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Stroke in General Population in Thailand: Risk factor and Prevention

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Abstract:

Stroke is a significant cause of death and disability. In Thailand, it imposes a major health burden, and the prevalence of stroke is increasing, particularly in patients with hypertension (HT), diabetes mellitus (DM), and dyslipidemia (DLP). We aimed to determine the trends in the prevalence of stroke and the associated factors among Thai patients with HT. Nationwide cross-sectional studies were conducted annually in 2014, 2015 and 2018 based on data obtained from the Thailand DM/HT study. Nationally, representative patients with HT in Thailand were sampled with stratified one-stage cluster sampling. A total of 104,028 participants were included in this study. The prevalence of stroke remained constant, with prevalence rates of 4.0%, 3.8%, and 3.9% in 2014, 2015 and 2018, respectively (p for trend = 0.221). Our findings suggested that the management of stroke patients who are covered by the universal coverage scheme should be evaluated. Effective interventions, including promoting smoking cessation, attenuating cholesterol levels, and controlling blood pressure should be provided to hypertensive patients to prevent ischemic stroke. Young adults with HT should be more concerned about the possibility of stroke. The use of prophylactic low-dose aspirin should be carefully monitored to prevent hemorrhagic stroke.

Keywords **—stroke, Thailand, risk factor,prevention**

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Introduction

Thailand is a country located in South-east Asia with an approximate current population of 67 million people. The total area of the country covers around 514,000 square kilometers which is similar in size with Spain. Thailand's tropical climate is generally hot and humid from March to November and very mild during the cooler seasons.Thai ethnics (75%) make up the majority of the population whereas those with Thai Chinese backgrounds account for 14%. Ninety-five percent of the population is Buddhist which is also the official religion.Life expectancy of the total population at birth is 73.83 years (71.45 years in male and 76.33 years in female). With a low population growth rate of 0.543% and an increase in life expectancy, Thailand's aging population is proportionally increasing.[1]

The Thai Ministry of Public Health has divided Thailand into 13 geographical areas. Each area covers a population of approximately 5 million with about 5,000 hospital beds.[2] There are approximately 12,000 physicians in Thailand. Roughly, the physician to population ratio would be one physician to 5,500 people. Currently, Thailand has about 300 active neurologists. However, more than two-thirds of this specialized group resides in the greater Bangkok metropolitan area and other neighboring provinces.[2] Therefore, the concentrated grouping of neurologists in Bangkok reveals that there is a shortage of neurologists across the country, especially in rural areas including the Northeastern and Southern parts of Thailand.[3]

Thailand, similar to most developing countries, has undergone significant economic and health transitions. It has gradually changed from a traditional agricultural base to that of a flourishing industrialized system.The shift from a predominantly rural community to an urbanized one has changed many lifestyle preferences as well. As a result, diet and physical activities have undergone complete transformations from healthy diets consisting of mainly rice and vegetables to more westernized diets that are rich in fat and sugar. Moreover, urbanization has led to greater competition in the community and less time at home. Family roles have shifted and traditional home cooked meals have been replaced by the convenience of fast food. Physical activity of the population has also progressively declined giving way to increased time of sedentary activities.[2,3] As a result, the incidence of cardiovascular diseases, particularly stroke, has increased.

As the leading cause of death and disability in Thailand, it is estimated that, there are more than 250,000 new stroke cases each year.Stroke claims approximately 50,000 lives annually.[3] Alarming statistics from the Ministry of Public Health, rank stroke the first most common cause of death among both women and men. Stroke related mortality is unfortunate but for survivors, stroke creates major burdens of disability for patients and their families. It carries the highest rank for disease burden in Thailand measured by disability-adjusted life years (DALYs) lost in female and the third in male.[4]

Epidemiological data of stroke in Thailand can be gathered from 2 main sources.First, general data collected from hospitals and the national health security service are reported in the official Country Report from the Ministry of Public Health. A Second more accurate data source comes from national surveys, registries, and cohort studies. A large cohort study among more than 20,000 Thais in various parts of Thailand or the Thai Epidemiological Stroke (TES) Study has provided salient data related to stroke prevalence and it is also the first study offering data on the incidence of stroke in Thailand.[5] Another study worth mentioning is the Thai Stroke Registry which has collected data from more than 1,000 stroke patients who were admitted to 76 hospitals around Thailand.[6] Information regarding risk factors and treatment are derived from other smaller studies.

