14th International Symposium on Thrombolysis, Thrombectomy and Acute Stroke Therapy

The 14th International Symposium on Thrombolysis, Thrombectomy and Acute Stroke Therapy (TTST) took place in Houston, Texas on October 21st and 22nd, 2018. TTST meetings began in 1990 during the initial simultaneous clinical investigations into thrombolysis taking place in the U.S, Europe, and Japan. Since then, TTST has brought together invited experts on reperfusion therapy for acute stroke every two years, and rotates among venues in Europe, North America, and Asia. TTST has provided opportunities for stimulating controversial discussions on data from recent clinical trials, the status of ongoing studies, and priorities for future research. Initially focused on thrombolytic therapy, recent TTST conferences have helped lay the groundwork for the success of thrombectomy clinical research.

The objective of TTST 2018 was to explore the changing landscape of acute ischemic stroke therapy and address current controversies in thrombolysis and thrombectomy. With the goal of reaching a consensus on how these therapies will evolve over the next several years, data of the relevant neuroscience was presented by experts of the field. Importantly, the emphasis was not only on scientific advances, but also on expanding access by a focus on systems of care with global relevance. Re-presentation of already-published data was discouraged. Invitees were selected to represent all specialties and regions involved in thrombolysis and thrombectomy. The format was a series of 3-4 talks on a general topic followed by an open discussion. Each talk was presented by a group of 3 experts and limited to 20 minutes. Another group of 3-4 experts led the subsequent discussion aimed at encouraging frank and open debate among all attendees. This manuscript summarizes the proceedings of TTST 2018.

1. Changing demographics of stroke and impact on thrombolysis and thrombectomy

Global incidence of stroke and projected future trends

Dominque Cadillac, George Howard, Anthony Kim

Annually, stroke is estimated to affect 15 million people worldwide, and is the third leading cause of disease burden.[1] In low and middle income countries (LMIC), 94% of deaths from stroke occur in people aged <70 years in contrast to 6% in high income countries (HIC).[2] A clear understanding of disease trends around the world is important. In the latest systematic review by Thrift and colleagues[3] it was confirmed that large geographical variations in stroke incidence and mortality persist, with the largest burden observed in Eastern European countries and China. However, data are lacking from many countries, making the world-wide assessment of the burden of stroke challenging. The Global Burden of Disease study has partially addressed this gap by providing estimates of the stroke burden in almost all countries. The estimates are derived by using evidence from the literature and modelling techniques to estimate stroke burden in countries with limited epidemiological information that is overseen by an expert group from 41 countries.[4,5]

Although there is evidence that stroke incidence rates have declined, and prevalence rates have remained similar, between 1990 and 2016 the absolute number of stroke survivors has almost doubled, and it is estimated that currently there are over 80 million people living with stroke (unpublished, Feigin 2018). Of great concern is that over 60% of people living with stroke are younger than 70 years. In HIC like Australia about 1 in 4 strokes now affects people aged 18-64 years, impacting their ability to work and their role in society.[6] However, the burden of stroke at lower ages is much larger in LMIC where stroke affects people at a younger age and where overall life expectancy is lower. In terms of disability and deaths, the greatest burden currently resides in developing countries, and the gap between developed and developing countries is increasing.[4] Increasing life expectancy and population growth explain some of these trends which are compounded by a global epidemic of people with metabolic risk factors such as obesity, type 2 diabetes and hypertension,[4] which are important risk factors for stroke.[5]

These changes in the burden of disease from stroke are the result of demographics shifts, as well as health sector and non-health sector trends. Population growth, particularly in the developing world, as well as aging, particularly in upper income and middle-income countries, both contribute to the increasing absolute stroke burden expected in the coming years.[7] Trends in population level for risk factors such as hypertension and the expected impact of both favorable and unfavorable trends vary across countries, with unfavorable trends in blood pressure and obesity in China and Brazil for instance, as compared to generally favorable trends in blood pressure and cholesterol in many developed countries, but not obesity.[5] The net impact of these factors is that there is a substantial increase in the

relative age-standardized burden of stroke in the developing world, while many developed countries continue long-term trends of improvement, but a substantial increase in the absolute burden of stroke is expected with any potential improvements in incident events outweighed by demographic shifts.[1]

In the US, the absolute age-adjusted mortality rate for stroke has potentially plateaued after decades of decline. Coupled with the continued "greying of America" where the population will continue to age in the coming decades, with substantial growth in the oldest of the old (age > 85) which will double from 5% to 10% of the population, there are accompanying changes in the race/ethnic distribution of the aged as well (**Figure 1**).[6] A forecasting model that combines estimates of population growth, assumed stroke incidence rates by age, sex, and race/ethnicity, predicts substantial shifts in the distribution of stroke events over the next 40 years. A more than doubling of the total number of stroke events is expected, with nearly all of this increase in the elderly where the proportion of strokes occurring at ages 75 and older increasing from 50% in 2010 to 61% in 2050. Projected changes will also have an impact on the race/ethnic distribution of stroke events with a decrease in the proportion of strokes that occur in whites from 75% to 56%, and an increase in Hispanics from 11% to 24%. These forecasts justify the need to expand capacity to treat patients with stroke, to refine interventions and therapies to the elderly population, and to focus on stroke care for minority populations in the future. We also need to ensure capacity building in LMIC countries to support efforts in the prevention and treatment of stroke, and overall, encourage routine and standardized data collection for better capturing the burden of stroke around the world.

Global rates of thrombolysis and thrombectomy
Dawn Kleindorfer, Werner Hacke, Kazunori Toyoda

Over the past decade, thrombolysis rates have increased particularly in a subset of patients arriving within 2 hours from time of symptom onset. Overall use of IV tPA in patients, without regarding time of arrival or contraindications for tPA administration, has remained similar.[8] Utilization rate in centers located in urban communities has increased but rural areas don't exhibit the same pattern. After the publication of pivotal RCTs, mechanical thrombectomy rates showed a significant increase in patients arriving up to 4.5 hours after symptom onset and an NIHSS > 5, with a significant 7% increase in all stroke patients, despite the fact that almost two-thirds of patients arrive in the late time window.[9] In Europe, Germany reached in 2016 a thrombolysis rate of 13.5% and a thrombectomy rate of 4.5%, with access to mechanical thrombectomy becoming available for patients from rural areas, although at a lower rate. The far majority of patients are being treated in high-volume centers with more than 25 cases/year and more than 50% are treated in centers with over 100 patients/year.[10] Asia exhibits very low thrombolysis and thrombectomy rates when compared to each individual country's population, as presented by Kazunori Toyoda, M.D by verbal communication. Access to thrombolysis and thrombectomy centers, along with patient eligibility at the time of hospital arrival may account for this trend.

Changing stroke demographics and characteristics as a result of preventive interventions and impact on thrombolysis and thrombectomy with focus on atrial fibrillation and LVO vs non-LVO stroke

Phil Bath, Mitch Elkind, Hooman Kamel

The concept of the "epidemiologic transition" has been used to explain the shift in the relative proportions of diseases that may occur in countries as they pass through different stages of development.[11] Epidemiologists described at least five stages of transition. In the first stage (pestilence and famine), nutritional deficiencies and infections dominate; in the world of stroke, Chagas disease could occur, for example. The second stage is characterized by diseases related to hypertension, such as hemorrhagic and small vessel stroke, and includes large parts of Asia, including China. In the third stage (degenerative and man-made diseases), high fat diets, sedentary lifestyles, and cigarette smoking allow chronic, degenerative, and "man-made" diseases, including cardiovascular disease and ischemic stroke, to become more prominent, as in urban India. In the fourth stage (delayed degenerative disorders), there are increased efforts to prevent, diagnose, and treat these lifestyle-related diseases, which allows for a delay in their age of onset as well as the increase in degenerative diseases affecting the elderly. Western Europe and North America are considered to be in this fourth stage of the epidemiologic transition. At this stage, we might expect an increase in large vessel occlusions due to atrial fibrillation and other sources of cardioembolic stroke, as well as effects of large artery atherosclerosis, amyloid angiopathy, and vascular dementia. Finally, a fifth stage of societal upheaval and social regression may exist in which existing health structures break down, leading to a resurgence of conditions seen in the first two stages, as well as to the effects of violence and accidents (parts of post-Soviet Russia has been suggested as an example). Here, vascular neurologists and stroke physicians would encounter traumatic hemorrhages of many types.

Empirical evidence of the epidemiologic transition in relation to stroke was well described in the Sino-MONICA-Beijing project.[12] In this community-based surveillance study, there were temporal trends in stroke incidence and subtype in Beijing over only two decades of rapid economic development, from 1984 to 2004. Four characteristics of the epidemiological transition were observed: declining incidence of hemorrhagic stroke due to improved treatment of hypertension, reduced case fatality due to improved treatment after stroke, increased age of stroke onset, and an expanded proportion of ischemic heart disease deaths with a decreased proportion of stroke deaths in the study population. Additionally, an increase in the incidence of ischemic stroke was found which was felt to be secondary to increased atherosclerotic risk factors. Though not a particular focus of this analysis, it is likely that cardioembolic stroke related to the aging of the stroke population and the increase in ischemic heart disease in particular, and thus large vessel occlusion, would be part of this picture.

Of course, the epidemiologic transition is not limited to the developing world, and disparities are reflected within nations. In the United States, racial minorities suffer increased stroke mortality and disability rates compared to non-Hispanic whites. African Americans have the highest mortality rates due to stroke and Hispanics have a higher stroke incidence than whites. In the southeastern United States, within a region referred to as the "Stroke Belt", stroke mortality and incidence rates are increased. The highest rates are found along the coast, in Georgia and North and South Carolina, in a region nicknamed the "Stroke Buckle". Variations in race or ethnicity of people comprising the population do not appear to fully explain the disparities in stroke mortality and incidence that exist in the southeastern United States, since African-Americans in the Stroke Belt have increased stroke risks compared to those in other parts of the country.[13] The difference may be attributable to socioeconomic factors limiting access to care, producing an increase in the prevalence of stroke risk factors.[14] In an analysis of the National Health and Nutrition Examination Survey, moreover, there is evidence that despite improving trends in the burden of cardiovascular risk factors among high income individuals in the US, low income populations are not sharing in these favorable trends. [15] Thus, while there have been improvements in the control of risk factors for cardiovascular disease in the US, it remains unclear that all socioeconomic strata have benefited equally, and as the population grows, we can expect more LVO to occur.

In this context, it is also important to ask if there are differences in the risk of LVO by sex or race/ethnicity. The two major stroke mechanisms leading to LVO are cardiac embolism and large-artery atherosclerosis. Although there is less atrial fibrillation (AF), the most common cardioembolic risk factor in women when adjusting for age,[16] this issue is less relevant at the time of stroke presentation since women generally present with stroke at a later age. In support of this, there was an essentially even distribution of men and women in trials of mechanical thrombectomy or other acute stroke therapies.[17] There are race/ethnicity-related differences in ischemic stroke subtypes, with Caucasians having a higher risk of cardioembolic stroke and Asians a higher risk of large-artery atherosclerosis.[18] However, given the contribution of large-artery atherosclerosis and cardiac embolism to LVO, there appear to be no race/ethnic differences in LVO risk.[19]

Discussion Panel

Joe Broderick, Devin Brown, Nicole Gonzales, Anjail Sharrief

With aging of the population and changes in racial demographics in the United States, we expect an increased number of strokes in Hispanics, elderly, females in the coming years and we need to be prepared for this. These changes raise a number of questions. Will we see an increase in patients with cardioembolic stroke requiring greater demand for EVT? Are we prepared? Do we have the interventionalists situated in the right regions? Currently rural areas are largely underserved. On the other hand, understanding the 'denominator'

helps to determine which patient population we are going to shift resources towards. The reality is that the percentage of patients eligible for EVT, while growing, is still small.

On a global level, there are very limited data in lower income countries where incidence of stroke is increasing. For these countries, the best use of resources may be in prevention. We should not exclude the possibility that some countries may have resources to provide thrombolytic therapy and we should support these countries in establishing stroke centers; however, setting up endovascular labs and advanced imaging does not seem plausible and the public health benefit of endovascular therapy much more limited. Even in the US, despite the exciting advances in endovascular treatment, the biggest public health benefits are still in prevention. Finally, it important for us to see input from physicians in lower income countries to determine the type of support that it is needed.

