

Anticoagulation Reversal: New Agents and Alternative Strategies

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Objectives

1. List considerations for urgent anticoagulation reversal
2. Review new therapies for direct oral anticoagulation (DOAC) reversal
3. Describe FDA-labeled warfarin reversal and off-label dosing strategies

Abbreviations

4-PCC – 4 factor prothrombin complex concentrate

3-PCC – 3 factor prothrombin complex concentrate

aPCC – activated 4 factor complex concentrate

rFVIIa – recombinant factor VII

FFP – fresh frozen plasma

DOAC- direct oral anticoagulant

Hbg- hemoglobin

ICH- intracranial hemorrhage

GCS- Glasgow coma scale

PRBC- packed red blood cells

Introduction

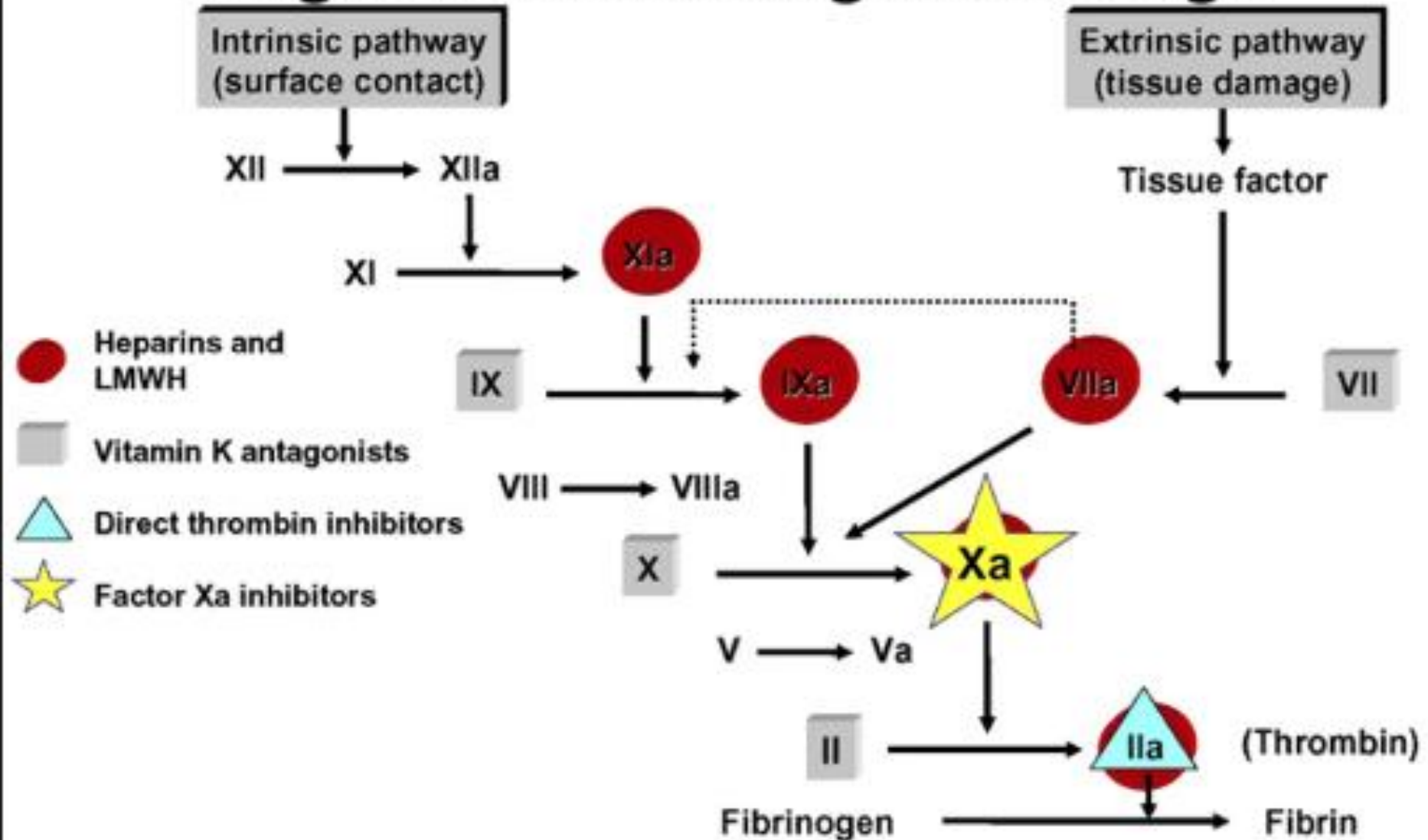
- DOAC use increasing
- New reversal agent approved May, 2018
- 4-PCC shortages reported nationwide



