

Health Outcomes in Acute Treatment of Cerebrovascular Disease

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9/22/2021

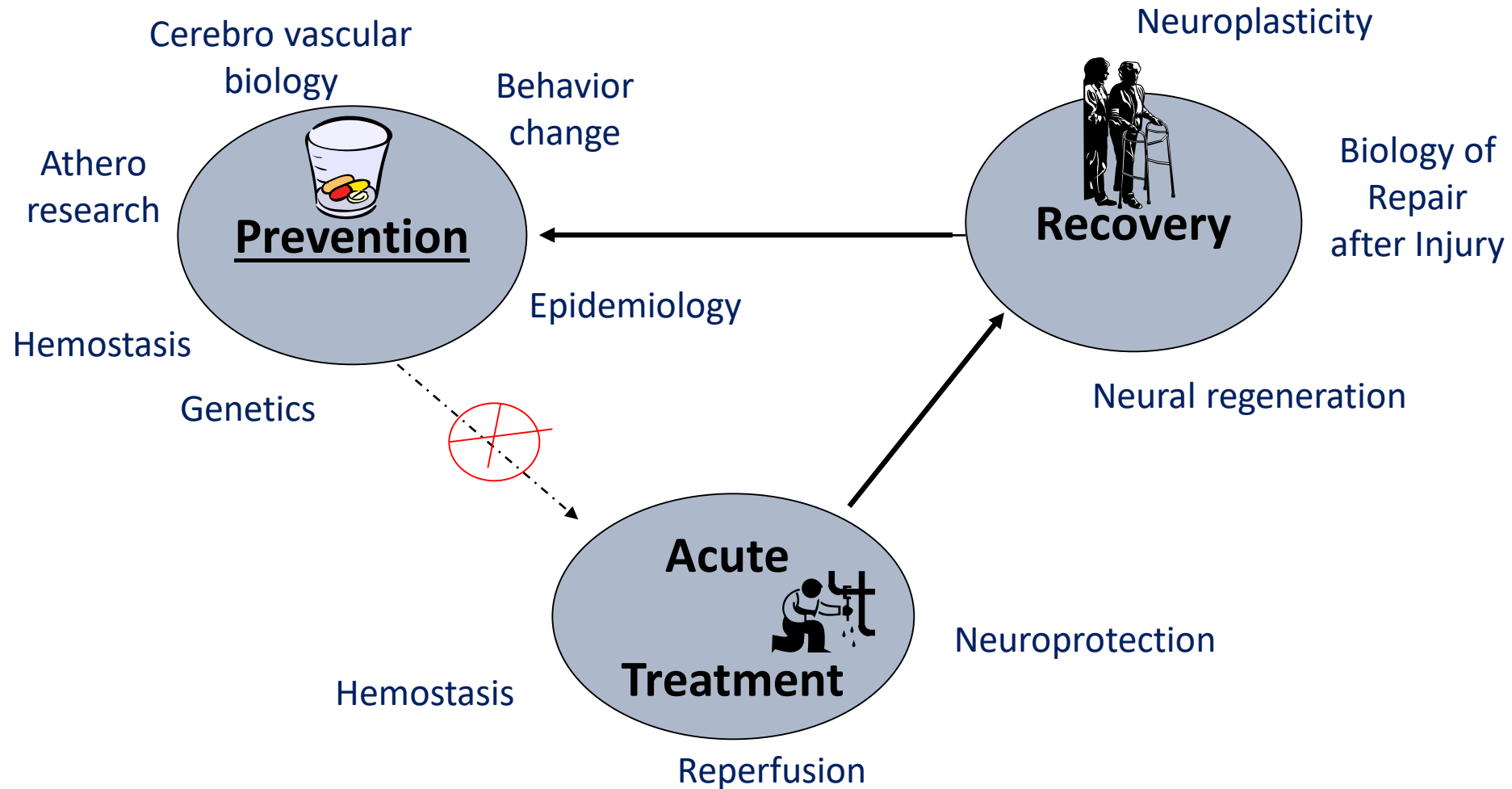
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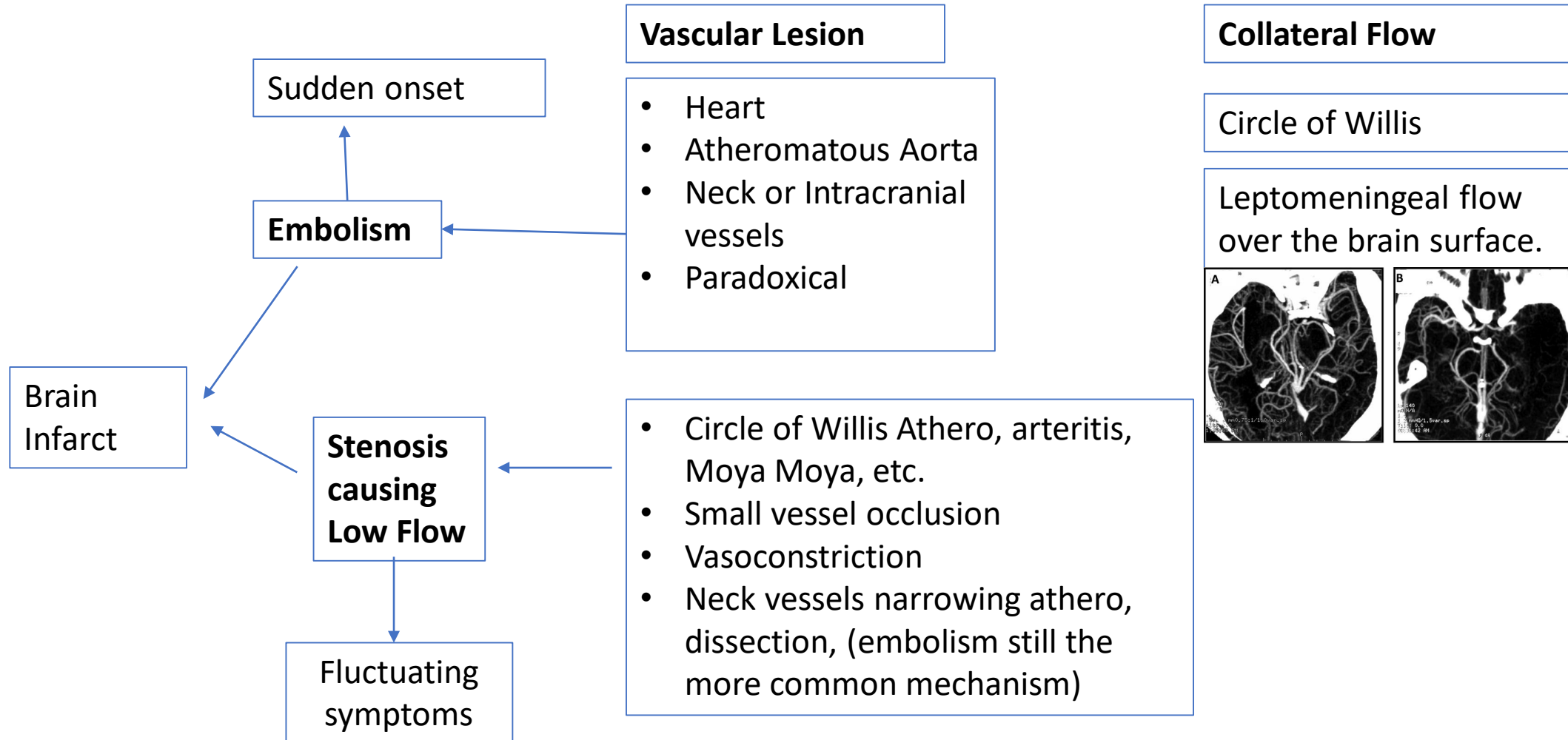
Disclosure

