Care of the Ischemic Stroke Patient: from ER to wards

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Disclosures

- none

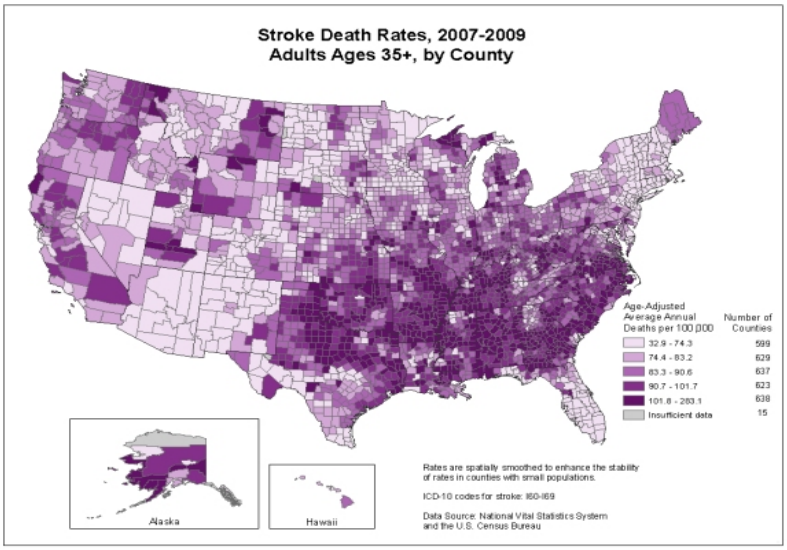
Outline

- **Epidemiology**
- Intravenous thrombolytic
- Thrombectomy
- Stroke management
- Post-stroke complications

Stroke Epidemiology

- 795,000 strokes are estimated to occur in the United States annually
  → 610,000 of these are first or new strokes
- 87% of these are ischemic strokes
- 130,000 Americans die from stroke annually
- Cost is estimated to be $ 36.6 billion annually
- In 2009, 34% of people hospitalized were younger than 65

Stroke Epidemiology



Stroke Epidemiology

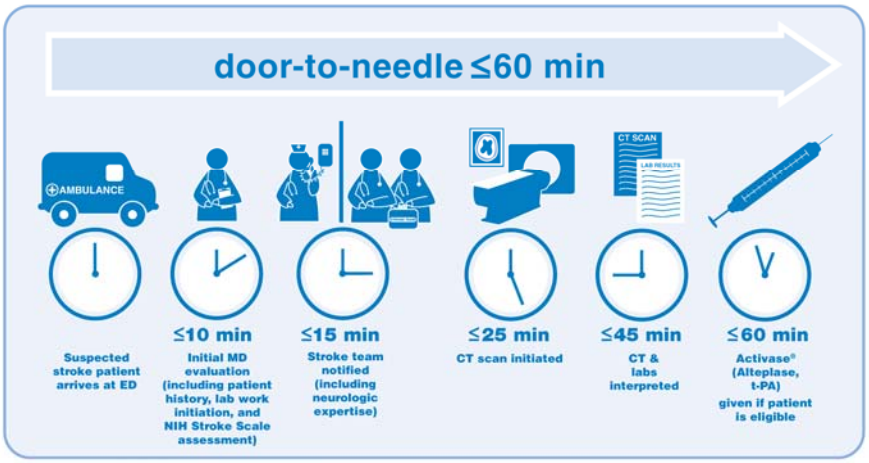
- stroke is 5th leading cause of death.
- However, public knowledge of stroke remains poor.
- Fewer than half of 911 calls for stroke were made within 1 hour of symptom onset and fewer than half of those callers thought stroke was cause of their symptoms

Outline

- Epidemiology
- **Intravenous thrombolytic**
- Thrombectomy
- Stroke management
- Post-stroke complications

NIH-recommended Emergency Department response times

The "golden hour" for evaluating and treating acute stroke



Reference: NINDS/NIH Web site: stroke proceedings.

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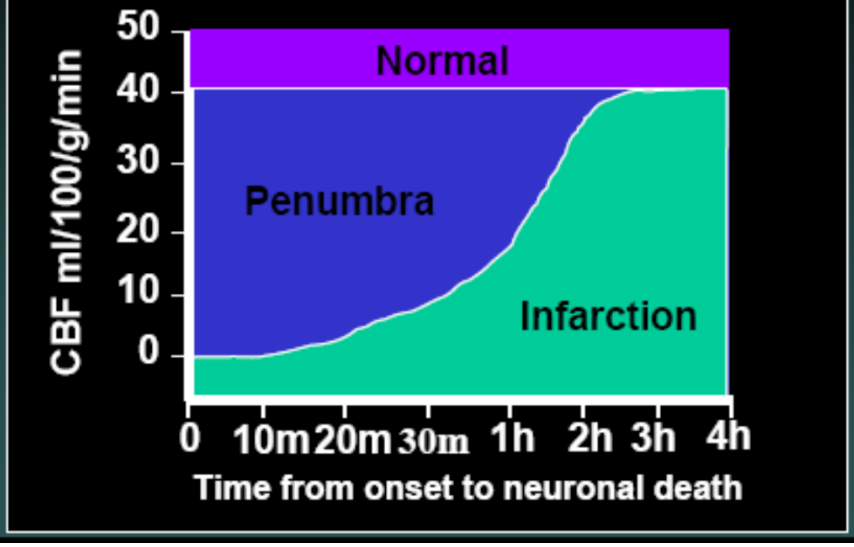
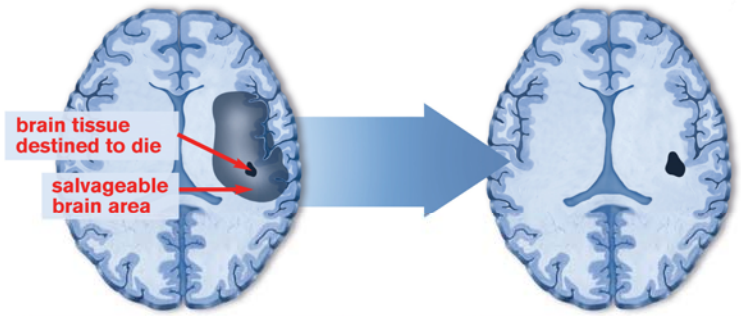
Relationship between duration and degree of cerebral blood flow (CBF) reduction



Potential to reverse neurologic impairment with thrombolytic reperfusion



The average stroke patient loses 32,000 brain cells every second[1]

Reperfusion offers the potential to reduce the extent of ischemic injury[2,3]

References: 1. AHA Stroke Journal Report. December 9, 2005. **2.** González. *Am J Neuroradiol.* 2006;27:728-735.
3. Donnan. *Lancet Neurol.* 2002;1:417-425.

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Patient Evaluation: Focused history

- Single most important historical information is time last known well
- Never ask: When or what time did this start?
- Rather, ask: How you were last well?
- Very important to have collateral information from friends/family

Patient Evaluation: Focused history

- Felt fine the night before
- Went to bed at 11pm
- Awoke at 7AM
- At 830AM, wife noticed words were slurred and he was weak on his right side
- Time last known well is…
- 11pm

Patient Evaluation: Focused history

- Felt fine the night before
- Went to bed at 11pm
- Awoke at 7AM
- At 715AM, son spoke to patient before leaving for work
- At 830AM, wife noticed words were slurred and he was weak on his left side
- Time last known well is…
- 715AM

Acute stroke: ED evaluation

- Check/Secure Airway/Breathing/Circulation
- Physician exam; including neuro exam
- **ED Nurse**: GCS, limb strength, facial droop q 2 hrs for ICU patient, every 4 hrs for med surg/telemetry patient. ******If tPA patient, see v/s neuro frequency below (utilize IV tPA flowsheet)
- 2 IV Lines-- IV normal saline 125cc/hr for hydration and BP, if tolerated
- O_2 4 liters per nasal cannula or ventilator to keep O_2 sat >92%
- Continued pulse ox
- Cardiac monitor
- Stat portable chest x-ray
- 12 lead EKG
- Bedside glucose STAT
- Labs- CBC w/diff & platelets, Comprehensive metabolic panel, PT/INR & PTT, Alcohol/drug screen

❖ **Target Door to Lab result ≤ 45 min.**

- Non-contrast head CT with ACLS transport
- **ED nurses to bring IV tPA to CT if Last Known well < 4.5 hours**.

