

The Relationship of 4 Factor PCC or Plasma to INR and Factor Levels: An Exploratory Analysis of 2 Clinical Trials

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INTRODUCTION

- Two Phase III randomized prospective clinical trials illustrated that non-activated 4 factor prothrombin complex concentrate (4F-PCC) [Kcentra/Beriplex], when used to reverse vitamin K antagonists (VKA) in patients with acute major bleeding or prior to an urgent surgery/invasive procedure, was successful in decreasing INR and achieving hemostatic efficacy.
- Many subjects had their post-treatment INR performed outside of the protocol window, leading to clinically relevant INR levels that were not included in the trial results.
- Successful INR reversal was considered ≤ 1.3 , even though many consider reversal "successful" at higher levels.

Dosing Protocol Used in the Clinical Trials

| INR | 4F-PCC (units/kg) | Plasma (mL/kg) | Vitamin K |
|---------|-------------------|----------------|-----------|
| 2 to <4 | 25 | 10 | 2-10 mg |
| 4 to 6 | 35 | 12 | |
| >6 | 50 | 15 | |

METHODS

Study design: Retrospective analysis of 2 prospective randomized controlled trials evaluating the safety and effectiveness of a non-activated 4F-PCC vs. plasma in patients on VKA therapy who had major bleeding or were in need of an urgent surgery/invasive procedure.

Inclusion criteria: All patients who had an initial post-reversal INR assessed, irrespective of timing of the lab draw

Exclusion criteria: None

Objectives:

- Examine the impact of 4F-PCC or plasma on INR reduction inclusive of all patients and times assessed
- Evaluate the percentage of patients receiving 4F-PCC or plasma returning factor levels to their lower limit of normal (LLN)
- Assess the temporal relationship of INR to vitamin K dependent factor (VKDF) levels

INR Reduction ≤ 1.3 at 30 Minutes After End of Infusion (+/- 15 minutes) per Clinical Trial Protocol

| | 4F-PCC | Plasma |
|----------------|--------------|--------------|
| Major Bleeding | 62.2% (n=98) | 9.6% (n=104) |
| Urgent Surgery | 55.2% (n=87) | 9.9% (n=81) |

RESULTS

Table 1 Integrated Study Data: INR Post Reversal (range 1-257 minutes after end of infusion)

