



# CLINICAL PRACTICE GUIDELINES

## Management of Ischaemic Stroke

3<sup>rd</sup> Edition  
2020



**STROKE COUNCIL**

*Malaysian Society of Neurosciences (Persatuan Neurosains Malaysia)*



Academy of Medicine Malaysia



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## **STATEMENT OF INTENT**

This guideline was developed to be a guide for best clinical practice, based on the best available evidence at the time of development. Specific attempts were made to use local data and publications to ensure local relevance. Adherence to this guideline does not necessarily lead to the best clinical outcome in individual patient care. Every healthcare provider is responsible for the management of his/her unique patient based on the clinical presentation and management options available locally.

## **REVIEW AND UPDATE OF THE GUIDELINE**

This guideline was issued in 2020 and will be reviewed in 2025 or earlier if important new evidence becomes available. When they are due for updating, the Chairman of the CPG or National Advisor of the related specialty will be informed about it. A discussion will be held on the need for a revision, including on the scope of the revised CPG. A multidisciplinary team will be formed, and the latest systematic review methodology used by MaHTAS will be employed.

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## TABLE OF CONTENTS

Chapter	Title	Page
-	STATEMENT OF INTENT REVIEW AND UPDATE OF THE GUIDELINE	3
-	MEMBER OF THE EXPERT PANELS	4-5
-	EXTERNAL REVIEWERS	6
-	TABLE OF CONTENTS	7
-	RATIONALE, OBJECTIVES AND PROCESS OF GUIDELINE DEVELOPMENT	8-11
-	KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS	12
-	GLOSSARY	13-16
-	UPDATES IN MANAGEMENT OF ISCHAEMIC STROKE CPG 2020	17
-	KEY RECOMMENDATIONS OF STROKE CPG 2020	18-21
-	RECOMMENDATIONS SUMMARY OF STROKE CPG 2020	22-36
<b>1</b>	EPIDEMIOLOGY, DEFINITION AND CLASSIFICATION OF STROKE	37-39
<b>2</b>	CAUSES AND PATHOPHYSIOLOGY	40-41
<b>3</b>	DIAGNOSIS AND INITIAL ASSESSMENT	42-44
<b>4</b>	PROGNOSIS	45-46
<b>5</b>	PREVENTION OF STROKE	47-65
<b>6</b>	INVESTIGATIONS	66-67
<b>7</b>	EMERGENCY MEDICINE SERVICES	68-73
<b>8</b>	ACUTE GENERAL MANAGEMENT	74-80
<b>9</b>	REPERFUSION OF ISCHAEMIC BRAIN	81-89
<b>10</b>	ENDOVASCULAR THROMBECTOMY	90-93
<b>11</b>	STROKE UNIT	94-96
<b>12</b>	STROKE IN THE OLDER PERSON	97-105
<b>13</b>	STROKE AND CARDIOEMBOLISM	106-109
<b>14</b>	STROKE IN SPECIAL CIRCUMSTANCES	110-117
<b>15</b>	MANAGEMENT OF STROKE IN PREGNANCY	118-120
<b>16</b>	STROKE THERAPIES WITH LIMITED EVIDENCE	121-122
<b>17</b>	QUALITY ASSURANCE	123
-	APPENDICES	124-129
-	REFERENCES	130-154
-	ACKNOWLEDGEMENT DISCLOSURE STATEMENT SOURCE OF FUNDING	155

## RATIONALE, OBJECTIVES AND PROCESS OF GUIDELINE DEVELOPMENT

### Rationale

Acute ischaemic stroke continues to be a major cause of morbidity and is currently the third leading cause of mortality in Malaysia. With current advancement, timely intervention, and early reperfusion either via medical thrombolysis or endovascular treatment, the outcome of stroke has improved significantly. The biggest challenge in Malaysia is the limited availability, not only in terms of a dedicated stroke unit in a major hospital but also the availability of reperfusion therapy, particularly mechanical thrombectomy. Furthermore, the lack of community awareness on the importance of timely hyperacute intervention for stroke in Malaysia is still prominent.

The 1st Clinical Practice Guideline (CPG) on the management of ischaemic stroke was published in 2006 and the second edition was published in 2012. Since then, there was a rapid development in the management of acute stroke, mainly with the improvement and advancement of reperfusion therapy, encompassing both medical thrombolysis and mechanical thrombectomy. Furthermore, the importance of timely intervention, especially in the emergency department, had significantly improved the outcome in stroke patients. Therefore, this current CPG emphasizes the hyperacute management and has introduced new chapters, for example, emergency medical services. With the growing numbers of elderly population in Malaysia, we have also included a new chapter on stroke in the older person. This 3rd edition was developed to provide a clear and concise approach based on current evidence with the focus being on the efforts to reduce time and improve pre-hospital care. We have summarised and adapted relevant clinical trials data and published literatures to our local practice.

This CPG has been prepared by a panel of committee members from the Malaysia Stroke Council (MSC), the Ministry of Health (MOH) and the Ministry of Higher Education (MOHE). The committee members were multidisciplinary and comprised of neurologists, internal medicine physicians, geriatricians, and emergency physicians from the government sector, private sector, and universities. The external reviewers included were also consultants from multidisciplinary branches of medicine. Patient and stroke carer groups were, however, not included as external reviewers.

### Objectives

- ❖ These guidelines are intended to provide awareness and education to reduce the morbidity and mortality associated with ischaemic stroke by:
  - Identifying symptoms and signs of stroke
  - Identifying the various types and causes of ischaemic stroke
  
- ❖ These guidelines are intended to provide evidence in:
  - Reducing the total ischaemic time
  - Updating the management of ischaemic stroke with respect to:
    - Diagnosis
    - Hyperacute management
    - Post hyperacute care
    - Primary prevention
    - Secondary prevention

These guidelines however do not cover:

- Management of cerebral haemorrhage
- Stroke rehabilitation
- Stroke in the paediatric aged-group population



## **Process**

The current CPG is the initiative of the Malaysia Stroke Council of the Malaysia Society of Neurosciences. A panel of committee members was appointed comprising of neurologists, internal medicine physicians, geriatricians, and emergency physicians from the Ministry of Health, universities, and private sector. Authors from the second CPG were invited to contribute on new updates that were discussed by the panel members. The discussion started from early 2018 till 2020 before being finalised and sent to the appointed reviewers. The panel members met several times throughout the development of the guidelines.

A review of the current medical literature on ischaemic stroke since the publication of the last CPG on 31<sup>st</sup> Jan 2012 was performed. Literature search was carried out using the following electronic databases – PubMed and Cochrane Database of Systematic Reviews. The search was conducted from the period of previous CPG publication until 31st July 2020. The relevant MeSH terms or free text terms were used either singly or in combination as the search strategy (refer **Appendix A**).

The search was filtered to clinical trials and reviews, involving humans, and published in the English language. The relevant articles were carefully selected from the retrieved list. In addition, the reference lists of all relevant articles retrieved were searched to identify further studies. Local CPGs were also studied. Experts in the relevant field were also contacted to obtain further information. International guidelines mainly from the American Heart Association/American Stroke Association (AHA/ASA) and the European Academy of Neurology/European Stroke Organisation (EAN/ESO) were used as the main references.

All literature retrieved were appraised and subsequently presented for discussion during the group meetings. All statements and recommendations formulated were agreed collectively by members of expert panels. Whereby the evidence was insufficient, the recommendations were agreed upon by consensus of the panel members. The draft was then sent to local external reviewers for comments. The level of recommendations and the grading of evidence used in this guideline was adapted from the U.S/Canadian Preventative Services Task Force and the Guidelines for Clinical Practice Guideline, Ministry of Health Malaysia 2003.

The principles and layout follow the methodology stated in the Guidelines for Clinical Practice Guidelines booklet published by the Medical Development Division of the Ministry of Health Malaysia. These guidelines have been presented to the Chairman of the Health Technology Assessment (HTA) and Clinical Practice Guidelines Council of the Ministry of Health Malaysia for review and approval.

## **Formulation Of Recommendation**

In formulating recommendations for the CPG, evidence from the literature i.e. systematic review, meta-analysis, randomized controlled trial or cohort study were critically appraised using CASP (critical appraisal skills program) checklist. Subsequently, the quality of each retrieved evidence and its effect size were carefully assessed/reviewed by the CPG Development Group.

In formulating the recommendations, the overall balances of the following aspects were considered in determining the strength of the recommendations:

1. Overall quality of evidence
2. Balance of benefits versus harms
3. Values and preferences
4. Resource implications
5. Equity, feasibility, and acceptability

## Clinical Questions Addressed:

There were several topics and subtopics that were formulated addressing the diagnosis and management of ischaemic stroke.

1. What is the current best practice for management of acute ischaemic stroke?
2. What are the strategies in stroke prevention?
3. What are the effective non-pharmacological modification in managing patients with stroke?

For **therapy**, the topics and subtopics were formulated using the PICO method as follows:

**P: Population-** Persons with ischaemic stroke and:

- Duration of stroke:
  - < 4.5 hours
  - < 6 hours
  - 6 to 24 hours (extended hours)
  - More than 24 hours
  - Wake up stroke
- Atrial Fibrillation
- Older persons
- Young stroke and special circumstances
- Pregnancy

**I: Intervention:**

- Reperfusion strategy:
  - Medical thrombolysis
  - Mechanical thrombectomy
  - Combined medical thrombolysis and mechanical thrombectomy
- Concomitant drug therapy
  - Anti-platelet therapy – single or dual
  - Direct oral anti-coagulants (DOACs)
  - Statins
  - Anti-hypertensive agents
  - Anti-diabetic agents

**C: Comparison:**

- Reperfusion vs no reperfusion
- Medical thrombolysis vs mechanical thrombectomy/combination therapy
- Single anti-platelet therapy vs dual anti-platelet therapy
- Clopidogrel vs cilostazol vs ticagrelor as a single/combination anti-platelet agent

**O: Outcome:**

- Functional outcome at 3 months
- Reduction of recurrent stroke
- Reduction in major cardiovascular disease event rate (MI, heart failure, cardiovascular (CV) death)
- Reduction in all-cause mortality

**Type of Question- Involves:**

- Therapy - Reperfusion strategy, concomitant drug therapy
- Harm
  - Increase of bleeding risk and stroke rate
  - Adverse effects due to pharmacotherapy
- Prognosis – Improvement of functional status, reduction of stroke recurrence or haemorrhagic transformation and improvement in all-cause mortality

**Type of Study**

- Systematic review and meta-analysis
- Randomised controlled studies
- Cohort studies

**Target Group:**

These guidelines are developed for all healthcare providers involved in the management of ischaemic stroke in adults.

**Target Population:**

These guidelines are developed to treat all adults with ischaemic stroke.

**Period of Validity of the Guidelines:**

These guidelines need to be revised at least every 5 years to keep abreast with recent developments and knowledge that is available.

**Applicability of the Guidelines and Resource Implications:**

This guideline was developed taking into account our local healthcare resources. At present medical thrombolysis is available at some government hospitals and private healthcare centres while mechanical thrombectomy is available likewise in limited centres. Stroke networks are being established in its early stages in some regions in Malaysia. We hope to have a nationwide stroke network in near future.

This guideline aims to educate health care professionals on strategies to optimise the available existing resources for the timely management of patients with ischaemic stroke.

**Facilitators and Barriers:**

The major barriers for the successful implementation of this CPG is the financial and resource implications of:

- transporting these patients to stroke ready hospitals as soon as possible using well-equipped ambulances and accompanied by trained pre-hospital care personnel or medical officers
- availability of medical thrombolysis/mechanical thrombectomy centres providing 24/7 service
- Medical thrombolysis/mechanical thrombectomy - costs of medications and thrombectomy instruments

**Implementation of the Guidelines:**

The implementation of the recommendations of a CPG is part of good clinical governance.

To ensure successful implementation of this CPG, we suggest:

- Increasing public awareness of ischaemic stroke in general and educating them on the importance of seeking early medical attention when they developed symptoms suggestive of stroke.
- Continuous medical education and training of healthcare providers on the importance of timely reperfusion and appropriate management of patients with ischaemic stroke. This can be done by roadshows, through the electronic media and in-house training sessions.

**Professor Dr Hj Hamidon Bin Basri**

Chairman

## KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE SCALE	
<b>I</b>	Evidence obtained from at least one properly randomized controlled trial
<b>II – 1</b>	Evidence obtained from well-designed controlled trials without randomization
<b>II – 2</b>	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group
<b>II – 3</b>	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
<b>III</b>	Opinions of respected authorities, based on clinical experience, descriptive studies and case reports; or reports of expert committees

Source: U.S./ CANADIAN PREVENTIVE SERVICES TASK FORCE

GRADES OF RECOMMENDATIONS	
<b>A</b>	At least one meta-analysis, systematic review, or randomized controlled trial (RCT), or evidence rated as good and directly applicable to the target population
<b>B</b>	Evidence from well-conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta-analysis, systematic review or RCT
<b>C</b>	Evidence from expert committee reports, or opinions and/or clinical experiences of respected authorities; indicates the absence of directly applicable clinical studies of good quality

Source: Guidelines for CLINICAL PRACTICE GUIDELINES, Ministry of Health Malaysia 2003

## GLOSSARY

Abbreviations	Descriptions
<b>ACA</b>	Anterior Cerebral Artery
<b>ACAS</b>	Asymptomatic Carotid Atherosclerosis
<b>ACCORD</b>	Action to Control Cardiovascular Risk in Diabetes
<b>ACE</b>	Angiotensin-Converting Enzyme
<b>ACST</b>	Asymptomatic Carotid Surgery Trial
<b>ADC</b>	Ambulance Dispatch Centre
<b>ADL</b>	Activities of Daily Living
<b>AED</b>	Anti-epileptic Drug
<b>AF</b>	Atrial Fibrillation
<b>AIS</b>	Acute Ischaemic Stroke
<b>ANCA</b>	Antineutrophil Cytoplasmic Antibodies
<b>aPTT</b>	activated Partial Thromboplastin Time
<b>ARB</b>	Angiotensin Receptor Blocker
<b>ARR</b>	Absolute Risk Reduction
<b>ARRIVE</b>	Aspirin to Reduce Risk of Initial Vascular Events
<b>ASCEND</b>	A Study of Cardiovascular Events in Diabetes
<b>ASCO</b>	Atherosclerosis, Small-vessel disease, Cardiac source, and Other causes
<b>ASCVD</b>	Atherosclerotic Cardiovascular Disease
<b>ASD</b>	Atrial Septal Defect
<b>ASTER</b>	Contact Aspiration vs Stent Retriever for Successful Revascularization
<b>AVERT</b>	A Very Early Rehabilitation Trial after stroke
<b>BP</b>	Blood Pressure
<b>CADASIL</b>	Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy
<b>CAS</b>	Carotid Angioplasty and Stenting
<b>CCS</b>	Causative Classification Systems
<b>CEA</b>	Carotid Endarterectomy
<b>CHA2DS2-VASc</b>	Congestive heart failure, Hypertension, Age $\geq$ 75 years, Diabetes mellitus, Stroke, or transient ischemic attack (TIA), Vascular disease, Age 65 to 74 years, Gender category
<b>CISS</b>	Chinese Ischaemic Stroke Classification
<b>CLOT</b>	Clots in Legs Or Stockings after Stroke
<b>CNS</b>	Central Nervous System
<b>CPAP</b>	Continuous Positive Airway Pressure
<b>CPG</b>	Clinical Practice Guideline
<b>CPSS</b>	Cincinnati Prehospital Stroke Scale
<b>CRP</b>	C-Reactive Protein
<b>CSP</b>	Cryosupernatant Plasma
<b>CT</b>	Computerized Tomography
<b>CTA</b>	Computerized Tomography Angiography
<b>CTB</b>	CT scans of the Brain
<b>CTP/MRP</b>	CT or MR Perfusion
<b>CV</b>	Cardiovascular
<b>CVD</b>	Cardiovascular Disease

<b>CVT</b>	Cerebral Venous Thrombosis
<b>DALYs</b>	Disability Adjusted Life Years
<b>DASH</b>	Dietary Action to Stop Hypertension
<b>DAWN</b>	Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo
<b>DEFUSE</b>	Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke
<b>DNA</b>	Deoxyribonucleic Acid
<b>DOAC</b>	Direct Oral Anticoagulant
<b>DSA</b>	Digital Subtraction Angiography
<b>DVT</b>	Deep Vein Thrombosis
<b>DWI-FLAIR</b>	MRI Diffusion Weighted Imaging – Fluid Attenuated Inversion Recovery
<b>DWI-MRI</b>	Diffusion-weighted imaging-MRI
<b>ECG</b>	Electrocardiogram
<b>ECHO</b>	Echocardiography
<b>EC-IC</b>	Extracranial – Intracranial
<b>ED</b>	Emergency Department
<b>EF</b>	Ejection Fraction
<b>eGFR</b>	estimated Glomerular Filtration Rate
<b>EMD</b>	Emergency Medical Dispatchers
<b>EMS</b>	Emergency Medical Services
<b>EMTS</b>	Emergency Medicine and Trauma Service
<b>ENT</b>	Ear, Nose, and Throat
<b>ESCT</b>	European Surgical Carotid Trial
<b>ESR</b>	Erythrocyte Sedimentation Rate
<b>ESUS</b>	Embolic Stroke of Undetermined Source
<b>EVT</b>	Endovascular Treatment
<b>FAST</b>	Face, Arm, Speech and Time
<b>FBC</b>	Full Blood Count
<b>FDA</b>	Food and Drug Administration
<b>FFP</b>	Fresh Frozen Plasma
<b>FOOD</b>	Feed or Ordinary Diet
<b>FORTA-A</b>	Fit For The Aged - Highly Beneficial
<b>FORTA-B</b>	Fit For The Aged - Beneficial
<b>FRS</b>	Framingham Risk Score
<b>FRS-CVD</b>	Framingham CVD Risk Score
<b>FSRS</b>	Framingham Stroke Risk Score
<b>GCS</b>	Glasgow Coma Scale
<b>GTN</b>	Glyceryl Trinitrate
<b>GXM</b>	Group and Crossmatch
<b>HAS-BLED</b>	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (age over 65), and Drugs/alcohol
<b>HCTZ</b>	Hydrochlorothiazide
<b>HELLP</b>	Haemolysis, Elevated Liver Enzyme levels, and Low Platelet levels.
<b>HHT</b>	Hereditary Haemorrhagic Telangiectasia
<b>HIV/AIDS</b>	Human Immunodeficiency Virus infection/Acquired Immune Deficiency Syndrome
<b>HOPE-3</b>	Heart Outcomes Prevention Evaluation-3
<b>IAS</b>	Intracranial Artery Stenting
<b>ICA</b>	Internal Carotid Artery
<b>ICP</b>	Intracranial Pressure
<b>ICU</b>	Intensive Care Unit

<b>IHD</b>	Ischaemic Heart Disease
<b>INR</b>	International Normalised Ratio
<b>IPC</b>	Intermittent Pneumatic Compression
<b>IV</b>	Intravenous
<b>IVT</b>	Intravenous Thrombolysis
<b>KPI</b>	Key Performance Indicator
<b>LAPSS</b>	Los Angeles Prehospital Stroke Screen
<b>LDL</b>	Low-Density Lipoprotein
<b>LDL-C</b>	Low-Density Lipoprotein Cholesterol
<b>LFT</b>	Liver Function Test
<b>LMIC</b>	Low and Middle-Income Countries
<b>LMWH</b>	Low Molecular Weight Heparin
<b>LSD</b>	D-lysergic acid diethylamide
<b>LV</b>	Left Ventricular
<b>LVO</b>	Large Vessel Occlusion
<b>MBS</b>	Modified Barium Swallow Examination
<b>MCA</b>	Middle Cerebral Artery
<b>MD</b>	Medical Doctor
<b>MECC</b>	Medical Emergency Coordination Centre
<b>MELAS</b>	Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes
<b>MPDS</b>	Medical Priority Dispatch System
<b>MR</b>	Magnetic Resonance
<b>MRA</b>	Magnetic Resonance Angiography
<b>MRC/BHF</b>	Medical Research Council/British Heart Foundation
<b>MRI</b>	Magnetic Resonance Imaging
<b>mRS</b>	Modified Rankin Scale
<b>mtDNA</b>	Mitochondrial DNA
<b>MTHFR</b>	Methylenetetrahydrofolate Reductase
<b>NASCET</b>	North American Symptomatic Carotid Endarterectomy Trial
<b>NBM</b>	Nil by Mouth
<b>NCCT</b>	Non-Contrast CT
<b>NES</b>	Neuroendovascular surgeon
<b>NG</b>	Nasogastric
<b>NHMS</b>	National Health Morbidity Survey
<b>NIHSS</b>	National Institutes of Health Stroke Scale
<b>NSAID</b>	Non-Steroidal Anti-Inflammatory Drug
<b>NSR</b>	Normal Sinus Rhythm
<b>NVAF</b>	Non-Valvular Atrial Fibrillation
<b>OAC</b>	Oral Anticoagulant
<b>OAC-FORTA</b>	Oral Anticoagulant – Fit for the Aged
<b>OCSP</b>	Oxford Community Stroke Project
<b>PACNS</b>	Primary Angiitis of the Central Nervous System
<b>PAN</b>	Polyarteritis Nodosa
<b>PAR</b>	Population-Adjustable Risk
<b>PCA</b>	Posterior Cerebral Artery
<b>PCC</b>	Prothrombin Complex Concentrate
<b>PCO2</b>	Partial Pressure of Carbon Dioxide
<b>PEG</b>	Percutaneous Endoscopic Gastrostomy
<b>PET</b>	Positron Emission Tomography
<b>PFO</b>	Patent Foramen Ovale
<b>PHC</b>	Pre-Hospital Care

<b>PREDIMED</b>	Prevención con Dieta Mediterránea (Prevention with Mediterranean Diet)
<b>PT</b>	Prothrombin Time
<b>RCT</b>	Randomized Clinical Trials
<b>RNA</b>	Ribonucleic Acid
<b>RP</b>	Renal Profile
<b>rtPA</b>	recombinant tissue Plasminogen Activator
<b>RVCL</b>	Retinal Vasculopathy with Cerebral Leukodystrophy
<b>RVCL</b>	Retinal Vasculopathy with Cerebral Leukodystrophy
<b>SAMMPRIS</b>	Stenting and Aggressive Medical management for prevention of Recurrent Stroke in Intracranial Stenosis
<b>sICH</b>	Symptomatic Intracranial Haemorrhage
<b>SLE</b>	Systemic Lupus Erythematosus
<b>SOCRATES</b>	Acute Stroke or Transient Ischaemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes
<b>SPRINT</b>	Systolic Blood Pressure Intervention Trial
<b>SSS-TOAST</b>	Stop-Stroke Study TOAST
<b>TB</b>	Tuberculosis
<b>TIA</b>	Transient Ischaemic Attack
<b>TLSW</b>	Time Last Seen Well
<b>TMS</b>	Transcranial Magnetic Stimulation
<b>TOAST</b>	Trial of Org 10172 in Acute Stroke Treatment
<b>TOE</b>	Trans-Oesophageal Echocardiogram
<b>TT</b>	Thrombin Time
<b>TTE</b>	Transthoracic Echocardiogram
<b>UFH</b>	Unfractionated Heparin
<b>US</b>	United States
<b>VDRL</b>	Venereal Disease Research Laboratory
<b>VFSE</b>	Video Fluoroscopic Swallowing Examination
<b>VISSIT</b>	Vitesse Intracranial Stent Study for Ischemic Therapy
<b>VKA</b>	Vitamin K Antagonists
<b>VTE</b>	Venous Thromboembolism
<b>WEAVE</b>	Wingspan Stent System Post Market Surveillance



## UPDATES IN MANAGEMENT OF ISCHAEMIC STROKE CPG 2020

1. New recommendations in this clinical practice guideline (CPG) refer to recommendations that are new from the previous Management of Ischaemic Stroke CPG 2012.
2. In this current CPG, new chapters have been added to update the previous CPG. Among the new chapters that have been added include:
  - a. Chapter 7: Emergency Medicine Services.
  - b. Chapter 12: Stroke in the Older Person
  - c. Chapter 16: Stroke Therapies with limited evidence.
  - d. Chapter 17: Quality Assurance
3. Management of Ischaemic Stroke CPG 2020, also emphasises the importance of hyperacute care of stroke, with the previous chapter on acute treatment, being further subdivided into three new chapters as following:
  - a. Chapter 8: Acute General Management
  - b. Chapter 9: Reperfusion of Ischaemic Brain – emphasizing on medical thrombolysis treatment.
  - c. Chapter 10: Endovascular Thrombectomy
4. The following chapters have also been updated:
  - a. Chapter 14: Stroke in Special Circumstances – with a new subsection on the management of patent foramen ovale (PFO) in stroke patients.
  - b. Chapter 15: Management of Stroke in Pregnancy.

## KEY RECOMMENDATIONS OF STROKE CPG 2020

### Chapter 1: Epidemiology, Definition and Classification Of Stroke

1. Stroke is a major cause of mortality and morbidity, and in Malaysia, stroke is the third leading cause of mortality.
2. Ischaemic stroke is the most common stroke, and hypertension was the most common risk factor followed by diabetes mellitus.
3. The new definition of stroke and transient ischaemic attack (TIA) involved either pathological imaging or clinical evidence of ischaemia and can be timed based on the presentation of symptoms.
4. Ischaemic stroke can be classified according to clinical, phenotypic or aetiologic classification.

### Chapter 2: Causes and Pathophysiology

1. Three main causes of ischaemic stroke include atherothrombosis of large vessels, intracranial small vessel disease, and embolism, which may contribute to up to 80% of the cases.
2. Cryptogenic infarction or stroke of undetermined aetiology may be responsible for around 20 to 40% of the cases despite extensive workup and usually would be a diagnosis of exclusion.

### Chapter 3: Diagnosis and Initial Assessment

1. The diagnosis of stroke is made by evaluating and analysing information derived from a good history, physical examination and selected diagnostic tests.
2. The symptoms and signs of stroke depend on the type, location, and the extent of the affected brain tissues.
3. A full neurological examination, including the patient's conscious level and tests of higher mental function is mandatory.
4. Stroke mimics commonly confound the clinical diagnosis of stroke.

### Chapter 4: Prognosis

1. Haemorrhagic stroke has a higher mortality than ischaemic stroke.
2. There is a decline in stroke mortality in both men and women suffering from ischaemic or haemorrhagic stroke due to the introduction of dedicated stroke units and improved control of stroke risk factors.
3. The recurrence rates are 3-4% in the first month and 12% in the first year.
4. Progress of time is an independent covariate which reflects the spontaneous recovery of bodily functions.

## Chapter 5: Prevention of Stroke

1. Stroke is a preventable disease and may be attributed to modifiable and non-modifiable risk factors.
2. Modifiable risk factors are the focus of primary prevention and can be clustered into three main groups i.e.
  - a) Lifestyle risk factors, i.e., smoking, physical inactivity, and unhealthy eating
  - b) Metabolic risk factors, i.e., high systolic BP, high cholesterol, high fasting blood glucose, low eGFR and high BMI.
  - c) Environmental factors, i.e., air pollution and lead exposure.
3. Secondary prevention of stroke involves the prevention of recurrent stroke, and this may involve medical interventions includes antiplatelet therapy, anti-hypertensive treatment, lipid-lowering agents, glycaemic control, prevention of cardio-embolism and re-vascularisation procedures in selected cases.

## Chapter 6: Investigations

1. Investigations carried out for stroke are aimed to confirm the diagnosis, determine the mechanism of stroke, stratify risk and to identify potential treatable vascular lesions.
2. Computed tomography (CT) brain is mandatory and preferred imaging in the emergency setting to differentiate haemorrhage from ischaemia, determine the site(s), cause, and extent of the lesion.
3. Advance imaging may be required in selected cases in the emergency settings, e.g., ruling out stroke mimics, reperfusion therapy in extended hours and determining potential re-vascularisation procedure.
4. Selected blood investigations and imaging will be required in certain patients to determine the aetiology of stroke.

## Chapter 7: Emergency Medicine Services

1. The public should be encouraged to call 999 if they suspect a person is having a stroke.
2. Emergency medical dispatcher and prehospital care providers should be trained to recognize and identify stroke and are able to provide rapid transportation of suspected acute stroke patient to nearest stroke ready hospital.
3. Assessment of patients with suspected acute stroke in emergency department should be prioritized in order to expediate the diagnosis of stroke and to determine the appropriate acute stroke interventions.
4. Audit of acute stroke care and training of emergency department personnel should be conducted to improve quality of care in acute stroke cases.

## Chapter 8: Acute General Management

1. Acute general management in stroke includes supportive care and treatment of acute complications in order to improve the mortality rate and functional disability.
2. General management includes management of blood pressure, glucose control, nutritional support, prevention of infection and DVT, and also to treat potential sequelae, e.g. raised intracranial pressure and seizure.

## Chapter 9: Reperfusion of Ischaemic Brain

1. Intravenous alteplase (0.9 mg/kg; maximum dose of 90mg) is recommended for the definite onset stroke for up to 4.5 hours from the onset. The treatment window can also be extended via CT perfusion with clinical evidence of penumbra-core mismatch up to 9 hours from the time of the last known to be well/midpoint of sleep or via MRI (DWI-FLAIR mismatch) done to identify possible stroke onset within the last 4.5 hours.
2. Intravenous tenecteplase (0.25 mg/kg; maximum dose of 25mg) is a possible treatment agent in acute stroke that presented within 4.5 hours with evidence of large vessel occlusion on imaging.

## Chapter 10: Endovascular Thrombectomy

1. Hyperacute endovascular thrombectomy is recommended for the definite onset of stroke with evidence of large vessel occlusion which is within 6 hours from the onset. The treatment window can be extended via CT/MR perfusion (penumbra-core mismatch) or MRI (clinical-imaging mismatch) with current evidence showed significant benefit up to 24 hours from the onset/time of last known to be well. However, treatment pathway should not be delayed, as the treatment outcome can be influenced by the imaging-to-recanalization time.
2. Drip & Ship (IVT prior to EVT) as per Chapter 9 is recommended for eligible patients.

## Chapter 11: Stroke Unit

1. The use of comprehensive specialized stroke care centres (stroke units) that incorporates rehabilitation services are able to reduce mortality and disabilities among stroke patients.

## Chapter 12: Stroke in The Older Person

1. All older persons with acute stroke should be assessed for fitness/frailty level using a validated instrument to facilitate a tailored and individualised treatment plan.
2. An older person can benefit from acute treatment for stroke including stroke thrombolysis and endovascular thrombectomy, providing the inclusion and exclusion criteria of the treatment are met.
3. An older person can benefit from and should receive treatment for stroke prevention with management of polypharmacy issues, individualised medication dosages and treatment targets as is tolerated, for stroke risk factors.
4. All older persons with stroke should be:
  - screened for delirium using a validated tool, and receive a tailored multicomponent intervention and management plan for delirium, when admitted with an acute stroke
  - offered falls and fragility fracture risk assessment and management during the rehabilitation period
  - assessed by a multidisciplinary team with an appropriate discharge plan
  - able to receive end-of-life care and recommendations when the prognosis is poor either from the stroke itself, complications, or other serious comorbid conditions

### Chapter 13: Stroke and Cardioembolism

1. Cardioemboli is a common cause of stroke. Stroke patient must have cardiac assessment to look for the presence of cardioemboli.
2. It causes more severe stroke and carry a higher morbidity and mortality rates.
3. Effective treatment to prevent cardioembolism is available and should be offered to patients at risk.
4. NOAC is preferred over VKA for NVAF.
5. Patient on VKA should have regular INR monitoring and aimed for time in therapeutic range (TTR) > 70%.
6. Antiplatelet is not recommended in NVAF for the prevention of stroke.

### Chapter 14: Stroke in Special Circumstances

1. Young onset stroke requires more comprehensive investigation to determine the stroke aetiology.
2. Diagnosis of cryptogenic stroke and embolic stroke of undetermined source (ESUS) is made after standard evaluation to rule out possible cause of stroke.
3. Further specialized investigations needed in the cryptogenic or ESUS stroke for example prolonged Holter monitoring to look for atrial fibrillation or to look for evidence of patent foramen ovale (PFO).
4. Cerebral venous thrombosis is one of the major cause of venous infarct and would require investigations to determine the cause of thrombosis. Treatment mainly directed at anticoagulation with adjunctive therapy to prevent associated complications.

### Chapter 15: Management of Stroke in Pregnancy

1. MRI of the brain (without gadolinium contrast) is the radiological modality of choice for investigating strokes in pregnancy.
2. Aspirin is the only choice of antiplatelet for pregnant patients with a well-defined low risk profile.

