A STUDY OF FACTORS ASSOCIATED WITH STROKES IN YOUNG ADULTS IN HOSPITAL UNIVERSITI SAINS MALAYSIA,KELANTAN

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Azrianna Nurfizan Azmi

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ABBREVIATIONS

AAICH	Anticoagulant associated intracerebral haemorrhage
ADVANCE	Action in Diabetes and Vascular Disease
AHA	American Heart Association
ASA	American Stroke Association
B	Regression Co Efficient
BI	Barthel Index
BMI	Body Mass Index
BP	Blood Pressure
CAD	Coronary Artery Disease
CEA	Carotid Endarterectomy
CI	Confident Interval
CPG	Clinical Practice Guideline
CSF	Cerebrospinal fluid
CT	Computed Tomography
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
GCS	Glasgow Coma Scale
HbA1c	Glycosylated Hemoglobin A1C
HPT	Hypertension
HUSM	Hospital Universiti Sains Malaysia

ICH	Intracerebral Haemorrhage
ICP	Intracranial Pressure
IHD	Ischaemic Heart Disease
IVH	Intraventricular Haemorrhage
LAA	Large Artery Atherosclerosis
MOH	Ministry Of Health
MRS	Modified Rankin Scale
NHMS	National Health Morbidity Survey
NIHSS	National Institute of Health Stroke Scale
OR	Odds Ratio
PROGRESS	Perindopril Protection Against Recurrent Stroke Study
ROC Curve	Receiver Operating Characteristic Curve
RTPA	Recombinant Tissue Plasminogen Activator
SAH	Subarachnoid Haemorrhage
SD	Standard Deviation
TIA	Transient Ischaemic Attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment
WARSS	Warfarin Aspirin Recurrent Stroke Study
WASID	Warfarin and Aspirin in Symptomatic Intracranial Arterial Stenosis

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ABSTRAK (BAHASA MELAYU)

Latarbelakang

Secara umumnya, strok pada usia muda menyebabkan mobiditi dan member kesan kepada sosioekonomi. Di Malaysia, maklumat berkenaan insiden dan prevalen penyakit strok adalah terhad. Satu kajian prospektif yang dijalankan di sebuah hospital, mendapati kes strok di usia muda disebabkan oleh aterosklerosis saluran arteri bersaiz besar dan penyumbatan saluran arteri bersaiz kecil dan risiko yang signifikan ialah diabetes mellitus, darah tinggi dan penyakit buah pinggang kronik. Objektif kajian ini adalah untuk mengenal pasti faktor – faktor yang berkaitan dengan strok jenis iskemia di usia muda. Maklumat berkenaan faktor-faktor yang berkaitan dengan strok jenis iskemia di usia muda di dalam masyarakat tempatan akan meningkatkan kualiti perawatan pesakit dan akhirnya dapat mengurangkan insiden strok di usia muda.

Metodologi

Satu kajian retrospektif mengkaji rekod perubatan 166 pesakit strok di usia muda, 99 daripadanya merupakan strok jenis iskemia dan 67 pesakit mempunyai strok jenis bukan iskemia. Faktor-faktor yang dikaji ialah darah tinggi, diabetes mellitus, dislipidemia, merokok, pengambilan alkohol,penyakit jantung koronari, penyakit injap jantung, atrial fibrilasi dan strok jenis iskemia terdahulu. Faktor yang mempunyai nilai $P \leq 0.25$ akan dimasukkan dalam analisis multivariasi. Nilai $P \leq 0.05$ di kira sebagai faktor yang signifikan.

Keputusan

Purata umur bagi pesakit strok jenis iskemia di usia muda ialah 38.6 tahun (±4.96). Faktor yang mempunyai kaitan dengan strok jenis iskemia di usia muda ialah darah tinggi (OR=1.85, 95% CI: 3.10, 12.98 dan $p<0.001$) dan diabetes mellitus merupakan faktor yang mempunyai kaitan dengan aterosklerosis saluran arteri bersaiz besar (OR=1.63, 95%CI: 1.86, 13.94 dan p=0.002).

Kesimpulan

Hasil kajian ini telah membuktikan darah tinggi merupakan faktor yang signifikan dengan strok jenis iskemia di usia muda dan diabetes mellitus merupakan faktor yang signifikan dengan aterosklerosis saluran arteri bersaiz besar. Rawatan yang optimum untuk penyakit darah tinggi dan diabetes mellitus di kalangan pesakit berusia muda adalah penting untuk mengurangkan risiko strok dan menghalang morbiditi dan mortaliti di kalangan pesakit ini.

ABSTRACT (ENGLISH)

Background

Stroke in young adults causes morbidity and it is responsible for significant socioeconomic losses worldwide. There are limited data regarding the incidence and prevalence of strokes in Malaysia. A prospective, hospital-based study concluded that large vessel atherosclerosis and small vessel occlusion are the most common types of strokes. Diabetes, hypertension and chronic renal disease were found to be significant risk factors for young ischaemic stroke. The objective of this study was to determine the association between risk factors and ischaemic strokes in young adults. Information regarding the factors associated with ischaemic stroke in young adults in a local setting would improve our quality of care and it might provide ways to reduce the incidence of such strokes.

Methodology

This is a retrospective cohort study of 166 young adult patients which 99 of suffered an ischaemic stroke, and 67 of which suffered a non ischaemic stroke. The variables included in this study were hypertension, diabetes mellitus, dyslipidemia, smoking, alcohol intake, ischaemic heart disease, valvular heart disease, atrial fibrillation and previous ischaemic stroke. Data were assessed using simple logistic regression analysis to look for associations with ischaemic strokes and large artery atherosclerosis. Any factors with a P value ≤ 0.25 were included in the multiple logistic regression analysis and P value ≤ 0.05 were considered to be significant.

Result

The mean/±SD age for ischaemic stroke patients was 38.6 (±4.96). Hypertension was found to be associated with young ischaemic stroke (OR=1.85, 95% CI: 3. 10, 12.98, p<0.001) and diabetes mellitus was associated with large artery atherosclerosis in young ischaemic stroke patients. (OR=1.63, 95%CI: 1. 86, 13.94, p=0.002).

Conclusion

This study showed that hypertension is significantly associated with ischaemic stroke and that diabetes mellitus was associated with large artery atherosclerosis in young adults. Optimal management of hypertension and diabetes mellitus in young patients is recommended to reduce the risk of stroke and to prevent significant morbidity and mortality in these patients.