Key Points:

- Stroke incidence forecasting models predict a more than doubling of the total number of stroke events, with nearly all of this increase in the elderly. The racial profile of stroke patients will also rapidly change in the next decade.
- While there have been improvements in the control of risk factors for cardiovascular disease in the US, it remains unclear that all socioeconomic strata have benefited equally, and as the population grows, we can expect more LVO to occur.
- At present, thrombolysis and thrombectomy rates around the world remain low relative to the clinical burden of stroke. This disparity raises serious questions as to our preparedness for the forecasted increased stroke numbers, and suggests a redoubling of efforts aimed at prevention.

2. Thrombolysis and thrombectomy—where, when, and who?

Existing and projected distribution of thrombolysis centers worldwide

Jeyaraj Pandian, Pooja Khatri

In the United States, the most recent analysis of the geographic distribution of thrombolysis centers from administrative data described access of the US population to all facilities that provided at least one case of IV r-tPA for acute ischemic stroke.[20] The 2011 US Medicare Provider and Analysis Review (MEDPAR) data set was used, although it was limited by excluding patients younger than 65 years of age, except transplant and permanently disabled patients. Based on this analysis, by ground, 81% of the US population may have access to intravenous-capable hospitals within 60 minutes and by air, 97% may have access to intravenous-capable hospitals within 60 minutes. These projections may overestimate,

since provision of one dose of alteplase may not guarantee an appropriate level of thrombolysis readiness. Similar good penetration of thrombolysis centers is likely in Canada, based on even older numbers from a 1998 publication using 1996 interim census numbers by Scott et al[7] They used Geographic Information System (GIS) just like the US study, but identified hospitals capable of delivering IV r-tPA as those with a CT scanner and a neurologist and EM specialist on staff, as opposed to the actual administration of at least one dose of IV rtPA. 67.3%, 78.2%, and 85.3% of the total Canadian population were within 32, 64, and 105 kilometers, respectively, of an identified hospital.

Among the South Asian countries, India and Thailand have organized stroke programs with thrombolysis and thrombectomy capable centers. The IV thrombolysis rates in India (1.25 to 4.58%) and Thailand (4.78%) are growing every year. There are 75 centers in India currently offering mechanical thrombectomy with an overall of 1,000 procedures a year. In India the government has approved the use of tenecteplase, a generic biosimilar which is cheaper than alteplase for acute stroke treatment. Over 4,800 patients have received tenecteplase in the country. In Thailand, 25 hospitals offer endovascular treatment for stroke. In Pakistan and Srilanka, IV thrombolysis is being used but only a few centers may provide EVT. For South Korea, government nationwide initiated 11 Regional Comprehensive Stroke Center since 2008. After the initiation, door-to-needle time for the intravenous thrombolysis was shortened to less than 30 minutes in the CSCs and the chance of intraarterial thrombectomy was increased from 30% to 47% in 2016 after the initiation of the CSCs. However, the quality of acute stroke management including thrombolytic therapy has not been clearly known in the provincial area of South Korea.[21]

Where and for whom should thrombolysis be done
Phil Scott, Henry Ma, Didier Leys

Use of thrombolytic therapy in acute ischemic stroke patients requires an initial recognition of stroke symptoms, confirmation of diagnosis and eligibility for therapy, proper delivery of thrombolytic agent, and a follow-up period post treatment. A prompt recognition of signs or symptoms associated with stroke in the prehospital setting is crucial in reducing delays to stroke identification and time from onset to hospital arrival, thus increasing the number of patients that may be eligible for thrombolytic therapy. Utilization of a single emergency number may speed healthcare access, along targeted education programs for physicians, hospital and EMS personnel have demonstrated utility in increasing thrombolytic treatment rates.

Confirmation of diagnosis requires a focused history and through neurological examination to rule out other causes of acute neurological deficits. Minimal neuroimaging requirements include a noncontrast head CT, with a CT angiogram as a tool to identify patients with a large vessel occlusion who would benefit from mechanical thrombectomy. New emerging technologies such as machine learning and biomarkers may aid in the near future to accurately define a positive stroke. As evidence from clinical trials becomes available and

the experience in thrombolytic administration increases, some of the exclusion criteria are changing from absolute to relative, allowing more patients to benefit from medical management. Therefore, the physician should evaluate on an individual case basis the benefits and risks of thrombolysis.

Delivery of thrombolytic therapy may occur in the field through mobile stroke units or in the emergency department/hospital. European systems of stroke care have demonstrated that the prehospital intravenous administration of alteplase can be accomplished effectively and increases the proportion of patients receiving thrombolysis within 60 minutes of onset. Prehospital administration of alteplase may translate into better outcomes in patients with pre-stroke dependency compared to in-hospital administration.[22] Generalization of pre-hospital delivery of thrombolytics faces challenges in non-densely populated regions and in non-resource rich communities.

Expanding Thrombolytic Use Safely

Minimal resources need to confirm eligibility for thrombolytic treatment are currently based on either a checklist approach identifying evidence based inclusion and exclusion criteria or utilizing physicians with stroke thrombolytic expertise, again, provided either at the bedside or remotely via telemedicine. Further minimal requirements include initial selection of a specific thrombolytic agent to be used (which includes cost, actual drug availability, physical drug stability, and physical drug delivery (availability of intravenous infusion pumps, etc.) which are important considerations in limited resource environments globally. Finally, minimal resource requirements for the management of post thrombolytic treated patients require cardiac and blood pressure monitoring and management capability. This can be implemented using, again, either a checklist approach by local post-thrombolytic care providers or accessing physicians with thrombolytic expertise either at the bedside or remotely via telemedicine and includes management of treatment complications.

Numerous points in the stroke chain of survival exist in which to improve and expand thrombolytic use safely. Improved prehospital systems reduce delays to stroke identification and treatment. Data indicate that public education to identify stroke symptoms and recognition of stroke as an emergency and that is sustained over time reduces delays. Utilization of a single emergency number (911 in the United States and 112 in the European Union) also speeds healthcare access. Targeted education programs for physicians, hospital personnel and EMS personnel have demonstrated utility in increasing thrombolytic treatment rates. Finally, consistent utilization of prehospital notification by EMS personnel has been demonstrated to reduce in-hospital delays to stroke treatment.

In communities where thrombolytics are administered only within a stroke unit, opportunities to expand use safely include starting treatment prior to stroke unit admission by providing remote neurologic expertise either in person or by telemedicine. Interactive

and multifaceted training programs for emergency physicians have demonstrated increased access to thrombolytics in the community setting. These programs frequently include an organized protocol for emergency evaluation.

The existing paradigm of excluding patients from thrombolytic use on the basis of time has the potential to yield to a future paradigm where patients are excluded on the basis of perfusion imaging. This reflects prominent advances in the fields of neuroimaging to provide meaningful information on local tissue viability in stroke. If ultimately proven efficacious, such a shift will remove the single most common barrier to thrombolytic treatment–time from symptom onset.

As experience with thrombolytic delivery increases and further data on thrombolytic use becomes available, some prior exclusion criteria are migrating from absolute to relative. Note should be made by the practicing clinician that the level of evidence for this migration frequently comes from non-randomized trials.

Discussion Panel

Chris Lewandowski, Wade Smith, Nerses Sanossian, Martin Ebinger

The use of intravenous thrombolysis in the Emergency Department is hindered by the limited clinical experience and teachings of the average emergency department physician. About 8 percent of emergency medicine consults corresponds to acute stroke, with 1 to 2% being ischemic stroke. It is estimated the ED doctor treats 2 acute ischemic stroke patients per decade with thrombolysis. The lack of experience and the low availability of neurologists on site doesn't allow for physicians in the front line to take a more active role in the care of stroke patients. It is thought that by simplifying the review of eligibility and providing support for the use of thrombolysis more physicians may feel comfortable delivering thrombolytics to patients. Telemedicine has proven to be an essential tool in this process, as well as involving nurses and advanced nurse practitioners in the stroke care.

In addition, further development of pre-hospital triage is needed. There have been major advances in the prehospital evaluation and triage of stroke in the last few decades. Progress has been made in education of the lay public about the importance of activating Emergency Medical Services (EMS) as soon as stroke is suspected, prehospital stroke identification, and routing of stroke patients to designated acute stroke center hospitals. Areas of active investigation in prehospital stroke include in-ambulance therapy (i.e. neuroprotective agents), mobile stroke unit ambulances with imaging capabilities, and multi-tiered routing protocols. The goal of any prehospital system of stroke care is to deliver patients quickly and safely to the most appropriate hospital.

Prehospital large vessel occlusion (LVO) triage may delay IV tPA in patients without LVO through longer transport times and bypass of closer hospitals, since treatment of AIS with IV tPA is time dependent and every 15-minute delay in IV tPA reduces the chance of

functional recovery.[23,24] A false-positive prehospital LVO stroke triage assessment (over-triage) may direct EMS to extend transport times by bypassing an IV tPA-capable hospital in favor of a more distant higher level of care, contributing to worse outcomes and may decrease efficiency of non-thrombectomy hospitals due to reduced case volume and experience,[25] whereas more specialized centers may become crowded with patients not requiring their advanced expertise and be unable to accept transfers of complex cases as a result of increased volume.[26]

On the other hand, stopping for IV tPA at a non-thrombectomy-capable hospital delays endovascular thrombectomy which, like IV tPAis highly time-dependent.[17,27,28] A false-LVO assessment may route a patient with AIS-LVO to a hospital without endovascular capabilities (under-triage). For patients requiring secondary transfer, inter-hospital transport delays EVT by 95-109 minutes,[29,30] and transfer delays of more than an hour are common.[31] Every 4-minute faster start of thrombectomy lowers the degree of 90-day disability (mRS shift) for 1 of 100 treated patients.[32] For dichotomous outcomes, mistriage is associated with an absolute 8% decrease in freedom from disability and an absolute 9% decrease in functional independence.[33]

We need to get the right patient to the right place in the right time. EMS exists to identify and stabilize patients with time dependent emergencies while ensuring the right patient gets to the right hospital in the right amount of time. This art of triage may bypass the closest facility for the most appropriate facility and, when performed correctly, improves outcomes after trauma,[34] acute myocardial infarction,[35,36] and out of hospital cardiac arrest.[37] Proper EMS triage can be the most cost-effective strategy in developing systems of care and is favored over creation of more specialty receiving facilities.[38] Under-triage, or taking a patient to a lower-level of care than optimal, introduces delays due to secondary transfer. Emergent definitive neurosurgical care with ventriculostomy, decompressive craniectomy, or aneurysmal clipping or coiling for ICH[39,40] and SAH[41-44] is unnecessarily delayed. Over-triage, or taking a patient to a higher level of care than required, can overwhelm highly-specialized centers and impact the ability to accept higher-acuity transfers due to capacity, can starve less-specialized centers of case volume and clinical experience, and can delay care for patients who do not need the advanced therapies offered at the specialty center (e.g., prolonged time IV tPA).

In the setting of stroke, almost all published experience with existing EMS triage tools focuses on identifying patients with LVO, which conflicts with the purpose of triage itself which is to get the right patient to the right place in the right amount of time, regardless of diagnosis. We need to refine prehospital assessment of stroke patients to focus not only on LVO but on how to best get patients the care they need to improve outcomes and increase disability. This may require a regional approach, but making thrombectomy available to the greatest numbers of individuals in the shortest time will require development of new prehospital tools.

Key Points:

- Earlier identification of stroke syndromes, particularly in pre-hospital settings, is crucial to ensure the right patient is treated in the right place.
- Minimal requirements for thrombolysis are being and should continue to be rethought, as treatments are moving out of specialized centers and closer to patients, particularly through Mobile Stroke Units.
- As thrombolysis becomes a viable treatment options for greater numbers of patients through increasingly complicated imaging and decision-making pathways, the need for additional availability of Neurology expertise, or training of ED physicians, gains heightened relevance. Options include telemedicine, checklists, and consistent messaging to ED providers.

