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### **Implementation and Outcomes Assessment of a 4-factor prothrombin complex concentrate (4F-PCC) Tiered Fixed Dosing Protocol in a Health System.**

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## OBJECTIVE

The aim of this study was to evaluate compliance to the newly implemented fixed dosing protocol while assessing for the need for repeat doses of 4F-PCC and the need for further invasive intervention to reverse the bleeding

## BACKGROUND

Patients presenting with an acute life-threatening bleed while taking warfarin or direct oral anticoagulants (DOAC) often require emergent reversal. In the setting of acute bleeding, while 4F-PCC has been routinely used as a reversal agent, its optimal dosing regimen remains controversial. Currently manufacturer dosing is pretreatment, INR restricted, and weight based as listed below:

Pre-treatment INR	2-4	4-6	Greater than 6
4F-PCC Dose	25 units/kg	35 units/kg	50 units/kg
Max dose	2500 units	3500 units	5000 units

Additionally, 4F-PCC only has a Food and Drug Administration (FDA) indication for warfarin reversal despite its common use in reversal of DOAC-related bleeding. A fixed dose strategy can have many advantages including shorter preparation time and thereby shorter time to administration, and overall lower doses resulting in reduced cost. In addition, the operational advantage of using a fixed dose is another contributor to the cost reduction of weight-based restriction doses.

In 2020, Parkview Health system in Fort Wayne, IN implemented a protocol utilizing a fixed-dose weight-based 4F-PCC dosing schedule in patients with life threatening warfarin or DOAC-related bleeding.

- Patient weight <50 kg = 4F-PCC 25 units/kg +/- 10%  
- Patient weight 50 kg-100 kg = 4F-PCC 2000 units +/- 10% (1800-2200 units)  
- Patient weight >100 kg = 4F-PCC 2500 units +/- 10% (2250-2750 units)  
- Re-dose with 4F-PCC 500 units +/- 10% as needed for continued bleeding

## METHODS

### Inclusion Criteria

- 18 years or older
- Received at least one dose of 4F-PCC within the Parkview Health system between November 1, 2020, to June 15, 2021.

