The use of PCC in warfarin reversal- reducing the need for FFP

Joost van Veen

Consultant Haematologist - Sheffield

Outline

- PCC vs FFP theoretical considerations

- Practical use of PCC
  - Avoiding delays in administration
  - Dose
  - Infusion times

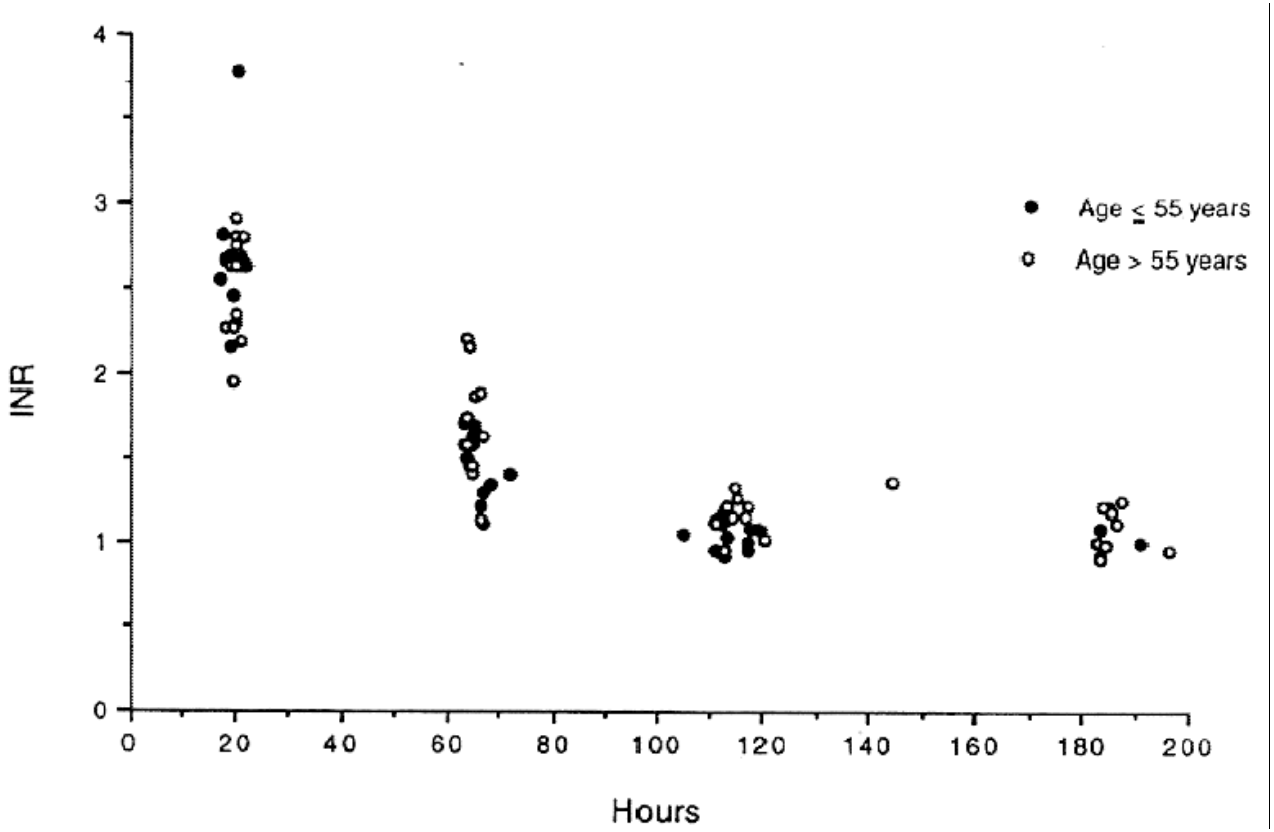
Conclusion

- PCC is the agent of choice for emergency warfarin reversal
- FFP should only be used if PCC is unavailable
- In strong suspicion of intracerebral haematoma after a clear head injury PCC should be given without prior INR or CT scanning
- Reduce delays in PCC administration
  - Standardised protocol independent of INR
  - Education of physicians and nursing staff particularly A&E
  - Availability of PCC at A&E
  - Haematology advice should not be mandatory
- Better planning of emergency procedures may reduce PCC use

