



# Emerging therapies for Intracerebral Hemorrhage

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# Learning objectives

Update on emerging trends in ICH for

- ✓ Blood pressure management
- ✓ Anticoagulation reversal
- ✓ Surgical advances

# Patient KK

- ✓ 80 year old male
- ✓ Very active, independent.
- ✓ Well controlled hypertension, hyperlipidemia, remote smoking, social EtOH.
- ✓ Collapsed in the bathroom, not moving left side, awake, dysarthric, right gaze preference, left hemiplegia, neglect, following commands.

110 cc right basal ganglia ICH with IVH.



# Audience question 1

Which of Mr. KK's risk factors put him at risk for the ICH?

- High cholesterol
- High blood pressure
- High blood sugar
- Smoking

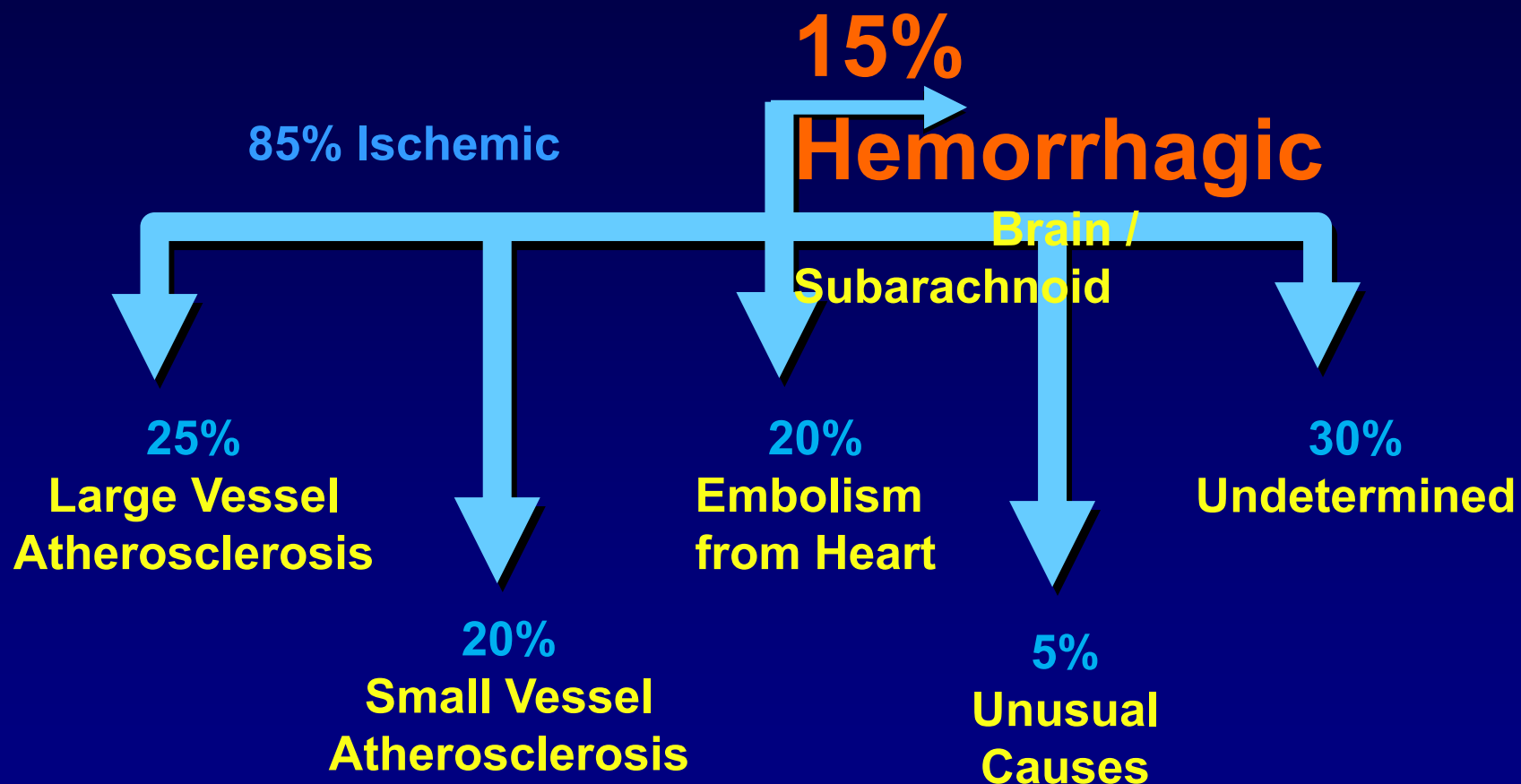
# Risk factors for primary ICH

1. Older age
2. Hypertension
3. ETOH abuse
4. Prior ICH
5. Anticoagulation
6. Carriers of apolipoprotein  $\epsilon$  2 or  $\epsilon$  4 allele

# Types of spontaneous (i.e. non-traumatic) Intracerebral Hemorrhage

- Primary (80-90%)
  - Hypertension
  - Cerebral amyloid angiopathy
- Secondary

# 'Tis a rare thing....But

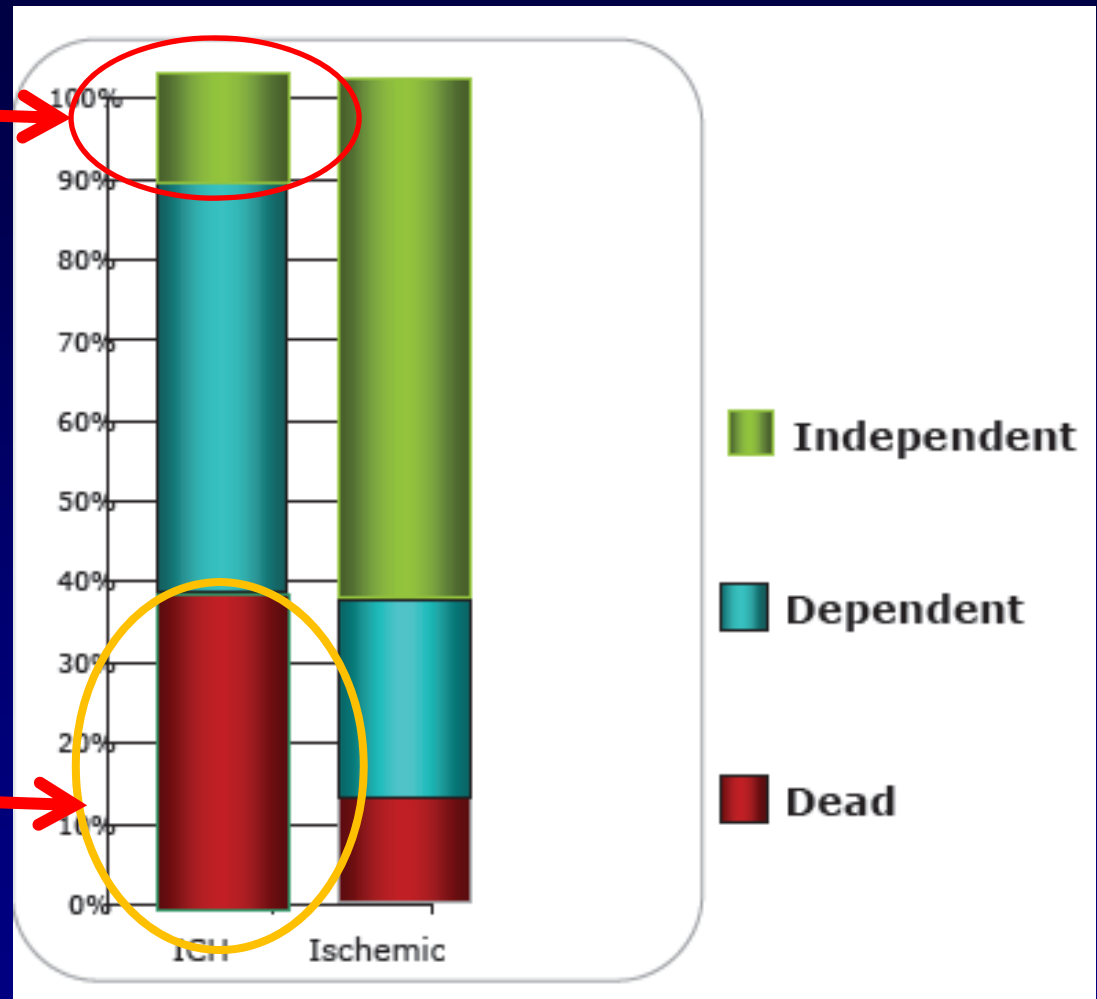




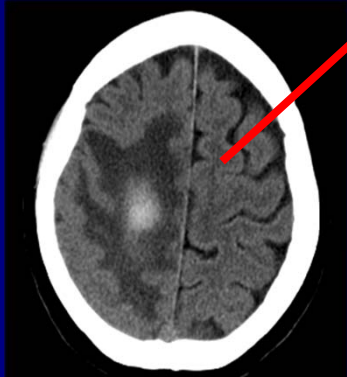
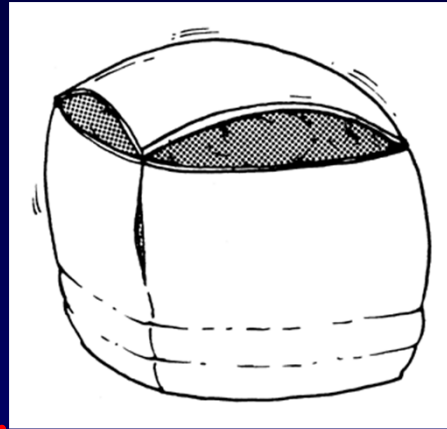
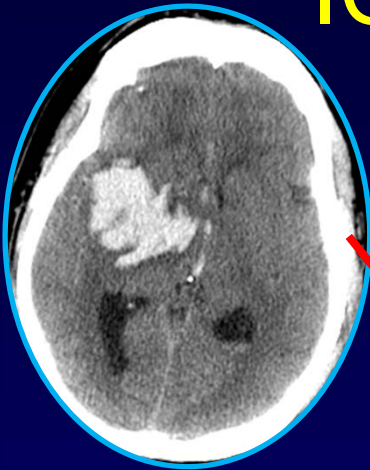
# ICH remains a devastating stroke.

