Hemorrhagic Stroke

Greater Cincinnati Stroke Consortium

11th Annual Symposium

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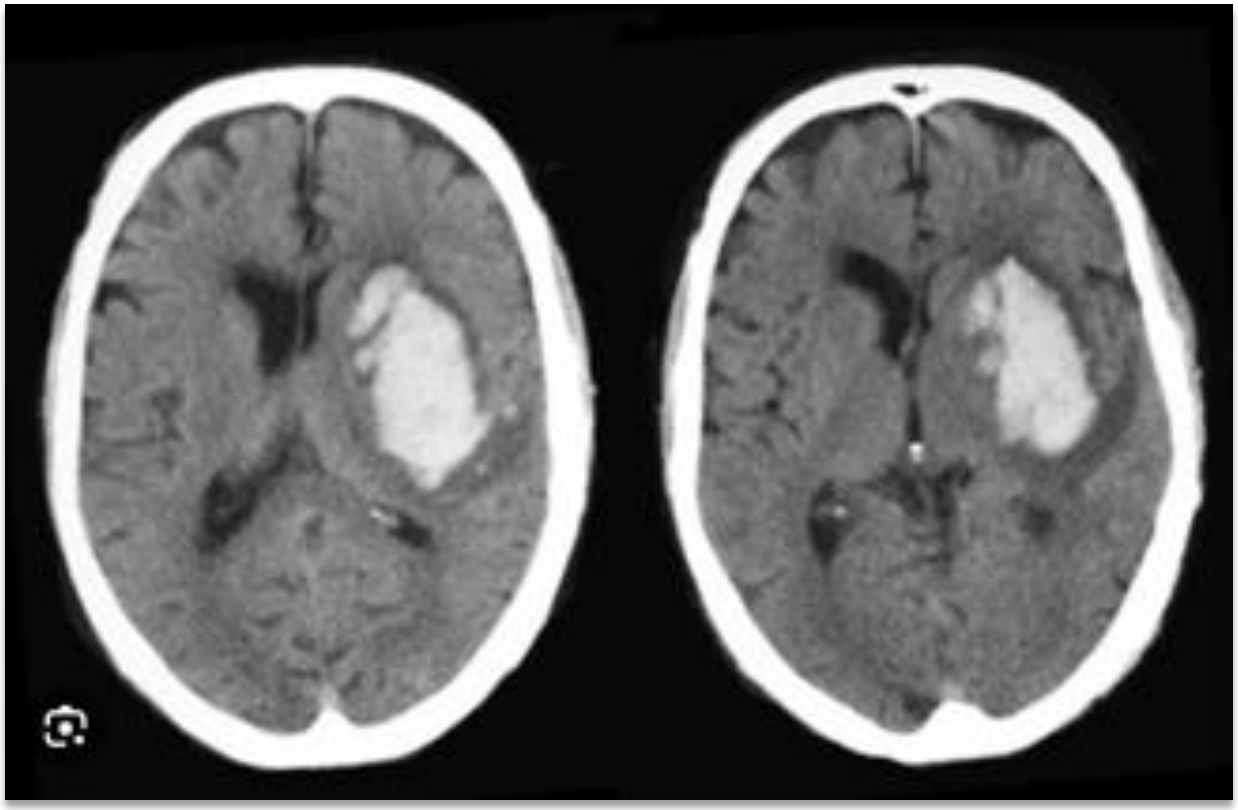
Outline – Hemorrhagic Stroke

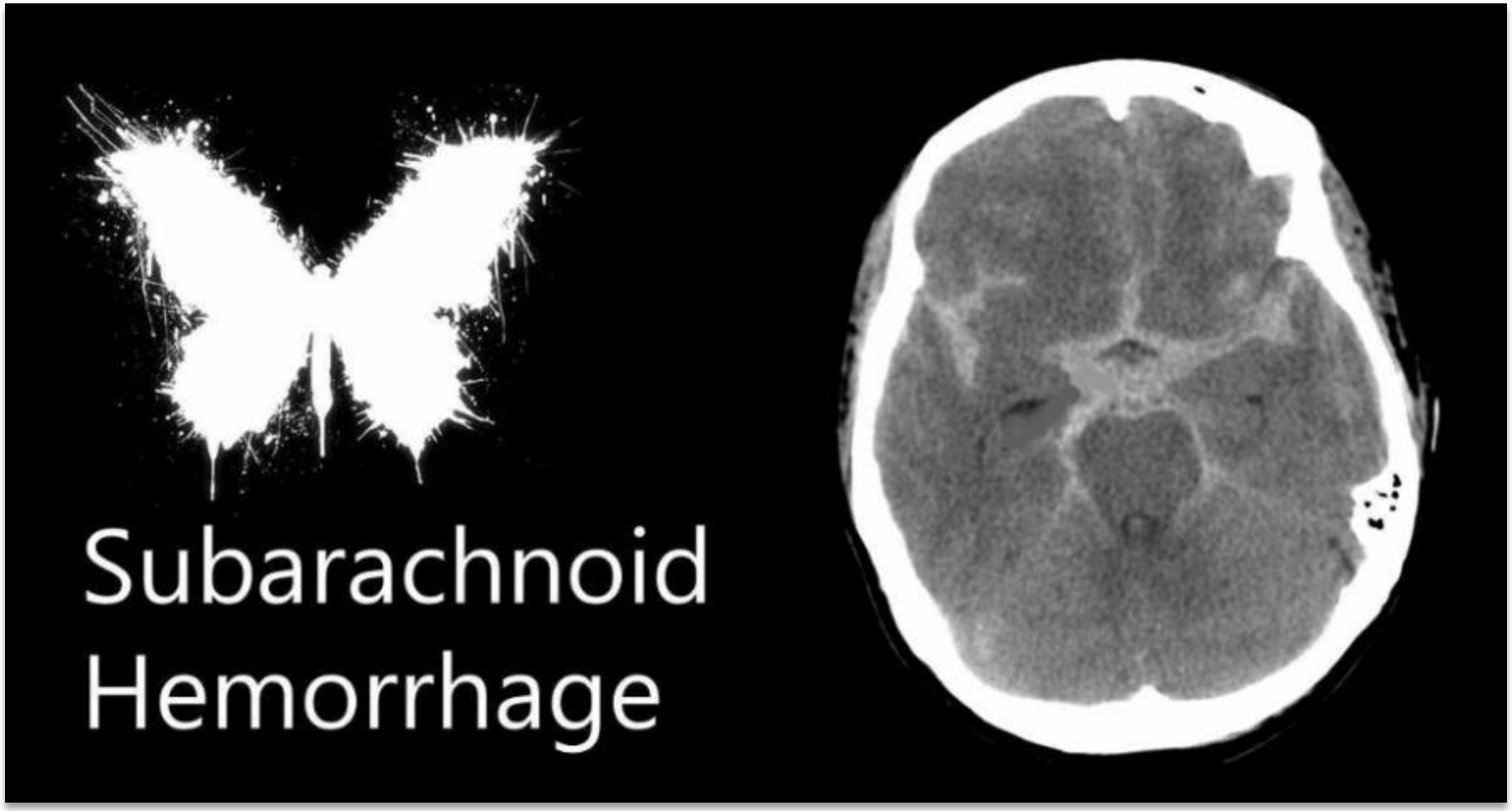
- What is a hemorrhagic stroke?
  - Intracerebral hemorrhage
  - Subarachnoid hemorrhage
- What it is not
  - Ischemic stroke
  - Traumatic/other intracranial hemorrhages
- Common symptoms
- Patient history
- Initial management

Intracerebral Hemorrhage - ICH

Spontaneous bleeding into the brain



Intracerebral Hemorrhage - ICH



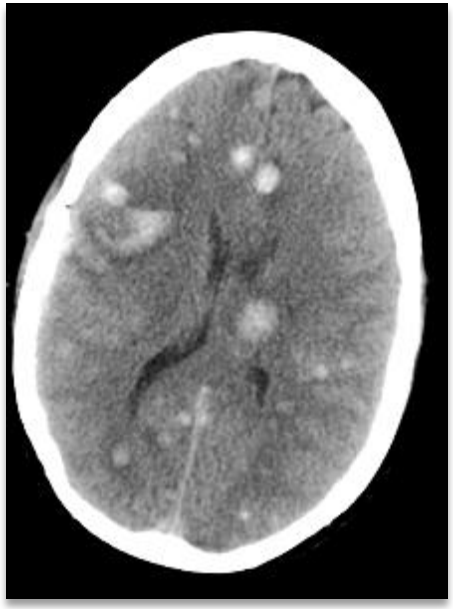
What a Hemorrhagic Stroke **Is Not** -

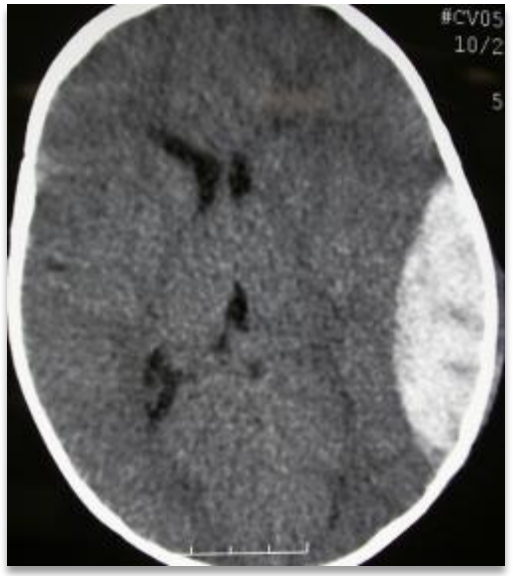
Ischemic Stroke

- Caused by a blockage in an artery
- ~80% of strokes

What a Hemorrhagic Stroke **Is Not** -

Other Types of Intracranial Bleeding





Intracerebral Hemorrhage

- ✓ 10-15% of all strokes, 50% of stroke mortality
- ✓ 60% of ICH patients die within the first year
- ✓ 74% of survivors remain functionally dependent at 12 months