### Chapter 16: Stroke Therapies with Limited Evidence

1. There are a variety of stroke medications and treatment modalities, but the evidence is very limited.

## RECOMMENDATIONS SUMMARY OF STROKE CPG 2020

### Chapter 5: Primary Prevention of Stroke

**Table 5.2: Primary Prevention and Management of Risk Factors**

Factors	Recommendations	Level of Evidence	Grade
Hypertension	Self-BP monitoring is recommended for all hypertensive patients. <i>New recommendation</i>	I	A
	Risk stratification for hypertension based on CVD risk, target organ damage and complications are recommended for optimizing therapy. <i>New recommendation</i>		
	Lifestyle changes if systolic BP is between 130-139mmHg and/or diastolic BP is between 80-89mmHg, with three to six-monthly review. <i>New recommendation</i>	I	A
	Treat medically if systolic BP is >140mmHg and/or diastolic BP is >90mmHg.	I	A
	Hypertension should be treated in the very elderly (age >80years) to reduce the risk of stroke. <i>New recommendation</i>	I	B
Diabetes Mellitus	Strict blood pressure control is important in patients with diabetes.	I	A
	More intensive HbA1c glycaemic control targets (<6.5%) may be required for optimal ischemic stroke prevention.	I	A
	Target BP for diabetics is systolic BP <130mmHg and diastolic BP <80mmHg, preferably <120mmHg if tolerated. <i>New recommendation</i>	I	A
Hyperlipidaemia	Treatment of dyslipidaemia / LDL-C is stratified based on risk.	I	B
	High-risk group: lowering LDL to <1.8 mmol/l is recommended. <i>New recommendation</i>		
	Intermediate and low risk: keep LDL <3.4mmol/l.		
	Low-risk group may benefit from cholesterol-lowering therapy with a statin. <i>New recommendation</i>		
No risk – keep LDL <4.2 mmol/L.			
Smoking	Cessation of smoking.	III	C
Aspirin therapy	Aspirin therapy is not recommended for primary prevention of stroke in the elderly, diabetics, or other high-risk groups. <i>New recommendation</i>	I	A
Post-menopausal Hormone Replacement Therapy	Oestrogen-based HRT is not recommended for primary stroke prevention.	II	B
Alcohol	Avoid heavy alcohol consumption or limit to < 1 drink per day. <i>New recommendation</i>	II-2	B
Physical Activity	Physical activity (occupational and leisure time) is recommended for all groups of patients. <i>New recommendation</i>	I	A
	Physical activity > 30mins/day or >150mins/week as part of a healthy lifestyle is recommended <i>New recommendation</i>	I	A

Diet	DASH diet is recommended to reduce BP. <i>New recommendation</i>	I	A
	Mediterranean diet (low glycaemic content with high intake of vegetables) supplemented with nuts and olive oil is beneficial. <i>New recommendation</i>	II	B
	Diet high in fruits and leafy green vegetables is beneficial. <i>New recommendation</i>	II	B

**Table 5.3: Secondary Prevention of Stroke**

Factors/Treatment	Recommendations	Level of Evidence	Grade
Antiplatelet (Single agent)			
Aspirin	The recommended dose of aspirin is 75mg to 325mg daily.	I	A
<i>Alternatives:</i>			
Clopidogrel	The recommended dose is 75mg daily.	I	A
Ticlopidine	The recommended dose is 250mg twice a day.	I	A
Triflusal	The recommended dose is 600mg daily	I	A
Cilostazol	The recommended dose is 100mg twice a day.	I	A
Double therapy	Combination therapy of Clopidogrel and Aspirin is recommended in patient with minor ischaemic stroke and high-risk TIA for 21 days. <i>New recommendation</i>	I	A
Antihypertensive treatment	ACE-inhibitor based therapy should be used to reduce recurrent stroke in normotensive and hypertensive patients.	I	A
	ARB-based therapy may benefit selected high risk populations.	II-1	B
Lipid lowering	Lipid reduction should be considered in all patients with previous ischaemic strokes.	I	A
	LDL target < 1.8 is recommended in all patients with previous ischaemic stroke. <i>New recommendation</i>	I	A
Diabetic control	All diabetic patients with a previous stroke should have good glycaemic control.	III	C
Cigarette smoking	All smokers should stop smoking.	III	C

**Table 5.4: Cardiac Conditions Predisposing to Ischaemic stroke**

Major Risk Conditions	Additional Risk Factors	Recommendations	Level of Evidence	Grade
Atrial Fibrillation	Risk factors to be assessed by CHA <sub>2</sub> DS <sub>2</sub> -VASc Score.	OAC to prevent cardioembolic stroke is recommended for all NVAf male patients with CHA <sub>2</sub> DS <sub>2</sub> -VASc score of 2 or more and female patients with a CHA <sub>2</sub> DS <sub>2</sub> -VASc score of 3 or more. <i>New recommendation</i>	I	A
		<b>Direct Oral Anticoagulant (DOAC) vs. Warfarin</b>		
		Dabigatran is superior (150mg bid) to and as effective (110mg bid) as compared to Warfarin, in preventing stroke and systemic embolism. Bleeding rates are similar with Warfarin at 150mg bid but with a lower bleeding rates at 110mg bid.	I	A
		Rivaroxaban was compared with adjusted-dose warfarin and was found to be non-inferior with regard to the primary composite end point of stroke or	I	A

		non-central nervous systemic embolism. <i>New recommendation</i>		
		Apixaban was compared with adjusted-dose warfarin and was found to be superior to warfarin in preventing stroke or systemic embolism. Apixaban also caused less major bleeding events as compared with warfarin and resulted in lower overall mortality. <i>New recommendation</i>	I	A
		Edoxaban* as compared to warfarin was found to be noninferior with regard to the primary efficacy end point and caused less bleeding. <i>New recommendation</i> *Currently not available in Malaysia.	I	A
Prosthetic Heart Valves (Mechanical)	<i>Moderate risk:</i> Bi-leaflet or tilting disk aortic valves in NSR	Lifelong Warfarin	II-2	B
	<i>High risk:</i> Bileaflet or tilting disk aortic valves in AF; Bileaflet or tilting disk mitral valve in AF or NSR.	Lifelong Warfarin (target INR 3.0; range 2.5-3.5)	II-3	B
	Caged-ball and caged-disk designs; Documented stroke/TIA despite adequate therapy with Warfarin.	Lifelong Warfarin (target INR 3.0; range 2.5-3.5) plus Aspirin 75-150mg daily	II-1	B
Bioprosthetic heart valves	<i>High risk:</i> AF; left atrial thrombus at surgery; previous stroke/TIA or systemic embolism.	If major risk factors are present, consider Warfarin for 3-12 months or longer.	III	C
		For all other patients, give Warfarin for 3 months post-op, then Aspirin 75-150mg daily.	III	C
Mitral Stenosis	<i>High risk:</i> AF; previous stroke/TIA; left atrial thrombus; left atrial diameter > 55mm on Echo.	If major risk factors are present, consider lifelong Warfarin.	II-3	B
		For all other patients start Aspirin 75-150mg daily.	II-2	B
MI and LV dysfunction	<i>High risk:</i> Acute/recent MI (<6 months); extensive infarct with anterior wall involvement; previous stroke/TIA. <i>Very high risk:</i> Severe LV dysfunction (EF < 28%); LV aneurysm; spontaneous echo contrast; LV thrombus; dilated non-ischaemic cardiomyopathies.	If risk factors are present without LV thrombus: consider Warfarin for 3-6 months followed by Aspirin 75-150mg daily.	III	C
		If LV thrombus is present, consider Warfarin for 6-12 months	III	C
		For dilated cardiomyopathies including peripartum, consider lifelong Warfarin	III	C
<i>Recommended Warfarin dose INR target 2.5 [range 2.0 to 3.0] unless stated otherwise</i>				



**Table 5.5: Anticoagulation for the Patient with Acute Cardioembolic Stroke**

Treatment	Recommendations	Level of Evidence	Grade
Warfarin	Adjusted-dose warfarin may be commenced within 2-4 days after the patient is both neurologically and medically stable.	II-2	C
Heparin (unfractionated)	Adjusted-dose unfractionated heparin may be started concurrently for patients at a very high risk of embolism.	III	C
Anticoagulant	Anticoagulant may be delayed for 1-2 weeks if there has been substantial haemorrhage.	III	C
	Urgent routine anticoagulation with the goal of improving neurological outcomes or preventing early recurrent stroke is not recommended.	I	A
	Urgent anticoagulation is not recommended for treatment of patients with moderate-to-large cerebral infarcts because of the high risk of intracranial bleeding.	I	A

**Table 5.6: Revascularisation Procedures**

Treatment	Recommendations	Level of Evidence	Grade
Carotid Endarterectomy (CEA)	<i>Primary Prevention</i> May be considered in patients with a high grade asymptomatic carotid stenosis (70-99%) when performed by surgeons with less than 3% morbidity/mortality rate.	I	A
	<i>Secondary Prevention</i> Indicated for most patients with a stenosis of 70-99% after a recent ischaemic event in centres with complication rates of less than 6%.	I	A
	Earlier intervention (within 2 weeks) is more beneficial.	II-1	B
	May be indicated for patients with a stenosis of 50-69% after a recent ischaemic event in centres with complication rates of less than 6%.	III	C
	Not recommended for patients with a stenosis of less than 50%.	I	A
	Patients should remain on antiplatelet therapy before and after surgery.	II-2	B
	Carotid angioplasty and stenting (CAS)	CAS represents a feasible alternative to carotid endarterectomy for secondary stroke prevention when surgery is undesirable, technically difficult, or inaccessible.	II-2
Distal protective devices should be used during the procedure.		I	A
Use of dual antiplatelet for at least 4 weeks after CAS.		I	A
The long-term safety (for 4 years) for CAS is as good as CEA.		I	A
Complex configuration of the aortic arch and internal carotid artery tortuosity increase the risk of cerebral ischemia in CAS.		II-2	B
Intracranial angioplasty & stenting (IAS)	Role of IAS in intra-cranial stenoses, asymptomatic stenoses and acute stroke is unclear and may not be recommended.	II-2	C

## Chapter 7: Emergency Medicine Services

**Table 7.1: Emergency Medicine Services**

Management	Recommendations	Level of Evidence	Grade
<b><i>Pre-Hospital Management</i></b>			
Public education	<p>Educational programmes</p> <ul style="list-style-type: none"> <li>- should be designed to create awareness and knowledge of stroke warning signs.</li> <li>- should include the timely recognition and need to seek emergency care by calling 999 promptly.</li> </ul> <p><i>New recommendation</i></p>	<p>II-1</p> <p>II-1</p>	<p>A</p> <p>A</p>
Emergency dispatch system	<p>ADC</p> <ul style="list-style-type: none"> <li>- should be familiar with common descriptors used by the public for stroke. Whenever the descriptors are used, EMD are trained to use the stroke protocols to identify suspected stroke patients</li> <li>- should have a protocol or tools that allow Emergency Medical Dispatchers (EMD) to identify suspected stroke patients. e.g. MDPS Stroke Diagnostic Tool, FAST stroke assessment.</li> <li>- should have a system to priorities suspected stroke calls to facilitate early arrival of patients to the ED.</li> </ul> <p><i>New recommendation</i></p>	<p>II-1</p> <p>II-1</p> <p>II-1</p>	<p>A</p> <p>A</p> <p>A</p>
Initial on-scene management	<p>PHC responders</p> <ul style="list-style-type: none"> <li>- should rapidly evaluate airway, breathing and circulation to identify life threatening situation, and manage them accordingly.</li> <li>- should use a validated and standardized stroke identification assessment tool such as FAST or BE-FAST stroke assessment</li> <li>- should be trained to identify hypoglycaemia as a stroke-mimic and apply appropriate management protocols</li> <li>- should ascertain the time of onset of stroke symptoms from the patient or witness(es).</li> </ul> <p>PHC Service Providers should ensure its responders are made aware of the nearest hospital capable of providing thrombolysis and hospital capable of performing endovascular stroke treatment, within their service area. A written protocol that ensures the ambulance diversion of the patient to such hospitals should be made available for use.</p> <p>All stroke patients from PHC with positive signs of stroke within the 4.5-hour time window for medical thrombolytic therapy should be transported immediately to an acute stroke ready hospital.</p> <p>Titrated dose of oxygen should be delivered to stroke patients with an oxygen saturation level of below 95%.</p> <p><i>New recommendation</i></p>	<p>II-1</p> <p>II-1</p> <p>I</p> <p>I</p> <p>I</p> <p>II-1</p> <p>II-3</p>	<p>A</p> <p>A</p> <p>A</p> <p>A</p> <p>A</p> <p>A</p> <p>B</p>
Pre-arrival communication	<p>PHC Responders should be trained to provide pre-arrival notification of stroke patients to receiving hospitals.</p> <p>MECC and associated stroke ready hospital(s) are recommended to have local regional stroke referral system/ network and agreement with the ED to facilitate the transport decision from PHC to ensure the treatment window of 4.5 hours is achieved.</p> <p><i>New recommendation</i></p>	<p>II-1</p> <p>I</p>	<p>A</p> <p>A</p>

<b>Emergency Department Management</b>			
ED Evaluation	All patients presenting to an ED with suspected acute stroke must have immediate clinical evaluation and investigations to establish the diagnosis and to determine the eligibility for intravenous thrombolytic therapy and/or EVT	I	A
	The use of clinical screening tools such as FAST or BE-FAST to identify stroke by ED staff can be beneficial  <i>New recommendation</i>	II-2	B
Initial Assessment in ED	ED staff should rapidly evaluate airway, breathing and circulation in patients with suspected acute stroke and manage accordingly	I	A
	All patients with suspected acute stroke should have their blood glucose level checked upon arrival at the ED	II-1	A
	A standardized stroke severity scale should be used such as the National Institutes of Health Stroke Scale (NIHSS) to assess stroke severity in the ED  <i>New recommendation</i>	II-1	A
Imaging	All patients with suspected stroke who are candidates for intravenous thrombolysis and/ or EVT should undergo at least CT scan immediately. All other suspected stroke patients should have an urgent CT brain.	II-1	A
	Interpretation of acute stroke imaging for thrombolysis decisions should only be made by healthcare professionals who have received appropriate training.  <i>New recommendation</i>	III	C
Other Considerations	Patients with acute stroke should only receive supplemental oxygen only if their oxygen saturation is below 95%.	II-3	B
	Hypotension and hypertension in patients with acute stroke should be identified and managed accordingly.	III	C
	Patients with acute stroke should have their swallowing ability screened as early as possible after arrival at the hospital and before being given any oral food, fluid, or medication  <i>New recommendation</i>	II-2	B
Quality Improvement	Joint multidisciplinary audit to review and monitor stroke care quality benchmarks, indicators, evidence-based practices, and outcomes should be performed periodically.	II-1	A
	ED personnel should undergo a standardized training in acute stroke management.  <i>New recommendation</i>	III	C

## Chapter 8: Acute General Management

**Table 8.1: Acute General Management**

Factors	Recommendations	Level of Evidence	Grade
Oxygen and Airway support	Patients with acute stroke should only receive supplemental oxygen if their oxygen saturation is below 95% and be titrated to achieve above 95%. <i>New recommendation</i>	II-3	B
Observation	Regular observation is mandatory to recognise impaired pulmonary function (pulse oxymeter), circulatory function (pulse rate, blood pressure), NIHSS score, head chart, GCS, and complications from mass effect.	III	C
Mobilisation	Mobilise early to prevent complications.	II-3	C
	High-dose, very early mobilisation within 24 hours of stroke onset should not be performed because it can reduce the odds of a favourable outcome at 3 months. <i>New recommendation</i>	I	-
Blood Pressure	Lowering BP initially by 15% is probably safe. Blood pressure reduction should not be drastic. <i>New recommendation</i>	III	C
	Do not treat hypertension if systolic BP is <220mmHg or diastolic BP is <120mmHg. Mild hypertension is desirable at 160-180/90-100 mmHg.	III	C
	<i>Recommended therapy:</i> Labetalol 10-20mg boluses at 10-minute intervals up to 150-300mg or 1mg/ml infusion, rate of infusion for Labetalol as 1-3mg/min or Captopril 6.25-12.5mg orally.	III	C
Blood Glucose	After an acute stroke, treat hyperglycaemia to keep the blood glucose levels between 6.0-10.0 mmol/L and ensure that hypoglycaemia is avoided. <i>New recommendation</i>	III	C
	Avoid very tight target of glucose control (4.0-7.5 mmol/L) in the first hours of acute ischaemic stroke. <i>New recommendation</i>	I	A
Nutrition	Perform a water swallowing test.	III	C
	Insert a nasogastric tube if the patient fails the swallowing test.	III	C
	PEG is superior to nasogastric feeding only if prolonged enteral feeding is required	II-1	B
	Enteral feeding should be started within 7 days of admission (oral or tube feeding). <i>New recommendation</i>	I	A
Infection	Search for the presence of infection if fever appears and treat it early with appropriate antibiotics.	III	C
Fever	Use anti-pyretics to control elevated temperatures.	II-1	B
Continence	The application of indwelling catheter should be used cautiously and should be removed as soon as possible. <i>New recommendation</i>	I	A
	All stroke patients should be assessed for urinary retention or incontinence, faecal incontinence, and constipation. <i>New recommendation</i>	III	C
Raised Intracranial Pressure	Hyperventilate to lower the intracranial pressure.	II-2	B
	Mannitol (0.25 to 0.5g/kg) intravenously administered over 20 minutes lowers the intracranial pressure and can be given every 6 hours.	II-2	B
	If hydrocephalus is present, drainage of cerebrospinal fluid via an intraventricular catheter can rapidly lower intracranial pressure.	III	C
	Hemicraniectomy and surgical decompressive therapy within 48	I	A

	hours after symptom onset is recommended to control intracranial pressure and prevent herniation among those patients with very large infarcts of the cerebral hemisphere.		
	Patients >60 years of age may be considered for decompressive craniectomy in selected cases. <i>New recommendation</i>	I	A
	Ventriculostomy and sub-occipital craniectomy are effective in relieving hydrocephalus and brain stem compression caused by large cerebellar infarctions.	II-2	B
Deep Vein Thrombosis Prophylaxis	For immobile stroke patients without contraindications, intermittent pneumatic compression (IPC) in addition to routine care (aspirin and hydration) is recommended over routine care alone to reduce the risk of deep vein thrombosis (DVT). <i>New recommendation</i>	I	A
	The benefit of prophylactic-dose subcutaneous heparin (unfractionated heparin [UFH] or LMWH) in immobile patients with AIS is not well established. <i>New recommendation</i>	III	C
	In ischaemic stroke, elastic compression stockings should not be used. <i>New recommendation</i>	I	A
Seizure	New-onset seizures in admitted patients with acute stroke should be treated using appropriate short-acting medications if they are not self-limiting. <i>New recommendation</i>	III	C
	A single, self-limiting seizure occurring at the onset, or within 24 hours after an ischemic stroke (considered an “immediate” post-stroke seizure) should not be treated with long-term anticonvulsant medications. The use of prophylactic anti-seizure medications is not recommended. <i>New recommendation</i>	III	C
	Patients that have an immediate post-stroke seizure should be monitored for recurrent seizure activity and should be treated as per treatment recommendations for seizures in as in other neurological conditions and treatment should be individualised. <i>New recommendation</i>	III	C

## Chapter 9: Reperfusion of Ischaemic Brain

**Table 9.1: Treatment of Acute Ischaemic Stroke with Intravenous Thrombolysis**

Treatment	Recommendations	Level of Evidence	Grade
Alteplase	Onset within 4.5 hours Dose: 0.9 mg/kg, max 90 mg, 10% bolus and remaining dose given as infusion over 1 hour.	I	A
	Onset >4.5 up to 9 hours if known onset or wake-up stroke guided by CT perfusion, with the presence of a significant penumbra core mismatch. <i>New recommendation</i>	II	B
	Uncertain onset and wake up stroke guided by MRI (DWI-FLAIR mismatch) <i>New recommendation</i>	II	B
Tenecteplase	Onset within 4.5 hours and eligible for thrombolytic treatment can be considered for intravenous Tenecteplase prior to EVT. Dose: 0.25mg/kg; maximum dose of 25mg <i>New recommendation</i>	II	B

## Chapter 10: Endovascular Thrombectomy

**Table 10.1: Acute Endovascular Thrombectomy Treatment**

Treatment	Recommendations	Level of Evidence	Grade
Acute Endovascular Thrombectomy (EVT)	EVT is indicated for AIS with large vessel occlusion; proximal middle cerebral artery segment 1 (M1)/proximal M2 occlusion/internal carotid artery (ICA), and presenting within 6 hours from onset. <i>New recommendation</i>	I	A
	EVT is indicated in selected patients who arrive after 6 hours and up to 24 hours of stroke onset with evidence of large vessel occlusion. <i>New recommendation</i>	I	A
EVT bridging with Alteplase (Drip & Ship)	AIS patients who arrive within 4.5 hours of stroke onset and are eligible for rtPA treatment should be considered for thrombolytic treatment prior to EVT. <i>New recommendation</i>	I	A
	For patients undergoing “Drip & Ship” (EVT following administration of IVT), there should be no delay in proceeding to EVT to determine the clinical effectiveness of Alteplase. <i>New recommendation</i>	I	A
EVT bridging with Tenecteplase	AIS patients who arrive within 4.5 hours of stroke onset and are eligible for thrombolytic treatment can be considered for intravenous Tenecteplase prior to EVT. <i>New recommendation</i>	II	B

## Chapter 11: Stroke Unit

**Table 11.1: Stroke Unit**

Factor	Recommendations	Level of Evidence	Grade
Stroke Unit	Every hospital should set up a stroke unit as it can significantly reduce deaths, dependency, institutionalisation, and length of hospital stay.	I	A
	The use of comprehensive specialized stroke care (stroke units) that incorporates rehabilitation is recommended.	I	A
	A stroke unit should be managed by a multidisciplinary stroke team.	I	A

## Chapter 12: Stroke in the Older Person

**Table 12.1: Stroke in the Older Person**

Management	Recommendations	Level of Evidence	Grade
Screening for Frailty	All older adults should be screened for frailty using a validated instrument suitable for the specific setting or context with a tailored management plan thereafter. <i>New recommendation</i>	III	C
Stroke Thrombolysis	An older person should receive and can benefit from intravenous thrombolysis. <i>New recommendation</i>	I	A
Endovascular thrombectomy	An older person can benefit from endovascular thrombectomy for anterior circulatory large vessel occlusion. <i>New recommendation</i>	I	A

Management of glucose level in the acute phase of stroke	After an acute stroke, treat hyperglycaemia to keep the blood glucose levels between 6.0-10.0 mmol/L (110-180 mg/dL) and ensure that hypoglycaemia is avoided. <i>New recommendation</i>	III	C
	Avoid very tight targets of glucose control (4.0-7.5 mmol/L) in the first hours of acute ischaemic stroke. <i>New recommendation</i>	I	A
Hypertension	Older persons who have one or more of the following: frailty, multiple comorbidities and/or cognitive impairment, require an individualised approach for blood pressure management. <i>New recommendation</i>	I	A
Diabetes Mellitus	Targets of blood glucose control in older persons with diabetes should be individualised taking into account their functional status, medical comorbidities, and likelihood of developing adverse events. <i>New recommendation</i>	III	C
Dyslipidaemia	Statins are recommended for stroke prevention in older persons with a less direct evidence of benefit for stroke prevention and primary prevention of vascular events in those aged over 75 years. <i>New recommendation</i>	I	A
Atrial Fibrillation	Older persons with atrial fibrillation can benefit from oral anticoagulant for stroke prevention with an individualised treatment plan taking into account medical co-morbidities, functional status, and social factors. <i>New recommendation</i>	I	A
Medication management in the older person with stroke	A comprehensive care plan for a frail older person should include management of polypharmacy. <i>New recommendation</i>	III	C
Delirium post-acute stroke	All post-stroke patients should be screened for delirium throughout hospitalization. <i>New recommendation</i>	II-2	B
	Screening for post-stroke delirium using the 4AT tool is recommended. <i>New recommendation</i>	II-2	B
	A multi-component intervention for post-stroke delirium prevention and management should be implemented to decrease the incidence and severity of delirium as well as to reduce the length of stay. <i>New recommendation</i>	II-2	B
Falls prevention post-stroke	All people with stroke should be offered falls and fragility fracture risk assessment and management during their rehabilitation period. <i>New recommendation</i>	III	C
Discharge planning and early supported discharge post stroke	Discharge planning for older persons with stroke should occur at the appropriate time following a multidisciplinary recommendation in where any decisions about care is made in the person's best interests. <i>New recommendation</i>	II-3	B
	Hospital in-patients with stroke who have mild to moderate disability should be offered early supported discharge, with treatment at home beginning within 24 hours of discharge. <i>New recommendation</i>	II-3	B
	An early stroke supported discharge team should be organised as a single multi-disciplinary team comprising of: <ul style="list-style-type: none"> <li>● Doctors</li> <li>● Nurses</li> <li>● Physiotherapists</li> </ul>	II-1	A

	<ul style="list-style-type: none"> <li>Occupational therapists</li> <li>Speech and language therapists</li> <li>Clinical psychologists</li> <li>Social workers</li> </ul> <p><i>New recommendation</i></p>		
	Older persons with stroke and their family members/carers should be involved in decisions about the discharge and are prepared to be involved in their care. <i>New recommendation</i>	III	C
	Discharge planning should include providing necessary equipment and support services including identification of follow-up treatment. <i>New recommendation</i>	III	C
	Evaluation of home environment by an occupational therapist should be carried out, by doing a home visit or conducting an interview about the home environment, including taking photographs or videos with the consent of the family members/carers. <i>New recommendation</i>	III	C
End-of-life care	The multidisciplinary stroke team should be trained in principles and practice of end-of-life care. <i>New recommendation</i>	II-3	C
	Burdensome treatment should be avoided at the end-of-life care and this should include decisions to continue oral feeding and hydration despite potential risk of aspiration. <i>New recommendation</i>	II-3	C
	Advanced care planning should be provided for individuals who are expected to have limited life expectancy. <i>New recommendation</i>	II-2	B
	Decisions to withhold and withdraw treatment should take into account prior expressed wishes of the individual with stroke which often needs to be established from the next-of-kin and close relatives. <i>New recommendation</i>	III	C
	Stroke teams should be prepared to facilitate the transfer of care of the individual dying of stroke to their own homes supported by local hospices and palliative care services if available. <i>New recommendation</i>	III	C

## Chapter 13: Stroke and Cardioembolism

**Table 13.1: Prevention of Stroke in Atrial Fibrillation Patients**

Treatment	Recommendations	Level of Evidence	Grade
<i>Stroke Prevention</i>			
Antiplatelet monotherapy	Antiplatelet monotherapy is not indicated for stroke prevention in patients with non-valvular atrial fibrillation (NVAF).	I	A
Oral anticoagulant (OAC)	OAC has been proven to be superior to no treatment or Aspirin in patients with NVAF.	I	A
	OAC is recommended to prevent cardioembolic stroke for all NVAF male patients with CHA <sub>2</sub> DS <sub>2</sub> -VASc score of 2 or more and female patients with a CHA <sub>2</sub> DS <sub>2</sub> -VASc score of 3 or more. <i>New recommendation</i>	I	A



	The OAC of choice for valvular AF (moderate-to-severe mitral stenosis) and mechanical heart valves patients is Vitamin K Antagonist (Warfarin).	I	A
<i>Secondary Stroke Prevention</i>			
Parenteral anticoagulant (heparin or low molecular weight heparin)	After a cardioembolic stroke, parenteral anticoagulant therapy (heparin or low molecular weight heparin) is not recommended to prevent secondary stroke.	I	A
DOACs	For secondary stroke prevention in an AF patient, the initiation of DOACs is recommended after excluding haemorrhagic transformation <i>New recommendation</i>	II	B
	DOACs are preferred over VKA and Aspirin in AF patients with a previous stroke. <i>New recommendation</i>	I	A
Aspirin	Aspirin could be considered before the initiation of OAC after an AF patient develops an ischaemic stroke.	III	C
Combination therapy of OAC and antiplatelet	The risk of bleeding is high after initiation of the combination therapy of OAC and antiplatelet for secondary stroke prevention. <i>New recommendation</i>	III	C
OAC	After an intracranial haemorrhage, OAC could be re-initiated after 4-8 weeks in a NVAF patient with high CHA <sub>2</sub> DS <sub>2</sub> -VASc score if the underlying cause and risk factors of bleeding have been treated. <i>New recommendation</i>	II	B

## Chapter 14: Stroke in Special Circumstances

**Table 14.2: Investigation of Young Stroke**

Investigation	Recommendations	Level of Evidence	Grade
Homocysteinaemia	Routine screening for hyperhomocysteinaemia among patients with a recent ischaemic stroke or TIA is not indicated.	III	C
Anti-phospholipid antibodies	Routine testing for anti-phospholipid antibodies is not recommended for patients with ischaemic stroke or TIA who have no other manifestations of the anti-phospholipid antibody syndrome and who have an alternative explanation for their ischaemic event, such as atherosclerosis, carotid stenosis, or AF.	III	C
Sleep study	A sleep study might be considered for patients with an ischaemic stroke or TIA.	II-2	B
Coagulation screening	The usefulness of screening for thrombophilic states in patients with ischaemic stroke or TIA is unknown.	II-2	C

**Table 14.3: Treatment of Stroke in Certain Circumstances**

Treatment	Recommendations	Level of Evidence	Grade
Aspirin	If the cause is not identified, Aspirin is usually given while additional tests are obtained to guide the choice between long-term antiplatelet or anticoagulant therapy.	III	C
	Antiplatelet therapy is recommended in patients who are found to have abnormal findings on coagulation testing after an initial ischaemic stroke or TIA if anticoagulant therapy is not used.	I	A
	For patients with ischaemic stroke or TIA who have an anti-phospholipid antibody but who do not fulfil the criteria for anti-phospholipid antibody syndrome, antiplatelet therapy is	I	B

	recommended		
	For patients with ischaemic stroke or TIA who meet the criteria for the anti-phospholipid antibody syndrome but in whom anticoagulation is not yet started, antiplatelet therapy is indicated	I	A
DOAC	<b>ESUS:</b> There is no role of anticoagulant in ESUS. <i>New recommendation</i>	I	A
	For patients with an ischaemic stroke or TIA and both a PFO and a venous source of embolism, anticoagulation is indicated, depending on the characteristics of the stroke. <i>New recommendation</i>	I	A
	Anticoagulation might be considered in patients who are found to have abnormal findings on coagulation testing after an initial ischaemic stroke or TIA, depending on the abnormality and the clinical circumstances. <i>New recommendation</i>	II-2	C
	For patients with ischaemic stroke or TIA who meet the criteria for APS, anticoagulant therapy might be considered depending on the perception of risk for recurrent thrombotic events and bleeding. <i>New recommendation</i>	II-2	C
Device	<b>PFO closure device therapy</b> PFO closure devices have moderate benefit in young and middle-aged patients with cryptogenic ischaemic stroke. PFO closure devices combined with antiplatelet therapy is also recommended. <i>New recommendation</i>	I	A
	<b>Continuous positive airway pressure (CPAP) machine</b> CPAP therapy might be considered for patients with ischaemic stroke or TIA and sleep apnoea given the emerging evidence in support of improved outcomes. <i>New recommendation</i>	II-2	B
Blood transfusion	For patients with sickle cell disease and prior ischaemic stroke or TIA, long-term blood transfusions to reduce the level of haemoglobin S to <30% of the total haemoglobin composition are recommended. <i>New recommendation</i>	I	B
Supplements	<b>Supplementation with folate, vitamin B6 and vitamin B12</b> In adults with a recent ischaemic stroke or TIA who are known to have mild to moderate hyperhomocysteinaemia, supplementation with folate, vitamin B6 and vitamin B12 safely reduces the homocysteine levels but has not been shown to prevent stroke. <i>New recommendation</i>	III	B

**Table 14.4: Investigation of Cerebral Venous Thrombosis**

Investigation	Recommendations	Level of Evidence	Grade
CTV/ MRV	Either CT or MR venography can be used as a reliable alternative to DSA for the diagnosis of CVT in patients with suspected CVT	II-3	B
Digital Subtraction Angiography (DSA)	DSA as a diagnostic modality is indicated in cases of suspected CVT when the diagnosis of CVT is doubtful with non-invasive imaging alone.	II-1	C
D-Dimer	Measurement of the D-dimer level before neuroimaging is recommended in patients with suspected CVT, except in those with isolated headache or prolonged duration of symptoms (high false negative rates).	II-2	B
Thrombophilia screening	Thrombophilia screening may be performed in patients with high pre-test probability of having severe thrombophilia (i.e. a personal and/or family history of venous thrombosis, a young age at CVT and/or CVT without a transient or a permanent risk factor) to	II-3	B

	prevent recurrent venous thrombotic events. However, routine thrombophilia screening is not recommended to reduce deaths, improve functional outcome, or prevent recurrent venous thrombosis in patients with CVT.		
Occult malignancy screening	Routine screening for occult malignancy in patients with CVT is not recommended to improve outcomes	II-3	B

**Table 14.5: Treatment of Central Venous Thrombosis**

<b>Treatment</b>	<b>Recommendations</b>	<b>Level of Evidence</b>	<b>Grade</b>
Acute anticoagulant treatment	Treatment of acute CVT adult patients with heparin in therapeutic dosage is recommended, including in those with intracerebral haemorrhage at baseline.	I	B
Type of heparin	Treatment of acute CVT patients with LMWH instead of UFH is recommended (unless fast reversal of the anticoagulant effect is required, or the patient has contraindications to LMWH).	I	B
Thrombolysis in acute CVT	Thrombolysis in acute CVT patients with a pre-treatment low risk of poor outcome is not recommended.	III	C
Endovascular therapy or Thrombectomy	Endovascular therapy or Thrombectomy may be considered in patients with clinical deterioration despite anticoagulation, with severe neurological deficits or in coma.	II-2	C
Warfarin	Using oral anticoagulants (vitamin K antagonists) for a variable period (3-12 months) after CVT is recommended to prevent recurrent CVT and other venous thromboembolic events. Patients with recurrent venous thrombosis or with an associated prothrombotic condition with a high thrombotic risk may need permanent anticoagulation. We suggest following specific recommendations for the prevention of recurrent venous thromboembolic events in such conditions.	III	C
DOACs	Treatment of CVT with DOACs is not recommended especially during the acute phase.	III	C
Therapeutic LP	Therapeutic LP is not recommended. However, it may be considered in patients with cerebral venous thrombosis and signs of intracranial hypertension, because of a potential beneficial effect on visual loss and/or headache, whenever its safety profile is acceptable.	III	C
Acetazolamide	Acetazolamide is not recommended in patients with acute CVT to prevent death or to improve the functional outcome. However, in isolated intracranial hypertension secondary to CVT, causing severe headaches or is threatening the vision, Acetazolamide may be considered if its safety profile is acceptable	III	C
Steroids	Steroids in patients with acute CVT without any co-existing inflammatory disease are not recommended to prevent death or to improve the functional outcome	III	C
Shunt	Routine shunting (without other surgical treatment) in patients with acute CVT and impending brain herniation due to parenchymal lesions is not recommended to prevent death	II-3	C
Decompressive surgery	Decompressive surgery for patients with acute CVT and parenchymal lesion(s) with impending herniation is recommended to prevent death.	II-1	B
Antiepileptic drugs (AEDs)	Antiepileptic drugs usage in patients with acute CVT with supratentorial lesions and seizures are recommended to prevent early recurrent seizures.	II-3	C

## Chapter 15: Management of Stroke in Pregnancy

**Table 15.1: Management of Stroke in Pregnancy**

Management	Recommendations	Level of Evidence	Grade
During pregnancy	In AIS, Aspirin up to 150mg daily is well tolerated during pregnancy. Pregnant patients with well-defined low risk conditions may be given UFH or LMWH in the first trimester, followed by a low dose aspirin in the second and third trimesters.	III	C
	In pregnant patients with well-defined low risk conditions, no antiplatelet other than Aspirin can be prescribed.	III	C
	In pregnant women with well-defined high-risk conditions, Vitamin K antagonists need to be avoided between the 6 <sup>th</sup> and 12 <sup>th</sup> weeks of pregnancy and also near to term. During this period, UFH or LMWH can be used.	II	B
	In addition, pregnant patients with well-defined high-risk conditions currently on direct oral anticoagulants (DOACs) should be given UFH or LMWH between the 6 <sup>th</sup> and 12 <sup>th</sup> weeks of pregnancy. <i>New recommendation</i>	III	C
	At other weeks of gestation, Warfarin can be given.	III	C
Labour induction	When the labour process is pharmacologically induced, Aspirin can be continued.	III	C
	UFH and LMWH need to be stopped 24 hours before the induction of labour.	III	C
	UFH and LMWH should be restarted within 24 hours of delivery if there are no contraindications.	III	C
	Vitamin K antagonists (without loading dose) may be restarted after 24 hours of delivery if there are no contraindications.	III	C

# 1

## EPIDEMIOLOGY, DEFINITION AND CLASSIFICATION OF STROKE

### 1.1 Epidemiology of Stroke

Stroke is a major cause of mortality and disability in many countries, including Malaysia. Global stroke estimates study reported that, in 2013, there were approximately 25.7 million stroke survivors, 6.5 million deaths, 113 million disability-adjusted life-years (DALYs) lost, and 10.3 million new cases of stroke.<sup>1</sup> The high burden of stroke was mainly observed in developing countries, and accounted for 75.2% of all stroke-related deaths and 81% of associated DALYs lost.

Statistics from the Department of Statistics, Malaysia showed that stroke emerged as one of the top five leading causes of mortality since 2000. Data in 2017 showed that cerebrovascular diseases contributed to 7.1% of all mortalities recorded in the Malaysian population (Table 1.1).