Factor

There were plenty of factors leading to stroke development which were divided into two main parts including non-modifiable and modifiable risk factors.

Non-modifiable risk factors

Age and gender

The relationship of gender to stroke risk depends on age. At young ages, females had a higher risk of stroke than males. Meanwhile at older ages, the relative risk was slightly higher for males.[15] Due to pregnancy, the post-partum state, and hormonal factors, these associated with the stroke development among female at younger ages. [15] Regarding hormonal factors, estrogen contraceptive increased a relative risk of stroke for 2.75. [11] In contrast, males were prone to develop hemorrhagic stroke. Stroke incidence increased significantly among middle-aged males which might be influenced by sex hormones or job strain.[32] These could stimulate the cortisol level contributing to risk factor developments such as abdominal obesity, hypertension, which are all associated with an increased risk of stroke. [9/10] In Thailand during 2014-2018, the prevalence of overall stroke was twice among males (5.6-6.0% for males, 2.7-2.8%for females).[12]

Stroke is a disease of aging. The incidence of stroke increased with age, with the incidence doubling for each decade after age 55. [15] The prevalence of overall stroke of Thai patients was found in patients under the age of 40 years, with prevalence rates of 0.9%, 1.3%, and 2.6% (p=0.020) in 2014, 2015, and 2018, respectively. Contrastingly, in patients aged between 50 and 59 years, the prevalence of overall stroke significantly decreased from 3.5% in 2014 to 3.4% in 2015 and further decreased to 2.8% in 2018 (p=0.007). [12]

In addition, the mean age of Thai was population at the onset of ischemic stroke approximately 65 years and the prevalence of stroke in males was higher than its in females. [3/12] However, the stroke onset of Thai patients was earlier than those in developed countries. Since, poorly controlled vascular risk factors in the Thai population.[3]

Stroke mortality

Stroke is the first leading cause of death in Thailand in both men and women. According to the Ministry of Public Heath in Thailand, there are more than 50,000 deaths from stroke annually.[1]Who data in 2004 reported that the

age-standardized death rate per 100,000 for cerebrovascular disease in Thailand is 100.[7]The finding that stroke causes more deaths than ischemic heart disease is consistent with the cardiovascular disease mortality pattern of East Asian countries.[8]

A large retrospective study of all-cause mortality among patients with cardiovascular diseases in Thailand was conducted in 2011. This study extracted data from the national database through the Central Office for Healthcare Information in 98,486 Thai patients. These patients were admitted in government hospitals due to established cardiovascular diseases (acute coronary syndrome, ischemic stroke, peripheral artery disease, congestive heart failure or atrial fibrillation). Nearly a quarter of the patients, 25,813, suffered from acute ischemic stroke in this study. Interestingly, it was found that stroke was the third leading cause of hospital admission among cardiovascular diseases with an in-hospital mortality rate of acute stroke of 11.9%.[9]

More information regarding in-hospital mortality of stroke was sourced from the Thai Stroke Registry where 1,222 acute ischemic stroke patients were prospectively registered throughout the country during 2008-2009. The data were collected from 3 different hospital levels; university, regional, and community hospitals.[10] In this particular study, the in-hospital death rate was only 3.2%.[6] The low mortality at the time of discharge in this study might be explained by a rather low median length of stay (4 days) and the type of participating hospital itself. Since hospital selection in the registry was voluntary, data from non-participating centers possibly with lower standards of care were not available.

According to the data from the Ministry of Public Health, the mortality rate of stroke in Thailand is increasing during the past 5 years. The mortality increased from 20.8 in the year 2008 to 30.7 per 100,000 populations in the year 2012. This may reflect the increased incidence of stroke in the country.[10]Figure 1 demonstrates the stroke mortality per 100,000 population according to data from the Ministry of Public Health.