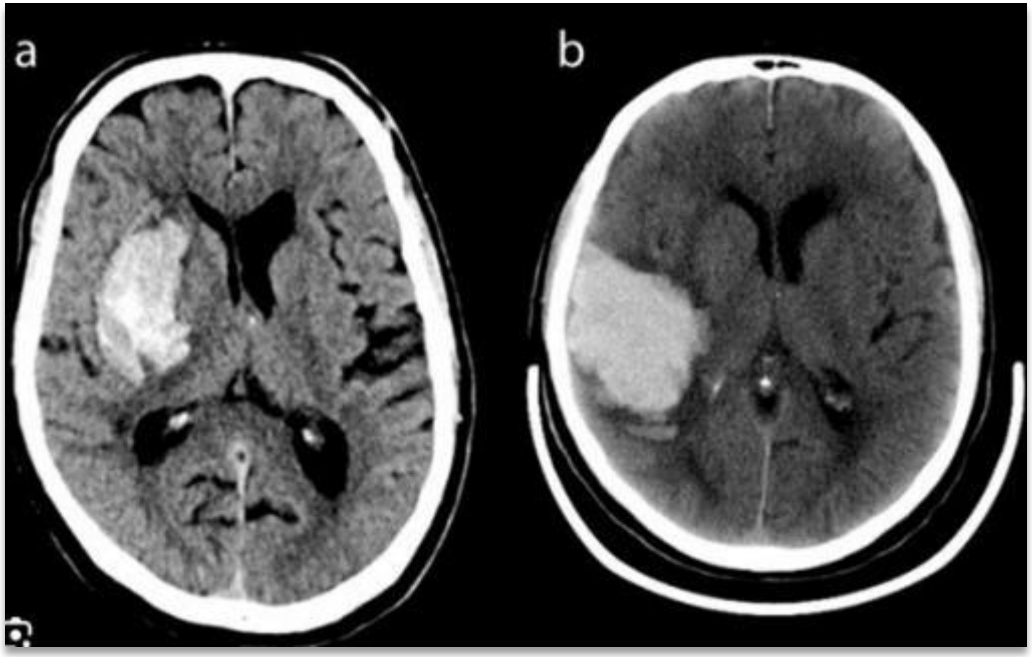
- ✓ For diagnosis, emergent brain imaging is needed:
  - Usually a CT scan

Intracerebral Hemorrhage

Symptoms:

- ✓ Generally, similar to ischemic stroke
- ✓ Dependent on the region of brain affected

- ✓ Weakness/numbness on one side of the body
- ✓ Speech difficulty
- ✓ Gaze deviation, neglect
- ✓ Visual field deficit
- ✓ Vertigo, unsteadiness with standing or walking


a
b

Intracerebral Hemorrhage

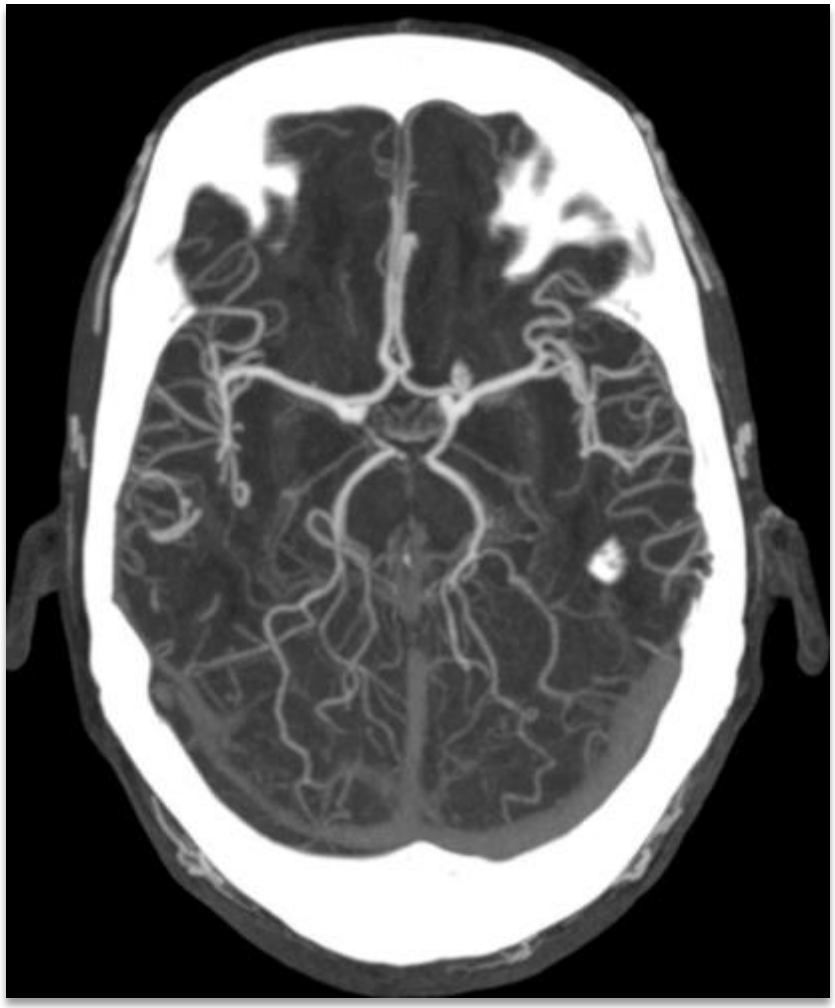
How to know ischemic vs. ICH?

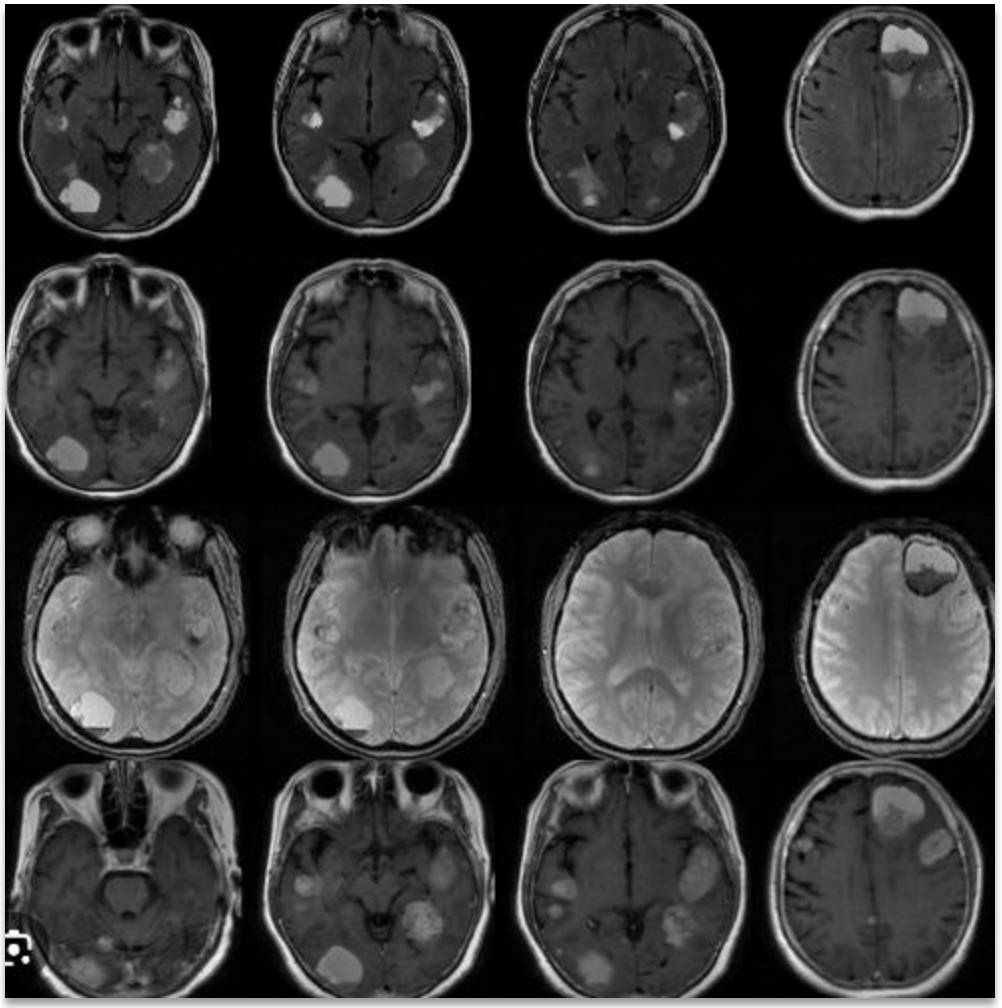
- CT scan

Symptoms more common for ICH vs. ischemic:

- Headache
- Decreased level of alertness
- Greater hypertensive response

Intracerebral Hemorrhage





Intracerebral Hemorrhage

Treatments:

Compared with ischemic stroke…

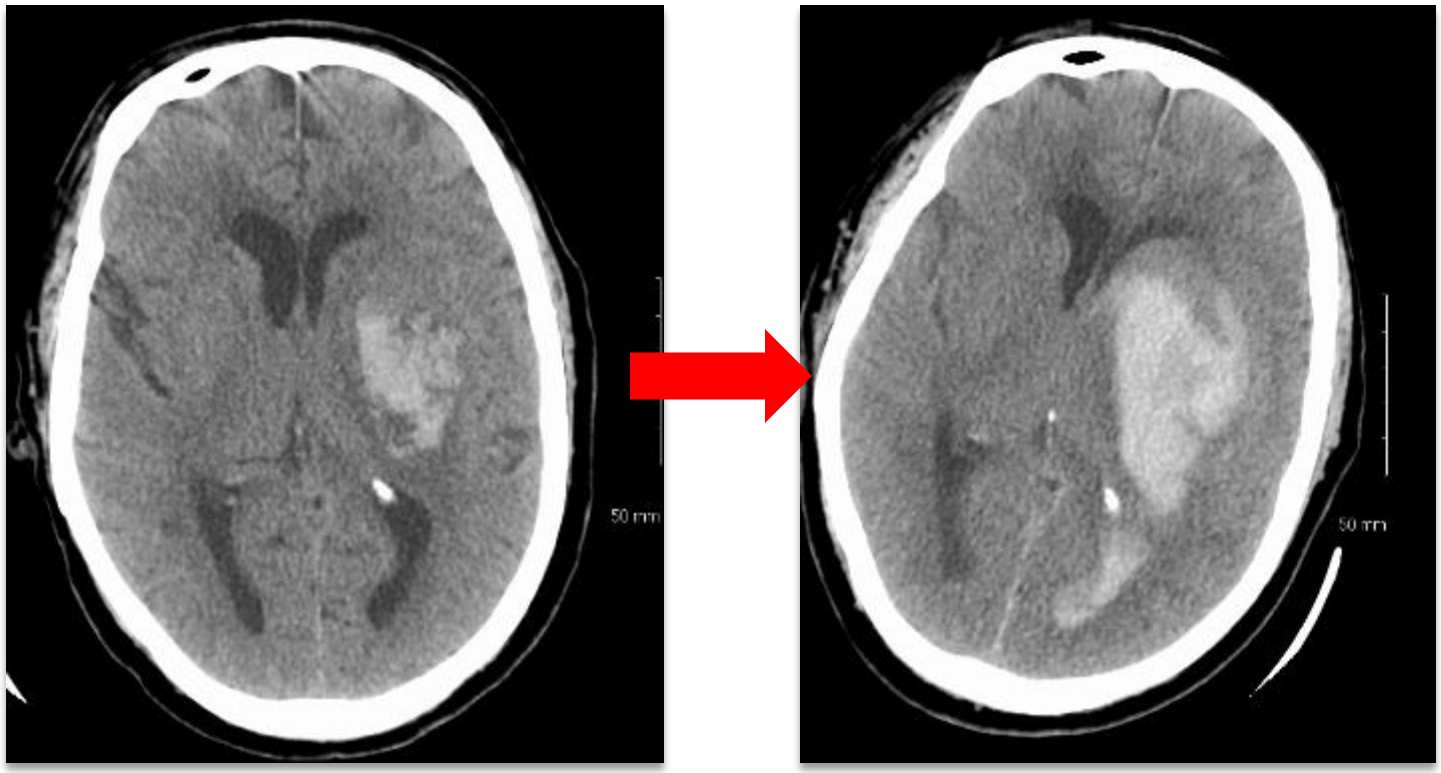
- Lower blood pressure
- Reverse anticoagulation

- In rarer cases….
  - Surgical removal of the hemorrhage
  - Treat increased pressure in the brain
  - Place an EVD

Intracerebral Hemorrhage

Why lower blood pressure and reverse anticoagulation?

Hematoma Expansion



Outline - ICH

Treatments:

- ***Elevated Blood Pressure***
- Vitamin K Antagonists (Warfarin)
  - Reversal
- Direct Oral Anticoagulants (DOACs, aka NOACs)
  - Monitoring of levels and Reversal
- Antiplatelet agents

Blood Pressure

AHA Guidelines

"As a primary recommendation, **lowering systolic BP (SBP)** to a target range of **130 to 140 mmHg** is safe and may be reasonable in improving functional outcome in patients presenting with acute ICH of mild to moderate severity and SBP between 150 and 220 mmHg."

"Initiating treatment as soon as possible and careful titration of BP-lowering therapy to ensure continuous smooth and sustained control of BP are recommended."

Blood Pressure

Common medications to acutely reduce blood pressure

- Nicardipine infusion
  - Clevidipine infusion
- Labetalol IV boluses
- Hydralazine IV boluses

INTERACT-2

Rapid Blood-Pressure Lowering in Patients with Acute Intracerebral Hemorrhage
N Engl J Med 2013;368:2355-2365

- 2839 patients with SBP 150-220 mmHg within 6 hours of ICH
- Randomized to intensive treatment (SBP <140 within 1 hr of randomization for 7 days) or standard treatment (SBP <180)
- Primary outcome: mRS ≥3 at 90 days

  52% intensive, 55.6% standard, (OR 0.87; P=0.06)

- Secondary outcomes: Better functional recovery and physical/mental QOL for intensive therapy

ATACH-2

Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage
N Engl J Med 2016;375:1033-1043

- 1000 patients within 4.5 hours of symptom onset - **SBP >180**
- Randomized to 24 hours to:
  intensive treatment (SBP 110-139) vs standard treatment (140-179)
- Stopped for futility
- Primary outcome: death or disability (mRS ≥4) at 90 days
  - 38.7% in intensive and 37.7% in standard (RR 1.04; CI 0.85 to 1.27)

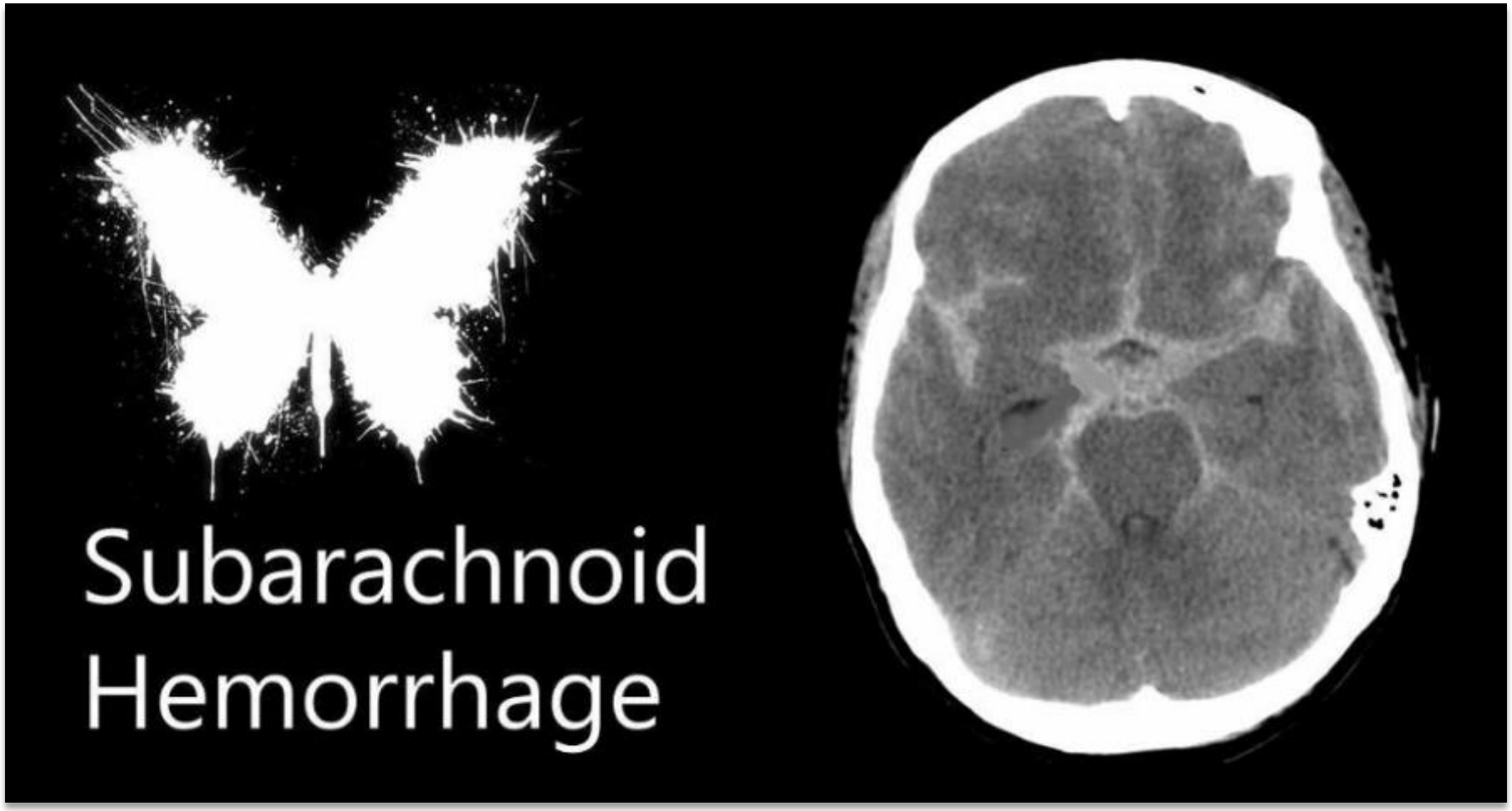
Blood Pressure Target

- SBP goal of 140? …. 180?
- No guidelines support allowing more extreme hypertension after ICH to be untreated
- Personalized targets?
- Also consider patient comorbidities, chronic hypertension
  - Time from ICH onset