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Patients and Methods: This is a retrospective cohort study of 166 young adult patients which 99 of suffered an ischaemic stroke, and 67 of which suffered a non ischaemic stroke. The variables included in this study were hypertension, diabetes mellitus, dyslipidemia, smoking, alcohol intake, ischaemic heart disease, valvular heart disease, atrial fibrillation and previous ischaemic stroke. Data were assessed using simple logistic regression analysis to look for associations with ischaemic strokes and large artery atherosclerosis. Any factors with a P value

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Conclusions: This study showed that hypertension is significantly associated with ischaemic stroke and that diabetes mellitus was associated with large artery atherosclerosis in young adults. Optimal management of hypertension and diabetes mellitus in young patients is recommended to reduce the risk of stroke and to prevent significant morbidity and mortality in these patients.

Dr. Sanihah Abd Halim: Supervisor

CHAPTER ONE

INTRODUCTION

1.1 Study Background and Rationale

Stroke is a clinical syndrome characterized by rapidly developing clinical symptoms and/or signs of focal and, at times global, loss of cerebral function, with symptoms lasting more than 24 hours or possibly leading to death, and with no apparent cause other than that of vascular origin(Hinkle and Guanci, 2007).Episodes of stroke and familial stroke have been reported since the 2nd millennium BC in ancient Mesopotamia and Persia(Ashrafian, 2010). Hippocrates (460 to 370 BC) was the first person to describe the phenomenon of sudden paralysis that is often associated with ischaemia. Apoplexy, from the Greek word meaning "struck down with violence," first appeared in Hippocratic writings to describe this phenomenon(Thompson, 1996).

Stroke is the second most common cause of mortality after heart disease, and it accounts for 5.7 million deaths annually. The World Health Organization (WHO) estimates that 90% of global stroke deaths occur in developing countries. As documented, the incidence of ischaemic stroke increases with age and ischaemic stroke among young patients constitutes about 5% of all strokes(Nencini *et al.*, 1988; Bevan *et al.*, 1990; Kristensen *et al.*, 1997).Stroke among young adults causes higher morbidity in this reproductive age group and the majority of survivors have emotional, social, or physical sequelae that impair their quality of life(Kappelle *et al.*, 1994).

Among young adults, acute stroke is responsible for significant socioeconomic losses worldwide. Many studies of hospital-based registries have demonstrated a broad spectrum of aetiologies and risk factors among this cohort. A study in Chennai, India found that the significant risk factors for strokes in young adults were; type A personality, tobacco and alcohol abuse, systemic hypertension, diabetes mellitus and cardiac disorders(Chitrambalam *et al.*, 2012). Meanwhile, a study in Malaysia that compared the patterns, risk factors and etiologies of ischaemic stroke among younger patients in Malaysia and Australia showed that diabetes, hypertension and chronic renal disease were significant risk factors(Tan *et al.*, 2010). A study in Pakistan by Razaq et al

(2002) found that most etiologies were undetermined (45.8%), followed by intracranial atherosclerosis (14.4%).The main risk factors for atherosclerosis in these patients were hypertension, diabetes and smoking. In Thailand, Dharmasaroja et al (2011) concluded that the most common (32%) etiology was undetermined etiology. For determined etiology, antiphospholipid syndrome and neurosyphilis were the top two causes.
In Malaysia, stroke is one of the top five diseases with the greatest burdens, based on disability-adjusted life years. However, prospective studies of stroke in Malaysia are limited. To date, neither the prevalence of stroke, nor its incidence have been recorded nationally(Loo and Gan, 2012a).

The aim of this study was to explore the factors associated with stroke in young adults of different ethnicities and socio-demographic background in Malaysia. This study provides local data, and discusses the factors associated with acute stroke among young adults. The information improves our quality of disease management and will ultimately reduce the incidence of strokes in young adults.

Furthermore, knowledge of the factors associated with stroke among young adults is important because will enable the implementation of preventive management strategies.

In addition, this study indirectly explains the similarities and differences in the etiologies of strokes in young adults as compared to the older population.

1.2 Epidemiology of Stroke

1.2.1 Epidemiology of Stroke Worldwide

The prevalence of stroke is estimated to affect 4.6 million people globally. Data from 2002 showed that cerebrovascular disease has a mortality rate of 11.9 per 100 000 population (Kappelle *et al.*, 1994).

Approximately 17 million people suffered a stroke in 2010, while 33 million people have previously suffered a stroke and survived. Between 1990 and 2010, the number of strokes decreased by approximately 10% in the developed world, while it increased by 10% in

the developing world. Overall, two- thirds of strokes occurred among those over 65 years old(Feigin *et al.*, 2005; Burke and Venketasubramanian, 2006).

The incidence of stroke increases from the age of 30 and above. The etiology also varies by age. Advanced age is one of the most significant stroke risk factors. Ninety five percent of strokes occurred among people aged 45 and older, and two-thirds of strokes occurred among those over the age of 65(Leys *et al.*, 2005). However, stroke can occur at any age, including during childhood.

Approximately 10% of all stroke cases were due to intracerebral haemorrhage (ICH) and 1 to 7% were due to subarachnoid haemorrhage (SAH)(Feigin *et al.*, 2005). The incidence of intracerebral haemorrhage is twice as common as SAH and it has a higher morbidity and mortality than cerebral infarction or SAH(Qureshi *et al.*, 2001).

1.2.2 Epidemiology of Stroke in Asia

Several studies, especially those incorporating hospital-based registries, have been successful in identifying the clinical features of stroke in Asia. These include the relatively high prevalence of intracerebral haemorrhage, lacunar infarction, intracranial atherosclerosis, and stroke among young patients(Taqui and Kamal, 2007).

Acute stroke is presently among the top four leading causes of death in the Association of Southeast Asian Nations (ASEAN) countries, with the crude death rate ranging from 10.9/100 000 to 54.2 per 100 000 (Burke and Venketasubramanian, 2006).It is the second or third leading cause of death in Hong Kong, Taiwan, South Korea and Singapore. Meanwhile, Malaysia, Thailand, the Philippines and Indonesia are countries with moderate hospital-based data on stroke. India is the only country that has some data on stroke prevalence(Singh *et al.*, 2000).The conservative assumptions made by the experts suggest that the absolute burden of stroke mortality is indeed likely to be greater in developing Asian countries. China, Taiwan and Japan rank the highest in terms of stroke mortality in the region. The mortality rates for cerebrovascular disease in these countries stand close to a hundred or higher per 100,000 population for men and women of all ages. Stroke is the leading cause of death in China, while in Taiwan it is currently ranked second, next to cancer, after being the main cause of death from 1963to 1982(Singh *et*

al., 2000). The major type of stroke in Taiwan is cerebral infarction while for Japan and China, it is cerebral haemorrhage (Shimamoto *et al.*, 1989).

