emorragica intraoperatoria
- Concentrazione>50ng/ml procedere con PCC 50U/Kg immediatamente prima dell'intervento e ripetere il dosaggio del farmaco 5 min dopo l'infusione. Se complicanza emorragica perioperatoria è possibile usare FEIBA 30 U/Kg o Novoseven

Somministrare carbone orale se ultima dose dabigatran≤2h

Dabigatran

- Concentrazione inferiore al limite inferiore di sensibilità del metodo: procedere con intervento
- Concentrazione superiore al limite di sensibilità del metodo: reverse con idarucizumab

Per i pazienti in duplice terapia anti-piastrinica (DAPT) in caso di evento traumatico con sanguinamento attivo in sedi critiche senza possibilità di emostasi meccanica immediata è indispensabile un trattamento di neutralizzazione nei seguenti casi:

1- Sanguinamento attivo in sedi critiche senza possibilità di emostasi meccanica immediata
2- Trauma cranico con necessità di intervento neurochirurgico
3- Trauma cranico senza necessità di intervento ma con lesione cerebrale emorragica (ematomi, emorragia subaracnoidea)

Nelle altre situazioni la neutralizzazione sistematica della DAPT non e' indispensabile e va valutato ogni singolo caso.
In caso di necessita' di neutralizzazione della DAPT si suggerisce in seguente protocollo:

1- Aspirina: trasfusione di PLT 0.5-0.7x10^{11}/ 10 kg di peso (dose standard)
2- Clopidogrel: 2 dosi standard di PLT (efficacia ridotta se assunzione clopidogrel <6 ore)
3- Prasugrel: 2 dosi standard di PLT (efficacia ridotta se assunzione prasugrel <6 ore)
4- Ticagrelor: -(a) ultima assunzione <24 ore: PLT inefficaci, considerare rFVIIa (nessuna evidenza)
   - (b) ultima assunzione >24 ore: dose standard di PLT ripetuta (neutralizzazione parziale).

Considerazioni per l'implementazione

Monitoraggio e valutazione

Priorità della ricerca

Opportunità di ricercare antidoti specifici per ciascuno dei farmaci con effetto anti-coagulante con un migliore profilo benefici/rischi e costo/benefici.

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Appendice A – Quesito clinico e strategia di ricerca

Review question: What is the most clinically and cost-effective regimen for reversal of pre-existing therapeutic anticoagulation (laboratory effect) in major trauma?	
Objective: To identify the optimal reversal regimen for children, young people and adults who have experienced a traumatic incident and are on pre-existing therapeutic anticoagulants.	
Population	Children, young people and adults who have experienced a traumatic incident and who are on pre-existing therapeutic anticoagulant therapy Anticoagulant classes: • Coumarins and phenindione • Direct thrombin inhibitors • Anti-platelet agents • Low molecular weight heparins
Intervention	Reversal agents: Fibrinogen concentrate Cryoprecipitate Platelets Vitamin K (Phytonadione) Fresh frozen plasma Prothrombin complex concentrates (PCCs) Recombinant factor vIIa
Comparison	A comparison of the above
Outcomes	Critical: Mortality at 24 hours, 30days/1month, and 12 months Health related quality of life Adverse effects (Stroke, MI, Thromboembolism (PA and venous) Reversal of anti-coagulation as measured by laboratory assessment (degree of reversal (reduction of INR)) Degree of resuscitation (units of blood transfused) Neurological outcome (brain injured patients) Important: Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing). Population size and directness: No limitations on sample size Studies with indirect populations will not be considered.
Exclusion	People with a major trauma resulting from burns
Search strategy	Databases: Medline, Embase, The Cochrane Library Date: All years Language: Restrict to English, German, Spanish, French, Italian Study designs: RCTs or Systematic reviews of RCTs - OBS

POPULATION trauma

Standard major trauma population

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}

INTERVENTION

Medline search terms

1.	exp warfarin/
2.	(marevan or warfarin or apo-wafarin or couma* or wafar* or sofarin or aldocumar or genwarfarin or tedicumar or jantoven or uniwarfin).ti,ab.
3.	exp acenocoumarol/
4.	(aceno#oum* or nicoumalon* or sint?rom* or syn#o?mar).ti,ab.
5.	(mini adj1 sintrom).ti,ab.
6.	exp phenindione/
7.	(phenindion* or pindion* or phenylin* or fenilin or phenylindan?dione or dindevan or hedulin).ti,ab.
8.	(apixaban or eliqu?s).ti,ab.
9.	(dabigatran or pradaxa or pradax or prazaxa).ti,ab.
10.	(rivaroxaban or xarel*).ti,ab.
11.	(clopidogrel or plavix).ti,ab.
12.	exp aspirin/
13.	(asprin or asa or dispril or polopiry* or zoeporin or colfarit or aloxiprimum or micristin or easprin or magnecyl or solprin or ecotrin or endosprin or acylpyrin or solopsan or acetysal).ti,ab.
14.	exp dalteparin/
15.	(dalteparin or tedelparin or fragmin*).ti,ab.
16.	exp enoxaparin/
17.	(enoxaparin or xaparin or clexan*).ti,ab.
18.	or/1-17

19.	exp fibrinogen/
20.	("factor i" or "factor1").ti,ab.
21.	(coagulation adj2 factor).ti,ab.
22.	("fibrinogen conc*" or haemocomplettan or riastrap).ti,ab.
23.	(cryoprecipitat* or ecryo or cryo).ti,ab.
24.	exp blood platelets/
25.	(platelet* or thrombolyte).ti,ab.
26.	(phytonadion* or phytomenadion*).ti,ab.
27.	exp vitamin k/
28.	("vitamin adj k" or konakion).ti,ab.
29.	(phyllohydroquinone or phylloquinone or mephton).ti,ab.
30.	exp plasma/
31.	exp blood component transfusion/
32.	(ffp or ((frozen or fresh) adj3 plasma)).ti,ab.
33.	(pcc* or ppsb or beriplex or "beriplex p n" or "beriplex b-n" or " beriplex p/n" or confidex or kaskadil or kcentra or octaplex or ocplex or cofact or prothar or ppconc or "protein c concentrate").ti,ab.
34.	("prothrombin complex" adj2 (concentrate* or preparation)).ti,ab.
35.	("prothrombin convert*" adj2 (complex or enzyme)).ti,ab.
36.	exp factor viia/
37.	(factor adj2 vii).ti,ab.
38.	("factor viia" or "factor 7a").ti,ab.
39.	proconvertin.ti,ab.
40.	(revers* or correct* or antidote* or counteract*).ti,ab.
41.	or/19-40
42.	18 and 41

Embase search terms

1.	exp *warfarin/
2.	(marevan or warfarin or apo-warfarin or couma* or wafar* or sofarin or aldocumar or genwarfarin or tidicumar or jantoven or uniwarfarin).ti,ab.
3.	exp *acenocoumarol/
4.	(aceno#oum* or nicoumalon* or sint?rom* or syn#o?mar).ti,ab.
5.	(mini adj1 sintrom).ti,ab.
6.	exp *phenindione/

7.	(phenindion* or pindion* or phenylin* or fenilin or phenylindan?dione or dindevan or hedulin).ti,ab.
8.	(apixaban or xarel*).ti,ab.
9.	(clopidogrel or plavix).ti,ab.
10.	exp *acetylsalicylic acid/
11.	(asprin or asa or dispril or polopiry* or zoeporin or colfarit or aloxiprimum or micristin or easprin or magnecyl or solprin or ecotrin or endosprin or acylpyrin or solosan or acetysal).ti,ab.
12.	(rivaroxaban or xarel*).ti,ab.
13.	(dabigatran or praxada or pradax or prazaxa).ti,ab.
14.	exp *dalteparin/
15.	(dalteparin or tedelparin or fragmin*).ti,ab.
16.	exp *enoxaparin/
17.	(enoxaparin or xaparin or clexan*).ti,ab.
18.	or/1-17
19.	exp *fibrinogen/
20.	(factor i or factor 1).ti,ab.
21.	(coagulation adj2 factor).ti,ab.
22.	("fibrinogen conc*" or haemocomplettan or oriastrap).ti,ab.
23.	(cryoprecipitat* or ecryno or cryo).ti,ab.
24.	exp *thrombocyte/
25.	(platelet* or thrombolyte).ti,ab.
26.	(phytonadion* or phytomenadion*).ti,ab.
27.	exp *vitamin k group/
28.	("vitamin adj k" or kontaktion).ti,ab.
29.	(phyllohydroquinone or phylloquinone or mephton).ti,ab.
30.	exp *plasma/
31.	exp *blood component/
32.	(ffp or ((frozen or fresh) adj3 plasma)).ti,ab.
33.	(pcc* or ppsb or beriplex or "beriplex p n " or "beriplex b-n" or "beriplex p/n" or confodex or kaskadil or kcentra or octaplex or cofact or prothar or ppconc or "protein c concentrate").ti,ab.
34.	("prothrombin complex" adj2 (concentrate* or preparation)).ti,ab.
35.	("prothrombin convert" adj2 (complex or enzyme)).ti,ab.
36.	exp *blood clotting factor 7a/
37.	(factor adj2 vii).ti,ab.
38.	("factor viia" or "factor 7a").ti,ab.
39.	proconvertin.ti,ab.

40.	(revers* or correct* or antidote* or counteract*).ti,ab.
41.	or/19-40
42.	18 and 41

Cochrane search terms

#1.	MeSH descriptor: [warfarin] explode all trees
#2.	(marevan or warfarin or apo-wafarin or couma* or wafar* or sofarin or aldocumar or genwarfarin or tedicumar or jantoven or uniwarfin):ti,ab
#3.	MeSH descriptor: [acenocoumarol] explode all trees
#4.	(acenocoum* or nicoumalon* or sint?rom* or synto?mar):ti,ab
#5.	mini near1/sintrom
#6.	MeSH descriptor: [phenindione] explode all trees
#7.	(phenindion* or pindion* or phenylin* or fenilin or phenylindan?dione or dindevan or hedulin):ti,ab
#8.	(apixaban or eliqu?s):ti,ab
#9.	(dabigatran or pradaxa or pradax or prazaxa):ti,ab
#10.	(rivaroxaban or xarel*):ti,ab
#11.	(clopidogrel or plavix):ti,ab
#12.	MeSH descriptor: [aspirin] explode all trees
#13.	(asprin or asa or dispril or polopiry* or zoeporin or colfarit or aloxiprimum or micristin or easprin or magnecyl or solprin or ecotrin or endosprin or acylpyrin or solopsan or acetysal):ti,ab
#14.	MeSH descriptor: [dalteparin] explode all trees
#15.	(dalteparin or tedelparin or fragmin*):ti,ab
#16.	MeSH descriptor: [enoxaparin] explode all trees
#17.	(enoxaparin or xaparin or clexan*):ti,ab
#18.	{or #1-#17}
#19.	MeSH descriptor: [fibrinogen] explode all trees
#20.	("factor i" or "factor1"):ti,ab
#21.	(coagulation near/2 factor):ti,ab
#22.	("fibrinogen conc*" or haemocomplettan or riastrap):ti,ab
#23.	(cryoprecipitat* or ecryo or cryo):ti,ab
#24.	MeSH descriptor: [blood platelets] explode all trees
#25.	(platelet* or thrombolyte):ti,ab
#26.	(phytonadion* or phytomenadion*):ti,ab

#27.	MeSH descriptor: [vitamin k] explode all trees
#28.	("vitamin near/ k" or konakion):ti,ab
#29.	(phyllohydroquinone or phylloquinone or mephton):ti,ab
#30.	MeSH descriptor: [plasma] explode all trees
#31.	MeSH descriptor: [blood component transfusion] explode all trees
#32.	(ffp or ((frozen or fresh) near/3 plasma)):ti,ab
#33.	(pcc* or ppsb or beriplex or "beriplex p n" or "beriplex b-n" or " beriplex p/n" or confidex or kaskadil or kcentra or octaplex or ocplex or cofact or prothar or ppconc or "protein c concentrate"):ti,ab
#34.	("prothrombin complex" near/2 (concentrate* or preparation)):ti,ab
#35.	("prothrombin convert*" near/2 (complex or enzyme)):ti,ab
#36.	MeSH descriptor: [factor viia] explode all trees
#37.	(factor near/2 vii):ti,ab
#38.	("factor viia" or "factor 7a"):ti,ab
#39.	proconvertin:ti,ab
#40.	(revers* or correct* or antidote* or counteract*):ti,ab
#41.	{or #19-#40}
#42.	#18 and #41

Appendice B – Caratteristiche degli studi inclusi ed elenco degli studi esclusi con motivazione

Caratteristiche degli studi inclusi

Study	**Agyabeng-Dadzie 2020**
Study type	Retrospective study
Number of studies/ number of participants	N=169 (n=102 reversal group (RV) group, n=67 no reversal group (NR) group)
Countries and Settings	Department of Surgery, Orlando Regional Medical Center, Orlando, FL, USA
Funding	None
Duration of study	Patient selection: adult TBI patients over a 4-year period were retrospectively reviewed
Age, gender, ethnicity	Age [mean (SE)]: Not reported; Gender (% F): Not reported; Ethnicity: Not reported
Patient characteristics	169 blunt TBI patients (age ≥16 years) on chronic antiplatelet therapy admitted to a Level I trauma center. Patients with penetrating TBI, blunt TBI without TICH on admission CT, those receiving warfarin, those not on chronic APT, or those who required immediate operative intervention were excluded. The remaining patients were divided into 2 groups: reversal group (RV) (patients receiving immediate platelet transfusion) versus no reversal group (NR) (patients who had no platelet transfusion). All patients had an initial and at least 1 follow-up CT scan.
Intervention	PFA testing utilized the VerifyNow Aspirin Assay (for patients on aspirin) and the VerifyNow P2Y12 Assay (for patients on adenosine diphosphate [ADP] inhibitors such as clopidogrel, prasugrel, ticagrelor, and ticlopidine). Abnormal PFA for aspirin was defined as <550 aspirin reactivity units and abnormal PFA for ADP inhibitors was defined as <194 platelet reactivity units (PRU).
Outcomes	. Admission PFA . transfer from outside facilities . intubation upon arrival . time from admission to first head CT and time from first head CT to second follow-up CT . HLOS . TBI-related complications . all cause mortality

Study	**Carothers 2017**
Study type	Retrospective chart review
Number of studies/ number of participants	N= 120 (n=89 control group, n=31 aPCC group)
Countries and Settings	Orlando Regional Medical Center, Florida, USA Institutional trauma registry database
Funding	Not reported
Duration of study	from January 2010 to November 2015
Age, gender, ethnicity	Age (mean (SD)): control group: 76.8 (8.5); aPCC group: 77.3 (11.6) Gender (% M): control group: 60.7%; aPCC group: 61.3% Ethnicity: control group: White 88.8%; African American 6.7%; Asian 3.4%; Other 1.1%; aPCC group: White 93.5%; African American 3.2%; Asian 3.2%; Other 0%
Patient characteristics	Patients were included in the study if they were admitted to the hospital with a traumatic brain injury (TBI), an Abbreviated Injury Scale (AIS) Head score3, had evidence of intracranial hemorrhage on imaging, and were on warfarin with an international normalized ratio (INR) 1.5. Patients were excluded if they were aged <18 years or if there was no repeat INR available.
Intervention	Protocol uses one vial (~1000 units) of activated PCC (aPCC) for warfarin reversal, regardless of the weight or presenting international normalized ratio (INR). The patients were divided into two study groups. The control group consisted of all patients who received fresh frozen plasma (FFP) vitamin K alone. Any patient who met the inclusion criteria and who received aPCC was included in the aPCC group.
Outcomes	The primary efficacy outcome of the study was to compare the rate of warfarin reversal between the two groups. Secondary efficacy outcomes included time to INR1.4 (up to 48 hours), need for neurosurgical intervention (defined as craniotomy/craniectomy, external ventricular drain placement, intracranial pressure bolt placement, or burr hole procedure), time to neurosurgical intervention (defined as time from first administration of FFP, vitamin K, or aPCC at our institution to either pre-procedure time-out or anesthesia induction), intensive care unit and hospital length of stay, mechanical ventilation days, incidence of acute respiratory distress syndrome, incidence of ventilator-associated pneumonia, adjunctive blood product and reversal agent usage, and mortality. The primary safety outcome was incidence of venous thromboembolism in each group.

Study	**Lumas 2020**
Study type	Retrospective
Number of studies/ number of participants	N=150 patients
Countries and Settings	Yale New Haven Hospital, an academic level 1 trauma center on preinjury warfarin, New Haven, Connecticut
Funding	None
Duration of study	Patients selection: from January 2013 to December 2018
Age, gender, ethnicity	Age [mean (SD)]: PCC group 81.9 (8.1); FFP group 81.2 (9.7); No reversal 81.3 (7.3) Gender (% M): PCC group 58.3%; FFP group 43.9%; No reversal 49.0% Ethnicity: PCC group: White 83.3%, Black 6.7%, Other 10.0%; FFP group: White 82.9%, Black 7.3%, Other 9.8%; No reversal: White 89.8%, Black 6.1%, Other 4.1%
Patient characteristics	All patients 65 y of age or older on pre-injury warfarin diagnosed with traumatic ICH admitted to Yale New Haven Hospital. The ICH types included were subarachnoid hemorrhage, subdural hemorrhage (SDH), epidural hemorrhage, and/or intraparenchymal hemorrhage identified through the trauma registry. Patients admitted for comfort measures only (n=18), deemed to have a nonsurvivable injury (n=3), had no follow-up head CT scan (n=12) or received both FFP and PCC (n=8) were excluded from analysis, yielding a final sample of 150 patients.
Intervention	All patients 65 y of age or older on pre-injury warfarin diagnosed with traumatic ICH. Follow-up CT scans were obtained at 6 h after the initial CT scan. All patients who had a change in mental status or underwent neurosurgical intervention had a follow-up CT. The study sample was then stratified based on type of urgent reversal agent used: PCC, FFP, or no reversal agent.
Outcomes	The primary outcomes were ICH progression on follow-up CT scan, need for craniotomy, and in-hospital mortality. Secondary outcomes included hospital length of stay (LOS), admission to the intensive care unit (ICU), ICU LOS, need for mechanical ventilation, ventilator days, change in neurologic examination, and number of hours from the time of emergency department arrival until INR decreased to a value of 1.7 or below

Study	**Alvikas 2020**
Study type	systematic review
Number of studies/ number of participants	N=12 studies included, 11 retrospective studies and 1 prospective observational study
Countries and Settings	
Funding	The work was supported by the following grants: R35 GM119526–04(PI: Matthew D. Neal, MD), R01 GM116929 (PI: Matthew R. Rosengart, MD, MPH), R01 GM082852 (PI: Matthew R. Rosengart, MD, MPH)
Duration of study	The study was conducted from January 1, 1987 to March 4, 2019
Age, gender, ethnicity	Age [mean]: Not reported Gender (% M): Not reported Ethnicity: Not reported
Patient characteristics	All studies investigating the effect of platelet transfusion after tICH in patients taking prehospital aspirin, dipyridamole, clopidogrel, ticagrelor, prasugrel, eptifibatide, or abciximab were eligible for inclusion. Commentaries (e.g., expert opinion), case reports, case series, reviews, and studies published in non–peer-reviewed journals were excluded.
Intervention	Determine whether or not platelet transfusions associated with survival, progression of intracranial hemorrhage or need for neurosurgical intervention in patients who have sustained tICH and were taking aspirin or P2Y12 inhibitors
Outcomes	The primary outcome of interest was all-cause in-hospital mortality. The secondary outcomes of interest were tICH progression and need for neurosurgical intervention.

Study	**Holzmacher 2018**
Study type	retrospective multicentre cohort study of prospectively collected
Number of studies/ number of participants	N= 66
Countries and Settings	6 trauma centre in the USA
Funding	Funding was provided by NCATS UL1TR000445 for REDCap (all authors), Vanderbilt Faculty Research Scholars Program (mbp); National Institutes of Health NHLBI R01HL111111 (mbp) and NIGMSR01GM120484 (mbp)
Duration of study	From 8/1/2015 to 12/31/2016
Age, gender, ethnicity	Age [mean (SD)]: transfusion group: 76.0 (9.3); no transfusion group: 78.0 (11.6) Gender (% M): transfusion group: 47.0%; no transfusion group: 34.8% Ethnicity: Not reported
Patient characteristics	Patients 18 years and older who were taking an antiplatelet pharmacologic agent and were noted to have radiographically evident, blunt traumatic brain injury were enrolled. Exclusion criteria included patients less than18 years old, penetrating brain injury, prisoners, pregnancy, patients transferred from outside hospitals to the trauma centre, patients who did not undergo TEG-PM testing on arrival to the trauma centre, inability to verify whether a patient was on an antiplatelet agent prior to injury, use of warfarin or a direct oral anticoagulant prior to injury, and platelet transfusion prior to obtaining a TEG-PM.
Intervention	Patients on antiplatelet medication with CT evident TBI after blunt injury were analyzed considering brain CT and TEG-PM results before/after platelet transfusion, length of stay (LOS), and injury severity score (ISS).
Outcomes	The primary outcomes were change in TEG-PM parameters following platelet transfusion and change in Marshall CT score over time. Secondary outcomes included need for operative intervention, ICU and hospital length of stay, and mortality

Study	**Leong 2015**
Study type	systematic review
Number of studies/ number of participants	N= 7 studies included, retrospective cohort studies
Countries and Settings	6 studies in United States and 1 Japanese
Funding	Not reported
Duration of study	From 1946 to June 2014
Age, gender, ethnicity	Age [mean (SD)]: Not reported Gender (% M): Not reported Ethnicity: Not reported
Patient characteristics	Studies were included if they were randomized or case controlled or cohort studies comparing outcomes in adult patients with APA-related traumatic or primary ICH who were treated, vs. those who were not treated with platelet transfusion; with results available in English.
Intervention	The use of platelet transfusion in the management of APA-related ICH
Outcomes	The primary outcome of interest was in-hospital mortality rate. Secondary outcomes included rates of craniotomy, neurological, medical, or radiological deterioration; mean length of hospital stay, delayed mortality, and functional status at discharge

Study	**Lokhandwala 2020**
Study type	retrospective cohort analysis
Number of studies/ number of participants	N= 343
Countries and Settings	American College of Surgeons verified level I trauma center
Funding	None
Duration of study	From 2014 to 2016
Age, gender, ethnicity	Age [mean (SD)]: PLT group 58(10); No-PLT group 60(11) Gender (% M): PLT group 59%; No-PLT group 57% Ethnicity (% White): PLT group 60%; No-PLT group 62%
Patient characteristics	All adult trauma patients (age≥18 y) admitted to level I trauma center with the primary diagnosis of TBI, only isolated TBI patients with an initial head computed tomography (CT) scan showing IB who were on an antiplatelet agent before being injured. We excluded patients with significant extracranial injuries (an extracranial abbreviated injury score [AIS]>2), those on preinjury anticoagulants, those with documented bleeding diathesis or chronic liver disease, and those who died within 24 h of injury. Patients were stratified into two groups: those who received aPLT and those who did not receive a PLT (No-PLT).
Intervention	All TBI patients were treated according to the Brain Trauma Foundation guidelines and Brain Injury Guidelines (BIG). We only consult neurosurgery if the TBI patient fulfills the BIG 3 criteria. Final verdicts regarding patient care were kept at the discretion of the trauma surgeons.
Outcomes	The primary outcomes of interest were: the progression of IB, the need for neurosurgical intervention, and in-hospital mortality

Study	**Ogunlade 2018**
Study type	Retrospective chart review
Number of studies/ number of participants	N= 72
Countries and Settings	2 level II US trauma center
Funding	None
Duration of study	From 2015 to 2018
Age, gender, ethnicity	Age [mean]: 75.38 Gender (% M): 56% Ethnicity: Not reported
Patient characteristics	Patients included in the study were adults, at least 40 years of age, who presented as a closed head injury trauma patient following a ground level fall, motor vehicle accident, or assault, and were diagnosed with an acute subdural hematoma on initial computerized tomography of the head (CTH) by an attending radiologist. All acute tSDH in this had a greatest thickness less than 1 cm and midline shift less than 5 mm, and were deemed non-surgical per neurosurgical guidelines. Patients with non-acute and non-traumatic subdural hematomas, history of previous subdural hematoma or intracranial hemorrhage, history of craniotomy or craniectomy, and depressed skull fracture on presentation were excluded. Patients were stratified into the four experimental groups (a) aspirin, (b) clopidogrel, (c) both, and (d) none. The four experimental groups were further stratified into platelet transfusion and no transfusion groups
Intervention	All patients received standard neurointensive care for acute tSDH including hourly neurological checks for at least 24 h, systolic blood pressure control 100–140 mmHg, repeat CTH 6–8 h after initial scan, seizure prophylaxis, HOB > 30 degrees, and appropriate pain control. The radiologist report final impression was used to classify the first repeat CTH as stable or unstable. Hematoma volumes greater than 10% of the initial scan were defined as unstable.
Outcomes	The primary outcome measure was no change in the SDH size on the repeat CTH (stable) or interval expansion of the SDH (unstable). The secondary outcome measure was progression of an expanded SDH to surgical criteria.