Subarachnoid Hemorrhage (SAH)

- SAH accounts for about 5% of all strokes
  - *Today discussing spontaneous, not traumatic*
- Ruptured aneurysms are the cause of about 85% of spontaneous SAH
- Most common initial symptom:
  sudden-onset severe headache
  - "Thunderclap" headache, worst headache of life
  - Vomiting, photophobia, focal neurological deficits, seizures

Subarachnoid Hemorrhage (SAH)



emblog.mayo.edu

SAH Diagnosis

CT Head (non-contrast) will detect the vast majority of aSAH

Especially within 6 hours of symptom onset

If the CT is negative for SAH, for additional workup:

Traditionally a lumbar puncture is performed

More recently, CT angiogram is also utilized

SAH: After the Diagnosis

- **Securing the aneurysm**
  - Risk of rebleeding
  - Lower blood pressure (SBP goal ~140 mmHg)
  - Reverse anticoagulation
- **Coiling vs. clipping**

Coiling: an endovascular procedure
Clipping: a neurosurgical procedure

SAH: After the Diagnosis

Secure the aneurysm

Prolonged ICU course follows

ICU care for 10 to 21 days to monitor for complications

Vasospasm

- Long term complications:
  Lack of adequate blood flow to brain, permanent damage can result

- Vasospasm is an incomplete term
  - More accurately "***delayed cerebral ischemia***"
  - Highest risk: days ~5 to 10 after SAH, but can vary substantially

Delayed Cerebral Ischemia (DCI)

"Delayed Neurological Deterioration"

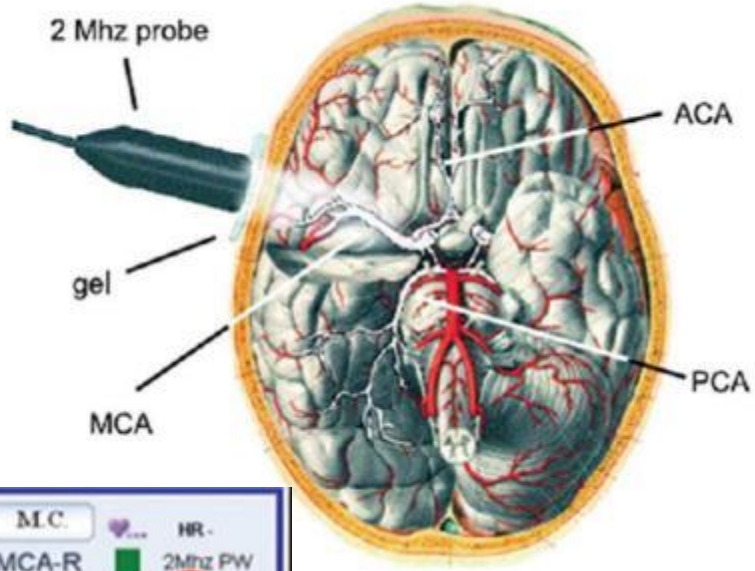
Multifactorial:

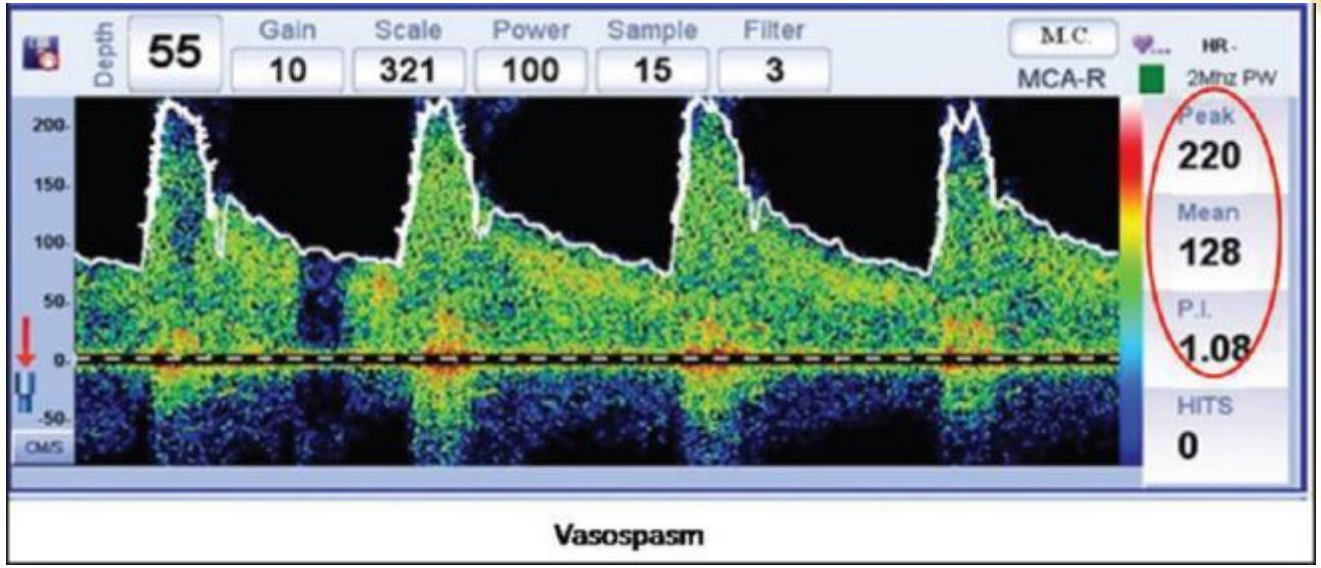
Not only vasospasm

- Cerebral vascular dysregulation
- Coagulation
- Cortical spreading depolarizations
- Neuroinflammation

DCI: Monitoring for Vasospasm

- Change in neurological examination
- Transcranial Doppler
- CT Angiogram
- Angiogram





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DCI Treatment

Nimodipine

- Calcium channel antagonist
- The only approved medication for aSAH in many countries

SAH ICU Treatment

- **Traditionally "Triple H" therapy**

  Hypervolemia, **H**ypertension, **H**emodilution

- Hypertension
  - Often patients "autoregulate" – i.e., BP will naturally increase
  - Pressors to induce hypertension
    - Improvement in neurologic status?

- Maintain normovolemia
  - Very close monitoring of fluid status
  - Give IV fluid boluses as needed

SAH ICU Treatment

- **Maintain normonatremia**
  - Treat abnormal blood sodium level
  - Salt wasting, SIADH, diabetes insipidus
  - Salt tablets, hypertonic saline infusion, fluid replacement
- **Maintain normothermia**
  - Treat fever TTM (hypothermia) devices if needed

SAH ICU Treatment

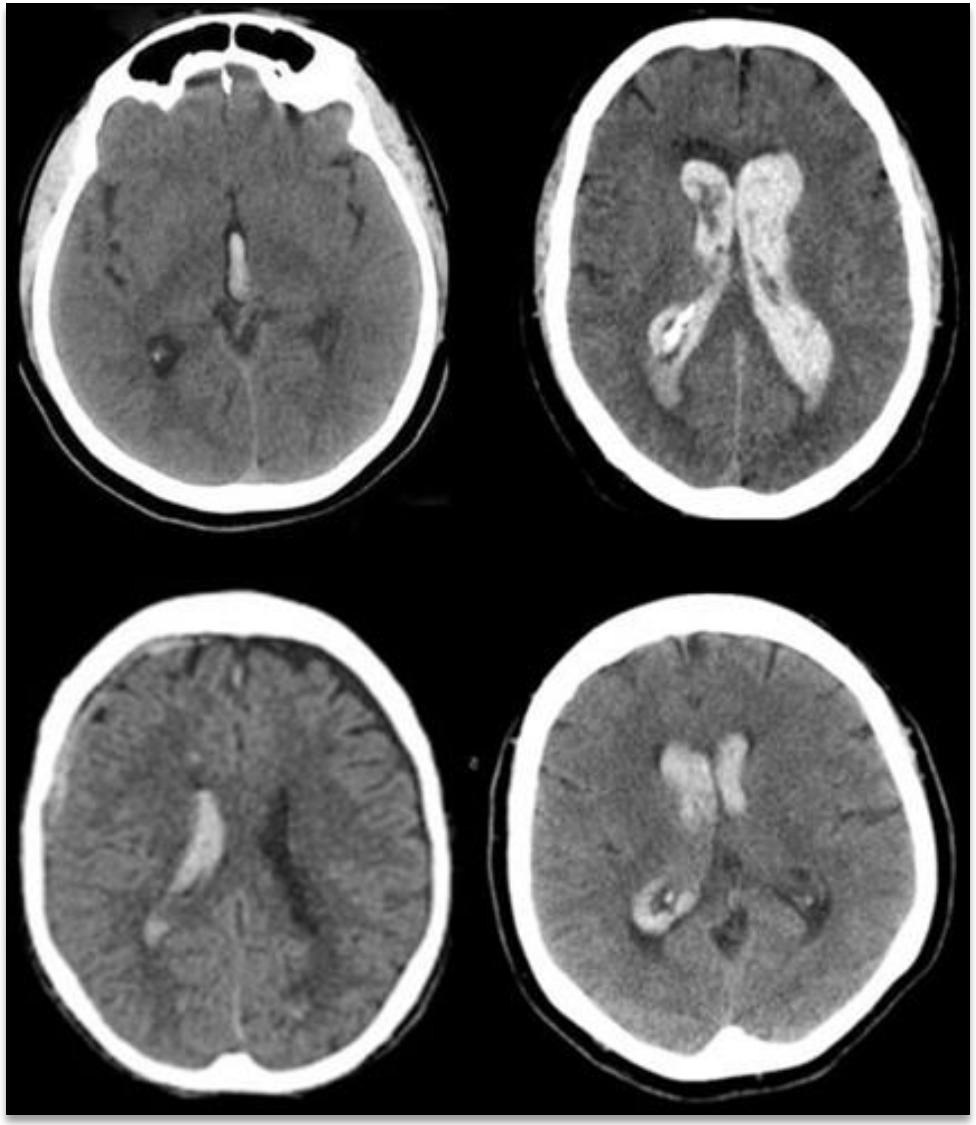
- **Maintain normoglycemia**
  - Hyperglycemia associated with poor outcomes
  - Treat glucose >180 mg/dL (???)
  - Risk of hypoglycemia
  - Maybe a higher glucose threshold is reasonable for SAH?

