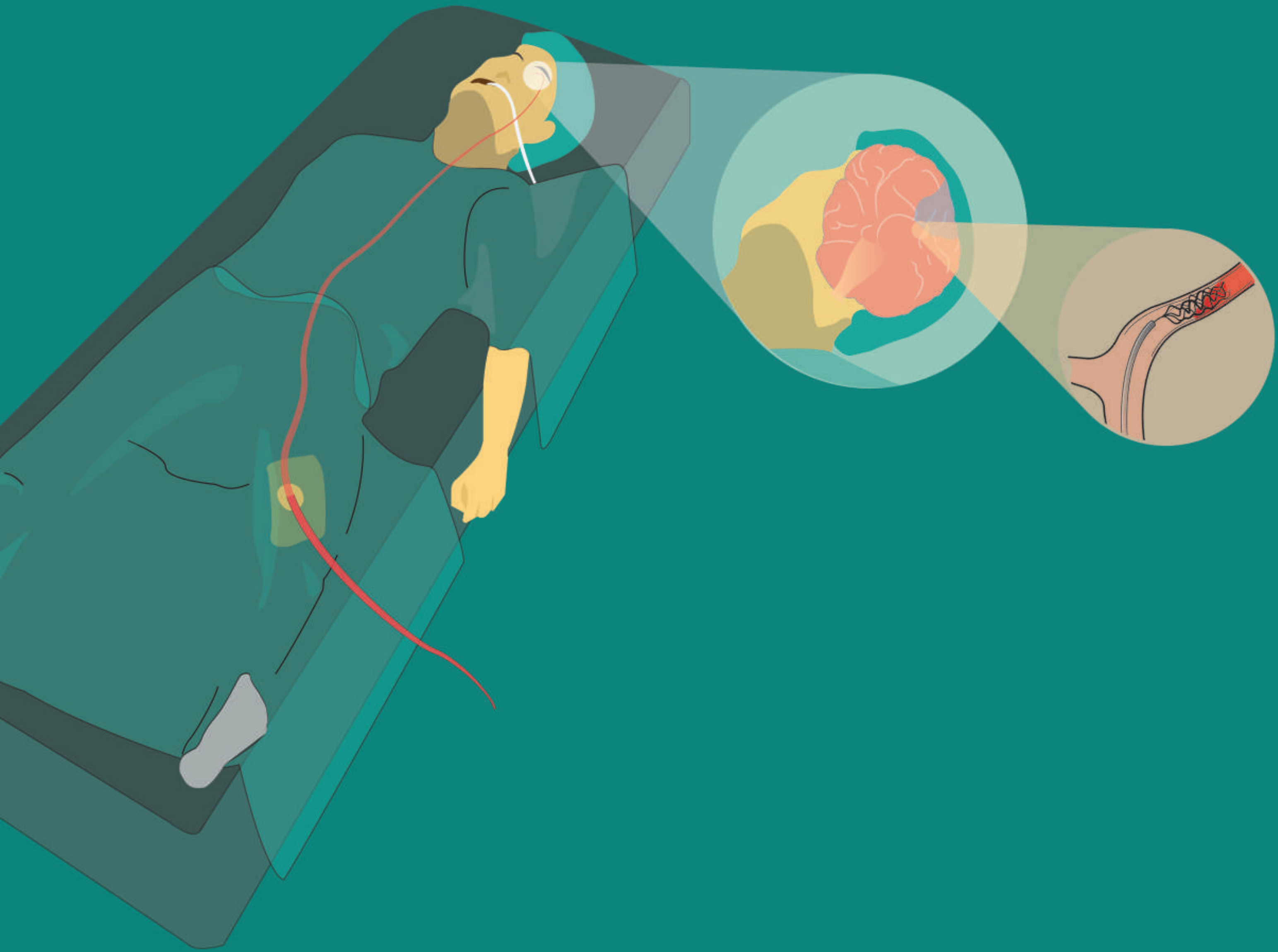
“Stroke policies are local, best practices are global”



STROKE MECHANICAL THROMBECTOMY

Building thrombectomy systems of care in your region; Why and How?

A White Paper

Prepared by
The Society of Vascular and Interventional Neurology (SVIN)

MT2020

MT2020 is a global non-profit campaign to rapidly accelerate access to Thrombectomy worldwide with public health interventions and sharing of best practices for stroke systems of care. Stroke poses a staggering health, economic and social burden across countries and age groups even though the incidence significantly increases after age 50. Stroke Thrombectomy is the new emergency standard of care for severe stroke due to large brain artery blockage since 2015. Stroke Thrombectomy preferably along with pharamacological thrombolysis when indicated is the most powerful brain and function saving treatment for stroke that is extremely effective when performed rapidly in the first 24 hours after a severe stroke symptoms start. This treatment has also been shown to be highly cost-effective despite being resource intensive across different income level countries. The MT2020 campaign was initiated in 2016 by Society for Vascular and Interventional Neurology (SVIN) and is now a multi-society, multi-stakeholder alliance to rapidly accelerate the growth of stroke Thrombectomy procedure capacity and systems that enable rapid access to this treatment worldwide through applying public health and policy best practices that are supported by scientific evidence.

Disclaimer

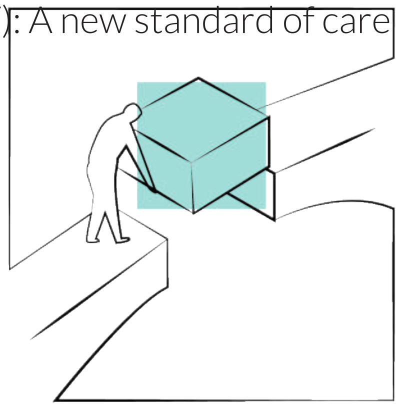
The opinions, findings, and conclusions expressed in this publication are those of the authors, who are responsible for the accuracy of the data presented herein. This white paper does not constitute a standard, specification, or regulation.

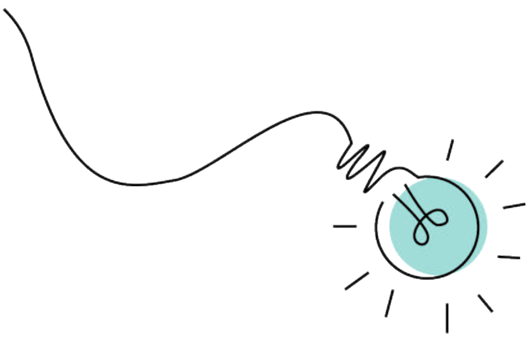
The report is prepared by the Society of Vascular and Interventional Neurology (SVIN).

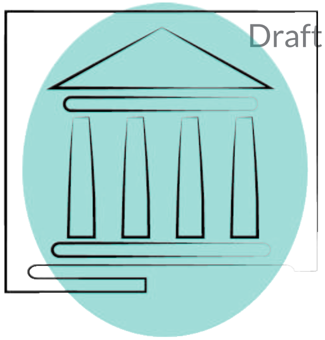
Compiled by
Supedit.com
HiiiH Innovations Pvt. Ltd.

January 2020

CONTENTS



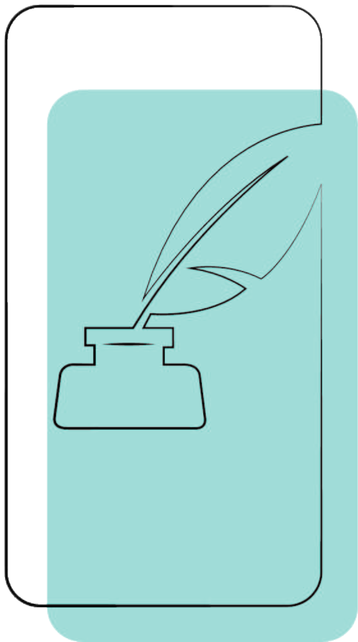




How can you implement MT in your region?

Recommendations for Policy Makers

Appendix



List of abbreviations

MT – Mechanical Thrombectomy

LVO – Large Vessel Occlusion

NIH - National Institutes of Health

SVIN - The Society of Vascular and Interventional Neurologists

ASA - American Stroke Association

AIS - Acute Ischemic Stroke

LMWH - Low Molecular Weight Heparins

IVT - Intravenous Thrombolysis

t-PA- tissue Plasminogen Activator

rt-PA – Recombinant tissue Plasminogen Activator

FDA – Food and Drug Administration

ICH – Intracranial Hemorrhage

RCT - Randomized Controlled Trial

AC – Anterior Circulation

DALY - Disability-Adjusted Life Years

BP – Blood Pressure

GBD - Global Burden of Disease

SDI- Socio-Demographic Index

ICA - Intracranial Internal Carotid Artery (ICA),

M1 - Proximal Middle Cerebral Artery,

M2 - Distal middle cerebral artery territory (M2)

BA - Basilar Artery

TIA – Transient Ischemic Attack

US – United States

PT – Prothrombin Time

aPTT = Activated partial thromboplastin time

INR – International Normalized Ratio

mRS - modified Rankin Scale score

NIHSS - National Institutes of health Stroke Scale

IV – Intravenous

EKG – Electrocardiogram

CT – Computed Tomography

MRI – Magnetic Resonance Imaging

CTA – Computed Tomography Angiography

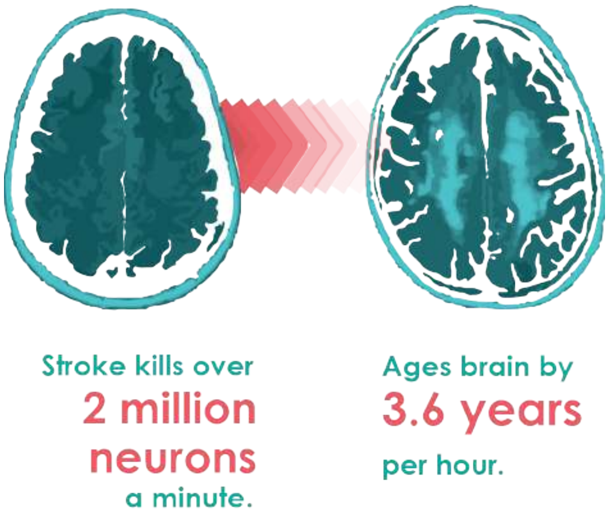
QALY - Quality Adjusted Life Year

IECR - Incremental Cost-Effectiveness Ratio

AHA – American Heart Association

Executive Summary

Brain attacks or strokes are the leading cause of disability[1-4] and the second leading cause of death worldwide.[5] While many other conditions impact patients over months, stroke victims are struck with sudden, potentially life-long paralysis that



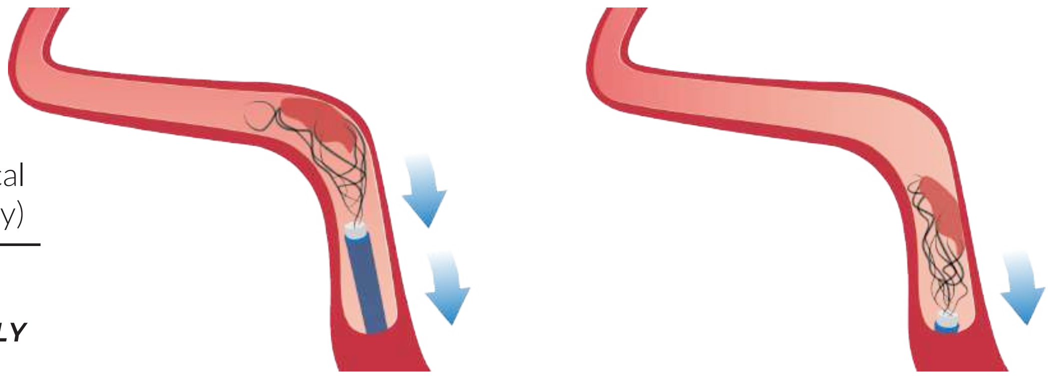
kills over 2 million brain cells a minute and ages the brain by 3.6 years per hour.[6] Until recently, the only intervention capable of improving outcomes was a clot-busting drug that had marginal benefits, but still left approximately two-thirds of patients with neurological symptoms,[7,8] with mortality rates up to 25%.[9-13] However, a minimally invasive procedure was proven effective in 2015 - Mechanical Thrombectomy (MT) - wherein a catheter is inserted into a major blood vessel within the thigh, navigated to the brain, and used to remove the clot.[10,14-18] This is similar to the approach used by interventional cardiologists who perform angioplasty procedures to remove blockages from the blood vessels that feed the heart.

MT procedures enable physicians to remove clots from 90% of stroke victims, so long as they are treated quickly,[19] and reduces the rate of neurological disability significantly. This procedure can transform stroke care, creating an opportunity to save tens of thousands of lives; but only if hospitals are capable of deploying this therapy wherever and whenever strokes occur.

In a majority of patients with large-vessel occlusions (LVO) stroke, the largest and deadliest type of stroke, MT now enables physicians to completely remove clots,[19] saving $23,000 per patient[20] in care costs, and doubling a patient's chances of avoiding permanent neurological harm.[24] Despite the benefits to patients and long-term cost savings to the healthcare system, MT is still performed at approximately 2000

MT (Mechanical Thrombectomy)

BLOCKAGE REMOVED MECHANICALLY

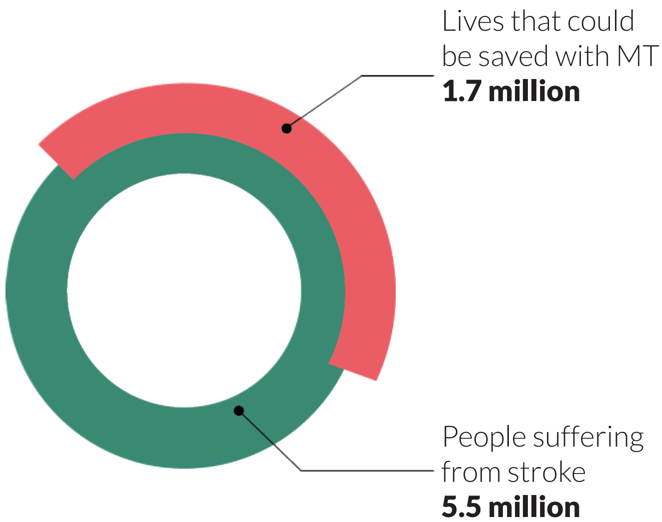


The Majority of the world does not have an MT centre

Out of a total of 2000 centres, 78% are in US, UK, Brazil, France, Germany and Australia.

thrombectomy systems of care (TSC), 900 of which are located in the United States and the rest in the United Kingdom, Australia, Brazil, Japan, France, Germany, and Spain,[21] indicating that this lifesaving stroke therapy is still unavailable to the majority of the global population.[22,23] While MT results far exceed the lifesaving potential of most vascular interventions, their benefits have not been distributed equally across global communities where stoke burden is significantly higher.

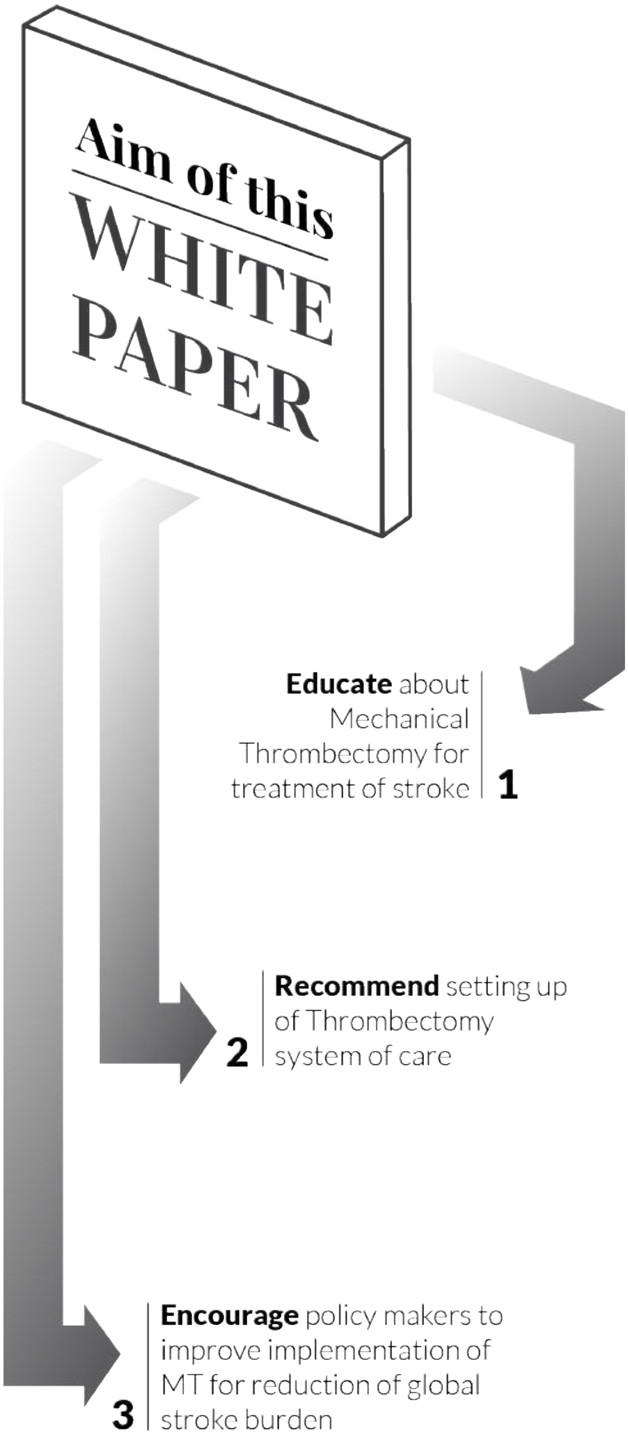
The greatest limiting factor is how quickly patients must be treated, with far better outcomes when treated sooner than later.[9,25,26] Emergency responders have created innovative ways to airlift or redirect patients to TSCs from some rural areas, but the vast majority of people are too far from a center to be transported within the required treatment window.[27] While physicians are rapidly working to improve the treatment methods, there is a critical need for the transformation of stroke care delivery at the system-wide level of healthcare policy in order to generalize these benefits from urban centers in developed countries to all communities, as stroke is a pervasive risk. If policies that effectively deliver clot removal therapies to a wider population are established, new stroke centers are funded, new



generations of stroke physicians are trained, and systems of emergency response are coordinated across the globe, it could save millions of lives,[28] and over $23,000 per patient in disability care.[20]

This issue is pressing not only because of the fact that more than 15,000 patients die every day from stroke,[5] but because a rapidly aging population is expected to have extraordinary increases in stroke burden, as most strokes afflict patients over the age of 65.[29,30] In fact, the American Heart Association (AHA) estimates that, while total stroke cost burden in the US was $71.6 billion in 2012, it will balloon to over $183.1 billion by 2030.[31] This cost exceeds the combined costs for the National Institutes of Health (NIH) yearly budget in 2020 for medical research, defense advanced research projects, NASA, the Department of Health and Human Services, the Energy Department, Homeland Security, and the Department of Housing and Urban Development.[31-38] Additionally, the economic burden will continue to grow in human and financial costs, unless addressed. It takes time to create stroke systems, but their effectiveness has been proven across 1077 patients in 9 randomized trials,[9,10,13-16,18,26,32] in 17 studies. These systems have been proven to save thousands of dollars per patient due to greatly improved patient outcomes.[33] If stroke systems are created to meet this growing burden of stroke and stroke-induced disability, our communities can not only save lives but also vastly reduce the long-term social cost of caring for patients that could not be delivered the best therapeutic option.

The Society of Vascular and Interventional Neurologists (SVIN) represents the advancement of interventional radiology with the goal of improving clinical care and patient outcomes with stroke and cerebrovascular diseases. In 2016, SVIN launched Mission Thrombectomy 2020, an



initiative to drive global efforts to improve stroke care by increasing the annual rate of thrombectomy procedures from 100,000 to 202,000 by 2020, leading to a worldwide decrease in stroke-related disability and potentially saving millions of lives. For carrying out this mission, SVIN is partnering with government agencies, medical non-profits, and industry leaders to improve public awareness and establish financial initiatives for supporting the development of thrombectomy systems of care.

Here, we have brought together thought leaders of the stroke community, from inventors of clot-retrieval devices to physicians and researchers at leading hospitals to the pioneers who instituted stroke systems across the world. This white paper has been created not just to educate on the magnitude of stroke's damage to society or the potential benefits of novel stroke therapies, but also to create a handbook on how to institute stroke systems worldwide. Our hope is for the wider medical community, healthcare administrators, and public policy makers to use this white paper to guide their valuable work deploying a vital therapy to help patients struck by a terrifying, debilitating paralysis that is growing in its threat to human health worldwide. We have assembled the following materials to assist this effort.

Background

Brain attack = STROKE

1. What is a brain attack or stroke?

A brain attack or stroke occurs when a blood vessel to the brain is either blocked or ruptured, causing a lack of oxygen and nutrients to a portion of the brain.[34] When this brain injury results from a sudden blockage of the blood vessel, it is called Acute Ischemic Stroke (AIS); if it's caused by a rupture of a blood vessel, it is called Hemorrhagic Stroke (HS). Permanent brain damage is possible after only a few minutes of reduced oxygen supply, which kills brain cells and causes notable physical symptoms like the sudden onset of numbness or weakness in the face, arm, or leg on one side of the body along with confusion, difficulty seeing, impaired walking, and severe headache.[41,35]

2. What is Large Vessel Occlusion (LVO) stroke?

Large Vessel Occlusion (LVO) stroke is a blockage of one of the four major blood vessels in the brain and neck.[52-59] LVO strokes represent approximately one-third of the total AIS population, and they correlate with significantly higher disability and deaths[58,60,61] due to the large size of the blockage and a greater area of brain damage.[62,63] The blockage is typically caused by the clotting of a vessel narrowed by fatty buildup or a clot from elsewhere in the body that travels to and lodges in the brain.[34]

3. What are the current treatment options?

Treatment for a patient with suspected AIS follows radiological imaging of the brain with CT (Computerized Tomography) and MRI (Magnetic Resonance Imaging) scans to rule out HS, following which, clot-dissolving medications and mechanical clot dislodgment procedures are considered, and general supportive care is administered. During the course of treatment, sudden medical or neurologic complications of stroke are anticipated and monitored. Finally, the most likely cause for stroke is evaluated, and treatment is directed towards preventing such events from occurring in the future.

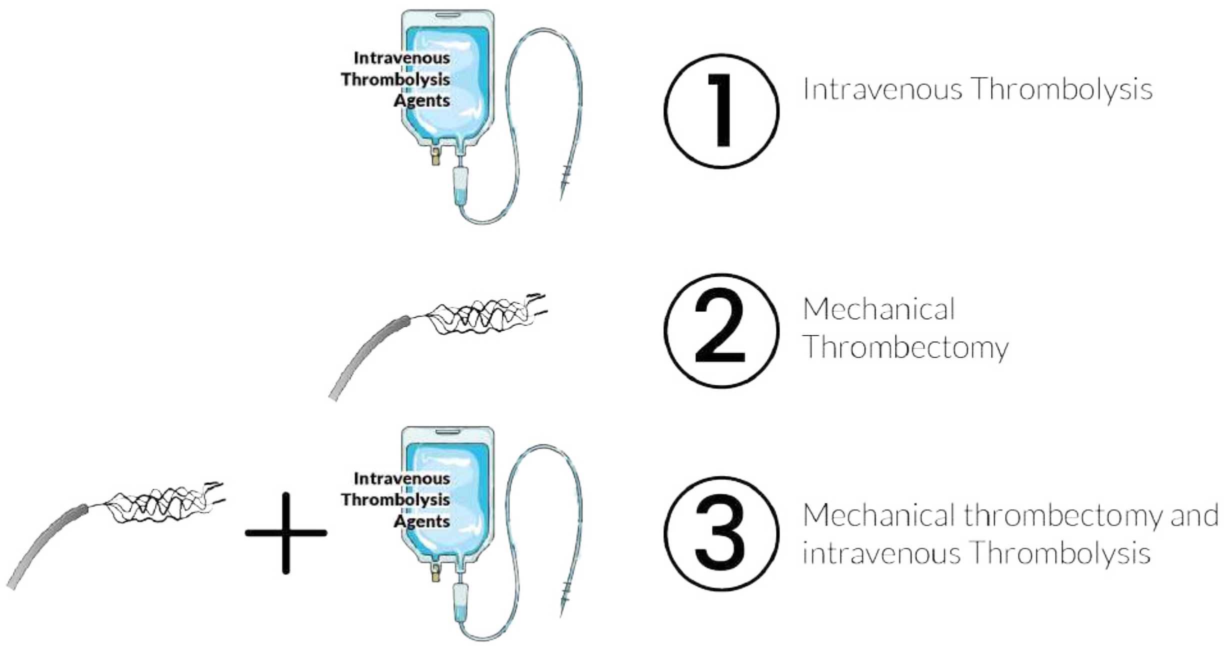
Depending on the capabilities of the treating facility, any of the following treatment methods are considered.

Intravenous Thrombolysis (IVT)

IVT or the use of clot-dissolving agents is the only US Food and Drug Administration (FDA)-approved medical therapy for the treatment of patients with AIS, and its use is associated with improved patient outcomes. Although some studies have suggested that genetic differences, race, and sex may influence the efficacy of IVT, only certain comorbidities such as hypertension (raised blood pressures) and hyperglycemia (elevated blood sugar levels) have been found to significantly and negatively impact its response in AIS patients.[70-74] However, IVT has a limited role in the treatment of LVO stroke as the size of blockage and burden of clot is very high.

Mechanical Thrombectomy (MT)

MT is a minimally invasive procedure wherein LVOs are removed using mechanical tools to reverse the injury to the brain.



During MT:

- A catheter is threaded into a large blood vessel in the groin region (or hand) and advanced up through the neck until it reaches the blood clot causing the stroke.
- Using X-ray guided imaging, a stent retriever (a slender mechanical tool that can remove the LVO) is inserted into the catheter.
- The stent reaches past the clot, expands to stretch the walls of the blood vessel resuming blood flow, and is "retrieved" – or pulled backward – which removes the clot.

MT combined with IVT

MT, in combination with IVT, significantly improves the odds of a good outcome after LVO stroke, when delivered within 24 hours of stroke onset, irrespective of age and over a broad range of stroke severity.[75] IVT, when used alone, has some important limitations, such as a narrow time window of 4.5 hours and an inability to dissolve a large burden of clot, making it ineffective for the treatment of LVO stroke;[75,76] however, a combined approach utilizing MT and IVT has overcome these limitations.[75]

4. Mechanical Thrombectomy(MT): A new standard of care

There is a great difficulty in treating stroke due to its quick onset and time-dependent nature. For each minute a stroke is not treated, 2 million brain cells, 14 billion nerve connections, and 12 km (7.5 miles) of nerve fibers are destroyed. Collectively, these age the brain by 3.6 years per hour, making it vital for a patient to receive rapid treatment.[6]

The time window for IVT is brief since it must be given to most patients within 4.5 hours,[151] and the outcome depends on the size of the clot, making it an ineffective choice for the treatment of LVO stroke.[78,79] Numerous studies have demonstrated that MT helps resume blood flow (recanalization) in blocked vessels rapidly, improves patient outcomes, and expands the treatment time window to 24 hours.[9,11,12,15,16,18,26,32]

MT involves a minimally invasive surgical procedure using a tiny catheter and tools to mechanically trap and remove the blood clot from a blocked blood vessel.

