Focus on Quality

heart.org/quality
Stroke Essentials: Beyond the tPA Window

*What else can be done?*

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Overview

- Introduction to Ischemic Stroke
- Historical perspective
- Medical Therapy - Systemic thrombolysis
- Surgical Intervention
- Building a stroke system
None

I will be discussing the use of non-FDA approved stroke treatments
What is stroke?

- A working definition of stroke: a sudden loss of oxygen delivery to a region of the brain

- Hemorrhagic stroke (15%)
  - a vessel or aneurysm ruptures causing bleeding in the brain

- Ischemic stroke (85%)
  - Blood flow is blocked (embolus >> thrombus/ICAD)
Why are neurosurgeons treating stroke?

Hemorrhagic may seem obvious

- aneurysms -> clip

- vascular malformations -> resect

- intraparenchymal/intraventricular -> CSF diversion, clot evacuation, ICP management
Why are neurosurgeons treating ischemic stroke?

Endovascular techniques were developed by both neuroradiologists (Guglielmi, 1995) and neurosurgeons (Serbinenko, 1970s)

Neurosurgeons gravitated towards these minimally-invasive techniques for treating brain AVMs and aneurysms
These techniques are directly applicable to stroke treatments, such as thrombectomy and thrombolysis.

Our neurocritical care training allows us to care for the stroke patient in the post-procedural setting as well.
Ischemic Stroke

- 85% of strokes are ischemic
- Leading cause of adult disability in the US
- 800,000 new strokes per year
- > 5 million stroke survivors
- $50,000,000,000 USD annually
- 1 in 6 adults will be affected
- 90% of survivors will have deficit
Evolution of Acute Stroke Treatment

FDA approved or positive trials in 1992

- Ischemic stroke: none
- Intracerebral hemorrhage (ICH): none
- Subarachnoid hemorrhage (SAH): nimodipine†
- Intraventricular hemorrhage (IVH): none

† Marginal reduction in delayed neurological ischemic deficit from vasospasm
Evolution of Acute Stroke Treatment

FDA approved or positive trials in 2012

- Ischemic
  Stroke unit care
  PO ASA < 48 h
  IV t-PA < 3 h
  IV t-PA 3-4.5 h
  IA fibrinolysis
  IA Merci retrieval < 8 h
  IA Penumbra device < 8 h
  IA Solitaire device < 8 h

- ICH
  Stroke unit care
  Temperature control

- SAH
  NICU care
  coil embolization
  Nimodipine
  Statins
  Magnesium
  Angioplasty for vasospasm

- IVH
  Stroke unit care
  IV tPA
  CSF diversion
The Golden Hour

1.9 million neurons lost
14 billion synapses lost
7.5 miles of myelinated white matter lost

PER MINUTE of ischemia

Brain ages 3.6 years per hour during stroke
The Ischemic Penumbra

Core infarct: brain is dead, no recoverable function

Ischemic penumbra: oxygen delivery has dropped below threshold for normal cell function

Restoration of blood flow will result in recovery to these cells
Systemic Thrombolysis

- Our goal is to reduce the *time to recanalization*
- IV/Systemic tissue plasminogen activator tPA
  - FDA approved in 1996 based on NINDS rt-PA SS
  - Pt must receive drug within **3 hours** of stroke onset
    - eventually expanded to 4.5 hours for select patients - not FDA approved
  - for every 100 Pts who receive IV tPA, 32 will benefit and 3 will be harmed
- Risk of intracranial hemorrhage
Diagnosing stroke

Think FAST

FACE
Does one side of the face droop?

ARMS
Is one arm weak or numb?

SPEECH
Is speech slurred?

TIME
Time is critical. Call 911 or get to the hospital immediately.
Don’t forget about the posterior circulation!

- Basilar, PICA, vertebral artery
- Ataxia
- Diplopia
- Ophthalmoplegia - disconjugate
- Dysarthria
- Waxing & waning symptoms
- Crescendo TIA
Limitations of IV-tPA

- Tight time window
- The brain does not have a clock
- Ineffective at recanalizing large clots
- Must be infused continuously (rapid hepatic clearance)
- rt-PA may be neurotoxic
- Exclusion criteria
IV t-PA exclusion criteria

