FASTEST:

NIH StrokeNet Trial utilizing EFIC

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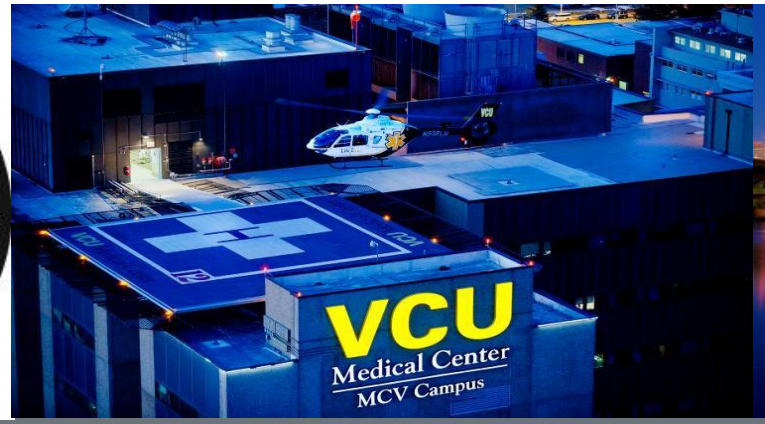

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rFVIIa for Acute Hemorrhagic Stroke Administered at Earliest Time (FASTEST) Trial

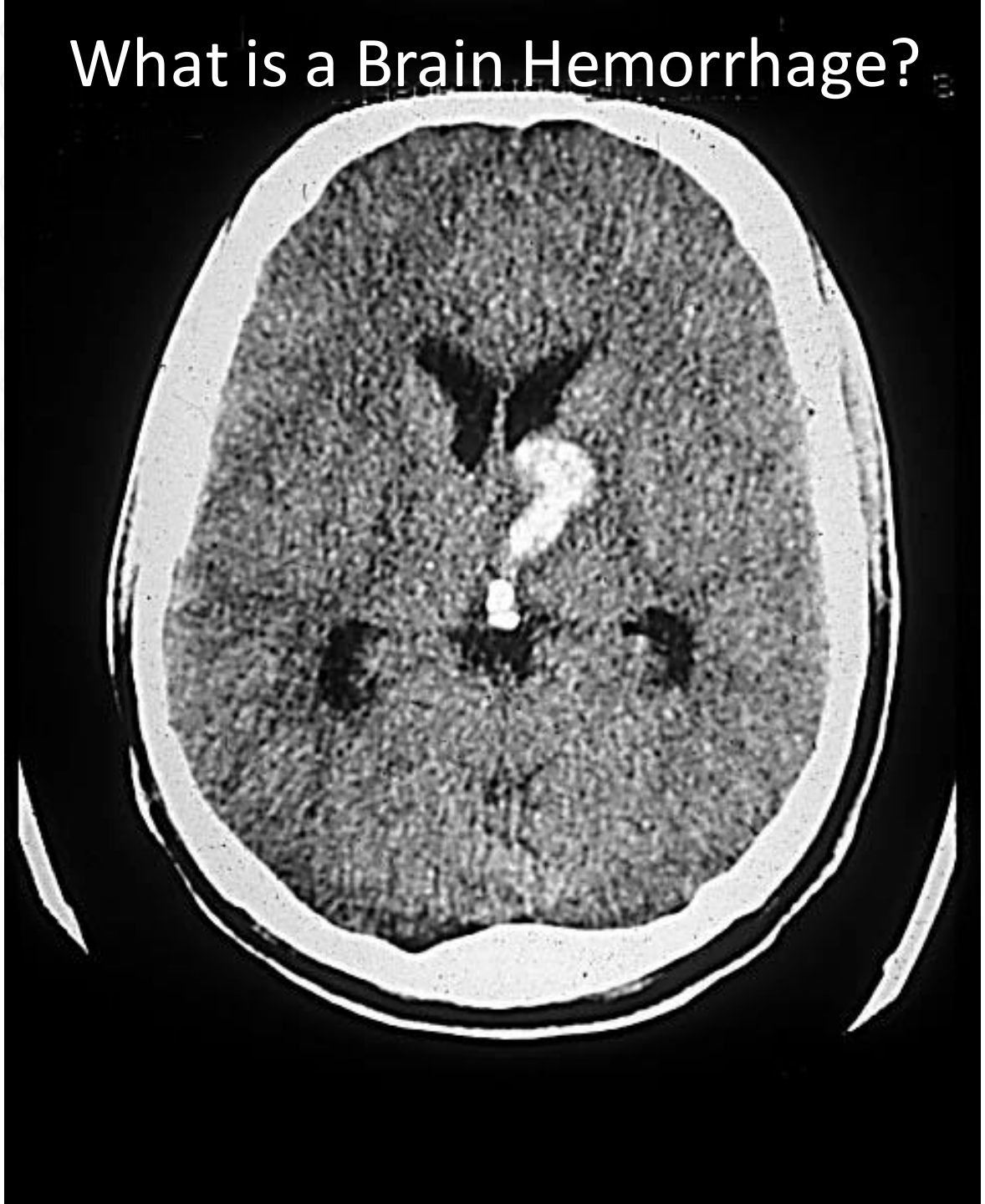
NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

Virginia Commonwealth University
VCU Medical Center

Outline for the FASTEST Trial Overview

- Discuss what is a brain hemorrhage or intracerebral hemorrhage (ICH)
- Explain what is recombinant Factor VIIa (rFVIIa)
- Explain the FASTEST Trial and what it is trying to accomplish
- Introduce emergency research and consent (Exception from Informed Consent (EFIC))

What is a Brain Hemorrhage?

