Stroke care and collaborative academic research in Latin America

Paula Muñoz-Venturelli, MD, PhD,[1-3] Francisca González, SLP, MPH,[1] Francisca Urrutia, SLP,[1] Enrico Mazzon, MD,[1,2] Victor Navia, MD,[1,2,4] Alejandro Brunser, MD,[2] Pablo Lavados, MD, MPH,[2] Verónica Olavarría, MD, MSc,[2] Juan Almeida, MD,[2,4] Rodrigo Guerrero, MD,[5] Alexis Rojo, MD,[6] Juan Pablo Gigoux, MD,[7] José Vallejos, MD,[8] Nathalie Conejan, MD,[9] Tomas Esparza, SLP,[9] Arturo Escobar, MD,[10] Alvaro Soto, MD, MSc,[11] Octavio Pontes-Neto, MD, PhD,[12] Antonio Arauz, MD, PhD,[13] Carlos Abanto, MD, MPH,[14] Cheryl Carcel, MD, PhD,[3] Jessica Hanae Zafra-Tanaka, MD, MSc,[15] Hueiming Liu, PhD,[3] Lili Song, MD, PhD,[16] J Jaime Miranda, MD, PhD,[3,15] Craig S Anderson, MD, PhD.[1,3]

Muñoz-Venturelli P, González F, Urrutia F, Mazzon E, Navia V, Brunser A, Lavados P, Olavarría V, Almeida J, Guerrero R, Rojo A, Gigoux JP, Vallejos J, Conejan N, Esparza T, Escobar A, Soto A, Pontes-Neto O, Arauz A, Abanto C, Carcel C, Zafra-Tanaka JH, Liu H, Song L, Miranda JJ, Anderson CS. Stroke care and collaborative academic research in Latin America. Salud Publica Mex. 2022;64(Supl 1):S40-S45.
https://doi.org/10.21149/12803

Muñoz-Venturelli P, González F, Urrutia F, Mazzon E, Navia V, Brunser A, Lavados P, Olavarría V, Almeida J, Guerrero R, Rojo A, Gigoux JP, Vallejos J, Conejan N, Esparza T, Escobar A, Soto A, Pontes-Neto O, Arauz A, Abanto C, Carcel C, Zafra-Tanaka JH, Liu H, Song L, Miranda JJ, Anderson CS. Cuidados del ataque cerebrovascular e investigación académica colaborativa en América Latina. Salud Publica Mex. 2022;64(Supl 1):S40-S45.
https://doi.org/10.21149/12803

Abstract

Objective. A narrative overview of regional academic research collaborations to address the increasing burden and gaps in care for patients at risk of, and who suffer from, stroke in Latin America (LA). **Materials and methods.** A summary of experiences and knowledge of the local situation is presented. No systematic literature review was performed.

Resumen

Objetivo. Realizar una revisión narrativa de la investigación colaborativa académica regional en accidente cerebrovascular (ACV), condición que ha aumentado su carga de enfermedad y presenta gran disparidad en prevención y tratamiento en América Latina (AL). **Material y métodos.** Se presenta un resumen de la experiencia y conocimiento de la situación

(1) Centro de Estudios Clínicos, Instituto de Ciencias e Innovación en Medicina, Facultad de Medicina Clínica Alemana Universidad del Desarrollo. Santiago, Chile.
(2) Unidad de Neurología Vascular, Servicio de Neurología, Departamento de Neurología y Psiquiatría, Facultad de Medicina Clínica Alemana Universidad del Desarrollo. Santiago, Chile.
(3) The George Institute for Global Health, Faculty of Medicine, University of New South Wales. Sydney, Australia.
(4) Servicio de Neurología, Hospital Padre Hurtado. Santiago, Chile.
(5) Servicio de Neurología, Hospital Santiago Oriente Doctor Luis Tisné Brousse. Santiago, Chile.
(6) Servicio de Neurología, Hospital Herminda Martín de Chillán. Chillán, Chile.
(7) Servicio de Neurología, Hospital Carlos Van Buren. Valparaíso, Chile.
(8) Servicio de Neurología, Hospital de la Florida Doctora Eloísa Díaz. Santiago, Chile.
(9) Servicio de Neurología, Hospital Base San José de Osorno. Osorno, Chile.
(10) Servicio de Neurología, Hospital Dr. Ernesto Torres Galdames de Iquique. Iquique, Chile.
(11) Unidad de Neurología, Hospital Dr. Hernán Henríquez Aravena. Temuco, Chile
(12) Stroke Service, Neurology Division, Department of Neuroscience and Behavioral Sciences, Ribeirão Preto Medical School, University of Sao Paulo. Ribeirão Preto, Sao Paulo, Brazil.
(13) Clínica de Enfermedad Vascular Cerebral, Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez. Ciudad de México, México.
(14) Departamento de Enfermedades Neurovasculares, Instituto Nacional de Ciencias Neurológicas. Lima, Perú.
(15) Cronicas, Centro de Excelencia en Enfermedades Crónicas, Universidad Peruana Cayetano Heredia. Lima, Perú.
(16) The George Institute China at Peking University Health Science Center. Beijing, China.