Only ~ 20% are fully independent at 6 months

Mortality:  
6 months, 30-50%

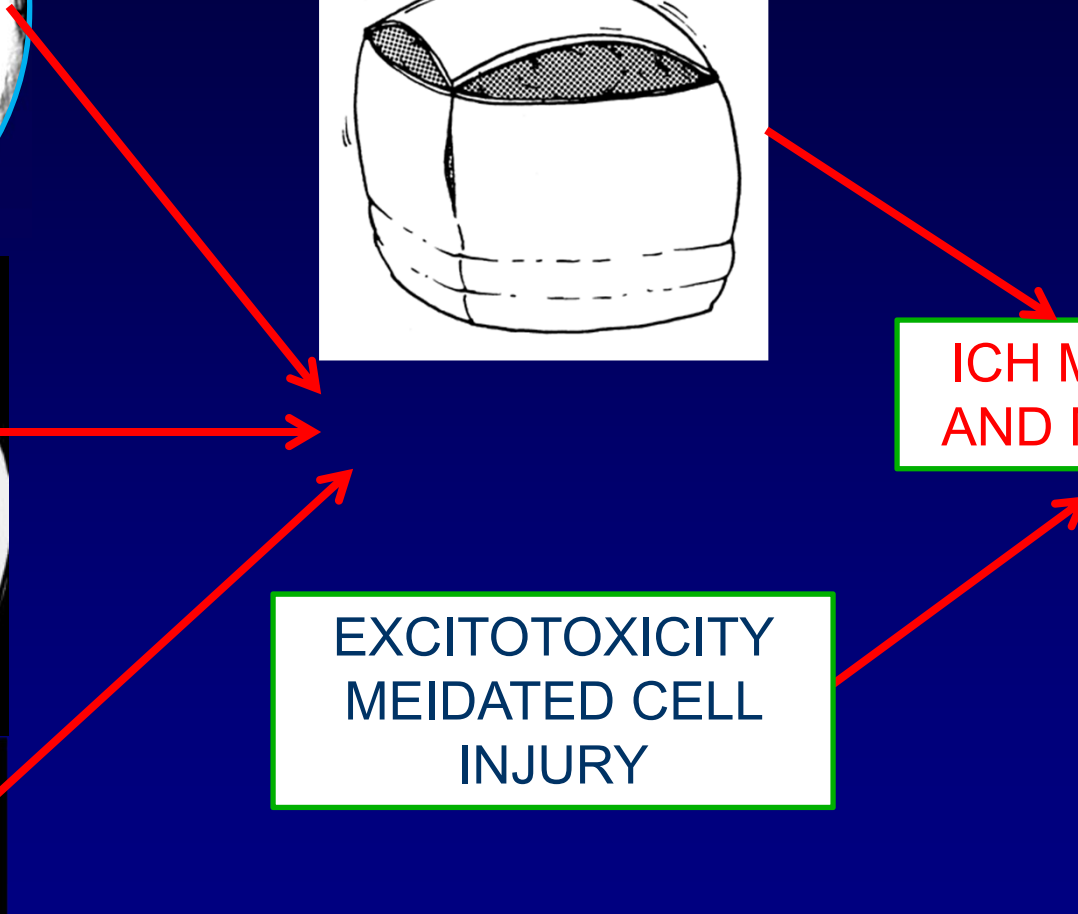


# ICH PATHOPHYSIOLOGY & OUTCOME



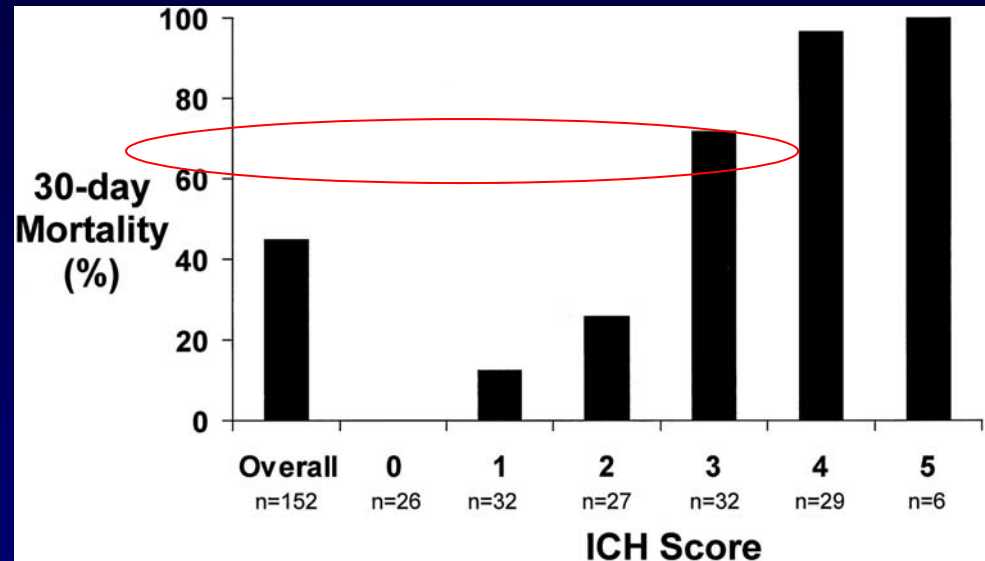
EXCITOTOXICITY  
MEIDATED CELL  
INJURY

ICH MORTALITY  
AND MORBIDITY



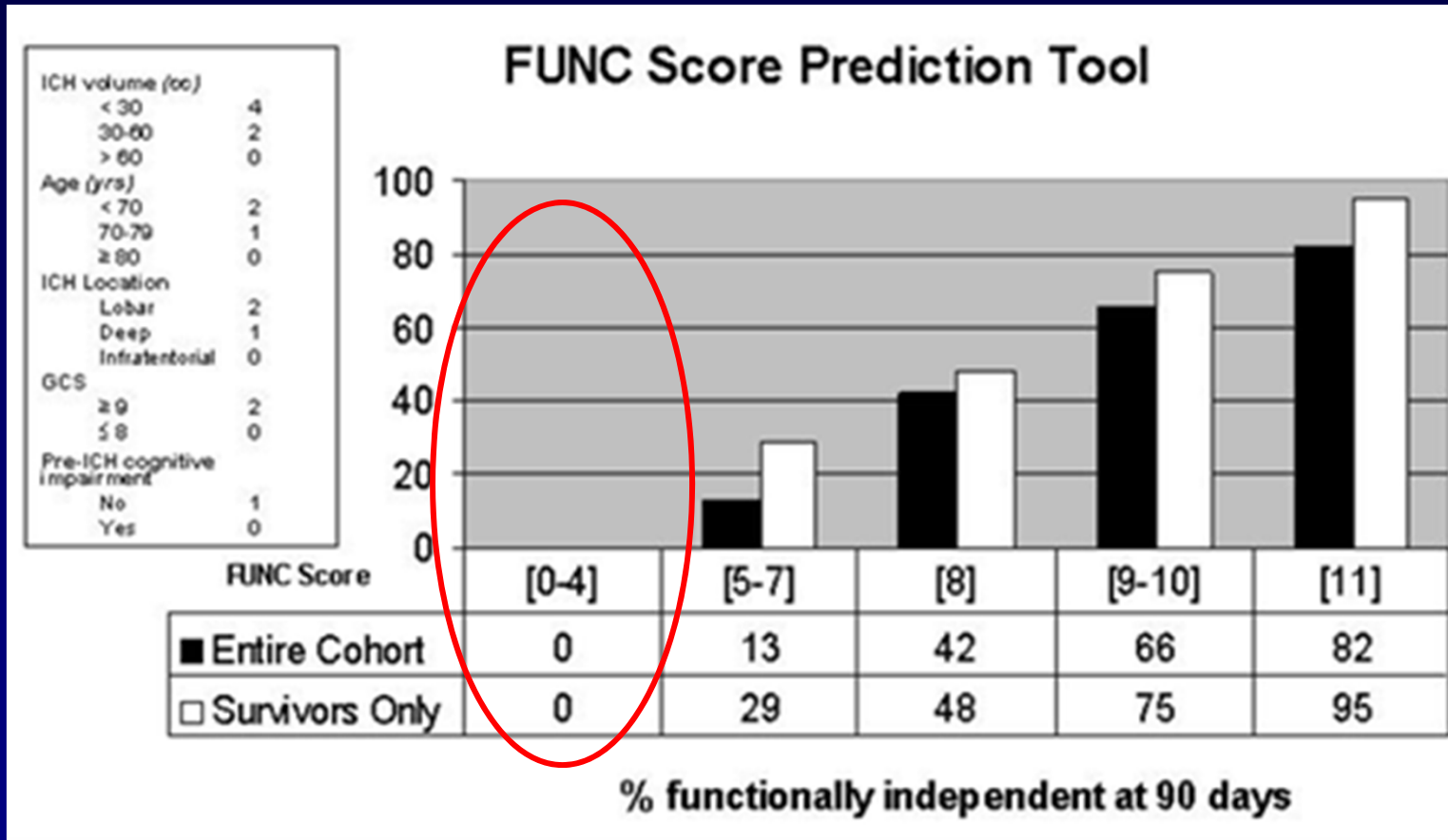
# ICH score and mortality at 1 month

GCS	
3-4	2 pts
5-12	1 pt
13-15	0 pts
ICH volume	
$\geq 30\text{cm}^3$	1 pt
$< 30\text{cm}^3$	0 pts
IVH	
Yes	1 pt
No	0 pts
Location	
Infratentorial	1 pt
Supratentorial	0 pts
Age	
$> 80\text{ yrs}$	1 pt
$< 80\text{ yrs}$	0 pts