1.	Ischaemic Heart Disease	13.9%
2.	Pneumonia	12.7%
3.	Stroke	7.1%
4.	Transport Accidents	4.6%
5.	Malignant Cancer	2.3%

(Source: Department of Statistics Malaysia, 2017)

Ischaemic stroke accounted for 79.4% of all stroke cases, followed by haemorrhagic stroke (18.2%), transient ischaemic attack (2%) and unclassified stroke (0.4%).<sup>2</sup>

Hypertension was the most common risk factor (72%), followed by diabetes mellitus (47%), dyslipidaemia (32%) and smoking (31%).<sup>3</sup> Hypertension remains the most common medical risk factor for stroke, whereas current smoking and physical inactivity are the most predominant lifestyle-related risk factors. In general, hypertension, diabetes mellitus and tobacco smoking tend to be more prevalent among men, whereas hypercholesterolaemia, physical inactivity and obesity were more prevalent among women.<sup>4</sup>

The mean age for ischaemic stroke in Malaysia was 62.8 years for the first stroke and 64.3 years for recurrent cases.<sup>2</sup> Malaysian women with a first-ever ischaemic stroke had a greater severity, higher number of risk factors and poorer functional outcomes, as compared to men. After post gender–age adjustment, the Malaysian population observed an increased incidence of stroke in women as compared to men. However, there was no difference between genders in terms of access to thrombolysis treatment.<sup>5</sup>

### 1.2 Conceptual Definitions

#### 1.2.1 Stroke

Stroke is defined as 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 leading to death, with no apparent cause other than that of a vascular origin.

The new definition of central nervous system (CNS) infarction which incorporates scientific and technological advances is “*brain, spinal cord, or retinal cell death attributable to ischaemia, based on either pathological imaging or other objective evidence of cerebrospinal cord or retinal ischaemic injury in a defined vascular distribution, or clinical evidence of ischaemic injury, based on symptoms persisting for greater than 24 hours.*”<sup>6</sup>

Strokes may be classified and timed as:<sup>7</sup>

- I. Early hyperacute (a stroke that is 0–6 hours old)
- II. Late hyperacute (6–24 hours)
- III. Acute (24 hours to 7 days)
- IV. Subacute (1–3 weeks)
- V. Chronic (more than 3 weeks)

### **1.2.2 Transient Ischaemic Attack (TIA)**

TIA originally had a time-based definition characterized by an acute loss of focal cerebral or monocular functions with symptoms lasting less than 24 hours and which is thought to be due to inadequate cerebral and ocular blood supply as a result of arterial thrombosis or embolism. However, a time-based definition is inadequate because there is risk of permanent tissue injury (i.e. infarction) even when focal transient neurologic symptoms last less than one hour.

TIA currently uses a tissue-based definition i.e. a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischaemia, without acute infarction.<sup>8</sup>

## **1.3 Classification of Stroke**

### **1.3.1 Why Classify Stroke?**

Stroke classification has numerous implications during the immediate supportive care and rehabilitation, for prognostic purposes, guiding cost-effective investigations for underlying causes as well as to aid decisions for therapy and secondary stroke prevention strategies. Apart from being useful in setting up stroke registries and data banks for epidemiological studies, proper classification of the causative mechanism of stroke is important for optimizing stroke treatment and prognosis.

### **1.3.2 What are Stroke Classification Systems that are Widely Used Nowadays?**

Ischaemic stroke classification can be categorized into:

- I. Clinical / Syndromic Classification
- II. Phenotypic Classification
- III. Aetiologic / Causative Classification

### **1.3.3 What Other Common Classification Systems are Being Used?**

There are a few other classification systems currently being used worldwide which have its own advantages and disadvantages:

- I. The **Oxford Community Stroke Project (OCSP)** which was developed based on clinical findings especially neurological symptoms.<sup>9</sup>
- II. The **Trial of Org 10172 in Acute Stroke Treatment (TOAST)** which is a valid straightforward and is currently the most widely used classification system based on stroke mechanism. This

classification system is further subclassified to **Stop-Stroke Study TOAST (SSS-TOAST)** which is more specific using algorithms.<sup>10</sup>

- III. The **Causative Classification Systems (CCS)** is a web-based system which uses multiple sources of clinical data and is highly dependent on the availability of modern diagnostic technology.<sup>11</sup>
- IV. **ASCO** is the first purely phenotypic classification in which every patient is characterized by **A-S-C-O acronym: Atherosclerosis, Small-vessel disease, Cardiac source, and Other causes**. **ASCOD Phenotyping of Ischaemic Stroke** is the modified version of the ASCO classification.<sup>12</sup>
- V. **Chinese Ischaemic Stroke Classification (CISS)** is a new two-step system that looks at the aetiology and underlying mechanism of stroke. It takes into account the importance of intracranial atheromatous branch disease affecting penetrating arteries and the underlying mechanisms of ischaemic strokes caused by large artery atherosclerosis, that commonly found in the Asian population.<sup>13</sup>

#### **Key Recommendations:**

1. Stroke is a major cause of mortality and morbidity, and in Malaysia, stroke is the third leading cause of mortality.
2. Ischaemic stroke is the most common stroke, and hypertension is the most common risk factor followed by diabetes mellitus.
3. The new definition of stroke and transient ischaemic attack (TIA) involved either pathological imaging or clinical evidence of ischaemia and can be timed based on the presentation of symptoms.
4. Ischaemic stroke can be classified according to clinical, phenotypic, or aetiologic classification.

## 2

## CAUSES AND PATHOPHYSIOLOGY

### 2.1 Principal Causes of Ischaemic Stroke

The three main causes of ischaemic stroke are:<sup>1</sup>

- I. Atherothrombosis of large vessels (20-50%)
- II. Intracranial small vessel disease (25%)
- III. Embolism (20%)

#### 2.1.1 Atherothrombosis

Atherothrombosis is defined as atherosclerosis with superimposed thrombosis.<sup>2</sup> Atherosclerosis affects large and medium-sized arteries. The process begins in childhood as fatty streaks and progresses over years with gradual build-up of fibrolipid plaque and infiltration of inflammatory cells. Thrombosis occurs when this atherosclerotic plaque is disrupted resulting in platelet aggregation. Atherothrombosis leads to local arterial occlusion with intraluminal propagation of the thrombus proximally or distally or it can result in distal embolism. Intracranial large artery disease is the main cause of ischaemic stroke among South Asian patients.<sup>3</sup>

#### 2.1.2 Intracranial Small Vessel Disease

Intracranial small vessel disease is thought to be due to lipohyalinosis, microatheroma and fibrinoid necrosis.<sup>4</sup> The clinical syndrome caused by this phenomenon is lacunar infarction due to occlusion of small perforating arteries. Table (2.1) exhibits the vascular risk factors associated with increased risk of stroke.<sup>5-7</sup>

**Table 2.1: Common Vascular Risk Factors of Stroke**

<b>Non-Modifiable</b>	<b>Modifiable</b>
Age	Hypertension
Male sex	Smoking
Ethnicity / Race	Diabetes mellitus
Family history of stroke	Atrial fibrillation
	Coronary artery disease
	Obesity & physical inactivity
	Raised homocysteine levels
	Heavy alcohol consumption
	Previous stroke

#### 2.1.3 Embolism

Cardioembolism causes approximately 20% of all ischaemic strokes.<sup>8</sup> Embolic material formed within the heart or large arteries travels through the arterial system, lodging in a vessel and partially or completely occluding it. The most common causes are atrial fibrillation and valvular heart disease. Rare causes of embolism include air, fat, cholesterol, bacteria, and tumour tissues.<sup>9</sup>

### 2.2 Other Causes

Other causes include non-atherosclerotic abnormalities of the cerebral vasculature such as arterial dissection, fibromuscular dysplasia, vasculitis, Moyamoya disease, hypercoagulable states,

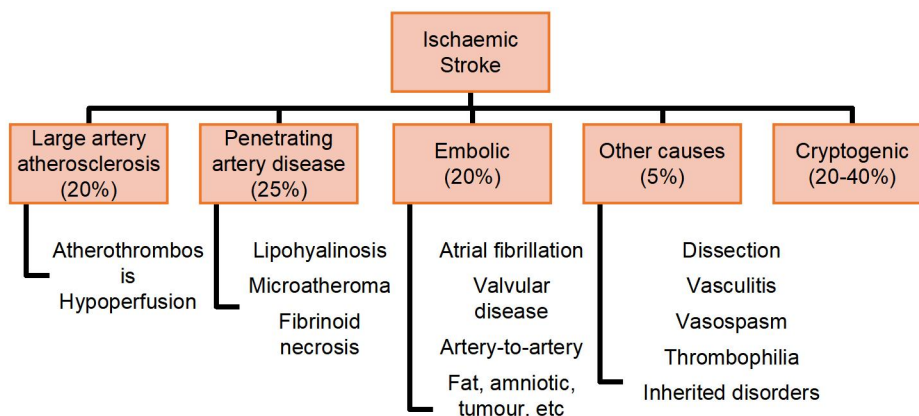


metabolic disorders, and inherited conditions such as Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL).

### 2.3 Cryptogenic Infarctions

Cryptogenic infarctions or stroke of undetermined aetiology are infarctions without a defined cause despite a complete work up and account for 20-40% of all ischaemic stroke. Possible mechanisms of cryptogenic stroke are embolism secondary to occult paroxysmal atrial fibrillation,<sup>10</sup> paradoxical embolism originating from the systemic venous circulation that enters the arterial circulation through a patent foramen ovale (PFO), atrial septal defect, ventricular septal defect or pulmonary arteriovenous malformation and sub-stenotic (<50% stenosis) atherosclerotic disease. A new terminology for non-lacunar cryptogenic stroke without proximal arterial stenosis or cardioembolic sources is Embolic Stroke of Undetermined Source (ESUS).<sup>11</sup> Cryptogenic stroke is a diagnosis of exclusion.

The algorithm as shown below outlines the pathophysiology of ischaemic stroke and the various causes.



#### Key Recommendations:

1. Three main causes of ischaemic stroke include atherothrombosis of large vessels, intracranial small vessel disease, and embolism which may contribute up to 80% of the cases.
2. Cryptogenic infarction or stroke of undetermined aetiology may be responsible for around 20 to 40% of the cases despite an extensive workout and is usually a diagnosis of exclusion.

# 3

## DIAGNOSIS AND INITIAL ASSESSMENT

### 3.1 General Aim

In general, the diagnosis of stroke is made by evaluating and analysing information derived from a good history and physical examination and is supplemented with selected diagnostic tests. Due to the nature of the illness and the dramatic manner in which the neurological deficit occurs, history is of utmost importance. Every effort must be made to obtain information from the patient, family members, friends, and witnesses.

The diagnosis should provide answers to the following questions:

- I. What is the neurological deficit?
- II. Where is the lesion(s)?
- III. What is the lesion?
- IV. Why has the lesion occurred?
- V. What are the potential complications and prognosis?

### 3.2 Symptoms and Signs

The symptoms and signs of stroke depend on the type, location, and the extent of the affected brain tissue. Stroke patients usually have a sudden or rapid onset of focal neurological symptoms, within minutes to an hour. Some patients may, however, have a stepwise or gradual worsening or waxing and waning of symptoms. A third of all strokes occur during sleep at night, therefore, the weakness is first recognized on waking up in the morning. Diagnosing stroke in the initial hours is very difficult, particularly when the onset is uncertain, the features are atypical or evolving, the patient is unwell or agitated, or when access to imaging is delayed, or when brain imaging is normal.<sup>1</sup>

A full neurological examination, including documenting the patient's conscious 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 lesion. These can be divided into 2 broad groups: a) clinical features that are caused by anterior circulation stroke (carotid artery); and b) those caused by posterior circulation stroke (vertebrobasilar system) (see Table 3.1).

**Table 3.1: Clinical Features of Stroke**

#### **Anterior (carotid) artery circulation**

##### ***Middle cerebral artery***

- Aphasia (dominant hemisphere)
- Hemiparesis / hemiplegia
- Hemisensory loss / disturbance
- Homonymous hemianopia
- Parietal lobe dysfunction, e.g. astereognosis, agraphesthesia, impaired two-point discrimination, sensory and visual inattention, left-right dissociation and acalculia

##### ***Anterior cerebral artery***

- Weakness of lower limbs more than the upper limbs

### Posterior (vertebrobasilar) artery circulation

- Homonymous hemianopia
- Cortical blindness
- Ataxia
- Dizziness or vertigo
- Dysarthria
- Diplopia
- Dysphagia
- Horner's syndrome
- Hemiparesis or hemisensory loss contralateral to the cranial nerves palsy
- Cerebellar signs

Less commonly, some patients present with atypical stroke symptoms (stroke “*chameleons*”) that can imitate other neurological diseases.<sup>2</sup> This is because the symptoms:

- I. are not anatomically localising (such as neuropsychiatric symptoms, confusion and/or altered consciousness),
- II. are positive (such as abnormal involuntary movements, rather than paralysis, due to an epileptic seizure, alien hand syndrome, isolated hemifacial spasms or hemiballismus),
- III. seems to be peripheral nerve in origin [vestibular syndrome, other cranial nerve palsy (especially third and seventh cranial nerve palsy), cortical hand syndrome, acute monoparesis], and
- IV. are isolated (isolated vertigo, binocular blindness, amnesia, headache, anosognosia, dysarthria, dysphagia, stridor, or foreign accent syndrome).<sup>2-4</sup> These atypical presentations are more likely to be due to a stroke if the patient has a known cardiovascular disease or risk factors.<sup>2</sup>

### 3.3 Differential Diagnoses

Stroke mimics commonly confound the clinical diagnosis of stroke (Table 3.2). In one study, 19% of patients diagnosed with acute ischaemic stroke by neurologists before cranial CT scanning actually had non-cerebrovascular causes for their clinical presentations.<sup>5</sup>

**Table 3.2: Differential Diagnosis of Stroke<sup>1,2,6,7</sup>**

- Metabolic / toxic encephalopathy (hypoglycaemia, non-ketotic, hyperglycaemia, hyponatraemia, Wernicke-Korsakoff syndrome or drug intoxication)
- Epileptic seizures (postictal Todd's paresis)
- Hemiplegic migraine
- Structural intracranial lesions (e.g. subdural haematoma, brain tumour or arteriovenous malformation)
- Brain infections e.g. encephalitis (e.g. herpes simplex virus), brain abscess or tuberculoma
- Head injury
- Hypertensive encephalopathy
- Relapsing Multiple Sclerosis
- Conversion disorders
- Hyperviscosity syndrome
- Peripheral nerve lesions (e.g. Guillain-Barre Syndrome)
- Systemic infection (sepsis)
- Memory disturbances due to delirium, dementia, or transient global amnesia

- Myelopathies (e.g. spinal stenosis, cervical myelopathy, etc.)
- Syncope
- Peripheral vestibulopathy (e.g. positional vertigo, labyrinthine disorder, etc.)

**Key Recommendations:**

1. The diagnosis of stroke is made by evaluating and analysing information derived from a good history, physical examination and selected diagnostic tests.
2. The symptoms and signs of stroke depend on the type, location, and the extent of the affected brain tissues.
3. A full neurological examination, including assessing the patient's conscious level and tests of higher mental function is mandatory.
4. Stroke mimics commonly confound the clinical diagnosis of stroke.

# 4

## PROGNOSIS

Prognosis of stroke depends on the type of stroke, size, and location of the lesion. Haemorrhagic stroke has a higher mortality than ischaemic stroke.<sup>1-4</sup> However, patients with haemorrhagic stroke show a better neurological and functional recovery.<sup>5</sup> Brainstem infarction, large hemispheric infarction and cardioembolic stroke also carry a poor prognosis.<sup>6</sup> Lacunar infarct has the lowest mortality rate.<sup>7</sup>

### 4.1 Survival after Stroke

There is a decline in stroke mortality in both men and women suffering from ischaemic or haemorrhagic stroke across all ages in many countries over the last few decades.<sup>8,9</sup> This can be attributed to the introduction of stroke units which provide organized stroke care and better control of stroke risk factors, resulting in milder strokes.<sup>10-15</sup>

A patient who survives the first 30 days after a first-ever stroke has an annual death risk of 9-10%.<sup>16,17</sup> Studies in recent years showed that case fatality rates after a first-ever stroke (all types combined) were 10% at one week, 14-20% at one month, 27-30% at one year, 47-60% at 5 years<sup>16,17</sup> and 76% at 10 years.<sup>18,19</sup> In a population study, more than 70% of patients either died or were disabled at 5 years after the index stroke.<sup>19</sup> Age (<75 years), verbal component of the Glasgow Coma Scale (orientated), arm power, ability to walk and pre-stroke dependency (Barthel Index  $\geq 12$  out of 20) are the 5 variables that have been shown to predict independent survival at 3 months and 12 months after stroke.<sup>20</sup>

In a local study published in 2003, the in-hospital mortality in ischaemic stroke was 11% while for haemorrhagic stroke, it was much higher, at 27.3%.<sup>21</sup>

Death occurring within the first 30 days after stroke is commonly due to the direct effect of brain damage.<sup>4</sup> There-after, mortality is usually caused by complications of immobilisation (e.g. bronchopneumonia, deep vein thrombosis, etc.), recurrent stroke and coronary heart disease.<sup>16</sup>

### 4.2 Risk Factors for Stroke Mortality

Previous use of antiplatelet drugs nearly halves the risk of early deaths in patients with ischaemic stroke, while old age, atrial fibrillation, ischaemic heart disease and diabetes mellitus increases the risk of early deaths.<sup>6</sup> Diabetes mellitus, both diastolic and systolic hypertension, smoking, increased cardiothoracic ratio and pre-existing coronary heart disease are risk factors for long-term stroke mortality.<sup>22</sup>

### 4.3 Recurrent Stroke

The recurrent rates are 3-4% in the first month and 12% in the first year. Thereafter the risk falls to about 4-5% per year and by 5 years, around 26.4-30% of patients will suffer a recurrent stroke.<sup>23-26</sup> Up to 40% of patients will have a recurrent event at 10 years.<sup>25</sup>

The risk is higher among individuals with cardiovascular risk factors, symptomatic atherosclerotic disease, an active source of thrombosis, or who have discontinued their antiplatelet and antihypertensive therapies.<sup>27</sup>

#### 4.4 Disability

Progress of time is an independent covariate which reflects spontaneous recovery of bodily functions. About 16-42% of improvements can be seen during the first 6 to 10 weeks of stroke onset.<sup>28</sup> Following a first-ever stroke, around 60% of patients may survive up to 5 years.<sup>18</sup> One-third of stroke survivors may exhibit some form of persistent disability after the initial episode of stroke. Up to 58% of patients who survive the first stroke will regain independence in activities of daily living (ADL), with most functional recovery occurring within the first 2 months of stroke. Less functional recovery is observed at the subsequent 4 to 5 months after stroke. Improvement in functional recovery is less than certain after 6 months, however the known predictors of disability were older age, very low premorbid level of activities before stroke and subsequent recurrent stroke.<sup>29</sup> Over a period of 10 years of follow-up, almost one half of survivors remained disabled, and one seventh required institutional care.<sup>26</sup>

#### Key Recommendations:

1. Haemorrhagic stroke has a higher mortality than ischaemic stroke.
2. There is a decline in stroke mortality in both men and women suffering from ischaemic or haemorrhagic stroke due to the introduction of stroke units and better control of stroke risk factors.
3. The recurrent rates are 3-4% in the first month and 12% in the first year.
4. Progress of time is an independent covariate which reflects spontaneous recovery of bodily functions.

## 5.1 Primary Prevention

### 5.1.1 *Epidemiology and Risk Factors of Stroke in Malaysia*

Stroke incidence and prevalence in Malaysia has increased steadily over the last 2 decades. Stroke is the third cause of mortality and the second leading cause of Disability Adjusted Life Years (DALY) in Malaysia.<sup>1</sup> The incidence and prevalence rate for both ischaemic and haemorrhagic stroke in Malaysia had increased steadily from 2010 to 2014.<sup>2</sup> Without effective interventions, stroke incidence will continue to rise, thus increasing the healthcare burden.<sup>2</sup>

Data from the National Stroke Registry showed that first ever strokes contributed to about 79.2% of all stroke cases in Malaysia, while 20.8% were due to recurrent strokes.<sup>2</sup> Therefore, primary prevention is the key to any national strategy to reduce the burden of stroke. Top modifiable risk factors associated with first ever strokes among Malaysians were hypertension (69.9%), diabetes mellitus (41.4%), smoking (26.3%), hyperlipidaemia (24.4%), family history of stroke (5.8%), ischaemic heart disease (IHD) and atrial fibrillation (3.4%). However, geographical and gender differences are observed.<sup>2</sup> Hypertension and diabetes were significantly higher in women compared to men, while smoking and IHD were higher in men. Within Peninsular Malaysia, the East Coast had the highest number of hypertensive patients, while the Southern regions had the highest number of patients with diabetes. East Malaysia reported the highest number of smokers.<sup>3</sup>

The INTERSTROKE study, which involved 32 countries including Malaysia, identified ten modifiable risk factors (hypertension, diabetes, hyperlipidaemia, waist-hip-ratio, poor diet, smoking, alcohol, cardiac cause, apo-lipoprotein levels and psychosocial factors) which accounted for 90% of population-adjustable risk (PAR) of stroke.<sup>4</sup> The Global Burden of Diseases 2013 study identified three clusters of modifiable risk factors associated with highest stroke burden in LMIC<sup>5</sup>:

- I. Lifestyle risk factors – smoking, physical inactivity, and unhealthy eating (74.1%)
- II. Metabolic risk factors – high systolic BP, high cholesterol, high fasting blood glucose, low eGFR and high BMI (72%)
- III. Environmental - air pollution and lead exposure (33.9%)

The National Health Morbidity Survey (NHMS) 2011 and 2015 highlighted an alarming trend in the prevalence of cardiovascular risk factors among Malaysians, with 63% of Malaysian adults (>18 years) having at least one CV risk factor (overweight/obesity, high blood pressure, high blood glucose and high blood cholesterol).<sup>6,7</sup> Based on NHMS 2015, the prevalence for the three major CV risk factors among Malaysian adults were<sup>7</sup>:

- Hypertension (known and undiagnosed) – 30.3%
- Diabetes mellitus (known and undiagnosed) - 17.5%
- Hypercholesterolaemia (known and undiagnosed) – 47.7%

## 5.2 Modifiable and Non-modifiable Risk Factors

### 5.2.1 Non-modifiable Risk Factors

Understanding the epidemiology of risk factors for stroke among Malaysians allows prioritization of primary prevention strategies specific to the needs of the population. Stroke risk factors can be categorized into modifiable and non-modifiable risk factors. Non-modifiable risk factors include age, sex, and family history.

**Age:** The cumulative effect of aging on the cardiovascular system and the progressive nature of stroke risk factors over a prolonged period of time substantially increase stroke risk. The risk of stroke doubles in each successive decade after 55 years of age.<sup>8,9</sup>

**Sex:** Stroke is more prevalent in men than women.<sup>8</sup> Overall, men have higher age-specific stroke incidence rates compared to women.<sup>10</sup> Exceptions are in the 35 to 44 year-olds and in those over 85 years of age, of whom women have slightly greater age-specific incidence than men.<sup>10</sup> Circumstances such as oral contraceptive use and pregnancy uniquely contributes to the risk of stroke in women.<sup>11-13</sup>

**Family History:** Both paternal and maternal history of stroke may be associated with an increased risk. This may be mediated through genetic and shared environmental factors.<sup>14,15</sup> Patients with a strong family history of recurrent subcortical infarcts and leucoencephalopathy should be investigated for CADASIL, Fabry's disease or mitochondrial diseases.

*(New recommendation)*

### 5.2.2 Modifiable Risk Factors

The National Stroke Registry has identified the following as the top modifiable risk factors for the first-ever stroke among Malaysians<sup>2</sup>:

- Hypertension
- Diabetes mellitus
- Hypercholesterolaemia
- Smoking
- IHD
- Atrial fibrillation

## 5.3 Risk Stratification and Monitoring

### 5.3.1 Cardiovascular Risk Estimates

For primary prevention strategies to be effective, understanding risk estimates is crucial for both the population at large and healthcare providers. Individualized risk estimation scores that takes into account both modifiable and non-modifiable risk factors, validated across multi populations such as the Framingham Stroke Risk Score Calculator, ASCVD and QRISK2 is helpful to create awareness and stratifying individuals according to cardiovascular risk categories.<sup>16,17</sup> The Revised FRS is shown to be better than the conventional FRS as it adjusts for temporal trends in stroke risk factors and has better discriminatory index for detecting stroke in various populations.<sup>18</sup> These risk estimations allow stratifying of individuals into risk categories for better preventive strategies.

The 2017 Malaysian Primary and Secondary Prevention of Cardiovascular Disease Clinical Practice Guideline (CPG) has advocated the use of FRS to stratify individuals into low risk, intermediate, high and very high risk based on their 10-year risks of developing cardiovascular events.<sup>19</sup>



- Low risk - FRS- CVD risk <10%
- Intermediate risk – FRS -CVD 10-20%
- High risk - FRS- CVD >20%
- Very high risk - FRS- CVD >30%

Patients with low risk should be counselled to maintain their status of health and to have regular reviews, while those with intermediate to high risks should be followed-up, and maintained on lifestyle interventions and pharmacotherapy for their specific risk factors, e.g. treatment of hypertension, LDL-C, smoking cessation, effective diabetes control, and encouraging physical activity and healthy eating.<sup>19</sup>

*(Level II, Grade B)*

### **5.3.2 Stroke Risk Estimates**

The Stroke Riskometer App, a smart phone-based application available in various languages (including the Malay language) allows for individualized stroke risk calculation, using 20 modifiable and non-modifiable risk factors. It contains educational videos for self-management of risk factors.<sup>20</sup> The app calculates individualized 5- and 10-year risks of stroke and is an effective tool for monitoring risk reductions associated with lifestyle and medical interventions. The Malay version has been validated for language and content (unpublished data).<sup>21</sup> Two interventional studies using Stroke Riskometer as a tool to reduce stroke risk have been completed among Malaysians with high risk (diabetics and stroke carers), with positive outcomes.<sup>22,23</sup>

The use of Stroke Riskometer and R-FRS Calculator may be beneficial in the community and in clinics for individualizing stroke risk and its management.<sup>20</sup>

*(Level II, Grade B)*

## **5.4 Prevention and Management of Risk Factors**

### **5.4.1 Lifestyle Changes**

The US Health Professionals and Nurses study showed that participants who achieved all five healthy lifestyle choices (not smoking, moderate intake of alcohol, BMI <25 kg/m<sup>2</sup>, daily exercise for 30 minutes and a healthy diet score in the top 40%), had their incidence of stroke reduced by 80% as compared to those who achieved none.<sup>24</sup>

A study among 11450 Swedish men with high cardiovascular risk (hypertensive, high cholesterol, diabetes, heart failure or atrial fibrillation) showed that adopting all five healthy lifestyle choices [(≥5 servings of fruits and vegetables and <30g/day of processed meat; not smoking; ≥150min of physical activity /week; BMI 18.5-25 kg/m<sup>2</sup>; low to moderate alcohol consumption (>0 to <30g/day)] had a 72% reduction of stroke incidence over 9 years as compared to those who were adherent to none or only one healthy behaviour.<sup>25</sup>

**Recommendation:** Adopting a healthy lifestyle (diets rich in fruits and vegetables, no smoking, daily exercise of >30 minutes or 150 minutes/week, low to moderate alcohol intake and maintaining a normal BMI of 18.5-25 kg/m<sup>2</sup>) reduces stroke incidence in normal and high-risk populations.<sup>24,25</sup>

*(New recommendation, Level I, Grade A)*

### **5.4.2 Hypertension**

Hypertension is the commonest and major risk factor for both ischaemic and haemorrhagic strokes in Malaysia, affecting 69.9% of patients with the first ever stroke.<sup>2</sup> The incidence of stroke increases in proportion to both systolic and diastolic blood pressures. Isolated systolic hypertension is an

important risk factor for stroke in the elderly (systolic blood pressure >140mmHg and diastolic blood pressure <90mmHg).<sup>26</sup>

Population specific and individualized strategies should be conducted to prevent the development of hypertension. Adopting healthy lifestyle such as smoking cessation, Dietary Action to Stop Hypertension (DASH) diet, increased physical activity and reducing salt consumption are shown to reduce the risk of developing hypertension.<sup>27</sup>

*(Level I, Grade A)*

#### **5.4.2.1 Primary Stroke Prevention in Specific High-risk Group with Hypertension**

The ACCORD BP trial showed that a lower target systolic value of 120 mmHg was superior to a target value of 140 mmHg in preventing any stroke and non-fatal stroke in diabetics, as secondary endpoint, but did not prevent other cardiovascular events.<sup>28</sup> The SPRINT (Systolic Blood Pressure Intervention Trial) study showed that intensive BP lowering regime to a target of ≤120 mmHg in high-risk non-diabetic hypertensive patients aged 50 years or older led to a reduction in all cardiovascular events and mortality but with an excess of adverse events in the intensive group.<sup>29</sup> However, there was no significant reduction in stroke event in these patients compared to the non-intensive group.

Large randomized controlled trials and meta-analyses have confirmed that reduction in blood pressure reduces first ever and recurrent stroke by 40%.<sup>30,31</sup>

*(Level I)*

Lowering the systolic blood pressure by 10mmHg is associated with a reduction in risk of stroke by about a third, irrespective of baseline blood pressure levels.<sup>31</sup>

*(Level I)*

For diabetics with hypertension, lowering systolic blood pressure to a target of 120 mmHg or below with careful monitoring of adverse events led to a significant reduction in stroke incidence.<sup>26</sup>

**Recommendation:** Target BP for diabetics is <130mmHg systolic and <80mmHg diastolic, preferably <120mmHg if tolerated.

*(New recommendation, Level I, Grade A)*

For high-risk non-diabetic hypertensive patients, intensive systolic BP lowering to below 120mmHg led to excess adverse events without reduction in stroke incidence.<sup>27</sup>

*(New recommendation, Level I, Grade B)*

**Recommendation:** Newly diagnosed hypertension in the very elderly (>80 years of age) should be treated.<sup>32</sup>

*(New recommendation, Level I, Grade B)*

#### **5.4.3 Smoking**

The Malaysian National Stroke Registry data showed that 51% of all patients with the first ever stroke were smokers. All forms of smoking, both active and passive, are a major risk factor for stroke.<sup>2</sup> Smokers who stopped for more than 5 years have the same risk as non-smokers.<sup>33</sup>

*(Level III)*

**Recommendation:** Cessation of smoking is strongly recommended.

*(Level III, Grade C)*

### 5.4.3.1 Smoking And Non Communicable Diseases

Smoking of tobacco and tobacco products (cigarette, electronic cigarette/vape, shisha, pipe, cigar etc.) can lead to various non-communicable diseases (NCDs). Worldwide, more than eight million people die every year because of this habit (WHO Tobacco Fact Sheet, 2020).

Hence, the decision to integrate smoking treatment with NCDs is important to reduce the prevalence of NCDs and their complications. This decision was made during the World Health Organization Framework Convention on Tobacco Control (WHO FCTC) Steering Committee Meeting in December 2019 chaired by the Honourable Health Minister of Malaysia.

The treatment for smoking should be initiated by the treating doctor based on the assessment and treatment of tobacco use disorder as in Table 1. Details on this can be found in the CPG on Treatment of Tobacco Use Disorder 2016, available at:

[https://www.moh.gov.my/moh/resources/Penerbitan/CPG/Respiratory/CPG\\_TobacoDisorder.pdf](https://www.moh.gov.my/moh/resources/Penerbitan/CPG/Respiratory/CPG_TobacoDisorder.pdf)

**Table 5.1: Assessment and treatment of tobacco use disorder**

<b>ASSESSMENT AND TREATMENT</b>	
1.	Ask and document smoking status for all patients.
2.	Provide brief advice on quit smoking at every visit to all smokers.
3.	Assess level of nicotine addiction using Modified Fagerström Test for Cigarette Dependence Questionnaire ( <b>COMPULSORY</b> ) and verify smoking status using carbon monoxide (CO) breath analyser ( <b>IF AVAILABLE</b> ).
4.	Offer pharmacotherapy to <b>all smokers</b> who are attempting to quit, unless contraindicated.
5.	If selected, use nicotine replacement therapy (NRT) for at least eight to twelve weeks, whereas varenicline should be used for at least twelve weeks.
6.	Combination therapy (e.g. two NRTs, a non-NRT, e.g. bupropion with an NRT) is better than monotherapy in smoking cessation treatment and may be most useful for those smokers at highest risk of relapse.
7.	Use smoking cessation medications with caution in special populations (e.g. children and adolescents, pregnant, breastfeeding women, psychiatric and substance abuse disorder patients).
8.	Arrange a minimum of six to eight face to face follow-up sessions for smoking cessation interventions in six months through counselling support team (health education officer, pharmacists or any officer trained for quit smoking services).

### 5.4.4 Alcohol

Alcohol consumption has been identified as one of the risk factors for global stroke burden.<sup>33</sup> Heavy alcohol drinking, of more than 4 units/day (1unit = 1glass wine = 1 pack of hard liquor), increases the risk of stroke.

**Recommendation:** Avoid heavy alcohol consumption or limit to < 1 drink per day.

*(New recommendation, Level II-2, Grade B)*

### 5.4.5 Post-menopausal Hormone Replacement Therapy

Stroke rates rapidly rise in women once they become menopausal. The Nurses' Health Study (6-year follow-up of 59,337 postmenopausal women) showed only a weak association between stroke and oestrogen replacement therapy. However, the Women's Health Initiative Estrogen Plus Progestin Study (E+P Study) showed a 31% increase in the risk of stroke due to E+ P.<sup>34</sup>

**Recommendation:** Post-menopausal hormonal therapy may increase the risk of stroke and is not recommended for primary stroke prevention.

*(Level II, Grade B)*

#### **5.4.6 Diabetes**

Case-control studies of stroke patients and prospective epidemiological studies have confirmed an independent effect of diabetes on ischaemic stroke, with an increased relative risk in diabetics ranging from 1.8- to nearly 6-folds.<sup>35</sup>

*(Level II-2)*

**Recommendation:** Tight control of hypertension in diabetics is recommended to reduce stroke incidence.<sup>27</sup>

*(Level I, Grade A)*

A systematic review and meta-analysis of observational cohort and nested case-control cohort studies showed that compared to controls with a normal HbA1c range (i.e. <5.7%), patients with diabetes mellitus with an abnormal HbA1c range (i.e. ≥6.5%) had an increased risk of first-ever stroke with an average HR [] of 2.15 [95% CI 1.76, 2.63]. In those with a pre-diabetes mellitus HbA1c range (i.e. 5.7– 6.5%) there was not increased risk of first-ever stroke (average HR 1.19 ,95% CI 0.87, 1.62).<sup>36</sup>

**Recommendation:** More intensive glycaemic control targets (HbA1c <6.5%) may be required for optimal ischemic stroke prevention.

