

Management of patent foramen ovale in embolic stroke of undetermined source patients: Malaysian experts' consensus

Stephenie Ann Albart, MD¹, Abdul Hanif Khan Yusof Khan, MMed (Int Med)^{2,3}, Wan Asyraf Wan Zaidi, MMed (Int Med)⁴, Annamalar Muthu Muthuppalaniappan, MRCP⁵, Geetha Kandavello, MRCP (Paeds)⁶, Koh Ghee Tiong, MRCPCH⁷, Leong Ming Chern, MRCPCH⁶, Liew Houng Bang, FRCP⁸, Ong Beng Hooi, MRCP⁹, Shanthy Viswanathan, MRCP¹⁰, Hoo Fan Kee, MRCPS (Glasgow)^{2,3}, Irene Looi, FRCP^{1,11}, Yap Yee Guan, FRCP¹², Law Wan Chung, MRCP¹³

¹Clinical Research Centre, Hospital Seberang Jaya, Ministry of Health Malaysia, Seberang Jaya, Pulau Pinang, Malaysia, ²Department of Neurology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Selangor, Malaysia, ³Department of Neurology, Hospital Pengajar Universiti Putra Malaysia, Universiti Putra Malaysia, Serdang, Selangor, Malaysia, ⁴Department of Medicine, Hospital Canselor Tuanku Muhriz (HCTM), Universiti Kebangsaan Malaysia, Kuala Lumpur, Wilayah Persekutuan Kuala Lumpur, Malaysia, ⁵Gleneagles Hospital Penang, George Town, Pulau Pinang, Malaysia, ⁶Institut Jantung Negara, Kuala Lumpur, Wilayah Persekutuan Kuala Lumpur, Malaysia, ⁷Paediatric Cardiology Unit, Hospital Serdang, Kajang, Selangor, ⁸Department of Cardiology, Hospital Queen Elizabeth II, Ministry of Health Malaysia, Kota Kinabalu, Sabah, Malaysia, ⁹Kedah Medical Centre, Alor Setar, Kedah, Malaysia, ¹⁰Department of Neurology, Hospital Kuala Lumpur, Ministry of Health Malaysia, Kuala Lumpur, Wilayah Persekutuan Kuala Lumpur, Malaysia, ¹¹Department of Medicine, Hospital Seberang Jaya, Ministry of Health Malaysia, Seberang Jaya, Pulau Pinang, Malaysia, ¹²Sunway Medical Centre, Petaling Jaya, Selangor, Malaysia, ¹³Department of Medicine, Hospital Umum Sarawak, Ministry of Health Malaysia, Kuching, Sarawak, Malaysia

ABSTRACT

Introduction: About 20 to 40% of ischaemic stroke causes are cryptogenic. Embolic stroke of undetermined source (ESUS) is a subtype of cryptogenic stroke which is diagnosed based on specific criteria. Even though patent foramen ovale (PFO) is linked with the risk of stroke, it is found in about 25% of the general population, so it might be an innocent bystander. The best way to treat ESUS patients with PFO is still up for discussion.

Materials and Methods: Therefore, based on current evidence and expert opinion, Malaysian expert panels from various disciplines have gathered to discuss the management of ESUS patients with PFO. This consensus sought to educate Malaysian healthcare professionals to diagnose and manage PFO in ESUS patients based on local resources and facilities.

Results: Based on consensus, the Malaysian expert recommended PFO closure for embolic stroke patients who were younger than 60, had high RoPE scores and did not require long-term anticoagulation. However, the decision should be made after other mechanisms of stroke have been ruled out via thorough investigation and multidisciplinary evaluation. The PFO screening should be made using readily available imaging modalities, ideally contrast-transsthoracic echocardiogram (c-TTE) or contrast-transcranial Doppler (c-TCD). The contrast-transesophageal echocardiogram (c-TEE) should be used for the confirmation of PFO diagnosis. The experts advised closing PFO as early as possible because there is limited evidence for late closure. For the post-closure follow-up management, dual antiplatelet therapy (DAPT) for one to three months, followed

by single antiplatelet therapy (APT) for six months, is advised. Nonetheless, with joint care from a cardiologist and a neurologist, the multidisciplinary team will decide on the continuation of therapy.

