



Emergency Treatment of Ischemic Stroke

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Conflicts of Interest

- None
- I will discuss therapies for treatment of stroke that are not approved by the FDA, including the administration of Alteplase at 3 – 4.5 hours after stroke



Outline

- Part 1
 - Ischemic stroke intro
 - Treatment of Acute Stroke
 - Other considerations
- Part 2
 - Endovascular treatment of stroke

Importance of Ischemic Stroke



- A leading cause of death and disability among Americans
 - Approximately 800,000 new strokes annually
- A leading cause of long-term disability
 - A leading cause of institutionalized care
- The frequency of stroke is increasing
 - Aging of the American population
 - Survival of high-risk patients with heart disease



Stroke in South Dakota

- Stroke is age-dependent
- Few rural critical access hospitals have neurology coverage
- Need for outpatient care
 - Risk of stroke is 1.34 times that in urban areas
 - ▣ Populations of elderly, poor, minorities
 - ▣ 19% relative increase in mortality



Emergency Stroke Therapy

- Ischemic stroke is a common and serious disease
 - ▣ Potential for death or severe incapacity
 - ▣ Affects patient and family
- An approved therapy of proven value is available
 - ▣ Intravenous thrombolysis within 3 hours is approved by the FDA
- Success is linked to early treatment
- Guidelines provide recommendations for care
 - ▣ Improve safety and efficacy of treatment
 - ▣ Failure to follow guidelines associated with poorer outcomes



Pre-Hospital Management

- Assess and manage ABCs
 - ▣ Treat SBP >210mmHg
- Initiate cardiac monitoring
- Provide O2 to maintain O2 saturation > 94%
- Establish IV access with saline
 - ▣ Do not give excess volume of fluid
 - ▣ Do not administer glucose-containing fluids unless patient has hypoglycemia
- Check blood glucose and treat accordingly
- Determine Last Known Normal (LKN)
- Obtain family information, preferably a cell phone

