LATEST IN STROKE TREATMENT

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PRESENTER DISCLOSURE INFORMATION

- Steve M. Cordina, MD
- Latest in Stroke Treatment

- Financial Disclosure: None

OUTLINE

- Stroke Pathophysiology
- Intravenous Thrombolytic Trials
- Intra-arterial Acute Stroke Trials
- Current evidence based recommendations
- Conclusions

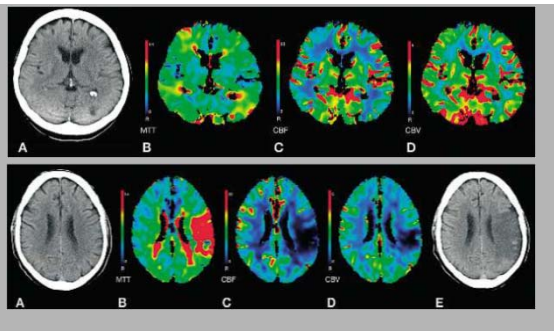
OUTLINE

- Stroke is the fifth leading cause of death and the leading cause of disability in the US.
- Each year, about 795,000 people suffer a stroke. About 600,000 of these are first attacks, and 185,000 are recurrent attacks.
- Of all strokes, 87 % are ischemic (IS), 10 % are intracerebral hemorrhage (ICH), and 3 % are subarachnoid hemorrhage (SAH).

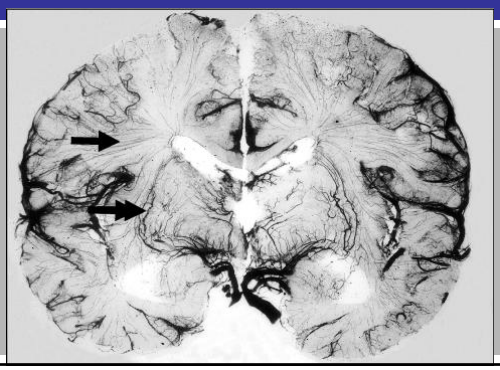
CEREBRAL BLOOD FLOW

- Normal cerebral blood flow (CBF) is approximately **50-to 60 ml/100g/ Min** and varies in different parts of the brain.
- In response to ischemia, the cerebral autoregulatory mechanisms compensate for a **reduction** in CBF by local vasodilatation, opening the collaterals, and increasing the extraction of oxygen and glucose from the blood.
- When the CBF is reduced to below 20 ml/100g/min, an electrical silence ensues and synaptic activity is greatly diminished in an attempt to preserve energy stores.
- CBF of less than 10ml/100g/min results in irreversible neuronal injury.

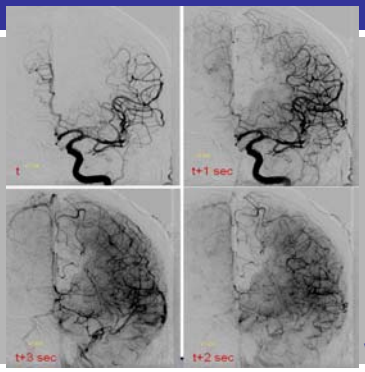
CEREBRAL BLOOD FLOW



CEREBRAL COLLATERALS



CEREBRAL COLLATERALS



IV THROMBOLYTIC TRIALS

RCTs	Intervention	Time window	(n)	Primary outcome result
MAST-E 1995	1) Placebo 2) SK	6 hrs	310	NEGATIVE
MAST-I 1995	1) Placebo 2) ASA 160 mg 3) SK 4) ASA + SK	6 hrs	622	NEGATIVE
ASK 1996	1) Placebo 2) SK	4 hrs	340	NEGATIVE
ECASS 1995	1) Placebo 2) IV rtPA (1.1 mg/kg)	6 hrs	620	NEGATIVE
ECASS II 1998	1) Placebo 2) IV rtPA (0.9 mg/kg)	6 hrs	800	NEGATIVE
ATLANTIS 1999	1) Placebo 2) IV rtPA (0.9 mg/kg)	3-5 hrs	667	NEGATIVE
NINDS 1995	1) Placebo 2) IV rtPA (0.9 mg/kg)	3 hrs	624	POSITIVE
ATLANTIS 2002	1) Placebo 2) IV rtPA (0.9 mg/kg)	3 hrs	91	POSITIVE
ECASS III 2008	1) Placebo 2) IV rtPA (0.9 mg/kg)	3-4.5 hrs	821	POSITIVE