Existing and projected distribution of thrombectomy centers worldwide
Raul Nogueira, May Nour, Olvert Berkhemer

The mismatch between lower resources and the increased stroke incidence is a devastating challenge that demands a timely solution. Despite the increased number of centers capable of carrying out mechanical thrombectomy, long travel times and delay in identification of patients with LVO who should be transferred to comprehensive stroke centers limit stroke care. In the United States, the two most prevalent certifying bodies are the Joint Commission and the DNV-GL. There are 194 CSCs accredited by the JC as a facility with NeuroInterventional coverage with a neurologist on site and a backup physician, with coverage for stroke neurology, neurosurgery, and neurocritical care coverage available 24/7. 67 current CSCs accredited by the DVNGL are required to provide only neurointerventional coverage 24/7 and have the ability to either accommodate or transfer out neurosurgical emergencies. In March 16, 2018, the JC in collaboration with the AHA/ASA certified the first Thrombectomy-capable Stroke Center (TSC) defined as a facility with EVT capability 24/7, have at least 15 patients with ischemic stroke in the past 12 months or at least 30 patients over the past 24 months, and was required to collect data for 13 standardized performance measures, and meet expectations of neurological expertise availability aligned with that of a CSC. These certifications served the goal of improving patient outcomes by facilitating access to care for stroke patients, so patients with a suspected LVO would get re-routed to the nearest CSC or TSC center rather than to a PSC. In Canada, thrombectomy access is evolving with a projected creation of 6 centers across the country. Latin America has a very limited distribution of thrombectomy centers when compared with the increase morbidity and mortality associated with acute stroke. In Europe 32% of the countries have overall EVT coverage, with the rest not providing EVT due to high costs and lack of trained personnel and facilities. 29% of eligible EVT patients were treated in 2016, and around 52% of centers are available 24/7.[45]

Where should thrombectomy be done—centralized vs distributed model; what do the guidelines say and how do they square with reality?
Tudor Jovin, Bernard Yan, Diogo Haussen

The American Stroke Association 2018 guidelines regarding the provision of thrombectomy services to acute ischemic stroke clearly recognizes that patients should be treated at experienced thrombectomy centers with rapid access, qualified neurointerventionists, and comprehensive periprocedural care team.[46] Evidence for other neurological diseases, such as subarachnoid hemorrhage and carotid endarterectomy, prove a worse clinical course in patients treated by lower volume operators at low-volume centers.[47-56] This is buttressed by similar experiences in the field of coronary percutaneous intervention and trauma.[57] Importantly, both operator and center volumes metrics are to be considered together, since one affects the other when evaluating for quality of care.[58] The data on mechanical thrombectomy has accrued and uniformly point towards improved outcomes in patients treated in higher volume centers.[59,60]

Significant concerns and unease were voiced by the presenters and the audience of the low volume (fewer than 15 thrombectomies per annum) required by the Joint Commission to qualify as a thrombectomy center, especially since most centers performing thrombectomies appear to have volume <10 thrombectomies per year (and therefore expected lower quality of care). The presenters also outlined different models of care including a decentralized model whereby high volume neurointerventionists travel to the spoke center to provide thrombectomy services.

Discussion Panel
Carlos Molina, Ed Jauch, Albert Yoo

The question of who should be performing EVT, both in terms of physician qualifications as well as hospital qualifications, was a central question during this meeting, and one that pervaded nearly all the discussions of the first day. In this discussion section, the speakers noted that there is an ongoing debate regarding manpower needs for mechanical thrombectomy and more broadly for neurointerventional procedures, which include treatments such as aneurysm coiling and AVM embolization. However, this debate ignores the fact that most neurointerventionists coming out of training do not move to underserved communities. They move to metropolitan areas where established practices already exist. Healthcare systems shoulder some of the blame. Despite the presence of nearby comprehensive stroke centers, in the United States hospitals are incentivized to become comprehensive or thrombectomy-capable centers to capture EMS traffic and the higher reimbursements associated with thrombectomy care. As a result, neurointerventional practices are competing for smaller and smaller case volumes, and the debate has naturally shifted to focus on the better outcomes at high-volume centers as an argument to stem this tide.

Meanwhile, populations residing in rural markets are being neglected. Patients who suffer a large vessel stroke in these communities must be transported to the closest major city. Unfortunately, transport can take several hours even with air transport. Despite publications projecting adequate neurointerventional availability to much of the US population, there is a clear need to better distribute thrombectomy expertise to underserved areas, given the highly time sensitive nature of large vessel stroke. If there are not enough aneurysms or AVMs to support a full-time neurointerventionist in a rural market, then other interventional disciplines (peripheral radiologists or when necessary even interventional cardiologists) may be trained to provide thrombectomy care. Alternatively, neurointerventional training and certification guidelines may need to be altered to accommodate this shift in modern neurointerventional practice, in which the largest need is for acute ischemic stroke, and as such requirements mandating high numbers of aneurysm and AVM treatments may be outdated. In such a system, additional thrombectomy-capable interventionists would be credentialed to treat large vessel strokes in regions where there is demonstrated need. Although thrombectomy care in the rural setting is likely to be less optimal than at high-volume centers in major cities, it may be better than the alternative which is to delay treatment by hours or to have a high proportion of cases that do not meet treatment criteria due to a combination of late arrival and large infarct volume (i.e., futile transfers).[61,62] The neurointerventional community along with other professional organizations should propose criteria for defining areas in need of local thrombectomy expertise and decide what constitutes adequate thrombectomy training and long-term quality assurance in these areas. Hybrid models including tele-neurointerventional expertise for intra-procedural decision making may help to bridge the quality gap. As technology continues to advance, remote robotic intervention may also be possible.

Key Points:

- At present, there is a palpable shortage of access to high quality EVT care. This shortage is present in developed as well as developing nations globally. This is an issue for both hospitals/stroke systems of care as well as physicians, and in particular, thrombectomy providers.
- Alternative models of stroke systems of care have developed to improve patient access. These models include improved pre-hospital routing paradigms, improved intra-hospital transfer paradigms, and models in which thrombectomy providers travel to outlying hospitals. All these systems however remain imperfect and limited, and ultimately, increased numbers of thrombectomy-capable physicians and provider teams are needed.
- There is a clear need for additional data examining outcomes data in low volume centers, and by low volume practitioners. The outcomes are likely to be poorer, but how much so? And is that decrement in outcome outweighed by the time delays associated with transfers?

Summary of new data from clinical trials of thrombolysis since ISC or ESOC

WAKE UP and ECASS 4 primary results and secondary analyses

Werner Hacke

The primary results of two trials testing the efficacy of rtPA in patients with longer or unknown time window using advanced imaging selection were presented at ESOC 2018 in Gothenburg. The WAKE-UP trial was terminated early for lack of funding. It selected wake up stroke patients on the basis of the DWI-FLAIR Mismatch concept. Despite the early termination the study showed a highly significant advantage in reaching mRS 0,1 for rtPA in patients with a positive DWI-FLAIR mismatch (OR 1.63 95% CI 1.09-2.36, p=.02,).[63]

ECASS 4 used the classic DWI-Perfusion mismatch in patients between 4.5-9h or in wake ups. It was also terminated prematurely because of futile recruitment because of massively increasing use of thrombectomy in this patient group. The OR point estimates were like anticipated in favor of rtPA treatment (OR 1.23 for the categorical shift, OR 1.38 for mRS 0,1), but the confidence intervals were wide and clearly overlapped unity because of the small sample size.[64]

Further ECASS 4 secondary analyses presented in Montreal (WSC 2018) indicated that this type of selection is more useful in known, late time window than in unknown time window. Using the FLAIR-DWI Mismatch paradigm in a non-predefined sub analysis of ECASS 4 showed also a clear trend towards better results in the DWI-FLAIR Mismatch cohort, but with the caveat of increased late (stroke unrelated mortality signal in the rtPA treated group). Again, due to the small sample size the CIs overlapped the unity line.

EXTEND

Henry Ma, Bruce Campbell, Mark Parsons, Stephen Davis, Geoffrey Donnan

EXTEND is a multicenter randomized double-blind placebo- controlled trial of alteplase in ischemic stroke patients presenting within 4.5-9 hours from onset or those with wake-up stroke (WUS). Selection was based on automated perfusion imaging software showing salvageable brain tissue. Primary outcome was excellent functional outcome (modified Rankin Score, mRS 0-1) adjusted for age and baseline NIHSS at 3 months.[65] Other prespecified outcomes included independent functional outcome (mRS 0-2), early reperfusion, clinical improvement with NIHSS reduction of 8 points or reaching 0-1 at 24 hours, death and symptomatic intracerebral hemorrhage (sICH). After 225 of the planned 310 patients had been randomized the study was terminated early after the publication of WAKE UP study and loss of clinical equipoise. Patients who received alteplase achieved significantly better functional outcomes at three months. Secondary end points including

reperfusion, early neurological improvement were superior in the alteplase group while mortality was not significantly different. EXTEND is the first positive thrombolytic trial in the extended time window using automated penumbral selection software.

3. Structuring Stroke Systems of Care

Drip and ship—safety, what is an acceptable time delay, what imaging should be done and where
Atte Meretoja, Sheryl Martin-Schild, Heinrich Audebert

The drip-and-ship model of treating with thrombolytics facilitates access to time-sensitive proven intervention to more patients with suspected stroke. One consequence of this model is that patients treated with thrombolytics are vulnerable to complications while in transit via ground or air ambulance. While remote guidance provides access to otherwise unavailable neurological expertise for decision making for ischemic stroke thrombolysis, the dripping sites usually have lower volume of acute strokes and may be less efficient in treating with thrombolytic than the hubs. This complicates the analysis of whether there is advantage for patients with suspected stroke stopping at a thrombolytic capable spoke versus bypassing in favor of access to the hub, where definitive care can be provided, particularly for patients who are candidates for thrombectomy. Reducing the door in-to-door out for sites who do not keep post-thrombolytic patients and for those patients who have emergent large vessel occlusion is a major opportunity for process improvement. In most ischemic stroke patients, the only imaging test necessary for decision-making is the non-contrast head CT. In our new world of treatment for stroke due to large vessel occlusion, access to and appropriate utilization of endovascular resources is critical. Vascular and penumbral imaging may evolve, particularly when thrombolytic is given. The "want to know" must be balanced with the "need to know" and is most relevant for sites who keep post-thrombolytic patients who do not require thrombectomy for large vessel occlusion. Depending on hub priorities and tolerance of limitations, clinical tools for identifying patients with large vessel occlusion may substitute vascular imaging and reduce the need for repeating studies upon arrival at the hub.

a) **Successful networks in resource rich and poor, urban and rural regions**
Lee Schwamm, Markku Kaste, Tsong-Hai Lee

Finland is presented as an example of a successful European network. After organizing acute stroke care and stroke unit care in Helsinki University Hospital, Dr. Kaste and the leadership team in Helsinki encouraged other Finnish university hospitals to follow their example. To ensure equal access to high-quality acute stroke care including thrombolysis for the entire population of Finland, the Helsinki team developed a telestroke program to support rural hospitals with low resources. These hospitals now have equally good results from thrombolysis as have been observed in Helsinki University Hospital. Through

telestroke, assistance to rural hospitals in recognizing thrombectomy candidates is given, and when appropriate, patients are transfer to the nearest university hospital applying the drip-and-ship method. The ways in which other European countries have done the same differ by country, but high-quality stroke care is ensured over much of western Europe.

In Asia, the resource-rich areas, mainly high-income countries, have sufficient support for acute stroke treatment networks in urban areas. However, in some rural areas where resources limited, there are still problems of lack of public awareness of stroke and limited access to mechanical thrombectomy. The establishment of stroke centers should be helpful in public and provider education, and the diagnosis and treatment of stroke.

Key components to implementing an effective Stroke System of Care (SSOC) include the need to factor in the nature of the First Responders (e.g., fire/police/volunteer, BLS, ALS, Paramedic, Flight Nurse) and how they can bring to bear various levels of education and training into a more standard approach to prehospital diagnosis (**Figure 2**); incorporate EMS assets effectively, taking into account EMS ground, air, ship and Mobile Stroke Units as available to provide the greatest coverage without depleting critical resources from a community for too long; create regionalized point of entry routing plans for suspected stroke destination so that the region fairly allocates suspected stroke patients to a level of capability that fits the resources. It will be important to maintain a strong PSC network while developing a broader plan for rapid access to EVT at TSC and CSC facilities; standardize stroke alert pre-arrival notification and severity scale use so that each community or state becomes comfortable in the use of a single scale and can thereby communicate more effectively; implement a tiered accreditation or designation of stroke centers that includes the recommended levels of Basic, Acute Stroke Ready, Primary and Comprehensive; these activities should ideally be done by national organizations, since national organizations provide greater transparency and uniformity, and potentially better outcomes. These systems should encourage high levels of participation in National QI programs with recognition for performance to ensure that systems are based on infrastructure and performance.

