Updates in Stroke

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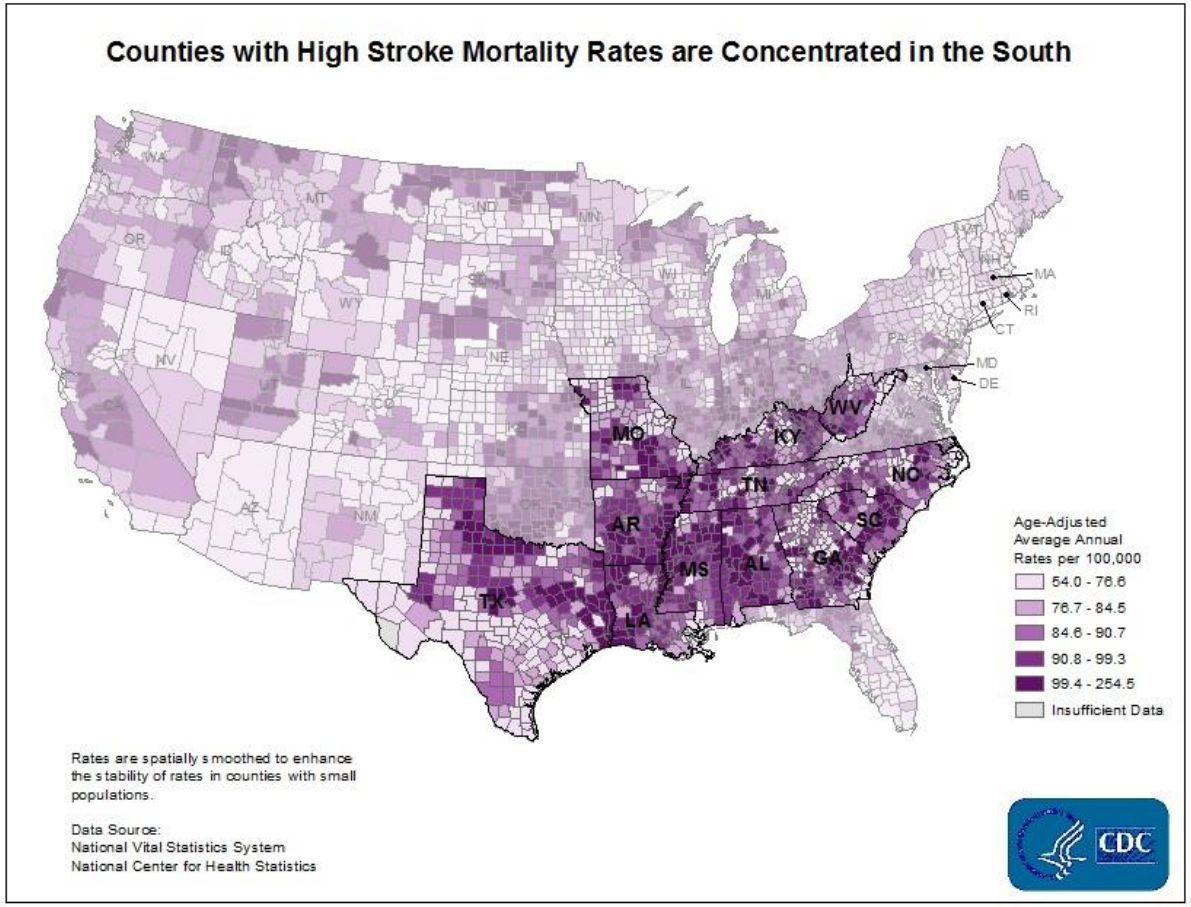
April 2, 2022

U.S. Stroke Statistics

- More than 795,000 people in U.S. have stroke annually (5th leading cause of death)
- **1 stroke every 40 seconds**
- 1 death from stroke every 4 minutes
- Approximately 87% of strokes are ischemic type
- Stroke related costs = $46 billion/ year (health care services, medicines for stroke treatment, missed days of work)



Centers for Disease Control and Prevention. Stroke Facts. https://www.cdc.gov/stroke/facts.htm. Accessed March 21, 2022.

Stroke Risk

- Risk of first stroke is almost twice as high for black people as for white. Black people have the highest mortality rate due to stroke.
- Overall death rates from stroke have declined for decades in all race/ethnicities except Hispanic people for whom rates have increased since 2013.
- 34% of people hospitalized for stroke were under age 65 in 2009.
- Major risk factors include high blood pressure, high cholesterol, smoking, obesity, and diabetes. 1 in 3 U.S. adults has at least one of these.

https://www.cdc.gov/stroke/facts.htm

Turning Points in Stroke Care

- Alteplase found to be effective for acute stroke therapy within 3 hours (1996)
- Alteplase shown to be effective up to 4.5 hours (2008)
- Mechanical thrombectomy shown to be effective for treatment of large vessel occlusions within 6 hours (2015)
- Mechanical thrombectomy treatment window extended to 24 hours (2018)

Mobile Stroke Units (MSU)

