

10th Anniversary of the Asia Pacific Stroke Organization: State of Stroke Care and Stroke Research in the Asia-Pacific

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Abstract

The Asia Pacific Stroke Organization is the largest international and professional stroke group in the region. It has worked consistently over the last 10 years to gain visibility and consistency across the Asia-Pacific and beyond. The 10-year journey will be reviewed in the background of many internal and external developments including changes in Asia-Pacific stroke epidemiology, stroke care systems, and stroke service developments as well as major research studies in the Asia-Pacific.

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Introduction

The 10th year of the Asia Pacific Stroke Organization (APSO) in 2021 is an accomplishment to be celebrated and at the same time an opportunity for reflection. As a regional stroke organization across a geographically and cultur-

ally diverse area, the journey of the APSO began with the main objectives of improving the standard of stroke care in the region as well as to provide a platform for stroke education and advocacy around the region [1, 2].

The key thrust of the APSO is training and updating neurologists, clinicians, and healthcare workers with evidence-based and up-to-date stroke management strategies, so that they can be utilized for the treatment of patients with stroke in this region at an affordable cost. The APSO also supports stroke survivors and their carers and stroke support organizations in their fight against stroke.

This 10th anniversary has also coincided with the COVID-19 pandemic, the greatest global healthcare disruption in the last 50 years with its impact affecting many aspects of stroke care delivery. This study will capture the zeitgeist of the last decade for the APSO with the corresponding major milestones, advances, and future challenges.

Historical Background

The APSO was established with the amalgamation of the Asian Stroke Forum (ASF) which was founded in Japan and the Asia Pacific Conference Against Stroke (AP-