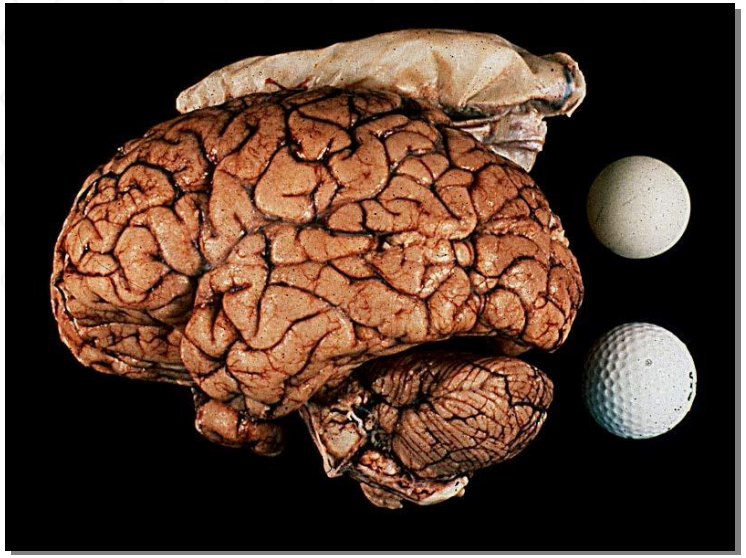


Background

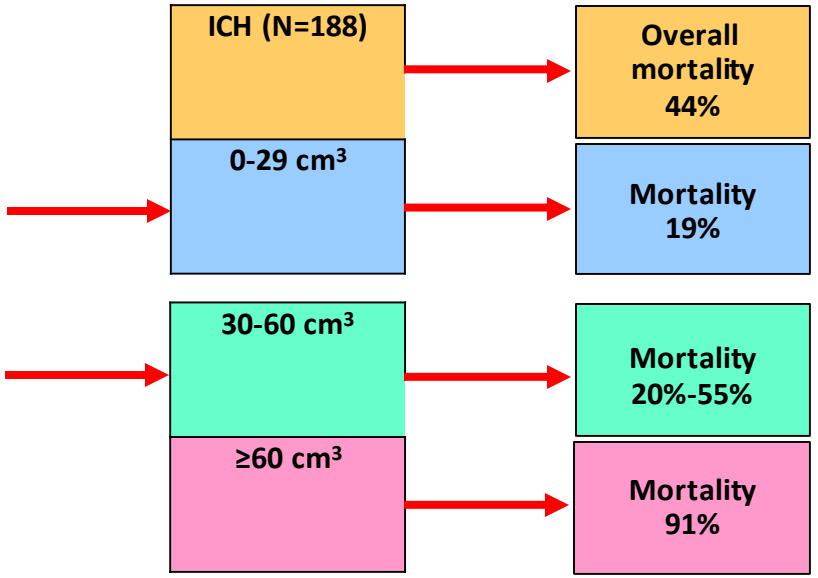
- Brain hemorrhage or intracerebral hemorrhage (ICH) is a type of stroke that accounts for more than 10% of the estimated 17 million strokes worldwide each year, or about 1,700,000 cases per year
- More than 40% of patients die and only 20% of survivors are functionally independent at 6 months
- The amount of blood in the brain is the most important determinant of outcome, and most bleeding occurs within 2-3 hours
- **There is no scientifically proven effective treatment for ICH**

SIZE MATTERS!

Small Increases in ICH Volume Cause Significant Increase in Mortality



Ping-pong ball vs. Golf ball
31 mL 41 mL



Only 1 of 71 patients with ICH volume ≥ 30 cm³ functioned independently at 30 days (Oxford Handicap Score ≤ 3)

Broderick, *Stroke*. 1993;24:987-993

Learn from patients, your wife, and your colleagues

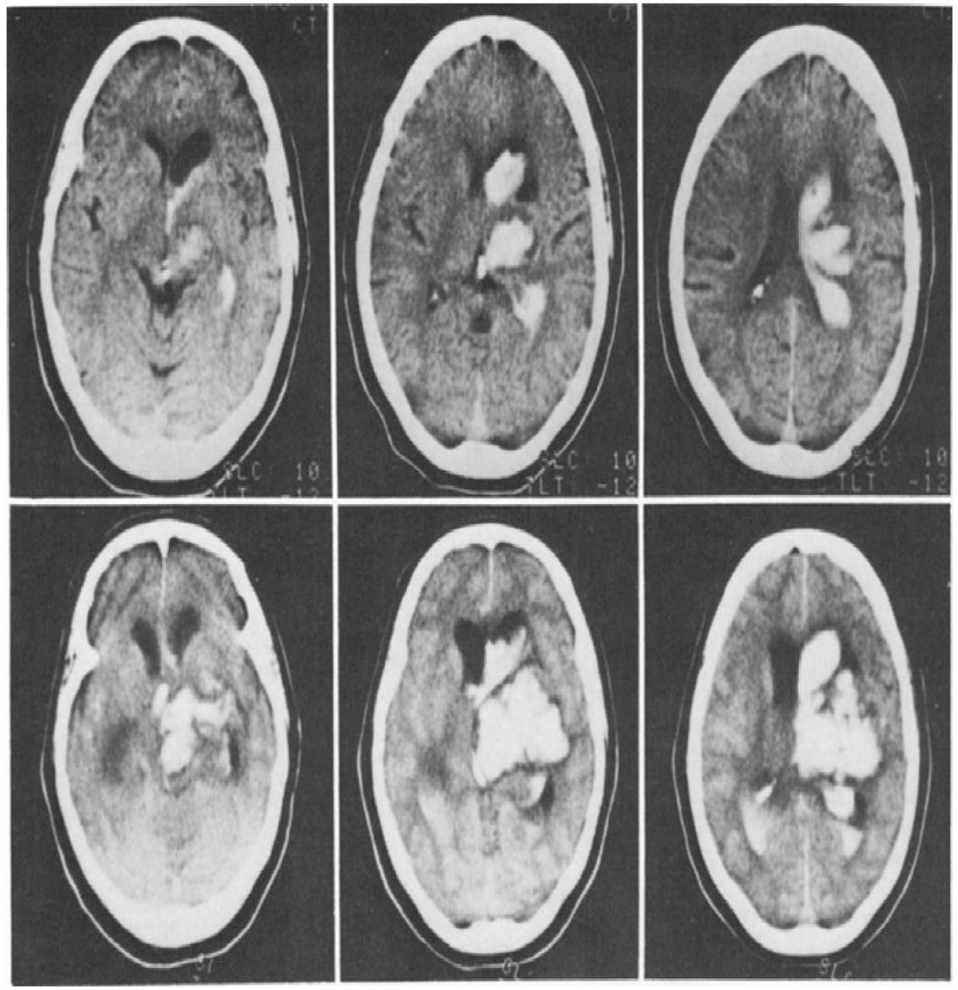


FIG. 2. Serial computerized tomography (CT) scans in Case 3. An increase in volume of hemorrhage from 8 to 35 cc was recorded between the first CT scans *(upper)*, obtained 50 minutes after onset of symptoms, and the second CT scans *(lower)*, obtained 210 minutes after onset.

TABLE 1

Times and results of serial computerized tomography (CT) scans

Case No.	Time of CT Scan*		Hemorrhage Volume (cc)		Origin of Bleed
	1st	2nd	1st CT	2nd CT	
1	35	105†	25	40	lt putamen
2	50	6000	20	36	rt putamen
3	50	210	8	35	lt thalamus
4	55	110†	71	72	lt frontal lobe
5	60	110†	14	20	rt putamen
6	75	105†	41	47	rt frontal lobe
7	95	185	17	48	rt thalamus
8	140	690	18	44	rt thalamus

* Time (in minutes) measured from onset of symptoms.
† Second CT scheduled prospectively, prior to deterioration.