IV THERAPY

- Tissue plasminogen activator for acute ischemic stroke *(NEJM 1995; 33: 1581-1587)*
  - 624 patients with ischemic stroke within 3 hours
  - Randomized to intravenous alteplase versus placebo

	Intravenous Alteplase	Placebo
Improvement at 24h	47%	39%
Favorable Outcome at 3m	43%	27%
Intracerebral Hemorrhage	6.4%	0.6%

IV THERAPY

- Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke (ECASS III)
  - 821 patients with ischemic stroke between 3 and 4.5 hours
  - Randomized to IV alteplase versus placebo

	Intravenous Alteplase	Placebo
Favorable Outcome at 3m	52.4%	45.2%
Symptomatic Intracerebral Hemorrhage	2.4%	0.2%

NEJM 2008; 359:1317-1329

RISK – BENEFIT OF IV TPA

IV t-PA administration window	NNT for good outcome in 1 patient	NNH one patient
0 – 90 min	3.6 patients	65 patients
91-180 min	4.3 patients	38 patients
180-270 min	5.9 patients	30 patients

After 270 minutes, iv TPA has no net benefit

IV THERAPY

- There is only 1 approved drug for treating an Acute Ischemic Stroke: IV rt-PA
- Successful administration of IV rt-PA has been proven to improve long term outcomes and reduces costs to the healthcare system, even in patients with low initial NIHSS

IV THERAPY

Study	Number of patients	Death or dependency in TPA arm
NINDS	312	57%
CASES	1135	44%
ECASS III	821	48%

CLOT BURDEN AND RECANALIZATION

- Site of Arterial Occlusion Identified by Transcranial Doppler Predicts the Response to Intravenous Thrombolysis for Stroke *(Stroke 2007; 38:948-954)*

Location of occlusion	Complete Recanalization within 2 hours of bolus	Favorable Outcome at 3 months (mRS ≤1)
Distal MCA	44%	52%
Proximal MCA	30%	25%
Tandem ICA + MCA	27%	21%
Terminal ICA	6%	18%
Basilar Artery	33%	25%

EARLY RECANALIZATION AND OUTCOME

- Is the benefit of early recanalization sustained at 3 months? A prospective cohort study. (Stroke 2003; 34:695-8)

	Favorable Outcome at 3 months with dramatic/early recovery within 2 hours of ivTPA	Favorable Outcome at 3 months
Complete Early Recanalization	78%	50%
Partial early Recanalization	66%	44%
No early recanalization	N/A	22%

INTRA-ARTERIAL THERAPY STUDIES

- Prolyse in Acute Cerebral Thromboembolism (PROACT) II *(JAMA 1999;282:2003-11)*
  - Multicenter Randomized Controlled Trial
  - 180 patients with occlusion of middle cerebral artery within 6 hours of onset
  - Randomized to intra-arterial pro-urokinase and heparin versus heparin alone
  - Primary outcome measure: modified Rankin score ≤2 at 90 days

INTRA-ARTERIAL THERAPY STUDIES

- Prolyse in Acute Cerebral Thromboembolism (PROACT) II *(JAMA 1999;282:2003-11)*

	Pro-Urokinase	Placebo
Recanalization	66%	18%
Symptomatic ICH	10%	2%
Favorable outcome (3 months)	40%	25%

BRIDGING (COMBINATION OF IV AND IA THERAPIES)

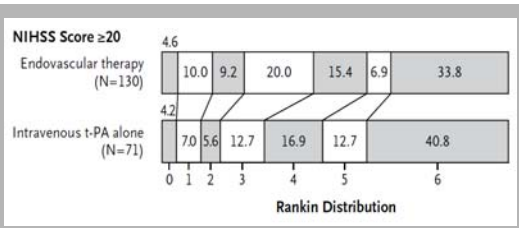
- Interventional Management of Stroke III

Phase III, randomized, multi-center, open-label clinical trial

- Purpose: To determine whether a combined IV/IA approach to recanalization is superior to standard IV rt-PA alone when initiated within 3 hours of stroke onset.
- Interim analysis April 2012 showed that the study had a very low likelihood of demonstrating the pre-specified, clinically significant difference in benefit between the treatment arms of the study.
- **No significant difference** in functional independence with endovascular therapy after intravenous t-PA, as compared with intravenous t-PA alone.