*(Level I, Grade A)*

#### **5.4.7 Hyperlipidaemia**

Although the relationship between high cholesterol and increased risk of coronary heart disease is stronger, epidemiological studies have also shown an association between raised serum lipids and risk of ischaemic stroke.<sup>37,38</sup>

The MRC/BHF, a RCT involving 20,536 high risk individuals showed that statin therapy significantly reduced the incidence of fatal and non-fatal strokes by 28%.<sup>39</sup> A meta-analysis of trials on statin therapy versus control in individuals with a 5-year risk of major vascular events lower than 10%, showed that each 1 mmol/L reduction in LDL cholesterol levels produced an absolute reduction in major vascular events of about 11 per 1000 over 5 years.<sup>40</sup>

The HOPE-3 trial studied 12,705 patients with intermediate risk and used fixed-dose BP lowering (Candesartan and HCTZ), cholesterol lowering (Rosuvastatin) or combination treatment regime. It was found that a low-dose Rosuvastatin therapy and combination treatment reduced stroke incidence by 30% and 44%, respectively.<sup>41</sup>

A prospective study involving 7484 elderly population (>65 years) with no history of vascular events showed that the use of statins or fibrates reduced stroke incidence by 30%.<sup>42</sup>

In the high-risk group (those with cardiovascular disease, occlusive arterial disease, or diabetes), statin therapy is recommended to reduce the incidence of coronary events and ischaemic strokes, even amongst individuals with normal cholesterol concentrations.<sup>39</sup>

*(Level I, Grade A)*

In the high-risk group, intensive lipid lowering therapy is superior in reducing stroke as compared to normal therapy.<sup>39</sup>

*(New recommendation, Level I)*

Low dose statin is beneficial in reducing stroke risk in patients with low and intermediate risk.<sup>41,42</sup>  
(*New recommendation, Level II, Grade B*)

Low dose statin is beneficial in reducing stroke risk in elderly patients with no vascular events.<sup>42</sup>  
(*New recommendation, Level II, Grade B*)

#### **5.4.8 Dietary Factors**

The PREDIMED study showed that a Mediterranean diet enriched with either olive oil or mixed nuts, reduced the incidence of stroke by 47% in 5 years as compared to a low fat diet.<sup>43</sup> A meta-analysis involving 20 prospective studies showed that diet rich in fruits and vegetables reduced stroke incidence with a linear inverse relationship between fruits and vegetables consumption and stroke incidence.<sup>44</sup>

**Recommendation:** A Mediterranean diet rich in olive oil and canola oil, with less meat and increased vegetables is beneficial for stroke prevention.<sup>43</sup>  
(*New recommendation, Level II, Grade B*)

**Recommendation:** A diet rich in fruits (citrus type) and vegetables (green leafy) is beneficial in reducing stroke.<sup>44</sup>  
(*New recommendation, Level II, Grade B*)

**Recommendation:** DASH diet that is high in vegetables and fruits and low in saturated fats is beneficial in reducing BP.<sup>45</sup>  
(*New recommendation, Level I, Grade A*)

#### **5.4.9 Physical Activity**

Physical activity is defined as any bodily movements involving skeletal muscles that results in energy expenditure and may involve occupational and leisure time activities such as walking, commuting and housework. However, meta-analyses of observational studies on physical activity and stroke showed that increased physical activity in healthy adults reduced stroke incidence by 20-25%<sup>46</sup> and stroke mortality by 17% irrespective of gender.<sup>47</sup> Analysis from the Japanese Diabetes Complications study showed that increased physical activity (30 minutes of walking daily) reduced stroke incidence in diabetics by 45%.<sup>48</sup>

**Recommendation:** Increased physical activity is recommended for stroke prevention in healthy adults and high-risk patients.<sup>46-48</sup>  
(*New recommendation, Level I, Grade A*)

**Asymptomatic Carotid Stenosis**

**See Revascularization Procedures**

**Atrial fibrillation**

**See Cardio-embolism & Stroke**

#### **5.4.10 Medical Therapy**

##### **5.4.10.1 Aspirin**

The ARRIVE trial which involved 12500 participants with moderate cardiovascular risk and low risk of bleeding, showed that Aspirin did not prevent the first occurrence of cardiovascular events and stroke as compared to placebo.<sup>49</sup>

Similarly, the Japanese Primary Prevention Project, a randomized controlled trial which involved elderly patients (60-85 years of age) with hypertension, diabetes and hyperlipidaemia did not show

the net benefit of Aspirin in stroke prevention. There were concerns that Aspirin use may lead to increased incidence of intracranial bleeding in Asian patients.<sup>50</sup>

The ASCEND Aspirin study, a RCT which involved 15480 diabetic patients did not show a net benefit of Aspirin in preventing stroke or cardiovascular events, but with an increased risk of bleeding.<sup>51</sup>

**Recommendation:** Daily Aspirin is not recommended for primary prevention of stroke in diabetics, moderate risk individuals or elderly patients in view of the high risk of bleeding which outweighs any benefits.<sup>49-51</sup>

*(New recommendation, Level I, Grade A)*

### Recommendations Summary:

Table 5.2: Primary Prevention and Management of Risk Factors			
Factors	Recommendations	Level of Evidence	Grade
Hypertension	Self-BP monitoring is recommended for all hypertensive patients. <i>New recommendation</i>	I	A
	Risk stratification for hypertension based on CVD risk, target organ damage and complications are recommended for optimizing therapy. <i>New recommendation</i>		
	Lifestyle changes if systolic BP is between 130-139mmHg and/or diastolic BP is 80-89mmHg with three to six-monthly review. <i>New recommendation</i>	I	A
	Treat medically if systolic BP is >140mmHg and/or diastolic BP is >90mmHg.	I	A
	Hypertension should be treated in the very elderly (age >80years) to reduce the risk of stroke. <i>New recommendation</i>	I	B
Diabetes Mellitus	Strict blood pressure control is important in diabetics.	I	A
	More intensive glycaemic control targets (HbA1c <6.5%) may be required for optimal ischemic stroke prevention.	I	A
	Target BP for diabetics is systolic BP <130mmHg and diastolic BP <80mmHg, preferably <120mmHg if tolerated. <i>New recommendation</i>	I	A
Hyperlipidaemia	Treatment of dyslipidaemia / LDL-C is stratified based on risk.	I	B
	High-risk group: lowering LDL to <1.8 mmol/l is recommended. <i>New recommendation</i>		
	Intermediate and low risk: keep LDL <3.4mmol/l.		
	Low-risk group may benefit from cholesterol-lowering therapy with a statin. <i>New recommendation</i>		
	No risk – keep LDL <4.2 mmol/L.		
Smoking	Cessation of smoking.	III	C
Aspirin therapy	Aspirin therapy is not recommended for primary prevention of stroke in the elderly, diabetics, or other high-risk groups. <i>New recommendation</i>	I	A

Post-menopausal Hormone Replacement Therapy	Oestrogen based HRT is not recommended for primary stroke prevention.	II	B
Alcohol	Avoid heavy alcohol consumption or limit to < 1 drink per day. <i>New recommendation</i>	II-2	B
Physical Activity	Physical activity (occupational and leisure time) is recommended for all groups of patients. <i>New recommendation</i>	I	A
	Physical activity > 30mins/day or >150mins/week as part of healthy lifestyle is recommended <i>New recommendation</i>	I	A
Diet	DASH diet is recommended to reduce BP. <i>New recommendation</i>	I	A
	Mediterranean diet – (low glycaemic and high in vegetables) supplemented with nuts and olive oil is beneficial. <i>New recommendation</i>	II	B
	Diet high in fruits and leafy green vegetables is beneficial. <i>New recommendation</i>	II	B

## 5.5 Secondary Prevention of Stroke

Secondary prevention strategies are aimed at preventing recurrent stroke. This should be tailored according to the individual's stroke pathogenesis based on neuroimaging and investigations (see Investigations).

The risk for recurrent vascular events after stroke or transient ischaemic attack is approximately 5% per year for stroke, 3% per year for myocardial infarction and 7% per year for any one of stroke, myocardial infarction or vascular death.<sup>52</sup> This figure is even higher in certain populations, especially in those with high cerebrovascular atherosclerotic burden and for patients with ipsilateral high grade (70%) extracranial carotid stenosis.<sup>53</sup>

### 5.5.1 Anti-platelet Therapy

**Aspirin:** There is substantial evidence to support the use of Aspirin. A 25% risk reduction of stroke was seen in all patients with stroke who received Aspirin.<sup>54</sup> Aspirin given within 48 hours had shown to be beneficial in reducing recurrent stroke and deaths.<sup>54-56</sup> Studies comparing the effects of different dosages of Aspirin had failed to show any differences in stroke recurrences.<sup>57-60</sup>

**Recommendation:** The recommended dose of oral Aspirin post-stroke is 75mg to 325mg daily.  
(Level I, Grade A)

Alternative anti-platelet medications can be considered for patients with Aspirin allergy, Aspirin failure, Aspirin intolerance or Aspirin contraindications based on the evidence presented below.

**Ticlopidine:** Previous clinical trials demonstrated that Ticlopidine is slightly superior to Aspirin.<sup>61,62</sup> Full blood count monitoring is essential as neutropenia is the most important side-effect.<sup>61</sup> Severe neutropenia usually occurs within the first 3 months of use. Thus, a baseline full blood count should be performed every 2-3 weeks during this time frame. Ticlopidine can also be used if the patient has recurrent symptoms despite Aspirin administration.

**Recommendation:** The recommended dose of oral Ticlopidine is 250mg twice a day.  
(Level I, Grade A)

**Clopidogrel:** Clopidogrel is a newer thienopyridine derivative. It is slightly superior to the 325 mg daily dosage of Aspirin.<sup>63</sup> It may be more beneficial than Aspirin in several settings, including patients with contraindications or having adverse effects due to Aspirin and in high risk subjects with multiple risk factors (i.e. with a previous stroke, peripheral artery disease, symptomatic coronary disease and diabetes)<sup>64</sup>

**Recommendation:** The recommended dose of oral Clopidogrel is 75mg daily.

(Level I, Grade A)

**Triflusal:** Triflusal is a viable alternative to Aspirin in secondary prevention of ischaemic stroke at a dosage of 600mg daily. There are less haemorrhagic complications compared to Aspirin. Triflusal is licensed in Malaysia for the secondary prevention of ischaemic stroke.<sup>65</sup>

**Recommendation:** The recommended dose of oral Triflusal is 600mg daily.

(Level I, Grade A)

**Cilostazol:** Cilostazol is another alternative in the secondary prevention of acute ischaemic stroke at a dosage of 100mg twice daily. Studies from Japan and China supports the safety and efficacy of Cilostazol for secondary stroke prevention in Asian populations. However, there are as yet no high-quality data regarding the use of Cilostazol for secondary stroke prevention in non-Asian ethnic groups.<sup>66,67</sup> The most recent meta-analysis showed that Cilostazol appeared to be effective for long-term secondary stroke prevention without increasing the risk of haemorrhage.<sup>68</sup> Combination use of cilostazol with aspirin or clopidogrel was explored in open-label trial in Japan that showed adult patients with non-cardioembolic ischemic stroke who had  $\geq 50\%$  stenosis of a major intracranial or extracranial artery, or two or more vascular risk factors, had lower recurrent ischaemic stroke compared to monotherapy (3% vs. 7%) with similar bleeding rates.<sup>69</sup>

**Recommendation:** The recommended dose of oral Cilostazol is 100mg twice a day.

(Level I, Grade A)

**Aspirin and Clopidogrel combination:** Recent evidence from 2 large trials in minor stroke and high risk TIA patients (NIHSS  $\leq 3$ , ABCD2  $\geq 4$ ), showed that those who received a combination of Clopidogrel and Aspirin had a lower risk of major ischaemic events for 3 weeks to 3 months, but a higher risk of major haemorrhage at 90 days than those who received Aspirin alone.<sup>70,71</sup>

**Recommendation:** Dual antiplatelet therapy (Clopidogrel and Aspirin) is recommended for 21 days in patients with high risk TIA or minor ischaemic stroke.

(New recommendation, Level I, Grade A)

**Ticagrelor:** In the SOCRATES trial, Ticagrelor was not superior to Aspirin in the prevention of fatal stroke, MI and death at 90 days in patients with minor stroke or TIA.<sup>72</sup> However, sub-analysis in the Asian population, showed a trend towards reduction in stroke, MI and death with Ticagrelor.<sup>73</sup> Since there were no significant safety differences in the 2 groups, Ticagrelor may be a reasonable alternative in stroke patients who have a contraindication to Aspirin.

(Level II, Grade B)

**Aspirin and Ticagrelor:** A recent trial examining the use of ticagrelor as combination therapy with aspirin in patients with mild-to-moderate acute non-cardioembolic ischaemic stroke (NIHSS score  $\leq 5$ ) or TIA who were not undergoing intravenous or endovascular thrombolysis, showed that the risk of the composite of stroke or death within 30 days was lower with ticagrelor–aspirin than with aspirin alone, but the incidence of disability did not differ significantly between the two groups. Severe bleeding was more frequent with the ticagrelor-aspirin combination therapy than with aspirin alone.

74



**Warfarin** is not indicated for secondary stroke prevention for patients with sinus rhythm in the absence of other conditions predisposing to cardioembolic risk.

*(Level I, Grade A)*

### **5.5.2 Anti-hypertensive Treatment**

Reduction of blood pressure after the acute phase of a cerebrovascular event results in further reduction of vascular events. This benefit was noted in both ischaemic and haemorrhagic stroke in hypertensive and normotensive subjects.<sup>75</sup> Meta-analyses of randomized controlled trials confirmed an approximate 30 – 40% reduction of stroke risk with blood pressure lowering.<sup>76</sup>

In one study, the combination of an ACE-inhibitor and thiazide diuretic was beneficial in both hypertensive and normotensive stroke patients when initiated two weeks after the event.<sup>77</sup>

Another study proved the superiority of an angiotensin receptor blocker (ARB), Losartan over a beta-blocker (Atenolol) in a specific group of high-risk patients with left ventricular hypertrophy, including subjects with previous stroke.<sup>78</sup>

**Recommendation:** In the post-stroke period (2 weeks or more after stroke), ACE-inhibitor based therapy has been shown to reduce recurrent stroke in normotensive and hypertensive patients.<sup>79</sup>

*(Level I, Grade A)*

**Recommendation:** Other classes of anti-hypertensive (ARB-based) therapy appear to be effective in selected high-risk populations.<sup>80,81</sup>

*(Level II-1, Grade B)*

The target blood pressure of absolute levels is not certain, but targets based on hypertension guidelines (local or international) can be followed and should be individualized.<sup>82</sup>

*(Level II-1, Grade B)*

The choice of antihypertensive drug therapy (single or in combination) should also be individualized based on current evidence and specific patient characteristics.<sup>83</sup>

*(Level II-1, Grade B)*

### **Carotid Endarterectomy (CEA)**

**See Revascularization Procedures**

### **5.5.3 Lipid Lowering**

Statins were proven to reduce vascular events among high risk patients including subjects with previous stroke.<sup>83,84</sup>

**Recommendation:** Lipid reduction should be considered in all patients with previous ischaemic strokes.

*(Level I, Grade A)*

The Treat Stroke to Target trial that involved 2860 patients with a history of ischaemic stroke or TIA showed that patients who achieved a target LDL of 1.8 mmol had a lower cardiovascular and stroke events at 3.5 years than those with a target LDL of 2.5 mmol/L.<sup>85</sup>

**Recommendation:** LDL target of 1.8 mmol/L is recommended.

*(New recommendation, Level I, Grade A)*

## 5.6 Other Risk Factors

The control of risk factors such as better glycaemic control in diabetes and smoking cessation has not been the subject of major randomized secondary prevention clinical trials. Although diabetes is recognized as an independent risk factor for ischaemic stroke, better diabetes control resulted only in the reduction of microvascular but not macrovascular complications.<sup>86</sup> Inferences can also be drawn from positive results of primary prevention trials (see primary prevention section). Nevertheless, better control of these risk factors should be advocated for better overall health after an ischaemic stroke.

**Recommendation:** All diabetic patients with a previous stroke should maintain a good glycaemic control.

(Level III, Grade C)

**Recommendation:** All smokers should stop smoking.

(Level III, Grade C)

### Recommendations Summary:

Table 5.3: Secondary Prevention of Stroke			
Factors/Treatment	Recommendations	Level of Evidence	Grade
Antiplatelet (Single agent)			
Aspirin	The recommended dose of aspirin is 75mg to 325mg daily.	I	A
<i>Alternatives:</i>			
Clopidogrel	The recommended dose is 75mg daily.	I	A
Ticlopidine	The recommended dose is 250mg twice a day.	I	A
Triflusal	The recommended dose is 600mg daily	I	A
Cilostazol	The recommended dose is 100mg twice a day.	I	A
Double therapy	Combination therapy of Clopidogrel and Aspirin is recommended in patient with minor ischaemic stroke and high-risk TIA for 21 days. <i>New recommendation</i>	I	A
Antihypertensive treatment	ACE-inhibitor based therapy should be used to reduce recurrent stroke in normotensive and hypertensive patients.	I	A
	ARB-based therapy may benefit selected high risk populations.	II-1	B
Lipid lowering	Lipid reduction should be considered in all patients with previous ischaemic strokes.	I	A
	LDL target < 1.8 mmol/L is recommended in all patients with previous ischaemic stroke. <i>New recommendation</i>	I	A
Diabetic control	All diabetic patients with a previous stroke should maintain a good glycaemic control.	III	C
Cigarette smoking	All smokers should stop smoking.	III	C

## 5.7 Cardioembolism

Cardioembolic stroke accounts for about 20% of all ischaemic strokes.<sup>87-89</sup> Generally, they are severe, prone to early recurrence, and more likely when there is documented source of embolism and involvement of different cerebrovascular territories or multiple infarctions. The predominant pathogenic process for stroke associated with cardiac disease is embolism due to formation of intra-atrial and intra-ventricular thrombus.

Atrial fibrillation (AF) whether chronic or paroxysmal, is the most common cause of cardioembolism and accounts for 50% of all cardiogenic emboli. Other high-risk conditions are having prosthetic heart valves, rheumatic mitral valvular disease, acute myocardial infarction, and severe left ventricular dysfunction. Non-thrombotic embolism may result from atrial myxoma and endocarditis. Investigations are directed at demonstrating cardiac sources of embolism in the absence of significant atherosclerosis or other vascular disease. All patients with stroke/TIA require a 12-lead electrocardiogram. A 72-hour Holter monitor is required to detect paroxysmal AF. In addition, all patients under 45 years of age and those in whom baseline investigations did not reveal an apparent cause for stroke will require a transthoracic echocardiogram (TTE). Patients in whom there is high suspicion of cardioembolism but have a normal TTE may undergo a trans-oesophageal echocardiogram (TOE). Conditions in which this method is superior to TTE include thrombi in the left atrium and left atrial appendage, patent foramen ovale, atrial septal aneurysm and aortic arch atheroma.<sup>89,90</sup>

Oral anticoagulant may reduce the risk of first and subsequent stroke for selected high-risk cardiac conditions but must be weighed against the risk of haemorrhagic complications.<sup>87,88,91,92</sup> (see table 5.4)

Patients with low risk cardiac conditions (such as mitral valve prolapse, mitral regurgitation, atrial septal aneurysm, and patent foramen ovale) without additional risk factors may be offered Aspirin 75-325mg/day for primary prevention of stroke.

*(Level III)*

If patients are Aspirin intolerant then consider: Clopidogrel 75mg daily, Ticlopidine 250mg bd or Dipyridamole 400mg daily.<sup>87</sup>

*(Level III, Grade C)*

Anticoagulation is not indicated for non-thrombotic causes of cardiac emboli and may cause substantial intracranial haemorrhage in infective endocarditis of native valves.<sup>87</sup>

Anticoagulation is not proven to reduce recurrent stroke in the first 14 days following an acute cardioembolic event [Level I] with the possible exception of prosthetic heart valves, recent MI, presence of intra-cardiac thrombus, AF with additional risk factors and previous stroke.<sup>89</sup> (see table 5.5)

*(Level III)*

Further details on stroke and cardioembolism in Chapter 13.

## Recommendations Summary:

**Table 5.4: Cardiac Conditions Predisposing to Ischaemic stroke**

Major Risk Conditions	Additional Risk Factors	Recommendations	Level of Evidence	Grade
Atrial Fibrillation	Risk factors to be assessed by CHA <sub>2</sub> DS <sub>2</sub> -VASc score.	OAC to prevent cardioembolic stroke is recommended for all NVAf male patients with CHA <sub>2</sub> DS <sub>2</sub> -VASc score of 2 or more and female patients with a CHA <sub>2</sub> DS <sub>2</sub> -VASc score of 3 or more. <i>New recommendation</i>	I	A
		<b>Direct Oral Anticoagulant (DOAC) vs. Warfarin</b>		
		Dabigatran is superior (150mg bid) to and as effective (110mg bid) as compared to Warfarin, in preventing stroke and systemic embolism. Bleeding rates are similar with Warfarin at 150mg bid but have a lower bleeding rates at 110mg bid. <sup>93</sup>	I	A
		Rivaroxaban was compared with adjusted-dose warfarin and found to be non-inferior with regards to the primary composite end point of stroke or non-central nervous systemic embolism. <sup>94</sup> <i>New recommendation</i>	I	A
		Apixaban was compared with adjusted-dose warfarin and found to be superior to warfarin in preventing stroke or systemic embolism. Apixaban also caused less major bleeding compared with warfarin and resulted in lower overall mortality. <sup>95</sup> <i>New recommendation</i>	I	A
		Edoxaban* as compared to warfarin was found to be non-inferior with regards to the primary efficacy end point and caused less bleeding. <sup>96</sup> <i>New recommendation</i> *Currently not available in Malaysia.	I	A
Prosthetic Heart Valves (Mechanical)	<i>Moderate risk:</i> Bileaflet or tilting disk aortic valves in NSR	Lifelong Warfarin	II-2	B
	<i>High risk:</i> Bileaflet or tilting disk aortic valves in AF; Bileaflet or tilting disk mitral valve in AF or NSR.	Lifelong Warfarin (target INR 3.0; range 2.5-3.5)	II-3	B
	Caged-ball and caged-disk designs; documented stroke/TIA despite adequate therapy with Warfarin.	Lifelong Warfarin (target INR 3.0; range 2.5-3.5) plus Aspirin 75-150mg daily	II-1	B
Bioprosthetic heart valves	<i>High risk:</i> AF; left atrial thrombus at surgery; previous stroke/TIA or systemic embolism.	If high-risk factors are present, consider Warfarin for 3-12 months or longer.	III	C
		For all other patients, give Warfarin for 3 months post-op, then Aspirin 75-150mg daily.	III	C

Mitral Stenosis	<i>High risk:</i> AF; previous stroke/TIA; left atrial thrombus; left atrial diameter > 55mm on Echo.	If high risk factors present, consider long-term Warfarin.	II-3	B
		For all other patients start Aspirin 75-150mg daily.	II-2	B
MI and LV dysfunction	<i>High risk:</i> Acute/recent MI (<6 months); extensive infarct with anterior wall involvement; previous stroke/TIA.  <i>Very high risk:</i> Severe LV dysfunction (EF < 28%); LV aneurysm; spontaneous echo contrast; LV thrombus; dilated non-ischaemic cardiomyopathies.	If risk factors are present without LV thrombus: consider Warfarin for 3-6 months followed by Aspirin 75-150mg daily.	III	C
		If LV thrombus is present, consider Warfarin for 6-12 months	III	C
		For dilated cardiomyopathies including peripartum, consider lifelong Warfarin	III	C
<i>Recommended Warfarin dose INR target 2.5 [range 2.0 to 3.0] unless stated otherwise</i>				

**Table 5.5: Anticoagulation for the Patient with Acute Cardioembolic Stroke**

Treatment	Recommendations	Level of Evidence	Grade
Warfarin	Adjusted-dose warfarin may be commenced within 2-4 days after the patient is both neurologically and medically stable.	II-2	C
Heparin (unfractionated)	Adjusted-dose unfractionated heparin may be started concurrently for patients at very high risk of embolism.	III	C
Anticoagulation	Anticoagulation may be delayed for 1-2 weeks if there has been substantial haemorrhage.	III	C
	Urgent routine anticoagulation with the goal of improving neurological outcomes or preventing early recurrent stroke is not recommended.	I	A
	Urgent anticoagulation is not recommended for treatment of patients with moderate-to-large cerebral infarcts because of the high risk of intracranial bleeding.	I	A

HAS-BLED stands for Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (age over 65), and Drugs/alcohol concomitantly; the maximum possible score is 9 with 1 point for each of the components (with abnormal renal/liver function, for example, a person scores 2 if both are present and similarly for drugs/alcohol).<sup>97,98</sup> "Drugs" refer to any medications that increases the bleeding risk during anticoagulation, such as Aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), or even steroids on top of Warfarin, and "alcohol" refers to alcohol abuse.

*(New recommendation)*

Risk of bleeding is as following (see chart):

HAS-BLED score	n	Bleeds, n	Bleeds/100 patients*
0	798	9	1.13
1	1286	13	1.02
2	744	14	1.88
3	187	7	3.74

## 5.8 Revascularisation Procedures

Surgical procedures in stroke management may be classified to procedures performed to prevent first stroke occurrence (primary prevention in asymptomatic patients) or following a stroke event (secondary prevention).

### 5.8.1 Primary Prevention

Carotid endarterectomy (CEA) has been compared to conservative medical therapy for asymptomatic patients without prior history of TIA or stroke for whom imaging of the carotid arteries reveals a definite stenosis. Of the 5 published randomized studies, only 2 were sufficiently powered to compare the outcomes between surgery and medical therapy. The absolute 5-year risk reduction for patients with 70-99% carotid artery stenosis (by ultrasound) was 5.4% in the recent follow-up of the ACST trial, which was consistent with the ACAS study from North America (5-year absolute risk reduction of 5.9%).<sup>99,100</sup> This translates into a 1% annual stroke rate reduction. Patients who are asymptomatic and receiving appropriate medical therapy face an annual stroke rate of 2% without CEA. Surgical morbidity and mortality often exceed this beneficial risk reduction. In the ACST and ACAS trials, surgery-related events were 3.1% and 2.3%, respectively.<sup>99,100</sup> In an unselected patient group undergoing CEA in a centre without proper auditing of the surgeon or the centre's operative records, the complications are likely to outweigh the benefits of CEA. Furthermore, asymptomatic patients should not be offered CEA if their 5-year probability of dying from unrelated causes is high. Finally, in the NASCET study, nearly 45% of all strokes occurring in patients with asymptomatic stenosis may be attributable to lacunar infarcts or cardioembolism.<sup>101</sup>

**Recommendation:** Endarterectomy may be considered in patients with high-grade asymptomatic carotid stenosis (70-99%) when performed by a surgeon with less than 3% morbidity/ mortality rate. (Level I, Grade A)

Careful patient selection, guided by comorbid conditions, life expectancy, and patient preference, followed by a thorough discussion of the risks and benefits of the procedure is required. It is important that asymptomatic patients receive appropriate medical treatment and be fully evaluated for other treatable causes of stroke.

### 5.8.2 Secondary Prevention

Two large randomized trials (NASCET and ECST) have compared the outcomes of patients with recent cerebrovascular symptoms treated conservatively or with carotid endarterectomy.<sup>102,103</sup> Long-term follow-up and a meta-analysis is available for these trials.<sup>104</sup> Standardizing the same measurements and definitions yielded highly consistent results among the 3 trials. In general, CEA is highly beneficial for patients with carotid stenosis (70-99%), producing a 16% absolute 5-year risk reduction (ARR). For patients with 50-69% stenosis, the 5-year ARR was 4.6%. No benefit was observed for patients with milder degrees of stenosis. Subgroup analyses revealed that benefits in surgery was the greatest in men, aged 75 years or older, and those randomized within 2 weeks of their stroke event. These studies excluded patients with medical co-morbidities, previous neck irradiation and recurrent stenosis following previous endarterectomy.

Extracranial-intracranial anastomosis between the superficial temporal and middle cerebral arteries (EC-IC Bypass) has not been shown to be beneficial for secondary stroke prevention by the EC/IC Bypass Study Group.

**Recommendation:** CEA is indicated for patients with carotid stenosis of 70-99% without a severe neurological deficit following a recent ischaemic event (less than 180 days) in centres with a perioperative complication rate for all strokes and deaths of less than 6%.

*(Level I, Grade A)*

**Recommendation:** Early CEA is indicated for patients with carotid stenosis of 70-99% without a severe neurological deficit within 2 weeks of recent ischaemic events in centres with a perioperative complication rate for all strokes and deaths of less than 6%.

*(Level II-1, Grade B)*

**Recommendation:** CEA may be indicated for patients with carotid stenosis of 50-69% without a severe neurological deficit with recent ischaemic event (less than 180 days) in centres with a perioperative complication rate for all strokes and deaths of less than 6%.

*(Level III, Grade C)*

**Recommendation:** CEA is not recommended for patients with carotid stenosis less than 50%.

*(Level I, Grade A)*

CEA should not be performed in centres not exhibiting low complication rates similar to those seen with NASCET or ECST.

*(Level I, Grade A)*

**Recommendation:** Patients should remain on antithrombotic therapy before and after surgery.

*(Level II-2, Grade B)*

**Recommendation:** External/internal carotid bypass is not recommended for secondary stroke prevention.

*(Level I, Grade A)*

## 5.9 Angioplasty or Stenting

This is a rapidly evolving field in stroke treatment and prevention. Several randomized trials have compared extra-cranial carotid angioplasty and stenting (CAS) to carotid endarterectomy (CEA).<sup>99,101,105,106</sup>

**Recommendation:** CAS represents a feasible alternative to carotid endarterectomy for secondary stroke prevention when surgery is undesirable, technically difficult, or inaccessible.<sup>107,109</sup>

*(Level II-2)*

In recent studies, the 4-year outcome in death, stroke and myocardial infarction was similar in CAS and CEA. However, the periprocedural rate of stroke was higher in the CAS group while the periprocedural rate of myocardial infarction was higher in the CEA group. Selection of patients for either CAS or CEA may require attention to age, with younger patients having a slightly better outcome with CAS and older patients having a better outcome with CEA.<sup>106-112</sup>

The criteria needed for a centre to do CAS:

- I. highly qualified surgeons and interventionists
- II. surgeons and interventionists that are credentialed
- III. must use distal embolic protection device
- IV. use of dual antiplatelet therapy after CAS for at least 4 weeks

**Recommendation:** Distal protection devices should be used during the procedure and use of dual antiplatelet for at least 4 weeks after CAS.

*(Level I, Grade A)*

**Recommendation:** Complex configuration of the aortic arch and internal carotid artery tortuosity increase the risk of cerebral ischemia in CAS.<sup>113</sup>

*(Level II-2, Grade B)*

Intracranial artery stenting (IAS) is also technically feasible but has not been proven to be an established treatment modality. A re-stenosis rate of up to 30% has been reported.<sup>105</sup> Clinical data has much less evidence with more controversy as compared to carotid angioplasty.<sup>105</sup> The SAMMPRIS and VISSIT randomized trials found that patients with symptomatic intracranial atherosclerosis treated with angioplasty and stenting had worse outcomes than those who received medical therapy<sup>114,115</sup>.

The role of CAS in intra-cranial stenoses, asymptomatic stenoses and acute stroke is unclear and may not be recommended.<sup>102,103,116</sup> However, the most recent study (WEAVE Trial) showed that with experienced interventionalists, and proper patient selection, the use of the stent for intracranial atherosclerotic disease demonstrated a low periprocedural complication rate and excellent safety profile.<sup>117</sup>

Therefore, careful selection with extensive multidisciplinary discussions by centres experienced in stroke management is recommended. As angioplasty with or without stenting is still an investigational procedure, it should be carried out under appropriate clinical trial protocols.

**Recommendation:** Role of IAS in intra-cranial stenoses, asymptomatic stenoses and acute stroke is unclear and may be recommended.

*(Level II-2, Grade C)*



**Table 5.6: Revascularisation Procedures**

Treatment	Recommendations	Level of Evidence	Grade
Carotid Endarterectomy (CEA)	<i>Primary Prevention</i> May be considered in patients with high grade asymptomatic carotid stenosis (70-99%) when performed by surgeons with less than 3% morbidity/mortality rate.	I	A
	<i>Secondary Prevention</i> Indicated for most patients with a stenosis of 70-99% after a recent ischaemic event in centres with complication rates of less than 6%.	I	A
	Earlier intervention (within 2 weeks) is more beneficial.	II-1	B
	May be indicated for patients with a stenosis of 50-69% after a recent ischaemic event in centres with complication rates of less than 6%.	III	C
	Not recommended for patients with a stenosis of less than 50%.	I	A
	Patients should remain on antiplatelet therapy before and after surgery.	II-2	B
Carotid angioplasty and stenting (CAS)	CAS represents a feasible alternative to carotid endarterectomy for secondary stroke prevention when surgery is undesirable, technically difficult, or inaccessible.	II-2	B
	Distal protection devices should be used during the procedure.	I	A
	Use of dual antiplatelet for at least 4 weeks after CAS.	I	A
	The long-term safety (for 4 years) for CAS is as good as CEA.	I	A
	Complex configuration of the aortic arch and internal carotid artery tortuosity increase the risk of cerebral ischemia in CAS	II-2	B
Intracranial angioplasty & stenting (IAS)	Role of IAS in intra-cranial stenoses, asymptomatic stenoses and acute stroke is unclear and may be recommended.	II-2	C

**Key Recommendations:**

1. Stroke is a preventable disease and may be attributed to modifiable and non-modifiable risk factors.
2. Modifiable risk factors are the focus of primary prevention and can be clustered into three main groups i.e.
  - a) Lifestyle risk factors, i.e., smoking, physical inactivity, and unhealthy eating
  - b) Metabolic risk factors, i.e., high systolic BP, high cholesterol, high fasting blood glucose, low eGFR and high BMI.
  - c) Environmental factors, i.e., air pollution and lead exposure.
3. Secondary prevention of stroke involves the prevention of recurrent stroke, and this may involve medical interventions includes antiplatelet therapy, anti-hypertensive treatment, lipid-lowering agents, glycaemic control, prevention of cardio-embolism and re-vascularisation procedures in selected cases.

# 6

## INVESTIGATIONS

### 6.1 Investigational Objectives

Investigations carried out for stroke patients are aimed to:

- I. Confirm the diagnosis
- II. Determine the mechanism of stroke
- III. Stratify risks and determine prognosis
- IV. Identify potential treatable large obstructive lesions of the cerebrovascular circulation

### 6.2 Types of Investigations

#### 6.2.1 Haematological Investigations

The required haematological investigations are displayed in Table 6.1.

**Table 6.1: Haematological Investigations Required**

Table 6.1: Haematological Investigations Required	
<b>On Admission</b>	
Full blood count	Exclude anaemia, polycythaemia, thrombocytosis, thrombocytopenia, etc.
Random blood glucose	Exclude hypoglycaemia or hyperglycaemia, new diagnosis of diabetes mellitus
Urea & electrolytes	Hydration status, excludes electrolyte imbalances
Clotting profile*	Baseline
<b>Next Day</b>	
Lipid profile (fasting)	
Glucose (fasting)	
<b>Optional Tests (in selected patients)</b>	
VDRL	
Autoimmune screen	ESR, anti-nuclear antibody, rheumatoid factor, anti-double stranded DNA antibodies, C3 and C4 levels, etc.
Thrombophilia screen & lupus anticoagulant	Serum fibrinogen, anti-thrombin III, protein C, protein S, factor V-Leiden, anti-phospholipid antibodies, etc.
Homocysteine (fasting)	
C-reactive protein	

\* If thrombolysis considered

#### 6.2.2 Other Baseline Investigations

Other baseline investigations that are crucial for the management of stroke are listed in Table 6.2.

**Table 6.2: Other Investigations**

12 lead ECG	- Mandatory
Ambulatory ECG	- For suspected arrhythmias or sinoatrial node disease

### 6.2.3 Imaging

Important imaging investigations for suspected stroke patients are shown in Table 6.3.