Review

MECHANISMS OF ACTION, DRUG ARMAMENTARIUM

Targets for Anticoagulant Drugs



Factor containing products

FFP – Factor V, VII, VII, X, XI, XIII, fibrinogen, plasma proteins, electrolytes

- 200-300 ml

PCC

- 3 factor – inactivated II, IX, X
- 4 factor – inactivated II, VII, IX, X- protein C &S, heparin

aPCC

- FEIBA (factor eight inhibitor bypass activity)
- Activated VII+ inactivated II, IX, X

rFVIIa

- Activated VII

Factor containing products

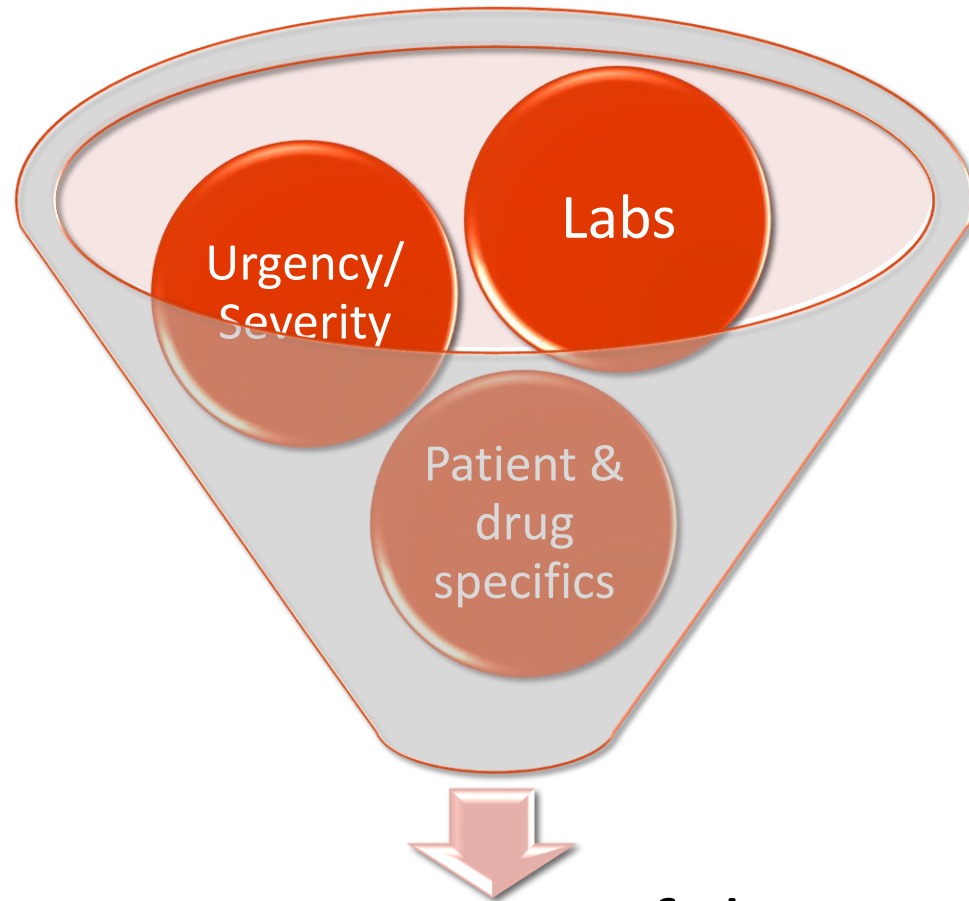
Vitamin K dependent Coagulation Factors	Recombinant Factor VIIa (rFVIIa)	Fresh Frozen Plasma (FFP)	3-factor prothrombin complex concentrate (3-PCC)	4-factor prothrombin complex concentrate (4-PCC)	aPCC (FEIBA*)
X		×	×	×	×
IX		×	×	×	×
VII	×	×	—	×	×
II		×	×	×	×

*Factor eight inhibitor bypassing activity

Case

- MH, 33 y/o M
- CC: HA, increased dizziness s/p fall from roof
- PMH: DVT 3/2018, depression
- Rx rivaroxaban 20mg PO daily
- What are your options for DOAC reversal?
- What other questions/considerations are there?