I have **NO** actual or potential financial disclosures or conflicts of interest with the materials included in this presentation

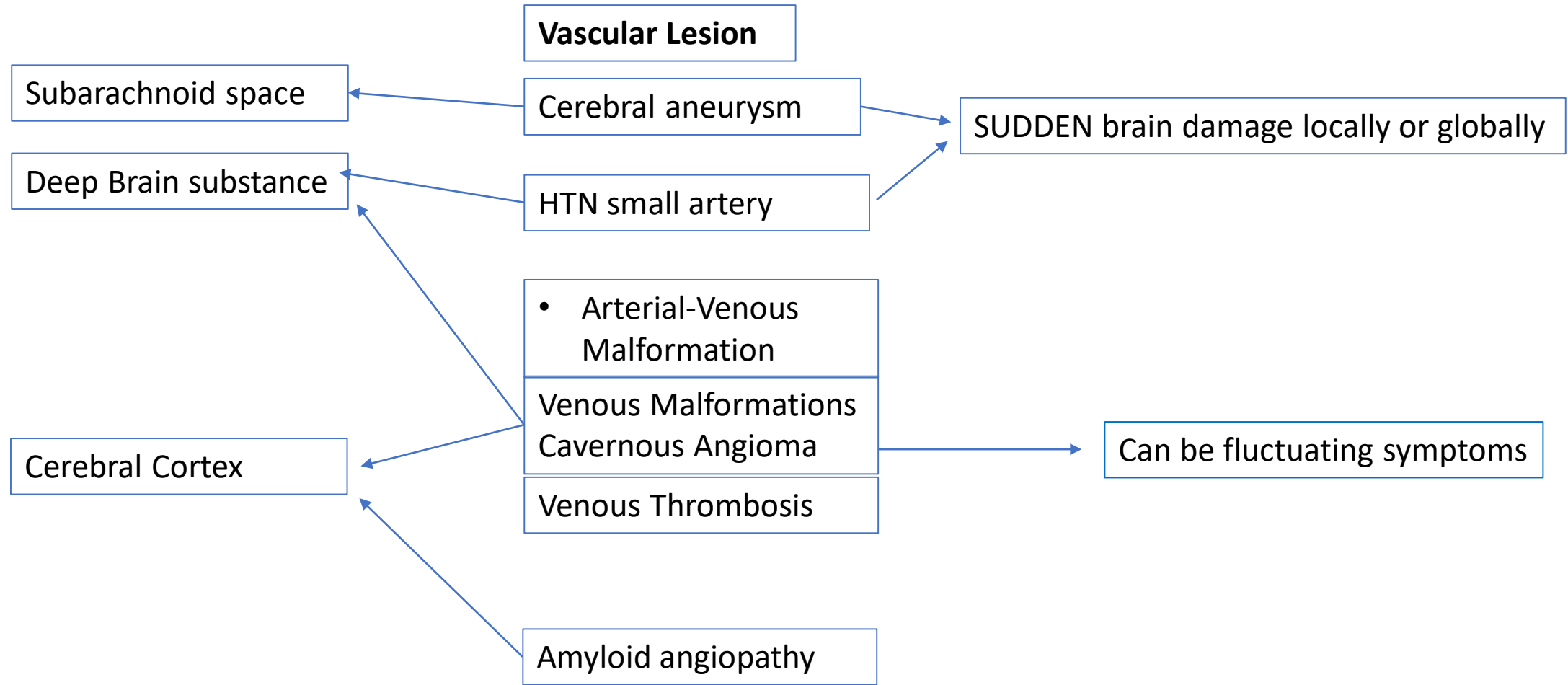
NIH supports research in stroke Prevention, Treatment and Recovery



Cerebrovascular Disease: multiple pathologies leading to infarction of brain tissue