Study	**Barletta 2020**
Study type	Retrospective cohort study
Number of studies/ number of participants	N= 202
Countries and Settings	Level I US trauma center
Funding	None
Duration of study	From July 2012 to May 2018
Age, gender, ethnicity	Age [mean (SD)]: 76 (12) Gender (% M): 63% Ethnicity: Not reported
Patient characteristics	Adult patients, age 18 years or older, who were admitted to our level I trauma center and prescribed pre-injury antiplatelet medications. Patients were excluded if their hospital length of stay was less than 24 h, if DDAVP was administered by any route other than intravenous, if they were prescribed a DDAVP dose<0.3 mcg/kg or there was no evidence of TBI on computed tomography (CT) scan. Patients were stratified into two groups based on the administration of DDAVP (yes or no)
Intervention	Pre-injury medication use was determined as per routine practice, which includes a thorough medication history, and consultation or verification with the dispensing pharmacy as needed. CT scans to be repeated at 6 h post-admission and at least every 24 h thereafter. Hematoma expansion was defined as expansion>20% from baseline or a new hematoma not present on initial CT scan. As a secondary measure, hematoma expansion>33% from baseline or a new hematoma was reported.
Outcomes	The primary outcome: the incidence of hematoma expansion was compared between groups. Thrombotic events were reviewed as a secondary outcome.

Study	**Hobbs 2016**
Study type	retrospective chart review
Number of studies/ number of participants	N= 120 patients; SOC group n= 89; aPCC group n=31
Countries and Settings	Level I trauma center
Funding	Not reported
Duration of study	From January 2010 to June 2015
Age, gender, ethnicity	Age [mean (SD)]: Not reported Gender (% M): Not reported Ethnicity: Not reported
Patient characteristics	Adult TBI patients with an INR≥1.5 on warfarin with evidence of intracranial hemorrhage were included, while patients with no repeat INR were excluded
Intervention	Patients were divided into two groups, SOC only vs SOC plus aPCC.
Outcomes	The primary outcome of the study was to compare the percent-age of patients in each group with an INR≤1.4 within 24 hours

Study	**Huang 2019**
Study type	retrospective cohort study
Number of studies/ number of participants	N= 77 patients: FFP group n=68 patients, PCC group n=7, n=2 received both
Countries and Settings	Single center, Level I trauma center Trauma registry
Funding	Not reported
Duration of study	From January 2014 to December 2015
Age, gender, ethnicity	Age [mean]: 78.91 Gender (% M): 53% Ethnicity: Not reported
Patient characteristics	Included patients were 18 and older, on warfarin with an INR>1.4, and had an urgent need to reverse coagulopathy. Excluded patients were younger than 18 or had no clinical indication for warfarin reversal
Intervention	Patients that received PCC (PCC group) were compared to those who received VitaminK/FFP (FFP group). Patients receiving both were excluded from comparison analyses.
Outcomes	Comparing outcomes between two treatment options: Prothrombin Complex Concentrate (PCC) and VitaminK/Fresh Frozen Plasma (FFP) in trauma patients needing urgent warfarin reversal.

Study	**Koyama 2021**
Study type	retrospective study
Number of studies/ number of participants	N= 20: VK group n=13, PCC group n=7
Countries and Settings	Department of Neurosurgery, Tokushima University Hospital, Tokushima, Tokushima, Japan
Funding	Not reported
Duration of study	From February 2016 to November 2019
Age, gender, ethnicity	Age [mean (SD)]: VK group 78.6 (7.2), PCC group 80 (6.6) Gender (% M): VK group 61.5%, PCC group 71.4% Ethnicity: Not reported
Patient characteristics	Adult patients (≥18 years old) admitted at hospital due to TICH within 12 post-injury hours. Among them, 35 patients underwent warfarin treatment with a PT-INR of ≥1.4. Seven patients were infused with FFP to treat coincidental systemic massive hemorrhage due to aortic, hepatic, or pulmonary injuries. They were excluded from the study population because the clinical status is different from the others. Patients with mild head injury or excessively severe trauma on admission who did not receive treatment for warfarin reversal effect were excluded.
Intervention	Immediately after TICH identification, all patients in the VK and PCC era were treated using intravenous administration of VK and PCC in combination with VK, respectively. All the patients underwent a computer tomography (CT) scan on admission and repeat scans at least twice within 3 and 4-24 hours after admission. PHI was evaluated on the repeat CT scans and defined as follows: the appearance of a new intracranial hematoma, including intracerebral, intraventricular, subdural, epidural, or subarachnoid hemorrhage not caused by redistributed hemorrhage or expansion of pre-existing hematoma indicated by a qualitative increase in the volume by 1.4 times greater than the volume on the admission CT. For warfarin reversal with and without PCC, the target PT-INR level was <1.40. Regarding reversal using PCC, PCC was intravenously administered immediately followed by intravenous VK administration (10–20 mg). The administered PCC dose was determined according to institutional protocol, which was approved by the medical safety commission of the hospital, as follows: 25 IU/kg, 35 IU/kg, and 50 IU/kg were given to patients with INR 1.4–4, 4.0–6.0, and >6, respectively. PCC was only administered once. Contrastingly, 10 mg VK was repeatedly administered in case the PT-INR was ≥1.4 in the follow-up test at 8–12 post-admission hours.
Outcomes	to evaluate the warfarin reversal effects of combination therapy of PCC with VK and VK monotherapy on TICH.

Study	**Drone 2015**
Study type	Retrospective chart review
Number of studies/ number of participants	N= 52
Countries and Settings	Not reported
Funding	Not reported
Duration of study	From 1 January 2012 to 1 November 2014
Age, gender, ethnicity	Age [mean (SD)]: Not reported Gender (% M): Not reported Ethnicity: Not reported
Patient characteristics	26 admitted adults who received a fixed dose of 1,500 units 4F-PCC with 26 patients who received a combination of factor IX complex and vitamin K, with or without FFP, for warfarin reversal.
Intervention	Patients have received a fixed dose of 1,500 units 4F-PCC or a combination of factor IX complex and vitamin K, with or without FFP, for warfarin reversal.
Outcomes	Primary outcomes included reversal to an INR of < 2 and reversal to an INR of < 1.6. Secondary outcomes included ICU and hospital length of stay (LOS), change in INR, INR nadir, potential cost savings from 4F-PCC versus traditional dosing, and major adverse effects.

Study	**Mangram 2016**
Study type	retrospective study
Number of studies/ number of participants	N= 64: 3F-PCC group n= 46, 4F-PCC group n= 18
Countries and Settings	2 affiliated American College of Surgeons verified trauma centers; one a level-I trauma center and the second, a level-III trauma center
Funding	Not reported
Duration of study	From January 2010 to October 2014
Age, gender, ethnicity	Age [mean (SD)]: 3F-PCC group 76 (13), 4F-PCC group 7 (8) Gender (% M): 3F-PCC group 54.3%, 4F-PCC group 55.5% Ethnicity: Not reported
Patient characteristics	Patients were included if they had a trauma-related admission diagnosis, received oral anticoagulation prior to admission and had a baseline INR ≥ 1.5. Patients were excluded if they did not have an INR assessment post-PCC administration or if they received both a 3F-PCC and a 4F-PCC product. Trauma patients with anticoagulation-related coagulopathy meeting inclusion/exclusion criteria were stratified into two groups based on the PCC product that was administered: 3F-PCCvs. 4F-PCC
Intervention	Adult patients who received either a 3F-PCC or 4F-PCC product and treated by the trauma service. There was no formal dosing protocol but institutional practices consisted of a dose range between 25–50 units/kg with the higher end of the range being considered for INR elevations that were considered extreme (i.e., greater than 5). All administered PCC doses (initial and subsequent if necessary) were included in the assessment
Outcomes	INR reversal, adverse effects and cost-effectiveness

Study	**Margraf 2020**
Study type	Retrospective chart review
Number of studies/ number of participants	N= 80, PCC3 group n= 57, PCC4 group n= 23
Countries and Settings	North Memorial Medical Center, an American College of Surgeons verified Level 1 Trauma Center.
Funding	None
Duration of study	From August 29,2007 to June 30, 2014
Age, gender, ethnicity	Age [mean]: PCC3 group 74, PCC4 group 66 Gender (% M): PCC3 group 63.2%, PCC4 group 52.2% Ethnicity: Not reported
Patient characteristics	Patients who receive PCC3 or PCC4 for emergent warfarin reversal (EWR) were identified Patients were included who had documented warfarin usage prior to admission, required EWR, an initial INR≥1.6, received either PCC3 or PCC4 at a dose range of 20–50 units/kg with an allowance for rounding to the nearest 500 unit vial, at least one INR value obtained pre PCC administration, and at least one INR obtained post PCC administration. Kcentra®, the PCC4 product used, is dosed in factor IX units, and contains 200 to 500 units of factor VII per 500 unit vial Profil-nine®, the PCC3 product used, contains no more than175 factor VII units per 500 factor IX units. Patients were excluded if they had an INR≤1.5 before PCC administration, received recombinant activated factor VII (rFVIIa), did not have an INR measurement before or after PCC administration, pre-PCC dose INR was drawn greater than 6 h from the dose given, or greater than 12 h elapsed from the pre-PCC dose INR to post-PCC dose INR. Administration of FFP units and vitamin K dose and route were not standardized by treatment protocol and were left to the discretion of the provider
Intervention	Administration of PCC3 or PCC4 at a dose range of 20–50 units/kg with an allowance for rounding to the nearest 500 unit vial, at least one INR value obtained pre PCC administration, and at least one INR obtained post PCC administration. Kcentra®, the PCC4 product used, is dosed in factor IX units, and contains 200 to 500 units of factor VII per 500 unit vial Profil-nine®, the PCC3 product used, contains no more than175 factor VII units per 500 factor IX units.
Outcomes	The primary outcome was achieving an INR≤1.5 post PCC. Secondary outcomes were the change in INR over time, post PCC INR, thromboembolic events (TE), and death during hospital stay

Study	**Martin 2016**
Study type	Retrospective study
Number of studies/ number of participants	N= 87: 3F-PCC+rVIIa group n=53, 4F-PCC group n=34.
Countries and Settings	academic level one trauma center, Department of Surgery, Oregon Health & Science University, Portland, USA institutional trauma registry single center
Funding	Not reported
Duration of study	From 2011 to 2015
Age, gender, ethnicity	Age [mean]: 3F-PCC+rVIIa group 80.8, 4F-PCC group 79.4 Gender (% M): 3F-PCC+rVIIa group 60.4%, 4F-PCC group 61.8% Ethnicity: Not reported
Patient characteristics	Traumatically injured patients taking warfarin before injury who were treated with a 4-factor PCC replacement regimen, either with 3F-PCC and rVIIa (3F-PCC1rVIIa) or 4F-PCC to treat an acute hemorrhage. Patients were included if they were treated with either 4F-PCC or 3F-PCC1rVII a specifically for the emergent reversal of warfarin because of the presence of an acute traumatic hemorrhage. Patients were excluded if the PCC was given for reasons other than an acute traumatic bleed (ie, before a nonemergent procedure during their admission)
Intervention	The administration of either 3F-PCC1rVIIa or 4F-PCC was performed according to established weight-based protocols. 3F-PCC was given at a dose of 50 units/kg, along with a fixed dose of 1 mg of rVIIa. 4F-PCC was given at different doses depending on the INR at presentation: for an INR ranging from 2.0 to 4.0, 25 units/kg of 4F-PCC were administered. For an INR of 4.0 to 6.0, 35 units/kg were given. DVT screening among traumatically injured patients is performed with weekly whole-leg duplex ultrasonography on patients determined to be at high risk for DVT. High-risk patients are defined as those with spinal cord injuries, immobility, lower extremity fractures and pelvic fractures, or prolonged intubation. Patients at medium risk of DVT are screened in the same fashion if they have a contraindication to DVT prophylaxis. Medium risk is determined by the presence of open extremity fractures, multiple closed extremity fractures, GCS score of 9 to 13, multiple rib fractures, spinal column injury without neuro-logic defects, or any known cardiac disease.
Outcomes	International normalized ratio (INR) reduction, in-hospital mortality, and diagnosis of deep venous thrombosis (DVT)

Study	**Cohen 2017**
Study type	Retrospective study
Number of studies/ number of participants	N= 194: 1500PCC group (n=70), 1000PCC group (n=124)
Countries and Settings	Level I trauma center and a tertiary care center
Funding	Not reported
Duration of study	From August 2014 to July 2015
Age, gender, ethnicity	Age [mean (SD)]: Not reported Gender (% M): Not reported Ethnicity: Not reported
Patient characteristics	Patients taking warfarin who received 4FPCC (Kcentra) for life-threatening bleeding or reversal for urgent procedures.
Intervention	Institutional protocol, patients received an initial dose of 1500 IU 4FPCC (1500PCC group) for intracranial bleeding and 1000 IU 4FPCC (1000PCC group) for extracranial bleeding.
Outcomes	The efficacy of two different protocolized non-weight-based doses of 4FPCC

Study	**Cohen 2018**
Study type	Retrospective study
Number of studies/ number of participants	N= 219:1500 PCC group (n=75),1000 PCC group (n=144)
Countries and Settings	Level I trauma center and a tertiary care center
Funding	Not reported
Duration of study	From August 2014 to July 2015
Age, gender, ethnicity	Age [mean (SD)]: Not reported Gender (% M): Not reported Ethnicity: Not reported
Patient characteristics	Patients taking warfarin who received 4FPCC for life-threatening bleeding or reversal for urgent procedure.
Intervention	Institutional protocol, patients received an initial dose of 1500+/-200 IU 4FPCC (1500 PCC group) for intracranial bleeding and 1000+/-200 IU 4FPCC (1000 PCC group) for extracranial bleeding.
Outcomes	The efficacy of two different protocolized non-weight-based doses of 4FPCC

Studi esclusi e motivi di esclusione

N	Titolo	Rivista	Autori	Motivo esclusione
1	A retrospective analysis of the realworld use of idarucizumab at two tertiary care centres in Toronto, Canada	Research and Practice in Thrombosis and Haemostasis	Abdulrehman, J. and Lindsay, D. and Elbaz, C. and Sholzberg, M. and Lin, Y. and Selby, R. and Sholzberg, M. and Selby, R.	wrong study design
2	Anticoagulation is associated with increased morbidity and mortality in concussive injury among elderly trauma patients	Chest	Akella, Krishna and Akella, Sraavya and Chendrasekhar, Akella	wrong intervention
3	Low-dose four-factor prothrombin complex concentrate in reversal of XA inhibitors in a neuro-ICU	Critical Care Medicine	Allison, Teresa and Hartman, Heather and Gass, Jennifer and Jen Lin, Pei and Chong, Kenneth and Choi, Huimahn and Escobar, Miguel	wrong study design
4	Evaluation of the Use of Low-Dose 4-Factor Prothrombin Complex Concentrate in the Reversal of Direct Oral Anticoagulants in Bleeding Patients	Journal of intensive care medicine	Allison Teresa, A. and Lin Pei, Jen and Gass Jennifer, A. and Chong, Kenneth and Hartman Heather, D. and https://orcid.org, Id Orcid and Prater Samuel, J. and Escobar Miguel, A.	wrong study design
5	Antiplatelet therapy is associated with a high rate of intracranial hemorrhage in patients with head injuries	Trauma surgery & acute care open	Alter Scott, M. and Mazer Benjamin, A. and Solano Joshua, J. and Shih Richard, D. and Clayton Lisa, M. and Greaves Spencer, W. and Hughes Patrick, G. and h	wrong intervention
6	Outcomes of geriatric trauma patients on preinjury anticoagulation: A multicenter study	American Surgeon	Ang, Darwin M. D. P. H. D. M. P. H. and Kurek, Stan and McKenney, Mark and Norwood, Scott and Kimbrell, Brian and Barquist, Erik and Liu, Huazhi and O'Dell, Annette and Hurst, James and Ang, Darwin M. D. P. H. D. M. P. H. and Liu, Huazhi and McKenney, Mark and Kurek, Stan and Barquist, Erik and Norwood, Scott and Kimbrell, Brian and Ziglar, Michele	wrong intervention
7	Delayed intracranial hemorrhage in patients with head trauma and antithrombotic therapy	Journal of Clinical Medicine,	Antoni, Anna and Schwendenwein, Elisabeth and Binder, Harald and Schauperl, Martin and Hajdu, Stefan and	wrong intervention

			Datler, Philip	
8	Idarucizumab reversal of anticoagulation in dabigatran -treated patients presenting with acute traumatic injuries: Interim results from the RE-VERSE AD Study	British Journal of Haematology	Austin, S. and Pollack, C. V. and Grunenfelder, F. and Kleine, E. and Kreuzer, J. and Eikelboom, J. and Hylek, E. and Mills, M. and Reilly, P. and Selke, F. and Kamphuisen, P. and Weitz, J.	wrong study design
9	Desmopressin for antiplatelet reversal in neurocritical care	Critical Care Medicine	Barletta, Jeffrey and Mankiewicz, Claire and Mangram, Alicia and Sucher, Joseph and Ali-Osman, Francis and Dz and u, James and Yusupov, Igor and Zach, Victor	duplicate
10	Newer and Better? Comparing Direct Oral Anticoagulants to Warfarin in Patients With Traumatic Intracranial Hemorrhage	The American surgeon	Billings Joshua, D. and Khan Abid, D. and Schroeppel Thomas, J. and Billings Joshua, D. and Khan Abid, D. and Schroeppel Thomas, J. and McVicker John, H.	wrong intervention
11	Fixed-dose activated prothrombin complex concentrate for oral factor Xa inhibitor reversal	Neurocritical Care	Birrer, Kara and Hobbs, Br and on and Spink, Tyler and De Ryke, Xi Liu and Giancarelli, Am and a	mixed population
12	Developing, Implementing, and Evaluating a Nurse-Driven Rapid Reversal Protocol for Patients With Traumatic Intracerebral Hemorrhage in the Presence of Preinjury Warfarin	Journal of trauma nursing : the official journal of the Society of Trauma Nurses	Blackmore Abigail, R. and Caputo Lisa, M. and Bourg Pamela, W. and Mains Charles, W.	out of scope
13	Platelet dysfunction and platelet transfusion in traumatic brain injury	The Journal of surgical research	Briggs, Alex and ra and Gates Jonathan, D. and Kaufman Richard, M. and Calahan, Christopher and Gormley William, B. and Havens Joaquim, M.	wrong intervention
14	Direct oral anticoagulants: a review on the current role and scope of reversal agents	Journal of thrombosis and thrombolysis	Chaudhary, Rahul and https://orcid.org/---385X, Id Orcid and Chaudhary, Rahul and https://orcid.org/---385X, Id Orcid and Sharma, Tushar and Sukhi, Ajaypaul and Tantry, Udaya and Garg, Jalaj and Bliden, Kevin and Gurbel, Paul and Turagam, Mohit and Lakkireddy, Dhanunjaya	wrong study design
15	Use of Aspirin and P2Y12 Response Assays in Detecting Reversal of Platelet Inhibition With	Neurosurgery	Choi Phillip, A. and Zusman Benjamin, E. and Parry Phillip, V. and Bauer Joshua, S.	wrong study design

	Platelet Transfusion in Patients With Traumatic Brain Injury on Antiplatelet Therapy		and Panczykowski David, M. and Puccio Ava, M. and Okonkwo David, O. and Bauer Joshua, S.	
16	Bleeding and treatment failure in patients taking direct oral anticoagulants referred to emergency department: A cohort management study	Journal of Thrombosis and Haemostasis	Compostella, C. and Rocca, F. D. and Vettore, G. and Jose, S. P. and Zoppellaro, G. and Denas, G. and Bracco, A. and Pengo, V.	wrong intervention
17	Assessing efficacy of four factor prothrombin complex concentrate (4FPCC) for reversal of direct factor XA inhibitors in intracranial hemorrhages at an academic medical center	Neurology	Coppiano, Lindsey and Wood, Kendyl Caroline and Rocker, Jody and Garcia, Klepper Alfredo and Shah, Manan	wrong study design
18	Coordinating emergent procedures after factor XA inhibitor (XAI) reversal with Andexanet Alfa	Research and Practice in Thrombosis and Haemostasis	Culbreth, S. and Rimsans, J. and Sylvester, K. and Connors, J. M.	wrong study design
19	Hemostatic Efficacy and Anti-FXa (Factor Xa) Reversal with Andexanet Alfa in Intracranial Hemorrhage: ANNEXA-4 Substudy	Stroke	Demchuk, Andrew M. M. D. and Yue, Patrick and Conley, Pamela B. and Curnutte, John T. and Zotova, Elena and Nakamya, Juliet and Xu, Lizhen and Eikelboom, John W. and Crowther, Mark and Connolly, Stuart J. and Milling, Truman J. and Ohara, Tomoyuki and Goldstein, Joshua N. and Middeldorp, Saskia and Verhamme, Peter and Lopez-Sendon, Jose Luis	wrong population
20	Use of a 4-factor prothrombin complex concentrate for management of direct Xa inhibitor-induced major bleeding	Research and Practice in Thrombosis and Haemostasis	Dobesh, P. and Trevarrow, B. and Malinowski, P. and Guiliano, K. and Duncan, C. and Gundabolu, K.	wrong study design
21	Efficacy and safety of four-factor prothrombin complex concentrate fixed, weight-based dosing for reversal of warfarin anticoagulation	Hematology (Amsterdam, Netherlands)	Endres, Kaitlin and St Bernard, Rosanne and Chin-Yee, Ian and Hsia, Cyrus and Lazo-Langner, Alej and ro and https://orcid.org, Id Orcid and Lazo-Langner, Alej and ro and https://orcid.org, Id Orcid	wrong population
22	Effect of antiplatelet therapy and ddavpÂ® on progression of traumatic brain injury in older patients	Academic Emergency Medicine	Fassassi, Catsim and Simon, Ronald and Walden, Heath and Patel, Krishan and Betro, Gerard and Qureshi, Mehr and	wrong population

			Motov, Sergey and Savel, Richard	
23	Trauma patients admitted taking warfarin or dabigatran -a comparison of management and outcomes	Critical Care Medicine	Feild, Carinda and Tran, Bao Anh and Johnson, Jeffery	wrong intervention
24	Temporary Warfarin reversal vs full oral anticoagulation reversal in the emergency setting	Academic Emergency Medicine	Goddard, Kara B. and Ubinas, George J. and Johnson, Michael and Sampson, Christopher S. and Quick, Jacob A. and Bedy, Starr-Mar'ee and Stilley, Julie A. W. and Miner, James	out of scope
25	Reversal of dabigatran with idarucizumab in five patients admitted to the emergency department of Centro Hospitalar Sao Joao, Porto	Research and Practice in Thrombosis and Haemostasis	Goncalves, L. and Carvalho, M. and Correia, F. and Oliveira, G. and Koch, C.	wrong study design
26	Administration of 4-Factor Prothrombin Complex Concentrate as an Antidote for Intracranial Bleeding in Patients Taking Direct Factor Xa Inhibitors	World neurosurgery	Gr and hi, Ramesh and Newman, W. Christopher and Okonkwo David, O. and Ducruet Andrew, F. and Zhang, Xiaoran and Harrison, Gillian and Moran, Colleen	wrong population
27	Reversal of anticoagulants: an overview of current developments	Thrombosis and haemostasis	Greinacher, Andreas and Thiele, Thomas and Selleng, Kathleen	wrong study design
28	Management of the Trauma Patient on Direct Oral Anticoagulants	Current Anesthesiology Reports	Grissom, Thomas E.	wrong study design
29	Four factor prothrombin concentrate utilization at A level 1 trauma center	American Journal of Hematology	Grunvald, Miles and Fabricant, Loic	wrong population
30	Efficacy and safety of 4- PCC for coagulopathy reversal stratified by FDA approval status	Critical Care Medicine	Helmink, Brady and King, Ben and Milling, Truman and Murphy, Melissa and Tabas, Irene and Murthy, Manasa and Shuman, Carrie and Daley, Mitchell	out of scope
31	4F- PCC for reversal of direct oral anticoagulant-associated traumatic subdural hematoma: Impact on hematoma expansion and outcomes	Neurocritical Care	Klavansky, Dana and Lin, Am and a and Temes, Richard	wrong study design
32	Reversal of direct oral anticoagulants with three-factor prothrombin complex concentrate : Real world experience from a tertiary centre in Hong Kong	Research and Practice in Thrombosis and Haemostasis	Kong, S. Y. and Yip, S. F. and Ha, C. Y.	wrong study design
33	Idarucizumab administration in emergency	Journal of neurology	Kupper, Clemens and Feil, Katharina and	duplicate

	situations: the Munich Registry of Reversal of Pradaxa Â® in clinical routine (MR REPAIR)		Klein, Matthias and Feuerecker, Regina and Dieterich, Marianne and Kellert, Lars and https://orcid.org/---639X, Id Orcid and Feil, Katharina and Dieterich, Marianne and Lucking, Marc and Thanbichler, Florian and Topka, Helge and Dietrich, Dennis and Zerkaulen, Irene and Zerkaulen, Irene and J and l, Mitja and Marziniak, Martin and Poppert, Holger and Wunderlich, Silke and Poppert, Holger and Dieterich, Marianne	
34	Idarucizumab administration in emergency situation-the Munich registry of reversal of Pradaxa Â® in clinicl routine (MR REPAIR)	European Stroke Journal	Kupper, C. and Heinrich, J. and Feil, K. and Kellert, L. and Feil, K. and Lu cking, M. and Thanbichler, F. and Topka, H. and Dietrich, D. and Zerkaulen, I. and Lechner, C. and Lechner, C. and J and l, M. and Marziniak, M. and Wunderlich, S. and Poppert, H. and Poppert, H. and Kellert, L.	wrong study design
35	Effect of platelet transfusion on TEG-PM in trauma patients taking antiplatelet medications	Critical Care Medicine,	Levins, Elizabeth and Barton, Cassie and Roberti, Gregory and Goodman, Andrew and Ran, Ran and Schreiber, Martin	wrong study design
36	Factor VIIa administration in traumatic brain injury: an AAST-MITC propensity score analysis	Trauma surgery & acute care open	Lombardo, Sarah and Millar, D. and Jurkovich Gregory, J. and Coimbra, Raul and Nirula, Ram	mixed population
37	Management of rivaroxaban or apixaban associated major bleeding with prothrombin concentrate: A prospective cohort study	Research and Practice in Thrombosis and Haemostasis	Majeed, A. and Agren, A. and Bruzelius, M. and Chaireti, R. and Odeberg, J. and Holmstrom, M. and Hempel, E. L. and Magnusson, M. and Frisk, T. and Majeed, A. and Agren, A. and Bruzelius, M. and Chaireti, R. and Odeberg, J. and Holmstrom, M. and Hempel, E. L. and Schulman, S. and Majeed, A. and Magnusson, M. and Frisk, T. and Schulman, S.	wrong population
38	Factor Eight Inhibitor Bypassing Agent (FEIBA) for Reversal of Target-Specific Oral	The Journal of emergency medicine	Mao, Gordon and King, Lauren and Young, Sarah and Kaplan, Richard	wrong intervention

