Acute Stroke management

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CANP state conference

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Overview

- Disclosures: None

- Epidemiology/Definition of stroke
- Guidelines for the assessment and treatment according to the American Heart Association
- Hemorrhagic stroke/Intracerebral hemorrhage (ICH) and the associated goals for care
- Recent and ongoing studies in ICH
- Case example

Objectives

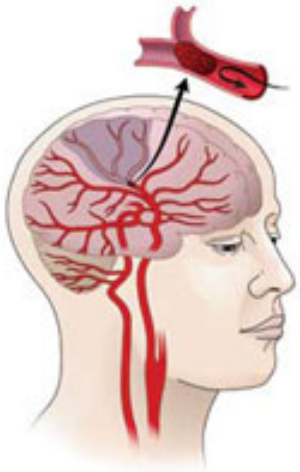
- Define the indications and contra-indications for tissue plasminogen activator (TPA) as a therapeutic agent.
- Understand assessment tools used in the evaluation of a patient suspected of having a stroke.
- Understand role of blood pressure management in the care of patients having suffered from hemorrhagic stroke.

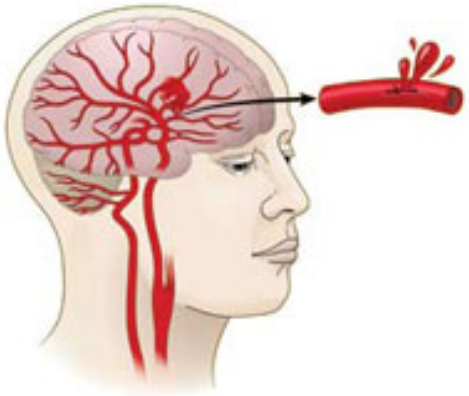
Definitions:

- A stroke, also known as a cerebrovascular accident (CVA), is the rapid loss of brain function(s) due to disturbance in the blood supply to the brain. This can be due to ischemia (lack of blood flow) caused by blockage (thrombosis, arterial embolism), or a hemorrhage (leakage of blood).

http://en.wikipedia.org/wiki/Stroke

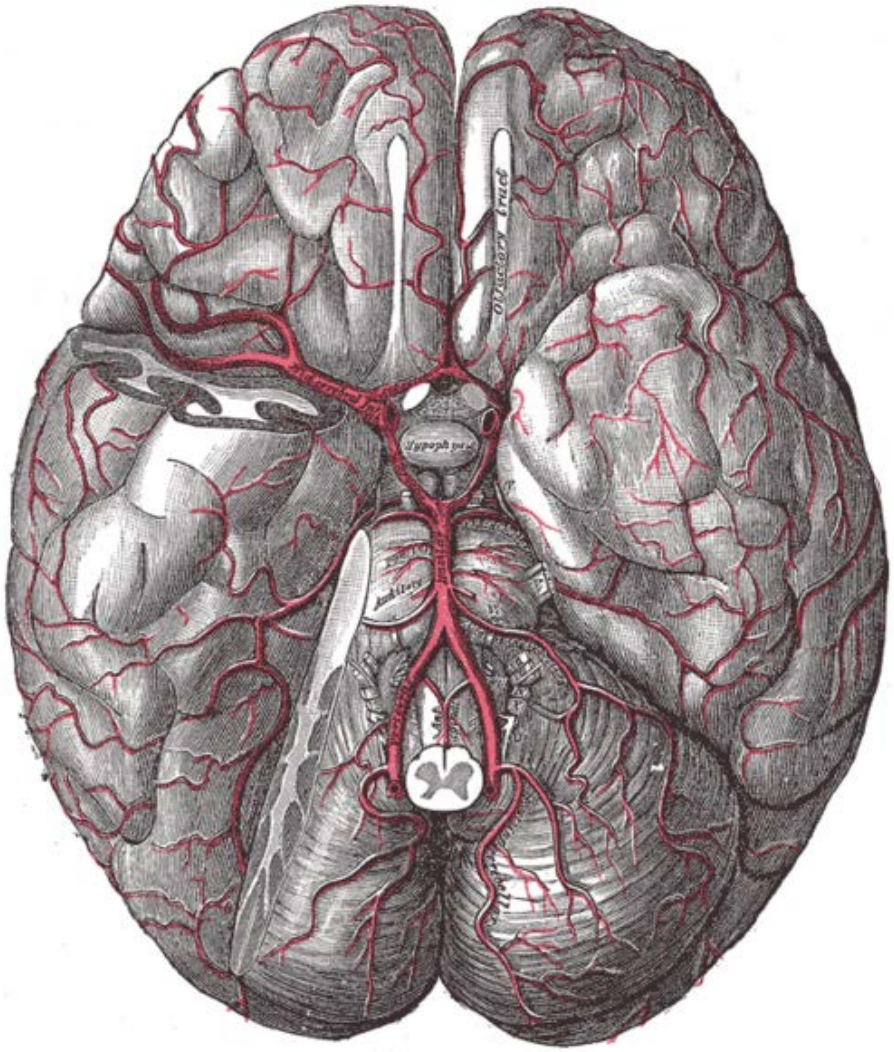
Pathophysiology of Stroke

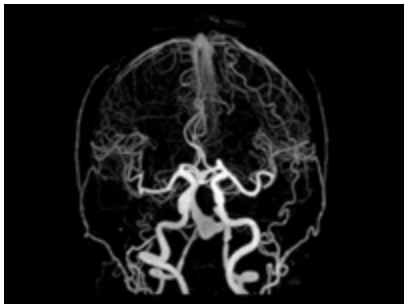




http://stroke.nih.gov/materials/strokechallenges.htm

Anatomy of cerebral vasculature





Brain facts

- Accounts for 2% body weight
- Receives 15% cardiac output
- 20% total body oxygen consumption
- 25% total body glucose utilization

Brain Anatomy

Epidemiology of Stroke

- About 795,000 Americans each year suffer a new or recurrent stroke. That means, on average, a stroke occurs every 40 seconds.
- Stroke kills more than 137,000 people a year. That's about 1 of every 18 deaths. It's the No. 3 cause of death.
- On average, every 4 minutes someone dies of stroke.
- About 40 percent of stroke deaths occur in males, and 60 percent in females.
- The 2006 stroke death rates per 100,000 population for specific groups were 41.7 for white males, 41.1 for white females, 67.7 for black males and 57.0 for black females.
- Americans will pay about $73.7 billion in 2010 for stroke-related medical costs and disability.

http://www.strokeassociation.org/STROKEORG/

Risk Factors

- **Uncontrollable Risk Factors:**
  - Age
  - Gender
  - Race
  - Family History
  - Previous Stroke or TIA
  - Fibromuscular Dysplasia
  - Patent Foramen Ovale

Risk factors

- **Controllable Risk Factors:**
  - High Blood Pressure
  - Atrial Fibrillation
  - High Cholesterol
  - Diabetes
  - Atherosclerosis
  - Circulation Problems
  - Tobacco Use and Smoking
  - Alcohol Use
  - Physical Inactivity
  - Obesity

Warning Signs of Stroke

Sudden numbness or weakness of the face, arm or leg, especially on one side of the body

Sudden confusion, trouble speaking or understanding

Sudden trouble seeing in one or both eyes

Sudden trouble walking, dizziness, loss of balance or coordination

Sudden, severe headache with no known cause

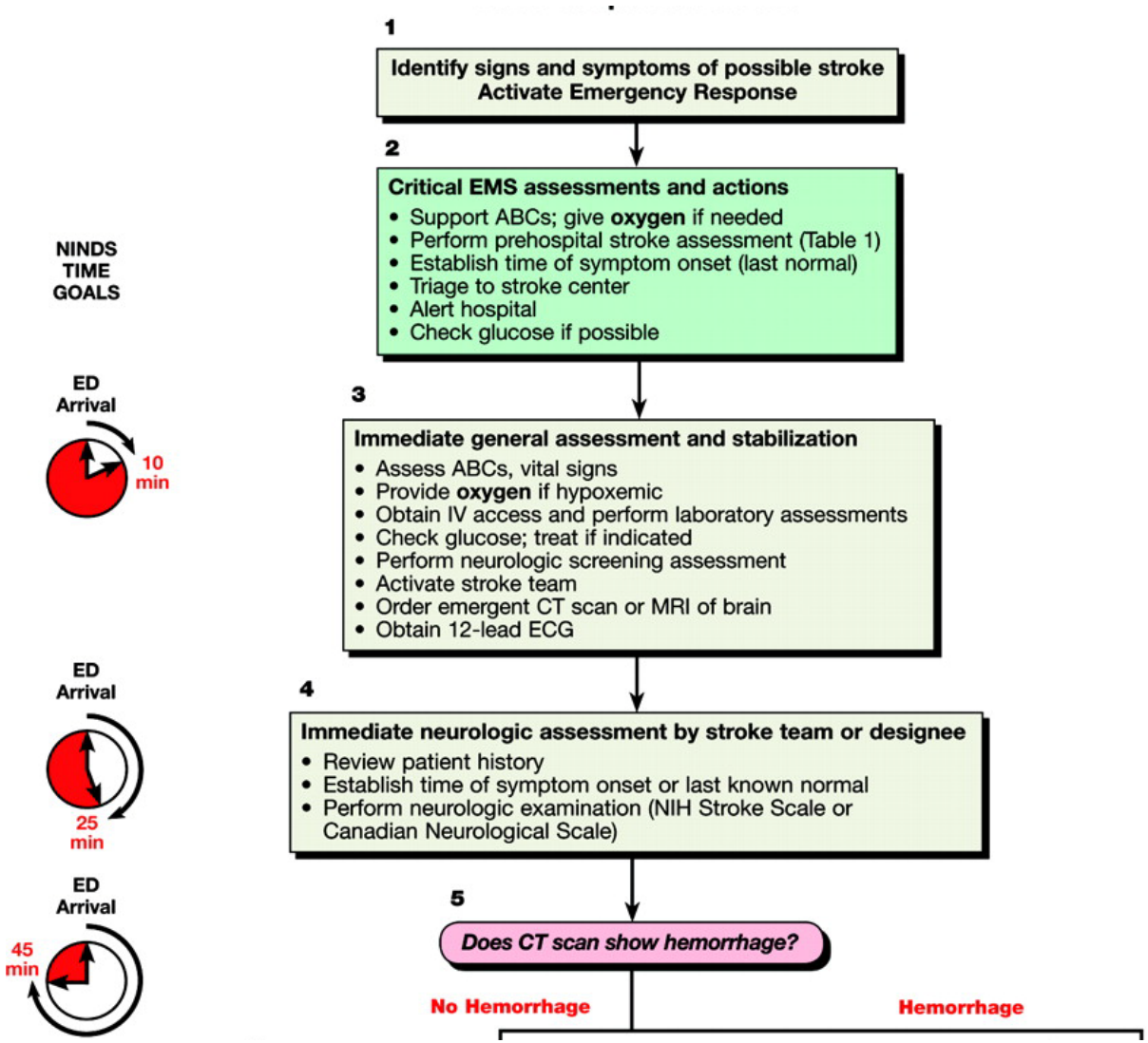
http://www.strokeassociation.org/STROKEORG/

Use the F.A.S.T. test for recognizing and responding to stroke symptoms:

- **F = FACE** Ask the person to smile. Does one side of the face droop?
- **A = ARMS** Ask the person to raise both arms. Does one arm drift downward?
- **S = SPEECH** Ask the person to repeat a simple sentence. Does the speech sound slurred or strange?
- **T = TIME** If you observe any of these signs, it’s time to call 9-1-1 or get to the nearest stroke center or hospital.


WITH A STROKE,
TIME LOST IS BRAIN LOST.