SAH ICU Treatment

A difficult hospital course

- 10 to 21 days in the ICU
- Neuro checks every hour
- Deterioration occurring ~1 week or more into the stay

Intraventricular Hemorrhage - IVH



Intraventricular Hemorrhage - IVH

External Ventricular Drain (EVD)

Reversal of Anticoagulation

Treatments

- ***Vitamin K Antagonists (Warfarin)***
  - ***Reversal***
- Direct Oral Anticoagulants (DOACs, aka NOACs)
  - Monitoring of levels and Reversal
- Antiplatelet agents

Anticoagulation

Medical history and medication list should be obtained as soon as possible

- Specifically, use of anticoagulant medication
  - When last dose was taken
- Urgent laboratory tests
  - CBC with platelet count, INR, Anti-factor Xa level?

Vitamin K Antagonists

- Recommend treatment for INR >1.4
- Vitamin K: 10 mg IV
- Fresh Frozen Plasma (FFP) vs. Prothombin Complex Concentrates (PCC)

- **FFP:** Contains all coagulation factors present in plasma
  - Factors I (fibrinogen), II, V, VII, IX, X, XI, XIII, and antithrombin
  - Large volumes of transfusion are often needed (10-15 ml/kg)
  - Time to prepare and administer

Vitamin K Antagonists

- Fresh Frozen Plasma (FFP) vs. Prothombin Complex Concentrates (PCC)

- **PCC:**
  - 3 Factor: 2, 9, 10
  - 4 Factor: 2, 7, 9, 10
  - Activated vs. inactivated
  - Faster reversal, less volume

FFP vs. PCC

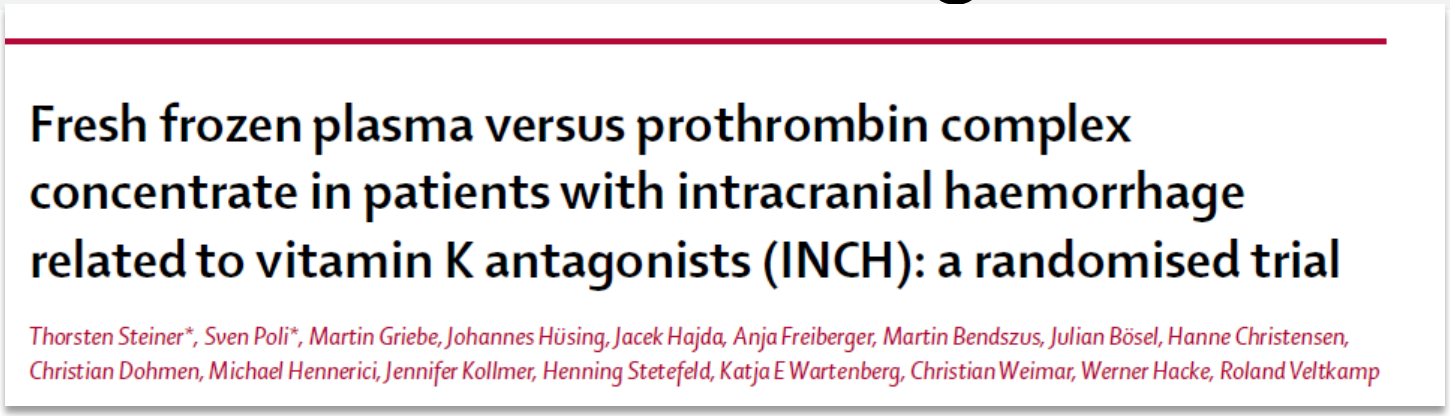
Pre-treatment INR	2–< 4	4–6	> 6
Dose of Kcentra (units of Factor IX) / kg body weight	25	35	50
Maximum dose (units of Factor IX)	Not to exceed 2500	Not to exceed 3500	Not to exceed 5000

PCC: 100 kg patient receives 2500 units in **100 mL** administered over **12 minutes**

FFP: 100 kg patient receives **1500 mL** administered over **150 minutes**

Kcentra®, Full Prescribing Information, CSL Behring

Vitamin K Antagonists



Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): a randomised trial

Thorsten Steiner, Sven Poli*, Martin Griebe, Johannes Hüsing, Jacek Hajda, Anja Freiberger, Martin Bendszus, Julian Bösel, Hanne Christensen, Christian Dohmen, Michael Hennerici, Jennifer Kollmer, Henning Stetefeld, Katja E Wartenberg, Christian Weimar, Werner Hacke, Roland Veltkamp*

- Randomized, open-label, blinded-endpoint trial
- ICH patients ≥ 18 years with VKA therapy
  - Within 12 hours of symptom onset
  - INR ≥ 2.0
- **FFP** 20 mL/kg or **4 factor PCC** 30 IU/kg within 1 hour of initial CT scan

INCH Trial

- Primary outcome: INR ≤ 1.2 within 3 hours of treatment
- 54 patients randomized and 50 received study drug
- Trial terminated early for safety
- 9% (n=2) FFP treated patients and 67% (n=18) PCC treated patients reached the primary endpoint
- PCCs seemed to be associated with less hematoma expansion

Rate of INR Correction

- Retrospective study, 55 ICH patients taking warfarin
- Outcome: ICH hematoma growth
- The differences between PCC and FFP no longer existed if INR was reversed within 2 hours

Outline

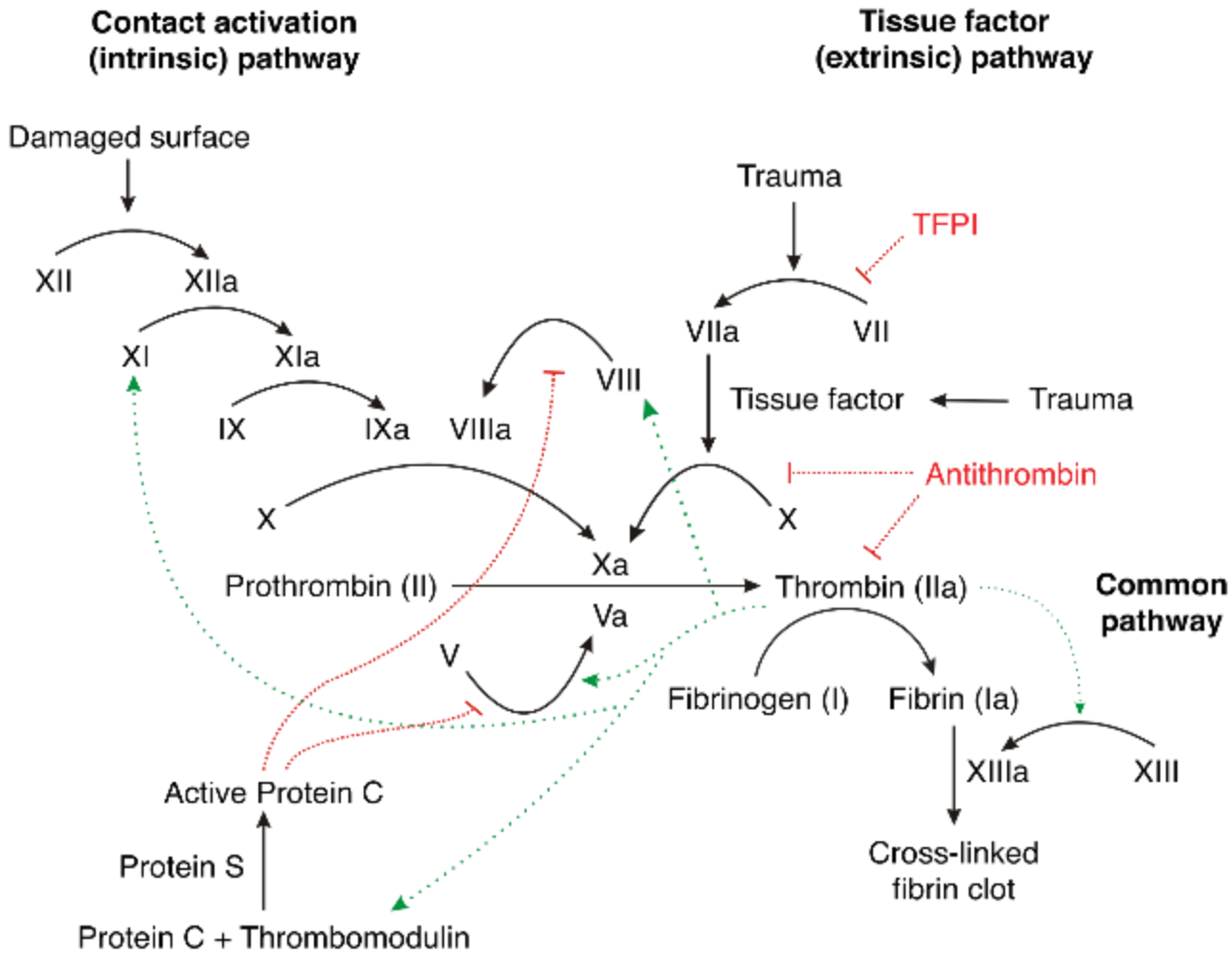
- Background: ICH Volume, Spot Sign, ICH Score
- Hematoma Expansion
  - Elevated Blood Pressure
  - Vitamin K Antagonists (Warfarin)
    - Reversal
  - ***Direct Oral Anticoagulants (DOACs, aka NOACs)***
    - ***Monitoring of levels and Reversal***
  - Antiplatelet agents