KEYWORDS:

Patent foramen ovale, embolic stroke of undetermined source, cryptogenic stroke, PFO closure, stroke

INTRODUCTION

Stroke is one of the major causes of mortality and disability worldwide. In Malaysia, stroke is the third-leading cause of death and the second-leading cause of combined death and disability.¹ Based on the National Health and Morbidity Survey in 2006 and 2011, there was an increase in stroke prevalence from 0.3% to 0.7% among the Malaysian population.^{2,4} From 2010 to 2014, the age-adjusted incidence and prevalence rates for ischaemic stroke almost tripled (34.2–96.2 per 100 000 and 42.8–118.7 per 100 000, respectively) in 5 years.⁵ A steady increase in the incidence of ischaemic stroke by 29.5% annually was observed.⁵ The Annual Report of the Malaysian Stroke Registry, 2009 to 2016, stated that 77% of stroke patients were between the ages of 50 and 79 years old, with the mean age of stroke onset being 62.5 years old.⁶ Hypertension, smoking, diabetes and hyperlipidaemia were the common risk factors for first and recurrent ischaemic strokes identified among the Malaysian population.^{5,7}

Ischaemic stroke is the most commonest type of stroke (79.4%), followed by haemorrhagic stroke (18.2%), transient ischaemic attack (2%) and strokes of unclassified causes

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Corresponding Author: Abdul Hanif Khan Yusof Khan

Email: ahaniifkhan@upm.edu.my

(0.4%).⁵ Based on pathophysiology, the causes of ischaemic stroke can be classified into large artery atherosclerosis (20%), small vessel occlusion (25%), cardio-embolism (20%), and other identified causes (5%).⁸ About 20-40% of ischaemic stroke causes remain undetermined and are classified as cryptogenic stroke.⁸ Cryptogenic stroke is further classified into three types: 1) multiple causes of stroke identified; 2) no causes identified due to insufficient diagnostic work-up; and 3) no causes identified despite extensive work-up.⁹ Embolic stroke of undetermined stroke (ESUS) is a sub-type of cryptogenic stroke which is diagnosed based on specific criteria. The diagnostics criteria for ESUS are described in the later section. The classification of stroke and the potential causes of ESUS and other types of strokes are shown in Figure 1 which is generated based on Ntaios et al.⁹ and Hart et al.¹⁰ One of the possible causes of ESUS is patent foramen ovale (PFO).¹⁰ PFO is the most common congenital cardiac abnormality in every 1 in 4 adults. The foramen ovale is a normal foetal heart structure that allows oxygenated placental blood to circulate from the right to the left atrium to reach the arterial circulation of the foetus. If the foramen ovale does not close naturally after birth during infancy, it is known as PFO.¹¹ The possible PFO-related stroke mechanisms are hypothesised as paradoxical embolism of a venous clot shunting through the PFO to the left atrium, in situ clot formation within the PFO, and atrial arrhythmias.¹²

There are a few treatment options available for secondary stroke prevention in ESUS patients with PFO, such as percutaneous transcatheter closure of PFO, antithrombotic therapy or a combination of both. Several clinical trials (CLOSURE, PC, RESPECT, CLOSE, REDUCE and DEFENSE-PFO trial) have been conducted to assess the efficacy and to compare the available treatments.¹³⁻¹⁹ However, the outcomes of the trials were inconsistent due to the differences in study design and efficacy of the device used. The optimal management of ESUS patients with PFO is still being debated.

PFO is common in 25% of the general population. Even though it is associated with an increased risk of stroke, it could be just an innocent bystander. While we search for the best treatment option for ESUS patients with PFO, it is also crucial to consider whether treating such patients is beneficial and outweighs the potential risk. Therefore, Malaysian expert panels have gathered their thoughts and recommendations on managing ESUS patients with PFO based on the current evidence and their expert opinion on such patients. This consensus mainly aimed to educate the healthcare professionals involved in the management of acute ischaemic strokes regarding the diagnosis and management of PFO in ESUS patients based on the availability and feasibility of local resources and facilities in Malaysia.