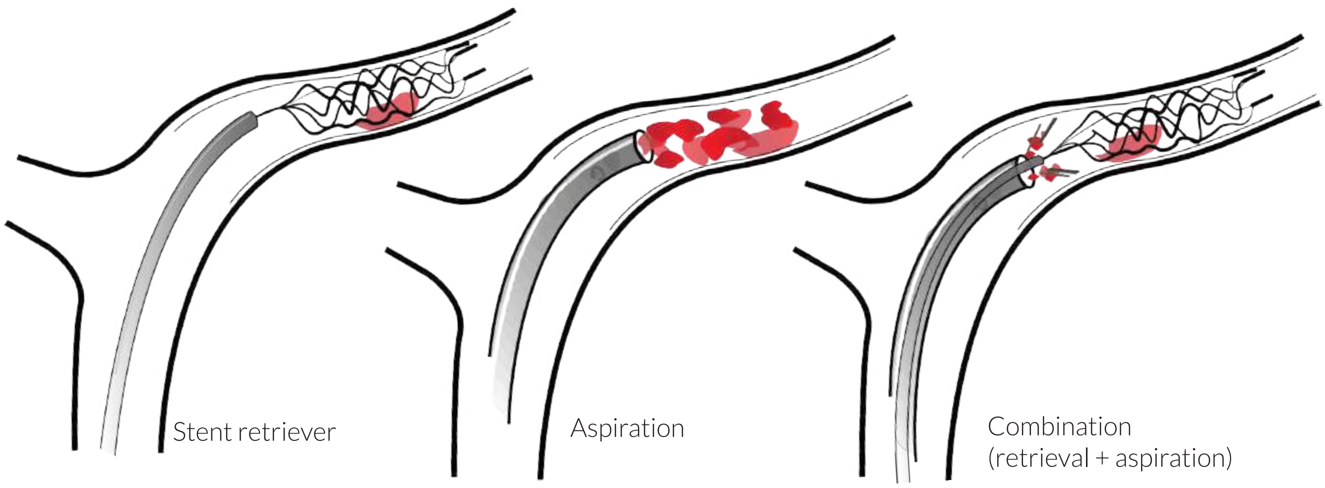
Tools that are used in MT can be classified into two different subtypes based on their mechanism of action:

(a) stent retriever
(b) aspiration

Stent retrievers are made of an expanding wire mesh tube intended to remove the clot in one piece. The retriever is placed using a delivery catheter. Once in place, the mesh expands, trapping the clot, and is then withdrawn into the catheter and removed from the patient.[80]

Aspiration catheters are flexible with a large inner diameter. A guidewire is inserted into the patient, followed by a small catheter that is used to guide the aspiration catheter toward the clot. When the clot is reached, it is broken into smaller pieces that are sucked through the catheter using a pump or manual suction.[154]

Combined interventions, using both stent retrievers and aspiration catheters, have shown promise in recent studies.[81] In this technique, aspiration of the clot, a cheaper alternative, is attempted first. If the aspiration fails, mechanical retrieval is attempted by inserting the stent retrievers via the aspiration catheter. Using this sequential or parallel combination, phenomenal recanalization rates of up to 95% have been achieved,[81] compared with stand-alone direct aspiration rates of 78%.



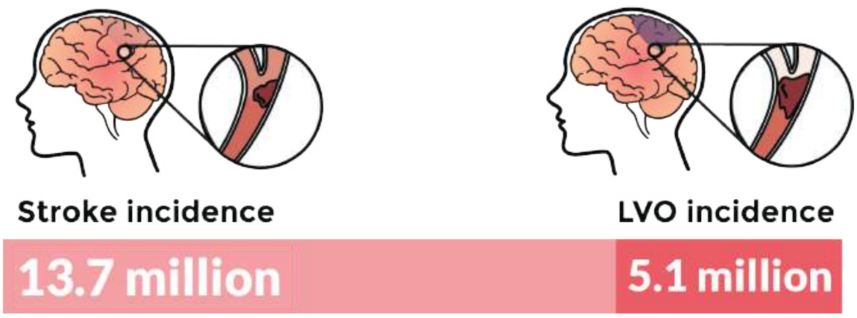
Techniques for Mechanical Thrombectomy

The global gap in the treatment of LVO stroke

1. Incidence of Stroke and LVO stroke: A global perspective

Stroke Demographics

A brain attack or stroke is currently the second leading cause of death and a major cause of disability worldwide.[51,82] In 2010, the global incidence of AIS was estimated to be 11.6 million; 63% of AIS and 80% of HS occurred in low and middle-income countries.[84]



The global incidence of stroke is 13.7 million.[3] In 2016, there were 5.5 million deaths attributable to strokes worldwide.[3] In the US, the incidence of stroke in adults between the ages of 35 and 44 is 30-120/100,000 per year, and 670-970/100,000 per year in those aged between 65 and 74.[107,108] Increased age is also associated with higher chances of death and a decreased quality of life (QOL) when compared to younger stroke patients.[109-114]

According to a Global Burden of Disease (GBD) study, the global lifetime risk of stroke in 2016 was estimated to be nearly 25% for those aged 25 years or older with a nearly equal occurrence in males and females.[126]

Incidence of LVOs – Across Demographics

Approximately half of all stroke-related deaths are attributable to AIS.[5] The presence of an LVO has been associated with significantly worse outcomes,[128] increasing the chances of death within 6 months by 4.5-fold.[60] AIS due to LVO has been reported in 11-46% of cases.[57,59,60,129-131]

United States

In the United States, on average, someone has a stroke every 40 seconds.[96,97] With an annual incidence of approximately 800,000, stroke is the fifth leading cause of death, resulting in more than 146,000 deaths (1 in 19) per year and is a major cause of serious disability, leaving many with long-term disability and an inability to work.[97]

[stroke is the second leading cause of death worldwide]

AIS due to LVO stroke accounts for an annual incidence estimated at 24/100,000 people per year, equaling nearly 80,000 LVO strokes annually.[59]

China

Stroke is the leading cause of death in China, accounting for 22.45% of all deaths.[131] In fact, more than 7 million individuals in China experience stroke, of which 65% are AIS.[134] Additionally, 35 - 40% of all AIS result from an LVO.[131]

Japan

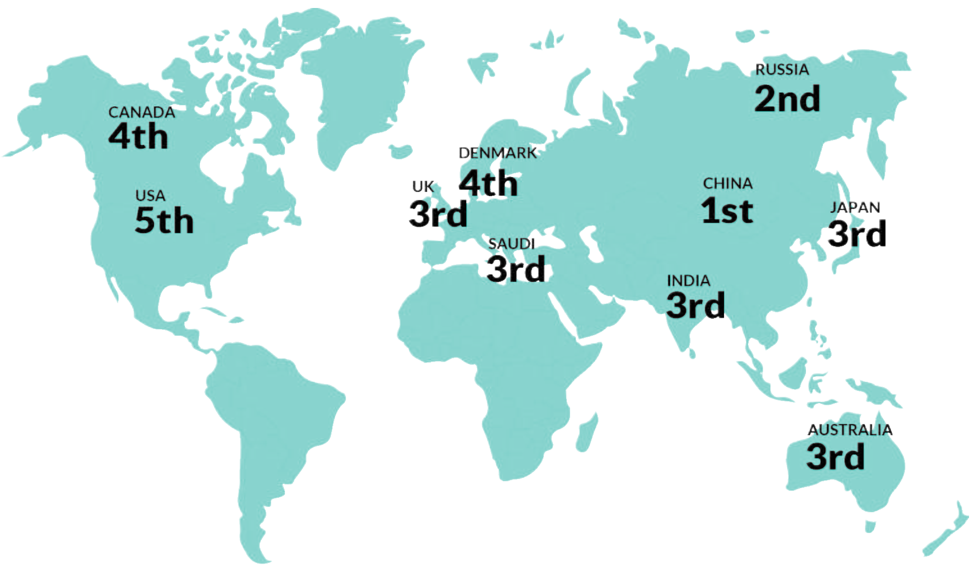
In 2017, stroke was the third leading cause of death in Japan[136] with a stroke incidence of 142.9/100,000 people per year. The incidence of AIS was 91.3/100,000 people per year.[137]

Middle Eastern Region: Saudi Arabia

Stroke incidence is 22.7 – 250/100,000 people per year. Strokes are more common in males than females with the mean age occurring in the sixth and seventh life decade. AIS is found to be the most prevalent type of stroke, while hypertension and diabetes were the most common stroke-associated risk factors.[138]

India

During the past two decades, the cumulative incidence of stroke in India is 105-152/100,000 people per year. In comparison to global estimates, these stroke incidence rates are higher than those of high-income countries.[146-148]



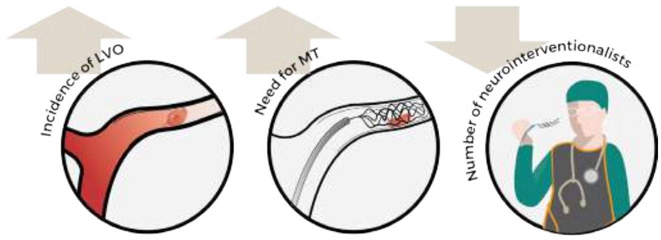
Global ranking based on leading cause of deaths due to stroke

2. Challenges to the effective treatment of LVO stroke

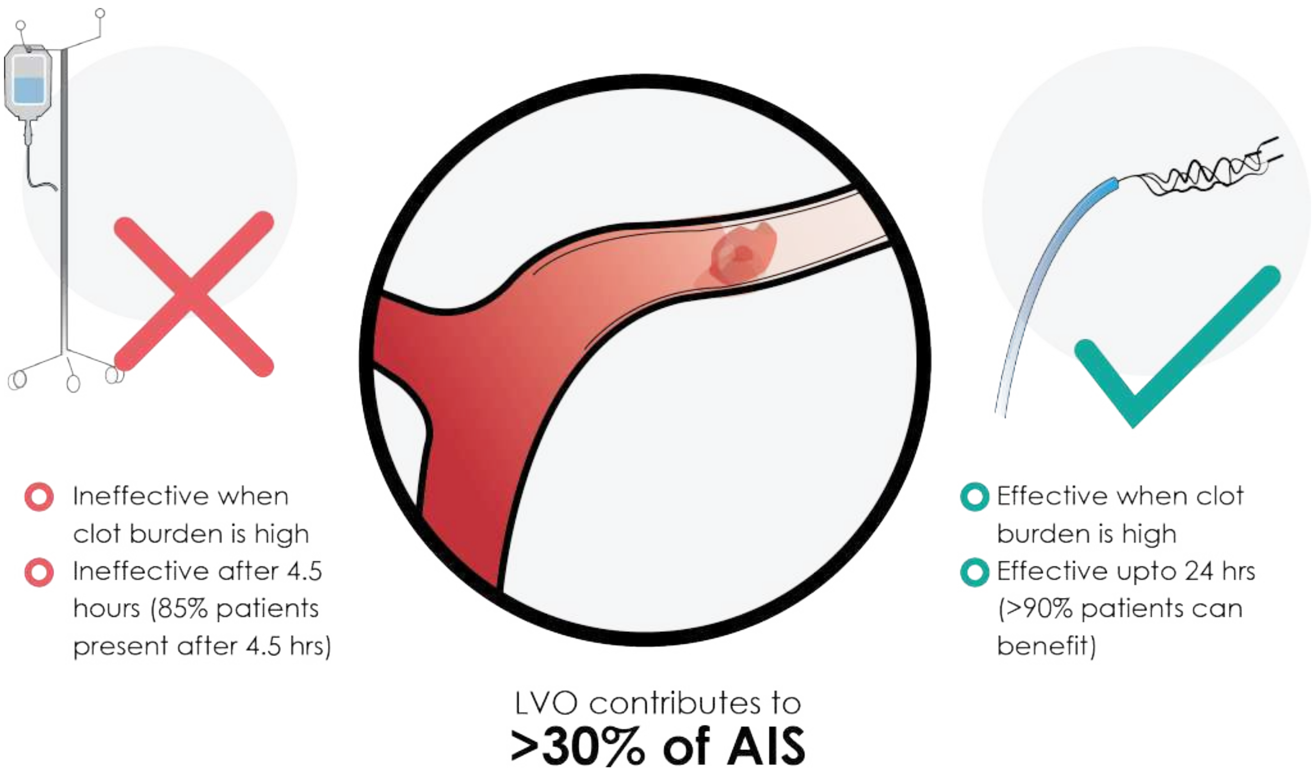
IVT does not work on LVO stroke

The only pharmaceutical drugs approved for the treatment of AIS are those used in IVT; however, these do not work in patients that have AIS due to an LVO, where the size of the clot is large, exceeding lengths of 8 mm.[165] Additionally, IVT needs to be administered within a narrow time window of up to 4.5 hours after symptom onset, which disqualifies usage in over 85% of the cases.[157-160]
For LVO stroke, MT is the standard of care as it can mechanically remove large blockages and can be carried out up to 24 hours from stroke symptom onset.[157-160]

Need for more MT procedures



MT is typically performed by a neurointerventionalist. Neurointerventionalists are a subspecialty of neuroradiology, in which minimally invasive therapy can be applied by advancing various devices within a blood vessel to a point of a previously identified lesion. An estimated yearly total of MT procedures is 3 per 100,000 people in the US, with 10,000 annual MTs.[59,61] Thus, the number of procedures falls considerably below the LVO stroke incidence, suggesting a need for further utilization and capacity of MT.



Contraindications applicable to the use of intravenous rtPA in acute ischemic stroke (AIS)

1. Onset of stroke symptoms more than 4.5 h

2. History of stroke or significant head trauma in the previous 3 months

3. Previous intracranial hemorrhage

4. Symptoms are suggestive of subarachnoid hemorrhage

5. Prolonged blood pressure elevation (systolic ≥185 mmHg or diastolic ≥110 mmHg)

6. Hypoglycemia (serum glucose 1.7, or PT > 15 s)

17. Heparin use within 48 h with an abnormally elevated aPTT

18. Arterial puncture at a non-compressible site in previous 7 days

19. History of gastrointestinal tract hemorrhage within 21 days

20. The recent history of major surgery intracranial or intraspinal surgery within 14 days

21. Previous history of a previous aneurysm, arteriovenous malformation, or intracranial neoplasm

22. Current use of a direct thrombin inhibitor or direct factor Xa inhibitors with an evidence of anticoagulation effect by laboratory tests such as aPTT, INR < ECT, TT, or relevant factor Xa activity assays

23. Early ischemic changes are visible on CT in more than one-third of MCA artery vascular territory consistent with irreversible injury or evidence of haemorrhage on CT scan.

As the aging population grows, these numbers are expected to increase. The growing incidence of LVO stroke is projected to increase the demand for neurointerventionalists, MT procedures and equipment, and MT-capable hospitals.[171]

Currently, there are 900 MT performing centers in the US, as per the definitive health database.[172] The market for stroke care in the US is growing rapidly, primarily due to the expansion of the AIS device market, which is expected to double by 2026.[172] The US stroke intervention model is moving toward specialized high-volume stroke facilities, and encourages bypassing patients to these TSCs in order to initiate treatment in a more timely manner. The accreditation process for TSCs is time-consuming and costly, which limits the growth of these centers, and rural/sparsely populated areas continue to be underserved as the costs to establish new facilities is often not justified in areas of insufficient population. However, because AIS devices and MT procedures are fully reimbursed in the US, stroke treatment volumes are expected to increase considerably over the next decade. However, supporting the establishment of TSCs in low and middle-income countries will continue to pose a challenge given the primary out-of-pocket expenditures for healthcare and limited insurance reimbursements.

There is a strong need for policymakers and governments to intervene in these countries and accelerate the adoption of MT in order to reduce the growing burden of LVO strokes, which is presently untreatable with IVT alone.

A revolutionary leap in the treatment of LVO stroke

1. The emergence of MT as a standard of care

A remarkable transformation of stroke care has occurred over the last two decades with the development of evidence-based stroke detection, increased access to advance care, and improved emergency management of stroke.[200] MT is considered a breakthrough in stroke treatment for LVO stroke. The mechanical removal of blood clots from blood vessels supplying the brain leads to better outcomes for stroke patients, including faster and greater independence and mobility.

Numerous clinical trials have established proof of better outcomes with MT, leading to widespread adoption. In fact, the total number of procedures doubled in just 3 years and is expected to grow by 25% annually to reach 202,020 in 2025. The 2018 American Stroke Association (ASA) guidelines recommend urgent thrombectomy for LVO stroke.[199]

MT has a number of advantages over other treatment options, which include:[202]

(a) Yields higher rates of revascularization and reduced rates of long-term functional dependence in patients with LVO stroke.[55]

(b) Extends the therapeutic time window for acute intervention up to 24 h from stroke onset, which is greatly increased compared to the 4.5 hours restricted time window for IVT, making IVT applicable to a small number of AIS patients.[26]

(c) Removes clots resistant to IVT, such as old and large clots, which are hardened and contain calcium and cholesterol crystals.[204]

2. Global cost- effectiveness of MT

The best outcomes from stroke care are time-sensitive with better chances of functional improvements, restoration of blood flow, survival of damaged brain tissue, being associated with shorter time between stroke onset and treatment.[9,10,14-18,26] These improved outcomes are associated with decreased economic burdens. In fact, a rapid treatment of AIS within 6 hours is accompanied by approximately 3–7 days of shorter hospital stays and 1-5 months of shorter rehabilitation stays, thus, lowering costs of $5,000-$5000 compared to those with longer time-to-treatment (>6 hours) or no recanalization.[205]

North America

	Onset-to-recanalization		
	≤ 6 hours	> 6 hours	No recanilization
Hospital stay	9.8±5.8	13.2±8.1	16.7±19.3
Rehabilitation stay (days)	87.2±136.4	133.7±152.4	224±130.3
1-year rehabilitation cost	$16,024±12,320	$21,002±15,504	$29,382±17,403
Functional dependence	70%	40%	6%
Home discharge	72%	50%	21%
Mortality	10%	16%	43%
Cost-utility ratio (compared to no-recanalization	($27,829/QALY)	($24,647/QALY)	Baseline

Table 1. Cost effectiveness of rapid recanalization using mechanical thrombectomy
Data obtained from a 2019 retrospective cost benefit analysis by Jeong et al.[155]

United States

In the United States, AIS is associated with a high economic burden, especially for patients discharged with a stroke-related disability who incur more than double the expense compared to non-disabled patients ($120,753 vs. $54,580).[206] Even though combination therapy (MT and

	Combination Therapy	Standard Care	P- value	Difference
Index Hospital cost [a]	9.8+5.8	13.2+8.1	<0.001	**$17,183**
90-day Cost [b]	$11,270	$16,174	0.014	**($4,904)**
QUAL trial [c]	0.131	0.105	0.005	**0.023**
QUAL lifetime [d]	6.79	5.05	—	**1.74**
Lifetime Cost [e]	($215,781)	($238,984)	—	**($23,203)**

Table 2. Cost-effectiveness of mechanical thrombectomy in the US
Data obtained from a 2017 prospective cost-effectiveness study conducted alongside the SWIFT-PRIME trial (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke) by Shireman et al.[20]
a Costs incurred for initial hospitalization.
b Costs incurred between discharge and 90 days.
c Quality of life years during trial.
d Projected lifetime quality of life years.
e Projected lifetime stroke-related costs. QUAL, Quality-adjusted life years.

IVT) has a higher cost for initial hospitalization ($17,183) than standard therapy (clot-disrupting IVT agents), it has a lifetime savings of $23,203 per patient because of the substantial reduction in disability, plus improvements in the overall quality of life. Additionally, it is associated with lower post-stroke rehabilitation and nursing care (90-day cost) and lifetime costs.[20]

Canada

The Canadian average annual cost of AIS is $2.8 billion, with an average per-patient cost of $75,353/year.[209] Similar to the data from the US, the average annual cost for patients with a stroke-related disability is more than double that of non-disabled patients ($107,883 vs. $48,339).[209] AIS treatment with combination therapy is estimated to save the Canadian healthcare system $321,334/year.[211]

Europe

	Combination Therapy	Standard Care	Difference
Costs	$64,757.28	$52,494.73	**($12,262,551)**
QALY	4.842	3.790	**1.052**
Net monetary benefit			
Lower	$95,031.35	$72,563.79	—
Upper	$174,925.66	$135,093.06	—

Table 3. Cost-effectiveness of mechanical thrombectomy in Europe
Data obtained from a 2015 model-based cost-utility analysis of mechanical thrombectomy by Ganesalingam et al. (2015).[163] Costs are based on 2013–2014 prices. The net monetary benefit is calculated at the lower and upper limits of the willingness-to-pay for a quality adjusted life year (QALY), which are $33000 (£20000) and $49500 (£30000) in the UK, respectively.

United Kingdom

Combination therapy in the UK is similarly associated with higher initial hospitalization costs than standard care ($64,757.28 vs. $52,494.73).[212] Combination therapy is not cost-effective in the short-term (90 days) but is estimated to be cost-effective over 20 years[163] and a lifetime horizon,[214] and if fully implemented, the projected value is estimated to be £1.3 billion ($1.7 billion) over five years.[214]

France

Mirroring the US results, in France, initial hospitalization costs are $2,116 more for combination therapy than standard care; however, these patients experience a 10.9% increase in functional independence 90 days post stroke. The estimated cost per one Quality Adjusted Life Year (QALY) gained is $14,880 and the estimated net monetary benefit is $2,757, indicating the cost-effectiveness of MT at one-year.[216]

Sweden

In Sweden, MT procedures increase intervention costs (+£9000 [$11,779]) but result in substantial overall cost savings in the long run due to a lower reliance on home medical (home help services - £13,000 [$17,014]) services or nursing home care (£26,000 [$34,027]).[218]

	Combination Therapy	Standard Care	Difference
1-year Cost QALYs ICER	€ 13,430.81 0.55 € 23,990.44	€ 9,352.44 0.38	**€ 4,078.37** **0.17**
2-year Cost QALYs ICER	€ 18,096.88 1.08 € 6,696.22	€ 15,895.04 0.75	**€ 2,201.84** **0.33**
3-year Cost QALYs ICER	€ 22,737.48 1.59 € 798.00	€ 22,353.22 1.11	**€ 384.26** **0.48**
4-year Cost QALYs ICER	€ 27,308.47 2.07	€ 28,678.84 1.44	**(€ 1.370,37)** **0.63**
5-year Cost QALYs ICER	€ 31.798,22 2.52	€ 34.854,90 1.75	**(€ 3.056,68)** **0.77**

Table 4. Cost-effectiveness of mechanical thrombectomy in Italy
Data obtained from a 2018 model-based cost effectiveness study by Ruggeri et al.[170] QUAL, Quality-adjusted life years.
ICER - Incremental cost-effectiveness ratio

Italy

From the perspective of the Italian National Healthcare System (NHS), combination therapy for LVO stroke is cost-effective between 1-3 years post-stroke and cost savings from year 4 onwards. At 1 year, MT is more expensive than standard care by €4.078,37 ($4,553.77) (€13,430.81 [$14,996.37] vs. €9,352.44 [$10,442.61]). At year 5, combination therapy is associated with a cost savings of €3,057 ($3,411) when compared to standard care (€31,798 [$35,483] vs. €34,855 [$38,895]).[220]

Spain

Matching the US results, from the perspective of the Spanish NHS, when compared to standard care, combination therapy has higher treatment costs (€8,428.00 [US $9,405] vs. €1,606.00 [US $1792]) and lower overall costs (€123,866 [US $138,228] vs. €168,244 [US $187,752]), along with a net monetary benefit of €119,744 (US $133,628).[221] Patients treated with combination therapy also have improved health outcomes with 1.17 life years gained. Therefore, combination therapy for LVO AIS patients is less costly and more beneficial than standard care alone.[221]

	Combination Therapy	Standard Care	Difference
Treatment Cost	€8,428.00	€1,606.00	**€6,822.00**
Long-term management	€105,624.00	€157,668.00	**(€52,044.00)**
Cost			
Total QALYs	7.62	5.11	**2.51**
Life Years Gained	11.708	10.536	**1.172**

Table 5: Cost-effectiveness of mechanical thrombectomy in Spain
Data obtained from a 2017 retrospective cost-effectiveness analysis by de Andrés-Nogales et al. (2017).[171] Quality adjusted life year (QALY).

Australia

Combination therapy has higher hospital costs ($10,666/patient) in Australia but results in a lifetime savings of more than $8,000/patient when compared to standard care.[222] For the first 90 days, average inpatient costs are less for patients receiving combination therapy compared to standard care ($15,689 vs. $30,569), counterbalancing the additional costs of inter-hospital transport (average $573) and the MT procedure (average $10,515), resulting in an average savings of $4,365/patient ($29,371 vs. $33,736). Patients treated with MT also have shorter hospital (5 vs. 8 days) and rehabilitation stays (0 vs. 27 days), and gain 4.4 life years than those treated with standard care.[11] As a result, it can be expected that increased use of combination therapy decreases the economic burden.[11]

	≤ 6 hours	Standard Care	Difference	P-value
Hospital stay	$29,371	$33,736	**($4,365)**	
Hospital stay (days)	5	8	**(3)**	0.04
Rehabilitation stay (days)	0	27	**(27)**	0.03
QALY	9.3	4.9	**4.4**	0.03
Utility score	0.91	0.65	**0.26**	0.005
DALY 15 years	5.5	8.9	**(3.4)**	0.02
Life Expectancy	15.6	11.2	**4.4**	0.02

Table 6. Cost-effectiveness of mechanical thrombectomy in Australia
Data obtained from a 2017 retrospective analysis of disability, quality of life, survival, and acute care costs associated with mechanical thrombectomy by Campbell et al.[11]
a Total in-hospital cost for the first 90 days post-stroke.
b Utility weighting of modified Rankin Score. Standard care and combination therapy refer to IV t-PA and MT+IV t-PA, respectively. DALY, disability-adjusted life years; QALY, quality-adjusted life-year.