Discussion Panel

George Tsvigoulis, Michael Lerario, Nate Bornstein, Claude Nguyen

Traditional hub and spoke networks for acute stroke treatment were developed to balance resource allocation in urbanized, resource rich regions and improve access to care in rural, resource poor regions. However, as the need for thrombectomy services expands and technology is increasingly used to improve triaging decisions, newer stroke systems have developed and compete with hub and spoke networks utilizing drip and ship protocols in both resource rich and poor regions.

Examples of stroke system innovations disrupting current drip and ship networks include those where field triage is performed to bypass suspected large vessel occlusion (LVO) patients directly to a hospital with thrombectomy services. Field triage can be

accomplished through standard emergency medical services staffing,[66] through telehealth,[67] or through the use of mobile applications[68] and may improve time efficiency and outcomes in time-sensitive stroke care. Mobile stroke units offer comparable services to primary stroke centers and can assist in the triaging of suspected LVO patients directly to endovascular centers without delaying thrombolysis times.[69] Prospective studies are underway to ascertain if these newer methods of stroke triaging will continue to supplement or even replace drip and ship networks.

Drip and ship networks alone cannot optimize resource utilization since false positive screens may occur up to 40-50% of the time if only clinical scores are used for LVO assessment,[70] and recanalization of an identified LVO may occur in 10-20% of patients during transport to the hub facility as a result of intravenous thrombolysis.[71,72] These factors generate confusion as to whether vessel imaging should occur at the hub or spoke facility and may result in overtriage of stoke patients to endovascular centers, when a primary stroke center may have been sufficient. Overtriage to advanced stroke centers could theoretically burden hub hospitals with unnecessary transfers and decrease volumes at spoke centers where competencies may be more difficult to maintain if patient numbers diminish.

Key Points:

- Stroke systems of care will need to be restructured to improve patient access to EVT. Key elements include reducing door-in-door-out times, determining whether clinical tools for evaluating for LVO may substitute for imaging, and improving access to subspecialty care with technology including telemedicine and mobile stroke units.
- Standardization of pre-hospital notifications and pre-hospital routing changes to avoid overtriage to comprehensive centers will be important.

Who is carrying out thrombolysis and who should do it in the future?

Andrew Demchuk, Steve Levine, Elizabeth Jones

Thrombolysis is carried out in hospitals, emergency departments and in the field with the help of mobile stroke units. IV tPA can be administered by non-vascular and vascular neurologists, emergency medicine physicians, residents and fellows in the training programs, physician assistants and advanced nurse practitioners. Telemedicine from the MSU has allowed for more patients, especially in the rural networks, to get access to thrombolysis and for neurology expertise to become readily available for decision-making. In controlled trials, telemedicine in stroke consultations within an organized system of care have demonstrated improved and safe IV tPA use and better patient outcomes than without

telemedicine coverage. Many networks, including hub and spokes, have developed telestroke coverage for their patients, including some rural networks.

In the near future, proper support for health providers from vascular neurologists should allow expanding and improvement of stroke patient care, empowering the autonomy of providers in the decision-making of thrombolysis. Guidance by a vascular neurologist, either on the field or through telemedicine, will lead to more patients getting the proper treatment, at the right time and the right place.

Who is carrying out thrombectomy and who should do it in the future?
Arthur Day, Marc Ribo, Reza Jahan

Almost all stroke programs across the United States are now led by a neurologically-trained subspecialist practitioners being either neuroradiologists, neurologists, or neurosurgeons who are doing intracranial thrombectomy, with only a small number of non-neurologic subspecialists with catheter skills due to their training and routine practice that are now venturing into the intracranial circuit, which may include vascular surgeons, cardiologists and interventional radiologists. (**Table** 1) The existing dichotomy on who should be doing thrombectomy in the future has on one side the scenario where more subspecialties should be able to deliver intracranial thrombectomy as the number of practitioners does not meet the needs of stroke care, while on the other hand, it is not a matter of available providers but a lack of an equally distributed and available expertise in small or rural communities.

The reason of a more restricted delivery of thrombectomy between providers is the complex access to the delicate intracranial vasculature which has a higher risk of perforation or distal embolization than the extracranial circulation, the need of a more comprehensive knowledge of the anatomical variants and functional anatomy of the collateral circulation, as well as the awareness of the physiology and pathophysiology of the disease which is entirely different from other organ systems suffering from infarction. This organ-specific expertise is what limits, to say, a neurosurgeon or radiologist from performing an arteriography and stenting in the management of a myocardial infarction. Future safe practice of intracranial thrombectomy requires a practitioner with highly skilled with intracranial catheter-based vascular techniques, with a firm knowledge base of the anatomy, pathophysiology, and treatment alternatives of the various cerebrovascular conditions that may arise during the evolution of a thrombotic stroke. **(Figure 2)** Further research will be needed to ascertain the number of trained physicians to meet the demands of stroke intervention, distribution of these physicians across the nation and better understanding of access of populations to stroke centers to help on planning regional stroke programs.

Current guidelines for training for thrombolysis and thrombectomy; appropriateness of current guidelines
Sunil Sheth, Don Heck, Diogo Hausen, Jim Grotta

Performance and training standards set by a multi-society consensus (CAST) for neuro-interventional training demands a proper 1-year minimum training under direction of multiple neurointerventionists at a high-volume center. Pre-requisites to training include neuroscience-based residency training. A distribution of diagnostic and interventional procedures, covering the breadth of neuro-interventional diseases including cerebral aneurysms, cerebral AVMs as well as spinal diseases is required. Final certification is obtained following the completion of such a training program as well as a review of two years of subsequent practice data, to ensure high quality outcomes after training.

Should the standards for stroke thrombectomy be different? On the one hand, there is a clear and present need to expand patient access to the therapy. This treatment is highly time sensitive – perhaps one of the most time sensitive in medicine – and as such delays in treatment such as those created by prolonged pre-hospital transports or inter-hospital transfers are costly. On the other hand, all the data supporting the efficacy of EVT at improving clinical outcomes after LVO stroke were derived from high volume hospitals and high volume neurointerventionalists. As such, treatment outside these specialized centers could be considered unproven.

Would it be beneficial then to train a group of neurointerventionalists for EVT alone, and forgo the remainder of neurointerventional training? Insisting that all providers to treat stroke also be proficient in aneurysm treatments, for example, would likely be mathematically impossible. But would a model in which some providers perform only EVT be even possible, whereby one can learn to effectively perform delicate and intricate intra-cranial thrombectomy without exposure to other cerebrovascular disorders?

Ultimately, these discussions should be framed in the context of what is best for patients, and not along specialty or "turf" considerations. As such, this topic is one that will need to be addressed with data, particularly from lower volume centers and lower volume physician practices, which are notoriously absent from traditional data generating mechanisms including clinical trials and clinical registries.

Discussion Panel
Mike Frankel, Gary Spiegel, Hen Hallevi, Jonathan Zhang

Since the FDA approval of tPA (Alteplase) for acute ischemic stroke in 1996 and the publication of consensus guidelines the acceptance by the medical community has been mixed. Although vascular neurologists have fully embraced the robust nature of the data supporting the benefit of tPA there has been reluctance to treat by general neurologists and emergency medicine physicians in large part due to fear of causing harm. As such, it is imperative that vascular neurologists work together to create more opportunities for clinical coverage through telestroke and education of general neurologists and emergency medicine physicians.

In the case of thrombectomy, adoption of the procedure has not been a problem. However, a strategy to equally distribute neurological expertise for thrombolysis and thrombectomy in both urban and rural areas may lead to certification of centers and physicians not fully competent to be involved in stroke care. Expanding certification of centers to deliver treatment to all population is only part of the solution, as more expertise from first responders and ways to reduce onset to door time play an important role in patient care. On the other hand, certifying non-neuroscience-based physicians, such as cardiologists or interventional radiologists, to perform thrombectomy requires a thorough review of training requirements and experience. It is clear that extracranial vessels differ enormously from intracranial vessels, hence a singular set of technical and cognitive expertise, as well as catheter-based skills and knowledge is necessary to better perform at the thrombectomy procedure.

Key Points:

- There is a need for an expansion of providers able to oversee thrombolysis treatments. Advanced practice providers including nurse practitioners, telemedicine, and MSUs may help address this issue.
- With the magnitude of benefit EVT confers on patients with AIS, and the resulting increase in need for proficient providers and suitable hospitals, there is a need to rethink hospital certification and training standards for NeuroIntervention. These standards, however, must be determined with the patients' best interest in mind.

4. Future of thrombolysis

Combining with anticoagulation

Andrew Barreto, Gary Ford, Opeolu Adeoye

Current reperfusion therapy with IV tPA alone in acute ischemic stroke is only able to recanalize approximately 50% of occluded arteries and 15 to 35% of patients who received thrombolysis experience early reocclussion within the first 2 hours. Although thrombectomy achieves higher recanalization rates, it is not available at many countries and patients may not be eligible when they arrive at CSC. Augmentation of IV tPA through the use of anticoagulants may have a potential significant public health impact if early administered, removing the need for transfer to a specialized center. Argatroban and eptifibatide have demonstrated efficacy in 6 phase II clinical trials with higher recanalization rates, no association with an increased risk for symptomatic intracerebral hemorrhage, and an increase in excellent functional outcome at 3 months. More clinical trials will define dosage of this anticoagulants and contribute to the proven efficacy of this combination therapy.

Combining thrombolysis with other approaches including magnetic enhanced lytics, perfluorcarbon, otaplimastat and glyburide
Keith Muir, Jong Kim, Taylor Kimberly

Turbulent flow in the arterial segment proximal to the occlusion alters delivery of the thrombolytic agent to the blood clot surface, as rtPA can only diffuse passively. In vitro studies of Magnetically Enhance Diffusion through iron nanoparticles with an externally applied magnetic field accelerates clot lysis and is now being pursued as an adjunct to IV rtPA and endovascular treatment in the setting of LVO is being evaluated in phase II clinical trials.

Perfluorocarbon nanoparticles are being studied in both transient and permanent MCAO models offering the potential to halt the evolution of ischemic damage by delivering oxygen to brain parenchyma beyond the site of occlusion and help to reduce infarct volumes. In addition, a phase II safety trial is evaluating the ability of this modality to provide imaging of the penumbra in combination with oxygen challenge (BOLD MRI).

Otaplimast is a new antioxidant agent that decreases free radicals by inhibiting iNOS expression, possesses an anti-inflammatory action by inhibiting inflammatory cell migration, and has also exhibited blood-brain barrier stabilization by metalloproteinases deactivation. It has been studied in phase I and phase II clinical trials showing smaller growth of infarct size, improved outcome and no significant increase in hemorrhagic transformation. A phase II study had a small sample size, so further studies are needed to confirm the efficacy.

An intravenous form of glyburide is under clinical development for the treatment and prevention of cerebral edema after a large hemispheric infarction. In an animal transient MCAO model of severe cerebral ischemia, glyburide reduces edema and hemorrhagic transformation, with similar findings observed when high-dose IV tPA was co-administered at the time of reperfusion, with a more pronounced effect of IV glyburide on plasma MMP-9 and water uptake in the subgroup treated with IV tPA. These data highlight a potential effect of IV glyburide in combination with IV tPA and/or with EVT in the setting of severe ischemia.

