

## Acute Intracerebral Hemorrhage: What is the Optimal Therapy in the Anticoagulated Patient?

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## Acknowledgement:

This session was initially developed by

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## Disclosure

- None



## Session Objectives

- Describe the current state of knowledge regarding reversal of anticoagulation in patients with acute intracranial hemorrhage
- Focus on warfarin reversal
- Review outcomes of activated Factor VII and prothrombin concentrate complex clinical trials



## Clinical Questions

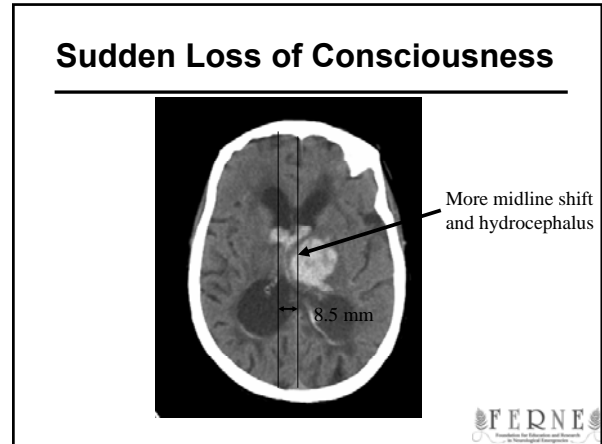
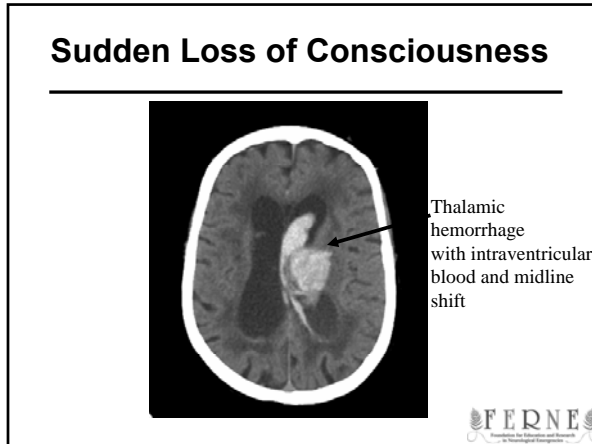
- What is the rationale for using warfarin anticoagulation?
- What risk does this pose?
- What options are available to reverse anticoagulation?
- How fast do they work?
- What is the risk of pro-coagulant complications?
- Does reduction in bleeding lead to better functional outcome or reduce mortality?



## Case Study: Acutely Unresponsive

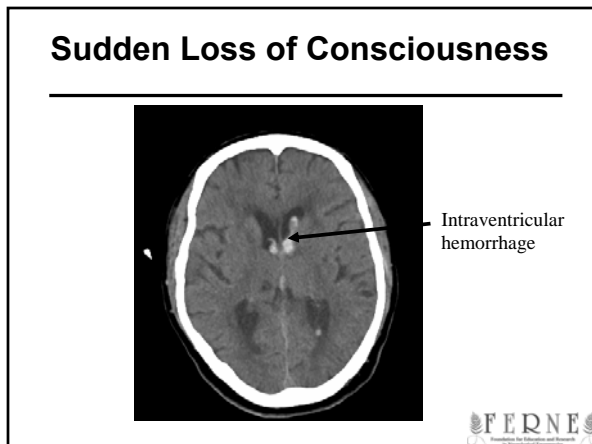
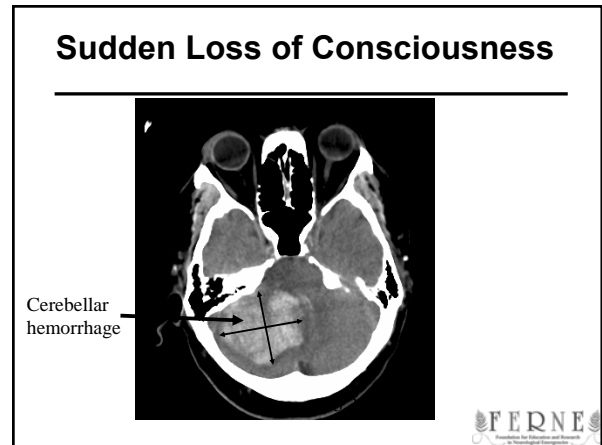