- Earlier stroke treatment leads to less disability
- Time is Brain
- Only 15-32% of stroke patients present to ED within 3 hours. 40-50% will be eligible for tPA
- Less than 5% of ischemic stroke patients are treated with thrombolytic therapy
- For good functional outcome, NNT = 4.5 at <1.5 hr,

NNT = 9 at 1.5-3 hr, NNT= 14.1 at 3-4.5 hr

Fang MC, Cutler DM, Rosen AB. Trends in thrombolytic use for ischemic stroke in the United States. *J Hosp Med*. 2010;5(7):406-409. doi:10.1002/jhm.689

Inside the MSU

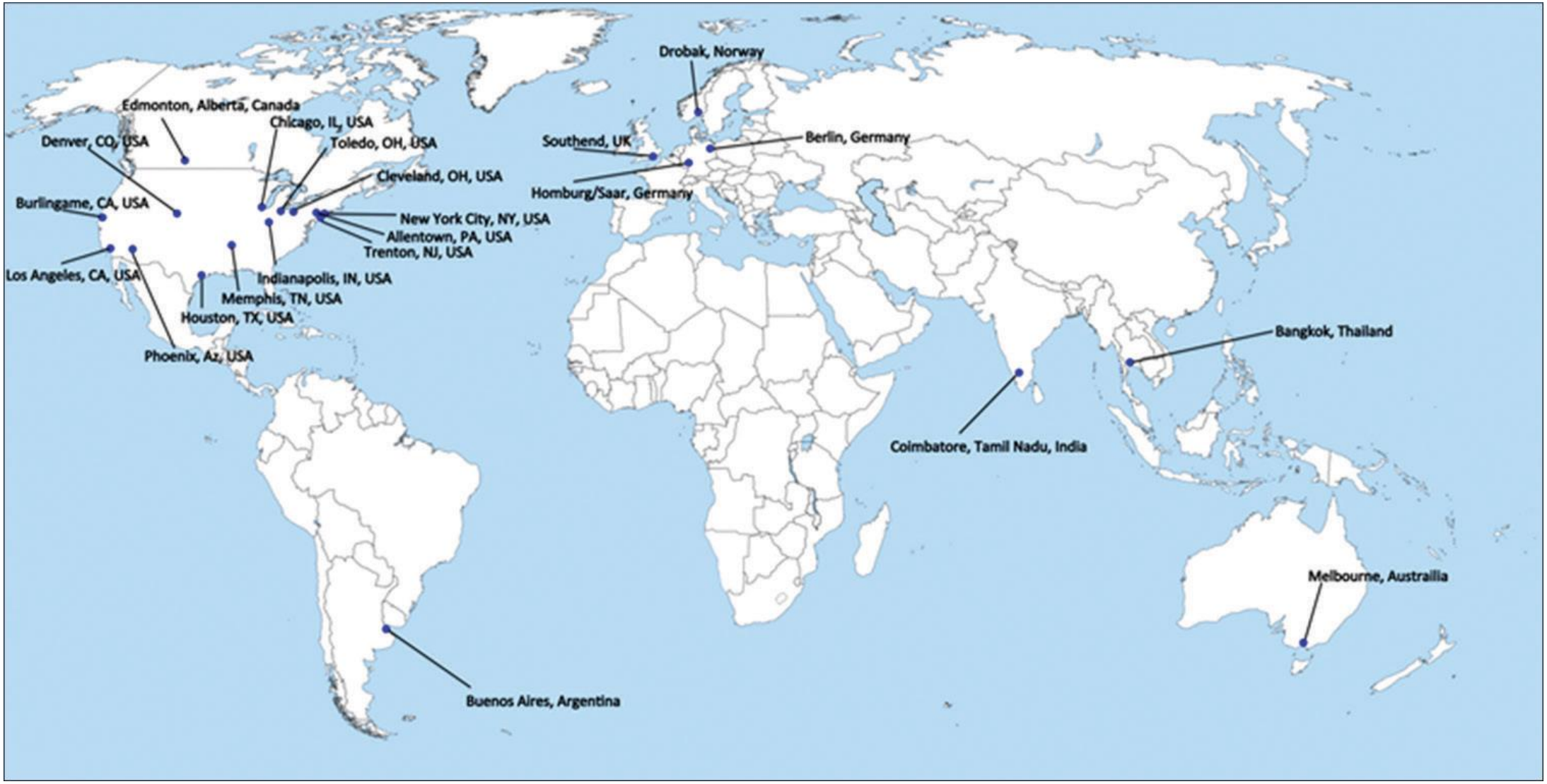
On the Unit

- Standard ambulance equipment/medications
- CT scanner
- Point of care lab equipment
- Telemedicine capability
- tPA

Team: Physician, EMT, CT technologist, Nurse

Towner J, Pieters T, Schmidt T, Pilcher W, Bhalla T. A History of Mobile Stroke Units and Review of Literature. Am J Interv Radiol 2018, **2**(9) 1-5.