❖ **Target Door to CT < 20 minutes of arrival to the ED**

❖ Neuro eval by Neurology/NRSG including NIHSS/swallow eval

- NPO, includes PO meds, until Stroke Team clears patient for swallowing

Stroke mimickers

Table 6. Features of Clinical Situations Mimicking Stroke

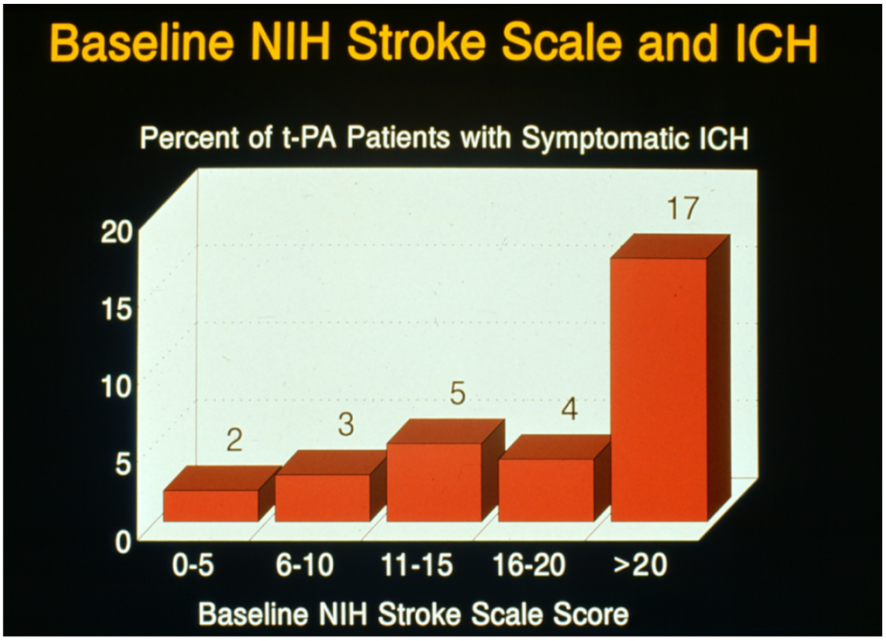
Psychogenic	Lack of objective cranial nerve findings, neurological findings in a nonvascular distribution, inconsistent examination
Seizures	History of seizures, witnessed seizure activity, postictal period
Hypoglycemia	History of diabetes, low serum glucose, decreased level of consciousness
Migraine with aura (complicated migraine)	History of similar events, preceding aura, headache
Hypertensive encephalopathy	Headache, delirium, significant hypertension, cortical blindness, cerebral edema, seizure
Wernicke's encephalopathy	History of alcohol abuse, ataxia, ophthalmoplegia, confusion
CNS abscess	History of drug abuse, endocarditis, medical device implant with fever
CNS tumor	Gradual progression of symptoms, other primary malignancy, seizure at onset
Drug toxicity	Lithium, phenytoin, carbamazepine

IV TPA

- Approved by FDA in 1996
- This was on basis of NINDS rtPA Stroke Trial in which 624 patients with ischemic strokes were treated with placebo or IV TPA.
- In Part 1, end point was neurological improvement at 24 hours
- In Part 2 (pivotal efficacy trial), end point was favorable outcome
- Treatment was associated with an increase in odds of a favorable outcome (OR 1.9)
  - In a subgroup analysis, OR was 2.11 when treatment was within 90 minutes [1.69 when treatment was 90-180 min]

IV TPA

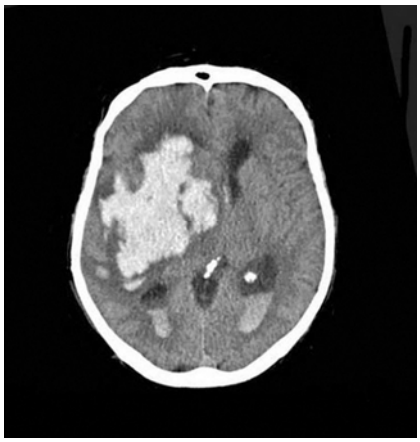
- Major risk is intracerebral hemorrhage.
- Occurred in 6.4% of patients and 0.6% of patients in placebo group
- However, mortality was similar at 3 months and at 1 year
- These results have been replicated in the ECASS I/II and ATLANTIS A/B trials



Broderick, *Stroke* 1997

IV TPA: ICH risk factors

- High stroke scale
- Blood Pressure/hypertension
- Hyperglycemia
- Age (in some studies)



Blood pressure (BP) management for patients eligible for Activase® (t-PA): pretreatment

AHA/ASA 2007 Guidelines for the Early Management of Adults With Ischemic Stroke

Indication that patient is eligible for Activase (t-PA)

If SBP >185 mm Hg or DBP >110 mm Hg

Labetalol 10–20 mg IV over 1–2 min; may repeat x 1;
-or-
Nitropaste 1–2 inches;
-or-
Nicardipine infusion, 5 mg/h; titrate up by 2.5 mg/h at intervals of 5–15 min (maximum dose 15 mg/h); when desired BP is attained, reduce to 3 mg/h

If BP does not decline and remains >185/110 mm Hg, do not administer Activase (t-PA)

AHA/ASA=American Heart Association/American Stroke Association.
SBP=systolic blood pressure.
DBP=diastolic blood pressure.
Reference: Adams et al. *Stroke.* 2007;38:1655-1711.

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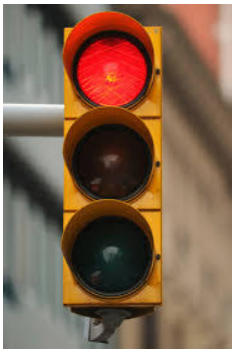
Absolute Contraindications

- Acute ICH
- History of ICH*
- BP > 185/110*
- Head trauma/stroke <3 months
- Thrombocytopenia/coagulopathy
- NOAC use



Relative Contraindications

- Advanced age
- Mild, improving symptoms
- Severe stroke
- Recent major surgery
- Recent GI hemorrhage

IV TPA: so what about 3-4.5 hours?

- ECASS III evaluated TPA in this window.
- Patients were randomized to tPA or placebo
- Had same inclusion/exclusion criteria as prior trials with the additional exclusion criteria of: age > 80, NIHSS > 25, taking oral anticoagulants, and combination of stroke and diabetes.
- OR of 1.28 of having a favorable outcome in the treatment group
- Mortality did not differ in the 2 groups
- Concluded that tPA can be safely given and can improve outcomes up to 4.5 hours in selected patients

IV TPA: so what about 3-4.5 hours?

- The European Medicines Agency expanded approval for IV tPA to 4.5 hours but FDA has not.
- However, this is recommended by AHA/ASA

Post-tPA care

- ICU admission
- Careful blood pressure monitoring: Goal <180/105
- No aspirin
- No anti-coagulation
- Monitor for swelling/edema

Outline

- Epidemiology
- Intravenous thrombolytic
- **Mechanical Thrombectomy**
- Stroke management
- Post-stroke complications

Pre-2015

- MERCI (2005)
- MULTI MERCI (2008)
- PENUMBRA (2009)
- IMS III (2013)
- SYNTHESIS (2013)
- MR RESCUE (2013)

Post-2015

- MR CLEAN (2014)
- EXTEND-IA (2015)
- ESCAPE (2015)
- SWIFT-PRIME (2015)
- REVASCAT (2016)

MR CLEAN

- Multicenter randomized clinical trial
- First positive trial demonstrating benefit with thrombectomy
- Study conducted across 16 centers in the Netherlands

Berkhemer, *NEJM,* 2015

MR CLEAN: inclusion criteria and methods

- Age > 18 with acute ischemic stroke caused by intracranial occlusion within the anterior circulation including distal ICA, M1 or M2, A1 or A2 seen on CTA or MRA
- Initiation of treatment had to be <6 hours from onset
- NIHSS > 2
- Patients randomized to intervention vs standard therapy
- Primary outcome was mRS at 90 days. Secondary outcome included NIHSS at 1, 5-7 days.