J. Neurosurg: 72: 195-199, 1990

Learn from patients, your wife, and your colleagues

- Ellipsoid volume $4/3\pi(A/2)(B/2)(C/2)$
- ABC/2

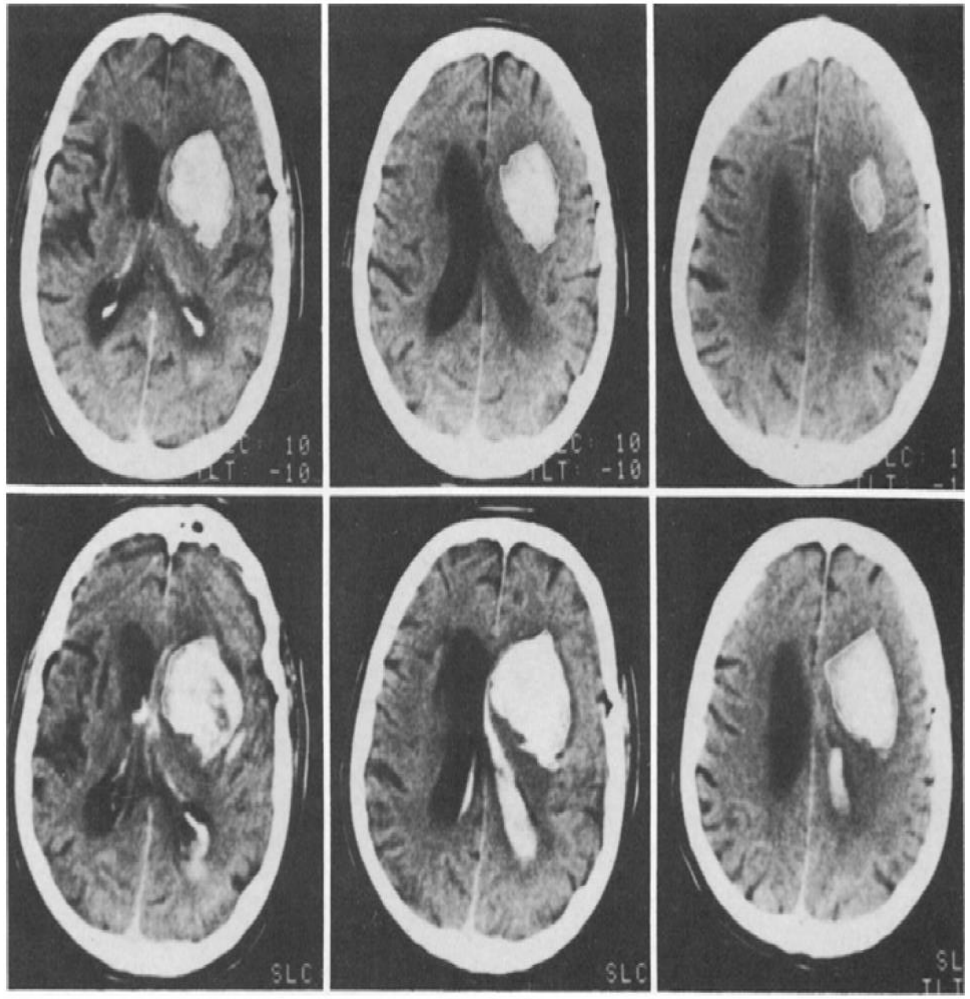


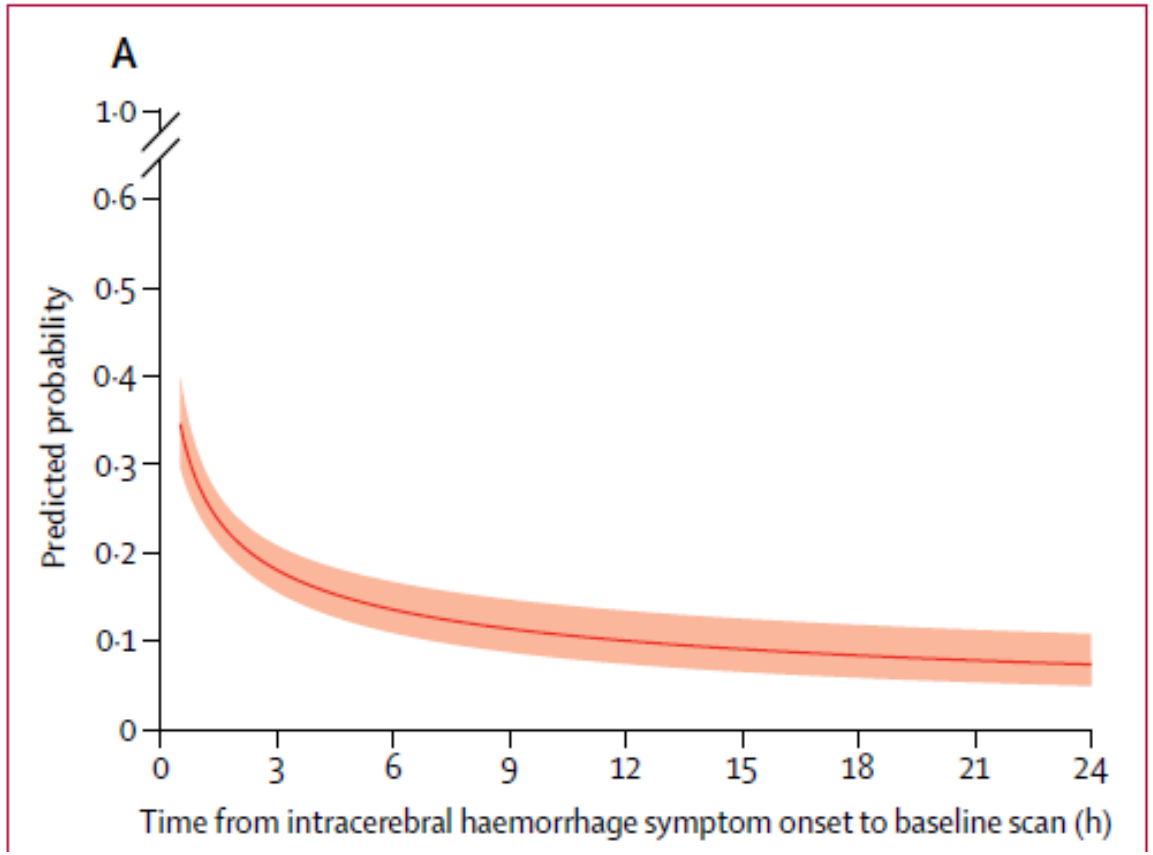
FIG. 1. Serial computerized tomography (CT) scans in Case 1. Measurement of the volume of hemorrhage revealed an increase from 25 to 44 cc between the first CT scans *(upper)*, obtained 35 minutes after onset of symptoms, and the second CT scans *(lower)*, obtained 105 minutes after onset.

Early hemorrhage growth in patients with ICH

- **First prospective study of ICH growth**
  - 103 patients scanned < 3 hours of onset
  - **38%** experienced significant hematoma growth (> 33% increase in volume)
    - **26%** between baseline and 1-hour scan
    - **12%** between 1- and 20-hour scan
  - ICH growth was associated with clinical deterioration on NIHSS

Brott, Broderick, et al 1997, *Stroke*. 1997;28:1
NINDS funded study

Physiologic time is critical for hemostatic therapy



Salman et al, Lancet Neurology, September, 2018 – Figure A, demonstrates the strong exponential relationship between time from onset and predicted probability of growth of ICH of > 6cc.