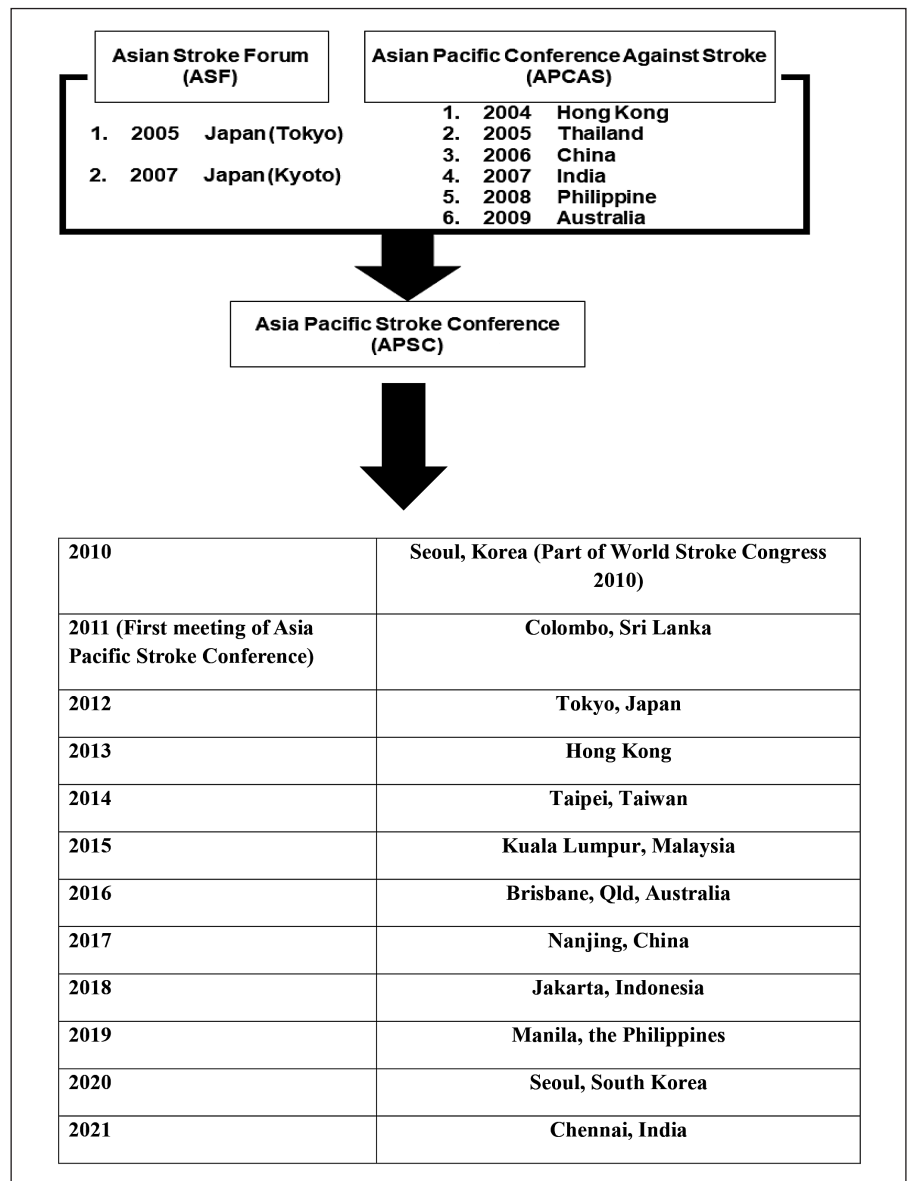


Fig. 1. Formation of the APSO and various annual conferences held by the ASF, AP-CAS, and APSO with the corresponding year of conference and country.

CAS). In September 2009, the APSO was registered as a charity in Hong Kong by Dr. Chen-Ya Huang. The first executive committee was formed in 2011 during the first Asia Pacific Stroke Conference in Sri Lanka. Dr. Chuanzhen Lu (China) was elected as the first President. From its inception, the banking and secretariat services were based in Hong Kong while the first website was registered in India. The website remained active in India from 2009 to 2015 before the domain name was transferred to Hong Kong.

One important objective of the APSO is the delivery of a high standard of stroke care to patients by enhancing

stroke knowledge and best practices among healthcare professionals in the Asia-Pacific by providing a platform for communication, cooperation, and engagement among stroke professionals and neurologists. This objective is achieved through annual Asia Pacific Stroke Conferences (APSCs), interactive workshops, and continuing medical education (CME). The key events in chronological order are captured in Figure 1. The flagship conference of the APSO, the APSC, replaced its predecessor regional conferences, APCAS and ASF.

Organizational Structure

The operational component of the APSO is the Executive Committee (EC) which consists of the President, President-Elect, Immediate Past-President, Secretary-General, Treasurer, and Chair of Continuing of Medical Education (CME). The members of the EC are elected every 2 years.

The General Executive Council (GEC) consists of the EC and representatives from member societies. There are 17 society members which include 5 sponsoring members (from Australia, Hong Kong, Japan, Korea, and Taiwan) and 12 affiliated stroke societies from Bangladesh, China, India, Malaysia, Mongolia, Nepal, Pakistan, Philippines, Singapore, Sri Lanka, Thailand, and Vietnam [3]. Efforts are continuing to enroll member societies from all countries in the Asia-Pacific region.

In the past, the EC meets at the Annual General Meeting which occurs at the same time as the annual APSCs [3]. There was a subsequent need for more frequent EC meetings as the number of activities organized by the APSO increased. The operational funds for the APSO have been acquired through running conferences, registration fees, and annual membership subscriptions. Main expenses include the cost of running a secretariat, website, related travel expenses, and numerous educational as well as travel grants.

Historical and Current Developments in Continuing Medical Education

Enhancing CME is one of the key objectives in the APSO. Several APSO initiatives run in parallel and were introduced incrementally over the years. The flagship conference is the annual APSC. As far as possible, the host country for APSC is rotated through various geographical regions in the Asia-Pacific. Many countries had the opportunity to host the conference at least once. The first Asia Pacific Stroke Conference was held in Sri Lanka in 2011 and the latest in India from 9 to 11 December 2021 <https://apscindia2021.com>. A balanced program is the objective, and it is usually performed with the engagement of the host country, and the scientific committee is drawn from the respective member countries.

