

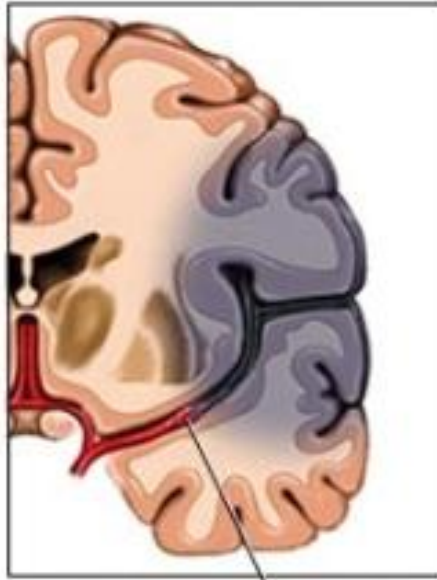
Rapid Reversal of Anticoagulation for Intracerebral Hemorrhage



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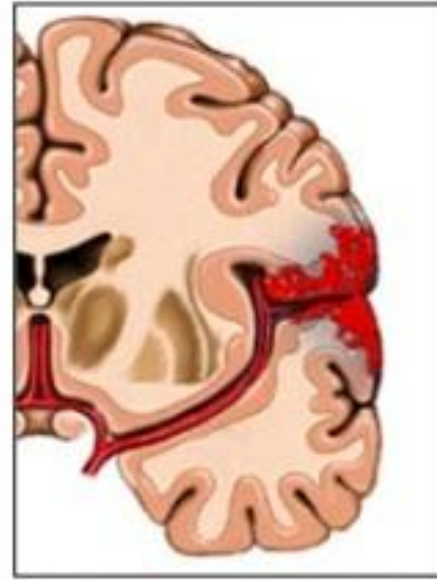
Two Types of Stroke

Ischemic stroke



A clot blocks blood flow
to an area of the brain

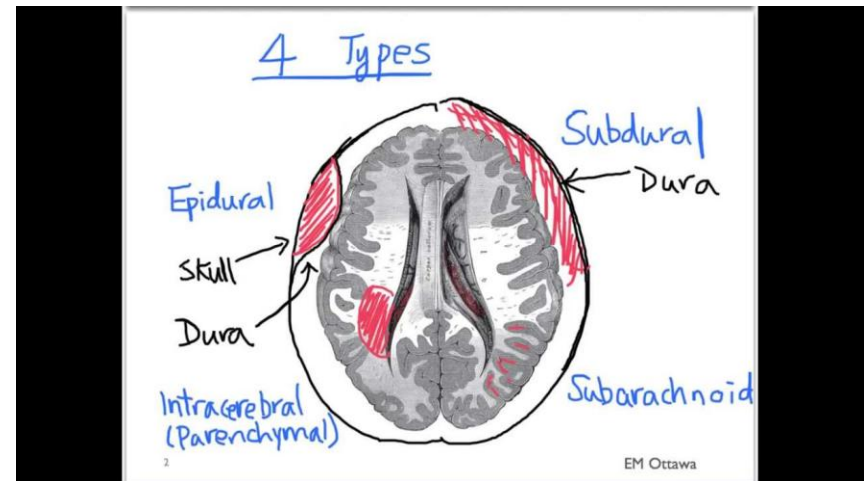
Hemorrhagic stroke



Bleeding occurs inside or
around brain tissue

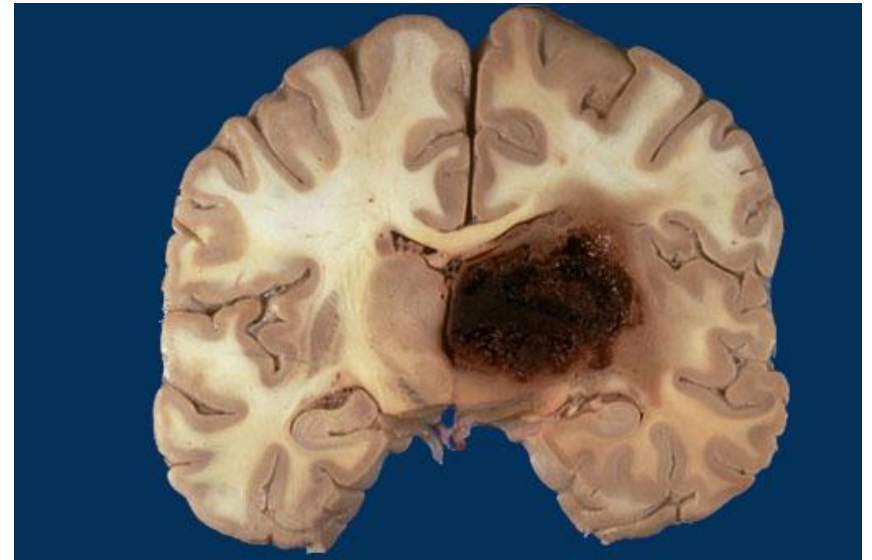
Intracranial Hemorrhage Facts

- 15% of all strokes
- 3 major types
 - SDH, SAH & ICH
- 15-30 cases per 100,000
 - African American & Asian
 - Risk doubles every 10 years after age 35
- 20,000 deaths per year
- 30 day mortality is 44%