Current treatment of ICH

- Admission to intensive care unit
- Treatment of blood pressure, which is often very elevated
- Often ventilator machine to help breathe
- Medical and surgical treatments to help relieve pressure in the brain
- Occasionally, surgery to remove blood
- **There is no scientifically proven effective treatment for ICH**

Medications that Plug Leak: PPC in Warfarin-ICH (INCH Trial)

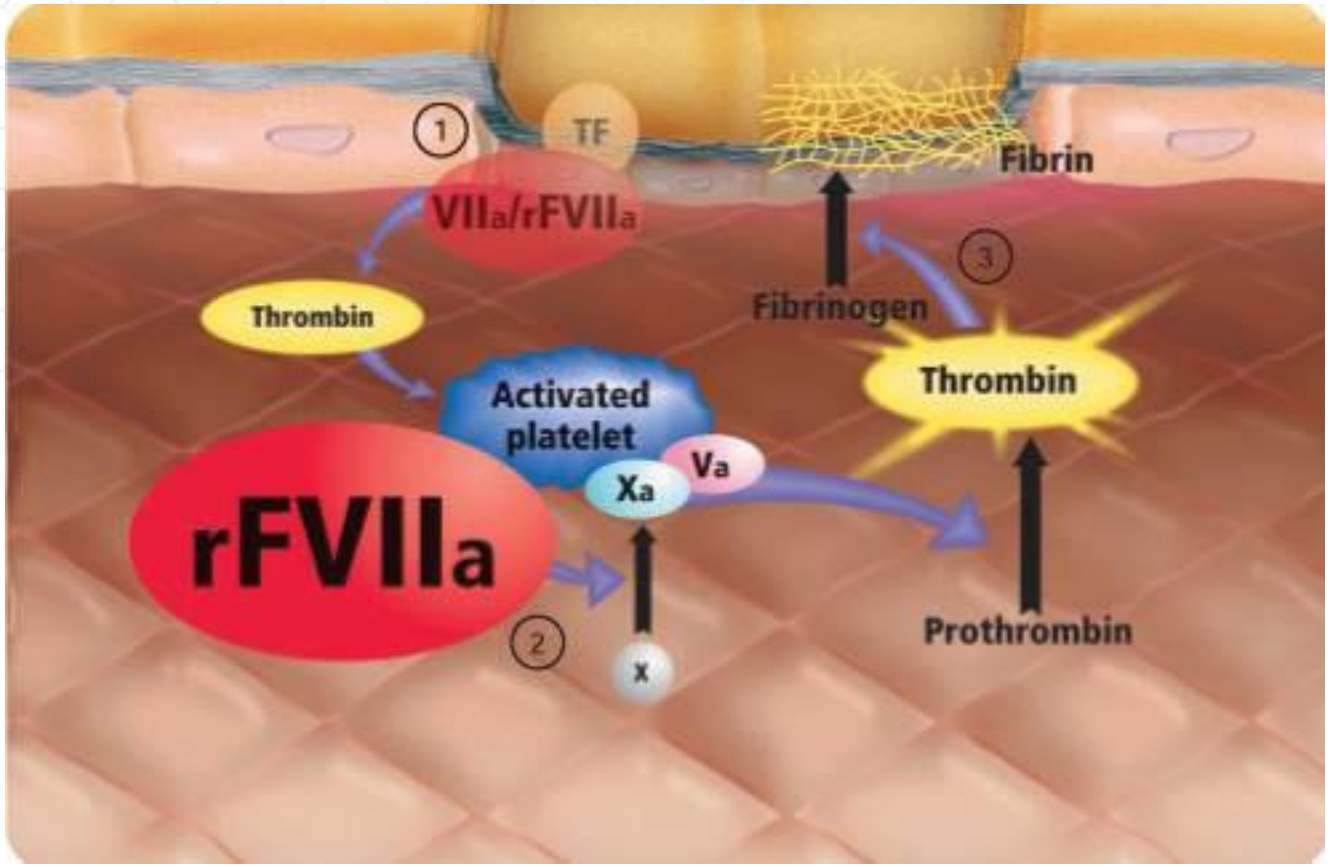
Outcome	FFP N=23	PCC N=27	P-value
INR<2 within 3 hours	2 (9%)	18 (67%)	0.003
Death at 90 days	8 (35%)	5 (19%)	0.14
ICH expansion at 24 hours (ccs)	**22.1 (27.1)**	**8.3 (18.3)**	**0.048**
>33% expansion at 24 hours	**12/20 (60%)**	**8/27 (30%)**	**0.024**

Steiner, et al. Lancet Neurology, 2016

What is recombinant Factor VIIa (rFVIIa)?

- Factor VIIa is a normal protein in our body that helps stop bleeding
- Recombinant Factor VIIa (identical to Factor VIIa but given in much larger amounts) is the only medication that has been shown to substantially decrease bleeding in patients with hemorrhage in the brain
- It is easily administered intravenously with rapid onset of action
- It is approved for other medical indications that involve bleeding (hemophilia) but not for brain hemorrhage
- Prior trials of rFVIIa showed that it slowed bleeding in the brain but that its benefits in improving outcomes are most likely when given within 2 hours of onset of symptoms

rFVIIa Accelerates and Strengthens Local Hemostasis via a Unique Mechanism of Action



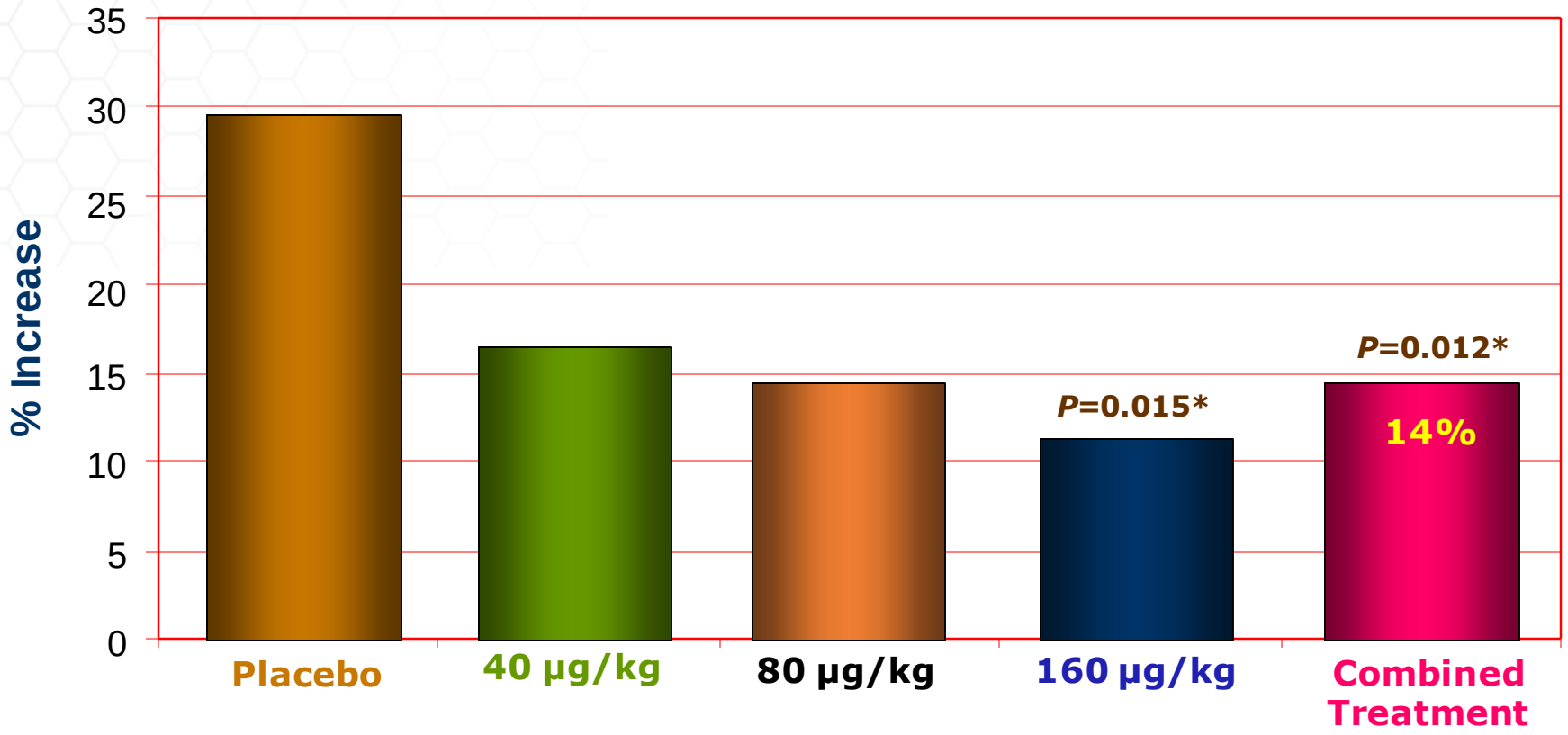
1. INITIATION: Tissue Factor/FVIIa interaction leads to thrombin generation
2. AMPLIFICATION: rFVIIa activates Factor X on the surface of activated platelets, leading to an enhanced thrombin burst at the site of injury
3. FIBRIN CLOT FORMATION: Thrombin converts fibrinogen into fibrin, producing a stable clot