MR CLEAN: results

Table 1. Baseline Characteristics of the 500 Patients.*

Characteristic	Intervention (N=233)	Control (N=267)
Age — yr		
Median	65.8	65.7
Interquartile range	54.5–76.0	55.5–76.4
Male sex — no. (%)	135 (57.9)	157 (58.8)
NIHSS score†		
Median (interquartile range)	17 (14–21)	18 (14–22)
Range	3–30	4–38
Location of stroke in left hemisphere — no. (%)	116 (49.8)	153 (57.3)
History of ischemic stroke — no. (%)	29 (12.4)	25 (9.4)
Atrial fibrillation — no. (%)	66 (28.3)	69 (25.8)
Diabetes mellitus — no. (%)	34 (14.6)	34 (12.7)
Prestroke modified Rankin scale score — no. (%)‡		
0	190 (81.5)	214 (80.1)
1	21 (9.0)	29 (10.9)
2	12 (5.2)	13 (4.9)
>2	10 (4.3)	11 (4.1)
Systolic blood pressure — mm Hg§	146±26.0	145±24.4
Treatment with IV alteplase — no. (%)	203 (87.1)	242 (90.6)
Time from stroke onset to start of IV alteplase — min		
Median	85	87
Interquartile range	67–110	65–116
ASPECTS — median (interquartile range)¶	9 (7–10)	9 (8–10)

Table 1. Baseline Characteristics of the 500 Patients.*

Characteristic	Intervention (N=233)	Control (N=267)
Intracranial arterial occlusion — no./total no. (%)‖		
Intracranial ICA	1/233 (0.4)	3/266 (1.1)
ICA with involvement of the M1 middle cerebral artery segment	59/233 (25.3)	75/266 (28.2)
M1 middle cerebral artery segment	154/233 (66.1)	165/266 (62.0)
M2 middle cerebral artery segment	18/233 (7.7)	21/266 (7.9)
A1 or A2 anterior cerebral artery segment	1/233 (0.4)	2/266 (0.8)
Extracranial ICA occlusion — no./total no. (%)‖**	75/233 (32.2)	70/266 (26.3)
Time from stroke onset to randomization — min††		
Median	204	196
Interquartile range	152–251	149–266
Time from stroke onset to groin puncture — min		
Median	260	NA
Interquartile range	210–313	

Berkhemer, *NEJM*, 2015

MR CLEAN: results

Table 2. Primary and Secondary Outcomes and Treatment Effects.*

Outcome	Intervention (N=233)	Control (N=267)	Effect Variable	Unadjusted Value (95% CI)	Adjusted Value (95% CI)†
Primary outcome: modified Rankin scale score at 90 days — median (interquartile range)	3 (2 to 5)	4 (3 to 5)	Common odds ratio	1.66 (1.21 to 2.28)	1.67 (1.21 to 2.30)
Secondary outcomes					
Clinical outcomes					
Modified Rankin score of 0 or 1 at 90 days — no. (%)	27 (11.6)	16 (6.0)	Odds ratio	2.06 (1.08 to 3.92)	2.07 (1.07 to 4.02)
Modified Rankin score of 0–2 at 90 days — no. (%)	76 (32.6)	51 (19.1)	Odds ratio	2.05 (1.36 to 3.09)	2.16 (1.39 to 3.38)
Modified Rankin score of 0–3 at 90 days — no. (%)	119 (51.1)	95 (35.6)	Odds ratio	1.89 (1.32 to 2.71)	2.03 (1.36 to 3.03)
NIHSS score after 24 hr — median (interquartile range)‡	13 (6 to 20)	16 (12 to 21)	Beta	2.6 (1.2 to 4.1)	2.3 (1.0 to 3.5)
NIHSS score at 5–7 days or discharge — median (interquartile range)§	8 (2 to 17)	14 (7 to 18)	Beta	3.2 (1.7 to 4.7)	2.9 (1.5 to 4.3)
Barthel index of 19 or 20 at 90 days — no./total no. (%)¶	99/215 (46.0)	73/245 (29.8)	Odds ratio	2.0 (1.3 to 2.9)	2.1 (1.4 to 3.2)
EQ-5D score at 90 days — median (interquartile range)‖	0.69 (0.33 to 0.85)	0.66 (0.30 to 0.81)	Beta	0.08 (0.00 to 0.15)	0.06 (-0.01 to 0.13)
Imaging outcomes					
No intracranial occlusion on follow-up CT angiography — no./total no. (%)**	141/187 (75.4)	68/207 (32.9)	Odds ratio	6.27 (4.03 to 9.74)	6.88 (4.34 to 10.94)
Final infarct volume on CT††					
Patients evaluated — no. (%)	138 (59.2)	160 (59.9)			
Median (interquartile range) — ml	49 (22 to 96)	79 (34 to 125)	Beta	20 (3 to 36)	19 (3 to 34)

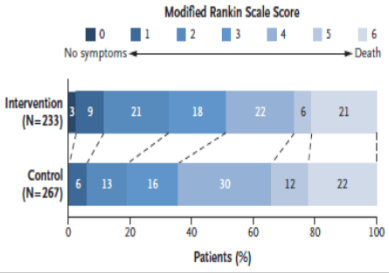


Figure 1. Modified Rankin Scale Scores at 90 Days in the Intention-to-Treat Population.

Berkhemer, *NEJM*, 2015

Positive thrombectomy trials

- MR CLEAN (2014)
- EXTEND-IA (2015) – smallest trial, relied on CT perfusion
- ESCAPE (2015) –used delayed CTA, fastest recanalization
- SWIFT-PRIME (2015) – highest recanalization rate
- REVASCAT (2016)

Positive thrombectomy trials

Table. Summary of Data From the 5 Trials

Trial N IAT+/CTL	NIHSS Range CTL	 IAT+	r-tPA	TICI 2B/3	LSN to Groin Mdn	mRS 0–2 at 90 d CTL	 IAT+	sICH CTL	 IAT+	Device Complications	Mortality CTL	 IAT+
MR CLEAN[12] 500 233/267	18 (14–21)	17 (14–22)	90%	59%	260	19%	33%	6.4%	7.7%	Embol. 13	22%	21%
ESCAPE[13] 315 165/150	17 (12–20)	16 (13–20)	76%	72%	200	29%	53%	2.7%	3.6%	Perfor.1	19%	10%
EXTEND IA[14] 70 35/35	13 (9–19)	17 (13–20)	100%	86%	210	40%	71%	6%	0%	Perfor.1 Embol.2	20%	9%
SWIFT PRIME[15] 196 98/98	17 (13–19)	17 (13–20)	98%	88%	224	36%	60%	3%	0%	SAH 4	12%	9%
REVASCAT[16] 206 103/103	17 (12–19)	17 (14–20)	73%	66%	269	28%	44%	1.9%	1.9%	Perfor. 5 Embol. 5	16%	18%

Grotta, *Stroke,* 2015

Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials

- HERMES collaboration
- Pooled data from 5 trials

	Intervention population (n=634)	Control population (n=653)
Demographic characteristics		
Median age (years)	68 (57-77)	68 (59-76)*
Men	330 (52%)	352 (54%)
Women	304 (48%)	301 (46%)
Past medical history		
Hypertension	352 (56%)	388 (59%)
Diabetes mellitus	82 (13%)	88 (13%)
Atrial fibrillation	209 (33%)	215 (33%)
Smoking (recent or current)	194 (31%)	210 (32%)
Clinical characteristics		
Baseline NIHSS score	17 (14-20)†	17 (13-21)‡
Baseline blood glucose (mmol/L)	6·6 (5·9-7·8)§	6·7 (5·9-7·8)¶
Imaging characteristics		
ASPECTS on baseline CT	9 (7-10)§	9 (8-10)¶
Intracranial occlusion location		
Internal carotid artery	133 (21%)	144 (22%)
M1 segment middle cerebral artery	439 (69%)	452 (69%)
M2 segment middle cerebral artery	51 (8%)	44 (7%)
Other	11 (2%)	13 (2%)
Treatment details and process times		
Treatment with intravenous alteplase	526 (83%)	569 (87%)
Treatment with intravenous alteplase documented within 180 min	442 (70%)	462 (71%)
Process times (min)		
Onset to randomisation	195·5 (142-260)‖	196 (142-270)*
Onset to intravenous alteplase	100 (75-133)**	100 (74-140)††
Onset to reperfusion	285 (210-362)	NA

Data are median (IQR), n (%), or mean (SD). NIHSS=National Institutes of Health Stroke Scale. ASPECTS=Alberta Stroke Program Early CT Score. *n=650. †n=631. ‡n=648. §n=620. ¶n=644. ‖n=632. **n=598. ††n=618.

Table 1: Baseline characteristics in the pooled data

Goyal, *The Lancet,* 2016.

Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials

	Intervention population	Control population	Risk difference (%)	Rate ratio (95% CI)	Odds ratio (95% CI)	Adjusted rate ratio (95% CI)	Adjusted odds ratio (95% CI)
mRS score reduction (shift analysis; primary outcome)*	..	..	..	..	2·26* (1·67-3·06); p<0·0001	..	2·49* (1·76-3·53); p<0·0001
mRS score 0-1 at 90 days	26·9% (170/633)	12·9% (83/645)	14·0	2·00 (1·54-2·60); p<0·0001	2·49 (1·84-3·35); p<0·0001	2·06 (1·59-2·69); p<0·0001	2·72 (1·99-3·71); p<0·0001
mRS score 0-2 at 90 days	46·0% (291/633)	26·5% (171/645)	19·5	1·7 (1·41-2·05); p<0·0001	2·35 (1·85-2·98); p<0·0001	1·73 (1·43-2·09); p<0·0001	2·71 (2·07-3·55); p<0·0001
NIHSS score 0-2 at 24 h	21·0% (129/615)	8·3% (52/630)	12·7	2·47 (1·79-3·41); p<0·0001	2·91 (2·06-4·12); p<0·0001	2·66 (1·92-3·67); p<0·0001	3·77 (2·49-5·71); p<0·0001
Early neurological recovery at 24 h	50·2% (309/616)	21·2% (134/633)	29·0	2·34 (1·91-2·87); p<0·0001	4·04 (2·75-5·93); p<0·0001	2·34 (1·91-2·87); p<0·0001	4·36 (3·03-6·27); p<0·0001

Data show the proportion of patients with outcome (n/N), unless otherwise stated. NIHSS=National Institutes of Health Stroke Scale. mRS=modified Rankin Scale. *Common odds ratio indicating the odds of improvement of 1 point on the mRS.

Table 2: Efficacy outcomes from the pooled data

Goyal, *The Lancet,* 2016.

Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials

	Intervention population	Control population	Risk difference (%)	Rate ratio (95% CI)	Odds ratio (95% CI)	Adjusted rate ratio (95% CI)	Adjusted odds ratio (95% CI)
Symptomatic intracranial haemorrhage	4·4% (28/634)	4·3% (28/653)	0·1	1·06 (0·63–1·80); p=0·82	1·07 (0·62–1·83); p=0·81	1·07 (0·62–1·80); p=0·81	1·07 (0·62–1·84); p=0·81
Parenchymal haematoma type 2	5·1% (32/629)	5·3% (34/641)	−0·2	0·99 (0·61–1·61); p=0·97	0·99 (0·60–1·63); p=0·97	1·04 (0·64–1·69); p=0·88	1·04 (0·63–1·72); p=0·88
Mortality	15·3% (97/633)	18·9% (122/646)	−3·6	0·82 (0·63–1·07); p=0·15	0·77 (0·54–1·10); p=0·16	0·82 (0·62–1·08); p=0·15	0·73 (0·47–1·13); p=0·16

Data show the proportion of patients with outcome (n/N), unless otherwise stated.

Table 4: Safety outcomes at 90 days

Goyal, *The Lancet,* 2016.

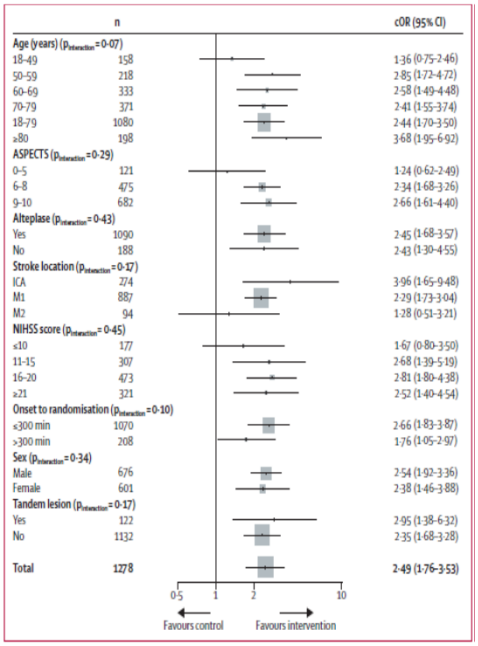


Figure 2: Forest plot showing adjusted treatment effect for mRS at 90 days in prespecified subgroups with p values for heterogeneity across subgroups

Goyal, *The Lancet,* 2016.

Thrombectomy beyond 6 hours: Dawn of a New Era

- Prospective, randomized open-label trial assessing thrombectomy versus standard therapy
- Patients with ICA or MCA occlusion with mismatch
- Thrombectomy occurred 6-24 hours
- Primary end point included mRS score and rate of functional independence
- Trial terminated early due to superiority of thrombectomy

DAWN trial

Table 1. Characteristics of the Patients at Baseline.*

Variable	Thrombectomy Group (N = 107)	Control Group (N = 99)
Age — yr	69.4±14.1	70.7±13.2
Age ≥80 yr — no. (%)	25 (23)	29 (29)
Male sex — no. (%)	42 (39)	51 (52)
Atrial fibrillation — no. (%)	43 (40)	24 (24)
Diabetes mellitus — no. (%)	26 (24)	31 (31)
Hypertension — no. (%)	83 (78)	75 (76)
Previous ischemic stroke or transient ischemic attack — no. (%)	12 (11)	11 (11)
NIHSS score†		
Median	17	17
Interquartile range	13–21	14–21
10 to 20 — no. (%)	78 (73)	72 (73)
Treatment with intravenous alteplase — no. (%)	5 (5)	13 (13)
Infarct volume — ml		
Median	7.6	8.9
Interquartile range	2.0–18.0	3.0–18.1
Type of stroke onset — no. (%)‡		
On awakening	67 (63)	47 (47)
Unwitnessed stroke	29 (27)	38 (38)
Witnessed stroke	11 (10)	14 (14)
Occlusion site — no. (%)§		
Intracranial internal carotid artery	22 (21)	19 (19)
First segment of middle cerebral artery	83 (78)	77 (78)
Second segment of middle cerebral artery	2 (2)	3 (3)
Interval between time that patient was last known to be well and randomization — hr		
Median	12.2	13.3
Interquartile range	10.2–16.3	9.4–15.8
Range	6.1–23.5	6.5–23.9
Time from first observation of symptoms to randomization — hr		
Median	4.8	5.6
Interquartile range	3.6–6.2	3.6–7.8

Nogueira, *NEJM,* 2018

DAWN trial

Table 2. Efficacy Outcomes.*

Outcome	Thrombectomy Group (N=107)	Control Group (N=99)	Absolute Difference (95% CI)†	Adjusted Difference (95% Credible Interval)‡	Posterior Probability of Superiority
Primary end points					
Score on utility-weighted modified Rankin scale at 90 days§	5.5±3.8	3.4±3.1	2.1 (1.2–3.1)	2.0 (1.1–3.0)	>0.999
Functional independence at 90 days — no. (%)¶	52 (49)	13 (13)	36 (24–47)	33 (21–44)	>0.999
				Risk Ratio (95% CI)	**P Value**
Secondary end points					
Early response — no. (%)‖	51 (48)	19 (19)	29 (16–41)	3 (2–4)	<0.001**
Recanalization at 24 hr — no. (%)††	82 (77)	39 (39)	40 (27–52)	2 (2–4)	<0.001**
Change from baseline in infarct volume at 24 hr — ml††					0.003‡‡
Median	1	13			
Interquartile range	0–28	0–42			
Infarct volume at 24 hour — ml††					<0.001‡‡
Median	8	22			
Interquartile range	0–48	8–68			
Grade of 2b or 3 on mTICI scale — no. (%)§§	90 (84)	NA			

Nogueira, *NEJM,* 2018

DAWN trial

- Rate of stroke-related death or symptomatic intracerebral hemorrhage did not differ
- Outcome were better in patients who were carefully selected based on imaging criteria with thrombectomy at 6-24 hours compared to standard medical therapy
- For every 2 patients who underwent thrombectomy, 1 additional patients had less disability

Thrombectomy beyond 6 hours: DEFUSE 3

- Randomized, open-label trial assessing endovascular therapy versus standard medical therapy
- Patients underwent intervention between 6 and 16 hours
- Patients were eligible if stroke volume was less than 70mL with an occlusion of ICA or MCA
- Primary outcome was mRS score