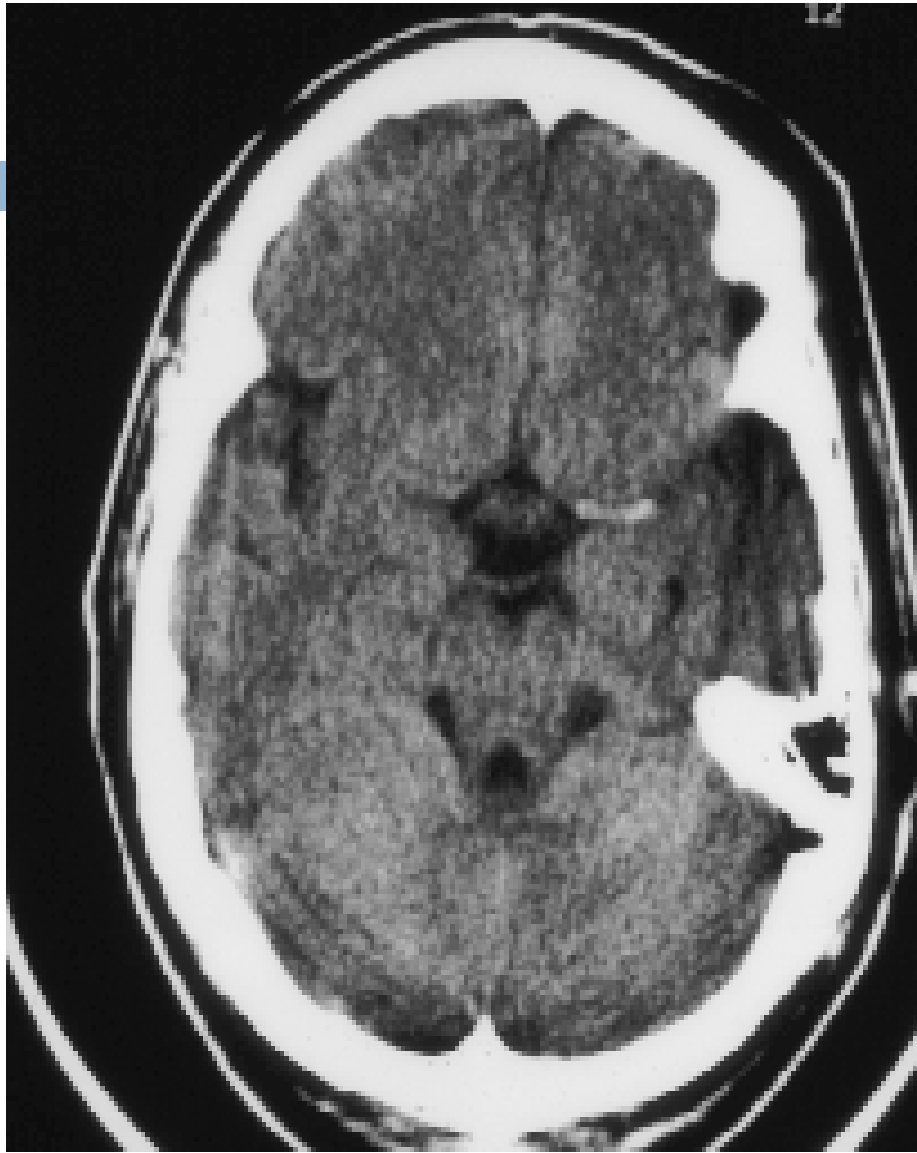
Jauch et al, Stroke, 2013



Emergency Diagnostic Studies

- Brain imaging***
 - May be either CT or MRI
 - CT generally more readily available, quick, non-invasive, and relatively inexpensive
 - Gives key information for emergency care
- Serum glucose***
- Complete blood count and platelet count, INR and aPTT
- Cardiac enzymes, renal studies
- Electrocardiogram
- Pulse oximetry

- *** Results must be known before treating with alteplase



General Emergency Management

- Similar to other acutely and seriously ill patients
- ABC of life support
 - ▣ Airway protection if decreased consciousness or brainstem dysfunction
 - ▣ Oxygen supplementation not needed unless hypoxic
- Monitor vital signs and neurological status
- Intravenous access
- Treat fever and look for source of fever
- Treat serious cardiac arrhythmias
- Symptomatic treatment – pain, nausea, agitation

Management of Arterial Hypertension



- Blood pressure elevations are common – underlying risk factor, stress, physiological response for perfusion
- Management is controversial because of minimal clinical trial evidence
- Aggressive lowering of blood pressure is not recommended because of risk of worsening of stroke
- Need to lower blood pressure to treat Alteplase
- Usually recommend IV administration of short-acting medications
 - Labetalol, nicardipine, hydralazine, sodium nitroprusside



Intravenous Thrombolysis

- Approved medical therapy for treatment of carefully selected patients with acute ischemic stroke
 - ▣ FDA approved for treatment < 3 hours
 - ▣ ASA/AHA Guidelines for treatment < 4.5 hours
- Improve neurological outcomes and “cure” patients
- Efficacy is time-linked
- Careful patient selection is key to minimize hemorrhage
- Effective therapy of limited usefulness because too few patients are being treated



Last Known Normal

- Harder than you think
- Stroke doesn't always start when symptoms are noticed.
- Wake up with symptoms
 - ▣ LKN is when they were last seen normal.
- Speech deficit, when did they last speak?
- “What were you doing?”



Last Known Normal

- Complicating factors
 - Patients “seemed off”
 - They had transient symptoms prior to fixed deficit
 - Hemineglect: patients pay no attention to problem
 - Anosagnosia: patients deny they have a problem
- If there is confusion around the LKN, keep asking questions.



Absolute Contraindications

- LKN >4.5h
- History of intracranial hemorrhage
- Platelets <100,000
- INR >1.7
- Heparin in prior 48h and elevated aPTT
- LMWH in prior 24h
- Direct oral anticoagulant use in prior 48h
- Uncontrolled hypertension (not responding to a drip)
- Uncontrolled hypoglycemia
- Stroke or severe head trauma within 3 months.

**American Heart Association
Guideline 2013¹****American Heart Association
Scientific Statement 2015¹²****US Food and Drug Administration
(FDA) Package Insert 2015¹³****Indications**

Diagnosis of ischemic stroke with measurable neurologic deficit

Same

Same

Symptom onset^a within 4.5 hours

Same

Within 3 hours

Age \geq 18 years

Same

Warning for age >77 years with risk factors for intracranial hemorrhage

Contraindications

Severe head trauma within 3 months

Same

Contraindicated

Ischemic stroke within 3 months

Risk increased, but degree is unclear

Removed^b

Arterial puncture at noncompressible site within 7 days

Risk uncertain

Not listed

Previous intracranial hemorrhage

Same

Warning for recent intracranial hemorrhage (contraindicated if active intracranial hemorrhage)