Best paper awards as well as travel grants for best abstracts have been presented to young investigators working in low- and low-middle income countries. These grants are used to encourage young clinicians and allied health personnel from Asia-Pacific countries to attend

APSCs. All previous APSC abstracts are freely available on the APSO website. Every effort is expended to keep registration fees for APSC affordable. The attendee numbers have ranged between 500 and 1,500. While the conferences have previously been held physically across many countries, APSCs from 2020 were held virtually. During this COVID-19 pandemic and as a build-up to APSC 2021 in India, the APSO organized a series of webinars in order to reach audiences in the region while covering contemporary issues in stroke care including hyperacute care, advanced imaging, secondary prevention, and intracerebral hemorrhage (ICH) [1].

The APSO Visiting Professorship program provides funding for member societies in the organization of local CME activities and includes support for air fares of invited stroke experts in order to conduct workshops and participate in national conferences. These grants have been given to support national meetings in Bangladesh (2016), Nepal (2017), Myanmar (2019), and Sri Lanka (2021). APSO Training Grants provide 2-week mini-fellowships for young stroke neurologists from countries with less resources to spend time in stroke centers of excellence in the Asia-Pacific region. This will allow the visiting fellow to learn directly from stroke experts and experienced stroke teams.

Epidemiology of Stroke in the Asia-Pacific

The progress of the APSO should be viewed in the context of the effect of stroke globally and in the Asia-Pacific. Epidemiological evidence showed that in 2019 alone, there were 12.2 million (95% UI: 11.0–13.6 million) incident stroke cases, 6.55 million (95% UI: 6.00–7.02 million) deaths from stroke, 101 million (95% UI: 93.2–111 million) prevalent stroke survivors, and 143 million (95% UI: 133–153 million) disability-adjusted life years (DALYs) lost due to stroke [4].

Sixty percent of the world's population live in Asia, in countries of varying population sizes, land area, socioeconomic status, and adequacy of healthcare systems. There is a wide range of age-standardized mortality rates, prevalence, and DALYs due to stroke, being in general highest in East Asia and Southeast Asia and lowest in South Asia [5–11]. Based on data from the Global Burden of Disease studies published in the last decade, country-specific, age- and sex-standardized mortality, and DALYs are highest in Mongolia (226/100,000 and 4,409.8/100,000, respectively) and lowest in Japan (43.4/100,000 and 706.6/100,000, respectively) [5]. There are also variations

within each region in Asia: stroke burden is highest and lowest, respectively, in Mongolia and Japan in East Asia, Pakistan and Bangladesh in South Asia, and Indonesia and Singapore in South East Asia [5].

While the absolute numbers have increased between 1990 and 2019 globally, the age-standardized rates for deaths and DALYs due to stroke declined substantially [4]. However, age-standardized death rates increased in some locations, including Indonesia and the Philippines [4], while stroke-related mortality has been decreasing in East-Asian countries such as Japan, Korea, Taiwan, and urbanized areas of China [5]. The decrease in high mortality, incidence, and morbidity, observed predominantly in high-income countries, may reflect the impact of the economic status of a country on health [5], as well as of the country's healthcare system [12].

There is a paucity of community-based incidence data, with few studies published in the last decade [5]. The highest incidence rates are in Japan [12] and Taiwan [13] and lowest are in Malaysia [14]. The availability of prevalence data from studies published in the last decade is greater than incidence data, but different study methods were used for case-finding, with different age bands studied, making direct comparisons difficult. Incidence rates may also vary according to the area surveyed with differences detected in rural-urban localities and between different provinces within the same country [5–7].