### Exclusion Criteria

- Eligible for and treated with massive transfusion protocol

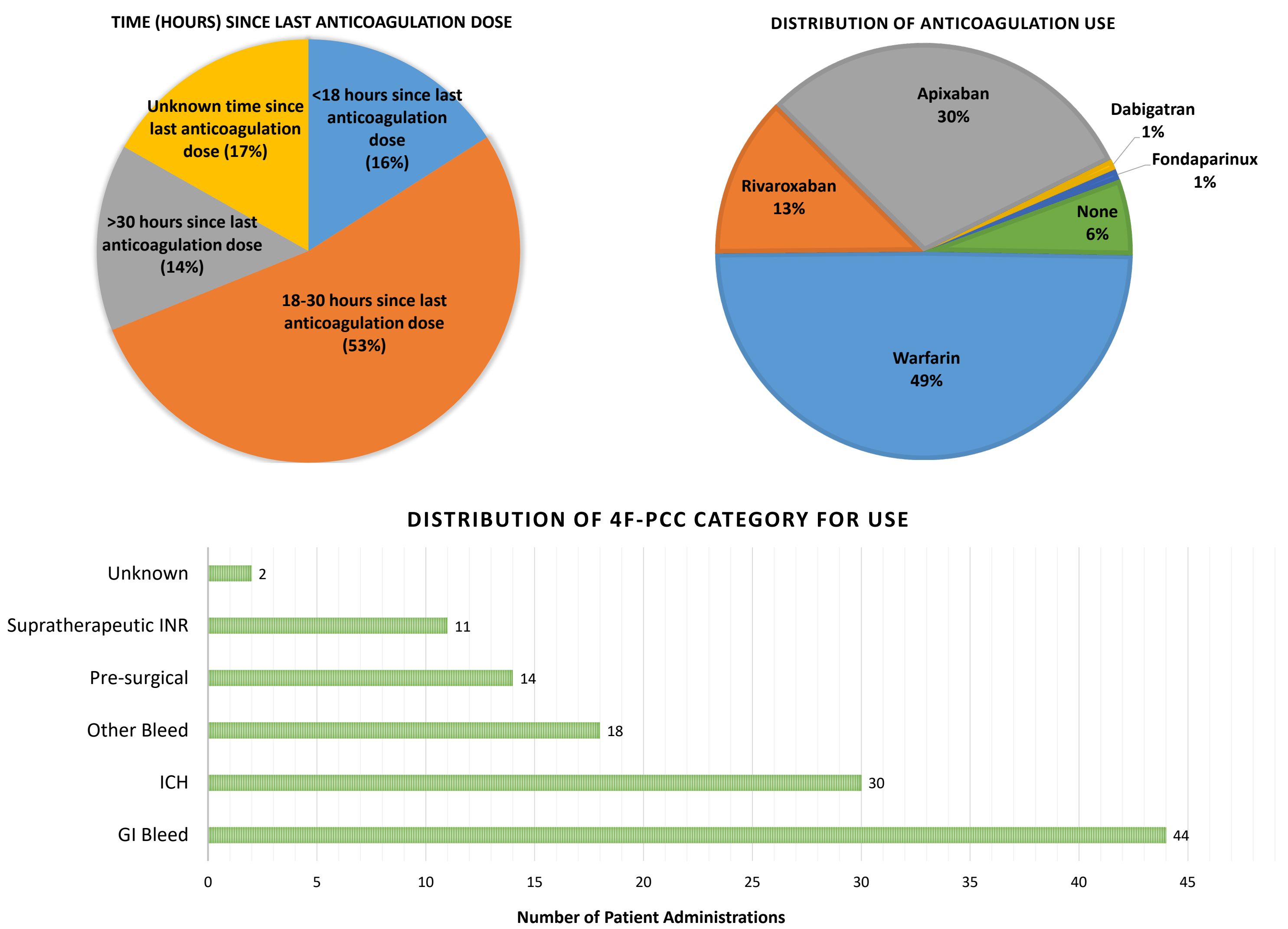
- We conducted an institutional review board exempt retrospective drug use evaluation extracting pertinent patient information from the electronic health record
- Main variables of interest collected: age, weight, classification for 4F-PCC use or location of bleed, type of anticoagulant prior to use, indication for anticoagulation, 4F-PCC dose information, use of blood products/phytonadione, and need for further invasive intervention.
- Any surgical procedure primarily intended for bleeding control within 48 hours post 4F-PCC administration was classified as invasive intervention.
- Further analysis compared actual dose administered with the package insert recommended dose to evaluate the difference in cost between fixed dosing and traditional dosing.
- Two models were used for cost-analysis due to the variability in dosing for non-warfarin related bleeding.
  - First model:** Utilized 4F-PCC package insert dose recommendations for warfarin-related bleeding reversal with INR-restricted weight-based dosing (25 units/kg if no INR available) with maximum dose adjustment for patients weighing over 100 kg.
    - For non-warfarin related bleeding reversal, 25 units/kg was used as standard recommended dosing with no maximum dose adjustment.
  - Second model:** The 4F-PCC package insert was utilized restricted by pretreatment INR and weight-based (25 units/kg if no INR available) with the same maximum dose adjustment.
    - For non-warfarin related bleeding reversal, 50 units/kg was used as the standard dosing with no maximum dose adjustment.
- Average wholesale price (AWP) of \$3.14/unit was used to estimate cost-savings between the different models and dosing strategies.

## RESULTS

# of administrations (n = 119)	
Age (years), average (SD)	74 (+/-12)
Sex (male) , n (%)	62 (52%)
Race (white), n (%)	104 (87%)
Not Hispanic or Latino, n (%)	115 (97%)
Weight (kg), average (SD)	89 (+/- 30)
Body Mass Index, average (SD)	30.2 (+/- 10.6)
Received at least one unit of PRBC, n (%)	41 (34.5%)
Average number of PRBC units received	2.3
Received at least one unit of platelets, n (%)	9 (8%)
Received at least one unit of FFP, n (%)	9 (8%)
Received at least one unit of cryoprecipitate, n (%)	1 (1%)

Table 1: Sample population characteristics | PRBC: Packed red blood cell; FFP: Fresh frozen plasma

- Nine encounters were excluded due to massive blood transfusion protocol
- Of the 119 administrations collected and analyzed, there was a single incidence of 4F-PCC redosing (post-operative surgical bleeding).
- The most common indication for any anticoagulant use was atrial fibrillation (76%) followed by venous thromboembolism (21%).
- Seventy-six percent of administrations (91 out of 119) complied with the health system dosing protocol based on accepted dosing range with the noted variability of available products.
- Overall, there was a lack of need for invasive intervention. Of the 119 administrations, 100 (84%) didn't require invasive intervention within 48 hours of 4F-PCC administration. Seven of those administrations were in the pre-surgical setting of 4F-PCC use where this attribute is not applicable. (Tables 2 and 3).