Suspected subarachnoid hemorrhage

Same

Contraindicated

Intracranial neoplasm, arteriovenous malformation (AVM), or aneurysm

Probably recommended if extraaxial neoplasm is present; not recommended if intraaxial neoplasm is present; risk unclear for AVM; probably recommended if unruptured unsecured aneurysm <10 mm is present, but risk unclear if greater size

Contraindicated



**American Heart Association
Guideline 2013¹**

**American Heart Association
Scientific Statement 2015¹²**

**US Food and Drug Administration
(FDA) Package Insert 2015¹³**

Recent intracranial or
intraspinial surgery
(within 3 months)

Same

Contraindicated

Active internal bleeding

Same

Contraindicated

Systolic blood pressure (BP)
>185 mm Hg or diastolic BP
>110 mm Hg

Same, but treatment recommended
if BP can be lowered safely

Contraindicated for severe uncontrolled
hypertension (BP values removed^b);
warning for BP >175/110 mm Hg

Bleeding diathesis

International normalized
ratio (INR) >1.7

Heparin within 48 hours with
abnormal activated partial
thromboplastin time

Platelets <100,000/mm³

Current use of direct thrombin
inhibitor or factor Xa inhibitor
with abnormal coagulation tests^c

Consider case by case in patients
with history of bleeding diathesis;
not recommended if INR >1.7,
low-molecular-weight heparinoid
within 24 hours, direct thrombin
inhibitor or factor Xa inhibitor
within 48 hours (unless coagulation
tests^c are normal)

Contraindicated for bleeding
diathesis (laboratory
values removed^b)

Blood glucose <50 mg/dL

Consider recombinant tissue
plasminogen activator (rtPA) if deficits
still present after glucose normalization

Removed^b

CT showing hypodensity >1/3
of the cerebral hemisphere

Same

Removed^b



American Heart Association Guideline 2013¹

American Heart Association Scientific Statement 2015¹²

US Food and Drug Administration (FDA) Package Insert 2015¹³

Relative contraindications

| | | |
|--|--|----------------------------|
| Minor stroke (typically National Institutes of Health Stroke Scale [NIHSS] score <5) | rtPA should be administered to patients with mild but disabling symptoms within 3 hours of onset; possible risk and benefit should be weighed in patients with nondisabling symptoms | Removed ^b |
| Rapidly improving symptoms | rtPA should be administered if symptoms are still disabling | Not listed |
| Pregnancy | rtPA may be considered in moderate to severe stroke when anticipated benefit outweighs the anticipated risk of uterine bleeding | Warning (Category C) |
| Seizure at onset with postictal residual deficits | rtPA administration is reasonable if residual deficits are thought to be caused by a stroke | Removed ^b |
| Major extracranial trauma within 14 days | rtPA can be considered | Warning for recent trauma |
| Major surgery within 14 days | rtPA can be considered in carefully selected cases | Warning for recent surgery |
| Gastrointestinal or genitourinary surgery within 21 days | Consider rtPA if no structural bleeding lesions | Warning |
| Acute myocardial infarction within 3 months | Administer rtPA (stroke dose) if concurrent stroke and acute myocardial infarction (MI); it is also reasonable to give rtPA after recent MI unless it was a STEMI involving the left anterior myocardium | Not listed |



Other Anticoagulants

- Direct Oral Anticoagulants (DOACs)
 - Apixaban (Eliquis)
 - Dabigatran (Pradaxa)
 - Rivaroxaban (Xeralto)
 - Edoxaban (Savaysa)
- Parenteral Direct thrombin inhibitors (for PCI)
 - Bivalirudin
 - Argatroban
 - Desirudin





Call Neurology

- AMG Neurology
 - 24/7
 - Telephone consultation
 - Most helpful when there is confusion around the LKN and/or relative contraindications.
 - Development of Telemedicine Stroke service is envisioned, difficult to implement.



Section Summary

- Patient selection is key
- Last Known Normal (LKN)
- As uncertainty and relative contraindications arise, the pace of the encounter should slow

Alteplase Administration

Time is Brain

Interval from Stroke Onset and Responses to Intravenous Alteplase



Pooled analyses of clinical trials

| Time | Odds of Favorable Outcomes |
|-------------------|----------------------------|
| < 90 minutes | 2.55 (1.44 – 4.52) |
| 91 – 180 minutes | 1.64 (1.12 – 2.40) |
| 180 – 270 minutes | 1.34 (1.06 – 1.68) |
| 270 – 360 minutes | 1.22 (0.92 – 1.61) |

Lees et al, Lancet, 2010; 375: 1695



Alteplase

- Alteplase is tPA
- Confusion with other thrombolytics
- We are trying to use “Alteplase”
- I still mess up sometimes