MSU Map



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MSU Efficacy (Early studies)

- Univ. of Saarland (1st RCT) showed 41 min decrease in time from stroke alert to treatment decision. No improvement in functional outcome at 7 days.
- Phantom-S pilot study showed decreased time to treatment. No adverse outcomes in those treated with tPA compared with treatment in the ED.
- Phantom-S RCT: 25 min decrease in treatment time, increased utilization of tPA, no changes in 7-day mortality or rate of hemorrhage.
  - Sub-study analysis showed increased rates of good functional outcome at 0-3 months and decreased 3-month mortality in MSU group.

Towner J, Pieters T, Schmidt T, Pilcher W, Bhalla T. A History of Mobile Stroke Units and Review of Literature. Am J Interv Radiol 2018, **2**(9) 1-5.

MSU Efficacy (BEST-MSU)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 9, 2021 VOL. 385 NO. 11

Prospective, Multicenter, Controlled Trial of Mobile Stroke Units

J.C. Grotta, J.-M. Yamal, S.A. Parker, S.S. Rajan, N.R. Gonzales, W.J. Jones, A.W. Alexandrov, B.B. Navi, M. Nour, I. Spokoyny, J. Mackey, D. Persse, A.P. Jacob, M. Wang, N. Singh, A.V. Alexandrov, M.E. Fink, J.L. Saver, J. English, N. Barazangi, P.L. Bratina, M. Gonzalez, B.D. Schimpf, K. Ackerson, C. Sherman, M. Lerario, S. Mir, J. Im, J.Z. Willey, D. Chiu, M. Eisshofer, J. Miller, D. Ornelas, J.P. Rhudy, K.M. Brown, B.M. Villareal, M. Gausche-Hill, N. Bosson, G. Gilbert, S.Q. Collins, K. Silnes, J. Volpi, V. Misra, J. McCarthy, T. Flanagan, C.P.V. Rao, J.S. Kass, L. Griffin, N. Rangel-Gutierrez, E. Lechuga, J. Stephenson, K. Phan, Y. Sanders, E.A. Noser, and R. Bowry

Grotta JC, Yamal JM, Parker SA, Rajan SS, Gonzales NR, Jones WJ, et al. Prospective, Multicenter, Controlled Trial of Mobile Stroke Units. N Engl J Med. 2021 Sep 9;385(11):971-981. doi: 10.1056/NEJMoa2103879. PMID: 34496173.

MSU Efficacy (BEST-MSU)

- Observational, prospective, alternating week trial enrolling at 7 sites (>70% from Houston site)
- Enrolled 1515 patients (1047 received tPA)
- Median stroke onset to tPA time 72 min in MSU group vs 108 minutes in EMS group
- Of tPA eligible patients, 97.1% in MSU group were treated vs 79.5% in EMS group
- 2.6% of patients in EMS group vs 32.9% in MSU group treated in “golden hour”

Grotta JC, Yamal JM, Parker SA, Rajan SS, Gonzales NR, Jones WJ, et al. Prospective, Multicenter, Controlled Trial of Mobile Stroke Units. N Engl J Med. 2021 Sep 9;385(11):971-981. doi: 10.1056/NEJMoa2103879. PMID: 34496173.

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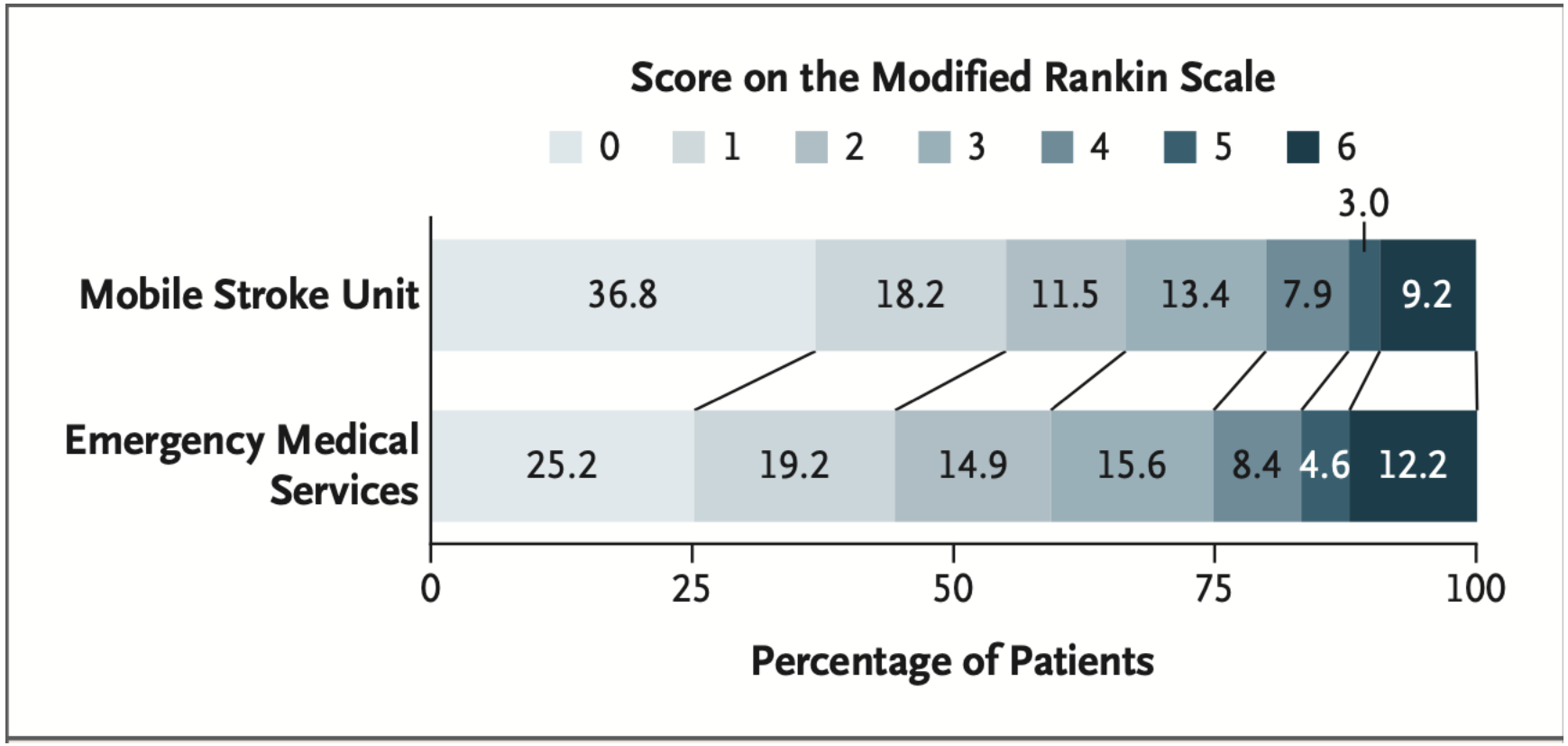

