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Editorial

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Stroke - the second leading cause of death

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In the World Health Organization (WHO) list of leading causes of death in the world, stroke is ranked second, behind heart disease (WHO, 2019). While the mortality rate of stroke is lower than that caused by the number one ailment (heart disease), disability after stroke carries a much greater burden than heart disease on quality of living. Disability after stroke creates a much more serious socioeconomic burden on survived patients, their families, and the society compared to heart disease. Prevention of stroke, rather than therapy, is the top priority in healthcare. Once stroke develops in a patient, the therapeutic options are limited. Approximately 87% of stroke is caused by cerebral ischemia following blockage of cerebral arteries secondary to atherosclerosis or blood clots dislodged from the heart or major cerebral arteries resulting in reduced cerebral blood flow in the region of the brain irrigated by the affected blood vessels[1]. Cerebral ischemia results in brain damage secondary to deprivation of oxygen and nutrients provided by cerebral blood flow. Ischemic brain injury can cause neurological dysfunctions including disorder in mental, motor, sensory, and other body functions. Starting in the 1980s, neurotoxicity caused by free radicals and endogenous neurotoxic substances, in particular glutamate, an excitatory neurotransmitter, had been identified to be the key pathogenetic mechanism underlying ischemic neuronal death[2]. Blocking the neurotoxic actions of free radicals and excitatory neurotransmitters, particularly glutamate, had been the top research field for developing therapeutic agents to treat ischemic stroke and restore neurological function for over a decade until 1995, after more than one thousand clinical trials failed to establish the therapeutic efficacy of any neuroprotective agent directed at free radicals or glutamate.

In 1995 in a multicenter clinical trial sponsored by the National Institute of Neurological Disorders and Stroke (NINDS) in the National Institutes of Health of the United States, an effective therapy was eventually established by dissolving the blood clots that occlude blood vessels supplying the brain using a fibrinolytic agent, alteplase, which is a recombinant tissue plasminogen activator (t-PA) (NINDS and Stroke rt-PA Study Group, 1995). Fibrinolytic therapy applying t-PA was found to be effective in improving functional outcome in patients with ischemic stroke in a double blind, placebo-controlled randomized trial. In this NINDS t-PA trial, published in the *New England Journal of Medicine*, functional recovery to normal or with minor neurological deficit was 30% more in the t-PA group than the control group[3]. However, the risk of developing symptomatic intracerebral hemorrhage was 10-fold higher in the t-PA group than the control group (6.4% *vs.* 0.6%). Another shortcoming of t-PA in the treatment of patients with ischemic stroke noted in this multicenter trial in the United States was the narrow therapeutic window, restricted to 3 h within stroke onset (extended to 4.5 h later). Until 2019, 24 years after the landmark NINDS trial of t-PA, advances in thrombolytic therapy were finally made in a multinational trial (EXTEND) under the global leadership of Prof. Steve Davis and Prof. Jeffrey Donnan (both were former Presidents of the World Stroke Organization). In this multinational clinical trial, the therapeutic window of t-PA for patients with ischemic stroke was extended from 4.5 to 9 h after stroke[3]. The EXTEND trial took the advantage of an innovative imaging software (RAPID) developed by the same investigator team led by Prof. Steve Davis and Prof. Jeffrey Donnan to define the penumbra region in the ischemic brain for identifying eligible stroke patients with ischemic but surviving brain region (penumbra) which is still eligible for salvaging with the restoration of blood flow by t-PA. The Australian stroke investigator group has developed another multinational stroke clinical trial aiming to broaden the therapeutic option by testing a new thrombolytic agent, teleplase. Compared to t-PAs such as alteplase, teleplase has the advantages of lower risk in causing intracerebral hemorrhage while carrying greater efficacy in thrombolytic action than t-PA. The TASTE trial comparing t-PA with teleplase has been a multinational clinical trial ongoing since 2017 under the leadership of another Australian stroke leader, Professor Mark Parsons.

Overall, therapeutic interventions for patients with stroke caused by cerebral ischemia have been limited to thrombolysis with intravenous t-PA for dissolving the blood clots that obstruct major cerebral blood vessels from delivering blood to the brain. The advance in the past 25 years is that the therapeutic window of t-PA has been extended from 4.5 to 9 h after stroke onset to allow a greater proportion of patients with acute ischemic stroke to have the benefit of receiving t-PA therapy because of the broadened therapeutic window from 4.5 to 9 h. Symptomatic intracranial hemorrhage has remained to be the major drawback. The multinational clinical stroke trial comparing the t-PA alteplase with teleplase (TASTE) is still ongoing under the global leadership of Prof. Mark Parsons, another commanding principal investigator from Australia. Prof. Henry Ma, the international coordinator of EXTEND, again has been serving the same for the TASTE trial[4].

It is a great honor that both Prof. Jeffrey Donnan and Prof. Steve Davis as well as Prof. Henry Ma, the outstanding global coordinator of the EXTEND and TASTE trials, have graciously agreed that each contributes an article for this special issue of Vessel Plus on stroke. The distinguished international leadership of the Australian stroke research group on the EXTEND trial has also broken new ground to broaden the therapeutic option for stroke patients beyond t-PA therapy. As referred to above, the TASTE trial which is ongoing aims to confirm that the thrombolytic agent tenecteplase is superior to alteplase in thrombolytic action but carries a lower risk of developing intracranial hemorrhage under the leadership of Prof. Mark Parson, the 4th global stroke research leader from Australia. The 5th Australian stroke trial leader, Prof. Bernard Yan, is the principal investigator on interventional trials applying thrombectomy. His research also covers a broad scope of stroke care and has included: (1) pre-hospital mobile unit