Table 6.3: Imaging for Stroke Patients	
<b>For all suspected stroke</b>	
Chest x-ray	- Mandatory
CT brain	- The emergency neuroimaging scan of choice for all patients - Differentiates haemorrhage from infarction and some stroke mimickers - Confirms site of lesion, cause of lesion and extent of brain affected
<b>In selected patients</b>	
Echocardiography (ECHO)	- For suspected cardio-embolism, assess cardiac function
Magnetic Resonance Imaging (MRI)	- Sensitive - Available in very selected setting, limited by cost - Useful tool to select patients for revascularization where available
Carotid Duplex Ultrasound	- Allows identification of extracranial vessel disease
\Transcranial Doppler Ultrasound	- Identifies intracranial vessel disease with prognostic and therapeutic implications
MR Angiography (MRA)	- Non-invasive tool to assess intra- and extra-cerebral circulation - Objective assessment of vessel stenosis
CT Angiography (Multi-slice CT scan) (CTA)	- Non-invasive tool to assess intra- and extra-cerebral circulation - Involves intravenous contrast injection
CT or MR Perfusion (CTP/MRP)	- Non-invasive tool, CTA with CTP, or MRI with DWI-MRI with or without MRP is useful for selecting candidate for thrombolysis and mechanical thrombectomy in the extended hours.
MR Venography	- In suspected cerebral venous thrombosis
Contrast Angiogram	- Gold standard assessment of cerebral vasculature - Reserved for patients planned for intervention

#### Key Recommendations:

1. Investigations carried out in stroke are aimed to confirm the diagnosis, determine the mechanism of stroke, stratify risk, and to identify potential treatable vascular lesions.
2. Computed tomography (CT) brain is mandatory and is the preferred imaging investigation in the emergency setting to differentiate haemorrhage, determine the site, cause, and extent of the lesion.
3. Advance imaging may be required in selected cases in the emergency settings, e.g., ruling out stroke mimics, reperfusion therapy in extended hours and determining potential re-vascularisation procedure.
4. Selected blood investigations and imaging will be required in certain patients to determine the aetiology of stroke.

Most people with acute stroke (95%) have their first symptoms out of hospital.<sup>1</sup> Based on data in other countries, approximately two-thirds of all patients who seek acute care for stroke arrive to the emergency department by ambulance.<sup>2</sup>

Specific therapies for acute stroke, namely intravenous thrombolysis, and endovascular treatment (EVT) are time-critical treatments. Thus, they are most effective when initiated soon after the onset of symptoms. Proper treatment and disposition of stroke patients begins from the out-of-hospital environment, subsequently continues in the emergency department (ED), and extends to the inpatient admission. Therefore, it is essential for Emergency Medicine and Trauma Service (EMTS) personnel, Medical Emergency Coordination Centre (MECC) or Ambulance Dispatch Centre (ADC) personnel, and/or pre-hospital care responders and ED personnel, to recognise stroke early and as accurately as possible. At the same time, a strong working relationship are required between pre-hospital care staffs, ED staffs and the stroke team to improve timely assessments and early management.

Emergency medicine management framework for acute stroke include two distinct phases:

- I. Pre-hospital care phase
- II. Emergency department clinical care phase

## 7.1 Pre-hospital Management

### 7.1.1 Public education<sup>3,4</sup>

**Recommendation:** Public or community educational programmes should be designed to create awareness and knowledge of stroke warning signs.

*(New recommendation, Level II-1, Grade A)*

**Recommendation:** The educational programmes should also include the timely recognition and need to seek emergency care by calling 999 promptly.

*(New recommendation, Level II-1, Grade A)*

### 7.1.2 Emergency dispatch system<sup>5,6</sup>

**Recommendation:** Ambulance Dispatch Centres (ADC) should be familiar with common descriptors used by public for stroke. Whenever the descriptors are used, Emergency Medical Dispatchers (EMD) are trained to use the stroke protocols to identify suspected stroke patients.

*(New recommendation, Level II-1, Grade A)*

**Recommendation:** ADC should have a protocol or tools that allow Emergency Medical Dispatchers (EMD) to identify suspected stroke patients. Examples of stroke assessment tools are the MDPS Stroke Diagnostic Tool used by MECC, FAST (Face, Arm, Speech, and Time) stroke assessment or CPSS (Cincinnati Prehospital Stroke Scale).

*(New recommendation, Level II-1, Grade A)*

**Recommendation:** ADC should have a system in place to allow suspected stroke calls to receive priority in response that will facilitate early arrival of patients to the Emergency Department (ED).

*(New recommendation, Level II-1, Grade A)*

### **7.1.3 Initial on-scene management** <sup>3-4, 7-10</sup>

PHC responders (a medically trained person who responds to pre-hospital calls, usually an Assistant Medical Officer or Staff Nurse) should be familiar with the detection and management of stroke patients. *(Level II-1, Grade A)*

**Recommendation:** PHC responders should rapidly evaluate the airway, breathing and circulation in patients with suspected acute stroke to identify life threatening situations, and manage accordingly. *(New recommendation, Level II-1, Grade A)*

There are several validated prehospital stroke screening tools which can be utilized to identify stroke (pre-hospital diagnostic screening tools) and to assess severity of stroke (pre-hospital stroke severity scales) (see **Appendix B**). Stroke severity assessment may be considered if patient demonstrate any signs of stroke.

**Recommendation:** For stroke identification, PHC responders should use a validated and standardized assessment tool such as FAST or BE-FAST (Balance, Eyes, Face, Arm, Speech, Time) stroke assessment. Other identification assessment tools that can be used include CPSS, LAPSS (Los Angeles Prehospital Stroke Screen). <sup>11-16</sup> *(New recommendation, Level II-1, Grade A)*

**Recommendation:** PHC responders should be trained to identify hypoglycaemia as a stroke-mimic and apply appropriate management protocols. *(New recommendation, Level I, Grade A)*

**Recommendation:** PHC responders should ascertain the time of onset of stroke symptoms from the patient or witness(es). *(New recommendation, Level I, Grade A)*

**Recommendation:** PHC Service Providers should ensure its responders are made aware of the nearest hospital capable of providing thrombolysis and hospital capable of performing endovascular stroke treatment, within their service area. A written protocol that ensures the ambulance diversion of the patient to such hospitals should be made available for use. *(New recommendation, Level I, Grade A)*

**Recommendation:** All stroke patients from PHC with positive signs of stroke within the 4.5-hour therapeutic window for medical thrombolytic therapy should be transported rapidly to an acute stroke ready hospital. *(New recommendation, Level II-1, Grade A)*

**Recommendation:** Titrated doses of oxygen should be delivered to stroke patients with oxygen saturation levels below 95%. *(New recommendation, Level II-3, Grade B)*

### **7.1.4 Pre-arrival communication (Stroke Alert)** <sup>3,4</sup>

**Recommendation:** PHC Responders should be trained to provide pre-arrival notification of stroke patients to receiving hospitals. Ambulance Dispatch Centres can be used as an intermediary to provide stroke alert communication to hospitals. *(New recommendation, Level II-1, Grade A)*

**Recommendation:** MECC and associated stroke ready hospital(s) are recommended to have local regional stroke referral system/ network and agreement with the ED to facilitate the transport decision from PHC to ensure the treatment window of 4.5 hours is achieved (Stroke system of care). *(New recommendation, Level I, Grade A)*

## 7.2 Emergency Department Management

### 7.2.1 ED Evaluation

**Recommendation:** All patients presenting to an ED with suspected acute stroke must have immediate clinical evaluation and investigations to establish the diagnosis and to determine the eligibility for intravenous thrombolytic therapy and/or EVT.<sup>2,3,17</sup>

*(New recommendation, Level I, Grade A)*

**Recommendation:** The use of clinical screening tools such as FAST or BE-FAST to identify stroke by ED staff can be beneficial.<sup>15-18 (add be fast)</sup>

*(New recommendation, Level II-2, Grade B)*

### 7.2.2 Initial Assessment of Stroke Patient in ED

**Recommendation:** ED staff should rapidly evaluate airway, breathing and circulation on patients with suspected acute stroke and manage accordingly.<sup>1-3</sup>

*(New recommendation, Level I, Grade A)*

**Recommendation:** All patients with suspected acute stroke should have their blood glucose concentration checked upon arrival at the ED. Hypoglycaemia should be corrected immediately.<sup>2,3</sup>

*(New recommendation, Level II-1, Grade A)*

**Recommendation:** A standardized stroke severity scale such as the National Institutes of Health Stroke Scale (NIHSS) should be used to assess stroke severity in the ED.<sup>2,3</sup>

*(New recommendation, Level II-1, Grade A)*

### 7.2.3 Imaging

**Recommendation:** All patients with suspected stroke who are candidates for intravenous thrombolysis and/ or EVT should undergo at least a CT scan immediately. All other suspected stroke patients should have an urgent CT-brain. In most cases, a non-contrast CT (NCCT) brain will provide necessary information to make decisions about acute management.<sup>1-3,17</sup>

*(New recommendation, Level II-1, Grade A)*

**Recommendation:** Interpretation of acute stroke imaging for thrombolysis decisions should only be made by healthcare professionals who have received appropriate training.<sup>1,19</sup>

*(New recommendation, Level III, Grade C)*

### 7.2.4 Other Considerations

**Recommendation:** Patients with acute stroke should only receive supplemental oxygen if their oxygen saturation is below 95%.<sup>1-4,17</sup>

*(New recommendation, Level II-3, Grade B)*

**Recommendation:** Hypotension and hypertension in patients with acute stroke should be identified and managed accordingly.<sup>2,3</sup>

*(New recommendation, Level III, Grade C)*

**Recommendation:** Patients with acute stroke should have their swallowing ability screened as early as possible after arrival at the hospital and before being given any oral food, fluid, or medication.<sup>1,2,17</sup>

*(New recommendation, Level II-2, Grade B)*

## 7.2.5 Quality Improvement

**Recommendation:** Joint multidisciplinary audits to review and monitor stroke care quality benchmarks, indicators, evidence-based practices and outcomes should be performed periodically. Quality improvement should be conducted to look at gaps and disparities in order to improve patient care and outcome.<sup>3</sup>

*(New recommendation, Level II-1, Grade A)*

**Recommendation:** ED personnel should undergo a standardized training in acute stroke management.<sup>3,17</sup>

*(New recommendation, Level III, Grade C)*

**Appendix C** lists and describes the terms related to this chapter.

### Recommendations Summary:

Table 7.1: Emergency Medicine Services			
Management	Recommendations	Level of Evidence	Grade
<b><i>Pre-Hospital Management</i></b>			
Public education	Educational programmes		
	<ul style="list-style-type: none"> <li>- should be designed to create awareness and knowledge of stroke warning signs.</li> <li>- should include the timely recognition and need to seek emergency care by calling 999 promptly.</li> </ul> <p><i>New recommendation</i></p>	II-1	A
Emergency dispatch system	ADC		
	<ul style="list-style-type: none"> <li>- should be familiar with common descriptors used by the public for stroke. Whenever the descriptors are used, EMD are trained to use the stroke protocols to identify suspected stroke patients</li> <li>- should have a protocol or tools that allow Emergency Medical Dispatchers (EMD) to identify suspected stroke patients. e.g. MDPS Stroke Diagnostic Tool, FAST stroke assessment.</li> <li>- should have a system to priorities suspected stroke calls to facilitate the early arrival of patients to the ED.</li> </ul> <p><i>New recommendation</i></p>	II-1	A
Initial on-scene management	PHC responders		
	<ul style="list-style-type: none"> <li>- should rapidly evaluate airway, breathing and circulation to identify life threatening situation, and manage them accordingly.</li> <li>- should use a validated and standardized stroke identification assessment tool such as FAST or BE-FAST stroke assessment</li> <li>- should be trained to identify hypoglycaemia as a stroke-mimic and apply appropriate management protocols</li> <li>- should ascertain the time of onset of stroke symptoms from the patient or witness(es).</li> </ul>	II-1	A
	PHC Service Providers should ensure its responders are made aware of the nearest hospital capable of providing thrombolysis and hospital capable of performing endovascular stroke treatment, within their service area. A written protocol that ensures the ambulance diversion of the patient to such hospitals should be made available for use.	I	A

	<p>All stroke patients from PHC with positive signs of stroke within the 4.5-hour time window for medical thrombolytic therapy should be transported rapidly to an acute stroke ready hospital.</p> <p>II-1</p> <p>A</p> <p>Titrated dose of oxygen should be delivered to stroke patients with an oxygen saturation level of below 95%.</p> <p>II-3</p> <p>B</p> <p><i>New recommendation</i></p>		
Pre-arrival communication	<p>PHC Responders should be trained to provide pre-arrival notification of stroke patients to receiving hospitals.</p> <p>II-1</p> <p>A</p> <p>MECC and associated stroke ready hospital(s) are recommended to have local regional stroke referral system/ network and agreement with the ED to facilitate the transport decision from PHC to ensure the treatment window of 4.5 hours is achieved.</p> <p>I</p> <p>A</p> <p><i>New recommendation</i></p>		
<b>Emergency Department Management</b>			
ED Evaluation	<p>All patients presenting to an ED with suspected acute stroke must have immediate clinical evaluation and investigations to establish the diagnosis and to determine the eligibility for intravenous thrombolytic therapy and/or EVT</p> <p>I</p> <p>A</p> <p>The use of clinical screening tools such as FAST or BE-FAST to identify stroke by ED staff can be beneficial</p> <p>II-2</p> <p>B</p> <p><i>New recommendation</i></p>		
Initial Assessment in ED	<p>ED staff should rapidly evaluate airway, breathing and circulation in patients with suspected acute stroke and manage them accordingly</p> <p>I</p> <p>A</p> <p>All patients with suspected acute stroke should have their blood glucose concentration checked upon arrival at the ED</p> <p>II-1</p> <p>A</p> <p>A standardized stroke severity scale should be used such as the National Institutes of Health Stroke Scale (NIHSS) to assess stroke severity in the ED</p> <p>II-1</p> <p>A</p> <p><i>New recommendation</i></p>		
Imaging	<p>All patients with suspected stroke who are candidates for intravenous thrombolysis and/ or EVT should undergo at least a CT scan immediately. All other suspected stroke patients should have an urgent CT-brain.</p> <p>II-1</p> <p>A</p> <p>Interpretation of acute stroke imaging for thrombolysis decisions should only be made by healthcare professionals who have received appropriate training.</p> <p>III</p> <p>C</p> <p><i>New recommendation</i></p>		
Other Considerations	<p>Patients with acute stroke should only receive supplemental oxygen only if their oxygen saturation is below 95%.</p> <p>II-3</p> <p>B</p> <p>Hypotension and hypertension in patients with acute stroke should be identified and managed accordingly.</p> <p>III</p> <p>C</p> <p>Patients with acute stroke should have their swallowing ability screened as early as possible after arrival at the hospital and before being given any oral food, fluid, or medication</p> <p>II-2</p> <p>B</p> <p><i>New recommendation</i></p>		



Quality Improvement	Joint multidisciplinary audit to review and monitor stroke care quality benchmarks, indicators, evidence-based practices, and outcomes should be performed periodically.	II-1	A
	ED personnel should undergo a standardized training in acute stroke management.  <i>New recommendation</i>	III	C

**Key Recommendations:**

1. The public should be encouraged to call 999 if they suspect a person is having a stroke.
2. Emergency medical dispatcher and prehospital care provider should be trained to recognize and identify stroke and are able to provide rapid transportation of suspected acute stroke patient to nearest stroke ready hospital.
3. Assessment of patient with suspected acute stroke in emergency department should be prioritized in order to expeditiously establish stroke diagnosis and to determine the best appropriate acute stroke interventions.
4. Audit of acute stroke care and training of emergency department personnel should be conducted to improve quality of care in acute stroke cases.

## 8.1 General Management

The primary aim of acute stroke management is for early reperfusion therapy which will be covered in Chapter 9 and 10. This chapter will cover the general management of acute stroke that includes supportive care and treatment of acute complications. This is important to improve the mortality rates and reduce the functional disability.

### 8.1.1 Oxygen and Airway Support

Adequate tissue oxygenation is imperative to prevent hypoxia and potential worsening of the neurological injury.<sup>1-5</sup>

*(Level II-3 to III)*

**Recommendation:** Patients with acute stroke should only receive supplemental oxygen if their oxygen saturation is below 95% and be titrated to achieve above 95%.<sup>6-9</sup>

*(New recommendation, Level II-3, Grade B)*

### 8.1.2 Observation

**Recommendation:** Regular observation is mandatory to recognise impaired pulmonary function (pulse oxymeter), circulatory function (pulse rate, blood pressure), NIHSS score, head chart, GCS, and complications from mass effect.<sup>1</sup>

*(Level III, Grade C)*

### 8.1.3 Mobilisation

Most patients are first treated with bed rest, but mobilisation should begin as soon as the patient's condition is judged to be stable.<sup>10-13</sup>

**Recommendation:** Mobilise early to prevent complications.

*(Level II-3, Grade C)*

Although two small RCTs showed that very early mobilisation (beginning within 24 hours) was feasible in an acute setting, the AVERT trial showed that very early, more frequent and higher dose of mobilisation focused on out-of-bed activities in addition to usual care was worse in terms of outcomes than usual care alone. Very early mobilisation reduced the odds of favourable outcomes at three months.<sup>14</sup>

**Recommendation:** High-dose, very early mobilisation within 24 hours of stroke onset should not be recommended.

*(New recommendation, Level I)*

### 8.1.4 Blood Pressure

In patients with AIS, early treatment of hypertension is indicated when required by comorbid conditions (e.g. concomitant acute coronary event, acute heart failure, aortic dissection, post-thrombolysis sICH, or preeclampsia/eclampsia). In patients with a BP of  $\geq 220/120$  mm Hg who have not received IV alteplase or EVT and have no comorbid conditions requiring acute antihypertensive treatment, the benefit of initiating or reinitiating treatment of hypertension within the

first 48 to 72 hours is uncertain. It might be reasonable to lower BP by 15% during the first 24 hours after the onset of stroke.<sup>15-20</sup>

**Recommendation:** Lowering BP initially by 15% is probably safe. Very high blood pressure should be reduced gradually.

*(New recommendation, Level III, Grade C)*

**Recommendation:** Do not treat hypertension if systolic BP is <220mmHg or diastolic BP is <120mmHg. Mild hypertension is desirable at 160-180/90-100 mmHg.

*(New recommendation, Level III, Grade C)*

**Recommendation:** Proposed drugs: Labetalol 10-20mg boluses at 10 minute intervals up to 150-300mg or 1mg/ml infusion, with the rate of infusion of 1-3mg/min or oral Captopril 6.25-12.5mg. Sublingual use of a calcium antagonist, such as Nifedipine, should be avoided because of the risk of rapid decline in blood pressure.<sup>21</sup>

*(Level II-3, Grade C)*

### **8.1.5 Blood Glucose**

Hyperglycaemia following acute stroke is strongly associated with subsequent mortality and impaired neurological recovery. This applies to both diabetics and non-diabetics.<sup>22,23</sup>

*(Level II-3, Grade C)*

The International Diabetes Federation published a comprehensive guideline on managing older people with type 2 diabetes which included a section on management of hyperglycaemia post-acute stroke.<sup>24</sup>

At present, the optimal level of blood glucose after a stroke is unclear. A systematic review of 11 RCTs concluded that the administration of intravenous insulin to maintain tight glucose control within a specific range (4.0-7.5 mmol/L) in the first few hours of acute ischaemic stroke does not provide benefit in terms of functional outcome, death, or improvement in final neurological deficit, but significantly increased the number of hypoglycaemic episodes.<sup>25</sup>

**Recommendation:** After an acute stroke, treat hyperglycaemia to keep the blood glucose levels between 6.0-10.0 mmol/L and ensure that hypoglycaemia is avoided.<sup>24</sup>

*(New recommendation, Level III, Grade C)*

**Recommendation:** Avoid very tight targets of glucose control (4.0-7.5 mmol/L) in the first few hours of acute ischaemic stroke.

*(New recommendation, Level I, Grade A)*

### **8.1.6 Nutrition**

Sustaining nutrition is important as malnutrition after stroke might interfere with recovery.<sup>26</sup> Persons with infarctions of the brain stem, multiple strokes, large hemispheric lesions, or depressed consciousness are at the greatest risk for aspiration. Swallowing impairments are associated with an increased mortality.

The FOOD RCT's showed that supplemented diet was associated with an absolute reduction in risk of death of 0.7% and that early tube feeding (within 7 days of admission) was associated with an absolute reduction in risk of death by 5.8% and a reduction in death or poor outcomes by 1.2%.<sup>27,28</sup>

**Recommendation:** Enteral feeding should be started within 7 days of admission (oral or tube feeding).

*(New recommendation, Level I, Grade A)*

A water swallowing test (refer to **Appendix C**) should be performed before the patient is allowed to eat or drink. A wet voice after swallowing, incomplete oral-labial closure, or coughing reflex on swallowing indicates high risk of developing aspiration. There is good evidence that a multi-item dysphagia screening protocol that includes at least a water intake test of 10 teaspoons and a lingual motor test was more accurate than screening protocols with only a single item.<sup>29</sup>

**Recommendation:** Perform a water swallowing test. Insert a nasogastric tube if the patient fails the swallowing test.

*(Level III, Grade C)*

An instrumental evaluation such as a video fluoroscopic swallowing examination (VFSE) or modified barium swallow examination (MBS) can be performed later if indicated.<sup>1,30</sup>

*(Level III, Grade C)*

If the patient fails the swallowing test, a nasogastric tube should be inserted to prevent aspiration. PEG tube is superior to nasogastric tube feeding if a prolonged need for devices is anticipated.<sup>31</sup>

**Recommendation:** PEG is superior to nasogastric feeding only if prolonged enteral feeding is required.

*(Level II-1, Grade B)*

### **8.1.7 Infection**

Infection is the commonest complication after an acute stroke especially pneumonia and urinary tract infection.<sup>32</sup>

The appearance of fever should prompt a search for infection and appropriate antibiotic therapy should be administered early.<sup>32</sup> Bladder catheters should be avoided if possible.<sup>1</sup>

**Recommendation:** Search for infection if fever appears and treat with appropriate antibiotics early.

*(Level III, Grade C)*

Routine use of prophylactic antibiotics has not been shown to be beneficial.

*(New recommendation, Level I, Grade A)*

### **8.1.8 Fever**

A meta-analysis suggested that fever after the onset of stroke was associated with marked increase in mortality and morbidity.<sup>33</sup>

**Recommendation:** Antipyretics should be used to control elevated temperatures in acute stroke patients.<sup>33,34</sup>

*(Level II-1, Grade B)*

The benefit of induced hypothermia for treating patients with ischaemic stroke is not well established.<sup>35-38</sup>

Hypothermia should be offered only in the context of on-going clinical trials.

*(New recommendation, Level I, Grade A)*

### 8.1.9 Continence

The application of indwelling catheter should be treated cautiously due to the risk of urinary tract infection.

**Recommendation:** If being used, daily assessment (with excellent perineum care) needs to be carried out and should be removed as soon as possible.<sup>39</sup>

*(New recommendation, Level I, Grade A)*

**Recommendation:** All stroke patients should be screened for urinary retention or incontinence, faecal incontinence, and constipation. The use of portable ultrasound machine (non-invasive) is recommended for assessing the post-void residual volume. A bladder training program should be implemented in patient who have urinary incontinence, including the use of intermittent catheterization based on post-void residual urine volume and bowel management procedures should be taught to patients/carers of patients with constipation and faecal incontinence.<sup>39</sup>

*(New recommendation, Level III, Grade C)*

### 8.1.10 Raised Intracranial Pressure

Cerebral oedema and increased intracranial pressure largely occur with large cerebral infarctions.

**Recommendation:** Hyperventilation is an emergency measure that acts almost immediately; a reduction of the PCO<sub>2</sub> by 5 to 10 mmHg can lower intracranial pressure by 25% to 30%.<sup>1,40</sup>

*(Level II-2, Grade B)*

Disability outcomes after acute stroke did not differ significantly between patients assigned to a lying-flat position for 24 hours and patients assigned to a sitting-up position with the head elevated to at least 30 degrees for 24 hours.<sup>41</sup>

*(Level I)*

**Recommendation:** Mannitol (0.25 to 0.5g/kg) administered intravenously over 20 minutes lowers intracranial pressure and can be given every 6 hours.<sup>42</sup> Maximum daily dose is 2g/kg.

*(Level II-2, Grade B)*

**Recommendation:** If hydrocephalus is present, drainage of cerebrospinal fluid via an intra-ventricular catheter can rapidly lower intracranial pressure.<sup>1</sup>

*(Level III, Grade C)*

The pooled result of RCTs demonstrated significant reduction in mortality when decompressive craniectomy was performed within 48 hours of malignant MCA infarction in patients <60 years of age, with an absolute risk reduction in mortality of 50% (95% CI 34–66%) at 12 months.<sup>43</sup>

There is evidence that patients aged >60 years can benefit from decompressive craniectomy. Hemicraniectomy increased survival without severe disability among patients aged 61 years or older with a malignant middle-cerebral-artery infarction. The majority of survivors required assistance with most of the bodily functional needs.<sup>44</sup>

**Recommendation:** Hemicraniectomy and surgical decompressive therapy within 48 hours after symptom onset is recommended to control intracranial pressure and prevent herniation among those patients with very large infarcts of the cerebral hemisphere.

*(New recommendation, Level I, Grade A)*

**Recommendation:** Patients >60 years of age may be considered for decompressive craniectomy in selected cases.

*(New recommendation, Level I, Grade A)*

**Recommendation:** Ventriculostomy and sub-occipital craniectomy are effective in relieving hydrocephalus and brain stem compression caused by large cerebellar infarctions.<sup>45,46</sup>

*(Level II-2, Grade B)*

### **8.1.11 Deep Vein Thrombosis**

Venous thromboembolism is a common, potentially avoidable cause of death and morbidity in patients, including those with stroke. Up to 50% of patients have thrombus in either the calf or thigh of the paretic limb.

Intermittent pneumatic compression (IPC) is an effective method of reducing the risk of DVT and to possibly improve survival in a variety of patients who are immobile after stroke.<sup>47</sup>

**Recommendation:** For immobile stroke patients without contraindications, intermittent pneumatic compression (IPC) in addition to routine care (aspirin and hydration) is recommended over routine care to reduce the risk of deep vein thrombosis (DVT).

*(New recommendation, Level I, Grade A)*

Prophylactic anticoagulants (unfractionated heparin or LMWH) were not associated with any significant effect on mortality or functional status at the final follow-up. There were statistically significant reductions in the incidences of symptomatic pulmonary embolisms and in DVTs, most of which were asymptomatic. There were statistically significant increases in the incidences of symptomatic intracranial haemorrhage and symptomatic extracranial haemorrhages.<sup>48</sup>

**Recommendation:** The benefit of prophylactic-dose subcutaneous heparin (unfractionated heparin [UFH] or LMWH) in immobile patients with AIS is not well established.

*(New recommendation, Level III, Grade C)*

The CLOTS 1 and 2 trials showed that graduated compression stockings were ineffective in preventing VTE or improving functional outcomes in stroke. Skin breaks, ulcers, blisters, and skin necrosis were significantly more common in patients allocated to graduated compression stockings than in those who avoided their use.<sup>49,50</sup>

**Recommendation:** In ischaemic stroke, elastic compression stockings should not be used.

*(New recommendation, Level I, Grade A)*

### **8.1.12 Seizure**

Early seizures after stroke are relatively uncommon, however if they do occur, it is associated with a poor outcome. Risk factors includes a more severe stroke severity and cortical involvement.

**Recommendation:** New-onset seizures in admitted patients with acute stroke should be treated using appropriate short-acting medications if they are not self-limiting.<sup>6,39</sup>

*(New recommendation, Level III, Grade C)*

**Recommendation:** A single, self-limiting seizure occurring at the onset, or within 24 hours after an ischemic stroke (considered an “immediate” post-stroke seizure) should not be treated with long-term anticonvulsant medications. The use of prophylactic anti-seizure medications is not recommended.<sup>6,39</sup>

*(New recommendation, Level III, Grade C)*

**Recommendation:** Patients that have an immediate post-stroke seizure should be monitored for recurrent seizure activity and should be treated as per treatment recommendations for seizures in other neurological conditions and treatment should be individualised.<sup>6,39</sup>

*(New recommendation, Level III, Grade C)*

## Recommendations Summary:

**Table 8.1 : Acute General Management**

Factors	Recommendations	Level of Evidence	Grade
Oxygen and Airway support	Patients with acute stroke should only receive supplemental oxygen if their oxygen saturation is below 95% and be titrated to achieve above 95%. <i>New recommendation</i>	II-3	B
Observation	Regular observation is mandatory to recognise impaired pulmonary function (pulse oxymeter), circulatory function (pulse rate, blood pressure), NIHSS score, head chart, GCS, and complications from mass effect.	III	C
Mobilisation	Mobilise early to prevent complications.	II-3	C
	High-dose, very early mobilisation within 24 hours of stroke onset should not be performed because it can reduce the odds of a favourable outcome at 3 months. <i>New recommendation</i>	I	-
Blood Pressure	Lowering BP initially by 15% is probably safe. Blood pressure reduction should not be drastic. <i>New recommendation</i>	III	C
	Do not treat hypertension if systolic BP is <220mmHg or diastolic BP is <120mmHg. Mild hypertension is desirable at 160-180/90-100 mmHg.	III	C
	<i>Proposed substances:</i> Labetalol 10-20mg boluses at 10-minute intervals up to 150-300mg or 1mg/ml infusion, rate of infusion for Labetalol is 1-3mg/min or oral Captopril 6.25-12.5mg.	III	C
Blood Glucose	After an acute stroke, treat hyperglycaemia to keep the blood glucose levels between 6.0-10.0 mmol/L and ensure that hypoglycaemia is avoided. <i>New recommendation</i>	III	C
	Avoid very tight targets of glucose control (4.0-7.5 mmol/L) in the first few hours of acute ischaemic stroke. <i>New recommendation</i>	I	A
Nutrition	Perform a water swallowing test.	III	C
	Insert a nasogastric tube if the patient fails the swallowing test.	III	C
	PEG is superior to nasogastric feeding only if prolonged enteral feeding is required	II-1	B
	Enteral feeding should be started within 7 days of admission (oral or tube feeding). <i>New recommendation</i>	I	A
Infection	Search for infection if fever appears and treat with appropriate antibiotics early.	III	C
Fever	Use anti-pyretics to control elevated temperatures.	II-1	B
Continence	The use application of indwelling catheter should be used treated cautiously due to the risk of urinary tract infection. <i>New recommendation</i>	I	A
	All stroke patients should be assessed for urinary retention or incontinence, faecal incontinence, and constipation. <i>New recommendation</i>	III	C
Raised Intracranial Pressure	Hyperventilate to lower the intracranial pressure.	II-2	B
	Mannitol (0.25 to 0.5g/kg) intravenously administered over 20 minutes lowers intracranial pressure and can be given every 6 hours.	II-2	B
	If hydrocephalus is present, drainage of cerebrospinal fluid via an intraventricular catheter can rapidly lower the intracranial pressure.	III	C
	Hemicraniectomy and surgical decompressive therapy within 48 hours after symptom onset is recommended to control the	I	A

	intracranial pressure and prevent herniation among those patients with very large infarcts of the cerebral hemisphere.		
	Patients >60 years of age may be considered for decompressive craniectomy in selected cases. <i>New recommendation</i>	I	A
	Ventriculostomy and sub-occipital craniectomy are effective in relieving hydrocephalus and brain stem compression caused by large cerebellar infarctions.	II-2	B
Deep Vein Thrombosis Prophylaxis	For immobile stroke patients without contraindications, intermittent pneumatic compression (IPC) in addition to routine care (aspirin and hydration) is recommended over routine care to reduce the risk of deep vein thrombosis (DVT). <i>New recommendation</i>	I	A
	The benefit of prophylactic-dose subcutaneous heparin (unfractionated heparin [UFH] or LMWH) in immobile patients with AIS is not well established. <i>New recommendation</i>	III	C
	In ischaemic stroke, elastic compression stockings should not be used. <i>New recommendation</i>	I	A
Seizure	New-onset seizures in admitted patients with acute stroke should be treated using appropriate short-acting medications if they are not self-limiting. <i>New recommendation</i>	III	C
	A single, self-limiting seizure occurring at the onset, or within 24 hours after an ischemic stroke (considered an “immediate” post-stroke seizure) should not be treated with long-term anticonvulsant medications. The use of prophylactic anti-seizure medications is not recommended. <i>New recommendation</i>	III	C
	Patients that have an immediate post-stroke seizure should be monitored for recurrent seizure activity and should be treated as per treatment recommendations for seizures in other neurological conditions and treatment should be individualised. <i>New recommendation</i>	III	C

### Key Recommendations:

1. Acute general management in stroke includes supportive care and treatment of acute complications in order to improve mortality and functional disability.
2. General management includes the management of blood pressure, glycaemic control, nutritional support, prevention of infection and DVT and also to treat potential sequelae, e.g. raised intracranial pressure and seizure.



# 9

## REPERFUSION OF ISCHAEMIC BRAIN

### 9.1 Introduction

In cerebral infarcts, restoration of perfusion to the ischaemic brain tissues is the key therapeutic strategy. The concept of existence of an ischaemic penumbra is fundamental to the current approach in the treatment of ischaemic stroke. Although the core infarcted tissues might not be salvageable, adjacent dysfunctional tissue might be saved if the circulation is restored and metabolism is normalized.

Reperfusion therapy is the single most important and beneficial treatment for acute ischaemic stroke. It would be considered unethical if no attempt at reperfusion is made. Reperfusion therapy can be achieved via intravenous thrombolysis (IVT) or/and endovascular thrombectomy (EVT).

IVT is indicated for patients with onset of symptoms within 4.5 hours of presentation, while EVT for large vessel occlusion (LVO) could be offered up to 24 hours using advanced imaging such as CT/MR perfusion scan. LVO include the ICA and M1 MCA occlusions. It is reasonable to include EVT for ACA, PCA and basilar artery occlusions.<sup>1</sup>

*(Level I, Grade A)*

Stroke treatment protocol and an organized stroke pathway is essential and should be established to achieve the recommended response time for IVT and EVT, in order to improve the clinical outcomes.<sup>1,2</sup> Stroke organizations should incorporate the emergency department (ED) including their pre-hospital care team, radiology department and stroke team. The management of acute ischaemic stroke at the pre-hospital care phase and emergency department phase were explained in Chapter 7.

### 9.2 Recommended NIH Emergency Response Time for AIS

	Time (Minutes)
Door to MD consult and initial work up	≤ 10 min
Door to neuro consult	≤ 15 min
Door to CT	≤ 25 min
Door to needle	≤ 60 min
Door to groin	≤ 120 min

Stroke teams may be composed of neurologists/physicians, medical officers with/without stroke nurses, neuro-interventional experts (interventional neuroradiologist or interventional neurologist/neurosurgeon), rehabilitation physicians, physiotherapists, occupational therapists, speech therapists, pharmacists, social workers, and psychologists. The composition of the stroke team depends on whether the hospital is a primary stroke centre or a comprehensive stroke centre. Roles of the stroke team during the acute presentation of ischaemic stroke include:

- to ascertain history and findings that are compatible with AIS
- perform NIHSS and mRS scoring
- exclude contraindications
- review neuroimaging
- making treatment decisions and to administer IVT and/or EVT
- to closely monitor and admit patients to the stroke care unit

**Recommendation:** All stroke patients should be nursed/ admitted to a stroke care unit.<sup>3</sup>  
(Level I, Grade A)

Suspected AIS patients within the reperfusion window should be sent to stroke ready hospitals or hospitals with a CT scan. Therefore, a regional stroke referral system should be developed to provide swift referral and transportation of the AIS patient to adjacent stroke ready hospitals which could be either a primary stroke centre or a comprehensive stroke centre. IVT can be initiated at the primary stroke centre prior to the transfer to a comprehensive stroke centre for EVT. Hospitals within the stroke care system should adhere to the protocol to provide the best standard of care available.