- 91 yo with HTN, dementia, old ischemic strokes
- Coumadin for history of atrial fibrillation
- 208/123, HR 76, Temp 37.2 C, RR 12
- Pupils 3mm and sluggish, conjugate deviation to right
- GCS 10-11, RUE motor 2/5, LUE 4/5
- Hgb 14.9, platelets 270K, INR 3.1





### Case 2: Sudden LOC


- 71 yo right handed Indian male with sudden LOC, vomiting, and 10 minutes of seizure activity
- On Naproxen for arthritis
- Vitals BP 200/90, HR 87, RR 14, Temp 36.7 C
- GCS 6, pupils 1mm and nonreactive bilaterally
- Flexure posturing R > L, toes equivocal
- No dolls eyes, but corneal and gag preserved
- Hgb 11, platelets 236K, INR 1.03, PTT normal



### ICH: Scope of the Problem

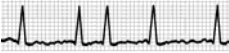


- 10-15% of first-ever strokes
- 30 day mortality 35-52%
- Only 20% are functionally independent at 6 months
- Hematoma growth associated with five-fold increase in clinical deterioration, poor outcome and death

*Silva Y, Leira R, Stroke 2005;86-91*




### Why Use Warfarin at all?

- **Atrial fibrillation: risk of embolic stroke 5% per year**
- **Rises to 12% per year with history of prior stroke**
- **4% per year with prosthetic mechanical valves**






### Warfarin Risk

- ICH: 0.3-0.6% per patient year
- 6-23% of all ICH are on warfarin
- 8-10,000/year in the USA
- OR of 6.2 for hematoma expansion and continues longer
- ICH risk doubles for each 0.5 INR unit > 4.5



*Flibotte JJ, Hagan N, Neurology 2004, 1059-64  
 Rosand J, Eckman MH, Arch IM, 2004, 880-4  
 Aguilar MI, Hart RG, Mayo Clin Proc, 2007*




### Anticoagulation Reversal for ICH

Management option	Time to anticoagulation reversal	Comments and cautions
Discontinuing warfarin therapy	5-14 d	
Vitamin K <sup>†</sup>	6-24 h to correct the INR	Replacement of factors IX and X takes longer than 24 hours, risk of anaphylaxis with intravenous injection, warfarin resistance in higher doses up to 1 wk
Fresh frozen plasma	3-6 h for infusion, typically 12-32 h for reversal	Volume (2-4 L to normalize INR) can be prohibitive
Prothrombin complex concentrate	15 min after 10-min to 1-h infusion	Limited availability, cost, variable cofactor content based on manufacturer, potentially prothrombotic
Factor VIIa concentrate	15 min after bolus infusion	Short half-life, cost, potentially prothrombotic, uncertain safety


\*INR = international normalized ratio.  
<sup>†</sup>A total of 10 mg intravenously by slow infusion throughout 10 minutes.

*Aguilar MI, Hart RG, Mayo Clin Proc, 2007*




### American College of Chest Physicians Guidelines, 2004

Condition	Description
INR < 5 No significant bleeding	Lower or omit next warfarin dose
INR >5 but <9 No significant bleeding	Omit next 1 or 2 warfarin doses Vitamin K up to 5mg po if increased bleeding risk
INR >9 No significant bleeding	Hold warfarin until therapeutic Vitamin K 5-10mg po
Any INR Serious bleeding	Hold warfarin Vitamin K 5-10mg IV FFP or PCC
Any INR Life-threatening bleeding	Hold warfarin Vitamin K 5-10mg IV PCC or Factor VIIa