N Engl J Med 2013. DOI: 10.1056/NEJMoa1214300

BRIDGING (COMBINATION OF IV AND IA THERAPIES)



Differences between the two treatment groups across the entire distribution of the mRS (p = 0.06, van Elterin test)

Broderick, Joseph, et. Al. Endovascular Therapy after Intravenous t-PA versus t-PA Alone for Stroke. NEJM. vol. 368 no. 10

TRIALS 2013

Study	Sites	EVT	Req. Imaging	LVO eval.	EVT	Iv TPA in EVT group	Control	Result
IMS III 2013 N=656	58	<6 h	NCCT	Y/N	IA TPA MERCI	Yes	IV TPA	40.8% vs 38.7% CI -6.1 to 9.1 sICH 6.2% vs. 5.9%
MR Rescue 2013 N=118	22	<8 h	NCCT	Yes	MERCI Penumbra	Yes	IV TPA or ASA	No difference 3.9 vs 3.9 Mortality 21% sICH 4% both groups
Synthesis 2013 N = 362	24	<6 h	NCCT	No	IA TPA Wire MERCI Heparin 5000U	No	IV TPA	No difference 30.4% vs. 34.8% sICH 6% both groups

STENT RETRIEVERS

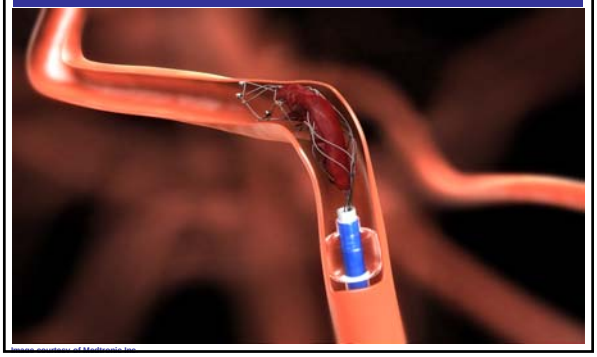


Image courtesy of Medtronic Inc

TRIALS 2014-2015

- MR CLEAN
- ESCAPE
- EXTEND IA
- SWIFT PRIME
- REVASCAT

TRIALS 2014-2015

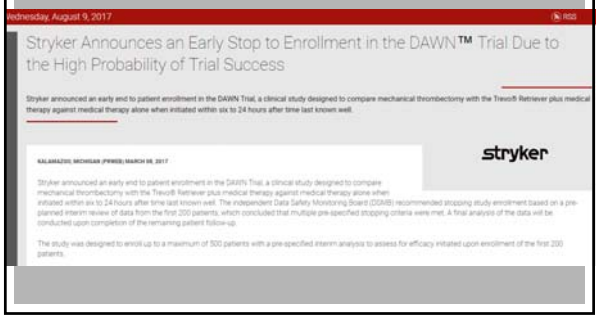
- Multi-center prospective randomized blinded trials
- IV tPA eligible patients treatable within 6 hours
- CT angiogram confirming large vessel occlusion
- Use of modern devices: stent retrievers
- Treatment at high volume centers
- ***ALL five trials were stopped early by each study's DSMB due to overwhelming efficacy of endovascular therapy.***

Safety: sICH no different from IV tPA alone (3-7%)

Elderly patients (>70, >80) benefited as much if not more

Trial	#Pts	IVtPA	Medical	Endovascular
MR CLEAN	500	89%	19.1%	32.5%
ESCAPE	316	75%	29.3%	53%
EXTEND IA	75	100%	40%	71%
SWIFT PRIME	196	100%	35.5%	60.2%
REVASCAT	206	73%	28.2%	43.7%

TRIALS 2017



Wednesday, August 9, 2017

Stryker Announces an Early Stop to Enrollment in the DAWN™ Trial Due to the High Probability of Trial Success

Stryker announced an early end to patient enrollment in the DAWN Trial, a clinical study designed to compare mechanical thrombectomy with the Trevo® Retriever plus medical therapy against medical therapy alone when initiated within six to 24 hours after time last known well.

stryker

KALAMAZOO, MICHIGAN (PRWEB) MARCH 08, 2017

Stryker announced an early end to patient enrollment in the DAWN Trial, a clinical study designed to compare mechanical thrombectomy with the Trevo® Retriever plus medical therapy against medical therapy alone when initiated within six to 24 hours after time last known well. The independent Data Safety Monitoring Board (DSMB) recommended stopping study enrollment based on a pre-planned interim review of data from the first 200 patients, which concluded that multiple pre-specified stopping criteria were met. A final analysis of the data will be conducted upon completion of the remaining patient follow-up.