MATERIALS AND METHODS

The Stroke Council of the Malaysian Society of Neurosciences (MSN) has scheduled three virtual meetings with neurologists, cardiologists, paediatric cardiologists, physicians and geriatricians from all regions of Malaysia: Central and South region in November 2021; North region in December 2021; and East Malaysia and the East Coast in January 2022. Each region was assigned to present and

discuss a few specific related topics. Experts from the Kuala Lumpur and Selangor regions reviewed the selection of patients for PFO closure, while experts from the North Zone discussed the preferred screening and diagnostic technique for PFO, as well as the timing of PFO closure in ESUS. Experts from East Malaysia and the East Coast discussed post-PFO closure care and follow-up, medical treatment if PFO is not closed despite an indication for closure, and the strategies to raise awareness about PFO closure in ESUS. The experts' recommendations and suggestions from these three meetings were compiled into a Google form and emailed to all the experts for voting on the level of consensus. Table I shows the description of the level of consensus which was adapted from Diener et al.²⁰ Twenty-eight out of fifty-two experts responded to the Google form, representing a 53% response rate. The data were retrieved and analysed to determine the percentages of the level of agreement for each consensus statement. The findings were presented to a small group of experts (14 volunteers) from all regions at the last meeting, held in March 2022. Those statements that lacked majority support or contradicted other guidelines were re-discussed before reaching the final consensus. The final consensus among Malaysian experts is presented in this article. The co-authors reviewed and commented on the first draft of the manuscript in June 2022. Subsequently, the draft was revised accordingly until no further comments were received from all the co-authors. The final draft was sent to experts listed in Appendix A from the Malaysian PFO-Stroke Working Group for review, and it was finalised in September 2022.

PREFERRED SCREENING AND DIAGNOSTIC STRATEGY

Diagnostic strategy for ESUS

A thorough investigation should be conducted to rule out any additional potential causes of the suspected ESUS before considering PFO closure.²¹

Hart et al. (10) suggested the diagnostic criteria for ESUS and the minimum diagnostic assessment that should be done.¹⁰ These are shown in Table II.

First of all, clinicians should get brain imaging from patients whose PFO closure is being investigated to confirm the size and distribution of the strokes and to look for embolic patterns or lacunar infarcts (which often involve a single deep perforator with a diameter of less than 1.5 cm).²¹

Occult atrial fibrillation (AF) is important in cryptogenic stroke as it is often asymptomatic and must be ruled out before considering PFO closure. A few screening methods are available to detect AF, such as 12-lead ECG, 24 to 48-hour Holter monitor, external event monitor, single-lead ECGs, in-patient cardiac telemetry and invasive methods such as implantable loop recorder.²² Even though prolonged cardiac monitoring might not be easy to get in some hospitals, at least a baseline ECG should be done to rule out persistent AF.^{21,23} However, comprehensive cardiac monitoring is advised whenever possible because studies have shown that it increases the likelihood of detecting AF.²⁴⁻²⁷ The best monitoring approach and duration are yet to be determined and can be based on effectiveness, cost and patient preference.²⁸ Some experts suggested continuous cardiac monitoring for at least 24 hours for AF detection.^{9,29} For

Table I: Description of the level of consensus

Consensus Level	Explanation
Should do this	Consensus to support a specific approach, treatment, or position
May do this	Limited evidence, and mixed opinions. Sufficient confidence and no contradictions regarding supported approach, treatment, or position
Should not do this	Consensus to discourage a specific approach, treatment, or position
Unsure	Insufficient data/experience, too many mixed opinions. Additional clinical evidence is required

Adapted from Diener et al. ²⁰

Table II: Diagnostic criteria and recommended work-up for ESUS

ESUS Criteria	Recommended Work-up
<ul style="list-style-type: none"> ■ Stroke detected by CT or MRI that is not lacunar ■ The absence of extracranial or intracranial atherosclerosis causes $\geq 50\%$ luminal stenosis in arteries supplying the area of ischaemia ■ No major-risk cardioembolic source of embolism* ■ No other specific cause of the stroke was identified* 	<ul style="list-style-type: none"> • Brain CT or MRI [Lacunar is defined as a subcortical infarct smaller than or equal to 1.5 cm (≤ 2.0 cm on MRI diffusion images) in the largest dimension.] • Imaging of both the extracranial and intracranial arteries supplying the area of brain ischaemia (catheter, MR, or CT angiography, or cervical duplex plus transcranial doppler ultrasonography) • 12-lead ECG • Precordial echocardiography • Prolonged cardiac monitoring with automated rhythm detection