Data from the Asian Stroke Advisory Panel (ASAP) revealed that the incidence of ICH ranged from 17 to 33% of all strokes, which is twice as high as in Western countries. In Thailand, the incidence of ICH was 30 % of all strokes(Niphon Poungvarin *et al.*, 2006).

1.2.3 Epidemiology of Stroke in Malaysia

Stroke is one of the top 10 causes of hospitalization in Malaysia. However, prospective studies of stroke in Malaysia have been limited. Hypertension has been found to be the major risk factor for stroke. The mean age of stroke patients in Malaysia is between 54.5 and 62.6 years(Loo and Gan, 2012b).

In Kuala Lumpur, 163 ischaemic stroke patients were admitted to Hospital Universiti Kebangsaan Malaysia from June 2000 to January 2001, with lacunar infarct (62.6%), middle cerebral infarct territory (26.4%), and other manifestations (11.0%). The mortality rate from ischaemic stroke was 11.7%, with a mean age of 62.2 years(Hamidon and Raymond, 2003b). In another hospital (University of Malaya Medical Centre), ischaemic stroke patients were admitted between June 2000 and November 2000; Chinese accounted for 40.9% of cases, followed by Malays (30.1%), Indians (27.7%), and other races (Loo and Gan, 2012a).

Of the 246 stroke patients admitted to Penang Hospital from December 1998 to November 1999, the majority were Chinese (55.7%), followed by the Malays (28.9%), and Indians (14.2%), while other races accounted for 3%. Again, this reflected the local population, as most of the people in Penang are of Chinese descent. It was observed that there were more ischaemic stroke cases (74.8%) than haemorrhagic stroke cases (25.2%)(Loo and Gan, 2012b).

1.2.4 Epidemiology of Stroke in Young Adults

Ischaemic stroke among young patients constitutes about 5% of all strokes (Nencini *et al.*, 1988; Bevan *et al.*, 1990; Kristensen *et al.*, 1997).

Previous studies of young adults with ischaemic stroke had varying definitions of the upper limit of "young", ranging from 15 to 50 years(Hilton-Jones and Warlow, 1985; Nencini *et al.*, 1988; Martin *et al.*, 1997; Lee *et al.*, 2002; Leys *et al.*, 2002; Putaala *et al.*, 2009b; Tan *et al.*, 2010; Dharmasaroja *et al.*, 2011; Tiamkao *et al.*, 2013).

Furthermore, differences in the methods of reporting the incidence of stroke makes it difficult to draw geographical comparisons. While the majority of population-based studies reported rates for all strokes combined (ischaemic and haemorrhagic, including SAH), were limited reports of the rates of ischaemic stroke alone.

The incidence of ischaemic stroke varies from 11 to 20/100,000 in different studies (Kappelle *et al.*, 1994; Wolfe *et al.*, 2000; Marini *et al.*, 2001; Razzaq *et al.*, 2002). During the past decade, several studies have been conducted to define the clinical patterns and etiology of stroke among young patients, with strikingly different results. The main reasons for this wide variation include geographic differences, new diagnostic tools such as trans-esophageal echocardiography, and previously unknown etiologies such as anti-phospholipid antibody syndrome and disorders of the inter-atrial septum (Bevan *et al.*, 1990).

Many studies conducted in Asia have shown an increased prevalence of stroke in the young (usually taken as age at onset of less than 45 years)(Mehndiratta *et al.*, 2004).

In Malaysia, a comparative study of ischaemic stroke patients in Malaysia and Australia showed that the mean age of Malaysian patients was 41.5 ± 7.4 years (range 16 to 49 years).There were significantly more large vessel atherosclerosis and small vessel occlusions among young Malaysians with ischaemic stroke compared with Australia(Tan *et al.*, 2010).

For haemorrhagic stroke, the incidence of ICH among people 35 years of age was estimated to be 0.3/100 000 while the frequency of ICH among a series of strokes among young adults varied from 0.7% to 40%(Ruíz-Sandoval *et al.*, 1999)

SAH accounts for only 5% of all strokes**.** The incidence of SAH is around six cases per 100,000 patient years. Although the incidence of SAH increases with age, one-half of patients are younger than 55 years(van Gijn *et al.*, 2007). Despite its relative rarity, the loss of productive life years in the general population as a result of SAH is comparable to that of cerebral infarction, the most common stroke subtype(Feigin *et al.*, 2005).

1.3 Definition and Classification

1.3.1 Definition of Stroke

Stroke is a clinical syndrome characterized by rapidly developing clinical symptoms and/or signs of focal, and at times global, loss of cerebral function, with symptoms lasting more than 24 hours and possibly leading to death, with no apparent cause other than that of vascular origin(Hinkle and Guanci, 2007).

1.3.2 Classification of Stroke

Classification of stroke is important to guide medical personnel during immediate stroke supportive care and rehabilitation, for prognostic purposes, and to guide cost-effective investigations of its underlying cause.

The classification should first distinguish between ischaemic and haemorrhagic stroke, SAH, cerebral venous thrombosis, and spinal cord stroke. The classification should also be based on the patient's medical history, physical examination, and diagnostic tests performed in good time.

The Stroke Data Bank Subtype Classification that was derived from the Harvard Stroke Registry classification, the National Institute of Neurological Disorders and Stroke (NINDS) Stroke Data Bank, recognized five major groups: brain haemorrhages, brain infarctions, including atherothrombotic and tandem arterial pathological abnormalities, cardioembolic stroke, lacunar stroke, and stroke from rare causes or undetermined etiology(Amarenco *et al.*, 2009).

1.3.3 Classification of Ischaemic Stroke

In the clinical classification by the Oxfordshire Community Stroke Project (OCSP), patients are classified into groups based on clinical grounds and computed tomography (CT) brain scans. The outcome of stroke is driven strongly by the severity of the stroke, which is well reflected in this classification, although it does not address the cause of the stroke. In this classification, ischaemic stroke is classified into lacunar infarct, total anterior circulation infarct, partial anterior circulation infarct and posterior circulation infarct(Amarenco *et al.*, 2009).

The other classification used for ischaemic stroke is the TOAST criteria (Trial of Org 10172 in Acute Stroke Treatment).In this classification the ischaemic stroke is classified into: (i) large artery atherosclerosis, (ii) cardioembolism, (iii) small vessel occlusion, (iv) stroke of other determined etiology and (v) stroke of undetermined etiology. The TOAST stroke subtype classification system is easy to use and has good inter observer agreement. This system should allow investigators to report responses to treatment among important subgroups of patients with ischaemic stroke(Adams *et al.*, 1993).