Life/limb threatening bleeding or emergency surgery on Warfarin

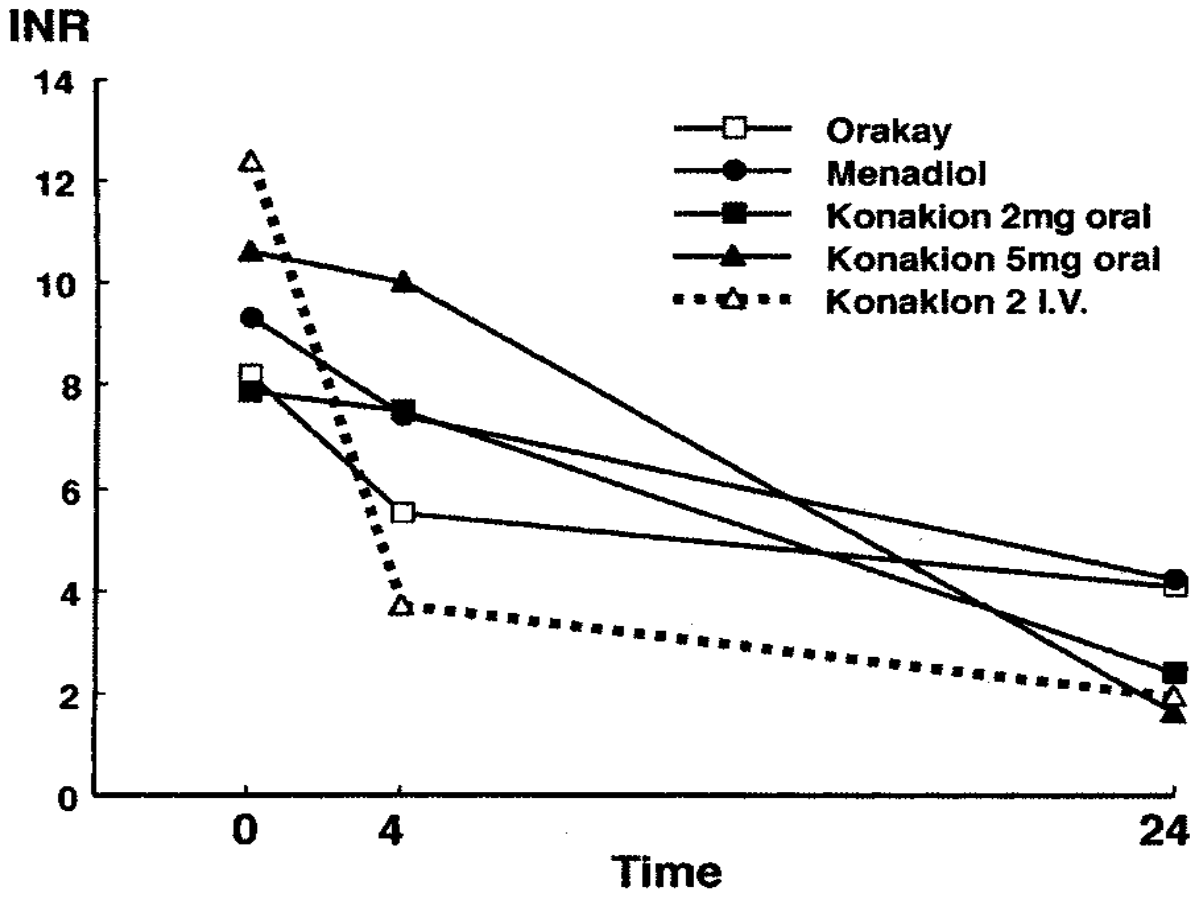
INR following discontinuation of warfarin

You need 4 days to reverse anticoagulation completely by withholding warfarin alone



White RH et al. Ann Int Med 1995; 122:40-42

4 hours correction iv is better than oral vit K



Watson HG et al Brit J Haematol 2001

Major, life-threatening bleeding

(will result in death or major disability if not treated within 6 hours)

