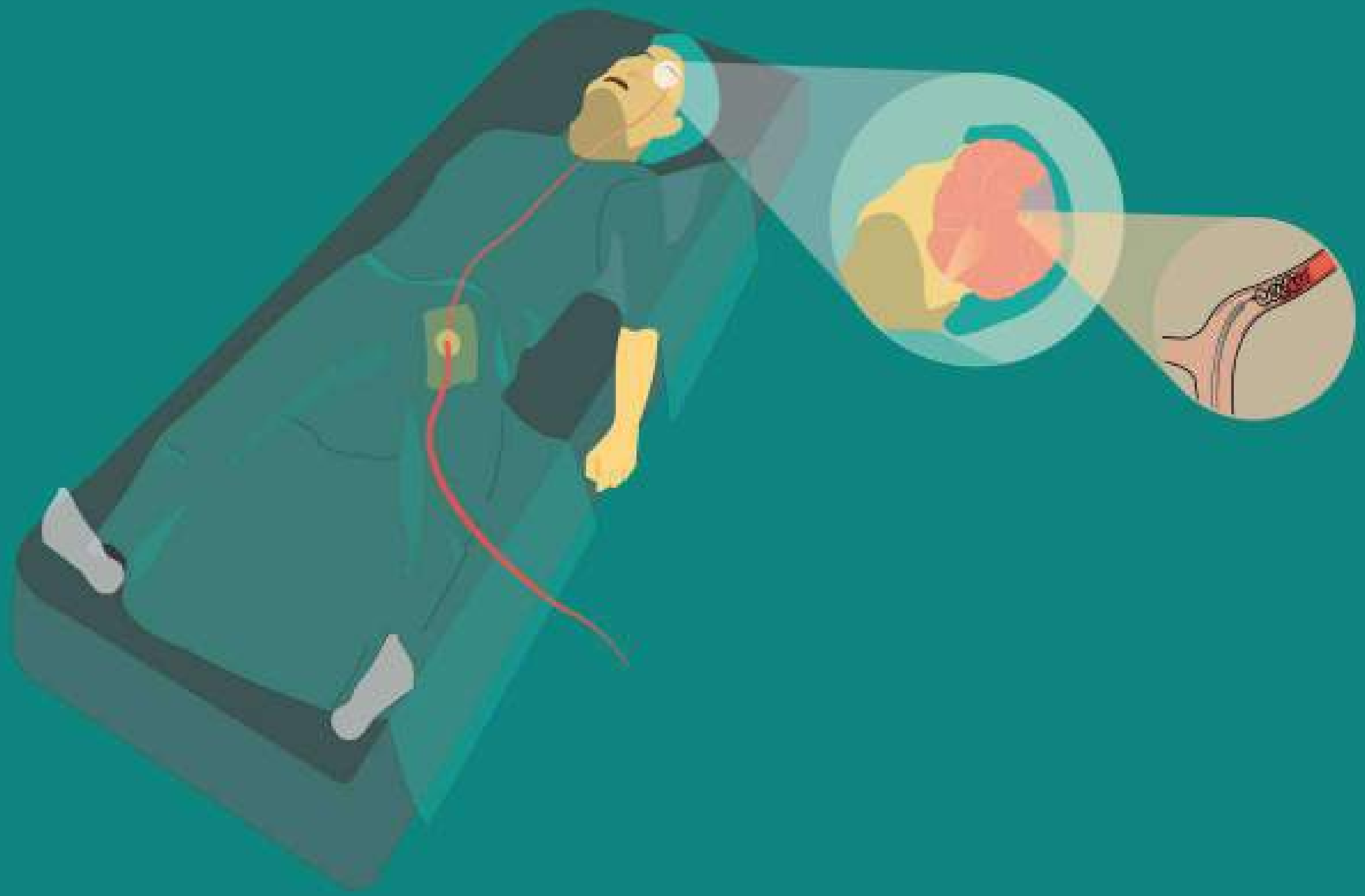

Mechanical Thrombectomy For Acute Stroke

Building Stroke Thrombectomy Systems Of Care In Your Region: Why & How?

A White Paper

Mission Thrombectomy 2020+ Global Executive Committee (MT2020+ GEC), October, 24th, 2020

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

Mission Thrombectomy 2020+ (MT2020+)

Stroke is the leading cause of neurological disability and second leading cause of death worldwide. Approximately 85% of all strokes are due to sudden blockage in or occlusion of an artery in the brain and are called acute ischemic strokes (AIS). Strokes due to occlusion of large arteries in the brain comprise around 1/3 of all AIS and are commonly referred to as large vessel occlusion (LVO) strokes. LVO strokes result in a disproportionate health burden in the population, causing three-fifths of dependency and more than nine-tenths of mortality after AIS. Mission Thrombectomy 2020+ (MT2020+) is a global non-profit campaign and multi-stakeholder alliance initiated by the Society of Vascular and Interventional Neurology (SVIN) in 2016, to accelerate access to emergency mechanical thrombectomy (MT) surgery for treatment of LVO stroke worldwide. The campaign aims to achieve its goals with the help of public health interventions (PHI) and by sharing best practices for stroke thrombectomy systems of care among different regions. Stroke poses a staggering health, economic and social burden across countries and age groups, although the incidence significantly increases after age 50. Since 2015, mechanical thrombectomy (MT), a catheter-based minimally invasive emergency surgery performed in an angiography suite, is the new standard of care for acute treatment of moderate to severe stroke caused by LVO.

MT by itself, or in combination with pharmacological thrombolysis when indicated, is an overwhelmingly effective and safe treatment for selected LVO stroke, when performed rapidly within the first 24 hours after symptoms begin. MT removes the blockage in the large vessel causing the stroke and restores blood flow to the brain tissue, and thereby saves portions of the brain that have not been irreversibly damaged from lack of oxygen, leading to restoration of neurological function. This treatment has also been shown to be cost-effective despite being resource intensive across different income level countries.

The overarching goal of MT2020+ is to accelerate the regional growth of thrombectomy procedure capacity and systems to enable access to this treatment worldwide, and increase overall LVO stroke thrombectomy rates through applying public health principles 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 in cooperation with the Society of Vascular and Interventional Neurology (SVIN) on behalf of the Mission Thrombectomy 2020 global executive community.

