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Global Epidemiology of Stroke and Access to Acute Ischemic Stroke Interventions

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Neurology® 2021;97:S6-S16. doi:10.1212/WNL.0000000000012781

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Abstract

Purpose of the Review

To provide an up-to-date review of the incidence of stroke and large vessel occlusion (LVO) around the globe, as well as the eligibility and access to IV thrombolysis (IVT) and mechanical thrombectomy (MT) worldwide.

Recent Findings

Randomized clinical trials have established MT with or without IVT as the usual care for patients with LVO stroke for up to 24 hours from symptom onset. Eligibility for IVT has extended beyond 4.5 hours based on permissible imaging criteria. With these advances in the last 5 years, there has been a notable increase in the population of patients eligible for acute stroke interventions. However, access to acute stroke care and utilization of MT or IVT is lagging in these patients.

Summary

Stroke is the second leading cause of both disability and death worldwide, with the highest burden of the disease shared by low- and middle-income countries. In 2016, there were 13.7 million new incident strokes globally; ≈87% of these were ischemic strokes and by conservative estimation about 10%–20% of these account for LVO. Fewer than 5% of patients with acute ischemic stroke received IVT globally in the eligible therapeutic time window and fewer than 100,000 MTs were performed worldwide in 2016. This highlights the large gap among eligible patients and the low utilization rates of these advances across the globe. Multiple global initiatives are underway to investigate interventions to improve systems of care and bridge this gap.

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Glossary

AHA/ASA = American Heart Association/American Stroke Association; **AIS** = acute ischemic stroke; **ASPECTS** = Alberta Stroke Program Early CT Score; **CI** = confidence interval; **DALY** = disability-adjusted life-year; **ED** = emergency department; **HS** = hemorrhagic stroke; **IS** = ischemic stroke; **IVT** = IV thrombolysis; **LVO** = large vessel occlusion; **MCA** = middle cerebral artery; **mRS** = modified Rankin Scale; **MSU** = mobile stroke unit; **MT** = mechanical thrombectomy; **MT2020+** = Mission Thrombectomy 2020+; **mTICI** = modified Thrombolysis in Cerebral Infarction; **NINDS** = National Institute of Neurological Disorders and Stroke; **OR** = odds ratio; **QALY** = quality-adjusted life-year; **RCT** = randomized clinical trial; **rtPA** = recombinant tissue plasminogen activator.

Stroke is the second leading cause of both disability and death worldwide[1] and poses a staggering burden at both individual and societal levels. Whereas advances in the treatment of hemorrhagic stroke (HS) have been slow, IV thrombolysis (IVT) and more recently mechanical thrombectomy (MT) for large vessel occlusion (LVO) have changed our ability to prevent long-term disability from acute ischemic stroke (AIS) in eligible patients. Outcomes from IVT and MT are highly time-sensitive and rapid access to these AIS interventions is lagging, especially from the global perspective. This review examines the global burden of stroke and the dramatic geographic disparities in stroke incidence as well in access to AIS interventions. Ongoing and planned approaches to address this are discussed.

Global Epidemiology of Stroke

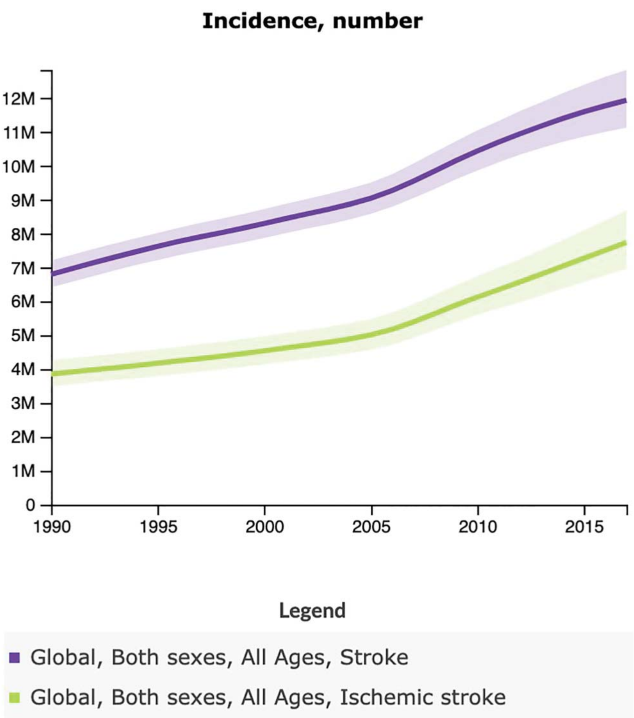
In 2010, the estimated number of incident ischemic strokes (IS) and HS across the globe was 11.6 million and 5.3 million, respectively; 63% of IS and 80% of HS occurred in low- and middle-income countries.[2,3] In 2016, the number of incident new strokes increased to 13.7 million (95% confidence interval [CI] 12.7–14.7; Figure 1).[1] In the same year, 5.5 million deaths worldwide were attributed to stroke; IS and HS accounted for 2.7 million and 2.8 million deaths, respectively.[1] A geographic distribution of the burden of stroke can be constructed with methodologic limitations including variability in research approaches for reporting incidence of stroke in different countries as well as a lack of information for many (Table 1).