Hoffman, M, et al. Thromb Haemost 2001;85:958

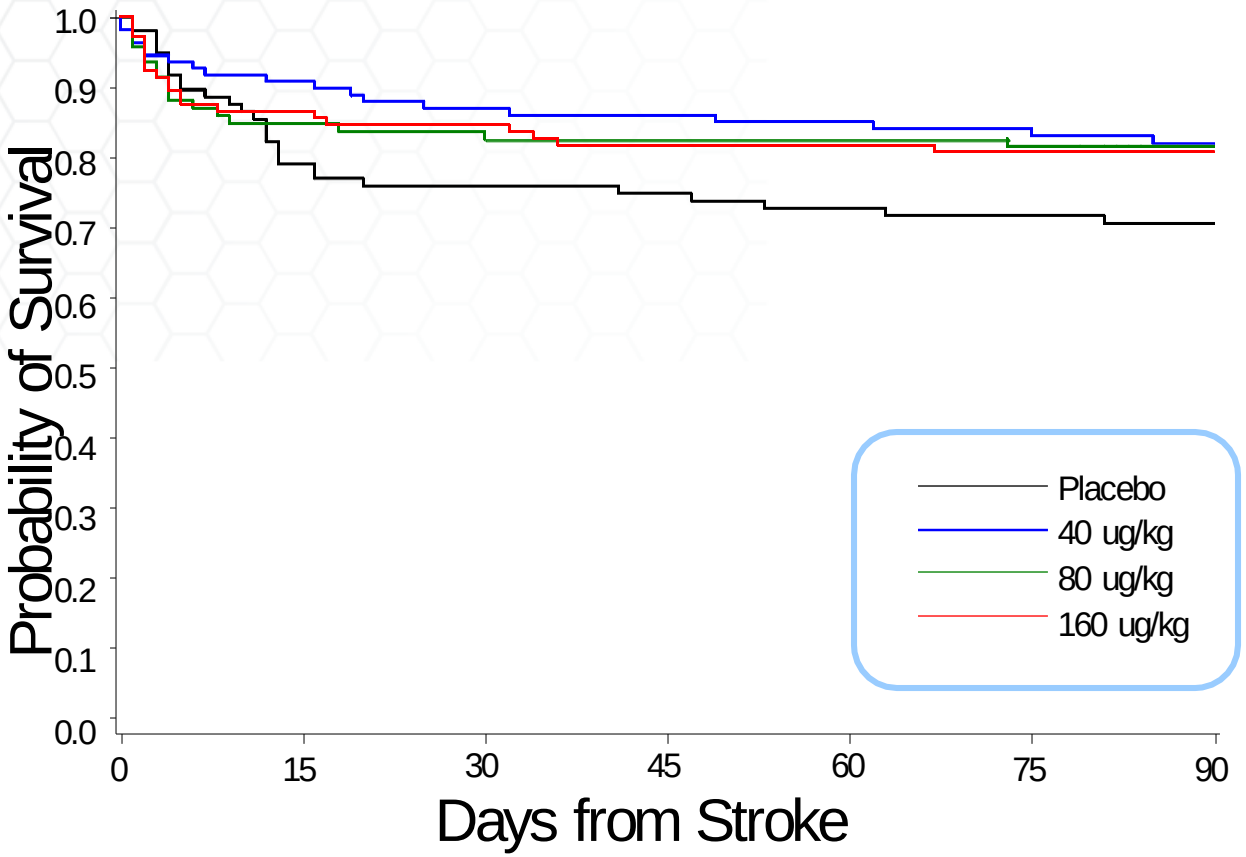
Potential risks of rFVIIa in patients with ICH

- Since rFVIIa helps stop bleeding by stimulating formation of and enhancing blood clots, patients with brain hemorrhage are also at risk for other vascular diseases and blood clots where there are damaged blood vessels – there is a risk of heart attack, stroke due to blockage of brain arteries, and clots in the lung
  - In prior studies, this occurred about 5% more commonly in persons treated with rFVIIa as compared to placebo