1. Stop warfarin – Yes
2. Intravenous vitamin K – Yes
3. FFP or PCC?

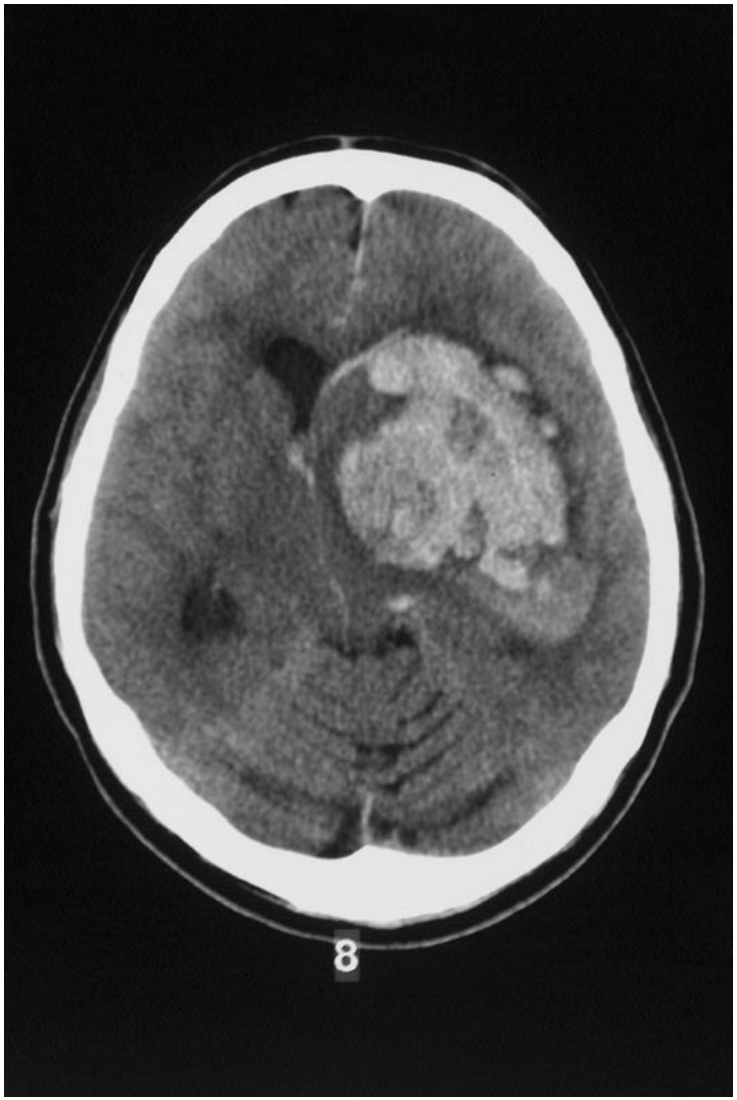
National comparative audit on the use of FFP 2009

Q6 - What was the underlying medical or surgical condition?	National (4635)	
Reversal of warfarin over-anticoagulation	14%	669
[redacted]		

Table 3: FFP given for Warfarin reversal

	Age 16+ years with Warfarin reversal				Age 1-15 years with Warfarin reversal			
	National (669)		Your site (1)		National (3)		Your site ()	
% non-bleeding*	56%	374/667	100%	1/1	33%	1/3	%	/0

- 291 (78%) of these 374 cases were treated in 115 hospitals that used PCC, 41 in 12 sites that did not use PCC and 43 in 9 sites where it was not known if PCC was used.



- Mild haemophilia B
- Factor IX 10% (0.1u/ml)
- Cerebral bleed
- Weight 70kg
- How should he be treated?

Cerebral bleed in mild haemophilia B

70kg, baseline IX 10%

- Most would correct the coagulopathy
  - Usually to 100% FIX:C but minimum will be 50%

- Options
  - Factor IX concentrate (plasma or recombinant)
    - Contains factor IX only
  - Prothrombin complex concentrate (PCC)
    - Contains factors II, IX, X plus variable VII
  - Fresh frozen plasma (FFP)
    - Contains all clotting factors

Cerebral bleed in mild haemophilia B

70kg, baseline IX 10%

	Dose required for target factor IX	
	50%	100%
Recombinant IX Plasma IX	4000u 2800u	9000u 6300u
PCC	2800u	6300u
FFP *	2800ml	6300ml

* FFP impractical due to large volume

- Patient on warfarin
- INR 7.0
  (FIX ~ 10%)
- Cerebral bleed
- Weight 70kg
- How should he be treated?