1.3.4 Classification of Haemorrhagic Stroke

Intracranial haemorrhage is the accumulation of blood anywhere within the skull vault. A distinction is made between intra-axial haemorrhage and extra-axial haemorrhage. Intra-axial haemorrhage is due to intraparenchymal haemorrhage or intraventricular haemorrhage. The main types of extra-axial hemorrhage are epidural haematoma, subdural haematoma and SAH.

For intracerebral haemorrhage, the classification was based on the location of the epicentre of the bleeding. It can be classified as lobar (frontal, parietal, temporal, occipital), thalamic, basal ganglia/internal capsule, cerebellar, or brain stem(Ruíz-Sandoval *et al.*, 1999).

1.4 Etiology of Strokes

The two major mechanisms causing brain damage in stroke are ischaemia and/or haemorrhage.

In the young adult population, ischaemic stroke is still the most common. However, the proportion of strokes due to SAH and intracranial haemorrhage is higher compared with the general stroke population (40-55% and 15-20% respectively) (Griffiths and Sturm, 2011).

1.4.1 Etiology of Ischaemic Stroke among Young Adults

For ischaemic stroke in young adults, the etiologies vary and are slightly different from those of the general population. However, in 35% of cases,the underlying etiology remains unclear(Kappelle *et al.*, 1994; Rohr *et al.*, 1996; Kristensen *et al.*, 1997; Martin *et al.*, 1997; Putaala *et al.*, 2009b).

In general, atherothromboembolism is the major cause of ischaemic stroke worldwide. It accounts for around 50% of the cases of ischaemic stroke. Meanwhile, 25% of ischaemic stroke is caused by intracranial small vessel disease (penetrating artery disease), and 20% of patients have cardiogenic embolism (Malaysia CPG Management of Acute Ischaemic Stroke, 2012). Another study, found that small vessel infarctions (lacunar infarcts) were more common among Asians than Caucasians (Caplan *et al.*, 1986; Feldmann *et al.*, 1990).

Among young adults, atherosclerosis remains an important risk factor (accounting for 15–25% of cases)(Varona, 2010).

In addition, cardioembolic stroke was more common among younger patients (15–35% of cases)and was found in 6–35% of young adult patients with ischaemic stroke in developed countries(Griffiths and Sturm 2011).

According to the TOAST category, "other" was the most common group (55%) with prothrombotic states in (15% of cases), vasculitis in 12%, and dissection in 7%(Hoffmann, 1998).

The causes that are more frequent among young people include extracranial artery dissection (2–25%ofcases)(Rohr *et al.*, 1996; Lee *et al.*, 2002; Nedeltchev *et al.*, 2005; Putaala *et al.*, 2009b; Varona, 2010) while up to 20% of young adults with ischaemic stroke had migraines (Bogousslavsky and Pierre, 1992).However, thorough studies that excluded alternate possible causes suggest that migraine contributes to only 1–5% of cases(Adams *et al.*, 1993; Kappelle *et al.*, 1994; Rohr *et al.*, 1996; Kristensen *et al.*, 1997), while drug use was found in up to 5% of cases, depending on the frequency of use in a given population (Rohr *et al.*, 1996).

In some populations, oral contraceptive use has been implicated in up to 8% of stroke cases in young adults(Carolei *et al.*, 1993), while, 5-10% of cases were caused by antiphospholipid antibody syndrome(Bogousslavsky and Pierre, 1992; Kappelle *et al.*, 1994; Rohr *et al.*, 1996; Kristensen *et al.*, 1997; Lee *et al.*, 2002), inherited coagulation disorders do not appear to play a large role in young stroke in the absence of right to left venoarterial shunting.

1.4.2 Etiology of Ischaemic Stroke among Young Adults in Asia

A number of factors have been postulated to account for the high prevalence of ischaemic stroke in Asia: (i) cardioembolic stroke(Luijckx *et al.*, 1993; Mehndiratta *et al.*, 2004)due to cardiac diseases, such as rheumatic heart disease, (ii) accelerated intracranial atherosclerosis, (iii) arteriovenous malformations, and (iv) increased prevalence of diseases such as Takayasu's arteritis and Moya-moya disease (Taqui and Kamal, 2007).

Another study was conducted in India revealed that stroke in young patients accounted for 13.5% (127 of 940) of all stroke cases over a period of nine years. It was found that the major risk factors for stroke in these young patients were hypertension, hypercholesterolemia, hypertriglyceridemia, and smoking. Oral contraceptives, alcohol and illicit drug use were infrequent risk factors, in contrast with Western studies. Cardioembolic stroke (29.4%) and atherosclerotic occlusive disease (22%) were the most common causes of ischaemic stroke(Mehndiratta *et al.*, 2004).

1.4.3Etiology of Haemorrhagic Stroke among Young Adults

The most common etiology for haemorrhagic stroke is hypertension, which was observed in a study on young stroke patients by Jacobs et al (2002) in Manhattan. The study concluded that there was an association between hypertension and ICH and an increased rate of intracranial haemorrhage was observed among young blacks in the US (Qureshi *et al.*, 1995; Jacobs *et al.*, 2002).

Ruiz-Sandoval et al. (1999) retrospectively ICH among 200 patients (mean age, 27 years; range, 15 to 40 years).He concluded that basal ganglia bleeding was caused by hypertension(Ruíz-Sandoval *et al.*, 1999).

Another study involving young adults (15 to 44 year old blacks) demonstrated an increased incidence of hypertensive and intracranial haemorrhage(Qureshi *et al.*, 1995). The study concluded that hypertensive intracerebral hemorrhage (64% of cases) was the most common subtype of intracerebral haemorrhage, andit was more frequently associated with stroke in young black than in non-black patients (55%).

Apart from a study in North India, this issue has not been thoroughly examined among young Asians. The study did not find an increased proportion of haemorrhagic to total strokes (only 14% of cases were haemorrhagic) (Mehndiratta *et al.*, 2004). In Western countries, a higher proportion of haemorrhagic stroke was reported (ranging 40 to 55%) (Bevan *et al.*, 1990; Marini *et al.*, 2001; Jacobs *et al.*, 2002).

Furthermore, a study by Woo et al (2004) conducted in the state of Kentucky in the US concluded that untreated hypertension is highly prevalent and an important risk factor for haemorrhagic stroke. They estimated that 17% to 28% of haemorrhagic strokes among hypertensive patients would have been prevented if the participant had been on hypertension treatment(Woo *et al.*, 2004).