Stroke incidence

To date, there is little information on the incidence of stroke in Thailand. It is currently being studied in a large cohort called the Thai Epidemiological Stroke (TES) Study. This study has collected data from over 20,000 subjects from the 5 major geographical regions of the country.[5]

Among the world population, age-adjusted stroke incidence rates in high-income countries have decreased from 163 per 100,000 person-years from 1970-1979 to only 94 per 100,000 person-years from 2000-2008. In contrast, the incidence of stroke has nearly doubled in low- to middle-income countries. (52 per 100,000 person-years to 117 per 100,000 person-years, respectively).[8]As a middle income country, it is believed that the stroke incidence in Thailand will follow this rising trend. The incidence of stroke is projected to increase as the Thai population ages and although further study is needed to support this projected trend, it is still approximated that at least one new stroke case occurs in Thailand every 2 minutes.

Stroke prevalence

The earliest prevalence study on stroke in Thailand was published in 1983. This study included subjects in the Bangkok metropolitan area who were over 20 years of age. It showed that the prevalence of stroke was 690 per 100,000 persons.[11]Another study among 3,036 elderly Thais over 60 years old in 4 geographical regions of the country conducted during 1994-1996 revealed a 1.12% prevalence of stroke with the highest prevalence found in the central region of Thailand.[12]

The most recent Thai Epidemiological Stroke Study found that the prevalence of stroke in populations over the age of 45 is 1.88%. Men had a higher prevalence of stroke than did women in all age groups. Stroke prevalence differed among the five geographic regions of the country with the highest prevalence in the capital city, Bangkok (3.34%) followed by central (2.41%), southern (2.29%,), northern (1.46%), and north-eastern regions (1.09%). A number of factors associated with higher stroke prevalence were also identified as older age, male gender, occupational class (manual class and unemployed), history of hypertension, diabetes mellitus and hypercholesterolemia.[5]In this particular study, the stroke prevalence was higher than those reported in previous studies in Thailand but still remains lower than that of developed countries, which may relate to the number of case fatalities.

Modifiable Risk factors

Age

Stroke occurs at any age but it is mainly a disease of the elderly. According to the Thai Stroke Registry, the mean age of patients at the onset of ischemic stroke in Thailand is approximately 65 years.[6]This age is similar to findings from previous reports from developing countries.[13-15]However, the onset of stroke in Thai patients is earlier than those in developed countries.[16-22]This may be due to poorly controlled vascular risk factors in the Thai population.

Hypertension

Hypertension is very common in the general population especially among the elderly. Data from the 2009 multistage cross-sectional Fourth National Health Examination Survey (NHES) of 18,629 Thai adults over the age of 20 years revealed that the prevalence of hypertension in Thailand is 21%.[23]Hypertension is the most common and wellestablished risk factor of stroke in most studies. In the Thai Stroke Registry, hypertension was found in 53% of the cases.[6]

Stroke risk factors focusing on hypertension were recently studied in a multicenter observational study between February 2010 and January 2011 at 24 selected stroke hospitals (8 academic hospitals, 9 regional referral center hospitals, and 7 provincial and other hospitals) in 6 geographical regions across Thailand. Self-reported hypertension prior to stroke was found in 62.5% of the patients. During acute periods of stroke, as expected, most patients with high blood pressure were not treated with antihypertensive agents. Surprisingly, only 49.1% of 558 stroke patients had good control of their blood pressure at 120 days after stroke. Therefore, more effort is still needed to increase the awareness of hypertension among physicians and patients in order to achieve a better control of blood pressure in the Thai population.[24]

Diabetes

According to the Fourth NHES, the age-adjusted prevalence of diabetes was 7.5% in adults over the age of 20 years. Among patients with diabetes, about one-third were undiagnosed. The prevalence of impaired fasting plasma glucose in the same population was 10.6%. Higher prevalence of diabetes was found in women, aging center hospital-based diabetes registry among 9037 diabetic patients in Thailand, the Thailand Diabetes populations, and those who live in urban areas. The prevalence of diabetes has slightly increased from 2004 to 2009[25] and was significantly higher in women than in men (8.3% vs. 6.6%). In a cross-sectional, multi- Registry Project, stroke was found in 3.5% of diabetic patients.[26]According to the Thai Stroke Registry, diabetes was found in 26% of stroke patients.[6]