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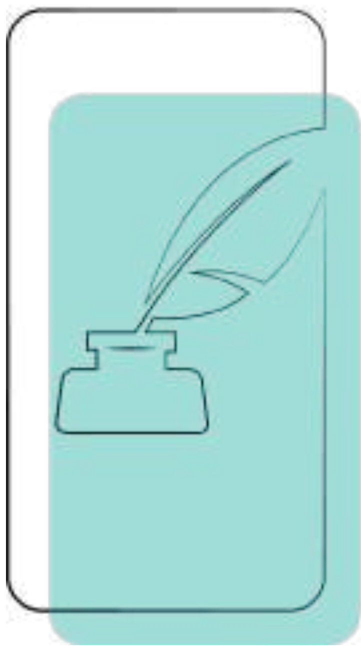


List of abbreviations

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

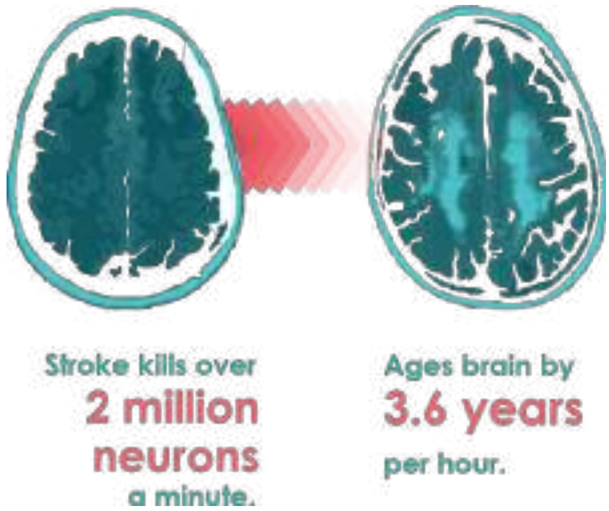
IECR - Incremental Cost-Effectiveness Ratio

AHA – American Heart Association

DIDO- Door-in-door-out

Executive Summary

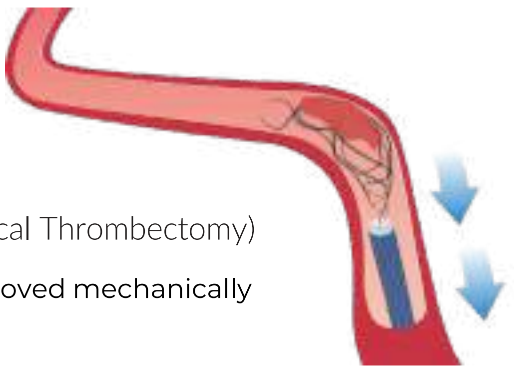
Brain attacks or strokes are the leading cause of disability[1-4] and the second leading cause of death worldwide.[5] While many other conditions affect patients over months, stroke victims are struck with sudden, potentially life-long paralysis that



kills over 2 million brain cells a minute and ages the brain by 3.6 years per hour.[6] Up to 85% of strokes are due to sudden blockages in brain arteries, referred to as acute ischemic strokes (AIS). The remainder are due to sudden rupture of brain arteries leading to hemorrhagic (bleeding) strokes. Strokes due to large vessel occlusion (blockages) (LVOs) in the brain constitute up to 30% of all AIS. LVO strokes are important as they disproportionately contribute to permanent stroke-related disability due to loss of large amounts of brain tissue.

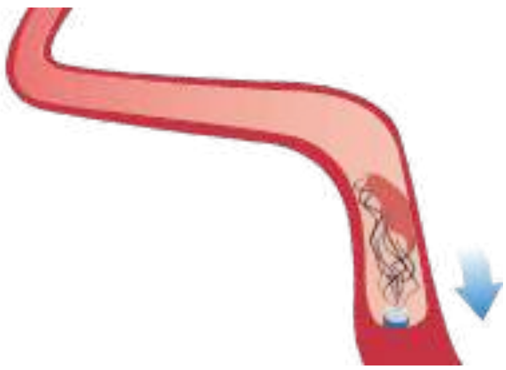
Until recently, the only intervention capable of improving outcomes in AIS was a clot-busting drug, rt-PA, administered intravenously within 4.5 hours from the beginning of stroke symptoms in eligible patients. While rt-PA is safe and effective, the delay in presentation of stroke patients and several instances where it cannot be given, for example in a patient on strong blood thinners, only a small fraction of stroke patients receive it. Also, intravenous rt-PA is specifically limited in its efficacy in LVO strokes with only a 10-25% chance of opening the blockage. However, an emergency minimally invasive procedure was proven highly effective and safe in 2015 - Mechanical Thrombectomy (MT) - for the treatment of LVO strokes. In MT, a catheter is inserted into a major blood vessel within the thigh or wrist, navigated to the brain, and used to remove the clot blocking the large brain arteries.[10,14-18] This is similar to the approach used by interventional cardiologists who perform emergency angioplasty with stent procedures to remove acute blockages from the blood vessels that feed the heart.

MT procedures enable specialized physicians to remove clots from up to 80-90% of LVO stroke victims, and reduce the rate of neurological disability significantly by 40-60%, so long as they are treated rapidly within 24 hours when patients are selected for treatment according to guidelines.[19]



MT (Mechanical Thrombectomy)

Blockage removed mechanically



The Majority of the world does not have an MT centre

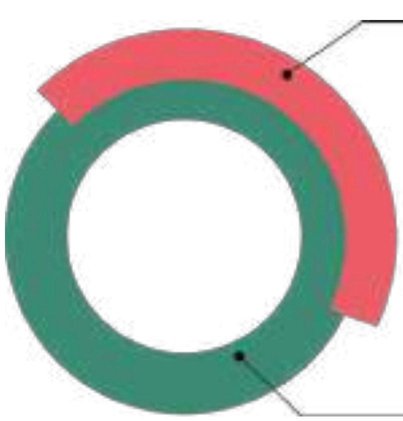
Out of a total of 2000 centres, 78% are in US, UK, Brazil, France, Germany and Australia.

This procedure can transform stroke care, creating an opportunity to save thousands of lives; but only if hospitals are capable of deploying this therapy wherever and whenever strokes occur. In a majority of patients with emergent large-vessel occlusions (LVO) stroke, the largest and deadliest type of stroke, MT now enables physicians to completely remove clots,[19] saving USD 23,000 per patient[20] in care costs, and doubling a patient's chances of avoiding permanent neurological disability.[24] Despite the benefits to patients and long-term cost savings to the healthcare system, adequate numbers of MT centers are only available in densely populated urban centers in North America, Europe, Japan and Australia[21] indicating that this life-saving 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, the benefits have not been distributed equally across global communities where stroke burden is significantly higher. The greatest hurdle is how quickly patients must be treated in order for them to get the maximal benefit from MT, with significantly better outcomes when treated sooner than later.[9,25,26.] Currently, even in the US, only 20% of the population has access to Thrombectomy Stroke Centers (TSCs).[27]

While physicians are rapidly working to improve the treatment methods that could make MT less time sensitive, 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 to all communities, as stroke is a pervasive risk.

