

## Background

- Factor-Xa inhibitors are frequently used for treatment of venous thromboembolism (VTE) and prevention of cardioembolic stroke in patients with atrial fibrillation
- The risk of major bleeding events associated with the use of factor-Xa inhibitors demands the need for an effective reversal agent
- Four-factor prothrombin complex concentrates (4F-PCC) have been used off-label for reversal of factor-Xa inhibitors
- With the recent FDA-approval of andexanet alfa for the reversal of factor-Xa inhibitors, the need to evaluate the effectiveness and safety of 4F-PCC for reversing factor-Xa inhibitors is requisite

## Objectives

### Primary objective:

- Hemostatic efficacy of 4F-PCC in patients requiring emergent reversal of factor-Xa-associated bleeding
  - Effectiveness of hemostasis categorized by criteria set forth by Sarode et. al.

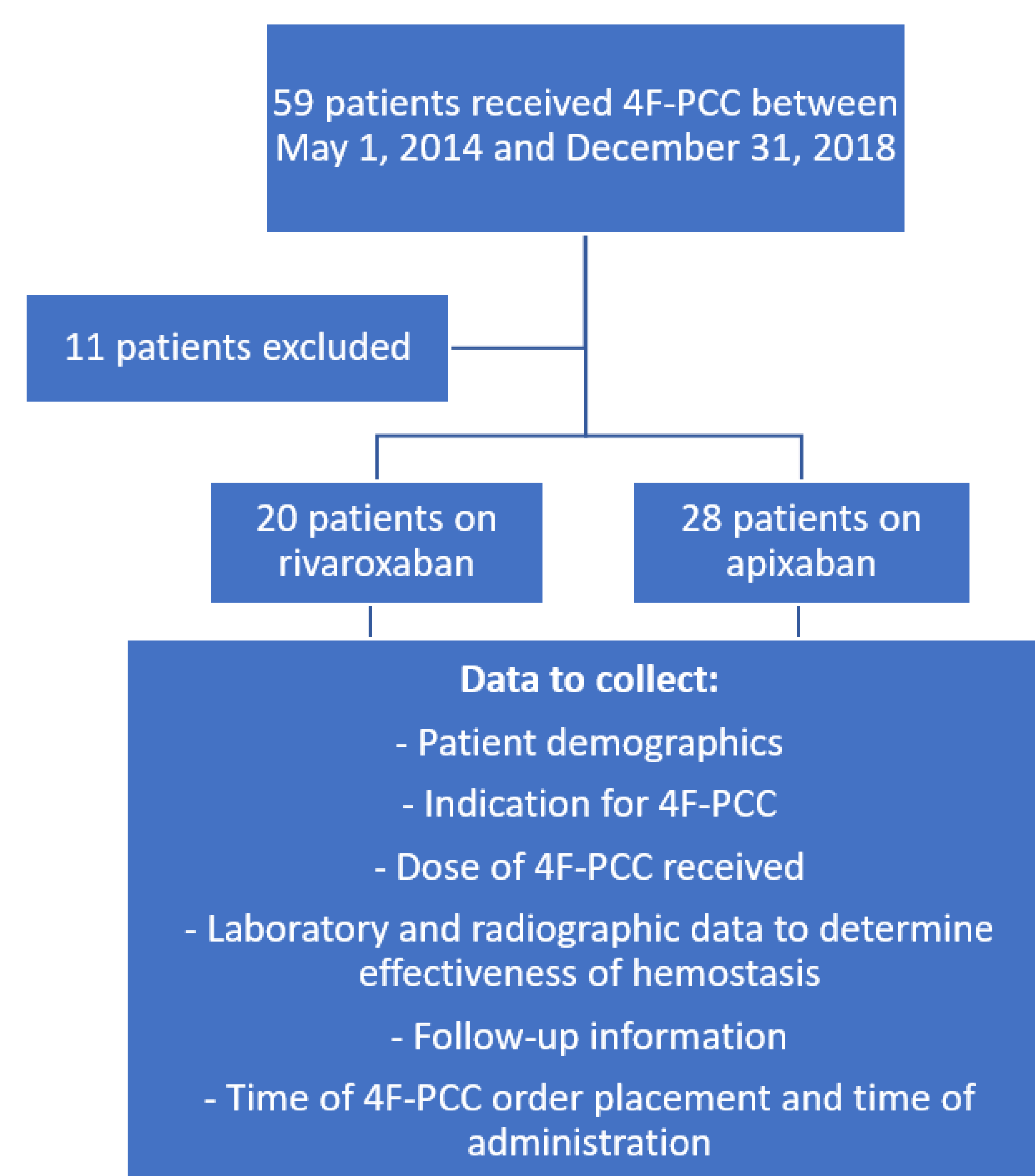
### Secondary objectives:

- Level of care required post-hospitalization
- Resumption of anticoagulation therapy following 4F-PCC use
- Time required to prepare and administer 4F-PCC following order placement

### Safety endpoints:

- Incidence of thromboembolic events within 30 days of 4F-PCC
- All-cause mortality within 30 days of 4F-PCC administration

## Methods



## Results

Variables	n=48
Age, years, median	74
Weight, kg, median	87.7
Male, n(%)	28 (58.3)
Creatinine Clearance, n(%)	
• <30 mL/min	7 (14.6)
• 30-60 mL/min	17 (35.4)
• >60 mL/min	24 (50)
Hemoglobin prior to 4F-PCC, median	11.7
Hemoglobin post 4F-PCC, median	10.5
Indication for anticoagulation, n (%)	
• Atrial fibrillation	36 (75)
• DVT/PE/CVA/Portal Vein Thrombosis	12 (25)
DOAC, n (%)	
• Apixaban	28 (58.3)
• Rivaroxaban	20 (41.7)
Type of Bleed, n (%)	
• Intracranial Hemorrhage	20 (41.7)
• Gastrointestinal Bleed	13 (27.1)
• Other	15 (31.3)
Intervention of surgery to stop bleeding, n (%)	
• Yes	8 (16.7)
• No	40 (83.3)