Worldwide stroke prevalence in 2016 was 80.1 million (95% CI 74.1–86.3): 41.1 million (38.0–44.3) in women and 39.0 million (36.1–42.1) in men.[1] In the United States, the prevalence of stroke is about 3% in adults 20 years or older, which accounts for ≈7 million strokes in the population.[4] Annually, ≈795,000 people experience a new or recurrent stroke in the United States; ≈610,000 of these are first time strokes.[4] This translates to a global stroke prevalence and incidence of ≈1,322 and 156 per 100,000 persons, respectively, in 2016, and US stroke prevalence and incidence of ≈2,320 and 184 per 100,000 persons, respectively, in 2016.[1,5]

The stroke case-fatality rate at 30 days ranged from ≈10% in Dijon, France (2000–2004) to as high as 42% in Kolkata, India (2003–2010).[6] This highlights the disparity in availability of resources to mitigate stroke burden and hence outcomes of stroke around the world. Figure 2 highlights the disproportionate distribution of age-standardized stroke incidence by country across the globe. Stroke is the second leading cause of disability and accounted for ≈116 million global disability-adjusted life-years (DALYs) lost in 2016.[1] From 1990 to 2010, although the age-standardized mortality rates for IS and HS decreased, the absolute number of people with incident IS and HS increased by 37% and 47%, respectively; the number of associated deaths increased by 21% and 20%, respectively; and DALYs lost increased by 18% and 14%, respectively.[3] Recent data from 2010 to 2017 continue to show alarming increase in stroke incidence and mortality by 5.3% each, prevalence by 19.3%, and DALYs lost by 2.7%.[7]

Most of the burden of this absolute increase in incidence of strokes is borne by low- and middle-income countries.[3] In a

Figure 1 Global Incidence of Stroke and Ischemic Stroke for All Ages and Both Sexes, From 1990 to 2017



Source: Institute for Health Metrics and Evaluation; ghdx.healthdata.org/gbd-results-tool. University of Washington, Seattle; 2015.[5]

Table 1 Age-Adjusted Incidence, Outcomes, and Utilization of Acute Interventions for Stroke Across the Globe[1,4,6,10,51-60]

	Incidence of stroke per 100,000 (95% CI)	Incidence of ischemic stroke per 100,000 (95% CI)	DALYs per 100,000 (95% CI)	Case-fatality 28 or 30 days, % (95% CI)	Mortality per 100,000 (95% CI)	Access to stroke unit, %	IVT use, % (year)	MT use, n (year)
Global	156.2 (145.5–167.9)	101.3 (91–113.6)	1,728.3 (1,655.6–1,797.7)	NA	80.7 (79.1–82.8)	NA	<5	<100,000
High income[b]								
Australia	76 (59–94; Adelaide 2009–2010); 67 (56–79; Perth 2000–2001)	55.1 (48.7–62.9) (2017)[c]	428 (386–470)	18 (14–24; Adelaide 2009–2010)	18.3/19.7 (F/M, 2015)	49.5	10 (2019)	1,907 (2019)
Barbados[g]	88 (79–98) (2001)	NA	1,080 (990–1,164)	29.9 (24.9–34.8) (2001)	45.1/59.5 (F/M, 2013)	NA	NA	NA
Canada	100.5 (92.5–110.2) (2017)[c]	66.8 (59.2–76.6) (2017)[c]	492 (438–547)		15/16.7 (F/M, 2015)	23	NA	NA
Estonia[d]	200 (181–218) (2016)		856 (733–1,036)	28 (Tartu 2001–2003)	37.1 (31.7–48.8) (2017)[c]	61	NA	NA
France	86.6 (83.9–89.3; Dijon, 1987–2012)	70.9 (68.5–73.4; Dijon, 1987–2012)	420 (380–461)	NA	13.9/18.8 (F/M, 2015)	33	NA	6,880 (2018)
Germany	85 (76–95; Erlangen 1995–1996)	73.9 (65.6–83.4) (2017)[c]	543 (486–599)	NA	19.6/25 (F/M, 2015)	70	NA	NA
Israel	97.5 (89.5–106.7) (2017)[c]	64.3 (56.9–74.1) (2017)[c]	443 (400–482)	NA	16.4/20.5 (F/M, 2015)	5	NA	NA
Italy	80.2 (73–87; Valley d'Aosta 2004–2008)	79.7% (Valley d'Aosta 2004–2008)	458 (422–498)	16.1 (Valley d'Aosta 2004–2008)	24.2/30.6 (F/M, 2015)	33	NA	NA
Japan	90.4 (77.4–107.7; Shiga 2011); 140 (130–163; Iwate state)	55.7 (46.5–68.4; Shiga 2011)	684 (620–747)	13.3–14.5 (Takashima 2001–2005)	17/31.5 (F/M, 2015)	Present (NA)	16.8 (Shiga 2011)	2.1 (Shiga 2011)
Saudi Arabia[f]	29.8–50.9	58.5%–87%	1,315 (1,169–1,470)	NA	20.6/25.4 (F/M, 2012)	Present (NA)	NA	NA
Spain	95.9 (88.3–104.5) (2017)	60.7 (53.4–69.5) (2017)[c]	464 (420–507)	NA	16.1/22.3 (F/M, 2016)	23	NA	NA
Sweden	126 (111–140; Orebro 1999–2000)	65.8 (58–75) (2017)[c]	518 (469–567)	19 (Orebro 1999–2000)	17.7/23.4 (F/M, 2016)	87.5	NA	NA
United Kingdom	73 (64–83; Oxfordshire 2002–2004)	56.8 (50.2–64.5) (2017)[c]	549 (511-5,840	15.9 (Scottish borders 1998–2000)	20.1/22.6 (F/M, 2016)	83	NA	NA
United States[a]	184.1 (170.6–199.8) (2016)[c]; 113 (102–126; Greater Cincinnati/Northern Kentucky 1999)	78.9 (70.6–89.3) (2017)[c]	692 (625–759)	NA	20.2/22.8 (F/M, 2016)	Present (NA)	10–15	11,469 (2016)
Upper middle income[b]								
Brazil[a,e]	137 (112–166.4; Matao 2003–2004)	91.9 (71.5–116.3; Matao 2003–2004)	2,342 (2,218–2,470)	18.5 (10.7–28.7; Matao 2003–2004)	41.8/60.4 (F/M, 2016)	Present (NA)	NA	NA
China[a]	354 (331–378) (2016); 297.4 (Tianjin 2014)	238.8 (Tianjin 2014)	3,136 (2,969–3,308)	NA	122.4 (118.6–126.7) (2017)[c]	Present (NA)	NA	NA
Iran[f]	203 (175–231; Mashhad 2006–2007)	167 (142–193; Mashhad 2006–2007)	1,141 (1,071–1,211)	NA	61.3 (59.2–65.1) (2017)[c]	NA	1.1 (2008)	NA
Mexico[a]	93 (86.2–100.1) (2017)[c]	53.8 (47.8–61) (2017)[c]	683 (656–713)	NA	29 (27.9–29.8) (2017)[c]	NA	NA	NA