Recommendations for Intravenous Thrombolysis



- IV administration of alteplase is recommended
 - ▣ 0.9 mg/Kg (maximum dose is 90 mg)
 - ▣ 10% as bolus, remainder infused over 1 hour
- Carefully selected patients < 3 (4.5) hours
- Can be associated with side effects
 - ▣ Overall risk of bleeding is 6%, higher with severe strokes
 - ▣ Does not increase mortality
 - ▣ Uncommon risk of angioedema
- Success in clinical settings is similar to that achieved in trials
- Success is linked to compliance with guidelines

Jauch et al, Stroke, 2013



Expanded Time Window for Intravenous Thrombolysis

- Impact on the numbers treated is relatively small
- Approved by European regulatory authorities
- Not approved by FDA
 - ▣ Did not find the data compelling
 - ▣ Requested another study in the US
 - ▣ Such a study is not likely to be done
- Guidelines continue to recommend the administration of Alteplase up to 4.5 hours after onset of stroke

Wechsler and Jovin, Stroke, 2012; 43: 2517

Decision Making Process

Intravenous Thrombolysis



- **Did the stroke happen in the last 3 – 4.5 hours?**
 - ▣ Stroke upon awakening or unwitnessed stroke
 - ▣ Minor symptoms with subsequent worsening
 - ▣ TIA followed by a second (new) event
- **Difference in criteria for those treated < 3 hours and those treated 3 – 4.5 hours**
- **If the stroke is > 3 hours but < 4.5 hours**
 - ▣ Age must be < 81 for treatment in 3 – 4.5 hours
 - ▣ No age restriction for treatment < 3 hours



- Any co-morbid disease or recent illness that could be associated with a high risk of bleeding complications?
 - ▣ History of prior cerebral hemorrhage
 - ▣ Recent stroke or myocardial infarction
 - ▣ Recent major trauma or surgery
 - ▣ Recent major bleeding
- Is the patient taking oral anticoagulants?
 - ▣ If taking warfarin, do not treat in 3 – 4.5 hours
 - ▣ If taking warfarin, treat in < 3 hours if INR is < 1.8
 - ▣ Aspirin, clopidogrel, dipyridamole, ticlopidine
 - ▣ DOACs



- **Are baseline coagulation tests normal?**
 - ▣ Primary issue is anticoagulant use or a history of bleeding
 - ▣ Abnormal coagulation tests preclude treatment
 - ▣ Tests take time to perform and may treat in some instances if tests are delayed
 - ▣ Finger stick test for INR
 - ▣ Prolonged aPTT as a marker for dabigatran effect
- **Is the patient a diabetic and has a history of a previous stroke?**
 - ▣ May treat < 3 hours but not in 3 – 4.5 hour time period
- **Is the patient taking an ACE-inhibitor?**
 - ▣ Not a contraindication
 - ▣ May be associated with increased risk of angioedema



- **Any neurological contraindication to treatment?**
 - ▣ Can treat a patient who has had seizures with stroke
 - ▣ Should avoid not treating because of “improvement”
- **Any medical contraindication to treatment?**
 - ▣ Most important is arterial hypertension
 - ▣ Blood pressure values
 - < 185 mm Hg systolic
 - < 110 mm Hg diastolic
 - ▣ Blood pressure may be lowered in order to treat patient
 - ▣ Be sure that the patient is not hypoglycemic



- **What is the score on the NIH Stroke Scale?**
 - ▣ No minimum score for treatment
 - Mild stroke may worsen subsequently
 - Composition of score may influence decision
 - A patient may be disabled despite a low score
 - ▣ No maximum score for treatment < 3 hours
 - Use caution with very severe stroke
 - Higher risk of bleeding complications
 - No increase risk in mortality
 - ▣ Maximum score for treatment in 3 – 4.5 hours
 - NIHSS score < 25



- **What are the findings on brain imaging?**
 - ▣ Presence of a hemorrhage – contraindication
 - ▣ Stroke appears to be older than 3 – 4.5 hours
 - ▣ Very large ischemic lesion is detected
 - ▣ Presence of a dense artery sign – usually a severe stroke
- **Are the patient/family aware of risks of treatment?**
 - ▣ Overall risk of symptomatic bleeding is approximately 6%
 - ▣ Hemorrhagic transformation of infarction or hematoma
 - ▣ Risk of bleeding greater in patients with severe strokes
 - ▣ FDA approved therapy and guidelines available