Discussion Panel
Sean Savitz, Bruce Campbell, Alastair Buchan, Mitch Elkind

In light of the recent successes with thrombolysis and thrombectomy, there is interest in reconsidering the role of neuroprotection and other strategies designed to limit reperfusion injury after stroke. It is unlikely, however, that the magnitude of benefit from these adjunctive therapies will be as large as those from thrombolysis or thrombectomy itself. Trials of such adjunctive therapies may therefore need to use trial approaches distinct from

those of the thrombolytic trials. Neuroprotection trials are likely to be require much larger sample sizes than thrombectomy trials. Alternatively, additional biomarker strategies could be used to identify patients most likely to benefit, and thereby improve trial efficiency. Imaging neuroinflammation or identifying serum-based biomarkers, such as complement levels, that predict a response to immunotherapy could help, for example.

In addition, a reassessment of trial outcomes of interest, and the time of assessment, may also be of value. Recent epidemiological evidence has shown that after a period of initial recovery, stroke patients experience decline in function[73] and cognition.[74] Animal models of stroke similarly show delayed cognitive decline after stroke.[75] Neuroimmune mechanisms, including the effect of infection occurring at the time of stroke, may contribute to this late decline.[76] Thus, we may also want to consider assessing outcome measures distinct from crude handicap scores, such as the modified Rankin scale, for some therapeutic effects. It is possible that some therapies, when given early, will have more of an effect on preventing later problems with cognition, depression, or fatigue, and scales focused on these outcomes may be increasingly relevant in trials patients undergoing thrombolysis. Most acute stroke trials collect outcomes out to 90 days, moreover, but some of these effects may not be seen for many months or even years after treatment; thus, longer follow-up assessments may be increasingly relevant.

The NIH have initiated the SNAP program to accelerate high quality preclinical stroke research using the principles of multi-laboratory reproducibility recommended in the STAIR consensus. Six laboratories with candidate molecules for stroke neuroprotection will be selected and each will test all 6 compounds in different stroke models with the most successful candidate taken forward into human clinical trials.

Key Points:

- Thrombolysis has experienced a number of recent successes, with preserved safety and efficacy in additional patient cohorts. Novel therapies that increase the efficacy of thrombolytics as well as freeze the penumbra and minimize the injury associated with reperfusion may continue this trend.

New lytics in the pipeline including TNK, plasmin, TAFI inhibitor
Carlos Garcia Esperon, Jeff Saver, Michel Piotin

Tenecteplase is a genetically engineered recombinant tissue plasminogen activator that is currently the first line treatment for thrombolysis in myocardial infarction. In acute ischemic stroke TNK shows a pharmacokinetic advantage over alteplase, as it is given in a single dose as bolus instead of a continuous infusion with alteplase, and it has less risk of hemorrhagic transformation. Current clinical trials are being conducted to determine if a high-dose TNK is superior than a low-dose TNK, with the EXTEND-IA TNK II study

exploring whether 0.4mg/kg dose is superior to 0.25mg/kg in producing early reperfusion. There is also limited information of the use of TNK in the late window after 4.5 hours of stroke onset. Parsons et al[77,78] showed in a small sample that both 0.1 and 0.25mg/kg dose of TNK had greater reperfusion than tPA up to 6 hours since onset (79% vs 55%, p=0.004) and similar sICH rate. The TWIST trial will aim to test 0.25 mg/kg TNK in a wake-up population, but only with non-contrast CT selection. Future trials (under design) will aim to define the role of TNK in the extended time window with multimodal imaging selection.

Future thrombolytic therapies in acute ischemic stroke

Early recanalization of the occluded artery represents the current therapeutic goal of AIS management. Intravenous fibrinolysis using recombinant tPA infusion is the only approved drug therapy in AIS. Recommended doses used in AIS lead to an increase of nearly 1000 times the physiological blood concentration of t-PA. T-PA is the major intravascular plasminogen activator. It converts plasminogen to plasmin, which is able to cleave fibrin strands contained in a thrombus in small fibrin degradation products leading to thrombolysis. However, these treatments have important limitations. Because of numerous contra-indications, very few patients are eligible to and receive tPA-mediated thrombolysis (~5 % of AIS patients). Moreover, IV tPA is associated with an increased risk of hemorrhagic transformation and often fails to achieve successful recanalization, especially in the case of large vessel occlusions (LVO). In this context, different research ways to improve AIS thrombolysis have been recently developed.

A first strategy could be to target circulating fibrinolysis inhibitors to increase the thrombolytic efficacy of IV t-PA.

TAFI

TAFI (thrombin activated fibrinolysis inhibitor) is the main circulating fibrinolysis inhibitor. Indeed, after activation by thrombin, thrombomodulin or plasmin, activated TAFI (TAFIa) is able to cleave C-terminal Lysine residues from fibrin networks, which prevents the formation of the ternary complex including plasminogen, t-PA and fibrin resulting in the inhibition of new plasmin generation. In blood samples during EVT using a microcatheter placed in contact to the thrombus, there is a local increase of activated TAFIa in patients previously treated with IV t-PA. This could contribute to t-PA induced thrombolysis resistance. In an experimental thrombo-embolic model of stroke, it was suggested that TAFIa inhibitor in association with suboptimal dose of t-PA was associated with a reduced ischemic lesion growth compared to full tPA dose. TAFIa alone, in this study had no impact.[79] Regarding clinical studies, there are two ongoing phases 1-2 clinical trials assessing the safety of administering of a TAFIa inhibitor developed (ClinicalTrials.gov Identifier: NCT02586233 and NCT03198715). The first one is recruiting non-selected AIS with a primary endpoint of safety. The second one is focused on AIS treated by EVT with also a primary endpoint of safety.

Von Willebrand Factor

The second strategy to enhance thrombolysis in AIS is to target non-fibrin AIS thrombus components. These thrombi contain platelet aggregates. Platelet cross-linking during

arterial thrombosis involves vWF multimers.[80] Therefore, proteolysis of VWF multimers appears promising to disaggregate platelet-rich thrombi and restore vessel patency in AIS. A first study from Denorme et al found that AIS thrombi contained about 20% of vWF. The authors suggested that targeting vWF with the specific VWF-cleaving protease (ADAMTS13) could exert a thrombolytic effect in an experimental thrombo-embolic model of stroke associated with a reduced infarct volume.[81]

A more recent publication assessed a potent thrombolytic effect of N-Acetylcysteine (NAC, a clinically approved mucolytic drug). NAC has the ability to break-up VWF multimers by reducing intrachain disulfide bonds in large polymeric proteins.

This publication founded an increased recanalization rate with NAC infusion compared to saline especially with concomitant treatment with anti-GPIIb/IIIa therapy, suggesting a synergistic action of these two treatments.[82]

Neutrophil extracellular traps

NETs (neutrophil extracellular traps) are an extracellular network of chromatin with double stand DNA from neutrophils. They exert a platform of coagulation activation and platelet aggregation.[83] NETs contribute to the composition of all AIS thrombi especially in their outer layers. The presence of neutrophils and NETs in AIS thrombi were investigated by immunofluorescence analysis. Immunofluorescence detection confirmed that areas containing extracellular DNA colocalized with citrullinated histones and granular neutrophils proteins (such as myeloperoxidase), which correspond to NETs. NETs were constitutively present in all AIS thrombi.[84] Ex vivo, recombinant DNAse 1 accelerated tPA-induced thrombolysis, whereas DNAse 1 alone was ineffective. Our results indicate that co-administration of DNAse 1 with tPA could be of interest in the setting of AIS with LVO.

Future thrombolytic therapies will involve an optimization of fibrinolysis therapy with TAFIa inhibitor infusion for example. But, in our opinion, the most promising way consists of targeting non-fibrin contents of thrombi, especially, platelets, vWF and NETs. This reasoning supports a pharmacological "cocktail" for the future of AIS treatment including therapies targeting different contents of thrombi. The development of such add-on therapies may represent a unique opportunity not only to improve recanalization therapy, but also to reduce tPA doses and the associated risk of intracranial bleeding, which is responsible for an increased mortality rate in tPA-treated AIS patients.

Do we need more exploration of dose?

Craig Anderson, Phil Gorelick, Kazunori Toyoda

Seminal dose-escalation studies of the US National Institute of Neurological Disorders and Stroke (NINDS) tPA study in the early 1990s determined a dose of 0.9mg/kg (10% bolus) of intravenous tPA, on the basis of both major neurological improvement and concomitant paucity of brain hemorrhage,[85,86] for administration in the subsequent positive phase III clinical trials in acute ischemic stroke (AIS).[87] The 0.9 mg/kg dose has become the standard

tPA treatment regimen for AIS in North America and much of the rest of the world, except in Asia, where lower doses of tPA are popular due to the: (i) perception of reduced major symptomatic intracranial hemorrhage (sICH), where the risks are considered higher in Asians; and flexibility of rounding to use of a single vial for reducing the cost of treatment in low resource settings.

Japan was one of the last countries to approve the commercial use of alteplase in AIS in 2005 but at a dose of 0.6 mg/kg, based on data from a dose-comparison study of duteplase[88] and the multicenter single-dose Japan Alteplase Clinical Trial.[89] Post-marketing studies, including the nationwide Japan post-Marketing Alteplase Registration Study (J-MARS)[90] and the multicenter Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry,[91] have shown similar efficacy and safety of alteplase at 0.6 mg/kg as compared the standard-dose of tPA among AIS patients registered with the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) in Europe.[92]

The only randomized evaluation of low-dose versus standard-dose alteplase has been in the international Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED). This large trial failed to clearly show non-inferiority in the primary outcome of death or disability, defined by conventional poor outcome scores 2 to 6 on the modified Rankin scale (mRS).[93] The results were likely due to insufficient power for the stringent non-inferiority margin imposed, as the ordinal shift analysis of the full range of mRS scores was significant for non-inferiority. Just as important, though, were the findings that sICH was halved, which translated into significant lower mortality at 7 days, in the low-dose group.

Overall, the evidence from observational studies, systematic reviews and meta-analyses,[94,95] is consistent in concluding, either of no clear difference or in favor of improved outcomes and reduced sICH with low-dose tPA. The findings are consistent in sensitivity analyses by fixed dose comparisons and in studies confined to Asian populations.

Our conclusions are that low-dose tPA offers lower cost, reduced bleeding risk particularly of sICH, and near non-inferiority in relation to efficacy compared to standard-dose tPA. Because use of low-dose tPA has been the subject of considerable evaluation in many Asian countries, clinicians there are likely to be more amendable to the utilization of this treatment. However, given the considerable challenges to accepting standard-dose tPA that have existed in many sectors of North America, and based on the interpretation of current evidence in the context of the FDA-approved dose, it may be difficult in successfully arguing in favor of using low-dose tPA outside of Asia.

Discussion Panel
Greg del Zoppo, Steve Davis, Ritvij Bowry, Ken Uchino

The potential of bolus-injection tenecteplase (TNK) replacing alteplase is based on the NORTEST trial (0.4 mg/kg TNK), which showed similar benefits in a mild stroke population. The EXTEND TNK trial showed that tenecteplase (0.25 mg/kg) compared with alteplase doubled reperfusion rates when administered before thrombectomy and was associated with improved clinical outcomes. An ongoing Phase III trial, TASTE, involves a head-to-head comparison of these thrombolytic agents. Regarding practical matters, the panel commented on the pricing of these agents which needs to be considered in the context of delivering these drugs across the world in specific markets such as USA, Europe, Asia and Australia. The major barrier to worldwide TNK or alteplase use includes its current lack of approval by influential regulatory bodies, such as the FDA. It is hoped that ongoing clinical trials of TNK will provide strong scientific evidence of its efficacy that will facilitate overcoming this barrier. Others raised concerns regarding the manner in which new thrombolytic agents might fit into clinical practice, and the contributions of clinical research protocols to these efforts. If the role is to dissolve thrombi before endovascular procedures, the time from infusion to puncture at comprehensive stroke centers is short and the capacity of drip-and ship facilities to conduct research is limited. Performing this research in the current infrastructure will be challenging, and would require novel approaches including remote electronic consent, or waiver or deferral of informed consent, telemedicine evaluation, and pre-hospital delivery of agents in a research setting.

In this context, the development of a new approach to intravenous thrombolysis will come under test. Recent work has demonstrated that t-PA exposes cleavage sites on fibrin so that pro-UK can bind and effect local plasminogen activation, and thrombus lysis. This approach will be tested prospectively for safety in patients presenting within 4.5 hours from symptom onset whereby t-PA (0.9 mg/kg) will be directly compared with low dose t-PA (5 mg) followed by the mutant Hispro-UK over 60 minutes in a phase II trial. Mutant Hispro-UK resists inhibition. It is expected that a lower incidence of intracerebral hemorrhage will be demonstrated, given the lower dose of t-PA. A published trial in acute myocardial infarction has demonstrated safety of the combination with comparable efficacy to t-PA.