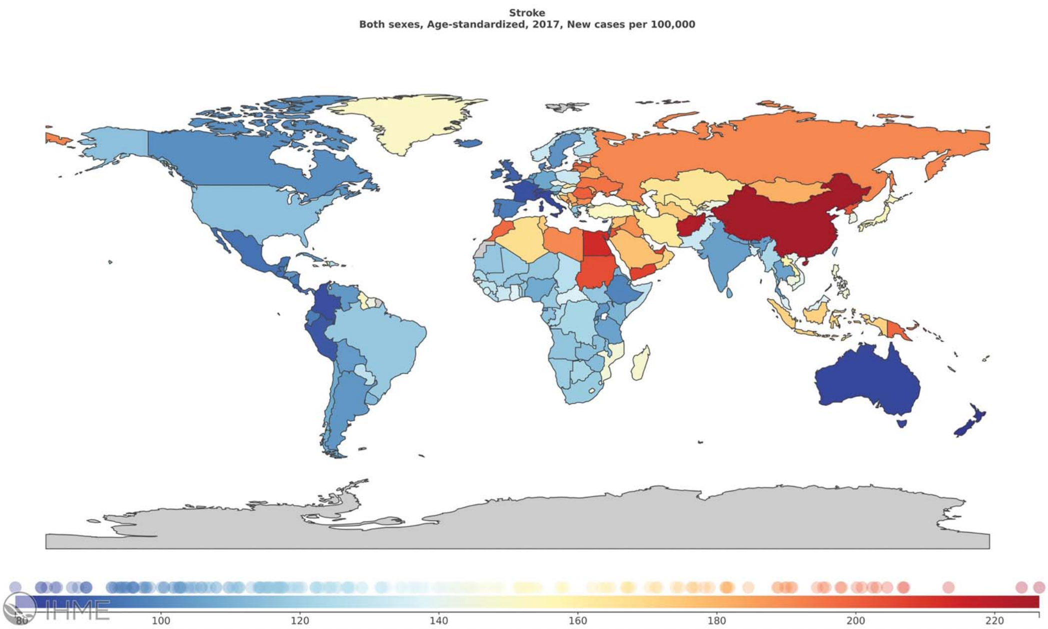
Continued

Table 1 Age-Adjusted Incidence, Outcomes, and Utilization of Acute Interventions for Stroke Across the Globe[1,4,6,10,51-60] *(continued)*

	Incidence of stroke per 100,000 (95% CI)	Incidence of ischemic stroke per 100,000 (95% CI)	DALYs per 100,000 (95% CI)	Case-fatality 28 or 30 days, % (95% CI)	Mortality per 100,000 (95% CI)	Access to stroke unit, %	IVT use, % (year)	MT use, n (year)
Russia[a]	190.9 (176.8–206) (2017)[c]	139.7 (126–155.6) (2017)[c]	2,511 (2,397–2,625)	22.7 (17.7–27.7; Novosibirsk 1992)	105.4/154.6 (F/M, 2013)	13	NA	NA
Lower middle income[b]								
Bangladesh[a]	135.7 (126.2–146.5) (2017)[c]	78.7 (70.2–88.7) (2017)[c]	2,870 (2,603–3,155)	NA	153 (138.8–168.2) (2017)[c]	NA	NA	NA
El Salvador[e]	89.3 (82.6–96.6) (2017)[c]	50.8 (44.8–58) (2017)[c]	683 (589–782)		15.6/18.8 (F/M, 2014)			
India[a]	130 (123–137; Ludhiana 2010–2013); 145.3 (120–175; Kolkata 2003–2005)	74.8 (66.3–83.2; Trivandrum, 2005)	1,592 (1,509–1,665)	22 (Ludhiana 2010–2013); 41.1 (Kolkata 2003–2005)	77.4 (72.7–81.1) (2017)[c]	Present (NA)	NA	NA
Indonesia[a]	171.5 (159.7–184.8) (2017)[c]	98.5 (87.3–110.9) (2017)[c]	3,481 (3,285–3,685)	NA	178.3 (167.6–189.7) (2017)[c]	NA	NA	NA
Pakistan[a]	131.6 (121.7–142.6) (2017)[c]	80.5 (71.6–90.5) (2017)[c]	2,534 (2,118–2,948)	NA	133.7 (112.7–155.7) (2017)[c]	Present (NA)	<2 (2,005–2,007)	NA
Nigeria[a,h]	60.7 (Ondo state, 2,010–2,011); 54.1 (Lagos state, 2007)	NA	1,252 (951–1,666)	16.2 (Lagos state, 2007)	NA	Present (NA)	NA	NA
Lower income[b]								
Afghanistan	223.9 (207.4–241.4) (2017)[c]	141 (125.2–157.2) (2017)[c]	3,665 (3,206–4,186)	NA	165.8 (144.3–188.2) (2017)[c]	NA	NA	NA
Madagascar[h]	148.8 (138.9–160.6) (2017)[c]	75.4 (66.4–85.1) (2017)[c]	2,661 (2,481–2,851)	NA	181.9 (153.4–213.6) (2017)[c]	NA	NA	NA
Rwanda[h]	96 (88.2–104.5) (2017)[c]	56.3 (49.3–63.8) (2017)[c]	1,390 (1,098–1,670)	NA	76 (58.2–93.7) (2017)[c]	NA	NA	NA
Somalia[h]	129 (119.2–139.3) (2017)[c]	71.2 (62.9–80.8) (2017)[c]	2,783 (2,139–3,511)	NA	136.2 (104.5–168.4) (2017)[c]	NA	NA	NA
Uganda[h]	102.4 (94.9–110.8) (2017)[c]	57.9 (50.9–65.5) (2017)[c]	1,476 (1,248–1,712)	NA	77.8 (64.8–91.3) (2017)[c]	NA	NA	NA