	Anticoagulants in Life-Threatening Intracranial Bleeding			
39	Retrospective evaluation of the efficacy and safety of 4-factor prothrombin complex concentrate compared to fresh frozen plasma for warfarin reversal in emergent surgery or invasive procedure	Anesthesia and Analgesia	Mazur, Hannah Dr and Young, Sarah and McGraw, Molly	not found
40	Single centre retrospective analysis of patients who underwent emergency reversal of warfarin anticoagulation	Blood,	Mohamed, Muhajir Bawa and Bates, Gerald and Hayes, Robert and Morse, Michael and Prakash, Ajay and Bates, Gerald and Basheer, Waheedha	wrong population
41	Reversal of warfarin and direct-acting oral anticoagulants in traumatic intracranial hemorrhage: Four factor prothrombin complex concentrates for all?	Trauma	Moore, Kerry K. and Barton, Cassie A. and Levins, Elizabeth S. and Oetken, Heath and Fleming, Michael and https://orcid.org, Id Orcid and https://orcid.org and Dewey, Elizabeth N. and Schreiber, Martin	wrong study design
42	Traumatic intracranial hemorrhage in the setting of 4-factor prothrombin complex concentrate	Neurocritical Care	Mushlin, Harry M. and Aarabi, Bizhan and Cunnion, Mary and Pajoum and , Mehrnaz and Stein, Deborah and Hines, Michele and Kufera, Joseph	wrong study design
43	Management of anticoagulation with rivaroxaban in trauma and acute care surgery: Complications and reversal strategies as compared to warfarin therapy	The journal of trauma and acute care surgery	Myers Sara, P. and Dadashzadeh Esmaeel, R. and Cheung, Jessica and Alarcon, Louis and Kutcher, Matthew and Brown Joshua, B. and Neal Matthew, D.	mixed population
44	FFP Versus PCC in Intracranial Hemorrhage	https://clinicaltrials.gov/show/NCT02429453	Nct	mixed population
45	Clinical course of intracranial bleeding in patients anticoagulated with factor XA inhibitors without the use of specific reversal agents	Clinical Neurosurgery	Nelton, Emmalin B. S. and Maragkos, Georgios and Richter, Sven and Filippidis, Aristotelis and Stippler, Martina	wrong intervention
46	Impact of Prothrombin complex concentrates on warfarin associated traumatic brain injury - A local experience	Surgical Practice	Ng, C. F. and Sham, J. K. and Mak, C. H. K. and Cheung, F. C. and Chiu, H. M.	not found
47	Andexanet alfa versus four-factor prothrombin complex concentrate (4F- PCC) for the reversal	Neurocritical Care	Nguyen, Keith and Hurley, Michael and Wdowiarz, Kathryn and Hassan, Ahmed	wrong population

	of intracranial hemorrhage (ICH) associated with rivaroxaban and apixaban : A retrospective comparative study			
48	Idarucizumab in major trauma patients: a single centre real life experience	European journal of trauma and emergency surgery : official publication of the European Trauma Society	Oberladstatter, Daniel and Voelckel, Wolfgang and Bruckbauer, Martin and Schochl, Herbert and https://orcid.org, Id Orcid and Zipperle, Johannes and Schochl, Herbert and https://orcid.org, Id Orcid and Grottke, Oliver and Ziegler, Bernhard	wrong study design
49	Comparison of the efficacy of 4-factor and 3-factor prothrombin complex concentrate for reversing warfarin in patients with intracranial hemorrhages	Neurocritical Care	Peck, Lauren H. and Tokumaru, Sheri S. and Chu, Cherie C. and Izumi, Kara K. and Nakagawa, Kazuma K.	mixed population
50	Use of vitamin K in a traumatology service	International Journal of Clinical Pharmacy	Pena, Celia Gomez and Fern and ez, Cristina Garcia and Romero, Rocio Moron and Gomez, Pelayo Nieto and Rustarazo, Susana Belda and Martinez, David Blanquez and Hidalgo, Inmaculada Casas and Corpas, Margarita Valle	wrong study design
51	Trauma victims requiring dabigatran reversal with idarucizumab in RE-VERSE AD	European Heart Journal	Pollack, C. and Van Ryn, J. and Reilly, P. and Levy, J. and Bernstein, R. and Weitz, J. L.	wrong study design
52	Health care resource utilization in patients requiring urgent surgical/ interventional management while taking dabigatran : Interim results from the reverse ad study	Journal of the American College of Cardiology	Pollack, Charles V. and Gruenenfelder, Fredrik and Levy, Jerrold H. and Reilly, Paul and Ustyugova, Anastasia and Kleine, Eva and Bernstein, Richard and Huisman, Menno and Hylek, Elaine and Sellke, Frank and Weitz, Jeffrey I.	wrong study design
53	Initial experience with idarucizumab in dabigatran -treated patients presenting with acute traumatic injuries: Interim results from the re-verse ad study	Annals of Emergency Medicine	Pollack Jr, C. V. and Gruenenfelder, F. and Eikelboom, J. and Hylek, E. and Mills, M. and Sellke, F. and Kamphuisen, P. and Reilly, P. and Kreuzer, J. and Weitz, J. I.	wrong population
54	Clinical outcome of using three-factor prothrombin complex concentrate in patients with major bleeding associated with factor XA	Research and Practice in Thrombosis and Haemostasis	Raksintham, T. and Chinthammitr, Y. and Ruchutrakool, T. and Suwannawiboon, B.	wrong study design

	inhibitor			
55	Idarucizumab, A specific reversal agent for dabigatran: mode of action, pharmacokinetics and pharmacodynamics, and safety and efficacy in phase 1 subjects	American journal of emergency medicine	Reilly, P. A. and van Ryn, J. and Grottke, O. and Glund, S. and Stangier, J.	wrong study design
56	Inactivated Four-Factor Prothrombin Complex Concentrate Dosing Practices for Reversal of Warfarin -Related Intracranial Hemorrhage	Neurocritical care	Rhoney Denise, H. and La, Mary and Merz, Molly and https://orcid.org, Id Orcid and Cook, Aaron and Owusu Kent, A. and Roels, Christina and Blunck, Joe and Shewmaker, Justin and Sangha Kiranpal, S. and Farrokh, Salia and Lewin, John and Chester Kathleen, W. and Human, Theresea and Bledsoe, Kathleen and Greene, Kristy and Levesque, Melissa and Rocker Jody, C. and Davis, Gary and Neyens, Ron and Lassiter Timothy, F. and Adriance Sarah, M.	wrong population
57	Andexanet alfa versus 4-factor pcc for reversal of intracranial hemorrhage associated with factor xa	Critical Care Medicine	Semon, Gregory and Ekeh, Akpofure and Straughn, Angela and Steel, Barbara and Hardman, Claire	mixed population
58	Idarucizumab for reversal of dabigatran anticoagulation in patients with intracranial hemorrhage: Sub analysis of re-verse AD	Neurocritical Care	Steiner, Thorsten and Reilly, Paul A. and Van Ryn, Joanne and Weitz, Jeffrey I. and Pollack, Charles V. and Bernstein, Richard A. and Steiner, Thorsten	wrong population
59	Safety of 4-factor prothrombin complex concentrate (4F- PCC) for emergent reversal of factor Xa inhibitors	Journal of intensive care	Tao, Jing and Bukanova Elena, N. and Akhtar, Shamsuddin and https://orcid.org, Id Orcid	wrong study design
60	Does usage of platelet or ddavp prevent progression of traumatic intracranial hemorrhage in patients on anti- platelet medication?	Journal of Neurotrauma	Ullman, Jamie and Chiluwal, Amrit and Wagner, Katherine and LeDoux, David and Bholat, Omar and Koutsouras, George	wrong study design
61	Off-label use of 4-factor prothrombin complex concentrate for direct oral anticoagulant reversal	Critical Care Medicine	Weaver, Cory and Rivosecchi, Ryan and Kane-Gill, S and ra and Smithburger, Pamela and Durkin, Joseph	wrong study design
62	Comparison of Low- Versus High-Dose Four-Factor Prothrombin Complex Concentrate (4F-	Journal of intensive care medicine	Wilsey, H. Andrew and https://orcid.org, Id Orcid and Bailey Abby, M. and Davis	mixed population

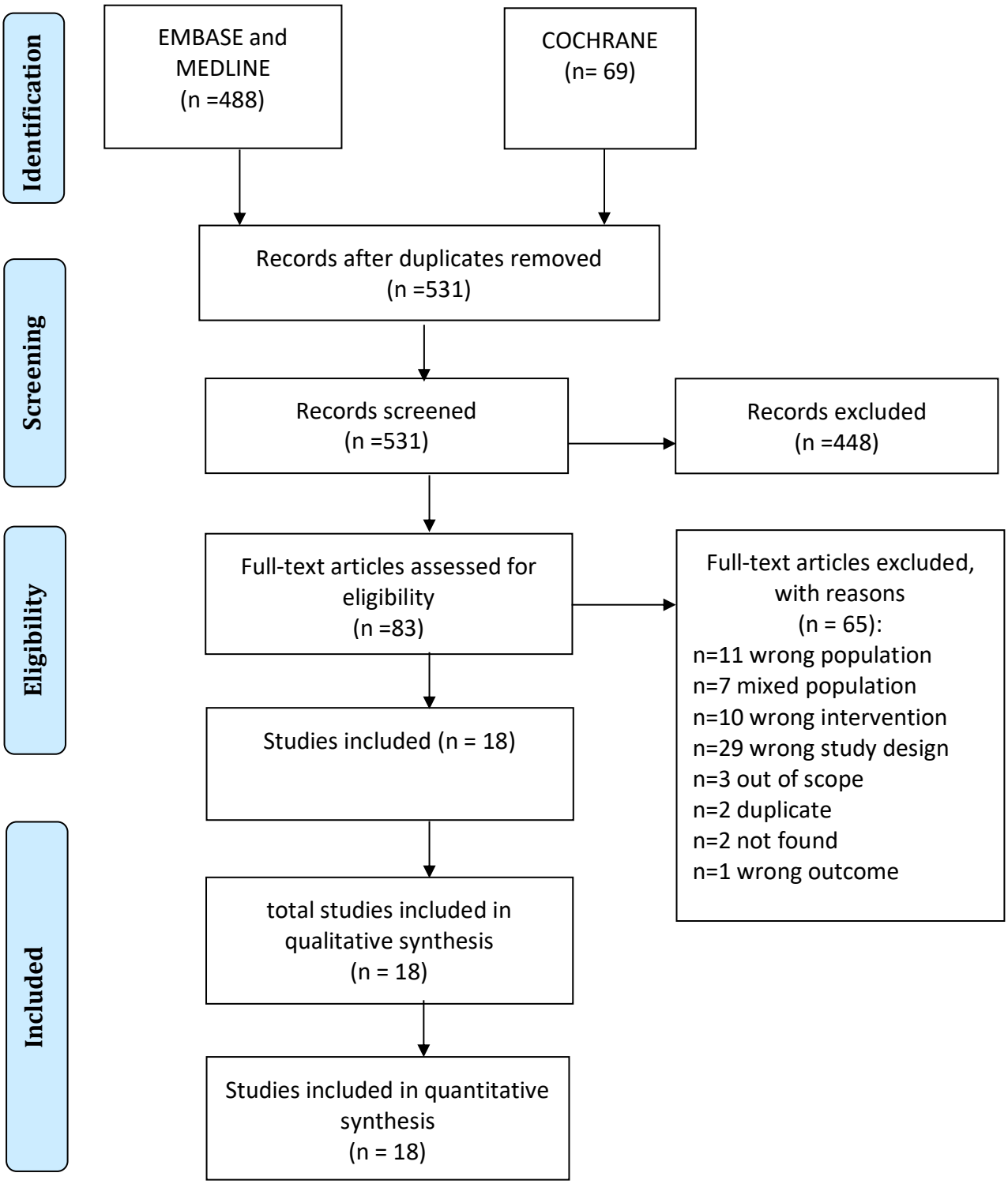
	PCC) for Factor Xa Inhibitor-Associated Bleeding: A Retrospective Study		George, A. and Nestor, Melissa and P and ya, Komal and Bailey Abby, M. and Schadler, Aric and Davis George, A. and Nestor, Melissa and P and ya, Komal and Schadler, Aric	
63	Traumatic intracranial hemorrhage and antiplatelet therapy: The efficacy of platelet transfusion	Critical Care Medicine	Wittmeyer, Richard and Poole, Christy and Cherico, Amy and Chen, Jennifer and Boyer, Br and on and Iaia, Alberto and Kolm, Paul and Cipolle, Mark	wrong outcome
64	Idarucizumab for Emergency Reversal of Anticoagulant Effects of Dabigatran : Interim Results of a Japanese Post-Marketing Surveillance Study	Cardiology and Therapy	Yasaka, Masahiro and Yokota, Hiroyuki and Suzuki, Michiyasu and Asakura, Hidesaku and Yamane, Teiichi and Ogi, Yukako and Nakayama, Daisuke and https://orcid.org, Id Orcid and Ochiai, Kaori	wrong study design
65	Evaluation of an indication-based prothrombin complex concentrates protocol for warfarin reversal	Critical Care Medicine,	Zhou, Chenshan and Blunck, Joseph	wrong study design

Appendice C – Sintesi delle evidenze

INDICE

Selezione degli studi

Figure 1. Flow Chart of study selection



Comparazioni di interesse

È stata effettuata una revisione sistematica della letteratura sulle banche dati Embase, Medline e Cochrane CENTRAL aggiornata al 15 giugno 2021. Sono stati individuati 531records da cui sono state selezionate 22 referenze che soddisfano i criteri per rispondere al quesito clinico proposto: 2 revisioni e 16 studi primari osservazionali. Inoltre, è stata interrogata la Linea guida NICE, senza aggiungere nessuna ulteriore pubblicazione.

Di seguito le comparazioni considerate negli studi inclusi:

A- Anticoagulanti versus no-reversal :

- A1. PLT vs no-reversal (2 review + 2 observational studies [1 with adjusted data and 1 without adjusted data])
- A2. PCC vs no-reversal (1 observational study with adjusted data*)
- A3. FFP vs no reversal (1 observational study with adjusted data*)
- A4. DDVAP vs no reversal (1 observational study with adjusted data)

*same study

B- Prothrombin complex concentrate (PCC) versus altro:

- B1. aPCC *versus* FFP (1 observational study without adjusted data)
- B2. aPCC+FFP + vitamin K *versus* FFP+vitamin K (1 observational study without adjusted data)
- B3. PCC *versus* FFP+vitamin K (2 observational studies of which 1 with adjusted data)*
- B4. PCC *versus* vitamin K * (1 observational study with adjusted data)

*uno studio ha 3 braccia: PCC *versus* FFP+vitamin K *versus* vitamin K

C- 4FPCC versus altro

- C1. 4FPCC versus 3FPCC+rFVIIa (1 observational study without adjusted data)
- C2. 4FPCC versus 3FPCC (2 observational studies with adjusted data)
- C3. 4FPCC versus Factor IX complex + vitamin K with or without FFP(1 observational study without adjusted data)

D- Dosi diverse 4FPCC a confronto

- D1. 4FPCC 1500 versus 4FPCC 1000 (2 observational studies of which 1 with adjusted data).

A. Anticoagulanti versus no-reversal

Gli studi identificati permettono di rispondere alle seguenti comparazioni:

- A1. PLT vs no-reversal (2 review [14 observational studies] + 2 new observational studies)
- A2. PCC vs no-reversal (1 observational study with adjusted data*) (Lumas)
- A3. FFP vs no reversal (1 observational study with adjusted data*) (Lumas)
- A4. DDVAP vs no reversal (1 observational study with adjusted data)

Di seguito le principali caratteristiche degli studi inclusi, in tabella 1a.

	Study design / adjusted or not adjusted data	**Population setting**	**Anticoagulation therapy**	**Type of reversal**	**Blunt trauma; ISS Baseline INR**
Alvikas 2020	Systematic review of observational studies (11 retrospective studies and 1 prospective observational study.)	Patients with traumatic intracranial hemorrhage (tICH) taking prehospital anticoagulation therapy	prehospital aspirin, dipyridamole, clopidogrel, ticagrelor, prasugrel, eptifibatide, or abciximab	platelet vs not platelet transfusion	any information NR
Leong 2015	Systematic review of observational studies (7 retrospective cohort studies: 4 on APA-related traumatic ICH, and on APA-related primary spontaneous IntraCranial Hemorrhage ICH)	Adult patients with APA-related traumatic or primary ICH	preinjury use of antiplatelet agents: aspirin and clopidogrel or aspirin and clopidogrel or extended release dipyridamole, aspirin, aspirin and clopidogrel, and clopidogrel or ticlopidine alone	platelet vs not platelet transfusion	About studies focussed on trauma: - Level I trauma centers (3 single-center studies and 1 conducted in two centers) - In all but one (Fortuna)of these studies, the platelet transfused and not-transfused groups were comparable in terms of baseline demographics, initial Glasgow Coma Scale (GCS) score, Injury Severity Score (ISS), mechanism of injury, and hospital LOS. -In all four studies, no mention of a protocol governing the timing and dosing of platelet transfusion.
Lokhandwala 2021	Observational study (retrospective) - adjusted data	patients on antiplatelet medications and traumatic brain injury (TBI)	Preinjury antiplatelet agent used (aspirin, clopidogrel, or both).	Group 1: PLT (n=253) Group 2: no PLT (n=90)	Group 1: Blunt: NR; ISS: 15 (11-26) INR: NR Group 2: Blunt: NR ISS: 12 (10-15)

					INR: NR
Agyabeng-dadzie 2020	Observational study (retrospective) - unadjusted data	Adult TBI patients (age ≥16 years). Patients with penetrating TBI, blunt TBI without TICH on admission CT, those receiving warfarin, those not on chronic APT, or those who required immediate operative intervention were excluded.	Antiplatelet medications: Aspirin, adenosine diphosphate [ADP] inhibitors such as clopidogrel, prasugrel, ticagrelor, and ticlopidine.	Group 1: reversal group (RV) (patients receiving immediate platelet transfusion) (n=102) Group 2: no reversal group (NR) (patients who had no platelet transfusion) (n=67)	The 2 groups were well matched with no significant differences in patient demographics or clinical characteristics (age, ISS, AIS-head, mechanism of injury, admission GCS, admission, and follow-up Marshall CT classification).
Lumas 2020	Observational study (retrospective) - adjusted data Adjusted for demographics, Admission INR, use of vitamin K, concomitant antiplatelet therapy, head Abbreviated Injury Scale (AIS) score, and Glasgow Coma Scale (GCS) score.	N=150 trauma patients with acute bleeding Baseline INR for inclusion: NR	Warfarin	Group 1: PPC (n = 60) Group 2: FFP (n=41) Group 3: no reversal (n=49)	Group 1: Blunt: NR; ISS: mean (SD) 15.8 (8.5) Group 2: Blunt: NR ISS: mean (SD) 15.2 (8.0) Group 3: Blunt: NR ISS: mean (SD) 13.6 (7.4)
Barletta 2020	Observational study (retrospective) - adjusted data Adjusted for hematoma expansion and risk factors	N=202 trauma patients with acute bleeding Baseline INR for inclusion: NR	Aspirin Group 1: 119 (75%) Group 2: 32 (73%) ADP-receptor antagonist 17 (11%) 8 (18%) Aspirin + ADP-receptor antagonist 22 (14%) 4 (9.1%) Oral anticoagulant (warfarin/apixaban) 9 (5.7%) 8 (18%)	Group 1: DDVAP (n=158) Group 2: no reversal (n=44)	Group 1: Blunt: NR; ISS: median IQR both groups 16 (11–20) Group 2: Blunt: NR ISS: median IQR both groups 16 (11–20)

In sintesi, in tabella 2a, gli outcome valutati:
Vs NO REVERSAL

Outcome	**PLT**	**PCC**	**FFP**	**DDVAP**
Mortality at 24 hours, 30days/1month, and 12 months	X	X	X	X
Health related quality of life				
Adverse effects (Stroke, MI, Thromboembolism (PA and venous) /comlications	X			X
Reversal of anti-coagulation as measured by laboratory assessment (degree of reversal (reduction of INR))		X		
Degree of resuscitation (units of blood transfused)	X			
Neurological outcome (brain injured patients)	X			X
Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing).	X	X	X	X
ICH progression	X	X	X	X
Need for neurosurgical surgey (craniotomy)	X	X	X	

A1. PLT vs NO REVERSAL

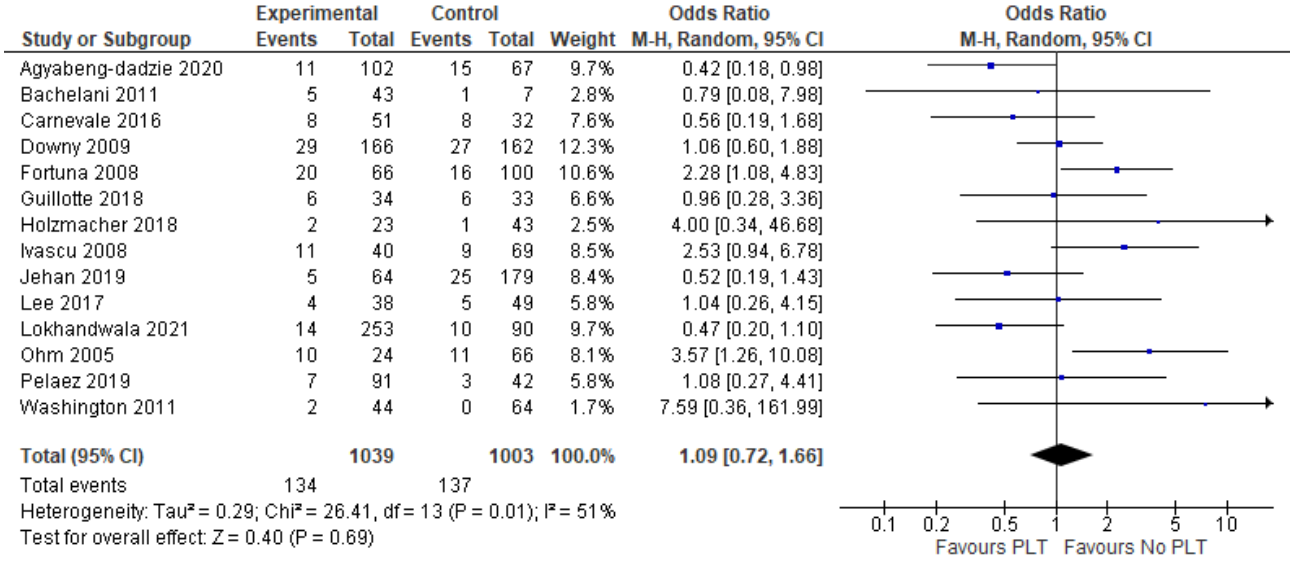
PLT vs No reversal	*Source*	*Mortality*	*Health related quality of life*	*Adverse effects (Stroke, MI, Thromboembolism (PA and venous) /comlications*	*Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing). Home/rehabilitation*	*Reversal of anti-coagulation as measured by laboratory assessment (degree of reversal (reduction of INR))*	*Degree of resuscitation (units of blood transf used)*	*Neurological outcome (brain injured patients)*	*Need for neurosurgical intervention*	*ICH progression*	*Adjustment planned*
Agyabeng-dadzie 2020	Our search	X		X					X		unadjusted
Bachelani 2011	Alvikas 2020	X							X	X	unclear/outcome not reported
Carneval e 2016	Alvikas 2020	X			X					X	yes
Downy 2009	Leong 2015	X									unclear/outcome not reported
Fortuna 2008	Leong 2015	X									unclear/outcome not reported
Guillotte 2018	Alvikas 2020	X								X	unadjusted
Holzmacher 2018	Alvikas 2020	X							X		unclear/outcome not reported
Ivascu 2008	Leong 2015	X									unadjusted
Jehan 2019	Alvikas 2020	X		X	x outcome reporitng bias			X	X	X	yes *
Lee 2017	Alvikas 2020	X					X			X	yes
Lokhandwala 2021	Our search	X							X	X	yes*
Ohm 2005	Alvikas	X									awating

	2020										assessment
Pelaez 2019	Alvikas 2020	X								X	not adjusted
Washington 2011	Leong 2015	X		X				X	X	X	awating assessment
Foreman 2019	Alvikas 2020								X		yes
Ogunlade 2018	Alvikas 2020									X	unadjusted

* not reproducible Confidence Intervals of published aOR

Mortality at 24 hours, 30days/1month, and 12 months

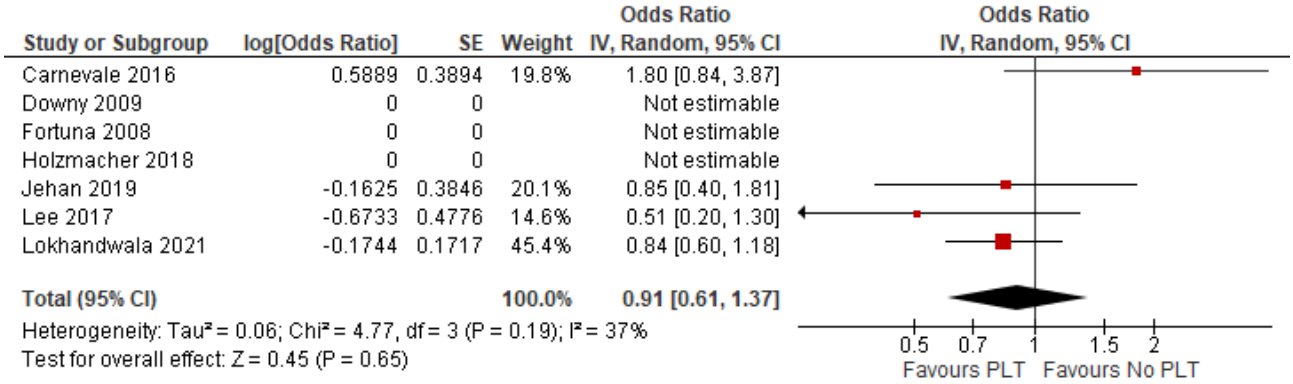
Overall Mortality NOT ADJUSTED (time not always specified): nessuna differenza statisticamente significativa fra gruppi (14 studi).