*Please refer to the examples of the major risk cardioembolic sources of embolism and other causes of stroke in Fig.1

Table III: The advantages, limitations, sensitivity (Sn), and specificity (Sp) of different modalities for PFO detection

Imaging Modalities	Advantages	Limitation	Weighted Mean Sn and Sp
Contrast transcranial Doppler (c-TCD)	<ul style="list-style-type: none"> • Non-invasive • Cost-effective • Can perform at the bedside • Can repeat at different body positions • Able to detect small shunts • Easy availability 	<ul style="list-style-type: none"> • Unable to distinguish intracardiac and intrapulmonary shunts • Unable to visualise cardiac structures 	Sn: 97% Sp: 93%
Contrast transthoracic echocardiogram (c-TTE)	<ul style="list-style-type: none"> • Non-invasive • Able to visualise cardiac structures • Easily available 	<ul style="list-style-type: none"> • Limitations in discriminating against a small amount of RLS 	Sn: 46% Sp: 99%
Contrast transesophageal echocardiogram (c-TEE)	<ul style="list-style-type: none"> • Able to visualise precise anatomy of PFO • Able to discriminate PFO shunt from intrapulmonary shunt 	<ul style="list-style-type: none"> • Semi-invasive • Valsalva manoeuvre may be difficult to perform due to sedation • Limitations in discriminating against a small amount of RLS 	Sn: 89.2% Sp: 91.4%

individuals who are older than 40 and have a high risk for AF, prolonged monitoring for AF detection for at least 28 days may be an option.^{9,21} High risks for atrial fibrillation include hypertension, obesity, sleep apnoea, an enlarged left atrium, elevated NT-proBNP, frequent premature atrial contractions, increased P-wave dispersion, a prolonged PR interval, multi-territorial infarcts, etc.

Complete vascular imaging (Computed Tomography Angiography (CTA) and Magnetic Resonance Angiography (MRA)) of the cervical and intracranial vessels should be obtained to look for dissection, vasculopathy and atherosclerosis.²¹

If the hypercoagulable condition is suspected, a complete blood count (haemoglobin and platelet count), factor V Leiden, protein C, protein S, antithrombin III, homocysteine

levels, prothrombin G20210A mutation and antiphospholipid antibodies test can be done.³⁰ Brain and pelvic Magnetic Resonance Venography (MRV) are recommended to look for cerebral venous sinus thrombosis and May-Thurner syndrome, respectively.³⁰

PFO Detection

PFO does not increase the risk of early stroke recurrence in ESUS patients.³¹ However, the risk of recurrent stroke is generally high in the first few weeks after a stroke. Therefore, Asian-Pacific experts suggested that recent ESUS patients should be given higher priority for PFO screening, which may be done within 2 weeks of stroke.²⁰

PFO can be diagnosed based on the direct or indirect visualisation of right-to-left shunting (RLS). A bubble contrast transthoracic echocardiogram (c-TTE), contrast