Received on: May 3, 2021 • **Accepted on:** September 10, 2021 • **Published online:** June 13, 2022
Corresponding author: Paula Muñoz Venturelli. Centro de Estudios Clínicos, Instituto de Ciencias e Innovación en Medicina, Facultad de Medicina Clínica Alemana Universidad del Desarrollo. Av. Plaza 680, Las Condes. 12461 Santiago, Chile.
email: paumunoz@udd.cl

Results. The rapidly increasing burden of stroke poses immense challenges in LA, where prevention and management strategies are highly uneven and inadequate. Clinical research is increasing through various academic consortia and networks formed to overcome structural, funding and skill barriers. However, strengthening the ability to generate, analyze and interpret randomized evidence is central to further develop effective therapies and healthcare systems in LA. **Conclusions.** Regional networks foster the conduct of multicenter studies –particularly randomized controlled trials–, even in resource-poor regions. They also contribute to the external validity of international studies and strengthen systems of care, clinical skills, critical thinking, and international knowledge exchange.

Keywords: cerebrovascular disorders; brain infarction; cerebral hemorrhage; Latin America; stroke

local. No se realizó una revisión sistemática. **Resultados.** El rápido aumento de la carga de enfermedad asociada con ACV presenta inmensos desafíos en AL, una región donde las estrategias de prevención y tratamiento aún son dispares e insuficientes. La investigación clínica ha aumentado gracias a redes y consorcios académicos formados para enfrentar barreras estructurales, presupuestarias y de capacidades. El fortalecimiento de las capacidades de generación, análisis e interpretación de evidencia aleatorizada es central para optimizar las terapias y sistemas de salud en AL. **Conclusiones.** Las redes regionales fomentan la realización de estudios multicéntricos, particularmente ensayos clínicos aleatorizados, incluso en regiones con desventajas. También contribuyen a la validez externa de los estudios internacionales, fortaleciendo sistemas de salud, capacidades clínicas, pensamiento crítico e intercambio de conocimiento internacional.

Palabras clave: trastornos cerebrovasculares; infarto cerebral; hemorragia cerebral; América Latina; accidente cerebrovascular

Globally, stroke remains a leading cause of death and disability.[1] Despite reductions in age-standardized rates of death and new events in many regions, the absolute and relative numbers of strokes are increasing as populations age, with over 80 million survivors and an increasing number of disability-adjusted life years (DALYs) lost worldwide. While stroke incidence is decreasing in some high-income countries, rates have more than doubled in many low- and middle-income countries (LMICs).[2] Locally relevant and scalable strategies to improve the prevention, management and rehabilitation of stroke in deprived populations are clearly urgent. Clinical research is important in providing contemporary data on the patterns of disease, as well as avenues for treatment and management with local relevance. Health professionals in Latin America (LA) have participated in several academic clinical stroke research initiatives in the region. Herein is a narrative overview of regional academic research collaborations organized to address the increasing burden and gaps in the care of patients at risk of, and who suffer from stroke in LA. No systematic literature review was performed; the authors summarized their experience and knowledge of the local situation.