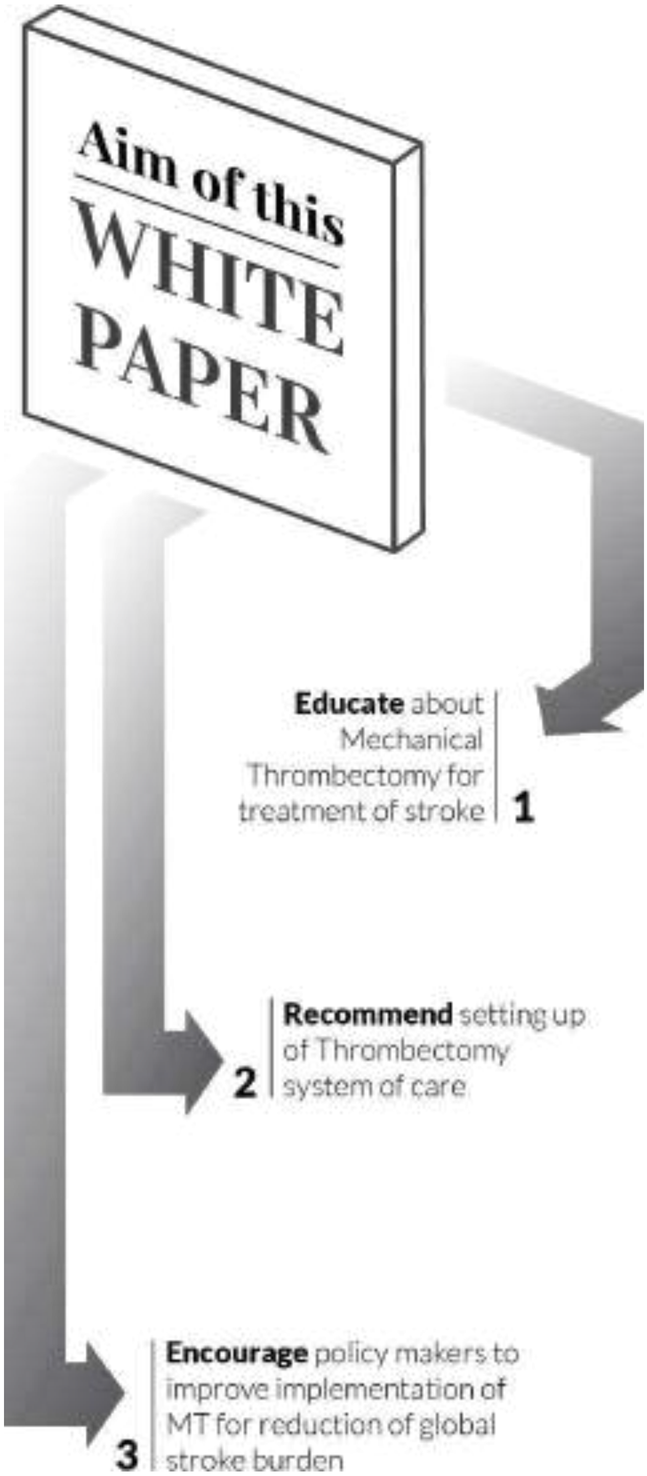
If regional system level policies are implemented to provide rapid access to MT for the majority of population, we could save millions of lives globally,[28] and have a substantial impact on reducing cost per patient in disability care.[20] Such policies could encourage direct bypass of emergency transport of suspected LVO patients to TSCs, facilitate funding of new TSCs, mediate the training of significantly more stroke and neuro-interventional physicians and coordinate systems of emergency response. This issue is pressing not only because of the fact that more than 15,000 patients die every day from stroke,[5] but also 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 increase 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 Agency (DARPA) 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. Although it takes time to create stroke systems, 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 owing 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 and prevent a lifetime of disability but also reduce the long-term societal cost of caring for patients that are severely disabled after an untreated LVO stroke.

The Society of Vascular and Interventional Neurologists (SVIN) has the overarching goal of improving clinical care and patient outcomes with stroke and cerebrovascular diseases. In 2016, SVIN launched Mission Thrombectomy 2020 (MT2020), a global campaign to drive regional public health efforts to improve stroke care by increasing the annual rates of thrombectomy procedures owing to the disproportionate impact of LVO stroke on overall long-term stroke disability. A simple metric of doubling thrombectomies every two years in all regions was chosen and the global goal was set to increase annual thrombectomies from 100,000 approximately in 2018 to 202,000 by 2020. For this mission, SVIN is partnering with government agencies including ministries of health at state and national levels, medical non-profits, and industry leaders to improve public



awareness and establish financial initiatives to support the development of thrombectomy systems of care. The campaign has recently been renamed as MT2020+ to signify its continuation beyond the year 2020.

Here, we have brought together respected leaders of the stroke community, from inventors of clot-retrieval devices and thrombectomy aspiration catheters 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 to help in building thrombectomy 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 work in deploying a vital therapy to reduce death and disability after stroke. We review the vast and growing literature to support our mission and recommendations. We detail the processes to implement the following recommendations to health policy makers to strengthen their regional stroke systems of care to rapidly improve access to thrombectomy for stroke:

- Create a regional task force that includes nurses, stroke coordinators, neurologists, neurointerventionalists, EMS personnel, community physicians, and administrators of hospitals who deal with a high volume of stroke cases.

- With the help of the expert task force, assess the efficacy of the existing systems in place for the management of stroke and identify key gaps.

- Assess the cost and therapeutic effective-ness of existing systems and conduct a detailed analysis of clinical and cost benefits to the patients in your region.

- Help in establishing local or regional accreditation programs for stroke hospitals to be recognized in delivering stroke services.

- Develop policies that aim to reduce the burden of stroke and improve clinical outcomes.

- Create funds for patients in resource-constrained settings who will benefit from MT for LVO stroke.

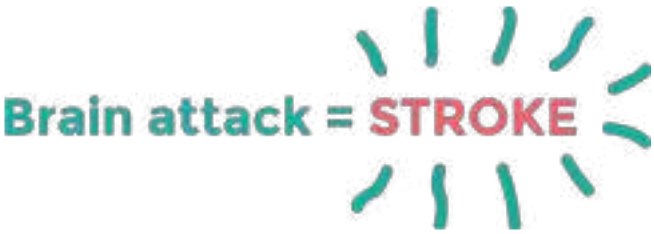
- Develop stroke education programs focusing on symptoms, the need to seek emergency care, and available stroke system resources.

- Set up and organize specialized regional thrombectomy systems of care that are equipped to carry out MT.

- Increase the number of training programs for neurointerventionalists with an aim to create adequate expertise for the management of LVO stroke.

- Modify key recommendations of stroke care to the local environment. Each recommendation should be adjusted to the needs and resources of each country.

Background



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), and this type of stroke comprises of approximately 85% of all strokes; if it is caused by a rupture of a blood vessel, it is called Hemorrhagic Stroke (HS) which comprises approximately 15% of strokes. Permanent brain damage is possible after only a few minutes of reduced oxygen supply, which kills brain cells and causes notable physical symptoms such as, but not limited to, a sudden onset of numbness or weakness in the face, arm, or leg on one side of the body, difficulty speaking, 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 large arteries in the brain.[52-59] LVO strokes represent approximately one-third of the total AIS population, and they correlate with significantly higher disability and death[58,60,61] owing to the large size of the blockage and a greater volume of brain damage as compared to non-LVO strokes.[62,63] The blockage is typically caused by migration of a clot (called an embolus) to the brain from the heart or a diseased vessel in the neck and its sudden enlodgement in a large brain artery, or sometimes clotting of a brain artery narrowed by atherosclerotic or 'fatty' buildup.[34]