Metabolic syndrome

The prevalence of metabolic syndrome in the Fourth NHES was 23.2% among adults aged 20 years or older, and was substantially higher in women than in men (26.8% in women compared to 19.5% in men). Among men, the prevalence of metabolic syndrome in urban areas was higher than those in rural areas, whereas in women, metabolic syndrome was more prevalent in rural areas than in urban areas.[27]

Obesity is also a rising health problem among Thais. According to the Fourth NHES, 35% of men and 44.9% of women were overweight with BMI≥23 kg/m2 using the Asian cut-points. Age was positively associated with being overweight in both genders.[3]

Smoking

Due to strong support and efforts by the Thai government to educate the public about the adverse effect of smoking, the smoking rate of the Thai population has steadily declined. According to the Ministry of Public Health, only 18.4% of Thais smoke. By gender, 36% of men are smokers while only 1.6% of women are smokers.

Dyslipidemia

Dyslipidemia especially defined as elevated low density lipoprotein cholesterol (LDL-C) is known to be a risk factor of atherosclerosis related ischemic stroke. According to the Thai Stroke Registry, hypercholesterolemia was found in 30% stroke cases.[6]However, the prevalence of dyslipidemia was much higher in a single center

hospitalbased study at our King Chulalongkorn Memorial Hospital where 80% of patients with ischemic stroke had a high LDL-C level of more than 100 mg/dL.

Atrial fibrillation

Atrial of fibrillation (AF) is a common problem especially among elderly. AF was found in 10% of patients who presented with acute ischemic stroke at King Chulalongkorn Memorial Hospital. Data from a retrospective study among patients who were diagnosed with AF and presented to the ambulatory care clinic at a university hospital in 2008 demonstrated that 52.8% of patients at intermediate risk and 70.3% patients at high risk according to CHADS2 score were prescribed warfarin. In the high risk group, 19.6% received only antiplatelets and 10.1% received no antithrombotic therapy.[28]

Stroke types and subtypes

Ischemic stroke is the major type of stroke in Thailand. However, when compared to Caucasian populations, there is a higher proportion of intracerebral hemorrhage. According to hospital based data, hemorrhagic stroke accounts for about 20% of all stroke cases.

Among patients with ischemic stroke, lacunar infarction is the most common subtype followed by large artery atherosclerosis, and cardioembolism. Similar to the findings among other East Asian and Southeast Asian countries, significant carotid atherosclerosis was found in only 11% of patients. In contrast, intracranial atherosclerosis was found more frequently, accounting for 23% of the cases. Furthermore, the number of patients with intracranial atherosclerosis is likely to be even higher since some of them may present clinically as lacunar infarction where sometimes CT scan is the only diagnostic imaging modality.[29]

Stroke care in Thailand

Intravenous thrombolysis with recombinant tissue plasminogen activator is now the standard treatment for patients with acute ischemic stroke and is recommended by the Thai Stroke Guidelines. The first patients ever treated with intravenous thrombolysis was in 1996 and later on, the stroke fast track program was developed, initiated, and implemented by and at King Chulalongkorn Memorial hospital.[30-31]The stroke fast track program is a hospital system designed to allow medical triage personnel at the hospital to identify patients with stroke early on in order to take proactive measures for prompt investigation and management with the stroke team. Leading to a higher number of acute stroke patients receiving intravenous thrombolysis within the critical window of time, the stroke fast track system has proven successful. At present, the fast track system has been adopted by many other university hospitals as well as regional, provincial, and some community hospitals.