Key Points:

- Newer thrombolytic agents including TNK, as well as future targets that enhance thrombolytic treatments may improve recanalization rates, and reduce hemorrhage.
- Low-dose tPA offers lower cost, reduced bleeding risk and near non-inferiority in relation to efficacy compared to standard-dose tPA. On the other hand, given the considerable challenges to accepting standard-dose tPA, it may be difficult in successfully arguing in favor of using low-dose tPA outside of Asia.

5. Future of thrombectomy

Summary of new data from clinical trials of thrombectomy since ISC or ESOC
Tudor Jovin

BEST Trial
The Basilar Artery Occlusion Endovascular Intervention versus Standard Medical Treatment (BEST) trial is a multicenter, prospective, randomized, controlled, open-label trial with blinded assessment of end points. Participants were allocated, in a 1:1 ratio, to receive endovascular treatment plus standard medical therapy (intervention group) or standard medical therapy alone (control group). Based on its pre-specified intention-to-treat analysis, the BEST trial failed to demonstrate a benefit of mechanical thrombectomy over medical therapy alone in the treatment of BAO within 8 hours of estimated occlusion time. After enrollment of 131 patients (66 in the intervention group, 65 in the control group) from April 2015 through September 2017, the study was terminated prematurely by the steering committee according to the recommendation of the DSMB due to excessive crossovers and progressive drop in valid recruitment. Results may have been confounded by the fact that equipoise was lost over the course of the study as demonstrated by the high cross-over rates and progressive drop in valid recruitment which eventually led to the early termination of the trial. Notably, patients who were actually treated with thrombectomy had significant better outcomes for all the primary and secondary functional endpoints on adjusted analysis.

A Trial Comparing Transfer to the Closest Local Stroke Center vs Direct Transfer to Endovascular Stroke Center of Acute Stroke Patients with Suspected Large Vessel Occlusion in the Catalan Territory (RACECAT) is a prospective, multicenter, cluster randomized controlled, open, blinded-endpoint trial of acute stroke patients with suspected acute large vessel occlusion (LVO) identified by EMS at first assistance on the field, in which two strategies are compared: transfer to the closest local stroke center (Local-SC) against direct transfer to an endovascular stroke center (EVT-SC). The current enrollment up to October 2018 is of 736 subjects.

AURORA Consortium
One would naturally anticipate that the benefits of a reperfusion therapy would be markedly diminished if treatment is delayed for many hours after symptom onset. Yet, the late window thrombectomy trials, DAWN and DEFUSE 3, reported treatment benefits that are larger than seen in the early window trials; this has been termed the "Late Window Paradox". The critical factors that explain the paradox are (1) about half of the patients with large vessel intracranial occlusions have very slow growth of the ischemic core for up to 12 hours or longer; (2) the favorable collateral circulation that is responsible for keeping the ischemic core size small eventually fails in most patients and infarct volumes ultimately increase; and (3) clinical outcomes in the control groups of the randomized trials are strongly influenced by whether or not tPA was administered. Recent data from DEFUSE 3 suggest that for about 20% of the medical control group, a favorable imaging profile

persists for up to 40 hours after last know well times. The "time is brain" concept requires a revision that allows the fortunate patients who have favorable collaterals and slow infarct growth to receive reperfusion therapy even in very late time windows. However, because it is not possible to immediately determine the growth rate of the ischemic core, it remains critical to evaluate and treat all stroke patients as urgently as possible.

Expanding candidates-later time window, milder strokes, large core, distal and posterior circulation

Greg Albers, Jay Mocco, Joey English

The anticipation of lack of benefit from reperfusion therapy in patients presenting after more than 6 hours from symptom onset was questioned by the trials DAWN and DEFUSE 3, which reported larger treatment benefit over patients treated in the early window trials. This late window paradox may be explained by the slow growth of infarct core in patients with LVO, the favorable collateral circulation and the influence of whether tPA was administered or not in the control group of RCT. With this evidence, time is becoming less of an exclusion criterion to allow patients who have favorable collaterals and slow infarct growth to receive reperfusion therapy in the late time window.

One of the most challenging stroke population are that of patient presenting with a low NIH Stroke Scale regardless of the ASPECTS or other neuroimaging characteristics, especially when it comes to the risk of therapy. About 50% of AIS patients present with minor stroke symptoms (MSS), with 70% of these patients not undergoing vessel imaging, and one quarter of MSS patients end up with a poor outcome.[96] Early neurological deterioration (END) develops in 23-41% of patients, and is associated with a worse outcome up to 60% of patients.[97]

The presence of a large vessel occlusion increases the risk for END by 2-fold and is found in 40% of patients with END.[98] MSS-LVO is associated with a 7-fold risk of poor outcome compared to MSS without an LVO, a 6% in overall mortality, and if left untreated, 32-45% have a poor outcome.[99] Sarraj et al[100] looked at 124 EVT and 90 medical patients with an MSS-LVO and determined there was an OR of 2.7 OR for good outcome in patients with ICAT and M1 occlusions, but distal occlusions showed no difference between treatment. Early rescue intervention showed a better outcome in 75% of patients when compared to delayed IAT, in which only 33% of patients had a good outcome.[101] IAT protects against END but it was found that the risk for intracranial hemorrhage was 12%.[101]

Currently, around 20% of patients in routine practice are being treated for M2 occlusions.[102] From the HERMES collaboration, only 94 patients had M2 occlusions but there is still a need for data that proves clear benefit from therapy. Good recanalization and good outcome were observed in about 60%, but the symptomatic intracranial hemorrhage

rate was 10%, higher than other trials.[17] Unfortunately, coverage from insurances varies between states, and some deem treatment for M2 occlusions to not be medically necessary. Regarding the BEST trial, there was a conclusion that a basilar occlusion was best left untreated. Currently posterior circulation strokes are being treated, and it represents 10% of all thrombectomies.[103] More data regarding the natural history, risks factors and outcomes is required but RCT lack clinical equipoise to be conducted, which makes this challenging. Contrary to M2 occlusions, treatment of basilar occlusions is considered only investigational and not medically necessary across all states.

Discussion Panel

Raul Nogueira, Aneesh Singhal, Reza Jahan, Alex Abou-Chebl

The benefit of thrombectomy can be expanded by investigating more subgroups, increasing community access, and developing adjunctive treatments. Investigation of various subgroups that may still benefit (e.g. large core, late time window) will require numerous trials and was discussed at length. It seems a lengthy and expensive process -- our tax dollars may be better spent ironing out "access" issues! In specific, the relatively low volume of thrombectomy precludes 24/7 coverage outside of academic medical centers; expanding the pool of interventionalists carries the risk of cardiac interventionalists 'taking over' thrombectomy with limited knowledge about stroke. One solution is to dissociate the technical (procedural) component from the decision-making component, with the latter restricted to stroke neurologists, and ensuring that compensation favors the decision-making component. Under this scenario thrombectomy could be expanded to the community by allowing interventionalists of any background (neurology, cardiology, radiology) to do the actual procedure, provided there is onsite or remote (telestroke) supervision by a stroke neurologist. This model would allow faster and widespread IA access, be economically viable for the smaller hospitals, and ensure a minimum quality of care. Neuro-interventionalists would receive both the technical and decision-making component. Other proceduralists will receive only the technical component and will require a minimum amount of cerebrovascular thrombectomy training. Other neuro-IR procedures such as aneurysm coiling would be restricted to neuro-interventionalists. Vascular neurologists would be more fairly compensated for their role in thrombectomy.

Adjunctive strategies include freezing the penumbra through neuroprotection. We all agree that the drug or strategy should be compatible with tPA as well as TNK, feasible to administer within a narrow time window (ideally pre-hospital), and safe in stroke mimicsGoing forward we need to be much less ambitious about effect size and reconsider outcome measures. The strategy of penumbral freezing with hypothermia, hyperoxia, etc. may require outcomes looking at 'immediate benefit' in addition to long term benefit at least in phase 2 trials -- confirmation of immediate benefit is important since early trials may not be adequately powered to show long term benefit. We need to better understand whether neuroprotection is more beneficial in "slow progressors" (i.e. milder strokes) or in

"rapid progressors" where even thrombectomy's benefit is controversial. Existing CTP/MRP criteria are optimized for selecting patients for thrombolysis/thrombectomy; for patient selection for neuroprotection, revised ADC or perfusion-imaging thresholds may be needed to identify less severe or even reversible ischemia. Lastly, with the ongoing national debate about drug pricing, the cost of drug development (trial size) will have more stringent limits and we may not have capacity to fail in mega-sized trials.

Key Points:

- Recent data, and upcoming trials, are expanding the indication for thrombectomy to broader groups of patients, including those with larger infarcts at presentation and presenting in later time windows.
- Adjunctive strategies including neuroprotection will receive a resurgence in this paradigm, as our ability to revascularize occluded vessels improves, and the need to "freeze the penumbra" becomes more relevant.
- With these thoughts in mind, however, access to EVT remains a key priority and perhaps a more important target for clinical trial investigation.

Technological advances in devices

Michel Piotin, Olvert Berkhemer

LVO pre-hospital detection

The benefit of EVT is highly time dependent, and every hour delay decreases the chance of functional independence by 20%.[32] Delivery of a patient eligible for mechanical thrombectomy to a non-thrombectomy center costs an average of 110 minutes.[30] Current existing triage methods relying on stroke severity clinical scales are lacking of sensibility and specificity to detect LVO.[104] Technology that could achieve similar speed, but with better sensitivity and specificity for LVO would have the potential to improve the rapidity of care. The volumetric impedance phase shift spectroscopy (VIPS) device experienced initial positive findings.[105] The system is placed on the patient's head for one minute, and utilizes VIPS to measure hemispheric asymmetry of the brain, correlating with severe stroke. Further validation studies are warranted to conclude if this device could be used in regular clinical setting.

New stent retrievers and aspirations devices

The recent development in stent retriever technology aimed at augmenting the "first pass effect," meaning obtaining a faster satisfactory reperfusion status (mTICI≥2b) and diminishing the rate of clot embolus into previously unaffected vascular territories. To do so this new generation of stent retrievers are designed to better conform to the vasculature, a key factor linked to the risk of thrombus fragment losses during the pullout phase of mechanical thrombectomy with stent retriever. Manufacturers are also developing larger

bore aspiration catheters as the aspiration technique (with or without the joint use of a stent retriever) is gaining wider acceptance.[106]

Regional cooling and other neuroprotection including NA-1, Uric acid
Michael Hill, Y Ding, Angel Chamorro

Therapeutic hypothermia has proven to offer neuroprotection and has significant potential in improving clinical outcomes due to multiple synergistic effects on decreasing damage from ischemia and reperfusion. Hypothermia slows pathways that cause excitotoxicity, apoptosis, inflammation and free radical production, as well as blood flow, cerebral metabolism and blood–brain barrier integrity. However, its clinical use has largely been limited due delayed cooling onset, prolonged duration to achieve a lowered core temperature, extensive medical and nursing efforts, as well as secondary complications. Previous studies have shown that the infusion of cold saline, i.e. intra-arterial regional cooling infusion (RCI), is a feasible technique for inducing selective hypothermia during endovascular treatment of intracranial occlusion and confers neuroprotection in ischemic stroke. RCI combined with endovascular recanalization can be safely achieved, leading to potential neuroprotection, in acute ischemic stroke patients. Future research will help to determine whether neuroprotection is beneficial in "slow progressors" (i.e. milder strokes) or in "rapid progressors" where even thrombectomy's benefit is controversial.