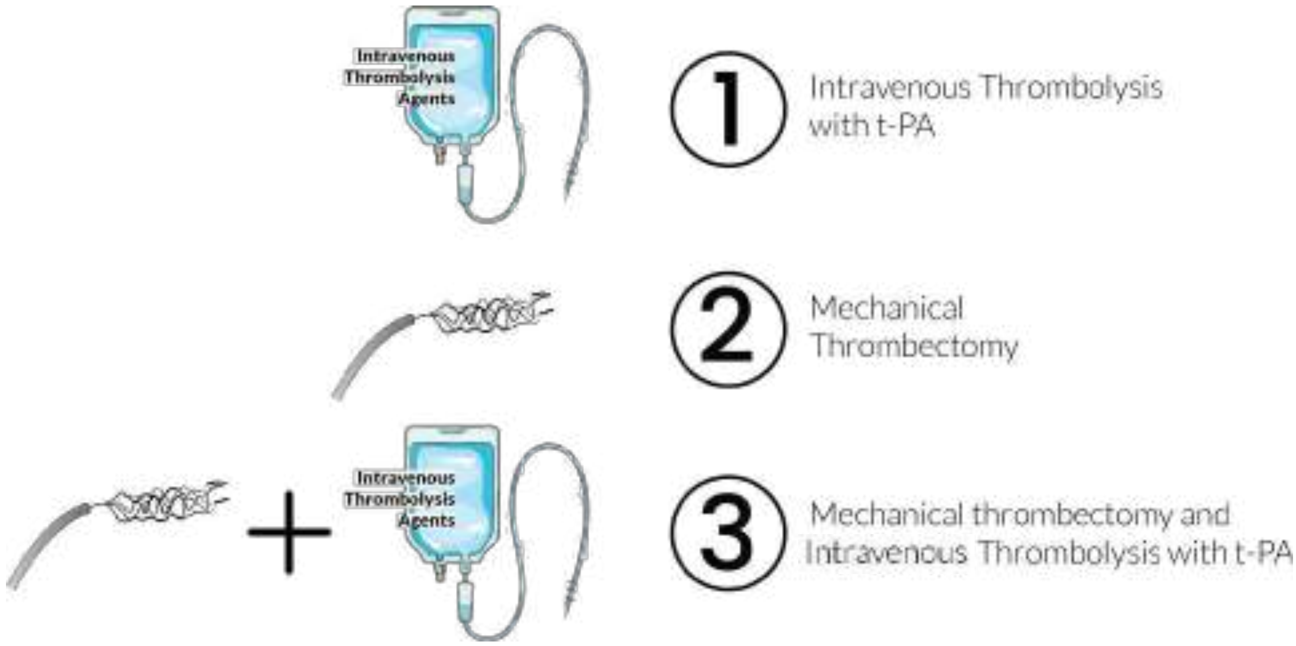
3. What are the current treatment options?

Current treatment for a patient with suspected LVO stroke starts with emergency imaging of the brain with specialized CT (Computerized Tomography) and MRI (Magnetic Resonance Imaging) scans to rule out a brain bleed, and emergent clot-dissolving medications given intravenously if the patient is eligible for them. After initiation of IV thrombolytics, additional CT or MR imaging is continued, ideally without moving the patient from the scanner, to image the arteries of the neck and brain to identify an LVO. In patients beyond 6 hours, a specialized perfusion scan to quantify blood supply in different parts of the brain is performed. If imaging identifies an LVO, the patient is rapidly transferred to the angiography suite for emergency mechanical thrombectomy to remove the clot blocking the large brain artery. During the course of treatment, sudden medical or neurologic complications of stroke are anticipated and managed. Finally, the most likely cause for stroke is evaluated, and treatment is directed toward 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 a clot-dissolving agent, Alteplase, given intravenously 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. Similar agents such as tenecteplase are also promising alternatives. Certain comorbidities such as hypertension (raised blood pressures) and hyperglycemia (elevated blood sugar levels) have been found to negatively affect its response in AIS patients.[70-74]



However, IVT alone has a limited efficacy in the treatment of LVO stroke as the size of blockage and burden of clot is very high and needs to be combined with mechanical thrombectomy to ensure the best chances for preventing long-term stroke disability.

Mechanical Thrombectomy (MT)

MT is a minimally invasive procedure wherein clots causing LVOs are removed using mechanical tools and blood flow is restored, saving brain tissue that was at risk of dying due to lack of blood supply.

During MT:

- A catheter is advanced into a large blood vessel in the thigh (or wrist) and navigated up through the neck until it reaches the blood clot causing the stroke.
- Using specialized X-ray guided imaging, a stent retriever (a slender mechanical tool that can remove the LVO) and/or an aspiration catheter is inserted into the blocked artery in the brain. The stent retriever and/or aspiration catheter engages the clot, and is “retrieved” (or pulled backward) to remove the blockage and restore the blood flow.

MTcombined with IVT

MT, in combination with IVT, significantly improves the odds of a good outcome after LVO stroke in patients selected with imaging criteria, 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.

For example, current guidelines only provide a Class 1A recommendation in the 0-3 hour time window and a Class 1B recommendation for the 3-4.5 hour time window. Additionally, IVT has limited ability to dissolve a large burden of clot, making it less effective for the treatment of LVO stroke;[75,76] however, a combined approach utilizing MT and IVT has overcome these limitations.[75]

4.MT for LVO Stroke: 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, with limited efficacy in large clots.[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.

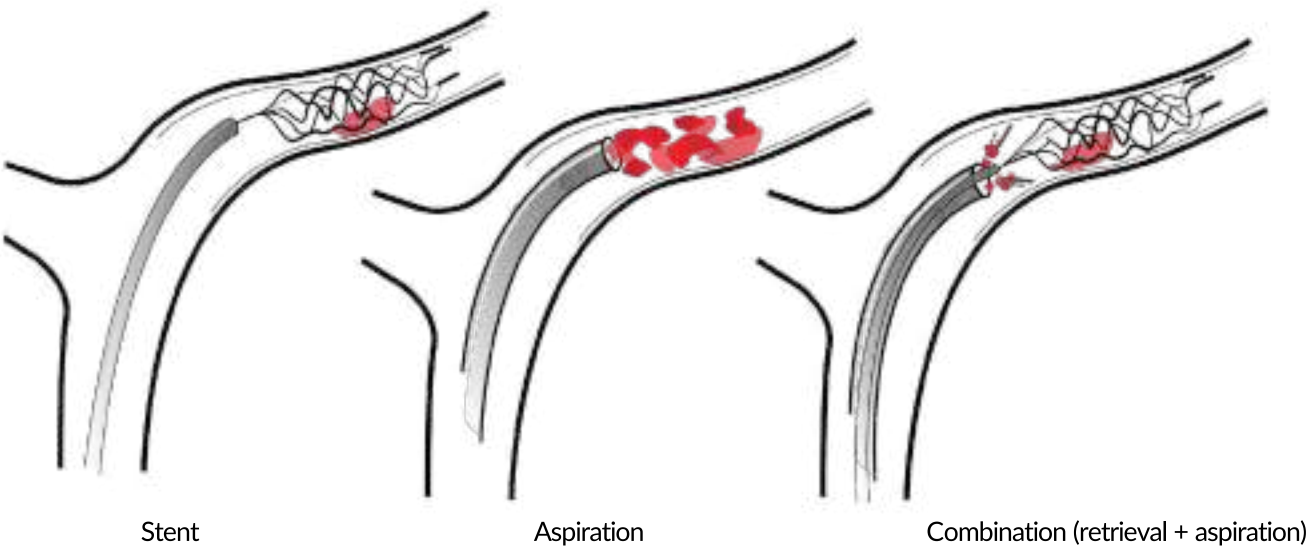
Tools that are used in MT can be classified into two different subtypes based on their mechanism of action:

(a) stent retriever
(b) aspiration catheters

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

Aspiration catheters for MT are flexible with a large inner diameter. A guidewire is inserted into the patient, with or without a microcatheter that is used to guide the aspiration catheter toward the clot, typically with suction force applied to the aspiration catheter at the end outside the body using a connected suction pump. When the clot is reached, it is engaged at the catheter tip and removed along with the catheter with continuous 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 lower cost 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, very high 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