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MSU Cost Effectiveness

- No difference in length of stay or proportion discharged home
- MSU patients had more days at home without nursing home or rehospitalization at 1 year
- MSU patients reported better subjective average quality of life
- MSU patients had higher healthcare utilization costs ($57,658 vs $54,898)
- MSU annual operation cost estimate: $436,457
- Using $190,000/QALY threshold, NNT = 100-150 tPA eligible patients/year

Rajan S., Yamal JM, Parker S,Jacob A,Wang M, Ganey C, Czap A, Bowry R, Grotta J. Economic Evaluation of the Benefits of Stroke Treatment Delivered Using a Mobile Stroke Unit Study [abstract]. In: Prceedings of the International Stroke Conference; 2022 Feb 9-11; New Orleans, Louisiana

MSU Implementation

- 20 MSU sites across the U.S. (2021)
- Houston and El Paso
- Improve Cost Effectiveness:
  - Reduce personnel using telemedicine
  - Determine number of units and placement to service a region efficiently
  - Expand scope to TBI, status epilepticus, intracranial hemorrhage
  - Improve accuracy of stroke identification algorithm from dispatch office

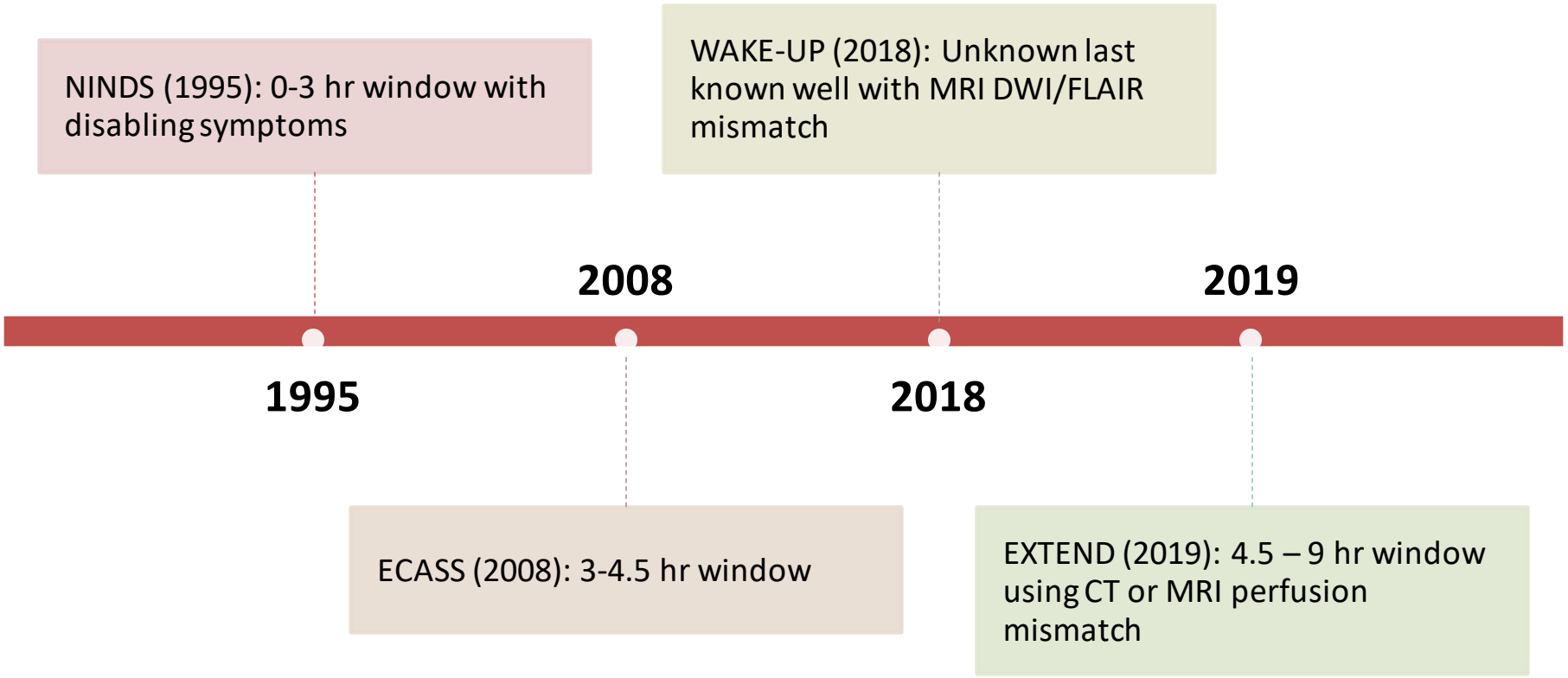
Fassbender K, Merzou F, Lesmeister M, *et al* Impact of mobile stroke units *Journal of Neurology, Neurosurgery & Psychiatry* 2021;**92:**815-822.