Overview of stroke in Latin America

LA is a heterogenous region, where large differences in culture, social fabric, and economic and political situation pose significant challenges to efforts aimed at unifying and standardizing stroke care and research. For example, according to the gross national income (GNI) per capita, Bolivia, El Salvador, Honduras, and Nicaragua are defined as lower middle-income countries, while Chile, Panama and Uruguay are high-income countries.[3] Moreover, stroke care mirrors patterns of social disparities in developing regions of the world, where countries are divided into the wealthier segment, which shares a similar profile to higher income countries according to the World Bank or a high development index where patients are able to pay for high-quality stroke care, and the poorer segment, which is the vast majority of the population, where patients have limited access to effective prevention, treatment, and acute and rehabilitation services.[4]

Reliable epidemiological data on stroke are limited to only a handful of LA countries; most of the data on the quality of stroke care have been derived from hospital-based registries. Epidemiological studies indicate the adjusted annual incidence of first-ever stroke varies widely: 83 per 100 000 (95%CI 66.6 to 102.4) in Matão, Brazil;[5] 88.1 per 100 000 (95%CI 78.5 to 98.5) in Tandil, Argentina;[6] 105.4 per 100 000 (95%CI 98.0 to 113.2) in Joinville, Brazil;[7] 108.2 per 100 000 (95.8 to 120.6) in Iquique, Chile;[8] 118.2 per 100 000 (95%CI 103.1 to 133.3) in Durango, Mexico,[9] and 121.7 per 100 000 (95% CI 113.7 to 130.1) in Ñuble, Chile,[10] all adjusted to the WHO world population. The most recent study[10] used a prospective community-based approach to research the incidence, risk factors, long-term prognosis, care, and life quality after stroke in a low-resource community in the southern Chilean Ñuble region. It showed a higher rate of first-ever stroke compared to an earlier epidemiological stroke study in a northern region of Chile,[8] partly explained by the older demographic profile, higher prevalence of risk factors, rural location, and higher level of poverty in Ñuble.[10]

Patients in LA show a similar profile of risk factors for stroke as in other regions of the world, with hyper-

tension being the leading factor, followed by diabetes mellitus, hypercholesterolemia, and cardiac disease.[11] Unfortunately, the intake of primary preventative medication remains low.[8] Although antihypertensive and antiplatelet medications are widely available and frequently prescribed, less than one third of patients with a history of stroke are actually taking them.[10] Of particular concern are the low rates of anticoagulation in patients with atrial fibrillation.[10,12]

Although there is strong evidence for a range of approaches to improving the outcome from acute stroke,[13,14] there are reports evaluating the success of management strategies and/or national prevention campaigns to fight stroke in LA; most patients rely on information provided by local stroke neurologists or other medical doctors.[4] Despite being one of the most relevant strategies, the availability of acute stroke units remains scarce in the region and is difficult to confirm.[15] In a broad effort to improve stroke care in the region, a recent pan-American meeting held in Brazil exposed considerable gaps in stroke care across the 13 countries in the region. In addition to large variations in the delivery of acute stroke care and rehabilitation, there are considerable differences in public health systems; although stroke centers were widely available, the numbers of patients who access this strategy vary substantially, and there are workforce skill issues.[15] For example, there was only one stroke unit described in Ecuador, compared to 156 centers in Brazil; few patients (usually <1%) had access to thrombolysis and/or thrombectomy, and very limited data existed on the availability of rehabilitation services and post-discharge care.[15]

Intravenous thrombolysis has revolutionized the management of acute ischemic stroke to improve patient outcomes. Yet, there are considerable ongoing barriers to its implementation, including the availability of skilled teams, drugs, community awareness, and triage systems, all of which have an impact on the efficiency in identifying and referring patients to key hospitals. Although the cost of thrombolysis is high and is often regarded as a key reason for the low use of thrombolysis in LMICs, cost-effectiveness analyses performed in the region have shown that such treatment is associated with shorter length of hospital stay, lower overall costs, reduced in-hospital complications, improved indirect costs related to improved productivity, and reduced absenteeism.[16] Similarly, thrombectomy is now an established strategy that has been shown to improve the outcome in those with acute ischemic stroke related to large vessel occlusion; however, until recently, most of the supporting evidence has come from developed countries.[13] Importantly, this treatment was shown to be viable, safe, and effective across the public health care system through a pioneering collaborative effort between the government and academic physicians in Brazil.[17] Nevertheless, the high costs of the intervention and the need to increase the local capacity and the number of trained professionals remain serious challenges across the region.