DEFUSE 3

Table 1. Baseline Characteristics of the Patients and Features of Thrombectomy.*

Characteristic	Endovascular Therapy (N = 92)	Medical Therapy (N = 90)
Median age (IQR) — yr	70 (59–79)	71 (59–80)
Female sex — no. (%)	46 (50)	46 (51)
Median NIHSS score (IQR)†	16 (10–20)	16 (12–21)
Stroke onset witnessed — no. (%)		
Yes‡	31 (34)	35 (39)
No		
Symptoms were present on awakening	49 (53)	42 (47)
Symptoms began during wakefulness	12 (13)	13 (14)
Treatment with intravenous t-PA — no. (%)§	10 (11)	8 (9)
Imaging characteristics¶		
Qualifying imaging — no. (%)		
CT perfusion imaging	69 (75)	64 (71)
Diffusion and perfusion MRI	23 (25)	26 (29)
Median volume of ischemic core (IQR) — ml	9.4 (2.3–25.6)	10.1 (2.1–24.3)
Median volume of perfusion lesion (IQR) — ml‖	114.7 (79.3–146.3)	116.1 (73.4–158.2)
Occlusion site on baseline CTA or MRA — no. (%)		
Internal carotid artery	32 (35)	36 (40)
Middle cerebral artery**	60 (65)	54 (60)
Median ASPECTS on baseline CT (IQR)††	8 (7–9)	8 (7–9)
Process measures — hr:min		
Median time from stroke onset to qualifying imaging (IQR)	10:29 (8:09–11:40)	9:55 (7:59–12:20)
Median time from stroke onset to randomization (IQR)	10:53 (8:46–12:21)	10:44 (8:42–13:04)
Median time from qualifying imaging to femoral puncture (IQR)	0:59 (0:39–1:27)	NA
Median time from femoral puncture to reperfusion (IQR)	0:38 (0:26–0:59)	NA

Albers, *NEJM,* 2018

DEFUSE 3

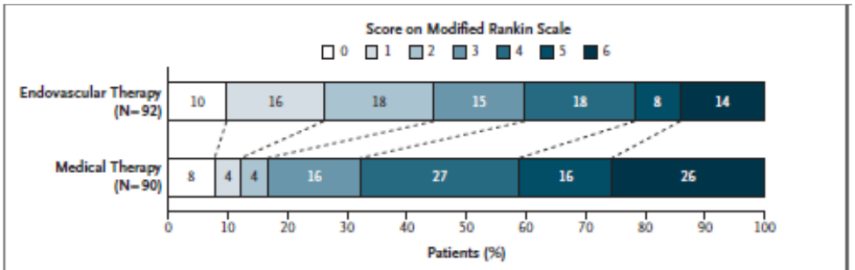


Figure 2. Scores on the Modified Rankin Scale at 90 Days.

Patients in the endovascular-therapy group received endovascular therapy plus standard medical therapy. Patients in the medical-therapy group received standard medical therapy alone. Scores on the modified Rankin scale range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. There was a significant difference favoring the endovascular-therapy group over the medical-therapy group in the overall distribution of scores (unadjusted common odds ratio, 2.77; 95% CI, 1.63 to 4.70; P<0.001).

Nogueira, *NEJM,* 2018

DEFUSE 3

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)	—	—	

Nogueira, *NEJM,* 2018

ASA recommendations

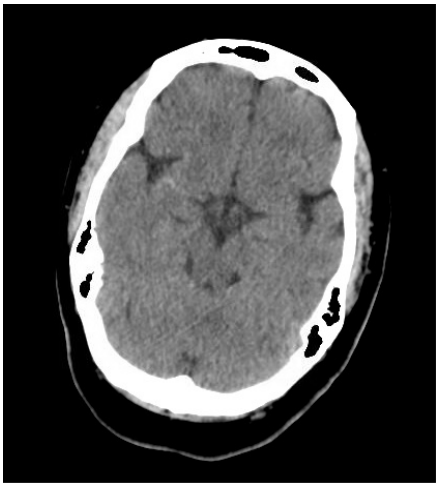
3. Patients should receive mechanical thrombectomy with a stent retriever if they meet all the following criteria: (1) prestroke mRS score of 0 to 1; (2) causative occlusion of the internal carotid artery or MCA segment 1 (M1); (3) age ≥18 years; (4) NIHSS score of ≥6; (5) ASPECTS of ≥6; and (6) treatment can be initiated (groin puncture) within 6 hours of symptom onset.	I	A	Recommendation revised from 2015 Endovascular.
7. In selected patients with AIS within 6 to 16 hours of last known normal who have LVO in the anterior circulation and meet other DAWN or DEFUSE 3 eligibility criteria, mechanical thrombectomy is recommended.	I	A	New recommendation.
8. In selected patients with AIS within 6 to 24 hours of last known normal who have LVO in the anterior circulation and meet other DAWN eligibility criteria, mechanical thrombectomy is reasonable.	IIa	B-R	New recommendation.

Powers, *Stroke,* 2018

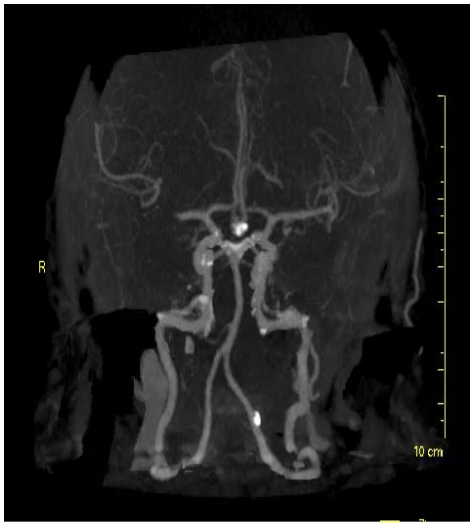
Case #1 – Patient KN

- 64 year woman with history of hypertension presents to ED with acute left sided weakness
- Witnessed onset of symptoms by husband 45 minutes prior to arrival while eating breakfast at a restaurant
- Normal finger stick BP 149/76
- R gaze preference, L field cut, L sided plegia, left sided neglect
- NIHSS 17
- CT negative

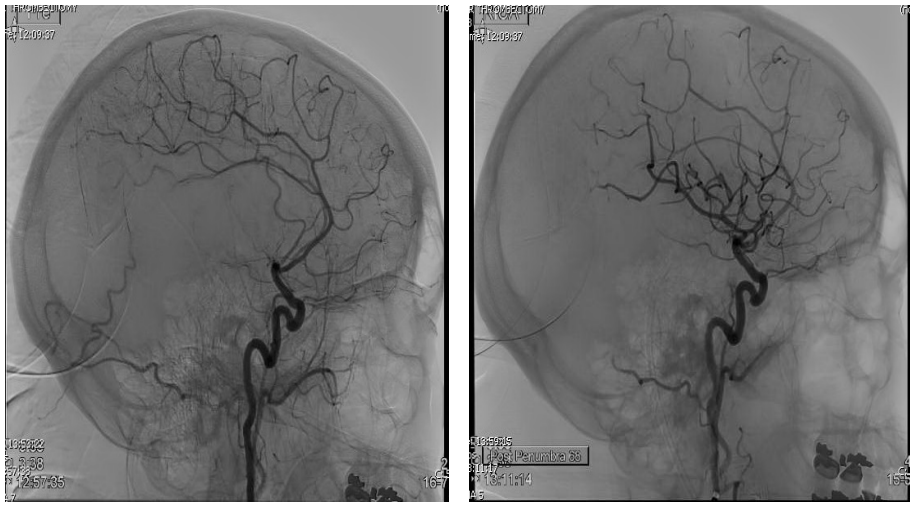
Patient KN



Patient KN

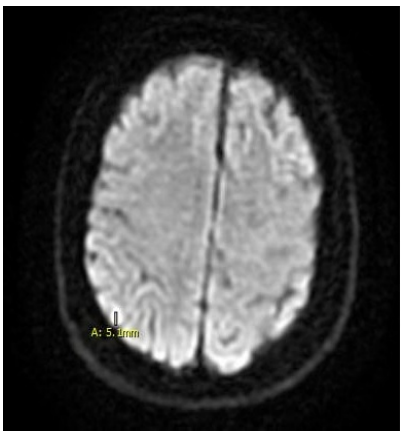


Patient KN



Patient KN

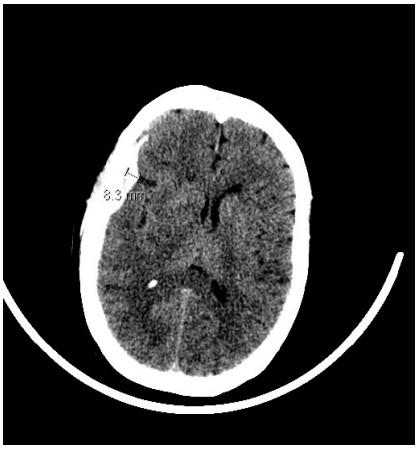
- Complete recovery post-procedure.
- NIHSS 0
- Discharged to home hospital day #3 with event monitor
- Paroxysmal atrial fibrillation identified
- Anticoagulation started