Thrombolytic Therapy: Alteplase

- Thrombolytic agent FDA approved for acute ischemic stroke, pulmonary embolism, acute MI, and occluded catheters.
- Mechanism: converts plasminogen to plasmin which lyses fibrin and fibrinogen
- Initial half life = 5 min
- Dose: 0.9 mg/kg given (10% given as IV bolus over 1 minute and 90% given as infusion over 1 hour)
- Adverse reactions: Bleeding, Angioedema, Anaphylaxis, Fever

Reed M, Kerndt CC, Nicolas D. Alteplase. [Updated 2020 Aug 21]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499977/

Thrombolytic Therapy: Alteplase

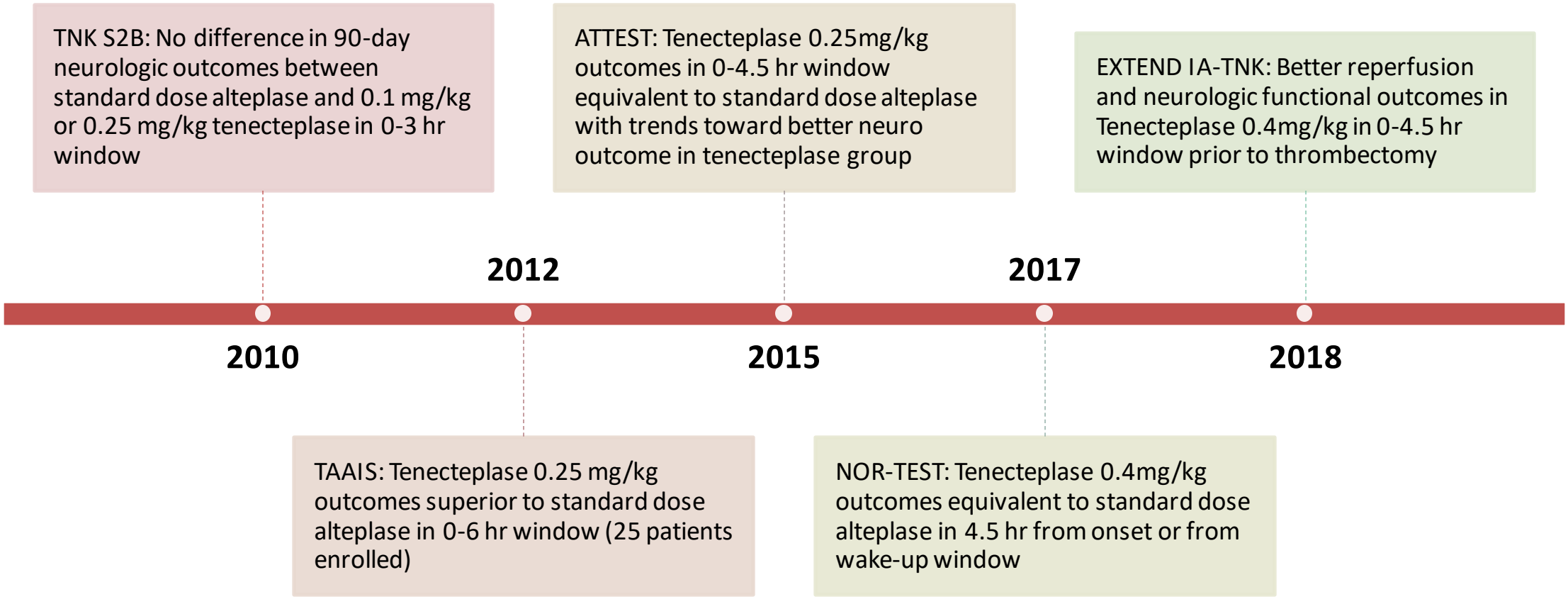


Thrombolytic Therapy: Tenecteplase

- A thrombolytic and tissue plasminogen activator
- Increased fibrin specificity which decreases systemic plasminogen activation and degradation of circulating fibrin
- Initial half life: 20-24 minutes
- Adverse reactions: Bleeding, Arrhythmia (in use for coronary thrombolysis), Angioedema, Anaphylaxis

Warach, S., Dula, A. and Milling, T., 2020. Tenecteplase Thrombolysis for Acute Ischemic. Stroke. *Stroke*, 51(11), pp.3440-3451.

Thrombolytic Therapy: Tenecteplase



Thrombolytic Therapy: Tenecteplase

Outcome measures	Measurements	Results
Rate of symptomatic hemorrhage	Baseline and after-treatment variables with symptomatic and asymptomatic	Following treatment with tenecteplase, there was a greater early clinical improvement with a median of 9 in comparison to alteplase's median of 1 [13].
	National Institutes of Health Stroke Scale score (NIHSS)	No significant difference between both scores because a majority of the score range fell between 0 and 4 for both interventions [16].
Functional outcome at 90 days	Modified Rankin Scale (mRS)	Both interventions shared the same effect [12, 16].
		A higher proportion of patients showed a significant recovery using the tenecteplase intervention [15].
		The proportion of patients with good functional outcome was 61% in the tenecteplase group and 57% in the alteplase group (odds ratio, 1.24; 95% CI 0.65–2.37).
Reperfusion rate after thrombectomy	Modified thrombolysis in cerebral infarction (mTICI)	Over the course of 90 days following the treatment, overall reperfusion rates were significantly higher than alteplase [13].
		Tenecteplase was associated with significantly better reperfusion (P=0.004) and clinical outcomes than alteplase (P<0.0001) [15].

Potla, N., Ganti, L. Tenecteplase vs. alteplase for acute ischemic stroke: a systematic review. *Int J Emerg Med* **15,** 1 (2022). https://doi.org/10.1186/s12245-021-00399-w

Thrombolytic Therapy: Tenecteplase

- TEMPO-2: TNK 0.25 mg/kg vs antiplatelet for minor stroke/TIA in the 0-12hr window (Dec 2023)
- TWIST: TNK 0.25 mg/kg vs standard of care in 4.5 hrs from onset or from wake up using non-contrast CT and CTA for selection (Dec 2022)
- TIMELESS: TNK 0.25 mg/kg vs placebo in LVO (MCA/ICA) patients in 4.5 – 24 hr window (April 2022)
- NOR-TEST 2: TNK 0.4 mg/kg vs alteplase 0.9 mg/kg in 0-4.5 hr or with 4.5 hr from wake-up window (May 2023)