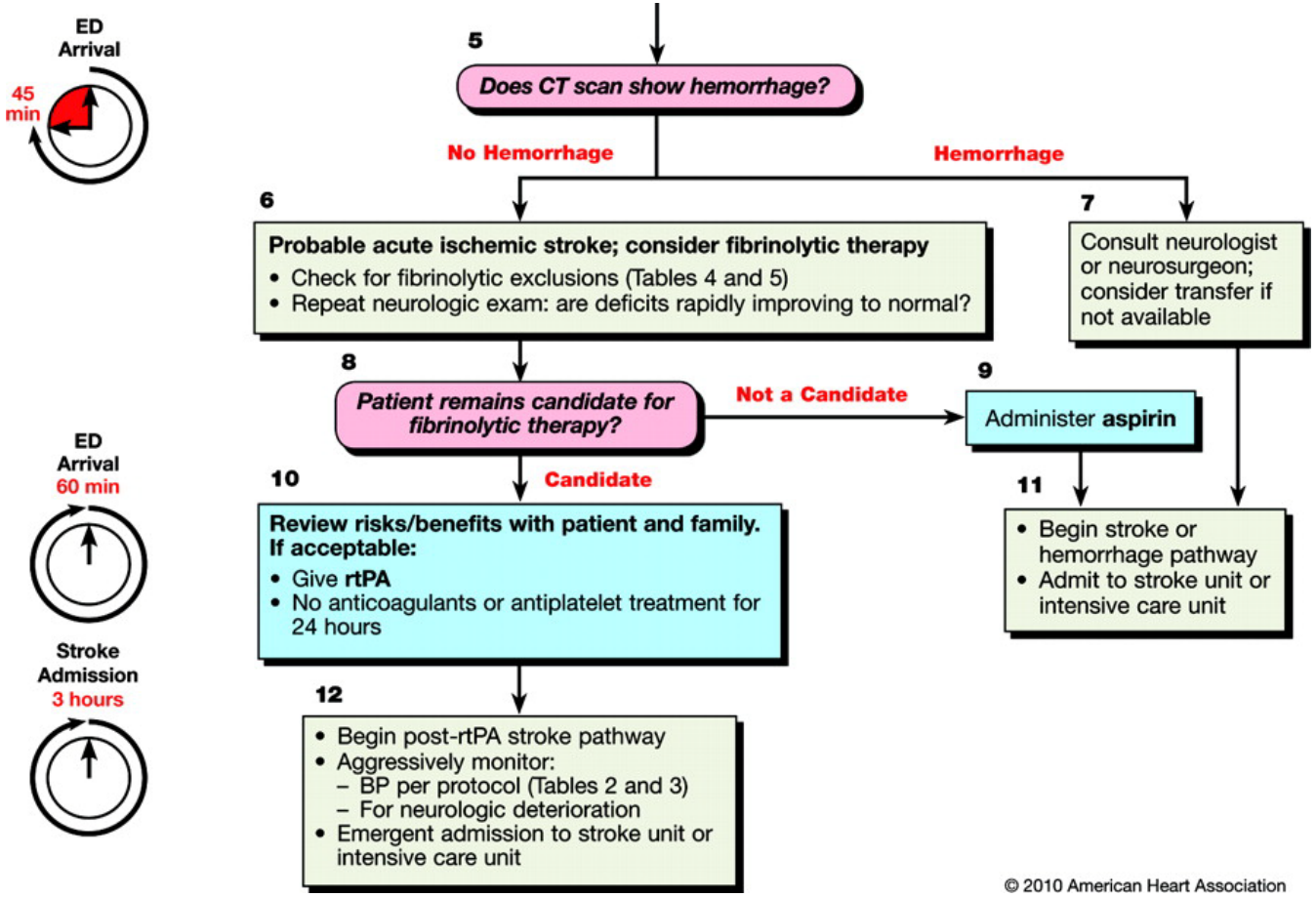
Goals for management of patients with suspected stroke.



Jauch E C et al. Circulation 2010;122:S818-S828

American Heart Association
Learn and Live

Goals for management of patients with suspected stroke.



Jauch E C et al. Circulation 2010;122:S818-S828

American Heart Association
Learn and Live

Assesment of Stroke

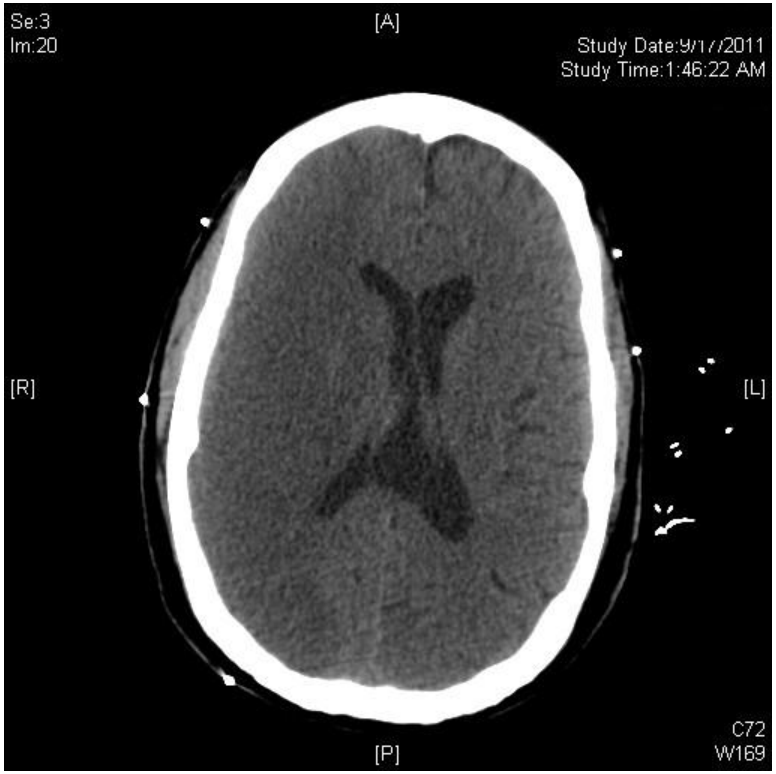
- National Institutes of Health Stroke Scale (NIHSS) - Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).

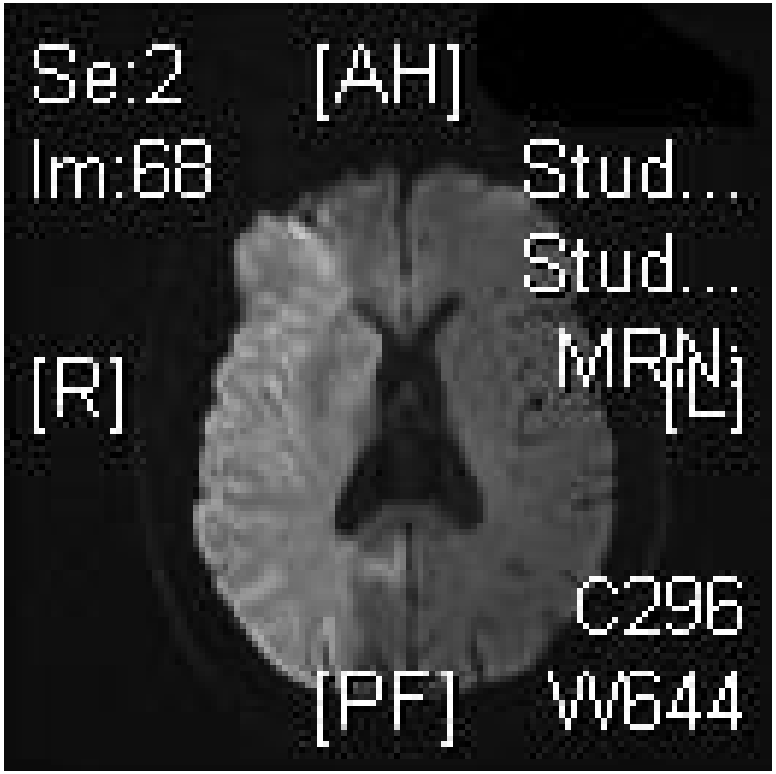
1A	Level of consciousness	0—alert 1—drowsy 2—obtunded 3—coma/unresponsive
1B	Orientation questions (2)	0—answers both correctly 1—answers one correctly 2—answers neither correctly
1C	Response to commands (2)	0—performs both tasks correctly 1—performs one task correctly 2—performs neither
2	Gaze	0—normal horizontal movements 1—partial gaze palsy 2—complete gaze palsy
3	Visual fields	0—no visual field defect 1—partial hemianopia 2—complete hemianopia 3—bilateral hemianopia
4	Facial movement	0—normal 1—minor facial weakness 2—partial facial weakness 3—complete unilateral palsy
5	Motor function (arm) a. Left b. Right	0—no drift 1—drift before 5 seconds 2—falls before 10 seconds 3—no effort against gravity 4—no movement

6	Motor function (leg)	0—no drift
	a. Left	1—drift before 5 seconds
	b. Right	2—falls before 5 seconds
		3—no effort against gravity
		4—no movement
7	Limb ataxia	0—no ataxia
		1—ataxia in 1 limb
		2—ataxia in 2 limbs
8	Sensory	0—no sensory loss
		1—mild sensory loss
		2—severe sensory loss
9	Language	0—normal
		1—mild aphasia
		2—severe aphasia
		3—mute or global aphasia
10	Articulation	0—normal
		1—mild dysarthria
		2—severe dysarthria
11	Extinction or inattention	0—absent
		1—mild (loss 1 sensory modality)
		2—severe (loss 2 modalities)

Imaging

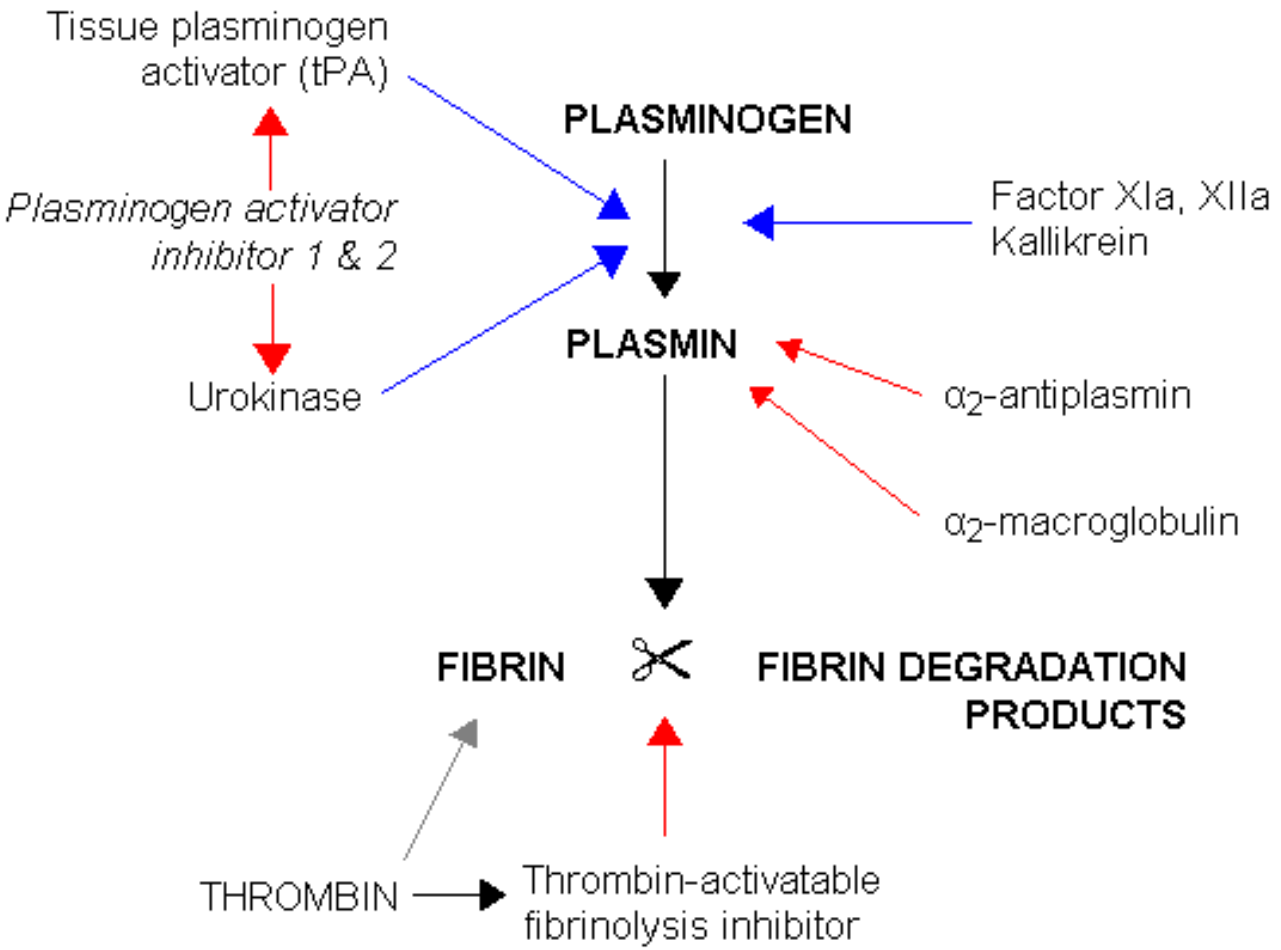
- CT
- MRI





Tpa

- What is it?



Tpa

- Role of medication: Intravenous administration of rtPA is the only FDA-approved medical therapy for treatment of patients with acute ischemic stroke.
- Inclusion Criteria
- Exclusion criteria

tPA IndicationsThese statements must be true in order to consider tPA administration:

- Ischemic stroke onset within 3 hours of drug administration.
- Measurable deficit on NIH Stroke Scale examination.
- Patient's computed tomography (CT) does not show hemorrhage or nonstroke cause of deficit.
- Patient's age is >18 years.

tPA Contraindications, Do NOT administer tPA if any of these statements are true:

- Patient's symptoms are minor or rapidly improving.
- Patient had seizure at onset of stroke.
- Patient has had another stroke or serious head trauma within the past 3 months.
- Patient had major surgery within the last 14 days.
- Patient has known history of intracranial hemorrhage.
- Patient has sustained systolic blood pressure >185 mmHg.
- Patient has sustained diastolic blood pressure >110 mmHg.
- Aggressive treatment is necessary to lower the patient's blood pressure.
- Patient has symptoms suggestive of subarachnoid hemorrhage.
- Patient has had gastrointestinal or urinary tract hemorrhage within the last 21 days.
- Patient has had arterial puncture at noncompressible site within the last 7 days.
- Patient has received heparin with the last 48 hours and has elevated PTT.
- Patient's prothrombin time (PT) is >15 seconds.
- Patient's platelet count is <100,000 uL.
- Patient's serum glucose is <50 mg/dL or >400 mg/dL.

tPA Relative Contraindications, If either of the following statements is true, use tPA with caution:

- Patient has a large stroke with NIH Stroke Scale score >22.
- Patient's CT shows evidence of large middle cerebral artery (MCA) territory infarction (sulcal effacement or blurring of gray-white junction in greater than 1/3 of MCA territory).