* Agyabeng-Dadzie 2020 riporta inoltre una mortalità specifica per traumatic brain injury: TBI-specific mortality (9 [9%] vs 9 [13%], P = 0.45).

° If data were not available in the primary studies we extracted them from the systematic reviews Alvikas 2020 and Leong 2015.

Overall Mortality ADJUSTED (time not always not specified): nessuna differenza statisticamente significativa fra gruppi (7 studi di cui solo 4 analizzabili).



*missing data/outcome non reporting bias: Bachelani unclear data of adjustment; aggiustato ma dato (adjusted OR) non riportato Downy 2009, Fortuna 2008, Holzmacher, Uncorrected confidence interval of adjusted OR Jehan and Lokhandwala. For judgement of outcome non reporting bias we followed: *Page MJ, Higgins JP. Rethinking the assessment of risk of bias due to selective reporting: a cross-sectional study. Syst Rev. 2016 Jul 8;5(1):108. doi: 10.1186/s13643-016-0289-2. PMID: 27392044; PMCID: PMC4938957*.

If data were not available in the primary studies we extracted them from the systematic reviews Alvikas 2020 and Leong 2015.

Health related quality of life

No outcome data

Adverse effects (Stroke, MI, Thromboembolism (PA and venous)

Tre studi indagano gli eventi avversi, ma considerato che ogni studio indaga eventi avversi differenti non è stato possibile cumulare i risultati (Agyabeng-dadzie 2020, Jenhan 2018, Washington 2011).

- Agyabeng-dadzie 2020 :"There were no differences between the reversal group versus no reversal group in **TBI-related complications**: burr hole (1 [1%] vs 2 [3%], P = 1.00), craniotomy due to TICH extension (1 [1%] vs 2 [3%], P = .56), TICH extension with no change in Marshall score (26 [26%] vs 14 [21%], P = .71), a TICH extension with increase in Marshall score by ≥1 point (9 [9%] vs 4 [6%], P = 0.77)"
- Jenhan 2018 riporta la pianificazione di **in-hospital complication** ma poi non riporta alcun dato nei risultati.
- Washington 2011 riporta il numero di **eventi cardiaci** non specificati per ogni gruppo con nessuna differenza significativa: 8/44 reversal, 8/64 no-reversal (p=0.41).

Reversal of anti-coagulation as measured by laboratory assessment (degree of reversal (reduction of INR))

No outcome data

Degree of resuscitation (units of blood transfused)

One study reported perioperative blood product transfusion volume of packed red blood cells (PRBCs), fresh frozen plasma (FFP), platelets, and cryoprecipitate (Lee 2017) only in the aspirin group.

Table 3. Aspirin Group: Comparison of Patients Who Received Preoperative or Intraoperative Platelet Transfusion (Platelets) to Patients Who Did Not (No Platelets)

Outcome	Platelets n = 38	No Platelets n = 49	Unadjusted OR	95% CI	P Value	Adjusted[a] OR	95% CI	P Value
Estimated blood loss >500 mL, n (%)	3 (7.9%)	1 (2.0%)	3.19	0.50–33.95	.224	2.34	0.33–25.45	.394
Postoperative intracranial hemorrhage[b] or in-hospital death, n (%)	7 (18.4%)	8 (16.3%)	1.16	0.38–3.47	.786	1.06	0.34–3.18	.918
Hospital length of stay (days > 15 or died), n (%)	12 (31.6%)	9 (18.4%)	2.01	0.76–5.48	.158	1.78	0.66–4.88	.251
ICU length of stay (days >5 or died), n (%)	10 (26.3%)	7 (14.3%)	2.09	0.74–6.18	.166	1.82	0.60–5.72	.283
In-hospital mortality, n (%)	4 (10.5%)	5 (10.2%)	1.06	0.27–4.01	.936	0.78	0.17–3.23	.732
Intra-/Postoperative[c] transfusion								
Packed red blood cells (received >350 mL), n (%)	7 (18.4)	3 (6.1%)	3.16	0.87–13.87	.082	2.81	0.60–16.31	.192
Fresh frozen plasma (any transfused), n (%)	7 (18.4%)	2 (4.1%)	4.52	1.12–25.46	.034	3.91	0.86–24.65	.078
Postoperative platelets[d] (any transfused), n (%)	3 (7.9%)	2 (4.1%)	1.87	0.35–11.77	.460	1.65	0.30–10.52	.563
Cryoprecipitate (any transfused), n (%)	0 (0%)	2 (4.1%)	0.25	0.00–3.15	.309	0.20	0.00–2.52	.231

Abbreviations: CI, confidence interval; GCS, Glasgow Coma Scale; ICU, intensive care unit; OR, odds ratio.
[a]OR <1.0 favors platelet transfusion; adjusted for differences in GCS score and incidence of coronary artery disease history.
[b]Postoperative intracranial hemorrhage defined as any intracranial bleeding after initial emergency neurosurgery and during same hospitalization that required repeat neurosurgical procedure.
[c]Intra-/postoperative transfusion defined as volume in mL of blood product given from surgery start time to as much as 48 hours after surgery end time (shorter if death or discharge occurred earlier after surgery end time).
[d]For platelets, only postoperative transfusion was considered as an outcome, because presence of either preoperative or intraoperative platelet transfusion was taken as the nondependent predictor in the secondary analysis.

Neurological outcome (brain injured patients)

Due studi non cumulabili (per diversa modalità di misurazione) studiano questo outcome (Jehan 2019, Washington 2011). Uno studio (Jehan 2019) riporta questo outcome come mediana del punteggio della scala di Glasgow (Jehan 2019) nei due gruppi "reversal" e "non reversal": differenze non statisticamente significative nei dati non aggiustati per gli outcome Discharge Glasgow Coma Scale (GCS), Discharge Glasgow outcome scale-extended (GOE-E).
*Median [IQR]

Table 3 — Outcomes.

Characteristics	No-PLT ($n = 179$)	PLT transfusion ($n = 64$)	P-value
In-hospital outcomes			
Progression of ICH	64% (115)	23% (15)	<0.01
Neurosurgical intervention	18% (32)	5% (3)	0.01
Hospital LOS	4 [1-2]	4 [1-2]	1.00
ICU LOS	1 [1-2]	1 [1-2]	1.00
Ventilator days	1 [0-1]	1 [0-1]	1.00
Discharge outcomes			
Discharge GCS	15 [14-15]	15 [14-15]	1.00
Discharge GOS-E	7 [7-8]	7 [7-8]	1.00
Discharge to SNiF	12% (21)	4% (3)	0.14
Mortality	14%(25)	8% (5)	0.26

LOS = Length of stay.

Lo studio di Washington 2011 mostra l'outcome categorizzato per punteggio della scala di GSC: nessuna differenza significativa fra i gruppi "reversal" e "no-reversal" per ogni singolo punteggio (p=0.16):

TABLE 4. Outcome Results Comparing Platelet Transfused and Nontransfused MTBI Patients Taking Antiplatelet Agents

	Platelet Transfusion		
	Mean ± SD or No. Patients (%)		
Antiplatelet Outcomes	Yes (N = 44)	No (N = 64)	*p*
Neurological decline	0	2 (3)	0.51*
Surgical intervention	2 (5)	0	0.16*
Medical decline	6 (14)	2 (3)	0.06*
Cardiac event	8 (18)	8 (12)	0.41*
Respiratory event	4 (9)	2 (3)	0.22*
Glasgow outcome			0.16†
1	2 (5)	0	
3	5 (11)	3 (5)	
4	7 (16)	11 (17)	
5	30 (68)	50 (78)	
HCT progression	5/41 (12)	4/58 (7)	0.48*

* *p* value by Fisher exact test.
† *p* value by Wilcoxon's test.

Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing).

Due studi riportano questo outcome (Jehan 2019, Carnevale 2018).
Jehan 2019: differenze non statisticamente significative nei dati non aggiustati per al discharge to skilled nursing facility (SNiF) mentre nell'analisi multivariata i dati al discharge to SNiF risultano staticamente significativi (p=0.02).

Table 3 – Outcomes.

Characteristics	No-PLT (*n* = 179)	PLT transfusion (*n* = 64)	*P*-value
In-hospital outcomes			
Progression of ICH	64% (115)	23% (15)	<0.01
Neurosurgical intervention	18% (32)	5% (3)	0.01
Hospital LOS	4 [1-2]	4 [1-2]	1.00
ICU LOS	1 [1-2]	1 [1-2]	1.00
Ventilator days	1 [0-1]	1 [0-1]	1.00
Discharge outcomes			
Discharge GCS	15 [14-15]	15 [14-15]	1.00
Discharge GOS-E	7 [7-8]	7 [7-8]	1.00
Discharge to SNiF	12% (21)	4% (3)	0.14
Mortality	14%(25)	8% (5)	0.26

LOS = Length of stay.

Table 4 – Multivariate regression analysis for outcomes.

Platelet transfusion	OR	95% Confidence interval	*P*-value
Progression of ICH	0.68	0.4-0.8	0.01
Neurosurgical intervention	0.80	0.3-0.9	0.03
Discharge to SNiF	0.75	0.5-0.8	0.02
Mortality	0.85	0.4-0.9	0.04

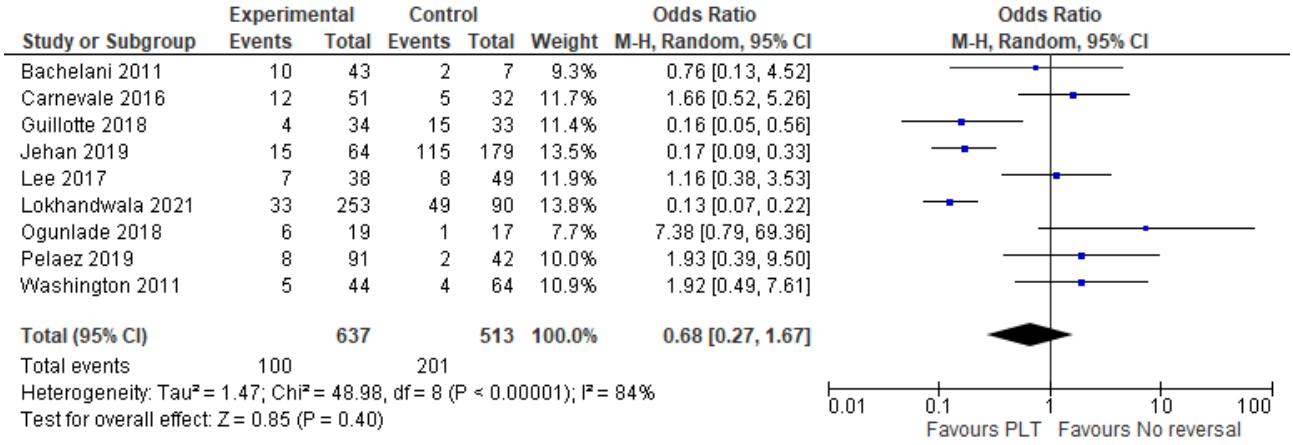
Reference: No platelet transfusion.

Carnevale 2018: "a non significant commensurate trend was observed between BAL and HPC (p = 0.0587). There were significant differences regarding age (p = 0.02), ISS (p = 0.004), NISS (p = 0.02), GCS score (p = 0.009), absolute platelet count (p = 0.023), presence of SDH (p =

0.05), and patient disposition, including discharge to home (p = 0.01) and discharge to hospice/death (p < 0.001). Looking closer at patient outcome, the group that was discharged home had a significantly lower proportion of patients who experienced HPC, while the group that was discharged to hospice or died had a significantly higher proportion of patients with HPC".

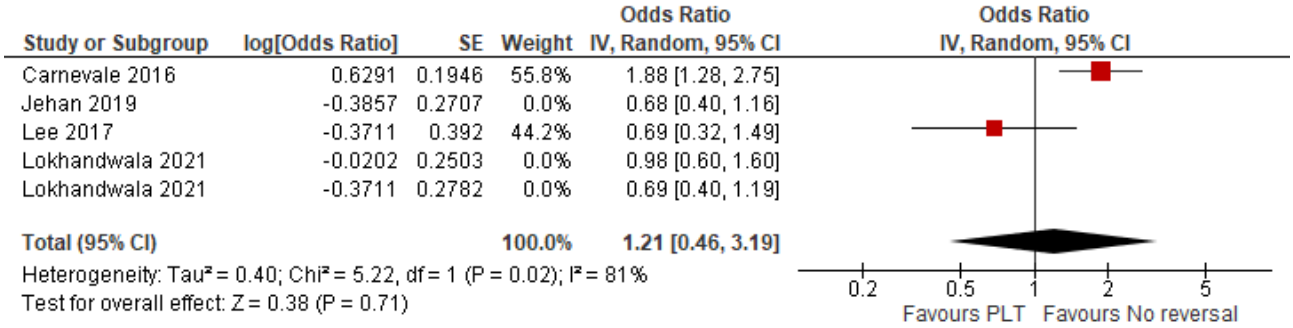
ICH progression

ICH progression NOT ADJUSTED: nessuna differenza statisticamente significativa fra gruppi.



If data were not available in the primary studies we extracted them from the systematic reviews Alvikas 2020 and Leong 2015.

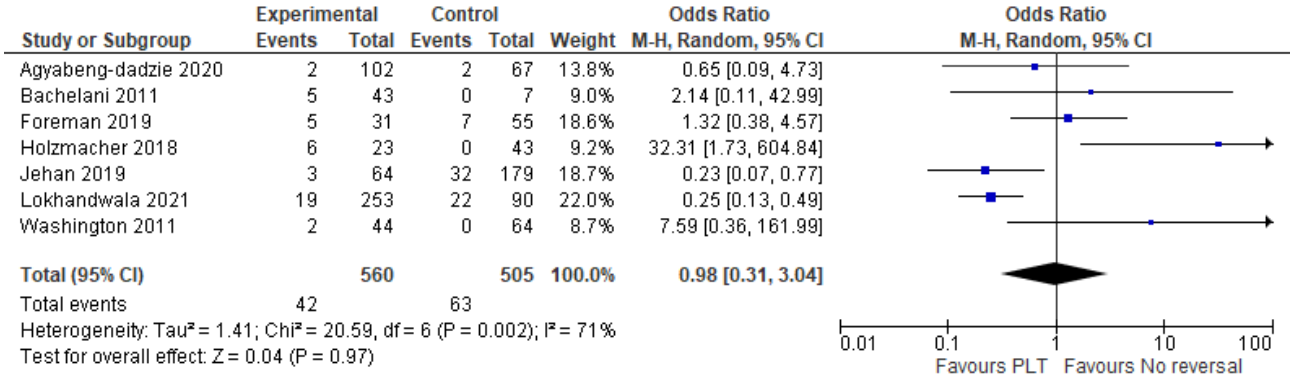
ICH progression ADJUSTED (time not always not specified): nessuna differenza statisticamente significativa a fra i gruppi.
In totale 4 studi riportano dati aggiustati sull'outcome di interesse, tuttavia 2 studi hanno aOR non riproducibili (uncorrected confidence intervals of adjusted OR in Jehan 2019 and Lokhandwala 2021 both 1 pack and two packs groups). Pertanto abbiamo evitato di riportare gli aOR non corretti, mostrando una metanalisi di 2 studi.



If data were not available in the primary studies we extracted them from the systematic reviews Alvikas 2020 and Leong 2015.

Need for neurosurgical surgery (craniotomy)

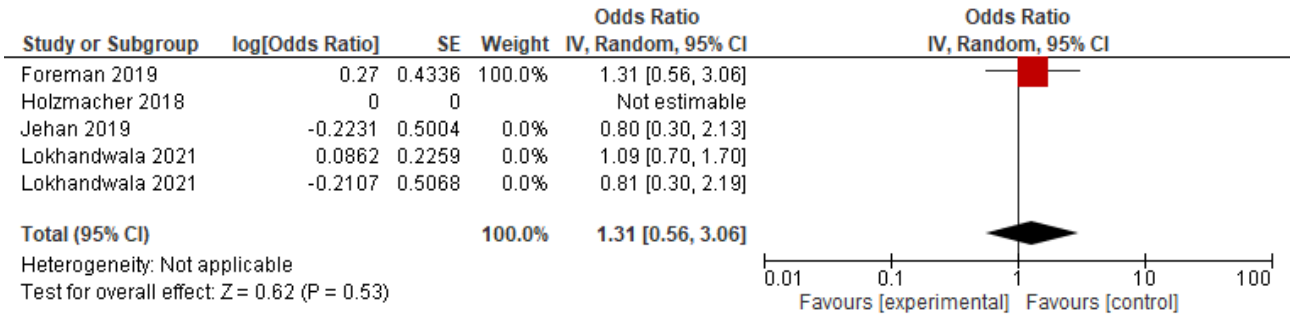
Need for neurosurgical surgery NOT ADJUSTED (time not always not specified): nessuna differenza statisticamente significativa fra gruppi.



If data were not available in the primary studies we extracted them from the systematic reviews Alvikas 2020 and Leong 2015.

Need for neurosurgical surgery ADJUSTED (time not always not specified): nessuna differenza statisticamente significativa fra gruppi. Abbiamo evitato di riportare aOR irriproducibili (Uncorrected confidence interval of adjusted OR Jehan and Lokhandwala).

4 studi riportano dati aggiustati sull'outocme di interesse, tuttavia 2 studi hanno aOR non riproducibili. Pertanto abbiamo evitato di riportare aOR non corretti (uncorrected confidence intervals of adjusted OR in Jehan 2019 and Lokhandwala 2021 both 1 pack and two packs groups). Inoltre uno studio (Holzmacher 2018) dichiara che aggiusta i dati con una regressione univariata ma non riporta i dati. Abbiamo riportato la rappresentazione grafica dell'unico studio che concorre alla metanalisi.



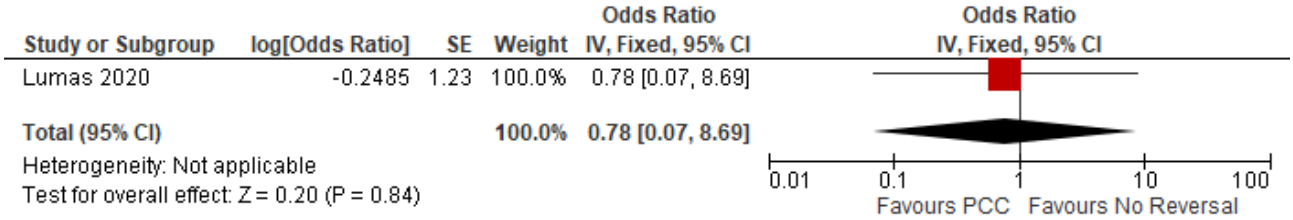
If data were not available in the primary studies we extracted them from the systematic reviews Alvikas 2020 and Leong 2015.

A2. PCC vs no-reversal

Un solo studio Lumas 2020 riporta dati sulla comparazione di interesse.

Mortality at 24 hours, 30days/1month, and 12 months

	Mortality						
	PCC		No reversal		Time point	Data adjusted	OR
	n(%)	tot	n(%)	tot			
Lumas 2020	2 (3.3)	60	2(4.1)	49	In hospital	Yes. Adjusted for demographics, admission INR, use of vitamin K, concomitant antiplatelet therapy, head Abbreviated Injury Scale (AIS) score, and Glasgow Coma Scale (GCS) score.	OR 0.78, 95% CI [0.07-8.96])



L'uso di PCC come reversal non riduce significativamente la mortalità intra-ospedaliera comparato al non uso di reversal in soggetti traumatizzati in trattamento con warfarin.

Health related quality of life

No outcome data

Adverse effects (Stroke, MI, Thromboembolism (PA and venous)

No outcome data

Reversal of anti-coagulation as measured by laboratory assessment (degree of reversal (reduction of INR))

	Time to INR <1.7 (h, median, IQR)					
	PCC		No reversal		Time point	Data adjusted
	Median	IQR	Median	IQR		
Lumas 2020	10.5	6 – 17.5	NA	NA		No

Degree of resuscitation (units of blood transfused)

No outcome data

Neurological outcome (brain injured patients)

No outcome data

Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing).

	Worsening of mental status						
	PCC		**No reversal**		**Time point**	**Data adjusted**	**OR**
	n(%)	**tot**	**n(%)**	**tot**			
Lumas 2020	18(30)	60	11(22.4)	49	Not specified	No	OR 1.48 (0.62 a 3.53)

L'uso di PCC come reversal sembra presentare percentuali lievemente superiore nel numero di soggetti con peggioramento dello stato mentale comparato al non uso di reversal in soggetti traumatizzati in trattamento con warfarin.

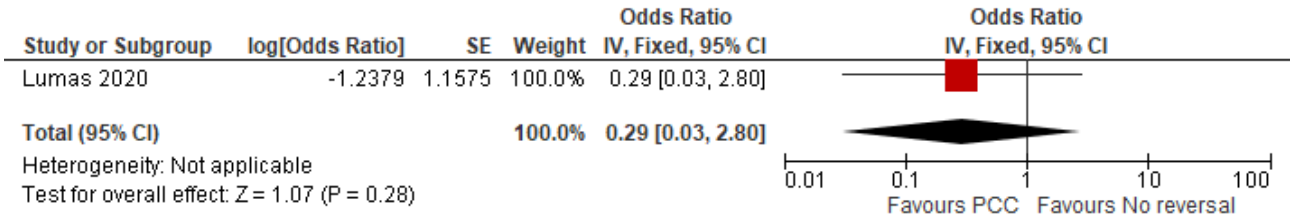
ICH progression

	ICH progression						
	PCC		**No reversal**		**Time point**	**Data adjusted**	**OR**
	n(%)	**tot**	**n(%)**	**tot**			
Lumas 2020	26(43.3)	60	10(20.4)	49	Not specified	No	OR 1.48 (1.26 a 7.06)

L'uso di PCC come reversal sembra presentare percentuali superiori di soggetti con progressione di emorragia intracranica comparato al non uso di reversal in soggetti traumatizzati in trattamento con warfarin.

Need for neurosurgical surgery (craniotomy)

	Need for craniotomy						
	PCC		**No reversal**		**Time point**	**Data adjusted**	**OR**
	n(%)	**tot**	**n(%)**	**tot**			
Lumas 2020	9(15)	60	3(6.1)	49	Not specified	Yes. Adjusted for demographics, admission INR, use of vitamin K, concomitant antiplatelet therapy, head Abbreviated Injury Scale (AIS) score, and Glasgow Coma Scale (GCS) score.	(OR 0.29, 95% CI [0.03-2.56])



L'uso di PCC come reversal non riduce in modo statisticamente significativo la necessità di craniotomia comparato al non uso di reversal in soggetti traumatizzati in trattamento con warfarin.

A3. FFP vs no reversal

Un solo studio Lumas 2020 riporta dati sulla comparazione di interesse.