Unfortunately, 45% of patients were unaware of the presence of hypertension, and in those in whom hypertension had been previously diagnosed, treatment was irregular.

Recurrence of haemorrhagic stroke was documented in 30% of surviving patients with hypertension(Ruíz-Sandoval *et al.*, 1999).

Another important etiology for haemorrhagic stroke is vascular malformations (aneurysms and arteriovenous malformations). Vascular malformations were found in 49% of patients in a retrospective evaluation of 200 cases of intracranial haemorrhage in a tertiary medical centre in Mexico (Ruíz-Sandoval *et al.*, 1999).

In developing countries, a high proportion of haemorrhagic stroke secondary to vascular malformations has also been reported, although formal angiography is less accessible and reported frequencies are lower (Mehndiratta *et al.*, 2004).

The possibility of drug used should be elicited in young adults presenting with haemorrhagic stroke. In a large population-based study in the US examined drug use among young patients hospitalized with haemorrhagic (n = 937) or ischaemic (n = 998) stroke, increased young haemorrhagic stroke rates were associated with increased rates of amphetamine and cocaine abuse over a period of three years (Westover *et al.*, 2007).

1.5 Pathophysiology of Stroke

It is known that the acute occurrence of neurological symptoms is caused by a vascular lesion in the brain, the brain stem or the cerebellum. Hemiparesis will be the most frequent neurological symptom in cerebral apoplexy, although other symptoms are also seen, for instance, aphasia, hemianopia and sensibility disturbances.

The definition of cerebrovascular disease consists of two main groups: intracerebral haemorrhage and cerebral ischaemic lesions.

The cerebral ischaemia can be subdivided into one group in which an arterial occlusion is demonstrable and another in which no arterial occlusion is demonstrable.

In ischaemic stroke, decreased or absent circulating blood deprives neurons of necessary substrates. The effects of ischemia are fairly rapid because the brain does not store glucose, its chief energy substrate, and it is incapable of anaerobic metabolism.

Intracerebral haemorrhage originates from deep penetrating vessels and causes injury to brain tissue by disrupting connecting pathways and causing localized pressure injury. In

either case, destructive biochemical substances released from a variety of sources play an important role in tissue destruction.

1.5.1 Pathogenesis of Cerebral Infarction

The three main mechanisms causing ischaemic strokes are: (a) thrombosis, (2) embolism and (3) global ischemia (hypotensive) stroke. Other infrequent causes of ischaemic strokes are vasospasm (migraine, following SAH and hypertensive encephalopathy) and some forms of "arteritis"(PAULSON, 1971).

In patients whom an arterial occlusion has been demonstrated, the cause of the ischaemic lesion may either be an embolus or a thrombus. The two causes cannot be distinguished in some individual cases. The embolic cases are presumably rather frequent, as they are often supposed to originate from the extracranial neck vessels and not from the heart.

i)Thrombosis

In thrombosis, atherosclerotic plaques can undergo pathological changes such as ulcerations, thrombosis, calcifications, and intra-plaque hemorrhage. The susceptibility of the plaque to disrupt, fracture or ulcerate depends on the structure of the plaque, as well as on its composition and consistency. Disruption of the endothelium can occur as a result of any of these pathological changes, which initiate a complicated process that activates many destructive vasoactive enzymes. These vasoactive enzymes cause mechanical "plugging" by leucocytes, erythrocytes, platelets and fibrin(Woodruff *et al.*, 2011) .

In addition to atherosclerosis, other pathological conditions that cause thrombotic occlusion of a vessel include clot formation due to a hypercoagulable state, fibromuscular dysplasia, arteritis and dissection of a vessel wall.

ii)Embolism

Embolic stroke (ES) can result from embolization of an artery in the central circulation from a variety of sources. In addition to clots, fibrin, and pieces of atheromatous plaque,

materials known to embolize into the central circulation include fat, air, tumors or metastaseis, bacterial clumps, and foreign bodies. Superficial branches of cerebral and cerebellar arteries are the most frequent targets of emboli. Most emboli lodge in the middle of the cerebral artery distribution because 80% of the blood carried by the large neck arteries flow through the middle cerebral arteries (Woodruff *et al.*, 2011).

The two most common sources of emboli are: the left sided cardiac chambers and large arteries, (e.g. “artery to artery” emboli that result from detachment of a thrombus from the internal carotid artery at the site of an ulcerated plaque).

iii) Global – Ischaemic or Hypotensive Stroke

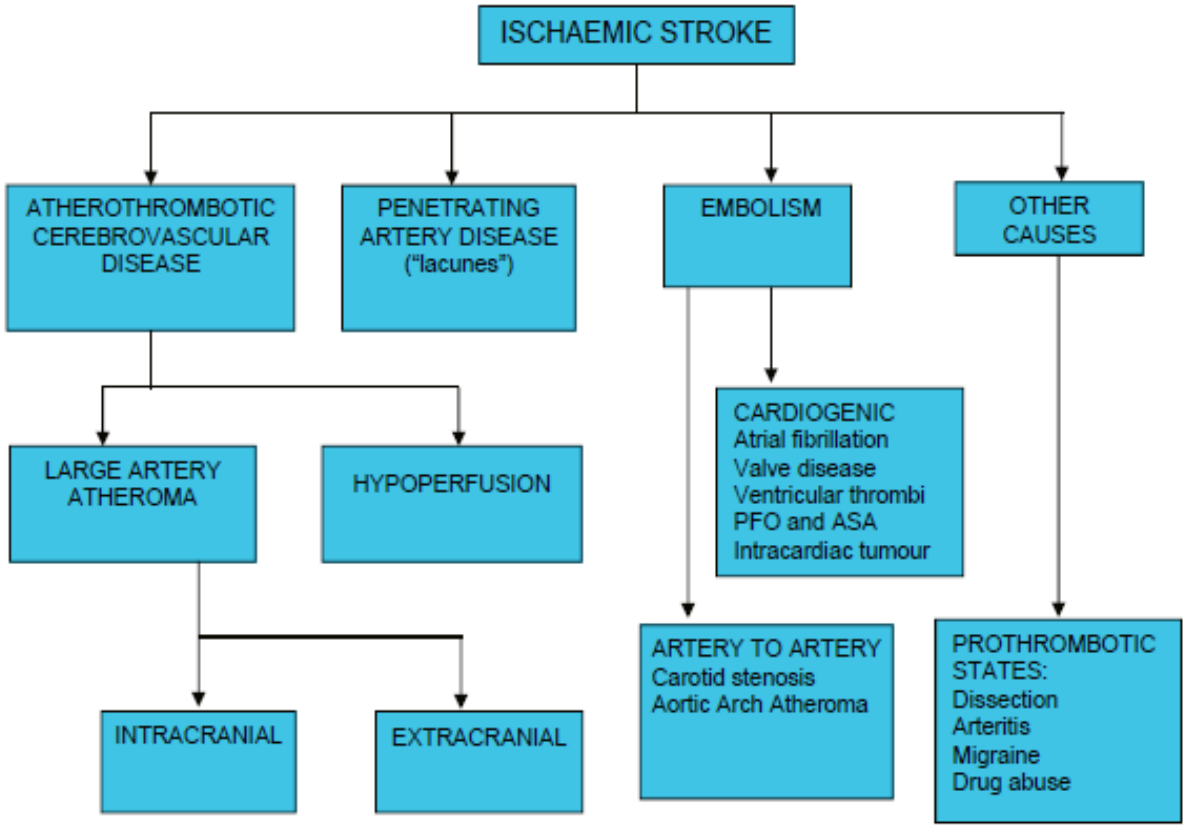
Hypotensive stroke occurs when there is profound reduction in systemic blood pressure for to any reason where some neurons are more susceptible to ischemia than others. These include the pyramidal cell layer of the hippocampus and the Purkinje cell layer of the cerebellar cortex.