Asia

China

In China, combination therapy is not considered cost-effective at 5 years post stroke, but at 6 years and thereafter, it is considered cost-effective.[223]

Conclusion

The cost-effectiveness of MT has been analyzed across the globe. MT compared to standard care is cost-effective over extended time horizons due to increased survival and quality of life and decreased long-term care (i.e., nursing and rehabilitation facilities). Economic studies of AIS come mostly from developed countries but are expanding to new areas, and costs may be stratified according to age, type of procedure, and baseline patient status.

	Combination Therapy	Standard Care	Difference
1-year			
Cost (CNY)	77,700	27,220	**50,480**
QALYs	0.405	0.326	**0.79**
ICER	638,987		
5-year			
Cost (CNY)	107,710	58,590	**49,120**
QALYs	1.765	1.392	**0.373**
ICER	131,689		
6-year			
Cost (CNY)	114,170	65,230	**48,940**
QALYs	2.029	1.599	**0.43**
ICER	113,814		
30-year			
Cost (CNY)	167,970	117,940	**50,030**
QALYs	3.773	2.979	**0.794**
ICER	63,010		

Table 7. Cost-effectiveness of mechanical thrombectomy in China
Data obtained from a 2018 retrospective cost-effective analysis by Pan et al. (2018).[173]
Renminbi, CYN; quality-adjusted life year (QALY); incremental cost ratio (ICER).

3. Recommended emergency steps in the care pathway of LVO stroke

Stroke systems of care allow for the coordination and integration of an entire stroke care continuum, which includes community education, prevention, emergency medical services, TSCs with a stroke care unit, treating specialists, capability of performing IVT and MT, and collaboration with rehabilitation facilities and services. Globally, an increased access to highly developed stroke systems has the potential to save nearly 2 million lives per year[28] but is dependent upon patient access.[187] Increasing access to TSCs is one of the main public health concerns of the decade due to aging and a rapidly growing incidence of LVO stroke.

Treatment of a stroke is a complex, multi-step process that requires timeliness and accuracy of diagnosis and treatment in order to increase the likelihood of a good outcome. When developing efficient stroke systems, it is important to understand the experience from the patient's perspective.

Patient or witness Calling Emergency Response

The first step in receiving acute stroke treatment is the recognition of LVO stroke itself. LVO strokes present with more prominent symptoms due to a larger area of affected brain. As a result, the patient may experience weakness of the limbs, speech disturbances, or a facial droop.[230] These symptoms can be for a short duration or persist for a longer time. The patient may call for help, report these symptoms to another person who can call for help, or these symptoms may be initially detected by a nearby witness. Stroke patients may be unable to communicate these symptoms, so bystanders' observations and knowledge of stroke symptoms can be vital to providing adequate and timely treatment. Early recognition of LVO stroke symptoms is critical as the decision to shift the patient to a TSC where MT can be performed can be made quickly.[230,231] Once any stroke is suspected, emergency medical services (EMS) should be called.

(One of the evidence-based best practices is to call EMS rather than trying to transport the patient. Relatives may not know where to take them and need pre-notification in the hospital)

Emergency paramedical ambulance response

Upon the arrival of an EMS, they will likely evaluate the patient by performing an initial assessment, which includes questioning the patient and/or witnesses to understand the patient's symptoms, events that led to calling EMS, and when the patient was last known to be well.[192,193] EMS may further inquire about the patient's medical history, including any risk factors for stroke, such as high blood pressure, diabetes, or irregular heartbeats, and any medications the patient is taking. They will also assess the patient's airway, breathing, and blood circulation, as with any other critical patient.[192] These initial evaluations collectively aid EMS professionals in identifying LVO strokes. EMS providers will also obtain intravenous (IV) access by inserting a needle into the blood vessels of the arm or wrist to administer fluids, like saline and dextrose, and assist in any imaging that will be done at the hospital.[192]

Paramedic/ambulance identification of LVO stroke

When examining the patient, some EMS providers utilize stroke scales, which are essentially a checklist of clinical signs, symptoms, and questions that can help identify an LVO stroke, such as the Fast Arm Speech Test (FAST), Cincinnati Prehospital Stroke Scale (CPSS), and Los Angeles Prehospital Stroke Screen (LAPSS).[191] These scores are useful in identifying patients with LVO strokes.

ER pre-notification

The patient is transported to the nearest stroke center. While in route, EMS professionals should provide pre-notification to the admitting hospital to initiate a stroke code in the hospital and prompt preparations for imaging, IVT, and MT.[192]

Stroke Alert in the ER

Once a stroke code is called, the physicians and hospital staff can prepare for the arrival of the patient. This allows the hospital to activate local protocols, ready necessary medications, prepare and hold the CT scanner, and be prepared to assess the patient upon arrival.[192,194]

ER bypass and urgent radiological assessment +/- IVT if indicated

Upon arrival at the emergency room, the prepared medical staff will obtain a medical history to ensure all relevant information is collected. One of the main objectives will be to rule out any stroke mimickers, such as a seizure, migraine (one-sided head ache), or hypoglycemia (low blood sugar).[193] A neurological examination will be performed on the patient, which usually involves testing muscular reflexes, eye movements, muscle strength, and language. The findings of this exam will yield a National Institutes of Health Stroke Scale (NIHSS) score, which assesses the severity of symptoms.[195] During this, the patient may be receiving IV hydration with normal saline, supplemental oxygen, insulin to control rising blood sugar, or antipyretics to reduce rising body temperatures, depending on the patient's status and requirements.[196] The patient may have an electrocardiogram (EKG) done for continuous cardiac monitoring, as well as blood tests.[196]

Following initial examination, the patient will be transported for radiological imaging. Imaging is necessary to differentiate an AIS from a HS, which is essential to determine and administer appropriate stroke-type-specific treatment. Patients demonstrating moderate to severe stroke symptoms should undergo CT, MRI, or CTA[193,196] imaging to diagnose stroke before receiving MT treatment.

If the brain imaging indicates stroke, the next step is to decide the type of therapy. Many AIS patients are treated with IVT, which must be administered 3-4.5 hours after symptom onset.[194,195] Earlier administration of IVT is associated with better outcomes; therefore, administration within 60 minutes from stroke onset is the goal of healthcare facilities.[194] If an LVO stroke is confirmed by CTA, then MT or combination therapy of MT and IVT is carried out.[195]

Thrombectomy Team Alert

MT is typically reserved for LVO strokes and can be used in patients who have received IVT or those who are eligible for the treatment and have missed the time cutoff for IVT.[194,196,197] It is given to those who were presented within 6 hours of symptom onset and, to some select patients, 6-24 hours after onset.[196] MT is performed by a neurointerventionalist, which begins procedure preparations once a stroke code is called, so that they can begin the procedure in a timely fashion once the patient is ready. The AHA/ASA published selection criteria for MT in AIS: functionally independent pre-stroke, AIS receiving IVT within 4.5 hours of onset, stroke caused by occlusion of one of the four major blood vessels supplying the brain (as per CTA), age ≥ 18 years old, and a significant NIHSS score.[194]

Groin Puncture

If a patient qualifies for MT, the first step of the procedure is the groin puncture (or via a major blood vessel in the hand), which should occur within 6 hours of symptom onset.[196]

Thrombectomy Pass of LVO stroke

This procedure involves placing a catheter into an artery at the groin (femoral artery) or hand (radial artery) and advancing it up through the neck until it reaches the blood clot. Using X-ray-guided imaging, a stent retriever and/or aspirator is inserted into the catheter. The stent reaches to a point beyond the clot, expands to stretch the walls of the artery, and is finally pulled back, or "retrieved", which removes the clot or the clot is aspirated out.[198]

Reperfusion

Removal of the clot should result in the restoration of blood flow in the vessel and reverse the temporary injury caused to the brain.

How can you implement MT in your region?

1. Educating communities about MT

Medical professionals and public health leaders need to develop stroke education programs focusing on symptoms, seeking emergency care, and available stroke system resources.[229] These programs should be implemented across all demographics within a community, tailoring to its economic, social, and ethical needs.[230] Increasing the awareness of stroke symptoms is vital for seeking timely treatment.[229] When compared to the general population, community minorities have a lower awareness of the risk factors and symptoms of a stroke. As a result, they are less likely to activate EMS, thus delaying necessary treatment.[231] When that treatment is delayed, it leads to an underutilization of proven therapy and to higher mortality.[232] The establishment of comprehensive stroke care and a greater emphasis on public stroke education have been shown to increase IVT and MT over time. Additionally, these programs should increase the awareness surrounding available emergency dispatch systems to decrease the time between the onset of a stroke and the arrival of EMS.[229] EMS activation and transport of stroke patients are independently associated with earlier arrival (onset-to-door time ≤3 hours), faster evaluation (more patients with door-to-imaging time ≤25 minutes), faster treatment delivery (more patients with door-to-needle time ≤60 minutes), and more patients being eligible for MT.[223]

2. Training initiatives for MT

EMS Training, Assessment, and Management

Stroke therapy has a small time-window for providing treatment. Thus, EMS professionals should be well-trained and experienced in recognizing, assessing, managing, treating, triaging, and transporting stroke patients quickly.[234] Improved patient outcomes have been associated with EMS dispatchers and field providers utilizing stroke assessment and identification tools to direct patients to the most suitable TSC.[235,236]

To prepare emergency personnel for a suspected LVO stroke patient, EMS should provide pre-arrival notification to the receiving hospital. In fact, this is associated with increased probability that patients receive IVT within 3 hours, decreased time between arrival and imaging, decreased door-to-needle, and decreased time between symptom onset to needle.[244] Additionally, EMS identification of patients suffering from LVO stroke allows transportation to the best-equipped stroke center, which is critical for positive patient outcomes.

Training Neurointerventionalists

Physicians providing MT must have sufficient training and experience in performing related techniques, which includes baseline training and ongoing professional education.[245,246] However, there are very few hospitals capable of offering adequate physician training for MT. Thus, specialized regional TSCs must be established to ensure adequate volume and operator experience for MT.[247]

Baseline Training and Qualifications

Residency training for physicians includes documented training in the diagnosis and management of AIS and interpretation of CTA and neuroimaging under the guidance of a board-certified neuroradiologist, neurologist, or neurosurgeon and ultimately achieving technical expertise. At the close of residency, they must obtain field-specific board certifications. Subsequently, they must also undertake specialized Interventional Neuroradiology at a high-volume facility under the supervision of a neurointerventionalist, where they receive AIS specific training.[245]

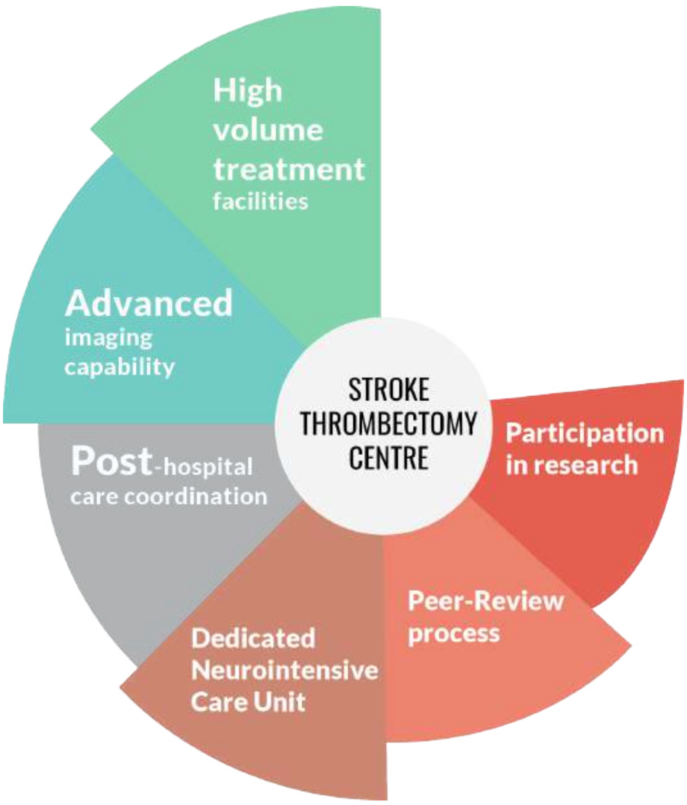
Maintenance of Physician Qualifications

The field of stroke therapy is constantly changing and, as a result, physicians should be required to engage in at least 16 hours of stroke education on a biannual basis. Additionally, physicians are encouraged to participate in quality and improvement monitoring programs. Such programs would review emergent interventional stroke therapy care and track associated outcomes.[245,246]

Training Stroke Teams

The outcomes of LVO stroke treatments are time-dependent, as has been demonstrated by the diminished therapeutic effects of IVT outside a 4.5-hour time window.[75] Similar time-dependent outcomes have been indicated for MT.[188] LVO stroke treatment algorithms combine IVT and MT to achieve better patient outcomes.[248] However, this approach requires an interdisciplinary, coordinated team approach. To minimize time-to-treatment and non-technical errors, simulation-based team trainings are recommended as a core component to any TSC.[249] Simulation-based interventions have been demonstrated to reduce door-to-needle times by 12 minutes and increasing the number of patients receiving IVT within 30 minutes of arrival.[250]

3. Building thrombectomy systems in your community



Numerous high quality clinical trials have shown significant clinical benefit for treatment with MT in LVO AIS patients.[10,14-16,18] Importantly, these trials were conducted in high-volume stroke centers staffed with stroke experts and the capabilities to provide complex care for this patient population. Facility-based stroke teams were comprised of emergency physicians, radiologists, neurointerventionists, neurologists, neurosurgeons, and stroke-trained support staff. These key players are vital for TSCs to provide efficient and effective treatment.[10,14-16,18,251]

In 2016, SVIN proposed recommendations to drive the development of LVO stroke systems, including MT as a treatment modality.[251] These recommendations are in addition to current eligibility requirements for comprehensive stroke centers, which include high-patient volume, advanced imaging capabilities, post-hospital care coordination, dedicated neurointensive care, quality control, participation in stroke research, and reporting of performance measures. The SVIN recommended additions to these criteria include the following:

- **High patient volume**

High-volume treatment facilities have been associated with positive patient outcomes.[252-255] A recommended requirement of 25-30 MT-treated patients per year and all TSC-affiliated neurointerventionalists should perform 10 MT per year (minimum).[251]

- **Advanced imaging capabilities**

It is recommended for all TSCs to have the capacity to manage the care of two simultaneous LVO stroke patients; therefore, requiring two of the following to be available at all times - neurointerinventionalists, stroke interventional labs, and associated support staff.[251]

- **Post-hospital care coordination**

A monitored and coordinated system between TSCs and rehabilitation facilities is recommended to ensure the continuity of care. Such post-stroke care institutions should be certified in stroke rehabilitation and staff should be trained in standardized outcome scales.[251]

- **Dedicated neurointensive care unit and expert neurointensivist and neurosurgical management**

Due to the complexity of care management of LVO stroke patients and the potential for complications, a multi-disciplinary team of vascular neurologists and neurocritical care specialists should be available at all times.[251]

- **Peer review process**

It is recommended for currently established peer reviews to include performance metrics related to the fast and efficient MT treatment of LVO stroke patients.[251]

- **Participation in stroke research**

A data management coordinator should be on staff at all TSCs to maintain a registry to improve quality, while contributing clinical data for analysis.[251]

4. Improving inter-hospital transfers for MT

Many landmark clinical trials have helped refine hospital workflow systems after direct patient admission, but pre-hospital time management and segregation of patients based on symptom severity (triage) continue to be the most important factors in optimizing logistical performance measures.[256] Longer door-in-door-out (DIDO) times adversely affect outcomes in stroke patients with LVO and is possibly the single largest modifiable factor in onset-to-MT time.[257]

Advantages and disadvantages of inter-hospital transfers

The benefits of MT have been demonstrated by several landmark trials.[10,14-16,18] As a result, the AHA/ASA have updated its 2013 guidelines to reflect the necessity for improved stroke care systems, which include pre-hospital triage, inter-hospital transfers, and certifications for TSC.[261] Inter-hospital transfers to TSC are required to provide access to MT. However, inter-hospital transfers before MT delay therapy and impact outcomes adversely for patients with LVO stroke.[262] Direct admission of patients to TSC with MT capabilities after earlier identification of LVO strokes has led to better outcomes;[264,265] therefore, EMS should bypass nearby hospitals and directly route patients to a TSC. To decrease transport time, all TSCs should be equipped to perform MT.[266]

Cause of futile transfers

Inter-hospital transfers for AIS increased by 33% between 2009 and 2014, representing the need for increased access to MT.[267] A French study demonstrated that 45% of the inter-hospital transfers for MT were futile and did not result in intervention, possibly due to clinical deterioration due to growth in the blockage of the blood vessel.[268]
[41]

Factors that affect delays in administering MT include awareness of first responders, efficiency of EMS, inter-hospital transfers, notifying the MT team, and intra-procedural delays.[270] Higher chances of MT after inter-hospital transfer were independently predicted by higher collateral score, a higher NIHSS score, and CTA imaging from the initial referring center.[43]

Delays during transfer and how to avoid them

DIDO times are the single largest modifiable factor in the onset to recanalization time, with longer DIDO times adversely affecting outcomes in stroke patients with LVO stroke.[257] Establishment of a Critical Care Resuscitation Unit decreases transfer time in inter-hospital transfers and aid in better outcomes for stroke patients with LVOs.[221]

Quality improvement in hospital workflow processes

Delays to MT in distant TSC can be decreased by quality improvement processes.[272] Many clinical trials have helped refine hospital workflow systems after direct patient admission, but pre-hospital time management and triage continue to be the most important factors in optimizing logistical performance measures, as shown by real-world data from regional stroke care systems.[18] Optimization of in-hospital workflow is important to prevent delays in inter-hospital transfer and the associated delay in administering MT.[49] A 2017 SVIN report recommends LVO stroke patients, who have escalated risk for morbidity and mortality, need to achieve reperfusion as soon as possible, a result depending on enhancing hospital processes and workflow.[50] Early notification to TSC, cloud data sharing, and CTA on arrival are some features of a standardized TSC protocol associated with improved outcomes for stroke patients with LVO stroke.[51][273] A detailed classification system on making decisions to transfer stroke patients from thrombectomy system of care to CSC can help reduce inappropriate transfers and improve outcomes.[53]

Trip and treat models

The trip-and-treat model of stroke care, where a mobile interventional stroke team provides intervention at TSC, was 79 minutes faster in comparison to the drip-and-ship model, where patients are transported to the nearest hospital to provide IVT. Hence, it is a potential alternative to inter-hospital transfers in urban settings.[274]

Telestroke options

Telestroke medicine, where doctors specializing in stroke medicine help treatment for stroke patients in other locations using technological measures, increases rates of MT for stroke patients and decreased inter-hospital transfers.[274]
[55]

Helicopter emergency medical services

The role of helicopter EMS (HEMS) needs to be addressed further for better ancillary care during transportation and to nullify disparities in access to MT based on geography.[275]

Recommendations for policy makers

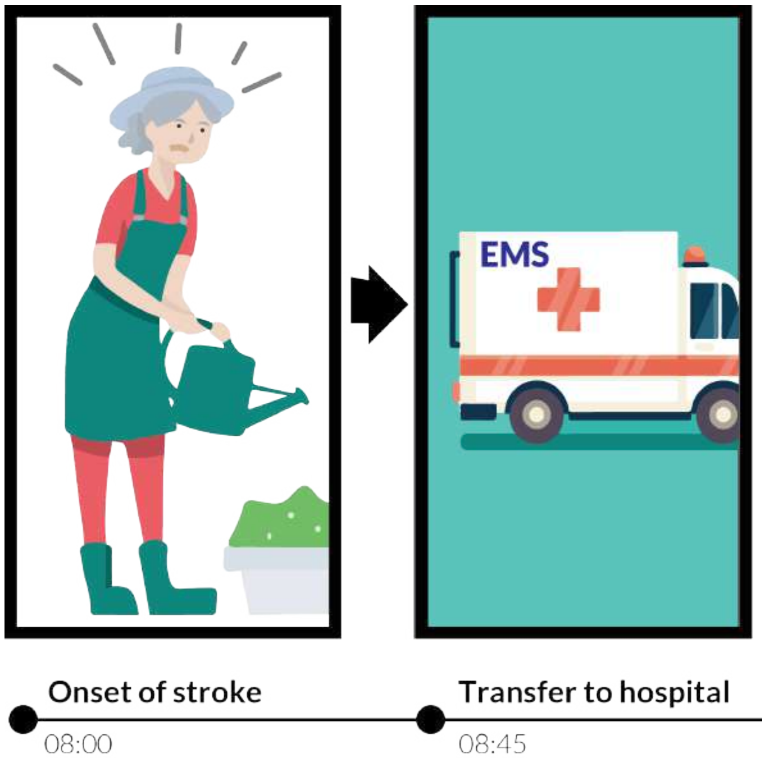
1. KEY RECOMMENDATIONS TO POLICY MAKERS

1. Physicians and administrators of hospitals who deal with a high volume of stroke cases.
2. Assess the burden of stroke and LVO in your region.
3. Assess the efficacy of the existing systems in place for the management of stroke and identify key gaps.
4. Assess the cost and therapeutic effectiveness of existing systems and a detailed analysis of clinical and cost benefits to the patients in your region.
5. Develop a policy that aims to reduce the burden of stroke and improve clinical outcomes.
6. Create funds for patients in resource-constrained settings who will benefit from MT for LVO.
7. Develop stroke education programs focusing on symptoms, seeking emergency care, and available stroke system resources.
8. Set up specialized regional stroke centers that are equipped to carry out MT.
9. Increase the number of training programs for neurointerventionalists with an aim to create adequate talent for the management of LVO.

2. Patient journey as recommended steps in care pathway

Clinical History

Elizabeth, a 62-year-old woman with atrial fibrillation on warfarin was presented with sudden-onset, left-sided weakness during her morning walk. A passer-by alerted the EMS who arrived on the scene within 15 minutes, recognized the signs of a stroke, and arranged for immediate transfer to a thrombectomy system of care.



Assessment in the Hospital

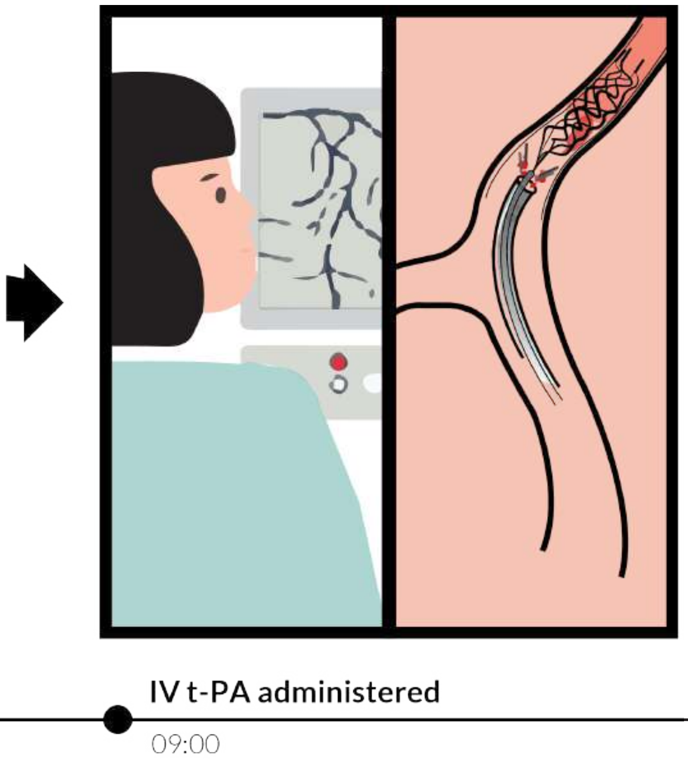
At the center, the symptoms were reassessed, and she was sent for a non-contrast head CT, which showed no early infarct changes or hemorrhage.

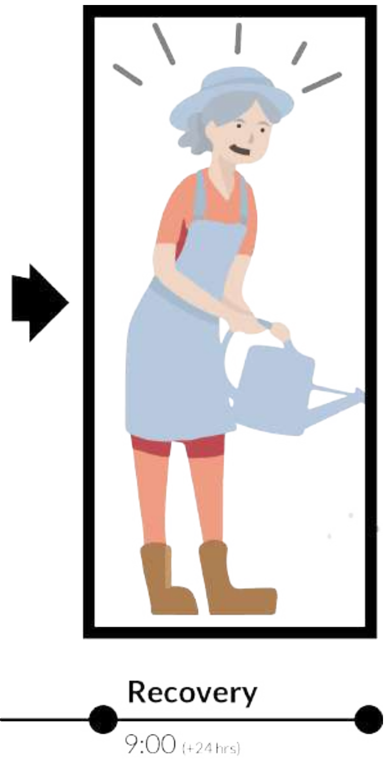
Management

She received IVT with a door-to-needle time of 45 minutes, 90 minutes after symptom onset. She was then taken for MT, where CTA confirmed an LVO stroke in the middle cerebral artery (MCA) and MT was performed with a combined use of a stent-retriever and intra-arterial thrombolysis in cerebral infarction recanalization. Follow-up imaging showed no infarct burden.

Outcome

The patient had an excellent clinical outcome. She left the hospital the very next day with complete functional independence.