management of stroke; (2) novel measures of similarity and asymmetry in upper limb activities for identifying hemiparetic severity in stroke survivors; (3) 7T MRI quantification of brain glutamate in acute ischemic stroke; (4) artificial intelligence decision support system to manage acute stroke; and (5) using disruptive technologies to transform pre-hospital care of stroke. Finally, Prof. Bruce Campbell, the 6th leader from Australia, Head of Stroke and Interim Head of Neurology at the Royal Melbourne Hospital, is also a professorial fellow in the Melbourne Brain Centre, an honorary professorial fellow at The Florey Institute of Neuroscience and Mental Health, and a fellow of the Australian Academy of Health and Medical Science. His research interest has been focused on the imaging and treatment of acute stroke. Prof. Campbell was a co-principal investigator and medical coordinator of the EXTEND-IA and EXTEND-IA TNK multi-center randomized trials on thrombectomy with trial results published in the *New England Journal of Medicine* in 2015 and 2018[5]. He is the Chair of Clinical Council, a Director of the Stroke Foundation, and Co-Chair of the Australian stroke "living" guidelines working party. He has been an inaugural member of the Victorian stroke telemedicine project and chairs the Victorian Statewide Stroke Reperfusion Therapy Committee. He also co-chairs the World Stroke Organization Young Stroke Professionals Committee and is the coordinator of the National Brainschool training program for neurologists in training.

In total, 6 of the 10 articles in this special issue of *Vessel Plus* on stroke, are authored by world-renowned stroke investigators from Australia, reflecting the robust clinical research activities on stroke in Australia in recent years.

The other global leaders on stroke research who have each contributed an article are Prof. Jin-Moo Lee, Prof. Adnan Qureshi, Prof. Kazunori Toyoda, and Prof. Shinn-Zong Lin, Prof. Jin-Moo Lee, the Norman J. Stupp Professor of Neurology at Hope Center, Washington University, is the Director of the Stroke Center at Washington University School of Medicine and Barnes-Jewish Hospital in St. Louis, Missouri, USA which has been ranked the number one stroke center in the United States by HealthGrades in 2001. In July 2021, Prof. Lee has been promoted to be Head of the Department of Neurology with a more prestigious endowed professorship, Andrew B. and Gretchen P. Jones Professor. Prof. Adnan Qureshi is a renowned international leader on stroke research. The widely applied Qureshi Grading System for angiographic evaluation of arterial occlusion and recanalization response to intra-arterial thrombolysis in the setting of acute ischemic stroke has been highly valuable in clinical practice during the evaluation and management of patients with acute ischemic stroke. Prof. Adnan Qureshi has also been the global principal investigator in a multinational clinical trial, ATACH II, which was sponsored by NINDS to explore the safety and efficacy of intense blood pressure regulation in improving the functional outcome of patients with intracranial hemorrhage in the acute setting. This multinational trial has had a major impact on clinical practice in treating patients with intracerebral hemorrhage. The key ATACH II trial results were published in the *New England Journal of Medicine*[6] with a series of follow-up publications in other high-impact journals such as *Lancet Neurology*, *Neurology*, *Stroke*, *International Journal of Stroke*, and other journals. Prof. Kazunori Toyoda, the Deputy Director General of the Hospital at the National Cerebral and Cardiovascular Center in Suita, Japan, has been directing a group of stroke investigators in Japan to join multicenter stroke trials including a number of landmark global trials in the development of better therapeutic measures for stroke. Prof. Kazunori Toyoda's group has published stroke trial results extensively in high-impact journals including *New England Journal of Medicine*, *Lancet*, *Circulation*, *Annals of Neurology*, and others. Prof. Shinn-Zong Lin, Professor of Neurosurgery and Superintendent of Tzu Chi Medical Center in Hualien, Taiwan, is a pioneer in applying stem cells to treat stroke. Prof. Shinn-Zong Lin was the first investigator in the world to show that stem cell therapy was able to restore lost neurological function in patients with chronic stroke.

Together, in this special issue of *Vessel Plus* on stroke, 10 world-class stroke leaders each has contributed an article based on their respective expertise in stroke research and clinical care of stroke patients to develop a special issue on stroke with up-to-date pioneering perspectives and world-renowned research achievements. Overall, an update of stroke research and therapy covering a broad scope of important topics are presented in this special issue of *Vessel Plus* reporting the topnotch and up-to-date perspectives and recent research accomplishments for treating a serious disease, with mortality ranked second by WHO and with surviving stroke patients carrying long-term disability which demands pioneering research by world-class stroke investigators to facilitate the development of safer and more effective therapeutic and restorative measures for relieving the long-term sufferings caused by disability after stroke.

Thrombectomy, an angiographic approach to remove blood clots from vessels that disrupt blood supply to the brain resulting in ischemic stroke, has been established for its safety and efficacy in a number of multinational trials. This is the first mechanical approach beyond surgical interventions to treat ischemic stroke. There were a series of publications in 2015 to report the safety and efficacy of thrombectomy for treating patient with ischemic stroke caused by occlusion of large vessels (i.e., carotid artery, vertebral artery, or proximal branches of the middle cerebral artery)[7-10]. Among the 10 authors for this special issue of *Vessel Plus*, both Prof. Bruce Campbell and Prof. Bernad Yan are leading experts on this invasive intervention for stroke. The Australian stroke team has also been conducting a multinational stroke trial (DIRECT-SAVE) exploring whether adding t-PA to thrombectomy can improve stroke outcome.

In conclusion, I am deeply honored to accept the call to invite 10 world-leading authoritative experts with each contributing an article to assemble a special issue on stroke for *Vessel Plus*, a new and rapidly uprising journal on vascular diseases.

DECLARATIONS

Authors' contribution

The author contributed solely to this article.

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Not applicable.

Consent for publication

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