From 12.2 million (95% UI: 11.0–13.6 million) incident stroke cases, 7.63 million (95% UI: 6.57–8.96 million) (62.4%) were ischemic strokes (IS), 3.41 million (95% UI: 2.97–3.91 million) (27.9%) were ICH, and 1.18 million (95% UI: 1.01–1.39 million) (9.7%) were subarachnoid hemorrhages [4]. Hospital-based stroke registries with high brain imaging rates in Asia have consistently shown a higher frequency of ICH than among Caucasian populations, ranging from 16.1% in Taiwan to 49.1% in India [5].

Small artery occlusion and intracranial stenosis are more frequent causes of IS in Asian than Caucasian populations, with increasing recognition of microatheroma of penetrating arteries in addition to atherosclerosis of the parent artery [15]. Among IS from hospital-based registries, large artery atherosclerosis comprises 14.6–54.1% in East Asia, 26–41% in South Asia, and 41–59% in South East Asia; small vessel disease comprises 21–39% in East Asia, 18–43% in South Asia, and 28.3–35% in South East Asia; cardioembolic stroke comprises 7.5–22.9% in East Asia, 6–10% in South Asia, and 3.4–10% in South East Asia [5]. Interestingly, in younger patients with IS (under the age of 50), a multicenter, international study [16] re-

ported similar proportions of large artery atherosclerosis (29.8%), small vessel occlusion (20.2%), and cardioembolism (15.1%). While these differences may be the result of regional differences, other possible reasons could be from the degree of investigations that were performed as well as the detection, frequency, and control of vascular risk factors. Other unusual mechanisms of stroke in Asia including *moya-moya* disease, radiation vasculopathy, and CADASIL have been reviewed recently [17]. Greater clarity on disease burden, mechanisms, outcomes, and trends will be obtained from the recent rise in nation-wide stroke registries as seen in China, Korea, Malaysia, and Singapore [18–21].

Stroke Care Systems

Given the rising burden of stroke in the Asia-Pacific region, existing stroke care systems come into focus. Stroke care systems are defined as healthcare processes that provide the platform for both stroke patients and professionals to raise public awareness of stroke and reduce the time for recanalization therapy in large vessel occlusions, as well as increase accessibility to acute stroke care through stroke unit admissions with long-term post-stroke management including rehabilitation and education. Among Asia-Pacific countries, the available stroke care systems are at various stages of developments and face numerous challenges in stroke care delivery with limitations in infrastructure and human resources [8, 22, 23].

Some countries have highly advanced care and reimbursement policies which allow most of the patients access to treatment. However, similar to the other parts of the world, higher mortality is evident in patients with acute stroke occurring in countries in lower socioeconomic strata with reasons such as lack of awareness of symptoms in patients and primary care physicians, delay in reaching healthcare facilities, lack of availability of thrombolysis and endovascular treatment, insufficient stroke unit beds, and lack of affordability of new interventional therapies [24, 25]. As for transportation, the majority of acute stroke patients in Asia still depend on non-EMS, e.g., private cars and public transportation, while on the other hand, mobile stroke units have been implemented in certain areas of India, China, and Thailand [26].

Recanalization therapy for large vessel occlusion is the most effective treatment currently accepted by neurologists and physicians in most countries. According to a

survey published in 2016, intravenous thrombolytic therapy was available in all 12 studied countries [8]. However, the number of patients receiving the treatment ranged from a single digit to many thousands. This number is closely related to the country's GDP and reimbursement policy. Most of the countries use the standard 0.9 mg/kg dose except for Japan where the recommended dose is 0.6 mg/kg. Endovascular treatment is also currently available in many countries, but the accessibility is still limited due to cost, lack of trained interventionalists, and inadequate resources in public hospitals [8, 25]. Stroke network systems and telemedicine is more widely used for acute stroke care in Asia such as in China, India, Japan, and Thailand. An international telestroke collaboration was also established between Thailand and Lao PDR in 2017 [27].

Stroke units with a multidisciplinary team approach is another standard treatment for acute stroke. In most countries, the number of stroke units has been rapidly increasing during the past decade. The establishment of a stroke unit in countries with limited resource countries may not require major infrastructure changes. The most crucial components are the leader physician, multidisciplinary team, re-orientation of the existing beds, and consensus care map [28].