ECASS III data

Additional Inclusion and Exclusion Characteristics of Patients With Ischemic Stroke Who Could Be Treated With rtPA From 3 to 4.5 Hours From Symptom Onset

Inclusion criteria

- ● Diagnosis of ischemic stroke causing measurable neurologic deficit
- ● Onset of symptoms 3 to 4.5 hours before beginning treatment

Exclusion criteria

- ● Age 80 years
- ● Severe stroke (NIHSS 25)
- ● Taking an oral anticoagulant regardless of INR
- ● History of both diabetes and prior ischemic stroke

Notes

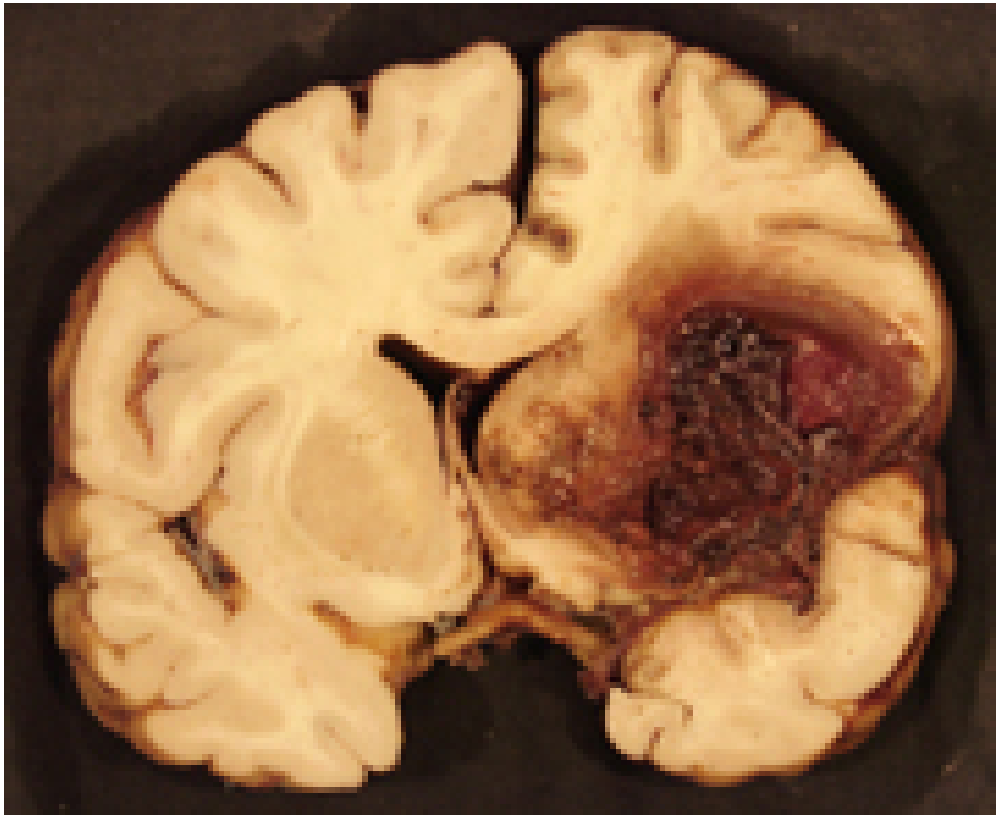
- ● The checklist includes some FDA-approved indications and
- contraindications for administration of rtPA for acute ischemic stroke.
- Recent guideline revisions have modified the original FDA criteria. A
- physician with expertise in acute stroke care may modify this list
- ● Onset time is either witnessed or last known normal
- ● In patients without recent use of oral anticoagulants or heparin, treatment
- with rtPA can be initiated before availability of coagulation study results
- but should be discontinued if INR is 1.7 or PT is elevated by local
- laboratory standards
- ● In patients without history of thrombocytopenia, treatment with rtPA can
- be initiated before availability of platelet count but should be discontinued
- if platelet count is 100 000/mm3

Jauch E C et al. Circulation 2010;122:S818-S828

Let’s change gears…

Intracerebral Hemorrhage

- ICH accounts for 10% of all stroke cases.



AHA/ASA Guideline

Guidelines for the Management of Spontaneous Intracerebral Hemorrhage

A Statement for Healthcare Professionals from the American Heart Association/American Stroke Association Council on Stroke
Co-Sponsored by the Council on Cardiovascular Nursing

The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.

The American Association of Neurological Surgeons (AANS) and Congress of Neurological Surgeons (CNS) have reviewed this document and affirm its educational content.

Morgenstern LB, et al; on behalf of the American Heart Association Stroke Council and Council on Cardiovascular Nursing. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2010: published online before print July 22, 2010, 10.1161/STR.0b013e3181ec611b.
http://stroke.ahajournals.org/cgi/reprint/STR.0b013e3181ec611b

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Definition of Classes and Levels of Evidence Used in AHA Stroke Council Recommendations

Class I	**Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective.**
Class II	**Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.**
Class IIa	**The weight of evidence or opinion is in favor of the procedure or treatment.**
Class IIb	**Usefulness/efficacy is less well established by evidence or opinion.**
Class III	**Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful.**

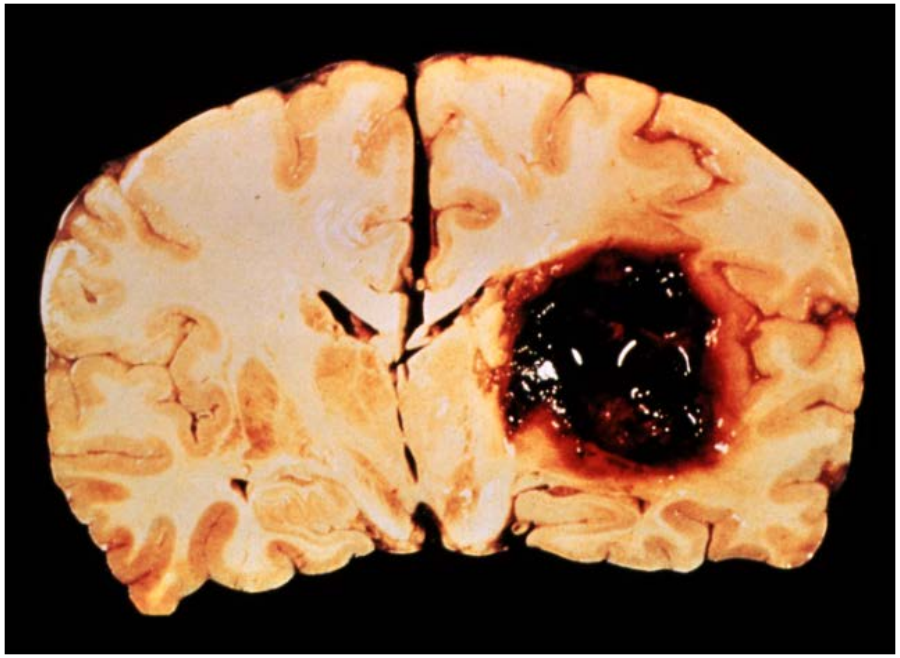
Therapeutic recommendations

Level of Evidence A	Data derived from multiple randomized clinical trials or metaanalyses
Level of Evidence B	Data derived from a single randomized trial or nonrandomized studies
Level of Evidence C	Consensus opinion of experts, case studies, or standard of care

Diagnostic recommendations

Level of Evidence A	Data derived from multiple prospective cohort studies using a reference standard applied by a masked evaluator
Level of Evidence B	Data derived from a single grade A study, or one or more case-control studies, or studies using a reference standard applied by an unmasked evaluator
Level of Evidence C	Consensus opinion of experts

Intracerebral Hemorrhage (ICH)



Gross specimen, coronal section of brain, large subcortical hypertensive ICH

Intracerebral Hemorrhage

Spontaneous, non-traumatic intracerebral hemorrhage (ICH) is a significant cause of morbidity and mortality throughout the world.

Excellent medical care has a potent, direct impact on ICH morbidity and mortality, even before a specific therapy is found.

The overall aggressiveness of ICH care is directly related to mortality from this disease.

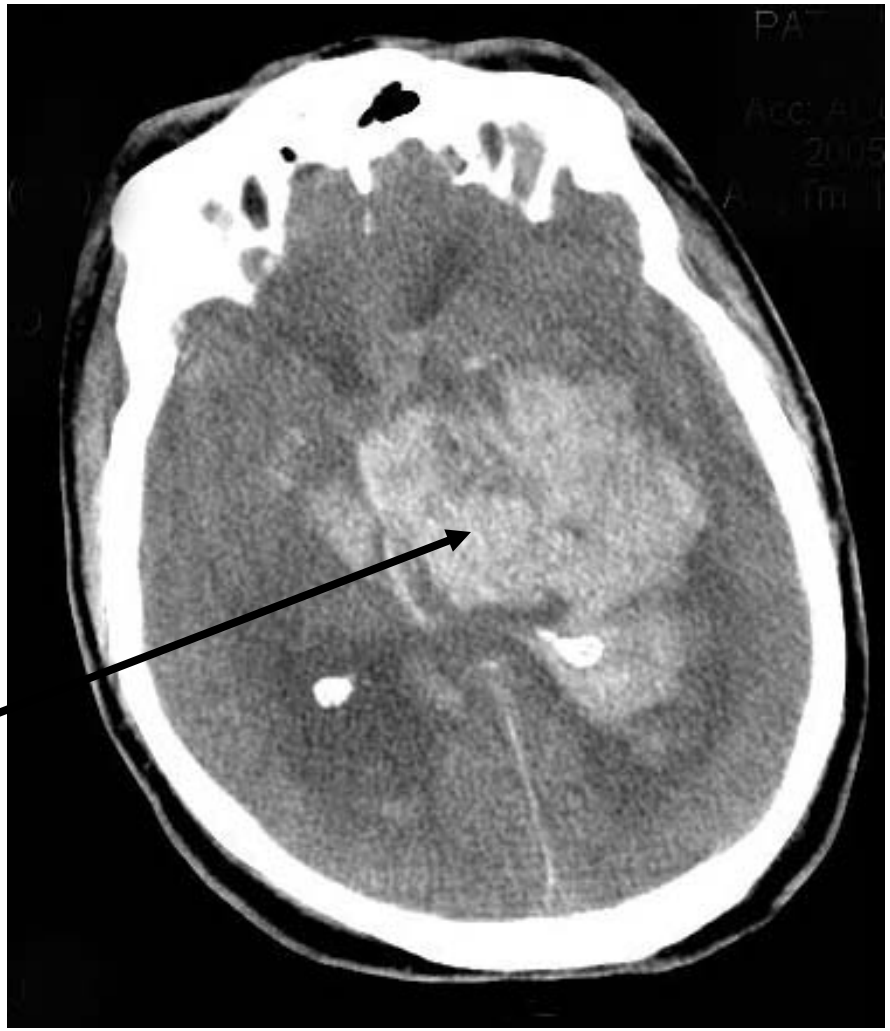
This guideline serves to update the prior guideline of 2007.