Abbreviations: CI = confidence interval; DALY = disability-adjusted life-years; IVT = IV thrombolysis; MT = mechanical thrombectomy; NA = not available.
[a] Top 10 most populous countries in the world (census.gov/popclock/world; updated on July 1, 2019).
[b] Countries are classified on income level according to the World Bank.
[c] Standardized by country as standardization by world population is not available; the rest are standardized by WHO world population.
[d] Countries based on region: Eastern Europe.
[e] Countries based on region: Latin America.
[f] Countries based on region: Middle East.
[g] Countries based on region: Caribbean.
[h] Countries based on region: Africa.

Figure 2 Age-Standardized Stroke Incidence by Country for Both Sexes, 2017



Source: Institute for Health Metrics and Evaluation; vizhub.healthdata.org/gbd-compare. University of Washington, Seattle; 2015.[5]

recent review on global stroke statistics, the authors observed a strong positive linear relationship in crude incidence rate of stroke by year in low-income countries but no such relationship was seen in high-income countries.[6]

Incidence of stroke is higher in older women (>50% higher incidence compared to men aged 75 years or older), the less educated population, and some racial or ethnic groups (for example, 1.91 per 1,000 in the Black population vs 0.88 per 1,000 in the White population).[4] Conventional projections show that by 2030, an additional 3.4 million US adults, representing 3.9% of the adult population, would have had a stroke and absolute stroke mortality would increase by ≈50%, which is ≈64,000 additional stroke deaths per year compared to 2012.[4,8] These values are higher in middle- or lower-income countries.

Over the past decade in India, the cumulative incidence of stroke ranged from 105 to 152 per 100,000 persons per year, and the crude prevalence of strokes ranged from 44.3 to 559 per 100,000 persons in different parts of the country.[9] A population-based study in Tianjin, China, from 1992 to 2014 showed that the age-standardized first-ever stroke incidence was 297 per 100,000 persons, which significantly increased across sex and strokes subtypes: increase of 6.3% overall, 5.5% for men and 7.9% for women, 4.6% for HS, and 7.3% for IS.[10]

Although the majority of strokes occur beyond the fifth decade, ≈10%–15% of strokes occur in patients 18–50 years of age.[11] The age at stroke onset tends to be lower in low- and middle-income countries, accounting for a relatively higher proportion of strokes (19%–30%), adding to the higher burden of disability and DALYs lost in the developing world.[6,10]

Ischemic Stroke

Of all strokes, ≈87% are ischemic, 10% are intracranial hemorrhage, and 3% are subarachnoid hemorrhage.[4] Global incidence of IS in 2017 was 101.3 (91–113.6) per 100,000 population.[5] A large meta-analysis of population- and hospital-based studies worldwide from 1993 to 2015 showed the following distribution of IS subtypes: cardioembolism accounted for ≈22% (95% CI 20–23), large artery atherosclerosis for 23% (95% CI 21–25), small vessel occlusion for 22% (95% CI 21–24), other determined causes 3% (95% CI 3–3), and undetermined cause 26% (95% CI 24–28).[2] In addition, the distribution of IS subtypes can vary among different racial or ethnic groups (for example, cardioembolism is the leading cause of IS in the White population [28%] vs secondary to large artery atherosclerosis in the Asian population [33%]).[2]

From 1993 to 2015, trends in IS subtypes showed a temporal increase in cardioembolic strokes in Whites (2.4% annually), large artery atherosclerosis in Asians (5.7% annually), and decrease in small vessel occlusion in Whites (−4.7% annually).[2,4] This finding of reduced small vessel disease incidence could in part be secondary to better control of conventional vascular risk factors in the Western population over time. Nevertheless, these differences highlight the role of genetics, environmental factors, socioeconomic status, and a differential distribution of vascular risk factors (hypertension, hyperlipidemia, diabetes, tobacco use, obesity, obstructive sleep apnea) in different racial or ethnic groups across the globe.

Large Vessel Occlusion

Acute LVOs are an important subset of IS as they are associated with more than double risk of death and permanent disability as compared to non-LVO IS. Large prospective studies from 2006 to 2013 found that LVOs contributed to ≈60% of post IS disability and 95% of post IS mortality.[12] LVOs accounts for 10%–46% of all AIS based on variations in the definition of LVO.[13] The initial randomized clinical trials (RCTs) included patients only with intracranial internal carotid artery or middle cerebral artery (MCA) M1 segment occlusion[14]; some studies also included M2 segment[15] and anterior cerebral artery A1 or A2 segment[14] occlusions. In addition, there is recent literature showing benefit in M3 segment[16] and posterior circulation (basilar and posterior cerebral artery) occlusions.[17]

Out of ≈675,000 annual AIS in the United States, MT-eligible patients may vary from 27,000 to 97,000 annually.[18] Another study estimated the annual incidence of LVO in the United States as ≈24 per 100,000 population, which translates to an absolute annual incidence of about 80,000 cases.[19] The total number of MTs performed in the United States in 2016 was around 11,500, highlighting a large gap between the need and MTs performed. The worldwide estimates of LVO if approximated at the lower end of the estimated range of 10% of all AIS yields a total of 1.3 million LVOs annually in 2016. The total number of MTs performed worldwide in 2016 was less than 100,000, indicating the enormous treatment gap and lack of highly beneficial therapy for the majority of patients with LVO stroke worldwide (Table 1).