Clotting factor deficiencies:
Haemophilia B and oral anticoagulants

	II	VII	IX	X
Haemophilia B				
Oral anticoagulation				

Fresh frozen plasma

- Widely available
- Contains all clotting factors
- All factors 1u/ml
- 250ml/unit
- Requires thawing
- Needs to be group specific
- Often not virally inactivated

	FFP (n=11)	
	Pre	Post
INR	8.95	2.0
Factor II	3	17
Factor VII	5	19
Factor IX	10	19
Factor X	6	20

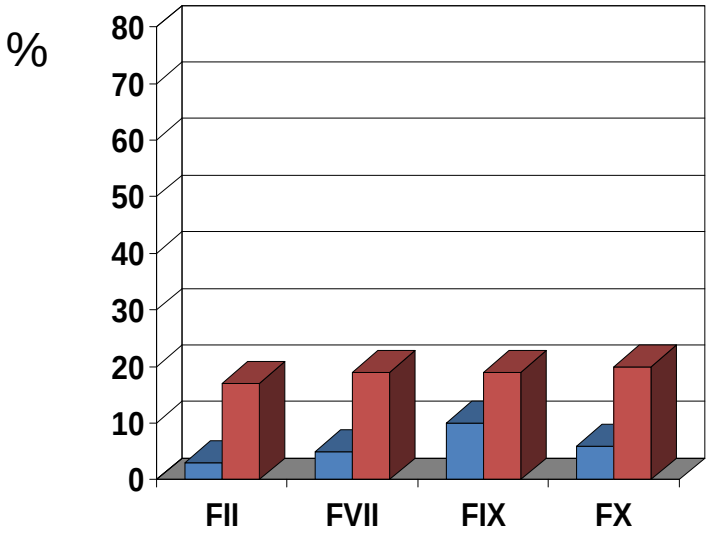
Median clotting factor levels in u/dl
Normal ranges 50-150u/dl

Prothrombin complex concentrate (PCC)

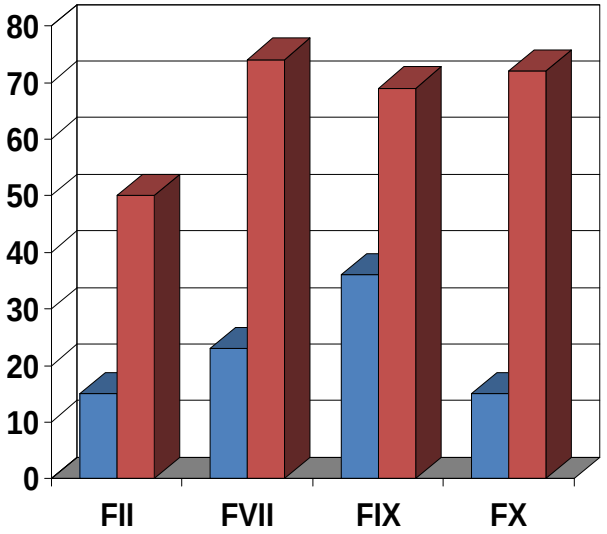
- Contain factors II, IX, X and variable VII
- Lyophilised concentrate
- Administered in 5-10 min
  (despite manufacturer recommendations)
- Corrects the INR within 5 minutes
- Beriplex and Octaplex licensed in UK

Emergency reversal of oral anticoagulation: FFP vs PCC

FFP (800 ml)



PCC (25-50u FIX / kg)



Makris M et al. Thromb Haemost 1997

Emergency Anticoagulation Reversal

	PCC	
	Pre	Post
INR	>20	1.1
Factor II	4.7	94
Factor VII	1.6	30
Factor IX	8.5	66
Factor X	1.1	91

Evans et al 2001

Median clotting factor levels in u/dl (Normal range 50-150%)

Comparison of FFP and Concentrate

	FFP	PCC
Volume	Large	Small
Availability	Widespread	Limited
Administration speed	Slow	Fast
Viral inactivation	Only for SD-FFP and MB-FFP	Yes
Pooled product	Yes for SD-FFP No for standard FFP	Yes
Blood group specific	Yes	No
Thrombogenicity	No	Yes
Cost	€300 per litre	€900 for 70kg person

Warfarin reversal – Guidelines[1]

- Emergency anticoagulation reversal in patients with major bleeding or emergency surgery within 6 – 12 hours should be with 25–50 u/kg four-factor PCC and 5 mg intravenous vitamin K (1B).
- Fresh frozen plasma produces suboptimal anticoagulation reversal and should only be used if prothrombin complex concentrate is not available (1C).
- Recombinant factor VIIa is not recommended for emergency anticoagulation reversal (1B).
- All hospitals managing patients on warfarin should stock a licensed four-factor prothrombin complex concentrate (1C).