Presentation Content Areas

- Neuroimaging of ICH
- Hemostasis
- Blood pressure management
- Inpatient management and prevention of secondary injury
- Intracranial pressure (ICP)/glucose/seizures/hydrocephalus
- Surgical treatment of ICH
- Intraventricular hemorrhage
- Withdrawal of technological support
- Prevention of recurrent ICH
- Rehabilitation and recovery

Neuroimaging of ICH

Computed tomography (CT) scan showing Left hemisphere intracerebral hemorrhage (ICH) with intraventricular extravasation



Large left intraparenchymal hematoma (ICH)

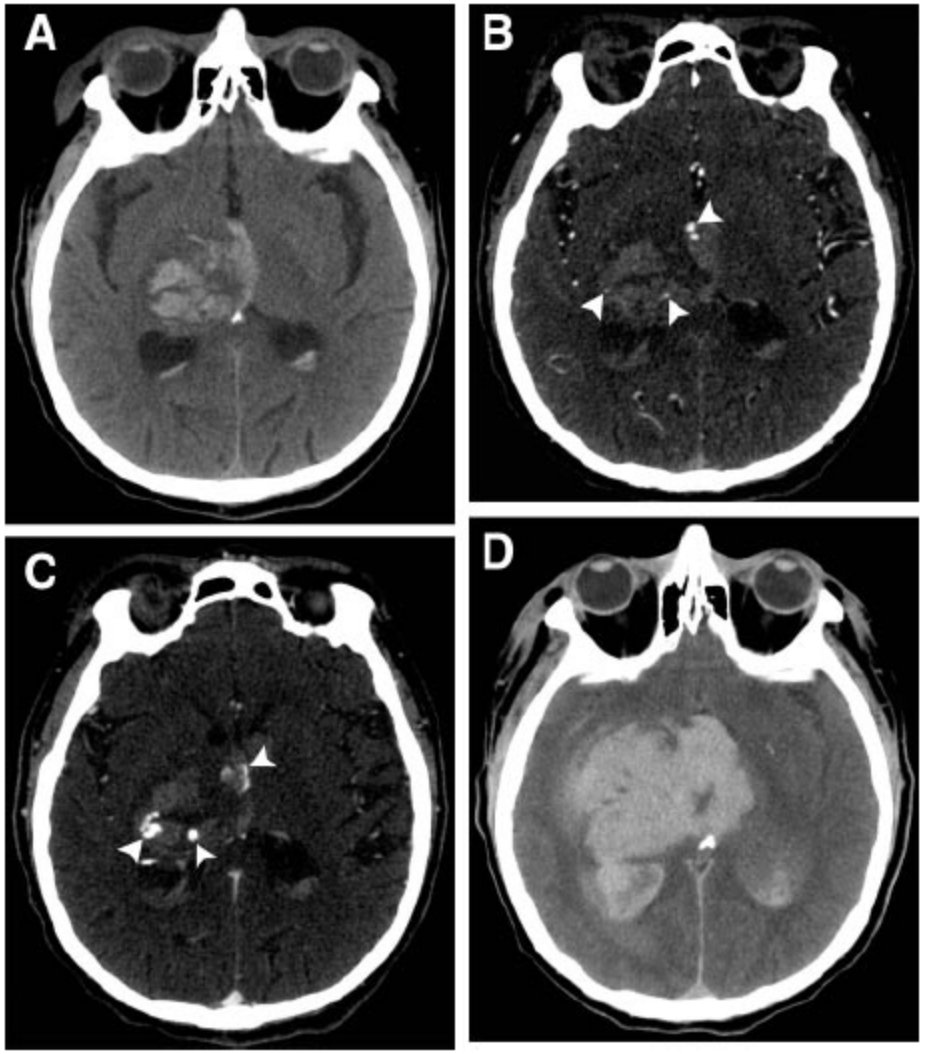
Image courtesy the UTHSCSA

Recommendations for Neuroimaging in ICH

Rapid neuroimaging with CT or MRI is recommended to distinguish ischemic stroke from ICH	**Class I, Level of Evidence A** *(Unchanged from the previous guideline).*
CT angiography and contrast-enhanced CT may be considered to help identify patients at risk for hematoma expansion	**Class IIb, Level of Evidence B**
CT angiography, CT venography, contrast-enhanced CT, contrast-enhanced MRI, MRA and MRV can be useful to evaluate for underlying structural lesions including vascular malformations and tumors when there is clinical or radiologic suspicion	**Class IIa, Level of Evidence B** (*New recommendation).*

CTA and ICH: SPOT sign

- CT contrast extravasates into hematoma
  - Spot sign, white arrows
- May predict hematoma expansion

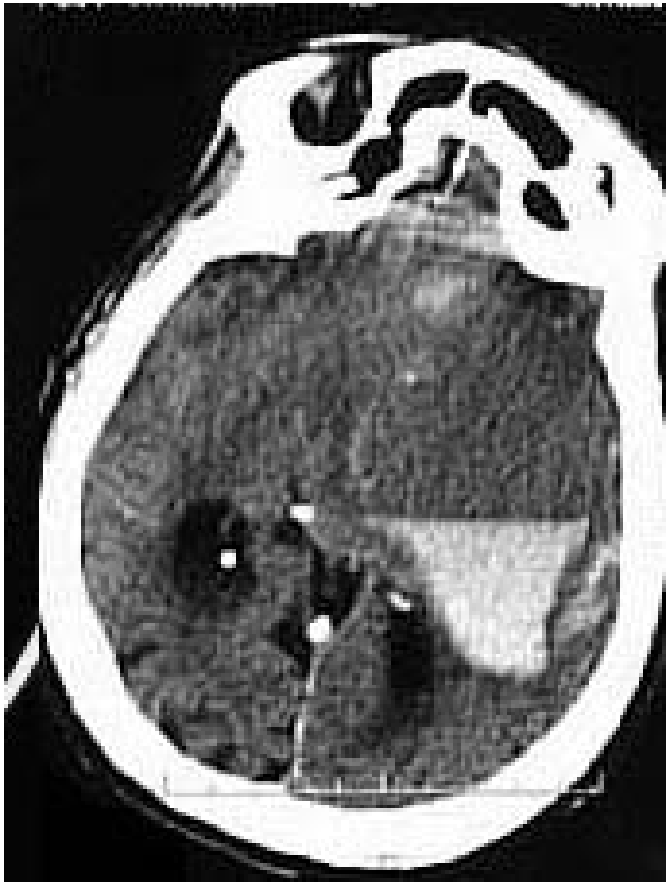


Delgado Almandoz et al. Stroke, 40 (9): 2994. 2009

Imaging of Underlying Structural Lesions?

- CTA/CTV, MRI with gadolinium, MRA/MRV can all be useful to evaluate for underlying structural lesions, including vascular malformations and/or tumors
  - When there is clinical or radiologic suspicion

Anticoagulation and ICH

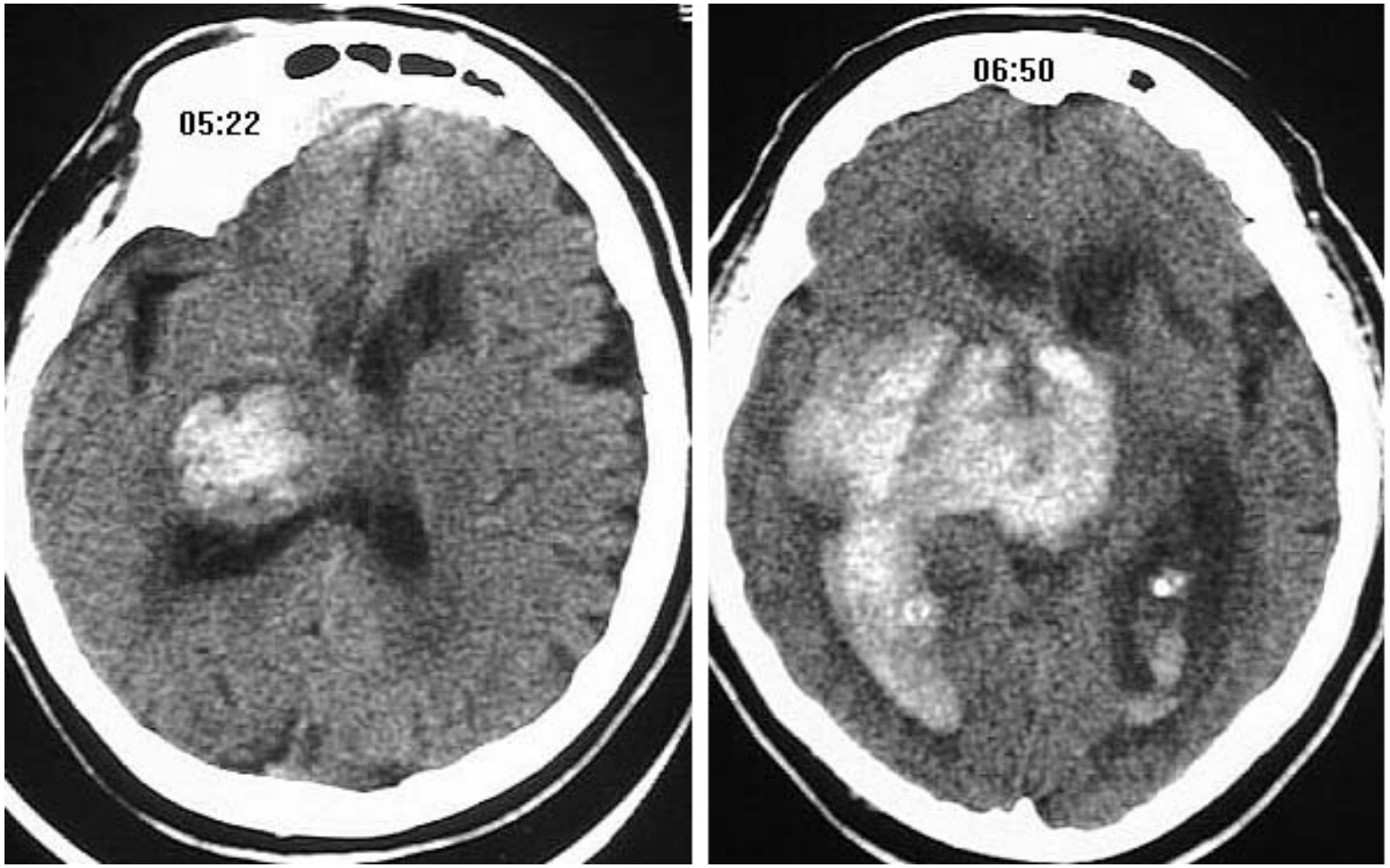


- Anticoagulation leads to more hematoma growth and higher mortality
  - Reverse warfarin promptly and aggressively
  - FFP or prothrombin complex concentrates (PCCs)
  - IV vitamin K
    - Faster than SQ/PO but a small risk of anaphylactoid reaction

Reversal of Anticoagulation in ICH patients

Patients with a severe coagulation factor deficiency or severe thrombocytopenia should receive appropriate factor replacement therapy or platelets, respectively	Class I, Level of Evidence C New Recommendation
Patients with ICH whose INR is elevated due to OAC's should have their warfarin withheld, receive therapy to replace vitamin K-dependent factors and correct the INR, and receive intravenous vitamin K	Class I, Level of Evidence C
PCCs have not shown improved outcome compared with FFP but may have fewer complications compared with FFP and are reasonable to consider as an alternative to FFP	Class IIa, Level of Evidence B
The usefulness of platelet transfusions in ICH patients with a history of antiplatelet use is unclear and is considered investigational	Class IIb, Level of Evidence B New Recommendation

Potential Treatments for ICH: The Problem of Hematoma Expansion



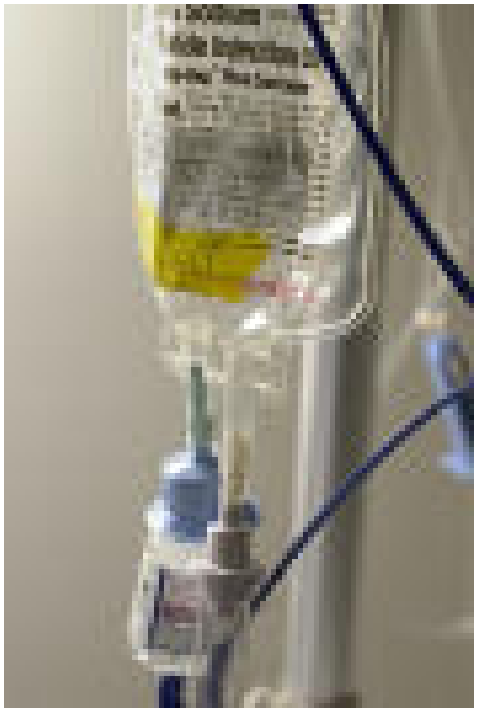
Hematoma Expansion is Common

- Brott, et al., 1997
  - 103 pts., prospective observational study with serial CT scanning (baseline, 1 hr and 20 hrs following ICH)
  - 26% showed >33% enlargement on 1 hr CT
  - 38% showed >33% enlargement on 20 hr CT
  - Neurologic deterioration correlated with hematoma expansion

Brott T et al, Stroke. 1997 Jan;28(1):1-5.

Recombinant Activated Factor VII*

- rFVIIa, NovoSeven©
- Used for hemophilia
- Induces local hemostasis when it binds to tissue factor
  - The complex can activate Factors IX and X
  - Factor Xa helps convert prothrombin to thrombin



*Not FDA approved for ICH

“FAST” Trials

- A phase II randomized trial showed that treatment with rFVIIa within four hours after ICH onset
  - limited hematoma growth
  - improved clinical outcomes relative to placebo
  - increased frequency of thromboembolic events (7% vs. 2%)

- A subsequent phase III study comparing placebo to 20 μg/kg and 80 μg/kg of rFVIIa:
  - both doses diminished hematoma enlargement
  - failed to show differences in clinical outcome
  - Overall serious thromboembolic adverse event rates were similar, the higher rFVIIa (80 μg/kg) group had significantly more arterial events than placebo.