For poststroke management, many stroke survivors in Asia still believe in traditional or alternative methods [29]. For example, almost all stroke patients in China use traditional Chinese medicine [30] as part of their long-term therapy, whereas in India, more than half of the patients use ayurvedic massage. In some remote areas of many countries, traditional healers still play a role in rehabilitation [31].

Stroke Service Development in the Asia-Pacific

Across the Asia-Pacific, in the last 10 years, improved strategies in hyperacute management of AIS (IV t-PA thrombolysis and mechanical thrombectomy) have enabled a rise of comprehensive stroke centers with well coordinated, multidisciplinary stroke teams in order to improve the care of stroke patients. In successful centers, there is significant association between the capacity of comprehensive stroke care centers and the volume of stroke interventions [32].

The recent network meta-analysis for stroke unit care re-affirmed the moderate-quality evidence that stroke patients who receive organized inpatient (stroke unit) care are more likely to be alive, independent, and living at

home 1 year after the stroke. The benefits were independent of patient's age, sex, initial stroke severity, or stroke type and were most obvious in units based in a discrete stroke ward [28]. For many countries, important considerations include workforce requirements and operational costs which will be greater when comprehensive stroke care centers are established, requiring careful planning in national finance and healthcare policies [30, 33, 34]. In addition, driven by the low number of stroke interventionalists in the Asia-Pacific, there has been a proposal for a neurointerventional fellowship program for neurologists, radiologists, and neurosurgeons to meet this shortfall of expertise [35].

Stroke Research in the Asia-Pacific Region

In the last decade, a noticeable rise in the number of clinical trials and research projects on stroke were conducted in the Asia-Pacific region, increased by international and inter-regional collaboration. Consequently, many publications in stroke research from the Asia-Pacific region, based on Google Scholar and PubMed searches with the keywords "stroke" and "Asia-Pacific," were found. These publications are briefly described in the following passages and summarized chronologically in Table 1.

Randomized Controlled Trials

Among the numerous trials done in the last decade, a clinical trial to compare low-dose with standard-dose intravenous alteplase in patients with acute stroke was performed involving predominantly Asian patients (ENCHANTED). There were significantly fewer symptomatic ICH with low-dose alteplase, although mortality at 90 days did not differ [36]. Intensive blood pressure reduction in acute cerebral hemorrhage trials (INTERACT I and II) reported that a significant blood pressure reduction decreased the hematoma expansion [37, 38]. In a large clinical trial for primary stroke prevention performed in China, folic acid therapy reduced the risk of first IS, but not a hemorrhagic stroke (CSPPT trial) [39].

Studies on secondary stroke prevention were mainly conducted on IS. The clopidogrel plus aspirin versus aspirin alone for reducing embolization in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR) trial revealed that the combination of clopidogrel and aspirin was more effective than aspirin alone in reducing microembolic signals in patients with symptomatic intracranial stenosis [40]. The clopidogrel in

Table 1. Asia-Pacific randomized controlled trials, stroke registries, and case-control studies in chronological order