In a situation where a radiologist/stroke-trained physician is not available, telemedicine may be utilized to assist in the management of AIS patient:

**Recommendation:** Tele-stroke could be beneficial for sites without in house neurology or neuroradiology services to hasten the IVT with Alteplase eligibility decision making and delivery.<sup>1, 4-6</sup>  
(New recommendation, Level II, Grade B)

**Recommendation:** Telephone consultation for physician is feasible, safe and may be considered if an in-house stroke team and tele-stroke are not available.<sup>7,8</sup>  
(New recommendation, Level III, Grade C)

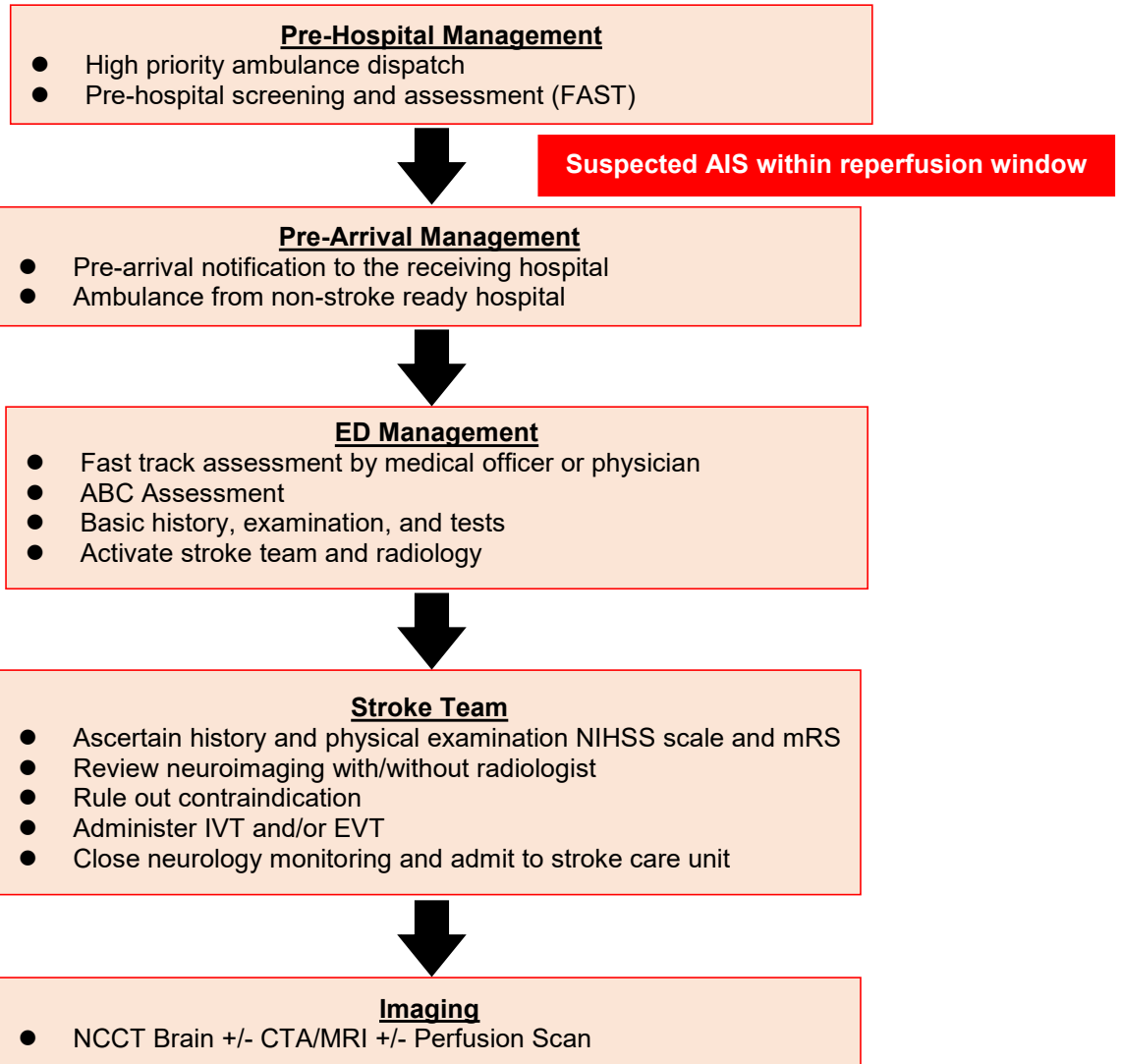


Figure 9.1: Acute Ischaemic Stroke Pathway

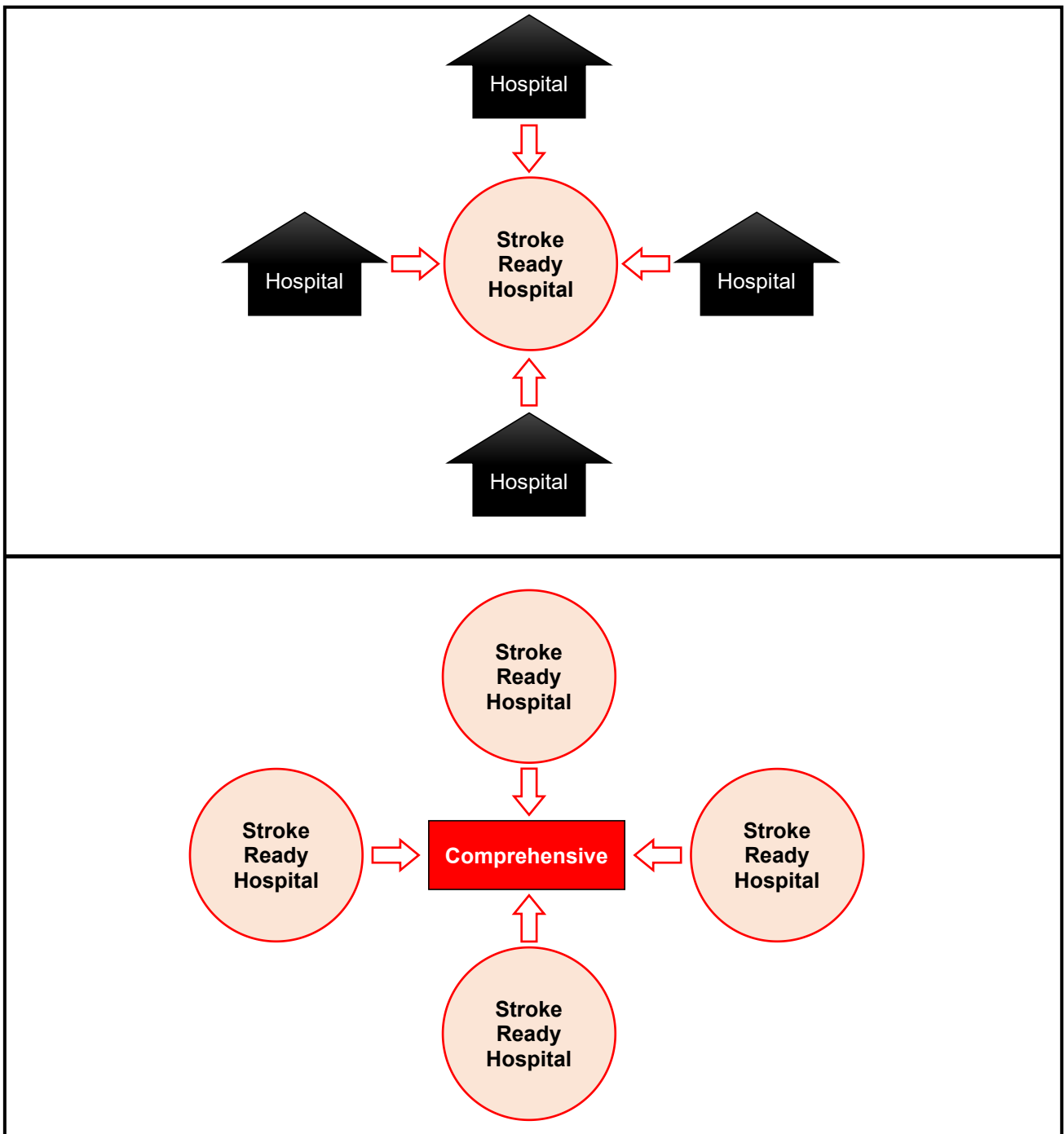


Figure 9.2: Regional Stroke Referral System Concept for Acute Ischaemic Stroke Management

### **9.3 Intravenous Thrombolysis**

For patients that are found to be eligible for IVT, the benefit of therapy is time dependent, and treatment should be initiated as quickly as possible. Thus, early detection and activation of the thrombolysis pathway is paramount and concerted effort should be made to deliver the treatment as soon as possible.

#### **9.3.1 Requirement for Thrombolysis (IVT)**

- I. Physicians with experience in treating hyperacute stroke
- II. Neuroimaging availability; NCCT ± CTA; MRI; perfusion scan
- III. Capability to manage complications of thrombolysis, particularly intracranial haemorrhage, and access to neurosurgical support

#### **9.3.2 Patient Eligibility for IVT**

- I. Clinical diagnosis of acute stroke at presentation.
- II. Acute disabling stroke within 4.5 hours of presentation or last known/seen to be well.<sup>9-15</sup>
- III. For patients who present with a wake-up stroke or stroke of unknown onset and are not eligible for EVT, IVT may be considered if the MRI shows stroke with DWI and FLAIR mismatch, and the lesion is not larger than 1/3 MCA territory.<sup>16</sup>
- IV. NCCT or MRI brain shows no haemorrhage or established large infarct core.
- V. For patients who meet the criteria for EVT, it is reasonable to proceed with CTA if indicated in patients with suspected intracranial LVO prior to obtaining the renal profile in patients without a history of renal impairment.<sup>17-22</sup> Criteria for CTA include NIHSS>6, presence of cortical signs or brain stem involvement.<sup>23</sup>
- VI. No contraindications.
- VII. Use of sono-thrombolysis as adjuvant therapy with IVT is not recommended.<sup>24</sup>
- VIII. Thrombolysis shall not be withheld for aphasic patients who cannot give consent and/or without any family members.

### **9.4 Contraindications for Intravenous Thrombolytic Therapy**

#### **9.4.1 Absolute Contraindication**

- I. Pre-treatment systolic BP is >185mmHg or diastolic BP is >110mmHg.
- II. A blood glucose <2.7mmol/l. IVT in patients with AIS who presents with initial glucose levels <2.7 mmol/l, and that is subsequently normalized and who are otherwise eligible, may be reasonable.
- III. Current use of treatment dose of LMWH within 24 hours.
- IV. Use of unfractionated heparin in the previous 24 hours and a prolonged partial thromboplastin time (aPTT).
- V. IVT could be considered when appropriate laboratory tests such as aPTT, INR, activated clotting time, thrombin time, or direct factor Xa activity assays are normal or when the patient has not taken a dose of these anticoagulants for >48 hours and the renal function is normal.
- VI. For patients on Dabigatran, reversing its anticoagulant effect with Idarucizumab prior to IVT may be reasonable for eligible patients.<sup>25,26</sup>
- VII. Prothrombin time (PT) >15 seconds, aPTT >40s or INR >1.7
- VIII. A platelet count <100,000/microliter

#### 9.4.2 **Relative Contraindication**

- I. Serious head injury in the previous 3 months
- II. Recent stroke within 3 months
- III. Recent myocardial infarction within 8 weeks
- IV. Gastrointestinal or urinary bleeding within the preceding 21 days
- V. Major surgery within the preceding 14 days
- VI. Arterial puncture at non-compressible site within the last 7 days
- VII. Prior intracranial haemorrhage of irremediable cause
- VIII. Seizure at the onset of stroke. IVT is reasonable in patients with a seizure at the time of onset of acute stroke if evidence suggests that residual impairments are secondary to stroke and not a post-ictal phenomenon
- IX. Premorbid mRS  $\geq 4$
- X. Peritoneal dialysis or haemodialysis
- XI. Pregnancy (up to 10 days of postpartum) or nursing mother with no bleeding tendency

#### 9.5 **Regimen for Treatment of Acute Ischaemic Stroke with Intravenous Thrombolysis**

1. Infuse 0.9mg/kg (maximum of 90 mg) over 60 minutes with 10% of the dose given as a bolus dose over 1 minute. A lower dose of IV Alteplase (0.6 mg/kg) was not shown to be of equivalent to standard-dose IV Alteplase for the reduction of disability at 90 days but had a reduced mortality rate.<sup>27</sup>

**Recommendation:** (Onset within 4.5 hours) Alteplase dose: 0.9 mg/kg, max 90 mg, 10% given as bolus and remaining dose infused over 1 hour.

*(Level I, Grade A)*

2. Admit the patient to an intensive care unit or a stroke unit for monitoring.
3. Perform neurological assessments\* every 15 minutes during the infusion of Alteplase and 1-hour post IVT, and every 30 minutes for the next 4 hours and then every hour until 24 hours lapses from the onset of treatment. (\*GCS and Blood pressure)
4. If the patient develops severe headache, acute hypertension, nausea or vomiting or worsening neurological symptoms with an increase of the NIHSS by 4 and reduction of the GCS by 2, discontinue the infusion and obtain a CT scan of the brain.
5. Closer blood pressure monitoring is required if a systolic BP of >180mmHg or diastolic BP of >105mmHg is recorded. Administer anti-hypertensive medications to maintain blood pressure at or below these levels.
6. Delay placement of nasogastric tubes, indwelling bladder catheters or intra-arterial pressure catheters.
7. Avoid antiplatelet and anticoagulation drugs for the first 24 hours after administration of Alteplase.
8. **Recommendation:** IV Alteplase maybe considered for acute stroke onset >4.5 up to 9 hours or in wake-up stroke or stroke of uncertain onset assisted by CT perfusion, with significant penumbra core mismatch.<sup>2,3</sup>

*(New recommendation, Level II, Grade B)*

9. **Recommendation:** IV Alteplase maybe considered for acute stroke of uncertain onset and wake-up stroke assisted by MRI (DWI-FLAIR mismatch).<sup>1</sup>  
*(New recommendation, Level II, Grade B)*
10. Tenecteplase might be considered as an alternative to Alteplase when Alteplase is not available.<sup>28-30</sup>
11. **Recommendation:** AIS patients who arrive within 4.5 hours of symptoms onset and are eligible for thrombolytic treatment can be considered for intravenous Tenecteplase prior to EVT.<sup>30</sup> (Tenecteplase dose of 0.25mg/kg; maximum dose of 25mg)  
*(New recommendation, Level II, Grade B)*
12. Streptokinase is contraindicated.  
*(Level I, Grade A)*

## 9.6 General Care

### 9.6.1 BP Control

Blood pressure should be kept  $\leq 180/105$  mmHg during and post thrombolysis.<sup>31-37</sup>  
*(New recommendation, Level I, Grade A)*

Hypotension and hypovolaemia should be corrected and avoided.  
*(New recommendation, Level I, Grade A)*

Patient otherwise are eligible for acute reperfusion therapy except that if BP is  $>185/110$  mmHg with:

- Labetalol 10–20 mg IV over 1–2 min, may repeat once; or
- Nicardipine 5 mg/h IV, titrate up by 2.5 mg/h every 5–15 min, maximum 15 mg/h; when desired BP reached, adjust to maintain proper BP limits; or
- Other agents (e.g., Hydralazine, Enalapril, GTN, Nimodipine) may also be considered
- GTN 5mg patch
- IV Nimodipine
- If BP is not maintained  $\leq 185/110$  mmHg, do not administer Alteplase

*(Level II-2, Grade B)*

Management of BP during and after Alteplase or other acute reperfusion therapy to maintain BP  $\leq 180/105$  mmHg:

- Monitor BP every 15 min for 2 hours from the start of Alteplase therapy, then every 30 min for 6 hours, and then every hour for 16 hours

*(Level II-2, Grade B)*

If systolic BP is  $>180$ – $230$  mmHg or diastolic BP is  $>105$ – $120$  mmHg:

- IV Labetalol 5-10 mg bolus followed by continuous IV infusion 2–8 mg/min; or
- IV Nicardipine 5 mg/h, titrate up to desired effect by 2.5 mg/h every 5–15 min, maximum 15 mg/h; or
- IV Nitroprusside. If BP not controlled, consider IV Nitroprusside in ICU setting if available. IV Nitroprusside should be administered at 0.5mcg/kg/minimum infusion (maximum of 8mcg/kg/min)
- Maximum dose of IV Labetalol bolus is 300 mg

*(Level II-2, Grade B)*

### **9.6.2 Blood Glucose Control**

Keep blood glucose level between 7.8-10.0 mmol/L.

Avoid hypoglycaemia.

*(Level I, Grade A)*

Hyperglycaemia within the first 24 hours of thrombolysis is associated with poorer outcomes and higher haemorrhage transformation.

*(Level III, Grade C)*

### **9.6.3 Temperature**

Fever (temperature >38°C) should be identified and treated.

*(Level I, Grade A)*

Hypothermia (temperature <37°C) and hyperthermia are associated with poorer outcome.<sup>38</sup>

*(Level II, Grade B)*

### **9.6.4 Others**

- Keep NBM and put on an IV drip to ensure adequate hydration. Avoid hypotonic solution.
- No nasogastric (NG) tube insertion, catheterization, and invasive procedure for 24 hours.
- Minimise physical handling and movement to avoid bruises and injury.
- Monitor neurological status deterioration and bleeding. Inform if it occurs.
- No antiplatelet or anticoagulation for the initial 24 hours.
- Repeat CT brain at 24 hours post thrombolysis.

## **9.7 Management of Complications**

### **9.7.1 Bleeding**

1. Stop IV Alteplase
2. Urgent CT brain if there is neurology deterioration
3. Send FBC, PT/PTT, GXM, fibrinogen. Repeat 2 hourly until bleeding is controlled.
4. Control BP
5. IV Cryoprecipitate 6-8 bags
6. IV Platelets 4 units or CSP 1 unit if platelet dysfunction is suspected
7. Consult neurosurgical team if ICH. Frequent neurology checks. Institute therapy for elevated ICP as needed.
8. Repeat Cryoprecipitate 6-8 bags if fibrinogen <200mg/dL
9. If PT/PTT prolonged despite normal fibrinogen, consider FFP (if negative, order Lupus anticoagulant and Anticardiolipin antibody)
10. Refer haematology team if coagulation still abnormal despite performing all the above measures
11. For severe life-threatening bleeding, consider the following treatment after weighing the risk of recurrent thrombotic stroke:
  - a) IV Tranexamic Acid 1g over 15 minutes, repeated every 8 hours as necessary
  - b) Recombinant Factor VIIa 40-160 µg/ kg BW as a single bolus over 1-2 minutes



### 9.7.2 Angioedema

1. Stop IV Alteplase
2. Maintenance of airway, breathing, and circulation
3. IV Diphenhydramine 50 mg
4. IV Ranitidine 50 mg
5. No improvement, give IV Methylprednisolone 100 mg
6. No improvement, give S/C Epinephrine 0.1% 0.3 mL or Nebuliser 0.5mls
7. Call ENT/Anaesthesia team
8. Icatibant if available and indicated

### 9.8 Administration of Intravenous Thrombolysis

We recommend administering intravenous thrombolysis in a hospital with trained general physicians, neurologists, geriatricians or emergency physicians experienced in administering, monitoring post-procedure, and managing the associated complications.

#### Recommendations Summary:

**Table 9.1: Treatment of Acute Ischaemic Stroke with Intravenous Thrombolysis**

Treatment	Recommendations	Level of Evidence	Grade
Alteplase	Onset within 4.5 hours Dose: 0.9 mg/kg, max 90 mg, 10% bolus and remaining dose as infusion over 1 hour.	I	A
	Onset >4.5 up to 9 hours if known onset or wake-up stroke guided by CT perfusion, with present significant penumbra core mismatch. <i>New recommendation</i>	II	B
	Uncertain onset and wake up stroke guided by MRI (DWI-FLAIR mismatch) <i>New recommendation</i>	II	B
Tenecteplase	Onset within 4.5 hours and eligible for thrombolytic treatment can be considered for intravenous Tenecteplase prior to EVT. Dose: 0.25mg/kg; maximum dose of 25mg <i>New recommendation</i>	II	B

#### Key Recommendations:

1. Intravenous alteplase (0.9 mg/kg; maximum dose of 90mg) is recommended for definite onset stroke for up to 4.5 hours from the onset or the treatment window can be extended via CT perfusion with evidence of penumbra-core mismatch up to 9 hours from the time of last known to be well/midpoint of sleep or via MRI (DWI-FLAIR mismatch) to identify possible stroke onset within 4.5 hours.
2. Intravenous tenecteplase (0.25 mg/kg; maximum dose of 25mg) is a possible treatment agent in acute stroke presented within 4.5 hours with evidence of large vessel occlusion.

### 10.1 Acute Endovascular Thrombectomy Treatment

Acute Endovascular Thrombectomy treatment (EVT) is considered as the standard of care since 2015 following the publications of 5 RCTs which have led to a major guideline revamp around the world.<sup>1-5</sup> EVT is indicated in acute ischaemic stroke that presents within 6-8 hours, and is equally beneficial in selected patients of up to 24 hours from the time last seen well (TLSW) with evidence of large vessel occlusion (LVO).<sup>1-7</sup>

EVT should be offered at the comprehensive stroke centre if the following are available and in coordination with the EMS:

- I. A stroke team consisting of stroke physician and radiologist with expertise in the diagnosis and management of stroke.
- II. A stroke team consisting of neuro-interventional experts (interventional neuro-radiologist or interventional neurologist/neurosurgeon).
- III. All AIS patients who are a candidate for EVT must at least undergo NCCT and CT angiography from arch of aorta-vertex with or without multiphase CTA or CT perfusion. MRI with MRA can be considered in selected cases if necessary and not as a routine modality to avoid any delays.

*(New recommendation, Level 1, Grade A)*

### 10.2 Indication for Acute Endovascular Thrombectomy

- I. Baseline functional status mRS of 0-2 or generally ADL independent.
- II. EVT is indicated in patients who have received intravenous Alteplase, but do not wait to assess response, and those who are not eligible for intravenous Alteplase with evidence of LVO.
- III. Patients who fulfil the imaging criteria via assessment of CT cerebral angiography prior to EVT as following:
  - a. Patients should have a LVO of the middle cerebral artery or/and internal carotid artery or proximal M2 occlusion.
  - b. For large artery occlusion of posterior circulation (e.g., basilar artery), the decision to treat should be based on the potential benefits and risks of treatment for the individual treatment.<sup>8</sup>
  - c. For patients who arrive between 6 and 24 hours of stroke onset or since the time last seen well, multimodal imaging is indicated (CT perfusion software which is capable to reproduce similar objective assessments for penumbra and infarct core) and may be subjected to EVT

NIHSS  $\geq$  10 and infarct core volume 0-21 mls, age  $\geq$  80 years old

*or*

Infarct core volume 0–31 mls, age < 80 years old

*or*

NIHSS  $\geq$  20 infarct core volume 31-51 mls, age < 80 years old

***\*(DAWN trial criteria)***

**OR**

Infarct core volume is < 70 mls, mismatch ratio is  $\geq$  1.8 and mismatch volume is >15 mls

***\*(DEFUSE 3 trial criteria)***

**Recommendation:** EVT is indicated for AIS with large vessel occlusion; proximal middle cerebral artery segment 1 (M1)/proximal M2 occlusion/internal carotid artery (ICA), and presenting within 6 hours from onset. <sup>1-5</sup>

*(New recommendation, Level I, Grade A)*

**Recommendation:** EVT is indicated in selected patients who arrive after 6 hours and up to 24 hours of stroke onset with evidence of large vessel occlusion. <sup>5,6</sup>

*(New recommendation, Level I, Grade A)*

### 10.3 Early Revascularization

Revascularization needs to be organized immediately. The majority of the EVT studies emphasise the importance of the early timing of recanalization through a properly organized stroke workflow, which was lacking in the previous neutral study. It is very important to understand that the treatment benefit declines over time; and despite recent evidence for extended hours for reperfusion therapy via EVT, there is no reason to delay recanalization in order to maximize the possible best outcome. <sup>6,7</sup>

**Recommendation:** AIS patients who arrive within 4.5 hours of stroke onset and are eligible for rtPA treatment should be considered for thrombolytic treatment prior to EVT. <sup>1-5</sup>

*(New recommendation, Level I, Grade A)*

**Recommendation:** For patients undergoing “Drip & Ship” (EVT following administration of IVT), there should be no delay in proceeding to EVT to determine the clinical effectiveness of Alteplase. <sup>1-5</sup>

*(New recommendation, Level I, Grade A)*

**Recommendation:** AIS patients who arrive within 4.5 hours of stroke onset and are eligible for thrombolytic treatment can be considered for intravenous Tenecteplase prior to EVT. <sup>9</sup>

*(New recommendation, Level II, Grade B)*

**Recommendation:** Transfer to high-volume centres has been associated with reduced mortality rates after endovascular treatment of acute stroke. This is likely to be achieved when high-volume centres have a well-organized acute stroke pathway. <sup>10</sup>

*(New recommendation, Level II, Grade B)*

### 10.4 Endovascular Thrombectomy Devices

Aspiration devices and Stent retriever are used widely for EVT, and these devices have been used almost exclusively in clinical trials within the past 5 years.

*(New recommendation, Level II, Grade B)*

### 10.5 Sedation vs General Anaesthesia

Procedural sedation is generally preferred over general anaesthesia and intubation in most patients undergoing EVT. General anaesthesia and intubation is however, appropriate, if medically indicated (e.g., for airway compromise, respiratory distress, depressed level of consciousness, severe agitation, or any other indication as determined by the treating physician) and in such cases, excessive and prolonged hypotension and time delays should be avoided.

*(New recommendation, Level II, Grade B)*

### 10.6 Endovascular Thrombectomy Work Flow

EVT should be offered at the comprehensive stroke centre when the following are available and in coordination with the EMS as following:

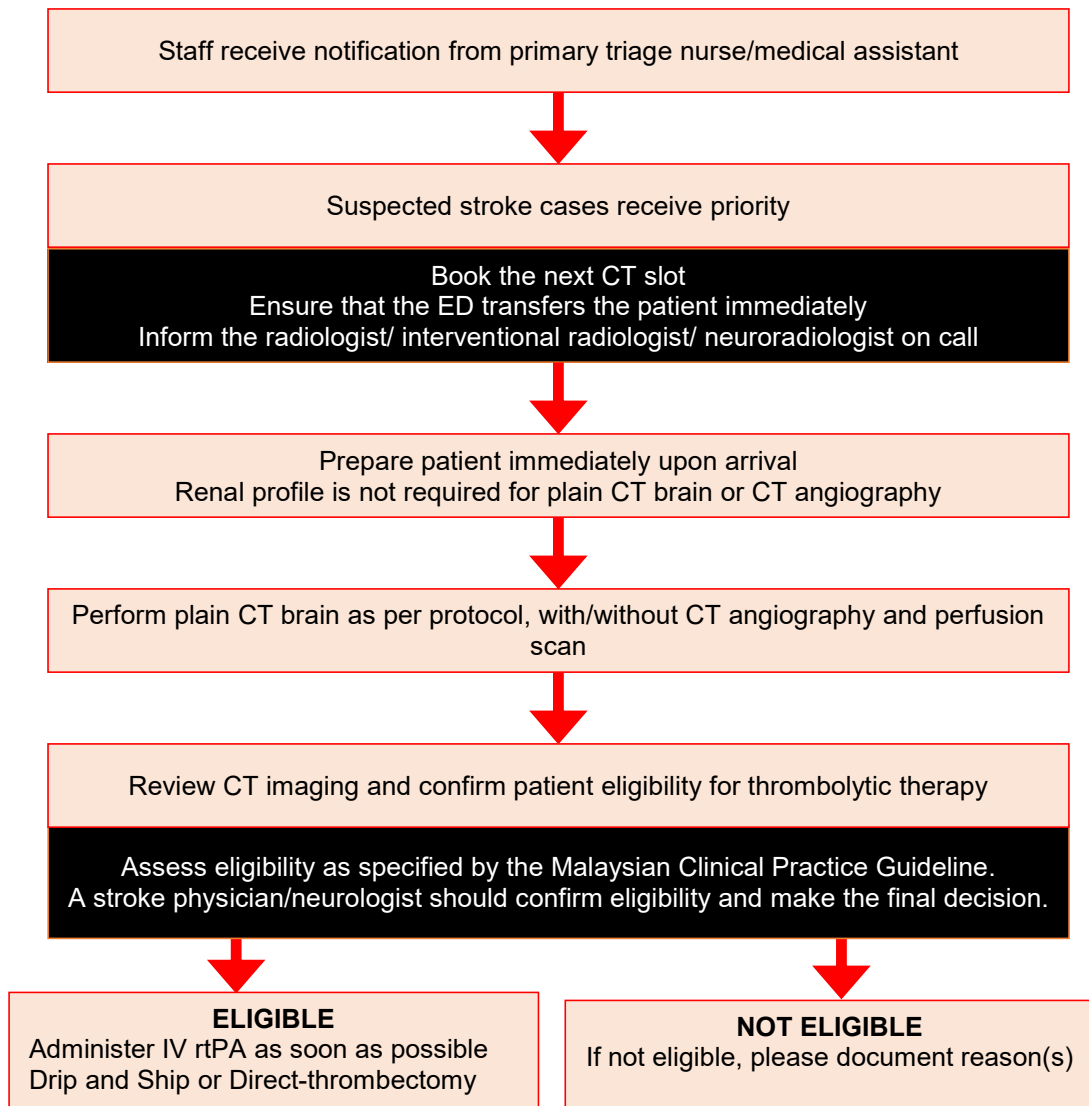


Figure 10.1: Endovascular Thrombectomy Work Flow

## Recommendations Summary:

**Table 10.1: Acute Endovascular Thrombectomy Treatment**

Treatment	Recommendations	Level of Evidence	Grade
Acute Endovascular Thrombectomy (EVT)	EVT is indicated for AIS with large vessel occlusion; proximal middle cerebral artery segment 1 (M1)/proximal M2 occlusion/internal carotid artery (ICA), and presenting within 6 hours from onset. <i>New recommendation</i>	I	A
	EVT is indicated in selected patients who arrive after 6 hours and up to 24 hours of stroke onset with evidence of large vessel occlusion. <sup>5,6</sup> <i>New recommendation</i>	I	A
EVT bridging with Alteplase (Drip & Ship)	AIS patients who arrive within 4.5 hours of stroke onset and are eligible for rtPA treatment should be considered for thrombolytic treatment prior to EVT. <i>New recommendation</i>	I	A
	For patients undergoing “Drip & Ship” (EVT following administration of IVT), there should be no delay in proceeding to EVT to determine the clinical effectiveness of Alteplase. <i>New recommendation</i>	I	A
EVT bridging with Tenecteplase	AIS patients who arrive within 4.5 hours of stroke onset and are eligible for thrombolytic treatment can be considered for intravenous Tenecteplase prior to EVT. <i>New recommendation</i>	II	B

### Key Recommendations:

- Hyperacute endovascular thrombectomy is recommended for definite onset stroke with evidence of large vessel occlusion which is within 6 hours from the onset or the treatment window can be extended via CT/MR perfusion (penumbra-core mismatch) or MRI (clinical-imaging mismatch) with current evidences showed significant benefit up to 24 hours from onset/time last known to be well. However, treatment pathway should not be delayed, as the treatment outcome can be influenced by the imaging-to-recanalization time.
- Drip & Ship (IVT prior to EVT) as per Chapter 9 is recommended for the eligible patients.

### 11.1 Stroke Unit

All patients with acute stroke should ideally have access to stroke units. There is clear evidence that the treatment of patients with stroke in stroke units significantly reduces death, dependency, institutionalisation, and length of hospital stay as compared to treatment in the general medical ward.<sup>1-7</sup>

**Recommendation:** Every hospital should set up a stroke unit as it can significantly reduce deaths, dependency, institutionalisation, and the length of hospital stay.

*(Level I, Grade A)*

This benefit is independent of the patients' age, gender, co-morbidities, and stroke severity.<sup>1,8</sup>

*(Level I)*

The benefits from treatment in a stroke unit are comparable to the effects achieved with intravenous administration of rtPA.<sup>9</sup>

*(Level III)*

A stroke unit is a dedicated unit in the hospital that exclusively manages stroke patients. A team of specially trained staff provide coordinated multidisciplinary care throughout the day for 24 hours to patients treated in a stroke unit. The core specialities of the stroke team are medical personnel (neurologists, geriatricians, or general physicians with interest in stroke), medical rehabilitation physicians, pharmacists, nurses, physiotherapists, occupational therapists, and speech therapists. In larger centres, the team may consist of neurosurgeons, social workers, and dieticians. The effectiveness of a stroke unit is not necessarily related to a certain medical specialty. A stroke unit run by general physicians, geriatricians, neurologists, or specialists in rehabilitation medicine may equally be effective.<sup>1</sup>

*(Level I)*

Ideally, a stroke unit should have/provide:

- I. A geographically defined unit
- II. A coordinated multi-disciplinary team that meets regularly for the exchange of information about inpatients with stroke
- III. Information, advice, and support for people with stroke and their family/carers
- IV. Management protocols for common problems based upon the best available evidence
- V. Close links with the primary care setting, community services and patient's welfare unit
- VI. Training for healthcare professionals in the specialty of stroke
- VII. The use of comprehensive specialized stroke care (stroke units) that incorporates rehabilitation services is recommended. It has been shown to reduce mortality and disabilities.<sup>1</sup>

**Recommendation:** The use of comprehensive specialized stroke care (stroke units) that incorporates rehabilitation services is recommended.

*(Level I, Grade A)*

Possible benefits of having stroke units include early treatment, reduced incidence of infection and systemic complications as well as early and more intense rehabilitation.<sup>10</sup>

*(Level I)*

## 11.2 Multidisciplinary Team in Stroke Unit

The core multidisciplinary team on a stroke unit should consist of healthcare professionals with stroke expertise including physicians, nurses, occupational therapists, physiotherapists, speech therapists, social workers, and dietitians.<sup>11</sup>

*(Level I, Grade A)*

Additional members of multidisciplinary team may include clinical pharmacists, discharge planner or case managers, psychologists, palliative care specialists, spiritual care providers and peer support groups.

*(Level II, Grade B)*

Role of multidisciplinary team:

- I. Should assess patients within 48 hours and formulate management plan.
- II. Assessment components include dysphagia screening, mood and cognition, mobility, functional assessment, temperature, nutrition, bowel and bladder function, skin breakdown and venous thromboembolism prophylaxis.
- III. Discharge planning and individualized assessment for post-acute rehabilitation services should also be discussed as soon as the patient has been stabilized.

**Recommendation:** A stroke unit should be managed by a multidisciplinary stroke team.

*(Level I, Grade A)*

Stroke units will work optimally if a well-established referral and rehabilitation network is available. Cooperation with primary care physicians is essential for the primary and secondary prevention of strokes.

Regular communications and coordinated care are key aspects of the stroke unit.