Table IV: Preferred screening and diagnostic strategy

No	Statements	Consensus Level
Diagnostic Strategy For ESUS		
1.	In patients being considered for PFO closure, perform a thorough evaluation to rule out alternative mechanisms of stroke.	Should do this
2.	In patients being considered for PFO closure, confirm stroke size and distribution, and assess for an embolic pattern or a lacunar infarct via brain imaging (MRI or CT).	Should do this
3.	In patients being considered for PFO closure, obtain complete vascular imaging (MRA or CTA) of the cervical and intracranial vessels to look for dissection, vasculopathy, and atherosclerosis.	Should do this
4.	In patients considered for PFO closure, perform a baseline ECG to look for atrial fibrillation.	Should do this
5.	In patients being considered for PFO closure, prolonged cardiac monitoring should be considered if there is a risk of atrial fibrillation.	May do this
PFO Detection		
6.	Highest priority: ensure that patients with recent ESUS are screened for PFO.	Should do this
7.	For PFO screening, use bubble contrast transthoracic echocardiography (c-TTE) or bubble contrast transcranial Doppler ultrasound (c-TCD) with and without Valsalva manoeuvre to assess for a right-to-left shunt and determine the degree of shunting.	Should do this
8.	Use contrast transesophageal echocardiography (c-TEE) for confirmation of PFO.	May do this
9.	Use the imaging modalities that are readily available in the hospital and on which the technical staff is best trained and most experienced (c-TTE, c-TCD, c-TEE, intracardiac echocardiography).	Should do this
10.	Ensure echocardiography is performed for imaging other cardiac structures to explore other sources of cardioembolic stroke.	Should do this
11.	Echocardiography is to be performed within two weeks after the stroke, depending on the local availability of services.	May do this

Table V: RoPE Score

Patient Characteristic	Points
No history of hypertension	+1
No history of diabetes mellitus	+1
No history of TIA or stroke	+1
Non-smoker	+1
Cortical infarct on imaging	+1
Age (y)	
18 to 29	+5
30 to 39	+4
40 to 49	+3
50 to 59	+2
60 to 69	+1
>70	+0
Total RoPE score	0-10

Adapted from Kent et al.⁴³

Table VI: Patent Foramen Ovale - Associated Stroke Causal Likelihood (PASCAL) classification

PFO-related stroke	Low RoPE Score (≤6)	High RoPE Score (>6)
High-risk PFO (e.g Large shunt PFO and/or ASA)	Possible	Probable
Low-risk PFO (e.g Small shunt without ASA)	Unlikely	Possible

Adapted from Kent et al.⁴⁹

transesophageal echocardiogram (c-TEE), and contrast transcranial Doppler (c-TCD) are the methods used to detect shunting from a PFO. TEE is the gold-standard method for detecting PFO. A bubble study is often performed together with an echocardiogram or a transcranial Doppler study (TCD) to assess the RLS when a PFO is suspected. In this study, the microbubbles (agitated saline or gaseous contrast agent) are injected into the peripheral vein. The patient is asked to perform a Valsalva manoeuvre to raise the pressure on the right side of the heart. The appearance of bubbles in the left atrium within three cardiac cycles during the echocardiogram confirms the presence of a shunt. Whereas

the appearance of at least one bubble in the middle cerebral artery within 40 seconds of agitated saline injection during the TCD confirms the presence of shunting.³⁰ (Note that late bubble arrival is also associated with extra-cardiac shunts)

A meta-analysis comparing c-TCD versus c-TTE showed that c-TCD is reliable in ruling out PFO, whereas c-TTE is reliable in diagnosing PFO. Contrast TCD appeared to have a higher overall diagnostic yield than c-TTE. In fact, contrast TCD (c-TCD) is more sensitive to RLS detection than contrast TTE (c-TTE) or contrast TEE (c-TEE). It is suitable for use as an initial screening approach for RLS.^{23,32-34} Nevertheless, this does not