Publication year	Study name	Results	Ref
<i>Randomized controlled trials</i>			
2010	Intensive blood pressure reduction in acute cerebral hemorrhage trial (INTERACT)	Early intensive BP-lowering treatment attenuated hematoma growth	37
2010	Clopidogrel plus aspirin versus aspirin alone for reducing embolization in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR)	Combination therapy with clopidogrel and aspirin is more effective than aspirin alone	40
2013	Clopidogrel with aspirin in acute minor stroke or transient ischemic attack (CHANCE)	Combination of clopidogrel and aspirin is superior to aspirin alone	41
2013	Rapid blood pressure lowering in patients with acute intracerebral hemorrhage (INTERACT2)	Intensive lowering of BP did not result in a significant reduction in the rate of the primary outcome of death or severe disability	38
2013	Chinese medicine neuroaid efficacy on stroke recovery (CHIMES)	No better than placebo in improving outcomes at 3 months ^a	45–6
2015	Efficacy of folic acid therapy in primary prevention of stroke among adults with hypertension in China (CSPPT)	Among adults with hypertension, the combined use of enalapril and folic acid, compared with enalapril alone, reduced the risk of first stroke	39
2016	Enhanced control of hypertension and thrombolysis stroke study (ENCHANTED)	Not show the noninferiority of low-dose alteplase to standard-dose alteplase	36
2017	Family-led rehabilitation after stroke in India (ATTEND)	No evidence that stroke rehabilitation services that shift tasks to family caregivers is beneficial for stroke patients	47
2018	Prevention of cardiovascular events in Asian patients with ischemic stroke at high risk of cerebral hemorrhage (PICASSO)	Cilostazol was noninferior to aspirin, but did not reduce the risk of hemorrhagic stroke	43
2020	A comparison of 2 LDL cholesterol targets after ischemic stroke	LDL cholesterol level <70 mg per deciliter had a lower risk of subsequent cardiovascular events	44
<i>Case-control study</i>			
2007	Phenylpropanolamine contained in cold remedies and risk of hemorrhagic stroke (ABBA)	PPA exposure significantly increased the risk of hemorrhagic stroke	48
2010	Parity and risk of hemorrhagic strokes (ABBA)	Increasing parity related to a higher risk of hemorrhagic stroke	50
2013	Excessive work and risk of hemorrhagic stroke (ABBA)	Longer regular working time may relate to an increased risk of hemorrhagic stroke	51
<i>Registry-based study</i>			
2009	Routine use of intravenous low-dose recombinant tissue plasminogen activator in Japanese patients (SAMURAI registry)	Three-month outcomes of low-dose intravenous rtPA therapy were similar to those from postmarketing surveys using 0.9 mg/kg alteplase	57
2010	Get with the guidelines-stroke performance indicators: surveillance of stroke care in the Taiwan stroke registry	Care quality and outcome	54
2013	Epidemiology and registry studies of stroke in Japan	Epidemiology	59
2014	Stroke: morbidity, risk factors, and care in Taiwan	Epidemiology	58
2011	Stroke care quality in China	Care quality	52
2018	Building linked big data for stroke in Korea: linkage of stroke registry and national health insurance claims data	Linkage of stroke registry and claim data	53
2020	Development of stroke identification algorithm for claims data using the multicenter stroke registry database	Stroke identification algorithm	56
2020	Characteristics and management of stroke in Korea: 2014–2018 data from Korean stroke registry	Epidemiology	19

^a But benefit seen at 6, 12, and 18 months.

high-risk patients with acute nondisabling cerebrovascular events (CHANCE) trial revealed that the risk of recurrent stroke was reduced by the dual antiplatelet therapy of clopidogrel and aspirin, compared with aspirin alone, in acute minor stroke or high-risk transient ischemic attack [41].

In contrast, the combination of clopidogrel and aspirin for prevention of early recurrence in acute atherothrombotic stroke (COMPRESS) trial did not show the superiority of combination therapy to prevent early recurrence in acute atherothrombotic stroke [42]. It was reported that cilostazol was comparable to aspirin for preventing cardiovascular events in IS patients at high risk of cerebral hemorrhage (PICASSO trial) [43]. A recent clinical trial performed in France and Korea to compare the effect of different levels of lowering LDL cholesterol after an IS of atherosclerotic origin suggested that lowering <70 mg/dL was better than 90–110 mg/dL to reduce the risk of subsequent cardiovascular events [44].