1. Evidence of intracranial hemorrhage on pretreatment CT scan
2. Minor or rapidly improving symptoms
3. Symptoms of subarachnoid hemorrhage, even with normal head CT
4. Active internal bleeding: Gastrointestinal or urinary bleeding within last 21 days or known bleeding risk, including but not limited to:
   a. Platelet count less than 100,000/mm3
   b. Heparin during the preceding 48 hours associated with elevated aPTT
   c. Currently taking oral anticoagulants (e.g. Warfarin sodium) or recent use with an elevated prothrombin time (PT) greater than 15 seconds or INR greater than 1.7
   d. Major surgery or other serious trauma during preceding 14 days
   e. Stroke, serious head trauma or intracranial surgery during preceding 3 months
   f. Recent arterial puncture at a non-compressible site
   g. Recent lumbar puncture during preceding 7 days
5. Systolic BP greater than 185 mm of Hg or diastolic BP greater than 110 mm of Hg at the time of t-PA infusion and/or patient requires aggressive treatment to reduce blood pressure to within these limits
6. History of intracranial hemorrhage, neoplasm, arteriovenous malformation, or aneurysm
7. Recent Acute Myocardial Infarction
8. Observed seizure at stroke onset
Get to know the NIHSS

Measures stroke severity

- 1b. LOC Questions: tests the patient's ability to answer questions correctly. Graded from 0-2.
- 1c. LOC Commands: tests the patient's ability to perform tasks correctly. Graded from 0-2.
- 4. Facial Palsy: tests the patient’s ability to move facial muscles. Graded from 0-3.

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<tr>
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<tr>
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<tr>
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<tr>
<td>21-42</td>
<td>severe</td>
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Advances in systemic thrombolysis

- Alteplase vs Tenecteplase
  - Tenecteplase: genetically engineered mutant tissue plasminogen activator
  - RCT IV Alteplase (rt-PA) vs Tenecteplase
    - NJEM March 2012
- Pt selected on the basis of CT perfusion
  - symptom onset within 6 hours
  - hemispheric perfusion lesion ≥ 20% core infarction volume on CTP
Advances in systemic thrombolysis

Outcome measures

- Perfusion volume at 24h post treatment (pMRI)
- NIHSS
- mRS at 90 days (secondary)

Significant improvement seen in all measures

STILL INVESTIGATIONAL - USE LIMITED TO CLINICAL TRIALS
Large Clot Burden

- The larger the vessel that is occluded, the less effective IV tPA is and the worse the outcome.

- MCA → intracranial ICA/carotid terminus → cervical carotid

- Site of occlusion *generally* correlates with stroke severity.

- Acute carotid occlusion with NIHSS > 10 → 0% probability of mRS 0-2 at 6 months.

We need to improve treatment for people with bad strokes and large vessel occlusions.
Beyond the tPA Window
IV tPA ineligible

- Outside of time window
- Stroke code activation 12 hours
- Contraindication to systemic thrombolysis
IA thrombolysis

- Decreased dose, direct delivery to clot
- Reduced systemic effects
- Prourokinase: mRS 0-2 40% treatment group vs 25% control (heparin)
- Recanalization 66%
- No difference in mortality
- SICH 10% treatment vs 2% control
- IA tPA 40-79%
Mechanical Thrombectomy
1st generation devices

Merci device (2004) ~70%
Penumbra device (2007) ~80%
Mechanical Thrombectomy
2nd generation devices

Solitaire (2011)
“stentriever”
~85%
Problems with intervention

- Time to recanalization *tends* to be inversely correlated with improved patient outcomes
- A few well-publicized randomized trials have not borne this out
Thrombectomy in the media

In 2013, 3 negative trials for thrombectomy were presented at ISC and published in NEJM

IMS III


MR RESCUE


SYNTHESIS

IMS III

- Inclusion criteria: IV tPA versus IV tPA + thrombectomy OR IA tPA
- symptom onset within 3 hours
- 656 patients, randomized in 2:1 ratio
- Prematurely terminated by DSMB
- mRS of 2 or less in 40% of patients with NO DIFFERENCE in bleeding or mortality
Problems with IMS-III

- Started collecting data in 2006
- Significant out-of-study use of thrombectomy
- Could enroll *without* CTA if NIHSS > 10
- Only 47% of enrolled pts had CTA
- 20% of IA arm had no thrombus or inaccessible clot
- Outdated technology
- Only 40% TICI 2b or 3 (versus 68% with stentrievers)
Inclusion criteria: symptom onset within 8 hours

Compared IV tPA to mechanical thrombectomy (Merci or Penumbra)

Further stratified patients by CT/MRI perfusion to identify a “penumbral pattern”

 Favorable penumbra: <70% of brain with decreased blood flow

Improved outcomes in patients with TICI flow > 2b
Problems with MR RESCUE

- Outdated technology
- Only 16/64 (27%) had TICI 2b flow or better
- Revascularization rates were *lower* in intervention arm than in control arm
MR RESCUE subgroup analysis