Keeling et al BJH, 2011:154;311–324

Warfarin reversal – Guidelines

- Patients on warfarin with a strong suspicion of intracerebral haematoma after a clear head injury should have their INR reversed with PCC immediately and before the CT and INR results are available[1].
  - Mortality of ICH on warfarin 20 – 67%[2]
  - Suggestions that early reversal may reduce haematoma expansion[3,4,5]

- Questions:
  - Effect on mortality?
  - What dose and infusion time?
  - How well is PCC used in practice?

1. Keeling et al BJH, 2011:154;311–324
2. Toth et al Blood transfusion 2012:10/10/2012 Doi 10.2450/2012.0113-12
3. Flibotte et al Neurology 2004 September 28; 63 (6): 1059-64
4. Cucchiara et al Stroke 2008 November; 39 (11): 2993-6.
5. Davis et al Neurology 2006 April 25; 66 (8): 1175-81.

Mortality and INR in warfarin reversal

Menzin et al JTH 2012;10:596-605

- Very little information
- 405 patients, 153 ICH, 283 GI bleed
- Mean INR 3.7 pre FFP, 39% INR >1.5 post FFP
- ICH 30 day mortality
  - 11% corrected INR
  - 26% not corrected
  - Extracranial haemorrhage no effect on mortality
- Other predictors
  - >85yrs, antiplatelet, INR>4

PCC dose (manufacturer recommendations)

Initial INR (Beriplex)	2.0 – 3.9	4.0 – 6.0	> 6.0
Approximate dose ml/kg body weight	1	1.4	2
Approximate dose IU (Factor IX)/ kg body weight	25	35	50
Maximum dose 5000 Units not more than 3 IU/kg/min, max. 210 IU/min, approximately 8 ml/min			

Initial INR (Octaplex)	2 – 2.5	2.5 – 3	3 – 3.5	> 3.5
Approximate dose (ml Octaplex/kg body weight)	0.9 –1.3	1.3 – 1.6	1.6 – 1.9	> 1.9
Maximum dose 3000 Units 1 ml per minute, followed by 2-3 ml per minute, using an aseptic technique.				

- Potential for delay in treatment:
  - INR measurements
  - Potentially long administration times
  - Haematology opinion

Dosing independent of INR

	All patients		ICH		GI haemorrhage		Emergency procedures	
	Median time (mean)	Number of patients	Median time (mean)	Number of patients	Median time (mean)	Number of patients	Median time (mean)	Number of patients
Presentation to INR	2 hours (4 hours)	88	1.3 hours (1.9 hours)	25	1.6 hours (3.8 hours)	26	3.1 hours (5.7 hours)	23
[redacted]								

From: Toth et al Blood transfusion 2012:10/10/2012 Doi 10.2450/2012.0113-12

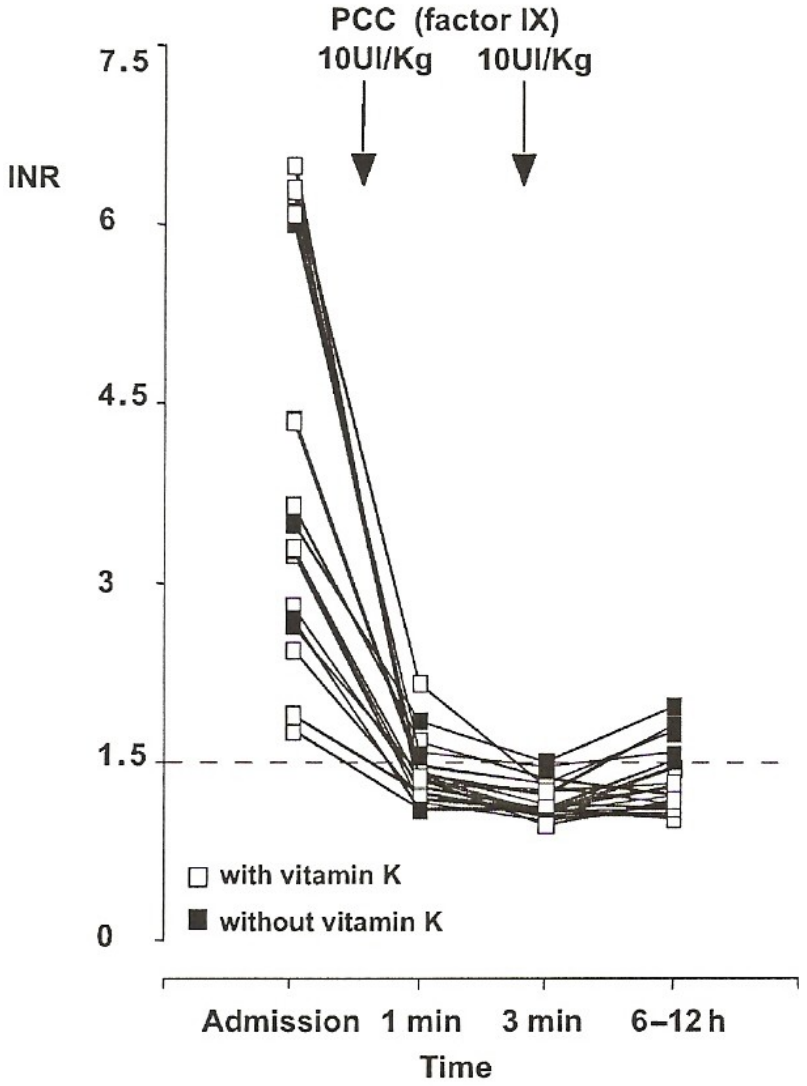
- Evans et al 2001[1]: 10 patients, median INR >20, given 30 U/kg Beriplex. Post INR 1.1.
- Sheffield: 30 U/kg, max 3000 Units over 5 minutes
  - Toth et al[2]: 131 patients. Median INR 3.1 (10.7% > 8). Given median 2000 units (26.8 U/kg). Median post INR 1.2, 85% < 1.5).