Spontaneous ICH Etiology

- Hypertension
- Cerebral amyloid angiopathy
- Arteriovenous malformation
- Aneurysmal rupture
- Hemorrhagic transformation ischemic infarct
- Cerebral venous thrombosis
- Intracranial neoplasm
- Vasculitis & Moyamoya
- Sympathomimetic drug abuse
- Bleeding disorders
 - Liver, thrombolytics, anticoagulants



Warfarin



1mg



3mg

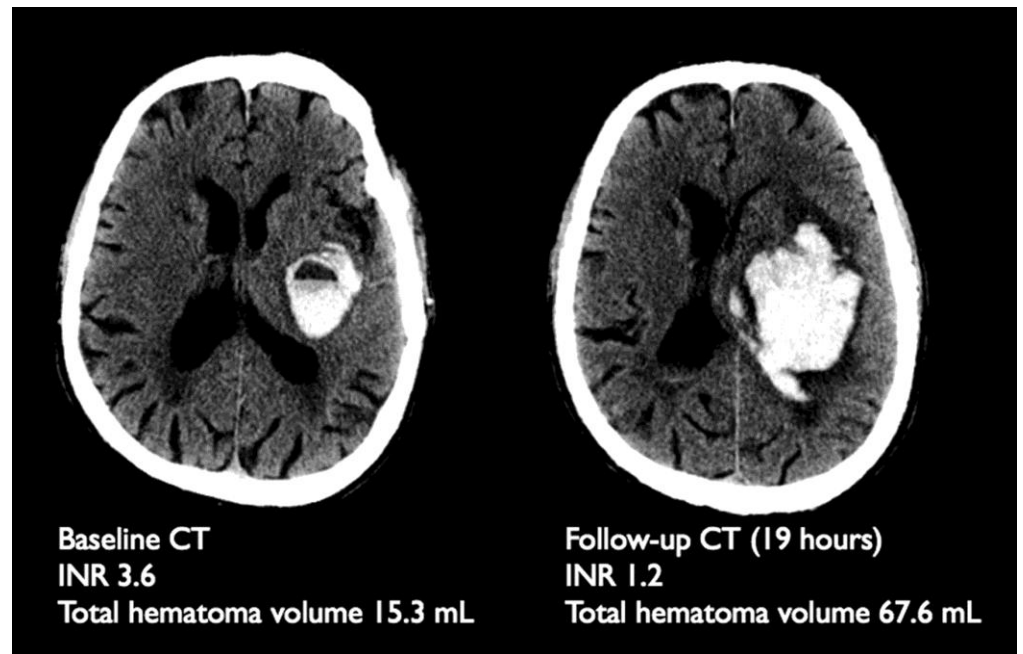


5mg

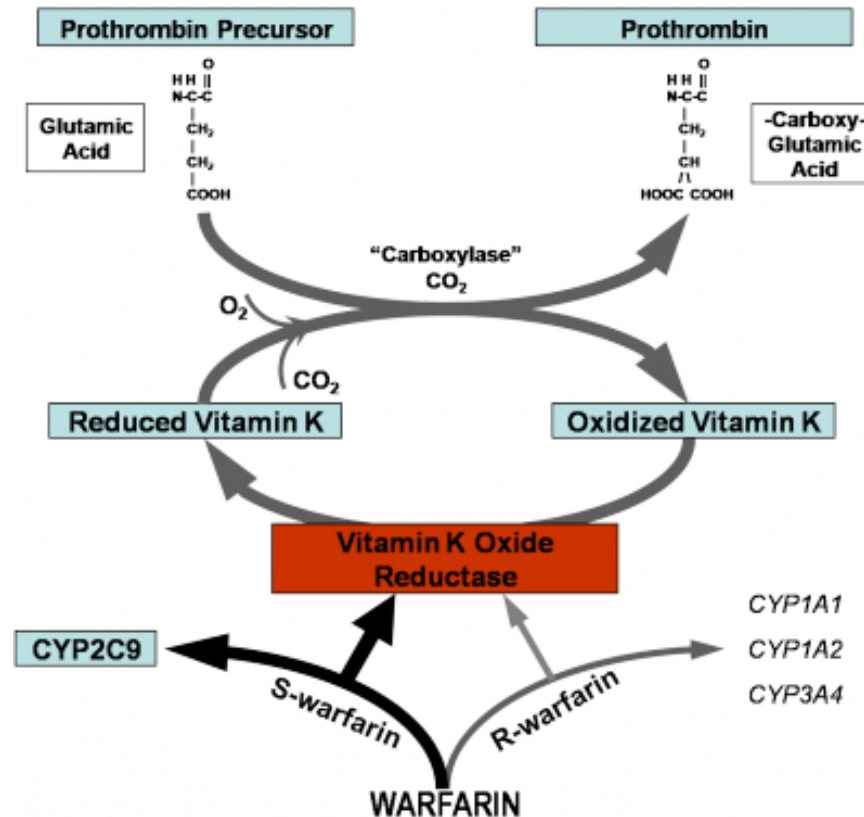
- 3 million patients prescribed warfarin
 - Atrial fibrillation, hypercoagulable states, stroke
- Narrow therapeutic window
 - INR 2.0-3.0 or 2.5-3.5
 - Patients outside window 30% of time
- Major side effect is bleeding
 - Black Box warning regarding bleeding risk
 - 15-20% of patients per year
 - 1-3% life-threatening and fatal
 - 2% suffer ICH with 44-68% mortality at 30 days
 - Warfarin accounts for 20% of all ICH