Hemorrhagic stroke



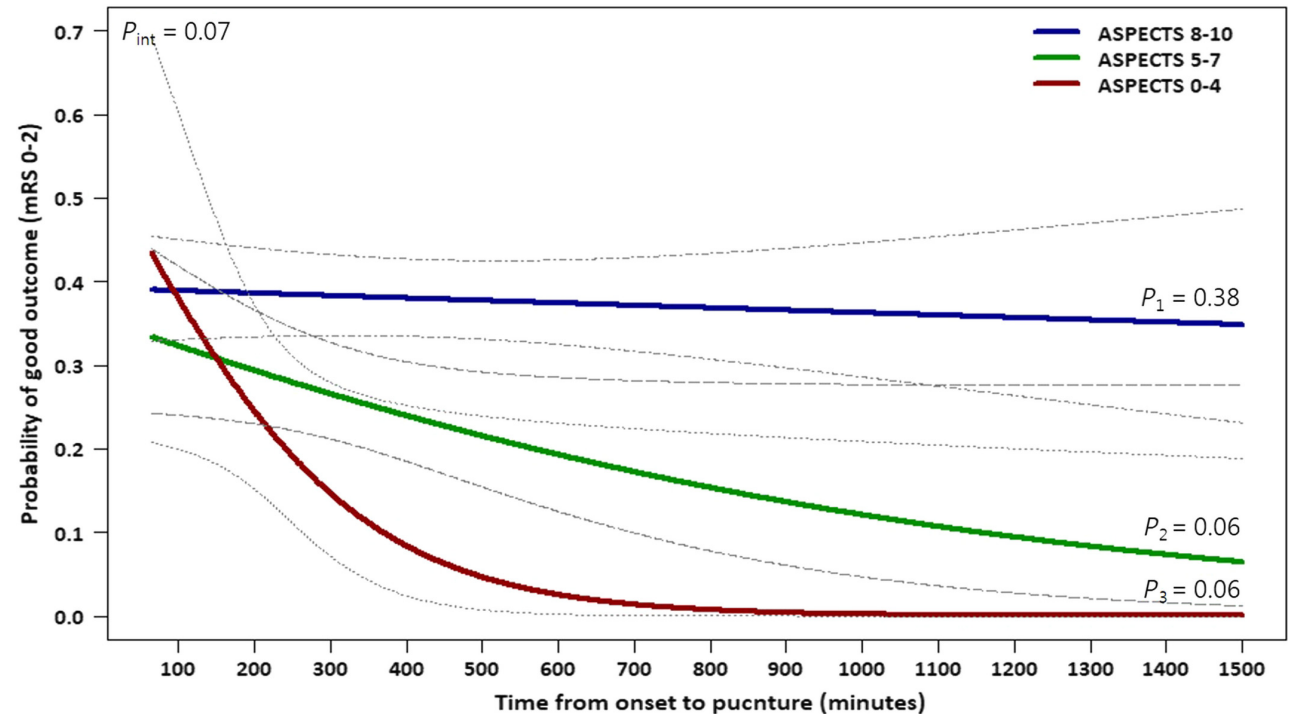
Ischemic brain damage

- Death of brain tissue occurs as a function of the Flow decrement x **Time**
 - **Goal of reperfusion therapy is to limit the time during which flow is reduced**
- Flow decrement is a function of the degree of vessel block and the level of collateral flow
- When first imaged there is generally a core with very low flow that can not be salvaged; surrounded by regions with better flow that can be prevented from dying if reperfusion occurs immediately
- Infarcts are basically cavities with complete wipe out of neurons and there is no regeneration of neural function
- A person's functional outcome depends on how the damage disturbs neural networks. Though the tissue does not repair itself, the networks seem to be able to re-wire for improved function over months, more slowly thereafter

Association between time to treatment and functional outcomes according to the Diffusion-Weighted Imaging Alberta Stroke Program Early Computed Tomography Score in endovascular stroke therapy

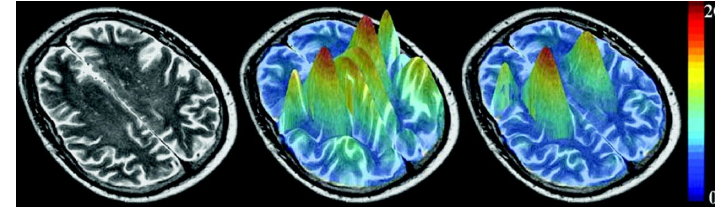
KIM JT, et. al., European Journal of Neurology, Volume: 27, Issue: 2, Pages: 343-351,, DOI: (10.1111/ene.14083)