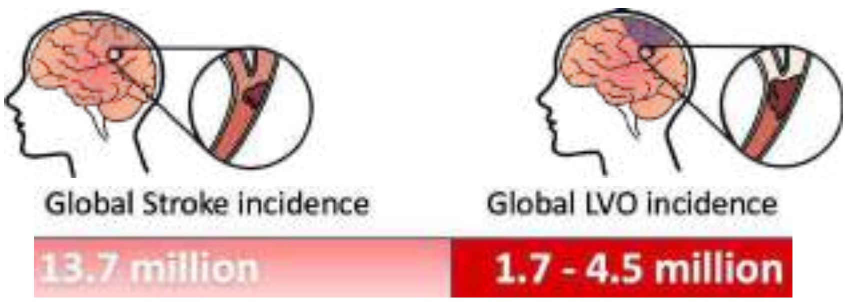
Stroke Demographics

A brain attack or stroke is currently the second leading cause of death and leading 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 all stroke was 13.7 million (12.7 to 14.7) in 2016, with 5.5 million deaths attributable to strokes worldwide.[3]

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]



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] There were 80.1 million (74.1 to 86.3) prevalent cases of stroke globally in 2016; 41.1 million (38.0 to 44.3) in women and 39.0 million (36.1 to 42.1) in men.

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. For survivors, it is a major cause of serious long-term disability, leaving many with 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% 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

Africa

Sub-Saharan Africa likely has the highest burden of stroke worldwide. However, due to lack of reliable data it is difficult to estimate the inci-dence of LVO as an etiology for stroke. However, in recent years hopeful signs are emerging in filling this gap in data as demonstrated by the Stroke Investigative Research and Education Network (SIREN), the largest case-control study of stroke to date in Africa, which studied a large number of patients from Ghana and Nigeria to determine the type and risk factors in young patients (<50 years old).[277]

France

By 2035 the incidence of stroke is expected to increase by 34% in Europe, which is mainly driv-en by the high prevalence of atrial fibrillation. Each year 140,000 people will experience a stroke in France, and for the past decade, the number of AIS admissions has increased by 32.8%. Across Europe it is expected by 2035, that there will be an increase of 34% of all stroke sub-types, mainly driven by the incidence of atrial fibrillation. Similarly, the number of endo-vascular procedures for LVO is consistently growing steadily with 2,822 treated patients in 2015 to 6,880 in 2018.[278] This corresponds to 56.2 endovascular interventions/million inhabit-ants. [277]

Mexico

Mexico has a stroke incidence of 232.3 per 100,000 inhabitants (IC 95% 27.8–436.9). The stroke prevalence has been calculated as 8 per 1,000 among people aged 35 years and older, and 18 per 1,000 among those aged 60 years or older. The rate of intravenous thrombolysis is 7.6%, with an in-hospital mortality rate of 3.2%. The most frequent AIS etiology is atherothrombotic (39%).[279,280]

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 advanced 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 its wide-spread 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 imaging-selected LVO strokes.[199]

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

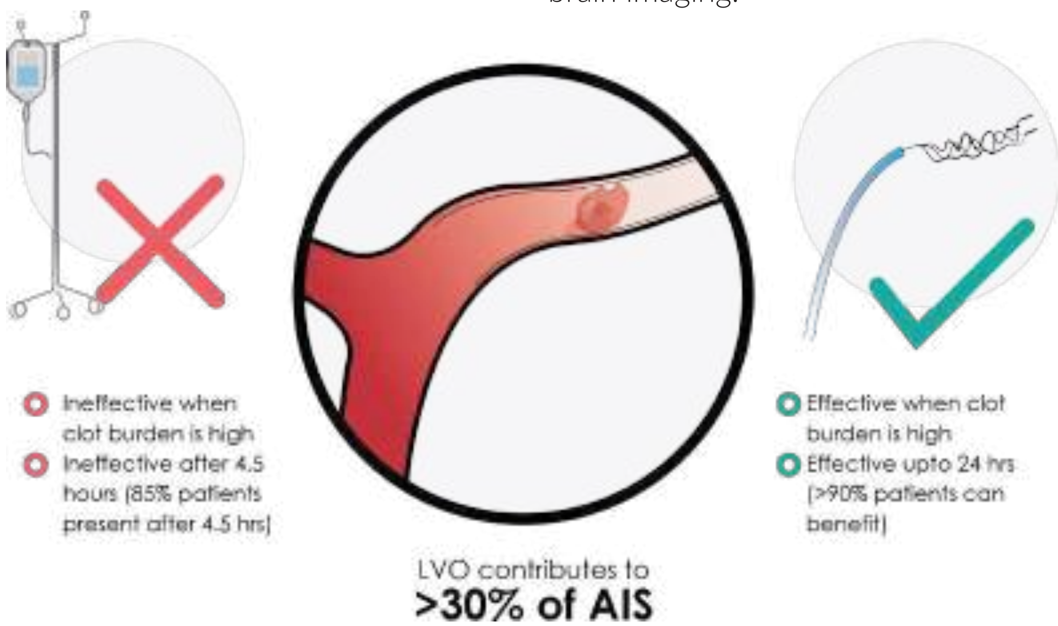
- Yields higher rates of revascularization and reduced rates of long-term functional dependence in patients with LVO stroke.[55]
- Extends the therapeutic time window for acute intervention up to 24h from stroke onset, which is greatly increased compared to the 4.5 hours restricted time window for IVT, allowing for a substantially larger number of LVO stroke patients to be eligible for reper-fusion treatment.[26]
- Removes clots resistant to IVT, such as older and larger clots blocking large arteries in the brain.[204]

2. Challenges to the effective treatment of LVO stroke

IVT may be less effective in LVO stroke.

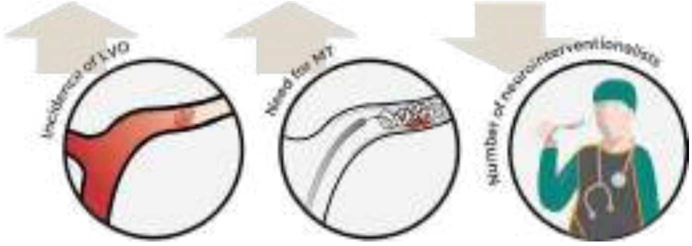
The only pharmaceutical drugs approved for the treatment of AIS are those used in IVT; however, these may be less effective in patients that have AIS due to an LVO, where the size of the clot is large, exceeding lengths of 8 mm.[165] Additionally, IVT must be administered within a narrow time window of up to 4.5 hours after symptom onset, which disqualifies usage in over 85% of the cases.[157-160]

For LVO stroke, MT with IVT when eligible, or without IVT 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 with standardized patient selection with brain imaging.[157-160]



Contraindications applicable to the use of intravenous rtPA in acute is-chemic 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 suggestive of subarachnoid hemorrhage
5. Prolonged blood pressure elevation (systolic ≥185 mmHg or diastolic ≥110 mmHg)
6. Hypoglycemia (serum glucose < 50 mg/dL)
7. INR > 1.7 or PT > 15
8. Heparin use within 48 h with an abnormally elevated aPTT
9. Arterial puncture at a non-compressible site in previous 7 days
10. History of gastrointestinal tract hemorrhage within 21 days
11. The recent history of major surgery in-tracranial or intraspinal surgery within 14 days
12. Previous history of a previous aneurysm, arteriovenous malformation, or intracranial neoplasm
13. Current use of a direct thrombin inhibitor or direct factor Xa inhibitors with evidence of anticoagulation effect by laboratory tests such as aPTT, INR < ECT, TT, or relevant factor Xa activity assays
14. Early ischemic changes are visible on CT in more than one-third of MCA artery vascular territory consistent with irreversible injury or evidence of hemorrhage on CT scan.