Warfarin ICH

- Associated with
 - Increased initial hematoma volume
 - Increased risk of hematoma expansion
 - Increased likelihood of IVH
 - Worse outcomes
 - Permanent disability
 - Death

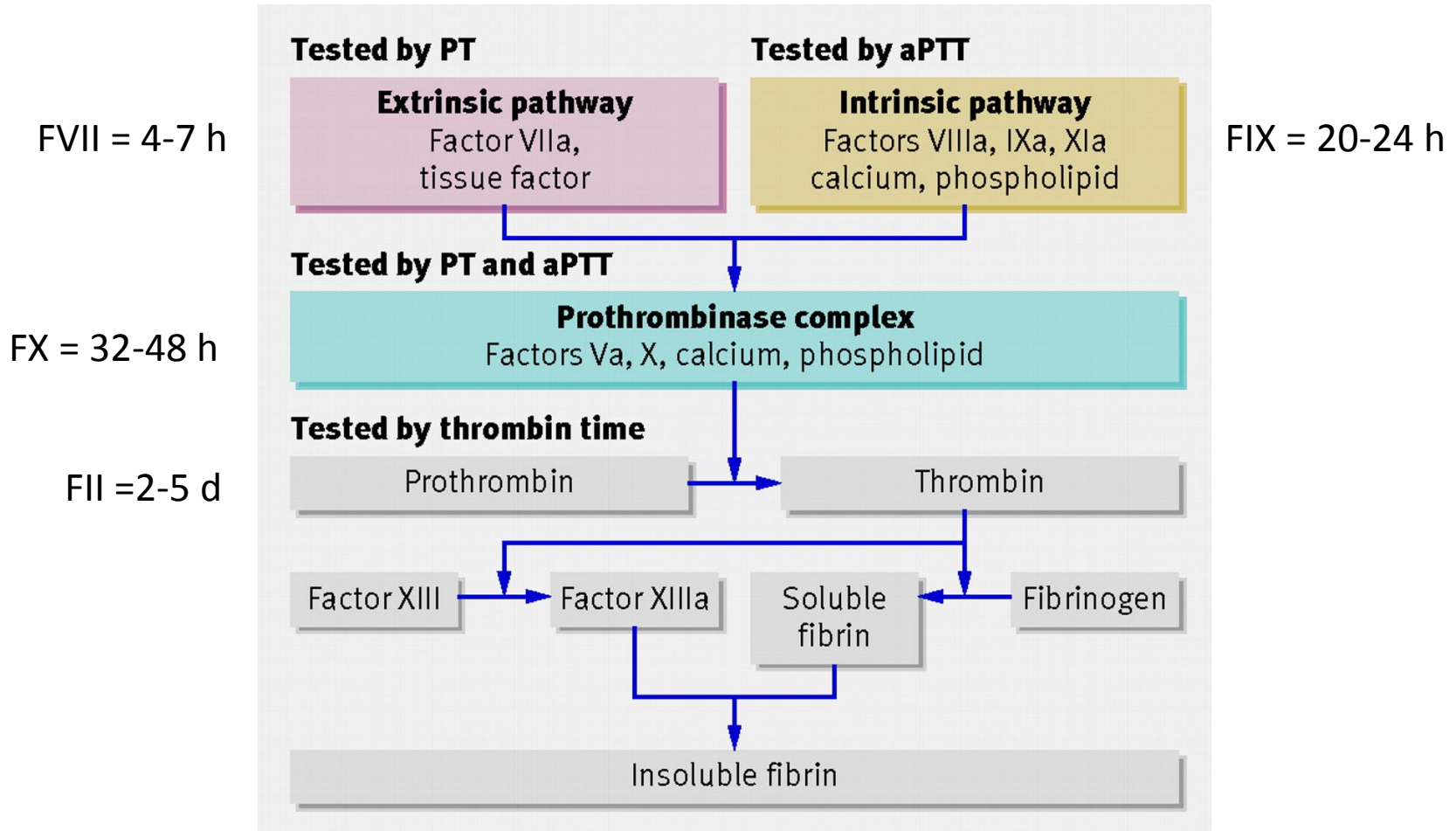


Warfarin Mechanism



Warfarin decreases Factor II, VII, IX & X activity

Warfarin Effect on Coagulation Pathway



INR & Coagulation Factor Levels

INR	FII	FVII	FIX	FX
1.5	60	100	120	90
2.0	40	40	60	20
2.5	25	35	40	15
2.8	20	25	35	15
Normal	50-150	50-150	50-150	50-150
MHC	20-40	10-20	25-50	10-25

Equilibrium levels of II, IX & X are 15-40% of normal at one week when INR is between 2.0 and 3.0

Oral Direct Factor Xa Inhibitors

- Rivaroxaban (Xarelto®)
 - Peak effect at 2-4 hours after dosing
 - Circulating half life is 11-13 hours
 - PT, INR, aPTT increased, but not reliable to assess degree of AC
- Apixiban (Eliquis®)
 - Peak effect at 1-2 hours after dosing
 - Circulating half life is 8-15 hours
 - PT, INR, aPTT not significantly increased