Mortality at 24 hours, 30days/1month, and 12 months

	Mortality						
	FFP		**No reversal**		**Time point**	**Data adjusted**	**OR**
	n(%)	**tot**	**n(%)**	**tot**			
Lumas 2020	0 (0)	41	2(4.1)	49	In hospital	Yes. Adjusted for demographics, admission INR, use of vitamin K, concomitant antiplatelet therapy, head Abbreviated Injury Scale (AIS) score, and Glasgow Coma Scale (GCS) score.	OR 0.29 (0.01 a 4.91)

L'uso di FFP come reversal non modifica? significativamente la mortalità intra-ospedaliera comparato al non uso di reversal in soggetti traumatizzati in trattamento con warfarin.

Health related quality of life

No outcome data

Adverse effects (Stroke, MI, Thromboembolism (PA and venous)

No outcome data

Reversal of anti-coagulation as measured by laboratory assessment (degree of reversal (reduction of INR))

No outcome data

Degree of resuscitation (units of blood transfused)

No outcome data

Neurological outcome (brain injured patients)

No outcome data

Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing).

	Worsening of mental status						
	FFP		**No reversal**		**Time point**	**Data adjusted**	**OR**
	n(%)	**tot**	**n(%)**	**tot**			
Lumas 2020	13(31.7)	41	11(22.4)	49	Not specified	No	OR 1.60 (0.63 a 4.10)

L'uso di FFP come reversal sembra presentare percentuali lievemente superiore nel numero di soggetti con peggioramento dello stato mentale comparato al non uso di reversal in soggetti traumatizzati in trattamento con warfarin.

ICH progression

	ICH progression						
	FFP		**No reversal**		**Time point**	**Data adjusted**	**OR**
	n(%)	**tot**	**n(%)**	**tot**			
Lumas 2020	21(51.2)	41	10(20.4)	49	Not specified	No	OR 4.09 (1.62 a 10.34)

L'uso di FFP come reversal sembra presentare percentuali superiori di soggetti con progressione di emorragia intracranica comparato al non uso di reversal in soggetti traumatizzati in trattamento con warfarin.

Need for neurosurgical surgery (craniotomy)

	Need for craniotomy						
	FFP		**No reversal**		**Time point**	**Data adjusted**	**OR**
	n(%)	**tot**	**n(%)**	**tot**			
Lumas 2020	8(19.5)	41	3(6.1)	49	Not specified	Yes. Adjusted for demographics, admission INR, use of vitamin K, concomitant antiplatelet therapy, head Abbreviated Injury Scale (AIS) score, and Glasgow Coma Scale (GCS) score.	OR 3.72 (0.92 a 15.08) (not adjusted)

L'uso di FFP come reversal non riduce in modo statisticamente significativo la necessità di craniotomia comparato al non uso di reversal in soggetti traumatizzati in trattamento con warfarin.

A4. DDVAP vs no reversal

Un solo studio, Barletta 2020, riporta la comparazione di interesse.

Mortality at 24 hours, 30days/1month, and 12 months

	Mortality						
	DDVAP		**NO reversal**		**P value**	**Time point**	**OR**
	N(%)	**tot**	**n**	**tot**			
Barletta 2020	5(3.2)	158	4(9.1%)	44	0.106	Not specified	OR 0.33 (0.08 a 1.27)

Non si presentano differenze statisticamente significative nella riduzione di mortalità tra soggetti traumatizzati in terapia anticoagulante che ricevono DDVAP come reversal e chi invece non riceve reversal.

Health related quality of life

No outcome data

Adverse effects (Stroke, MI, Thromboembolism (PA and venous)

	Thrombosis						
	DDVAP		**NO reversal**		**P value**	**Time point**	**OR**
	N(%)	**tot**	**n**	**tot**			
Barletta 2020	4(2.5%)	158	2(4.5%)	44	0.613	Not specified	OR 0.55 (0.10 a 3.08)
Venous	2		2				
Arterial	2						

Non si presentano differenze statisticamente significative nella presenza di complicazione (ie. Trmbosi) tra soggetti traumatizzati in terapia anticoagulante che ricevono DDVAP come reversal e chi invece non riceve reversal.

Reversal of anti-coagulation as measured by laboratory assessment (degree of reversal (reduction of INR))

No outcome data

Degree of resuscitation (units of blood transfused)

No outcome data

Neurological outcome (brain injured patients)

	Glascow Coma Scale at discarge					
	DDVAP		NO reversal		P value	Time point
	Median (IQR)	tot	Median(IQR)	tot		
Barletta 2020	15 (14 - 15)	158	15 (14 – 15)	44	0.106	Discharge

Non si presentano differenze statisticamente significative nella Glascow Coma Scale alla dimissione tra soggetti traumatizzati in terapia anticoagulante che ricevono DDVAP come reversal e chi invece non riceve reversal.

Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing).

	Home or rehabiltiation						
	DDVAP		NO reversal		P value	Time point	OR
	N(%)	tot	N(%)	tot			
Barletta 2020	96(61%)	158	30 (68%)	44	0.369	Home/rehabilitation after hospitalization	OR 0.72 (0.36 a 1.47

Non si presentano differenze statisticamente significative nel numero di soggetti che alla dimissione ritorna a domicilio o si trasferisce in riabilitazione tra coloro che ricevono DDVAP come reversal e chi invece non riceve reversal.

ICH progression

Table 5 Hematoma expansion—multivariate analysis

Model	Variables	OR (95% CI)	*p* value
Final	Age	1.046 (1.008–1.086)	0.019
	DDAVP	0.259 (0.103–0.646)	0.004
	High-dose aspirin	2.869 (1.094–7.524)	0.032
	Multi-compartmental injury	2.774 (1.209–6.367)	0.016
	Platelet transfusion	1.854 (0.822–4.178)	0.137
	Oral anticoagulant	1.922 (0.541–6.831)	0.313

ADP adenosine diphosphate, *DDAVP* desmopressin, *ISS* injury severity score

Adjustment for: age, ISS, DDAVP administration, pre-injury high-dose aspirin (> 81 mg), pre-injury adenosine diphosphate (ADP)-receptor antagonist (i.e., clopidogrel), pre-injury oral anticoagulant, multi-compartmental head injury (> 1 head injury classification), PCC administration and platelet transfusion.

Need for neurosurgical surgery (craniotomy)

No outcome data

B. Prothrombin complex concentrate (PCC) versus altro

Gli studi identificati permettono di rispondere alle seguenti comparazioni:

- B1. aPCC vs (FFP + vitamin K) (2 studies without adjusted data)
- B2. (aPCC + Vitamin K + FFP) versus (FFP + Vitamin K) (1 study without adjusted data)
- B3: (PCC + vitamin k) versus Vitamin K (1 study without adjusted data)
- B4: PCC vs FFP (1 study with adjusted data)

Di seguito le principali caratteristiche degli studi inclusi, in tabella 1b.

	Study design / adjusted or not adjusted data	**Population setting**	**Anticoagulation therapy**	**Type of reversal**	**Blunt trauma; ISS Baseline INR**
Lumas 2020	Observational study (retrospective) - adjusted data adjusted for demographics, Admission INR, use of vitamin K, concomitant antiplatelet therapy, head Abbreviated Injury Scale (AIS) score, and Glasgow Coma Scale (GCS) score.	N=150 trauma patients with acute bleeding Baseline INR for inclusion: NR	Warfarin	Group 1: PPC (n = 60) Group 2: FFP (n=41) Group 3: no reversal (n=49)	Group 1: Blunt: NR; ISS: mean (SD) 15.8 (8.5) Group 2: Blunt: NR ISS: mean (SD) 15.2 (8.0) Group 3: Blunt: NR ISS: mean (SD) 13.6 (7.4)
Carothers 2018	Observational study (retrospective) - unadjusted data	N=120 trauma patients with acute bleeding Baseline INR for inclusion: ≥ 1.5	Warfarin	Group 1: FFP + vitamin K (n = 89) Group 2: aPCC (n=31)	Group 1: Blunt: NR; ISS: median (IQR) 10 (9-16) Group 2: Blunt: NR ISS: median (IQR) 17 (9-24.5)
Hobbs 2016	Observational study (retrospective) - unadjusted data	N=120 trauma patients with acute bleeding Baseline INR for inclusion: ≥ 1.5	Warfarin	Group 1: FFP + VitaminK (n = 89) Group 2: VitaminK + FFP + aPCC (n=31)	Group 1: Blunt: NR ISS: NR Group 2: Blunt: NR ISS: NR
Huang 2019	Observational study (retrospective) - unadjusted data	N=77 trauma patients with acute bleeding (2 patients received both interventions)	Warfarin	Group 1: VitaminK + FFP (n = 68) Group 2: PCC (n=7)	Group 1: Blunt: NR ISS: mean between groups 16.53 Group 2: Blunt: NR

		Baseline INR for inclusion: ≥ 1.4			ISS: mean between groups 16.53
Koyama 2021	Observational study (retrospective) - adjusted data Univariate regression adjusted for: not specified	N=20 trauma patients with acute bleeding Baseline INR for inclusion: NR	Warfarin	Group 1: PCC + vitamin k (n = 7) Group 2: Vitamin K (n=13)	Group 1: Blunt: NR ISS: NR Group 2: Blunt: NR ISS: NR

In sintesi, in tabella 2b, gli outcome valutati:

Outcome	aPCC vs (FFP + vitamin K)	(aPCC+FFP + vitamin K) versus (FFP+vitamin K)	(PCC + vitamin K) versus vitamin K	PCC vs FFP
Mortality at 24 hours, 30days/1month, and 12 months	X	X		X
Health related quality of life				
Adverse effects (Stroke, MI, Thromboembolism (PA and venous)	X		X	
Reversal of anti-coagulation as measured by laboratory assessment (degree of reversal (reduction of INR))	X	X		X
Degree of resuscitation (units of blood transfused)	X			
Neurological outcome (brain injured patients)				
Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing).	X			X
ICH progression			X	X
Need for neurosurgical surgey (craniotomy)	X	X		X

B1. aPCC vs (FFP + vitamin K)

Due studi osservazionali, Carothers 2018 e Huang 2019 (abstract con dati) riportano la comparazione di interesse.

Mortality at 24 hours, 30days/1month, and 12 months

Un solo studio riporta dati di mortalità, Carothers 2018.

	Mortality							
	aPCC		**FFP + vitamin K**		**Time point**	**Data adjusted**	**P value**	**OR**
	n(%)	**tot**	**n(%)**	**tot**				
Carothers 2018	11 (35.5)	31	20 (22.5)	89	In hospital	No	0.162	OR 1.90 (0.78 a 4.61)

Non ci sono differenze statisticamente significative nella riduzione di mortalità tra il gruppo aPCC e il controllo (FFP+ Vitamin K)

Health related quality of life

No outcome data.

Adverse effects (Stroke, MI, Thromboembolism (PA and venous)

Un solo studio riporta dati di eventi avversi, Carothers 2018: "in regard to the safety outcome evaluated, there were no incidences of thrombosis in either group"

Table 2 – Primary and secondary outcomes.

Variables	Control ($n = 89$)	aPCC ($n = 31$)	P-value
Thrombosis, *n* (%)	0 (0)	0 (0)	1

Reversal of anti-coagulation as measured by laboratory assessment (degree of reversal (reduction of INR))

Due studi riportano l'outcome di interesse, con dati non aggiustati.
Cartohers 2018: in tabella sono riportate le 3 misurazioni del grado di reversal

Table 2 – Primary and secondary outcomes.

Variables	Control ($n = 89$)	aPCC ($n = 31$)	P-value
Achieved INR $\leq$ 1.4, *n* (%)	62 (69.7)	28 (90.3)	0.029
Postintervention INR, mean $\pm$ SD	1.36 $\pm$ 0.3	1.20 $\pm$ 0.2	<0.001
Time to INR $\leq$ 1.4* (h), median (IQR)	6.75 (4.75-13.5)	3.75 (2-10)	0.003

Carothers 2018 riporta differenze statisticamente significative in termini di soggetti che raggiungono INR ≤1.4, valori medi di INR al post intervention e tempo (ore) al raggiungimento di INR ≤1.4 a favore del gruppo con aPCC comparato al controllo FFP+Vitamin K.

Huang 2019: riporta come misura di reversal

- Tempo (giorni) alla correzione della coagulopatia: "PCC corrected coagulopathy faster than FFP (0.21 vs 1.03 days, p<.002)"
- valori INR post trattamento: "The INR values after reversal were PCC=1.357, FFP=1.362 (p=.935)."

Degree of resuscitation (units of blood transfused)

Un solo studio riporta dati dell'outcome di interesse, Carothers 2018.

Table 2 – Primary and secondary outcomes.

Variables	Control (*n* = 89)	aPCC (*n* = 31)	P-value
Received FFP, *n* (%)	85 (95.5)	16 (51.6)	<0.001
FFP, units, median (IQR)	4 (2.5-6)	1 (0-2)	<0.001
aPCC dose, median (IQR)	-	906 (811-1000)	-
Received vitamin K, *n* (%)	54 (70.7)	22 (71)	0.388
Vitamin K dose, median (IQR)	5 (0-10)	10 (0-10)	0.550

Ci sono differenze statisticamente significative in termini di FFP (numero di soggetti e numero mediano di unità ricevute) tra chi riceve aPCC e il controllo (FFP+vitaminK).

Neurological outcome (brain injured patients)

No outcome data

Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing).

Un solo studio, Carothers 2018, riporta dati in merito alla destinazione dopo la dimissione.

Table 2 – Primary and secondary outcomes.

Variables	Control (*n* = 89)	aPCC (*n* = 31)	P-value
Discharge disposition, *n* (%)			
Home	11 (12.4)	8 (25.8)	0.091
Home with home health	7 (7.9)	1 (3.2)	0.678
Skilled nursing facility	18 (20.2)	4 (12.9)	0.431
Rehab/long-term care	14 (15.7)	3 (9.7)	0.555
Acute-care hospital	12 (13.5)	2 (6.5)	0.516
Hospice	7 (7.9)	2 (6.5)	1
Death	20 (22.5)	11 (35.5)	0.162

Non si evidenziano differenze statisticamente significative in merito alla destinazione dopo dimissione (riabilitazione/domicilio/hospice.) tra chi riceve aPCC e il controllo (FFP+Vitamink).

ICH progression

No outcome data

Need for neurosurgical surgey (craniotomy)

Un solo studio, Carothers 2018, riporta dati in merito alla necessità di intervento di neurochirurgia.

Table 3 – Neurosurgical intervention.

Variables	Control ($n = 89$)	aPCC ($n = 31$)	P-value
Required neurosurgical intervention, *n* (%)	19 (21.3)	7 (22.6)	1
Time to neurosurgical intervention (h), median (IQR)	7.3 (4.7-14.8)	4.9 (1.3-5.7)	0.069
Neurosurgical procedure (%)	($n = 19$)	($n = 7$)	
Craniotomy/ craniectomy	16 (84.2)	4 (57.1)	0.293
EVD placement	0 (0)	2 (28.6)	0.065
ICP bolt	2 (10.5)	1 (14.3)	1
Bur hole	1 (5.2)	0 (0)	1

EVD = external ventricular drain; ICP = intracranial pressure; IQR = interquartile range.

Non si evincono differenze statisticamente significative tra chi riceve aPCC e il controllo (FFP+VitaminK).

B2. (aPCC + Vitamin K + FFP) versus (FFP + Vitamin K)

Un solo studio, Hobbs 2016, riporta la comparazione di interesse (abstract con dati).

Mortality at 24 hours, 30days/1month, and 12 months

"There were no significant differences in clinical outcomes including mortality (35.5% aPCC vs. 22.2% SOC, p= 0.162) between the two groups."

Health related quality of life

No outcome data

Adverse effects (Stroke, MI, Thromboembolism (PA and venous)

No outcome data

Reversal of anti-coagulation as measured by laboratory assessment (degree of reversal (reduction of INR))

"For the primary outcome, significantly more patients in the aPCC group achieved an INR ≤1.4 compared to the SOC group (90% vs. 70%, p= 0.029). The median time to reversal of anticoagulation was also significantly shorter in the aPCC group vs. SOC (3.75 hours vs. 6.75 hours, p= 0.003)."

Degree of resuscitation (units of blood transfused)

No outcome data

Neurological outcome (brain injured patients)

No outcome data

Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing).

No outcome data

ICH progression

No outcome data

Need for neurosurgical surgey (craniotomy)

"patients requiring neurosurgical intervention, median time to intervention was significantly shorter in the aPCC group (2 hours vs 7.25 hours, p=0.038)."

B3. PCC + vitamin k versus Vitamin K

Un solo studio, Koyama 2021, riporta la comparazione di interesse.

Mortality at 24 hours, 30days/1month, and 12 months

No outcome data.

Health related quality of life

No outcome data.

Adverse effects (Stroke, MI, Thromboembolism (PA and venous)

L'autore riporta che nessun paziente nei gruppi PCC+Vitamin K e Vitamin K ha presentato complicazioni trombotiche.

Reversal of anti-coagulation as measured by laboratory assessment (degree of reversal (reduction of INR))

No outcome data.

Degree of resuscitation (units of blood transfused)

No outcome data.

Neurological outcome (brain injured patients)

No outcome data.

Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing).

No outcome data.

ICH progression

L'autore riporta in un abstract/conference proceedings con dati, che: "PHI predictors were evaluated using univariate regression analyses. Warfarin reversal using PCC had a significant negative association with PHI (odds ratio: 0.03, 95%confidence interval: 0.00–0.41, P = 0.004)."
Perciò, l'uso di PCC+ vitamin K non aumenta in modo statisticamente significativo la progressione di emorragia intracranica rispetto al gruppo con vitamin K.

Need for neurosurgical surgery (craniotomy)

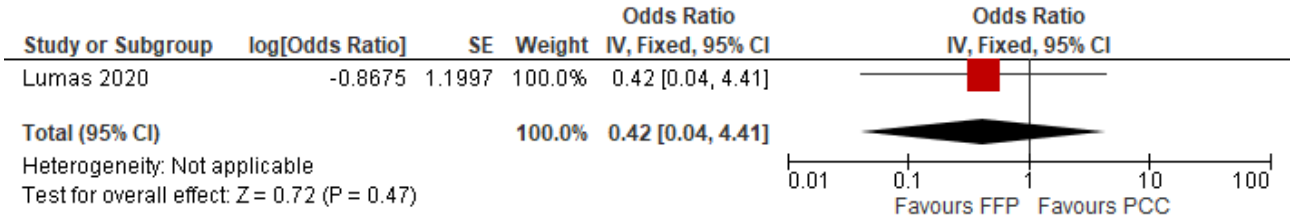
No outcome data.

B4. PCC vs FFP

Un solo studio, Lumas 2020, riporta la comparazione di interesse. In tutti e tre i bracci di intervento veniva somministrata la Vitamina K nella maggior parte dei soggetti.

Mortality at 24 hours, 30days/1month, and 12 months

	Mortality						
	PCC		**FFP**		**Time point**	**Data adjusted**	**OR**
	n(%)	**tot**	**n(%)**	**tot**			
Lumas 2020	2 (3.3)	60	0(0)	41	In hospital	Yes. Adjusted for demographics, admission INR, use of vitamin K, concomitant antiplatelet therapy, head Abbreviated Injury Scale (AIS) score, and Glasgow Coma Scale (GCS) score.	(OR 0.42, 95% CI [0.04-4.44])



L'uso di FFP come reversal non riduce significativamente la mortalità intra-ospedaliera comparato al non uso di reversal in soggetti traumatizzati in trattamento con warfarin.

Health related quality of life

No outcome data

Adverse effects (Stroke, MI, Thromboembolism (PA and venous)

No outcome data

Reversal of anti-coagulation as measured by laboratory assessment (degree of reversal (reduction of INR))

Table 2 – Primary and secondary outcomes of patients who received PCC, FFP, and no reversal agent.

Patient characteristic	PCC (n = 60)	FFP (*n* = 41)	No reversal (*n* = 49)	P-value
ICH progression (n, %)	26 (43.3)	21 (51.2)	10 (20.4)	0.006*
Need for craniotomy (n %)	9 (15)	8 (19.5)	3 (6.1)	0.157
Mortality (n, %)	2 (3.3)	0 (0)	2 (4.1)	0.448
LOS (d, median, IQR)	4 (3-7)	6 (3-13)	4 (2-5)	0.024*
ICU admit (n, %)	34 (56.7)	23 (56.1)	19 (38.8)	0.128
ICU LOS (median, IQR)	2 (1, 5)	7 (4, 13)	4 (2, 15)	0.422
Mechanical ventilation (n, %)	4 (6.7)	9 (22)	4 (8.2)	0.041*
Vent days (median, IQR)	0 (0, 0)	1 (0, 4)	0 (0, 0)	<0.001*
Worsening mental status (n, %)	18 (30)	13 (31.7)	11 (22.4)	0.563
Time to INR <1.7 (h, median, IQR)	10.5 (6, 17.5)	21 (15, 36)	N/A	0.002*

LOS = length of stay; ICU = intensive care unit.
*P < 0.05.

Degree of resuscitation (units of blood transfused)

No outcome data

Neurological outcome (brain injured patients)

No outcome data

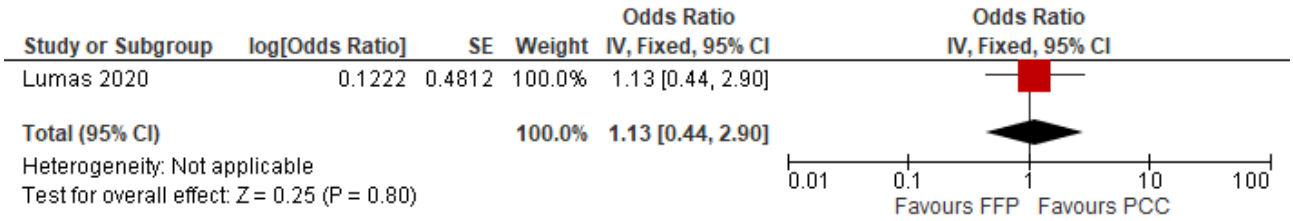
Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing).

	Worsening of mental status						
	PCC		**FFP**		**Time point**	**Data adjusted**	**OR**
	n(%)	**tot**	**n(%)**	**tot**			
Lumas 2020	18(30)	60	13(31.7)	41	Not specified	No	OR 0.92 (0.39 a 2.18)

L'uso di PCC come reversal sembra presentare percentuali simili nel numero di soggetti con peggioramento dello stato mentale comparato all'uso di FFP in soggetti traumatizzati in trattamento con warfarin.

ICH progression

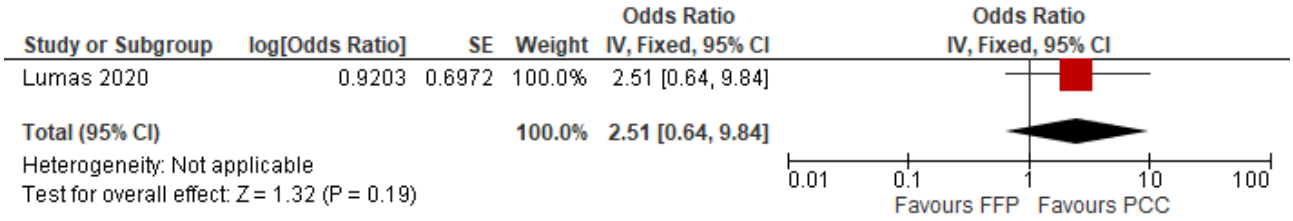
	ICH progression						
	PCC		**FFP**		**Time point**	**Data adjusted**	**OR**
	n(%)	**tot**	**n(%)**	**tot**			
Lumas 2020	26(43.3)	60	21(51.2)	41	Not specified	Yes	(OR 1.13, 95% CI [0.44-2.90])



L'uso di PCC come reversal sembra presentare percentuali superiori di soggetti con progressione di emorragia intracranica comparato all'uso di FFP in soggetti traumatizzati in trattamento con warfarin tuttavia non statisticamente significativa.

Need for neurosurgical surgery (craniotomy)

	Need for craniotomy						
	PCC		**FFP**		**Time point**	**Data adjusted**	**OR**
	n(%)	**tot**	**n(%)**	**tot**			
Lumas 2020	9(15)	60	8(19.5)	41	Not specified	Yes. Adjusted for demographics, admission INR, use of vitamin K, concomitant antiplatelet therapy, head Abbreviated Injury Scale (AIS) score, and Glasgow Coma Scale (GCS) score.	(OR 2.51, 95% CI [0.64-9.93]).



L'uso di PCC come reversal non riduce in modo statisticamente significativo la necessità di craniotomia comparato all'uso di FFP in soggetti traumatizzati in trattamento con warfarin.

C- 4FPCC versus altro

Gli studi identificati, di cui in Tabella 1 sono riportate le caratteristiche generali, permettono di analizzare le seguenti comparazioni:

- C1. 4FPCC versus 3FPCC+rFVIIa (1 observational study without adjusted data, Martin et al.)
- C2. 4FPCC versus 3FPCC (2 observational studies with adjusted data, Mangram et al-Margraf et al.)
- C3. 4FPCC versus Factor IX complex + vitamin K with or without FFP (1 observational study without adjusted data, Drone et al.)