Pharmacological treatments or mechanical thrombectomy are frequently powerless to fully reperfuse the ischemic brain despite achieving a high rate of recanalization. Former experimental models of transient brain ischemia identified the lack of reflow at the brain microcirculation despite complete recanalization of proximal arterial occlusions. More recently, oxidative and nitrosative stress were found to play a major role in "no reflow" as the result of a rich expression of pro-oxidant NADPH oxidases (NOX) in brain endothelium, vascular smooth muscle, adventitia and capillary pericytes. Other sources of high concentrations of reactive species included the mitochondria, the activity of cyclooxygenase enzymes, NOX expressed by neurons, and infiltrating neutrophils, and the hypoxic-dependent conversion of xanthine dehydrogenase (XDH) into xanthine oxidase (XO). Amongst the more than 4000 free radicals or non-radicals which have been described, peroxynitrite is an especially attractive molecular target for therapeutic intervention because is highly toxic, it crosses readily biological membranes, and interacts with most critical bio-molecules. Likewise, under experimental conditions peroxynitrite is largely generated in the ischemic penumbra where it builds up for about 6 to 12 hours, thus giving strong biological rationale and a realistic time window of opportunity for therapeutic intervention. Uric acid (UA) is a potent peroxynitrite scavenger whose safety was demonstrated in a cohort of 421 patients treated with alteplase within 4.5 hours of stroke onset in the URICOICTUS trial. A preplanned nested study of the URICOICTUS trial showed that UA therapy showed a 19% absolute increase in the proportion of good outcome compared with placebo in patients who in addition to intravenous alteplase also received rescue mechanical thrombectomy. The ease of UA administration (a 90-minute

intravenous infusion during the endovascular procedure) and long elimination half-life of 44 hours (one single administration), are additional advantages of this treatment modality that deserves appropriate validation in a larger confirmatory trial of stroke patients with LVO treated with mechanical thrombectomy.

NA-1 is a small eicosopeptide (20 amino acids) constructed from components of the NR2b-subunit of the NMDA receptor and HIV envelope protein TAT. The TAT protein moiety allows easy passage across a lipid bilayer and across the blood-brain barrier. The NR2b subunit moiety is analogous to the binding site of a PDZ-binding domain for a series of a catalytic protein on the cytosolic surface of the receptor. Competitive inhibition of the binding site prevents activation of the protein cascade, that is triggered by calcium entry through the VGCC function of the NMDA receptor, that results in intracellular production of nitric oxide.

NA-1 was tested in multiple animal species including old-world primates (cynomolgus macaques) and in a phase 2 study in humans undergoing aneurysm coiling. The ESCAPE-NA1 study is 50% enrolled and attempting to demonstrate efficacy of NA-1 in human stroke using a paradigm that mimics the cynomolgus macaques experiment.

Discussion Panel
Enrique Leira, Bernard Yan, Julian Bosel, Thabele Leslie-Mazwi

The panel agreed that further progress is needed in the devices used for mechanical thrombectomy. An important feature for new devices should show improved effectiveness (e.g rate of TICI 3), including speed and simplicity of use in achieving successful reperfusion (e.g. at first pass). Current devices are suited for embolic thrombus however none are designed to address intracranial atherosclerotic disease, an entity that to this day remains poorly treatable. Metrics that allow greater comparison between devices (first-pass effect, mTICI 3 reperfusion result, etc) will allow small differences in devices to be better understood, but the diversity of patient anatomy and vascular occlusion requires a range of device options remain available. Approaches to improved device-based reperfusion should be broader than simply clot-device interaction, including base catheter systems and a full evaluation of intra-arterial lytic options.

Penumbral imaging may help selection of the best patients for clinical trials to evaluate the use of neuroprotection in the thrombectomy setting, as current research fails to adequately rank the merit of these interventions. The concept of combined neuroprotection (i.e. sequence of different substances for different phases of stroke and/or different settings such as ambulance and angio-suite) is appealing. However, the challenge to transfer preclinical data, including that of the potential interaction of these agents, to the corresponding clinical setting, deserves more prospective research as by pilot studies.

Key Points:

- New devices for thrombectomy are being developed and should focus on effective reperfusion on the first pass. The definition of device superiority, relative to existing devices, however, is unclear. Further, the interaction with these devices on intracranial atherosclerosis, a disease that remains poorly treated, should be addressed.
- Neuroprotective strategies including NA-1, uric acid, and hypothermia have shown some success, raising the question of the profile of patient (i.e. penumbral status) in whom they will be the most effective.

Imaging selection—how will we reach a consensus on imaging selection?
Bruce Campbell, Amrou Sarraj, David Liebeskind

Some of the key controversies in the field of stroke imaging are if acquiring more than NCCT/CTA in patients is beneficial and if CTP/MRI is obtained how will imaging influence in reperfusion decisions. The concept of patient selection within the 0-6hr time window based on any single clinical or imaging parameter is naïve. HERMES meta-analyses of the positive endovascular trials have indicated consistent treatment effect across a broad range of age, clinical severity, non-contrast CT ASPECTS, CTA collaterals, CTP/diffusion MRI ischemic core volume etc. All these factors are, however, strongly prognostic and the presence of multiple negative prognostic features may lower the absolute probability of meaningful outcome sufficiently to justify regarding reperfusion as "futile".

The choice of imaging strategy for diagnostic and prognostic purposes needs to be distinguished from selection criteria used to determine eligibility for endovascular thrombectomy. Performing a CT perfusion scan does not imply or require any particular selection criteria for thrombectomy. Indeed, advanced imaging is not simply about excluding patients from thrombectomy. It can also include more patients and provide diagnostic benefits. Despite the positive trials of reperfusion >6hr all using CT perfusion or MRI selection, there are attempts to simply use non-contrast CT for selection in the late window on the grounds that this will expand the population who benefit. However, many patients are not at the extremes of excellent or very poor non-contrast CT appearance. In the intermediate zone there are patients who would be excluded by an ASPECTS threshold yet who would have met ischemic core volume<70mL criteria due to the poor volumetric correspondence and inter-rater variability with ASPECTS rating. Synthesizing the non-contrast CT and CT perfusion information is likely to provide more informed decision-making and improve the inter-rater reliability. Rather than accepting arguments around expertise, equipment, cost and treatment delay that are often provided as justification for not performing more advanced imaging, the field needs to find creative solutions to bring

more informative imaging to routine practice in both primary and comprehensive stroke centers.

Future imaging to help selection; new sequences; new physiologic information
Chris Levi, Steve Warach, Alexander Thiel

The field of acute stroke reperfusion therapy is undergoing a paradigm shift. The screening and selection criteria for treatment have evolved from being primarily driven by the time from last known well, the window for which closed at 4.5 hours, toward an approach that prioritizes the identification of patient-specific, treatment-related biological targets, by which treatment efficacy is less dependent on the time elapsed from last known well to the initiation of treatment. Thus, the succinctly stated principle that clinical efficacy of reperfusion therapy in ischemia is time dependent ('Time is Brain') requires an updating and qualification.

In considering reperfusion therapy for ischemic stroke, the time elapsed from last known well to initiation of treatment is not the most important predictor of benefit from thrombolysis or thrombectomy. Further, reperfusion treatment opportunities are better defined by the demonstration of a treatment relevant acute ischemic target than by the time from last known well. In addition, the duration and severity of focal cerebral ischemia in viable, vulnerable, and salvageable tissue determines the probability of infarction. Finally, in the presence of an ischemic target, the clinical efficacy of reperfusion is time dependent.

Consensus statements of imaging selection and outcomes in stroke clinical trials issued by the Stroke Imaging Research (STIR) international collaborative[107-109] have recognized the need for standardization in image acquisition and analysis as well as the importance image data pooling and sharing. The STIR/VISTA-Imaging stroke MRI repository has been one such effort available to the community of stroke researchers (http://stir.dellmed.utexas.edu/). STIR's 2007 call for development of a tool for standard imaging processing of CT or MR images, vendor neutral, to reliably identify core and penumbra within the time constraints needed to assist in treatment decisions[107] encouraged and energized the efforts resulting in RAPID, the software that has been central to the success of the recent clinical trials that broke through the early time windows.

The most important advances on the horizon for imaging will not be so much the development of new scanning techniques, but rather in the pooling of large datasets to best define the limits of image-based treatment target selection and in disseminating the advanced clinical image methods to the centers where patients are assessed for acute stroke intervention.

"Big data" to accelerate definition of patient profiles

Compared to large-scale imaging network initiatives in other areas of neuroscience (Human Connectome project, Human Brain Project) and clinical neurology (ADNI, Autism research), the acute stroke imaging community is presently underutilizing pooled

imaging data analysis to advance the development of patient selection for individualization of acute stroke therapy. Although the need for imaging-data repository has been identified in the past[107-109], present initiatives (STIR-repository, VISTA-imaging) suffer from several challenges: the numbers of data-sets are small (several hundred), processed rather than raw data are archived, data have been acquired in the context of sponsored clinical trials using standardized acquisition protocols within but not necessarily between trials, and the reluctance of clinical trial initiatives to share data for pooled analysis. As a consequence, imaging research in the field has mainly been correlational[110-112] not drawing on the strength of modern event-causal modelling approaches which have recently been used successfully to define e.g. "therapeutic fingerprints" of individual patients in other fields of clinical neuroscience.[113] Defining patient profiles for therapy selection, consisting of imaging, demographic and medical parameters has been identified as a research priority. Driving this process by animal experiments, pilot studies and subsequent RCT's however is inefficient with respect to time, resources and cost, given the large parameter space to be explored. Highly efficient parallel processing on distributed neuroimaging platforms like CBRAIN[114] can identify and test the validity of identified profiles in several thousands of imaging and behavioral data sets thus accelerating the transition to clinical use compared to traditional development cycles.

Implementing ischemic target definitions

There is now sufficiently robust evidence to support more widespread adoption of imaging-based selection for reperfusion therapies in routine practice, both in the hyperacute and extended time window situations. Additional refinements such as clinical decision assistance underpinned by accurate predictive algorithms for reperfusion therapy response will develop using "big data mining" and artificial intelligence approaches as described above. However, the history of research knowledge translation suggests that adoption of both the current and the future evidence will require the establishment of an international portfolio of implementation research projects in advanced stroke imaging, all aiming to avoid the often quoted on-average 17-year latency in translation of clinical discoveries into routine practice. There is now a major opportunity for the stroke research community to begin to engage in and focus on a research agenda aiming at the development of locally effective strategies for adoption and diffusion of the emerging new knowledge in acute stroke imaging science. This will require the establishment of interdisciplinary teams that span radiology, imaging science, computer science, vascular neurology, implementation science and health service management. Ideally, it would also involve the formation of international consortia to share methodological knowledge, implementation enablers and knowledge and skills and have proven effective in achieving adoption across a variety of health systems.

Discussion Panel

Michael Hill, Jean Marc Olivot, Teruyuki Hirano, Albert Yoo

Multimodal imaging could be an important help for the diagnosis of acute brain infarction by non-vascular specialist in remote places and may therefore help to increase the number of cases treated. Due to the limited reliability of the ASPECTS score to assess the volume of the infarct core in the first hours after cerebral infarction, and regarding the last publication from HERMES investigators, future stroke trial investigating the benefit of thrombectomy among patients with "large infarctions" may rather use objective core volume measurement than low ASPECTS. Such approach will therefore give a robust demonstration of the benefit of thrombectomy in that subset of patient.

Key Points:

- Given the enormity of the effect size seen in endovascular trials using advanced imaging, in practice, treatment criteria (i.e. infarct size at presentation) may need to be relaxed to allow maximal benefit to patients with AIS.
- Deciding which imaging study is optimal in screening patients is important, but ultimately these studies are supportive tools. Practical considerations, in terms of availability may be the greatest deciding factor for imaging protocols.
- There continues to exist a need for large AIS imaging databases for improved understanding of target definitions and patient profiles.

6. Speeding thrombolysis and thrombectomy

How can we expand telestroke and other innovations?
Teddy Wu, Lee Schwamm, Larry Wechsler

Stroke is a rare event, accounting for less than 5% of emergency medical dispatches, emergency department visits and hospital admissions. Telestroke extends the reach of acute stroke expertise to rural and community hospitals increasing appropriate delivery of thrombolytic therapy and identifying patients eligible for mechanical thrombectomy. Most telestroke networks limit evaluations to the acute stroke setting either in the emergency department or in-house stroke alerts. When patients remain at originating hospitals after acute evaluation subsequent hospital care may not be the same as care delivered by vascular neurologists at a stroke center. Providing telestroke follow-up throughout the episode of care for stroke patients promotes efficient and cost-effective testing and selection of optimal treatment, reducing length of stay and improving outcomes.