Assessment of the
bleeding patient

Patient Characteristics

- Renal function assessment
- Anticoagulant & indication
- Time of last known ingestion
- Co-medications
- Religious preferences
- Allergies

Pharmacologic Properties

Oral Anticoagulant	Time to Peak concentration (hr)	Half-life	Renal Excretion
Dabigatran	1-3	7-9, 17	80-85%
Rivaroxaban	2-4	7-17	36%
Apixaban	1-2	8-14	25%
Edoxaban	1-2	6-11	26-45%

Urgency of Reversal

- Life threatening bleeding
 - Major often defined as: hemodynamic instability, Hgb decrease by ≥ 2 g/dL or ≥ 2 U PRBCs administration
- Urgent/emergent procedure
 - Critical bleeding site
 - High bleeding risk
- Planned vs. unplanned

Labs

- Tests &/or point of care devices readily available?
- Lab turn around time?

TABLE 3 Suggestions for Laboratory Measurement of DOACs When Specialized Assays are not Available

Drug	Clinical Objective			
	Exclude Clinically Relevant* Drug Levels		Determine Whether On-Therapy or Above On-Therapy Levels Are Present	
	Suggested Test	Interpretation	Suggested Test	Interpretation
Dabigatran	TT, aPTT	Normal TT excludes clinically relevant* levels Prolonged TT does not discriminate between clinically important and insignificant levels Normal aPTT usually excludes clinically relevant* levels, if a sensitive reagent is used.	aPTT	Prolonged aPTT suggests that on-therapy or above on-therapy levels are present Normal aPTT may not exclude on-therapy levels, particularly if a relatively insensitive aPTT reagent is used
Apixaban	None	Normal PT and aPTT do not exclude clinically relevant* levels	PT	Prolonged PT suggests that on-therapy or above on-therapy levels are present Normal PT may not exclude on-therapy or above on-therapy levels, particularly if a relatively insensitive PT reagent is used
Edoxaban or rivaroxaban	None	Normal PT and aPTT do not exclude clinically relevant* levels	PT	Prolonged PT suggests that on-therapy or above on-therapy levels are present Normal PT may not exclude on-therapy levels, particularly if a relatively insensitive PT reagent is used