It is important to approach this problem in a 3-pronged fashion: first, to educate the public on the urgency of AIS as a medical emergency and seek immediate help; second, to increase the utilization of available technology to ensure faster arrival of these patients to hospitals and improve infrastructure to provide IVT or MT to as many eligible patients as possible; and third, to identify deficiencies in current preventative strategies to better identify patients at higher risk of LVOs. The first 2 points are discussed in detail in the following sections. The third point is better elucidated by a recent single-center study performed at one of the largest county hospitals in the United States, where 21.7% patients with LVO undergoing MT had known atrial fibrillation but were not adequately anticoagulated.[20] The frequency is even higher in elderly patients, where ≈1 in 4 LVO cases were not adequately anticoagulated prior to incident LVO.[20]

Eligibility for Acute Stroke Intervention

Time to stroke intervention is the most important quality metric in providing acute stroke interventions. A systematic review of 123 peer-reviewed studies across the globe from 1987 to 2007 showed a trend of 6% annual decline in hours/year in symptom onset to emergency department (ED) arrival and ≈10% annual decline each in ED to neurologic evaluation and ED to CT scan across the study period.[21] In-hospital delay in stroke care has drastically declined with establishment of focused and organized stroke units, leading to long-term reduction in death, dependency, and need for institutional care.[22] On the other hand, prehospital delay continues to contribute the largest proportion of prolonged time to acute stroke care, which is worse in low- and middle-income countries.

IV Thrombolysis

IVT has been studied as a potential treatment for AIS since the 1950s. The ECASS trial, published in 1995, failed to show a difference in efficacy of IV recombinant tissue plasminogen activator (rtPA; Genentech Inc.) vs control within 6 hours of symptom onset when compared to the control arm. The same year, the National Institute of Neurological Disorders and Stroke (NINDS) trial successfully showed that patients given IV rtPA within 3 hours of symptoms onset had significant reduction in disability at 90 days; 50% of those treated had minimal or no disability vs 38% of controls.[23] In 2008, the ECASS III trial demonstrated the efficacy of IV rtPA within 3–4.5 hours from symptom onset with 52.4% of patients achieving functional independence at 90 days compared to 45.2% patients receiving placebo.[24]

At present, the European Medicines Evaluation Agency has approved the use of IV rtPA for AIS up to 4.5 hours from symptom onset, whereas in contrast, its American counterpart, the Food and Drug Administration, has only approved the same until 3 hours from symptom onset. An advisory meeting led by the American Heart Association/American Stroke Association (AHA/ASA) came to a consensus to use IV rtPA in the extended 4.5-hour time window, which is now a Class I, Level of Evidence B recommendation. About 25% patients with AIS arrive within 3 hours of symptom onset, and expansion of the tissue plasminogen activator window to 4.5 hours increases potentially eligible patients by 6.3%.[25]

Across the globe, only ≈30% of countries have reported IV rtPA use in the literature. Among these nations, the utilization of rtPA ranges from ≈10%–15% in high-income countries to less than 2% in low- and middle-income countries (Table 1). In the United States, from 2004 to 2016, IV rtPA use increased by ≈500% in both men (1.8%–11.6%) and women (1.3%–10.9%) but by 2016 marked disparity still existed by age and sex (Table 2). A cost-effectiveness analysis performed in the United States showed that each patient treated with IV rtPA resulted in ≈$600 net cost savings. In the same analysis, it was estimated that every 2% increase in utilization of IV rtPA would result in approximate savings of $7 million US dollars annually.[26]

Unknown time of stroke onset, including wake-up stroke, was initially considered a contraindication to IVT. The challenge to extend the IV rtPA window has been debated since the

Table 2 Frequency of IV Thrombolysis and Mechanical Thrombectomy (MT) Utilization in Acute Ischemic Stroke Admissions in the United States From 2004 to 2016 According to Sex and Age Groups, Using National Inpatient Sample Database