Many other clinical trials in the Asia-Pacific have harnessed the collaboration of many international centers in South East Asia. These include The Chinese Medicine NeuroAid Efficacy on Stroke Recovery (CHIMES) trial, CHIMES-Extension Study (CHIMES-E), and The Family-led Rehabilitation after Stroke in India (ATTEND) trial. The first 2 studies were randomized, placebo-controlled, double-blinded trials of a traditional Chinese medicine MLC 601 (Neuroaid) among patients with cerebral infarction of intermediate severity, treated within 72 h of stroke onset. MLC601 was statistically no better than placebo in improving primary end points at 3 months and at 2 years [45]. Interestingly, the odds of functional independence increased at 6 months and persisted up to 18 months in an extended follow-up study [46].

The ATTEND trial involving 14 centers investigated whether family-led stroke rehabilitation, initiated in hospital and continued at home, is superior to usual care. It showed that task shifting to family caregivers, an attractive option in a low-resource setting, did not reduce death or dependency at 6 months [47].

Case-Control Studies

The Acute Brain Bleeding Analysis (ABBA) study, a multicenter case-control study conducted in Korea, revealed that phenylpropanolamine in cold medicines increased the risk of hemorrhagic stroke. Furthermore, the secondary analyses showed the association between caffeine-containing medicines, multiparity, heavy work duties, and unhealthy dietary habits with the overall risk of hemorrhagic stroke [48–51].

Registry-Based Studies

There were large, comprehensive national registries on stroke: the China National Stroke Registry (CNSR) [18, 52], Korean Stroke Registry (KSR) [53], and the Taiwan Stroke Registry (TSR) [54]. These are collaborative national registries that collect clinical data on acute stroke and TIA which serve to assess stroke care quality and provide feedback on evidence-based performance measures. In addition, many detailed studies including stroke epidemiology and stroke care quality improvements have been performed, using these clinical registries by linking big data of the National Health Insurance Database [53–56]. These registries provide contrasting details compared to countries that do not have comprehensive National Health Insurance [18, 20, 21].

In Japan, the SAMURAI registry investigated the association of risk factors and initial stroke features with thrombolytic outcomes [57]. These specific stroke registries provide important information on secular trends of risk factors, management, and prognosis [58, 59].

Challenges and Future Direction

The future of the APSO lies in the engagement of its members and a unified vision for regional stroke service development and education. One important direction will be to allocate resources for countries with lower income. This can be done through the sharing of expertise, with subsequent production and dissemination of educational content across the region. Practical training modules and best practice guidelines for the region may also be viable projects for the future. In research, possible projects include funding of small research grants to answer specific questions and to address research gaps. The APSO will also need to offer opportunities and engage like-minded and suitably motivated younger clinicians to continue the work.

The APSO is well positioned to further support stroke service development. In the future, the APSO can work with local member societies in communication and negotiation with government regulators and health policy planners to obtain more resources and allocation while being cognizant that each country has its own unique practice and regulatory environment as well as insurance status.

While the APSO has made steady improvements in the last decade, many challenges remain at this 10-year milestone. These include reducing fragmented stroke care within countries, between countries, and regionally, im-

proving access to relevant educational material, addressing a lack of epidemiological data in some regions, and moderating the cost of interventional devices in acute stroke. A rebalancing and optimization of stroke care resources, currently disrupted by the COVID-19 pandemic, is also expected. For the APSO, the lessons learnt during the pandemic will be used to enhance international engagement as well as to improve the quality and delivery of conferences upon its eventual return in the future.

Conclusion

The first decade of the APSO is a reminder of a challenging but rewarding journey, forged by the contributions of many individuals and national societies, in the name of regional cooperation. The advances gained in the APSO are more meaningful in the background of Asia-Pacific stroke epidemiology, stroke care systems, stroke service developments, and major research publications.

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Author Contributions

K.S.T. conceptualized the format of the manuscript, co-wrote the first draft in its entirety, and revised the subsequent drafts for content, clarity, length, and accuracy before approval and submission of the final version. N.V. co-wrote many sections with K.S.T. while improving content and accuracy. N.V., B.W.Y., N.S., M.M., and R.T.L. contributed equally in their respective sections, reviewed the first draft, and made corrections for content before approving the final version.

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