NEXT STEPS

1. Discuss this white paper with the members of SVIN to understand how MT may potentially benefit your region
2. Have an internal discussion with key stakeholders and decision-makers for stroke management in your healthcare ecosystem
3. Organize a meeting with clinical experts and decision-makers for policymaking in your region to evaluate the need for improvement in management for LVO

References

1. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet.* 2006;367(9524):1747-1757.
2. Warlow CP. Epidemiology of stroke. *Lancet.* 1998;352 Suppl 3:SIII1-4.
3. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. *Circulation.* 2015;131(4):e29-322.
4. Donkor ES. Stroke in the 21(st) Century: A Snapshot of the Burden, Epidemiology, and Quality of Life. *Stroke Res Treat.* 2018;2018:3238165.
5. Collaborators GS. Global, regional, and national burden of stroke, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* 2019;18(5):439-458.
6. Saver JL. Time is brain--quantified. *Stroke.* 2006;37(1):263-266.
7. Goyal M, Almekhlafi M, Dippel DW, et al. Rapid Alteplase Administration Improves Functional Outcomes in Patients With Stroke due to Large Vessel Occlusions. *Stroke.* 2019;50(3):645-651.
8. Robinson DJ. Should physicians give tPA to patients with acute ischemic stroke? For: thrombolytics in stroke: whose risk is it anyway? *West J Med.* 2000;173(3):148-149.
9. Albers GW, Marks MP, Kemp S, et al. Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. *N Engl J Med.* 2018;378(8):708-718.
10. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med.* 2015;372(1):11-20.
11. Campbell BCV, Mitchell PJ, Churilov L, et al. Endovascular Thrombectomy for Ischemic Stroke Increases Disability-Free Survival, Quality of Life, and Life Expectancy and Reduces Cost. *Front Neurol.* 2017;8:657.
12. Khoury NN, Darsaut TE, Ghostine J, et al. Endovascular thrombectomy and medical therapy versus medical therapy alone in acute stroke: A randomized care trial. *J Neuroradiol.* 2017;44(3):198-202.
13. Mocco J, Zaidat OO, von Kummer R, et al. Aspiration Thrombectomy After Intravenous Alteplase Versus Intravenous Alteplase Alone. *Stroke.* 2016;47(9):2331-2338.
14. Campbell BC, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med.* 2015;372(11):1009-1018.
15. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med.* 2015;372(11):1019-1030.
16. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med.* 2015;372(24):2285-2295.
17. Munich SA, Mokin M, Snyder KV, Siddiqui AH, Hopkins LN, Levy EI. Guest Editorial: An Update on Stroke Intervention. *Neurosurgery.* 2015;77(3):313-320.
18. Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med.* 2015;372(24):2296-2306.
19. Alawieh A, Vargas J, Fargen KM, et al. Impact of Procedure Time on Outcomes of Thrombectomy for Stroke. *J Am Coll Cardiol.* 2019;73(8):879-890.
20. Shireman TI, Wang K, Saver JL, et al. Cost-Effectiveness of Solitaire Stent Retriever Thrombectomy for Acute Ischemic Stroke: Results From the SWIFT-PRIME

Trial (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke). *Stroke.* 2017;48(2):379-387.
21. McCarthy DJ, Diaz A, Sheinberg DL, et al. Long-Term Outcomes of Mechanical Thrombectomy for Stroke: A Meta-Analysis. *ScientificWorldJournal.* 2019;2019:7403104.
22. Luby M, Warach SJ, Albers GW, et al. Identification of imaging selection patterns in acute ischemic stroke patients and the influence on treatment and clinical trial enrollment decision making. *Int J Stroke.* 2016;11(2):180-190.
23. Mullen MT, Branas CC, Kasner SE, et al. Optimization modeling to maximize population access to comprehensive stroke centers. *Neurology.* 2015;84(12):1196-1205.
24. Mullen MT, Wiebe DJ, Bowman A, et al. Disparities in accessibility of certified primary stroke centers. *Stroke.* 2014;45(11):3381-3388.
25. Jovin TG, Nogueira RG, Investigators D. Thrombectomy 6 to 24 Hours after Stroke. *N Engl J Med.* 2018;378(12):1161-1162.
26. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. *N Engl J Med.* 2018;378(1):11-21.
27. Gorelick PB. Primary and comprehensive stroke centers: history, value and certification criteria. *J Stroke.* 2013;15(2):78-89.
28. EurekAlert. SVIN announces 'Stroke: Mission thrombectomy 2020': An initiative to reduce disability from stroke worldwide Web site. https://www.eurekalert.org/pub_releases/2016-11/lpl-sa112116.php. Published 2016. Updated 21 Nov 2016. Accessed 31 Dec 2019.
29. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation.* 2017;135(10):e146-e603.
30. Feigin VL, Lawes CM, Bennett DA, Anderson CS. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. *Lancet Neurol.* 2003;2(1):43-53.
31. Ovbiagele B, Goldstein LB, Higashida RT, et al. Forecasting the future of stroke in the United States: a policy statement from the American Heart Association and American Stroke Association. *Stroke.* 2013;44(8):2361-2375.
32. Bracard S, Ducrocq X, Mas JL, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. *Lancet Neurol.* 2016;15(11):1138-1147.
33. Sevick LK, Ghali S, Hill MD, et al. Systematic Review of the Cost and Cost-Effectiveness of Rapid Endovascular Therapy for Acute Ischemic Stroke. *Stroke.* 2017;48(9):2519-2526.
34. Clinic C. Stroke. https://my.clevelandclinic.org/health/diseases/17519-stroke. Published 2018. Updated 2018, Oct. 17. Accessed.
35. Lisabeth LD, Brown DL, Hughes R, Majersik JJ, Morgenstern LB. Acute stroke symptoms: comparing women and men. *Stroke.* 2009;40(6):2031-2036.
36. Reeves M, Bhatt A, Jajou P, Brown M, Lisabeth L. Sex differences in the use of intravenous rt-PA thrombolysis treatment for acute ischemic stroke: a meta-analysis. *Stroke.* 2009;40(5):1743-1749.
37. Barr J, McKinley S, O'Brien E, Herkes G. Patient recognition of and response to symptoms of TIA or stroke. *Neuroepidemiology.* 2006;26(3):168-175.
38. Centers for Disease C, Prevention. Prehospital and hospital delays after stroke onset--United States, 2005-2006. *MMWR*

Morb Mortal Wkly Rep. 2007;56(19):474-478.
39. Cheung RT. Hong Kong patients' knowledge of stroke does not influence time-to-hospital presentation. *J Clin Neurosci.* 2001;8(4):311-314.
40. Engelstein E, Margulies J, Jeret JS. Lack of t-PA use for acute ischemic stroke in a community hospital: high incidence of exclusion criteria. *Am J Emerg Med.* 2000;18(3):257-260.
41. Foerch C, Misselwitz B, Humpich M, et al. Sex disparity in the access of elderly patients to acute stroke care. *Stroke.* 2007;38(7):2123-2126.
42. Jungehulsing GJ, Rossnagel K, Nolte CH, et al. Emergency department delays in acute stroke - analysis of time between ED arrival and imaging. *Eur J Neurol.* 2006;13(3):225-232.
43. Mandelzweig L, Goldbourt U, Boyko V, Tanne D. Perceptual, social, and behavioral factors associated with delays in seeking medical care in patients with symptoms of acute stroke. *Stroke.* 2006;37(5):1248-1253.
44. Menon SC, Pandey DK, Morgenstern LB. Critical factors determining access to acute stroke care. *Neurology.* 1998;51(2):427-432.
45. Rose KM, Rosamond WD, Huston SL, Murphy CV, Tegeler CH. Predictors of time from hospital arrival to initial brain-imaging among suspected stroke patients: the North Carolina Collaborative Stroke Registry. *Stroke.* 2008;39(12):3262-3267.
46. Yu RF, San Jose MC, Manzanilla BM, Oris MY, Gan R. Sources and reasons for delays in the care of acute stroke patients. *J Neurol Sci.* 2002;199(1-2):49-54.
47. Chong J, Sacco RL. Risk factors for stroke, assessing risk, and the mass and high-risk approaches for stroke prevention. In: Gorelick PB, ed. *Continuum: Stroke Prevention.* Hagerstwon, Maryland: Lippincott Williams and Wilkins; 2005:18-34.
48. Johnston SC, Mendis S, Mathers CD. Global variation in stroke burden and mortality: estimates from monitoring, surveillance, and modelling. *Lancet Neurol.* 2009;8(4):345-354.
49. Feigin VL, Norrving B, Mensah GA. Global Burden of Stroke. *Circ Res.* 2017;120(3):439-448.
50. Gorelick PB. The global burden of stroke: persistent and disabling. *Lancet Neurol.* 2019;18(5):417-418.
51. Katan M, Luft A. Global Burden of Stroke. *Semin Neurol.* 2018;38(2):208-211.
52. Goyal N, Tsivgoulis G, Malhotra K, et al. Medical Management vs Mechanical Thrombectomy for Mild Strokes: An International Multicenter Study and Systematic Review and Meta-analysis. *JAMA Neurol.* 2019.
53. Griessenauer CJ, Medin C, Maingard J, et al. Endovascular Mechanical Thrombectomy in Large-Vessel Occlusion Ischemic Stroke Presenting with Low National Institutes of Health Stroke Scale: Systematic Review and Meta-Analysis. *World Neurosurg.* 2018;110:263-269.
54. Heldner MR, Hsieh K, Broeg-Morvay A, et al. Clinical prediction of large vessel occlusion in anterior circulation stroke: mission impossible? *J Neurol.* 2016;263(8):1633-1640.
55. Li H, Zhang Y, Zhang L, et al. Endovascular Treatment of Acute Ischemic Stroke Due to Intracranial Atherosclerotic Large Vessel Occlusion : A Systematic Review. *Clin Neuroradiol.* 2019.
56. The Joint Commission. Specifications Manual for Joint Commission National Quality Measures (v2018B1). https://manual.jointcommission.org/releases/TJC2018B1/DataElem0771.html. Published 2018.

Accessed.
57. Dozois A, Hampton L, Kingston CW, et al. PLUMBER Study (Prevalence of Large Vessel Occlusion Strokes in Mecklenburg County Emergency Response). *Stroke.* 2017;48(12):3397-3399.
58. Malhotra K, Gornbein J, Saver JL. Ischemic Strokes Due to Large-Vessel Occlusions Contribute Disproportionately to Stroke-Related Dependence and Death: A Review. *Front Neurol.* 2017;8:651.
59. Rai AT, Seldon AE, Boo S, et al. A population-based incidence of acute large vessel occlusions and thrombectomy eligible patients indicates significant potential for growth of endovascular stroke therapy in the USA. *J Neurointerv Surg.* 2017;9(8):722-726.
60. Smith WS, Lev MH, English JD, et al. Significance of large vessel intracranial occlusion causing acute ischemic stroke and TIA. *Stroke.* 2009;40(12):3834-3840.
61. Rennert RC, Wali AR, Steinberg JA, et al. Epidemiology, Natural History, and Clinical Presentation of Large Vessel Ischemic Stroke. *Neurosurgery.* 2019;85(suppl_1):S4-S8.
62. Fink JN, Selim MH, Kumar S, Voetsch B, Fong WC, Caplan LR. Insular cortex infarction in acute middle cerebral artery territory stroke: predictor of stroke severity and vascular lesion. *Arch Neurol.* 2005;62(7):1081-1085.
63. Kodumuri N, Sebastian R, Davis C, et al. The association of insular stroke with lesion volume. *Neuroimage Clin.* 2016;11:41-45.
64. Cooray C, Fekete K, Mikulik R, Lees KR, Wahlgren N, Ahmed N. Threshold for NIH stroke scale in predicting vessel occlusion and functional outcome after stroke thrombolysis. *Int J Stroke.* 2015;10(6):822-829.
65. Heldner MR, Zubler C, Mattle HP, et al. National Institutes of Health stroke scale score and vessel occlusion in 2152 patients with acute ischemic stroke. *Stroke.* 2013;44(4):1153-1157.
66. Al Kasab S, Holmstedt CA, Jauch EC, Schrock J. Acute ischemic stroke due to large vessel occlusion. *Emerg Med Rep.* 2018;39(2):13-22.
67. Brouns R, De Deyn PP. The complexity of neurobiological processes in acute ischemic stroke. *Clin Neurol Neurosurg.* 2009;111(6):483-495.
68. Bansal S, Sangha KS, Khatri P. Drug treatment of acute ischemic stroke. *Am J Cardiovasc Drugs.* 2013;13(1):57-69.
69. Bruno A, Biller J, Adams HP, Jr., et al. Acute blood glucose level and outcome from ischemic stroke. Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators. *Neurology.* 1999;52(2):280-284.
70. Catanese L, Tarsia J, Fisher M. Acute Ischemic Stroke Therapy Overview. *Circ Res.* 2017;120(3):541-558.
71. del Rio-Espinola A, Fernandez-Cadenas I, Giralt D, et al. A predictive clinical-genetic model of tissue plasminogen activator response in acute ischemic stroke. *Ann Neurol.* 2012;72(5):716-729.
72. Fernandez-Cadenas I, Del Rio-Espinola A, Giralt D, et al. IL1B and VWF variants are associated with fibrinolytic early recanalization in patients with ischemic stroke. *Stroke.* 2012;43(10):2659-2665.
73. Mehta RH, Cox M, Smith EE, et al. Race/Ethnic differences in the risk of hemorrhagic complications among patients with ischemic stroke receiving thrombolytic therapy. *Stroke.* 2014;45(8):2263-2269.
74. Savitz SI, Schlaug G, Caplan L, Selim M. Arterial occlusive lesions recanalize more frequently in women than in men after intravenous tissue plasminogen activator administration for acute stroke. *Stroke.* 2005;36(7):1447-1451.

75. Emberson J, Lees KR, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet.* 2014;384(9958):1929-1935.
76. Riedel CH, Zimmermann P, Jensen-Kondering U, Stingele R, Deuschl G, Jansen O. The importance of size: successful recanalization by intravenous thrombolysis in acute anterior stroke depends on thrombus length. *Stroke.* 2011;42(6):1775-1777.
77. del Zoppo GJ, Higashida RT, Furlan AJ, Pessin MS, Rowley HA, Gent M. PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. PROACT Investigators. Prolyse in Acute Cerebral Thromboembolism. *Stroke.* 1998;29(1):4-11.
78. Furlan A, Higashida R, Wechsler L, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. *JAMA.* 1999;282(21):2003-2011.
79. National Institute of Neurological D, Stroke rt PASSG. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med.* 1995;333(24):1581-1587.
80. *Mechanical thrombectomy devices for acute ischaemic stroke.* United Kingdom: National Institute for Health and Care Excellence;2018.
81. Hu YC, Stiefel MF. Force and aspiration analysis of the ADAPT technique in acute ischemic stroke treatment. *J Neurointerv Surg.* 2016;8(3):244-246.
82. Group GBDNDC. Global, regional, and national burden of neurological disorders during 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Neurol.* 2017;16(11):877-897.
83. Global Burden of Disease Study 2016. Global Burden of Disease Study 2016 (GBD 2016) results. . http://ghdx.healthdata.org/gbd-results-tool. . Accessed 21 January 2020, 2020.
84. Krishnamurthi RV, Feigin VL, Forouzanfar MH, et al. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet Glob Health.* 2013;1(5):e259-281.
85. Yang Q, Tong X, Schieb L, et al. Vital Signs: Recent Trends in Stroke Death Rates — United States, 2000–2015. *Morbidity and Mortality Weekly Report.* 2017;66(35):933-939.
86. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* 2012;380(9859):2095-2128.
87. Boehme AK, Esenwa C, Elkind MS. Stroke Risk Factors, Genetics, and Prevention. *Circ Res.* 2017;120(3):472-495.
88. O'Donnell MJ, Chin SL, Rangarajan S, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet.* 2016;388(10046):761-775.
89. Larsson SC, Wallin A, Wolk A, Markus HS. Differing association of alcohol consumption with different stroke types: a systematic review and meta-analysis. *BMC Med.* 2016;14(1):178.
90. Suk SH, Sacco RL, Boden-Albala B, et al. Abdominal obesity and risk of ischemic stroke: the Northern Manhattan Stroke Study. *Stroke.* 2003;34(7):1586-1592.

91. Zhang X, Shu L, Si C, et al. Dietary Patterns and Risk of Stroke in Adults: A Systematic Review and Meta-analysis of Prospective Cohort Studies. *J Stroke Cerebrovasc Dis.* 2015;24(10):2173-2182.
92. Boehme C, Toell T, Mayer L, et al. The dimension of preventable stroke in a large representative patient cohort. *Neurology.* 2019;93(23):e2121-e2132.
93. Hachinski V, Donnan GA, Gorelick PB, et al. Stroke: working toward a prioritized world agenda. *Stroke.* 2010;41(6):1084-1099.
94. Pistoia F, Sacco S, Degan D, Tiseo C, Ornello R, Carolei A. Hypertension and Stroke: Epidemiological Aspects and Clinical Evaluation. *High Blood Press Cardiovasc Prev.* 2016;23(1):9-18.
95. Weiss J, Freeman M, Low A, et al. Benefits and Harms of Intensive Blood Pressure Treatment in Adults Aged 60 Years or Older: A Systematic Review and Meta-analysis. *Ann Intern Med.* 2017;166(6):419-429.
96. Benjamin EJ, Virani SS, Callaway CW, et al. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. *Circulation.* 2018;137(12):e67-e492.
97. Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. *Circulation.* 2019;139(10):e56-e528.
98. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ.* 2009;338:b1665.
99. Lackland DT, Carey RM, Conforto AB, Rosendorff C, Whelton PK, Gorelick PB. Implications of Recent Clinical Trials and Hypertension Guidelines on Stroke and Future Cerebrovascular Research. *Stroke.* 2018;49(3):772-779.
100. Lau LH, Lew J, Borschmann K, Thijs V, Ekinci EI. Prevalence of diabetes and its effects on stroke outcomes: A meta-analysis and literature review. *J Diabetes Investig.* 2019;10(3):780-792.
101. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. *BMJ.* 2006;332(7533):73-78.
102. Peters SA, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775,385 individuals and 12,539 strokes. *Lancet.* 2014;383(9933):1973-1980.
103. Emerging Risk Factors C, Sarwar N, Gao P, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet.* 2010;375(9733):2215-2222.
104. Banerjee C, Moon YP, Paik MC, et al. Duration of diabetes and risk of ischemic stroke: the Northern Manhattan Study. *Stroke.* 2012;43(5):1212-1217.
105. Sui X, Lavie CJ, Hooker SP, et al. A prospective study of fasting plasma glucose and risk of stroke in asymptomatic men. *Mayo Clin Proc.* 2011;86(11):1042-1049.
106. Kissela BM, Khoury J, Kleindorfer D, et al. Epidemiology of ischemic stroke in patients with diabetes: the greater Cincinnati/Northern Kentucky Stroke Study. *Diabetes Care.* 2005;28(2):355-359.
107. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics--2011 update: a report from the American Heart Association.

Circulation. 2011;123(4):e18-e209.
108. Ovbiagele B, Nguyen-Huynh MN. Stroke epidemiology: advancing our understanding of disease mechanism and therapy. *Neurotherapeutics*. 2011;8(3):319-329.
109. Arboix A, Garcia-Eroles L, Massons J, Oliveres M, Targa C. Acute stroke in very old people: clinical features and predictors of in-hospital mortality. *J Am Geriatr Soc*. 2000;48(1):36-41.
110. Dennis MS, Burn JP, Sandercock PA, Bamford JM, Wade DT, Warlow CP. Long-term survival after first-ever stroke: the Oxfordshire Community Stroke Project. *Stroke*. 1993;24(6):796-800.
111. Di Carlo A, Lamassa M, Pracucci G, et al. Stroke in the very old : clinical presentation and determinants of 3-month functional outcome: A European perspective. European BIOMED Study of Stroke Care Group. *Stroke*. 1999;30(11):2313-2319.
112. Kammersgaard LP, Jorgensen HS, Reith J, et al. Short- and long-term prognosis for very old stroke patients. The Copenhagen Stroke Study. *Age Ageing*. 2004;33(2):149-154.
113. Pohjasvaara T, Erkinjuntti T, Vataja R, Kaste M. Comparison of stroke features and disability in daily life in patients with ischemic stroke aged 55 to 70 and 71 to 85 years. *Stroke*. 1997;28(4):729-735.
114. Rojas JI, Zurru MC, Romano M, Patrucco L, Cristiano E. Acute ischemic stroke and transient ischemic attack in the very old--risk factor profile and stroke subtype between patients older than 80 years and patients aged less than 80 years. *Eur J Neurol*. 2007;14(8):895-899.
115. Krishnamurthi RV, Moran AE, Feigin VL, et al. Stroke Prevalence, Mortality and Disability-Adjusted Life Years in Adults Aged 20-64 Years in 1990-2013: Data from the Global Burden of Disease 2013 Study. *Neuroepidemiology*. 2015;45(3):190-202.
116. Danaei G, Finucane MM, Lin JK, et al. National, regional, and global trends in systolic blood pressure since 1980: systematic analysis of health examination surveys and epidemiological studies with 786 country-years and 5.4 million participants. *Lancet*. 2011;377(9765):568-577.
117. Norrving B, Kissela B. The global burden of stroke and need for a continuum of care. *Neurology*. 2013;80(3 Suppl 2):S5-12.
118. de los Rios F, Kleindorfer DO, Khoury J, et al. Trends in substance abuse preceding stroke among young adults: a population-based study. *Stroke*. 2012;43(12):3179-3183.
119. Zaridze D, Brennan P, Boreham J, et al. Alcohol and cause-specific mortality in Russia: a retrospective case-control study of 48,557 adult deaths. *Lancet*. 2009;373(9682):2201-2214.
120. Hu SS, Kong LZ, Gao RL, et al. Outline of the report on cardiovascular disease in China, 2010. *Biomed Environ Sci*. 2012;25(3):251-256.
121. Jha P, Jacob B, Gajalakshmi V, et al. A nationally representative case-control study of smoking and death in India. *N Engl J Med*. 2008;358(11):1137-1147.
122. Persky RW, Turtzo LC, McCullough LD. Stroke in women: disparities and outcomes. *Curr Cardiol Rep*. 2010;12(1):6-13.
123. Roy-O'Reilly M, McCullough LD. Age and Sex Are Critical Factors in Ischemic Stroke Pathology. *Endocrinology*. 2018;159(8):3120-3131.
124. Appelros P, Nydevik I, Viitanen M. Poor outcome after first-ever stroke: predictors for death, dependency, and recurrent stroke within the first year. *Stroke*. 2003;34(1):122-126.

125. Bots SH, Peters SAE, Woodward M. Sex differences in coronary heart disease and stroke mortality: a global assessment of the effect of ageing between 1980 and 2010. *BMJ Glob Health.* 2017;2(2):e000298.
126. Collaborators GLRoS, Feigin VL, Nguyen G, et al. Global, Regional, and Country-Specific Lifetime Risks of Stroke, 1990 and 2016. *N Engl J Med.* 2018;379(25):2429-2437.
127. Collaborators GBDCoD. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet.* 2017;390(10100):1151-1210.
128. Zhu W, Churilov L, Campbell BC, et al. Does large vessel occlusion affect clinical outcome in stroke with mild neurologic deficits after intravenous thrombolysis? *J Stroke Cerebrovasc Dis.* 2014;23(10):2888-2893.
129. Beumer D, Mulder MJHL, Saiedie G, et al. Occurrence of intracranial large vessel occlusion in consecutive, non-referred patients with acute ischemic stroke. *Neurovasc Imaging.* 2016;2(11).
130. Hansen CK, Christensen A, Ovesen C, Havsteen I, Christensen H. Stroke severity and incidence of acute large vessel occlusions in patients with hyper-acute cerebral ischemia: results from a prospective cohort study based on CT-angiography (CTA). *Int J Stroke.* 2015;10(3):336-342.
131. Miao Z, Huo X, Gao F, et al. Endovascular therapy for Acute ischemic Stroke Trial (EAST): study protocol for a prospective, multicentre control trial in China. *Stroke Vasc Neurol.* 2016;1(2):44-51.
132. Lakomkin N, Dhamoon M, Carroll K, et al. Prevalence of large vessel occlusion in patients presenting with acute ischemic stroke: a 10-year systematic review of the literature. *J Neurointerv Surg.* 2019;11(3):241-245.
133. Writing Group M, Mozaffarian D, Benjamin EJ, et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation.* 2016;133(4):e38-360.
134. Wang Y, Liao X, Zhao X, et al. Using recombinant tissue plasminogen activator to treat acute ischemic stroke in China: analysis of the results from the Chinese National Stroke Registry (CNSR). *Stroke.* 2011;42(6):1658-1664.
135. Tsang ACO, You J, Li LF, et al. Burden of large vessel occlusion stroke and the service gap of thrombectomy: A population-based study using a territory-wide public hospital system registry. *Int J Stroke.* 2019:1747493019830585.
136. Institute for Health Metrics and Evaluation, IHME - Measuring what matters. University of Washington. Japan Web site. Published 2019. Accessed 21 Dec 2019, 2019.
137. Takashima N, Arima H, Kita Y, et al. Incidence, Management and Short-Term Outcome of Stroke in a General Population of 1.4 Million Japanese- Shiga Stroke Registry. *Circ J.* 2017;81(11):1636-1646.
138. El-Hajj M, Salameh P, Rachidi S, Hosseini H. The epidemiology of stroke in the Middle East. *Eur Stroke J.* 2016;1(3):180-198.
139. Alahmari K, Paul SS. Prevalence of stroke in kingdom of Saudi Arabia – through a physiotherapist diary. *Mediterr J Soc Sci.* 2016;7:228-233.
140. al-Rajeh S, Larbi EB, Bademosi O, et al. Stroke register: experience from the eastern province of Saudi Arabia. *Cerebrovasc Dis.* 1998;8(2):86-89.
141. Al-Senani F, Al-Johani M, Salawati M, et al. A national economic and clinical model

for ischemic stroke care development in Saudi Arabia: A call for change. *Int J Stroke.* 2019;14(8):835-842.
142. Alhazzani AA, Mahfouz AA, Abolyazid AY, et al. Study of Stroke Incidence in the Aseer Region, Southwestern Saudi Arabia. *Int J Environ Res Public Health.* 2018;15(2).
143. Alanazy MH, Barakeh RB, Asiri A, et al. Practice Patterns and Barriers for Intravenous Thrombolysis: A Survey of Neurologists in Saudi Arabia. *Neurol Res Int.* 2018;2018:1695014.
144. Horton R, Das P. Indian health: the path from crisis to progress. *Lancet.* 2011;377(9761):181-183.
145. Dalal P, Bhattacharjee M, Vairale J, Bhat P. UN millennium development goals: Can we halt the stroke epidemic in India? *Ann Indian Acad Neurol.* 2007;10(3):130-136.
146. Kamalakannan S, Gudlavalleti ASV, Gudlavalleti VSM, Goenka S, Kuper H. Incidence & prevalence of stroke in India: A systematic review. *Indian J Med Res.* 2017;146(2):175-185.
147. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol.* 2009;8(4):355-369.
148. Bennett DA, Krishnamurthi RV, Barker-Collo S, et al. The global burden of ischemic stroke: findings of the GBD 2010 study. *Glob Heart.* 2014;9(1):107-112.
149. Huded V, Nair RR, de Souza R, Vyas DD. Endovascular treatment of acute ischemic stroke: an Indian experience from a tertiary care center. *Neurol India.* 2014;62(3):276-279.
150. Truelsen T, Hansen K, Andersen G, et al. Acute endovascular reperfusion treatment in patients with ischaemic stroke and large-vessel occlusion (Denmark 2011-2017). *Eur J Neurol.* 2019;26(8):1044-1050.
151. von Kummer R, Allen KL, Holle R, et al. Acute stroke: usefulness of early CT findings before thrombolytic therapy. *Radiology.* 1997;205(2):327-333.
152. Lees KR, Bluhmki E, von Kummer R, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet.* 2010;375(9727):1695-1703.
153. Kwiatkowski TG, Libman RB, Frankel M, et al. Effects of tissue plasminogen activator for acute ischemic stroke at one year. National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study Group. *N Engl J Med.* 1999;340(23):1781-1787.
154. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med.* 2008;359(13):1317-1329.
155. Balami JS, Hadley G, Sutherland BA, Karbalai H, Buchan AM. The exact science of stroke thrombolysis and the quiet art of patient selection. *Brain.* 2013;136(Pt 12):3528-3553.
156. Paciaroni M, Inzitari D, Agnelli G, et al. Intravenous thrombolysis or endovascular therapy for acute ischemic stroke associated with cervical internal carotid artery occlusion: the ICARO-3 study. *J Neurol.* 2015;262(2):459-468.
157. Yoo AJ, Pulli B, Gonzalez RG. Imaging-based treatment selection for intravenous and intra-arterial stroke therapies: a comprehensive review. *Expert Rev Cardiovasc Ther.* 2011;9(7):857-876.
158. Fisher M, Albers GW. Advanced imaging to extend the therapeutic time window of acute ischemic stroke. *Ann Neurol.* 2013;73(1):4-9.