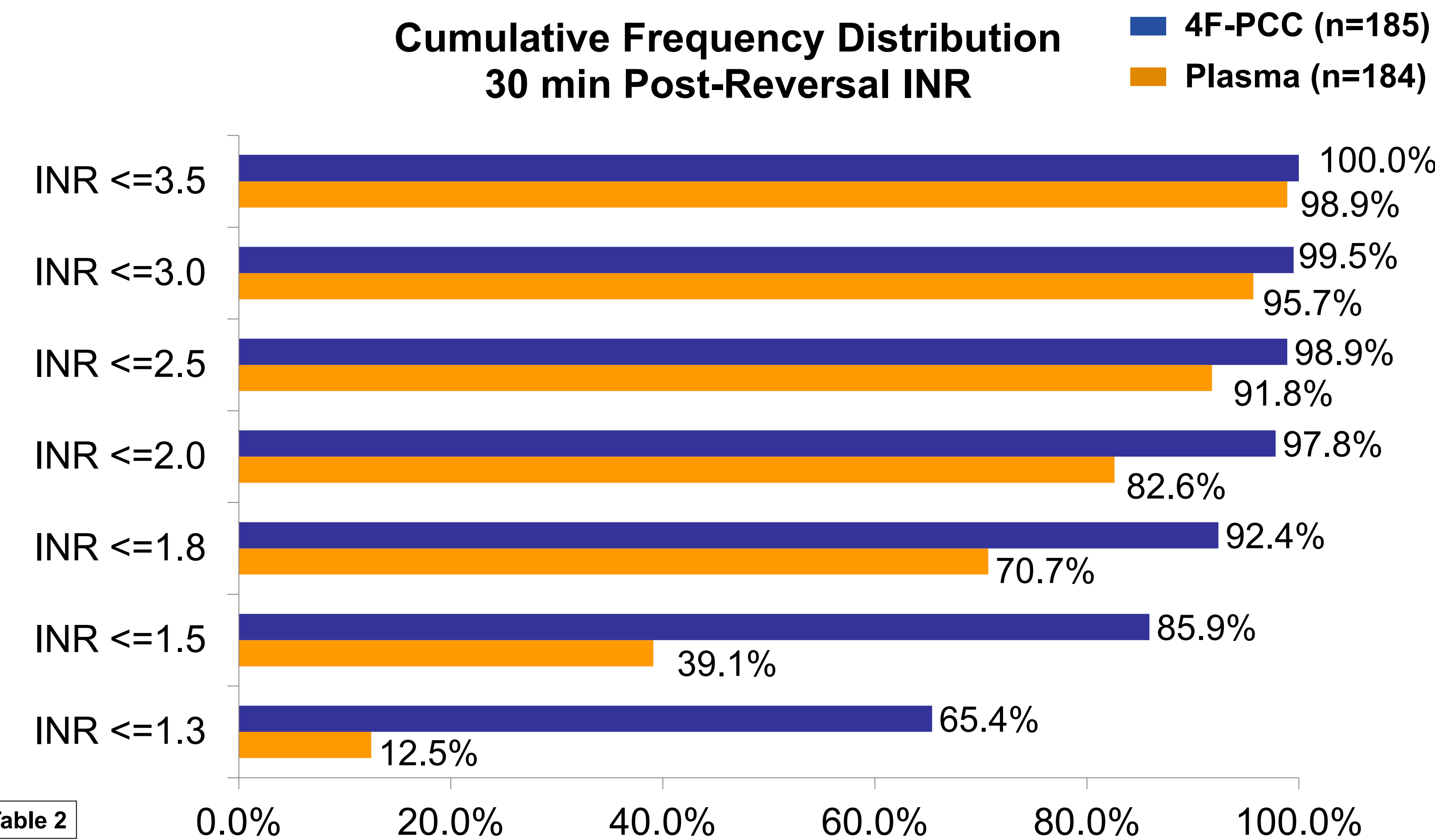


Table 2

| Factor (Normal range %) | % of Patients \geq LLN | | | Mean factor levels | |
|-------------------------|--------------------------|------------|---------|--------------------|------------|
| | 4F-PCC (%) | Plasma (%) | p-value | 4F-PCC (%) | Plasma (%) |
| II (70-146) | | | | | |
| 30 minutes | 72.3 | 9.2 | <0.0001 | 88.2 | 31.0 |
| 3 hours | 73.1 | 8.6 | <0.0001 | 85.5 | 46.1 |
| 24 hours | 67.6 | 25.4 | <0.0001 | 79.8 | 57.5 |
| VII (67-143) | | | | | |
| 30 minutes | 26.0 | 10.4 | 0.0003 | 57.3 | 32.8 |
| 3 hours | 25.6 | 13.9 | 0.01 | 61.3 | 50.9 |
| 24 hours | 66.5 | 74.0 | 0.13 | 94.4 | 90.4 |
| IX (55-163) | | | | | |
| 30 minutes | 76.1 | 43.6 | <0.0001 | 76.9 | 47.5 |
| 3 hours | 76.3 | 52.3 | <0.0001 | 73.7 | 23.7 |
| 24 hours | 82.1 | 91.3 | 0.01 | 90.2 | 93.5 |
| X (70-152) | | | | | |
| 30 minutes | 76.7 | 7.4 | <0.0001 | 95.5 | 21.9 |
| 3 hours | 81.4 | 6.6 | <0.0001 | 89.6 | 37.6 |
| 24 hours | 65.9 | 27.2 | <0.0001 | 81.8 | 56.8 |