Patient KK's ICH score = 3

# Functional outcome at 90 days



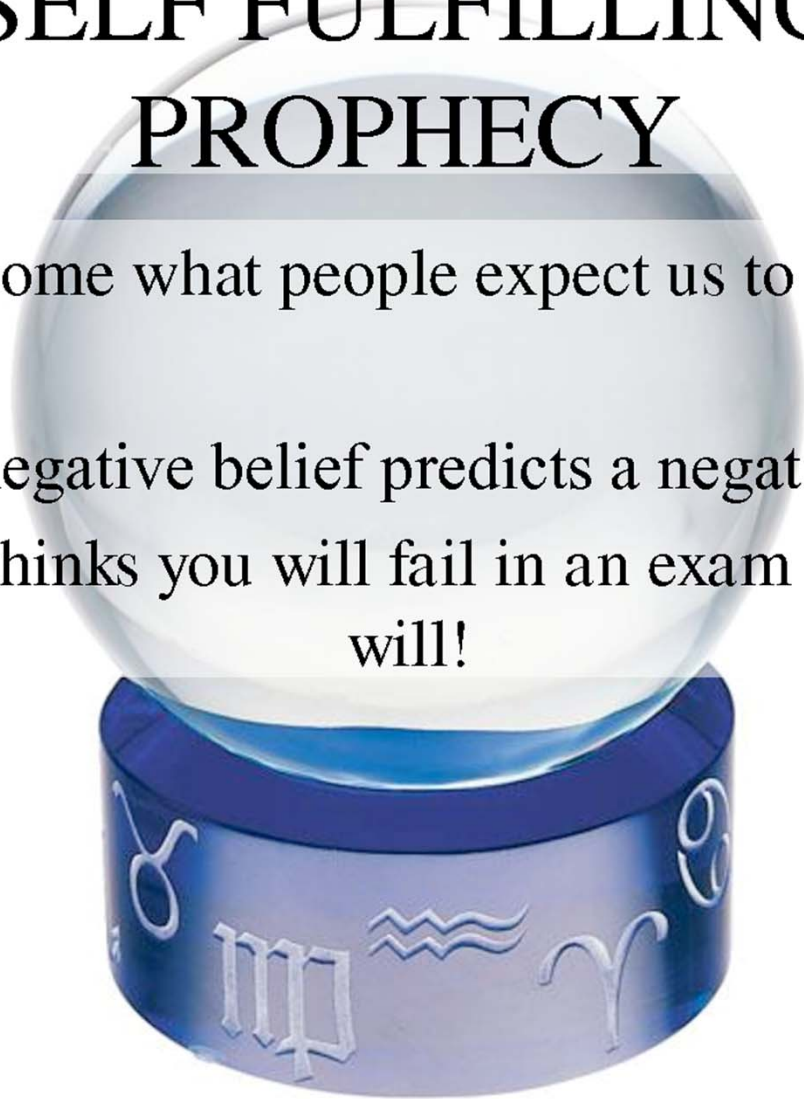
# Dilemma

- With a predicted 70% mortality at 1 month and 0% chance of functional recovery, in this 80 year old male, what should I advise him and his family?
- Oh, BTW, his daughter is an ICU nurse at my hospital.

# SELF FULFILLING PROPHECY

We become what people expect us to become

... and so a negative belief predicts a negative behaviour  
If a teacher thinks you will fail in an exam you probably  
will!



# The self fulfilling prophecy in ICH

- Current methods of prognostication in individual patients early after ICH are likely biased by failure to account for the influence of withdrawal of support and early DNR orders.
- Aggressive full care early after ICH onset and postponement of new DNR orders **until at least the second full day** of hospitalization is probably recommended.

# How I view ICH related outcome

- Excellent medical care has a potent, direct impact on ICH morbidity and mortality, even before a specific therapy is found.
- In many cases, it is *the aggressiveness of clinical care that determines the direct mortality* from the disease.



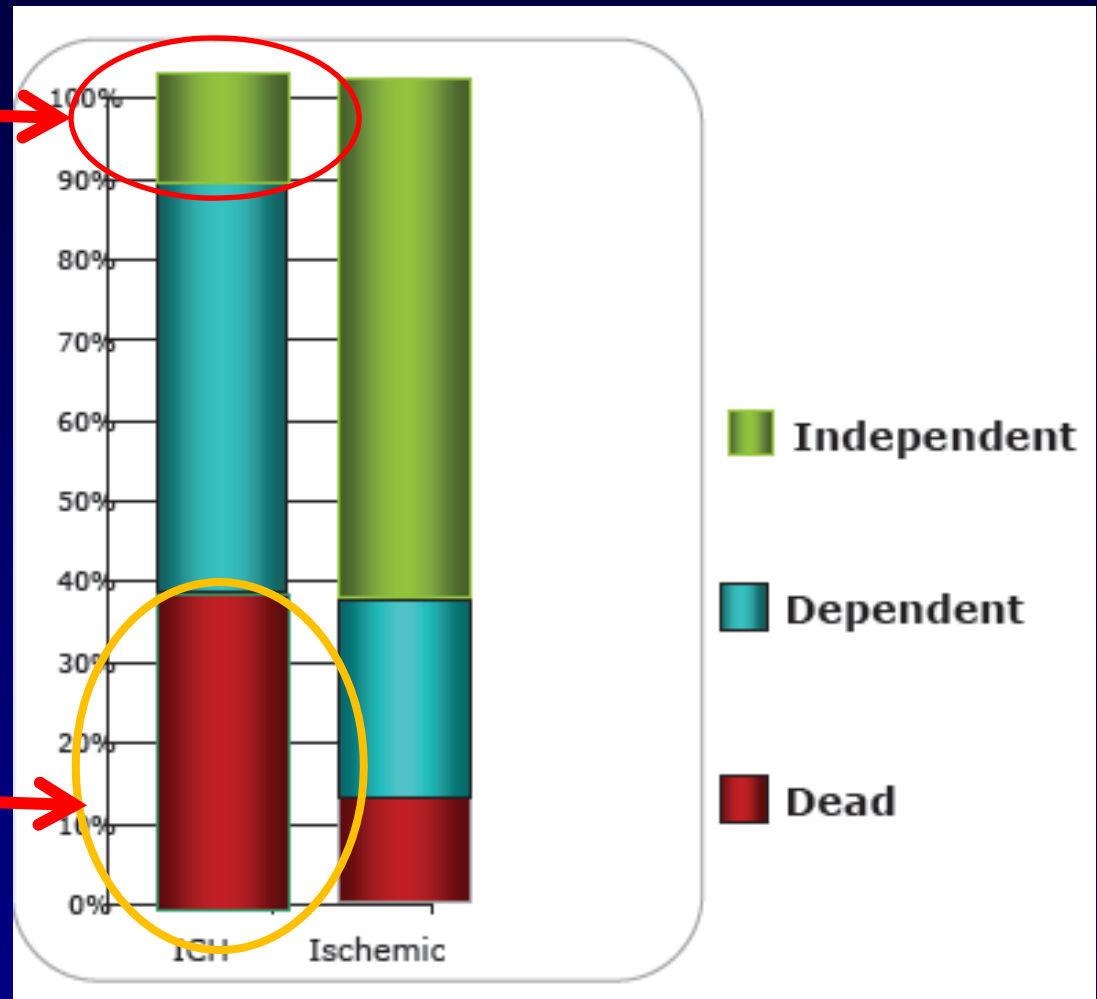
# ICH outcomes are improved in a neuroICU

- Initial monitoring and management of ICH patients should take place in **an intensive care unit with physician and nursing neuroscience intensive care expertise**  
**Class 1 recommendation.**

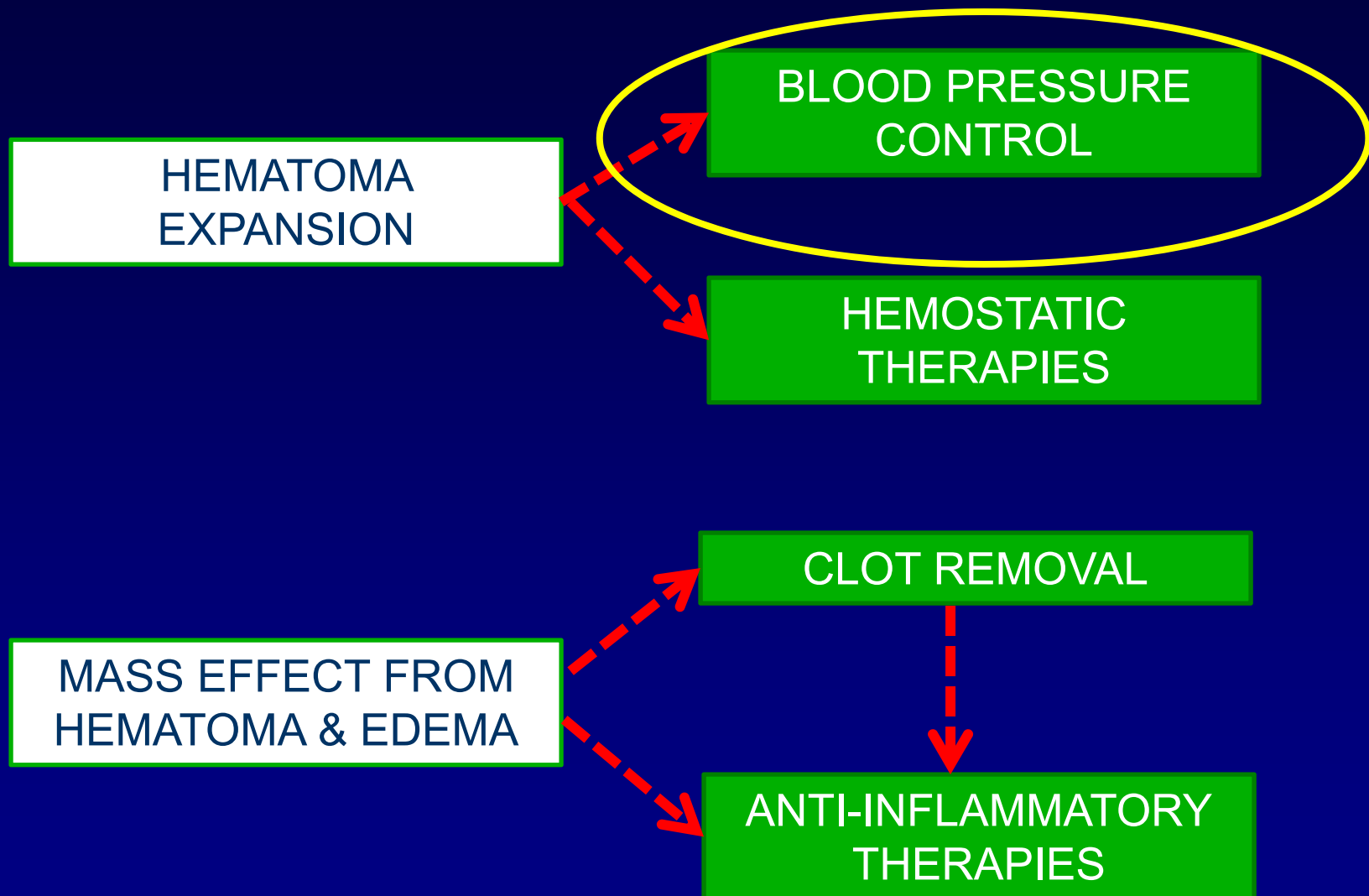
# Can we and if so, how to change ICH outcome?