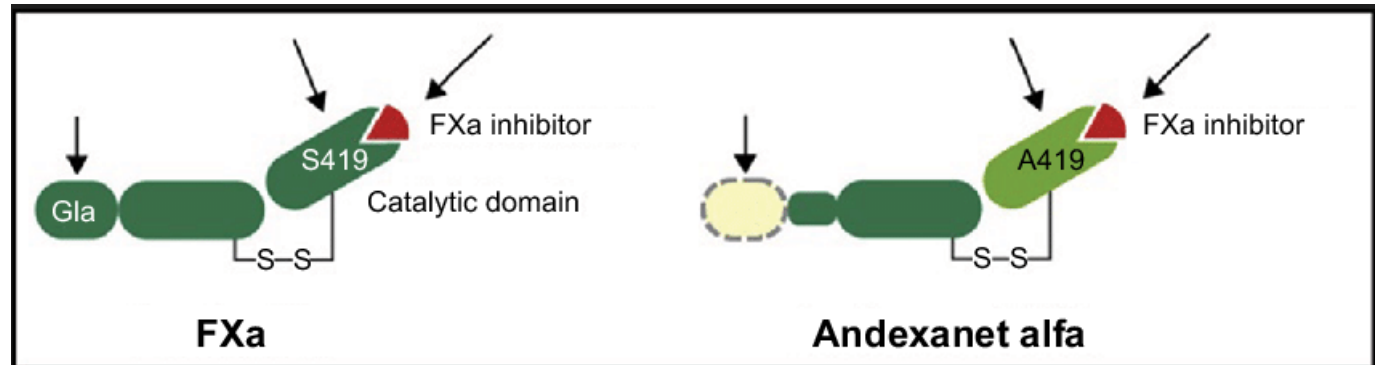
New Agents

ANDEXANET ALFA

Andexanet Alfa

Recombinant modified human factor Xa
“decoy” protein

Binds direct and indirect
factor Xa inhibitors



Andexanet alfa dosing

High dose = 800mg → 8mg/min

Low dose = 400mg → 4 min/min

Andexanet alfa Dose Based on Apixaban or Rivaroxaban Dose			
FXa inhibitor	FXa inhibitor last dose	Timing of FXa Inhibitor Last Dose Before Andexanet alfa Initiation	
		<8 Hours or Unknown	≥8 Hours
Apixaban	≤5 mg	Low dose	Low dose
	>5 mg/unknown	High dose	
Rivaroxaban	≤10 mg	Low dose	
	>10 mg/unknown	High dose	

100 mg = \$3,300 AWP

ANNEXA-4

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

Stuart J. Connolly, M.D., Truman J. Milling, Jr., M.D., John W. Eikelboom, M.D.,
C. Michael Gibson, M.D., John T. Curnutte, M.D., Ph.D., Alex Gold, M.D.,

- Ongoing, multicenter, prospective, open-label, single group study
- 67 patients with acute major bleeding
- Primary outcomes:
 - % change in anti-Xa activity
 - Rate of good or excellent hemostatic efficacy 12 hours after infusion
- All patients received bolus → 2 hour infusion

ANNEXA-4

INCLUSION

- Age > 18
- Rivaroxaban, apixaban, enoxaparin within 18 hours
- Acute major bleeding
 - Potentially life threatening overt bleeding with hemodynamic instability
 - Hgb decrease by at least 2g/dL or Hgb < 8 g/dL
 - Critical bleeding site

EXCLUSION

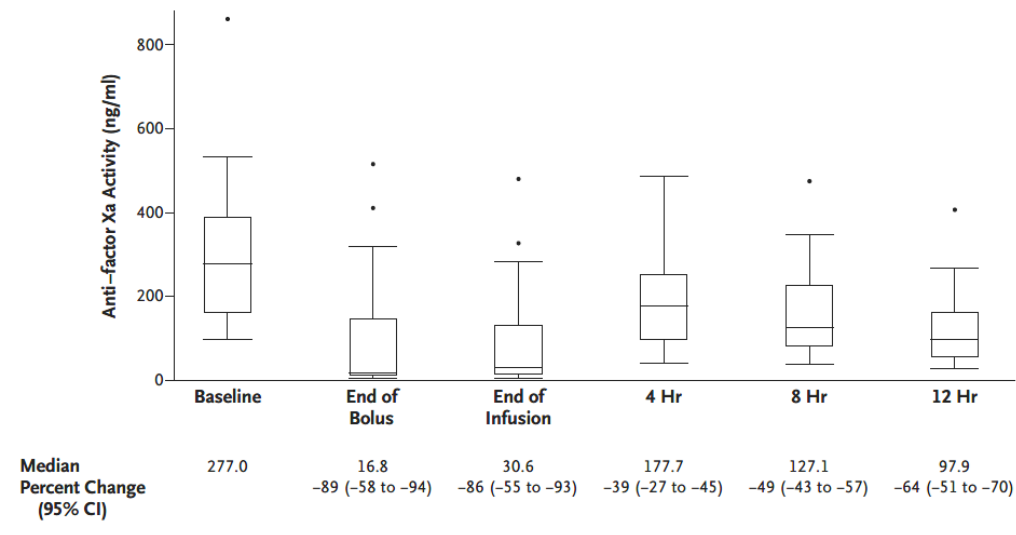
- Scheduled surgery within < 12 hours
- ICH with GCS < 7
- ICH volume > 60 ml
- Survival expected < 1 mo.
- Major thrombotic event in previous 2 weeks

Baseline Characteristics (Efficacy n=47)