### Anticoagulation Reversal Options

- Vitamin K
- Fresh frozen plasma
- Platelet transfusion
- rFVIIa
- Prothrombin complex concentrate
- Tranexamic acid
- Desmopressin



### Vitamin K<sub>1</sub>

- Takes at least 6 hours to normalize INR, 24 hours for full effect
- Given 10 mg IV (small risk of anaphylaxis) or subq
- Necessary but not sufficient
- AHA/ASA Class I, Level of evidence B



## Reversal of Heparin

- Protamine sulfate
- 1 mg per 100 units of heparin if heparin stopped just prior to protamine
- Reduced dose the longer the heparin has been off (0.25-0.375 mg/100 units after 2 hours)
- Slow IV < 5 mg/min to avoid hypotension
- AHA/ASA Class I recommendation, Level of evidence B



## Fresh Frozen Plasma

- Replenishes vitamin K dependent clotting factors inhibited by warfarin
- 12-20 ml/kg = 1400ml = 6 units
- Volume overload and time
- Unpredictable factor levels and low factor IX
- "impractical"



## Activated Factor VII

- rFVIIa approved for hemophilia bleeding
- Mechanism:
  - Interacts with tissue factor and stimulates thrombin generation directly
  - Activates factor X on platelet surface which also activates thrombin
  - Converts fibrinogen to fibrin = stable clot
- Half life of 2.6 hours



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

### Recombinant Activated Factor VII for Acute Intracerebral Hemorrhage

- Phase II dose finding trial
- 399 patients diagnosed with ICH within 3 hrs
- Primary outcome: change in hematoma volume at 24 hrs
- Clinical outcomes at 90 days

Mayer SA, Brun NC, NEJM, 2005



## Activated Factor VIIa Trial Outcomes

- Hematoma growth: 29% placebo vs 16, 14, 11% in three treatment groups (p = .01)
- 69% in placebo group dead or severely disabled vs. 53% in three treatment groups (p = .004, 95% CI 4.5-25%)
- Serious clots elsewhere: 7% vs 2% placebo (p= .12)

Mayer SA, Brun NC, NEJM, 2005, 777-85



## Problems with aFVIIa Trial

- Industry sponsored
- Excluded:
  - anticoagulated patients
  - coagulopathy patients
  - Patients with known thrombo-embolic disease
- Placebo group had more brainstem strokes, more men, lower GCS at entry = worse outcome
- Not powered to detect increase in thrombotic events (2 vs. 7%)
- 2/9 thrombotic strokes fatal
- Other series: 10% symptomatic MI vs. 1%

Mayer SA, Brun NC, NEJM, 2005  
Greenberg SM, Neurology 2006



**AHA/ASA Guideline for Activated Factor VIIa Use: 2007**

- “has shown promise”
- “efficacy and safety must be confirmed in phase III trials before it can be recommended outside of clinical trials”
- **Class IIb recommendation, Level of evidence B**



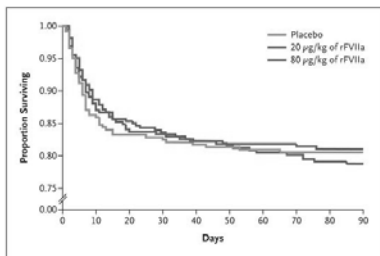
**FAST Trial Results**

- Randomized placebo-controlled trial of 821 patients
- ICH within 3 hours onset
- **Outcome: Death or severe disability at 90 days**
- **Reduced hematoma growth**
  - 26% growth with placebo
  - 18% with lower dose
  - 11% higher dose (p=0<.004 for the higher dose)