Need for more MT procedures

MT is typically performed by neurointerventionalists, physicians who are specialized by virtue of focused substantial training in the use of minimally invasive endovascular approaches to treat neurovascular disease. The 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.

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. A more urgent need, however, is supporting the establishment of TSCs in low and middle- income countries (LMICs) which will continue to be challenging given the primary out-of-pocket expenditures for healthcare and limited insurance reimbursements.

In LMICs, thrombectomy is mainly available in private hospitals but is scarce in public medical centers. The MERR (Mexican Endovascular Reperfusion Registry) showed that thrombectomy is effective as all other clinical reports, but mainly feasible in private hospitals, creating an enormous inequity in endovascular access.[279]

The main barrier to access to thrombectomy is the lack of funding to cover the treatment. Despite the high burden of disease that stroke presents, scarce public funding is assigned to treatment of the disease. The high cost of the medical supplies for MT represent the second main barrier to access thrombectomy. The RESILIENT trial from Brazil proved that thrombectomy is a cost-effective intervention for the public sector.[278]

Nonetheless, the study highlights the relevance of having adequate funding for endovascular devices. For example, in Mexico the average cost of thrombectomy supplies is USD 20,000 approximately. In a public hospital, the patient pays out-of-pocket for the devices to perform endovascular procedures. Another well-established barrier is the poor knowledge of stroke symptoms at the general population level, which limits timely access to IVT and MT. A Mexican nationwide study reported less than 25% of patients arrive during the first three hours since stroke onset, with no difference between public and private hospitals.[280]

3. Global cost-effectiveness of MT

The best outcomes from stroke care are time-sensitive, with better chances of functional improvements, restoration of blood flow and 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 long-term economic burdens. In fact, rapid treatment of AIS within 6 hours is accompanied by approximately 3–7 fewer days of hospital stays and fewer than 1-5 months of rehabilitation stays.[205] Mechanical thrombectomy performed for acute stroke within 8 hours of symptom onset was found to be cost-effective in a US study finding that the incremental cost of mechanical thrombectomy over standard medical therapy is $12,000 per quality adjusted life years (QALY) gained. This cost-effectiveness ratio is well below the generally accepted cost-effectiveness threshold of $50,000 per QALY gained.[281,282] In the SWIFT-PRIME trial, using lifetime projections, MT+tPA was associated with substantial gains in quality-adjusted life years (6.79 versus 5.05) and significant cost savings of $23,203 per patient when compared with tPA alone treatment.[20] For patients beyond the 6 hour window in the DAWN and DEFUSE studies, MT had a probability greater

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	($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]

	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 store-related costs. QALY, Quality-adjusted life years

than 99.9% of being cost-effective vs standard treatment alone at a threshold of $100,000/QALY as well as at a threshold of $50,000/QALY.[283]

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 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

United Kingdom

Combination therapy with MT and IVT 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]

	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.

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]

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 out-comes 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
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	 € 33,737.48 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.[119]
QUALYs, Quality Adjusted life years
INCER - Incremental Cost-Effectiveness Ratio

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 interhospital 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]

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 with or without IVT 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.

	≤ 6 hours	Standard Care	Difference	P-value
Hospital stay	$29,371	$33,736	($4,365)	
Hospital stay5 (days)		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 5. 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 IVt-PA and MT+IVt-PA, respectively. DALY, disability adjusted life years : QALY, quality adjusted life year.

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

	Combination Therapy	Standard Care	Difference
1-year Cost (CNY) QALYs ICER	 77.700 0,405 638.987	 27.220 0.326	 50,480 0.79
5-year Cost (CNY) QALYs ICER	107,710 1.765 131.689	58,590 1.392	49,120 0.373
6-year Cost (CNY) QALYs ICER	 114.170 2.029 113.814	 65.230 1.599	 48,940 0.43
30-year Cost (CNY) QALYs ICER	 167.970 3.773 63.010	 117,940 2.979	 50,030 0.794

Table 7. Cost effectiveness of mechanical thrombectomy in China
Data obtained from a 2018 retrospective cost effective analysis by Pan et al.(2018).[177]
Renminbi, CYN; quality adjusted life year (QALY); incremental cost ratio (ICER)

4. Emergency care pathway for 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, treatment specialists with 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, multistep 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.[190,192] 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.[190] 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.[230]

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 assessment & emergency radiological exams +/- 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[193,194] 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.[193,195] 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.[196,196,197] 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.[196]

Arterial 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, tailored 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 therapies 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.[245,24]

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 neuro-surgeon in order to ultimately achieve 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

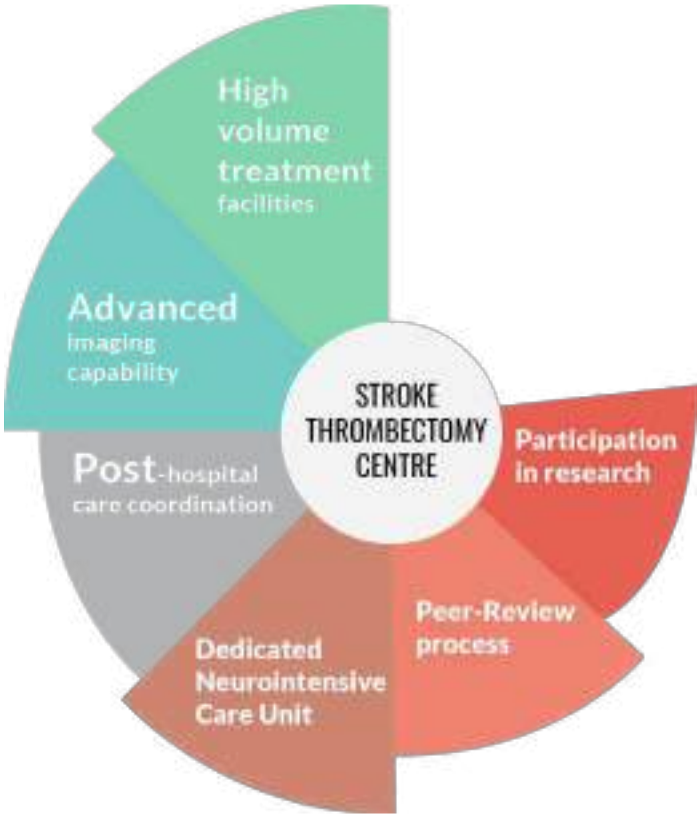
The field of stroke therapy is constantly changing and, as a result, physicians should be required to engage in at least 16 hours of stroke education on a biannual basis. Additionally, physicians are encouraged to participate in quality and improvement monitoring programs. Such programs would review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

Training Stroke Teams

The outcomes of LVO stroke treatments are time-dependent, as 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 increase 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 MTs 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 neuro-interinventionalists, 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 neuro-surgical management**

Owing 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 has 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 affect 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 that 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 a 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]

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 for global and regional policy makers

The following are selected recommendations from MT2020+ GEC that have broader global relevance. There are additional recommendations that may be useful for your regions of focus. MT 2020+ regional committees will engage with respective policy makers, if helpful, to identify and outline region-specific recommendations.