There is a clear need for systems to be better organized, which will require greater investment in resources to increase the ability of patients to access the best available treatment, including rehabilitation and post-discharge care.[18] While the promotion of national projects could guide the development of high standards of stroke care relevant to the local characteristics, needs and available resources, there is also a need to build research capacity in order to better understand the burden of disease, expose gaps in care to inform policies and services, and identify widely applicable and affordable strategies for prevention and care across populations and in those individuals at increased risk. A recent initiative, for example, is that of the Global Stroke Alliance involving continuing education and the certification of standards for acute stroke units in order to improve the outcomes.[19,20]

Examples of collaborative academic stroke research

Several initiatives have been developed to enhance collaboration in academic stroke research across LA, most of them being health registries. The Ibero-American Stroke Organization (*Sociedad Iberoamericana de Enfermedades Cerebrovasculares*, SIECV-IASO), for example, established a joint regional project within the Safe Implementation of Treatments in Stroke (SITS) Registry to obtain up-to-date systematic information about the characteristics of patients and their management of stroke across Ibero-American countries as a basis for quality improvement, using a common in-hospital stroke registry (SITS-SIECV).[18] In one of its recent reports, less than 10% of patients with acute ischemic stroke were treated with intravenous thrombolysis, although this is likely an overestimation, given the selection bias of active participating centers. The Angels Stroke Initiative also allows sites to register their process of care for quality purposes (Res-Q).[21]

In order to translate evidence-based interventions into clinical practice (knowledge translation research) and to understand how health systems influence outcomes in stroke (for example, with cluster randomized trials), a LA network has participated in several influential global stroke research projects over the last decade.[22-25] This work has strengthened local research capacity, allowed knowledge generation, and improved

population health care, which further underpins the importance of international linkage. In particular, various collaborations with The George Institute for Global Health have allowed large numbers of participants from several countries to be included, developed familiarity in the use of novel methodologies, and allowed affordable and widely available strategies to be assessed in relevant, locally representative patients.

Over the last decade, many LA researchers have participated in several large pragmatic academic clinical trials that have required the collection of minimal essential data to allow the testing of low-cost interventions within the context of routine clinical practice. For example, the University of Development (*Universidad del Desarrollo*) in Santiago, Chile, provided regional coordination and monitoring for the second Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2, ClinicalTrials.gov Identifier: NCT00716079). This landmark study determined the effectiveness of early intensive blood pressure lowering treatment in 2 839 adult patients with acute spontaneous intracerebral hemorrhage (ICH) and high systolic blood pressure (SBP 150-220 mmHg**),** recruited at 144 hospitals in 21 countries, worldwide, including 50 (1.8%) patients from Argentina, Brazil and Chile.[22] The trial intervention considered the use of routinely available antihypertensive drugs to reach the specified BP goal. A crucial challenge for this study was the inclusion criteria of a short time window (<6 hours) from symptom onset to randomization. As many centers were located in areas of suboptimal population awareness, patient recruitment was compromised by delays in arrival and busy emergency departments.

Another project was the Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED, ClinicalTrials.gov Identifier: NCT01422616), designed to compare low-dose with standard-dose intravenous thrombolysis and intensive versus guideline-recommended blood pressure management in patients with acute ischemic stroke.[24,25] For the dose arm in this quasi-factorial design, 3 310 patients were randomized at 111 clinical centers in 13 countries between March 2012 and August 2015, including 324 (9.8%) patients from Brazil, Chile and Colombia. The sites used recombinant tissue plasminogen activator (rTPa) approved in the different countries but with different doses (low dose 0.6 mg/kg or standard dose 0.9 mg/kg) as per the trial's randomization. Again, rapid recruitment, efficient informed consent, and randomization process were often challenges for many researchers who were overwhelmed by clinical workload in the emergency departments of participating hospitals.

Finally, in the Head Position in Acute Stroke Trial (HeadPoST, ClinicalTrials.gov Identifier: NCT02162017) —the largest stroke care trial, involving 11 093 adults who were randomly allocated to the lying flat or sitting up head positions at 114 hospitals in nine countries from March 2015 to November 2016—,[23] there were 910 (8.2%) participants from Chile, Brazil and Colombia. Participants were assigned lying flat (0º) or sitting up (≥30°) head position for the first 24 hours after hospital admission for an acute stroke. The randomized cluster crossover design and guardian consent process were highly innovative for the region, allowing the rapid inclusion of patients; however, the monitoring of patients and fidelity to the protocol and reporting were still challenging to many investigators with limited research experience.