Only ~ 20% are fully independent at 6 months

Mortality:  
6 months, 30-50%



# THERAPEUTIC TARGETS IN ICH



# Emergency ICH management Principles



- Stop ongoing bleeding
- Prevent hematoma expansion



- Accelerate removal blood from the brain

# Emergency ICH management Principles



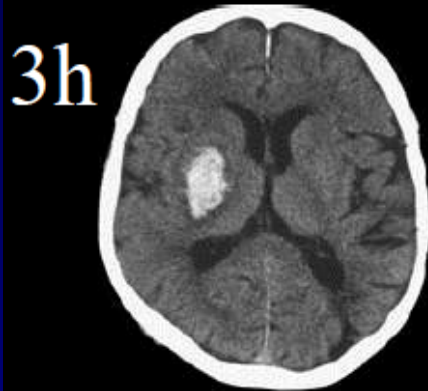
- Stop ongoing bleeding
- Prevent hematoma expansion

# Strategies to limit ICH expansion.

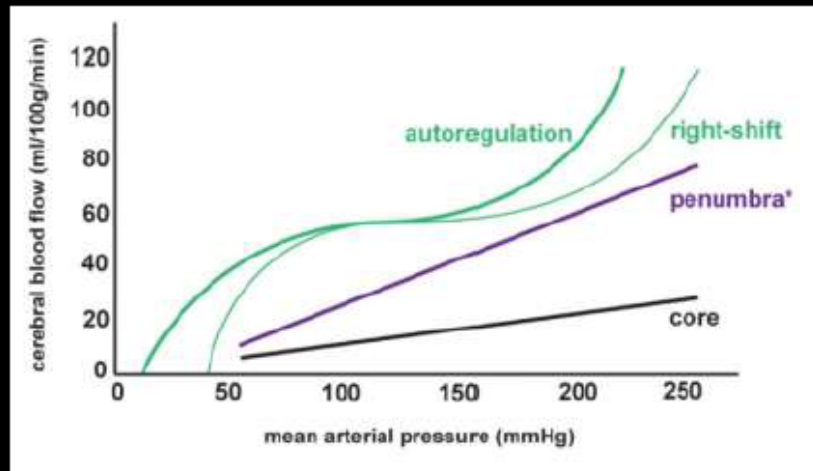
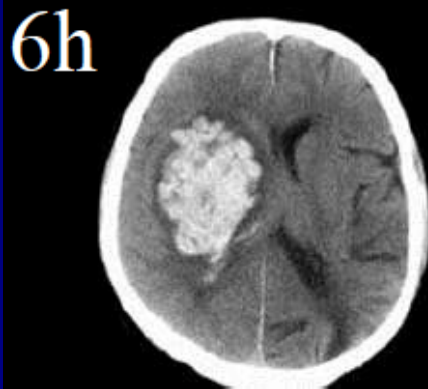
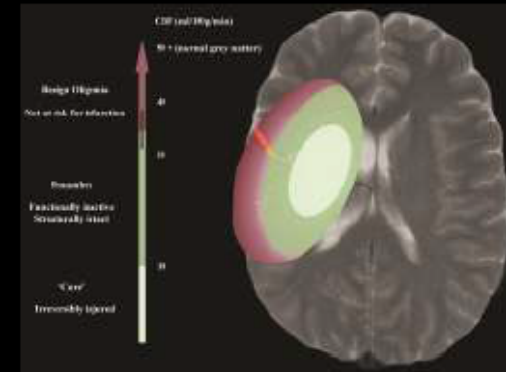
- Reducing the driving force (i.e. Blood pressure).
- Treating the compromised coagulation.

# BP lowering after ICH: Competing interests Hematoma expansion Vs penumbra

↓ Hematoma Expansion



↓ Cerebral Blood Flow







## Audience question 2

- The optimal systolic blood pressure goal for blood pressure lowering in the first day after ICH is
  - 180 mm Hg
  - 160 mm Hg
  - 140 mm Hg

# My approach to BP lowering in ICH

*(in 2013)*

- For small ICH (< 25 cc)- BP lowering to SBP < 140 mm Hg seems reasonably safe. (*Interact 2 study*)
- For larger ICH- I lower to SBP < 160 mm Hg or MAP of < 110 mm Hg (*AHA guideline, Class 2b*)
- In young normotensives, coagulopathy, vascular lesion- < 140 mm Hg is reasonable.
- ATACH-2: NIH funded, Phase 3, RCT, iv nicardipine, < 140 Vs 140-180 mm Hg.

# Emergency ICH management Principles

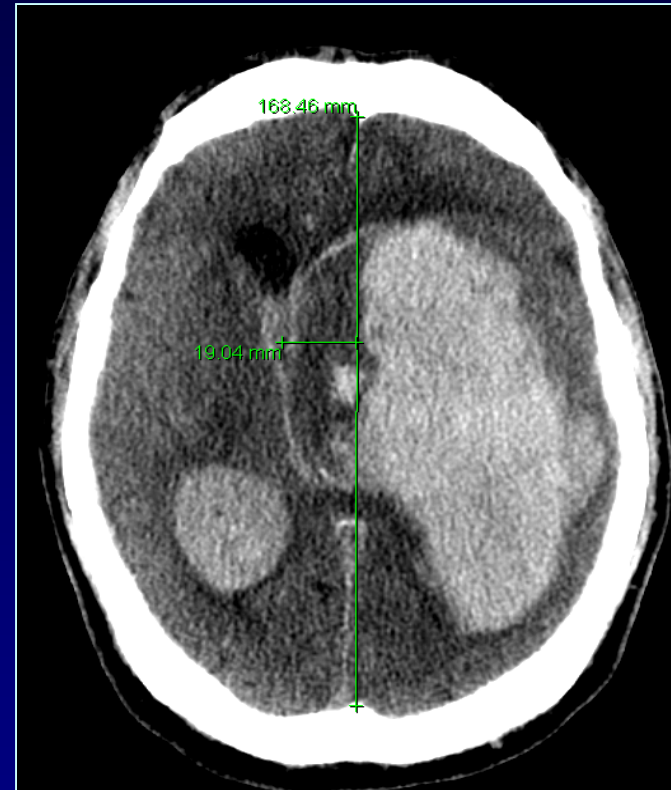


- Stop ongoing bleeding
- Prevent hematoma expansion

# 76yo M, ICH, INR=5.5



Non-Con CT @ 60 mins post sx onset

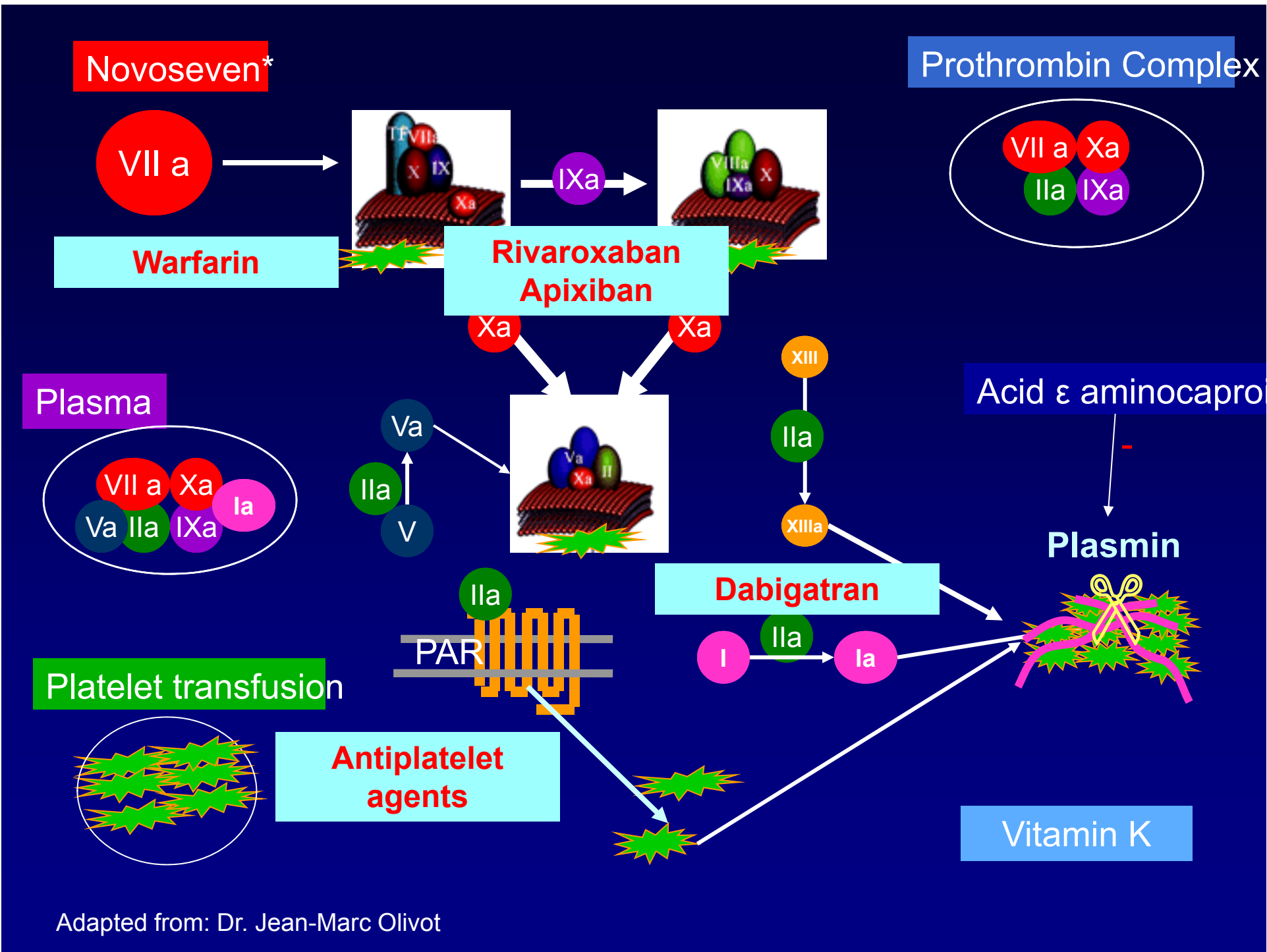


R pupil becomes fixed in ED, follow-up CT  
140 mins later shows interval expansion

# Audience response question # 3

Which of the following is the best strategy for emergency warfarin reversal?