1. British J Haematology 2001: 115, 998-1001
2. Blood transfusion 2012:10/10/2012 Doi 10.2450/2012.0113-12

30 U/ kg, max 3000 Units is an effective dose regardless of INR

PCC infusion times

- Vigue et al[1]: PCC given over 3 min, no adverse events
- Sheffield: 30 U/kg, max 3000 Units over 5-10 minutes
  - Toth et al[2]: 131 patients, no immediate complications, thrombotic rate 1.5% in the first week, 3.8% at 60 days.
    - Similar to recent meta-analysis (1.4% in 1032 patients in 4 days)[3]



1. Intensive Care Med 2007 April; 33 (4): 721-5.
2. Blood transfusion 2012:10/10/2012 Doi 10.2450/2012.0113-12
3. Thromb Haemost 2011 September; 106(3): 429-38

Short infusion times (5 – 10 min) appear safe

PCC use: other practical points

- Audit of 131 patients over a 1 year period in Sheffield.
- 47.3% of PCC administered at A&E

Indication for warfarin	Number of patients (%)
Atrial fibrillation	57/131 (43.5%)
Venous Thromboembolism	32/131 (24.4%)
Prosthetic heart valve	22/131 (16.8%)
Ischemic stroke	2/131 (1.5%)
Cardiomyopathy	1/131 (0.8%)
Thromboprophylaxis	1/131 (0.8%)
Unknown	16/131 (12.2%)

Indication for PCC	Number of patients (%)
Emergency surgery	39/131 (29.8%)
GI haemorrhage	36/131 (27.5%)
ICH	35/131 (26.7%)
Large haematoma*	9/131 (6.9%)
Pulmonary haemorrhage	5/131 (3.8%)
Aortic rupture/dissection	4/131 (3%)
Other	3/131 (2.3%)

From: Toth et al Blood transfusion 2012:10/10/2012 Doi 10.2450/2012.0113-12

PCC use: other practical points

	All patients		ICH		GI haemorrhage		Emergency procedures	
	Median time (mean)	Number of patients	Median time (mean)	Number of patients	Median time (mean)	Number of patients	Median time (mean)	Number of patients
Presentation to INR	2 hours (4 hours)	88	1.3 hours (1.9 hours)	25	1.6 hours (3.8 hours)	26	3.1 hours (5.7 hours)	23
Presentation to vitamin K	3.6 hours (8.9 hours)	82	2.7 hours (3.0 hours)	24	3.5 hours (7.1 hours)	22	17.4 hours (22 hours)	18
Presentation to PCC	5.2 hours (11.5 hours)	85	3.0 hours (3.9 hours)	24	7.3 hours (11.8 hours)	28	15.9 hours (20.6 hours)	21

From: Toth et al Blood transfusion 2012:10/10/2012 Doi 10.2450/2012.0113-12

- Delays in sending INR
- Delay in obtaining INR result and PCC administration
- Better planning of surgical procedures can avoid PCC: use vitamin K instead
- Stock PCC in A&E

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