	Study design / adjusted or not adjusted data	**Population setting**	**Anticoagulation therapy**	**Type of reversal**	**Blunt trauma; ISS Baseline INR**
Martin et al. 2016	Observational study (retrospective) - unadjusted data	N=87 trauma patients with acute bleeding Baseline INR for inclusion: not specified	Warfarin	Group 1: 3F-PCC + VIIa (n = 53) Group 2: 4F-PCC (n=34)	Group 1: Blunt: 100%; ISS: 19 (17, 26) Group 2: Blunt: 100%; ISS: 18 (16, 26)
Mangram 2016	Observational study (retrospective) - adjusted data *Adjustment*: multivariate logistic regression model (age, baseline INR, time INR assessed post-dose, vitamin K administration	N=64 trauma-patients, baseline INR for inclusion: ≥ 1.5	Warfarin, n=61 (95.3%) Rivaroxaban, n=3 (4.7%)	Group 1: 3F-PCC (n=36) Group 2: 4F-PCC (n=18)	Group 1: Blunt: NR ISS: 10.9 ± 8.6 Group 2: Blunt: NR ISS: 11.9 ± 6.3
Margraf 2020	Observational study (retrospective) - adjusted data *Adjustment*: Propensity score adjustment accounting for age, sex, actual body weight, dose, initial INR value, and time between INR measurements	N=80 Adults at Level 1 Trauma center Baseline INR for inclusion: ≥1.6	Warfarin	Group 1: PCC3 (n= 57) Group 2: PCC4 (n= 23)	Group 1: Blunt: NR ISS: NR Group 2: Blunt: NR ISS: NR
Drone 2015	Observetional study (retrospective) – unadjusted data	N=52 Adults at level 1 trauma center Baseline INR for inclusion: not specified	Warfarin	Group 1: 1,500 units 4F-PCC (n=26) Group 2: factor IX complex + vitamin K, with or without FFP (n=26)	Not reported

Tabella 1. Caratteristiche degli studi inclusi.

Di seguito, in tabella 2c, gli outcome analizzati:

Outcome	C1. 4FPCC versus 3FPCC+rFVIIa	C2. 4FPCC versus 3FPCC	C3. 4FPCC versus Factor IX complex + vitamin K with or without FFP
Mortality at 24 hours, 30days/1month, and 12 months	X	X	
Health related quality of life			
Adverse effects (Stroke, MI, Thromboembolism (PA and venous)	X	X	X
Reversal of anti-coagulation as measured by laboratory assessment (degree of reversal (reduction of INR))	X	X (adjusted data)	X
Degree of resuscitation (units of blood transfused)		X	
Neurological outcome (brain injured patients)			
Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing).			
ICH progression			
Need for neurosurgical surgey (craniotomy)	X		

Tabella 2. Sintesi degli outcomes analizzati.

C1. 4FPCC versus (3FPCC+rFVIIa)

Un solo studio, Martin 2016, risponde alla comparazione di interesse
(1 observational study without adjusted data).

Mortality at 24 hours, 30days/1month, and 12 months

	Mortality						
	3F-PCC + rVIIa		4F-PCC		P value	Time point	OR
	n	tot	n	tot			
Martin 2016	9 (17%)	53	1 (2.9%)	34	0.08	In-hospital – not defined	OR 0.15 (0.02 a 1.23)

L'uso di 4F-PCC comporta un minor rischio di mortalità rispetto all'uso di 3F-PCC + rVIIa in pazienti traumatizzati, con una differenza non statisticamente significativa seppur con dati non aggiustati.

Health related quality of life

No outcome data

Degree of resuscitation (units of blood transfused)

No outcome data

Adverse effects.

	Adverse events: New diagnosis of DVT						
	4F-PCC		3F-PCC + rVIIa		P value	Time point	OR
	N (%)	tot	n	tot			
Martin 2016	1(2.9%)	34	12 (22.6 %)	53	0.01	Not reported	OR 0.10 (0.01 a 0.84)

L'uso di 4F-PCC comporta una minor insorgenza di complicazioni (ie. Trombosi venosa profonda) rispetto all'uso di 3F-PCC + rVIIa in pazienti traumatizzati, con una differenza statisticamente significativa seppur con dati non aggiustati.

Reversal of anti-coagulation as measured by laboratory assessment (degree of reversal (reduction of INR))

Martin 2016 include dati in merito a (1) INR change pre post e (2) successful degree of reversal (INR <1.5)

Table 3 Effect of PCCs

	3F-PCC+rFVIIa n= 53	4F-PCC n=34	P value
INR prereversal	2.65 (2.23, 3.36)	2.35 (2.02, 3.26)	.14
INR postreversal	.75 (.69, 1.00)	1.28 (1.13, 1.36)	<.001
ΔINR	(n= 48)	(n = 34)	.001
	−1.82 (−1.33, −2.44)	−1.17 (−.69, −1.97)	
First INR below 1.5	46 (93.9%)	33 (97.1%)	.51
Dose PCC (units/kg)	46 (39, 51)	25 (23, 28)	<.001
Dose rVIIa	12 (10, 15)	NA	NA
Vitamin K given	51 (96.2%)	30 (88.2%)	.15
FFP given	23 (43.4%)	10 (29.4%)	.19

Data presented as median (IQR) or as percentage of whole.
FFP = fresh frozen plasma; INR = international normalized ratio; IQR = interquartile range; NA = not applicable; PCC = prothrombin complex concentrate.

(1) INR change pre post: La differenza tra pre-post INR tra i due gruppi è statisticamente significativa con un decremento maggiore a favore del gruppo di soggetti a cui è stato somministrato 3F-PCC + rFVIIa.
(2) successful degree of reversal (INR <1.5): Entrambi i gruppi raggiungono alte percentuali di soggetti con INR<1.5 dopo la somministrazione dei reversal tuttavia, non vi è una differenza statisticamente significativa tra uso di 3F-PCC + rFVIIa e 4F-PCC.

Neurological outcome (brain injured patients)

No outcome data

Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing).

No outcome data

ICH progression

No outcome data

Need for neurosurgical surgey

	Neurosurgical procedure							
	4F-PCC		**3F-PCC + rVIIa**		**P value**	**Data adjusted**	**Time point**	**OR**
	n	**tot**	**n**	**tot**				
Martin 2016	2	34	9	53	0.19	No	Not reported	OR 0.31 (0.06 a 1.51)

Non ci sono differenze statisticamente significative, seppur con dati non aggiustati, nella necessità di neurochirurgia (es. craniotomia) tra soggetti traumatizzati che ricevono 4F-PCC verso 3F-PCC + rVIIa.

C2. 4FPCC versus 3FPCC

Due studi, Mangram 2016 e Margraf 2020, rispondono alla comparazione di interesse (2 observational studies with adjusted data)

Mortality at 24 hours, 30days/1month, and 12 months

	Mortality						
	4F-PCC		3F-PCC		P value	Data adjusted	Time point	OR
	n	tot	n	tot				
Mangram 2016	2	18	2	46	0.313	No	Not reported	
Margraf 2020	8	23	14	57	0.52	No	During hospitalization	
								Pooled OR 1.83 (0.72 a 4.64)

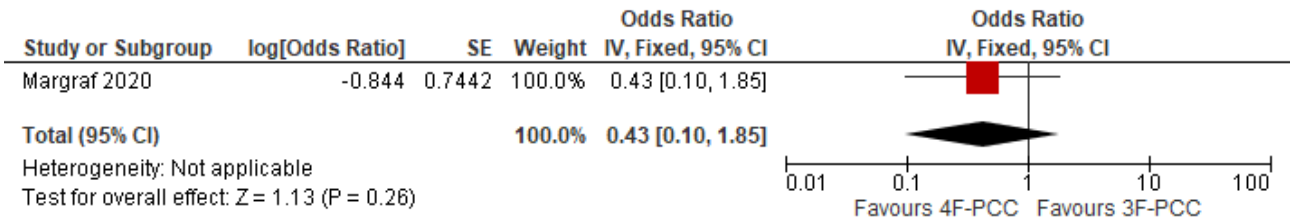
Non ci sono differenza statisticamente significative tra l'uso di 4F-PCC e 3F-PCC nella riduzione di mortalità, seppure con dati non aggiustati.

Health related quality of life

No outcome data

Adverse effects (Stroke, MI, Thromboembolism (PA and venous)

	Thrombolic events						
	4F-PCC		3F-PCC		P value	Data adjusted	OR adjusted
	n	tot	n	tot			
Mangram 2016	0	18	7	46	.177	No	
Margraf 2020	2	23	5	57	1.0	Yes Propensity score accounted for age, sex, actual body weight, PCC dose, initial INR value, and time from the first and second INR measurement.	aOR 0.43 (0.10–1.79)



Non ci sono differenza statisticamente significative tra l'uso di 4F-PCC e 3F-PCC nell'insorgenza di complicanze (ie. Eventi trombotici). Infatti, osservando i risultati di Margraf

2020, aggiustati per co-variabili, non ci sono differenze statisticamente significative tra i due gruppi di trattamento.

Reversal of anti-coagulation as measured by laboratory assessment (degree of reversal (reduction of INR))

Sono stati trovati due studi che riportano l'outcome di interesse espresso in INR change pre to post e numero di soggetti con successo di reversal.

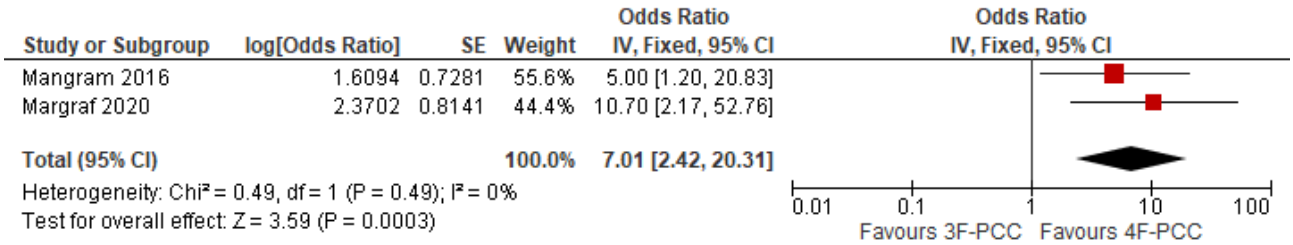
- **INR change pre to post**

	INR change pre to post								
	4F-PCC			**3F-PCC**			**P value**	**Adjustment**	**MD**
	Median	**Range IQR**	**N**	**Median**	**Range IQR**	**N**			
Margraf 2020	2.3	1.2-3.3	23	1.1	0.6 – 2	57	Not reported	Yes propensity score accounted for age, sex, actual body weight, PCC dose, initial INR value, and time from the first and second INR measurement.	Not reported After propensity score adjustment, the estimated mean change in INR in the PCC3 group was 1.39, and the PCC4 group was 0.30 higher on average (p = 0.56).

After propensity score adjustment, the estimated mean change in INR in the PCC3 group was 1.39,
and the PCC4 group was 0.30 higher on average (p = 0.56).
Non ci sono differenza statisticamente significative tra l'uso di 4F-PCC e 3F-PCC nella differenza pre-post INR tra i due gruppi di trattamento.

	Successful anticoagulation reversal (INR < 1.5)						
	4F-PCC		3F-PCC		P value	Adjustment	OR
	n	tot	n	tot			
Mangram 2016	15	18	23	46	0.021	(age, baseline INR, time INR assessed post-dose, vitamin K administration, administration of 4F- PCC Yes	aOR 5 (95% CI: 1.2 to 19.6)
Margraf 2020	20	23	18	57	< 0.0001	propensity score accounted for age, sex, actual body weight, PCC dose, initial INR value, and time from the first and second INR measurement	aOR 10.7 (95% CI: ,: 2.17–51.24)

- **Successful anticoagulation reversal (INR < 1.5)**



In figura la meta-analisi con dati aggiustati - Successful anticoagulation reversal (INR<1.5)

L'odds ratio aggiustato dimostra che l'uso di 4F-PCC permette di aumentare in modo statisticamente significativo il numero di soggetti con INR<1.5 rispetto all'uso di 3F-PCC.

Degree of resuscitation (units of blood transfused)

	pRBC transfused post PCC administrations (units/pt)					
	4F-PCC		3F-PCC		P value	Time point
	Mean	Sd	Mean	sd		
Mangram 2016	0.8	1.7	0.4	0.8	.663	Not reported

	FFP transfused post PCC administrations (units/pt)					
	4F-PCC		3F-PCC		P value	Time point
	Mean	Sd	Mean	sd		
Mangram 2016	0.6	1.5	0.5	1.3	.748	Not reported

	Platalets transfused post PCC administrations (units/pt)					
	4F-PCC		3F-PCC		P value	Time point
	Mean	Sd	Mean	sd		
Mangram 2016	0.3	0.7	0.1	0.4	.215	Not reported

Non ci sono differenze statisticamente significative tra l'uso di 4F-PCC e 3F-PCC nella richiesta/uso di emocomponenti e trasfusioni tra i due gruppi di trattamenti, seppur con dati non aggiustati.

Neurological outcome (brain injured patients)

No outcome data

Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing).

No outcome data

ICH progression

No outcome data

Need for neurosurgical surgey (craniotomy)

No outcome data

C3. 4FPCC versus (Factor IX complex + vitamin K with or without FFP)

Uno studio, Drone 2016, riporta la comparazione di interesse (1 observational study without adjusted data)

Mortality at 24 hours, 30days/1month, and 12 months

No outcome data

Health related quality of life

No outcome data

Adverse effects (Stroke, MI, Thromboembolism (PA and venous)

Drone et al 2016, include 26 adulti che ricevevano una dose fissa di 1500 unità 4F PCC e 26 pazienti che ricevevano una combinazione di factor IX complex e vitamina K, con e senza FFP, per warfarin reversal ammessi in trauma center dal 1 Gennaio 2012 al 1 Novembre 2014.
In termini di eventi avversi, l'autore non riporta differenze in percentuali tra gruppi.

Reversal of anti-coagulation as measured by laboratory assessment (degree of reversal (reduction of INR))

Drone et al 2016, include 26 adulti che ricevevano una dose fissa di 1500 unità 4F PCC e 26 pazienti che ricevevano una combinazione di factor IX complex e vitamina K, con e senza FFP, per warfarin reversal ammessi in trauma center dal 1 Gennaio 2012 al 1 Novembre 2014.
L'INR è stato riportato < 2 nel 100% dei pazienti nel gruppo 4F-PCC contro? l'84.6% dei pazienti nel gruppo factor IX complex (p……?).

L'INR è stato ridotto a <1.6 nel 90.8% dei pazienti nel gruppo 4f-PCC verso il 50% del gruppo factor IX complez (p<0.05).
Nei gruppi 4F-PCC e factor IX complex l e medie del pre reversal INRs erano rispettivamente di 3.5 (range 1.1-10) e 4 (range1.3-10) (p=0.29).

Degree of resuscitation (units of blood transfused)

No outcome data

Neurological outcome (brain injured patients)

No outcome data

Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing).

No outcome data

ICH progression

No outcome data

Need for neurosurgical surgey (craniotomy)

No outcome data

D. Dosi diverse 4FPCC a confronto

Gli studi identificati permettono di analizzare le seguenti comparazioni (tabella 1d):

- 4FPCC 1500 versus 4FPCC 1000 (2 observational studies of which 1 with adjusted data)

Tabella 1d					
	Study design / adjusted or not adjusted data	**Population setting**	**Anticoagulation therapy**	**Type of reversal**	**Blunt trauma; ISS Baseline INR**
Cohen 2017	Observational study (retrospective) - unadjusted data	N=194 patients for life-threatening bleeding or reversal for urgent procedures Baseline INR for inclusion: not specified	Warfarin	Group 1: 1500PCC (n = 70) Group 2: 1000PCC (n=124)	Group 1: Blunt: NR ISS: NR Group 2: Blunt: NR ISS: NR
Cohen 2018	Observational study (retrospective) - adjusted data Adjustment for baseline INR	N=219 patients for life-threatening bleeding or reversal for urgent procedures Baseline INR for inclusion: not specified	Warfarin	Group 1: 1500PCC (n = 75) Group 2: 1000PCC (n=144)	Group 1: Blunt: NR ISS: NR Group 2: Blunt: NR ISS: NR

Di seguito, in tabella 2c, gli outcome analizzati:

Outcome	**D1.** 4FPCC 1500 versus 4FPCC 1000
Mortality at 24 hours, 30days/1month, and 12 months	X (1 study)
Health related quality of life	
Adverse effects (Stroke, MI, Thromboembolism (PA and venous)	X (1 study)
Reversal of anti-coagulation as measured by laboratory assessment (degree of reversal (reduction of INR))	X (1 study unadjusted, 1 study adjusted)
Degree of resuscitation (units of blood transfused)	
Neurological outcome (brain injured patients)	
Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing).	
ICH progression	
Need for neurosurgical surgey (craniotomy)	

D1. 4FPCC 1500 versus 4FPCC 1000 (2 observational studies of which 1 with adjusted data)

Mortality at 24 hours, 30days/1month, and 12 months

Dati di mortalità vengono riportato da Cohen et 2018, che include 219 pazienti: 75 nel gruppo 1500 PCC e 144 nel gruppo 1000 PCC. Non si evince nessuna differenza statisticamente significativa in mortalità per tutte le cause tra i due gruppi.

Health related quality of life

No outcome data

Adverse events

Dati di eventi avversi (ie. Eventi trombotici) vengono riportato da Cohen et 2018, che include 219 pazienti: 75 nel gruppo 1500 PCC e 144 nel gruppo 1000 PCC. Non si evince nessuna differenza statisticamente significativa in eventi trombotici tra i due gruppi.

Reversal of anti-coagulation as measured by laboratory assessment (degree of reversal (reduction of INR))

Sono stati inclusi due studi, di cui è disponibile soltanto abstract con dati aggiustati e non aggiustati.
Nello studio di Cohen et al. 2017 con dati non aggiustati per co-variabili, sono stati inclusi 194 pazienti, divisi in due gruppi: gruppo 1500 PCC (n=70) e gruppo 1000PCC (n=124). Sia i valori della media baseline INR (media±sd; 3.50 [±2.44] vs 4.48 [±2.87], p=0.013) sia la media al post trattamento INR (1.51 [±0.64] vs 1.77 [±0.45], p<0.001) erano più bassi in modo significativo nel gruppo 1500 PCC. Inoltre, nel gruppo 1500 PCC più pazienti hanno raggiunto un INR < 2 rispetto al gruppo 1000 PCC (93% vs 71%, p=0.003) Similmente, nel gruppo 1500 PCC più pazienti hanno raggiunto un INR < 1.5 rispetto al gruppo 1000PCC (76% vs 31%, p<0.0001).
Concludendo che una prescrizione di dose 1500 PCC può risultare in una più efficace riduzione di INR < 1.5 al post trattamento rispetto a una dose di 1000 PCC.

Successivamente, Cohen et al pubblica nel 2018 un aggiornamento arrivando a includere 219 pazienti: 75 nel gruppo 1500 PCC e 144 nel gruppo 1000 PCC. Sia la media INR al baseline [±SD] INR (3.3 [±2.1] vs. 5.0 [±3.8], p<0.001) e al post trattamento INR (1.4 [±0.2] vs. 1.8 [±0.5] p<0.001) avevano valori più bassi nel gruppo 1500 PCC. Inoltre, un maggior numero di pazienti ha raggiunto un INR < 2 nel gruppo 1500 PCC rispetto al gruppo 1000 PCC (95% vs 74%, p<0.001). Similmente, un maggior numero di pazienti aveva raggiunto un INR < 2 nel gruppo 1500 PCC (76% vs. 28.5%, p<0.0001). Aggiustando per la media INR al baseline, è stata riportata una riduzione nel post intervento di 0.27 IU fra i gruppi (da bassa ad alta dose).
Concludendo che usando una dose di 1500 PCC risulta più efficace rispetto alla dose 1000 PCC nel raggiungere un INR al post trattamento minore di 2 e di 1.5.

"In the 1500PCC group (n=75) compared to the 1000PCC group (n=144), both the baseline mean [±SD] INR (3.3 [±2.1] vs. 5.0 [±3.8], p<0.001) and the post-treatment INR (1.4 [±0.2] vs. 1.8 [±0.5] p<0.001) were significantly lower. More patients achieved an INR < 2.0 in the 1500PCC than the 1000PCC group (95% vs 74%, p<0.001). Similarly, more patients achieved

an INR < 1.5 in the 1500PCC than the 1000PCC group (76% vs. 28.5%, p<0.0001). After adjusting for the baseline INR, there is a 0.27 IU average decrease in post 4FPCC INR going from the low to the high dose group."

Degree of resuscitation (units of blood transfused)

No outcome data

Neurological outcome (brain injured patients)

No outcome data

Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing).

No outcome data

ICH progression

No outcome data

Need for neurosurgical surgey (craniotomy)

No outcome data

Appendice D – Valutazione della qualità metodologica degli studi inclusi

Revisioni sistematiche (AMSTAR2)

	Alvikas 2020	Leong 2015
Total studies included in the RS; last date search update	12 studies: retrospective cohort (n = 11), prospective cohort (n = 1) ; search from January 1, 1987 to March 4, 2019	7 studies: retrospective cohort (n = 7), 6 studies in United States and 1 Japanese; search from 1946 to June 2014
	treated vs. not treated with platelet transfusion	treated vs. not treated with platelet transfusion
Type of evidence synthesis	Quantitative and qualitative	Quantitative and qualitative
overall quality	**Moderate**	**Critically low**
1-Question and inclusion	yes	yes
2-Protocol	yes	yes
3-Study design	no	no
4-Comprehensive search	partial yes	partial yes
5-Study selection	yes	yes
6-Data extraction	yes	yes
7-Excluded studied justification	partial yes	no
8-Included studied details	yes	yes
9-Risk of Bias	yes	yes
10-Source of funding of included studies	no	no
11-Appropriate statistical methods for analysis	yes	no
12-Rob on meta-analyses	yes	yes
13-Rob on individual studies	yes	yes
14-Explanation for heterogeneity	yes	no
15-Publication bias	yes	no
16-Conflict of interest	yes	no

STUDI OSSERVAZIONALI (Newcastle-Ottawa Scale)

	SELECTION				COMPARABILITY	OUTCOME			
Cohort study	**Representativeness of the exposed cohort**	**Selection of the non exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at start of study**	**Comparability of cohorts on the basis of the design or analysis**	**Assessment of outcome**	**Was follow-up long enough for outcomes to occur**	**Adequacy of follow up of cohorts**	**tot**
1_Agyabeng-Dadzie2020	*	*	*	*	*	*	*	*	8
2_Carothers,2017	*	*	*	*		*	*	*	7
3_Lumas 2020	*	*	*	*	*	*	*	*	8
4_Holzmacher2018	*	*	*	*	*	*	*	*	8
5_Lokhandwala 2020	*	*	*	*	*	*	*	*	8
7_Ogunlade 2018	*	*	*	*		*	*	*	7
9_Barletta 2020	*	*	*	*	*	*	*	*	8
10_Hobbs 2016 (abstract)	*	*	*	*		*	*	*	7
11_Huang 2019 (abstract)	*	*	*	*	*	*	*	*	8
12_Koyama 2021	*	*	*	*		*	*	*	7
13_Drone 2015(abstract)	*	*	*	*		*	*	*	7
14_Managram 2016	*	*	*	*	*	*	*	*	8
15_Margraf 2020	*	*	*	*	*	*	*	*	8
16_Martin 2016	*	*	*	*		*	*	*	7
17_Cohen 2017(abstract)	*	*	*	*		*	*	*	7
18_Cohen 2018(abstract)	*	*	*	*		*	*	*	7

INDICE

A- Anticoagulanti versus no-reversal:

A1-PLT vs no-reversal (2 review (with 14 observational studies) + 2 observational studies [1 with adjusted data and 1 without adjusted data])

Certainty assessment							№ di pazienti		Effetto		Certezza evidenza	Importanza
№ degli studi	Disegno dello studio	Rischio di distorsione	Mancanza di riproducibilità dei risultati	Mancanza di generalizzabilità	Imprecisione	Ulteriori considerazioni	PLT	no reversal	Relativo (95% CI)	Assoluto (95% CI)		
In hospital Mortality NOT ADJUSTED												
14	studi osservazionali	serio [a]	non importante	non importante	molto serio [b,c]	nessuno	134/1039 (12.9%)	137/1003 (13.7%)	**OR 1.09** (0.72 a 1.66)	**10 più per 1.000** (da 34 meno a 71 più)	⨁◯◯◯ MOLTO BASSA	
In hospital mortality ADJUSTED												
7 (solo 4 analizzati)	studi osservazionali	non importante	non importante	non importante	molto serio [b,c]	bias di pubblicazione fortemente sospetto [d]	31/406 (7.6%)	48/350 (13.7%)	**OR 0.91** (0.61 a 1.37)	**11 meno per 1.000** (da 49 meno a 42 più)	⨁◯◯◯ MOLTO BASSA	
Health related quality of life												
0									non stimabile		-	
Adverse effects (Stroke, MI, Thromboembolism (PA and venous)												
3	studi osservazionali	non importante	non importante	non importante	molto serio [b,c]	bias di pubblicazione fortemente sospetto [d]	2 studi riportano i dati tuttavia con eventi avversi differenti e non cumulabili. In generale, nessuna differenza significativa tra i due gruppi				⨁◯◯◯ MOLTO BASSA	
Reversal of anti-coagulation as measured by laboratory assessment (degree of reversal (reduction of INR))												
0									non stimabile		-	
Degree of resuscitation (units of blood transfused, perioperative platelet transfusion)												
1	studi osservazionali	non importante	non importante	non importante	serio [c]	forte associazione	3/38 (46.0%)	2/49 (8.3%)	**OR 2.01** (0.32 – 12.71)	**38 più per 1.000** (da 27 meno a 310 più)	⨁⨁◯◯ BASSA	
Neurological outcome (brain injured patients)												
2	studi osservazionali	non importante	non importante	non importante	serio [e]	nessuno	Nessuna differenza significativa con dati NON aggiustati tra i due gruppi				⨁◯◯◯ MOLTO BASSA	
Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing)												
2	studi osservazionali	non importante	non importante	non importante	serio [e]	bias di pubblicazione fortemente sospetto [d]	21/179 (11.7%)	3/64 (4.7%)	**OR 0.75** (0.50 a 0.80)	**11 meno per 1.000** (da 23 meno a 9 meno)	⨁◯◯◯ MOLTO BASSA	