For all Thai citizens, treatment costs can be reimbursed from the Universal Coverage Program provided by the National Health Security Office.[13] According to the Ministry of Public Health, the proportion of patients receiving intravenous thrombolysis among those with acute ischemic stroke or acute stroke in Thailand has increased from 0.38% in 2008 to 1.95% in 2012. Although this figure is encouraging, one significant gap in acute stroke care is public education regarding stroke warning signs and act on stroke in Thailand.[34]

The Stroke Unit is a critical component towards the betterment of stroke care in the country.[32]Current data show that there are more than 110 stroke units across Thailand, mostly in regional and provincial hospitals.[35] However, according to the Thai Stroke Registry, only one-fourth of patients were admitted to a specialized acute stroke care unit.[35] The proportion of stroke unit admission was higher in university hospitals (50%) compared to 17.1% and 3.4% in regional and community hospitals, respectively. In the acute period, most ischemic stroke patients received aspirin within 48 hours of admission (71%).

As for secondary stroke prevention, antiplatelet was used in 80% of the cases. High rates of statin treatments were also noted.[39] Seventy-three percent of patients received statin on discharge. After discharge, most Thai patients return home and are taken care of by family members.[32] There are very few patients placed in nursing care facilities.[36] This is due to cultural influences of Thai families where large extended families provide care for ailing family members.

In conclusion, stroke is a major health burden in Thailand. It is the leading cause of death and longterm disability.[19] The incidence of stroke in Thailand is now being studied in a large cohort. The estimated prevalence of stroke is 1.88% among adults 45 years and older.[37] Stroke is more prevalent in men and the mean age of stroke

onset is 65 years. Hypertension, diabetes, dyslipidemia, metabolic syndrome, and atrial fibrillation are major risk factors of stroke in the Thai population. Significant economic and health transitions from predominantly rural to urbanized communities may be responsible for the increasing prevalence of these risk factors. Similar to other parts of the world, ischemic stroke accounts for the majority of strokes but there is a higher proportion of hemorrhagic stroke when compared to Caucasian populations.[38] Among patients with ischemic stroke, lacunar stroke accounts for almost half followed by atherosclerotic disease. Intravenous thrombolysis has been used in Thailand for over 20 years. Its cost is reimbursed by the national health care system but its use is still limited. With the introduction of the stroke fast track system and acute stroke unit, prompt stroke treatment across the country is ensured.

Among patients with ischemic stroke, lacunar infarction is the most common subtype followed by large artery atherosclerosis, and cardioembolism.[39] Similar to the findings among other East Asian and Southeast Asian countries, significant carotid atherosclerosis was found in only 11% of patients. In contrast, intracranial atherosclerosis was found more frequently, accounting for 23% of the cases. Furthermore, the number of patients with intracranial atherosclerosis is likely to be even higher since some of them may present clinically as lacunar infarction where sometimes CT scan is the only diagnostic imaging modality.

Paraphrasing

To the best of our knowledge, this is the first and largest epidemiological study in Southeast Asia to focus on stroke and its associated factors among Thai patients with HT. These results revealed the constant trends in the prevalence of stroke among Thai patients with HT from 2014 to 2018. The prevalence of overall stroke in this population ranged from 3.8 to 4.0% . Unsurprisingly, the prevalence of ischemic stroke was higher than that of hemorrhagic stroke. In patients with HT, the prevalence of stroke was 5.1% in Madrid, Spain[19], and 11.6% in Southern Piauí, Brazil[20]. In Thailand, the prevalence of overall stroke in patients with HT was relatively low. This may be the result of improvements in the stroke management system. Indeed, in Thailand, a stroke fast track system was initiated and has been improved over the past two decades[21]. As a consequence, more acute stroke patients are treated within the golden period.