Mayer et al. NEJM 2008; 358 (20): 2127



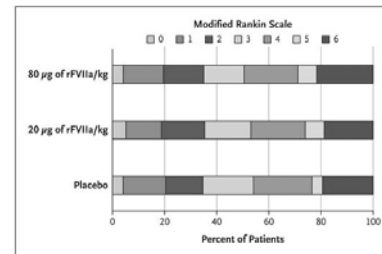
**FAST Trial Results**



Mayer et al. NEJM 2008; 358 (20): 2127



**FAST Trial Results**



Mayer et al. NEJM 2008; 358 (20): 2127



**FAST Trial Results**

**Acute Thrombotic Events**

Arterial Thrombosis	rFVIIa	rFVIIa	placebo
	20 mcg/kg	80 mcg/kg	
Acute MI	5%	8%	4%
Cerebral Infarction	4%	5%	3%

Mayer et al. NEJM 2008; 358 (20): 2127



**FAST Trial Results**

- **No significant effect on mortality/disability:**
  - 24% controls
  - 26% low dose
  - 29% higher dose
- **Why? 2005 placebo group did poorly (29% mortality vs. 19% in the FAST trial)**
  - Lower GCS, more brainstem bleeds, more intraventricular bleeds, more men
- **Surrogate markers are often misleading**

Mayer et al. NEJM 2008; 358 (20): 2127



## rFVIIa Utilization



## Broader Literature on rFVIIa

- Cochrane Review April, 2007
- Non-hemophiliac population search
- Randomized placebo-controlled
- 13 trials
  - 6 (n=724) for prevention
  - 7 (n= 1214) for treatment
- No differences between groups that could not be due to chance

Stanworth SJ, Birchall J, Cochrane Database of Systematic Reviews, 2007, Issue 2



## rFVIIa in Warfarin-associated ICH

- 4 studies of 27 total patients
- Two trials (n=14) also gave FFP and Vitamin K
- May not reverse coagulopathy of all vit K dependent factors
- No studies of rFVIIa vs. Prothrombin Factor IX concentrates in ICH



## Prothrombin Complex Concentrate

- Beriplex P/N, Proplex-T, Autoplex T, FEIBA, Bebulin, Profilnine HT, Konyne 80
- Factor IX complex concentrate has high levels of II, VII, and X
- 8 Studies of 107 patients with warfarin-associated ICH
- Not widely available in the US
- Restricted to hematology?
- AHA/ASA Class IIb recommendations

Aguilar MI, Hart RG, Mayo Clin Proc, 2007



## Prothrombin Complex Concentrate

- Dose based on Factor IX component
- 25-50 IU/kg total dose = 3500 IU
- First 500-1000 IU at 100 IU/min max over 10 min, then 25 IU/min
- Goal INR: 1.2
- Check after 30 minutes
- Cost \$1500 per dose
- Repeat if necessary

Aguilar MI, Hart RG, Mayo Clin Proc, 2007



## Beriplex P/N

- Beriplex® P/N is a highly purified, lyophilized human plasma fraction containing balanced amounts of the coagulation factors of the prothrombin complex (II, VII, IX and X) and of protein C and protein S.




### Prothrombin Complex Concentrate

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- 58 patients needing emergent surgery treated, median age 75
- 25-50 units/kg of PCC
- INR measured before and < 1 hr after treatment
- Median pretreatment INR 3.8 (1.4-52.8)
- < 1hr later median INR was 1.3 (0.9-5.7)
- Only two patients with INR > 2.0
- All got Vitamin K too, and 50% got FFP