- A. Subcutaneous Vit K + FFP
- B. Intravenous Vit K + FFP
- C. Intravenous Vit K + Profilnine (3F- PCC)
- D. Intravenous Vit K + Kcentra (4F-PCC)



Novoseven\*

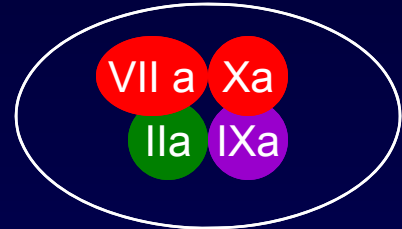
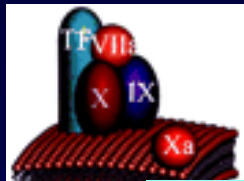
Prothrombin Complex

Plasma

Platelet transfusion

Antiplatelet agents

Adapted from: Dr. Jean-Marc Olivot



Warfarin

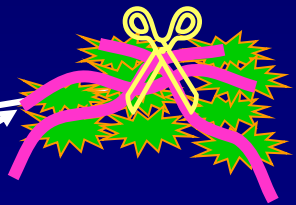
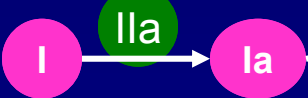
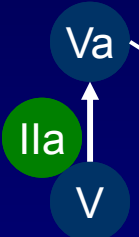
Rivaroxaban Apixiban

Acid ε aminocapro

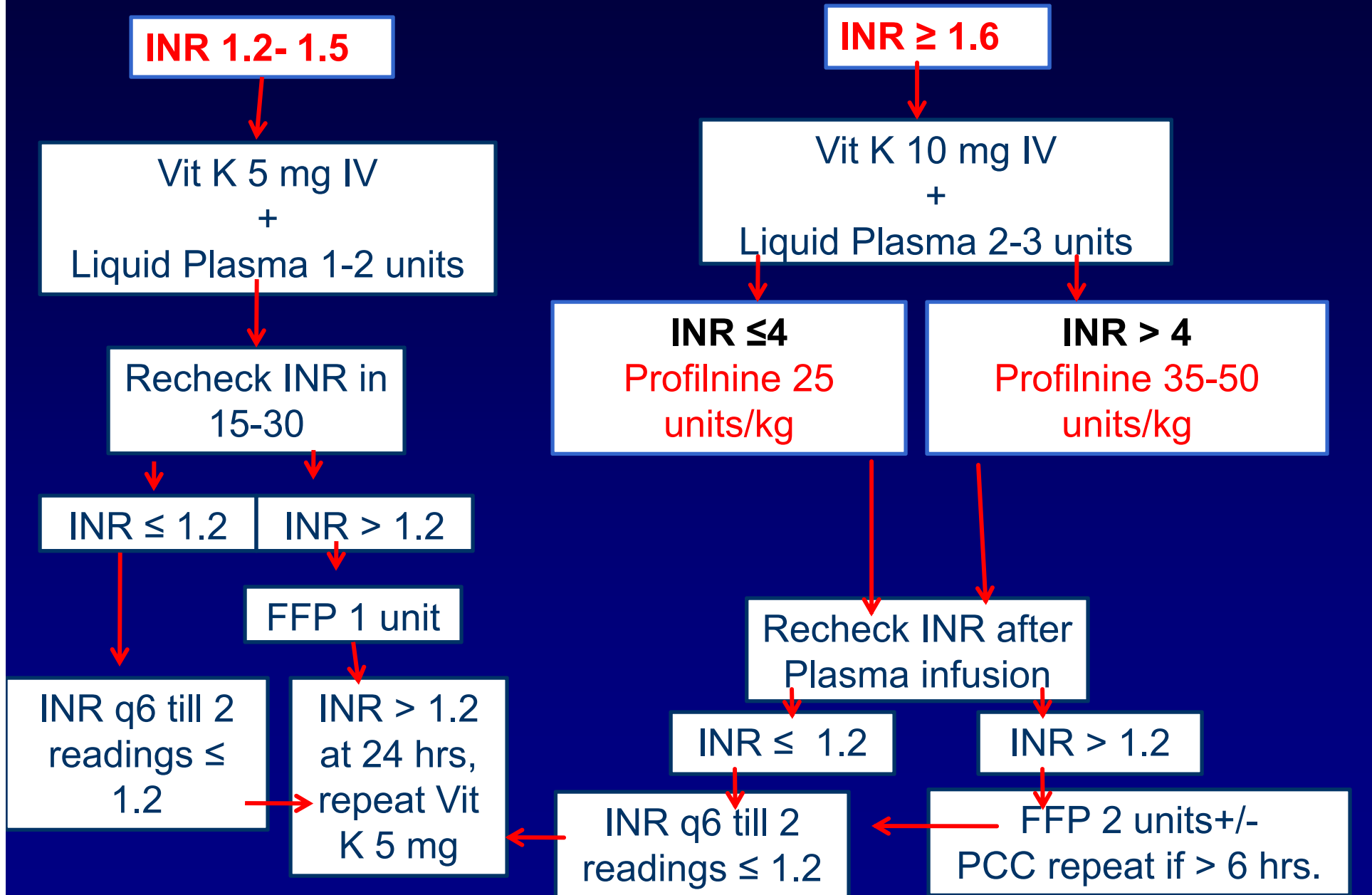
Plasmin

Dabigatran

Vitamin K



# Stanford emergency warfarin reversal protocol



# Does the protocol work?



80 year old woman with  
INR 18.9.

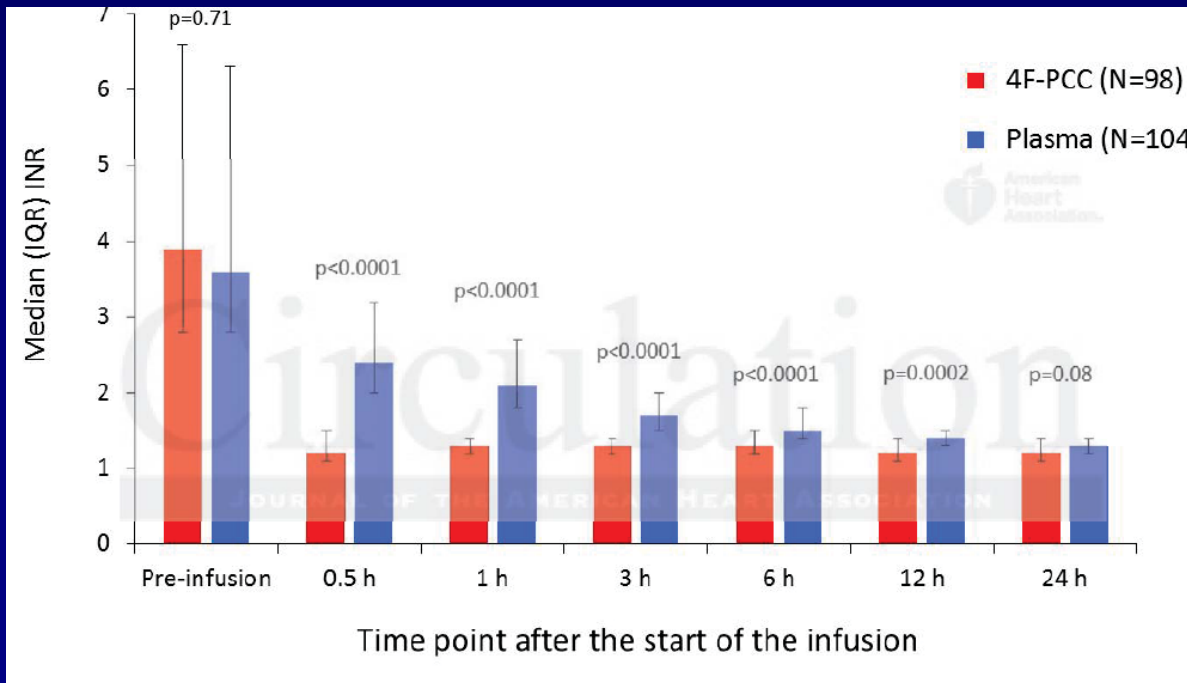


The warfarin reversal protocol was implemented  
INR 1.1 reached within 2 hours. She has since  
returned home with minimal deficits.