Estimated Mean Percent Change in ICH at 24 Hours: Phase 2b Trial



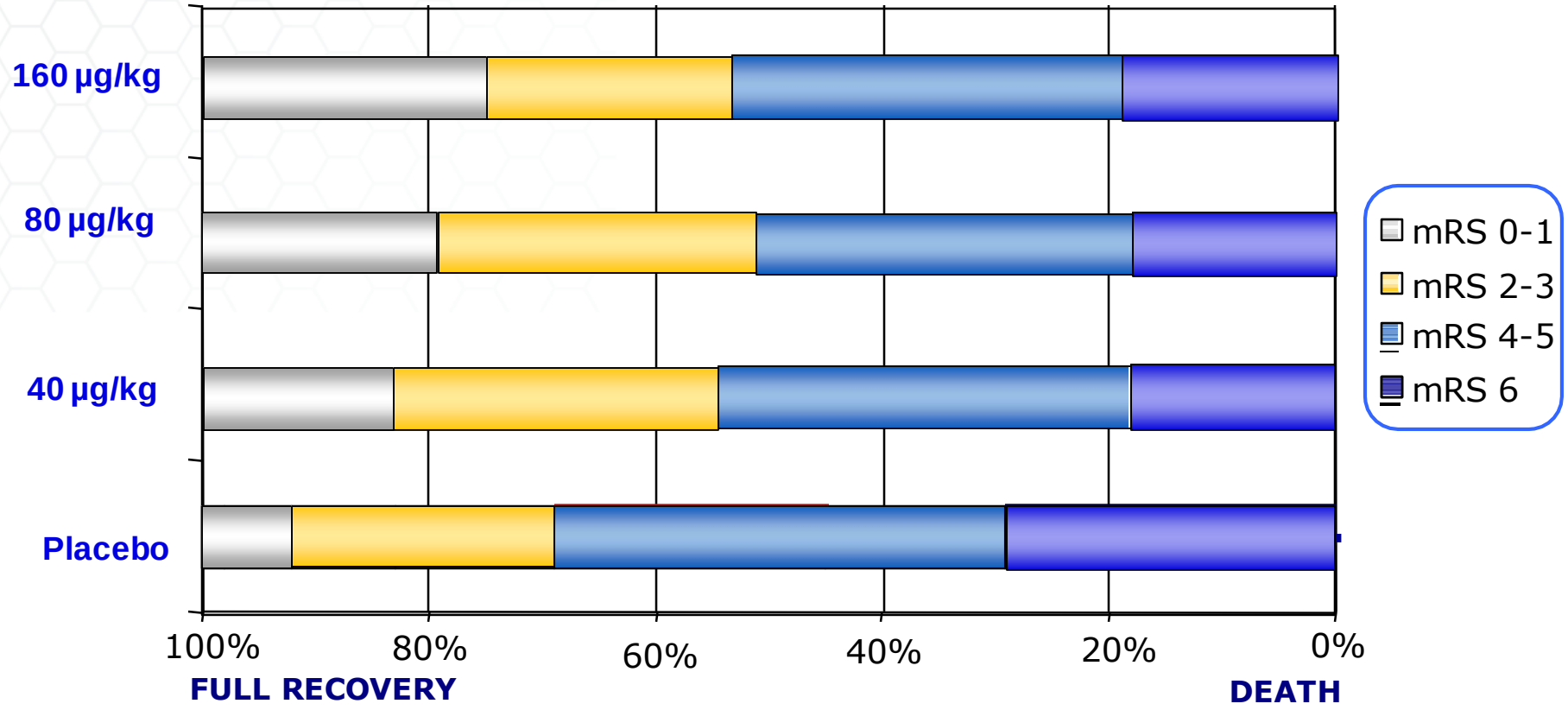
Kaplan-Meier Survival Curves: Phase 2b Trial



P=0.02, rFVIIa combined vs. placebo

New Engl J Med 2005;352:777-785

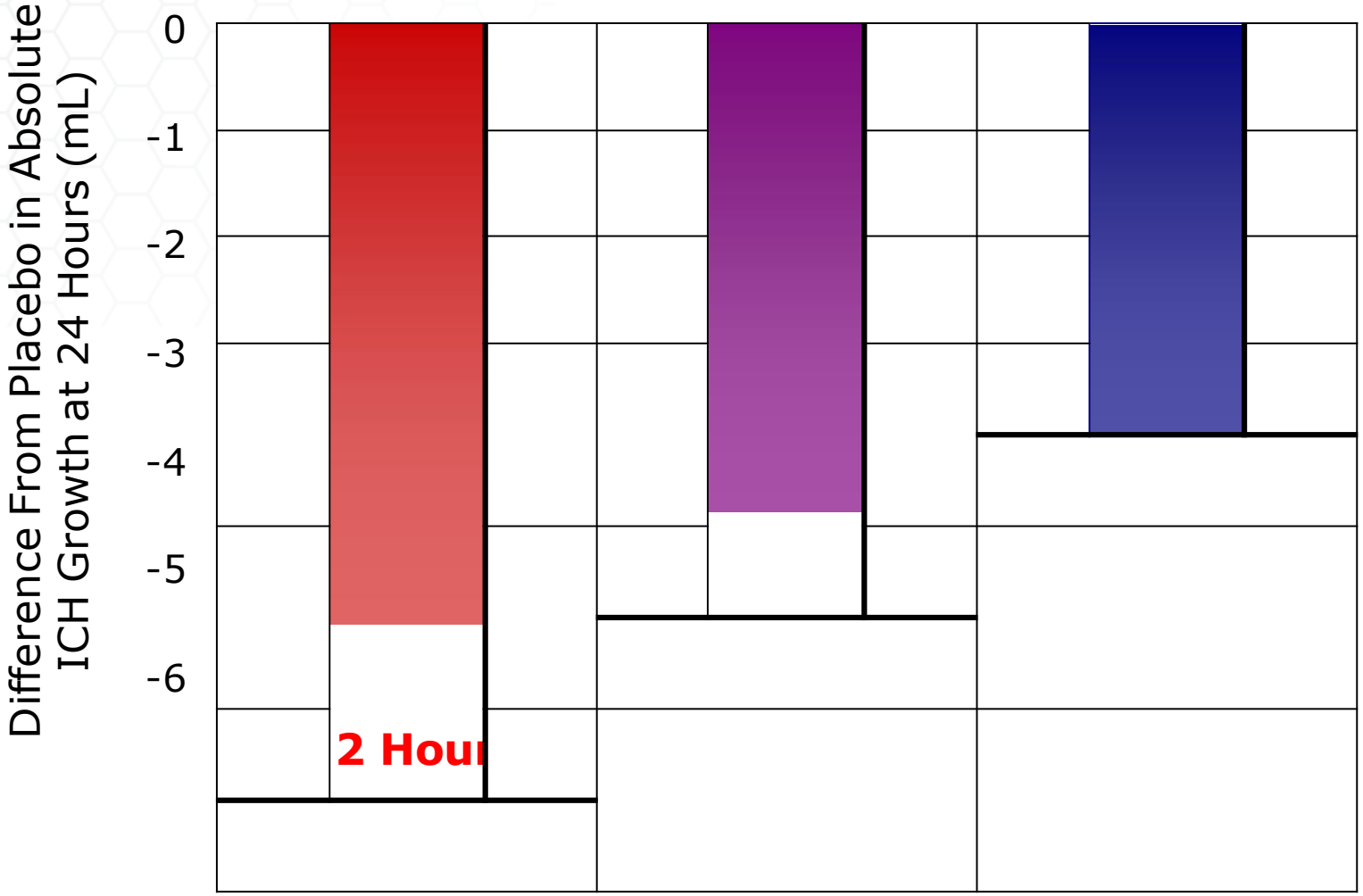
Modified Rankin Scale at Day 90: Phase 2b Trial