- “Favorable” penumbra pattern correlated with improved outcomes
- These patents may have had more robust pre-existing collateral circulations
- Acute ischemic stroke is a highly heterogeneous disease
- underscores need to stratify patients non-invasively
SYNTHESIS

- Multi-center Italian trial
- Randomized 326 patients
- IV rt-PA within 4.5h or IA therapy within 6h
- No difference in mRS outcome at 3 months
Problems with SYNTHESIS

- If randomized to IA arm, straight to diagnostic angiogram
- no IV tPA (Class I therapy)
- 10% had no LVO
- On average 1h delay in onset of treatment compared to IV arm
- 165/181 in intervention arm got procedure
- 109/165 got IA thrombolysis +/- wire manipulation
- Only 56/165 got mechanical thrombectomy
What can we learn from these trials?
Understanding the negative stroke trials

- These trials failed to demonstrate *superiority* of intervention
- Safety profile of intervention is confirmed in each of these studies
- Severe strokes (NIHSS > 20) benefit more from intervention
  - IMS-III 24% versus 17%
- Subgroup analysis confirms that patients with LVO, high NIHSS do better with rapid restoration of high-quality (TICI 2b or greater) flow
Understanding the negative stroke trials

We are trying to identify patients with bad strokes and LVO because they do poorly with medical treatment alone
More lessons from NEJM trials

- Pre-procedure arterial imaging (CTA, MRA) is essential in stratifying stroke patients
- Identify LVO
- IA intervention provides benefit to patients with LVO when revascularization is timely and adequate
NEJM Thrombectomy trials

- IMS-III & SYNTHESIS did not identify LVO prior to enrollment
- Revascularization rates were significantly lower in all three trials than with current 3rd generation devices

CONCLUSION:

Outdated technology used in poorly selected patients is not effective in treating stroke
Where we need to go

CARDIOLOGY

suspected MI
↓
EKG
↓
troponin
↓
cath lab

Door-to-needle: 45 minutes
How do we improve?

1. Identifying patients
   - No biomarker for the brain (troponin)
     - Still in lab
   - No reliable physiological study (EKG)
   - CT/MR perfusion are being investigated in clinical trials
   - highly device & technologist dependent - cross-site reproducibility is poor
   - Most patients are not candidates for therapy due to “last known normal”
How do we improve?

2. Refining protocols, streamlining workflow
   - Door to needle 120 min -> 90 min -> 45 min
   - Field activations

3. Faster, better recanalization
   - Technological improvement
Building a stroke system

- Comprehensive stroke centers are money and resource intensive
- Most strokes do not require emergency intervention
- Knowing treatment options and regional resources are key
- Creation of regional stroke networks
Stroke treatment in the modern era

- Teleneurology
- Phone/Internet consultation with neurologist, interventionalist
- “Drip and Ship”
Methodist Dallas Health System Stroke & Cerebrovascular Coverage 2013
In conclusion

- Strokes are common and a serious cause of morbidity
- Most money is spent on rehabilitation
- New stroke treatments are available that can significantly improve patient outcomes
- Stroke treatment requires a regional network and telepresence to rapidly identify and treat stroke patients
Thank you

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# American Heart Association
## Contact Information

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<th>Region</th>
<th>Contact 1</th>
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<tbody>
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Will be posted on [www.heart.org/swaquality](http://www.heart.org/swaquality) within one week of webinar.

Password: STROKE 2
Save the Date

April 29, 12:00 -1:00 pm

Stroke Essentials: Together to End Stroke – Ideas for Stroke Community Education

http://www.strokeassociation.org/STROKEORG/General/Together-to-End-Stroke_UCM_448718_SubHomePage.jsp
If we have time…

Current management of intracranial atherosclerotic disease
Intracranial atherosclerotic disease

- Large vessel atherosclerotic disease accounts for around 10% of ischemic strokes
- Used to treat with coumadin, then with antiplatelet agents
- WASID trial
Medical therapy

- SAMMPRIS looked at angioplasty and stenting
- Antiplatelet agents worked better than expected
- Procedural complications with PTAS higher than expected
- Study ended early, device withdrawn
Still a valuable tool

- Refractory symptoms despite adequate medical therapy
- basilar stenosis
- 1 year mortality for symptomatic basilar artery stenosis is 50%
Basilar occlusion

54 yo man
acute onset dysarthria
NIHSS 14
Load with ASA, Plavix
Progressive symptoms
Now somnolent
Angioplasty

Angioplasty with Gateway 2.5 x 9mm
Stent

Wingspan
2.5 x 15 mm stent
Conclusion

- Stroke is a big problem. We need to get better at treating it.
- Time is brain.
- Anatomic -> physiological studies as basis for guiding treatment
- This is an exciting time, many promising therapies are on the horizon