- The authors noted imbalances in treatment groups, particularly intraventricular hemorrhage in the higher dose rFVIIa group

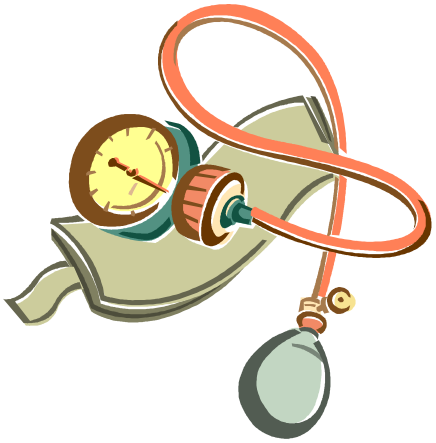
Mayer SA, et al for the FAST Trial Investigators., N Engl J Med. 2008 May 15;358(20):2127-37.
Mayer SA for the FAST Trial Investigators. N Engl J Med. 2005 Feb 24;352(8):777-85.

Factor VIIa

- Factor VIIa can limit hematoma expansion in non-coagulopathic patients, but also increases thromboembolic risk.
  - *rFVIIa is not recommended in unselected patients*
- rFVIIa does NOT replace clotting factors, even though INR normalizes
  - *rFVIIa is not recommended as the only agent to reverse INR in ICH patients*

Mayer SA, et al for the FAST Trial Investigators., N Engl J Med. 2008 May 15;358(20):2127-37.
Mayer SA for the FAST Trial Investigators. N Engl J Med. 2005 Feb 24;352(8):777-85.

Blood Pressure and ICH: Is it safe to lower BP in the acute setting?



INTERACT

- 404 ICH pts, randomized into:
  - Target SBP of 140mmHg within 1 hr OR
  - Target SBP of 180mmHg
- Trend towards lower hematoma growth
- No increase in adverse events related to BP-lowering
- No differences in clinical outcome/QOL
  - Not powered for clinical endpoints

Anderson CS, et al. *Lancet Neurol.* 2008;7(5):391-399.

ATACH

- 80 ICH pts
- 4-tier, dose escalation of IV nicardipine-based lowering of BP
- Confirmed safety and feasibility of early rapid BP lowering

Qureshi AI, et al, for the ATACH Investigators Arch Neurol. 2010 May;67(5):570-6.

Summary of New BP Lowering in ICH Trials

- These new studies have shown that intensive BP lowering is clinically feasible and potentially safe
- BP targets, duration of therapy is unknown
- No studies have shown clinical benefit so far

Blood Pressure Recommendations

Until ongoing clinical trials of BP intervention for ICH are completed, physicians must manage BP on the basis of the present incomplete efficacy evidence.	Class IIb, Level of Evidence C *Unchanged from the previous*
In patients presenting with a systolic BP of 150-220 mmHg, acute lowering of systolic BP to 140 mmHg is probably safe	Class IIa, Level of Evidence B *New recommendation*

Recommended BP Treatment Targets

- If SBP is >200 mmHg or MAP is >150 mm Hg, then consider aggressive reduction of blood pressure with continuous intravenous infusion, with frequent blood pressure monitoring every 5 minutes.

- If SBP is >180 mmHg or MAP is >130 mm Hg and there is the possibility of elevated ICP, then consider monitoring ICP and reducing blood pressure using intermittent or continuous intravenous medications while maintaining a cerebral perfusion pressure $\geq$ 60 mmHg.

Recommended BP Treatment Targets

- If SBP is >180 mmHg or MAP is >130 mm Hg and there is not evidence of elevated ICP, then consider a modest reduction of blood pressure (eg, MAP of 110 mm Hg or target blood pressure of 160/90 mm Hg) using intermittent or continuous intravenous medications to control blood pressure, and clinically reexamine the patient every 15 minutes.

ICP Monitoring and Ventriculostomy

Patients with a GCS score of 8 or less, those with clinical evidence of transtentorial herniation, or those with significant IVH or hydrocephalus might be considered for ICP monitoring and treatment. A CPP of 50-70 mmHg may be reasonable to maintain depending on the status of cerebral autoregulation	Class IIb, Level of Evidence C New recommendation
Ventricular drainage as treatment for hydrocephalus is reasonable in patients with decreased level of consciousness	Class IIa, Level of Evidence B New Recommendation
Although intraventricular administration of rt-PA in IVH appears to have a fairly low complication rate, efficacy and safety of this treatment is uncertain and is considered investigational	Class IIb, Level of Evidence B New Recommendation

STICH Trial

- 902 ICH pts randomized trial of early hematoma evacuation (<96 hrs) vs medical
  - Excluded cerebellar ICH
- If ICH >1 cm from cortical surface, OR

  GCS $\leq$ 8
  - Surgical patients tended to do worse than medical
- If ICH < 1cm from surface
  - Trended toward better outcomes with surgery, but not significant (OR 0.69, 95% CI 0.47-1.01)

Mendelow AD, et al for the STICH Investigators. *Lancet* 2005;365(9457):387-397

Surgical ICH Trials

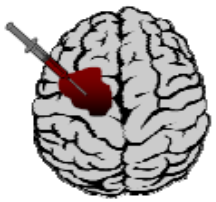
- Timing of surgery: What is “early”?
  - Trials have been done using <24, 48, 72, and 96 hours
  - Regardless of definition, no clear benefit for surgery
- Minimally invasive techniques are being studied

Surgical Recommendations

For most patients with ICH, the usefulness of surgery is uncertain	Class IIb, Level of Evidence New Recommendation
Patients with cerebellar hemorrhage who are deteriorating neurologically or who have brain stem compression and/or hydrocephalus from ventricular obstruction should undergo surgical removal of the hemorrhage as soon as possible	Class I, Level of Evidence B Revised recommendation
Initial treatment of these cerebellar hemorrhage patients with ventricular drainage alone rather than surgical evacuation is not recommended	Class III, Level of Evidence C). New Recommendation

Surgical Recommendations

For patients presenting with lobar clots >30 cc and within 1 cm of the surface, evacuation of supratentorial ICH by standard craniotomy might be considered	Class IIb, Level of Evidence B Updated recommendation
The effectiveness of minimally invasive clot evacuation utilizing either stereotactic or endoscopic aspiration with or without thrombolytic usage is uncertain and is considered investigational	Class IIb, Level of Evidence B New Recommendation
While theoretically attractive, no clear evidence at present indicates that ultra-early removal of supratentorial ICH improves functional outcome or mortality rate. Very early craniotomy may be harmful due to increased risk of recurrent bleeding	Class III, Level of Evidence B Revised from the previous guideline



Minimally Invasive (Stereotactic) Surgery + rt-PA for ICH Extraction (MISTIE)

A phase II, safety, and efficacy study of ICH treatment
Sponsored by the NIH/NINDS

Leadership 2012

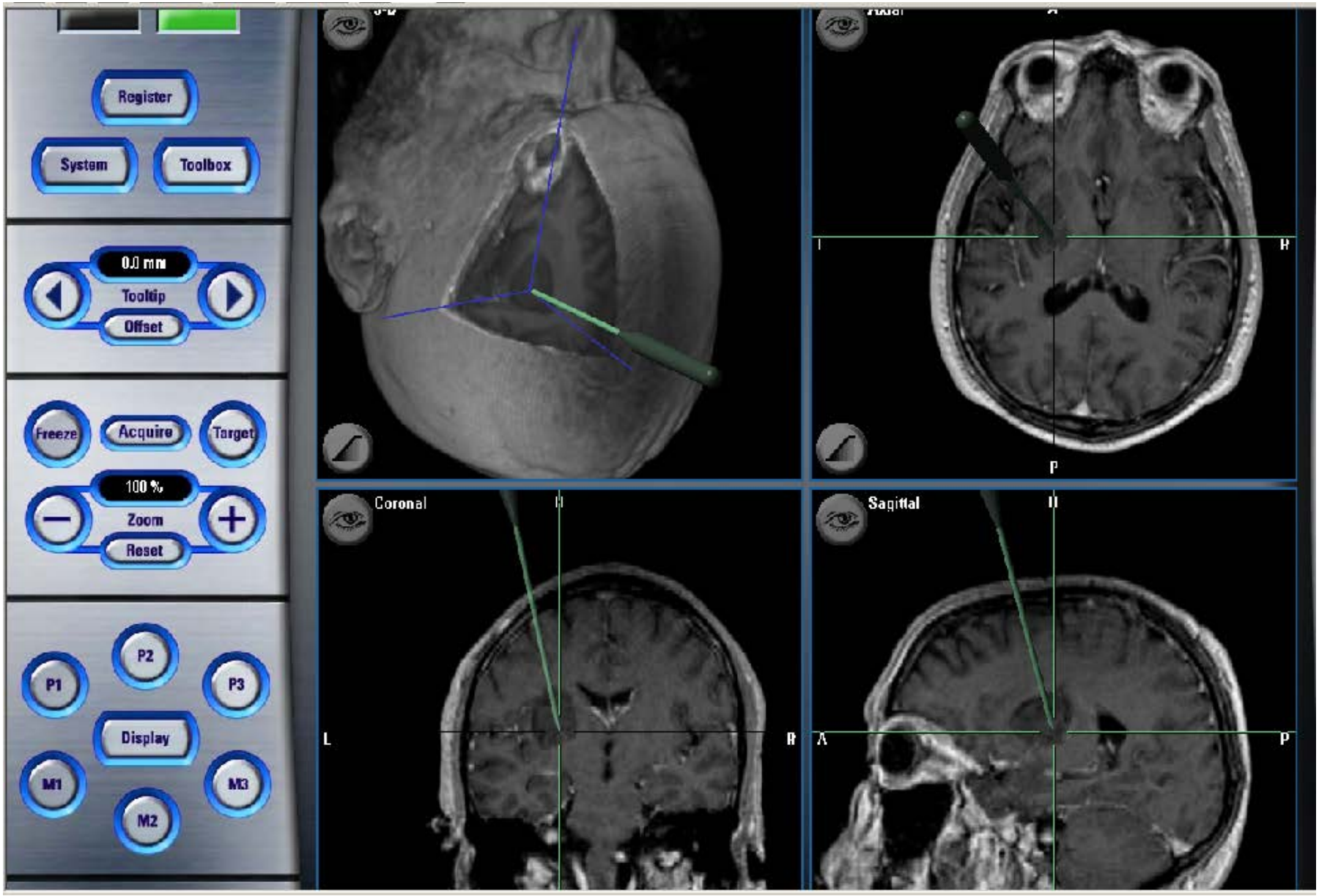
Daniel F. Hanley, MD co-PI Mario Zuccarello, MD co-PI

(Surgical Center)
William Broaddus, MD
Issam Awad, MD
Judy Huang, MD
E. Francois Aldrich
Paul Camarata

(Endoscopy Center)
Neil Martin, MD
Paul Vespa, MD

Joshua Bederson, MD

Start date: January 1, 2004


Register
System
Toolbox
0.0 mm
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Acquire
Target
100 %
Zoom
Reset
P2
P1
P3
Display
M1
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Coronal
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Sagittal
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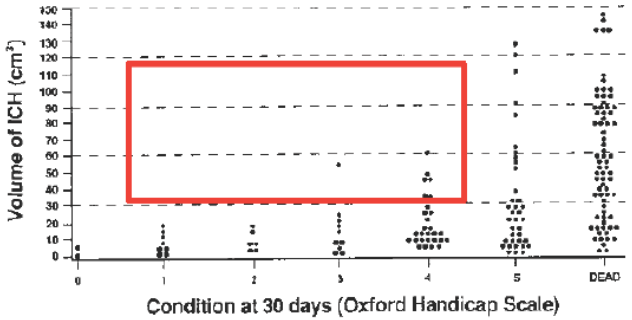
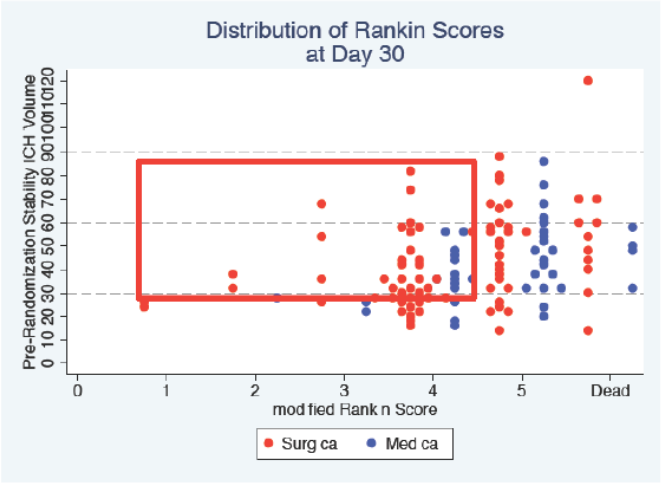
MISTIE II data