In addition to the sense of achievement in contributing to the impactful results of these trials, there was increased awareness of stroke among the health professionals, who facilitated the development of local systems and pathways for the assessment and treatment of patients.

We are currently participating in INTERACT3 (ClinicalTrials.gov Identifier: NCT03209258) in Chile, Peru, Brazil and Mexico, and in the Triple Therapy Prevention of Recurrent Intracerebral Disease Events Trial (Trident) (ClinicalTrials.gov Identifier: NCT02699645) in Brazil. Unfortunately, clinical trials in post-discharge care or rehabilitation are still limited in the region, where the scarce data and variable services create challenges in delivering continuing care to address multimorbidity and to facilitate the integration of systems and records.

Such large-scale stroke trial academic collaborations have provided data of the main results to inform local guideline recommendations and allowed research to participate in further secondary and exploratory analyzes in order to understand relevant gaps and barriers in stroke care systems.[26,27]

Challenges in academic research

We provide examples which prove that high-quality minimally-funded academic research can be conducted within busy clinical workloads and low-resourced health systems in LA. However, considerable efforts are required to further develop a sustainable program of stroke research in LA allowing researchers to undertake their own trials and even lead global trials.

One major challenge to developing research capacity in the region lies in attracting and retaining talented individuals to be trained in research.[28] As the public health system does not incorporate full-time or fractional research appointments, those interested in and committed to research need to find outside funding, where there are often limited opportunities. This is

particularly challenging for clinical trials where there is a demands for efficiency over recruitment and adherence to quality and reporting.

Clinical trials require strong organization, but these are generally established around individual projects rather than programs for sustainability. Thus, a key strategy is to convince authorities of the importance of investing in local infrastructure and human resources to foster research centers of excellence.[15,29] The availability of research staff within the public system would allow to offer a wide range of research activities, including registry projects, as well as clinical trials to promote research and train new researchers and assistants. Understanding the barriers, opportunities, and array of financial and non-financial incentives is critical to genuine engagement with local professionals, as academic achievements are not always considered important for a successful career. Many health professionals work between public and private systems for financial reasons and do not have protected time for academic or research work when their workload is high; besides, there are few rewards. Effective research capacity building within health systems will require this work to be appropriately valued, quarantined, and funded.

When health professionals have a passion to develop an academic or research career, the limited research funds restrict them to undertaking small single center studies rather than large-scale projects of international significance.[30] Although researchers have been successful in Brazil, research funding elsewhere in LA is generally insufficient to sustain highly impactful trials. This has led them to form networks and apply for international grants to access financing.

Another issue is that few professionals have experience in the design, organization and analysis of collaborative multicenter clinical trials or evaluations of health systems in the region, which requires familiarity with the management of human resources and financial systems for salaries and reimbursements of direct costs and overheads, as well as processes to obtain ethics and regulatory approvals and to negotiate legal frameworks for contracts, insurance and agreements. Efficient negotiation through these various areas is critical to avoid delays resulting in various research risks, including delays in set-up, conduct and close-out, poor data quality, serious adverse events, and litigation.[31]

Learning and development require overcoming new challenges. This will strengthen collaborations between local academic institutions and build interdisciplinary teams that will extend from hospitals, universities, and other institutions into the community.

Conclusions

Given that stroke is a leading cause of death and disability, it is a key health priority across all countries of LA. Proven therapies and interventions exist to prevent and manage stroke, but these are still underutilized in this large and highly populous region of the world.

Considerable work has been undertaken to build an academic network for stroke research in LA, with increasing participation in landmark trials. However, there is a need to generate more and better local data in order to enhance understanding of stroke and find solutions for reducing its burden in the region.

Building capacity to increase the production and quality of research should positively impact health outcomes. Knowledge, capability and capacity in different countries and areas are critical aspects to allow high quality collaborative academic research to be efficiently implemented. In addition to increased resources, this requires the development of a clear research-oriented professional career path to facilitate work in academic research as part of the training and development programs for professionals.

Implementation science has recently been recognized as critical to evaluate proven interventions in real world conditions and to answer questions that matter to health professionals and consumers. Better solutions to local problems in LA can be found by creating a network of academic researchers eager to answer clinical questions and to test the implementation of different strategies in our local scenarios. Practical and widely available strategies for stroke care are essential to improving patient outcomes and promoting healthier societies in LA.

