Low- & fixed-dose prothrombin complex concentrate:

therapeutic, pharmacoeconomic, & operational outcomes

❶Objective:

Evaluate the clinical and operational outcomes resulting from a conservative dosing strategy for four-factor prothrombin complex concentrate (4F-PCC) for anticoagulation reversal.

❷Methods:

Anticoagulation reversal protocols were updated to reflect a multi-tiered approach (Fig. 1). Patients on warfarin were reversed with a fixed dose of 4F-PCC, patients on direct oral anticoagulants (DOACs)—specifically apixaban & rivaroxaban—were given a 25 unit/kg dose, and andexanet alfa was excluded from the Salina Regional Health Center (SRHC) formulary [1]. Order sets were updated to include an entry to consult pharmacy to dose when searching for 4F-PCC. This study was approved by the SRHC Institutional Review Committee & all data was obtained via retrospective chart review for calendar year 2020.

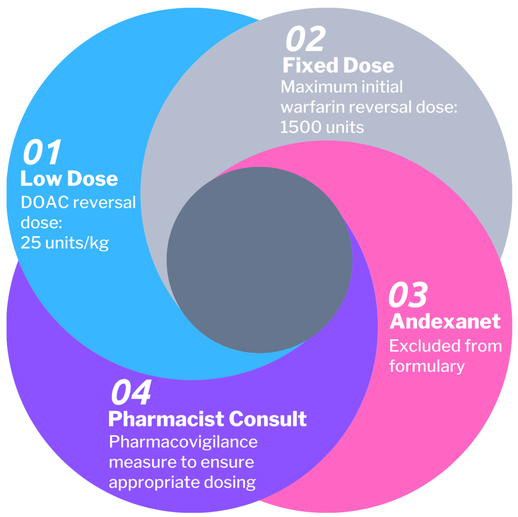

Figure 1: Multi-tiered approach

4-F PCC	WARFARIN REVERSAL	DOAC REVERSAL	ANDEXANET EXCLUSION
Standard dosing	Weight- & INR-based	50 units/kg	Low- & high-dose regimens
Low/fixed dose	INR-based, 1500 units max	25 units/kg	None (use 4F-PCC)
Average dose	1462 units	2000 units	---
Number of vials spared	31 (13 patients)	67 (17 patients)	---
Cost savings	$32,654	$70,576	$1,009,800
Hemostasis achieved	91%	90%	82% [2]

Figure 2: Summary of results

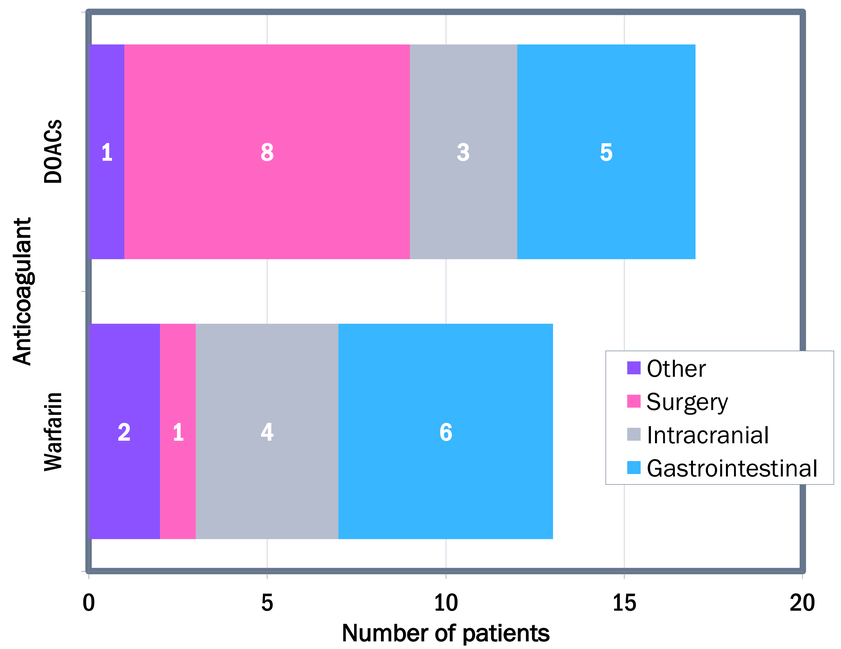

Figure 3: Location of bleed/indication for anticoagulant reversal

❸Results:

Using the updated 4F-PCC dosing strategies, SRHC used **98 fewer vials** over the course of calendar year 2020 when compared to traditional dosing (Fig. 2). There was no clinically meaningful change in therapeutic efficacy as **90-91% of patients** for whom data was available achieved hemostasis with an INR of 1.7 or less after treatment. Only 1 patient in each anticoagulation group required a repeat dose of 4F-PCC per protocol. No patient experienced a documented thrombotic event. Overall, drug cost avoidance from the multi-tiered strategy totals **$1,113,030** when including drug expenditures related to andexanet alfa. When pharmacists were consulted, average time to drug administration was **45 minutes**, compared to 67 minutes without pharmacist consult.

❹Conclusions:

A conservative dosing approach to anticoagulant reversal seems to be effective from a therapeutic, pharmacoeconomic, & operational standpoint.

In this data set, two patients did not achieve adequate INR reversal and one patient did but nonetheless was given a repeat dose of 4F-PCC with no explanation noted. The following baseline characteristics were compared amongst these three patients:

- Anticoagulant agent
- Baseline & post-treatment INR
- Comorbid malignancy
- Location of bleed (Fig. 3)
- Platelet count/concomitant anti-platelet therapy
- Serum creatinine (SCr)
- Time to administration
- Weight and body mass index (BMI)

Patients had no discernible similarities, sometimes dramatically so (e.g. INRs ranging from 3 to 20, SCr ranging from 0.66 to 5.12). No single measure alone (INR, anti-Xa, clinical correlation) is known to be sufficient to predict hemostasis [2]. This absence of a clinically meaningful pattern may lend support to use of more sophisticated assessment techniques, such as viscoelastic testing (eg thromboelastogram) [3].

Zahra Nasrazadani, PharmD, BCPS
Salina Regional Health Center
✉ znasrazada@srhc.com
@zahranasr

References
1) Tomaselli et al. 2017 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants. J Amer Coll Card 2017; 70:3042-67.
2) Connolly et al. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors (ANNEXA-4). NEJM 2019; 380:1326-35.
3) Bugaev et al. Thromboelastography and rotational thromboelastometry in bleeding patients with coagulopathy. J Trauma Acute Care Surg 2020; 89:999-1017.