Potential Pitfalls

Intravenous Thrombolysis

- Weight-based dosage
 - ▣ 0.9 mg/Kg – to a maximum of 90 mg
 - ▣ Accurate estimate of weight
- Medication is in a 100 mg bottle that is mixed by nurse or pharmacist
 - ▣ Must dispose of 10 mg before treating patient
 - ▣ Must be swished not shaken when preparing
- 10% given as a bolus and remainder infused over 1 hour
 - ▣ Infusion rates need to be accurate

Potential Pitfalls

Intravenous Thrombolysis



- Heparin during the acute evaluation is avoided
 - ▣ Results in patient not being treated with Alteplase
 - ▣ Contraindication
 - ▣ No evidence of efficacy of heparin
 - ▣ Evidence of increased risk of bleeding
- No antiplatelet agent or anticoagulant is started within the first 24 hours after treatment
 - ▣ Concern about bleeding complications
 - ▣ Usually do a follow-up CT at 24 hours before starting an antithrombotic agent



Legal Implications

- Not treating a patient may violate the rule of “doing no harm”
- The primary legal issue is not prescribing Alteplase
 - ▣ Need a well-documented reason for not treating
 - ▣ Clearly state reasons in the medical record
- Medication may be prescribed by any physician
 - ▣ Neurological consultation improves diagnosis and treatment
 - ▣ Workflow for consultation should be in place
- The size of the hospital is not a defense
 - ▣ Expected to have a plan for emergency treatment of stroke



Other Considerations

- Psychogenic overlay can be hard to distinguish from neurologic deficits. (Conversion disorder?)
- Risk of hemorrhage in IV Alteplase MI patients:
 - ▣ 1.4%
- Permanent disability must be considered.
- Gives them an “out” vs repeat performance.



Safety and Outcomes of Intravenous Thrombolysis in Stroke Mimics

A 6-Year, Single-Care Center Study and a Pooled Analysis of Reported Series

Georgios Tsivgoulis, MD; Andrei V. Alexandrov, MD; Jason Chang, MD; Vijay K. Sharma, MD; Steven L. Hoover, MD; Annabelle Y. Lao, MD; Wei Liu, MD; Elefterios Stamboulis, MD; Anne W. Alexandrov, PhD; Marc D. Malkoff, MD; James L. Frey, MD

Table 3. Prevalence and Outcomes of SM Among Patients Treated With IVT Across Different Stroke Registries

| Registry | IVT (No.) | SM (No., %) | sICH in SM (No., %) | OE in SM (No., %) | FI in SM (No., %) |
|-------------------------|-----------|---------------------------------|---------------------------------|---------------------------------|------------------------------------|
| Michigan ^d | 151 | 6 (4%) | 0 | NA | 1 (17%) [†] |
| Basel ^e | 250 | 7 (3%) | 0 | 0 | 6 (86%) [‡] |
| Houston ^f | 512 | 69 (13%) | 0 | 0 | 60 (87%) [†] |
| Pittsburgh ^g | 254 | 9 (4%) | NA | NA | NA |
| Phoenix | 539 | 56 (10%) | 0 | 0 | 54 (96%) [†] |
| Overall | 1706 | 147 (9%) (95% CI, 7% to 10%) | 0 (0%) (95% CI,* 0% to 2.3%) | 0 (0%) (95% CI,* 0% to 2.4%) | 121 (88%) (95% CI,* 81% to 93%) |

SM indicates stroke mimic; IVT, intravenous thrombolysis; sICH, symptomatic intracranial hemorrhage; OE, orolingual edema; FI, functional independence defined as a modified Rankin Scale score of 0 to 1; NA, not available.