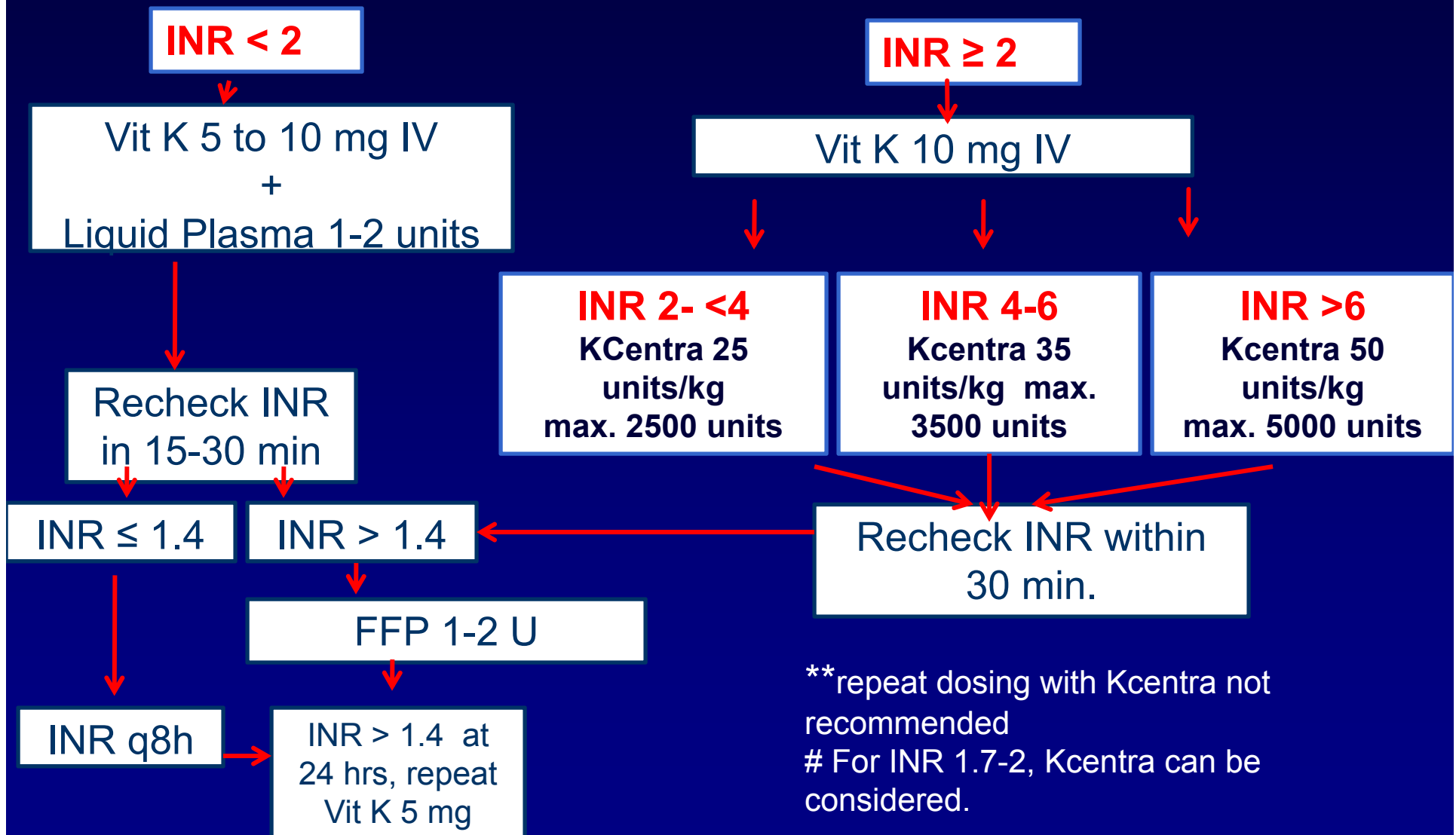
# FDA approves Kcentra- 4 factor PCC, 4/2013

- 4F PCC- 2, 7, 9, 10, protein C & S
- **Kcentra + Vitamin K Vs FFP + Vitamin K (n=212)**
  - INR < 1.3 at 30 minutes in 63% Vs 9%
  - 87% less volume (~ 100 cc Vs 900 cc)
  - 7 fold faster infusion time (24 min Vs 3 hrs)



*Sarode, Circulation, 2013.*

# Stanford emergency warfarin reversal protocol



# Reversal of newer oral anticoagulants

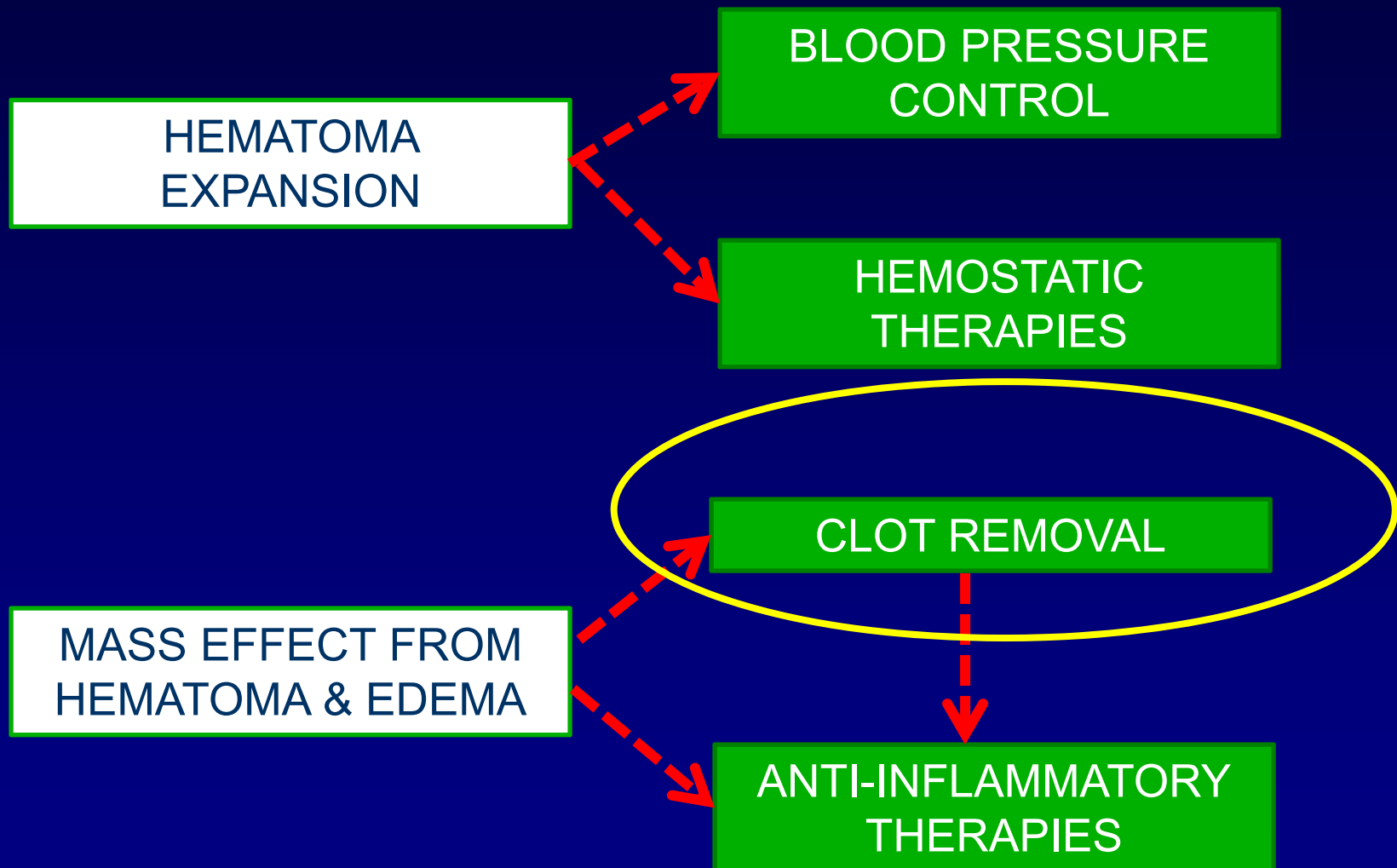
- No specific antidote yet
- Pilot trial of dabigatran reversal agent is being planned
- For now
  - Hemodialysis for dabigatran if within 6 hours
  - 4F- PCC as off label use for apixiban and rivaroxaban.

# Emergency ICH management Principles



- Accelerate removal  
blood from the brain

# THERAPEUTIC TARGETS IN ICH

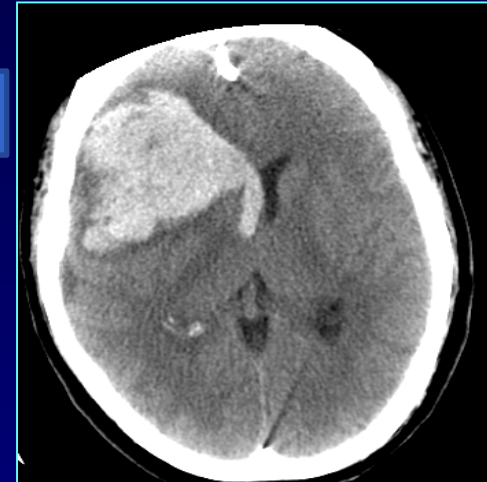


# Audience question

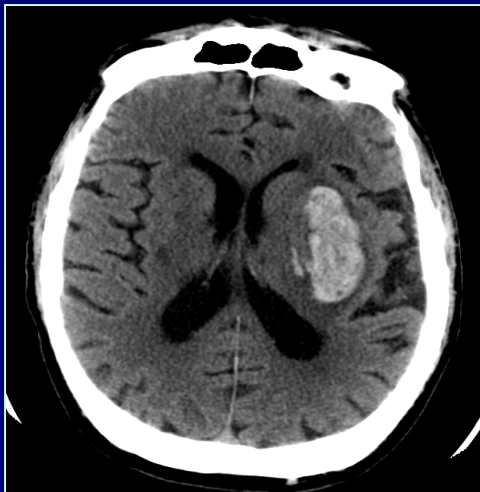
Open craniotomy is currently recommended for which of the following hematomas?