- Indications
 - Reduce risk stroke and thromboembolism in NV-AF
 - Treat DVT and PE
 - DVT prophylaxis

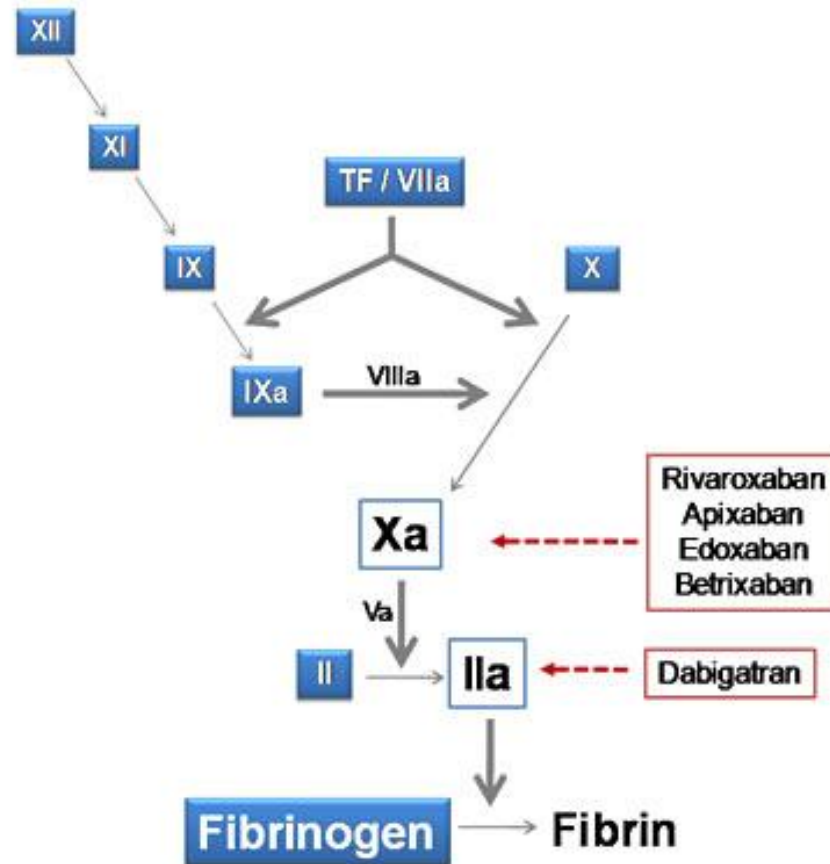
Direct Fxa Inhibitor Bleeding Risk

Event	Rivaroxaban	Apixiban	Warfarin
Major bleeding	3.6% per year	3.6% per year	3.4% per year
ICH	0.5% per year	0.3% per year	0.7% per year
GI bleed	3.2% per year	0.8% per year	0.9-2.2% per year

ROCKET study, NEJM 2009;361:1139

ARISTOTLE study, NEJM 2011;365:981

Direct Fxa Inhibitor Mechanism



Emergent Reversal of Fxa Inhibitors

- Challenges
 - Difficult to assess level of anticoagulation
 - No specific antidote
 - No standard procedure to reverse effect
- Recommendations
 - Discontinue the drug
 - Supportive care
 - Nonactivated 3 or 4 factor PCC
 - Excess Fxa neutralizes drug effect

Warfarin Reversal Strategies

- Vitamin K replacement
- Plasma infusion
- 3-Factor Prothrombin Complex Concentrate
 - Alone or with rFVIIa (NovoSeven)
- 4-Factor Prothrombin Complex Concentrate