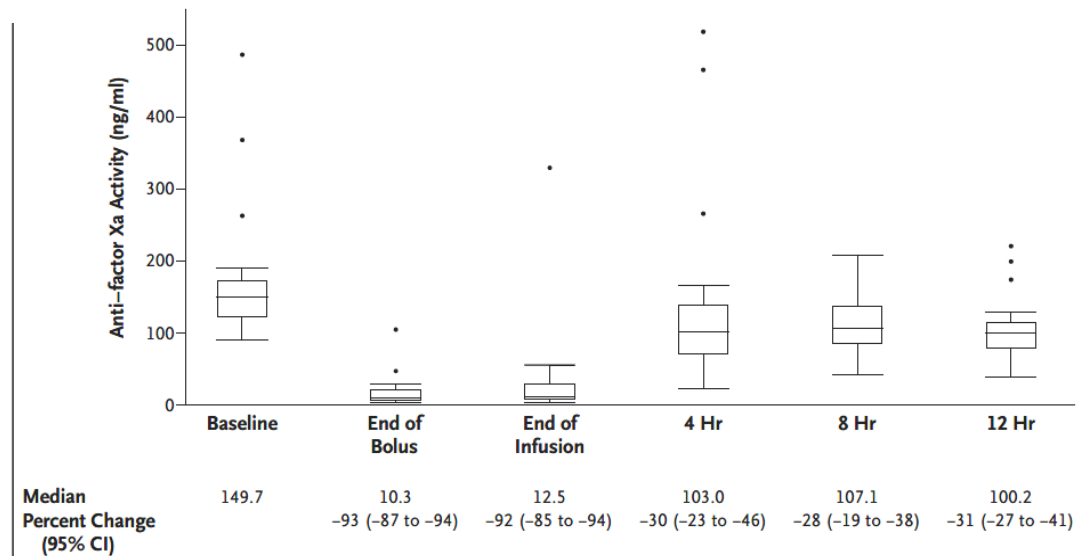
- Bleeding site
 - GI = 53%
 - Intracranial bleeding = 43%
 - Baseline GCS 14.1 ± 1.17
 - 67% hematoma < 10 ml
- Age 77.1 years
- 55% male
- Time from presentation until bolus:
 - 4.8 ± 1.8 hr
- Time from last dose to andexanet administration
 - Rivaroxaban: 12 ± 4.1 hr
 - Apixaban: 11 ± 4.7 hr

ANNEXA- 4 – Primary Outcomes

RIVAROXABAN, N = 26



APIXABAN, N =20



Good or excellent hemostatic efficacy 12 hours after infusion = 79% overall at 12 hours

ANNEXA -4 Safety Outcomes

NEJM '16 PUBLICATION

- Thrombotic event rate 12/67 (18%)
- 15% of patients died in 30-day follow-up period

Session 409 - Late-Breaking Clinical Trials: Interventional

409-14 - Interim Report on the ANNEXA-4 Study: Andexanet For Reversal of Anticoagulation in Factor Xa - Associated Acute Major Bleeding

- Interim safety analysis presented at ACC 2018
- Safety on 227 patients
 - 12% died
 - 11% thrombotic event
- Efficacy on 132 patients
 - Excellent or good hemostasis in 83%

ANDEXANET CRITIQUE

PROS

- First FDA- Approved product for anti-Xa inhibitors

CONS

- No control group
- Quick off-set
- Cost
 - CMS add on payment Oct.1, 2018
- Unavailable to many institutions
 - Gen 2 product expected early 2019



New Agents

IDARUCIZUMAB

Idarucizumab (Praxbind[®])

- Humanized monoclonal antibody that binds to dabigatran
- Accelerated FDA approval October 16, 2015
 - RE-VERSE AD
- N = 503
 - Group A n = 301 – uncontrolled bleeding
 - Group B n = 202 in urgent procedure
- Primary endpoint: maximum % reversal of anticoagulant effect at 4 hours (dTT or ECT)
- Secondary endpoints: restoration of hemostasis and safety measures