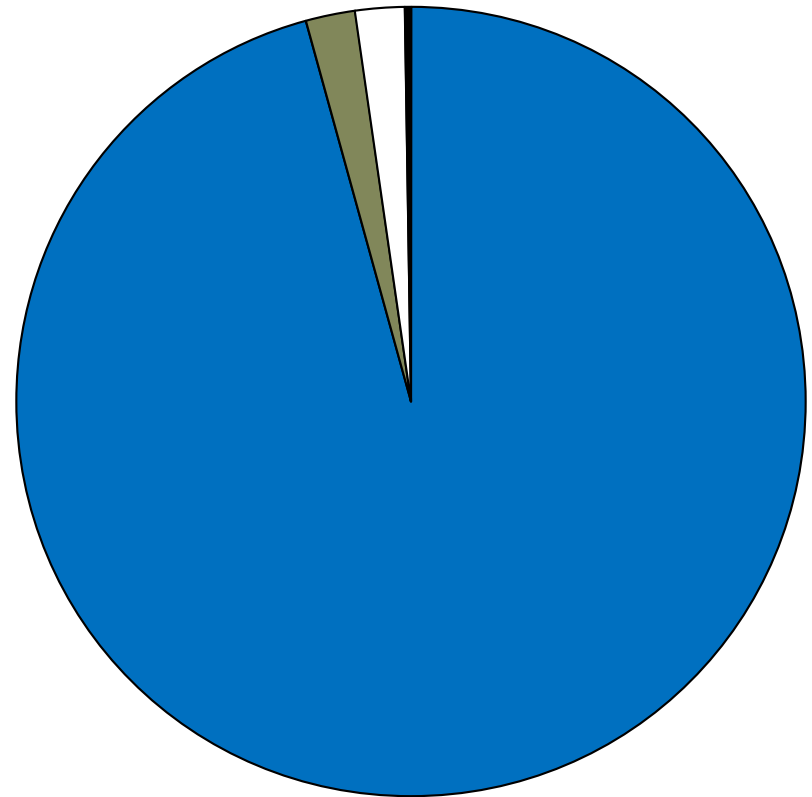
*Calculated by the Adjusted Wald method.

[†]At hospital discharge.

[‡]At 3 mo.

Current Management of Ischemic Stroke

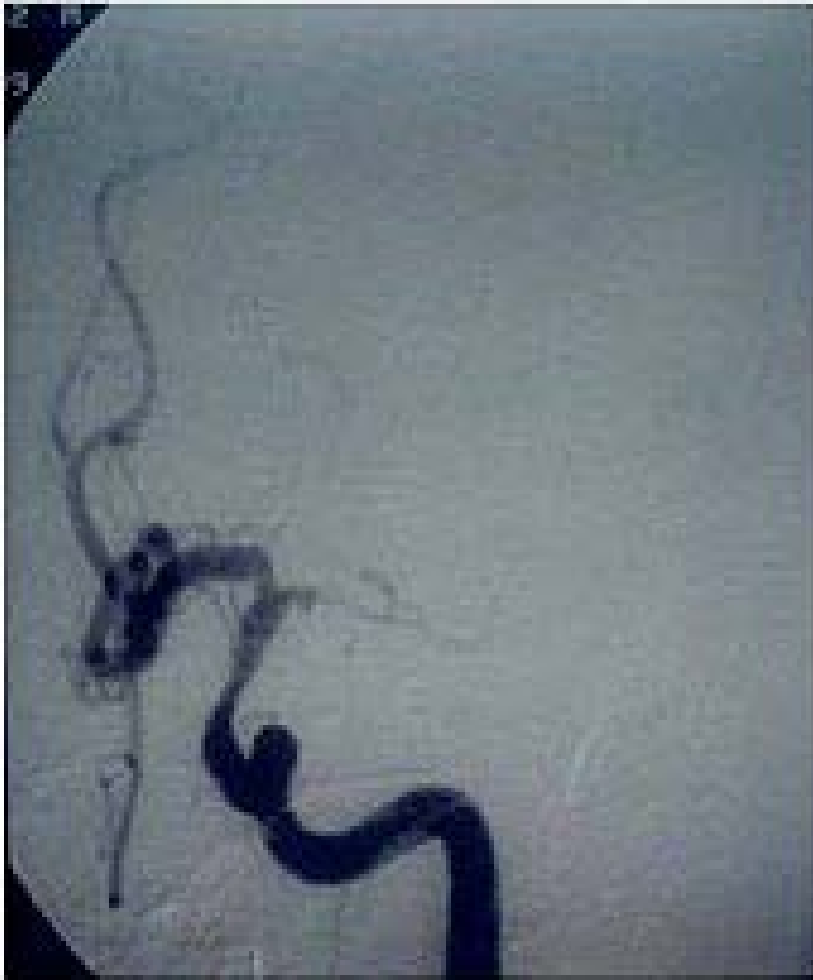
- Most patients are not treated with reperfusion therapy
- Most patients arrive too late for treatment or their strokes are considered to be mild
- Overall impact of intravenous thrombolysis is limited
- Impact of intra-arterial interventions is very small