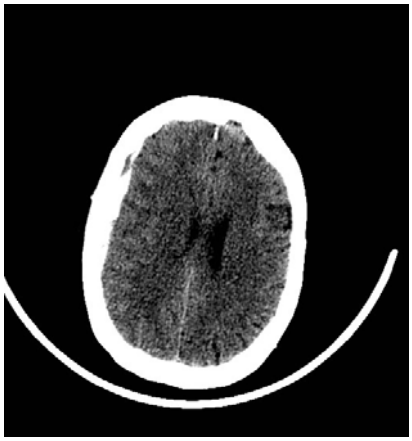


Patient #2 - JH

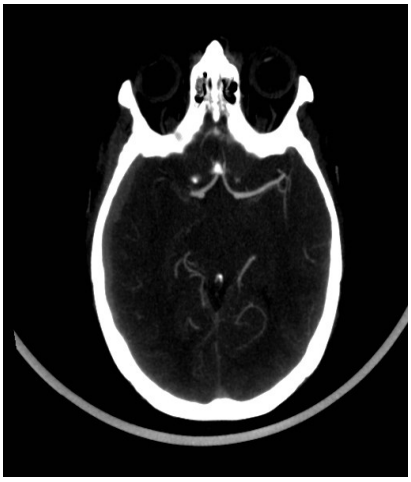
- 78 year old woman presenting with left sided weakness upon waking up
- She had history of atrial fibrillation and was taken off Coumadin but taken off due to recent subdural hematoma
- Last known normal was last night
- NIHSS 16

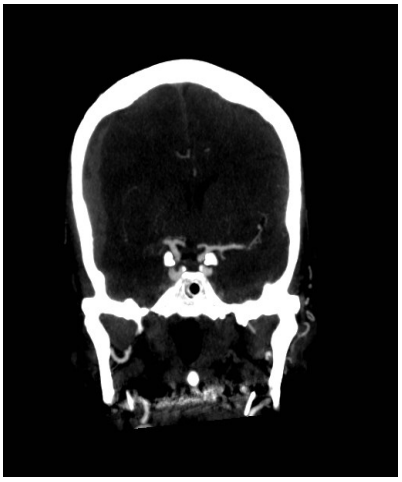
Patient JH



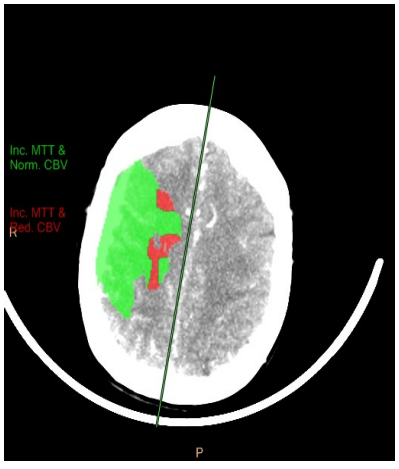


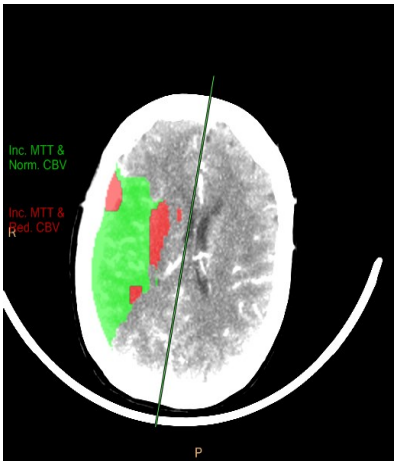
Patient JH





Patient JH



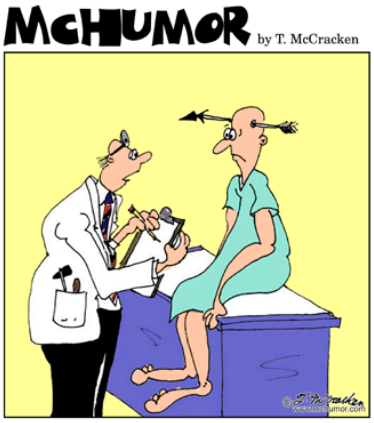


Outline

- Epidemiology
- Intraveneous thrombolytics
- Thrombectomy
- **Stroke management**
- Post-stroke complications

Stroke work-up

- MRI
- CT angiogram
- Aspirin
- Statin
- Cholesterol level
- Diabetes screen
- Echocardiogram
- Swallow screen
- Dvt prophylaxis
- Rehab evaluation
- Telemetry monitoring
- Blood pressure management



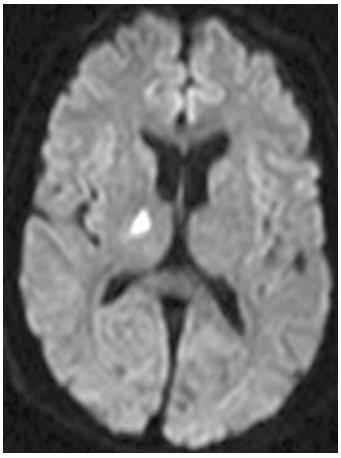
"Off hand, I'd say you're suffering from an arrow through your head, but just to play it safe, I'm ordering a bunch of tests."

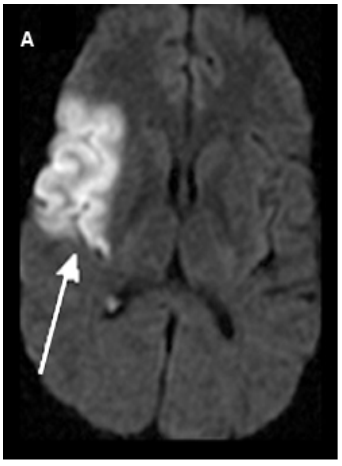
Imaging

6.1. Brain Imaging	COR	LOE	New, Revised, or Unchanged
1. Routine use of brain MRI in all patients with AIS is not cost-effective and is not recommended for initial diagnosis or to plan subsequent treatment.	III: No Benefit	B-NR	New recommendation.
2. In some patients with AIS, the use of MRI might be considered to provide additional information for initial diagnosis or to plan subsequent treatment, although the effect on outcomes is uncertain.	IIb	C-EO	New recommendation.
2. In patients with AIS, routine noninvasive imaging by means of CTA or MRA of the intracranial vasculature to determine the presence of intracranial arterial stenosis or occlusion is not recommended to plan subsequent secondary preventive treatment.	III: No Benefit	A	New recommendation.
3. In some patients with AIS, noninvasive imaging by means of CTA or MRA of the intracranial vasculature to provide additional information to plan subsequent secondary preventive treatment may be reasonable, although the effect on outcomes is uncertain.	IIb	C-EO	New recommendation.
4. Routine use of echocardiography in all patients with AIS to plan subsequent secondary preventive treatment is not cost-effective and is not recommended.	III: No Benefit	B-NR	New recommendation.
5. In selected patients with AIS, echocardiography to provide additional information to plan subsequent secondary preventive treatment may be reasonable.	IIb	B-R	New recommendation.

Powers, *Stroke*, 2018

Imaging





Cholesterol

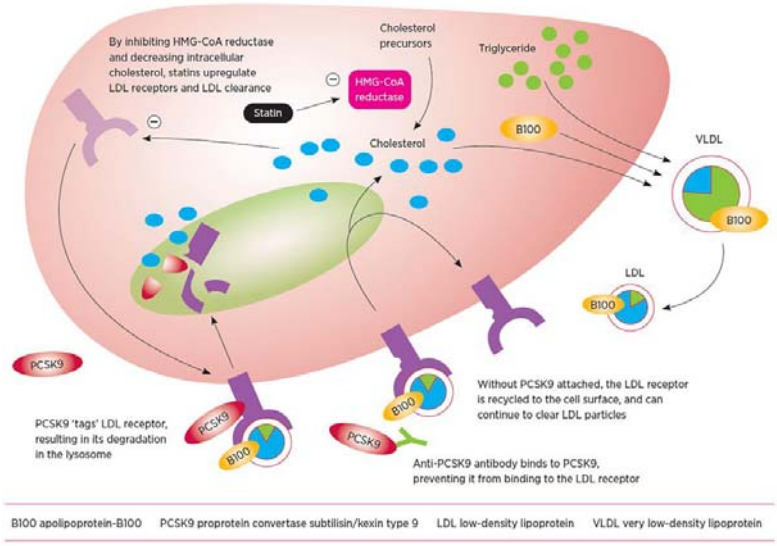
6.5. Cholesterol	COR	LOE	New, Revised, or Unchanged
1. Routine measurement of blood cholesterol levels in all patients with ischemic stroke presumed to be of atherosclerotic origin who are not already taking a high-intensity statin is not recommended.	III: No Benefit	B-R	New recommendation.
2. Measurement of blood cholesterol levels in patients with ischemic stroke presumed to be of atherosclerotic origin who are already taking an optimized regimen of statin therapy may be useful for identifying patients who would be candidates for outpatient proprotein convertase subtilisin/kexin type 9 inhibitor treatment to reduce the risk of subsequent cardiovascular death, MI, or stroke.	IIb	B-R	New recommendation.