Acknowledgments

We thank all our colleagues for their commitment and efforts, as well as the many patients, families and friends who have contributed in various ways to developing research and health care in Latin America.

Declaration of conflict of interests. The authors declare that they have no conflict of interests.

References

1. Global Health Data Exchange. GBD Results Tool [internet]. Seattle: GHDx [cited 2021 Aug 17]. Available from: http://ghdx.healthdata.org/gbd-results-tool

2. Krishnamurthi RV, Ikeda T, Feigin VL. Global, Regional and Country-Specific Burden of Ischaemic Stroke, Intracerebral Haemorrhage and Subarachnoid Haemorrhage: A Systematic Analysis of the Global Burden of Disease Study 2017. Neuroepidemiology. 2020;54(2):171-9. https://doi.org/10.1159/000506396
3. The World Bank. World Bank Country and Lending Groups [internet]. Washington DC: The World Bank [cited 2021 Aug 17]. Available from: http://data.worldbank.org/about/country-classifications/country-and-lending-groups
4. Avezum Á, Costa-Filho FF, Pieri A, Martins SO, Marin-Neto JA. Stroke in Latin America: Burden of Disease and Opportunities for Prevention. Global Heart. 2015;10(4):323-31. https://doi.org/10.1016/j.gheart.2014.01.006
5. Minelli C, Cabral NL, Ujikawa LT, Borsetti-Neto FA, Langhi-Chiozzini EM, Dos Reis GC, *et al*. Trends in the Incidence and Mortality of Stroke in Matão, Brazil: The Matão Preventing Stroke (MAPS) Study. Neuroepidemiology. 2020;54(1):75-82. https://doi.org/10.1159/000503005
6. Bahit MC, Coppola ML, Riccio PM, Cipriano LE, Roth GA, Lopes RD, *et al*. First-Ever Stroke and Transient Ischemic Attack Incidence and 30-Day Case-Fatality Rates in a Population-Based Study in Argentina. Stroke. 2016;47(6):1640-2. https://doi.org/10.1161/STROKEAHA.116.013637
7. Cabral NL, Gonçalves ARR, Longo AL, Moro CHC, Costa G, Amaral CH, *et al*. Trends in stroke incidence, mortality and case fatality rates in Joinville, Brazil: 1995-2006. J Neurol Neurosurg Psychiatry. 2009;80(7):749-54. https://doi.org/10.1136/jnnp.2008.164475
8. Lavados PM, Sacks C, Prina L, Escobar A, Tossi C, Araya F, *et al*. Incidence, 30-day case-fatality rate, and prognosis of stroke in Iquique, Chile: a 2-year community-based prospective study (PISCIS project). Lancet. 2005;365(9478):2206-15. https://doi.org/10.1016/S0140-6736(05)66779-7
9. Cantu-Brito C, Majersik JJ, Sánchez BN, Ruano A, Quiñones G, Arzola J, *et al*. Hospitalized Stroke Surveillance in the Community of Durango, Mexico The Brain Attack Surveillance in Durango Study. Stroke. 2010;41(5):878-84. https://doi.org/10.1161/STROKEAHA.109.577726
10. Lavados PM, Hoffmeister L, Moraga AM, Vejar A, Vidal C, Gajardo C, *et al*. Incidence, risk factors, prognosis, and health-related quality of life after stroke in a low-resource community in Chile (ÑANDU): a prospective population-based study. Lancet Glob Heal. 2021;9(3):e340-51. https://doi.org/10.1016/S2214-109X(20)30470-8
11. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, *et al*. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet. 2010;376(9735):112-23. https://doi.org/10.1016/S0140-6736(10)60834-3
12. Muñoz-Venturelli P, Sacks C, Madrid E, Lavados PM. Long-term adherence to national guidelines for secondary prevention of ischemic stroke: A prospective cohort study in a public hospital in Chile. J Stroke Cerebrovasc Dis. 2014;23(3):490-5. https://doi.org/10.1016/j.jstrokecerebrovasdis.2013.04.013
13. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, *et al*. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2019;50(12):E344-418. https://doi.org/10.1161/STR.0000000000000211
14. Hemphill JC, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, *et al*. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2015;46(7):2032-60. https://doi.org/10.1161/STR.0000000000000069