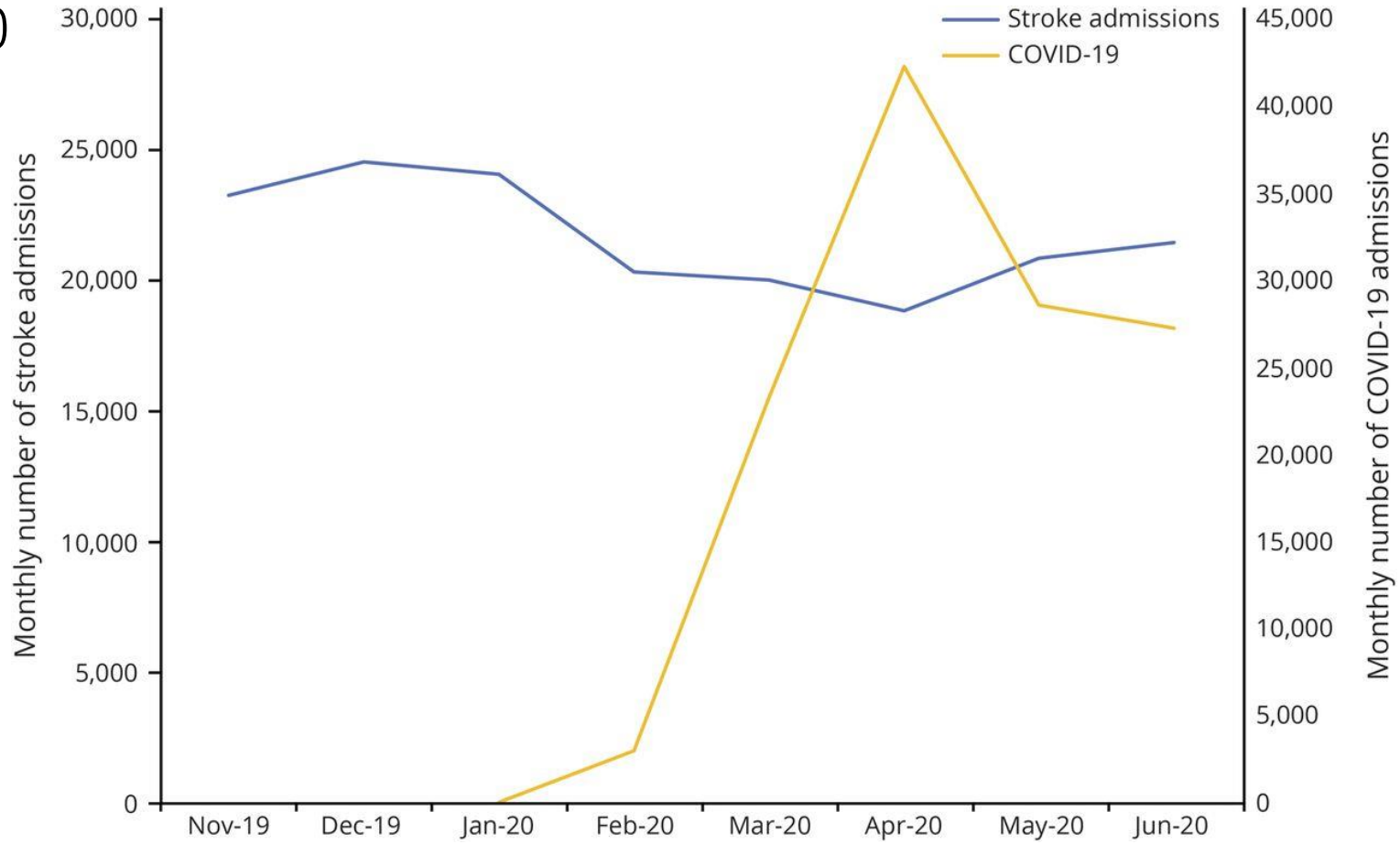
Thrombolytic Therapy: Tenecteplase

- Non-inferior to alteplase
- Superior safety profile
- Easier administration
- Potential for decreased medication errors
- Improvements in door to thrombolytic time

Hailu K, Cannon C, Hayes S. Tenecteplase use in the management of acute ischemic stroke: Literature review and clinical considerations. Am J Health Syst Pharm. 2022 Jan 10:zxac010. doi: 10.1093/ajhp/zxac010. PMID: 35020806.

Stroke and Covid-19