1. Create a task force that includes neurologists, neurointerventionalists, EMS personnel, community physicians, stroke-trained nurses, stroke coordinators and administrators of hospitals who deal with a high volume of stroke cases.

2. Assess the stroke disease and economic burden of stroke and LVO stroke in your region of focus.

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 public and private health systems and conduct a detailed analysis of clinical and cost benefits to the patients and overall population in your region.

5. Help in establishing local or regional certification programs for stroke hospitals to be recognized in offering stroke services

6. Develop a policy framework and specific policies that aim to reduce the burden of stroke and improve clinical outcomes. Each region may need a unique set of policies but there are examples of effective policies globally that can serve as starting points for your region.

7. Create government-supported funding mechanisms for patients in resource- constrained settings who will benefit from MT for LVO stroke.

8. Develop stroke education programs focusing on symptoms, seeking emergency care, and available stroke system resources.

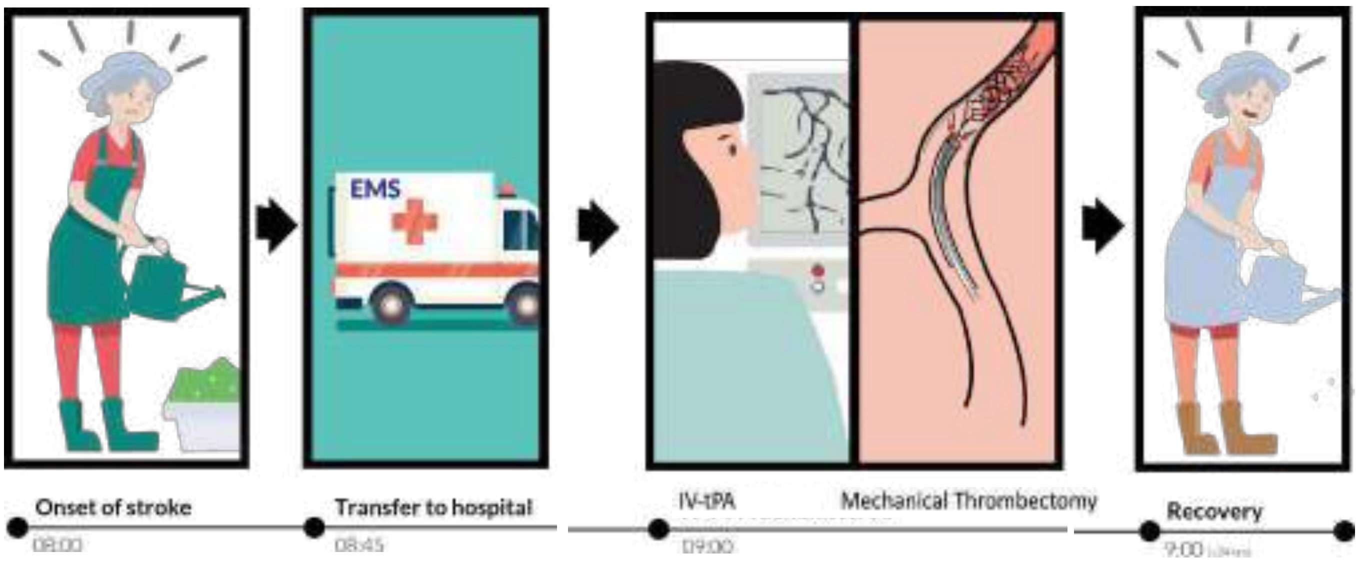
9. Set up specialized regional thrombectomy systems of care that are equipped to carry out MT.

10. Increase the number of training programs for neurointerventionalists with an aim to create adequate talent for the management of LVO stroke.

2. Patient journey as recommended steps in care pathway

Clinical History

Elizabeth, a 62-year-old woman with atrial fibrillation on warfarin, 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 FOR HEALTH POLICY MAKERS

1. Discuss this white paper with the Regional MT2020+ Committee members to understand how MT may potentially benefit your region.

2. Conduct discussions with key stakeholders and decision-makers for stroke management in your healthcare ecosystem to build consensus on top 5 Public Health Interventions for accelerating access to MT for LVO stroke.

3. Organize a meeting with clinical experts and decision-makers for policy-making in your region to evaluate the need for improvement in the management of LVO stroke.

4. Outline a draft regional MT policy framework with key components with the stakeholder group.

REGIONAL COMMITTEE ACTION PLAN FOR 2020

1. White Paper Communication to regional Health Policy Makers and health system stakeholders (such as hospital CEOs)

2. Regional electronic MT survey to establish baseline quantitative picture of MT numbers in your region.

3. Develop regional top 5 Public Health Interventions (PHI) for 2021 and a detailed implementation plan for your region.

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About the authors

SVIN: Society of Vascular and Interventional Neurolgy

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 Brain Attack or 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 owing 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, feeling lightheaded, change in mental state or consciousness, 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 popula-tion 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)?

A 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] owing to their larger infarct size[62,63] and more severe initial deficits than other stroke sub-types.[64,65]

LVOs can develop through four mechanisms – (1) occlusion at a primary arterial site secondary to the development of atherosclerosis of an intra-cranial artery, (2) extra-cranial artery atheroscle-rotic embolism or plaque rupture that results in the occlusion of an intracranial vessel, (3) car-dio-embolic events related to cardiac disease such as atrial fibrillation resulting in intracranial vessel occlusion, and (4) cryptogenic causes of vessel occlusion.[66]

LVOs often result in insufficient blood flow to brain tissue, causing damage to cells and in-flammation that culminate in the death of neu-rons, glia, and endothelial cells.[60] Although is-chemic changes occur within minutes, the ulti-mate 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 current 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 toward preventing recurrent ischemic events.

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

Intravenous Thrombolysis

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 backward – which removes the clot.

Mechanical Thrombectomy Combined with Intravenous thrombolysis

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 pretreatment 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 Trials (RCTs) 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,[151] and the outcome depends on the size of the clot, length of time between the onset of symptoms and recanalization as well as recanalization success, making it an ineffective choice for the treatment of LVO stroke.[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 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, and once in place, the mesh expands, trapping the clot, and then is 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 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 or parallel combination, phenomenal recanalization rates of up to 95% have been achieved [81], compared with stand-alone direct aspiration rates of 78%.

5. Incidence of Stroke and LVO: 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 globally was estimated to be 11.6 million; 63% of AIS and 80% of hemorrhagic strokesoccurred 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 mm-Hg 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 lives (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 in sub-Saharan Africa, had lower estimated lifetime stroke risk owing 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

Approximately half of all stroke-related deaths are attributable to ischemic stroke.[5] Yet all strokes are not created equal; the presence of a LVO has been associated with significantly worse outcomes,[128] increasing the odds of mortality within 6 months by 4.5-fold.[60] Ischemic stroke due to LVO has been reported in 11-46% of cases.[57,59,60,129-131] The most common definitions of LVO include the intracranial internal carotid artery (ICA), proximal middle cerebral artery (M1), distal middle cerebral artery territory (M2) and basilar artery (BA). Additional arterial territory with variable acceptance as LVO include the vertebral artery (VA), posterior cerebral artery, and anterior cerebral artery. Depending on the classification used, angiographic studies have shown LVO accounts for 31-46% of ischemic strokes and only 13% of transient ischemic attack (TIA).[60,129] Currently, LVO-related ischemic stroke data by country or global region is not available.