Standardized stroke orders or integrated stroke pathways improve adherence towards the best practices for the treatment of patients with stroke.<sup>12,13</sup>

Nine KPI are used as the measurement index for the effectiveness of a stroke unit as shown below:

### The 9 KPI's Recommended by the Stroke Council Malaysian Society of Neurosciences (MSN) 2011 *(Used in Malaysian National Stroke Registry)*

1. Thrombolytic Therapy Administered
2. Antithrombotic Therapy by End of Hospital Day Two
3. Dysphagia Screening
4. Deep Vein Thrombosis (DVT) Prophylaxis
5. Patients with Atrial Fibrillation Receiving Anticoagulant Therapy
6. Stroke Education
7. Assessed for Rehabilitation.
8. Discharged on Anti Thrombotic Therapy
9. Discharged on Cholesterol Reducing Medication

## Recommendations Summary:

**Table 11.1: Stroke Unit**

<b>Factor</b>	<b>Recommendations</b>	<b>Level of Evidence</b>	<b>Grade</b>
Stroke Unit	Every hospital should set up a stroke unit as it can significantly reduce deaths, dependency, institutionalisation, and the length of hospital stay.	I	A
	The use of comprehensive specialized stroke care (stroke units) that incorporates rehabilitation services is recommended.	I	A
	A stroke unit should be managed by a multidisciplinary stroke team.	I	A

### **Key Recommendations:**

The use of comprehensive specialized stroke care (stroke units) that incorporates rehabilitation services are able to reduce mortality and disabilities among stroke patients.



## 12.1 Introduction

An older person is defined as those aged 60 years and above by the Malaysian Ministry of Health. As the average age of getting a stroke in Malaysia is 63 years, a significant number of stroke survivors are in the older age group.

Older persons are heterogenous in nature and their physical and functional status can range from very fit to very severely frail. An older person may also have cognitive function ranging from excellent to severe dementia. Older age alone should not be an exclusion criterion for stroke treatment without considering functional status and medical co-morbidities. This is providing that the older person fulfils the inclusion and exclusion criteria for the treatment.

Frailty is defined as reduced physiological reserve causing a person to be more susceptible to insults. A useful scale in determining an older person's fitness/frailty level is the Clinical Frailty Scale.<sup>1</sup> A fit older person's treatment plan can have goals that approximate those of a younger person. However, a hallmark of frailty is that the person has reduced tolerance to medical treatment and interventions.

Hence, frail older persons need to be assessed closely for side effects and adverse events from treatment. Few randomized controlled trials (RCTs) for stroke treatment examine frailty as a factor associated with outcomes. Therefore, the clinician needs to make individualised decisions for treatment based on each older person's characteristics.

**Recommendation:** All older adults should be screened for frailty using a validated instrument suitable for the specific setting or context with a tailored management plan thereafter.<sup>2</sup>

*(New recommendation, Level III, Grade C)*

## 12.2 Treatment of acute stroke

### 12.2.1 Stroke Thrombolysis

The Cochrane review and meta-analysis shows that older patients benefit at least as much as those below the age of 80 years, so there is no upper age limit for stroke thrombolysis treatment, particularly within the first 3 hours.<sup>3</sup> Patients with mild and severe stroke and those with early signs of infarction on initial brain imaging also benefit from treatment, as long as early radiological changes are consistent with the stated time of onset.

**Recommendation:** An older person should receive and can benefit from intravenous thrombolysis.

*(New recommendation, Level I, Grade A)*

### 12.2.2 Endovascular Thrombectomy

A meta-analysis of five randomised controlled trials with 1287 patients, on endovascular thrombectomy for anterior circulation large vessel ischaemic stroke versus control, showed that there was benefit across all age-groups in significantly reducing post-stroke dependency at 90 days, including in those aged 80 years and above.<sup>4</sup>

**Recommendation:** An older person can benefit from endovascular thrombectomy for anterior circulatory large vessel occlusion.

*(New recommendation, Level I, Grade A)*

### 12.2.3 Management of glucose level in the acute phase of stroke

The International Diabetes Federation published a comprehensive guideline on managing older people with type 2 diabetes which included a section on management of hyperglycaemia post-acute stroke.<sup>5</sup>

At present, the optimal level of blood glucose after a stroke is unclear. A systematic review of 11 RCTs concluded that administration of intravenous insulin to maintain tight glucose control within a specific range (4.0-7.5 mmol/L) in the first few hours of acute ischaemic stroke does not provide benefit in terms of functional outcome, death, or improvement in final neurological deficit, but significantly increased the number of hypoglycaemic episodes.<sup>6</sup>

**Recommendation:** After an acute stroke, treat hyperglycaemia to keep the blood glucose levels between 6.0-10.0 mmol/L (110-180 mg/dL) and ensure that hypoglycaemia is avoided.<sup>5</sup>  
*(New recommendation, Level III, Grade C)*

**Recommendation:** Avoid very tight targets of glucose control (4.0-7.5 mmol/L) in the first few hours of acute ischaemic stroke.  
*(New recommendation, Level I, Grade A)*

### 12.3 Management of risk factors for stroke prevention

#### 12.3.1 Hypertension

Older persons may develop orthostatic hypotension, have falls and syncope when prescribed with multiple antihypertensive medications. Home BP monitoring may supplement clinic BP measurements for a more reflective picture of the overall BP control.

Older persons with high frailty levels, advanced cognitive impairment, or terminal illness, requires accurate prognostication, risk stratification and setting of treatment goals. These population groups are not represented in large RCTs and therefore have no demonstrated safety data for intensive BP lowering.<sup>7</sup>

**Recommendation:** Older persons who have one or more of the following: frailty, multiple comorbidities, cognitive impairment, require an individualised approach for blood pressure management.  
*(New recommendation, Level I, Grade A)*

#### 12.3.2 Diabetes Mellitus

In older people, therapeutic decisions on blood glucose control should be based on comprehensive assessment and individualized risk stratification of key risk factors. Hypoglycaemia, hyperglycaemia and their consequences, comorbidities, frailty, falls, pain, medication adherence, and medicine related adverse events, and life expectancy should be considered when planning and monitoring care for older people with diabetes mellitus.<sup>5,8</sup>

**Recommendation:** Targets of blood glucose control in older persons with diabetes should be individualised taking into account their functional status, medical comorbidities, and likelihood of developing adverse events.  
*(New recommendation, Level III, Grade C)*

#### 12.3.3 Dyslipidaemia

A meta-analysis of 28 RCTs with 186,854 participants of whom 14483 (8%) were aged 75 years and above, showed that statin therapy produced significant reductions in major vascular events including

stroke, regardless of age. However, there is less direct evidence of benefit among patients older than 75 years for the purpose of primary prevention of vascular events. In particular, in patients aged over 75 years, the reduction in stroke rates was not found to be significant.<sup>9</sup>

**Recommendation:** Statins are recommended for stroke prevention in older persons with less direct evidence of benefit for stroke prevention and primary prevention of vascular events in those aged over 75 years.

*(New recommendation, Level I, Grade A)*

#### **12.3.4 Atrial Fibrillation**

Older persons with atrial fibrillation can benefit from anticoagulation for stroke prevention, either with warfarin or a direct oral anticoagulant (DOAC). DOACs were found to have a better efficacy/risk ratio as compared to warfarin.<sup>10,11</sup> However, the cost of DOACs are considerably higher than warfarin, in terms of the medications themselves.

It is important to follow the individual DOACs prescription guidelines taking into consideration their age, body weight and creatinine clearance to determine the appropriate dose of the DOAC. A higher percentage of older persons have impaired renal function, low body weight and sarcopenia. Prescribing a DOAC without following the prescription guidelines results in a higher number of strokes and adverse events.<sup>12</sup>

Falls and dementia are not absolute contraindication to anticoagulation, the decision needs to be made on an individualised basis. Falls prevention measures and carer education are important in these circumstances.

The 2019 Beers criteria recommend that rivaroxaban and dabigatran are prescribed with caution in older persons aged 75 years and above due to the higher risk for gastrointestinal bleeding.<sup>13</sup>

The OAC-FORTA (Oral Anticoagulant – Fit for the Aged) guidelines recommend apixaban as FORTA-A (highly beneficial) in older persons and the other DOACs and warfarin as FORTA-B (beneficial).<sup>11</sup>

**Recommendation:** Older persons with atrial fibrillation can benefit from oral anticoagulant for stroke prevention with an individualised treatment plan taking medical co-morbidities, functional status, and social factors into consideration.

*(New recommendation, Level I, Grade A)*

#### **12.4 Medication management in the older person with stroke**

Older persons, especially those who had a stroke and several stroke risk factors, are more likely to experience polypharmacy ( $\geq 5$  medications) with high pill burden, adverse events from medications, drug-drug interactions, drug-disease interactions and the high cost of treatment.

When prescribing for an older person, it is advisable to

- simplify the medication regime
- choose where possible, medications that require once a day administration
- consider renal and liver function, and presence of anaemia
- consider swallowing function
- check the body weight
- deprescribe or reduce dosages or number of medications by prioritising medical conditions, reviewing targets of treatment and side effects
- check for potential drug-drug and drug-disease interactions

**Recommendation:** A comprehensive care plan for a frail older person should include management of polypharmacy.<sup>2</sup>

*(New recommendation, Level III, Grade C)*

## 12.5 Delirium post-acute stroke

Delirium is a common complication of stroke, affecting at least 1 in 4 acute stroke patients.<sup>14</sup> Delirium in post-stroke is associated with higher mortality, increased length of stay and worse functional outcome.<sup>15-17</sup> Risk of developing post-stroke delirium is higher in patients with advanced age, pre-stroke cognitive impairment, atrial fibrillation, previous stroke, left cortical stroke, visual disturbances, more severe stroke and platelet to white-cell count ratio < 20.<sup>22</sup> .<sup>14,16-18</sup> A majority of delirium were detected on the first day of admission and the remainder appeared within the next 5 days.<sup>14,18</sup>

The 4AT is a validated tool to screen for delirium in acute stroke patients (sensitivity 90 - 100%; specificity 65 - 86%). It allows assessment for all (including non-verbal) patients.<sup>19</sup>

**Recommendation:** All post-stroke patients should be screened for delirium throughout hospitalization.<sup>14,20</sup>

*(New recommendation, Level II-2, Grade B)*

**Recommendation:** Screening for post-stroke delirium using the 4AT tool is recommended.

*(New recommendation, Level II-2, Grade B)*

**Recommendation:** A multi-component intervention for post-stroke delirium prevention and management should be implemented to decrease incidence of delirium and its severity as well as to reduce the length of stay.<sup>21,22</sup>

*(New recommendation, Level II-2, Grade B)*

## 12.6 Falls prevention post-stroke

Falls are common adverse events post-stroke. The incidence is 7% in the first week but can be as high as 73% one year after suffering a stroke.<sup>23,24</sup> Post-stroke falls may result in serious injury (such as fragility fracture), fear of falling, activities limitation, increased dependence and higher cost of care.<sup>25,26</sup> Although any patients with residual difficulties following a stroke are at risk of falls, patients with modified Rankin Scale (mRS) score of 2 are at greater risk of falls.<sup>27</sup> This inverse U-shaped relationship suggests interplay between opportunities of falling and susceptibility to falls.<sup>28</sup>

Although interventions for preventing falls after stroke are largely ineffective other than those involving exercises, people with stroke should be offered falls and fragility fracture risk assessment and management as part of their stroke rehabilitation.<sup>29,30</sup>

**Recommendation:** All people with stroke should be offered falls and fragility fracture risk assessment and management during their rehabilitation period.

*(New recommendation, Level III, Grade C)*

## 12.7 Discharge planning and early supported discharge post stroke

The process of recovering from a stroke includes treatment, spontaneous recovery, rehabilitation, and the return to community living.

After receiving acute care, rehabilitation which is typically complex for older persons is offered as soon as possible. Decisions about rehabilitation are made by the patients, family, and a multidisciplinary team. Some patients may not need rehabilitation as they fully recover or have a mild neurological deficit that does not interfere with their daily activities.

A very important stage of stroke recovery is called discharge planning and it begins with the person's return to community living after acute care and/or rehabilitation.<sup>31</sup> Discharge planning is an important and complex process following acute stroke management to ensure a smooth transition from one level of care to another where the patient's level of care is matched to the site of care provision. The objective of discharge planning is to maintain the benefits of rehabilitation after the patient has been discharged from the hospital once their goals are attained.<sup>32</sup>

The benefits of discharge planning include reduced length of stay and readmission rate, and improved quality of life.<sup>33</sup>

Elements of discharge planning are:

1. Ensuring the stroke survivor has a safe place to live after discharge
2. Determining the level of care, assistance, or special equipment that are needed
3. Coordinating rehabilitation services or other services in the home (such as visits by a primary care clinic's domiciliary care team or a home health aide)
4. Determining the health care provider who will monitor the person's health and medical needs
5. Determining and training the caregiver of the patient to provide daily care and assistance
6. Helping the stroke survivor explore employment opportunities or volunteer activities and maintaining their social activities where possible

**Recommendation:** Discharge planning for older persons with stroke should occur at the appropriate time following a multidisciplinary recommendation where any decisions about care is made in the person's best interests.

*(New recommendation, Level II-3, Grade B)*

**Recommendation:** Hospital in-patients with stroke who have mild to moderate disability should be offered early supported discharge, with treatment at home beginning within 24 hours of discharge.

*(New recommendation, Level II-3, Grade B)*

**Recommendation:** A stroke early supported discharge team should be organised as a single multi-disciplinary team including:

*(New recommendation, Level II-1, Grade A)*

- Doctor
- Nurse
- Physiotherapist
- Occupational therapist
- Speech and language therapist
- Clinical psychologist
- Social worker

**Recommendation:** Older persons with stroke and their family/carers should be involved in decisions about the discharge and are prepared to be involved in their care.

*(New recommendation, Level III, Grade C)*

**Recommendation:** Discharge planning should include equipment and support services necessary including identification of the follow-up treatment.

*(New recommendation, Level III, Grade C)*

**Recommendation:** Evaluation of home environment by an occupational therapist should be carried out, by doing a home visit or through interview about the home environment, including photographs or videos taken with consent given by the family members/carers.

*(New recommendation, Level III, Grade C)*

## 12.8 End-of-life care

Stroke is often the mode of death for older persons, either as a primary incident or exacerbated by other acute conditions. The recognition that lifespan is limited or that the patient is dying should be considered positively. Death should be recognized as an inevitability of life, and hence palliative care should be considered a core competency of those accredited to deliver stroke care. Treatment at the end-of-life for stroke patients needs to prioritize patient dignity and the need to facilitate a good death.

Common burdensome symptoms at the end of life in stroke include anxiety, agitation, decubitus ulcers, pain and issues with hydration and nutrition.<sup>34</sup> Studies involving caregivers of those who died of stroke revealed limited preparations for the end of life with the use of the term palliative care equated to 'last days of life'.<sup>35</sup> The quality of intervention studies in palliative care in general is limited, with available studies conducted mainly in cancer patients. Available registry studies have supported implementation of the palliative care principles and encounters.<sup>34,36</sup>

**Recommendation:** The multidisciplinary stroke team should be trained in principles and practice of end-of-life care.

*(New recommendation, Level II-3, Grade C)*

**Recommendation:** Burdensome treatment should be avoided at the end-of-life care and this should include decisions to continue oral feeding and hydration despite the potential risk of aspiration.

*(New recommendation, Level II-3, Grade C)*

**Recommendation:** Advanced care planning should be provided for individuals who are expected to have a limited life expectancy.

*(New recommendation, Level II-2, Grade B)*

**Recommendation:** Decision to withhold and withdraw treatment should take into account prior expressed wishes of the individual with stroke which often needs to be established from the next-of-kin and close relations.

*(New recommendation, Level III, Grade C)*

**Recommendation:** Stroke teams should be prepared to facilitate the transfer of care of the individual dying of stroke to their own homes supported by local hospices and palliative care services if available.

*(New recommendation, Level III, Grade C)*

## Recommendations Summary:

**Table 12.1: Stroke in the Older Person**

Management	Recommendations	Level of Evidence	Grade
Screening for Frailty	All older adults should be screened for frailty using a validated instrument suitable for the specific setting or context with a tailored management plan thereafter. <i>New recommendation</i>	III	C
Stroke Thrombolysis	An older person should receive and can benefit from intravenous thrombolysis. <i>New recommendation</i>	I	A
Endovascular thrombectomy	An older person can benefit from endovascular thrombectomy for anterior circulatory large vessel occlusion. <i>New recommendation</i>	I	A
Management of glucose level in the acute phase of stroke	After an acute stroke, treat hyperglycaemia to keep the blood glucose levels between 6.0-10.0 mmol/L (110-180 mg/dL) and ensure that hypoglycaemia is avoided. <i>New recommendation</i>	III	C
	Avoid very tight targets of glucose control (4.0-7.5 mmol/L) in the first few hours of acute ischaemic stroke. <i>New recommendation</i>	I	A
Hypertension	Older persons who have one or more of the following: frailty, multiple comorbidities, cognitive impairment, require an individualized approach for blood pressure management. <i>New recommendation</i>	I	A
Diabetes Mellitus	Targets of blood glucose control in older persons with diabetes should be individualized taking into account their functional status, medical comorbidities, and likelihood of developing adverse events. <i>New recommendation</i>	III	C
Dyslipidaemia	Statins are recommended for stroke prevention in older persons with less direct evidence of benefit for stroke prevention and primary prevention of vascular events in those aged over 75 years. <i>New recommendation</i>	I	A
Atrial Fibrillation	Older persons with atrial fibrillation can benefit from oral anticoagulant for stroke prevention with an individualized treatment plan taking medical co-morbidities, functional status, and social factors into consideration. <i>New recommendation</i>	I	A
Medication management in the older person with stroke	A comprehensive care plan for a frail older person should include the management of polypharmacy. <i>New recommendation</i>	III	C
Delirium post-acute stroke	All post-stroke patients should be screened for delirium throughout hospitalization. <i>New recommendation</i>	II-2	B
	Screening for post-stroke delirium using the 4AT tool is recommended. <i>New recommendation</i>	II-2	B
	A multi-component intervention for post-stroke delirium prevention and management should be implemented to decrease the delirium incidence and severity as well as to reduce the length of stay. <i>New recommendation</i>	II-2	B

Falls prevention post-stroke	All people with stroke should be offered falls and fragility fracture risk assessment and management during their rehabilitation period. <i>New recommendation</i>	III	C
Discharge planning and early supported discharge post stroke	Discharge planning for older persons with stroke should occur at the appropriate time following a multidisciplinary recommendation where any decisions about care is made in the person's best interests. <i>New recommendation</i>	II-3	B
	Hospital in-patients with stroke who have mild to moderate disability should be offered early supported discharge, with treatment at home beginning within 24 hours of discharge. <i>New recommendation</i>	II-3	B
	A stroke early supported discharge team should be organised as a single multi-disciplinary team including: <ul style="list-style-type: none"> <li>● Doctor</li> <li>● Nurse</li> <li>● Physiotherapist</li> <li>● Occupational therapist</li> <li>● Speech and language therapist</li> <li>● Clinical psychologist</li> <li>● Social worker</li> </ul> <i>New recommendation</i>	II-1	A
	Older persons with stroke and their family/carers should be involved in decisions about the discharge and are prepared to be involved in their care. <i>New recommendation</i>	III	C
	Discharge planning should include equipment and support services necessary including identification of the follow-up treatment. <i>New recommendation</i>	III	C
	Evaluation of home environment by an occupational therapist should be carried out, by doing a home visit or through interview about the home environment, including photographs or videos taken with consent given by the family members/carers. <i>New recommendation</i>	III	C
	End-of-life care	The multidisciplinary stroke team should be trained in principles and practice of end-of-life care. <i>New recommendation</i>	II-3
Burdensome treatment should be avoided at the end-of-life care and this should include decisions to continue oral feeding and hydration despite the potential risk of aspiration. <i>New recommendation</i>	II-3	C	
Advanced care planning should be provided for individuals who are expected to have a limited life expectancy. <i>New recommendation</i>	II-2	B	
Decision to withhold and withdraw treatment should take into account prior expressed wishes of the individual with stroke which often needs to be established from the next-of-kin and close relations. <i>New recommendation</i>	III	C	
Stroke teams should be prepared to facilitate the transfer of care of the individual dying of stroke to their own homes supported by local hospices and palliative care services if available. <i>New recommendation</i>	III	C	



### **Key Recommendations:**

1. All older persons with acute stroke should be assessed for fitness/frailty level using a validated instrument to facilitate a tailored, individualised treatment plan.
2. An older person can benefit from acute treatment for stroke including stroke thrombolysis and endovascular thrombectomy providing the inclusion and exclusion criteria of the treatment are followed.
3. An older person can benefit from and should receive treatment for stroke prevention with management of polypharmacy, individualised medication dosages and treatment targets as tolerated, for stroke risk factors.
4. All older persons with stroke should be:
  - screened for delirium using a validated tool, and receive a tailored multicomponent intervention and management plan for delirium, when admitted with an acute stroke
  - offered falls and fragility fracture risk assessment and management during their rehabilitation period
  - assessed by a multidisciplinary team with appropriate discharge planning
  - able to receive end-of-life care and recommendations when the prognosis is poor either from the stroke itself, complications, or other serious comorbid conditions

### 13.1 Cardioembolic Stroke

Cardioembolic stroke accounts for about 20% of all ischaemic strokes.<sup>1-3</sup> They are generally severe, prone to early recurrence, more likely to happen when there is documented source of embolism and involve different cerebrovascular territories or multiple infarctions. The predominant pathogenic process for stroke associated with cardiac disease is embolism due to the formation of intra-atrial and intra-ventricular thrombi.

Atrial fibrillation (AF) whether chronic or paroxysmal, is the most common cause of cardioembolism and accounts for 50% of all cardiogenic emboli. Other high-risk conditions are prosthetic heart valves, rheumatic mitral valvular disease, acute myocardial infarction, and severe left ventricular dysfunction. Non-thrombotic embolism may result from atrial myxoma and endocarditis.

Investigations are directed at demonstrating cardiac sources of embolism in the absence of significant atherosclerosis or other vascular disease. All patients with stroke/TIA require a 12-lead electrocardiogram. A 72-hour Holter monitor is required to detect paroxysmal AF. In addition, all patients under 45 years of age and those in whom baseline investigations do not reveal an apparent cause for stroke will require a transthoracic echocardiogram (TTE). Patients in whom there is high suspicion of cardioembolism not found on TTE may undergo a trans-oesophageal echocardiogram (TOE). Conditions in which this method is superior to TTE include identifying thrombi in the left atrium and left atrial appendage, patent foramen ovale, atrial septal aneurysm and aortic arch atheroma.<sup>3,4</sup>

### 13.2 Stroke Prevention in Atrial Fibrillation Patients

**Recommendation:** Antiplatelet monotherapy is not indicated for stroke prevention in non-valvular atrial fibrillation (NVAf) patients.

*(Level I, Grade A)*

**Recommendation:** Oral anticoagulant (OAC) has been proven to be superior to no treatment or Aspirin in patients with NVAf.

*(Level I, Grade A)*

**Recommendation:** OAC to prevent cardioembolic stroke is recommended for all NVAf male patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 2 or more and female patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 3 or more.

*(New recommendation, Level I, Grade A)*

**Recommendation:** The choice of OAC for valvular AF (moderate-to-severe mitral stenosis) and mechanical heart valves patients is a Vitamin K Antagonist (Warfarin).

*(Level I, Grade A)*

Recommendation of treatment according to CHA<sub>2</sub>DS<sub>2</sub>-VASc Score:

CHA <sub>2</sub> DS <sub>2</sub> -VASc Score			
Male		Female	
≥2	OAC	≥3	OAC
1	Consider OAC	2	Consider OAC
0	No treatment	0-1	No treatment

### 13.3 Secondary Stroke Prevention in Atrial Fibrillation Patients

**Recommendation:** After a cardioembolic stroke, parenteral anticoagulant therapy (heparin or low molecular weight heparin) is not recommended to prevent secondary stroke. *(Level I, Grade A)*

**Recommendation:** For the secondary stroke prevention in an AF patient, the initiation of direct oral anticoagulants (DOACs) is recommended as below after excluding haemorrhagic transformation: *(New recommendation, Level II, Grade B)*

#### 1-3-6-12 Day Rule

Type of stroke	NIHSS score	Day to start OAC
TIA		1
Mild	<8	3
Moderate	8-15	6
Severe	≥16	12

**Recommendation:** DOACs are preferred as compared to VKA or Aspirin in AF patients with a previous stroke. *(New recommendation, Level I, Grade A)*

**Recommendation:** Aspirin could be considered before the initiation of OAC after an AF patient suffers from an ischaemic stroke. *(Level III, Grade C)*

**Recommendation:** The risk of bleeding is high after initiation of combination therapy of OAC and antiplatelet for secondary stroke prevention. *(New recommendation, Level III, Grade C)*

**Recommendation:** After intracranial haemorrhage, OAC could be re-initiated after 4-8 weeks in a NVAf patient with high CHA<sub>2</sub>DS<sub>2</sub>-VASc score if the underlying cause and risk factors of the bleeding have been treated. *(New recommendation, Level II, Grade B)*

### 13.4 General Measures for DOACs in Bleeding and Emergency Intervention

- Mechanical compression if possible
- IV access at 2 sites
- Determine timing of last DOAC dose
- FBC, RP, LFT
- Plasma expanders
- Consider activated charcoal if DOAC ingestion is < 2 hours
- Notify on-call haematologist

The following chart refers to specific measures of intervention:

OAC Category	Name of OAC	Blood tests	Specific Reversal Agent	Alternative Treatment Options
Vitamin K antagonist	Warfarin	INR	Vitamin K	1. PCC 2. Recombinant Factor VIIa 3. IV Tranexamic Acid 4. FFP 5. *Haemodialysis only for Dabigatran
DOAC	Dabigatran	aPTT, TT	Idarucizumab 5g IV (2 times infusions of 2.5 grams)	
	Rivaroxaban	Anti-Factor Xa	Andexanet alfa*	
	Apixaban	Anti-Factor Xa	Andexanet alfa*	

*\*Not available at the time of writing, boxed warning (FDA) for thromboembolic risks, ischaemic risks, cardiac arrest, and sudden death*

#### Recommendations Summary:

**Table 13.1: Prevention of Stroke in Atrial Fibrillation Patients**

Treatment	Recommendations	Level of Evidence	Grade
<i>Stroke Prevention</i>			
Antiplatelet monotherapy	Antiplatelet monotherapy is not indicated for stroke prevention in non-valvular atrial fibrillation (NVAf) patients.	I	A
Oral anticoagulant (OAC)	OAC has been proven to be superior to no treatment or Aspirin in patients with NVAf.	I	A
	OAC to prevent cardioembolic stroke is recommended for all NVAf male patients with CHA <sub>2</sub> DS <sub>2</sub> -VASc score of 2 or more and female patients with a CHA <sub>2</sub> DS <sub>2</sub> -VASc score of 3 or more. <i>New recommendation</i>	I	A
	The choice of OAC for valvular AF (moderate-to-severe mitral stenosis) and mechanical heart valves patients is Vitamin K Antagonist (Warfarin).	I	A
<i>Secondary Stroke Prevention</i>			
Parenteral anticoagulant (heparin or low molecular weight heparin)	After a cardioembolic stroke, parenteral anticoagulant therapy (heparin or low molecular weight heparin) is not recommended to prevent secondary stroke.	I	A
DOACs	For secondary stroke prevention in an AF patient, the initiation of DOACs is recommended after excluding haemorrhagic transformation <i>New recommendation</i>	II	B

	DOACs are preferred over VKA and Aspirin in AF patients with a previous stroke. <i>New recommendation</i>	I	A
Aspirin	Aspirin could be considered before the initiation of OAC after an AF patient suffers from an ischaemic stroke.	III	C
Combination therapy of OAC and antiplatelet	The risk of bleeding is high after initiation of combination therapy of OAC and antiplatelet for secondary stroke prevention. <i>New recommendation</i>	III	C
OAC	After intracranial haemorrhage, OAC could be re-initiated after 4-8 weeks in a NVAf patient with high CHA <sub>2</sub> DS <sub>2</sub> -VASc score if the underlying cause and risk factors of the bleeding have been treated. <i>New recommendation</i>	II	B

### Key Recommendations:

1. Cardioembolism is a common cause of stroke. Stroke patient must have cardiac assessment to look for cardioemboli.
2. It causes more severe stroke and carry a higher morbidity and mortality rates.
3. Effective treatment to prevent cardioembolism is available and should be offered to patient at risk.
4. DOAC is preferred over VKA for NVAf.
5. Patient on VKA should have regular INR monitoring and aim time in the therapeutic range (TTR) > 70%.
6. Antiplatelet is not recommended for NVAf for the prevention of stroke.

### 14.1 Stroke in Young Adults

The incidence of stroke in young adults (18 to 45 years) is increasing and the prevalence is reported to be approximately 10-15% of all stroke patients.<sup>1</sup> The causes and risk factors of stroke in young adults is distinct from those in older patients, in which cardiac embolism and other aetiologies are more common, notably non-atherosclerotic arteriopathies and haematological disorders.<sup>2,3</sup> Therefore, the diagnostic evaluation and management strategy are usually more comprehensive and challenging. This chapter will cover the aetiology and risk factors in young adults with stroke, in addition to the diagnosis and management of specific causes of stroke in young adults.

### 14.2 Young Stroke Aetiology

The causes of ischaemic stroke in young adults are diverse and vary by age, gender, and geographic region.<sup>4</sup> The causes may be classified according to the TOAST classification. Non-atherosclerotic arteriopathies such as arterial dissection as well as premature atherosclerosis due to hypertension, cigarette smoking and hyperlipidaemia are collectively the most common causes of ischaemic stroke in young individuals.<sup>3,5</sup> But often, the cause of the stroke is unknown.<sup>6</sup>

Cryptogenic stroke is defined as stroke without any probable cause identified after adequate diagnostic evaluation.<sup>7-10</sup> Cryptogenic stroke has been reported in up to 40% of young stroke cases.<sup>4</sup> In 2014, the clinical construct of “embolic stroke of undetermined source” (ESUS) was introduced to identify patients with non-lacunar cryptogenic ischaemic strokes in whom embolism was the likely stroke mechanism. About 1/6 of stroke patients are labelled as ESUS and they are generally younger patients with milder stroke but are associated with a higher risk of stroke recurrence.<sup>7,8</sup> To date, there is no evidence to suggest the role of anticoagulants in the management of ESUS.

**Table 14.1: Aetiology of Young Stroke**

#### Large artery atherosclerosis

- Uncommon before the age of 40 but incidence increases with age
- Classic vascular risk factors are present
- Management is similar with stroke in older populations

#### Cardiogenic embolism

- Cardiac tumours commonly found in the left atrium and apex (atrial myxoma, papillary fibroelastoma)
- Arrhythmia – atrial fibrillation, sick sinus syndrome, etc.
- Cardiomyopathy
- Infection and non-bacterial thrombotic endocarditis
- Rheumatic valvular heart disease<sup>9</sup>
- Patent foramen ovale (PFO), atrial septal defect (ASD), etc.

#### Small vessel disease

- Genetic: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) -Notch 3 mutation<sup>11</sup>
- Sporadic: classic vascular risk factors are present
- Management is long-term antiplatelet therapy

### Stroke of other determined cause

- Haematological causes based on abnormal blood components:<sup>12</sup>
- Erythrocytes: polycythaemia vera, sickle-cell disease, paroxysmal nocturnal haemoglobinuria, etc.
- Leucocytes: leukaemias, Waldenstrom macroglobulinaemia, multiple myeloma, hypereosinophilic syndrome, etc.
- Platelets: essential thrombocythaemia; thrombotic thrombocytopenic purpura, heparin induced thrombocytopenia, etc.

#### *Coagulation disorders:*

- Protein C deficiency
- Protein S deficiency
- Antithrombin deficiency
- Factor V Leiden
- Prothrombin G20210A mutation
- Disseminated intravascular coagulation
- Antiphospholipid syndrome
- Hypercoagulable states – malignancy, pregnancy, oestrogens dehydration
- Management is anticoagulants

#### *Illicit drug use:*

- Cocaine and amphetamines cause cerebral vasospasm, cardiac arrhythmias, cardiomyopathy, accelerated atherosclerosis, vasculitis, and direct toxic effects on cerebral vessels
- Management is supportive treatment

#### *Arterial dissections:*

- Spontaneous or secondary to trauma or primary arteriopathy such as cystic medial necrosis, fibromuscular dysplasia
- Extracranial cause: carotid artery dissection
- Intracranial cause: vertebral artery, etc.
- Management is antiplatelet treatment, endovascular treatment

#### *Vasculitis / inflammatory arteriopathy:*

- Vasculitis: primary / secondary to infection / drug-related
- Primary: SLE, polyarteritis nodosa (PAN), Takayasu's arteritis (affecting large blood vessels, including major aortic branches); granulomatous angiitis, primary angiitis of the CNS (PACNS) affecting medium and small blood vessels; Behçet disease, Churg-Strauss syndrome, Kohlmeier-Degos disease<sup>13</sup>
- Complication of infection: TB meningitis<sup>14</sup> (mainly perforators and cortical branches), syphilis, post varicella, fungal, HIV/AIDS, etc.
- Drug related: heroin, LSD, cocaine, amphetamines, ephedrine, phenylpropanolamine
- Management is immunosuppressive treatment for primary causes

#### *Inherited arteriopathy:<sup>11</sup>*

- Fabry disease: a X-linked sphingolipidosis caused by deficiency of  $\alpha$ -galactosidase A ( $\alpha$ -gal)
- Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke like episodes (<40years old): mostly due to mitochondrial DNA (mtDNA) A-to-G transition at nucleotide 3243 of the transfer RNA of leucine
- Others: fibromuscular dysplasia, dolichoectasia, Susac syndrome,<sup>15</sup> CADASIL, retinal

vasculopathy with cerebral leukodystrophy (RVCL) due to TREX1 mutation, hyperhomocysteinaemia due to methylenetetrahydrofolate reductase (MTHFR) gene polymorphism,<sup>16,17</sup> neurofibromatosis type 1 and homocystinuria

*Miscellaneous:*

- Sleep apnoea
- Moyamoya disease<sup>18</sup> – progressive stenosis of intracranial arteries and proximal branches (primary or secondary to other causes)
- Radiation-induced arteriopathy - post radiation at head and neck area, stenosis of distal internal carotid artery
- Reversible cerebral vasoconstriction syndrome - precipitating factors includes hypertension, illicit drug use and medications
- Migraine – risk is controversial, needs further research
- Hereditary haemorrhagic telangiectasia (HHT) - stroke caused by paradoxical embolism due to pulmonary arteriovenous malformations

**Stroke of undetermined cause**

*Cryptogenic stroke:*

- “Cryptogenic” after standard evaluation vs “cryptogenic” after additional, specialized evaluation
- “Highly cryptogenic” (i.e., with no probable and no possible cause discovered) vs “of possibly determined origin” (i.e., with no probable, but one or more possible, causes identified)

*Embolic Stroke of Undetermined Source (ESUS):*

- Sub-group of patients with cryptogenic ischaemic strokes with a high possibility of an occult embolic source of stroke (e.g. undetected paroxysmal AF, aortic arch plaque, and occult cancer).
- Criteria: (1) non-lacunar stroke detected by CT or MRI; (2) absence of extracranial or intracranial atherosclerosis causing 50% luminal stenosis in arteries supplying the ischaemic area; (3) absence of a major-risk cardiac source of embolism; and (4) absence of any other specific cause of index stroke. Lacunar stroke is defined as a subcortical infarct 1.5 cm in its largest dimension and in the distribution of the small, penetrating arteries.
- Management is long-term antiplatelet with no evidence for oral anticoagulants. One RCT showed direct oral anticoagulants (Rivaroxaban) is not superior to aspirin in prevention of recurrent stroke and associated with higher risk of bleeding. Prolonged ambulatory ECG monitoring to detect AF is more important as occult AF occurs in about 25% of all ESUS.