- SVIN Registry review of 254,000 global stroke admissions in early months of the pandemic
- 11.5% monthly stroke hospitalizations seen in first months
- 13.2% drop in thrombolytic therapy



Raul G. Nogueira, Muhammad M. Qureshi, Mohamad Abdalkader, Sheila Ouriques Martins, et al. on behalf of the SVIN COVID-19 Global Stroke Registry Neurology Jun 2021, 96 (23) e2824-e2838; DOI:10.1212/WNL.0000000000011885

Stroke and Covid-19

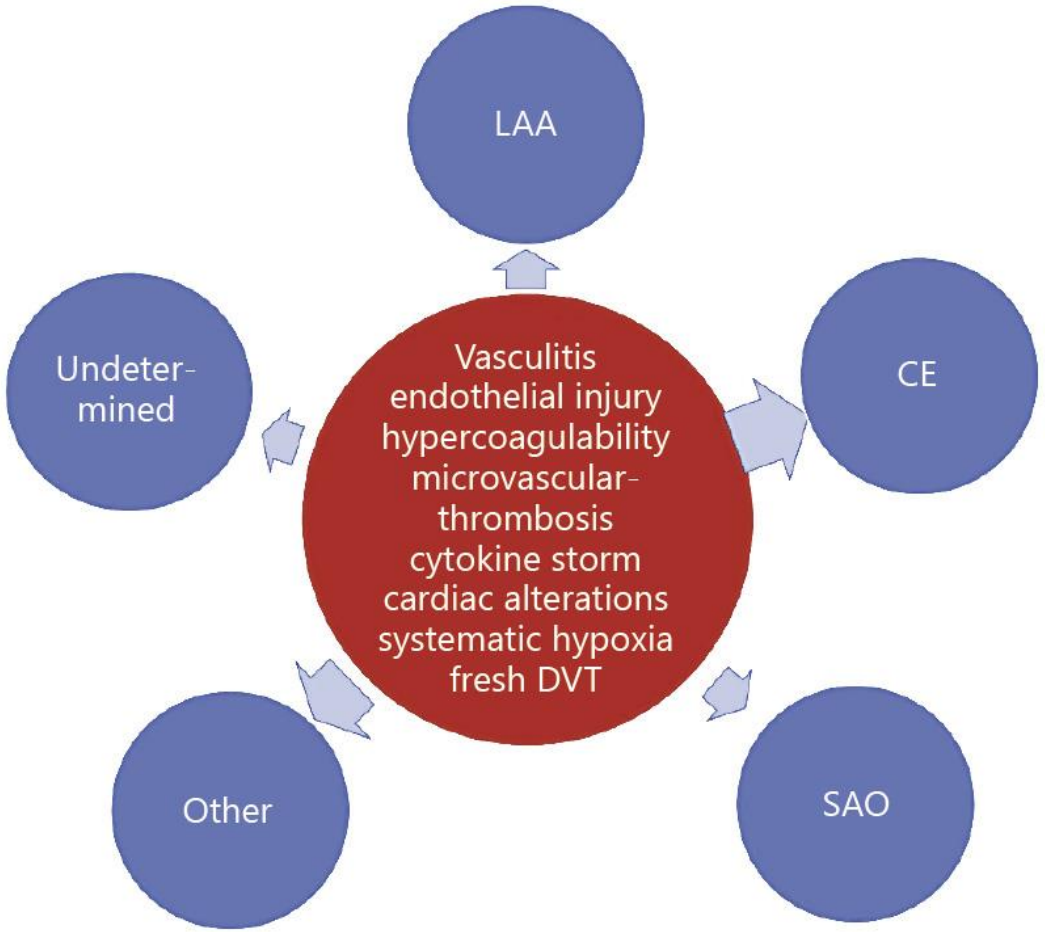
Table e-5. Proportion of Patients with COVID-19 and Concomitant Diagnosis of Stroke.