Dabigatran (Pradaxa®)

- Direct Thrombin Inhibitor (DTI)
- Inhibits thrombin preventing conversion of fibrinogen to fibrin
- FDA approved in October 2010

Rivaroxaban (Xarelto®)

- Factor Xa inhibitor, reduces thrombin production
- FDA approved July 2011



Apixaban (Eliquis®)

The NEW ENGLAND JOURNAL of MEDICINE

Apixaban versus Warfarin in Patients with Atrial Fibrillation

Authors: Christopher B. Granger, M.D., John H. Alexander, M.D., M.H.S., John J.V. McMurray, M.D., Renato D. Lopes, M.D., Ph.D., Elaine M. Hylek, M.D., M.P.H., Michael Hanna, M.D., Hussein R. Al-Khalidi, Ph.D., +25 , for the ARISTOTLE Committees and Investigators* Author Info & Affiliations

Published September 15, 2011 | N Engl J Med 2011;365:981-992 | DOI: 10.1056/NEJMoa1107039

VOL. 365 NO. 11 | Copyright © 2011

- Factor Xa inhibitor, reduces thrombin production
- FDA Approval December 2012

Idarucizumab (Praxbind®)

The NEW ENGLAND JOURNAL of MEDICINE

Idarucizumab for Dabigatran Reversal

Authors: Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., +10 , and Jeffrey I. Weitz, M.D. Author Info & Affiliations

Published August 6, 2015 | N Engl J Med 2015;373:511-520 | DOI: 10.1056/NEJMoa1502000 | VOL. 373 NO. 6

- Interim analysis: 90 patients
- Conclusion: "Idarucizumab completely reversed the anticoagulation effects of dabigatran within minutes."

Idarucizumab For Dabigatran Reversal

- Clinical outcomes:
  - In patients with serious bleeding, hemostasis restored at a median of 11.4 hours
    - Difficult to assess in patients, e.g. with intracranial or retroperitoneal bleeding

- Adverse events: DVT and PE 2 days after treatment in 1 patient
- All other thrombotic events: 7 days or longer after treatment

Andexanet alfa (Andexxa®)

Xa Inhibitor Reversal – Rivaroxaban, Apixaban

- Coagulation factor Xa (recombinant)
- Modified Xa decoy protein
- FDA approved May 2018

Andexanet alfa (Andexxa®)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors

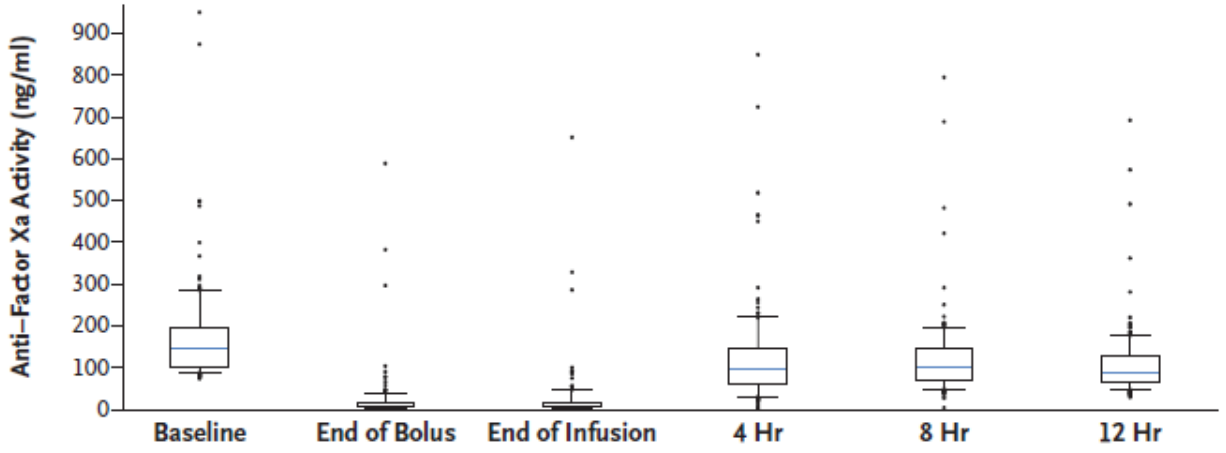
S.J. Connolly, M. Crowther, J.W. Eikelboom, C.M. Gibson, J.T. Curnutte, J.H. Lawrence, P. Yue, M.D. Bronson, G. Lu, P.B. Conley, P. Verhamme, J. Schmidt, S. Middeldorp, A.T. Cohen, J. Beyer-Westendorf, P. Albaladejo, J. Lopez-Sendon, A.M. Demchuk, D.J. Pallin, M. Concha, S. Goodman, J. Leeds, S. Souza, D.M. Siegal, E. Zotova, B. Meeks, S. Ahmad, J. Nakamya, and T.J. Milling, Jr., for the ANNEXA-4 Investigators*

N ENGL J MED 380;14 NEJM.ORG APRIL 4, 2019

ANNEXA-4

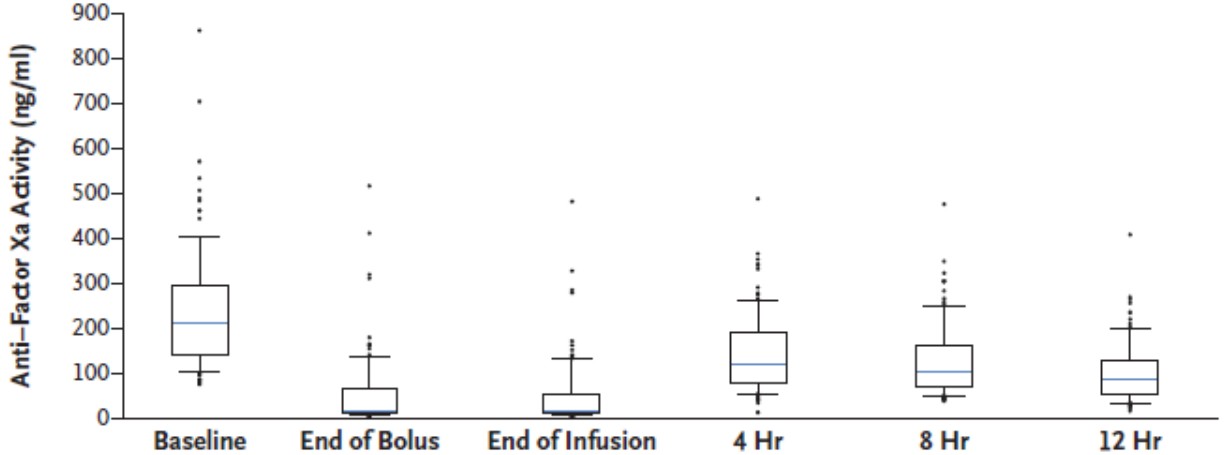
- 479 patients with acute major bleeding
  - Within 18 hours of taking Xa inhibitor
  - 64% of patients with intracranial bleeding
- 80% (273/342) of patients had excellent or good hemostasis
- For Apixaban and Rivaroxaban:
  - 93% decrease in Anti Factor Xa activity

A Patients Who Received Apixaban



	Baseline	End of Bolus	End of Infusion	4 Hr	8 Hr	12 Hr
Median	149.7	11.1	11.5	97.2	104.6	91.2
Percent Change		–92	–92	–32	–34	–38
(95% CI)		(–93 to –91)	(–93 to –91)	(–38 to –29)	(–36 to –27)	(–41 to –34)