Previously, the central part of Thailand was reported to have the highest prevalence of stroke, followed by the southern, northern, and northeastern regions; the northeastern region has been reported to have the lowest prevalence of stroke in Thailand[8]. In this study, however, the geographic distribution of the prevalence of stroke in patients with HT was slightly different. We found that ischemic stroke was most prevalent in the southern part of Thailand, whereas the northeastern region still had the lowest stroke prevalence. However, there was a significant increasing trend in the prevalence of ischemic stroke in patients with HT residing in the northeastern part of Thailand from 2014 to 2018. With regard to hemorrhagic stroke, the prevalence was also lowest in the northeastern region, and the risk of stroke nearly doubled in patients with HT residing in other regions of the country . The most plausible explanation of the lowest prevalence of both ischemic and hemorrhagic strokes being found in the northeastern part of Thailand is that agriculture is the main occupation of people residing in this area with a lower rate of industrialization. Their lifestyles are still conservative; for example, healthy diets consisting of mainly rice and vegetables and regular physical activity related to their occupation may lower the risk of stroke. However, further investigation is required to identify the associated factors contributing to a significant increasing trend in the prevalence of ischemic stroke in this area and the change from the central to the southern region where the highest prevalence of ischemic stroke was observed.

Interestingly, in Thai patients with HT, we found that the prevalence of both ischemic and hemorrhagic strokes was higher in patients who were admitted to regional and provincial hospitals than in those admitted to community hospitals. This can be explained by the fact that stroke patients are likely to be referred to tertiary care centers. Specialists and essential medical facilities are not available in health-promoting and community hospitals; as a result, patients with stroke in such hospitals may have limited access to neurologists. At present, Thailand has fewer than 400 active neurologists. More than two-thirds of this specialized group lives in Bangkok and the surrounding provinces[5]. The concentration of neurologists in Bangkok results in a shortage of neurologists across the country, particularly in rural areas. In addition, we found that the highest prevalence of both ischemic and hemorrhagic strokes was observed in hypertensive patients who were under the universal health coverage scheme, which is the major healthcare coverage scheme in Thailand. The most plausible explanation is that there are imbalances between the demand and supply of treatment for stroke that affect the management system within the universal health

coverage scheme. The need for longitudinal studies on the outcomes of stroke at different hospital levels and the impact of universal health coverage schemes on the outcome of stroke is suggested. Collectively, these findings indicated that stroke should be a focus in regional and provincial hospitals and that opportunities to prevent stroke should be considered by providing more intensive preventive strategies to hypertensive patients, especially those who are under the universal health coverage scheme.

The present study revealed that male sex was a risk factor for both ischemic and hemorrhagic strokes in Thai patients with HT. These results were consistent with previous studies performed in southwestern China[10] and in Thailand, particularly in patients older than 35 years old[22]. An analysis of 471,971 participants from the UK Biobank cohort study demonstrated that the incidence of stroke was higher among males[23]. However, this remains controversial, as opposite results have been reported. In the USA, the incidence and prevalence of stroke were higher in females[24-25]. It was reported that estrogen was a protective factor against the development of ischemic stroke[26]. Therefore, the higher prevalence of stroke in males may be related to a lower level of female hormones. However, menopausal and postmenopausal females may lose this protective effect, which results in an increased susceptibility to ischemic brain changes.[26]

Although stroke can occur at any age, it is mainly a disease of the elderly population. We found that the risk of ischemic stroke increased with increasing age group among Thai patients with HT in a dose–response relationship. The average age of patients at the onset of ischemic stroke in Thailand, according to the Thai Stroke Registry, is approximately 65 years[6]. This age is consistent with the average age of onset of ischemic stroke reported in other developing countries[26,27,29]. Nevertheless, from 2014 to 2018, the prevalence of overall and ischemic strokes continuously increased in patients with HT who were younger than 40 years. In addition, the present study also found an inverse dose–response relationship between age and the risk of hemorrhagic stroke. These results indicated that young Thai people with HT should be more concerned about the possibility of stroke. Interestingly, in Western countries, the proportion of patients with hemorrhagic stroke is dramatically higher in the young adult subpopulation: 15–20% of the general stroke population has hemorrhagic stroke, while 40–55% of young adult diagnosed with stroke has hemorrhagic stroke[30-33]. In a large American study, fivefold and 2.33-fold increased risks of hemorrhagic stroke were observed in young adults who abused amphetamine and cocaine, respectively[34]. Mechanistically, amphetamine can induce cerebral vasculitis[35-36], whereas cocaine is involved in hypertensive surges following its administration[37-38]. However, it was revealed that, rather than the direct effects of the drugs, the higher risk of hemorrhagic stroke in those young adults was potentially associated with underlying vascular malformations[39]. The proportion of patients with hemorrhagic stroke has not been well investigated among young Asians.