Certainty assessment							№ di pazienti		Effetto		Certezza evidenza	Importanza
№ degli studi	Disegno dello studio	Rischio di distorsione	Mancanza di riproducibilità dei risultati	Mancanza di generalizzabilità	Imprecisione	Ulteriori considerazioni	PLT	no reversal	Relativo (95% CI)	Assoluto (95% CI)		
Hemorrhage progression NOT ADJUSTED												
9	studi osservazionali	non importante	serio [f]	non importante	serio [b]	nessuno	100/637 (15.7%)	201/513 (39.2%)	**OR 0.68** (0.27 a 1.67)	**87 meno per 1.000** (da 244 meno a 126 più)	⨁◯◯◯ MOLTO BASSA	
Hemorrhage progression ADJUSTED												
2	studi osservazionali	non importante	serio [f]	non importante	serio [c]	bias di pubblicazione fortemente sospetto [d]	19/89 (21.3%)	13/81 (16.0%)	**OR 1.21** (0.46 a 3.19)	**27 più per 1.000** (da 80 meno a 218 più)	⨁◯◯◯ MOLTO BASSA	
Neurosurgical intervention NOT ADJUSTED												
7	studi osservazionali	non importante	non importante	non importante	serio [c]	nessuno	42/560 (7.5%)	63/505 (12.5%)	**OR 0.98** (0.31 a 3.04)	**2 meno per 1.000** (da 82 meno a 178 più)	⨁◯◯◯ MOLTO BASSA	
Neurosurgical intervention ADJUSTED												
1	studi osservazionali	non importante	non importante	non importante	molto serio [b,c]	bias di pubblicazione fortemente sospetto [d]	5/31 (16.1%)	7/55 (12.7%)	**OR 1.31** (0.56 a 3.06)	**33 più per 1.000** (da 52 meno a 181 più)	⨁◯◯◯ MOLTO BASSA	

CI: Confidence interval; **OR:** Odds ratio

Spiegazioni

a. Not all included studies reported adjusted data
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
d. Outcome non-reporting bias
e. small sample size <400 participants
f. I2>75%

A2-PCC vs no-reversal (1 observational study with adjusted data*)

Certainty assessment							№ di pazienti		Effetto		Certezza evidenza	Importanza
№ degli studi	Disegno dello studio	Rischio di distorsione	Mancanza di riproducibilità dei risultati	Mancanza di generalizzabilità	Imprecisione	Ulteriori considerazioni	PCC	NO reversal	Relativo (95% CI)	Assoluto (95% CI)		
Mortality ADJUSTED												
1	studi osservazionali	non importante	non importante	non importante	molto serio [a,b]	nessuno	2/60 (3.3%)	2/49 (4.1%)	**OR 0.78** (0.07 a 8.69)	**9 meno per 1.000** (da 38 meno a 229 più)	⨁◯◯◯ MOLTO BASSA	
Health related quality of life												
0									non stimabile		-	
Adverse effects (Stroke, MI, Thromboembolism (PA and venous)												
0									non stimabile		-	
Reversal of anti-coagulation as measured by laboratory assessment (degree of reversal (reduction of INR))												
1	studi osservazionali	non importante	non importante	non importante	serio [a]	bias di pubblicazione fortemente sospetto [c]	Time to INR <1.7 (h, median, IQR): PCC: 10.5 (6, 17.5); No reversal: N/A				⨁◯◯◯ MOLTO BASSA	
Degree of resuscitation (units of blood transfused)												
0									non stimabile		-	
Neurological outcome (brain injured patients)												
0									non stimabile		-	
Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing).												
1	studi osservazionali	non importante	non importante	non importante	serio [a]	nessuno	18/60 (30.0%)	11/49 (22.4%)	**OR 1.48** (0.62 a 3.53)	**75 più per 1.000** (da 72 meno a 281 più)	⨁◯◯◯ MOLTO BASSA	
ICH progression												
1	studi osservazionali	non importante	non importante	non importante	serio [a]	nessuno	26/60 (43.3%)	10/49 (20.4%)	**OR 2.98** (1.26 a 7.06)	**229 più per 1.000** (da 40 più a 440 più)	⨁◯◯◯ MOLTO BASSA	
Need for neurosurgical surgery (craniotomy) ADJUSTED												
1	studi osservazionali	non importante	non importante	non importante	molto serio [a,b]	nessuno	9/60 (15.0%)	3/49 (6.1%)	**OR 0.29** (0.03 a 2.80)	**43 meno per 1.000** (da 59 meno a 93 più)	⨁◯◯◯ MOLTO BASSA	

CI: Confidence interval; **OR:** Odds ratio

Spiegazioni

a. events <300 rule of thumb

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. Outcome non-reporting bias

A3-FFP vs no reversal (1 observational study with adjusted data*)

Certainty assessment							№ di pazienti		Effetto		Certezza evidenza	Importanza
№ degli studi	Disegno dello studio	Rischio di distorsione	Mancanza di riproducibilità dei risultati	Mancanza di generalizzabilità	Imprecisione	Ulteriori considerazioni	FFP	No reversal	Relativo (95% CI)	Assoluto (95% CI)		
Mortality												
1	studi osservazionali	non importante	non importante	non importante	molto serio [a,b]	nessuno	0/41 (0.0%)	2/49 (4.1%)	**OR 0.29** (0.01 a 4.91)	**29 meno per 1.000** (da 40 meno a 132 più)	⨁◯◯◯ MOLTO BASSA	
Health related quality of life												
0									non stimabile		-	
Adverse effects (Stroke, MI, Thromboembolism (PA and venous)												
0									non stimabile		-	
Reversal of anti-coagulation as measured by laboratory assessment (degree of reversal (reduction of INR))												
0									non stimabile		-	
Degree of resuscitation (units of blood transfused)												
0									non stimabile		-	
Neurological outcome (brain injured patients)												
0									non stimabile		-	
Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing).												
1	studi osservazionali	non importante	non importante	non importante	molto serio [a,b]	nessuno	13/41 (31.7%)	11/49 (22.4%)	**OR 1.60** (0.63 a 4.10)	**92 più per 1.000** (da 70 meno a 318 più)	⨁◯◯◯ MOLTO BASSA	
ICH progression												
1	studi osservazionali	non importante	non importante	non importante	serio [b]	nessuno	21/41 (51.2%)	10/49 (20.4%)	**OR 4.09** (1.62 a 10.34)	**308 più per 1.000** (da 89 più a 522 più)	⨁◯◯◯ MOLTO BASSA	
Need for neurosurgical surgery (craniotomy)												
1	studi osservazionali	non importante	non importante	non importante	molto serio [a,b]	nessuno	8/41 (19.5%)	3/49 (6.1%)	**OR 3.72** (0.92 a 15.08)	**134 più per 1.000** (da 5 meno a 435 più)	⨁◯◯◯ MOLTO BASSA	

CI: Confidence interval; **OR:** Odds ratio

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

A4-DDVAP vs no reversal (1 observational study with adjusted data)

Certainty assessment							№ di pazienti		Effetto		Certezza evidenza	Importanza
№ degli studi	Disegno dello studio	Rischio di distorsione	Mancanza di riproducibilità dei risultati	Mancanza di generalizzabilità	Imprecisione	Ulteriori considerazioni	DDVAP	No reversal	Relativo (95% CI)	Assoluto (95% CI)		
Mortality at 24 hours, 30days/1month, and 12 months												
1	studi osservazionali	non importante	non importante	non importante	molto serio [a,b]	nessuno	5/158 (3.2%)	4/44 (9.1%)	**OR 0.33** (0.08 a 1.27)	**59 meno per 1.000** (da 83 meno a 22 più)	⨁◯◯◯ MOLTO BASSA	
Health related quality of life												
0									non stimabile		-	
Adverse effects (Stroke, MI, Thromboembolism (PA and venous)												
1	studi osservazionali	non importante	non importante	non importante	molto serio [a,b]	nessuno	4/158 (2.5%)	2/44 (4.5%)	**OR 0.55** (0.10 a 3.08)	**20 meno per 1.000** (da 41 meno a 82 più)	⨁◯◯◯ MOLTO BASSA	
Reversal of anti-coagulation as measured by laboratory assessment (degree of reversal (reduction of INR))												
0									non stimabile		-	
Degree of resuscitation (units of blood transfused)												
0									non stimabile		-	
Neurological outcome (brain injured patients) (valutato con: GCS)												
1	studi osservazionali	non importante	non importante	non importante	serio [c]	nessuno	DDVAP: 15 (14 - 15), tot: 158 No reversal: 15 (14 – 15), tot: 44				⨁◯◯◯ MOLTO BASSA	
Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing).												
1	studi osservazionali	non importante	non importante	non importante	molto serio [a,b]	nessuno	96/158 (60.8%)	30/44 (68.2%)	**OR 0.72** (0.36 a 1.47)	**75 meno per 1.000** (da 246 meno a 77 più)	⨁◯◯◯ MOLTO BASSA	
ICH progression												
1	studi osservazionali	non importante	non importante	non importante	serio [b]	nessuno	22/158 (13.9%)	13/44 (29.5%)	**OR 0.259** (0.103 a 0.646)	**197 meno per 1.000** (da 254 meno a 82 meno)	⨁◯◯◯ MOLTO BASSA	
Need for neurosurgical surgery (craniotomy)												
0									non stimabile		-	

CI: Confidence interval; **OR:** Odds ratio

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
c. sample size <400 participants

B- Prothrombin complex concentrate (PCC) versus altro:

B1-aPCC vs FFP + vitamin K (2 studies without adjusted data)

Certainty assessment							№ di pazienti		Effetto		Certezza evidenza	Importanza
№ degli studi	Disegno dello studio	Rischio di distorsione	Mancanza di riproducibilità dei risultati	Mancanza di generalizzabilità	Imprecisione	Ulteriori considerazioni	aPCC	FFP + vitamin K	Relativo (95% CI)	Assoluto (95% CI)		
Mortality at 24 hours, 30days/1month, and 12 months												
1	studi osservazionali	non importante	non importante	non importante	molto serio [a,b]	nessuno	11/31 (35.5%)	20/89 (22.5%)	**OR 1.90** (0.78 a 4.61)	**130 più per 1.000** (da 40 meno a 347 più)	⨁◯◯◯ MOLTO BASSA	
Health related quality of life												
0									non stimabile		-	
Adverse effects (Stroke, MI, Thromboembolism (PA and venous)												
1	studi osservazionali	non importante	non importante	non importante	serio [b]	nessuno	0/31 (0.0%)	0/89 (0.0%)	non stimabile		⨁◯◯◯ MOLTO BASSA	
Reversal of anti-coagulation as measured by laboratory assessment (degree of reversal (reduction of INR)) (valutato con: POST INR)												
2	studi osservazionali	non importante	non importante	non importante	serio [c]	bias di pubblicazione fortemente sospetto [e]	Huang 2019, valori INR post trattamento: PCC=1.357, FFP+Vitamin K =1.362, p=0.935 Carothers 2018, soggetti che raggiungono INR ≤1.4: PCC=28 (90.3%), FFP+Vitamin K =62 (69.7%), p=0.029				⨁◯◯◯ MOLTO BASSA	
Degree of resuscitation (units of blood transfused) (valutato con: Number of subjects recevied FFP)												
1	studi osservazionali	non importante	non importante	non importante	serio [b]	nessuno	16/31 (51.6%)	85/89 (95.5%)	**OR 0.05** (0.01 a 0.17)	**440 meno per 1.000** (da 780 meno a 172 meno)	⨁◯◯◯ MOLTO BASSA	
Neurological outcome (brain injured patients)												
0									non stimabile		-	
Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing).												
1	studi osservazionali	non importante	non importante	non importante	serio [d]	nessuno	Discharge disposition, n (%) 1)Home: FFP+vitamin K:11 (12.4), aPCC 8 (25.8) p=0.091 2)Home with home health FFP+vitamin K :7 (7.9), aPCC 1 (3.2) p=0.678 3)Skilled nursing facility FFP+vitamin K: 18 (20.2), aPCC 4 (12.9) p=0.431 4)Rehab/longterm care FFP+vitamin K:14 (15.7), aPCC 3 (9.7) p=0.555				⨁◯◯◯ MOLTO BASSA	
ICH progression												
0									non stimabile		-	
Need for neurosurgical surgey (craniotomy)												

Certainty assessment							№ di pazienti		Effetto		Certezza evidenza	Importanza
№ degli studi	Disegno dello studio	Rischio di distorsione	Mancanza di riproducibilità dei risultati	Mancanza di generalizzabilità	Imprecisione	Ulteriori considerazioni	aPCC	FFP + vitamin K	Relativo (95% CI)	Assoluto (95% CI)		
1	studi osservazionali	non importante	non importante	non importante	serio [b]	nessuno	7/31 (22.6%)	19/89 (21.3%)	**OR 1.07** (0.40 a 2.87)	**12 più per 1.000** (da 116 meno a 224 più)	⨁◯◯◯ MOLTO BASSA	

CI: Confidence interval; **OR:** Odds ratio

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
c. sample size < 400 participants or event <300 rule of thumb
d. sample size < 400 participants
e abstract without full publication

B2-aPCC+FFP + vitamin K *versus* FFP+vitamin K (1 observational study without adjusted data)

Certainty assessment							№ di pazienti		Effetto		Certezza evidenza	Importanza
№ degli studi	Disegno dello studio	Rischio di distorsione	Mancanza di riproducibilità dei risultati	Mancanza di generalizzabilità	Imprecisione	Ulteriori considerazioni	aPCC + Vitamin K + FFP	FFP + Vitamin K	Relativo (95% CI)	Assoluto (95% CI)		
Mortality at 24 hours, 30days/1month, and 12 months												
1	studi osservazionali	non importante	non importante	non importante	serio [a]	bias di pubblicazione fortemente sospetto [b]	35.5% aPCC (31 soggetti) vs. 22.2% FFP + Vitamin K (89 soggetti), p= 0.162				⨁◯◯◯ MOLTO BASSA	
Health related quality of life												
0									non stimabile		-	
Adverse effects (Stroke, MI, Thromboembolism (PA and venous)												
0									non stimabile		-	
Reversal of anti-coagulation as measured by laboratory assessment (degree of reversal (reduction of INR))												
1	studi osservazionali	non importante	non importante	non importante	serio [a]	bias di pubblicazione fortemente sospetto [b]	For the primary outcome, significantly more patients in the aPCC group achieved an INR ≤1.4 compared to the FFP+Vitamin K group (90% vs. 70%, p= 0.029). The median time to reversal of anticoagulation was also significantly shorter in the aPCC group vs. FFP+Vitamin K (3.75 hours vs. 6.75 hours, p= 0.003)				⨁◯◯◯ MOLTO BASSA	
Degree of resuscitation (units of blood transfused)												
0									non stimabile		-	
Neurological outcome (brain injured patients)												
0									non stimabile		-	
Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing).												
0									non stimabile		-	
ICH progression												
0									non stimabile		-	
Need for neurosurgical surgey (craniotomy)												
1	studi osservazionali	non importante	non importante	non importante	serio [a]	bias di pubblicazione fortemente sospetto [b]	patients requiring neurosurgical intervention, median time to intervention was significantly shorter in the aPCC group (2 hours vs 7.25 hours, p=0.038)				⨁◯◯◯ MOLTO BASSA	

CI: Confidence interval

Spiegazioni

a. sample size <400 participants
b. bias di pubblicazione fortemente sospetto [d]

B3-PCC+ vitamin K *versus* vitamin K (1 observational studies without adjusted data)

Certainty assessment							№ di pazienti		Effetto		Certezza evidenza	Importanza
№ degli studi	Disegno dello studio	Rischio di distorsione	Mancanza di riproducibilità dei risultati	Mancanza di generalizzabilità	Imprecisione	Ulteriori considerazioni	PCC + vitamin k	Vitamin K	Relativo (95% CI)	Assoluto (95% CI)		
Mortality at 24 hours, 30days/1month, and 12 months												
0									non stimabile		-	
Health related quality of life												
0									non stimabile		-	
Adverse effects (Stroke, MI, Thromboembolism (PA and venous)												
1	studi osservazionali	non importante	non importante	non importante	serio [a]	nessuno	nessun paziente nei gruppi PCC+Vitamin K e Vitamin K ha presentato complicazioni trombotiche				⨁◯◯◯ MOLTO BASSA	
Reversal of anti-coagulation as measured by laboratory assessment (degree of reversal (reduction of INR))												
0									non stimabile		-	
Degree of resuscitation (units of blood transfused)												
0									non stimabile		-	
Neurological outcome (brain injured patients)												
0									non stimabile		-	
Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing).												
0									non stimabile		-	
ICH progression												
1	studi osservazionali	non importante	non importante	non importante	serio [a]	nessuno	Warfarin reversal using PCC had a significant negative association with pregressive Hemorragic Injuries (odds ratio: 0.03, 95%confidence interval: 0.00–0.41, P = 0.004)				⨁◯◯◯ MOLTO BASSA	
Need for neurosurgical surgey (craniotomy)												
0									non stimabile		-	

CI: Confidence interval

Spiegazioni

a. events <300 rule of thumb

B4-PCC *versus* FFP (in all arms patients take vitamin K) * (1 observational study with adjusted data)

Certainty assessment							№ di pazienti		Effetto		Certezza evidenza	Importanza
№ degli studi	Disegno dello studio	Rischio di distorsione	Mancanza di riproducibilità dei risultati	Mancanza di generalizzabilità	Imprecisione	Ulteriori considerazioni	PCC	FFP	Relativo (95% CI)	Assoluto (95% CI)		
Mortality at 24 hours, 30days/1month, and 12 months ADJUSTED												
1	studi osservazionali	non importante	non importante	non importante	serio [a]	nessuno	2/60 (3.3%)	0/41 (0.0%)	**OR 0.42** (0.04 a 4.41)	**0 meno per 1.000** (da 0 meno a 0 meno)	⨁◯◯◯ MOLTO BASSA	
Health related quality of life												
0									non stimabile		-	
Adverse effects (Stroke, MI, Thromboembolism (PA and venous)												
0									non stimabile		-	
Reversal of anti-coagulation as measured by laboratory assessment (degree of reversal (reduction of INR)) (valutato con: TIme to INR < 1.7, h/median)												
1	studi osservazionali	non importante	non importante	non importante	serio [b]	nessuno	Time to INR <1.7 (h, median, IQR) PCC: 10.5 (6, 17.5), FFP:21 (15, 36), p= 0.002				⨁◯◯◯ MOLTO BASSA	
Degree of resuscitation (units of blood transfused)												
0									non stimabile		-	
Neurological outcome (brain injured patients)												
0									non stimabile		-	
Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing). (valutato con: Worsening mental health)												
1	studi osservazionali	non importante	non importante	non importante	serio [a]	nessuno	18/60 (30.0%)	13/41 (31.7%)	**OR 0.92** (0.39 a 2.18)	**18 meno per 1.000** (da 164 meno a 186 più)	⨁◯◯◯ MOLTO BASSA	
ICH Progression ADJUSTED												
1	studi osservazionali	non importante	non importante	non importante	serio [a]	nessuno	26/60 (43.3%)	21/41 (51.2%)	**OR 1.13** (0.44 a 2.90)	**30 più per 1.000** (da 196 meno a 241 più)	⨁◯◯◯ MOLTO BASSA	
Need for neurosurgical surgery (craniotomy) ADJUSTED												
1	studi osservazionali	non importante	non importante	non importante	molto serio [a,c]	nessuno	9/60 (15.0%)	8/41 (19.5%)	**OR 2.51** (0.64 a 9.84)	**183 più per 1.000** (da 61 meno a 509 più)	⨁◯◯◯ MOLTO BASSA	

CI: Confidence interval; **OR:** Odds ratio

Spiegazioni

a. events <300 rule of thumb
b. sample size< 400 participants
c. 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- 4FPCC versus altro

C1-4FPCC versus 3FPCC+rFVIIa (1 observational study without adjusted data)

Certainty assessment							№ di pazienti		Effetto		Certezza evidenza	Importanza
№ degli studi	Disegno dello studio	Rischio di distorsione	Mancanza di riproducibilità dei risultati	Mancanza di generalizzabilità	Imprecisione	Ulteriori considerazioni	4FPCC	3FPCC+rFVIIa	Relativo (95% CI)	Assoluto (95% CI)		
Mortality												
1	studi osservazionali	non importante	non importante	non importante	molto serio [a,b]	nessuno	1/34 (2.9%)	9/53 (17.0%)	**OR 0.15** (0.02 a 1.23)	**140 meno per 1.000** (da 166 meno a 31 più)	⨁◯◯◯ MOLTO BASSA	
Health related quality of life												
0									non stimabile		-	
Degree of resuscitation (units of blood transfused)												
0									non stimabile		-	
Adverse effects. (valutato con: New diagnosis of DVT)												
1	studi osservazionali	non importante	non importante	non importante	serio [a]	nessuno	1/34 (2.9%)	12/53 (22.6%)	**OR 0.10** (0.01 a 0.84)	**198 meno per 1.000** (da 223 meno a 29 meno)	⨁◯◯◯ MOLTO BASSA	
Reversal of anti-coagulation as measured by laboratory assessment (degree of reversal (reduction of INR)) (valutato con: Subject with successful degree of reversal (INR <1.5))												
1	studi osservazionali	non importante	non importante	non importante	molto serio [a,b]	nessuno	33/34 (97.1%)	46/53 (86.8%)	**OR 5.02** (0.59 a 42.79)	**103 più per 1.000** (da 73 meno a 129 più)	⨁◯◯◯ MOLTO BASSA	
Neurological outcome (brain injured patients)												
0									non stimabile		-	
Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing).												
0									non stimabile		-	
ICH progression												
0									non stimabile		-	
Need for neurosurgical surgey (valutato con: Neurosurgical procedure)												
1	studi osservazionali	non importante	non importante	non importante	molto serio [a,b]	nessuno	2/34 (5.9%)	9/53 (17.0%)	**OR 0.31** (0.06 a 1.51)	**110 meno per 1.000** (da 158 meno a 66 più)	⨁◯◯◯ MOLTO BASSA	

CI: Confidence interval; **OR:** Odds ratio

Spiegazioni

a. events <300 rule of thumb

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.

C2-4FPCC versus 3FPCC (2 observational studies with adjusted data)

Certainty assessment							№ di pazienti		Effetto		Certezza evidenza	Importanza
№ degli studi	Disegno dello studio	Rischio di distorsione	Mancanza di riproducibilità dei risultati	Mancanza di generalizzabilità	Imprecisione	Ulteriori considerazioni	4FPCC	3FPCC	Relativo (95% CI)	Assoluto (95% CI)		
Mortality at 24 hours, 30days/1month, and 12 months UNADJUSTED												
2	studi osservazionali	non importante	non importante	non importante	molto serio [a,b]	nessuno	10/41 (24.4%)	16/103 (15.5%)	**OR 1.83** (0.72 a 4.64)	**96 più per 1.000** (da 38 meno a 305 più)	⨁◯◯◯ MOLTO BASSA	
Health related quality of life												
0									non stimabile		-	
Adverse effects (Stroke, MI, Thromboembolism (PA and venous) ADJUSTED												
1	studi osservazionali	non importante	non importante	non importante	molto serio [a,b]	nessuno	2/23 (8.7%)	5/57 (8.8%)	**OR 0.43** (0.10 a 1.85)	**48 meno per 1.000** (da 78 meno a 63 più)	⨁◯◯◯ MOLTO BASSA	
Successful anticoagulation reversal (INR < 1.5) ADJUSTED												
2	studi osservazionali	non importante	non importante	non importante	serio [a]	nessuno	35/41 (85.4%)	41/101 (40.6%)	**OR 7.01** (2.42 a 20.31)	**421 più per 1.000** (da 217 più a 527 più)	⨁◯◯◯ MOLTO BASSA	
Degree of resuscitation (units of blood transfused)												
1	studi osservazionali	non importante	non importante	non importante	non importante	nessuno	pRBC transfused post PCC administration (units/pt); 3FPCC: 0.4 ± 0.8, 4FPCC: 0.8 ± 1.7, p=0.663 FFP transfused post PCC administration (units/pt); 3FPCC: 0.5 ± 1.3, 4FPCC: 0.6 ± 1.5, p=0.748 Platelets transfused post PCC administration (units/pt); 3FPCC: 0.1 ± 0.4, 4FPCC: 0.3 ± 0.7, p=0.215				⨁⨁◯◯ BASSA	
Neurological outcome (brain injured patients)												
0									non stimabile		-	
Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing).												
0									non stimabile		-	
ICH progression												
0									non stimabile		-	
Need for neurosurgical surgey (craniotomy)												
0									non stimabile		-	

CI: Confidence interval; **OR:** Odds ratio

Spiegazioni

a. events <300 rule of thumb

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.