Global ischaemia causes the greatest damage to areas between the territories of the major cerebral and cerebellar arteries, known as the “boundary zone” or “watershed area”.

Watershed infarction in this area causes a clinical syndrome consisting of paralysis and sensory loss predominantly involving the arm while the face is not affected and speech is spared. Watershed infarcts make up approximately 10% of all ischemic strokes and almost 40% of these occur in patients with carotid stenosis or occlusion (Woodruff *et al.*, 2011).

A summary of ischaemic stroke pathophysiology is shown in Figure 1.

Figure 1: Ischaemic Stroke Pathophysiology Algorithm



Adapted from:Clinical Practice Guideline (Malaysia) Management of Ischaemic Stroke 2nd Edition 2012

1.5.2 Pathogenesis of Intracerebral Haemorrhage

The majority of the patients with ICH have hypertension and it is a frequent cause of death in patients with malignant hypertension (PAULSON, 1971; Woo *et al.*, 2004).

Hypertension induces smooth muscle cell proliferation in the arterioles. This process is termed hyperplastic arteriolosclerosis. Over time, smooth muscle cells die and the tunica media is replaced by collagen, resulting in vessels with decreased tone and poor compliance. The arterioles ultimately undergo ectasia and aneurysmal dilation. These microaneurysms, called Charcot-Bouchard aneurysms, are susceptible to rupture leading

to cerebral haemorrhage and were proposed by Charcot and Bouchard in 1868 as a key element of deep ICH(Takebayashi and Kaneko, 1983).

In another theory, the haemorrhage is caused by a primary rupture of an artery that is weak due to chronic degenerative changes(PAULSON, 1971).

1.5.3 Mechanisms of Neuronal Injury

The ischaemic cascade occurs when the thrombosis or emboli causes a decrease in blood supply to the brain tissue. Neurons and support cells require a careful balance of variables such as temperature, pH, nutrition, and waste removal in their environment to function optimally (Hinkle and Guanci, 2007).

At a molecular level, the development of hypoxic- ischaemic neuronal injury is greatly influenced by “overreaction” of certain neurotransmitters, primarily glutamate and aspartate. This process called “excitotoxicity” is triggered by the depletion of cellular energy stores. Glutamate, which is normally stored inside the synaptic terminals, is cleared from the extracellular space by an energy dependent process. The greatly increased concentration of glutamate (and aspartate) in the extracellular space in a depleted energy state results in the opening of calcium channels associated with N-methy1-D-asapartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxanole propionate (AMPA) receptors. Persistent membrane depolarization causes influx of calcium, sodium, and chloride ions and an efflux of potassium ions(Rothman and Olney, 1986; Kristián and Siesjö, 1998).

Intracellular calcium is responsible for the activation of a series of destructive enzymes such as proteases, lipases, and endonucleases which allow the release of cytokines and other mediators, resulting in the loss of cellular integrity.

In ICH, the presence of a hematoma initiates edema and neuronal damage in the surrounding parenchyma. Fluid begins to collect immediately in the region around the hematoma, and edema usually persists for up to five days, although it has been observed for as long as two weeks after a stroke. Early edema around the hematoma results from the release and accumulation of osmotically active serum proteins from the clot.

Vasogenic edema and cytotoxic edema subsequently follow owing to the disruption of the blood brain barrier, the failure of the sodium pump, and the death of neurons(Qureshi *et al.*, 2001).

1.5.4 Neuronal Death

Neuronal death occurs via coagulation necrosis (CN) and apoptosis. CN is a process in which individual cells die without eliciting an inflammatory response. This type of cell death is attributed to the effects of physical, chemical, or osmotic damage to the plasma membrane. Within 8-12 hours of arterial occlusion, the cell will experience irreversible injury. This was demonstrated in eosinophilic cytoplasm and shrunken nuclei(Kristián and Siesjö, 1998).

In apoptosis, cerebral neurons are “programmed” to die under certain conditions, such as ischaemia. During apoptosis, nuclear damage occurs first while the integrity of the plasma and mitochondrial membrane is maintained until late in the process(Lee *et al.*, 2000).

1.6 Risk Factors for Stroke in Young Adults

1.6.1 Non-modifiable Risk Factors

In terms of etiology and risk factors, most data come from clinical series and case-control studies. The majority of these cases examined adults less than 45 years of age, while the Helsinki Young Stroke registry examined stroke etiology among adults less than 49 years of age. In as many as 35% of cases, the underlying etiology remains unclear. Atherosclerosis remains an important risk factor (15 to 25% of strokes among young adults, and an even greater proportion among certain ethnicities)(Putaala *et al.*, 2009b).

This is supported by a study by Feldmann, who found that there is a greater predominance of intracranial atherosclerotic vascular disease compared with extracranial or carotid artery disease in Asians(Feldmann *et al.*, 1990).

Furthermore, Stewart et al. (1999) reported an association between ethnicity and stroke incidence, even after adjusting for social class. The study concluded that the incidence rates of stroke are higher in the black population and that this was not explained by confounders, such as social class, age and sex(Stewart *et al.*, 1999).
In Singapore, Sharma et al. (2012) found that Indian stroke patients were younger than Malays and they had more severe strokes compared with the Chinese(Sharma *et al.*, 2012).

In regard to sex differences in the incidence of stroke in young adults, stroke rates are greater among men than women in the 35 to 44 year old age group. Some population-based studies demonstrated an increased incidence among women less than 30 years old , as did several case-series(Griffiths and Sturm, 2011).