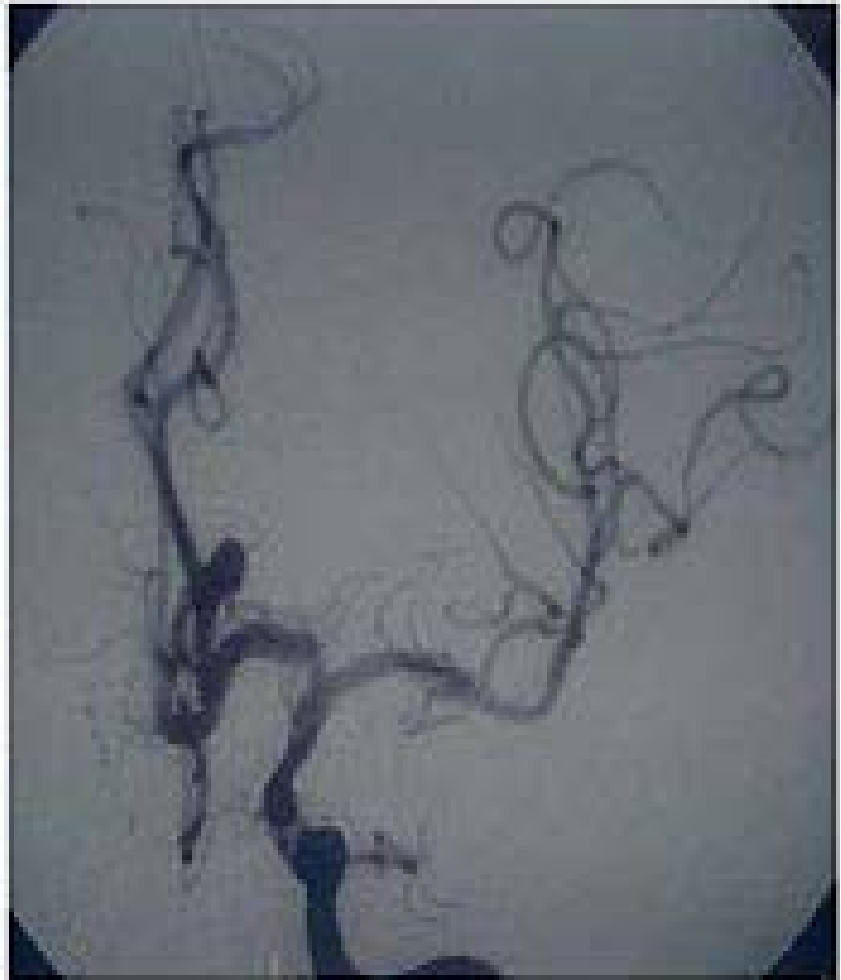


Endovascular Therapy

Angiography of a Large Vessel Occlusion



Before



After Intra-arterial Thrombolysis



Endovascular Therapy

- Intravascular catheterization of the major arteries of the brain for thrombectomy (removing the clot)
 - Clot retrieval devices
 - Intrarterial Alteplase
 - Can follow IV Alteplase!
 - Don't wait for a response
 - Can be used even if Alteplase can't in selected patients

Indications for Endovascular Tx (6h)



- Treatment initiated within 6 hours.
- Large Vessel Occlusion (LVO)
 - ▣ Middle Cerebral Artery (Proximal section)
 - ▣ Internal Carotid Artery
 - ▣ Need a CT-Angiogram (or MRA)
- NIHSS ≥ 6
- Minimal early changes on CT Head



Endovascular Therapy evidence

- Multiple Positive trials
 - ▣ MR CLEAN, SWIFT PRIME, EXTEND-IA, ESCAPE, REVASCAT, THRACE
 - ▣ Class I, Level of Evidence A Studies
 - ▣ Pooled data:
 - Outcome measure: Normal or minimal disability
 - OR 2.41
 - 95% CI 1.51-3.84