Vitamin K



- Vitamin K is only specific antidote to warfarin
- Sustained reversal of warfarin effect
- IV administration begins correct INR within 4h
 - Too slow to prevent hematoma expansion
 - Cannot be used alone
- Vitamin K should be given with PCC or plasma
 - Factor VII has short half life of 7 hours
 - Factor IX has a large volume of distribution

Plasma Products

- 175 – 250 mL per bag
- Thaw time
- ABO compatible
- Each bag ↑ level of any coagulation factor by 2-3%
- 15 mL/Kg → 10% increase
- Usual adult dose is 2-4 bags per transfusion
- Long infusion time
- Short term effect
- Risk of TACO



INR Correction w/ Plasma

Pre-transfusion INR	INR correction per Unit of Plasma
1.0 – 1.5	0 – 0.1
1.6 – 1.8	0 – 0.3
1.9 – 2.6	0.1 – 0.5
2.7 – 4.9	0.3 – 1.1
5.0 – 9.9	0.8 – 2.5
10.0 – 14.0	4.0 – 6.0
14.1 – 20.0	5.8 – 8.4

INR of plasma is 1.2 – 1.3

3 Factor Prothrombin Complex Concentrate

- Profilnine SD Factor IX Complex (Grifols)
- FDA licensed for Rx of hemophilia B
- Contains Factors II, IX & X
 - Trace amount of Factor VII
- Labeled with FIX potency in IU
 - SLHS stocks vials with ~1000 IU of FIX
- Can supplement 1 mg NovoSeven (rFVIIa)
 - FDA licensed for Rx of Hemophilia A/B inhibitors

4-Factor Prothrombin Complex Concentrate

- Kcentra in U.S. & Beriplex in Europe & Canada
 - CLS Behring
- 4 factor complex concentrate
 - Factors II, VII, IX, X, Protein C & S
 - Lower risk of thrombosis?
- Dosing based on Factor IX
- FDA approval on April 29, 2013
 - urgent reversal of warfarin in adults
 - Acute major bleeding or urgent invasive procedure

Plasma vs PCC

Plasma

- ABO compatibility
- Thaw time
- Large volume (500-1000)
- Low specific activity
- IV drip – 30 to 60 minutes
- Less expensive
 - ~\$60/bag

PCC

- Blood type not necessary
- Reconstitution time
- Small volume (80-120 mL)
- High specific activity
- IV push – 3 minutes
- More expensive
 - \$1.27 to \$1.39 per U

ICH Treatment Recommendations

2012 ACCP & 2010 AHA/ASA

- Stop all anticoagulant & antiplatelet Rx
- Confirm Dx with noncontrast head CT
- 10 mg Vitamin K by slow IV infusion
- Infuse rapid reversal reagent
 - 4-factor PCC or
 - 3-factor PCC supplemented with plasma or
 - Plasma

3F-PCC ICH order set

April 1, 2013

Discontinue antithrombotic & antiplatelet medications
If warfarin, give 10 mg Vitamin K IV in 50 mL D5W over 1h
Give PCC per orders below:

INR	<70 kg	70-100 kg	>100 kg
1.5 – 3.0	2000 U PCC	3000 U PCC	4000 U PCC
>3.0	3000 U PCC	4000 U PCC	5000 U PCC

1 mg vial of rFVIIa if on warfarin & INR>1.4

Check PT/INR at 30 minutes post-infusion

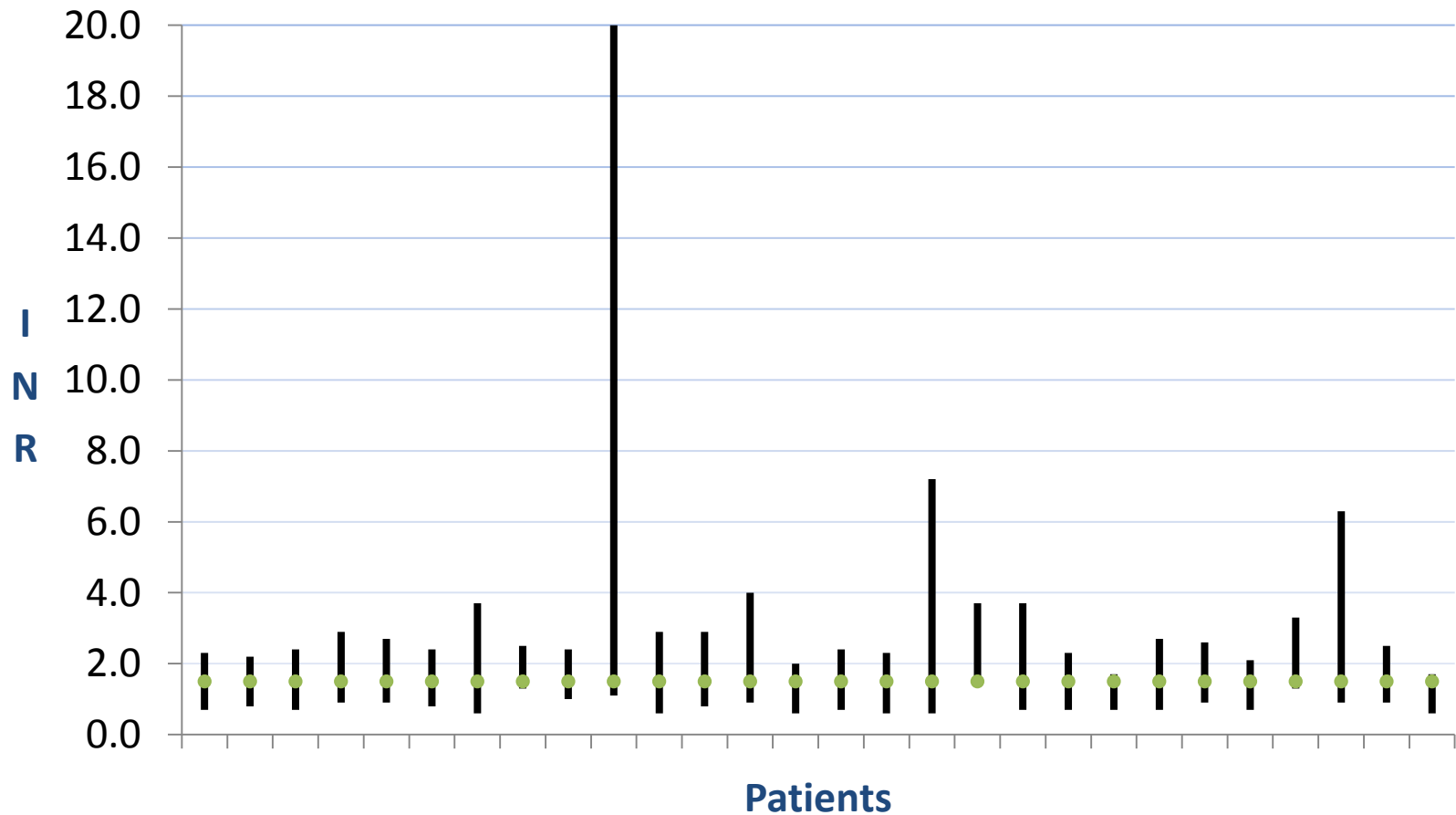
Consider repeat dose if INR remains >1.4

If patient taking apixiban or rivaroxaban use INR>3.0 dose

3F-PCC + rFVIIa Experience

- 33 patients treated from Apr 1 – Oct 31, 2013
- 32 taking warfarin & 1 rivaroxaban
- Very effective correction of INR
 - Average post-INR was 0.8
 - Post-INR often ≤ 0.7
- 2 patients had thrombosis
 - 1 had history of APLA syndrome
 - 1 with history of severe CAD & PAD
- Inpatient mortality was 21% (7/34)

INR Correction with PCC + rFVIIa



Combination Protocol Concerns

- Off label use of both products
- Confusion in ordering, issuing & reconstituting 2 different products
- Over-correction of INR
- Expense
- Reimbursement



Kcentra

- 4 factor Prothrombin Complex Concentrate
- FDA approved Apr 2013 for urgent reversal of acquired coagulation deficiency in adults with major bleeding or needing invasive procedure



Kcentra Reconstitution & Infusion

- Stock 500 & 1000 U vials
- Reconstitute with 20 or 40 mL sterile water
- Administer each vial over 3 minutes IV push
- Use separate infusion line
- Check INR/Protime within 30 minutes

4F-PCC ICH Order Set

Nov 6, 2013

Discontinue antithrombotic & antiplatelet medications

If warfarin, give 10 mg Vitamin K IV in 50 mL D5W over 1h

Give PCC per orders below:

INR	<79 Kg	≥80 Kg
≤3.9	2000 IU	2500 IU
≥4.0	3000 IU	3500 IU

Check PT/INR at 30 minutes post-infusion

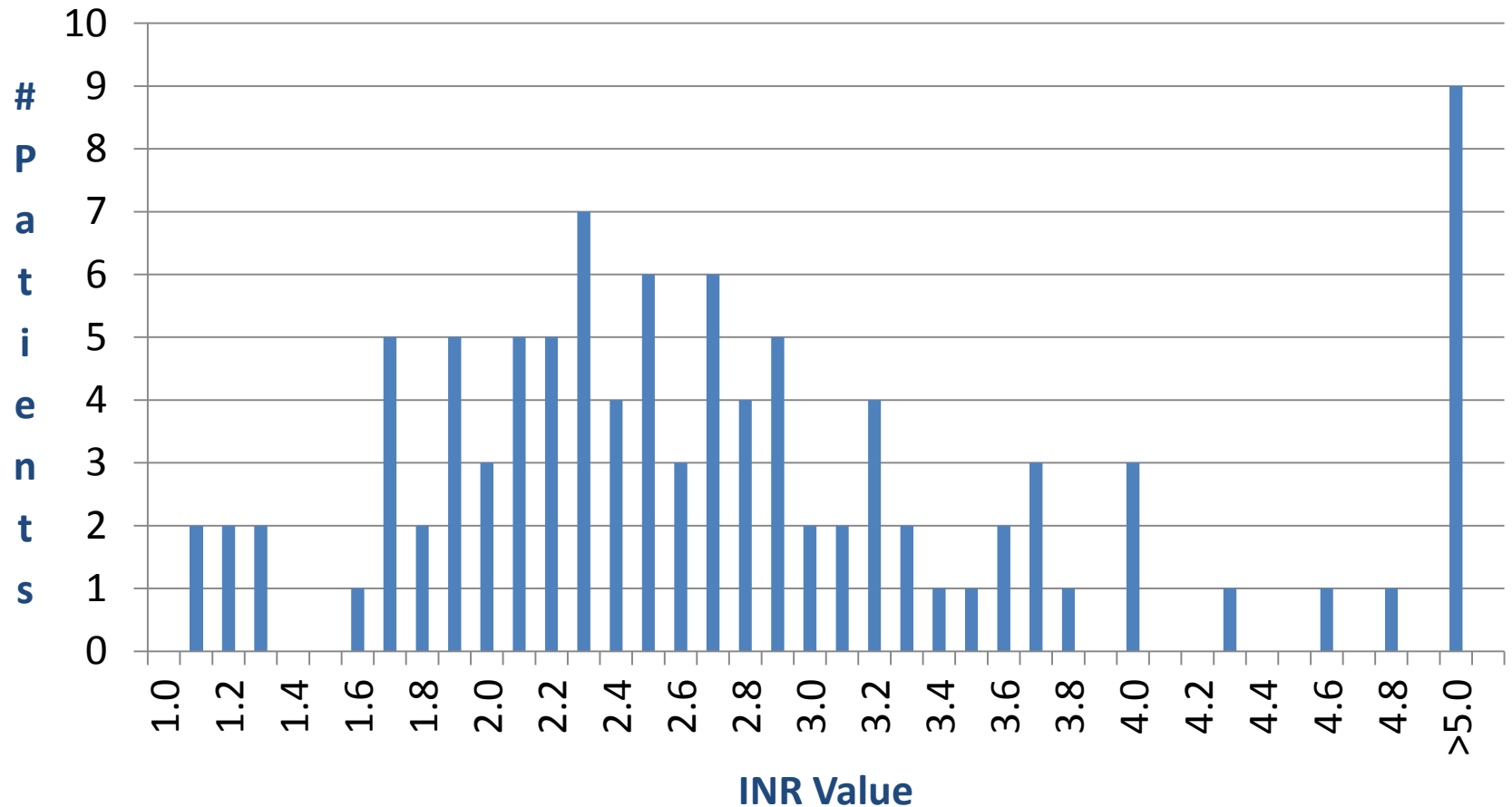
Consider repeat dose if INR remains >1.4