Meanwhile , Lee et al. (2002) found that 71.4% of young ischemic stroke patients in Taiwan were men, which was similar to studies in Korea (75.2%) and India (76.3%), but different from those in Western countries (44.1% to 58.9%)(Lee *et al.*, 2002).
For haemorrhagic stroke, a study by George et al. (2011) concluded that females aged 15 to 34 years and males aged 35 to 44 years showed a decrease in the prevalence of hospitalizations for SAH, whereas females aged 5 to 14 years showed increased rates of SAH (George *et al.*, 2011).

1.6.2 Modifiable Risk Factors

The modifiable, vascular risk factors associated with an increased risk of stroke are high blood pressure, cigarette smoking, diabetes mellitus, atrial fibrillation, coronary artery disease, hyperlipidemia, obesity, physical inactivity, high dietary salt intake, heavy alcohol consumption, previous stroke and increased homocysteine levels.

Several studies have determined the etiology and risk factors of stroke in young adults. An increased risk of cerebral infarction among young adults with conventional vascular risk factors was observed, particularly in developing countries due to increasing smoking rates and urbanization(Griffiths and Sturm, 2011).

Furthermore, a hospital based prospective observational study involving all young adults admitted to Hamad General Hospital in Qatar with first-ever ischaemic stroke instances concluded that the most common risk factors were hypertension (40%), diabetes mellitus (32.5%), hypercholesterolemia (27.5%), smoking (27.5%), and alcohol intake (22.5%)(Khan, 2007).
According to George et al. (2011),hypertension, diabetes, obesity, lipid disorders, and tobacco use were among the most common coexisting conditions, and their prevalence among adolescents and young adults (aged 15 to 44 years) hospitalized with acute ischaemic stroke increased from 1995 to 2008.

In Asia, a study in Thailand was conducted to evaluate the causes of ischaemic stroke among Thai adults (16-50 years old).The study found that undetermined cause were responsible for the majority of strokes and hyperlipidemia, smoking and hypertension were the common risk factors(Dharmasaroja *et al.*, 2011).

In addition, a study by University of Malaya involved all consecutive ischaemic stroke patients aged of 18 to 49 years old. The study compared the differences in risk factors for Malaysia versus Australia. There was a higher proportion of patients with conventional atherothrombotic risk factors for diabetes and hypertension was more likely to be associated with related complications, such as chronic renal failure in Malaysians as compared with Australians. The background population in Malaysia has been observed to have a rising prevalence of diabetes, reaching twice the prevalence in Australia in recent years(Tan *et al.*, 2010).

For local data, Loo and Gan (2012) found that the risk factors for stroke in Kelantan and Penang were smoking, diabetes, heart disease, and hypercholesterolemia, with hypertension being the highest risk factor. Patients from Kelantan had a lower mean age

(59·3 years) of stroke occurrence compared with patients from Penang (65 years).(Loo and Gan, 2012a).

1.6.3Modifiable Risk Factors for Haemorrhagic Stroke in Young Adults

In previous population-based, case-control studies, ICH has been consistently associated with advancing age, race (black and Asian populations), hypertension, anticoagulant use, and heavy alcohol use(Feldmann *et al.*, 2005).

Moreover, a systematic review of case control and longitudinal studies by Feigin et al2005) revealed that smoking, hypertension, and excessive alcohol intake have statistically significant and consistent associations with an increased risk of SAH (Feigin *et al.*, 2005).

The same conclusion was made by Kurth et al. (2003) in a prospective cohort study. The study revealed an increased risk of total haemorrhagic stroke, ICH and SAH in current cigarette smokers with a graded increase in risk that was dependent on how many cigarettes were smoked. The effect of smoking on ICH was about the same magnitude as the effect of smoking on ischaemic stroke.

Monforte et al. (1990) found that high ethanol intake among young and middle aged people was an independent risk factors for ICH, which tended to be located in the cerebral lobes(Monforte *et al.*, 1990).

Another common cause of ICH is anticoagulant associated ICH (AAICH). This is the most feared complication of anticoagulant use. Anticoagulants have been shown to be effective for prevention of venous thromboembolism and systemic embolism in patients with atrial fibrillation or prosthetic valves(Hirsh *et al.*, 2001). Other risk factors for AAICH include advanced age, history of hypertension, simultaneous use of antiplatelet agents, cerebral amyloid angiopathy, apolipoprotein genotype e2, and presence of leukoaraiosis on neuroimaging (Testai and Aiyagari, 2008).

1.7 Diagnosis

Generally, the diagnosis of stroke is made by evaluating and analysing information derived from a good history and physical examination and this information is supplemented with selected diagnostic tests.
It is important to assess and recognize the stroke in the pre-hospital phase. Emergency medical technicians and ambulance staff members need training to recognise the signs and symptoms of stroke. Tools such as the Face Arm Speech Test (Nor *et al.*, 2004) and the shortened National Institutes of Health Stroke Scale (NIHSS) (Tirschwell *et al.*, 2002) have been tested and found to be effective in increasing the diagnostic accuracy of ambulance staff.

When the patient arrives at the emergency department, the essential data to include in the history are a quick history of the timing of the event, pertinent past medical history, and risk factors.

The signs and symptoms of a stroke depend on the type, location and the extent of the affected brain tissue. Stroke patients usually have a rapid within minutes to one hour, onset of focal neurological symptoms. One- third of all strokes occur during night sleep, therefore, the symptoms are first noted upon waking in the morning.

In haemorrhagic stroke, the classic clinical presentation includes the onset of a sudden, focal neurological deficit while the patient is active, which progresses over minutes to hours. This smooth symptomatic progression of a focal deficit over a few hours is uncommon in ischaemic stroke and rare in SAH. Headache is more common with ICH than with ischaemic stroke, although it is less common than in SAH. Vomiting is more common with ICH than with either ischaemic stroke or SAH. Increased blood pressure and an impaired level of consciousness are common. However, clinical presentation alone, although helpful, is insufficient to reliably differentiate ICH from other stroke subtypes(Broderick *et al.*, 1999).

A full neurological examination, including the patient's consciousness level and tests of higher mental function (such as the mini-mental state examination), is mandatory. Every positive and negative finding should point to the site of the lesion. These can be divided

into two broad groups: a) clinical features that are caused by anterior circulation stroke (carotid artery), and b) those caused by posterior circulation stroke.