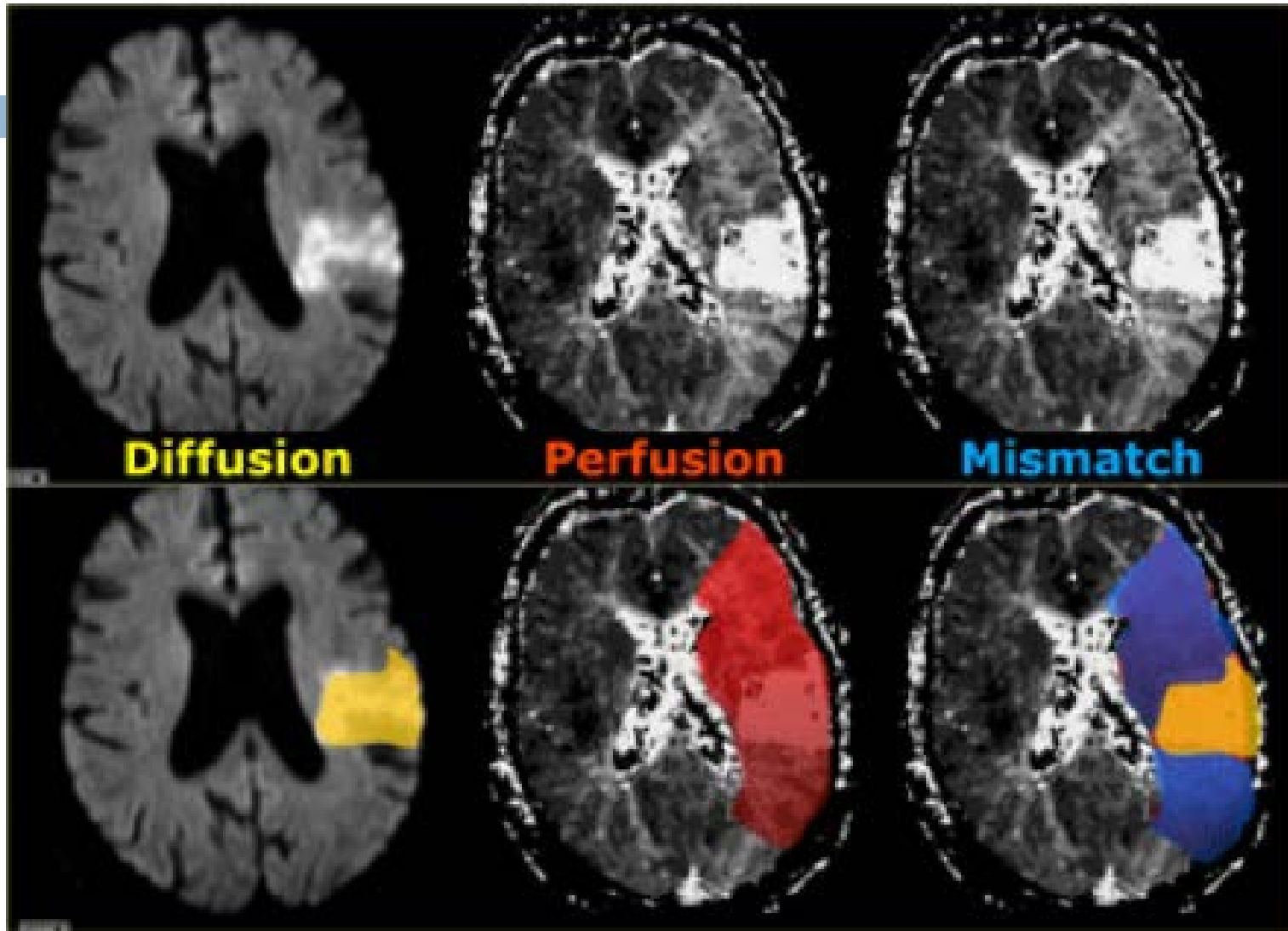
Is there brain to save?

- For patients > 6 hours out from LKN
- Dead vs Dysfunctional brain cells
 - ▣ Infarcted vs Ischemic
 - ▣ A *Mismatch* in the amount of brain that is dead and the amount of brain supplied by the artery.
 - ▣ Blood comes from other vascular territories.



Mismatch

- CT-Perfusion
- Infarcted brain
 - Low Cerebral Blood Volume
 - No flow
- Ischemic brain
 - ▣ Normal or elevated Cerebral Blood Volume
 - ▣ Slow blood flow





Clinical Trials

- DAWN
 - LKN 6-24h
- DEFUSE 3
 - LKN 6-16h
- Carefully selected patients
 - Primarily the CT-Perfusion



Clinical Trial Outcomes

- Large Vessel Occlusion, LKN 6-24h, Mismatch
- Moderate disability or better
- DAWN
 - Endovascular: 49%
 - Conservative: 13%
 - Adjusted Difference 33%, CI: 21-44%
- DEFUSE 3
 - Endovascular: 44.6%
 - Conservative: 16.7%, RR: 2.67, CI: 1.6-4.48



Section Summary

- Endovascular Tx is for large vessel occlusions (LVO)
- All LVOs if LKN is less than 6 hours.
- For LKN at 6-24 hours, Endovascular Tx is indicated if a CT-Perfusion scan shows there is brain to save.
- Call Neurology if NIHSS ≥ 6 within these time windows.