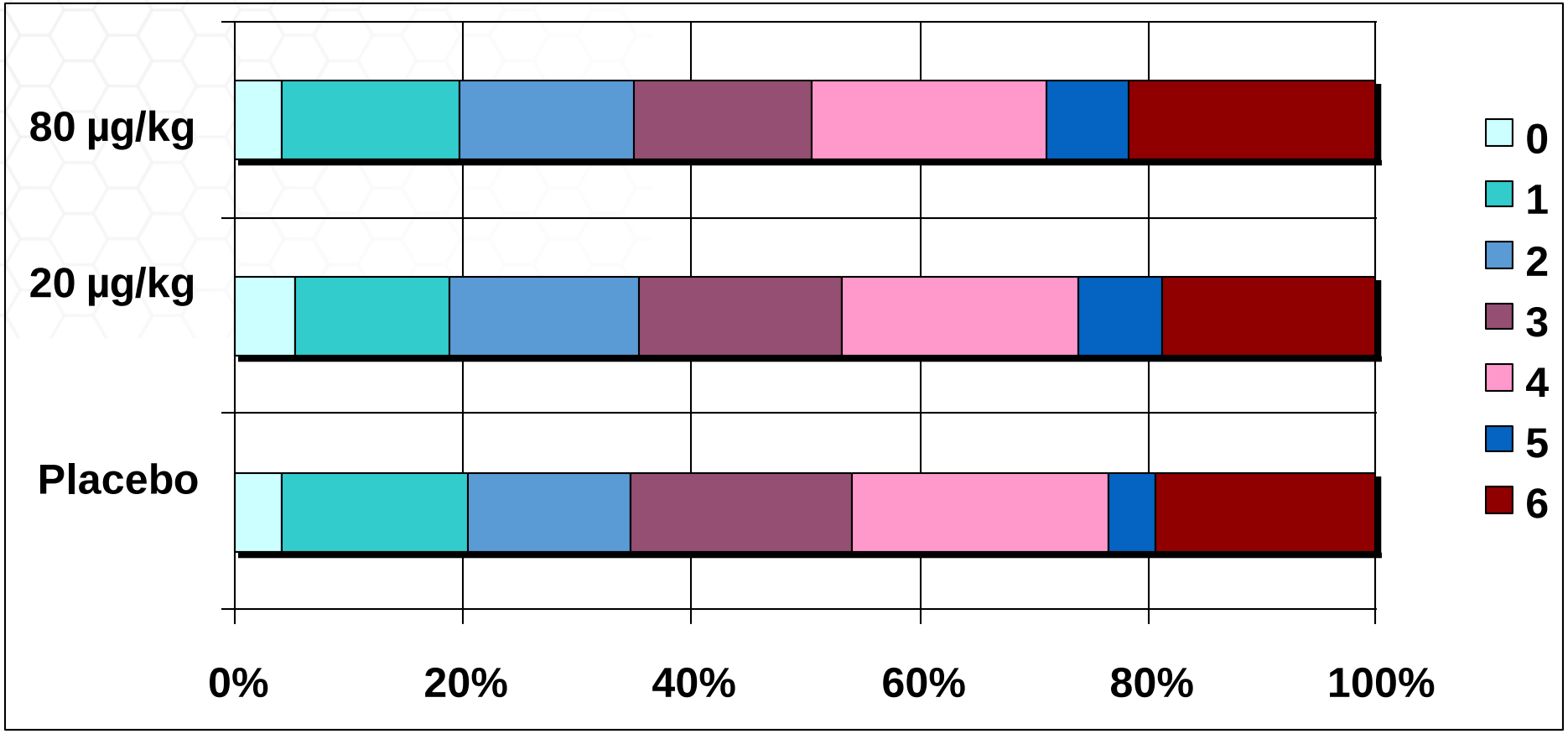
Global adjusted odds ratio for improvement on mRS 2.2, P=0.004

New Engl J Med 2005;352:777-785

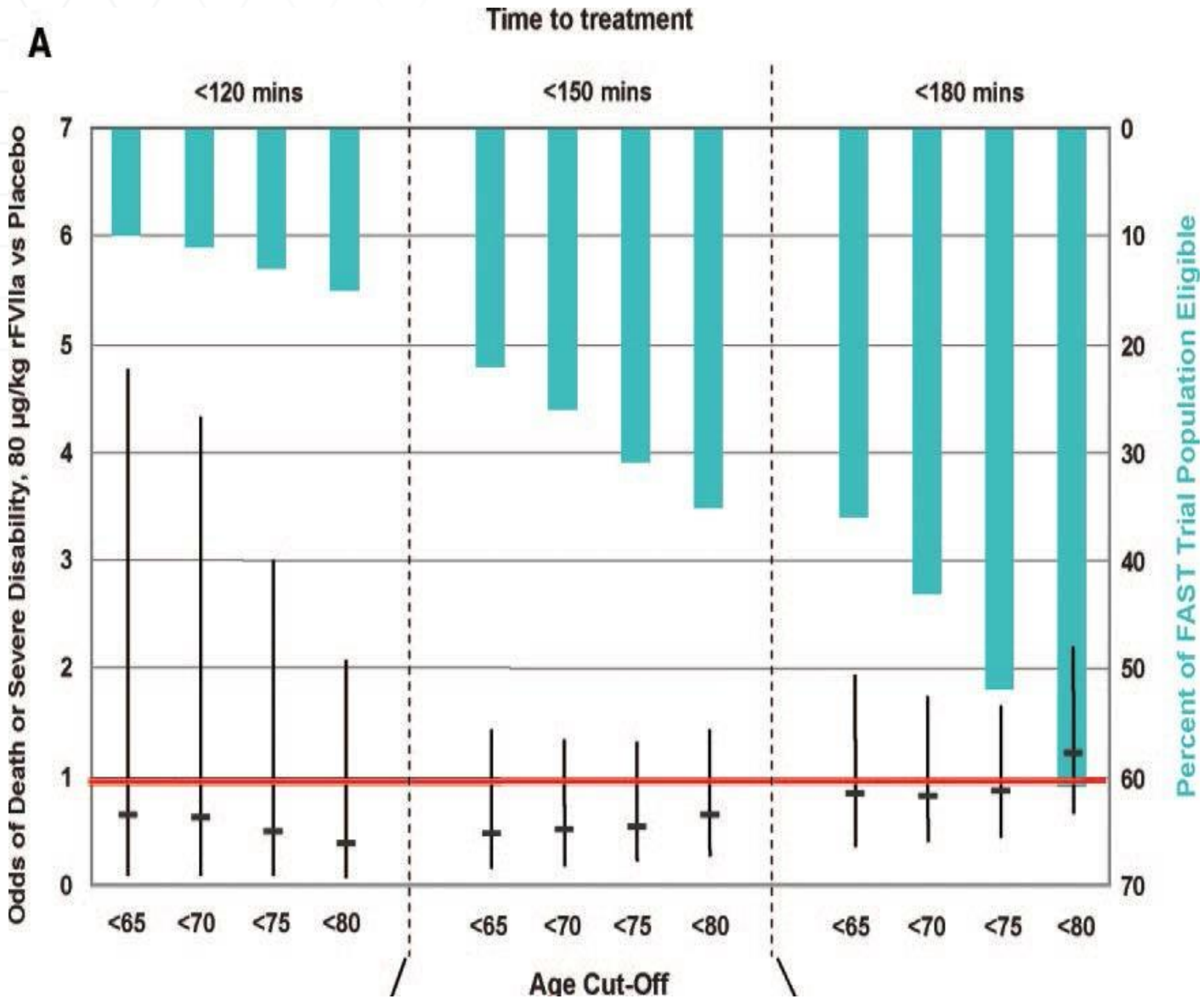
FAST Trial: Absolute Reduction in ICH Growth (mL) 80 µg/kg by Treatment Time