It is important to determine the dominant hemisphere as it is primarily responsible for language function. Handedness determines dominance for most people. Right-handed people are left-hemisphere dominant; left-handed people are also left-hemisphere dominant about 60% of time. The clinical features that are more common with a dominant left cerebral hemisphere lesion include aphasia, agraphia, acalculia, apraxias, a left gaze preference, a right visual field deficit along with right-sided hemiparesis, and a right-sided hemisensory loss. Common features of a non-dominant right cerebral hemisphere include neglect (left-sided hemiinattention), right gaze preference, left visual field deficit, dysarthria, flat affect, left-sided hemiparesis, and left-sided hemisensory loss (Bader and Palmer, 2006).

Once diagnosis of stroke is made, the NIHSS can be used to guide the neurologic assessment. The NIHSS provided the most prognostic information. A cut point of 13 on the NIHSS best predicted 3-month outcomes (Muir *et al.*, 1996).

To measure disability or dependence in activities of daily living in stroke victims, the Modified Rankin Scale (MRS) and Barthel Index (BI) are most commonly used.

Previous studies have revealed higher score on the BI, with better survival after stroke(Hankey *et al.*, 2000).However, the BI is susceptible to ceiling effects,(Kwon *et al.*, 2004), which may limit its application in the evaluation of stroke patients with mild to moderate severity. The MRS, which is a global outcome measure consisting of seven grades ranging from0 to 6, has been used for functional evaluation of patients with stroke, and it is considered to have less of a ceiling effect(Chiu *et al.*, 2012).

1.8 Investigations

Despite the differences in clinical presentation between hemorrhagic and ischaemic strokes, no collection of clinical features has sufficient predictive value to forego brain imaging(Broderick *et al.*, 1999). CT is the key part of the initial diagnostic evaluation. First, it clearly differentiates haemorrhagic from ischaemic stroke. In addition, CT demonstrates the size and location of the haemorrhage and may reveal structural abnormalities such as aneurysms, arteriovenous malformations, and brain tumors causing the ICH as well as structural complications such as herniation, intraventricular hemorrhage, or hydrocephalus. Administration of contrast by the radiologist can often highlight suspected vascular abnormalities.

The American Heart Association (AHA) Guidelines state that the diagnostic studies are important to confirm stroke and to detect early, potentially life-threatening complications, thereby enabling the provision of direct and specific care (Broderick *et al.*, 1999; Adams *et al.*, 2007). A CT scan without contrast is recommended to all patients to confirm the type of stroke (ischaemic or haemorrhagic).It is also important to rule out the presence of a hemorrhagic stroke that would preclude the use of thrombolysis in ischaemic stroke(Muir *et al.*, 2006).Other imaging studies may include a CT angiogram, magnetic resonance imaging (MRI), and cerebral angiography. A CT angiogram can be used to identify large vessel stenosies or occlusions. MRI allows for better visualization of possible infarcted areas, and angiography is used when intra-arterial (IA) thrombolysis is indicated or when surgical interventions are being considered.

Other investigations include electrocardiogram and cardiac biomarkers to exclude acute coronary syndrome or cardiac arrhythmias, complete blood counts, renal function tests, blood glucose and coagulation profiles. In selected cases, the patient may need a chest radiograph, an arterial blood gas assessment, a toxicology screen, as well as other investigations that may contribute to their diagnosis and management (Adams *et al.*, 2007).

Among young adults suffering ischaemic stroke, several investigations can identify the cause or predisposing factor. The investigations should include a search for classical

vascular risk factors, special diagnostic tests (e.g: Fasting homocysteine), autoantibody screen including antiphospholipid antibodies and a coagulation screen if indicated (e.g: serum fibrinogen, antithrombin III, protein C, protein S and Factor V-Leyden).

1.9 Management

1.9.1General Management

In general, management of acute stroke includes supportive care and treatment of acute complications. This is important to improve mortality and functional disability.

In acute care, the management include oxygen and airway support. It is important to ensure adequate tissue oxygenation which is imperative to prevent hypoxia and potential worsening of the neurological injury**.** Other supportive general management includes monitoring with a pulse oxymeter to recognize impaired pulmonary function , circulatory function (pulse rate, blood pressure), NIHSS, Head Chart, and to recognise complications from mass effects (Adams *et al.*, 2007).

i) Blood Pressure (BP) Management

During the first hours after the onset of the symptoms of stroke, treatment of severe hypertension is problematic, because a precipitous decline in arterial pressure may cause harmful decreases in local perfusion. There is currently no evidence that antihypertensive therapy is beneficial in patients with stroke, even above the blood pressure treatment thresholds recommended by various consensus panels (systolic pressure thresholds range from >200 to 220 mm Hg, and diastolic pressure thresholds range from >110 to 120 mm Hg)(Wood *et al.*, 2000).

For ischaemic stroke, hypertension following stroke is quite common. However, its optimal management has not been established(Adams *et al.*, 2007). Yong et al. (2005) found that higher baseline systolic blood pressure (SBP) or diastolic blood pressure (DBP) was associated with favourable outcomes after stroke. This study again raised the question of whether it is beneficial to reduce the initial blood pressure in acute ischaemic stroke, especially when hypertension is moderate(Yong *et al.*, 2005).

A summary of blood pressure management in acute ischaemic stroke is shown in Figure 2:

AHA/ASA Recommendations for BP Management in Acute Ischaemic Stroke
1.Patients eligible for treatment with intravenous thrombolytics or other acute reperfusion intervention and SBP>185 mmHg or DBP > 110 mmHg should have BP lowered before intervention. A persistent SBP>185 mmHg or DBP > 110 mmHg is a contraindication to intravenous thrombolytic therapy. After perfusion therapy, keep SBP <180 mmHg and DBP<105 mmHg for at least 24 hours.
2.Patients who have other medical indications for aggressive treatment of BP should be treated.
3.For those not receiving thrombolytic therapy, BP may be lowered if it is markedly elevated (SBP>220mmHg or DBP>120mmHg).A reasonable goal would be to lower BP by approximately 15% during the first 24 hours after the onset of stroke.
4. In hypotensive patients, the cause of hypotension should be sought. Hypovolumia and cardiac arrhythmias should be treated and in exceptional circumstances, vasopressors may be prescribed in an attempt to improve cerebral blood flow.

Figure 2: AHA/ASA recommendations for BP management in acute ischaemic stroke

Adapted from Circulation AHA: Guidelines for the Early Management of Adults with Ischaemic Stroke 2007

For haemorrhagic stroke (primary ICH), very little prospective evidence exists to support a specific blood pressure threshold. The previous recommendation was to maintain a SBP of 180 mm Hg or less and/or a mean arterial pressure (MAP) less than 130 mm Hg. The