A



B



C



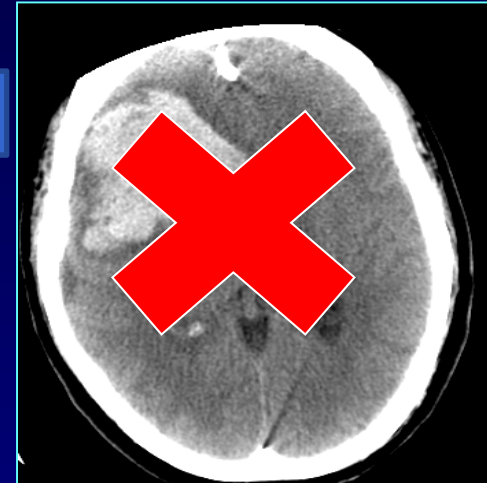
D

# Audience question

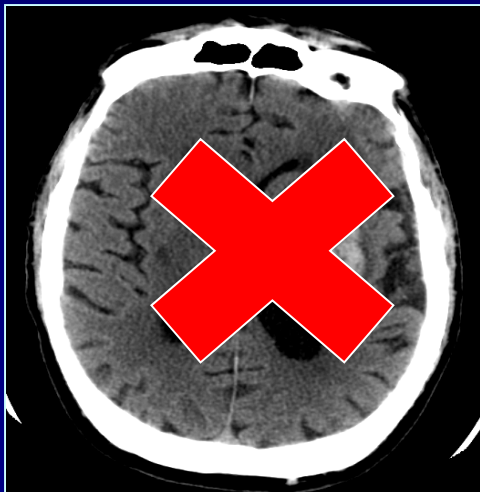
Open craniotomy is currently recommended for which of the following hematomas?



A



B



C



D

# When do I call the neurosurgeon?

- ?? Moderate or large lobar/superficial hemorrhage when deteriorating
- Cerebellar hemorrhage > 3cm with deterioration or brainstem compression and/or hydrocephalus
- Nonsurgical candidates: small ICH / minimal neurologic deficits and a low LOC



# How about minimally invasive surgery?

Das ist dz and  
der instrument / vñ  
das dyenet mer ob  
en vff dz haubt / das  
sunst darnebe / oder  
hinden. darumb dz  
es nit breyte gleych  
hat / als dz nechst in  
strumēt hye vor ver  
zeychnet. Vnd dyen  
et auch / wann die  
hyrnschal ingeschla  
gen ist / das man sye  
mit disē instrument  
wider vffschraub.



**MISTIE- minimally invasive  
surgery + tpA for ICH  
evacuation**

# What happened to Mr. KK?

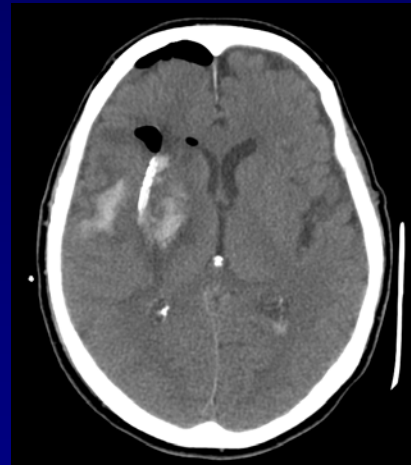
Pre-surgery



Immediate post op.



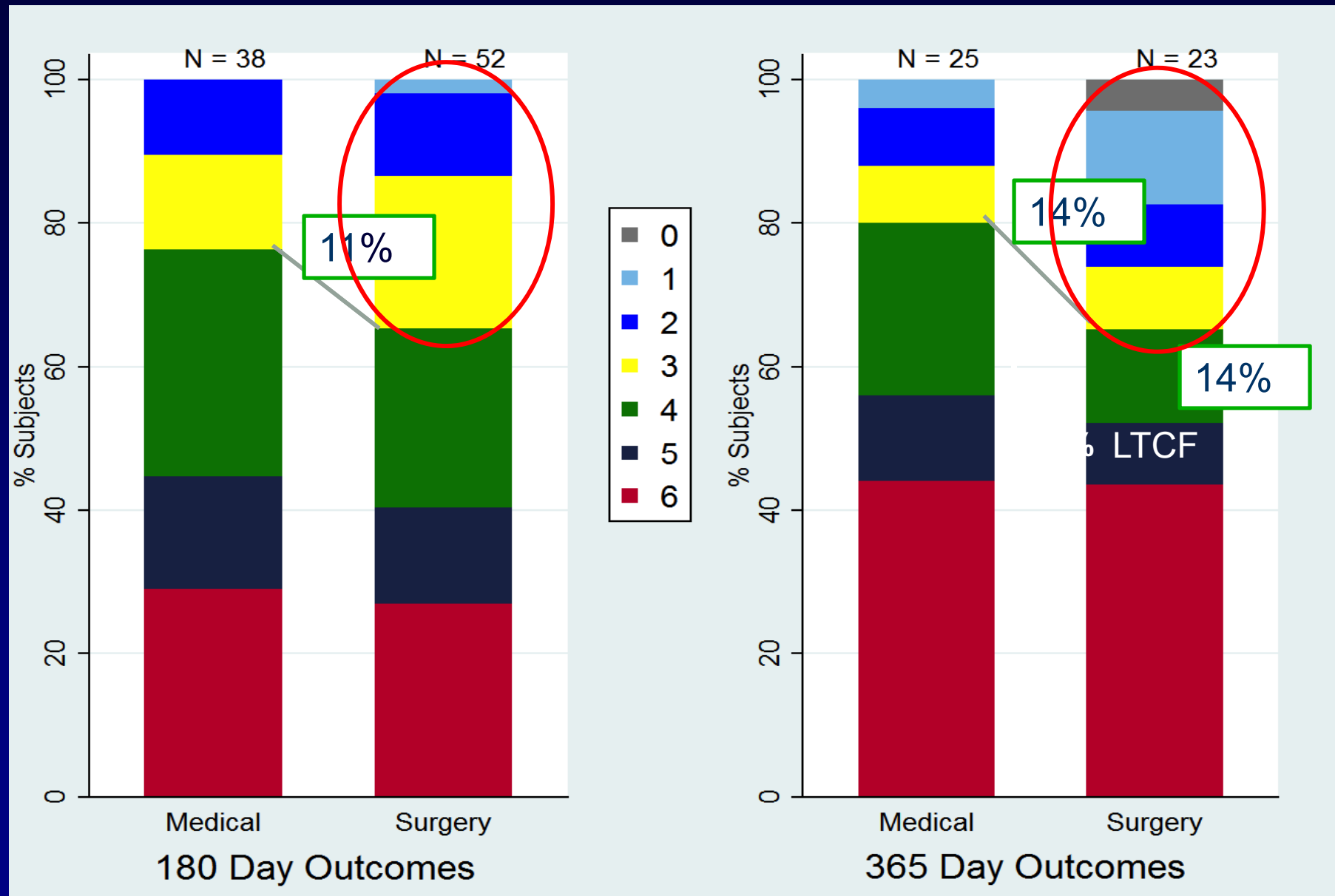
1 dose tpa.