Figure 1 Factor II Levels Post 4F-PCC

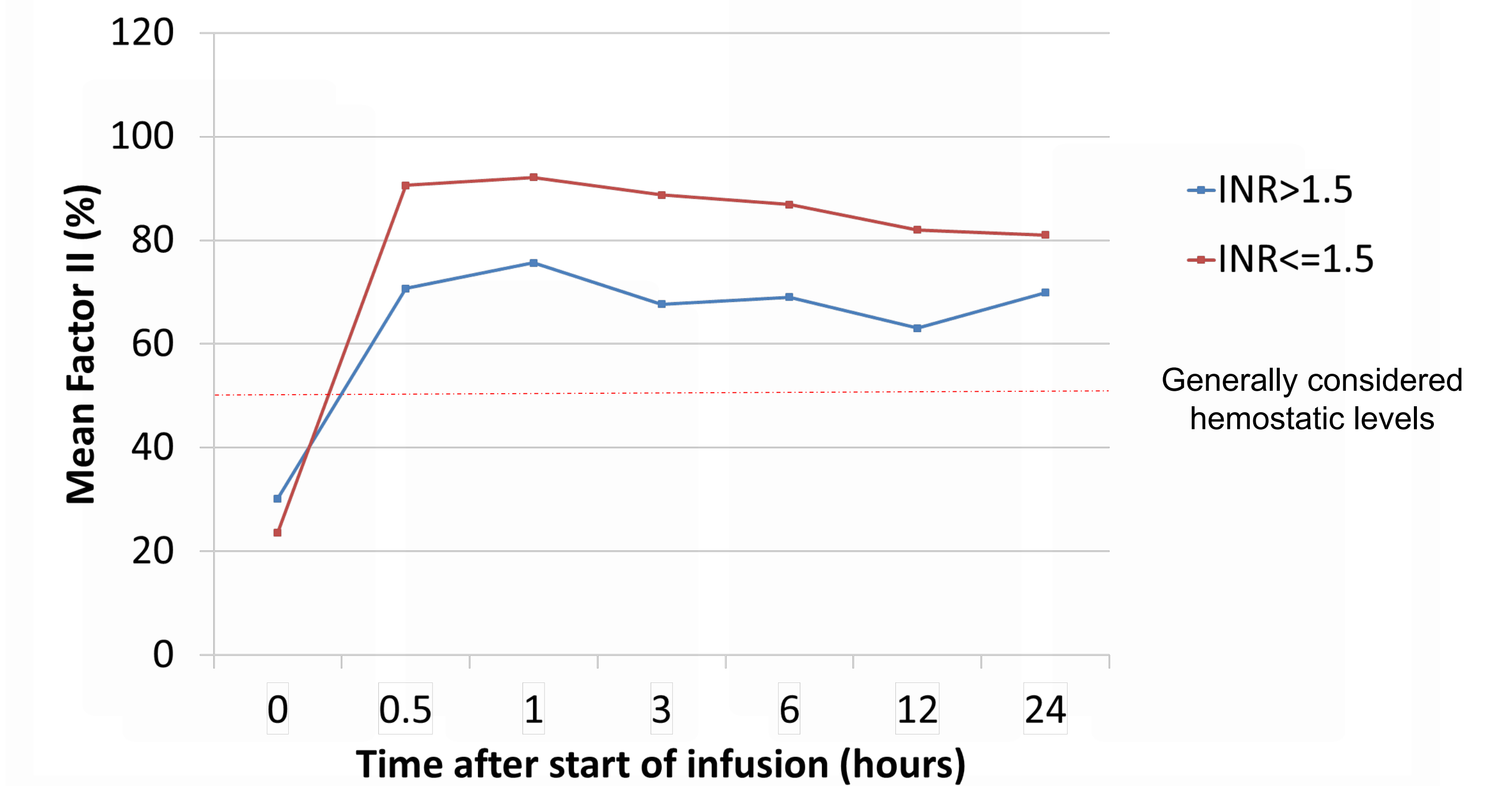
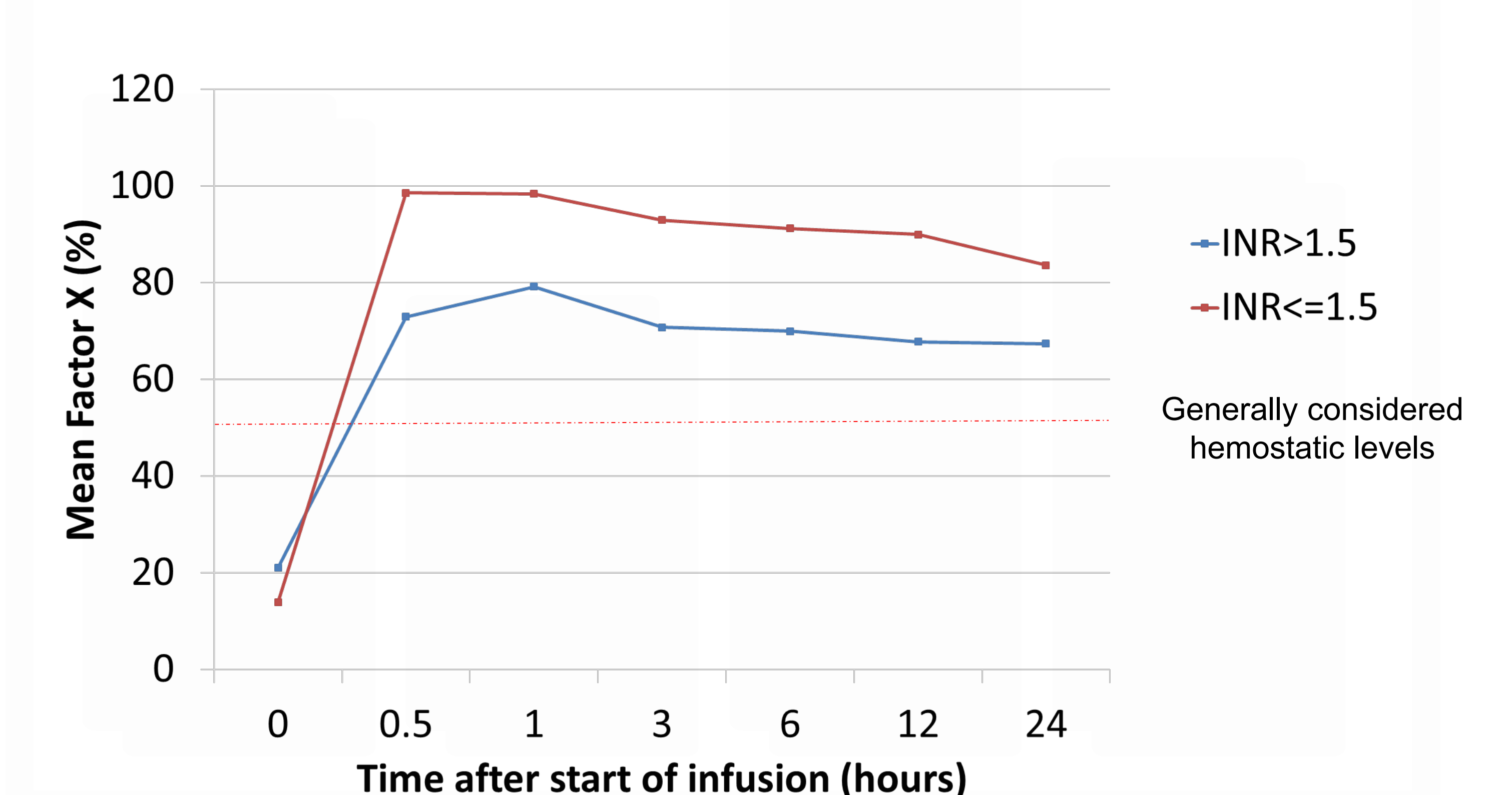


Figure 2 Factor X Levels Post 4F-PCC



CONCLUSIONS

- 4F-PCC effectively reduces the INR to ≤ 1.5 in ~86% of patients.
- 4F-PCC restores factor levels to their normal levels by ~30 minutes at a significantly higher rate than plasma.
- All factor levels were above 50% as early as 30 minutes after administration of 4F-PCC, regardless of achieving INR ≤ 1.5 or > 1.5 . FII and FX levels were significantly higher in those patients who reached an INR ≤ 1.5 post reversal.