159. Duffis EJ, Al-Qudah Z, Prestigiacomo CJ, Gandhi C. Advanced neuroimaging in acute ischemic stroke: extending the time window for treatment. *Neurosurg Focus.* 2011;30(6):E5.
160. Sandhu GS, Sunshine JL. Advanced neuroimaging to guide acute stroke therapy. *Curr Cardiol Rep.* 2012;14(6):741-753.
161. Medlin F, Amiguet M, Vanacker P, Michel P. Influence of arterial occlusion on outcome after intravenous thrombolysis for acute ischemic stroke. *Stroke.* 2015;46(1):126-131.
162. Hong JH, Sohn SI, Kang J, et al. Endovascular Treatment in Patients with Persistent Internal Carotid Artery Occlusion after Intravenous Tissue Plasminogen Activator: A Clinical Effectiveness Study. *Cerebrovasc Dis.* 2016;42(5-6):387-394.
163. Paciaroni M, Balucani C, Agnelli G, et al. Systemic thrombolysis in patients with acute ischemic stroke and Internal Carotid ARtery Occlusion: the ICARO study. *Stroke.* 2012;43(1):125-130.
164. Saqqur M, Tsivgoulis G, Molina CA, et al. Residual flow at the site of intracranial occlusion on transcranial Doppler predicts response to intravenous thrombolysis: a multi-center study. *Cerebrovasc Dis.* 2009;27(1):5-12.
165. Saqqur M, Uchino K, Demchuk AM, et al. Site of arterial occlusion identified by transcranial Doppler predicts the response to intravenous thrombolysis for stroke. *Stroke.* 2007;38(3):948-954.
166. Rubiera M, Ribo M, Delgado-Mederos R, et al. Tandem internal carotid artery/middle cerebral artery occlusion: an independent predictor of poor outcome after systemic thrombolysis. *Stroke.* 2006;37(9):2301-2305.
167. Khandelwal P, Yavagal DR, Sacco RL. Acute Ischemic Stroke Intervention. *J Am Coll Cardiol.* 2016;67(22):2631-2644.
168. Liu X. Beyond the time window of intravenous thrombolysis: standing by or by stenting? *Interv Neurol.* 2012;1(1):3-15.
169. Wolpert SM, Bruckmann H, Greenlee R, Wechsler L, Pessin MS, del Zoppo GJ. Neuroradiologic evaluation of patients with acute stroke treated with recombinant tissue plasminogen activator. The rt-PA Acute Stroke Study Group. *AJNR Am J Neuroradiol.* 1993;14(1):3-13.
170. Stroke, Cerebrovascular Accident. World Health Organization. http://www.emro.who.int/health-topics/stroke-cerebrovascular-accident/index.html. Published 2019. Accessed.
171. Demand for Neurovascular Thrombectomy Devices to Surge on Account of Growing Incidences of Acute Ischemic Stroke. BioSpace. https://www.biospace.com/article/demand-for-neurovascular-thrombectomy-devices-to-surge-on-account-of-growing-incidences-of-acute-ischemic-stroke/. Published 2019. Accessed.
172. Li YY. *Stroke Devices Medtech 360 Market Analysis US 2018.* 2018.
173. Zaidat OO, Lazzaro M, McGinley E, et al. Demand-supply of neurointerventionalists for endovascular ischemic stroke therapy. *Neurology.* 2012;79(13 Suppl 1):S35-41.
174. Fiorella D, Cloft H. Demand-supply of neurointerventionalists for endovascular ischemic stroke therapy. *Neurology.* 2013;81(3):305.
175. Gupta R, Horev A, Nguyen T, et al. Higher volume endovascular stroke centers have faster times to treatment, higher reperfusion rates and higher rates of good clinical outcomes. *J Neurointerv Surg.* 2013;5(4):294-297.
176. Avasarala J, Wesley K. Optimization of acute stroke care in the emergency department:

a call for better utilization of healthcare resources amid growing shortage of neurologists in the United States. *CNS Spectr.* 2018;23(4):248-250.
177. Sigsbee B, Bernat JL. Physician burnout: A neurologic crisis. *Neurology.* 2014;83(24):2302-2306.
178. Dall TM, Storm MV, Chakrabarti R, et al. Supply and demand analysis of the current and future US neurology workforce. *Neurology.* 2013;81(5):470-478.
179. Vanacker P, Lambrou D, Eskandari A, Mosimann PJ, Maghraoui A, Michel P. Eligibility and Predictors for Acute Revascularization Procedures in a Stroke Center. *Stroke.* 2016;47(7):1844-1849.
180. Tawil SE, Cheripelli B, Huang X, et al. How many stroke patients might be eligible for mechanical thrombectomy? *Eur Stroke J.* 2016;1(4):264-271.
181. Wahlgren N, Moreira T, Michel P, et al. Mechanical thrombectomy in acute ischemic stroke: Consensus statement by ESO-Karolinska Stroke Update 2014/2015, supported by ESO, ESMINT, ESNR and EAN. *Int J Stroke.* 2016;11(1):134-147.
182. Kuntze Soderqvist A, Andersson T, Ahmed N, Wahlgren N, Kaijser M. Thrombectomy in acute ischemic stroke: estimations of increasing demands. *J Neurointerv Surg.* 2017;9(9):830-833.
183. Wanted: More interventionalists. NeuroNews International. https://neuronewsinternational.com/wanted-more-interventionalists/. Published 2017. Accessed.
184. Urimubenshi G, Cadilhac DA, Kagwiza JN, Wu O, Langhorne P. Stroke care in Africa: A systematic review of the literature. *Int J Stroke.* 2018;13(8):797-805.
185. Al-Senani F, Salawati M, AlJohani M, Cuche M, Seguel Ravest V, Eggington S. Workforce requirements for comprehensive ischaemic stroke care in a developing country: the case of Saudi Arabia. *Hum Resour Health.* 2019;17(1):90.
186. Fujiwara K, Osanai T, Kobayashi E, et al. Accessibility to Tertiary Stroke Centers in Hokkaido, Japan: Use of Novel Metrics to Assess Acute Stroke Care Quality. *J Stroke Cerebrovasc Dis.* 2018;27(1):177-184.
187. Brinjikji W, Starke RM, Murad MH, et al. Impact of balloon guide catheter on technical and clinical outcomes: a systematic review and meta-analysis. *J Neurointerv Surg.* 2018;10(4):335-339.
188. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet.* 2016;387(10029):1723-1731.
189. Minnerup J, Wersching H, Teuber A, et al. Outcome After Thrombectomy and Intravenous Thrombolysis in Patients With Acute Ischemic Stroke: A Prospective Observational Study. *Stroke.* 2016;47(6):1584-1592.
190. Mellon L, Doyle F, Williams D, Brewer L, Hall P, Hickey A. Patient behaviour at the time of stroke onset: a cross-sectional survey of patient response to stroke symptoms. *Emerg Med J.* 2016;33(6):396-402.
191. Glober NK, Sporer KA, Guluma KZ, et al. Acute Stroke: Current Evidence-based Recommendations for Prehospital Care. *West J Emerg Med.* 2016;17(2):104-128.
192. Elizabeth K Powell HGC, Natalie P Kreitzer. Acute Stroke: From Prehospital Care to In-Hospital Management. *Journal of Emergency Medical Services.*43(5).
193. Waqas M, Vakharia K, Munich SA, et al. Initial Emergency Room Triage of Acute Ischemic Stroke. *Neurosurgery.*

2019;85(suppl_1):S38-s46.
194. Chang P, Prabhakaran S. Recent advances in the management of acute ischemic stroke. *F1000Res.* 2017;6.
195. Hasan TF, Rabinstein AA, Middlebrooks EH, et al. Diagnosis and Management of Acute Ischemic Stroke. *Mayo Clinic Proceedings.* 2018;93(4):523-538.
196. Zweifler RM. Initial Assessment and Triage of the Stroke Patient. *Prog Cardiovasc Dis.* 2017;59(6):527-533.
197. Mayo Clinic Staff. Stroke. Mayo Foundation for Medical Education and Research (MFMER). https://www.mayoclinic.org/diseases-conditions/stroke/diagnosis-treatment/drc-20350119. Accessed December 21, 2019.
198. Azzam EI, Jay-Gerin JP, Pain D. Ionizing radiation-induced metabolic oxidative stress and prolonged cell injury. *Cancer Lett.* 2012;327(1-2):48-60.
199. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/ American Stroke Association. *Stroke.* 2018;49(3):e46-e110.
200. Powers WJ, Derdeyn CP, Biller J, et al. 2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/ American Stroke Association. *Stroke.* 2015;46(10):3020-3035.
201. Saver JL, Fonarow GC, Smith EE, et al. Time to treatment with intravenous tissue plasminogen activator and outcome from acute ischemic stroke. *JAMA.* 2013;309(23):2480-2488.
202. Fanous AA, Siddiqui AH. Mechanical thrombectomy: stent retrievers vs. aspiration catheters. *Cor et vasa.* 2016;58(2):e193-203.
203. Lee W, Sitoh YY, Lim CC, Lim WE, Hui FK. The MERCI Retrieval System for the management of acute ischaemic stroke--the NNI Singapore experience. *Ann Acad Med Singapore.* 2009;38(9):749-755.
204. Alshekhlee A, Pandya DJ, English J, et al. Merci mechanical thrombectomy retriever for acute ischemic stroke therapy: literature review. *Neurology.* 2012;79(13 Suppl 1):S126-134.
205. Jeong HS, Shin JW, Kwon HJ, et al. Cost benefits of rapid recanalization using intraarterial thrombectomy. *Brain and behavior.* 2017;7(10):e00830.
206. Mu F, Hurley D, Betts KA, et al. Real-world costs of ischemic stroke by discharge status. *Current medical research and opinion.* 2017;33(2):371-378.
207. Rai AT, Crivera C, Kalsekar I, et al. Endovascular Stroke Therapy Trends From 2011 to 2017 Show Significant Improvement in Clinical and Economic Outcomes. *Stroke.* 2019;50(7):1902-1906.
208. Kunz WG, Hunink MG, Dimitriadis K, et al. Cost-effectiveness of Endovascular Therapy for Acute Ischemic Stroke: A Systematic Review of the Impact of Patient Age. *Radiology.* 2018;288(2):518-526.
209. Mittmann N, Seung SJ, Hill MD, et al. Impact of disability status on ischemic stroke costs in Canada in the first year. *Can J Neurol Sci.* 2012;39(6):793-800.
210. Xie X, Lambrinos A, Chan B, et al. Mechanical thrombectomy in patients with acute ischemic stroke: a cost-utility analysis. *CMAJ Open.* 2016;4(2):E316-325.
211. Koto PS, Hu SX, Virani K, et al. A Cost-Utility

Analysis of Endovascular Thrombectomy in a Real-World Setting. *Can J Neurol Sci*. 2019:1-11.

212. Pizzo E, Dumba M, Lobotesis K. Cost-utility analysis of mechanical thrombectomy between 6 and 24 hours in acute ischemic stroke. *Int J Stroke*. 2019:1747493019830587.

213. Ganesalingam J, Pizzo E, Morris S, Sunderland T, Ames D, Lobotesis K. Cost-Utility Analysis of Mechanical Thrombectomy Using Stent Retrievers in Acute Ischemic Stroke. *Stroke*. 2015;46(9):2591-2598.

214. Heggie R, Wu O, White P, et al. Mechanical thrombectomy in patients with acute ischemic stroke: A cost-effectiveness and value of implementation analysis. *Int J Stroke*. 2019:1747493019879656.

215. Lobotesis K, Veltkamp R, Carpenter IH, Claxton LM, Saver JL, Hodgson R. Cost-effectiveness of stent-retriever thrombectomy in combination with IV t-PA compared with IV t-PA alone for acute ischemic stroke in the UK. *J Med Econ*. 2016;19(8):785-794.

216. Achit H, Soudant M, Hosseini K, et al. Cost-Effectiveness of Thrombectomy in Patients With Acute Ischemic Stroke: The THRACE Randomized Controlled Trial. *Stroke*. 2017;48(10):2843-2847.

217. Kabore N, Marnat G, Rouanet F, et al. Cost-effectiveness analysis of mechanical thrombectomy plus tissue-type plasminogen activator compared with tissue-type plasminogen activator alone for acute ischemic stroke in France. *Rev Neurol (Paris)*. 2019;175(4):252-260.

218. Steen Carlsson K, Andsberg G, Petersson J, Norrving B. Long-term cost-effectiveness of thrombectomy for acute ischaemic stroke in real life: An analysis based on data from the Swedish Stroke Register (Riksstroke). *International journal of stroke : official journal of the International Stroke Society*. 2017;12(8):802-814.

219. Aronsson M, Persson J, Blomstrand C, Wester P, Levin LA. Cost-effectiveness of endovascular thrombectomy in patients with acute ischemic stroke. *Neurology*. 2016;86(11):1053-1059.

220. Ruggeri M, Basile M, Zini A, et al. Cost-effectiveness analysis of mechanical thrombectomy with stent retriever in the treatment of acute ischemic stroke in Italy. *J Med Econ*. 2018;21(9):902-911.

221. de Andres-Nogales F, Alvarez M, de Miquel MA, et al. Cost-effectiveness of mechanical thrombectomy using stent retriever after intravenous tissue plasminogen activator compared with intravenous tissue plasminogen activator alone in the treatment of acute ischaemic stroke due to large vessel occlusion in Spain. *Eur Stroke J*. 2017;2(3):272-284.

222. Arora N, Makino K, Tilden D, Lobotesis K, Mitchell P, Gillespie J. Cost-effectiveness of mechanical thrombectomy for acute ischemic stroke: an Australian payer perspective. *Journal of medical economics*. 2018;21(8):799-809.

223. Pan Y, Cai X, Huo X, et al. Cost-effectiveness of mechanical thrombectomy within 6 hours of acute ischaemic stroke in China. *BMJ Open*. 2018;8(2):e018951.

224. Muir KW, Ford GA, Messow CM, et al. Endovascular therapy for acute ischaemic stroke: the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) randomised, controlled trial. *J Neurol Neurosurg Psychiatry*. 2017;88(1):38-44.

225. Flynn D, Francis R, Halvorsrud K, et al. Intra-arterial mechanical thrombectomy

stent retrievers and aspiration devices in the treatment of acute ischaemic stroke: A systematic review and meta-analysis with trial sequential analysis. *Eur Stroke J.* 2017;2(4):308-318.

226. Saver JL, Jahan R, Levy EI, et al. Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. *Lancet.* 2012;380(9849):1241-1249.
227. *Mechanical thrombectomy for acute ischaemic stroke: An implementation guide for the UK*. Oxford Academic Health Science Network;2019.
228. Boudour S, Barral M, Gory B, et al. A systematic review of economic evaluations on stent-retriever thrombectomy for acute ischemic stroke. *J Neurol.* 2018;265(7):1511-1520.
229. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke.* 2019;50(12):e344-e418.
230. Adeoye O, Nystrom KV, Yavagal DR, et al. Recommendations for the Establishment of Stroke Systems of Care: A 2019 Update. *Stroke.* 2019;50(7):e187-e210.
231. Ojike N, Ravenell J, Seixas A, et al. Racial Disparity in Stroke Awareness in the US: An Analysis of the 2014 National Health Interview Survey. *J Neurol Neurophysiol.* 2016;7(2).
232. Hassan AE, Kassel DH, Adil MM, Tekle WG, Qureshi AI. Are There Disparities in Thrombolytic Treatment and Mortality in Acute Ischemic Stroke in the Hispanic Population Living in Border States versus Nonborder States? *J Vasc Interv Neurol.* 2016;9(2):1-4.
233. Ekundayo OJ, Saver JL, Fonarow GC, et al. Patterns of emergency medical services use and its association with timely stroke treatment: findings from Get With the Guidelines-Stroke. *Circ Cardiovasc Qual Outcomes.* 2013;6(3):262-269.
234. Crocco TJ, Grotta JC, Jauch EC, et al. EMS management of acute stroke--prehospital triage (resource document to NAEMSP position statement). *Prehosp Emerg Care.* 2007;11(3):313-317.
235. Berglund A, Svensson L, Wahlgren N, von Euler M, collaborators H. Face Arm Speech Time Test use in the prehospital setting, better in the ambulance than in the emergency medical communication center. *Cerebrovasc Dis.* 2014;37(3):212-216.
236. De Luca A, Giorgi Rossi P, Villa GF, Stroke group Italian Society pre hospital emergency S. The use of Cincinnati Prehospital Stroke Scale during telephone dispatch interview increases the accuracy in identifying stroke and transient ischemic attack symptoms. *BMC Health Serv Res.* 2013;13:513.
237. Bray JE, Martin J, Cooper G, Barger B, Bernard S, Bladin C. Paramedic identification of stroke: community validation of the melbourne ambulance stroke screen. *Cerebrovasc Dis.* 2005;20(1):28-33.
238. Bray JE, Martin J, Cooper G, Barger B, Bernard S, Bladin C. An interventional study to improve paramedic diagnosis of stroke. *Prehosp Emerg Care.* 2005;9(3):297-302.
239. Kidwell CS, Saver JL, Schubert GB, Eckstein M, Starkman S. Design and retrospective analysis of the Los Angeles Prehospital Stroke Screen (LAPSS). *Prehosp Emerg Care.*

1998;2(4):267-273.
240. Kidwell CS, Starkman S, Eckstein M, Weems K, Saver JL. Identifying stroke in the field. Prospective validation of the Los Angeles prehospital stroke screen (LAPSS). *Stroke.* 2000;31(1):71-76.
241. Navalkele D, Vahidy F, Kendrick S, et al. Vision, Aphasia, Neglect Assessment for Large Vessel Occlusion Stroke. *J Stroke Cerebrovasc Dis.* 2020;29(1):104478.
242. Teleb MS, Ver Hage A, Carter J, Jayaraman MV, McTaggart RA. Stroke vision, aphasia, neglect (VAN) assessment-a novel emergent large vessel occlusion screening tool: pilot study and comparison with current clinical severity indices. *J Neurointerv Surg.* 2017;9(2):122-126.
243. Ver Hage A, Teleb M, Smith E. An Emergent Large Vessel Occlusion Screening Protocol for Acute Stroke: A Quality Improvement Initiative. *J Neurosci Nurs.* 2018;50(2):68-73.
244. Lin CB, Peterson ED, Smith EE, et al. Emergency medical service hospital prenotification is associated with improved evaluation and treatment of acute ischemic stroke. *Circ Cardiovasc Qual Outcomes.* 2012;5(4):514-522.
245. Lavine SD, Cockroft K, Hoh B, et al. Training Guidelines for Endovascular Ischemic Stroke Intervention: An International Multi-Society Consensus Document. *AJNR Am J Neuroradiol.* 2016;37(4):E31-34.
246. Meyers PM, Schumacher HC, Alexander MJ, et al. Performance and training standards for endovascular ischemic stroke treatment. *J Stroke Cerebrovasc Dis.* 2009;18(6):411-415.
247. Grigoryan M, Chaudhry SA, Hassan AE, Suri FK, Qureshi AI. Neurointerventional procedural volume per hospital in United States: implications for comprehensive stroke center designation. *Stroke.* 2012;43(5):1309-1314.
248. Goyal M, Jadhav AP, Bonafe A, et al. Analysis of Workflow and Time to Treatment and the Effects on Outcome in Endovascular Treatment of Acute Ischemic Stroke: Results from the SWIFT PRIME Randomized Controlled Trial. *Radiology.* 2016;279(3):888-897.
249. Tahtali D, Bohmann F, Rostek P, Wagner M, Steinmetz H, Pfeilschifter W. Setting Up a Stroke Team Algorithm and Conducting Simulation-based Training in the Emergency Department - A Practical Guide. *J Vis Exp.* 2017(119).
250. Tahtali D, Bohmann F, Kurka N, et al. Implementation of stroke teams and simulation training shortened process times in a regional stroke network-A network-wide prospective trial. *PLoS One.* 2017;12(12):e0188231.
251. English JD, Yavagal DR, Gupta R, et al. Mechanical Thrombectomy-Ready Comprehensive Stroke Center Requirements and Endovascular Stroke Systems of Care: Recommendations from the Endovascular Stroke Standards Committee of the Society of Vascular and Interventional Neurology (SVIN). *Interv Neurol.* 2016;4(3-4):138-150.
252. Boogaarts HD, van Amerongen MJ, de Vries J, et al. Caseload as a factor for outcome in aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. *J Neurosurg.* 2014;120(3):605-611.
253. Demetriades D, Martin M, Salim A, Rhee P, Brown C, Chan L. The effect of trauma center designation and trauma volume on outcome in specific severe injuries. *Ann Surg.* 2005;242(4):512-517; discussion 517-519.
254. McGrath PD, Wennberg DE, Dickens JD, Jr., et al. Relation between operator and hospital volume and outcomes following percutaneous

coronary interventions in the era of the coronary stent. *JAMA*. 2000;284(24):3139-3144.

255. Prabhakaran S, Fonarow GC, Smith EE, et al. Hospital case volume is associated with mortality in patients hospitalized with subarachnoid hemorrhage. *Neurosurgery*. 2014;75(5):500-508.
256. Kollikowski AM, Amaya F, Stoll G, Mullges W, Schuhmann MK, Pham M. Impact of landmark endovascular stroke trials on logistical performance measures: a before-and-after evaluation of real-world data from a regional stroke system of care. *J Neurointerv Surg*. 2019;11(6):563-568.
257. McTaggart RA, Moldovan K, Oliver LA, et al. Door-in-Door-Out Time at Primary Stroke Centers May Predict Outcome for Emergent Large Vessel Occlusion Patients. *Stroke*. 2018;49(12):2969-2974.
258. Ng FC, Low E, Andrew E, et al. Deconstruction of Interhospital Transfer Workflow in Large Vessel Occlusion: Real-World Data in the Thrombectomy Era. *Stroke*. 2017;48(7):1976-1979.
259. Choi PMC, Tsoi AH, Pope AL, et al. Door-in-Door-Out Time of 60 Minutes for Stroke With Emergent Large Vessel Occlusion at a Primary Stroke Center. *Stroke*. 2019;50(10):2829-2834.
260. Venema E, Lingsma HF, Chalos V, et al. Personalized Prehospital Triage in Acute Ischemic Stroke. *Stroke*. 2019;50(2):313-320.
261. Mokin M, Gupta R, Guerrero WR, Rose DZ, Burgin WS, Sivakanthan S. ASPECTS decay during inter-facility transfer in patients with large vessel occlusion strokes. *J Neurointerv Surg*. 2017;9(5):442-444.
262. Froehler MT, Saver JL, Zaidat OO, et al. Interhospital Transfer Before Thrombectomy Is Associated With Delayed Treatment and Worse Outcome in the STRATIS Registry (Systematic Evaluation of Patients Treated With Neurothrombectomy Devices for Acute Ischemic Stroke). *Circulation*. 2017;136(24):2311-2321.
263. Venema E, Groot AE, Lingsma HF, et al. Effect of Interhospital Transfer on Endovascular Treatment for Acute Ischemic Stroke. *Stroke*. 2019;50(4):923-930.
264. Jayaraman MV, Hemendinger ML, Baird GL, et al. Field triage for endovascular stroke therapy: a population-based comparison. *J Neurointerv Surg*. 2019.
265. Seker F, Bonekamp S, Rode S, Hyrenbach S, Bendszus M, Mohlenbruch MA. Direct Admission vs. Secondary Transfer to a Comprehensive Stroke Center for Thrombectomy : Retrospective Analysis of a Regional Stroke Registry with 2797 Patients. *Clin Neuroradiol*. 2019.
266. Grotta JC. Interhospital Transfer of Stroke Patients for Endovascular Treatment. *Circulation*. 2019;139(13):1578-1580.
267. George BP, Pieters TA, Zammit CG, Kelly AG, Sheth KN, Bhalla T. Trends in Interhospital Transfers and Mechanical Thrombectomy for United States Acute Ischemic Stroke Inpatients. *J Stroke Cerebrovasc Dis*. 2019;28(4):980-987.
268. Sablot D, Dumitrana A, Leibinger F, et al. Futile inter-hospital transfer for mechanical thrombectomy in a semi-rural context: analysis of a 6-year prospective registry. *J Neurointerv Surg*. 2019;11(6):539-544.
269. Morey JR, Dangayach NS, Shoirah H, et al. Major Causes for Not Performing Endovascular Therapy Following Inter-Hospital Transfer in a Complex Urban Setting. *Cerebrovasc Dis*. 2019:1-6.
270. Asif KS, Lazzaro MA, Zaidat O. Identifying delays to mechanical thrombectomy for acute

stroke: onset to door and door to clot times. *J Neurointerv Surg*. 2014;6(7):505-510.
271. Al Kasab S, Almallouhi E, Harvey J, et al. Door in door out and transportation times in 2 telestroke networks. *Neurol Clin Pract*. 2019;9(1):41-47.
272. Sablot D, Farouil G, Laverdure A, Arquizan C, Bonafe A. Shortening time to reperfusion after transfer from a primary to a comprehensive stroke center. *Neurol Clin Pract*. 2019;9(5):417-423.
273. McTaggart RA, Yaghi S, Baird G, Haas RA, Jayaraman MV. Decreasing procedure times with a standardized approach to ELVO cases. *J Neurointerv Surg*. 2017;9(1):2-5.
274. Wei D, Oxley TJ, Nistal DA, et al. Mobile Interventional Stroke Teams Lead to Faster Treatment Times for Thrombectomy in Large Vessel Occlusion. *Stroke*. 2017;48(12):3295-3300.
275. Leira EC, Stilley JD, Schnell T, Audebert HJ, Adams HP, Jr. Helicopter transportation in the era of thrombectomy: The next frontier for acute stroke treatment and research. *Eur Stroke J*. 2016;1(3):171-179.
276. Vaughan Sarrazin M, Limaye K, Samaniego EA, et al. Disparities in Inter-hospital Helicopter Transportation for Hispanics by Geographic Region: A Threat to Fairness in the Era of Thrombectomy. *J Stroke Cerebrovasc Dis*. 2019;28(3):550-556.