*Lankiewicz MW, Hays J, J Thromb Haemost, 2006.*




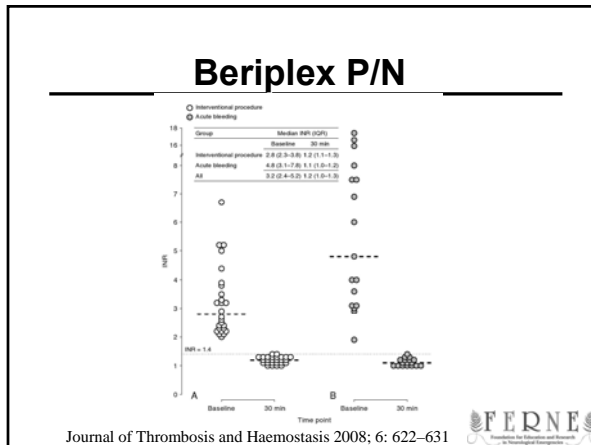
**ORIGINAL ARTICLE**

### Prothrombin complex concentrate (Beriplex® P/N) for emergency anticoagulation reversal: a prospective multinational clinical trial

1. PABINGER, \* B. BRENNER,† U. KALINA,‡ S. KNAUB,‡ A. NACYS §¶¶ H. OSTERMANN§ FOR THE BERIPLEX® P/N ANTICOAGULATION REVERSAL STUDY GROUP

- Open, uncontrolled, multinational phase III study
- 26 patients who required emergency surgery and 17 who had acute bleeding (43 total) were treated with Beriplex® P/N based on baseline INR.
- A rapid correction of INR ( $\leq 1.3$ ) was achieved in 40 of the 43 patients (95%). The remaining 3 patients had an INR of 1.4.
- There was good/satisfactory hemostatic efficacy of 98% as assessed by the investigator.

*Journal of Thrombosis and Haemostasis 2008; 6: 622–631*





### Prothrombin Complex Concentrate

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- Thrombosis 4/57 pts (7%) where this was reported
- Early mortality of 24% (15/64) where this was reported
- Overall risk of thrombosis not clear
- “Probably safe”


*Aguilar MI, Hart RG, Mayo Clin Proc, 2007*



### Tranexamic Acid

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- Trade name Cyclokapron (US) or Transamin (Asia)
- Antifibrinolytic competitively inhibits conversion of plasminogen to plasmin which, in turn, degrades fibrin
- Fibrin basic to blood clot formation and stability
- 8 times the activity of an  $\epsilon$ -aminoacaproic acid (Amicar)




### Tranexamic Acid

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- 2004 Cochrane review of 89 RCTs/8,580 patients
  - elective surgery: 74 cardiac, 8 ortho, 4 liver, 3 vascular
- Reduced patients needing transfusion by 1/3
- Reduced transfusion one unit on average
- Cut need for further surgery by 50%
- Mortality reduction RR = 0.85 (95% CI 0.63–1.14)
- 25 mg/kg IV
- 15 ongoing trials at [clinicaltrials.gov](http://clinicaltrials.gov)
- None with ICH or warfarin

*Henry DA, Moxey AJ, Cochrane Database Syst Rev. 2004*



## CRASH 2 Trial of Tranexamic Acid

- "A Large Randomized Placebo Controlled Trial Among Trauma Patients With, or at Risk of, Significant Hemorrhage, of the Effects of Antifibrinolytic Treatment on Death and Transfusion Requirement"
- Primary Outcome: Death within four weeks
- Secondary Outcome: transfusion, further surgery, venous thromboembolism
- Goal: 20,000 patients under recruitment 2005-09



## Reversal of Clopidigrel

- **Selectively inhibits ADP binding to platelet receptor and activation of GPIIb-IIIa complex**
- **Inhibits aggregation for platelet lifespan (7 days)**
- **No active metabolite, so no effect on new platelets after two hours**
- **Wears off in 5-7 days, or new platelets will work**
- **"Platelet transfusion may be used to reverse the pharmacological effects of clopidogrel when quick reversal is required."**

Bristol Myers Squibb package insert



## Reversal of Platelet Inhibition

- **Renal failure, liver failure and NSAID use**
- **Three strategies:**
  - Desmopressin (DDAVP)
  - Dialysis in renal failure
  - Platelet transfusion?
- **Desmopressin**
  - Not studied for ICH
  - Some effectiveness in renal failure patients
  - Increases Von Willibrand factor levels/activity
  - shortens bleeding time with aspirin and ticlopidine
  - In vitro, "may improve" platelet dysfunction caused by glycoprotein IIb/IIIa inhibitors or aspirin

Mannucci PM, Vicente V. *Blood*, 1986

Churchill WH. *Hematology, Transfusion Therapy*, 2000.