The present study demonstrated inverse dose–response relationships between BMI and the risk of both ischemic and hemorrhagic strokes in Thai patients with HT, with a higher risk of stroke in hypertensive patients who had lower BMI values. These results were consistent with those of a previous study conducted in 67,086 American patients with DM[40]. More clinical and molecular insights are, however, still needed to explain these findings.

Heavy metals and other toxins in tobacco smoke promote vascular endothelial dysfunction and inflammation, ultimately resulting in atherosclerosis[41]. In addition, smoking also promotes a global procoagulant state[42] which results in a decrease in cerebral blood flow[43], leading to blood clot formation and ischemic stroke development. While the relationship between intracerebral hemorrhage and smoking is weak and inconsistent, an increased risk of subarachnoid hemorrhage tends to be associated with the increased incidence of aneurysms seen in smokers. A strong association between smoking and stroke risk has been reported, with current smokers having at least a two- to fourfold higher risk of stroke than nonsmokers or ex-smokers who quit smoking more than 10 years prior[41]. A number of studies have indicated that ex-smokers have a lower risk of stroke than current smokers[43-46]and may have the same risk as nonsmokers[47-48]. Nonetheless, we found that both current smokers and ex-smokers with HT had an elevated risk of ischemic but not hemorrhagic stroke. Therefore, for the greatest benefit, smoking cessation should be listed in preventive rather than therapeutic strategies for stroke. Physiologically, smoking cessation can lead to a reversal of the procoagulant state to baseline. However, the full return to the risk status of a nonsmoker depends on various factors, including the level of atherosclerosis developed during smoking, the duration of smoking, and the duration since smoking cessation[41]. Unfortunately, this information was not available in our database.

HT is the most common and well-established risk factor for both ischemic and hemorrhagic strokes. In ischemic stroke, HT places a strain on the blood vessels and predisposes them to damage, which ultimately causes atherosclerosis[49]. HT is implicated in hemorrhagic stroke when a weakened blood vessel in the brain bursts and blood leaks into the brain. In our study, uncontrolled HT was identified as a factor associated with ischemic stroke in Thai patients with HT. Therefore, controlling blood pressure is a critical management strategy that can reduce the risk of ischemic stroke in hypertensive patients. Unexpectedly, we found that uncontrolled HT was no longer associated with hemorrhagic stroke. This result was supported by a previous study reporting that there was no association between the use of antihypertensive drugs and the outcome of cerebral small vessel disease[50]. However, these findings were only described in minority reports. The pooling of data from one hundred forty-seven randomized clinical trials demonstrated that 10 mmHg systolic and 5 mmHg diastolic reduction of blood pressure was associated with an average 41% reduction in stroke in all trials[51]. In fact, in a systemic review, all eleven case–control studies showed a positive correlation between HT and intracerebral hemorrhage, with an overall OR of 3.68 (95% CI, 2.52 to 5.38)[52]. The incidence of HT increases with age; hence, HT is a more common risk factor for intracerebral hemorrhage in older people. The stronger association between younger age groups of hypertensive patients and hemorrhagic stroke in this study potentially explains the lack of a correlation between HT and hemorrhagic stroke.

DLP is known to be a risk factor for atherosclerosis-related ischemic stroke. Our study revealed an association between comorbid DLP and the risk of ischemic stroke in Thai patients with HT (Table 3), indicating that lipid profiles should be regularly tested. However, a relationship between DLP and hemorrhagic stroke was not observed. It has been reported that attenuating cholesterol levels can reduce the risk of stroke. Regarding statins versus placebo and more versus less statin therapy, the pooled results of twenty-six clinical trials demonstrated that there was a reduction in ischemic stroke with an overall relative risk (RR) of 0.79 (95% CI, 0.74 to 0.85), whereas there was a nonsignificant increase in hemorrhagic stroke with an overall RR of 1.12 (95% CI, 0.93 to 1.35) per 1 mmol/L reduction in low-density lipoprotein cholesterol (LDL-C)[53]. Gemfibrozil reduces serum triglycerides and raises high-density lipoprotein cholesterol (HDL-C). In the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) conducted in 2,531 men with coronary heart disease, it was reported that gemfibrozil reduced strokes by 31% (95% CI, 2% to 52%), and there were five and six hemorrhagic strokes in the placebo and gemfibrozil arms, respectively[54].