If patient on rivaroxaban or apixiban use INR ≥4.0 dose

Kcentra Contraindications

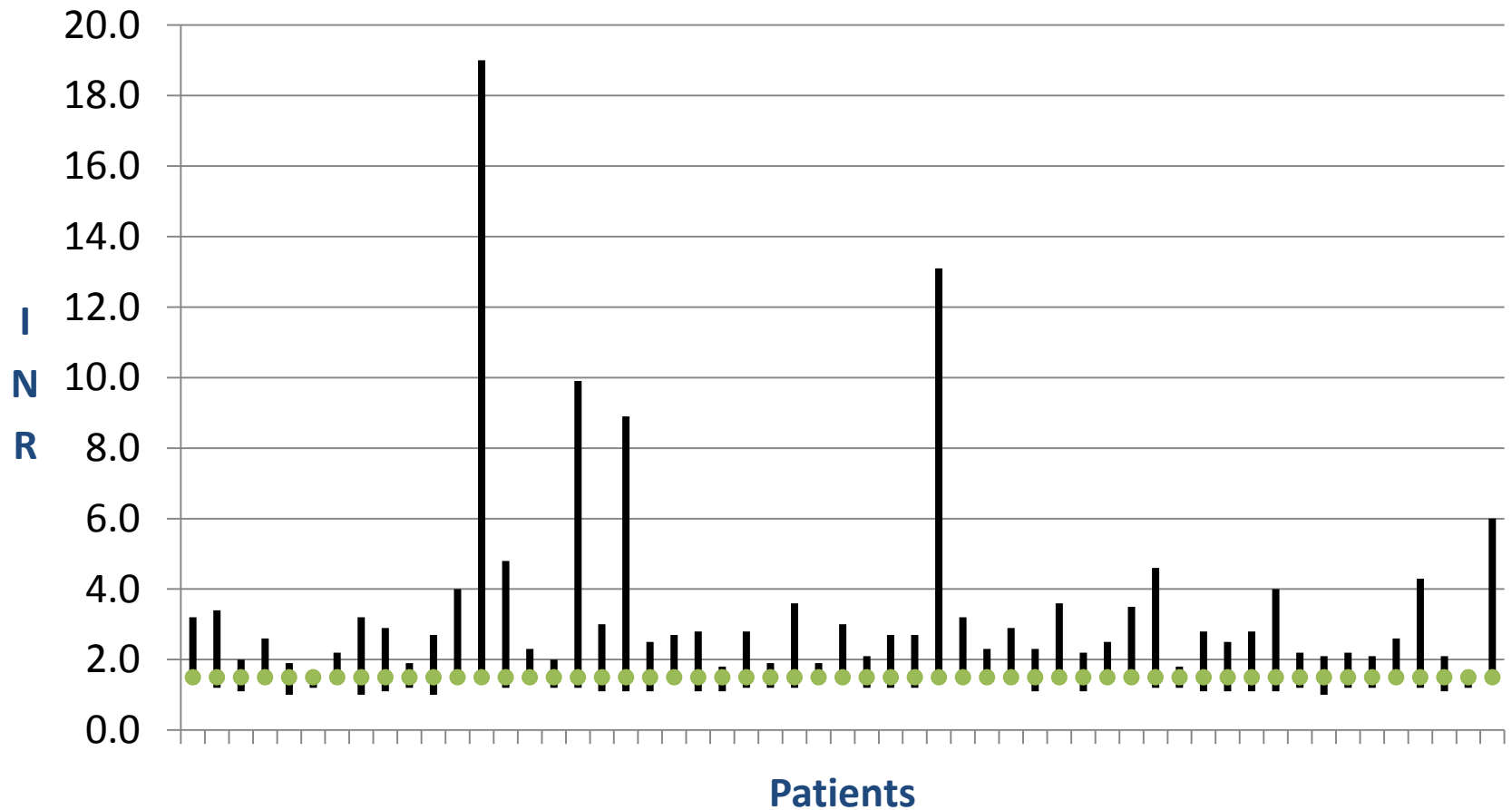
- Known anaphylactic or severe systemic reactions to albumin, factors or heparin
- Disseminated intravascular coagulation
- Heparin induced thrombocytopenia
- Thromboembolic event in past 3 months

Pretreatment INR Values



Apixiban INR 1.1-1.4 & Rivaroxaban INR 1.1 – 1.9

INR Correction with 4F-PCC



4F-PCC Protocol Experience

- 69 cases Nov 6, 2013 through Mar 24, 2015
 - 57 warfarin, 7 rivaroxaban, 5 apixiban
- All warfarin patients corrected to INR <1.5
 - Average post-INR was 1.2
- 3 patients developed DVT (2) or PE (1) during stay
 - >24 hours after 4F-PCC
 - 1 had APLA syndrome
- 15 patients had neurosurgery (14 survived)
- Inpatient mortality was 14% (10/69)
 - 9 on warfarin (9/57 = 16%)
 - 1 on rivaroxaban (1/7 = 14%)

Outcomes Comparison

Endpoint	Plasma	3F-PCC + rFVIIa	4F-PCC
%Pt w/ INR <1.5*	24%	100%	100%
Average Post-INR*	1.9	0.8	1.2
%Pt w/ INR <1.0*	0%	92%	0%
Ave time to INR <1.5	1229 min	148 min	98 min
In hospital mortality	32%	19%	14%
Acquisition cost	\$134	\$4171	\$3600

*Post-INR statistics measured on warfarin patients

Need to measure modified Rankin scale at 90 days and 1 year

Summary

- 4F-PCC rapidly reversed OAC
 - 12x faster than plasma
- Simplified dosing schedule corrected INR to 1.5 or lower regardless of initial value
- Inpatient mortality reduced from 32% to 14%
 - Mortality same for warfarin & rivaroxaban
- Acquisition cost increased 26 fold compared to plasma
- Reimbursement has been adequate
- To do
 - Determine 90d and 1y outcomes (modified Rankin Scale)
 - Determine impact on hematoma expansion

Original Investigation

Anticoagulant Reversal, Blood Pressure Levels, and Anticoagulant Resumption in Patients With Anticoagulation-Related Intracerebral Hemorrhage

CONCLUSIONS AND RELEVANCE

Among patients with OAC-associated ICH, reversal of INR <1.3 within 4 hours and systolic BP <160 mmHg at 4 hours were associated with lower rates of hematoma enlargement

JAMA. 2015;313(8):824-836. doi:10.1001/jama.2015.0846