Change in Outcome with intervention

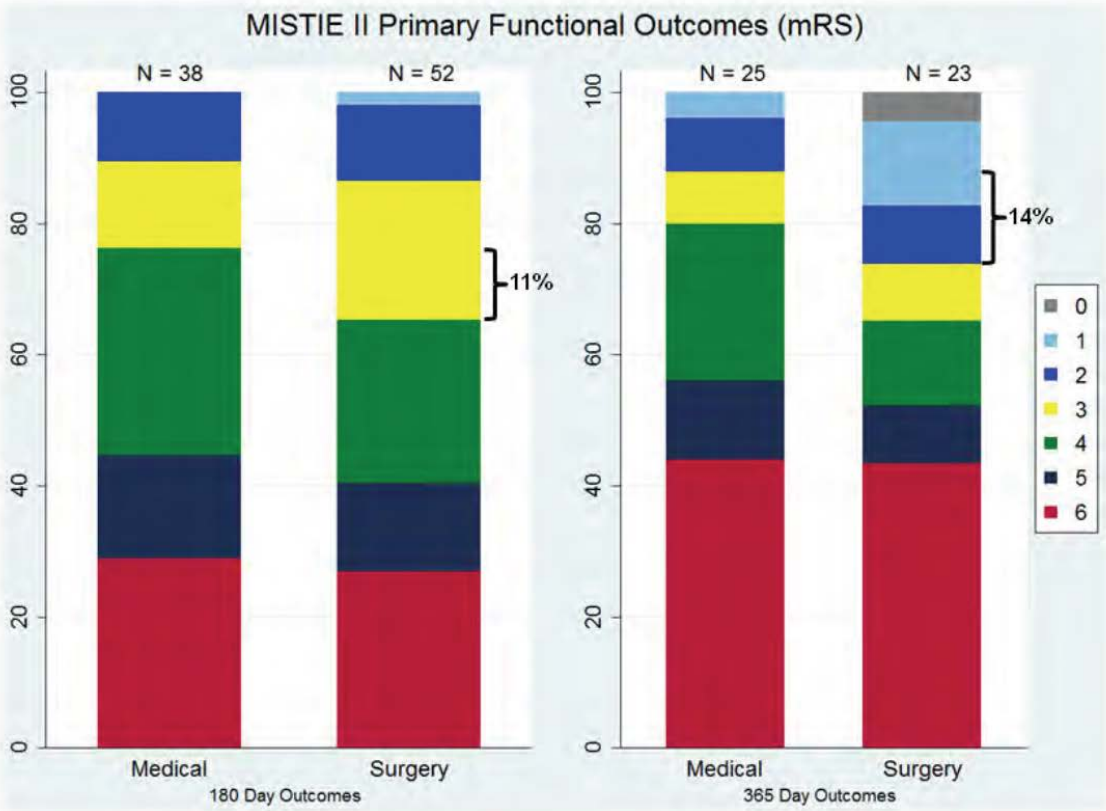
30 day Cincinnati 1988



30 day MISITE II 2004-2010



MISTIE II data



Altered mental status?

New studies to evaluate blood pressure management following ICH….

BACKGROUND
THE ATACH TRIAL ("ATACH-I")

Determine the tolerability of the treatment.

- three different systolic blood pressure goals
- intravenous nicardipine infusion for 18 to 24 hours post-ictus
- subjects with ICH who present within 6 hours of symptom onset

Define the safety of three escalating systolic blood pressure treatment goals

- rate of neurological deterioration during treatment
- serious adverse events, using intravenous nicardipine infusion.

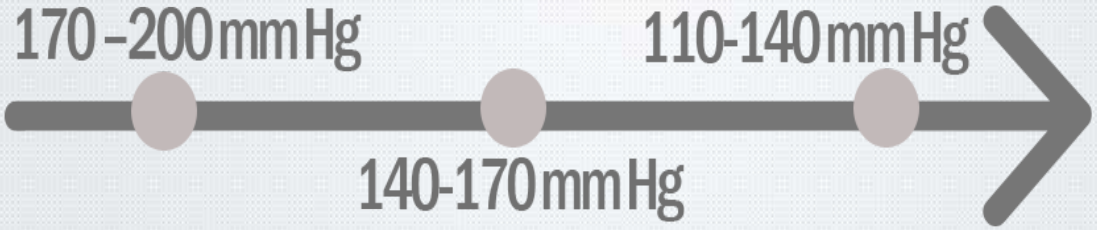
Funded by National Institute of Neurological Disorders and Stroke.

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

ATACH-I
ESCALATING SBP GOALS

INITIAL SYSTOLIC BLOOD PRESSURE

(within 6 hours of system onset)



ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

ATACH-I
SAFETY THRESHOLDS

- The safety-stopping rule in the ATACH trial mandated a cessation of enrollment if the rate of neurological deterioration exceeded 45%, the upper limit of the 95% confidence interval expected for the disease based on previous literature.

- Interim evaluations were required after every 3 neurological deteriorations and/or deaths or after four serious adverse events.

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

ATACH-I
SAFETY RESULTS

INITIAL SYSTOLIC BLOOD PRESSURE

(wit

Safety stopping rule was not activated in any tier

DSMB reviews adjudicated **that event rate was not higher than anticipated based on natural history**

Qureshi AI, ATACH Investigators, Neurocrit Care.2007;6(1):56-66.

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

ATACH-I
3 MONTH OUTCOMES

	S B P 170-200 mmHg (n=18)	S B P 140-170 mmHg (n=20)	S B P 110-140 mmHg (n=20)
3 MONTH FAVORABLE OUTCOME (mRS 0-2)	**44%**	**45%**	**32%**

NO SIGNIFICANT DIFFERENCE IN TIERS

(adjusted for Age, initial Glasgow Coma Scale (GCS) score, hematoma volume, and intraventricular extension)

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

ATACH-I
SAFETY - CONCLUSION

- It is safe to proceed with further research examining whether early and more intensive lowering of SBP in ICH patients will improve outcomes.

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

ATACH-I
OUTCOMES - CONCLUSION

- The underlying mechanism for an expected beneficial effect of intensive SBP treatment is through a reduction in the rate and magnitude of hematoma expansion observed in approximately 73% of patients with acute ICH.
- Data from the ATACH trial (and also the INTERACT trial) showed that a reduction in hematoma volume expansion with more intensive and early lowering of SBP was likely.
- These results indicated that further research was justified.

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

ATACH-II
CONCEPT (PHASE III TRIAL)

- The ATACH-II phase III trial will have important public health implications by providing necessary information regarding the efficacy and safety of antihypertensive treatment of acute hypertension in subjects with ICH.
  - BP treatment represents a strategy that can be made widely available without the need of specialized equipment and personnel and therefore, if effective, can make a major impact upon outcome in patients with ICH.

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

ATACH-II
PHASE III TRIAL INITIATION

- The ATACH-II phase III clinical trial received NINDS high-priority research funding in August, 2010. Since then, at least one ancillary study has also received NIH funding.
  - The December 2003 report from a National Institute of Neurological Disorders and Stroke (NINDS) Workshop on priorities for clinical research in intracerebral hemorrhage (ICH) recommended clinical trials for evaluation of blood pressure (BP) management in acute ICH as a leading priority.
  - The Special Writing Group of the Stroke Council of the American Heart Association in 1999 and 2007 emphasized the need for clinical trials to ensure evidence-based treatment of acute hypertension in ICH.

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

PROTOCOL SYNOPSIS

PROTOCOL TITLE

- **ATACH-II**

Antihypertensive **T**reatment of **A**cute **C**erebral **H**emorrhage (ATACH)-II: A **Phase III** Randomized **Multicenter Clinical Trial** of Blood Pressure Reduction for Hypertension in Acute Intracerebral Hemorrhage

PRIMARY STUDY OBJECTIVE

<140 vs <180

To determine the therapeutic benefit of intensive SBP treatment (SBP < 140 mmHg) compared with standard SBP treatment (SBP < 180 mmHg) in reducing the proportion of patients with death and disability (mRS of 4 – 6) at day 90 among subjects with ICH treated within 4.5 hours of symptom onset

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

PROTOCOL SYNOPSIS

To Date **635/1280** patients enrolled

//STUDY SITES

University of Minnesota
Clinical Coordinating Center and Fiscal Management Office

Medical University of South Carolina
Statistical and Data Coordination Center

~125 Recruiting Centers
International & Domestic

//STUDY PERIOD

Planned enrollment period
4 Years
Planned duration of the study
5 years

//STUDY POPULATION

Acute
ICH
patients

//SAMPLE SIZE

1,280
subjects randomized in a
1:1 RATIO
to either intensive SBP treatment or standard SBP treatment

//PRIMARY OUTCOME MEASURE

Death or Disability
(mRS of 4 to 6)
at 90 days from randomization

//STUDY DESIGN

- **Multicenter**
- **Randomized**
- **Concurrently-controlled**
- **Parallel arms design**

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

INCLUSION CRITERIA

- Age 18 years or older.
- IV nicardipine can be initiated within **4.5 hours** of symptom onset.
- Clinical signs consistent with the diagnosis of ICH
- Total **GCS score of 5 or greater** at time of ED arrival.
- CT scan demonstrates intraparenchymal hematoma with manual hematoma **volume measurement <60 cc**.
- INR value < 1.5
- Informed consent obtained by subject, legally authorized representative, or next of kin.

For subjects randomized prior to infusion start: **SBP greater than 180 mmHg*** prior to antihypertensive treatment (this includes pre-hospital treatment) AND WITHOUT spontaneous SBP reduction to below 180 mmHg at the time of randomization.
-- OR --

For subjects randomized after antihypertensive administration: Admission SBP greater than 180 mmHg prior to IV antihypertensive treatment (this includes pre-hospital treatment) AND WITHOUT SBP reduction to below 140 mmHg at the time of randomization.

- * Note: Patients with SBP < 180 should be monitored for 4.5 hours from symptom onset as their SBP may rise to eligible levels before the eligibility window closes.

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

EXCLUSION CRITERIA

- ICH is due to previously known neoplasms, AVM, or aneurysms.
- Intracerebral hematoma considered to be related to trauma.
- ICH located in infratentorial regions such as pons or cerebellum.
- IVH associated with intraparenchymal hemorrhage and blood completely fills one lateral ventricle or more than half of both ventricles.
- Patient to receive immediate surgical evacuation.
- A platelet count less than 50,000/mm^3.
- Use of dabigatran within the last 48 hours.
- Current pregnancy, or parturition within previous 30 days, or active lactation
- Known sensitivity to nicardipine.
- Pre-morbid disability requiring assistance in ambulation or activities of daily living.
- Subject's living will precludes aggressive ICU management.
- Subject is currently participating in another interventional clinical trial.

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

STUDY FLOW I

+ ICH on CT & + under 4 hour since LKWT = NCC team paged by Stroke Fellow in ER

Patient with symptoms of stroke arrives to ED

Patient screened by ED staff or stroke team

Failed Screening

Not randomized

Screening Passed

Patient eligibility assessed by stroke team

Not Eligible

Eligible

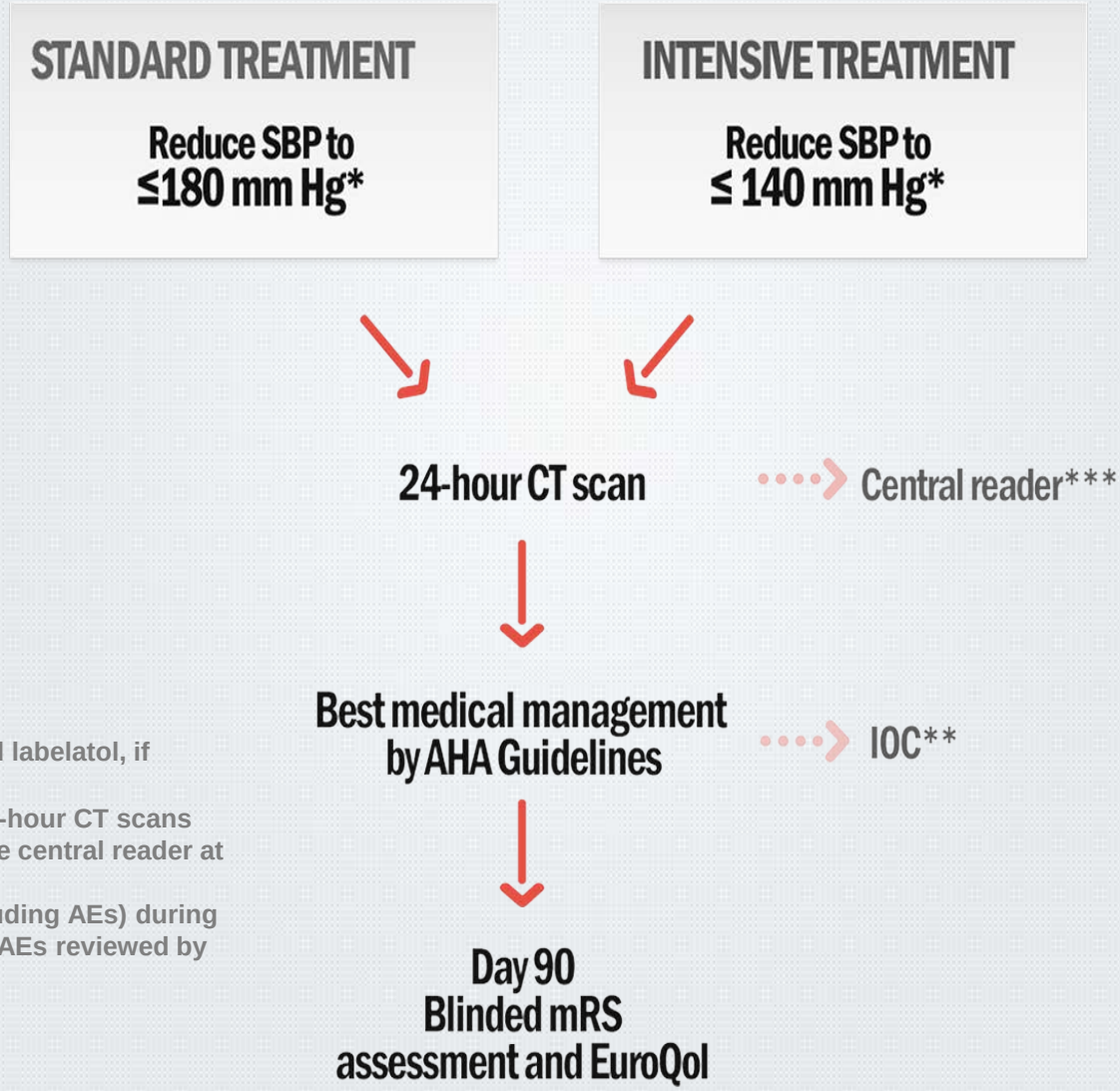
Randomize 1:1

Start study drug infusion within 4.5 hours of symptom onset

(WebDCU™: https://dcu.musc.edu/ctms/)