Relations between OTP and good outcome by 3 DWI-ASPECTS categories



Drivers of Outcomes after Brain Infarction

- Short term: @ 1-7 day assessment
 - Location of infarct in brain
 - Size of the infarct
 - Secondary hemorrhage into the infarct
 - Ischemic brain swelling leading to elevated intracranial pressure
 - Co-morbid conditions, *i.e.*, infection
- Long term: @ 90 day assessment
 - Age of individual
 - Previous brain injury and possibly the presence of diffuse white matter disease



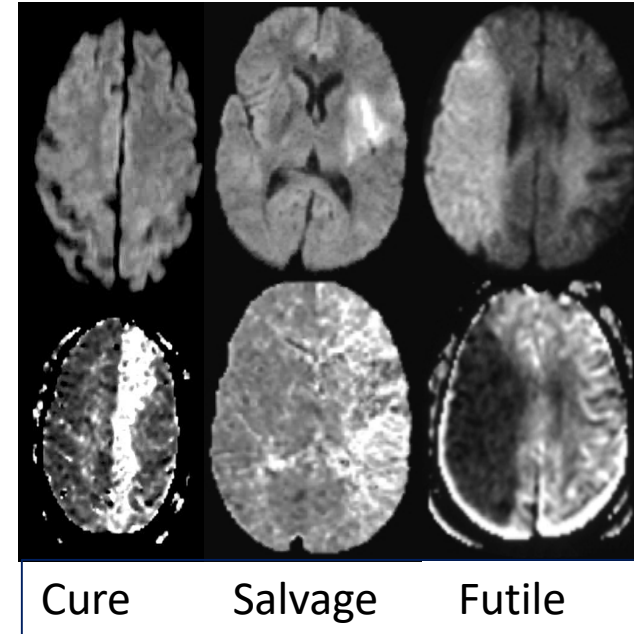
The Real Estate Factor: Quantifying the Impact of Infarct Location on Stroke Severity
[Menezes](#) MM et.. al., Stroke. 2007;38:194–197

Goal of Acute Ischemic Stroke Therapy: Reperfusion ASAP

- Intravenous thrombolysis- fast, relatively simple to administer, fairly effective for smaller vessel embolic /thrombotic occlusion with treatment <3-4.5 hours. Less effective for Circle of Willis occlusion
- Endovascular therapy- prior IV thrombolytic therapy not a contraindication, treatment of choice for large vessel occlusion and some may benefit at longer time windows 6-12 hours. Important characteristics include:
 - Success rate of opening vessel(s)
 - Speed of opening vessel
 - Risk of arterial injury (brain, or vessels between puncture site and brain)
 - Risk of sending embolic material into distal vascular bed

What will matter most to the person?

- How well did the treatment limit extent of infarction (size and location)?
 - Can be measured as preventing growth of infarct on sequential imaging
- Did the treatment cause secondary brain injury?
 - Distal embolic infarcts from clot instrumentation
 - Perforation of artery with clinically significant subarachnoid hemorrhage
 - Reperfusion injury: parenchymal hemorrhage into infarct, promote malignant brain edema
- Did the acute treatment create co-morbidities?
 - Aspiration pneumonia during imaging or procedures
 - Sepsis from instrumentation



How and when will the person know if they benefited from endovascular treatment?