Description	Total	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	*p* trend
Any IV thrombolysis, %[a]															
tPA, male	7.0	1.8	2.3	2.9	3.4	4.1	5.9	7.2	7.4	8.4	9.5	10.3	11.2	11.6	<0.001
tPA, female	6.1	1.3	1.7	2.5	2.9	3.4	5.0	6.6	6.6	7.5	8.9	9.7	10.3	10.9	<0.001
Male, age, y, %															
18–39	9.6	3.3	3.6	4.7	6.1	5.0	8.2	9.5	10.1	10.1	13.8	15.5	14.4	14.1	<0.001
40–59	7.8	2.3	2.7	3.7	3.7	4.7	6.4	8.4	8.2	9.7	10.4	10.9	12.3	12.4	<0.001
60–79	7.1	1.9	2.4	2.9	3.6	4.0	6.0	7.3	7.3	8.5	9.4	10.3	11.0	11.7	<0.001
≥80	5.7	1.0	1.6	2.0	2.8	3.4	5.1	5.6	6.4	6.6	8.1	9.0	9.9	10.4	<0.001
Female, age, y, %															
18–39	9.5	2.7	2.5	4.1	5.4	6.2	7.6	8.6	11.2	9.2	14.2	14.7	14.7	15.7	<0.001
40–59	7.2	1.8	2.1	2.8	3.5	3.7	5.5	7.5	8.1	8.5	9.8	11.3	12.0	12.7	<0.001
60–79	6.2	1.4	1.7	2.9	2.9	3.7	5,1	7.0	6.7	7.6	9.0	9.5	10.0	10.6	<0.001
≥80	5.4	0.9	1.4	2.0	2.5	2.9	4.6	5.8	5.7	7.0	8.2	9.1	9.5	10.3	<0.001
Any MT[a]															
Weighted number, %	318	1,280	1,858	1,811	3,922	3,788	5,055	5,311	6,945	7,860	8,970	9,980	11,469	N/A	
MT, male	1.2	0.1	0.4	0.6	0.6	1.1	1.1	1.4	1.4	1.8	1.9	2.2	2.2	2.4	<0.001
MT, female	0.9	0.1	0.3	0.4	0.4	0.9	0.8	1.1	1.1	1.5	1.7	1.8	2.0	2.4	<0.001
Male, age, y, %															
18–39	3.9	0.3	2.5	2.8	2.9	4.6	3.7	4.9	3.3	4.1	6.1	6.1	3.6	4.1	<0.001
40–59	1.8	0.2	0.7	1.2	0.9	1.9	1.8	2.0	2.0	2.8	2.7	2.7	2.6	2.5	<0.001
60–79	1.1	0.1	0.3	0.4	0.5	0.9	1.0	1.3	1.4	1.6	1.7	2.2	2.3	2.4	<0.001
≥80	0.5	0.0	0.2	0.3	0.2	0.3	0.5	0.6	0.6	0.8	1.0	1.1	1.5	1.9	<0.001
Female, age, y, %															
18–39	3.4	0.7	1.9	2.3	2.4	3.7	2.6	3.3	4.7	3.8	5.5	5.4	4.2	4.4	<0.001
40–59	1.5	0.2	0.6	0.7	0.9	1.4	1.4	2.0	1.9	2.2	2.3	2.5	2.0	2.2	<0.001
60–79	1.0	0.1	0.3	0.4	0.4	1.0	0.9	1.2	1.2	1.6	1.8	1.9	2.2	2.4	<0.001
≥80	0.5	0.0	0.1	0.1	0.1	0.5	0.5	0.6	0.5	0.9	1.1	1.2	1.7	2.3	<0.001

Abbreviation: tPA = tissue plasminogen activator.
[a] Saini V, Otite F; unpublished data; 2020.

sentinel ECASS and NINDS trials in 1995. In 2018, the WAKE-UP and EXTEND trials demonstrated a significant benefit from IV rtPA use in the extended window up to 9 hours from when the patient was last seen well based on fluid-attenuated inversion recovery–diffusion-weighted imaging mismatch and permissive CT perfusion imaging criteria, respectively.[27,28] The 2019 update of the AHA/ASA guidelines for AIS management included the extended window IV rtPA use based on the WAKE-UP trial criteria. With this new guideline, the proportion of patients eligible for IVT will significantly increase, specially in low- and middle-income countries, where one of the major barriers to treatment is delayed arrival to hospitals. This could be further broadened in the future with the ongoing TIMELESS trial evaluating the efficacy of a new thrombolytic agent, tenecteplase, up to 24 hours from last seen well.

An analysis of Get With the Guidelines data on 58,353 patients in 2013 demonstrated that faster onset to needle times for IV rtPA was associated with a reduced rate of symptomatic

ICH, faster recovery or ambulation at discharge, and an increased chance of discharge to home.[29] It is estimated that approximately every hour of delay in acute stroke intervention results in a loss of ≈120 million neurons, which translates to the number of neurons lost with 3.6 years of normal aging.[30] Therefore the importance of rapid access to reperfusion therapy remains paramount. Successful recanalization of LVO occurs in about 10% patients treated with IVT alone, with a resulting good clinical outcome in 61.7% of these patients.[31] Therefore, implementing strategies to address availability and delays in IVT has the potential of improving LVO outcomes globally, as it is implementable even in settings where resources limit establishment of thrombectomy centers.

Mechanical Thrombectomy

In 2015, MR CLEAN, EXTEND-IA, and SWIFT PRIME trials established MT as the standard of care for patients with anterior circulation LVO presenting within 6 hours of symptoms onset.[14] The REVASCAT and ESCAPE trials showed benefit up to 8 hours and 12 hours, respectively,[14] and more recently the DAWN[32] and DEFUSE 3[33] trials expanded the therapeutic window to 24 hours in patients with favorable perfusion imaging. The number needed to treat with MT within 6 hours and 6–24 hours of symptom onset to reduce disability by at least 1 point on the modified Rankin Scale (mRS) scale was 2.6 and 3–4, respectively.[14] Absolute improvement, defined as mRS 0–2 at 90 days in these MT trials, ranged from 13.5% to 31%, as compared to the 13% improvement reported in the NINDS trial with IV rtPA use alone.[23] The response to IVT alone is influenced by the site and characteristics of the vessel occlusion; IVT is less effective if there is a terminal internal carotid artery or proximal MCA occlusion, if there is no detectable residual flow signal across the occlusion, or if the size of the clot exceeds 8 mm in length.[34] These findings highlight the utility of MT in achieving successful reperfusion with or without adjunctive IV rtPA.

Saver et al.[35] showed in the HERMES collaboration that each 1-hour delay in reperfusion with MT is associated with less favorable degree of disability (odds ratio [OR] 0.84, 95% confidence interval [CI] 0.76–0.93) and less functional independence (OR 0.81, 95% CI 0.71–0.92) specially within the first 6-hour window. However, the DAWN and DEFUSE 3 trials revealed that brain tissue may be viable in the 6- to 24-hour time window, likely related to favorable collateral blood flow. A tissue-based (rather than time-based) selection criterion in these trials allowed for the identification of patients who would continue to benefit from reperfusion therapy in the late time window. Real-world clinical practice registries such as TRACK[36] and NASA[37] have confirmed similar rates of good clinical outcomes compared to those reported in RCTs (48% and 42%, respectively).