B Patients Who Received Rivaroxaban

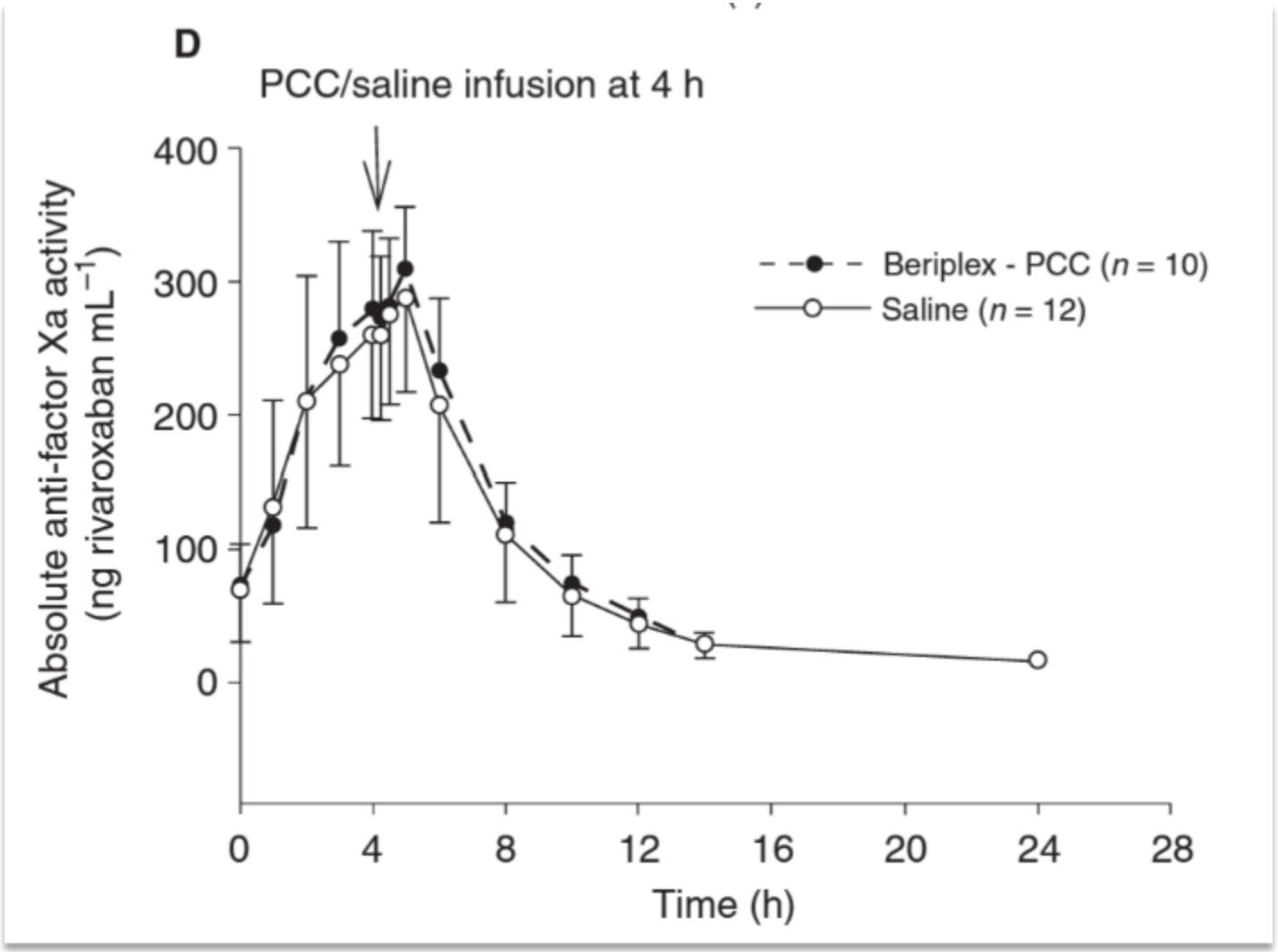


	Baseline	End of Bolus	End of Infusion	4 Hr	8 Hr	12 Hr
Median	211.8	14.2	16.5	121.7	101.4	85.5
Percent Change		–92	–90	–42	–48	–62
(95% CI)		(–94 to –88)	(–93 to –87)	(–45 to –36)	(–52 to –45)	(–65 to –58)

DOACs

- **Rivaroxaban, Apixaban**
- Factor Xa inhibitors

- PCCs for reversal of Apixaban or Rivaroxaban?
  - No known effect on Anti factor Xa levels


D
PCC/saline infusion at 4 h
Absolute anti-factor Xa activity
(ng rivaroxaban mL^{-1})
400
300
200
100
0
0
4
8
12
16
20
24
28
Time (h)
Beriplex - PCC (n = 10)
Saline (n = 12)

Retrospective, observational study of 3030 patients hospitalized for FXa inhibitor related bleeding:

Of the 3030 total subjects:

	In-hospital mortality	
	All	Intracranial
342 : Andexxa	4%	9%
733 : Kcentra	10%	25%
925 : FFP	11%	27%
794 : All other agents	8%	23%
438 : No reversal or replacement	8%	23%

Annexa I

Phase 4, randomized, multinational, open-label trial comparing Andexxa vs usual care in patients with intracerebral hemorrhage

(taking FXa inhibitor and within 6 hours of symptom onset)

Annexa I

Usual Care: 85.5% received PCCs

Table 2. Efficacy End Points.

End Point	Andexanet (N=224)	Usual Care (N=228)	Adjusted Difference per 100 Patients (95% CI)*	P Value*
	no./total no. (%)		*percentage points*	
Hemostatic efficacy	150/224 (67.0)	121/228 (53.1)	13.4 (4.6 to 22.2)	0.003
Hematoma volume change ≤35%†	165/215 (76.7)	137/212 (64.6)	12.1 (3.6 to 20.5)	
NIHSS score change <7 points	188/214 (87.9)	181/218 (83.0)	4.6 (–2.0 to 11.2)	
No receipt of rescue therapy between 3 hr and 12 hr	218/224 (97.3)	213/228 (93.4)	3.8 (–7.6 to 0.0)	
Hematoma volume increase ≥12.5 ml‡	24/216 (11.1)	36/214 (16.8)	–5.6 (–12.0 to 0.8)	
Hemostatic efficacy, excluding patients nonevaluable for administrative reasons	150/218 (68.8)	121/225 (53.8)	14.5 (5.7 to 23.4)	

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Annexa I

Table 3. Thrombotic Events and Deaths at 30 Days.*

Event	Andexanet (N=263)	Usual Care (N=267)	Increase per 100 Patients (95% CI)†	P Value†
	no. of patients (%)		*percentage points*	
≥1 Thrombotic event	27 (10.3)	15 (5.6)	4.6 (0.1 to 9.2)	0.048
Transient ischemic attack	0	0	—	
Ischemic stroke	17 (6.5)	4 (1.5)	5.0 (1.5 to 8.8)	
Myocardial infarction	11 (4.2)	4 (1.5)	2.7 (–0.2 to 6.1)	
Deep-vein thrombosis	1 (0.4)	2 (0.7)	–0.4 (–2.4 to 1.5)	
Pulmonary embolism	1 (0.4)	6 (2.2)	–1.9 (–4.5 to 0.2)	
Arterial systemic embolism	3 (1.1)	2 (0.7)	0.4 (–1.7 to 2.7)	
Death	73 (27.8)	68 (25.5)	2.5 (–5.0 to 10.0)	0.51

Andexxa or PCCs?

It Depends….

Take into account:

- ICH characteristics
- Underlying thrombotic risk
- Time from ICH onset
- Time from DOAC dose
- Lab testing?

Outline - ICH

- Background: ICH Score
- Hematoma Expansion
  - Elevated Blood Pressure
  - Vitamin K Antagonists (Warfarin)
    - Reversal
  - Direct Oral Anticoagulants (DOACs, aka NOACs)
    - Monitoring of levels and Reversal
  - ***Antiplatelet agents***

Antiplatelet Therapy

- **Antiplatelet agents:**
  - Aspirin
  - Clopidogrel (Plavix)

- **Anticoagulants**
  - Warfarin (Coumadin)
  - Dabigatran (Pradaxa)
  - Rivaroxaban (Xarelto)
  - Apixaban (Eliquis)

Antiplatelet Therapy

- Clinical practice widely varies for ICH patients taking antiplatelets
  - Empiric platelet transfusion
  - Potential transfusion pending platelet function tests
  - No platelet transfusion

PATCH TRIAL:

- 190 patients with supratentorial ICH
- Patient taking antiplatelet agents for ≥ 7 days, GCS ≥ 8
- Randomized to standard care vs. platelet transfusion (within 6 hrs of onset and 90 minutes of imaging)

Antiplatelet Therapy

PATCH trial *(continued)*

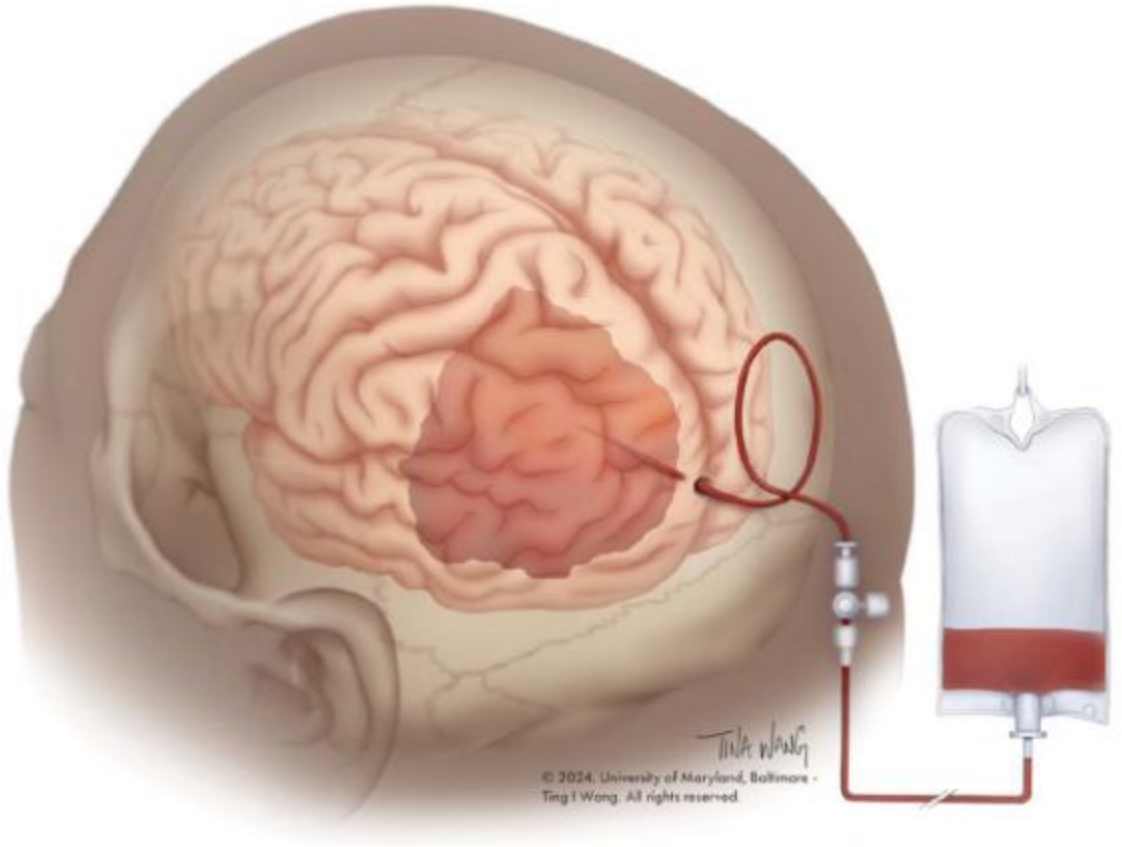
- More death/dependence at 3 months with platelet transfusion
  - Adjusted common odds ratio 2.05, P=0.0114
- Serious adverse event during hospital stay
  - **42%** with transfusion, **29%** with standard care
- Died during hospital stay
  - **24%** with transfusion, **17%** with standard care
- Most patients were on aspirin only
- Those undergoing neurosurgical procedures were excluded

Surgery?