C3-4FPCC versus Factor IX complex + vitamin K with or without FFP (1 observational study without adjusted data)

Certainty assessment							№ di pazienti		Effetto		Certezza evidenza	Importanza
№ degli studi	Disegno dello studio	Rischio di distorsione	Mancanza di riproducibilità dei risultati	Mancanza di generalizzabilità	Imprecisione	Ulteriori considerazioni	4FPCC	Factor IX complex + vitamin K with or without FFP	Relativo (95% CI)	Assoluto (95% CI)		
Mortality at 24 hours, 30days/1month, and 12 months												
0									non stimabile		-	
Health related quality of life												
0									non stimabile		-	
Adverse effects (Stroke, MI, Thromboembolism (PA and venous)												
1	studi osservazionali	non importante	non importante	non importante	serio [a]	bias di pubblicazione fortemente sospetto [b]	no difference between groups (4FPCC n=26, factor IX complex e vitamina K, con e senza FFP n=26)				⨁◯◯◯ MOLTO BASSA	
Reversal of anti-coagulation as measured by laboratory assessment (degree of reversal (reduction of INR))												
1	studi osservazionali	non importante	non importante	non importante	serio [a]	bias di pubblicazione fortemente sospetto [b]	L'INR è stato riportato < 2 nel 100% dei pazienti nel gruppo 4F-PCC verso l'84.6% dei pazienti nel gruppo factor IX complex. L'INR è stato ridotto a <1.6 nel 90.8% dei pazienti nel gruppo 4f-PCC vero il 50% del gruppo factor IX complez (p<0.05). La media del pre reversal INRs erano 3.5 e 4 e avevano un range di 1.1 – 10, e da 1.3 a 10 rispettivamente nei gruppi 4F-PCC e factor IX complex (p=0.29); (4FPCC n=26, factor IX complex e vitamina K, con e senza FFP n=26)				⨁◯◯◯ MOLTO BASSA	
Degree of resuscitation (units of blood transfused)												
0									non stimabile		-	
Neurological outcome (brain injured patients)												
0									non stimabile		-	
Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing).												
0									non stimabile		-	
ICH progression												
0									non stimabile		-	
Need for neurosurgical surgey (craniotomy)												
0									non stimabile		-	

CI: Confidence interval

Spiegazioni

a. events <300 rule of thumb
b. abstract without full publication

D- Dosi diverse 4FPCC a confronto

4FPCC 1500 versus 4FPCC 1000 (2 observational studies of which 1 with adjusted data)

Certainty assessment							№ di pazienti		Effetto		Certezza evidenza	Importanza
№ degli studi	Disegno dello studio	Rischio di distorsione	Mancanza di riproducibilità dei risultati	Mancanza di generalizzabilità	Imprecisione	Ulteriori considerazioni	4FPCC 1500	4FPCC 1000	Relativo (95% CI)	Assoluto (95% CI)		
Mortality at 24 hours, 30days/1month, and 12 months												
1	studi osservazionali	non importante	non importante	non importante	serio [a]	bias di pubblicazione fortemente sospetto [b]	75 nel gruppo 1500 PCC e 144 nel gruppo 1000 PCC. Non si evince nessuna differenza statisticamente significativa in mortalità per tutte le cause tra i due gruppi				⨁◯◯◯ MOLTO BASSA	
Health related quality of life												
0									non stimabile		-	
Adverse events												
1	studi osservazionali	non importante	non importante	non importante	serio [a]	bias di pubblicazione fortemente sospetto [b]	Dati di eventi avversi (ie. Eventi trombotici) vengono riportato da Cohen et 2018, che include 219 pazienti: 75 nel gruppo 1500 PCC e 144 nel gruppo 1000 PCC. Non si evince nessuna differenza statisticamente significativa in eventi trombotici tra i due gruppi.				⨁◯◯◯ MOLTO BASSA	
Reversal of anti-coagulation as measured by laboratory assessment (degree of reversal (reduction of INR))												
2	studi osservazionali	non importante	non importante	non importante	serio [a]	bias di pubblicazione fortemente sospetto [b]	Cohen et al. 2017 con dati non aggiustati per co-variabili, sono stati inclusi 194 pazienti, divisi in due gruppi : dose 1500 PCC può risultare in una più efficace riduzione di INR < 1.5 al post trattamento rispetto a una dose di 1000 PCC. Cohen et al.2018: 75 nel gruppo 1500 PCC e 144 nel gruppo 1000 PCC. Aggiustando per la media INR al baseline, è stata riportata una riduzione nel post intervento di 0.27 IU fra i gruppi (da bassa ad alta dose).				⨁◯◯◯ MOLTO BASSA	
Degree of resuscitation (units of blood transfused)												
0									non stimabile		-	
Neurological outcome (brain injured patients)												
0									non stimabile		-	
Patient-reported outcomes (pain/discomfort, return to normal activities, psychological wellbeing).												
0									non stimabile		-	
ICH progression												
0									non stimabile		-	
Need for neurosurgical surgey (craniotomy)												
0									non stimabile		-	

CI: Confidence interval

Spiegazioni

a. events <300 rule of thumb
b. abstract without full publication

Appendice F – Bibliografia degli studi inclusi.

	TITLE	JOURNAL	YEAR	AUTHORS
1	Antiplatelet Agent Reversal Is Unnecessary in Blunt Traumatic Brain Injury Patients Not Requiring Immediate Craniotomy	The American surgeon	2020	Agyabeng-Dadzie, Kojo and Hunter Jocelyn, E. and Smith Timothy, R. and Jordan, Monica and Safcsak, Karen and Ibrahim Joseph, A. and Cheatham Michael, L. and Bhullar Indermeet, S.
2	A systematic review and meta - analysis of traumatic intracranial hemorrhage in patients taking prehospital antiplatelet therapy: Is there a role for platelet transfusions?	The journal of trauma and acute care surgery	2020	Alvikas, Jurgis and Myers Sara, P. and Wessel Charles, B. and Okonkwo David, O. and Joseph, Bellal and Pelaez, Carlos and Doberstein, Cody and Guillotte Andrew, R. and Rosengart Matthew, R. and Neal Matthew, D.
3	Activated prothrombin complex concentrate for warfarin reversal in traumatic intracranial hemorrhage	The Journal of surgical research	2017	Carothers, Chancey and Giancarelli, Am and a and Ibrahim, Joseph and Hobbs, Br and on
4	Comparison of two fixed doses of four factor prothrombin complex concentrate for rapid warfarin reversal	Journal of the American College of Surgeons	2017	Cohen, Jessica Dr and Georgiades, Maria D. and Klein, Eric and Bank, Matthew A.
5	Optimal dosing of 4-factor prothrombin complex concentrate for reversal of warfarin associated coagulopathy	Journal of Hospital Medicine	2018	Cohen, Jessica M. D. and Klein, Eric and Sfakianos, Maria and Chhibber, Vishesh and Logdberg, Lennart and Rosenberg, David and Bank, Matthew
6	Evaluation of fixed dose four-factor prothrombin complex concentrate for warfarin reversal at a level 1 trauma center	Critical Care	2015	Drone, H. and Jancik, J. and Gorlin, J. and McCarthy, M.
7	Fixed, low-dose activated prothrombin complex concentrate for warfarin reversal in tbi patients	Critical Care Medicine	2016	Hobbs, Br and on and Carothers, William and Giancarelli, Am and a and Ibrahim, Joseph

8	Platelet transfusion does not improve outcomes in patients with brain injury on antiplatelet therapy	Brain injury	2018	Holzmacher Jeremy, L. and Maluso, Patrick and Gamsky, Nathaniel and Amdur, Richard and Sarani, Babak and https://orcid.org, Id Orcid and Reynolds, Cass and ra and Patel, Mayur and Holl and , Seth and Hancock, Heather and Moore, Henry and Acquista, Elizabeth and Carrick, Matthew and Metzler, Michael and Dunn, Julie
9	Warfarin trauma patients: Comparing prothrombin complex concentrate to vitamin K / fresh frozen plasma	Critical Care Medicine,	2019	Huang, Gregory and Hileman, Barbara and Chance, Elisha and Steiner, Dena and March and , Tiffany and Gianetti, Emily
10	Combination Therapy Using Prothrombin Complex Concentrate and Vitamin K in Anticoagulated Patients with Traumatic Intracranial Hemorrhage Prevents Progressive Hemorrhagic Injury: A Historically Controlled Study	Neurologia medico chirurgica	2021	Koyama, Hiroshi and Yagi, Kenji and Hara, Keijiro and Matsubara, Shunji and Tao, Yoshifumi and Uno, Masaaki and Koyama, Hiroshi
11	Is Platelet Transfusion Effective in Patients Taking Antiplatelet Agents Who Suffer an Intracranial Hemorrhage?	Journal of Emergency Medicine	2015	Leong, Lim Beng Mbbs and David, Teng Kuan Peng
12	Platelet Transfusion After Traumatic Intracranial Hemorrhage in Patients on Antiplatelet Agents	The Journal of surgical research	2020	Lokh and wala Adil, M. and Asmar, Samer and Khurrum, Muhammad and Chehab, Mohamad and Bible, Letitia and Castanon, Lourdes and Ditillo, Michael and Joseph, Bellal
13	Choosing the Best Approach to Warfarin Reversal After Traumatic Intracranial Hemorrhage	The Journal of surgical research	2020	Lumas Shunella, G. and Hsiang, Walter and Becher Robert, D. and Maung Adrian, A. and Davis Kimberly, A. and Schuster Kevin, M.
14	Is there a difference in efficacy, safety, and cost-effectiveness between 3-factor and 4-factor prothrombin complex concentrates among trauma patients on oral	Journal of critical care	2016	Mangram, Alicia and Oguntodu Olakunle, F. and Dz and u James, K. and Hollingworth Alexz and ra, K. and Hall, Scott and Cung, Christina and Rodriguez, Jason and

	anticoagulants?			Yusupov, Igor and Barletta Jeffrey, F.
15	Propensity score adjusted comparison of three-factor versus four-factor prothrombin complex concentrate for emergent warfarin reversal : a retrospective cohort study	BMC emergency medicine	2020	Margraf David, J. and Chapman Scott, A. and Seaburg, Scott and Beilman Gregory, J. and Wolfson, Julian and Gipson Jonathan, C.
16	Emergent reversal of vitamin K antagonists: addressing all the factors	American journal of surgery	2016	Martin David, T. and Barton Cassie, A. and Dodgion, Christopher and Schreiber, Martin
17	Efficacy of platelet transfusion in the management of acute subdural hematoma	Clinical neurology and neurosurgery	2018	Ogunlade, John and Wiginton James, G. th and Ghanchi, Hammad and Wacker, Margaret and Menoni, Rosalinda and Miulli, Dan and Al-Atrache, Zein
18	The Role of Desmopressin on Hematoma Expansion in Patients with Mild Traumatic Brain Injury Prescribed Pre-injury Antiplatelet Medications	Neurocritical Care	2020	Barletta JF, Abdul-Rahman D, Hall ST, Mangram AJ, Dzandu JK, Frontera JA, Zach V.

Appendice G – Costi e costo-efficacia.

INDICE

Selezione degli studi

fonti- Revisione della letteratura

È stata effettuata una revisione sistematica della letteratura sulle banche dati Embase, Medline e Cochrane Library. Sono stati individuati 5 records (al netto delle duplicazioni). Di questi sono stati esclusi tutti i lavori: (1) che non riportavano esplicitamente analisi dei costi intese come metodologia di identificazione, misurazione e valorizzazione delle risorse assorbite o analisi costo efficacia; (2) che fossero concentrati su prestazioni sanitarie non inerenti il trauma (ad esempio chirurgia vascolare).

fonti-Studi considerati nella linea guida NICE

In aggiunta alle evidenze reperite con la revisione della letteratura, laddove queste fossero insufficienti o nulle, sono state considerate evidenze riportate dalla linea guida N39 del NICE.

fonti-Studi considerati da altre fonti (strategia di ricerca per efficacia quesito Q15)

Sono stati selezionati 3 studi fra quelli già inclusi per gli outcomes critici e importanti provenienti dalla stringa di ricerca per efficacia clinica.

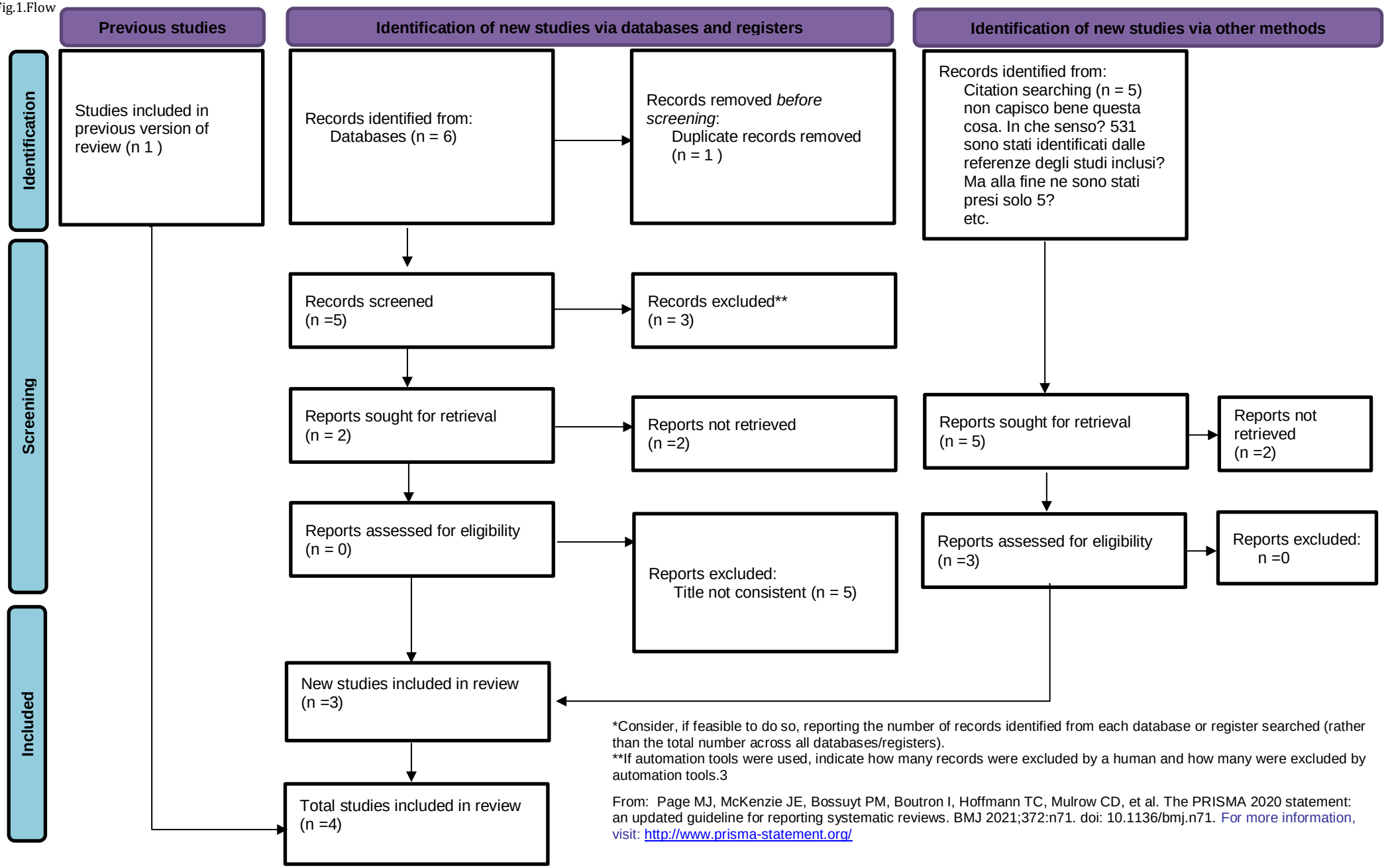
fonti- Costi italiani

Per quanto riguarda i costi inerenti la realtà italiana dei trattamenti, si è fatto riferimento al prontuario farmaceutico AIFA.

In totale sono stati inseriti 4 lavori, di cui uno proveniente da revisioni precedentemente pubblicate (Guest, 2010) e tre identificati con altri metodi (stringa di ricerca inerente all'efficacia). Nessun lavoro proveniente dalla stringa di ricerca inerente gli spetti economici è stato inserito.

Dei 4 articoli inclusi: 2 sono relativi ad analisi costo efficacia e 2 relativi ad analisi dei costi. La **figura 1** mostra i risultati della revisione sistematica della letteratura.

Fig.1.Flow



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.3

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Risultati

Costi

Costi internazionali

Relativamente all'analisi dei costi, i records inclusi riguardano abstract di convegni (Cohen 2018, Drone 2015). Ambedue gli articoli conducono una valutazione dei costi dei complessi protrombinici. Cohen (2018) ha l'obiettivo di determinare il dosaggio ottimale. I risultati del lavoro mostrano come il dosaggio di 1500 UI sia meno costoso del dosaggio 1000 UI con un risparmio di circa $ 1.075 per paziente).

Il lavoro di Drone et al. (2015), invece, conduce una valutazione dei costi del complesso protrombinico concentrato 4 fattori (4F-PCC) contro il complesso protrombinico concentrato 3 fattori (3F-PCC). I risultati mostrano come il 4F-PCC conduca ad un risparmio di $802,63.

In aggiunta a questo update, la linea-guida NICE NG39 aggiornata al 2016 identificava i seguenti costi britannici per i relativi interventi di reversal negli adulti (Table 59) e nei bambini (Table 60):

Table 59: Cost of interventions and resources

Resource	Cost	Unit	Source
Fibrinogen concentrate	£500	1-mg vial	GDG contact
Cryoprecipitate	£181	Pooled cryoprecipitate (5 pack) Mean: 199 ml per pooled pack	NHS Blood and transplant price list 2014/15[105]
Platelets	£197	1 adult therapeutic dose	NHS Blood and transplant price list 2014/15
Vitamin K	£0.38	10 mg vial	BNF [73]
FFP	£28	1 pack Mean: 271 ml per pack (240-280 is common)	NHS Blood and transplant price list 2014/15
PCC	£600	1000 International Units	Manufacturer website
Factor VIIa	£667		Blood Products, Band 1 (Factor VIIa (recombinant)) (Mean cost per episode of care where used). NHS reference cost 2012-2013. Health Resource Groups code XD05Z [37]
Additional blood product resources			
Red blood cells	£122	1 pack 220-300 ml per pack	NHS Blood and transplant price list 2014/15 [105]

Source: Unit information sourced from GDG contact and internet.

Table 60: Intervention costs for children and young people

Resource	Cost	Unit	Source
FFP			
Paediatric MBFFP (Non-UK Sourced)	£178	1 pack Mean: 226 ml per bag Range: 200 -320 ml	NHS Blood and transplant price list 2014/15 [105]
Octaplas LG	£64	1 pack 200 ml	GDG contact
Cryoprecipitate			
MB cryoprecipitate-pooled (non-UK sourced)	£1,080	Pooled cryoprecipitate (6 pack) Mean: 275 ml per pooled pack	NHS Blood and transplant price list 2014/15

Costi italiani

Per i prezzi degli interventi in Italia è stato consultato il prontuario AIFA. È possibile notare come i costi unitari delle varie formulazioni siano molto eterogenei. Tuttavia, rispetto a tali costi è necessario prendere in considerazione l'efficacia incrementale rispetto alla popolazione di riferimento. Nella Tabella 1 si riportano i costi unitari dei regimi reversal attualmente utilizzati in Italia, con la relativa fascia di rimborso.

Tabella 1. Costi unitari delle varie formulazioni reversal.

REVERSAL	CLASSE	prezzo ex factory
IDARUCIZUMAB	H	2.493,75 €
COMPLESSO PROTROMBINICO CONCENTRATO 4 FATTORI	C	208,13 €
PLASMA FRESCO CONGELATO	H	20,00-40,00€
COMPLESSO PROTROMBINICO ATTIVATO	H	460,00 €
PROTAMINA CLORIDRATO	H	4,38 €
COMPLESSO PROTROMBINICO CONCENTRATO 3 FATTORI	H	1.224,31 €
FATTORE VII RICOMBINANTE	H	466,72 €
ANDEXANET ALFA	C	23.407,34 €

Costo efficacia

La prima evidenza inserita è proveniente dalle linee guida emanate dal NICE (Guest et al., 2010). L'articolo è relativo alla valutazione costo efficacia del plasma fresco congelato versus protrombina.

Il lavoro mostra come l'utilizzo della protrombina abbia un profilo di costo efficacia molto favorevole rispetto al plasma fresco congelato, con un rapporto costo efficacia incrementale ampiamente al di sotto delle soglie critiche di accettabilità (£ 35.000/QALY) in tutti gli scenari

considerati. Nell'analisi di sensibilità probabilistica, venivano inoltre effettuate 1.000 simulazioni delle quali il 100% restituiva un ICER inferiore ai £ 16.000/QALY.

Certainty of Evidence: la valutazione economica è difficilmente applicabili a pazienti con trauma, dato che la popolazione oggetto di studio era soggetta ad emorragie non da trauma, di tipo gastrointestinale, intracranico e retroperitoneale.

PCC è cost-effective nella comparazione PCC vs FFP per reversal del warfarin.

Table 58: Economic evidence profile: PCC versus FFP

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Guest 2010[57,57] (UK)	Partially applicable[a]	Potentially/ very serious limitations[b]	Probabilistic decision tree with a lifetime horizon comparing PCCs with FFP for three different types of haemorrhage: intracranial, gastrointestinal and retroperitoneal in patients receiving anti-coagulant therapy using warfarin.[c]	Intracranial £3,246 Gastrointestinal £401 Retroperitoneal £534	Intracranial 2.1 QALYs Gastrointestinal 0.14 QALYs Retroperitoneal 0.71 QALYs	Intracranial £1,600 per QALY Gastrointestinal £2,900 per QALY Retroperitoneal £800 per QALY	PSA with 10,000 iterations was performed, with variation in probabilities, utilities, unit costs and resource use in the model. The probability of PCC being cost-effective was ≥ 90% at a threshold of £10,000 per QALY for all types of haemorrhage. Deterministic sensitivity analyses were also performed. All sensitivities for all types of haemorrhage resulted in a cost per QALY of ≤ £16,000 for treatment with PCC.

Fonte: Linea guida NICE NG39

Il secondo lavoro (Mangram et al., 2016) è stato identificato con metodi alternativi alla stringa di ricerca. Questo lavoro ha l'obiettivo di valutare l'efficacia, la sicurezza e la costo efficacia del 4F-PCC contro il 3F-CC. Per quanto riguarda l'analisi economica, il lavoro dimostra che, sebbene il 4F-PCC sia più costoso del 3F-PCC, il costo per reversal ottenuto si dimostra favorevole ($ 5.382 vs $ 3.797).

Valutazione della qualità delle evidenze

La valutazione della qualità delle evidenze di costo-efficacia è stata condotta a due livelli.

In prima analisi è stata applicata la checklist CHEERS - Consolidated Health Economics Evaluations Reporting Standards- (Husereau 2013) per una valutazione della qualità metodologica degli studi. In secondo luogo è stata applicata la checklist per la valutazione della generalizzabilità (Drummond, 2005; Ruggeri, 2015) dei risultati ottenuti.

L'analisi della generalizzabilità può dar luogo a tre tipi di risultati diversi:

1. Analisi context-specific: nel caso in cui lo studio non rispetti più di due requisiti richiesti dalla checklist;
2. Analisi adattabile: nel caso in cui lo studio non rispetti un requisito richiesto dalla checklist;
3. Analisi generalizzabile: nel caso in cui lo studio rispetti tutti i requisiti richiesti dalla checklist.

Nel caso in cui ci si trovi in presenza di analisi adattabili, questo adattamento può essere condotto attraverso un'analisi bayesiana che trasformi i risultati dello studio in quantili di una distribuzione stocastica. Questa analisi dà luogo ad una distribuzione probabilistica che può essere interpretata come il livello di affidabilità dello studio rispetto al contesto di riferimento.

La costruzione dell'analisi stocastica avviene considerando i valori medi dei risultati costo efficacia degli studi ritenuti adattabili e le relative deviazioni standard, che servono a popolare una distribuzione di tipo *gamma.*

Il lavoro di Guest et al. (2010), cosi come anche specificato nelle linee guida del NICE, non è relativo a pazienti con trauma e di conseguenza risulta non adattabile.

Per quanto riguarda il lavoro di Mangram et al. (2016), invece, nel lavoro non sono presenti informazioni utile per poter applicare la checklist di valutazione della qualità metodologica secondo gli standard CHEERS. Non sono presenti informazioni in merito al disegno dello studio economico, al metodo di stima dei costi, all'orizzonte temporale ecc... Per questo motivo la qualità delle evidenze risulta essere molto bassa e ciò rende impossibile anche effettuare una valutazione della generalizzabilità.

Conclusioni

Dalla analisi delle evidenze relative ai costi ed al costo efficacia, non risultano attualmente evidenze che, considerata la qualità ed il livello di generalizzabilità, possano essere considerate applicabili al contesto italiano.

Tuttavia, i risultati ottenuti in un contesto UK ed inclusi nelle linee guida NICE, ed uno studio inerente al contesto US, che non sono adattabili ad un contesto italiano mostrano che

- La protrombina è costo efficace rispetto al plasma fresco congelato;
- Nell'ambito dei complessi protrombinici quelli a 4 fattori risultano essere meno costosi o comunque costo efficaci rispetto a quelli a 3 fattori.

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