### 14.3 Stroke Patients with Patent Foramen Ovale (PFO)

**Recommendation:** PFO closure devices have moderate benefit to young and middle-aged patients with cryptogenic ischaemic stroke. PFO closure devices combined with antiplatelet therapy is also recommended.<sup>19</sup>

*(New recommendation, Level I, Class A)*

In patients with ischaemic stroke or transient ischaemic attack (TIA) and a patent foramen ovale (PFO) who are not treated with anticoagulation treatment, antiplatelet therapy is recommended.<sup>20</sup>

*(New recommendation, Level II-1, Class B)*

**Recommendation:** Among ischaemic stroke or TIA patients who have both a PFO and a venous source of embolism, anticoagulation is indicated based on the characteristics of stroke.<sup>20</sup>

*(New recommendation, Level I, Class A)*



When anticoagulant therapy is contraindicated, an inferior vena cava filter can be inserted.<sup>20</sup>

*(New recommendation, Level III, Class C)*

In patients with PFO and deep vein thrombosis (DVT), PFO closure with a transcatheter device may be considered depending on the risk of recurrent DVT.<sup>20</sup>

*(New recommendation, Level III, Class C)*

PFO closure during pregnancy is not recommended.<sup>21</sup> Low-dose oral Aspirin is the first line of treatment.<sup>21</sup> If a pregnant patient with a known PFO is at increased risk of venous thrombosis, prophylactic low molecular weight heparin (LMWH) doses can be considered.<sup>21</sup>

In one study, in patients who had a recent cryptogenic stroke due to PFO with an associated atrial septal aneurysm or large interatrial shunt, the rate of stroke recurrence was lower in patients with combined PFO closure/antiplatelet therapy compared to patients with antiplatelet therapy alone.<sup>22</sup> However, the closure of PFO was associated with a higher frequency of atrial fibrillation.<sup>22</sup>

#### **14.4 Investigation of Young Stroke**

Identify the cause / predisposing factor<sup>6</sup>

- A. Search for the classical vascular risk factors
- B. Special diagnostic tests (see section on Investigations)
  - I. ESR, CRP and fasting homocysteine<sup>16</sup>
  - II. FBC, RP, PT/aPTT, pregnancy test
  - III. Serum and urine toxicology screen
  - IV. *Auto-antibody screen*: including antiphospholipid antibodies, antinuclear antibody, antibody to double-stranded DNA, rheumatoid factor, anticardiolipin antibodies, complement levels, cryoglobulin level, neutrophil cytoplasm antibody (cANCA and pANCA), Scl-70 antibody, anti-centromere antibody, anti-Ro (SSA) and anti-La (SSB) cytoplasmic antibodies, serum angiotensin-converting enzyme, anti- proteinase 3
  - V. Infectious disease panel tests: varicella-zoster virus, herpes simplex virus, Epstein-Barr virus, HIV, hepatitis B and C viruses, tuberculosis, syphilis, Lyme disease and others
  - VI. Genetic tests:<sup>23</sup> for conditions such as CADASIL (notch 3 mutation), RVCL (trex 1 mutation), Hyperhomocysteinaemia (MTHFR 677C-T pleomorphism) and others
  - VII. Plasma  $\alpha$ -gal activity for Fabry's disease
  - VIII. MELAS: Increased lactate and pyruvate levels in serum and cerebrospinal fluid; lactate/pyruvate ratio, ragged-red fibres strongly positive succinate dehydrogenase staining in muscle biopsy
  - IX. Sleep study to detect sleep apnoea
  - X. Coagulation screen if indicated:
    - i. Serum fibrinogen
    - ii. Anti-thrombin III level
    - iii. Protein C and Protein S
    - iv. Factor V-Leyden
    - v. Prothrombin gene mutation

- C. Radiological investigations - standard (see chapter on Investigations) and specialised:
- I. MRI/MRA brain and intra and extracranial carotids / Carotid Doppler ultrasounds
  - II. Transthoracic Echocardiography (to detect atrial myxoma or any lesion in the heart)
  - III. Trans-esophageal echocardiography (TOE), Lower extremity ultrasound, pelvic CT, or MR venography (in patients with PFO)
  - IV. Advanced brain imaging: axial fat-suppressed T1-weighted MRI, high-resolution (3T) contrast- enhanced T1-weighted MRI, PET scan, MR spectroscopy, transcranial Doppler ultrasound studies, percutaneous cerebral angiography.
- D. Others: 24-hour Holter monitoring, prolonged ambulatory ECG monitoring, sleep study.

**Recommendations:**

**Table 14.2: Investigation of Young Stroke**

Investigation	Recommendations	Level of Evidence	Grade
Homocysteinaemia	Routine screening for hyperhomocysteinaemia among patients with a recent ischaemic stroke or TIA is not indicated.	III	C
Coagulation screening	The usefulness of screening for thrombophilic states in patients with ischaemic stroke or TIA is unknown.	II-2	C
Anti-phospholipid antibodies	Routine testing for anti-phospholipid antibodies is not recommended for patients with ischaemic stroke or TIA who have no other manifestations of the anti-phospholipid antibody syndrome and who have an alternative explanation for their ischaemic event, such as atherosclerosis, carotid stenosis or AF.	III	C
Sleep study	A sleep study might be considered for patients with an ischaemic stroke or TIA.	II-2	B

**Table 14.3: Treatment of Stroke in Certain Circumstances**

Treatment	Recommendations	Level of Evidence	Grade
Aspirin <sup>24,25</sup>	If the cause is not identified, Aspirin is usually given while additional tests are obtained to guide the choice between long-term antiplatelet or anticoagulant therapy.	III	C
	Antiplatelet therapy is recommended in patients who are found to have abnormal findings on coagulation testing after an initial ischaemic stroke or TIA if anticoagulant therapy is not administered.	I	A
	For patients with ischaemic stroke or TIA who have an anti-phospholipid antibody but who do not fulfil the criteria for anti-phospholipid antibody syndrome, antiplatelet therapy is recommended	I	B
	For patients with ischaemic stroke or TIA who meet the criteria for the anti-phospholipid antibody syndrome but in whom anticoagulation is not yet started, antiplatelet therapy is indicated	I	A
DOAC	<i>ESUS:</i> There is no role of anticoagulant in ESUS. Rivaroxaban was not superior to aspirin with regard to the prevention of recurrent stroke after an initial embolic stroke of undetermined source and was associated with a higher risk of bleeding. <sup>26</sup> <i>New recommendation</i>	I	A

	<p>For patients with an ischaemic stroke or TIA and both a PFO and a venous source of embolism, anticoagulation is indicated, depending on the stroke characteristics.<sup>27</sup></p> <p><i>New recommendation</i></p>	I	A
	<p>Anticoagulation might be considered in patients who are found to have abnormal findings on coagulation testing after an initial ischaemic stroke or TIA, depending on the abnormality and the clinical circumstances.</p> <p><i>New recommendation</i></p>	II-2	C
	<p>For patients with ischaemic stroke or TIA who meet the criteria for the APS, anticoagulant therapy might be considered depending on the perception of risk for recurrent thrombotic events and bleeding.</p> <p><i>New recommendation</i></p>	II-2	C
Device	<p><i>PFO closure device therapy</i></p> <p>PFO closure devices have moderate benefit to young and middle-aged patients with cryptogenic ischaemic stroke. PFO closure devices combined with antiplatelet therapy is also recommended.<sup>19</sup></p> <p><i>New recommendation</i></p>	I	A
	<p><i>Continuous positive airway pressure (CPAP) machine</i></p> <p>CPAP therapy might be considered for patients with ischaemic stroke or TIA and sleep apnoea given the emerging evidence in support of improved outcomes.<sup>28</sup></p> <p><i>New recommendation</i></p>	II-2	B
Blood transfusion	<p>For patients with sickle cell disease and prior ischaemic stroke or TIA, long-term blood transfusions to reduce haemoglobin S to &lt;30% of total haemoglobin composition are recommended.<sup>29</sup></p> <p><i>New recommendation</i></p>	I	B
Supplements	<p><i>Supplementation with folate, vitamin B6 and vitamin B1</i></p> <p>In adults with a recent ischaemic stroke or TIA who are known to have mild to moderate hyperhomocysteinaemia, supplementation with folate, vitamin B6 and vitamin B12 safely reduces the levels of homocysteine but has not been shown to prevent stroke.</p> <p><i>New recommendation</i></p>	III	B

## 14.5 Cerebral Venous Thrombosis

CVT is a type of stroke where the thrombosis occurs in the venous side of the brain circulation, leading to occlusion of one or more cerebral veins and dural venous sinus. The age and gender distribution of CVT is different from that of ischaemic stroke, CVT being more frequent in young adults and women. The incidence is higher in developing countries. CVT is associated with prothrombotic conditions either due to transient causes or permanent primary causes. In around 13% of adult with CVT, no risk factors are identified. The European Stroke Organization guideline addresses both diagnostic and therapeutic topics in CVT.<sup>10</sup> CVT in pregnancy is outlined in the chapter of stroke in pregnancy.

### Recommendations:

**Table 14.4: Investigation of Cerebral Venous Thrombosis**

Investigation	Recommendations	Level of Evidence	Grade
CTV/ MRV	Either CT or MR venography can be used as a reliable alternative to DSA for the diagnosis of CVT in patients with suspected CVT	II-3	B
Digital Subtraction Angiography (DSA)	DSA as a diagnostic modality is indicated in cases of suspected CVT when the diagnosis of CVT doubtful with non-invasive imaging alone. <sup>30</sup>	II-1	C
D-Dimer	Measurement of D-dimer before neuroimaging is recommended in patients with suspected CVT, except in those with isolated headache or prolonged duration of symptoms (high false negative rates)	II-2	B
Thrombophilia screening	Thrombophilia screening may be performed in patients with high pre-test probability of having severe thrombophilia (i.e. a personal and/or family history of venous thrombosis, young age at CVT, CVT without a transient or a permanent risk factor) to prevent recurrent venous thrombotic events. However, routine thrombophilia screening is not recommended to reduce deaths, improve functional outcome, or prevent recurrent venous thrombosis in patients with CVT.	II-3	B
Occult malignancy screening	Routine screening for occult malignancy in patients with CVT is not recommended to improve outcomes	II-3	B

**Table 14.5: Treatment of Central Venous Thrombosis**

Treatment	Recommendations	Level of Evidence	Grade
Acute anticoagulant treatment	Treatment of adult patients with acute CVT with heparin in therapeutic dosage is recommended, including in those with intracerebral haemorrhage at baseline.	I	B
Type of heparin	Treatment of patients with acute CVT with LMWH instead of UFH is recommended (unless fast reversal of the anticoagulant effect is required, or the patient has contraindications to LMWH).	I	B
Thrombolysis in acute CVT	Thrombolysis in acute CVT patients with a pre-treatment low risk of poor outcome is not recommended.	III	C
Endovascular therapy or Thrombectomy	Endovascular therapy or Thrombectomy may be considered in patients with clinical deterioration despite anticoagulation, or with severe neurological deficits or in coma. <sup>30</sup>	II-2	C

Warfarin	Using oral anticoagulants (vitamin K antagonists) for a variable period (3-12 months) after CVT is recommended to prevent recurrent CVT and other venous thromboembolic events. Patients with recurrent venous thrombosis or with an associated prothrombotic condition with a high thrombotic risk may need permanent anticoagulation. We suggest following specific recommendations for the prevention of recurrent venous thromboembolic events in such conditions.	III	C
DOACs	Treatment of CVT with DOACs is not recommended especially during the acute phase.	III	C
Therapeutic LP	Therapeutic LP is not recommended. However, it may be considered in patients with cerebral venous thrombosis and signs of intracranial hypertension, because of a potential beneficial effect on visual loss and/or headache, whenever its safety profile is acceptable.	III	C
Acetazolamide	Acetazolamide is not recommended in patients with acute CVT to prevent deaths or to improve the functional outcomes. However, in isolated intracranial hypertension secondary to CVT, causing severe headaches or is threatening the vision, Acetazolamide may be considered if its safety profile is acceptable	III	C
Steroids	Steroids in patients with acute CVT without any co-existing inflammatory diseases are not recommended to prevent deaths or to improve the functional outcomes	III	C
Shunt	Routine shunting (without other surgical treatment) in patients with acute CVT and impending brain herniation due to parenchymal lesions is not recommended to prevent death	II-3	C
Decompressive surgery	Decompressive surgery for patients with acute CVT and parenchymal lesion(s) with impending herniation is recommended to prevent death.	II-1	B
Antiepileptic drugs (AEDs)	Antiepileptic drugs in patients with acute CVT with supratentorial lesions and seizures are recommended to prevent early recurrent seizures.	II-3	C

### Key Recommendations:

5. Young onset stroke requires more comprehensive investigation to determine the stroke aetiology.
6. Diagnosis of cryptogenic stroke and embolic stroke of undetermined source (ESUS) is made after standard evaluation to rule out possible cause of stroke.
7. Further specialized investigations needed in the cryptogenic or ESUS stroke for example prolonged Holter monitoring to look for atrial fibrillation or to look for evidence of patent foramen ovale (PFO).
8. Cerebral venous thrombosis is one of the major cause of venous infarct and would require investigations to determine the cause of thrombosis. Treatment mainly directed at anticoagulation with adjunctive therapy to prevent associated complications.

### 15.1 Burden and Aetiology

The incidence of pregnancy-associated stroke is 10.2 per 100 000 deliveries.<sup>1</sup> The incidence rate of stroke in pregnancy is higher in the peripartum and postpartum period, especially in the first six to twelve weeks after delivery.<sup>2-5</sup> In a Japanese study, most pregnancy-associated strokes were haemorrhagic strokes (73.5%), less than a quarter (24.5%) were ischaemic strokes and rarely, there were mixed strokes (2%).<sup>6</sup>

In a previous study, 75.7% of the patients with ischaemic stroke were arterial infarcts and 24.3% were venous infarctions.<sup>6</sup> Main causes of ischaemic stroke in pregnancy were congenital heart diseases, valvular heart diseases, atrial fibrillation (AF) and inheritable coagulation abnormalities.<sup>1</sup> Most common aetiologies of cerebral haemorrhage were aneurysm (19.8%), arteriovenous malformation (17.1%), pregnancy-induced hypertension (11.7%) and HELLP syndrome.<sup>1</sup>

### 15.2 Investigations

Magnetic resonance imaging (MRI) of the brain (without gadolinium contrast) is the radiological modality of choice for investigating strokes in pregnancy.<sup>5</sup> MRI of the brain in the antenatal period is not associated with increased adverse events to the foetus.<sup>7-9</sup> However, MRI of the brain should be used carefully.<sup>8</sup> MRI of the brain should only be used when the test can answer the patient's clinical question and provides medical benefits to the pregnant patient.<sup>8</sup> However, antenatal exposure to gadolinium contrast was reported to increase the risk of stillbirth, neonatal death, rheumatological, inflammatory and infiltrative skin conditions in one study.<sup>9</sup>

### 15.3 Management

Blood pressure should be reduced to less than 160/110 mmHg.<sup>10</sup> In cases of preeclampsia or severe hypertension with neurological symptoms, the aim is to achieve an urgent and sustained reduction of blood pressure to less than 160/110 mmHg to reduce the risk of maternal stroke.<sup>10</sup> In acute haemorrhagic stroke in pregnancy, blood pressure can be controlled with Methyldopa, Labetalol and long acting Nifedipine.<sup>10</sup> The goal is to correct the blood pressure to <160/110 mmHg, followed by titration of the anti-hypertensive medications to reduce the blood pressure consistently to <140/90 mmHg.<sup>10</sup> The coagulopathies should also be corrected.<sup>10</sup>

**Recommendation:** In ischaemic arterial strokes, Aspirin up to 150mg daily is well tolerated during pregnancy.<sup>5</sup> Pregnant patients with a well-defined low risk conditions may be given UFH or LMWH in the first trimester, followed by a low dose of aspirin in the second and third trimesters.<sup>11</sup>

*(Level II, Grade B)*

**Recommendation:** In pregnant patients with a well-defined low risk conditions, no antiplatelet other than Aspirin can be prescribed.<sup>11</sup>

*(Level III, Grade C)*

**Recommendation:** In pregnant women with a well-defined high-risk condition, Vitamin K antagonists need to be avoided between the 6<sup>th</sup> and 12<sup>th</sup> weeks of pregnancy and also near the term.<sup>11</sup>

During this period, UFH or LMWH can be used.<sup>11</sup>

*(Level II, Grade B)*

**Recommendation:** In addition, the pregnant patients with a well-defined high-risk condition on DOACs should be given UFH or LMWH between the 6<sup>th</sup> and 12<sup>th</sup> weeks of pregnancy.<sup>11</sup>

*(New recommendation, Level III, Grade C)*

**Recommendation:** At other weeks of gestation, Warfarin can be given.<sup>11</sup>

*(Level III, Grade C)*

**Recommendation:** When the labour process is pharmacologically induced, Aspirin can be continued.<sup>11</sup>

*(Level III, Grade C)*

**Recommendation:** UFH and LMWH need to be stopped 24 hours before the induction of labour.<sup>11</sup>

*(Level III, Grade C)*

**Recommendation:** UFH and LMWH should be restarted within 24 hours of delivery if there are no contraindications.<sup>11</sup>

*(Level III, Grade C)*

**Recommendation:** Vitamin K antagonists (without a loading dose) may be restarted after 24 hours of delivery if there are no contraindications.<sup>11</sup>

*(Level III, Grade C)*

Patients with cerebral venous thrombosis (CVT) can be administered with either unfractionated heparin (UFH) or low molecular weight heparin (LMWH) till at least six weeks postpartum.<sup>12</sup> The management of the patients with dissection of the carotid and vertebral arteries includes monitoring only or using low-dose Aspirin.<sup>12</sup> LMWH can be considered in some cases in which dissection is in the highest thrombotic risk period (peri-partum to six weeks post-partum).<sup>12</sup>

There is lack of evidence regarding the safety of statins in pregnancy.<sup>12</sup> Statins should be stopped during preconception and throughout pregnancy.<sup>12</sup> In general, stroke management decisions are based on symptom severity, maternal medical conditions, and wishes of the patient and her family.<sup>10</sup> Rehabilitation should be started early.<sup>10</sup> Rehabilitation is based on a multidisciplinary team discussions and decisions.<sup>10</sup>

## Recommendations Summary:

**Table 15.1: Management of Stroke in Pregnancy**

Management	Recommendations	Level of Evidence	Grade
During pregnancy	In AIS, Aspirin up to 150mg daily is well tolerated during pregnancy. Pregnant patients with a well-defined low risk conditions may be given UFH or LMWH in the first trimester, followed by a low dose aspirin in the second and third trimesters.	III	C
	In pregnant patients with a well-defined low risk conditions, no antiplatelet other than Aspirin can be prescribed.	III	C
	In pregnant women with a well-defined high-risk condition, Vitamin K antagonists need to be avoided between the 6 <sup>th</sup> and 12 <sup>th</sup> weeks of pregnancy and also near to term. During this period, UFH or LMWH can be used.	II	B
	In addition, the pregnant patients with a well-defined high-risk condition on direct oral anticoagulants (DOACs) should be given UFH or LMWH between the 6 <sup>th</sup> and 12 <sup>th</sup> weeks of pregnancy. <i>New recommendation</i>	III	C
	At other weeks of gestation, Warfarin can be given.	III	C
Labour induction	When the labour process is pharmacologically induced, Aspirin can be continued.	III	C
	UFH and LMWH need to be stopped 24 hours before the induction of labour.	III	C
	UFH and LMWH should be restarted within 24 hours of delivery if there are no contraindications.	III	C
	Vitamin K antagonists (without a loading dose) may be restarted after 24 hours of delivery if there are no contraindications.	III	C

### Key Recommendations:

1. MRI of the brain (without gadolinium contrast) is the radiological modality of choice for investigating strokes in pregnancy.
2. Aspirin is the only choice of antiplatelet for pregnant patients with a well-defined low risk condition.



# 16

## STROKE THERAPIES WITH LIMITED EVIDENCE

A variety of medicines and treatment modalities have been used for stroke. Although yet to be proven effective, they may be considered for treatment in acute stroke (Table 16.1).

**Table 16.1: Stroke Therapy Modalities**

Therapy	Description
<b>NeuroAid</b>	The medicine did not demonstrate any statistically significant benefit after 3 months although some small studies showed that it could be effective in improving functional independence and motor recovery, and is safe for patients with a primarily non-acute stable stroke. <sup>1-3</sup>
<b>Citicoline</b>	Citicoline is widely used after stroke but is not proven statistically to be beneficial in the treatment of acute stroke. <sup>4,5</sup>
<b>Cerebrolysin</b>	Cerebrolysin is also not proven in the management of acute stroke. <sup>6-8</sup>
<b>Edaravone</b>	Meta-analysis of Edaravone showed some benefits in improving neurological impairment in acute ischaemic stroke and intracerebral haemorrhage but was not proven to reduce death and long-term disability in both types of stroke. <sup>9</sup>
<b>Gingko</b>	There was limited evidence on to support the use of gingko biloba in terms of improving quality of life and other stroke events. As such, more studies are needed before it can be recommended for routine use in improving neurological and cognitive function in patients with acute ischaemic stroke. <sup>10</sup>
<b>Vitamin B</b>	Based on the Vitatops trial, Vitamin B supplements did not help in secondary stroke prevention but showed some benefit if the patient had concomitant hyperhomocysteinaemia. <sup>11,12</sup>
<b>Folic Acid</b>	Folic acid supplementation did not demonstrate a major effect in preventing stroke. However, potential mild benefits in primary stroke prevention, especially when folate is combined with B vitamins and in male patients, requires further investigation. <sup>13</sup>
<b>Selective Serotonin Reuptake Inhibitors</b>	Fluoxetine 20 mg given daily for 6 months after acute stroke does not seem to improve the functional outcomes. A study showed that even though the treatment reduced the occurrence of depression, it increased the frequency of bone fractures. Therefore, recent evidence does not support the routine use of fluoxetine either for the prevention of post-stroke depression or to promote recovery of function. <sup>14</sup>
<b>Acupuncture</b>	Acupuncture, from multiple trials, did not show any significant benefit and efficacy in terms of functional recovery after stroke. <sup>15-17</sup> A recent meta-analysis concluded that the apparent reduction in dependency and improvement in neurological recovery associated with the use of acupuncture in acute stroke are confounded by the use of open controls. However the adverse events associated with acupuncture were generally reported to be minor and usually did not result in stopping treatment. <sup>18</sup>
<b>Transcranial Magnetic Stimulation (TMS)</b>	TMS has shown some promising results in improving the motor recovery after stroke. However, it may need more evidence before it can be used as a daily rehabilitation tool for r stroke. <sup>19-22</sup>
<b>Tocovid (Tocotrienol)</b>	Tocovid (tocotrienol) has only been proven in animal studies to be effective as neuroprotective treatment in stroke, but not in human studies. <sup>23-25</sup> However, one study showed that tocotrienol may attenuate the progression of white matter lesion <sup>26</sup> .
<b>Selenium</b>	Selenium levels have been shown to be on the lower side during an acute stroke. However, there is still no evidence of benefit from Selenium

	supplementation in acute stroke although a few animal studies have shown some benefits. <sup>27-29</sup>
<b>Piracetam</b>	Piracetam played a limited role in the rehabilitation of the overall language impairment and only showed benefit as regards to the written language ability based on a meta-analysis. Its effect on the overall linguistic level and written language tends to emerge within a short period and declines thereafter. Piracetam also did not significantly improve neurologic or functional outcome in acute stroke patients. <sup>30,31</sup>

### **Key Recommendations:**

1. There are a variety of stroke medications and treatment modalities, but the evidence is very limited.

Stroke Care Quality Measures to Monitor for Hospitals providing Thrombolysis and/or Thrombectomy Services in Malaysia<sup>1-11</sup>

Stroke Care Quality		Minimal measures
1	Percentage of Ischemic Stroke (IS) patients receiving IV Thrombolytic therapy (IV rt-PA), < 35 minutes of CT Brain initiation (CT Brain initiation to needle time)	≥ 65%
2	Percentage of all suspected stroke patients who underwent CT or MRI Brain imaging within 24 hours of presenting themselves to the emergency department.	≥ 90%
3	Percentage of newly confirmed stroke patients who underwent bedside screening for dysphagia	≥ 90%
4	Percentage of Ischemic Stroke patients discharged with antiplatelets (if there were no contraindications)	≥ 80%
5	Percentage of AF- related stroke patients given anticoagulants before discharge or planned for eventual anticoagulation (if there were no contraindications)	≥ 80%
6.	Percentage of admitted post-stroke patients were discharged with proper discharge plan: <ul style="list-style-type: none"> <li>- Cardiovascular risk factors addressed</li> <li>- Rehabilitation team referral</li> <li>- Stroke education</li> <li>- Smoking cessation education</li> </ul>	> 90%

## APPENDICES

**Appendix A. MeSH terms or free text terms used for literature search**  
*(Reference: Rationale, Objectives And Process Of Guideline Development)*

Chapter	Related Topics	Search Terms Used
-	Stroke	Stroke Brain infarct* Brain ischemia Brain isch?emi* Cerebral infarct* Cerebrovascular accident* CVA Cerebrovascular infarct* Acute ischemi* stroke Carotid artery thrombosis Anterior cerebral artery infarction Middle cerebral artery infarction Posterior cerebral artery infarction Anterior circulation occlusion
-	<b>AND</b>	
<b>OR</b>	Epidemiology, Definition and Classification of Stroke	Epidemiology Prevalence Definition Description Classification Categorization
<b>OR</b>	Causes and Pathophysiology	Causes Aetiology Pathophysiology Mechanism
<b>OR</b>	Diagnosis and Initial Assessment	Diagnosis Differential diagnosis Sign Symptoms Clinical features Clinical presentation initial assessment
<b>OR</b>	Prognosis	Prognosis Survival Mortality Disability Recurrent Progress
<b>OR</b>	Prevention of Stroke	Prevention Primary prevention Secondary prevention Predisposing factor Risk factor Modifiable risk factor Non modifiable risk factor Risk stratification Risk estimate Management of risk factor

		Revascularisation Carotid endarterectomy CEA Carotid angioplasty Stenting Intracranial angioplasty
<b>OR</b>	Investigations	Investigations Imaging Assessment
<b>OR</b>	Emergency Medicine Services	Emergency medicine services EMS Pre-hospital management Pre arrival Emergency department Initial management/evaluation/assessment
<b>OR</b>	Acute Management	Acute management General management
<b>OR</b>	Reperfusion of Ischaemic Brain	Reperfusion Intravenous thrombolysis IVT Alteplase Tenecteplase
<b>OR</b>	Endovascular Thrombectomy	Endovascular thrombectomy Thrombectomy Percutaneous thrombectomy Endovascular procedures Mechanical thrombectomy Neuro-thrombectomy Embolectomy Cerebral revascularization Endovascular embolectomy Intraarterial embolectomy Intra-arterial thrombectomy Balloon angioplasty Stent Mechanical thrombolysis Endovascular therapy Endovascular treatment
<b>OR</b>	Stroke Unit	Stroke unit Stroke team
<b>OR</b>	Stroke in the Older Person	Older person Elderly Age above 60
<b>OR</b>	Stroke and Cardioembolism	Cardioembolism Atrial fibrillation
<b>OR</b>	Stroke in Special Circumstances	Young adult Cryptogenic Embolic stroke of undetermined source ESUS Patent foramen ovale PFO Cerebral venous thrombosis
<b>OR</b>	Management of Stroke in Pregnancy	Pregnancy During pregnancy Labour induction
<b>OR</b>	Stroke Therapies with Limited Evidence	Stroke therapy Limited evidence Treatment modalities

**Appendix B. Prehospital Stroke Screening Tool**  
(Reference Chapter: Chapter 7)

**Acute Stroke Pre-Hospital Diagnostic Screening Tools**

Assessment Tools	Items/ Scoring
Face Arm Speech Test (FAST)	<ol style="list-style-type: none"> <li>1. Facial palsy,</li> <li>2. Arm weakness,</li> <li>3. Speech disturbance.</li> </ol> <p>Abnormality demonstrated on one or more items is indicative of suspected stroke</p>
Balance, Eye, Face Arm Speech Test (BEFAST)	<ol style="list-style-type: none"> <li>1. Balance</li> <li>2. Eyesight changes</li> <li>3. Facial weakness</li> <li>4. Arm Weakness</li> <li>5. Speech Difficulties</li> </ol> <p>Abnormality demonstrated on one or more items is indicative of suspected stroke</p>
Cincinnati Prehospital Stroke Scale	<ol style="list-style-type: none"> <li>1. Presence/absence of facial pals</li> <li>2. Unilateral arm weakness</li> <li>3. Speech impairment.</li> </ol> <p>Abnormality demonstrated on one or more items is indicative of suspected stroke</p>
Los Angeles Prehospital Stroke Screen (LAPSS)	<ol style="list-style-type: none"> <li>1. Age &gt; 45</li> <li>2. History of seizures absent</li> <li>3. Symptom duration &lt; 24 hr</li> <li>4. At baseline, patient is not wheelchair bound or bedridden</li> <li>5. Blood sugar between 60 and 400 mg/dL</li> <li>6. Obvious asymmetry (right versus left)</li> <li>7. Facial smile/grimace</li> <li>8. Grip</li> <li>9. Arm strength</li> </ol> <p>If 1–5 are yes with asymmetry on exam then LAPS criteria are met indicating suspected stroke</p>

*\*note: There are several other Pre-Hospital Diagnostic Screening Tools available for use as screening tools.*

## Pre-Hospital Stroke Severity Scale

Assessment Tools	Items/ Scoring
Field Assessment Stroke Triage for Emergency Destination (FAST-ED)	<p>6-items</p> <ol style="list-style-type: none"> <li>1. Facial palsy (0-1)</li> <li>2. Arm weakness (0-2)</li> <li>3. Speech changes (0-2)</li> <li>4. Eye deviation (0-2)</li> <li>5. Denial/neglect (0-2)</li> <li>6. Time (documentation for decision making) not scored</li> </ol> <p>Total possible score: 9 Large vessel occlusion (LVO) is possible if score 4 or more</p>
The Los Angeles Motor Scale (LAMS)	<p>3 items</p> <ol style="list-style-type: none"> <li>1. Facial droop (absent=0, present=1)</li> <li>2. Arm drift (absent=0, drifts down=1, falls rapidly=2)</li> <li>3. Grip strength (normal=0, weak=1, no grip=2)</li> </ol> <p>Total possible score 5 LVO is possible if score 4 or more</p>
Cincinnati Prehospital Stroke Severity Scale	<p>3 items</p> <ol style="list-style-type: none"> <li>1. Conjugate gaze deviation (<math>\geq 1</math> on NIHSS item for gaze) (0-2)</li> <li>2. Incorrectly answers to at least 1 of 2 LOC questions (age or current month) and does not follow at least 1 of 2 commands (close eyes, open and close hand). (0-1)</li> <li>3. Cannot hold arm (left, right or both) up for 10 seconds. (0-1)</li> </ol> <p>Total possible score 4 LVO is possible if score 1 or more</p>
Vision, Aphasia, and Neglect (VAN)	<p>Patients are asked to raise both arms up and hold them up for 10 s. If the patient demonstrates any level of drift, weakness or paralysis, the assessment continues. Otherwise, patient is VAN negative and screen ends.</p> <p>Items</p> <ol style="list-style-type: none"> <li>1. Visual disturbances: field cut, double vision, new-onset blindness (present/absent)</li> <li>2. Aphasia: Expressive, receptive, mixed (present/absent)</li> <li>3. Neglect: Forced gaze, unable to feel both sides at same time or does not recognize arm, ignoring one side (present/absent)</li> </ol> <p>Scoring: None If weakness present + <math>\geq 1</math> positive finding =VAN positive (LVO is possible)</p>

*\*note: There are several other Pre-Hospital Stroke Severity Scales available for use as screening tools. The above list are just few examples of Pre-Hospital Stroke Severity Scales.*

**Appendix C. Operational definition - Terms and Descriptions**  
 (Reference Chapter: Chapter 7)

Terms	Descriptions
<b>Bypass</b>	Ambulances are directed to other facilities by bypassing the original destination. It is to ensure the stroke patient is sent to the nearest stroke centre rather than a facility that is not capable of thrombolysing the stroke patient.
<b>Call taker</b>	A trained person in MECC who receives calls from the public through 999 and manages the call.
<b>Dispatch priority</b>	Level of priority assigned to each case according to the clinical urgency. There are 4 levels of priority: Priority 1, priority 2, priority 3 and priority 4. Priority 1 is the highest priority level in the dispatch system.
<b>Dispatching system</b>	A computerized system in MECC manned by the call taker to manage all incoming 999 calls from the public and dispatches the appropriate response team to the scene.
<b>PHC responder</b>	A medically trained person (usually an Assistant Medical Officer / Staff Nurse) who responds to pre-hospital calls.
<b>Pre-arrival alert</b>	Providing notification of an incoming case prior to the patient's arrival.



## Appendix D. Types of Swallowing Test

(Reference Chapter: Chapter 8)

### Types of Swallowing Tests

#### Kidd Water Test

**Description:** Clinical examination includes pharyngeal sensation assessed by orange stick, tongue and facial movement, speech, sensory and perceptual function and muscle strength also assessed. Ability to swallow also assessed by patient swallowing 50 ml of water in 5 ml allotments.

**Source:** Kidd D, Lawson J, Nesbitt R, MacMahon J. Aspiration in acute stroke: a clinical study with video fluoroscopy. *Quarterly Journal of Medicine*. 1993; 86:825-829.

#### Nishiwaki et al.

**Description:** Scores 6 items including lip closure, tongue movement, palatal elevation, gag reflex, voice quality and motor speech function. Also includes a saliva swallowing test. After patient swallows 1 teaspoon of water twice, asked to drink the rest of the water from a cup for a total of 30 ml.

**Source:** Nishiwaki K, Tsuji T, Liu M, Hase K, Tanaka N, Fujiwara T. Identification of a simple screening tool for dysphagia in patients with stroke using factor analysis of multiple dysphagia variables. *J Rehabil Med*. 2005; 37(4):247-51.

#### CODA Standardized Swallowing Assessment (SSA)

**Description:** Pre-swallowing check list if passed is followed by teaspoon sips of water 3 times, followed by half glassful of water (*Grade A, strong evidence Westergren, 2006*).

**Source:** Perry, L. Screening swallowing function of patients with acute stroke. Part one: identification, implementation and initial evaluation of a screening tool for use by nurses. *Journal of Clinical Nursing* 2001; 10: 463-473.

#### Toronto Bedside Swallowing Screening Test (TOR-BSST)

**Description:** The test is divided into three sections. First section is oral exam (3 items), followed by section on water swallowing. The third section is examination of voice after swallow. The TOR-BSST has been validated in stroke survivors and is a simple accurate tool to identify stroke patients with dysphagia regardless of severity and setting.

**Source:** Martino R, Silver F, Teasell R, Bayley M, Nicholson G, et al. The Toronto Bedside Swallowing Screening Test (TOR-BSST). *Stroke*. 2009; 40: 555-561.

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The Development Group members have completed the disclosure forms. None of them hold shares in pharmaceutical firms or act as consultants to such firms.

(Details are available upon request from the CPG secretariat)

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