The study was designed to enroll up to a maximum of 500 patients with a pre-specified interim analysis to assess for efficacy initiated upon enrollment of the first 200 patients.

LARGE VESSEL OCCLUSION

Common: 40-50% of all ischemic stroke.

Severe: 5 x higher mortality, 3 fold reduction in good outcome.

Respond poorly to intravenous thrombolytic (tPA).

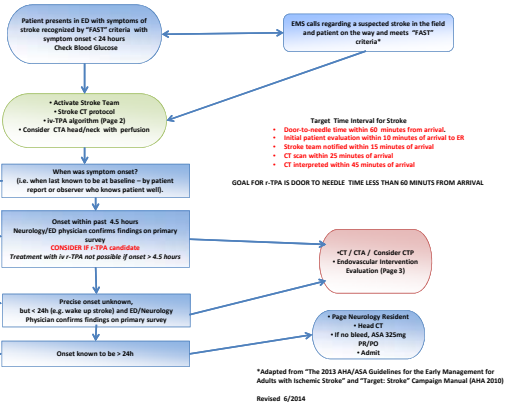
Successful opening of the artery associated with improved outcome.

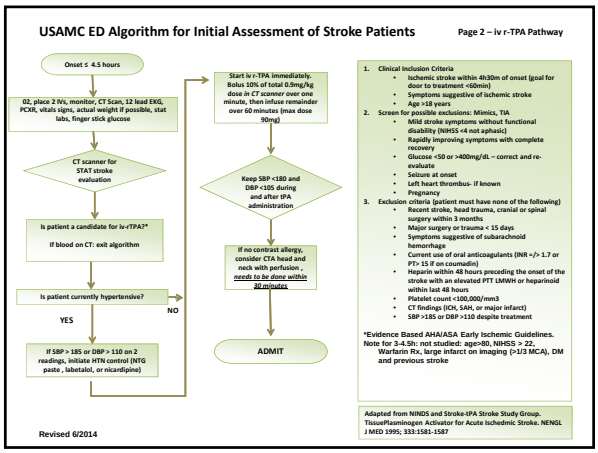
Multiple randomized clinical trials comparing endovascular therapy with stent retrievers to intravenous tPA have provided powerful LEVEL 1A evidence of clinical benefit with endovascular therapy. This is the first major advancement in the treatment.

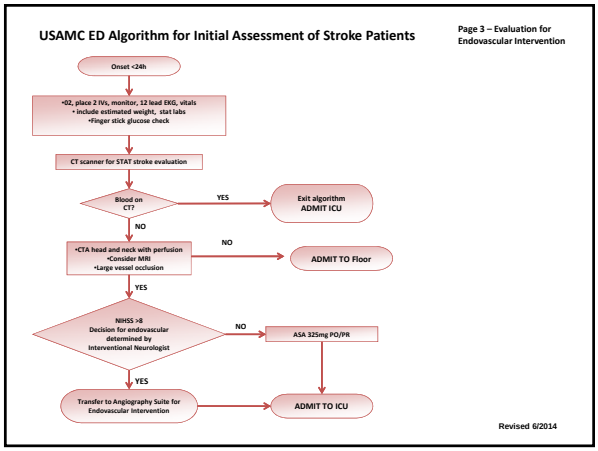
Effective treatment of these patients requires a very efficient protocol of care involving coordination between primary and comprehensive stroke hospitals.