In AF, the chaotic rhythm may cause blood to pool in the upper chambers of the heart and form clots that can dislodge and block blood flow to other organs, including the brain. The present study identified that AF was a strong associated factor for ischemic stroke in Thai patients with HT. This result was consistent with previous studies[55-58]. However, it remains unclear whether occult AF is related to stroke. According to the Prevalence of Sub-Clinical Atrial Fibrillation Using an Implantable Cardiac Monitor in Patient with Cardiovascular Risk Factors (ASSERT-II) study, the rate of occurrence of subclinical AF in those with or without a history of stroke, systemic embolism, or transient ischemic attack was not significantly different[59]. With regard to stroke prevention, ongoing clinical trials are evaluating appropriateness and the risks and benefits of screening for occult AF and the use of anticoagulants in occult AF patients, including the Systematic ECG Screening for Atrial Fibrillation Among 75 Year Old Subjects in the Region of Stockholm and Halland, Sweden (STROKESTOP) trial (NCT01593553) and the Apixaban for the Reduction of Thromboembolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation (ARTESIA) trial (NCT01938248).

Given its cost-effectiveness and widespread availability, low-dose aspirin is a key therapeutic option for the secondary prevention of myocardial infarction and ischemic stroke[60]. Aspirin at a dose of 81 mg was the main prophylactic antiplatelet medication prescribed to the patients in our study. We found that low-dose aspirin use was a risk factor for hemorrhagic stroke in patients with HT (Table 4). Therefore, patients taking prophylactic low-dose aspirin should be closely monitored. In a systemic review, the pooled results of eight randomized clinical trials showed an association between low-dose aspirin use and an elevated risk of intracranial bleeding, with an overall RR of 1.37 (95% CI, 1.13 to 1.66)[61]. The pooling of data from four randomized clinical trials demonstrated that the strongest relationship was between low-dose aspirin use and subdural or extradural hemorrhage, with an overall RR of 1.53 (95% CI, 1.08 to 2.18). Moreover, it was concluded that Asians were at higher risk than other ethnicities.

There were some limitations of our study. First, patients with HT visiting university hospitals were not included; therefore, it is possible that the prevalence of stroke in hypertensive patients was underestimated. Second, the data

were obtained from the Thailand DM/HT study. Therefore, the diagnosis of stroke and comorbidities in this study was based on the ICD-10 codes determined by clinicians. Third, the subclassifications of ischemic and hemorrhagic strokes were not further investigated because of the limited information available from the Thailand DM/HT database. Fourth, the study employed serial cross-sectional surveys; therefore, cause-and-effect relationships could not be identified between the associated risk factors and stroke. Although there were some data missing from the surveys, this was compensated for by the recruitment of a large number of participants from all geographic regions across the country. Hence, the associations between the outcomes and the risk factors were still robust. The strength of our study was that it was a large, nationwide epidemiological study focusing on stroke in Thai patients with HT. Our results can be generalized to the entire country and similar populations.

Conclusion

We identified a constant trend in the prevalence of stroke among Thai patients with HT over the period from 2014 to 2018. Our findings suggested that the management of stroke patients who are covered by the universal health coverage scheme needs to be evaluated. Effective interventions, including promoting smoking cessation, attenuating cholesterol levels, and controlling blood pressure should be provided to all patients with HT to prevent ischemic stroke. Young adults with HT should be more concerned about the risk of stroke. The use of prophylactic low-dose aspirin should be more focused and carefully monitored to prevent hemorrhagic stroke.

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