- Negative trials of surgical evacuation (STICH, STICH II)

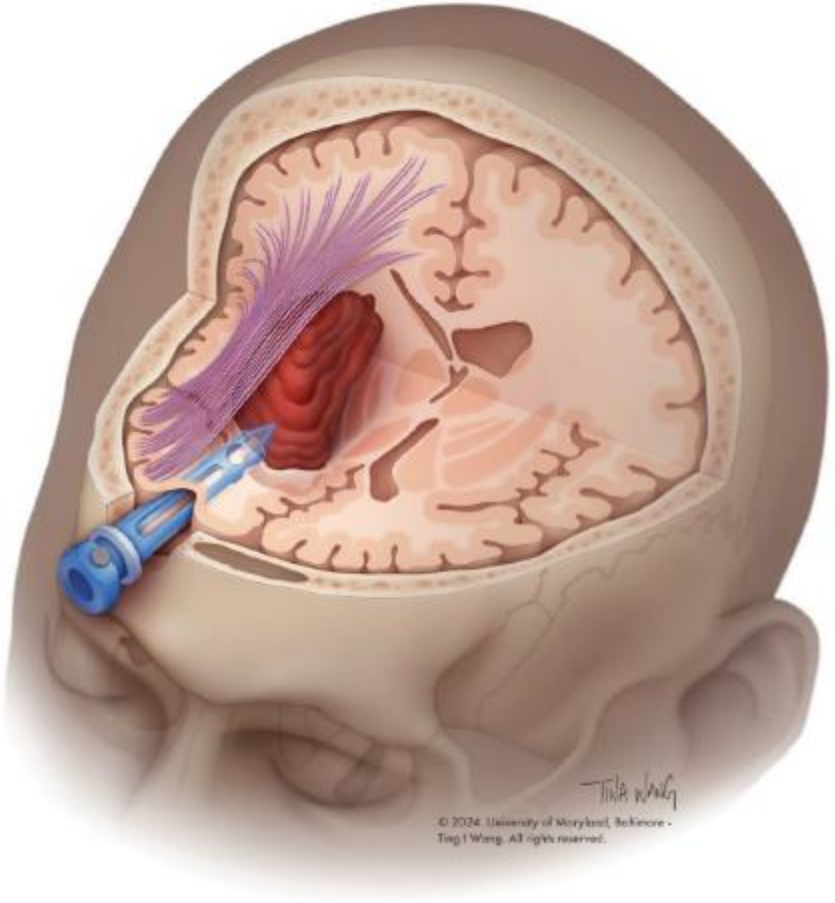
- MISTIE III Trial

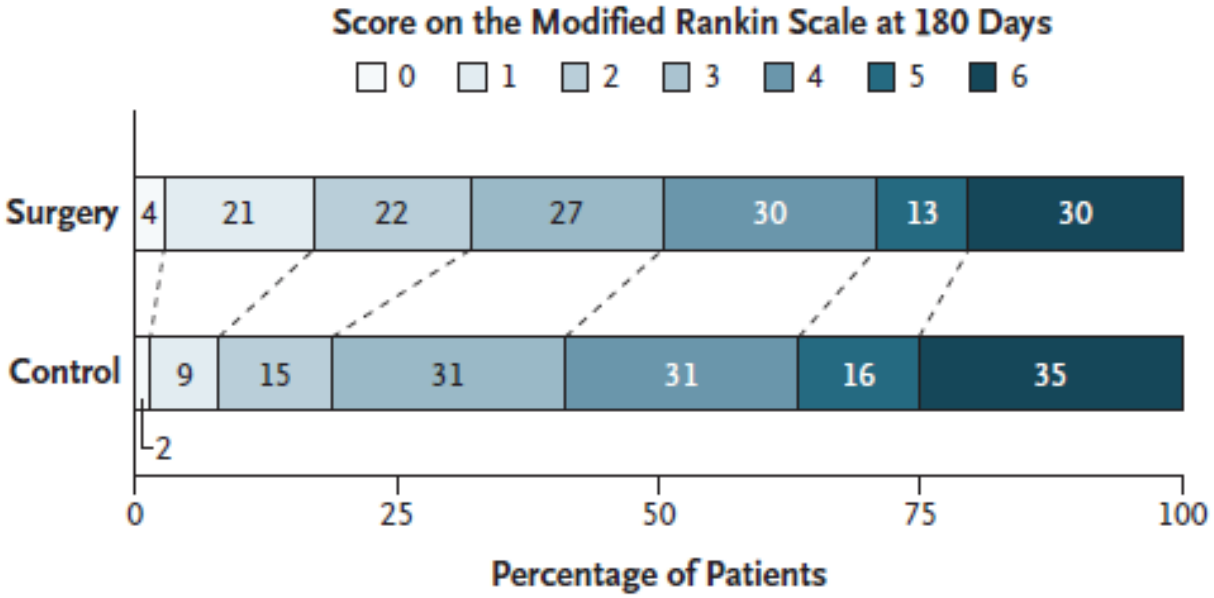
  Published March 2019



Surgery?

ENRICH Trial





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ENRICH – Who Qualifies?

Patients presenting with ICH:
2 to 4% eligible

Many exclusions (~22) including:

ICH volume < 30 cc,

disability pre-ICH, thalamic ICH, ESRD, Age >80, > 50% IVH

Stroke

BRIEF REPORT

Projecting US Population Eligibility for Minimally Invasive Surgical Evacuation of Intracerebral Hemorrhage

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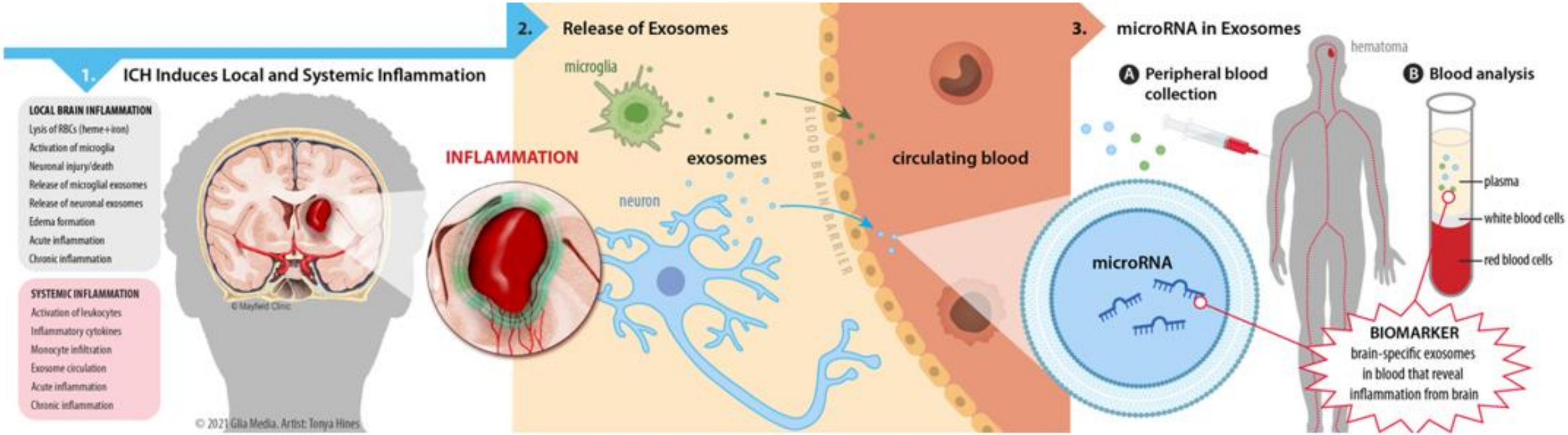
Conclusion - SAH

- Diagnosis
  - LP vs. CTA
- Blood pressure management
- Securing the aneurysm
  - Coiling vs. clipping
- Vasospasm/Delayed Cerebral Ischemia (DCI)
  - Nimodipine
  - Triple H Therapy
  - Other

Conclusion - ICH

ED/ICU Treatments

- Elevated Blood Pressure
- Vitamin K Antagonists (Warfarin)
  - Reversal
- Direct Oral Anticoagulants (DOACs, aka NOACs)
  - Monitoring of levels and Reversal
- Antiplatelet agents
- Surgery



UC STROKE TEAM

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THANK YOU

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