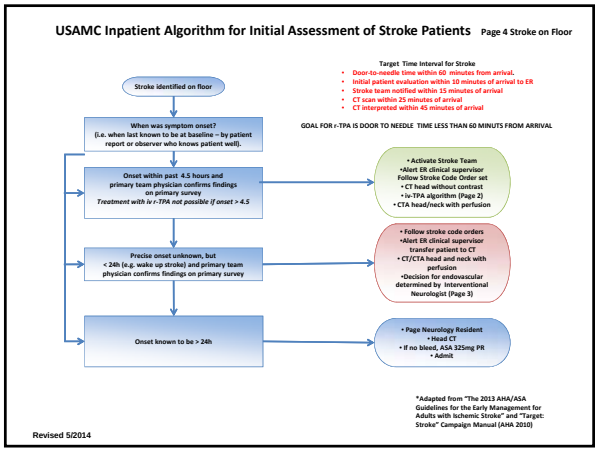
1. Smith WS et al. Significance of large vessel intracranial occlusion causing acute ischemic stroke and TIA. Stroke. 2009; Dec; 40(12): 38340-40.
2. Riedel et al. The Importance of Size: Successful Recanalization by Intravenous Thrombolysis in Acute Anterior Stroke Depends on Thrombus Length. Stroke 2011; 42:1775-7.
3. *Powers et al. 2015 AHA/ASA Focused Update of the 2013 Guidelines for the Early Management of Patients with Acute Ischemic Stroke Regarding Endovascular Treatment. Stroke. Epub ahead of print.*

USAMC ED Algorithm for Initial Assessment of Stroke Patient




USAMC ED Algorithm for Initial Assessment of Stroke Patients
Page 2 – iv r-TPA Pathway
Onset ≤ 4.5 hours
02, place 2 IVs, monitor, CT Scan, 12 lead EKG, PCXR, vitals signs, actual weight if possible, stat labs, finger stick glucose
CT scanner for STAT stroke evaluation
Is patient a candidate for iv-rTPA?*
If blood on CT: exit algorithm
Is patient currently hypertensive?
YES
NO
If SBP > 185 or DBP > 110 on 2 readings, initiate HTN control (NTG paste , labetalol, or nicardipine)
Start iv r-TPA immediately. Bolus 10% of total 0.9mg/kg dose in CT scanner over one minute, then infuse remainder over 60 minutes (max dose 90mg)
Keep SBP <180 and DBP <105 during and after tPA administration
If no contrast allergy, consider CTA head and neck with perfusion , needs to be done within 30 minutes
ADMIT
1. Clinical Inclusion Criteria
• Ischemic stroke within 4h30m of onset (goal for door to treatment <60min)
• Symptoms suggestive of ischemic stroke
• Age >18 years
2. Screen for possible exclusions: Mimics, TIA
• Mild stroke symptoms without functional disability (NIHSS <4 not aphasic)
• Rapidly improving symptoms with complete recovery
• Glucose <50 or >400mg/dL – correct and re-evaluate
• Seizure at onset
• Left heart thrombus- if known
• Pregnancy
3. Exclusion criteria (patient must have none of the following)
• Recent stroke, head trauma, cranial or spinal surgery within 3 months
• Major surgery or trauma < 15 days
• Symptoms suggestive of subarachnoid hemorrhage
• Current use of oral anticoagulants (INR =/> 1.7 or PT> 15 if on coumadin)
• Heparin within 48 hours preceding the onset of the stroke with an elevated PTT LMWH or heparinoid within last 48 hours
• Platelet count <100,000/mm3
• CT findings (ICH, SAH, or major infarct)
• SBP >185 or DBP >110 despite treatment
*Evidence Based AHA/ASA Early Ischemic Guidelines. Note for 3-4.5h: not studied: age>80, NIHSS > 22, Warfarin Rx, large infarct on imaging (>1/3 MCA), DM and previous stroke
Adapted from NINDS and Stroke-tPA Stroke Study Group. TissuePlasminogen Activator for Acute Ischedmic Stroke. NENGL J MED 1995; 333:1581-1587
Revised 6/2014


USAMC ED Algorithm for Initial Assessment of Stroke Patients
Page 3 – Evaluation for Endovascular Intervention
Onset <24h
•02, place 2 IVs, monitor, 12 lead EKG, vitals
• include estimated weight, stat labs
•Finger stick glucose check
CT scanner for STAT stroke evaluation
Blood on CT?
YES
Exit algorithm ADMIT ICU
NO
•CTA head and neck with perfusion
•Consider MRI
•Large vessel occlusion
NO
ADMIT TO Floor
YES
NIHSS >8
Decision for endovascular determined by Interventional Neurologist
NO
ASA 325mg PO/PR
YES
Transfer to Angiography Suite for Endovascular Intervention
ADMIT TO ICU
Revised 6/2014