A study from a large comprehensive stroke center in the United States showed that due to the strict imaging criteria of patient enrollment in the DAWN and DEFUSE 3 trials (National Institutes of Health Stroke Scale score >5, Alberta Stroke Program Early CT Score [ASPECTS] 6–10, infarct core less than 70 mL with penumbra:core ratio >1.7), as many as 70% patients with LVO in the 6- to 24-hour window did not meet the eligibility criteria for MT, most commonly due to large core infarct (38%).[38] Desai et al.[38] showed that 26% of these DAWN or DEFUSE 3 ineligible patients underwent MT and ≈30% of them achieved good functional outcomes (mRS 0–2). The 2018 AHA/ASA guidelines recommended urgent thrombectomy for patients with LVO stroke up to 24 hours from symptom onset. More recently, Sarraj et al.[39] showed that patients with LVO and large infarct cores (initial ASPECTS score of 0–5 or core infarct volume >50 mL) on initial CT perfusion imaging within 24 hours of symptom onset benefited from MT, with 31% of patients achieving functional independence at 90 days (mRS 0–2). Ongoing trials, such as TESLA, SELECT 2, and RESCUE Japan LIMIT, will help provide more information about the safety and efficacy of MT in patients with large baseline IS defined by CT ASPECTS score of 2–5 or ischemic core volumes >50 mL. At present, there is limited data on the utility of thrombectomy beyond 24 hours.

With the rapid evolution of acute stroke interventions over the past decade, the systems of care to establish widespread availability of MT have lagged behind, as only 56% of the US population has access to MT treatment capable hospitals within 60 minutes by ground transport.[40] Similar statistics in most developing countries are not available. Furthermore, lack of advanced perfusion imaging modalities in low- and middle-income countries and rural areas in high-income countries makes evaluation of patients' eligibility for MT within a 6- to 24-hour window a challenge. In addition, there is no central data repository to identify the number of MTs being performed on a national scale for most countries. Therefore, a better MT procedural count tracking can be performed using a triangulation method that includes device company sales, independent research organizations, and public hospital and procedure statistic databases. The US device industry estimates suggests an increase in MT from 10,000 procedures in 2015 to around 70–80,000 estimated procedures in 2020. Similarly, device industry worldwide estimates of MT range from ≈79,000 procedures performed in 2016 (11,500 in the United States, 27,000 in Europe, and 30,000 in Asia and Australia combined) to a projected increase to ≈200,000 in 2020. Saini et al. (unpublished data, 2021) have found that the rate of MT use in the United States increased by ≈20-fold from 2004 to 2016 in both sexes (from 0.1% to 2.4%) and the proportion of younger patients (18–39 years) receiving MT was higher compared to other age groups among both men and women (Table 2).

In a cost-effectiveness study performed in Italy, MT with IVT was found to be cost-effective from year 1 through year 3 and cost-saving from year 4 onwards. The total estimated cost of MT plus IV rtPA and IV rtPA alone is ≈€34,855 and €31,798, respectively.[41] In a US study, based on fees paid for institutional rehabilitation for a year post MT, the cost utility of patients successfully revascularized within 6 hours of symptoms onset group was $35,557/quality-adjusted life-year (QALY) (US dollar) higher than that of the >6 hours group, and $27,829/QALY higher than the no-revascularized group.[42] Successful revascularization reduces the length of both hospital and rehabilitation stays by ≈3–7 days and 1–5 months, respectively.[42] In addition, lifetime QALYs incrementally increased with every grade of improved reperfusion. Overall, in lifetime projections, a successful MT results in average cost savings of about $23,203 (US dollars) per patient.[43]

Global Utilization and Access to Acute Stroke Interventions

In order to make a collective effort to target the growing burden of stroke across the globe, we need to understand the characteristics and effect of stroke on individual countries, as bottlenecks to implementing successful preventative and therapeutic strategies may differ in underdeveloped, developing, and developed nations. The expanding armamentarium of therapeutic options for AIS from extending the window for IVT beyond 4.5 hours to MT up to 24 hours for eligible patients with LVO has reignited the efforts to improve access to these advances across the globe. Availability is constrained by information, facilities, physicians, and finances. Consensus is that most high-income countries have enough neurointerventionalists in training and in current practice to meet the growing demand for MT. But consensus on the right approach to allow other specialty trained physicians such as cardiology or vascular surgery to perform MT especially in low- and middle-income countries where there are not enough neurointerventionalists is lacking. The overarching goal for each national or global stroke campaign is to shorten the time to access to acute stroke interventions including IVT and MT. Furthermore, the measures needed to achieve this goal have to be individualized to each country based on resource availability to allow a better implementation of customized recommendations.

The added cost of establishing acute stroke care vs treating patients in a general ward in a hospital can range from $5,000 to $10,000 (US dollars), but with reduced length of in-hospital and rehabilitation stay, the initial cost incurred can be recovered within a year of its operation.[44] This does not include costs for any additional staff. The use of IV rtPA within 3 hours of symptom onset continues to remain cost-effective even if as high as 30% of the patients treated are stroke mimics.[45] Therefore, lack of advanced imaging such as MRI in low- or medium-income countries or rural areas in high-income countries should not deter appropriate utilization of IV rtPA in eligible patients.