Advancement of stroke care is dependent on completion of clinical trials. Traditional ways of patient recruitment into acute ischemic stroke trials at tertiary care centers can be inefficient and often patients at remote hospitals lack access to such trials. Transfer delays from remote hospitals to larger tertiary centers may preclude enrollment of these patients into time-sensitive acute stroke clinical trials. Telemedicine has the potential to enable stroke specialist to conduct acute stroke trials at remote hospitals to potentially enhance

enrollment while also increasing access and opportunities for stroke patients at rural and community hospitals to receive promising new therapies.

Mobile Stroke Units—status and future perspective
Klaus Fassbender, Steve Davis, Anne Alexandrov

Staffing on mobile stroke units varies among existing programs, and is dependent on manpower availability, technology requirements, and regulatory and credentialing mandates. Programs should consider models that are sustainable based on personnel expense and the local availability of expertise. Most countries and local governing authorities will require at least the presence of a licensed prehospital provider, such as a paramedic and/or emergency medical technician on board any vehicle that is licensed as an ambulance. Computed tomography (CT) technologists are required to perform all CT imaging acquisition functions. The main difference between MSU program staffing lies in the area of stroke expertise, with use of vascular neurologists, nurse practitioners, or telemedicine operations. Regardless of the staffing model utilized, MSU teams must collaborate closely to support optimal stroke diagnostic and treatment outcomes.

Discussion Panel
Martin Ebinger, Sandy Middleton, Silke Walter

The discussion evolved around the role of nurses in future stroke care. Patients cared for in stroke units who received facilitated implementation to manage fever, hyperglycemia and swallowing using the FeSS Protocols (fever, sugar, swallow) had 16% reduced death and disability[115], with a sustained effect in terms of 20% increased likelihood of being alive out to a median of four years.[116] It also has been shown to result in a $AUD 281M saving if only 60% of all eligible patients received this care over 12 months. This is as a result of evidence-based nursing care. Further, stroke unit coordinators, most usually nurses, have been shown to improve uptake of evidence-based stroke care and improve patient outcomes.[117] However, the QASC Europe study is demonstrating the variable level of autonomy of stroke nurses across the world. Advancing stroke nursing care requires active support by neurologists. How can neurologists advance the role of the stroke nurse within their services? Can they identify nurses with potential who could lead FeSS protocol implementation and support introduction of other evidence-based stroke care processes to improve patient outcomes?

Involving stroke nurses in MSUs would support autonomy of nurses and strengthen their role in the service.[22,118] In addition, a recent good example of the multifaceted uses of MSUs took place in Houston in 2017, when Hurricane Harvey caused power breakdown of a hospital. The Mobile Stroke Unit partly replaced the emergency department in this exceptional situation providing head CT imaging. This report sparked fantasies about Mobile Stroke Units replacing Stroke Units in underserved areas, though the panelists also

reminded the audience that a Stroke Unit is more than the CT-scanner and a laboratory. Apart from nurses and doctors, Stroke Units consist of a dedicated team that also includes physiotherapists, occupational therapists, speech therapists, and social workers.

Key Points:

- Telemedicine and MSUs shrink the gap between patient, provider, and treatment.
- Nurses and advanced practice providers are well suited for deployment in these roles.

Other approaches to increasing perfusion

Andrei Alexandrov, Italo Linfante, Rolf Blauenfeldt

The principle behind remote ischemic conditioning (RIC) is based in applying short-lasting, non-lethal ischemia in a distant tissue to protect against long-lasting ischemic injury. In practice, it is applied by holding pressure to the target tissue for 5 minutes, and then allow a reperfusion stage for 5 minutes. These 2 stages are one cycle, and it is then repeated for a total of 5 cycles. RIC seems to target multiple neuroprotectants and cause an anti-inflammatory shift, as showed in many preclinical studies.[119]

Ongoing RIC Trials

1. RICA– This clinical trial is being conducted in China. It is the largest trial looking at a population with either AIS or TIA with symptomatic ICAD. Patients are treated with RIC once daily for one year and were then followed up to assess for stroke recurrence. Sample size is 2600 with its enrollment almost completed. Results are expected to be published in 2020.
2. RESCUE BRAIN – Clinical trial in France, with 10 participating centers where RIC is given within 6 hours from symptom onset in the in-hospital setting for AIS patients treated with either tPA or IAT. Primary endpoint is infarct growth rate and enrollment has been completed. Results are expected early in 2019.
3. REMOTE-CAT – Pre-hospital trial in which RIC is started within 8 hours from symptom onset in the ambulance. Target population is AIS patients who do or don't receive reperfusion therapy. Primary endpoint is dichotomized modified Rankin scale.
4. ReCAST-2 – Dose escalation study in the UK looking at the application of RIC in the in-hospital setting for AIS patients. Enrollment has been completed and results will be analyzed for planning of a large efficacy trial (ReCAST-3).
5. RESIST – Danish trial for pre-hospital RIC given within 4 hours from symptom onset in patients presenting with stroke symptoms. If patients are confirmed of having an AIS or ICH, patients are treated once again in-hospital after 6 hours. Current enrollment is 170 patients out of 1500 patients.

The effect of improved functional outcome is likely to be small, but RIC treatment is a cheap and feasible therapy without serious adverse events risk. Questions regarding which subset of patients will benefit from this intervention, and standardized timing and dosing of cycles are yet to be answered.

Recent data showing increasing blood flow in the leptomeningeal anastomosis by administering Hemoglobin Oxygen Carriers and Carboxyhemoglobin Transporters in Middle Cerebral Artery Occlusion (MCAO) may represent a way to slow down core progression by increasing collateral circulation and transporting oxygen in acute ischemic brain tissue.

Sonothrombolysis is another approach for improved thrombolytic efficacy. CLOTBUSTER (NCT01098981) had a signal of efficacy for in subgroup analysis (publication pending). A new phase III international trial called TRUST (NCT03519737) will include patients diagnosed with large vessel occlusions by CT-angiography who will also be eligible for intravenous tPA treatment within conventional time window at spoke hospitals and transferred for mechanical thrombectomy. The primary end-point is recanalization on diagnostic catheter angiography assessment prior to mechanical thrombectomy. The lead-in phase testing a novel therapeutic ultrasound device is being launched now at 4 US hub-and-spokes systems.

Other new and exciting updates
Pat Lyden, Dileep Yavagal, Simon de Meyer

Reperfusion of the ischemic territory that occurs too late can also exacerbate tissue damage by reperfusion injury. This problem does not only occur after successful thrombolysis but also often complicates stroke outcome after successful mechanical thrombectomy. Hence, there continues to be a critical need for novel therapies for AIS, including better ways for thrombolysis and better ways to guarantee neuroprotection upon recanalization.

Many previous neuroprotectant failures (promising drugs emerge from pre-clinical development only to fail in large stroke patient trials) might be traced to a fundamental dogmatic misconception of the mammalian brain. New understanding of the neurovascular unit indicates the brain uses at least 7 main categories of cell types: neurons, astrocytes, endothelial cells, oligodendroglia, pericytes, ependymal cells and microglia. Recently, emerging data suggests the elements of the NVU respond to injury (ischemia, trauma) differently, and then respond to treatment differentially. Understanding this differential susceptibility to injury—and subsequent differential response to therapy—has led to a novel, striking re-interpretation of prior clinical therapeutic trial failures.

In some patients however, tPA can cause internal bleeding and other complications. 3K3A-APC, is a pleiotropic cytoprotectant and may reduce thrombolysis associated hemorrhage. 3K3A-APC's cytoprotective properties may be useful in protecting ischemic brain tissue

from further damage, while reducing the risk of treatment-related bleeding. The NeuroNEXT trial NN104 (RHAPSODY) trial established the safety, tolerability and activity of 3K3A-APC, following the use of tissue plasminogen activator (tPA) in subjects who have experienced moderately severe acute hemispheric ischemic stroke. Results were presented at the International Stroke Conference in January, 2018 and confirmed that 3K3A-APC appears safe and tolerable, and that a suggestion of vasculoprotection (reduced hemorrhage) requires confirmation in a larger trial. The next phase of development includes further pre-clinical development, hopefully via the new Stroke Pre-clinical Assessment Network (SPAN) and further dose finding studies in patients via StrokeNET. Together, these development efforts will not only advance one drug to Phase 3 trial, these joint efforts among SPAN and StrokeNET will establish the validity of rigorous pre-clinical development in parallel and in concert with early proof of efficacy in stroke patients. The paradigm challenges the dogma "bench-to-bedside-to-bench" in favor of a more realistic, collaborative joint development effort in which basic and translational scientists work together in real-time.

The natural history of stroke recovery depends on endogenous stems cells in the adult and pediatric brain. This recovery is incomplete in most patients and exogenous cell-based therapy shows great promise to significantly enhance this stroke recovery. Among different cell types, mesenchymal stem cells (MSCs) are most attractive for clinical translation. MSCs are adult stem cells that are multipotent, non-hematopoietic stem cells found in the stromal fraction of the bone marrow, along with the connective tissue of most organs. They are an appealing cell source due to the relative ease in which they can be retrieved, developed, and expanded for therapeutic application. Among various routes of cell delivery for ischemic stroke, the intra-arterial (IA) route of stem cell transport is most attractive as it targets delivery of cells to the ischemic brain bypassing systemic trapping of cells seen with intravenous delivery and much less invasive than direct stereotactic or intraventricular delivery. Furthermore, IA delivery of cells leads to a wide distribution of cells in the ischemic brain as MSCs home in to ischemic tissue via the vasculature using the CXCR4-SDF-1 signaling pathway. Thus, IA cell delivery leads to a substantial number of MSCs in the core and penumbra of the infarct optimizing the trophic mechanism of benefit for stroke recovery: anti-inflammation, neuroprotection and stimulation of endogenous stem cells. This suggests great potential for clinical translation of IA delivered MSCs for ischemic stroke, especially considering the growing clinical application of endovascular treatment for AIS.

A major concern for IA delivery of cells is the potential for brain ischemia that could result from administered cells compromising blood flow in the microcirculation. Pre-clinical work addressing this issue shows that such ischemia depends on the dose of IA delivery and can be fully mitigated by lowering cell doses in small and larger animal models. Furthermore, the lower (MTD) dose of cells, when given at 24-48 hours after stroke onset is efficacious for functional recovery and reduction of infarct volume in rodent stroke models. The first randomized trial (Phase 2a) of IA cell therapy in 48 patients, RECOVER-

Stroke was presented at the European Stroke Conference in 2015 and recently accepted for publication. The study showed safety of autologous IA cell delivery in anterior circulation ischemic stroke at a median of 18 days from stroke onset with no difference in efficacy. A larger phase 2b clinical trial with allogenic MSCs given between 24-36 hours is planned to move towards clinical translation of this this promising approach.

Limited data exist on clot composition and detailed characteristics of arterial thrombi associated with large vessel occlusion in acute ischemic stroke. Advances in endovascular thrombectomy and related imaging modalities have created a unique opportunity to analyze thrombi removed from cerebral arteries. Insights into thrombus composition may lead to future advancements in acute ischemic stroke treatment and improved clinical outcomes. Such detailed information can reveal novel insights and open improved recanalization. Some thrombi are particularly rich in von Willebrand factor, leading to the concept of developing a novel thrombolytic strategy using the von Willebrand factor-cleaving enzyme ADAMTS13. Similarly, the remarkable amount of extracellular DNA (derived from neutrophil extracellular traps) had led to using DNase1 as a prothrombolytic drug in experimental studies. The testing hypothesis that will be presented is one of using a thrombolytic cocktail (tPA + ADAMT13 + DNAse) instead of tPA alone.

Discussion Panel
Clark Haley, Antoni Davalos, Markku Kaste, Chris Levi

Key Points:

- Existing treatment with thrombolysis and thrombectomy still leave half of patients with disability and substantial room for new experimental approaches.

- Ongoing approaches along this line include remote ischemic preconditioning, enhancing collaterals through oxygen carriers or sonothrombolysis, targeting the multiplicity of vulnerable cell populations in the neurovascular unit, stem cells, and a better understanding of clot composition.

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