Table 1: Background Characteristics and Demographics

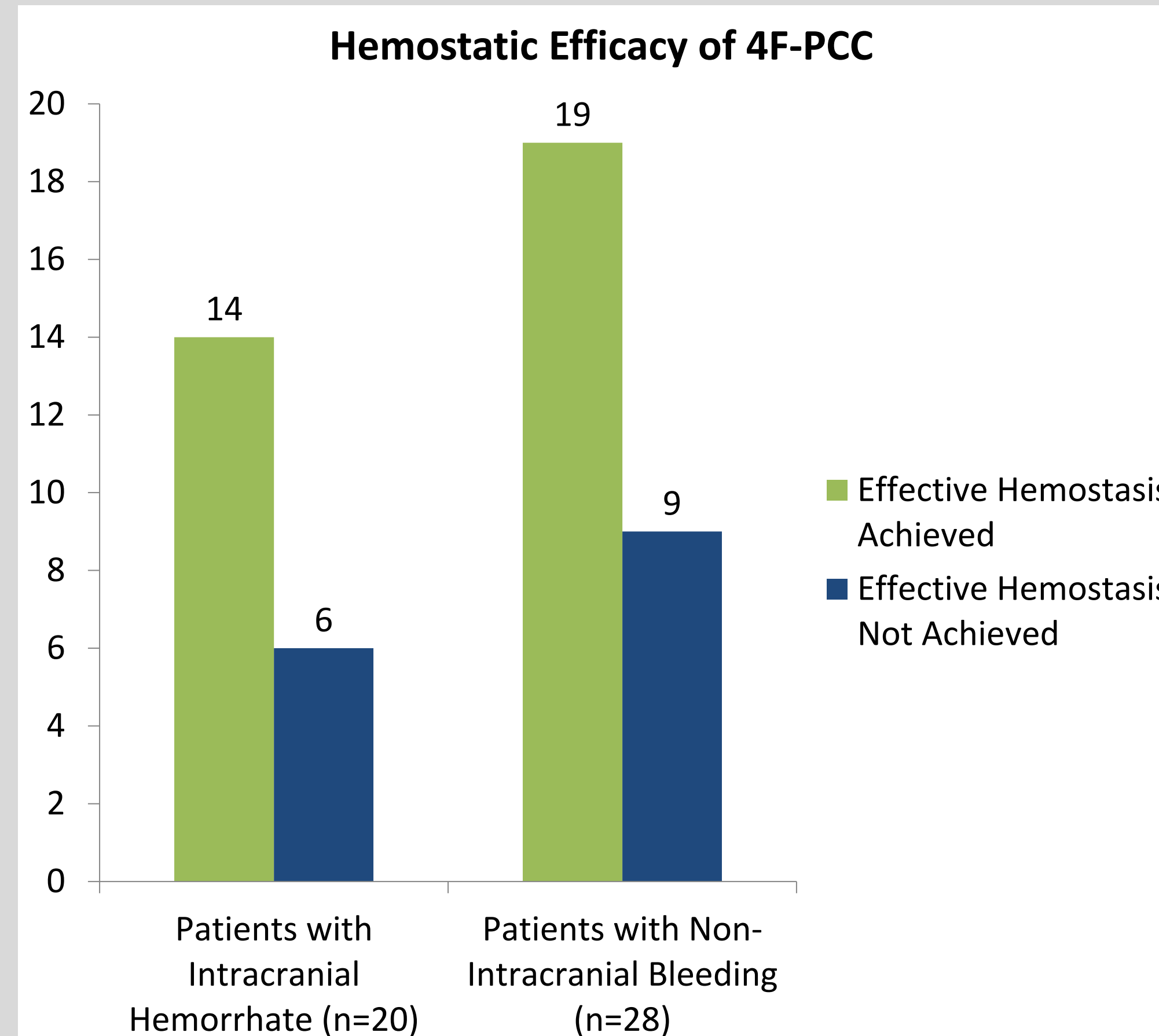


Chart 1: Primary Outcome – Hemostatic Efficacy of 4F-PCC

Patient	Anticoagulant (AC)	Bleeding Site	Thromboembolic Event	Anticoagulant Restart Day post 4F-PCC
Patient 1	Apixaban	Rectal Sheath Hematoma	Midbrain Infarct	Day 10
Patient 2	Rivaroxaban	Epidural Hematoma	Superficial Thrombus in RUE	Day 14
Patient 3	Apixaban	GI Bleed	Acute Ischemic Stroke	Never Restarted
Patient 4	Rivaroxaban	Subdural Hemorrhage	Acute Pulmonary Emboli	Day 24

Table 3: Patient Information for Thromboembolic Events

Agents	Result
Dose of 4F-PCC, units, mean	4136.33
Dose of 4F-PCC, n (%)	
• 25 units/kg dosing	2 (4.2)
• Actual Dose, mean, units/kg	23.6
• 50 units/kg dosing	46 (95.8)
• Actual Dose, mean, units/kg	48.5
Repeat Dose of 4F-PCC, n (%)	0 (0)
4F-PCC order-to-needle time, minutes, median (n=46)	36
Blood Products, n (%)	
• Blood Product Given	25 (52.1)
• Fresh Frozen Plasma Given	3 (6.3)