About the authors

SVIN: Society of Vascular and Interventional Neurology

This white paper is authored by leading Vascular and interventional Neurologists who are a part SVIN which represents the advancement of interventional radiology with the goal of improving clinical care and patient outcomes with stroke and cerebrovascular diseases. In 2016, SVIN launched Mission Thrombectomy 2020, an initiative to drive global efforts to improve stroke care by increasing the annual rate of thrombectomy procedures from 100,000 to 202,000 by 2020, leading to a worldwide decrease in stroke-related disability and potentially saving millions of lives. To carry out this mission, SVIN is partnering with government agencies, medical non-profits, and industry leaders to improve public awareness and establish financial initiatives for supporting the development of comprehensive stroke centers.

Appendix

A. Literature review and detailed scientific evidence for mechanical thrombectomy for acute stroke

1. What is a stroke?

According to the American Stroke Association (ASA), a stroke occurs when a blood vessel to the brain is either blocked by a blood clot or ruptures, causing a lack of oxygen and nutrients to a portion of the brain. Acute Ischemic Stroke (AIS) occurs when the blood flow is suddenly slowed or immediately cut off from the brain due to a blockage in an artery leading to the brain.[34] The blockage is typically caused by the clotting of a vessel narrowed by fatty buildup or a clot from elsewhere in the body that travels to and lodges in the brain. Permanent brain damage is possible after only a few minutes of oxygen deprivation.[34] Oxygen deprivation rapidly kills brain cells, causing notable physical symptoms like sudden onset of numbness or weakness in the face, arm, or leg on one side of the body, confusion, difficulty seeing, impaired walking, and severe headache. Rarer, non-traditional symptoms include pain in the face, arm, or leg on one side of the body, lightheadedness, change in mental state or consciousness, headache, general neurological symptoms (nausea, hiccups, non-focal weakness), and non-neurological symptoms (chest pain, palpitations, shortness of breath).[41,35]

Studies have shown that women are more likely to report non-traditional symptoms of stroke,[35] resulting in 30% lower odds of receiving intravenous thrombolysis than men,[36] and some other studies have reported greater out-of- and in-hospital delays in women with stroke.[37-46] Additionally, stroke used to be considered a disease of the aging population with most cases occurring in those older than 65 years of age[29,30] and incidence doubling for each decade after the age of 55;[47,48] however, the prevalence of stroke in young and middle-aged adults is on the rise due to an increase in obesity and diabetes mellitus.[49] As a result, the growing and aging populations are expected to experience increased stroke prevalence rates worldwide.[50,51]

2. What is LVO in Acute Ischemic Stroke (AIS)?

Large vessel occlusion (LVO), is a blockage of one of the four major arteries in the brain and neck.[52-59] While LVOs represent approximately one-third of the total AIS population, they correlate with significantly higher post-stroke dependence or death at three months and mortality rates [58,60,61] due to their larger infarct size[62,63] and more severe presenting deficits than other stroke subtypes.[64,65]

LVOs can develop through four mechanisms - occlusion at the primary arterial site secondary to the development of atherosclerosis of an intracranial artery, extra-cranial artery atherosclerotic embolism or plaque rupture that results in the occlusion of an intracranial vessel, cardio-embolic events related to cardiac disease such as atrial fibrillation resulting in intracranial vessel occlusion, and cryptogenic causes of vessel occlusion.[66] LVOs often result in insufficient blood flow to brain tissue, causing damage to cells and inflammation that culminate in the death of neurons, glia, and endothelial cells.[60] Although ischemic changes occur within minutes, the ultimate volume of infarcted tissue is determined by the degree and length of hypoperfusion,[67] with the level of collateral flow to an ischemic area playing a large role in stroke progression.

3. What are the treatment options?

Treatment for a patient with suspected AIS follows neuro-imaging to exclude intracranial hemorrhage after which thrombolytic agents and endovascular device therapies are considered, and general supportive care is administered. During the management, acute medical or neurologic complications of stroke are anticipated and monitored. Finally, the most likely cause for the stroke is evaluated, and treatment is directed towards preventing recurrent ischemic events.

Depending on the capabilities of the stroke center, any of the following treatment methods are considered

Intravenous Thrombolysis with clot dissolving agents (Intravenous t-PA)

Intravenous thrombolysis (IVT) or the use of clot dissolving agents (administration of alteplase or tissue Plasminogen Activator, tPA) is the only US Food and Drug Administration (FDA)-approved medical therapy for the treatment of patients with AIS, and its use is associated with improved patient outcomes. Although some studies have suggested that genetic differences, race, and sex may influence the efficacy of tPA, only certain comorbidities such as hypertension (raised blood pressures) and hyperglycemia (elevated blood sugar levels) have been found to significantly and negatively impact thrombolytic response in AIS patients.[70-74]

Mechanical Thrombectomy

MT is used to remove LVOs and reverse neurological deficits.
During the mechanical thrombectomy:
- A catheter is threaded into an artery in the groin and up through the neck, until it reaches the blood clot causing the stroke
- Using x-ray guided imaging, a stent retriever is inserted into the catheter
- The stent reaches past the clot, expands to stretch the walls of the artery so blood can flow, and is "retrieved" – or pulled backwards – which removes the clot.

Mechanical Thrombectomy Combined with Intravenous t-PA

IVT with tPA significantly improves the odds of a good outcome after AIS when delivered within 4.5 hours of stroke onset, irrespective of age and over a broad range of stroke severity, and despite an increased risk of intracranial hemorrhage (ICH). Therefore, in the absence of contraindications, IVT is the standard therapy for all patients presenting with an AIS within 4.5 hours after symptom onset.[75] However, IVT has some important limitations, such as a narrow time window with a rapidly decreasing efficacy and a rapidly increasing number of AIS cases that need treatment[75] , the overall increase of fatal ICH compared with placebo,[75] a poor recanalization rate in patients with large thrombus burden,[76] and various contraindications, such as pre-treatment with oral anticoagulants and unclear time of symptom onset.

Mechanical thrombectomy (MT) in combination with IVT (i.e. bridging thrombolysis) has the potential to overcome some limitations of IVT, especially the poor recanalization rate of patients with large vessel occlusions (LVOs).[75]

Since December 2014, 8 Randomized Controlled Trial's (RCT's) testing newer devices have consistently shown that MT in addition to best medical treatment (with and without IV tPA) improves outcome in anterior circulation (AC) ischemic stroke patients with LVO, as compared to the best medical treatment alone.[10]

4. Mechanical Thrombectomy: A new standard of care

There is great difficulty in treating stroke due to its acute, time-dependent nature. For each minute a stroke is not treated, 2 million neurons, 14 billion synapses, and 12 km (7.5 miles) of myelinated fibers are destroyed. Collectively, these neurological changes age the brain by 3.6 years per hour, making it vital for a patient to receive rapid treatment.[6]

The time window for effective thrombolysis is brief since it must be given to most patients within 4.5 hours,[77] and the outcome depends on the length of time between the onset of symptoms

Aspiration catheters are flexible with a large inner diameter. A guide wire is inserted into the patient, followed by a small access catheter that is used to guide the aspiration catheter toward the clot. When the clot is reached, it is broken into smaller pieces that are aspirated through the catheter using a pump or manual suction.[154]

Combined interventions, using both suction embolectomy with large bore catheters and mechanical retrieval using stent retrievers, have shown promise in recent studies.[81] In this technique, aspiration of the clot, a cheaper alternative, is attempted first using a large bore microcatheter. If the aspiration fails, mechanical retrieval is attempted by inserting the stent retrievers via the aspiration catheter. Using this sequential combination, phenomenal recanalization rates of up to 95% have been achieved,[81] compared with stand-alone direct aspiration rates of 78%. This narrow time window of 4.5 h along with the multitude of contraindications, prevent many patients from receiving treatment with only less than 3% of patients presenting with AIS receive IV-rtPA.[9]

and recanalization, as well as recanalization success.[78,79] Numerous randomized trials have demonstrated that MT accelerates recanalization, improves patient outcomes, and expands the treatment time window compared to thrombolysis.[9,11,12,15,16,18,26,32]

MT involves a minimally invasive surgical procedure using a microcatheter and other thrombectomy devices to mechanically trap and remove the blood clot from an occluded artery.

MT devices can be classified into different subtypes based on their mechanism of action:
(a) coil retriever
(b) aspiration
(c) stent-retriever
(d)mechanical clot disruption, using laser or ultrasound.

Retrievers and aspiration techniques are the most widely performed. Stent retrievers are made of an expanding wire mesh tube intended to remove the clot in one piece. The retriever is placed using a delivery catheter, and once in place, the mesh expands, trapping the clot, and then is withdrawn into the catheter and removed from the patient.[80]

5. Incidence of Stroke and LVO: A global perspective

Stroke Demographics

Stroke is currently the second leading cause of death and a major cause of disability worldwide.[51,82] In 2016, the global prevalence of ischemic stroke was 67.6 million and that of hemorrhagic stroke was 15.3 million.[83] The highest prevalence rates of ischemic stroke are found among countries in Eastern Europe, Central Asia, and East Asia.[83] In 2010, the global incident of ischemic stroke was estimated to be 11.6 million; 63% of ischemic strokes and 80% of hemorrhagic strokes occurred in low- and middle-income countries in that same year.[84]

In 2016, there were 5.5 million deaths attributable to cerebrovascular disease worldwide. While the number of deaths increased by 28.2% between 1990 and 2016, the age-standardized death rate decreased by 36.2%;[84] however, a more recent report suggests the prior decline in stroke death rates have not continued in recent years in the United States.[85] Countries in Eastern Europe and central East Asia have among the highest mortality rates attributable to ischemic stroke.[84] In 2010, an estimated 39.4 million disability-adjusted life years (DALY) were lost because of ischemic stroke.[84] In that same year, the mean age of stroke related death in high income countries was 80.4 years compared with 72.1 years in low- and middle-income countries.[86]

Stroke is associated with several modifiable and non-modifiable risk factors. Age, sex, race, and ethnicity are non-modifiable risk factors for stroke, while hypertension, diabetes, atrial fibrillation, obesity, carotid or other artery disease, smoking, diet, physical inactivity, hyperlipidemia, waist-to-hip ratio, psychosocial factors, cardiac causes, and alcohol consumption are considered modifiable risk factors.[87-91] Globally, these factors account for nearly 90% of the modifiable risks for strokes.[88] It is estimated that 50% of strokes are preventable through control of the top five most relevant modifiable risk factors (hypertension, hypercholesterolemia, atrial fibrillation, smoking and overweight);[92] thus, the international community of leaders in the field have prioritized stroke prevention.[93]

Of the modifiable risk factors for stroke, hypertension is the most prevalent in developed and developing countries,[94] and is the single most important risk factor for stroke. In a recent meta-analysis, nine trials showed that blood pressure (BP) control to <150/90 mmHg reduces stroke, and six trials demonstrated that lower targets (≤140/85 mmHg) are associated with significant decreases in stroke.[95-97] Another meta-analysis of clinical trials demonstrated that antihypertensive therapy was associated with an average decline of 41% in stroke incidence with systolic BP reductions of 10 mmHg or diastolic BP reductions of 5 mmHg.[98] A recent special report identified the positive global implications of hypertension treatment on stroke risk reduction around the world.[99]

As determined by a multi-nation, meta-analysis, diabetes is an established independent risk factor for stroke with one-third of all stroke patients having diabetes.[100] The effect of diabetes is more prominent in women than men.[101,102] Additionally, diabetic adults have a two-fold excess risk for stroke[103] and stroke accounts for nearly 20% of deaths in this patient population.[104,105] Duration of diabetes is also associated with an increased ischemic stroke risk,[104] where the prevalence of diabetes in ischemic stroke is 33%.[100] Interestingly, diabetic ischemic stroke patients tend to be younger (before age 55 in African Americans and age 65 in whites), more likely to be African American, and more likely to have at least one comorbidity, such as hypertension, hypercholesteremia, and myocardial infarction when compared to nondiabetic patients.[106]

Stroke used to be considered a disease of the aging population with most strokes occurring in those older than 65 years of age[29,30] and the incidence doubling for each decade after the age of 55.[47] In the US, incidence of strokes in adults between the ages of 35 and 44 is 30-120/100,000 per year, and 670-970/100,000 per year in those aged between 65 and 74.[107,108] Increased age is also associated with higher rates of mortality and decreased quality of life when compared to younger stroke patients.[109-114] However, over the last few decades, the incidence of stroke in people younger than 65 years has increased worldwide by 25%,[115] especially in low- and middle-income countries, such as Russia, China, and India. This shift in stroke burden is suspected to be a result of the rising epidemic of cardiovascular risk in younger age groups.[51,116-121] Gender is also known to affect incidence and outcomes of stroke. Overall, women have a higher prevalence of stroke because they have a longer average life expectancy than men; however, men have a higher stroke incidence throughout most of their life (these data trends were not specific to a geographical region).[36,96,122-125]

According to the Global Burden of Disease (GBD) Study 2016 Lifetime Risk of Stroke Collaborators, the global lifetime risk of stroke in 2016 was estimated to be nearly 25% for those aged 25 years or older with a nearly equal occurrence in males and females.[126] Risk of ischemic stroke was higher than hemorrhagic stroke. Additionally, lifetime risk was found to vary according to Socio-demographic Index (SDI) and GBD region. Highest and lowest stroke risks were associated with high-middle-SDI and low-SDI, respectively; however, the observed low risk of stroke is attributed to a high occurrence of a multitude of mortality causes and not necessarily a decreased risk of stroke.[49,126,127] Global comparisons reveal the highest estimated lifetime risks to be found in East Asia, Central Europe, and Eastern Europe and the lowest risk in eastern sub-Saharan Africa.[126] These estimates were determined using estimates of stroke incidence and competing risks of death from any other cause besides stroke. In general, low-SDI countries with young populations, such as sub-Saharan African, had lower estimated lifetime stroke risk due to a high risk of death from all other causes; therefore, the decreased risk may not indicate a lower stroke incidence in these countries.[126]

6. Incidence of LVOs – Across Demographics

The incidence rate of LVO is estimated at 24 per 100,000 person-years in the US population,[47,56] with AIS cases estimated at 800,000 per year.[3,47] In the US, approximately 80,000 of AIS cases are due to large vessel occlusions (LVO).[47] Approximately half of all stroke related deaths are attributable to ischemic stroke.[5] Ischemic stroke due to LVO has been reported in 11- 46% of cases.[47,53,55,114-116] Occlusion of large intracranial vessels, such as internal carotid artery (ICA) terminus, middle cerebral artery (MCA), and basilar artery (BA), is considered severe and is associated with high rates of mortality and morbidity.

According to a 10-year systematic review (2019) carried out by Lakomkin et al on prevalence of LVO in patients AIS, despite institutional variability in definitions and reporting methodology limiting, the precision of estimates, the prevalence of LVO among patients with AIS is greater than previously thought.[87] The prevalence of LVO among patients with AIS ranged from 7.3% to 60.6% among the identified studies. Of the 17 groups of patients (Vanacker et al described both a derivation and validation cohort of AIS patients),[57] the mean prevalence of LVO exceeded was 31.1% across all studies, and 29.3% when weighted by the number of patients included in each study.[87]

United States

In the United States, with an annual incidence of approximately 800,000, stroke is the fifth leading cause of death, resulting in more than 146,000 deaths (1 in 19) per year and is a major cause of serious disability, leaving many with long-term disability and rendering them unable to work.[117] The prevalence of stroke within the US is 2.7% for those 20 years or older (7.2 million total), which increases with age. Prevalence rates for those over 60 and 80 years of age are 6% and 13%, respectively.[117] Considering all stroke types, AIS account for nearly

87%.[43]

Ischemic strokes due to LVO, where the occlusions of the MCA, ICA terminus, and BA, the annual incidence has been estimated at 24/100,000 people per year, equaling nearly 80,000 LVOs annually.[47] Several recent randomized control trials investigated patients with anterior LVOs (including ICA).[10,14,15,26] The mean patient age ranged between 65 and 70 years of age with no consistent differences of sex. Taken together, these studies found smoking, diabetes mellitus, atrial fibrillation, and hypertension to be significantly correlated with LVO.[10,14,15,26]

China

At 22.45%, stroke is the leading cause of death in China, of which 65% are AIS.[118] Additionally, 35-40% of all AIS result from proximal large vessel atherosclerotic stenosis or occlusion.[116] A recent Chinese population-based study from 6,809 AIS patients in the main emergency healthcare revealed LVO patients were older (mean of 80.5 years vs. 71.4 years), had a higher 30-day mortality rate (31.1% vs. 4.6%), and longer mean hospital stay (mean 38.6 vs. 21.1 days) than non-LVO AIS patients.[119]

Japan

In 2017, stroke was the third leading cause of death in Japan,[120] with an age- and sex-adjusted stroke incidence of 142.9/100,000 person-years (determined using the 2013 European Standard Population; 95% CI 123.3–168.5). The incidence of ischemic stroke was 91.3/100,000 person-years.[121]

Middle Eastern Region: Saudi Arabia

The transformation of social, economic, and environmental conditions in the Middle East Region has led to drastic lifestyle changes, leading to a high burden of stroke.[122] A recent systematic review included 64 stroke-related articles in the Middle East between 1980 to May 2015.[122] Stroke incidence and prevalence ranged between 22.7 and 250 per 100,000 population per year and 508 and 777 per 100,000 population, respectively. Strokes were more common in males than females and a mean age occurring in the sixth and seventh life decade. Ischemic stroke was the prevalent type of stroke, while hypertension and diabetes were the most common stroke associated risk factors.[122]

Prevalence of stroke in Saudi Arabia is estimated at 0.67%.[123] In 1998, the first stroke incidence was reported at 29.8/100,000 person-years;[124] however, considering current demographics, incidence is estimated to have increased to 50.9/100,000.[125] A recent study examined stroke incidence in the Aseer Region, South-western Saudi Arabia and include 1249 first-time stroke patients admitted to an Aseer hospital between 1 January 2016 till 31 December 2016.[126] From the patient population, an incidence rate of 57.64/100,000 persons per year was determined, which is similar to the estimated value; however, incidence rate increased with age and reached 851.81/100,000 persons aged 70 years and older. Stroke was found to be more common in males.[126] The standard of care for stroke patients in Saudi Arabia lags behind other developed countries and, as a result, nearly 95% of patients receive treatment at non-specialized stroke centers and are only treated with non-reperfusion therapy regardless of stroke type, even LVOs.[127]

India

India has transgressed through significant demographic, economic, and epidemiological changes,[128] resulting in increased life expectancy and a growing aging population.[129,130] This is further indicated by a 42% decrease in stroke incidence (163/100,000 person-years in 1970-1979 to 94/100,000 person-years in 2000-2008) in India's high-income regions.[131] A 2014 retrospective study analyzed patient outcomes for endovascular treatment of AIS with LVO in an Indian tertiary care center.[132] All patients had contraindications to or failed intravenous thrombolysis prior to endovascular treatment. 45 patients were included with a mean age of 49±14 years and 71% (32/45) were male. At 90-day follow-up, 64% of patients had good outcomes, while 36% had poor outcomes including 18% deaths.[132]

Denmark

A recent retrospective study analyzed national data from the Danish Stroke Registry from 2011 to 2017 for all acute endovascular reperfusion treatment procedures in AIS patients with LVO.[133] 1,720 patients were included with a median age of 70 years and 58% were male. The number of stroke-LVO patients markedly increased from 128 in 2011 to 409 in 2017. At 3 months, 45% of patients had good outcomes, while 43% had poor outcomes. Overall, 1-year mortality was 22% and the survival rate increased considerable from 96 in 2011 to 994 in 2016.[133]

7. Gaps in the management of LVO

An overwhelming number of studies and clinical trials confirm the efficacy of thrombolytic therapy, in a given therapeutic window, in improving the clinical outcome and recovery of AIS patients.[79,151-154] The primary therapeutic goal for patients with AIS is the timely restoration of blood flow to salvageable ischemic brain tissue that is not already infarcted.[155] Reperfusion therapy using thrombolysis[156], including IV t-PA and endovascular interventions such as MT, are the only approved treatments for AIS. Both these treatment options have limitations when used as monotherapies. The only pharmaceutical agent approved for the treatment of AIS is IV-rtPA (Recombinant t-PA); however, it is not effective in patients with AIS due to LVO, where the clot burden is very high. This significantly limits the options for effective management of LVO.

In such patients, MT has proven more effective. Currently, the primary criterion for candidate selection in reperfusion is the time from stroke symptom onset. Reperfusion therapy must be administered within a narrow time window of up to 4.5 h after symptom onset for IV-tPA, and up to 6-8 h for MT. The restriction on IV-tPA treatment beyond 4.5 h disqualifies the majority of stroke patients admitted beyond this time-window eligible population.[157-160] (around 85%), thereby drastically limiting the eligible population.[157-160]

Other limitations of IV-rtPA are:

(a) Increased rate of mortality and intracranial bleeding in internal carotid artery occlusion (ICA)[156,161-163] or other disabling strokes, such as those with no detectable residual flow signals,[164-166]

(b) Low recanalization rate ranging from 13 to 50% in LVO, such as the proximal middle cerebral artery (MCA), the ICA, or the basilar artery[167] and

(c) Unresponsiveness to large thrombi (especially when the thrombus length exceeds 8 mm or location is proximal, such as terminal carotid artery occlusion[165]

One study found only 10 and 25% of ICA and proximal MCA occlusions are recanalizable by IV-rtPA.[168] Incomplete recanalization is often observed in patients treated with IV-rtPA. For instance, 70% of patients who received IV-rtPA were found to have angiographically confirmed residual thrombus requiring complimentary intra-arterial treatment such as clot angioplasty.[169]

In addition to limitations, there are several contraindications applicable to the use of intravenous rtPA in acute ischemic stroke (AIS)[167]

These limitations and contraindications significantly limit the treatment options for stroke patients, in particular, the majority of those with LVO. Considering that constraints of intravenous tPA administration resulted in its use in less than 3% of stroke patients, the expansion of stroke treatment lies not in the realm of systemic thrombolytics, but rather in the purview of the endovascular intervention such as MT.

8. Shortage of neurointerventionalists

Neurointerventionalists are a subspecialty of neuroradiology, in which minimally invasive therapy can be effected by advancing various devices within a blood vessel to a point of a previously identified lesion. An estimated yearly total of thrombectomy procedures is 3 per 100,000 people in the US, with 10,000 annual thrombectomies.[47,56] Thus, the number of procedures falls considerably below the LVO incidence, suggesting a need for future utilization and capacity of thrombectomy.

The World Health Organization estimates that 5 million people die every year due to stroke.[134] As the aging population grows, these numbers are expected to increase. The growing prevalence of LVO strokes is projected to increase the demand for neurothrombectomy devices, neurointerventionalists, thrombectomy procedures, thrombectomy-capable hospitals.[135]

Currently, there are over 200 comprehensive stroke centers in the US.[136] The market for stroke care in the US is growing rapidly, primarily due to the expansion of AIS device market, which is expected to double by 2026.[136] US stroke intervention model is moving toward specialized high-volume stroke facilities, and encourages bypassing patients to these comprehensive thrombectomy capable centers in order to initiate treatment in a more timely manner. The accreditation process is time consuming and costly, which limits the growth of these centers, and rural/sparsely populated areas continue to be underserved as the costs to establish new facilities is often not justified in areas of insufficient population. However, because AIS devices and thrombectomy procedures are fully reimbursed in the US, stroke treatment volumes are expected to increase considerably over the next decade.

A 2012 study by Zaidat et al estimated the annual demand of AIS patients meeting the criteria for MT and the supply of trained neurointerventionalists.[137] The number of neurointerventionalists was estimated at approximately 800, practicing within a 50-mile radius of major metropolitan areas, covering more than 95% of the US population. Approximately 40 neurointerventionalist fellows graduate yearly from US training programs. The number of neurointerventionalists 10 years from the study was estimated at 1,200. The number of MT cases per year is estimated at 22-81 per year for each neurointerventionalist. The study concluded that the current and projected number of neurointerventionalists adequately supplies the future need even as the number of AIS cases requiring MT increases.

This finding has been corroborated by other experts in the field. A letter by David Fiorella and Harry Cloft in response to Zaidat's article claims that new graduates will continue to overpopulate areas already adequately covered by neurointerventional services.[138] Excess growth in the number of neurointerventionalists decentralizes care and reduces volume at centers of excellence, and as a result, care could worsen as volume reduces per neurointerventionalist. Volume criteria area are recommended by professional societies, as patient outcomes are shown to be better with increased case volumes and operator experience.[139]

However, the overabundance of neurointerventionalists has been contested by other studies. Avasarala and Wesley discussed the burden neurointerventionalists bear in the ever-changing stroke care system, based on the results of an observational email survey.[140] Neurologists have to be at the stroke patient's bedside within 15 minutes of arrival. Additionally, physician burnout is escalating based on data from national surveys, with some studies calling it a crisis.[141] Studies have estimated a neurologist shortfall of 19% by 2025.[142]

Europe

Across Europe, the need for neurointerventionalists varies considerably between countries. Countries like Germany have an adequate number of neurointerventionalists capable of providing thrombectomy procedures, while others do not. A presentation by Urs Fischer (University of Bern, Switzerland), at the European Society for Minimally Invasive Neurological Therapy (ESMINT) annual meeting in 2017 (Nice, France) estimated the eligibility of patients for MT in Europe at 20% based on the studies below.

A study from Switzerland showed that 10.5% of stroke patients coming to a comprehensive stroke center within 6 hours of symptoms onset are eligible for MT based on AHA/ASA guideline-based eligibility.[143]

In Glasgow, roughly 15% of patients present within the first 6 hours might be eligible for MT based on real-world data.[144] The study found that clinical trial eligibility criteria are much more strict; around 1% of patients from this study fulfilled criteria for all recent trials. A study from a Swedish hospital estimated the future need for thrombectomy. New treatment recommendations by European professional organizations were published in 2016,[145] with less stringent criteria for MT compared to previous guidelines. The authors estimated that the number of potential thrombectomies would have been 5 times higher if the recommendations were released in 2013.[146]

Thus, out of the 1.3 million acute stroke patients across Europe, it is estimated that 130,000-230,000 patients per year might be candidates for endovascular therapy.[147]

Africa

A systematic review of stroke care in Africa highlights limited available data, and identified gaps in the availability of stroke care in Africa, which frequently falls below the recommended standards with variations across countries and settings.[148] Publications were available from only 14/54 (25.9%) of African countries. Areas with the most common shortages included medical transportation, CT/MRI imaging technology, stroke units, medications/thrombolysis, rehabilitation services, and health care personnel. Urimubenshi et al concluded that policy makers and health care professionals in Africa need to combine efforts and improve stroke care, ensure access, and organize stroke care as much as possible.