- Most clear when neurological recovery occurs temporally associated with successful reperfusion (Walk off the angiographic phenomenon)
- Improved NIH Stroke Scale from pre-Rx
 - to post 24 hours if no worsening that follows
 - to day 7 (or day of discharge) factors in potential procedural comorbidities
- Evaluation of function at 90 days
 - factors in time of greatest rate of recovery of function after ischemic stroke. (longer is necessary for TBI, some forms of hemorrhagic stroke)

Outcome and Time Course of Recovery in Stroke. Part II: Time Course of Recovery. The Copenhagen Stroke Study

Henrik S. Jørgensen, MD, Hirofumi Nakayama, MD, Hans O. Raaschou, MD, Jørgen Vive-Larsen, MD, Mogens Støier, MD, Tom S. Olsen, MD, PhD

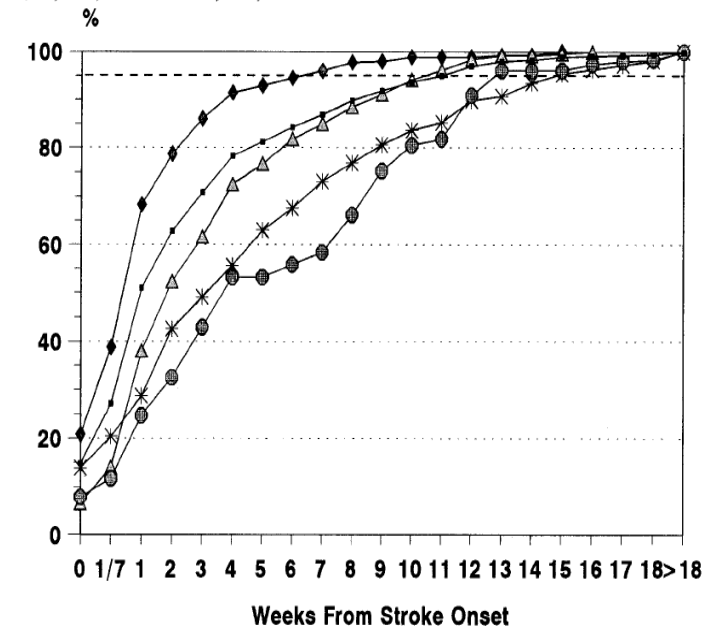


Fig 1—The time course of recovery in survivors shown as the cumulated rate of patients having reached their best neurological outcome. Rates are given for all patients, ■; for patients with initial mild stroke severity, ♦; for patients with initial moderate stroke severity, ▲; for patients with initial severe stroke severity, *; for patients with initial very severe stroke severity, ●. The

Stroke Scales

- NIH Stroke Scale- a global neurologic deficit scale built to detect change due to reperfusion in preparation for IV thrombolysis trials
 - Surveys for presence and estimate of severity of neurologic deficits as opposed to a fine measure of impact on function. Utility in emergency setting
- Modified Rankin Scale (mRS)- functional scale
 - 7 bins to detect large changes in functional levels which occur due to occlusion of major cerebral arteries, and which can be prevented by early reperfusion. A person's preference may not differ for the severe scores (*i.e.*, mRS 5,6,7)
 - Bins are crude enough that can estimate in emergency setting
 - Though prediction of mRS outcome due to major cerebral artery stroke is somewhat variable, mRS >2 is common. mRS ≤ 2 is therefore considered a relatively good outcome in top of carotid, MCA M1 or Basilar occlusion. mRS ≤ 3 may be more realistic for ICH trials
- Functional Independence Measure (FIM) scale
 - more fine-grained measure (18 items scored 1-7) of function and sensitive to change over weeks/months post stroke. Would be difficult to assess pre-stroke in emergency setting
- Barthel Index for Independent Living
 - 10 items scored with 100 points total. Would be difficult to assess in emergency setting

NINDS Notice of Interest in Research in the Endovascular Treatment of Acute Ischemic stroke

- Many questions remain about the **potential for benefit or harm** of thrombectomy
 - in specific subgroups of patients
 - In certain ischemic stroke phenotypes
- Also of interest are considerations such as **pre-hospital care and peri-procedural management** strategies that lead to better functional outcomes
- Promising **neuroprotectants** that failed in trials that predated successful reperfusion, as well as newer agents that have potential but remain untested, are ripe for consideration in this new environment to **widen the time window** for saving brain tissue and **limiting reperfusion injury**

The NINDS is interested in **master protocols to enable platform trials** that answer the above questions using a seamless rolling approach. Trials that further refine patient groups that do or do not benefit from mechanical thrombectomy, and using which management approaches, will also open the door to testing neuroprotectant strategies in an efficient, timely, and cost-effective manner

Can we enhance the effectiveness of intravenous reperfusion therapy?