Need for further invasive intervention	GI Bleed n=44	ICH n=30	Other Bleed n=18	Pre-surgical n=14	Supratherapeutic INR n=11	Unknown n=2	Grand Total
Yes	6 (14%)	3 (10%)	3 (17%)	0	0	0	12 (10%)
No	38 (86%)	27 (90%)	15 (83%)	7 (50%)	11 (100%)	2 (100%)	100 (84%)
N/A	0	0	0	7 (50%)	0	0	7 (6%)

Table 2: Need for further invasive intervention encounters classified by each bleed type.

Need for further invasive intervention	Warfarin n=59	Rivaroxaban n=15	Apixaban n=36	Dabigatran n=1	Fondaparinux n=1	None n=7
Yes	4 (7%)	3 (20%)	5 (14%)	0	0	0
No	53 (90%)	12 (80%)	26 (72%)	1 (100%)	1 (100%)	7 (100%)
N/A	2 (3%)	0	5 (14%)	0	0	0

Table 3: Need for further invasive intervention patient encounters classified by anticoagulation used.

## RESULTS

Of the 59 patients with warfarin use prior to reversal, 51 also received phytonadione as recommended with use of 4F-PCC. We saw phytonadione use with 4F-PCC in non-warfarin related bleeds including 5 patients with DOAC use prior to reversal and in 5 patients with no anticoagulation use.

A comparison in the number of 4F-PCC units (Table 4) administered to standard recommended dosing showed considerable dose reductions in warfarin and non-warfarin reversal. Regardless of which model, fixed dosing resulted in considerable cost reduction when compared to standard dosing. Given the potential variability in cost reduction, the two models provide a range of savings that can be expected.

	Model 1		Model 2	
	Difference in units	Cost reduction (\$)	Difference in units	Cost reduction (\$)
All anticoagulants	-52,295	\$164,206.30	-160,460	\$503,844.40
Warfarin only	-25,926	\$81,407.64	-25,926	\$81,407.64
DOACs only	-26,308	\$82,607.12	-119,674	\$375,776.36
Other	-61	\$191.54	-14,860	\$46,660.40

Table 4: Difference in number of units and cost (\$) between using the health system protocol and standard recommended dosing (stratified by the anticoagulant type needing reversal)

Other includes encounters where no anticoagulation or fondaparinux is used; DOACs include rivaroxaban, apixaban, and dabigatran.

## DISCUSSION & CONCLUSIONS

- During a seven-month period, 4F-PCC was administered adherent to hospital dosing protocol with minimal need for redosing. Although the assessed dosing regimen is clear, it can be difficult to accurately dose 4F-PCC when considering variability of the available products and the dosage vials manufactured.
- The most common reversal need for bleeding was in atrial fibrillation patients on-warfarin therapy. Least commonly, 4F-PCC was used in supratherapeutic INR and in dabigatran or fondaparinux anticoagulant use reversal which are not indicated treatments.
- Utilization of this dosing protocol for 4F-PCC is associated with considerable cost minimization. Both models comparing the two dosing regimens showed dose reductions and therefore cost reductions when using the fixed dose weight-restricted dosing schedule compared to the standard dose recommendations.
- The assessed dosing regimen was also associated with certain positive outcomes including limited needs for redosing and minimal requirements of invasive intervention for bleeding control.
- These results show that weight-restricted fixed dosing is an alternative for dosing 4F-PCC in both warfarin and DOAC-related bleeding reversal.
  - It can be advantageous especially in patients weighing over 100 kg particularly in cost reduction.
  - This dosing strategy is useful in dosing 4F-PCC for DOAC-related bleeding reversal as there is no standard, package insert recommended dosing.
- The clinical features in this subset were found to be consistent with values prior to implementation of the fixed-dose protocol.
- Overall hemostasis, a commonly evaluated outcome, was not evaluated in our present study thereby presenting a possible limitation of measuring efficacy.
- Further limitations include the off-indication use of 4F-PCC. Occasionally, 4F-PCC was used when there was no bleed or for reversal in DOAC-related bleeds; which may impact cost-analysis and stand-in outcomes.

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### Disclosure

The authors of this presentation have the following to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation:  
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