USAMC Inpatient Algorithm for Initial Assessment of Stroke Patients
Page 4 Stroke on Floor
Target Time Interval for Stroke
• Door-to-needle time within 60 minutes from arrival.
• Initial patient evaluation within 10 minutes of arrival to ER
• Stroke team notified within 15 minutes of arrival
• CT scan within 25 minutes of arrival
• CT interpreted within 45 minutes of arrival
GOAL FOR r-TPA IS DOOR TO NEEDLE TIME LESS THAN 60 MINUTS FROM ARRIVAL
Stroke identified on floor
When was symptom onset? (i.e. when last known to be at baseline – by patient report or observer who knows patient well).
Onset within past 4.5 hours and primary team physician confirms findings on primary survey
Treatment with iv r-TPA not possible if onset > 4.5
• Activate Stroke Team
•Alert ER clinical supervisor Follow Stroke Code Order set
• CT head without contrast
• iv-TPA algorithm (Page 2)
• CTA head/neck with perfusion
Precise onset unknown, but < 24h (e.g. wake up stroke) and primary team physician confirms findings on primary survey
• Follow stroke code orders
•Alert ER clinical supervisor transfer patient to CT
• CT/CTA head and neck with perfusion
•Decision for endovascular determined by Interventional Neurologist (Page 3)
Onset known to be > 24h
• Page Neurology Resident
• Head CT
• If no bleed, ASA 325mg PR
• Admit
*Adapted from "The 2013 AHA/ASA Guidelines for the Early Management for Adults with Ischemic Stroke" and "Target: Stroke" Campaign Manual (AHA 2010)
Revised 5/2014

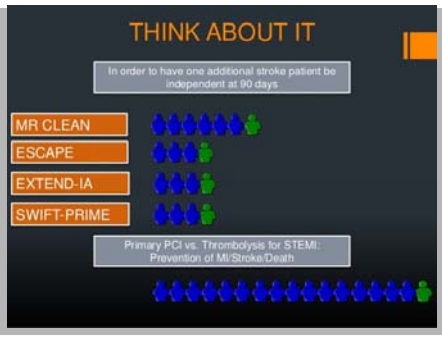
CONCLUSION

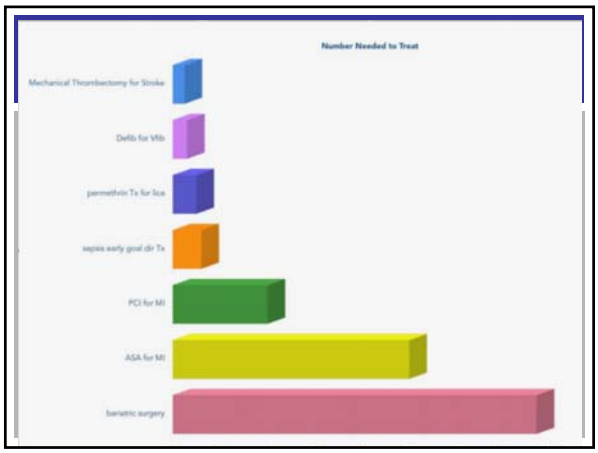
- **Time is brain**, IV rt-PA only IV FDA approved medication for the treatment of ischemic stroke
  - **Window 0-3 hours (FDA), 3-4.5 hours (AHA recommended, non-FDA approved)**
- **Endovascular interventions decrease morbidity and mortality AND improve outcomes** in selected patients at Comprehensive Stroke Centers
  - CTA confirmed Large Vessel Occlusion,
    - ***Treat within 8 hours of onset***
    - ***(Up to 24 hours of onset possible, based on DAWN)***
  - No large core established stroke on initial CT imaging
- **Endovascular Therapy is now Standard of Care.**

CONCLUSION

- **Standard of Care is now ivTPA followed by thrombectomy in eligible patients.**
- **Transfer of confirmed Large Vessel Occlusion is *now necessary* if hospital lacks capability for IA treatment.**
- **IV TPA Drip and Ship model to be employed in these situations**
- **Expedited transfer is mandatory, most patients are subject to an 8 hour time window.**
- **Recommend locating regional Stroke Centers that offer comprehensive stroke treatment and setting up appropriate transfer protocols.**

CONCLUSION




Number Needed to Treat
Mechanical Thrombectomy for Stroke
Defib for Vfib
permethrin Tx for lice
sepsis early goal dir Tx
PCI for MI
ASA for MI
bariatric surgery

THANK YOU