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

STUDY FLOW II



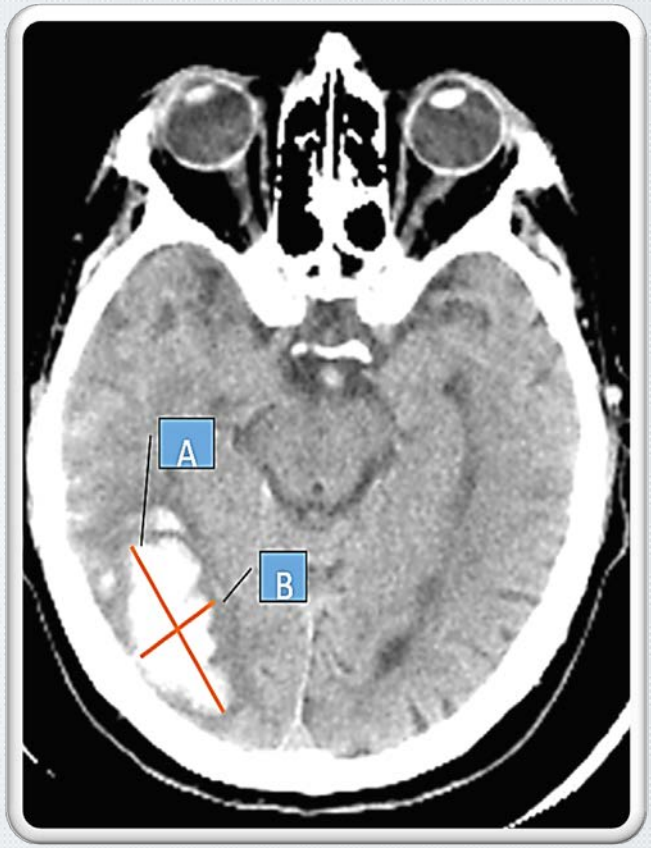
* Using nicardipine (and labelatol, if necessary)
*** Both baseline and 24-hour CT scans must be submitted to the central reader at UMN
** Intensity of care (including AEs) during hospitalization and all SAEs reviewed by the IOC

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

HEMATOMA VOLUME

A·B·C /2 <60

- **A** represents greatest hemorrhage diameter by CT
- **B** is the diameter 90 degrees to A
- **C** is the approximate number (of 10 mm slices) with hemorrhage



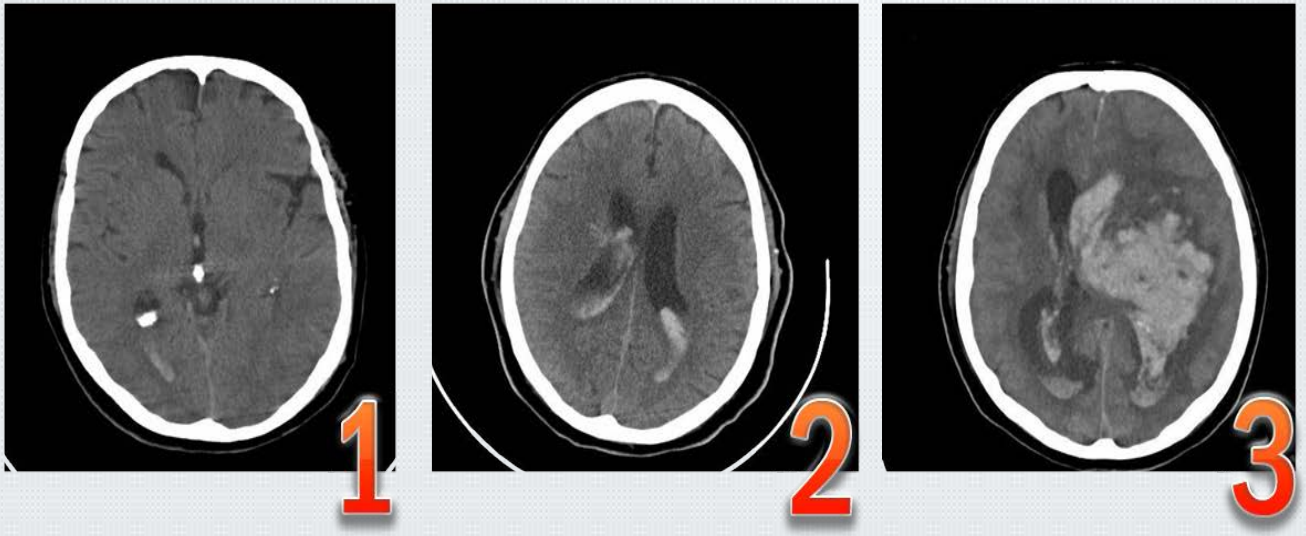
ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

INTRAVENTRICULAR BLOOD

Exclude Patients:

- blood completely filling one lateral ventricle
- more than half of both ventricles

Patient #



Patients 1 and 2 are eligible

Patient 3 is excluded

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

NICARDIPINE TITRATION & BP MANAGEMENT

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

NICARDIPINE ADMINISTRATION

- Nicardipine IV * should be started according to patient need, and may be started prior to randomization of a potential subject into the ATACH-II study.

	STARTING	INCREASE BY	MAXIMUM
Nicardipine Dose	**5 mg/hr**	**2.5 mg/hr**	**15 mg/hr**

- Cornerstone Therapeutics supplies Cardene® (nicardipine hydrochloride), a calcium ion influx inhibitor, to US sites. Cardene® may be supplied in Ready-to-Use Premixed IV Bags for efficiency in use. However, the specific IV nicardipine source and formulation to be used at each site is determined at that site to maximize safety. The use of nicardipine hydrochloride in the ATACH-II study is according to the manufacturer's standard administration recommendations.

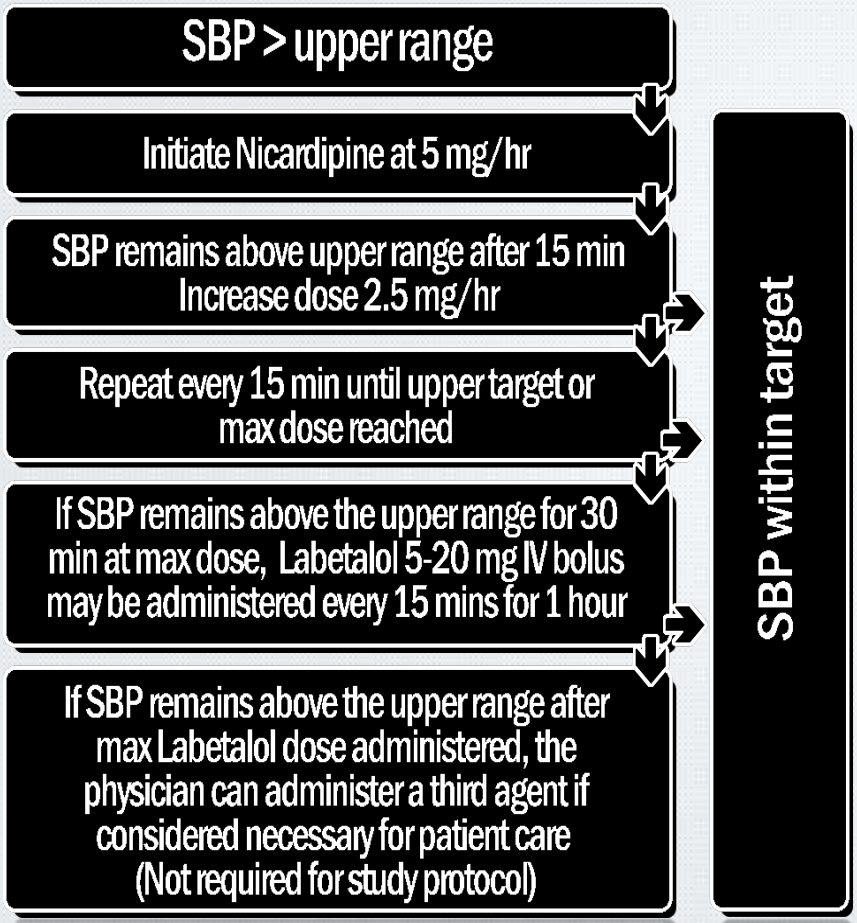
ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

SYSTOLIC BLOOD PRESSURE MANAGEMENT

STANDARD TREATMENT	INTENSIVE TREATMENT
Reduce SBP to ≤180 mm Hg*	Reduce SBP to ≤ 140 mm Hg*

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

BLOOD PRESSURE MANAGEMENT



STANDARD TREATMENT

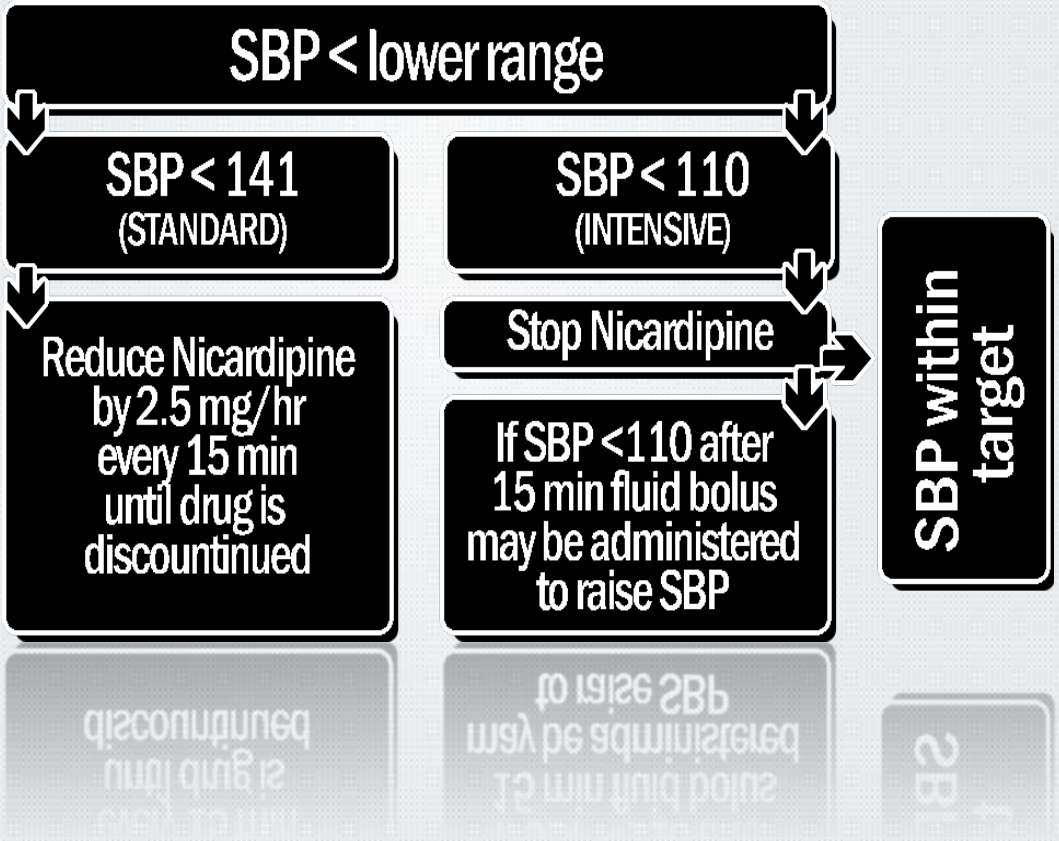
Reduce SBP to
≤180 mm Hg*

INTENSIVE TREATMENT

Reduce SBP to
≤ 140 mm Hg*

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

BELOW RANGE
MANAGEMENT



ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

BELOW RANGE MANAGEMENT

Important to Note as not USUAL B/P Monitoring ** Please be sure RN is aware**

BLOOD PRESSURE MONITORING:

- **During the first hour after nicardipine started:**

a) Every **5 minutes** for the first 15 minutes after nicardipine is started
b) Every **15 minutes** for the remainder of the first hour, unless the dose is being adjusted (see next bullet point)

- **From one hour to 24 hour after nicardipine initiation:**

a) Every 5 minutes (recommended) to **15 minutes** (mandatory) during dose adjustments
b) At least **every 30 minutes** while receiving nicardipine (at least hourly if nicardipine is turned off)

After the 24-hour study drug maintenance infusion period has ended, new orders for blood pressure management are needed which may or may not include nicardipine.
Blood pressures should be monitored closely

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

BELOW RANGE
MANAGEMENT

BLOOD PRESSURE MONITORING:

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ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

HYPOTENSION

- The most important side effect of the study drug is hypotension.
- Severe or prolonged hypotension may cause hypoperfusion of organs which can result in ischemic injury.
- If SBP is below the target range, either the infusion rate is to be decreased until SBP goes up to target range again or the nicardipine infusion should be discontinued.
- If SBP ≤110 mmHg, or if the subject develops symptoms of hypotension even after stopping nicardipine infusion, IV fluids should be given.