Powers, *Stroke,* 2018

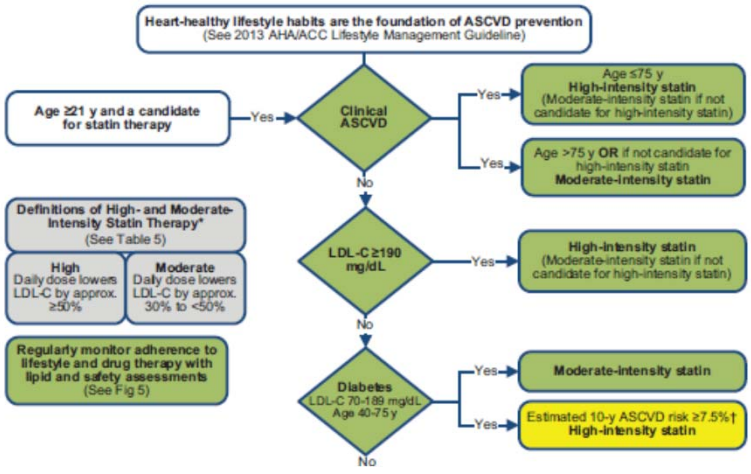
PCSK9 antibody: future standard therapy?

- Proprotein convertase subtilisin-kexin type 9
- PCSK9 bind to LDL receptors and promotes its degradation
- PCSK9 inhibitors allow LDL receptors to remove LDL
- Two agents: alirocumab, evolocumab
- Cost $200 vs $14,000

PCSK9



2013 AHA guideline



Stone, et al. 2013

Types of statin therapy

Table 5. High-, Moderate-, and Low-Intensity Statin Therapy (Used in the RCTs Reviewed by the Expert Panel)*

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL-C, on average, by approximately ≥50%	Daily dose lowers LDL-C, on average, by approximately 30% to <50%	Daily dose lowers LDL-C, on average, by <30%
Atorvastatin (40†)–80 mg	**Atorvastatin 10 (*20*) mg**	*Simvastatin 10 mg*
Rosuvastatin 20 (*40*) mg	**Rosuvastatin (*5*) 10 mg**	**Pravastatin 10–20 mg**
	Simvastatin 20–40 mg‡	**Lovastatin 20 mg**
	Pravastatin 40 (*80*) mg	*Fluvastatin 20–40 mg*
	Lovastatin 40 mg	*Pitavastatin 1 mg*
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg BID	
	Pitavastatin 2–4 mg	

Stone, et al. 2013

Swallow screen

4.6. Dysphagia Screening	COR	LOE
1. Dysphagia screening before the patient begins eating, drinking, or receiving oral medications is reasonable to identify patients at increased risk for aspiration.	**IIa**	**C-LD**

Dysphagia, a common (37%–78%) complication of acute stroke, is a risk factor for aspiration pneumonia and is associated with higher mortality and worse patient outcomes. The evidence review committee completed a systematic review to determine whether dysphagia screening, compared with no screening or usual care, decreased outcomes of pneumonia, death, or dependency.[4,231–233] There were insufficient data to determine whether implementation of a dysphagia screening protocol reduces the risk of death or dependency. However, insufficient evidence does not mean that dysphagia screening is ineffective. Joundi et al[234] determined that patients who failed dysphagia screening were older, had a higher rate of multiple comorbidities (including prior stroke and dementia), more often came from a long-term care facility, more often presented with weakness and speech deficits, had a lower level of consciousness, and had a higher stroke severity. Patients who failed dysphagia screening were more likely to develop pneumonia (13.1% versus 1.9%), to have more severe disability (52.4% versus 18.0%), and to be discharged to a long-term care institution (14.0% versus 4.3%). Early dysphagia screening is reasonable to identify patients at higher risk for adverse outcomes.

Powers, *Stroke,* 2018

Dvt prophlyaxis

4.8. Deep Vein Thrombosis Prophylaxis	COR	LOE
1. In immobile stroke patients without contraindications, intermittent pneumatic compression (IPC) in addition to routine care (aspirin and hydration) is recommended over routine care to reduce the risk of deep vein thrombosis (DVT).	I	B-R
CLOTS (Clots in Legs or stockings After Stroke) 3 was a multicenter trial enrolling 2867 patients in 94 centers in the United Kingdom and comparing the use of IPC with routine care to no IPC with routine care in immobile stroke patients for venous thromboembolism prophylaxis. Eligible patients were enrolled within 3 days of the acute stroke and could not mobilize to the toilet without the help of another person. Routine care was defined as the use of aspirin for nonhemorrhagic stroke, hydration, and possible compression stockings. A total of 31% of the patients received prophylactic or full-dose heparin or LMWH, but these patients were evenly distributed between both groups. After the exclusion of 323 patients who died before any primary outcome and 41 who had no screening, the primary outcome of DVT occurred in 122 of 1267 IPC participants (9.6%) compared with 174 of 1245 no-IPC participants (14.0%), giving an adjusted OR of 0.65 (95% CI, 0.51–0.84; *P*=0.001). Among patients treated with IPC, there was a statistically significant improvement in survival to 6 months (HR, 0.86; 95% CI, 0.73–0.99; *P*=0.042) but no improvement in disability. Skin breaks were more common in the IPC group (3.1% versus 1.4%; *P*=0.002). Contraindications to IPC include leg conditions such as dermatitis, gangrene, severe edema, venous stasis, severe peripheral vascular disease, postoperative vein ligation, or grafting, as well as existing swelling or other signs of an existing DVT.[409] A meta-analysis including this trial and 2 smaller trials confirmed these results.[240]		
2. The benefit of prophylactic-dose subcutaneous heparin (unfractionated heparin [UFH] or LMWH) in immobile patients with AIS is not well established.	IIb	A
The most recent and comprehensive meta-analysis of pharmacological interventions for venous thromboembolism prophylaxis in AIS included 1 very large trial (n=14 578) and 4 small trials of UFH, 8 small trials of LMWHs or heparinoids, and 1 trial of a heparinoid.[240] Prophylactic anticoagulants were not associated with any significant effect on mortality or functional status at final follow-up. There were statistically significant reductions in symptomatic pulmonary embolisms (OR, 0.69; 95% CI, 0.49–0.98) and in DVTs, most of which were asymptomatic (OR, 0.21; 95% CI, 0.15–0.29). There were statistically significant increases in symptomatic intracranial hemorrhage (OR, 1.68; 95% CI, 1.11–2.55) and symptomatic extracranial hemorrhages (OR, 1.65; 95% CI, 1.0–2.75). There may be a subgroup of patients in whom the benefits of reducing the risk of venous thromboembolism are high enough to offset the increased risks of intracranial and extracranial bleeding; however, no prediction tool to identify such a subgroup has been derived.[197,198,240]		

Powers, *Stroke,* 2018

Dvt prophlyaxis

- Recommendation based on a meta-analysis of 5 trials
- Anticoagulation was not associated with any significant effect on mortality or functional status
- Lower rates of PE and DVT (most were asymptomatic)
- Higher rate of ICH and extracranial hemorrhage

CLOTS study

- Clots in Legs or stockings after stroke
- Enrolled ~2900 patients
- Randomized to pneumatic compression
- DVT occurred in 122 patients in treatment group versus 174 (OR 0.65,p=0.001)
- In treatment group, also an improvement in survival