A recent study in the United States estimated LVO incidence of 24 per 100,000 person-years (95% CI 20 to 28), whereas the current MT utilization rate was only at 3 procedures per 100,000, highlighting the need for developing better systems of care to be able to bridge this gap of underutilization of this life-saving therapy.[19] As the aging population in high-income countries such as the United States grows, these numbers are expected to increase. With projected increase in LVO stroke, the demand for neurointerventionalists, MT equipment, and MT-capable hospitals will increase. Currently, there are ≈2,000 MT-capable comprehensive stroke centers across the globe, and 900 of these centers are in the United States. The market for acute stroke care in the United States is growing rapidly, fueled in parallel by the expansion of the AIS device market, which is expected to double by 2026.

Rate of successful reperfusion in recent MT trials, defined as modified Thrombolysis in Cerebral Infarction (mTICI) grade 2b, 2c, or 3 (representing 50%–90%, 90%–99%, and 100% reperfusion, respectively), was ≈70%.[14] With the advent of 3rd- and 4th-generation devices and rapidly advancing technology, the proportion of patients undergoing successful reperfusion is expected to improve. Recent literature already supports achieving mTICI 2c or 3 reperfusion grades as the feasible new aim of MT as rate of favorable outcomes with mTICI 2c/3 are significantly better than in patients with mTICI 2b.[46] Even a modest 10% increase in mTICI 2c/3 reperfusion rates in patients undergoing MT annually in the United States would yield an additional 3,656 QALYs and save $21 million/$36.8 million (US dollars) in health care costs, respectively.[47] For context, stroke costs ≈$34 billion annually in the United States.[4]

Studies in low- or medium- or high-income countries have shown that utilization of MT within 6 hours is cost-effective and we expect a similar trend for patients treated within 24 hours.[4] Primary out-of-pocket costs and limited insurance reimbursements are an important deterrent to both IVT use and rapid expansion of MT-capable centers in low- and middle-income countries. In addition, the infrastructure to identify and rapidly transport patients from the field to MT-capable centers is largely lacking, leading to increased prehospital delay in acute stroke care in these countries. A large systematic review including publications from 14 out of 54 African countries showed that the median time from stroke onset to hospital admission was 31 hours, and there was a large variation in the proportion of patients with stroke (10%–43%) arriving within 3 hours of stroke onset across the continent.[48] An effective collaboration between local government, the health care sector and international campaigns such as the WHO noncommunicable disease programs can help improve timely access to IVT and successfully accelerate the adoption of MT, thus reducing the growing burden of IS in these countries.

Mobile stroke units (MSUs), compared to standard prehospital care and transport, are the latest approach to improving acute stroke care delivery and can mitigate significant costs in administration of stroke care. Results from the B_PROUD trial showed that a higher proportion of eligible patients assigned to MSUs received IVT compared to conventional treatment on arrival to hospital (60% vs 48%).[49] MSUs shortened time to IVT by an average of 20 minutes and resulted in reduced likelihood of severe disability and death at 3 months by 26%.[49] In addition, MSUs helped reduce time to MT, resulting in ≈24.6 DALYs saved.[50]

Ongoing Efforts

Multiple international organizations are leading global missions with ideologic focus ranging from education of the population about stroke to providing local regional centers and practicing physicians the tools to increase utilization of available acute stroke interventions; for example, the WHO is leading World Stroke campaigns; NINDS is leading an international campaign, Know Stroke, to educate the public about symptoms of stroke and the importance of seeking care quickly; the Society of Vascular and Interventional Neurologists is leading Mission Thrombectomy 2020+ (MT2020+), with an aim to double global access to MT every 2 years. The MT2020+ mission is unique as it aims to bring together leaders in the stroke and neurointerventional community in every region, organized stroke and interventional societies, industry representatives from thrombectomy and thrombolysis device companies, health administrators, and government policymakers on a common platform to work in tandem to develop better systems of care worldwide. It provides a roadmap for making local hospitals into primary or comprehensive stroke centers based on local availability of resources and outreach neurointervention training programs. Wide geographic distribution of stroke thrombectomy centers is critical for rapid access to thrombectomy. Hence MT2020+ takes a public health intervention approach to increasing access to thrombectomy in a geographically distributed manner.

Stroke Alliance for Europe recently launched "Burden of Stroke in Europe," which is an excellent resource on stroke burden and care comparison between different European Union countries. The WHO's "Package of Essential Noncommunicable Disease Interventions for Primary Health Care in Low-Resource Settings" provides guideline for cardiovascular and stroke prevention strategies for low-income countries.

Summary

Between 2015 and 2035, the estimated total direct medical stroke-related costs are projected to more than double, from \$36.7 billion to \$94.3 billion.[7] Acute stroke care is cost-effective across the board in low-, middle-, or high-income countries, therefore the call of the hour is to encourage a collaborative effort to bridge the gap in rapid therapeutic advances and its access to patients eligible to receive them across the globe.

Study Funding

No targeted funding reported.

Disclosure

V. Saini and L. Guada report no disclosures. D.R. Yavagal reports the following: consultant for Carenovous, Deck Therapeutics, GLG Consulting, Guidepoint Consulting, Mosaic Consulting, and Neuralanalytics; speaker and member of Clinical Trial Steering Committee for SWIFT-Prime–RAPID; medical consultant and member of the steering committee for the TIGER and CALM2 trials, Medtronic, Vascular Dynamics, and Poseydon Medical LLC. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* June 27, 2020. Accepted in final form June 23, 2021.

Appendix Authors

Name	Location	Contribution
Vasu Saini, MD	Jackson Memorial Hospital and University of Miami Miller School of Medicine	Designed and conceptualized the review study; drafted the manuscript for intellectual content
Luis Guada, MD	Jackson Memorial Hospital and University of Miami Miller School of Medicine	Revised the manuscript for intellectual content
Dileep R. Yavagal, MD	Jackson Memorial Hospital and University of Miami Miller School of Medicine	Designed and conceptualized the review study; revised the manuscript for intellectual content

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