FAST Trial: Modified Rankin Scale – Distribution at Day 90
No Difference Between Treatment Groups



Post-hoc analysis of subgroup from FAST Trials



Mayer et al, Stroke, 2009

FASTEST subgroups from FAST and Phase 2b studies

FAST

Minutes from onset to treatment in patients age ≤ 80	mRS 0-2 FVIIa	mRS 0-2 Placebo	Absolute % in mRS 0-2 in favor of rFVIIa at 90 days
≤ 150	42%	42%	0%
≤ 140	46%	41%	5%
≤ 130	49%	41%	9%
≤ 120*	**52%**	**38%**	**14%**

Minutes from onset to treatment in patients age ≤ 70	mRS 0-2 FVIIa	mRS 0-2 Placebo	Absolute % in mRS 0-2 in favor of rFVIIa at 90 days
≤ 150	53%	39%	14%
≤ 140	59%	38%	21%
≤ 130	62%	38%	24%
≤ 120	**69%**	**33%**	**36%**

*N=25 in FVIIa and 32 in placebo group

Phase 2b

Minutes from onset to treatment in patients age ≤ 80	mRS 0-2 FVIIa	mRS 0-2 Placebo	Absolute % in mRS 0-2 in favor of rFVIIa at 90 days
≤ 150	42%	32%	10%
≤ 140	47%	30%	17%
≤ 130	50%	25%	25%
≤ 120	**50%**	**20%**	**30%**

FASTEST Trial: Objective

- The objective of the rFVIIa for Acute Hemorrhagic Stroke Administered at Earliest Time (FASTEST) Trial is **to establish the first treatment for acute ICH within a time window and subgroup of patients that is most likely to benefit**

NIH Funded: 1U01NS110772-01

Design

- Randomized, double-blind controlled efficacy trial of rFVIIa plus best standard therapy vs. placebo plus best standard therapy (including INTERACT 2 goal of target systolic blood pressure of 140 mm Hg)
- Includes patients:
  - Age 18-80, inclusive
  - Baseline volume of spontaneous ICH ≥ 2 cc and < 60 cc (measured by ABC/2 or by an FDA-cleared automated ICH volume imaging software (e.g., VIZ.ai))
  - No or small volume of IVH (IVH score ≤ 7)
  - **Treated within 120 minutes of stroke onset/last known well** (goal: ½ treated within 90 minutes)

FASTEST

Who does not qualify for FASTEST?

- Persons who already are in a deep coma, or who have very large areas of bleeding in the brain and are already destined to die
- Persons with recent heart attacks, strokes, or blood clots (within the prior 3 months)
- Persons on blood thinners, such as warfarin
- Women known to be pregnant
- Persons who have an opt-out card

FASTEST

How to Minimize Time to Treatment

- Exception from Informed Consent (EFIC)
  - Including remote and eConsent options in the event a legally authorized representative or family member is available to provide prospective consent
- Mobile stroke units (MSUs)
- Improved acute stroke treatment processes, as for ischemic stroke, including automated calculation of ICH volume, door to needle, etc.

FASTEST

Intervention

- Randomize participants in a 1:1 ratio to intravenous rFVIIa or placebo at a dose of 80 µg/kg (maximum 10,000 µg or 10 mg) and administered intravenously over 2 minutes – all investigators and participants will be blinded throughout the course of the trial
  - **Enrollment and randomization in the trial will occur upon injection of the study medication**
- Only a baseline non-contrast CT is required
- CT angiogram will be collected, if done, but is not required

FASTEST

Additional Key Study Procedures

- Participants will receive AHA guideline-supported management of acute ICH; acute blood pressure management with a target systolic blood pressure of 140 mm Hg is required
- Participants will get another CT of the head within 24 hours from stroke onset/last known well to measure if there was hemorrhage growth
- Participants will have follow-up visits remotely at Day 30 and Day 90 and in-person at Day 180

FASTEST

Primary Outcome

- The primary outcome measure is **the following distribution of the ordinal mRS at 180 days: 0-2, 3, and 4-6**

Study Population

- Number of subjects to be enrolled: 860
- Approximate number of trial sites: 115 hospitals and 15 mobile stroke units
- Countries participating: U.S., Canada, Germany, Spain, U.K., and Japan
- Target FPFV: October 1, 2020
- Target recruitment period: 3½ years

How are emergency studies different?

- In most studies, investigators describe what will happen, discuss potential risks and benefits, answer questions, and then eligible patients decide whether or not to participate – the process of informed consent
- In emergency studies, such as FASTEST, eligible patients cannot make a decision if they want to participate due to their medical condition, and treatment is needed to be started often before the patient's legally authorized representative or family member is available to decide for the patient

FASTEST

So how do we do emergency research?

- Specific federal regulations allow for **exception from informed consent for emergency research (EFIC)** only when:
  - The condition under study is life-threatening
  - Existing treatments are unproven or inadequate
  - There is potential benefit for participants
  - Informed consent cannot feasibly be obtained

What Is Planned Emergency Research?

- Clinical investigation
- Subject incapacitated
- Life threatening situation
- No time to obtain traditional consent
- No way to identify subjects in advance
- Not practical to conduct research without an exception to informed consent

Example:
Experimental blood plasma product for trauma patients

Regulation 21 CFR 50.24—Summary of Key Points

See the full text of the regulation here:
https://www.govinfo.gov/content/pkg/CFR-2012-title21-vol1/pdf/CFR-2012-title21-vol1-sec50-24.pdf

- 50.24(a)—IRB can approve a clinical investigation with an exception to informed consent *under certain circumstances* and in consultation with a licensed physician not involved in the research *[paraphrased)*

The Requirements—Summary of Key Points

- 50.24(a)(1)—Life threatening situation, unproven or unsatisfactory standard treatments, collection of safety and efficacy data is necessary. *[paraphrased]*

- 50.24(a)(2)—Obtaining prospective consent is not feasible because there is no reasonable way to identify in advance who will become eligible. *[paraphrased]*

- 50.24(a)(3)—Research holds the prospect of direct benefit to the incapacitated subject who is in an emergency situation and the risks are reasonable in relation to their situation. *[paraphrased]*

The Requirements—Summary of Key Points

- 50.24(a)(5)—Investigator must commit to attempting to get consent from subject's LAR during the potential therapeutic window before initiating intervention without consent; these contact efforts must be summarized for the IRB at continuing review. *[paraphrased]*

- 50.24(a)(6) & (7)(v)—If LAR is not available, the investigator must also commit to attempting to contacting a family member to ask if they object to the subject's participation; these efforts likewise must be summarized for the IRB. *[paraphrased]*

EFIC – why is it used in the FASTEST Trial?

- Patients had a stroke that caused intracerebral brain hemorrhage (ICH), which can be life threatening
- Study drug (Recombinant Factor Vlla) may stop or slow growth of ICH if administered in a short time window (2 hours from symptom onset)
- Testing the study drug against placebo
- Patients typically are unconscious or in a coma so unable to consent
- Legally authorized representative/family member may not be available to provide consent

https://redcap.research.cchmc.org/surveys/

Enter Code: LWP9YE97Y

English

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