Middle East

A recent Saudi Arabian study by Al-Senani et al published in 2019 found that the current availability of staff and stroke services are inadequate to keep up with the projected increase in stroke cases, particularly in the area of acute and rehabilitation services.[149] The authors concluded that the re-organization of existing staff and services is needed, along with significant investment in new staff across several disciplines in order to meet these needs. The total cost of additional staff over a 10-year period was estimated at approximately US$230,000,000.

Asia

In Japan, the availability of stroke specialists is similar to that of the US. Accessibility varied by region, with rural areas with low populations having the lowest accessibility.[150] Up to 17.5% of elderly individuals lived 60 minutes or more from a treatment facility. Furthermore, the distribution of stroke specialists did not match the number of hospital beds and medical doctors.

9. Protocol for implementation of MT

Stroke systems of care allow for the coordination and integration of an entire stroke care continuum, which includes community education, prevention, emergency medical services, comprehensive stroke centers equipped with a stroke care unit, interventional specialists, capability of performing thrombolysis and MT, and collaboration with rehabilitation facilities and services. Globally, increased access to highly developed stroke systems has the potential to save nearly two million[28] lives per year[28], but is dependent upon patient access.[187] Increasing access to comprehensive stroke systems is one of the main acute public health concerns of the decade due to the aging and rapidly growing prevalence of vascular diseases.

MT added to thrombolysis more than doubles the odds of achieving a good neurological (modified Rankin Scale score (mRS) 0-2) outcome in patients with AIS due to LVO.[188] In a meta-analysis of five major clinical trials assessing the safety and efficacy of MT compared to thrombolysis alone, 46% of patients treated with MT had an mRS score of 0-2 at 90 days compared to only 26.5% of those treated with thrombolysis alone.[188] Additionally, 26.9% patients reach major neurological recovery (mRS 0-1) with MT, compared to only 12.9% of patients treated with thrombolysis alone.[188] Furthermore, in a prospective, observational study designed to determine the safety and efficacy of MT compared to thrombolysis alone found 90.4% (458/504) of patients treated with MT alone and 92.4% (557/603) of patients with a combination of MT and thrombolysis achieved partial or complete revascularization.[189] This is a drastic improvement over treatment with thrombolysis alone, where only 60.0% (926/1543) of patients achieve significant revascularization.[189] In fact, for every 100 patients treated with MT, 38 will experience less stroke related-disability than those treated with thrombolysis, and 58 will achieve neurological recovery and functional independence.[188]

The treatment of a stroke is a complex, multi-step process that requires timeliness and efficiency in order to increase the likelihood of a good prognosis. When developing efficient stroke systems, it is important to understand the experience from the patient's perspective.

10. Clinical benefits of MT

MT is considered a breakthrough in stroke treatment. Removing blood clots from the brain leads to better outcomes for stroke patients, including greater independence and mobility. Previous endovascular interventions were unable to remove clots quickly and safely enough.
In the initial trials establishing the efficacy of MT for LVOs up to 6 hours after stroke onset, patients with large infarcts were excluded in order to maximize the amount of salvageable tissue and increase the chances of procedural benefit.[14-16,18] This salvageable tissue is called penumbra, which is the region around the ischemic tissue that is at risk of progressing into infarction (tissue death) but can be prevented if reperfused. Subsequent clinical trials have utilized computed tomography, or magnetic resonance-perfusion imaging, to differentiate the ischemic penumbra, which has delayed perfusion/near normal blood flow, from the core infarct, the region most affected by stroke that has significantly decreased bloodflow.[9,26,87] These trials have demonstrated the efficacy of MT for select LVO patients with favorable penumbra/core ratios up to 24 hours from symptom onset.[9,26,87]

A remarkable transformation of stroke care has occurred over the last two decades with the development of evidence-based stroke detection, increased access to advance care, and improved emergency management of stroke.[88] Prior to 2015, stroke was treated with clot "busting" t-PA agents, which were limited by a narrow treatment window of 4.5 hours from stroke onset,[89,90] precluding many patients from receiving treatment for AIS. Since then, treatment of AIS has drastically changed with the development of new endovascular devices that are inserted into the femoral artery and navigated through the vascular system up through the neck, advancing until it reaches the clot to capture and remove it. While these tools went through several evolutions, 2015 was a landmark year - 5 randomized trials proved mechanical thrombectomy far more effective at removing clots and saving brain function than medical therapies, which subsequent studies have corroborated (MR CLEAN, EXTEND-IA, ESCAPE, SWIFT PRIME, REVASCAT, DAWN, and DEFUSE).[9,10,14-18,26] The profound benefit of MT up to 24 hours after stroke onset shown in these studies has revolutionized stroke care by transforming it from a medicine-only approach to an intensive intervention that has increased the number of patients achieving functional outcome by an average of 21.4%.[9,10,14-18,26]

These trials have led to widespread adoption, with total procedures doubling in just 3 years and expected to grow by 25% annually to reach 103,000 in 2025. The 2018 American Stroke Association guidelines recommended urgent thrombectomy for AIS.[87]

11. Economic benefits of MT

The effectiveness of stroke care is time-sensitive with increased rates of functional outcomes, recanalization, reperfusion, and mortality being associated with shorter time between stroke onset and treatment.[9,10,14-18,26] These improved outcomes are associated with decreased economic burdens. In fact, rapid treatment of AIS (≤6 hours) is accompanied by shorter hospital and rehabilitation stays, thus, lowering costs compared to those with longer time-to-treatment (>6 hours) (Table 1).[205] Therefore, combination therapy (MT and IV t-PA) leading to successful recanalization within 6 hours after stroke onset leads to markedly improved outcomes compared to longer treatment windows or no recanalization.

North America

United States

In the United States, AIS is associated with a high economic burden, especially for patients discharged with a stroke-related disability, who incur more than double the expense compared to non-disabled patients ($120,753 vs. $54,580).[206] Even though combination therapy (MT and IV t-PA) has a higher cost for initial hospitalization ($17,183) than standard therapy (clot-disrupting pharmaceutical agents), it has a lifetime savings of $23,203 per patient because of the substantial reduction in disability, plus improvements in the overall quality of life. Additionally, it is associated with lower post-stroke rehabilitation and nursing care (90-day cost) and lifetime costs, while also increasing QALY by 1.74 (Table 2).[20]

A 2019 study of 11,800 patients treated with MT found a significant decrease in length of hospital stay compared to standard care (8.7 vs. 11.7 days), increased rate of discharge-to-home (17.7% vs. 29.6%) and decreased mortality (21.6% vs. 12.8%) rates.[207] Collectively, the public and personal economic burden of AIS is decreased when MT is utilized.

A 2018 meta-analysis evaluated the cost-effectiveness of combination therapy in relation to patient age (range 50 to 100 years).[208] 50-year-old patients were found to have the greatest incremental effectiveness (2.61 QALYs) and cost-savings (health care perspective: $99,555; societal perspective: $146,385) when treated with mechanical thrombectomy. The incremental effectiveness (1.13 QALYs) and incremental costs ($19,041) of treatment in 80-year-old patients is associated with an incremental cost-effectiveness ratio (ICER) of $16,870 per quality life year gained from successful combination therapy. At a willingness-to-pay threshold of $50,000/QALY, the acceptability rate is high at 97.8%. The cost-effectiveness ratio increases to $35,802/QALY for 90-year-old patients, but the acceptability rate remains high at 81.4%, 99.1%, and 99.8% at willingness-to-pay thresholds of $50,000, $100,000, and $150,000/QALY, respectively. Therefore, in patients younger than age 79, combination stroke therapy decreases lifetime direct and indirect costs, regardless of higher procedure costs when compared to standard care alone. Patients aged 80-100 years experience the benefit of added quality-adjusted life years with only a small rise in lifetime costs.[208]

Canada

The Canadian average annual cost of AIS is $2.8 billion total, with an average per patient cost of $75,353/year.[209] Similar to data from the US, the average annual cost for patients with stroke-related disability is more than double that of non-disabled patients ($107,883 vs. $48,339).[209] Over a 5-year time horizon, LVO AIS patients treated with combination therapy experienced slightly higher total costs than standard therapy ($126,939 vs. $124,419), along with increased QALY (1.484 vs. 1.273 QALYs) with an associated ICER of $11,990/QALY. At a willingness-to-pay threshold of $50,000/QALY and $100,000/QALY, the acceptability rate is high at 89.7 and 99.6.[210] AIS treatment with combination therapy is estimated to save the Canadian healthcare system $321,334/year.[211]

Europe

United Kingdom

Combination therapy in the UK is similarly associated with higher initial hospitalization costs than standard care ($64,757.28 vs. $52,494.73); however, the incremental cost per QALY was determined to be $1,564 (£1219), $5,253 (£4096), and $3,712 (£2894) at 6, 12, and 24 hours, respectively; therefore, demonstrating this treatment is cost-effective up to 24 hours post stroke onset and should be implemented by the UK NHS.[212] Interestingly, in the UK, combination therapy is not cost-effective in the short-term (90 days) but is estimated to be cost-effective over 20 years[213] and a lifetime horizon,[214] and if fully implemented, the projected value is estimated to be £1.3 billion (US $1.7 billion) over five years.[214]

Compared to standard care, combination therapy has an incremental cost of $12,262/patient and is associated with a gain of 1.05 QALY per patient over 20 years. It also has a higher net monetary benefit compared to standard care (Table 3) and an overall savings of £33,190 (US $43,437)/patient,[215] indicating the cost-effectiveness of MT in AIS patients.[213]

France

Mirroring the US results, in France, initial hospitalization costs are $2,116 more for combination therapy than standard care; however, these patients experience a 10.9% (53% vs. 42.1%, P=0.028) increase in functional independence at 90-days post-stroke. For every one case of gained functional independence, the ICER is estimated at $19,379, which is below the willingness-to-pay threshold of $36,351 (as of 2015) with a net monetary benefit of $1,853; therefore, the benefit of combination therapy outweighs the index procedure costs.[216]

At one-year post-stroke, combination therapy patients have higher QALY scores than those treated with standard care (0.58 vs. 0.46). The estimated cost per one QALY gained is $14,880 and the estimated net monetary benefit is $2,757, indicating the cost-effectiveness of mechanical thrombectomy at one-year.[216] At 10 years post-stroke, cost effectiveness remains high at 98% with a willingness-to-pay threshold of €50,000 (US $55,797) per QALY gained.[217]

Sweden

In Sweden, MT procedures increase intervention costs (+GBP 9000 [US $11,779]) but result in substantial overall cost savings in the long run due to less reliance on home medical (home help services - GBP 13,000 [US $ 17,014]) services or nursing home care (nursing home care - GBP 26,000 [US $34,027]).[218] Additionally, combination therapy increases quality of life (0.99 QALY), life-expectancy (0.40 life years), and cost savings (US $221).[219]

Italy

From the perspective of the Italian NHS, combination therapy for LVO AIS is cost-effective between years one and three post-stroke and cost savings from year four onwards. At one-year, MT is more expensive than standard care by €4.078,37 (US $4,553.77) (€13,430.81 [US $14,996.37] vs. €9,352.44 [US $10,442.61]) with an incremental QALY of 0.17 and an ICER of €23,990.44 [US $26,786.89]. At years 2 and 3 , a decreasing difference in total cost per patient and an increasing difference in effectiveness with an ICER of €6,696 (US $7476.52) and €798 (US $891.02). At year 5, combination therapy is associated with a cost savings of €3,057 (US $3,411) when compared to standard care (€31,798 [US $35,483] vs. €34,855 [US $38,895]), and has an incremental QALY of 0.77 (Table 4). Therefore, combination therapy for LVO AIS patients is associated with lower total costs and better outcomes when compared to standard care.[220]

Spain

Matching the US results, from the perspective of the Spanish NHS, when compared to standard care, combination therapy has higher treatment costs (€8,428.00 [US $9,405] vs. €1,606.00 [US $1792]) and lower overall costs (€123,866 [US $138,228] vs. €168,244 [US $187,752]), along with a net monetary benefit of €119,744 (US $133,628) (willingness-to-pay threshold of €30,000 [US $33478]/quality adjusted life-year) (Table 5).[221] Patients treated with combination therapy also have improved health outcomes with 1.17 life years gained and 2.51 QALYs. Therefore, combination therapy for LVO AIS patients is less costly and more effective than standard care alone.[221]

Australia

Matching the US results, combination therapy has higher index hospital costs ($10,666/patient) and quality of life in Australia but results in a lifetime savings of more than $8,000/patient when compared to standard care.[222] For the first 90 days, average inpatient costs are less for patients receiving combination therapy compared to standard care ($15,689 vs. $30,569, P=0.008), counterbalancing the additional costs of inter-hospital transport (average $573) and the MT procedure (average $10,515), resulting in an average savings of $4,365/patient ($29,371 vs. $33,736). Patients treated with MT also have shorter hospital (5 vs. 8 days) and rehabilitation stays (0 vs. 27 days), decreased loss of healthy life years (DALYs), increased life quality (9.3 vs. 4.9 QALYs), and a gain of 4.4 life years than those treated with standard care (Table 6).[11] As a result, it can be expected that increased use of combination therapy decreases the economic burden. Importantly, patient centered utilities (such as mobility, self-care, everyday activities, pain/discomfort, and anxiety/depression) associated with modified Rankin Score (mRS) had the most significant impact on patient outcomes.[11]

Asia

China

In China, combination therapy is not considered cost-effective at 5 years post-stroke, but at 6 years and thereafter, it is considered cost-effective with the significant gains in quality life years (Table 7). Combination therapy is associated with a lifetime gain of 0.794 QALYs at an additional cost of CNY 50,030 (US $7,700), resulting in a cost of CNY 63,010 (US $96,90) per QALY gained.[223]

Conclusion

The cost-effectiveness of MT has been analyzed across the globe. MT, compared to standard care, is cost effective over extended time horizons due to increased survival and quality of life and decreased long-term care (i.e., nursing and rehabilitation facilities). Economic studies of acute ischemic stroke (AIS) come mostly from developed countries, but are expanding to new areas, and costs may be stratified according to age, type of procedure, and baseline patient status.

12. Challenges of implementing MT

Reliability of data that claims superior benefits of MT

The benefits of MT have been demonstrated in a wide range of healthcare systems – clinical trials[174] have included patients from 9 countries across Western Europe, the USA, Canada, Korea, Australia, and New Zealand.[9,12-16,18,26,32,188,224] After the MR CLEAN trial reported results in October 2014,[18] most MT trials were stopped early.[12-14,16,26] However, most trials had accumulated sufficient data to demonstrate that a predefined efficacy stopping point favoring MT had been reached.[13,14,16] Trials with more delayed MT (>6 hours) were smaller and used different selection criteria, so evidence for the benefit of delayed MT is not as strong as that for MT up to 6 hours. Sequential trials showed no change in the odds ratio for treatment outcome compared to medical therapy alone.[12,13,16,18,26,32,224] A meta-analysis of trial data indicated that MT does not confer a significant mortality advantage, although there is a trend for a 20% reduction [225,226]

MT Procedural Safety

MT is associated with a number of intra-procedural and postoperative complications (Table 8),[227] which need to be effectively minimized and managed to maximize the benefits. Overall, the risk of complications from MT with sequelae for the patient is approximately 15%.[9,12-16,18,26,32,188,224] Some complications are life threatening, and may increase the length of stay in intensive care and stroke units, while others increase costs and delay rehabilitation. Some complications may be preventable, and the impact of others can be minimized with early detection and appropriate management. Neurointerventionists need to be aware of risk factors, strategies for prevention, and management of complications related to MT. Nonetheless, procedure-related morbidity and mortality nearly always occur within 30 days and so are incorporated within the net benefit of MT on 90-day outcomes, which strongly favor MT.[227]

Areas of Uncertainty

Current meta-analyses include few patients with posterior circulation LVO. Although recanalization results of MT in the posterior circulation match those of the anterior in non-randomized studies, the clinical benefit remains to be confirmed in posterior circulation strokes, and trials are ongoing. Recently, the Chinese trial of basilar artery occlusion was stopped early due to excess crossovers, and information has been presented but not published, indicating there was no benefit for MT on the intention-to-treat group but benefit in the as-treated group.[227]

Trials are needed to investigate whether less selective brain imaging can be used to select patients undergoing delayed MT, as well as whether there is benefit from the use of advanced brain imaging in early presenters, use of general versus local anesthesia in a real-world situations, and use of MT in patients with pre-stroke disability. [227,228]

13. Community education for MT

Medical professionals and public health leaders need to develop stroke education programs focusing on symptoms, seeking emergency care, and available stroke system resources.[229] These programs should be implemented across all demographics within a community, tailoring to its economic, social, and ethical needs.[230] Increasing awareness of stroke symptoms is vital for seeking timely treatment.[229] When compared to the general population, community minorities have a lower awareness of the risk factors and symptoms of a stroke. As a result, they are less likely to activate EMS, thus delaying necessary treatmen.[231] When that treatment is delayed, it leads to an underutilization of proven therapy and to higher mortality.[232] The establishment of comprehensive stroke care and a greater emphasis on public stroke education have been shown to increase intravenous thrombolysis and MT over time. Additionally, these programs should increase awareness of the available emergency dispatch systems to decrease the time between the onset of a stroke and the arrival of emergency systems.[229] EMS activation and transport of stroke patients are independently associated with earlier arrival (onset-to-door time ≤3 hours), faster evaluation (more patients with door-to-imaging time ≤25 minutes), faster treatment delivery (more patients with door-to-needle time ≤60 minutes), and more patients are eligible for intravenous tissue-type plasminogen activator (IV tPA) (67% vs. 44%).[233]

14. Training initiatives for MT

EMS Training, Assessment, and Management

Stroke therapy has a small therapeutic time window, making it imperative for EMS professionals to be well trained and experienced in recognizing, assesses, managing, treating, triaging, and transporting stroke patients.[234] Improved patient outcomes have been associated with EMS dispatchers and field providers utilizing stroke assessment and identification tools.[235,236] The Los Angeles Prehospital Stroke Screen (LAPSS), Cincinnati Prehospital Stroke Scale (CPSS), and Melbourne Ambulance Stroke Screen (MASS) have demonstrated sensitivities of greater than 90% for stroke assessment.[237-240] An additional screening tool is the vision, aphasia, and neglect (VAN) assessment, which evaluates neurovascular function without a scoring system but has been demonstrated to effectively identify stroke patients with emergent LVO on arrival and outperformed beyond a severity threshold of NIHSS ≥6, which is one of the most commonly used measures to determine the degree of impairment caused due to stroke. It quickly identifies ischemic stroke patients eligible for endovascular treatments and high-risk intracerebral hemorrhage patients more likely to undergo brain surgery.[14,15] It has also proven effective in hospital environments in comparison to NIHSS and other established prehospital LVO screening tools.[241] In fact, while both VAN and NIHSS scale have 100% sensitivity, VAN has been shown to be superior to the NIHSS ≥6 tool, in terms of higher positive predictive value (74% vs 58% respectively) and specificity (90% vs 74%).[242] Additionally, VAN implementation significantly reduces door to computed tomographic angiography (CTA) times (77 [±43] vs 27 [±23] minutes, P<0.05).[243]

To prepare emergency personnel for a suspected stroke patient, EMS should provide pre-arrival notification to the receiving hospital. In fact, this is associated with increased probability that patients receive IV t-PA within 3 hours (82.8% vs. 79.2%), decreased time between arrival and imaging (26 vs. 31 minutes), decreased door-to-needle (78 vs. 80 minutes), and decreased time between symptom onset to needle (141 vs. 145 minutes).[244] Additionally, EMS identification of patients suffering from AIS with LVO, allows transport to the best equipped stroke center, which is critical for positive patient outcomes.

Training Neurointerventionalists

Physicians providing emergent endovascular stroke interventions must have sufficient training and experience performing the related techniques, which includes baseline training and ongoing professional education.[245,246] However, there are a limited number of hospitals capable of offering adequate physician training for MT Thus, specialized regional stroke centers must be established to ensure adequate volume and operator experience for neurointerventional procedures.[247]

Baseline Training and Qualifications

Residency training for physicians includes documented training in the diagnosis and management of acute stroke and interpretation of cerebral arteriography and neuroimaging under the guidance of a board certified neuroradiologist, neurologist, or neurosurgeon and ultimately achieving technical expertise. At the close of their residency, they must obtain field-specific board certifications. Subsequently, they must also undertake specialized interventional neuroradiology training at a high-volume facility, under the supervision of a neurointerventionalist, where they receive AIS specific therapy experience, such as how to overcome challenging anatomy to gain access, microcatheter navigation within cerebral circulation, and how to avoid and manage procedural complications.[245]

Maintenance of Physician Qualifications

The field of stroke therapy is constantly changing and, as a result, physicians should be required to engage in at least 16 hours of stroke education on a biannual basis. Additionally, physicians are encouraged to participate in quality and improvement monitoring programs. Such programs would review emergent interventional stroke therapy care and track associated outcomes.[245,246]

Training Stroke Teams

Efficacy of stroke treatments are time-dependent, as has been demonstrated by the diminished therapeutic effects of IV t-PA outside a 4.5-hour time window.[75] Similar time-dependent outcomes have been indicated for endovascular therapies, such as MTs.[188] LVO AIS treatment algorithms combine IV t-PA and MT to achieve better patient outcomes;[248] however, this approach requires an interdisciplinary, coordinated team approach. To minimize time to treatment and non-technical errors, simulation based team trainings are recommended as a core component to any CSC.[249] Simulation-based interventions have been demonstrated to reduce median door-to-needle times by 12 (43.0 (IQR 29.8–60.0, n=122) to 31 (IQR 240–420, n=112) minutes (P<0.001)), and increasing the number of patients receiving thrombolysis treatment within 30 minutes of arrival (41.5% to 59.6% (P<0.001)).[250]

15. Development of stroke thrombectomy centers

Five multicenter, prospective, randomized, open-label, blinded end point clinical trials showed significant clinical benefit for treatment with MT in LVO AIS patients.[10,14-16,18] Importantly, these trials were conducted in high-volume cerebrovascular centers staffed with stroke experts with the capabilities to provide complex care for AIS patients. Facility based stroke teams were comprised of emergency physicians, radiologists, neuro-interventionalists, neurologist, neurointensivists, neurosurgeons, and stroke-trained support staff. These key players are vital for thrombectomy centers to provide efficient and effective treatment.[10,14-16,18,251]

In 2016, the Society of Vascular and Interventional Neurology (SVIN) proposed recommendations to drive the development of LVO AIS stroke systems including MT as a treatment modality.[251] These recommendations are in addition to current eligibility requirements for CSCs, which include high-patient volume, advanced imaging capabilities, post-hospital care coordination, dedicated neurointensive care, a peer review process for quality control, participation in stroke research, and reporting of performance measures. The SVIN recommended additions to these criteria include the following:

High Patient Volume

High-volume treatment facilities have been associated with positive patient outcomes.[252-255] A recommended requirement of 25-30 MT-treated patients per year and all CSC-affiliated neurointerventionalists should perform 10 MT per year (minimum).[251]

Advanced Imaging Capabilities

It is recommended for all comprehensive stroke centers (CSC) to have the capacity to manage the care of two simultaneous LVO AIS patients; therefore, requiring two of the following to be available at all times: neurointerinventionalists, stroke interventional labs, and all associated support staff.[251]

Post-hospital Care Coordination

A monitored and coordinated system between CSCs and rehabilitation facilities is recommended to ensure continuity of care. Such post-stroke care institutions should be certified in stroke rehabilitation and staff should be trained in standardized outcome scales.[251]

Dedicated Neurointensive Care Unit and Expert Neurointensivist and Neurosurgical Management

Due to the complexity of care management of LVO AIS patients and the potential for complications, a multi-disciplinary team of vascular neurologists and neurocritical care specialists should be available at all times.[251]

Peer Review Process

It is recommended for currently established peer reviews to include performance metrics related to the fast and efficient MT treatment of LVO AIS patients. English et al.[251] provides a comprehensive list of these metrics.

