## Evidence Tables

**PHAR5:** a) For patient with acute warfarin-associated haemorrhagic stroke what is the safety and efficacy of i) vitamin K ii) fresh frozen plasma iii) prothrombin complex conjugate?

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
<th>Evidence level</th>
<th>Number of patients</th>
<th>Patient characteristics</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Length of follow-up</th>
<th>Outcome measures</th>
<th>Source of funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cartmill M, Dolan G, Byrne JL et al. Prothrombin complex concentrate for oral anticoagulant reversal in neurosurgical emergencies. <em>British Journal of Neurosurgery</em>. 2000; 14(5):458-461. Ref ID: 62</td>
<td>Prospective case series</td>
<td>single centre 3</td>
<td>N=12</td>
<td>Patients admitted to a neurosurgical unit with spontaneous intracranial haemorrhage associated with warfarin</td>
<td>Prothrombin complex concentrate (PCC) 50μ/kg plus 10 mg i.v vitamin K N=6</td>
<td>Fresh frozen plasma (FFP) 4 units (approx 800 ml) plus 10mg i.v vitamin K N=6</td>
<td>180 minutes</td>
<td>Mean International Normalised Ratios</td>
<td>None reported</td>
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<td>PCC patients: 3 males and 3 females with a median age of 69 yrs (range 45-77). Pathologies included spontaneous intracerebral haemorrhage, acute subdural haematoma and subarachnoid haemorrhage</td>
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<td>FPP patients: 3 males and 3 females with a median age of 71 yrs (range 48-77). Their pathologies were identical to the PCC patients.</td>
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</table>

*INR

PCC pre-treatment and post-treatment mean INRs were 4.86 (range 2.50 to 10.0) and 1.32 (range 1.09 to 1.49) (within-group comparison p<0.001), respectively. All patients treated with PCC had corrected INRs below the haematologically recommended safe surgical level of 1.50.

FFP pre-treatment and post-treatment mean INRs were 5.32 (range 2.40 to 10.0) and 2.30 (range 1.30 to 2.30) (NS). Only one patient in the FFP group had the recommended INR below the recommended level of 1.50. One patient had incomplete reversal owing to the development of pulmonary oedema following the infusion of FFP.

*Correction time

Correction time (from commencement of treatment to receiving the result from the laboratory) was 41 mins (range 30 to 60) in the PCC group (within group comparison p<0.001) compared to 115 minutes (range 60 to 180) in the FFP group.
This includes two patients who required a second FFP infusion.

*Serial INRs
Serial INRs were performed as part of standard post treatment monitoring. In the PCC group the INR remained reversed at 48 hrs in five patients ranging from 0.98 to 1.31. The sixth patient died from neurological deterioration.

Patients in the FFP group had a wide range of INRs in the 48 hrs following treatment (range 1.6 to 2.8)


<table>
<thead>
<tr>
<th>Effect</th>
<th>Reaction Level Scale</th>
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</thead>
<tbody>
<tr>
<td>None reported</td>
<td></td>
</tr>
</tbody>
</table>

**Prothrombin time**
In patients treated with PCC, the mean prothrombin time decreased from 2.83 to 1.22 International Normalised Ratio (INR) within 4.8 hrs compared with a decrease from 2.97 to 1.74 within 7.3 hrs in those given FFP (p<0.001)

* Reaction Level Scale
After treatment signs and symptoms of intracerebral haemorrhage, measured on an eight-point Reaction Level Scale, progressed on average 0.2 grades in patients treated with PCC compared with 1.9 grades in those given FFP (p<0.05).

| Goldstein JN, Thomas SH, Frontiero V et al. Timing of fresh | Retrospective case series, single centre 3 | N=69 | Patients with warfarin-related intracerebral haemorrhage | Fresh Frozen Plasma (FPP) (dosage not stated) | Vitamin K (dosage not stated) | INR reversal (any follow-up INR ≤1.4 within 24 hrs of arrival in the) | 3 months | American Academy of Neurology Foundation, National Stroke Association, National Institute of Neurological Disorders and |
frozen plasma administration and rapid correction of coagulopathy in warfarin-related intracerebral hemorrhage. [see comment]. *Stroke.* 2006; 37(1):151-155. Ref ID: 1613