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal — Full Cohort Analysis

Idarucizumab – Full Cohort Results

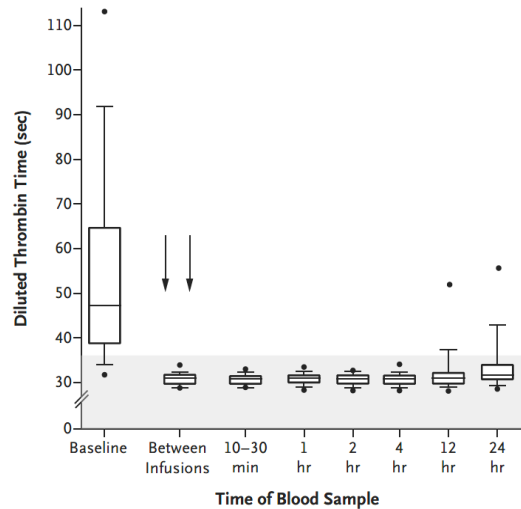
PRIMARY ENDPOINT

- Median maximum % reversal: 100%

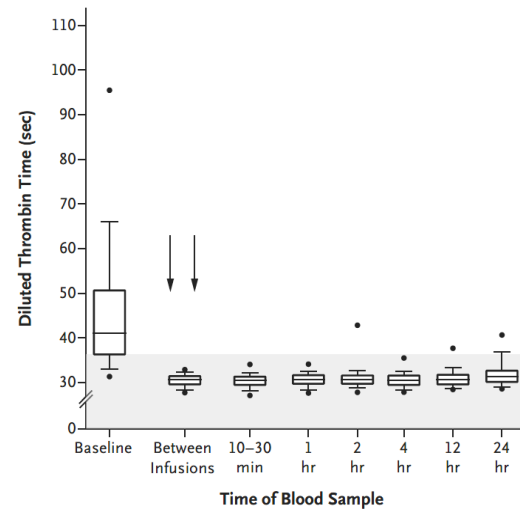
SECONDARY ENDPOINTS

- Time to cessation of bleeding:
 - Group A: 2.5 hours
 - Group B: 1.6 hours
- Periprocedural hemostasis
 - Normal: 93.4%
- Safety- 90 day thrombotic event rate:
 - 6.3% Group A
 - 7.4% Group B
- Mortality: 18.8-18.9%

A Diluted Thrombin Time in Group A



B Diluted Thrombin Time in Group B



Warfarin Reversal

4-PCC for Warfarin Reversal

- FDA Indications: VKA reversal in patients with acute major bleeding or need for urgent surgery/invasive procedure

Labeled dosing:

Pre-treatment INR	Dose	Maximum Dose
2 - < 4	25 units/kg	2,500 units
4-6	35 units/kg	3,500 units
>6	50 units/kg	5,000 units

4-PCC

Acute Major Bleeding

- n= 212, 202 in mITT
 - 98 PCC, 104 FFP
- FFP 10,12, or 15 ml/kg (based on INR)
- Primary endpoints:
 - Hemostatic efficacy 72.4% PCC vs 65.4% - non-inferiority
 - Reduction in INR to 1.3 or less at 30 minutes after end of infusion: 62.2% PCC and 9.6% FFP- superiority

Urgent Invasive or Surgical Intervention

- n =181, 168 in ITT
 - 87 PCC, 81 FFP
- Primary endpoints
 - Hemostatic efficacy 90% PCC vs. 75% FFP- non-inferiority
 - Reduction in INR to 1.3 or less at 30 minutes after end of infusion: 55% PCC and 10% FFP - superiority

4-PCC Shortage

- Both 1000 & 500 unit vials affected
- Estimated Resupply Dates – CSL Behring is releasing Kcentra® weekly
- ASHP Alternative Agents & Management Strategies:
 - Reserve supplies for patients on warfarin with life threatening bleeding. Consider fixed dosing to conserve supply.
 - Consider aPCC (FEIBA) as alternative
 - FFP

4-PCC – Fixed Dosing Strategies

4-PCC – Fixed Dosing Strategies

- Purpose: Evaluate experience with 1500 IU fixed-dose protocol
- Retrospective review
- Results, n =39
 - 71.8% were ICH
 - Median pre-treatment INR = 3.3, post-treatment INR 1.14 ($p < 0.001$)
 - 92.3% (36 of 39) achieved INR < 2 ; 71.8% (28) achieved INR 1.5 or less
 - No thrombotic events
 - Author conclusions: fixed dose 1500 IU 4-PCC leads to high rates of successful INR reversal and no related thrombotic at 7 days.