	Number of Centers	COVID-19 with Any Stroke	Any COVID-19 Hospitalization	%	95% CI	
Overall	264*	1,778	119,967	1.48	1.41	1.55
Asia	61	317	20,858	1.52	1.36	1.70
North America	97	615	49,237	1.25	1.16	1.35
Europe	62	507	36,871	1.38	1.27	1.50
South America	27	291	9,865	2.95	2.63	3.30
Oceania	7	1	257	0.39	0.07	2.49
Africa	10	47	2,879	1.63	1.23	2.16

*In this analysis of the proportion of patients with COVID and concomitant diagnosis of stroke, 5 centers were excluded due to incomplete COVID-19 hospitalization data

Nogueira RG, Qureshi MM, Abdalkader M, Martins SOet al. SVIN COVID-19 Global Stroke Registry. Global Impact of COVID-19 on Stroke Care and IV Thrombolysis. Neurology. 2021 Jun 8;96(23):e2824-e2838. Epub 2021 Mar 25. PMID: 33766997

Stroke and Covid-19

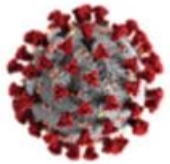


Potential mechanisms:

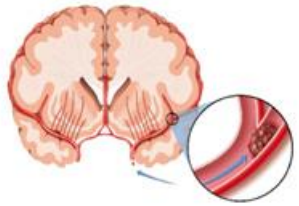
- Hypercoagulable state (antiphospholipid antibodies, DIC, paradoxical emboli)
- Vasculitis (endothelial dysfunction, cytokine storming
- Cardiomyopathy (myocarditis, stress cardiomyopathy)

Spence JD, de Freitas GR, Pettigrew LC, Ay H, et al. Mechanisms of Stroke in COVID-19. Cerebrovasc Dis. 2020;49(4):451-458. doi: 10.1159/000509581. Epub 2020 Jul 20. PMID: 32690850

Stroke and Covid-19



Acute Ischemic Stroke
41,971 Patients from 458 Hospitals



	With COVID-19 (n=1,143)	**Without COVID-19** (n=40,828)
Characteristics	↑Non-Hispanic Black, Hispanic, and Asian ↑Large Vessel Occlusion	↑Age ↑Hypertension ↓Diabetes
Diagnostics	↑Door to Brain Imaging Time	
Treatment	↑Door to Needle Time ↑Door to EVT Time ↔ Intravenous Thrombolytic Use ↔ Endovascular Therapy Use ↔ GWTG Achievement Measures	
Outcomes	↑In-Hospital Mortality ↑Discharge to Skilled Nursing	↑Discharge mRS 0-2 ↑Discharge Home ↑Discharge Inpatient Rehabilitation

Srivastava PK, Zhang S, Xian Y, Xu H, Rutan C et al. Acute Ischemic Stroke in Patients With COVID-19: An Analysis From Get With The Guidelines-Stroke. Stroke. 2021 May;52(5):1826-1829. Epub 2021 Mar 17. PMID: 33728926.

Stroke and Covid-19

- Potential prevention and treatment of stroke in COVID-19 patients
  - Ongoing trials for antithrombotic and immunomodulatory drugs
  - Focus on timely revascularization
  - Further investigation into use of telemedicine in stroke assessment
  - Study of association and potential causal relationship between coronavirus and stroke
  - Longitudinal study of long-term disability

Sagris D, Papanikolaou A, Kvernland A, Korompoki E, et al. COVID-19 and ischemic stroke. Eur J Neurol. 2021 Nov;28(11):3826-3836. doi: 10.1111/ene.15008. Epub 2021 Jul 17. PMID: 34224187; PMCID: PMC8444875.

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Thank you


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