Many landmark trials have helped refine hospital workflow systems after direct patient admission, but prehospital time management and triage continue to be the most important factors in optimizing logistical performance measures.[256] Longer DIDO times adversely affected outcomes in stroke patients with emergent LVO and are possibly the single largest modifiable factor in onset-to-recanalization time.[257] Even high-volume Primary stroke centers (PSC) in a metropolitan “hub-and-spoke” network, in which a single designated CSC provides thrombectomy support for PSC, have long DIDO times and transportation times (median time: 106 minutes) from PSC doors to CSC doors (median transfer time of 128 minutes).[258] Therefore, it is recommended that DIDO is a routine performance measure that needs to be actively reduced. Continuous quality improvement programs have been shown to reduce median DIDO times to <60 minutes in a PSC.[259] Risks of LVO, driving times in rural or urban areas, and hospital workflow times must be considered in designing a personalized prehospital transportation strategy for optimal outcomes in patients with AIS.[260]

Advantages and Disadvantages of Inter-hospital Transfer

The benefits of intra-arterial thrombectomy have been demonstrated by several landmark trials,[10,14-16,18] and as a result, the American Heart Association/American Stroke Association (AHA/ASA) updated their 2013 guidelines to
reflect the necessity for improved stroke care systems, which included prehospital triage, interhospital transfers, and certifications for PSCs and CSCs.[261] These guidelines have been maintained in the latest 2019 ASA guidelines with continued emphasis on prehospital care, urgent and emergency evaluation and treatment with intravenous and intra-arterial therapies, and in-hospital management. Interhospital transfers to endovascular-capable centers are required to provide access to MT. However, interhospital transfers before thrombectomy delays therapy and affects outcomes adversely for patients with anterior-circulation LVOs in AIS.[262] These outcomes were consistent with a study conducted in The Netherlands, where the distances between centers are relatively short.[263] Direct admission of patients to CSCs with endovascular capabilities after field identification of LVOs has led to better outcomes.[264,265] As result, EMS should bypass nearby PSC and directly route patients to a CSC, and, therefore, to decrease transport time, all PSCs should be equipped to perform MT.[266]

Cause of Futile Transfers

Interhospital transfers for ischemic stroke increased by 33% between 2009 and 2014, representing the need for increased access to MT.[267] A French study demonstrated 45% of the interhospital transfers for MT were futile and did not result in intervention, possibly due to clinical deterioration due to infarct growth.[268] The major reasons a MT is not performed after interhospital transfer include established infarct, recanalized LVO, and clinically improved symptoms.[269] Additionally, approximately one-third of patients became ineligible for thrombectomy because of deterioration according to the Alberta Stroke Program Early CT Score (ASPECTS) during inter-hospital transfer.
41

Factors affecting delays in administering endovascular therapy include awareness of first responders, efficiency of EMS, interhospital transfers, notifying the endovascular team, and intraprocedural delays.[270] Higher chances of thrombectomy after interhospital transfer were independently predicted by a higher collateral score, a higher NIHSS score, and CTA imaging from the initial referring center.[4344]

Delays During Transfer

DIDO times are the single, largest modifiable factor in onset to recanalization time with longer DIDO times adversely affecting outcomes in stroke patients with emergent LVO.[257] Analysis of DIDO times at two large rural telestroke networks in the US showed CTA performed before interhospital transfer increases the time from the door-in to groin puncture at thrombectomy-capable centers.[271] DIDO times and times from PSC doors to CSC doors are also higher even for high-volume PSC in a metropolitan network.[258]

Quality Improvement in Hospital Workflow Processes

Delays to reperfusion therapy in distant CSCs can be decreased by quality improvement processes.[272] The landmark trials have also helped refine hospital workflow systems after direct patient admission, but prehospital time management and triage continue to be the most important factors in optimizing logistical performance measures, as shown by real-world data from regional stroke care systems.[18] Optimization of in-hospital workflow is important to prevent delays in inter-hospital transfer and its associated delay in administering thrombectomy.[49] A 2017 SVIN report recommends LVO patients, who have escalated risk for morbidity and mortality, need to achieve reperfusion as soon as possible, a result dependent on enhancing hospital processes and workflow.[50] Early notification to CSC, cloud data sharing, and CTA on arrival are some features of a standardized PSC care protocol associated with improved outcomes for stroke patients with emergent LVO.[51] In a single institution study, procedure times, such as overall time from puncture to final recanalization decreased significantly from 68.2 to 37.0 min after standardizing the medical protocol and the equipment for treating emergent LVO.[52,273] A detailed classification system on making decisions to transfer stroke patients from PSC to CSC can help reduce inappropriate transfers and improve outcomes.[53]

Trip and Treat Models

The trip-and-treat model of stroke care, where a mobile interventional stroke team provides intervention at PSCs, was 79 minutes faster ($P<0.0001$) by the initial door-to-recanalization time in comparison to the drip-and-ship model, where patients are transported to the nearest hospital that provide endovascular treatment; hence, it is a potential alternative to interhospital transfers in urban settings.[274]

Telestroke Options

Telestroke medicine, where doctors specializing in stroke medicine help provide treatment for stroke patients in remote locations using technological measures, increases MT rates for these patients and decreased interhospital transfers.[274] Hawaii’s Telestroke Program resulted in a leap in yearly telestroke consultations from 11 in 2012 to 203 in 2016. Consequently, more revascularization therapies are incorporated at hospitals with limited neurological capabilities, representing a potential treatment option to address disparities.[55]

Helicopter Emergency Medical Services

The role of helicopter EMS (HEMS) needs to be addressed further for better ancillary care during transportation to nullify disparities in access to thrombectomy based on geography.[275] A disparity to be addressed in the United States is the differential use of HEMS for Hispanic stroke patients in comparison to non-Hispanic whites, which delays or nullifies the chances of timely thrombectomy procedures.[276]

B. COMMUNITY EDUCATION GUIDELINES

2016	**A Community-Engaged Assessment of Barriers and Facilitators to Rapid Stroke Treatment** https://www.ncbi.nlm.nih.gov/pubmed/27545591
2007-2012	**Heart Disease and Stroke in Illinois: Now is the time for Public Health Action** http://www.idph.state.il.us/heartstroke/state_plan_book2.pdf
2013	**American Heart Association Guide for Improving Cardiovascular Health at the Community Level: A Statement for Public Health Practitioners, Healthcare Providers, and Health Policy Makers from the American Heart Association Expert Panel on Population and Prevention Science** https://www.ahajournals.org/doi/full/10.1161/cir.0b013e31828f8a94
2010	**A Population-Based Policy and Systems Change Approach to Prevent and Control Hypertension.** https://www.ncbi.nlm.nih.gov/books/NBK220093/

C. PRIMORDIAL/PRIMARY PREVENTION GUIDELINES

2019	**Stroke Prevention** https://emedicine.medscape.com/article/323662-overview
2019	**Guidelines for the Early Management of Patients with Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association** https://pubmed.ncbi.nlm.nih.gov/31662037-guidelines-for-the-early-management-of-patients-with-acute-ischemic-stroke-2019-update-to-the-2018-guidelines-for-the-early-management-of-acute-ischemic-stroke-a-guideline-for-healthcare-professionals-from-the-american-heart-associationamerican-stroke-association/?from_term=2018+Guidelines+for+the+Early+Management+of+Patients+With+Acute+Ischemic+Stroke%3A+A+Guideline+for+Healthcare+-Professionals+From+the+American+Heart+Association%2FAmerican+Stroke+Association&from_page=1&from_pos=2
2018	**2018 Guidelines for the Early Management of Patients with Acute Ischemic Stroke: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association** https://www.bmc.org/sites/default/files/Patient_Care/Specialty_Care/Stroke_and_Cerebrovascular_Center/Medical_Professionals/Protocols/2018%20AHA%20Ischemic%20Stroke%20Guideline%20Update%202018.pdf
2018	**Recent Advances in Primary and Secondary Prevention of Atherosclerotic Stroke** https://www.j-stroke.org/journal/view.php?number=225

2017	**Blood Pressure Reduction and Secondary Stroke Prevention: A Systematic Review and Metaregression Analysis of Randomized Clinical Trials** https://pubmed.ncbi.nlm.nih.gov/27802419-blood-pressure-reduction-and-secondary-stroke-prevention-a-systematic-review-and-metaregression-analysis-of-randomized-clinical-trials/?from_term=Current+Recommendations+for+Secondary+Stroke+Prevention&from_pos=6
2016	**Stroke Prevention** https://www.ncbi.nlm.nih.gov/pubmed/27816341
2014	**Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association** https://www.ncbi.nlm.nih.gov/pubmed/24788967
2014	**Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association** https://www.ahajournals.org/doi/abs/10.1161/01.str.0000442009.06663.48
2014	**Guidelines for the Primary Prevention of Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association** https://www.ahajournals.org/doi/10.1161/STR.0000000000000046
2008	**Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and transient ischemic attack** https://www.ahajournals.org/doi/abs/10.1161/strokeaha.107.189063

D. EMS RESPONSE GUIDELINES

2018	**2018 guidelines for the early management of patients with actue ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association** https://www.ahajournals.org/doi/abs/10.1161/STR.0000000000000158
2013	**Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association** https://www.ahajournals.org/doi/abs/10.1161/str.0b013e318284056a
2007	**EMS management of acute stroke--prehospital triage (resource document to NAEMSP position statement)** https://www.tandfonline.com/doi/abs/10.1080/10903120701347844
2005	**Recommendations for the Establishment of Stroke Systems of Care: Recommendations from the American Stroke Association's Task Force on the Development of Stroke Systems** https://www.ahajournals.org/doi/full/10.1161/01.cir.0000154252.62394.1e

E. HOSPITAL-BASED ACUTE STROKE MANAGEMENT GUIDELINES

2019	**Recommendations for the Establishment of Stroke Systems of Care: A 2019 Update** https://www.ncbi.nlm.nih.gov/pubmed/?term=Recommendations+for+the+Establishment+of+Stroke+Systems+of+Care%3A+A+2019+Update
2019	**Guidelines for the Early Management of Patients with Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association** https://www.ncbi.nlm.nih.gov/pubmed/31662037
2019	**Management of Acute Ischemic Stroke: a Review of Pertinent Guideline Updates** https://www.uspharmacist.com/article/management-of-acute-ischemic-stroke-a-review-of-pertinent-guideline-updates
2019	**Ischemic Stroke: Management by the Nurse Practitioner** https://www.npjournal.org/article/S1555-4155(18)30500-2/fulltext
2019	**Society of Interventional Radiology Training Guidelines for Endovascular Stroke Treatment** DOI: https://doi.org/10.1016/j.jvir.2019.08.018
2019	**2019 Update of the Korean Clinical Practice Guidelines of Stroke for Endovascular Recanalization Therapy in Patients with Acute Ischemic Stroke** https://doi.org/10.5853/jos.2019.00024
2019	**European Stroke Organisation (ESO) - European Society for Minimally Invasive Neurological Therapy (ESMINT) Guidelines on Mechanical Thrombectomy in Acute Ischemic Stroke** https://www.ncbi.nlm.nih.gov/pubmed/30808653

2018	**2018 Guidelines for the Early Management of Patients with Acute Ischemic Stroke: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association** https://www.ncbi.nlm.nih.gov/pubmed/29367334
2018	**Canadian Stroke Best Practice Recommendations for Acute Stroke Management: Prehospital, Emergency Department, and Acute Inpatient Stroke Care, 6th Edition, Update 2018** https://www.ncbi.nlm.nih.gov/pubmed/30021503
2018	**Get with The Guidelines® - Stroke Clinical Tools** https://www.heart.org/en/professional/quality-improvement/get-with-the-guidelines/get-with-the-guidelines-stroke/get-with-the-guidelines-stroke-clinical-tools
2018	**Diagnosis and Management of Acute Ischemic Stroke** https://doi.org/10.1016/j.mayocp.2018.02.013
2018	**TREATMENT OF ACUTE ISCHEMIC STROKE** https://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=6438
2018	**Complications of endovascular treatment for acute ischemic stroke: Prevention and management** https://www.ncbi.nlm.nih.gov/pubmed/29171362
2018	**International Comparison of Patient Characteristics and Quality of Care for Ischemic Stroke: Analysis of the China National Stroke Registry and the American Heart Association Get With The Guidelines--Stroke Program.** https://www.ncbi.nlm.nih.gov/pubmed/30371291

2018	**Multisociety Consensus Quality Improvement Revised Consensus Statement for Endovascular Therapy of Acute Ischemic Stroke** https://www.ncbi.nlm.nih.gov/pubmed/29478797
2018	**The organisation of the acute ischemic stroke management: key notes of the Italian Neurological Society and of the Italian Stroke Organization** https://www.ncbi.nlm.nih.gov/pubmed/29181655
2018	**Standards of Practice in Acute Ischemic Stroke Intervention: International Recommendations** https://www.ncbi.nlm.nih.gov/pubmed/30442688
2017	**A systematic comparison of key features of ischemic stroke prevention guidelines in low- and middle-income vs. high-income countries** https://www.ncbi.nlm.nih.gov/pubmed/28008094
2017	**Differences in Acute Ischemic Stroke Quality of Care and Outcomes by Primary Stroke Center Certification Organization** https://www.ncbi.nlm.nih.gov/pubmed/28008094
2017	**Brazilian guidelines for endovascular treatment of patients with acute ischemic stroke** https://www.ncbi.nlm.nih.gov/pubmed/28099563
2017	**The Chinese Stroke Association scientific statement: intravenous thrombolysis in acute ischaemic stroke** https://www.ncbi.nlm.nih.gov/pubmed/28989804
2016	**Guidelines for Adult Stroke Rehabilitation and Recovery: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association** https://www.ncbi.nlm.nih.gov/pubmed/27145936
2016	**Diagnosis and Initial Treatment of Ischemic Stroke** https://www.icsi.org/wp-content/uploads/2019/01/Stroke.pdf
2016	**Quality Improvement in Acute Ischemic Stroke Care in Taiwan: The Breakthrough Collaborative in Stroke** https://doi.org/10.1371/journal.pone.0160426
2016	**Training Guidelines for Endovascular Ischemic Stroke Intervention: An International multi-society consensus document** https://www.ncbi.nlm.nih.gov/pubmed/26888954
2015	**Canadian Association of Emergency Physicians position statement on acute ischemic stroke** https://www.ncbi.nlm.nih.gov/pubmed/26120643
2010	**Acute Stroke Practice Guidelines for Inpatient Management of Ischemic Stroke and Transient Ischemic Attack (TIA)** https://www.heart.org/idc/groups/heart-public/@private/@wcm/@hcm/documents/downloadable/ucm_309996.pdf

F. SECONDARY PREVENTION/POST-ACUTE CARE GUIDELINES

2020	**Overview of secondary prevention of ischemic stroke** https://www.uptodate.com/contents/overview-of-secondary-prevention-of-ischemic-stroke
2019	**Recommendations for the Establishment of Stroke Systems of Care: A 2019 Update.** https://www.ahajournals.org/doi/10.1161/STR.0000000000000173
2019	**Ischemic Stroke: Management by the Nurse Practitioner** DOI: https://doi.org/10.1016/j.nurpra.2018.07.019

2019	**Antithrombotic treatment for secondary prevention of stroke and other thromboembolic events in patients with stroke or transient ischemic attack and non-valvular atrial fibrillation: A European Stroke Organisation guideline** https://journals.sagepub.com/doi/full/10.1177/2396987319841187
2019	**Secondary prevention of stroke in patients with atrial fibrillation: factors influencing the prescription of oral anticoagulation at discharge** https://www.ncbi.nlm.nih.gov/pubmed/31662037
2018	**2018 Guidelines for the Early Management of Patients with Acute Ischemic Stroke: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association** https://www.ncbi.nlm.nih.gov/pubmed/29367334
2018	**Canadian stroke best practice consensus statement: Secondary stroke prevention during pregnancy** https://www.ncbi.nlm.nih.gov/pubmed/29171360
2018	**Recent Advances in Primary and Secondary Prevention of Atherosclerotic Stroke** https://www.j-stroke.org/journal/view.php?number=225
2017	**Canadian stroke best practice recommendations: Secondary prevention of stroke, sixth edition practice guidelines, update 2017** https://www.ncbi.nlm.nih.gov/pubmed/29171361 https://journals.sagepub.com/doi/full/10.1177/1747493017743062
2017	**Secondary Prevention of Stroke: 6th Edition 2017 UPDATE** https://www.strokebestpractices.ca/recommendations/secondary-prevention-of-stroke

2016	**Stroke and Stroke Rehabilitation: Quality Measurement Set Update** https://www.aan.com/siteassets/home-page/policy-and-guidelines/quality/quality-measures/15strokeandrehabmeasureset_pg.pdf
2016	**Quality-Based Procedures: Clinical Handbook for Stroke (Acute and Postacute)** http://health.gov.on.ca/en/pro/programs/ecfa/docs/qbp_stroke.pdf
2016	**National clinical guideline for stroke – SSNAP** https://www.strokeaudit.org/SupportFiles/Documents/Guidelines/2016-National-Clinical-Guideline-for-Stroke-5t-(1).aspx
2016	**Guidelines for Management of Hyperlipidemia: Implications for Treatment of Patients with Stroke Secondary to Atherosclerotic Disease** https://www.ncbi.nlm.nih.gov/pubmed/26838351
2016	**Secondary Prevention of Stroke** http://www.ebrsr.com/sites/default/files/Chapter%208_Secondary%20Prevention%20of%20Stroke.pdf
2015	**Quality-Based Procedures: Clinical Handbook for Stroke (Acute and Postacute)** http://www.hqontario.ca/Portals/0/Documents/evidence/clinical-handbooks/community-stroke-20151802-en.pdf
2015	**Antithrombotic Management of Patients with Nonvalvular Atrial Fibrillation and Ischemic Stroke or Transient Ischemic Attack: Executive Summary of the Korean Clinical Practice Guidelines for Stroke** https://www.ncbi.nlm.nih.gov/pubmed/26060808
2014	**Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association.** https://www.ncbi.nlm.nih.gov/pubmed/24788967

2014	**2014 Chinese guidelines for secondary prevention of ischemic stroke and transient ischemic attack.** https://www.ncbi.nlm.nih.gov/pubmed/28381199
2014	**Canadian Stroke Best Practice Recommendations: secondary prevention of stroke guidelines, update 2014.** https://www.ncbi.nlm.nih.gov/pubmed/25535808
2013	**Key articles and guidelines in the acute management and secondary prevention of ischemic stroke** https://www.ncbi.nlm.nih.gov/pubmed/23401103
2012	**Stroke Clinical Care Programme Model of Care – HSE** https://www.hse.ie/eng/services/publications/clinical-strategy-and-programmes/stroke-model-of-care.pdf
2012	**Model of Stroke Care 2012** https://ww2.health.wa.gov.au/~/media/Files/Corporate/general%20documents/Health%20Networks/Neurosciences%20and%20the%20Senses/Model-of-Stroke-Care.pdf
2012	**Chinese guidelines for the secondary prevention of ischemic stroke and transient ischemic attack 2010.** https://www.ncbi.nlm.nih.gov/pubmed/22313945
2012	**Inclusion of stroke in cardiovascular risk prediction instruments: a statement for healthcare professionals from the American Heart Association/American Stroke Association.** https://www.ncbi.nlm.nih.gov/pubmed/22627990
2011	**AHA/ASA Guidelines on Prevention of Recurrent Stroke** https://www.aafp.org/afp/2011/0415/p993.html
2011	**Subacute Management of Ischemic Stroke** https://www.aafp.org/afp/2011/1215/p1383.html
2010	**New Zealand Clinical Guidelines for Stroke Management 2010** https://www.health.govt.nz/system/files/documents/publications/nzclinicalguidelinesstrokemanagement2010activecontents.pdf
2010	**Clinical Guidelines for Stroke Management 2010** https://extranet.who.int/ncdccs/Data/AUS_D1_Clinical%20Guidelines%20for%20Stroke%20Management.pdf
2010	**Management of Stroke Rehabilitation** https://www.healthquality.va.gov/stroke/str_full_220.pdf
2010	**Current Recommendations for Secondary Stroke Prevention** https://www.uspharmacist.com/article/current-recommendations-for-secondary-stroke-prevention
2009	**Stroke and Transient Ischaemic Attacks - Ministry of Health** https://www.moh.gov.sg/docs/librariesprovider4/guidelines/cpg_stroke-and-transient-ischaemic-attacks.pdf

G. STROKE REHABILIATION GIDELINES

2019	**Evidence-Based Guidelines and Clinical Pathways in Stroke Rehabilitation-An International Perspective** https://www.ncbi.nlm.nih.gov/pubmed/?term=Evidence-Based+Guidelines+and+Clinical+Pathways+in+Stroke+Rehabilitation%E2%80%94An+International+Perspective
2019	**The Management of Stroke Rehabilitation: A Synopsis of the 2019 U.S. Department of Veterans Affairs and U.S. Department of Defense Clinical Practice Guideline** https://www.ncbi.nlm.nih.gov/pubmed/31739317
2019	**Assessment and Management of Patients at Risk for Suicide: Synopsis of the 2019 U.S. Department of Veterans Affairs and U.S. Department of Defense Clinical Practice Guidelines** https://www.ncbi.nlm.nih.gov/pubmed/31450237

2019	**VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF STROKE REHABILITATION** https://www.healthquality.va.gov/guidelines/Rehab/stroke/VADoDStrokeRehabCPGFinal8292019.pdf
2019	**Stroke rehabilitation: therapy** https://pathways.nice.org.uk/pathways/stroke
2019	**The Subacute Rehabilitation of Childhood Stroke, Clinical Guideline 201** https://informme.org.au/en/Guidelines/Childhood-stroke-guidelines
2019	**Clinical Practice Guideline for Cardiac Rehabilitation in Korea.** https://www.ncbi.nlm.nih.gov/pubmed/31404368 https://www.ncbi.nlm.nih.gov/pubmed/31311260
2019	**Clinical Practice Guideline for Cardiac Rehabilitation in Korea: Recommendations for Cardiac Rehabilitation and Secondary Prevention after Acute Coronary Syndrome.** https://www.ncbi.nlm.nih.gov/pubmed/31646772
2018	**Guidelines for Adult Stroke Rehabilitation and Recovery** https://www.ncbi.nlm.nih.gov/pubmed/?term=JAMA+Guidelines+for+Adult+Stroke+Rehabilitation+and+Recovery
2018	**Elderly Stroke Rehabilitation: Overcoming the Complications and Its Associated Challenges** https://www.hindawi.com/journals/cggr/2018/9853837/
2018	**Systematic review of clinical practice guidelines to identify recommendations for rehabilitation after stroke and other acquired brain injuries** https://www.ncbi.nlm.nih.gov/pubmed/29490958
2018	**Korean Clinical Practice Guidelines for Aneurysmal Subarachnoid Hemorrhage.** https://www.ncbi.nlm.nih.gov/pubmed/29526058

2017	**Stroke Rehabilitation: Current American Stroke Association Guidelines, Care, and Implications for Practice** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6143585/
2017	**Stroke in childhood - clinical guideline for diagnosis, management and rehabilitation** https://www.rcpch.ac.uk/resources/stroke-childhood-clinical-guideline-diagnosis-management-rehabilitation#fullclinicalguideline
2016	**Guidelines for Adult Stroke Rehabilitation and Recovery: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association** https://www.ncbi.nlm.nih.gov/pubmed/27145936
2016	**EVIDENCE-BASED REVIEW OF STROKE REHABILITATION (18th Edition)** http://www.ebrsr.com/sites/default/files/documents/v18-SREBR-ExecutiveSummary-2.pdf
2016	**Clinical Practice Guideline for Stroke Rehabilitation in Korea 2016** https://synapse.koreamed.org/Synapse/Data/PDFData/0176BN/bn-10-e11.pdf
2016	**2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR).** https://www.ncbi.nlm.nih.gov/pubmed/27222591

2016	**2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR).** https://www.ncbi.nlm.nih.gov/pubmed/27664503
2016	**Assessing and treating pain associated with stroke, multiple sclerosis, cerebral palsy, spinal cord injury and spasticity. Evidence and recommendations from the Italian Consensus Conference on Pain in Neurorehabilitation** https://www.ncbi.nlm.nih.gov/pubmed/27579581
2016	**Canadian Stroke Best Practice Recommendations: Managing transitions of care following Stroke, Guidelines Update 2016.** https://www.ncbi.nlm.nih.gov/pubmed/27443991
2015	**Stroke Rehabilitation | Canadian Stroke Best Practices** https://www.strokebestpractices.ca/recommendations/stroke-rehabilitation
2015	**Canadian stroke best practice recommendations: Stroke rehabilitation practice guidelines, update 2015** https://www.ncbi.nlm.nih.gov/pubmed/27079654
2015	**Guidelines for the Management of Spontaneous Intracerebral Hemorrhage** Guidelines for the Management of Spontaneous Intracerebral Hemorrhage
2014	**Physical activity and exercise recommendations for stroke survivors: a statement for healthcare professionals from the American Heart Association/ American Stroke Association** https://www.ncbi.nlm.nih.gov/pubmed/24846875

2014	**Best practice guidelines for stroke in Cameroon: An innovative and participatory knowledge translation project** https://www.ncbi.nlm.nih.gov/pubmed/28729996
2013	**Clinical Guideline on Stroke Rehabilitation** https://extranet.who.int/ncdccs/Data/MNG_D1_2.%20Rehabilitation%20guideline%20of%20Stroke.pdf
2013	**Stroke rehabilitation in adults: Clinical guideline [CG162]** https://www.nice.org.uk/guidance/cg162
2012	**Rehabilitation for Cerebrovascular Disease: Current and new methods in Japan** https://www.ncbi.nlm.nih.gov/pubmed/25237224
2011	**VII. Rehabilitation** https://www.ncbi.nlm.nih.gov/pubmed/21835355
2011	**The South African guideline for the management of ischemic stroke and transient ischemic attack: recommendations for a resource-constrained health care setting** https://www.ncbi.nlm.nih.gov/pubmed/21745347
2010	**Clinical Guidelines for Stroke Management 2010 – PEDro** https://www.pedro.org.au/wp-content/uploads/CPG_stroke.pdf
2010	**Pathway for Stroke Rehabilitation** https://www.sahealth.sa.gov.au/wps/wcm/connect/dd39a9804b32fb628730afe79043faf0/Stroke+Rehabilitation+Pathway.pdf?MOD=AJPERES&CACHEID=ROOTWORKSPACE-dd39a9804b32fb628730afe79043faf0-mMz0iEE
2010	**Management of patients with stroke: Rehabilitation, prevention and management ofcomplications, and discharge planning** https://www.sign.ac.uk/assets/sign118.pdf

2010	**Comprehensive overview of nursing and interdisciplinary rehabilitation care of the stroke patient: a scientific statement from the American Heart Association** https://www.ncbi.nlm.nih.gov/pubmed/20813995
2009	**A review of the evidence for the use of telemedicine within stroke systems of care: a scientific statement from the American Heart Association/American Stroke Association.** https://www.ncbi.nlm.nih.gov/pubmed/19423852

H. PALLATIVE AND END-OF-LIFE CARE GIDELINES

2018	**Canadian Stroke Best Practice Recommendations for Acute Stroke Management: Prehospital, Emergency Department, and Acute Inpatient Stroke Care, 6th Edition, Update 2018.** https://www.ncbi.nlm.nih.gov/pubmed/30021503
2016	**Palliative Care and Cardiovascular Disease and Stroke: A Policy Statement from the American Heart Association/ American Stroke Association.** https://www.ncbi.nlm.nih.gov/pubmed/27503067
2014	**Palliative and end-of-life care in stroke: a statement for healthcare professionals from the American Heart Association/ American Stroke Association.** https://www.ncbi.nlm.nih.gov/pubmed/24676781
2012	**National clinical guideline for stroke: Fourth Edition** http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.476.6093&rep=rep1&type=pdf
2012	**Symptomatic and palliative care for stroke survivors.** https://www.ncbi.nlm.nih.gov/pubmed/22258916

I. CONTINUOUS QUALITY IMPROVEMENT GIDELINES

2018	**Multisociety Consensus Quality Improvement Revised Consensus Statement for Endovascular Therapy of Acute Ischemic Stroke: From the American Association of Neurological Surgeons (AANS), American Society of Neuroradiology (ASNR), Cardiovascular and Interventional Radiology Society of Europe (CIRSE), Canadian Interventional Radiology Association (CIRA), Congress of Neurological Surgeons (CNS), European Society of Minimally Invasive Neurological Therapy (ESMINT), European Society of Neuroradiology (ESNR), European Stroke Organization (ESO), Society for Cardiovascular Angiography and Interventions (SCAI), Society of Interventional Radiology (SIR), Society of NeuroInterventional Surgery (SNIS), and World Stroke Organization (WSO).** https://www.ncbi.nlm.nih.gov/pubmed/29478797
2017	**Stroke care quality in China: Substantial improvement, and a huge challenge and opportunity.** https://www.ncbi.nlm.nih.gov/pubmed/?term=Stroke+care+quality+in+China%3A+Substantial+improvement%2C+and+a+huge+challenge+and+opportunity
2017	**Standards for providing safe acute ischaemic stroke thrombectomy services (September 2015).** https://www.ncbi.nlm.nih.gov/pubmed/27974152

2016	**Quality Improvement in Acute Ischemic Stroke Care in Taiwan: The Breakthrough Collaborative in Stroke.** https://www.ncbi.nlm.nih.gov/pubmed/?term=Quality+improvement+in+acute+ischemic+stroke+-care+in+Taiwan%3A+the+Breakthrough+Collaborative+in+Stroke
2016	**The Danish Stroke Registry.** https://www.ncbi.nlm.nih.gov/pubmed/27843349