Exclusion criteria: < 18 yrs, lack of emergency department records, ICH secondary to head trauma, ischemic stroke with haemorrhagic transformation, do-not-resuscitate orders

Patient population: 53% male, 54% ≤75 yrs, Hypertension 15%, antiplatelets use 26%, Initial INR: <2.0 12%, 2.0-3.0 39%, >3.0 49%, hematoma volume: < 30 mL 35%, 30 to 60 mL 28%, >60 mL 19%, Haemorrhage location: deep 61%, lobar 39%, time from symptom onset

Emergency Dept. was scored as positive
Mortality
Glasgow Coma Scale

Stroke
Timing of fresh frozen plasma (FFP) was associated with a successful INR reversal. Median time to first dose of FFP was 90 minutes (range 60 to 205) for patients that had an INR ≤1.4 within 24 hrs, and 210 (100 to 375) minutes in those who did not (p=0.02).

No demographic or clinical variables predicted INR reversal. A low initial INR was not associated with an increased likelihood of INR reversal (NS). Initial INR was not associated with FFP dose (NS) or timing (NS) or vitamin K dose (NS) or timing (NS).

Time to FFP was associated with both dose of FFP (>4 units 120 ± 108 vs <4 units 190 ± 140; p<0.001) and time to vitamin K (>100 min 112 ± 85 vs >100 min 198 ± 152; p<0.002) “suggesting that timing of FFP administration reflects more aggressive overall care”.

Every 30-minute delay in FFP administration was independently associated with a 20% decrease in the probability of a successful INR reversal within 24 hrs (OR 0.8; 95%CI 0.65 to 0.98).

Ref ID: 7

Effect

* Haematoma growth
6/31 (19.3%) of patients treated with PCC alone or in combination with FFP or vitamin K showed haematoma growth compared with 6/18 (33.3%) treated with FFP alone or in combination with vitamin K and 3/6 (50%) of patients treated with vitamin K alone ($\chi^2 p<0.01$ for PCCs). There were no significant differences between the groups on the extent of haematoma growth. When patients treated with PCC were compared with those treated with FFP or vitamin K alone, there was a significantly lower incidence of haematoma growth (6/31 (19.3%) vs 9/24 (37.5%) $\chi^2 p<0.01$).

*INR reversal

Patient population: mean 70 yrs, median Glasgow Coma Scale 10, 60% male, haematoma location: deep (ganglionic and thalamic) 41.8%, lobar (lobar or subcortical nonbasal ganglia haemorrhage) 36.3% or posterior fossa 21.8%

criteria: evidence of primary subdural, epidural or subarachnoid haemorrhage or patients with haematoma surgically evacuated

Effect

* Haematoma growth
6/31 (19.3%) of patients treated with PCC alone or in combination with FFP or vitamin K showed haematoma growth compared with 6/18 (33.3%) treated with FFP alone or in combination with vitamin K and 3/6 (50%) of patients treated with vitamin K alone ($\chi^2 p<0.01$ for PCCs). There were no significant differences between the groups on the extent of haematoma growth. When patients treated with PCC were compared with those treated with FFP or vitamin K alone, there was a significantly lower incidence of haematoma growth (6/31 (19.3%) vs 9/24 (37.5%) $\chi^2 p<0.01$).

*INR reversal
<table>
<thead>
<tr>
<th>Condition</th>
<th>Treated with PCC</th>
<th>Treated with FFP</th>
<th>Treated with Vitamin K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete INR reversal (within 2 hrs)</td>
<td>26/31 (83.8%)</td>
<td>7/18 (38.8%)</td>
<td>0/6 (0%)</td>
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<tr>
<td>($\chi^2$ p&lt;0.01)</td>
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*Functional outcome

There were no significant differences between the groups on the proportion of patients with an mRS of 4 to 6 (PPC 24/31 (78%), FFP 14/18 (78%) and Vitamin K 5/6 (83%); NS).