## ASA: Platelet Transfusion?

- Not studied for ICH
- RR of death at 3 months is 2.5 (CI 1.3-4.6) with ASA use
- Aspirin associated with hematoma growth in first week
- ASA half life only 20 minutes (metabolites 2 hours)
- Platelet transfusion theoretically beneficial
- "Whether the benefits of...platelet transfusion outweigh the risks in aspirin-associated ICH requires further study"
- "Transfusion is appropriate in a bleeding patient whose platelet count is adequate but whose platelets are nonfunctional as a result of medications such as aspirin NSAIDs or uremia"

Saloheimo P, Ahonen M. *Stroke*, 2006

Churchill WH. *Hematology, Transfusion Therapy*, 2000.



## Case Study: Coumadin Anticoagulation

- **Vitamin K 10 mg IV**
- **FFP 6 units IV**
- **Prothrombin Complex Concentrate 50 units/kg = 3500 units IV**
- **No proven benefit to activated factor VIIa**



## Case 2: NSAID Use

- **Desmopressin**
  - **0.3 mcg/kg = 2 mcg = 0.5 cc IV diluted in 100 cc over 15 minutes**
- **Platelet transfusion?**
  - Unclear benefit
  - One unit raises platelet count 5-10K
  - Common to give 10 units in life threatening bleeds



### Should I Call or Transfer to a Neurosurgeon?

- Cerebellar ICH > 3 cm with deterioration, brainstem compression (coma) and/or hydrocephalus should....ASAP (Class I, Level B)
- Lobar clots within 1 cm of surface... "might be considered" (Class IIb, Level B)
- Routine evacuation of supratentorial ICH is not recommended

AHA/ASA Guidelines, *Circulation*, 2007

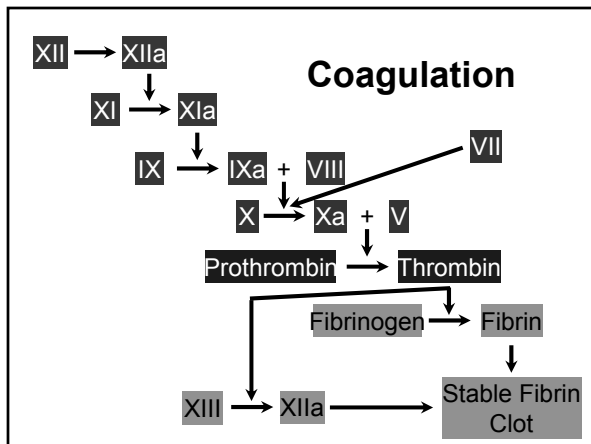


### Conclusions

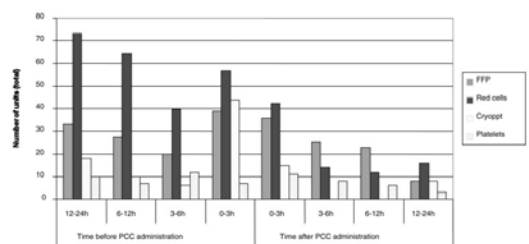
- Coagulopathy puts patients at high risk for ICH
- Vitamin K effective but too slow
- FFP effective but slow and volume overload
- Protamine works to reverse heparin
- Prothrombin Complex Concentrates promising
- Platelet transfusion might help for clopidogrel
- Factor VIIa unproven and expensive
- Tranexamic acid promising/under intense study



### Questions?



### Units of blood products administered: Before and after PCC administration



Bruce and Nokes, *Critical Care* 2008; 12:r105