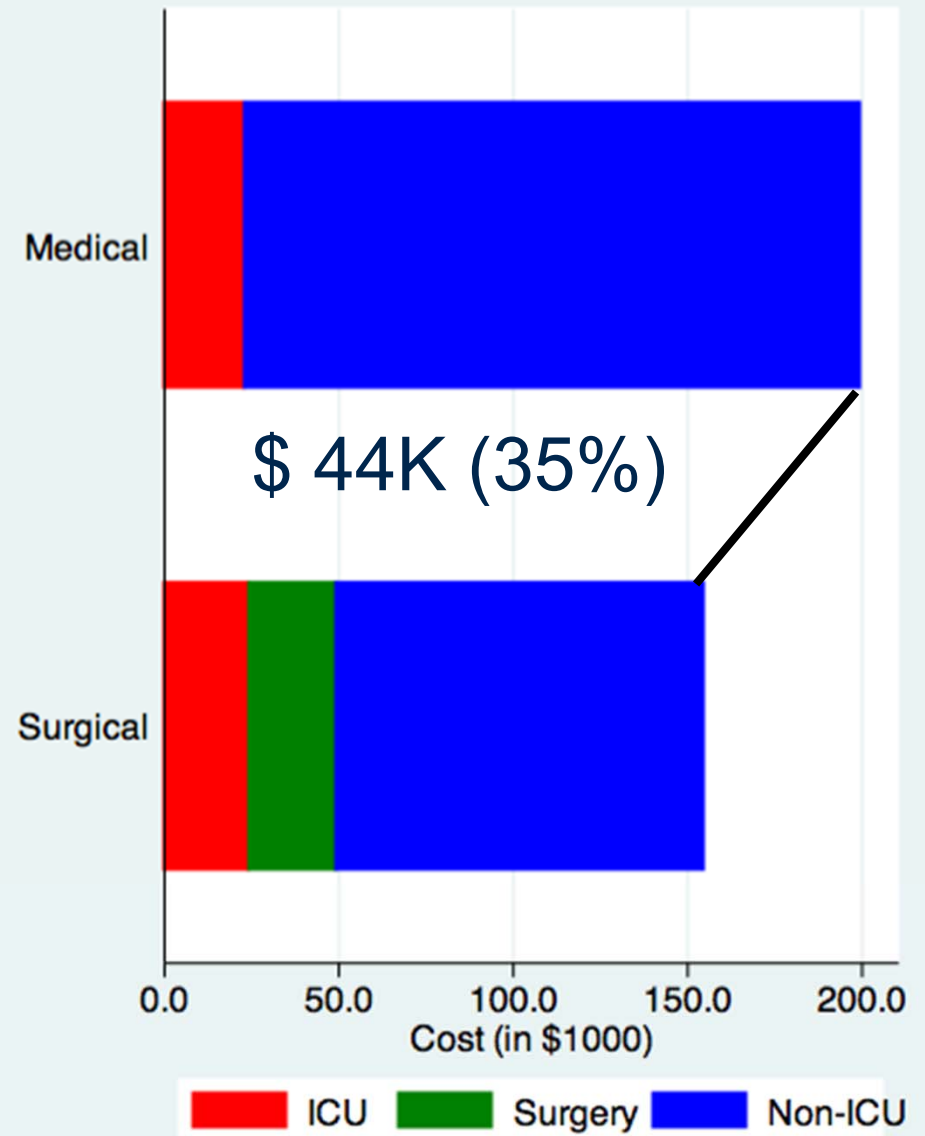
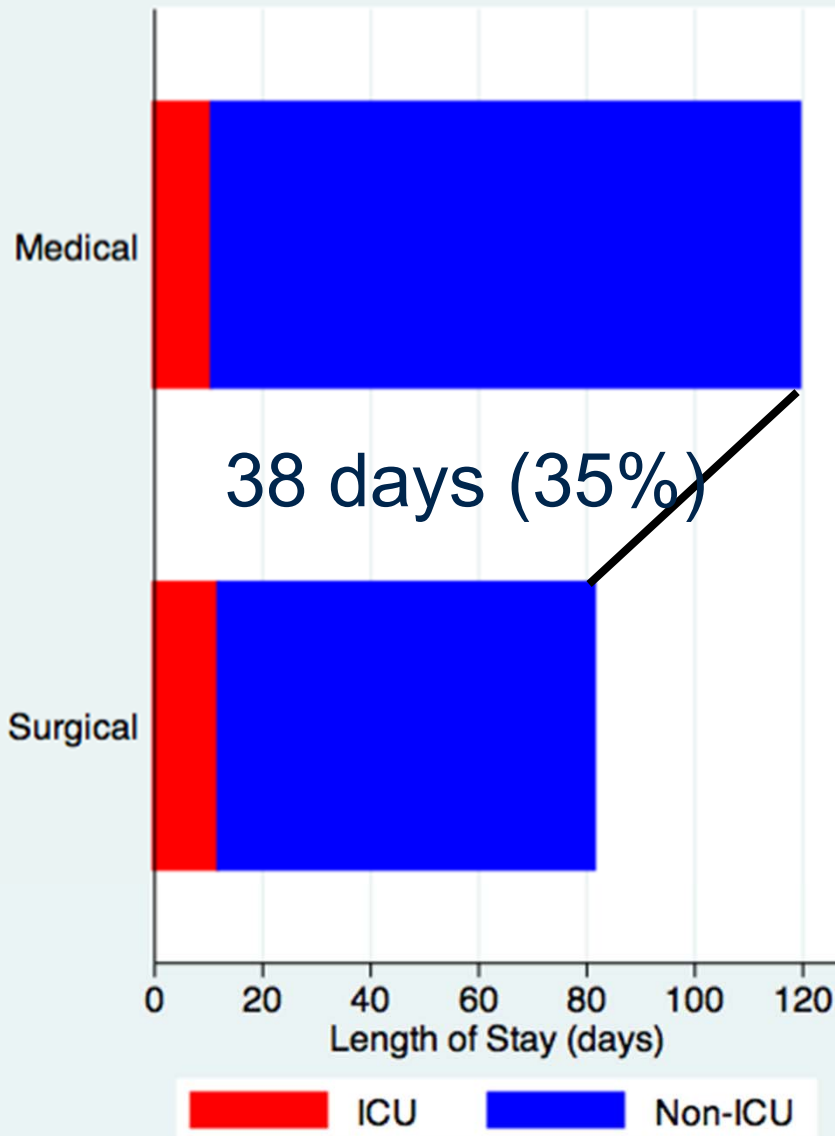
48 hours.



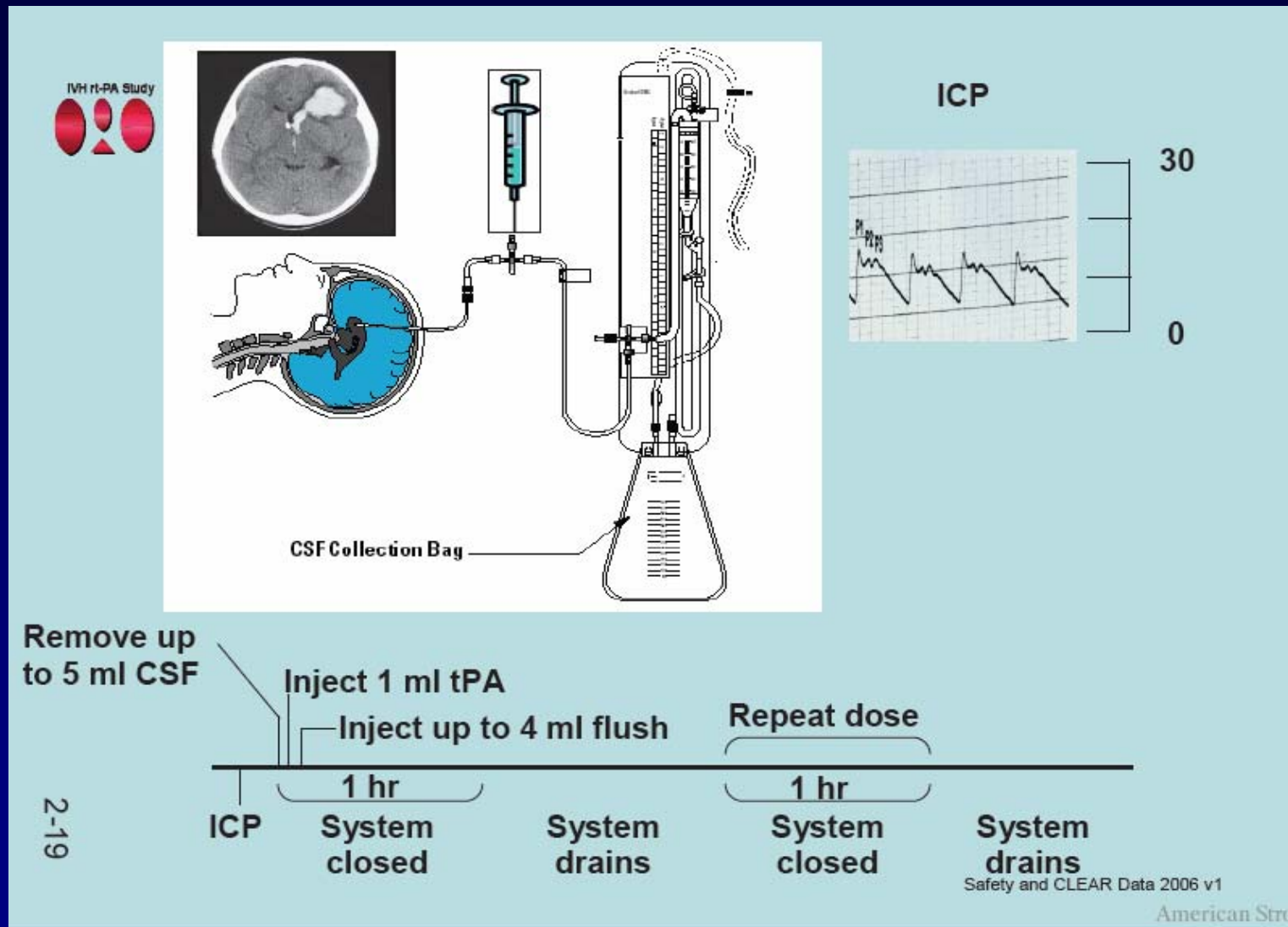
# 180 & 365-Day modified Rankin Scale



## Length of Stay and Cost by Treatment Arm



# TPA Accelerates Intraventricular Clot Lysis.

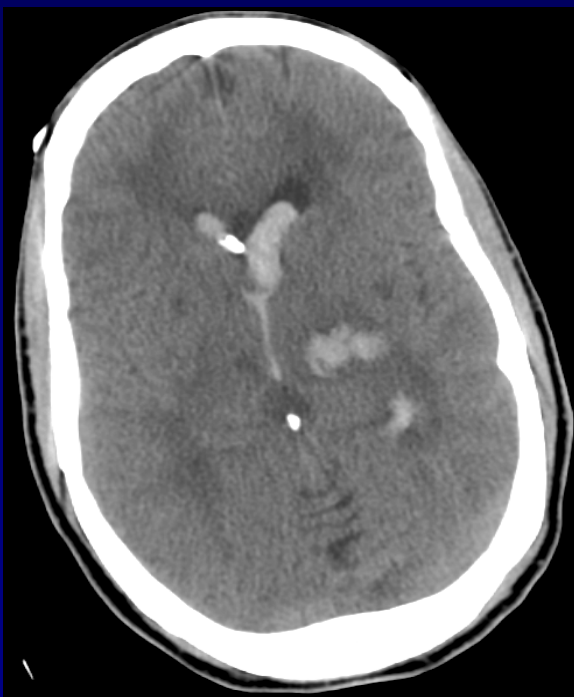




**Low-Dose Recombinant Tissue-Type Plasminogen Activator Enhances Clot Resolution in Brain Hemorrhage: The Intraventricular Hemorrhage Thrombolysis Trial**

Neal Naff, Michael A. Williams, Penelope M. Keyl, Stanley Tuhim, M. Ross Bullock, Stephan A. Mayer, William Coplin, Raj Narayan, Stephen Haines, Salvador Cruz-Flores, Mario Zuccarello, David Brock, Issam Awad, Wendy C. Ziai, Anthony Marmarou, Denise Rhoney, Nichol McBee, Karen Lane and Daniel F. Hanley, Jr

*Stroke*. 2011;42:3009-3016; originally published online August 25, 2011;



Intraventricular  
tpA- 2 doses



# How did Mr. KK do?

- Was never intubated
- Went to acute rehab after 3 weeks
- Is now home; in great spirits
- Able to stand with assistance (2 months after ICH), left neglect improving
- Can wheel himself around, cognitively intact, speaking well.



# Take home points

1. ICH patients need aggressive treatment in a neuroscience ICU.
2. BP can probably be safely reduced to 140/90 mm Hg over the first 24 hours.
3. Anticoagulation should be promptly reversed.
4. Surgery is indicated only in select patients.
5. Prognostication is best done by an expert keeping in mind that 1/3<sup>rd</sup> of patients improve up to one year and beyond.

# The Stanford Stroke Center