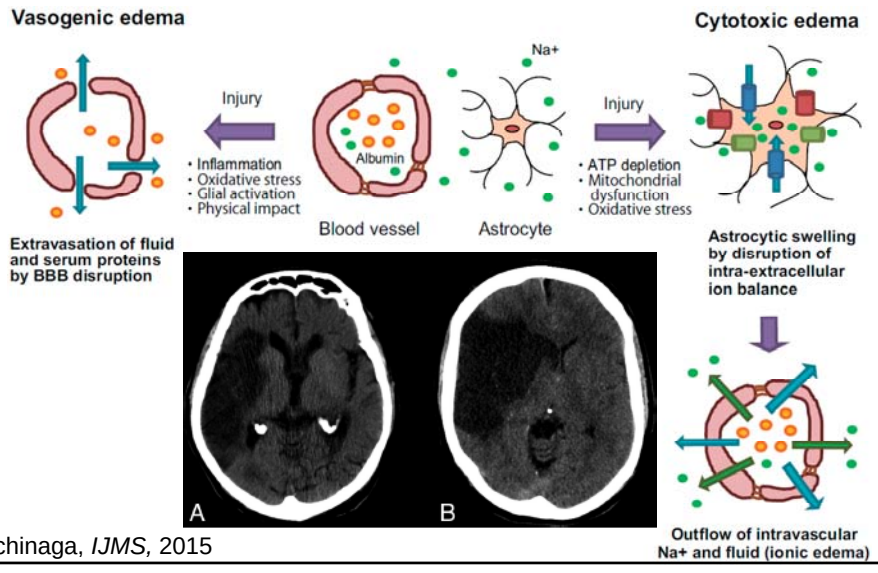
Outline

- Epidemiology
- Intravenous thrombolytic
- Thrombectomy
- Stroke management
- **Post-stroke complications**

Stroke Complications

- Infection
- DVT
- Hemorrhage
- Re-stroke
- Cerebral/malignant edema

Cerebral edema



Michinaga, *IJMS,* 2015

Malignant edema

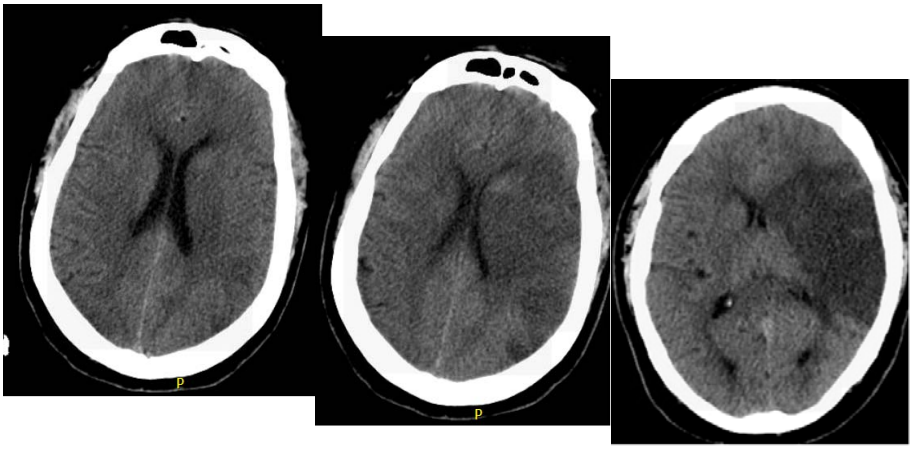
- Defined as edema severe enough to cause increased intracranial pressure and lead to herniation and death
- Predictors include:
  - Younger age
  - Carotid occlusion
  - History of hypertension

Treatment

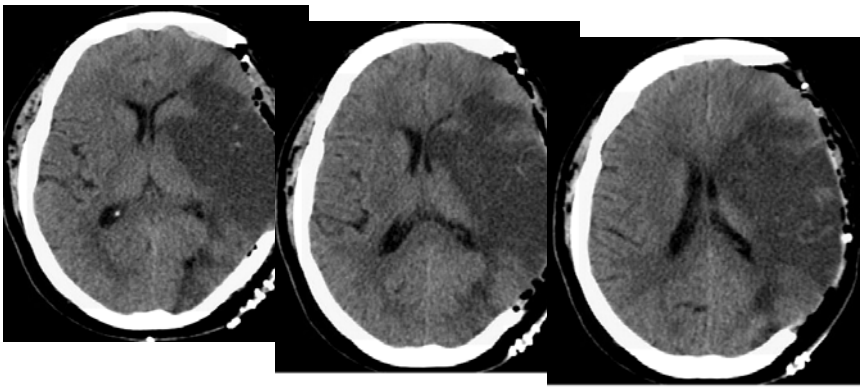
- Intubation/hyperventilation
- Sedation
- Head elevation
- Mannitol
- Hypertonic saline
- Decompressive craniectomy

Patient RR

- 46 year man with large L MCA syndrome
- Was not a candidate for tpa or thrombectomy



Post-OR



Decompressive craniectomy

Table 2 Study characteristics

Name, publication year and reference number, country, first author surname	Duration from symptoms onset to treatment	Age (years) inclusion; median age years (mean)	n treatment/ n control; % females	Rationale for timing of termination
DESTINY II 2014,[17] Germany, Jüttler	Within 48 hours after the onset of symptoms	Over 60 years; 70	47/62; 50%	Anticipated sample size ~130 patients. Sequential analysis allowed for repeated interim analyses; trial stopped as soon as reached statistical significance for 'success' (proportion mRS 4 or less).
DESTINY I 2007,[38] Germany, Jüttler	>12 to <36 hours	18–60 years; 44.5	17/15; 53%	Planned sample size of 188 patients; and after inclusion of 32 patients, the trial was interrupted according to the protocol because reached significance for the 30-day mortality end point.
DECIMAL 2007,[37] France, Vahedi	Within 24 hours	18–55 years; (43.4)	20/18; 53%	Anticipated sample size of 60 patients; sequential analysis planned, stopped after the 38th patient due to slow recruitment, a large difference in mortality between the two groups, and a planned meta-analysis with ongoing European trials[36 39]
HAMLET 2009,[39] Netherlands, Hofmeijer	Within 4 days (96 hours)	18–60 years; (48.7)	32/32; 41%	Planned sample size 112, stopped early apparently because of large significant effect.
HeADDFIRST 2014 pilot,[35] USA and Canada, Frank	Within 4 days (96 hours)	18–75 years; 54	14/10; 38%	Planned sample size was 75 patients, trial stopped after 26 patients randomised because of judgement that 'we had achieved our aims for the pilot study' without further details.
Decompressive Hemicraniectomy 2012,[36] China, Zhao	Within 48 hours	18–80 years; 64	24/23; 28%	Planned sample size was 110; trial was stopped after 47 patients recruited because of large, significant effect.

Alexander, *BMJ,* 2016

Decompressive craniectomy

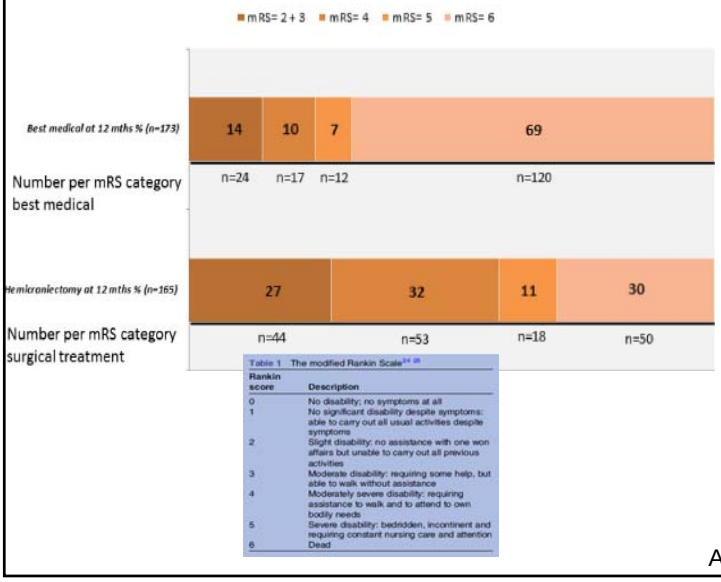


Table 1 The modified Rankin Scale[34 35]

Rankin score	Description
0	No disability; no symptoms at all
1	No significant disability despite symptoms: able to carry out all usual activities despite symptoms
2	Slight disability: no assistance with one won affairs but unable to carry out all previous activities
3	Moderate disability: requiring some help, but able to walk without assistance
4	Moderately severe disability: requiring assistance to walk and to attend to own bodily needs
5	Severe disability: bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Alexander, *BMJ,* 2016

Controversy: should age matter?

- Hemicraniectomy clearly results in improved survival
- However, this is potentially offset by a higher rate of severe disability
- Lot of debate about potential age restrictions (first trial excluded patients over age of 60)

When is it the right time?

- Edema thought to peak ~3-5 days
- Question remains when to take patients to OR
- Two general options: Take high risk patients early or wait until there is objective signs of edema
- General consensus to monitor closely and operate

Summary

- Stroke remains a significant burden and leading cause of disability
- Intravenous thrombolytic remains first line therapy for majority of ischemic strokes
- Mechanical thrombectomy can be beneficial in carefully selected patients up to 24 hours from last known well
- Stroke work-up should be guided by type of stroke
- Several complications are possible after acute stroke including cerebral edema in large hemispheric stroke

References

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