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

HYPOTENSION

- Nicardipine has a rapid onset (within 1-5 minutes) and short half-life of 10-15 minutes, so most subjects should show an increase in BP within 10-15 minutes after stopping the infusion. Delayed nicardipine metabolism can occur, however, or other medications may influence its effects.
- If SBP remains < 110 mmHg with signs of organ hypoperfusion, the treating physician may start vasopressor agents.
- Symptoms of hypoperfusion include changes in level of consciousness, new or worsening of focal neurological deficits, myocardial ischemia, and oliguria.

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

NEUROLOGICAL DETERIORATION

- Neurological deterioration is defined as a decrease of ≥ 2 on GCS or increase of ≥4 points on NIHSS (from baseline) that is not related to sedation/hypnotic use and is sustained for at least 8 hours.

- Each episode of neurological deterioration is to be evaluated and managed under the direct supervision of a stroke neurologist or neurointensivist.

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

OTHER RISKS

- Another important side effect is non-responsiveness to nicardipine.
  - According to the study protocol, if SBP is higher than the target range for longer than 30 minutes despite the maximum dose of nicardipine, IV boluses of a second agent (Labetalol) can be used for another hour.
  - If SBP still remains above the target range, further management is left to the discretion of the treating physician.
- Other side effects of nicardipine are:
  - Headache (the most commonly reported side effect)
  - Nausea or vomiting
  - Tachycardia
- Cardiac and SpO_2 as well as renal functions are monitored [illegible] safety, as appropriate with any vasoactive drip.

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

INTERVENTION
DISCONTINUATION

Study agent should be discontinued if any of the following occur:

- Suspected anaphylactic reaction.
- Need for emergency surgery.
- Investigator determination that discontinuation is in the subject's best interest, for example:
  - Suspected study drug-related SAE
  - Withdrawal of consent by the subject (or the subject's legally authorized representative).

ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

Case Integration:

- The patient is a 71-year-old female with a history of hypertension. The patient was in her normal state of health and was driving home when she acutely developed left hemiplegia, left hemisensory loss, and acute onset of "fatigue." This caused her to crash into a parked car that was stopped at a red light. The patient denies loss of consciousness and was wearing her seatbelt. The patient was retrieved by the paramedics and was found to be plegic on the left and brought in to UCLA as a stroke code.

Case continued

PAST MEDICAL HISTORY:

1. Hypertension.
2. "Fast heartbeat."
3. The patient denies history of stroke, seizure, cancer, traumatic brain injury, or intracerebral hemorrhage.

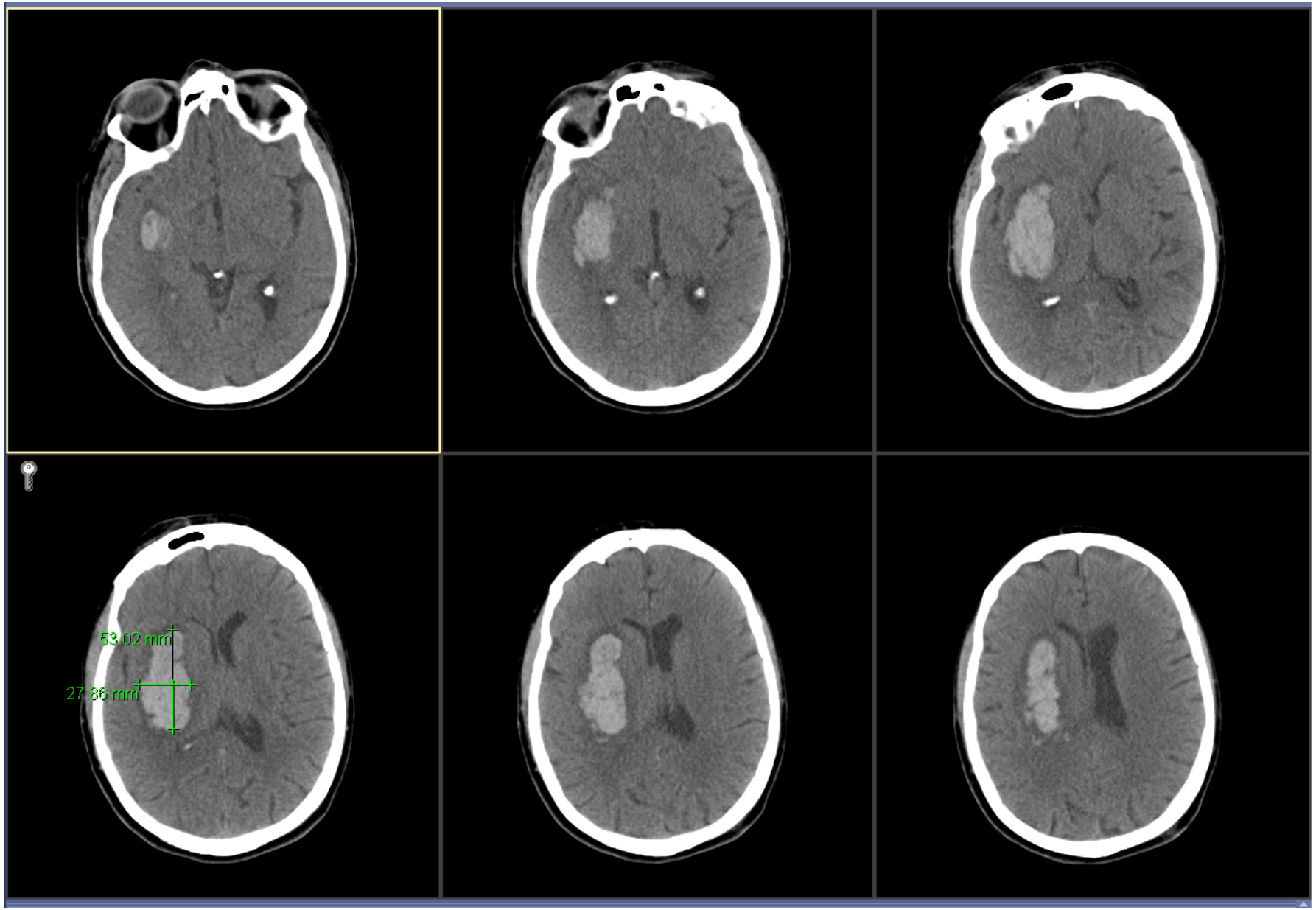
PAST SURGICAL HISTORY:

1. Hysterectomy.
2. Bilateral carpal tunnel surgery for carpal tunnel syndrome.
3. Right knee arthroscopy and microfracture surgery.

HOME MEDICATIONS:
Diovan and Toprol.

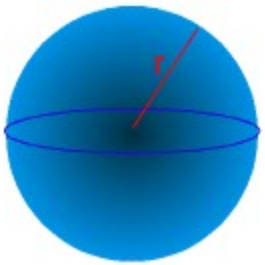
The patient denies history of aspirin, Plavix, and Coumadin usage.

ALLERGIES:
No known drug allergies.

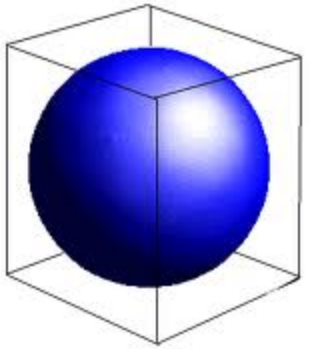

53.02 mm
27.86 mm

Volume of ICH

- CT of the head at UCLA demonstrated a 5.3 x 2.8 x 4.0 cm right basal ganglia intracerebral hemorrhage that occupies the right lentiform nucleus. There was minimal midline shift.



$$V = \frac{4}{3} \pi r^3$$



What do we do?

- Predicted mortality
- Management

Determination of the ICH score

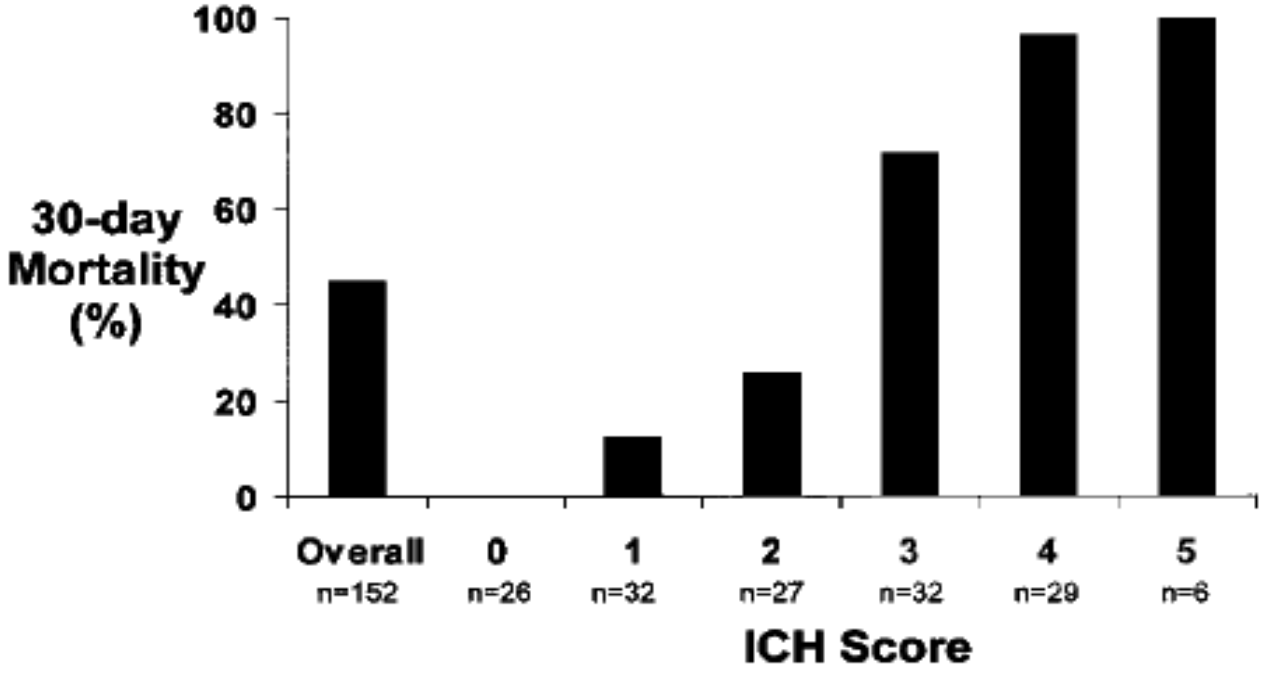
TABLE 3. Determination of the ICH Score

Component	ICH Score Points
GCS score	
3–4	2
5–12	1
13–15	0
ICH volume, cm^3	
≥30	1
<30	0
IVH	
Yes	1
No	0
Infratentorial origin of ICH	
Yes	1
No	0
Age, y	
≥80	1
<80	0
Total ICH Score	0–6

GCS score indicates GCS score on initial presentation (or after resuscitation); ICH volume, volume on initial CT calculated using *ABC*/2 method; and IVH, presence of any IVH on initial CT.

Hemphill et. al. Stroke 2001.

Predicted Mortality



The ICH Score and 30-day mortality. Thirty-day mortality increases as ICH Score increases. No patient with an ICH Score of 0 died. All patients with an ICH Score of 5 died. No patient in the UCSF ICH cohort had an ICH Score of 6, although this would be expected to be associated with mortality.

Management

- Prevent hemotoma expansion
- Blood pressure management
- PT/OT

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