Table 2: 4F-PCC Dosing, Blood Products, and Other Dosing Information

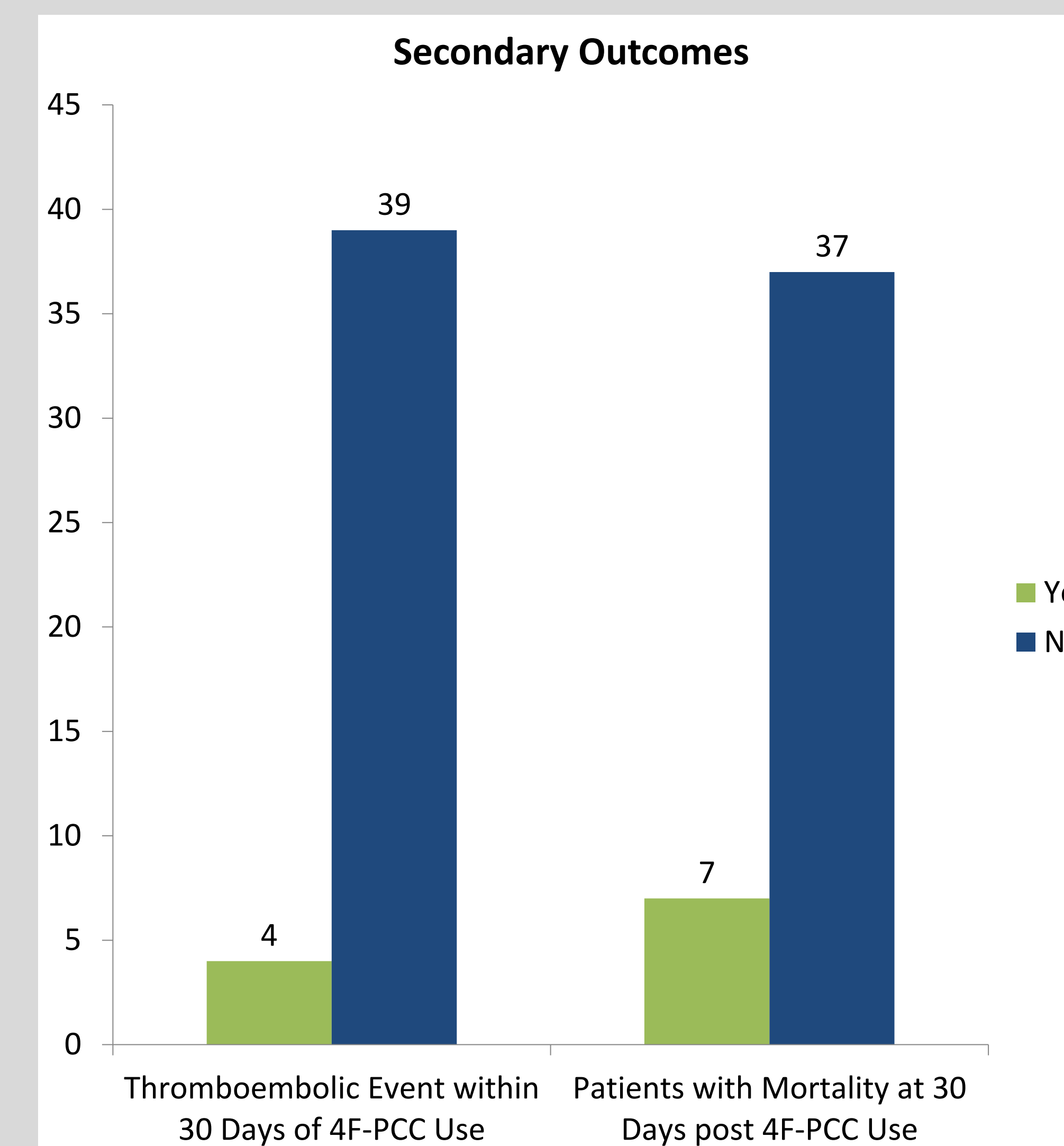


Chart 2: Secondary Outcomes – Thromboembolic Events and Mortality within 30 Days

### Discharge Destination (n=48)

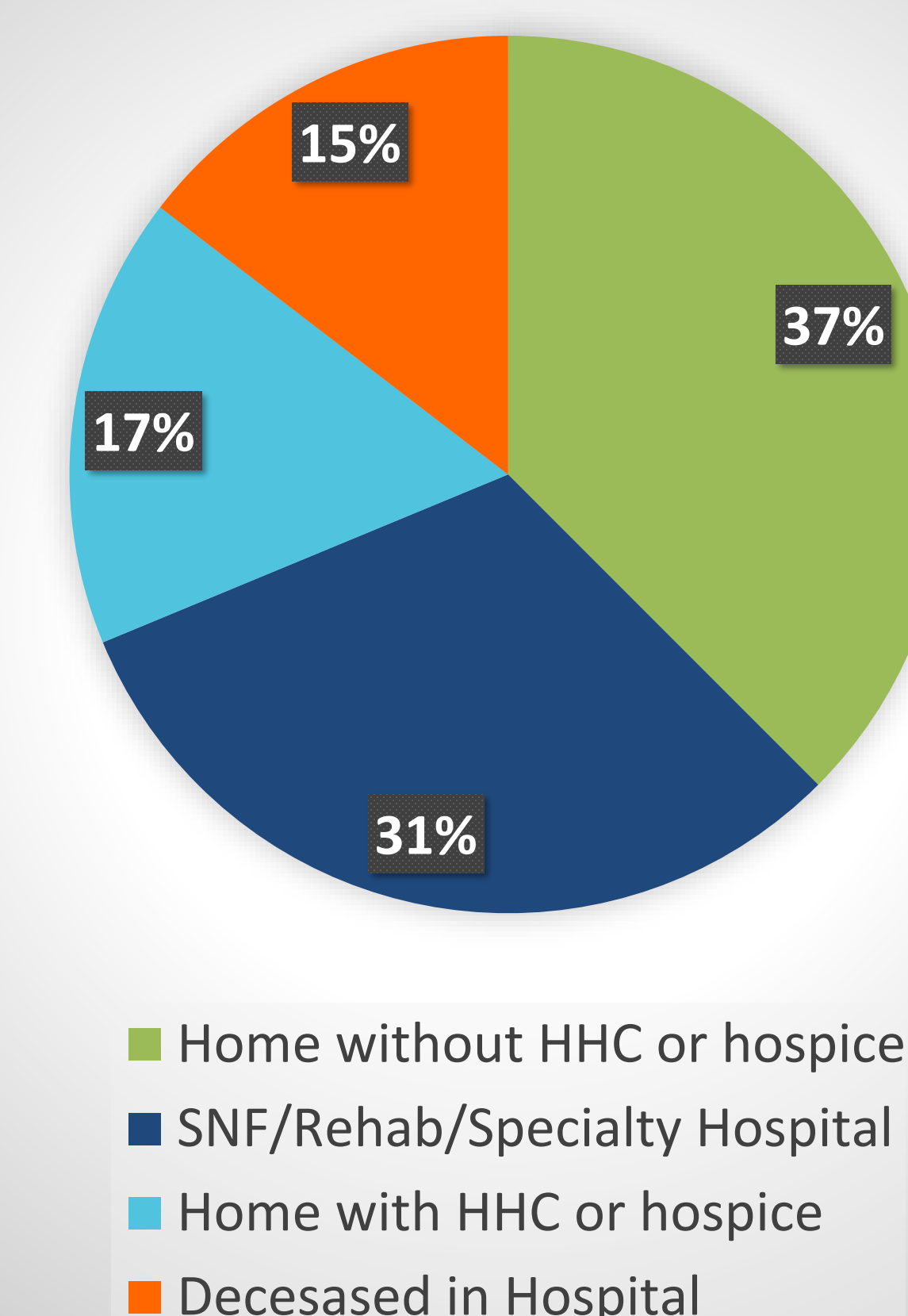


Chart 3: Discharge Destination

## Discussion

- While andexanet alfa is the only FDA approved reversal agent for apixaban and rivaroxaban, there is currently limited data available regarding its use
- Use of 4F-PCC may be favorable to the use of andexanet alfa for apixaban- and rivaroxaban-related bleeding for the following reasons:
  - Multiple studies have shown that 4F-PCC is safe and effective for anti-factor Xa reversal
  - More restrictive inclusion criteria in andexanet alfa clinical trials
  - Paucity of clinical experience using andexanet alfa
  - Shorter preparation time
  - Lower acquisition cost
- Our institution did not add andexanet alfa to formulary as it may be beneficial to continue using 4F-PCC for anti-factor Xa reversal until more data is available for andexanet alfa

## Conclusion

- This analysis shows that four-factor prothrombin complex concentrate is effective for stopping intracranial hemorrhages and non-intracranial hemorrhages associated with anti-factor Xa use
- This analysis study is limited due to its small sample size, retrospective design, and the lack of a comparator group
- More studies are warranted to prove the safety and efficacy of 4F-PCC for the reversal of bleeds associated with anti-factor Xa medications

## Author Disclosures

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:

- Zachary Hitchcock: Nothing to disclose
- Spencer Smith: Nothing to disclose
- Lamanh Le: Nothing to disclose
- Lauren Lees: Nothing to disclose
- Matthew Brandt: Nothing to disclose

## References

- ANDEXXA. Coagulation factor Xa (recombinant), inactivated-zhzo. [prescribing 172 information] South San Francisco, CA; Portola Pharmaceuticals; 2018.
- Sarode R, Milling TJ Jr, Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin 199 complex concentrate in patients on vitamin K antagonists presenting with major bleeding: 200 a randomized plasma-controlled, phase IIIb study. *Circulation*. 2013 Sep 10;128(11):1234-43.