4-PCC – Fixed Dosing Strategies

- Purpose: Evaluate efficacy of 1500 IU fixed dose 4-PCC to decrease INR to ≤ 1.5 in warfarin treated patients requiring emergent reversal
- Retrospective evaluation
- n=37
- ~ 75% ≤ 1.5 after 1500 & 100% INR ≤ 2
- Median pre-INR: 3.06, post: 1.32

Fixed dose 4-factor prothrombin complex concentrate for the emergent reversal of warfarin: a retrospective analysis



4-PCC – Fixed Dosing Strategies

- 1000 units 4-PCC for ICH vs. weight based (Cofact®)
- Before and after study design
- 1750 IU in weight based n =25 and 1000 IU n=28
- ITT analysis 96% achieved $\text{INR} \leq 1.5$ – wt based & 68% in fixed dose
- 8% in wt based & 32% in fixed received additional dose
- Median door – to – PCC:
 - 81 vs. 60 min ($p = 0.42$)
- Author Conclusions: fixed dose needs more PCC infusions more frequently to achieve $\text{INR} \leq 1.5$; no significant changes in door –to- PCC time, clinical outcome effects remain unknown

neurocritical care society Neurocrit Care (2017) 26:64–69
DOI 10.1007/s12028-016-0248-8



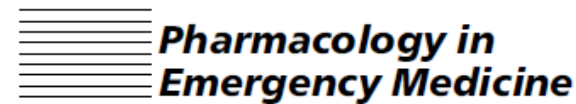
ORIGINAL ARTICLE

Fixed Versus Variable Dosing of Prothrombin Complex Concentrate in Vitamin K Antagonist-Related Intracranial Hemorrhage: A Retrospective Analysis

Rahat Amadkhan Abdoellakhan^{1,2} · Ishita Parveen Miah³ · Nakisa Khorsand² · Karina Meijer¹ · Korné Jellema³

4-PCC – Fixed Dosing Strategies

- Purpose: Compare fixed dose of 1000 IU 4-PCC to that of weight-based dosing in ICH
- Primary endpoint: INR < 1.5
- Secondary endpoints: in-hospital mortality, patient disposition, reversal defined by INR < 1.6
- n= 61 (31 weight based, 30 fixed)
- Baseline INR 2.98, 2.84, 71% INR < 1.5 wt based, 53% in fixed (p=.15), 81% achieved INR < 1.6 wt based & 73% in fixed (p=0.49). No difference in other secondary endpoints
- Author Conclusions: non-statistically significant difference in warfarin reversal to an INR < 1.5 between weight-based and 1000 IU 4-PCC



EVALUATION OF FIXED-DOSE FOUR-FACTOR PROTHROMBIN COMPLEX CONCENTRATE FOR EMERGENT WARFARIN REVERSAL IN PATIENTS WITH INTRACRANIAL HEMORRHAGE

Rachael Scott, PHARM^D,* Brian Kersten, PHARM^D, BCPS, BCCCP,* Jeanne Basior, MD,† and Megan Nadler, PHARM^D, BCPS*

Alternative Warfarin & DOAC Reversal Strategies

Alternative Reversal Strategies

Warfarin

- 3-PCC: 20 -50 IU/kg
- aPCC: 50 -100 IU/kg
- FFP: 10-15 ml/kg

DOAC

- aPCC: 50-100 IU/kg
- rFVIIa: 90 u/kg
- 3-PCC: 50 IU/kg

TABLE 5 Available Reversal Agents and Suggested Use

Reversal Agent	Vitamin K Antagonists (Warfarin)	Factor IIa Inhibitor (Dabigatran)	Factor Xa Inhibitor (Apixaban, Edoxaban and Rivaroxaban)
4F-PCC (56)	First line	Second line	First line
aPCC	Not indicated	Second line	Second line
Idarucizumab	Not indicated	First line	Not indicated
Plasma	If 4-PCC is unavailable	Not indicated	Not indicated

4F-PCC = 4-factor prothrombin complex concentrate; aPCC = activated prothrombin complex concentrate.

Case - Revisited

- MH
- What are your options for DOAC reversal?
- Would your regimen change if patient was taking warfarin instead?

Conclusions

- Reversal of oral anticoagulation requires many considerations, many of which are patient and bleeding site specific
- Standard lab assays may not represent anticoagulation from oral anticoagulant, gold-standard assays are generally not readily available
- Andexanet alfa is the only FDA-approved reversal agent for oral factor Xa inhibitors
- 4-PCC conservations strategies and alternatives should be considered during times of drug shortage

References

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Questions?

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