15. Ouriques-Martins SC, Sacks C, Hacke W, Brainin M, de Assis Figueiredo F, Marques Pontes-Neto O, *et al*. Priorities to reduce the burden of stroke in Latin American countries. Lancet Neurol. 2019;18(7):674-83. https://doi.org/10.1016/S1474-4422(19)30068-7
16. Araújo DV, Teich V, Passos RB, Martins SC. Analysis of the cost-effectiveness of thrombolysis with alteplase in stroke. Arq Bras Cardiol. 2010;95(1):12-20. https://doi.org/10.1590/s0066-782x2010005000067
17. Martins SO, Mont'Alverne F, Rebello LC, Abud DG, Silva GS, Lima FO, *et al*. Thrombectomy for Stroke in the Public Health Care System of Brazil. N Engl J Med. 2020;382(24):2316-26. https://doi.org/10.1056/NEJMoa2000120
18. De Leciñana MA, Mazya M V, Kostulas N, Del Brutto OH, Abanto C, Massaro AR, *et al*. Stroke Care and Application of Thrombolysis in Ibero-America: Report from the SITS-SIECV Ibero-American Stroke Register. Stroke. 2019;50(9):2507-12. https://doi.org/10.1161/STROKEAHA.119.025668
19. Global Stroke Alliance. Educational Tools [internet] [cited 2021 Aug 17]. Available from: http://www.globalstrokealliance.com/en/certification/educational-tools/
20. The Lancet Neurology. The fight against stroke must go on. Lancet Neurol. 2020;19(5):369. https://doi.org/10.1016/S1474-4422(20)30107-1
21. Angels Initiatives. Angel Awards [internet] [cited 2021 Aug 17]. Available from: https://www.angels-initiative.com/angels-awards
22. Anderson CS, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, *et al*. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med. 2013;368(25):2355-65. https://doi.org/10.1056/NEJMoa1214609
23. Anderson CS, Arima H, Lavados P, Billot L, Hackett ML, Olavarria VV, *et al*. Cluster-randomized, crossover trial of head positioning in acute stroke. N Engl J Med. 2017;376(25):2437-47. https://doi.org/10.1056/NEJMoa1615715
24. Anderson CS, Robinson T, Lindley RI, Arima H, Lavados PM, Lee TH, *et al*. Low-Dose versus Standard-Dose Intravenous Alteplase in Acute Ischemic Stroke. N Engl J Med. 2016;374(24):2313-23. https://doi.org/10.1056/NEJMoa1515510
25. Anderson CS, Huang Y, Lindley RI, Chen X, Arima H, Chen G, *et al*. Intensive blood pressure reduction with intravenous thrombolysis therapy for acute ischaemic stroke (ENCHANTED): an international, randomised, open-label, blinded-endpoint, phase 3 trial. Lancet. 2019;393(10174):877-88. https://doi.org/10.1016/S0140-6736(19)30038-8
26. Muñoz Venturelli P, Robinson T, Lavados PM, Olavarría VV, Arima H, Billot L, *et al*. Regional variation in acute stroke care organisation. J Neurol Sci. 2016;371:126-30. https://doi.org/10.1016/j.jns.2016.10.026
27. Venturelli PM, Li X, Middleton S, Watkins C, Lavados PM, Olavarría VV, *et al*. Impact of evidence-based stroke care on patient outcomes: a multilevel analysis of an international study. J Am Heart Assoc. 2019;8(13):e012640. https://doi.org/10.1161/JAHA.119.012640
28. Bonini BB, Araya R, Quayle J, Silva Evangelista M, Price LN, Menezes PR. LATIN-MH: a model for building research capacity within Latin America. Glob Ment Heal. 2017;4(e2):1-10. https://doi.org/10.1017/gmh.2016.32
29. Pandian JD, William AG, Kate MP, Norrving B, Mensah GA, Davis S, *et al*. Strategies to improve stroke care services in low- and middle-income countries: a systematic review. Neuroepidemiology. 2017;49(1-2):45-61. https://doi.org/10.1159/000479518
30. Estenssoro E, Friedman G, Hernández G. Research in Latin America: opportunities and challenges. Intensive Care Medicine. 2016;42:1045-7. https://doi.org/10.1007/s00134-016-4342-3
31. Alger J, Francisco BP, Kennedy A, Martinelli E, Cuervo LG. National health research systems in Latin America: a 14-country review. Rev Panam Salud Publica. 2009;26(5):447-57.