- The goal is to determine the safety/effectiveness of **combining** the thrombolytic agent, tissue plasminogen activator (**tPA or TNK**) within 3 hours of onset- with a direct thrombin inhibitor, **argatroban**; or a potent anti-platelet agent, **eptifibatide** within 6 hours of onset
- 150th to the 500th subject enrollment, response adaptive randomization (RAR) will favor the active arm showing the greatest benefit based on accrued data
- **The primary outcome measure** for the MOST trial will be the 90-day mRS scores translated to **patient-centered utilities**. Safety outcomes are related to brain hemorrhage

Utility Scores for Each modified Rankin Score							
mRS Score	0	1	2	3	4	5	6
MOST Trial utility scores	10	9.1	7.6	6.5	3.3	0	0

Pre-Specified Secondary Outcomes:

- proportion of participants with NIHSS ≤ 2 at 24 hours
- change from baseline to 24-hour NIHSS
- proportion with 90-day mRS 0 or 1, and 0-2;
- 90-day ordinal analysis of the mRS;
- 90-day EuroQuol-5D;
- proportion of participants who have thrombectomy



ORIGINAL ARTICLE

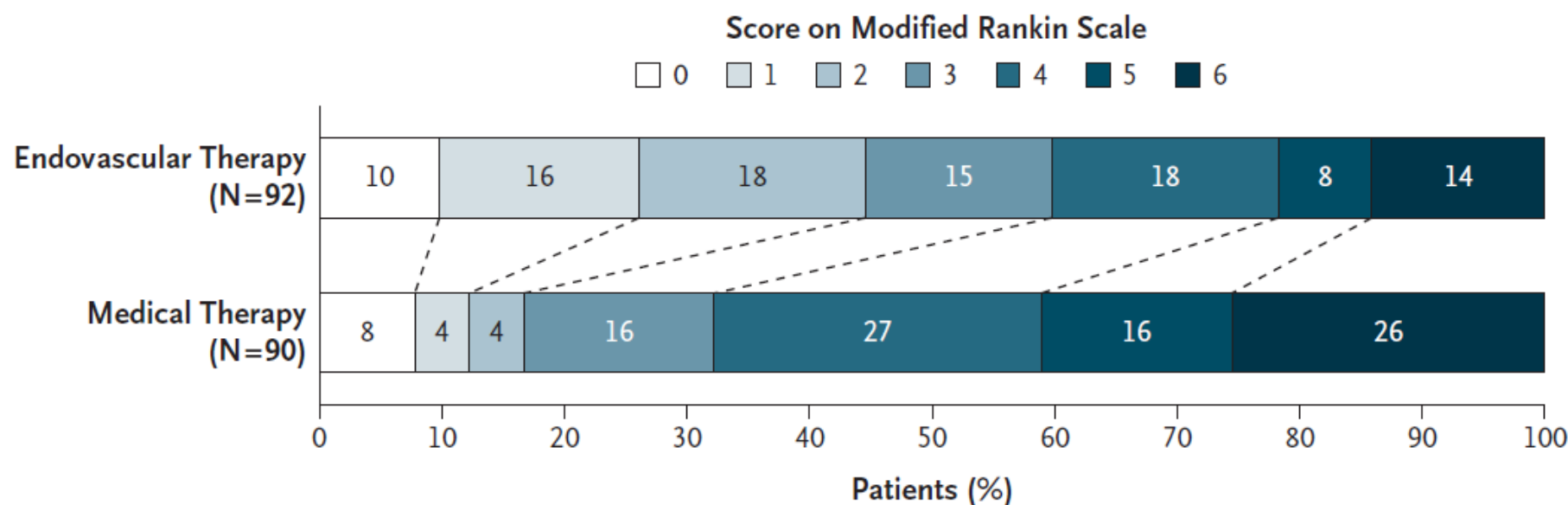
Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging

G.W. Albers, M.P. Marks, S. Kemp, S. Christensen, J.P. Tsai, S. Ortega-Gutierrez, R.A. McTaggart, M.T. Torbey, M. Kim-Tenser, T. Leslie-Mazwi, A. Sarraj, S.E. Kasner, S.A. Ansari, S.D. Yeatts, S. Hamilton, M. Mlynash, J.J. Heit, G. Zaharchuk, S. Kim, J. Carrozzella, Y.Y. Palesch, A.M. Demchuk, R. Bammer, P.W. Lavori, J.P. Broderick, and M.G. Lansberg, for the DEFUSE 3 Investigators*

- Prospective randomized Phase III multicenter controlled trial of endovascular therapy in an extend time window ending in 2017
- Patients with acute stroke due to large anterior artery occlusion treated between 6-16 hours of stroke onset with endovascular thrombectomy therapy vs. control
- **Perfusion/CTA or MRI DWI/PWI/MRA** studies prior to randomization.
 - Patients with ICA or MCA M1 occlusion & a Target Mismatch Profile
 - Randomized in a 1:1 ratio to treatment with one or more DEFUSE 3 approved thrombectomy device

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Procedure related complications-

- vasospasm in 1
- arterial perforation with Subarachnoid hemorrhage and clinical worsening in another

Parenchymal hematoma with mass effect (PH2) in 9% of endovascular and 3% of medical treated, ($p=0.21$)

Table 2. Clinical and Imaging Outcomes.

Outcome	Endovascular Therapy (N = 92)*	Medical Therapy (N = 90)	Odds Ratio or Risk Ratio (95% CI)†‡	P Value
Primary efficacy outcome: median score on modified Rankin scale at 90 days (IQR)‡	3 (1–4)	4 (3–6)	2.77 (1.63–4.70)§	<0.001
Secondary efficacy outcome: functional independence at 90 days — no. (%)¶	41 (45)	15 (17)	2.67 (1.60–4.48)	<0.001
Safety outcomes — no. (%)				
Death at 90 days	13 (14)	23 (26)	0.55 (0.30–1.02)	0.05
Symptomatic intracranial hemorrhage	6 (7)	4 (4)	1.47 (0.40–6.55)	0.75
Early neurologic deterioration	8 (9)	11 (12)	0.71 (0.30–1.69)	0.44
Parenchymal hematoma type 2	8 (9)	3 (3)	2.61 (0.73–14.69)	0.21
Imaging outcomes**				
Median infarct volume at 24 hr (IQR) — ml	35 (18–82)	41 (25–106)	—	0.19
Median infarct growth at 24 hr (IQR) — ml	23 (10–75)	33 (18–75)	—	0.08
Reperfusion >90% at 24 hr — no./total no. (%)	59/75 (79)	12/67 (18)	4.39 (2.60–7.43)	<0.001
Complete recanalization at 24 hr — no./total no. (%)	65/83 (78)	14/77 (18)	4.31 (2.65–7.01)	<0.001
TICI score of 2b or 3 — no./total no. (%)	69/91 (76)	—	—	

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Efficacy and safety of minimally invasive surgery with thrombolysis in intracerebral haemorrhage evacuation (MISTIE III): A randomised, controlled, open-label, blinded endpoint phase 3 trial

- Acute intracerebral hemorrhage trial to determine whether catheter evacuation of blood followed by cavity infusion of tPA would decrease clot size to 15m or less and thereby improve functional outcome
- Primary outcome was proportion of patients with mRS 0-3 at one year adjusted for group differences in prespecified variables such as age, intraventricular hemorrhage, clot location, Coma score, size and stability of the hemorrhage

At 1 year 45% of patients in the MISTIE group and 41% patients in the standard medical care group had achieved an mRS score of 0–3 (absolute risk difference 4% [95% CI –4 to 12]; p=0.33)