According to a 10-year systematic review carried out by Lakomkin et al,[132] despite variability in institutional LVO definition and reporting methodology, the prevalence of LVO among patients with AIS is greater than previously thought. The prevalence of LVO in AIS patients ranged from 7.3% to 60.6% among the included studies.[132] The weighted mean prevalence was 29.3% (weighted by the number of patients included in each study).[132]

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 unable to work.[97] Prevalence of stroke in 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.[97] Considering all stroke types, AIS account for nearly 87%.[96,97,133]

Ischemic strokes due to LVO stroke, where the occlusions of the MCA, ICA terminus, and BA occur, the annual incidence has been estimated at 24/100,000 people per year, equaling nearly 80,000 LVO strokes annually.[59] Several recent randomized control trials investigated patients with anterior LVO strokes (including ICA).[10,14,15,26] The mean patient age ranged between 65 and 70 years with no consistent differences of sex. Taken together, these studies found smoking, diabetes mellitus, atrial fibrillation, and hypertension to be significantly correlated with LVO stroke.[10,14,15,26]

China

Stroke is the leading cause of death in China, accounting for 22% of all deaths.[131] In fact, more than 7 million individuals in China experience stroke, of which 65% are ischemic.[134] Additionally, 35 - 40% of all AIS result from proximal large vessel atherosclerotic stenosis or occlusion.[131] A recent Chinese population-based study on 6,809 AIS patients in emergency health care revealed LVO stroke patients were older (mean age 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.[135]

Japan

In 2017, stroke was the third leading cause of death in Japan,[136] with 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.[137]

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.[138] A recent systematic review included 64 stroke-related articles in the Middle East between 1980 to May 2015.[138] 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.[138]

The prevalence of stroke in Saudi Arabia is estimated at 0.67%.139 In 1998, the first stroke incidence was reported at 29.8/100,000 person-years;[140] however, considering current demographics, incidence is estimated to have increased to 50.9/100,000.[141] A recent study examined stroke incidence in the Aseer Region, South-western Saudi Arabia and included 1249 first-time stroke patients admitted to an Aseer hospital between 1 January 2016 and 31 December 2016.[142]

Additionally, stroke was found to be more common in males.[142] The standard of care for stroke patients in Saudi Arabia lags behind other developed countries. As a result, nearly 95% of patients receive treatment at non- specialized stroke centers and do not receive reperfusion therapy regardless of stroke type, even for LVO strokes.[143]

India

India has transgressed through significant demographic, economic, and epidemiological changes,[144] resulting in increased life expectancy and a growing aging population.[145,146] In fact, during the past two decades, the cumulative incidence (105 to 152/100,000 persons per year) and crude prevalence (44.29 to 559/100,000) of stroke ranged greatly across different parts of the country.[146] In comparison to global estimates, these stroke incidence and prevalence rates are higher than those of high-income countries.[146-148] A 2014 retrospective study analyzed patient outcomes for endovascular treatment of AIS with LVO stroke in an Indian tertiary care center.[149] All patients had contraindications to or failed intravenous thrombolysis prior to endovascular treatment. Forty-five 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; half of these died.[149]

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 patients with AIS from a LVO stroke.[150] One-thousand seven-hundred twenty patients were included with a median age of 70 years with 58% male. The number of LVO stroke 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 considerably from 96 in 2011 to 994 in 2016.[150]

7. Challenges in the effective treatment of LVO stroke

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 Intravenous Thrombolysis 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 recombinant intravenous thrombolysis; however, it is not effective in patients with AIS due to LVO stroke, where the clot burden is very high, especially when the thrombus length exceeds 8 mm or location is proximal, such as terminal carotid artery occlusion.[165] This significantly limits the options for effective management of LVO stroke.

For LVO stroke, MT is the standard of care. 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 Intravenous Thrombolysis, and up to 24 h for MT. The restriction on Intravenous Thrombolysis treatment beyond 4.5 h disqualifies the majority of stroke patients admitted beyond this time- window (around 85%), thereby drastically limiting the eligible population.[157-160] This resulting low recanalization rate ranges from 13 to 50% in LVO of the proximal middle cerebral artery (MCA), the ICA, or the basilar artery.[16] 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. 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 neuro-thrombectomy devices, neurointerventionalists, thrombectomy procedures, and thrombectomy-capable hospitals.[135] 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 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 de-mand 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 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 CSC within 6 hours of symptoms onset are eligible for MT based on AHA/ASA guideline based eligibility.[143]

In Glasgow, roughly 15% of patients presenting 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 stricter; 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 addi-tional staff over a 10-year period was esti-mated at approximately US $230,000,000.

Asia

In Japan, the availability of stroke specialists is similar to that of the US. Accessibility var-ied by region, with rural areas with low populations having the lowest accessibil-ity.[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.

8. Protocol for implementation of MT

Stroke systems of care allow for the coor-dination 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 devel-oped stroke systems has the potential to save nearly two million28 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.

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.

9. 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 blood flow.[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 ad-vance 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 as 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, EXTENDIA, 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]

10.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] There-fore, combination therapy (MT and IV t-PA) lead-ing to successful recanalization within 6 hours after stroke onset leads to markedly improved outcomes compared to longer treatment win-dows 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 im-provements in the overall quality of life. Addi-tionally, 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 de-creased 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-effec-tiveness of combination therapy in relation to patient age (range 50 to 100 years).[208] Fifty year-old patients were found to have the great-est 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 willing-ness-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 expe-rience 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 pa-tient cost of $75,353/ year.[209] Similar to data from the US, the average annual cost for pa-tients 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 high-er total costs than standard therapy ($126,939 vs. $124,419), along with increased QALY (1.484 vs. 1.273 QALYs) with an associ-ated 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 com-bination therapy is estimated to save the Ca-nadian healthcare system $321,334/ year.[211]

Europe

United Kingdom

Combination therapy in the UK is similarly associated with higher initial hospitali-zation 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 sub-stantial 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 in-creases 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 onward. 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 in-creasing 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 com-pared to standard care.[220]

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 combina-tion therapy compared to standard care ($15,689 vs. $30,569, P=0.008), counterbal-ancing the additional costs of inter-hospital transport (average $573) and the MT proce-dure (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 5).[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]

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 6).[221] Patients treated with combination therapy also have improved health out-comes 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]

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.

11. 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 upto 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- proce-dural 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 threat-ening, and may increase the length of stay in in-tensive care and stroke units, while others in-crease 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]

12. 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 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 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]

13. 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 to ultimately achieve 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 is time-sensitive, 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 training is 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]

14. 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, neurointerventionalists, neurologists, 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

Owing 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 Interhospital 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 an 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.[43,44]

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 into 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 stand-ardizing 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 and improve outcomes.

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 GUIDELINES

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/Child-hood-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=JA-MA+Guidelines+for+Adult+Stroke+Rehabilita-tion+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-child-hood-clinical-guideline-diagnosis-management-reha-bilitation#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/PDF-Data/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 GUIDELINES

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 GUIDELINES

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