Table VII: Patient selection for PFO closure

No	Statements	Consensus Level
1.	PFO closure in patients younger than 60 with an embolic-appearing infarct with no other mechanism of stroke was identified.	May do this
2.	PFO closure in patients with RoPE score >6.*	Should do this
3.	PFO closure in patients with RoPE score ≤6 is on a case-by-case basis where no other attributable causes for the cryptogenic stroke are identified and where the benefit outweighs the immediate and long-term risk.*	May do this
4.	PFO closure in patients with a lacunar stroke by imaging (single, small, deep infarct (infarct size <1.5cm)).	Insufficient data
5.	PFO closure in younger patients (e.g., <30 years) with a lacunar stroke (single, small, deep infarct (infarct size <1.5cm)), a large shunt, and absence of any vascular risk factors.	May do this / Insufficient data
6.	PFO closure in patients with a large PFO shunt (defined by the passage of > 20 microbubbles or maximum separation of septum of ≥2mm).*	May do this
7.	PFO closure in patients with an atrial septal aneurysm.*	May do this
PFO in Patients Aged More Than 60 Years		
8.	PFO closure in patients over 60 years of age who are in biologically good condition and with strong indications of PFO causality in the embolic stroke mechanism, e.g., significant right-to-left shunt, atrial septal aneurysm.	May do this / Insufficient data
9.	PFO closure in patients over 60 years of age without high-risk PFO.	Should not do this
PFO Closure in Patient Requiring Oral Anticoagulant (OAC)		
10.	PFO closure in patients with evidence of thrombi/ emboli and requirement for prolonged but not indefinite OAC (likely to be related to deep venous thrombosis).	May do this
11.	PFO closure in patients with an unrelated requirement for indefinite OAC.	Should not do this
Multidisciplinary Approach		
12.	Before undergoing PFO closure, clinicians with expertise in stroke assess patients and ensure that the PFO is the most plausible mechanism of stroke.	Should do this
13.	Before undergoing PFO closure, clinician with expertise in assessing the degree of shunting and anatomical features of a PFO, and performing PFO closure, to assess whether the PFO is anatomically appropriate for closure, to ascertain whether other factors are present that could modify the risk of the procedure, and to address post procedural management.	Should do this
14.	In a patient for whom PFO closure is being considered, a shared decision-making approach between clinicians and the patient is to be used.	Should do this
15.	Comply with indications for PFO closure according to international/global guidelines/consensus statements.	Should do this

*Note that PASCAL classification can be considered for patient selection for PFO closure.

Table VIII: Timing of PFO closure in ESUS

No	Statements	Consensus Level
1.	ESUS with evidence of significant PFO: Close as early as possible.	Should do this
2.	Late (> 1 year) PFO closure in ESUS patients with evidence of significant PFO and no additional risk factors developed since the stroke.	May do this

Table IX: Post-PFO closure treatment and follow-up

No	Statements	Consensus Level
1.	Dual antiplatelet therapy (DAPT) for one to three months, followed by single APT for six months. The decision on continued therapy is to be made by the multidisciplinary team.	Should do this
2.	Echocardiography to assess erosion and other major devices-, procedures-, or cardiac-related complications when there is a high index of suspicion.	Should do this
3.	Follow-up by echocardiography every three months depending on the resources (in case of a residual shunt to inform the decision on DAPT)	May do this
4.	Monitoring of patients is based on the remnant risk of stroke, and the frequency is based on patients' needs and local resources. For centers that do not have resources to monitor and quantify residual shunt, patients should be referred to the appropriate clinicians with expertise and resources.	Should do this
5.	In the event of a rare residual shunt after PFO closure, the subsequent management is to be individualised with the team approach to weighing the options of the repeat procedure and/or antiplatelet regimes based on the patient's overall risk assessment. Such patients are on lifelong follow-up because risk assessment is dynamic as age increases and other comorbidities may develop in the future.	May do this
6.	In case of recurrent ischemic stroke: explore any secondary cause and confirm (non-) compliance to antithrombotic therapy.	Should do this

Table X: Medical therapy if the PFO is not closed despite an indication for closure

No	Statements	Consensus Level
1.	In patients who opt to receive medical therapy alone without PFO closure, clinicians may recommend either an antiplatelet medication such as aspirin or anticoagulation (using a vitamin K antagonist, a direct thrombin inhibitor, or a factor Xa inhibitor).	May do this

Table XI: Creating awareness about PFO closure in ESUS

No	Statements	Consensus Level
1.	Industry's role: continue supporting training and education programmes at general neurology meetings and events.	Should do this
2.	Set up online training and national forums.	Should do this
3.	Conferences: create awareness and organise screening training for technicians.	Should do this
4.	Hospital CMEs	Should do this

preclude echocardiography to rule out cardio-embolism mechanisms and confirm the presence of an intracardiac shunt, of which c-TCD is unable to differentiate.^{20,21,24} Contrast TTE, however, showed limitations in diagnosing PFO with the small or delayed shunt.³⁵ Therefore, HSC/HSO experts suggested that c-TCD and/or c-TTE should be used for initial screening of RLS to diagnose PFO.⁹ AAN also emphasised using bubble contrast, with and without Valsalva manoeuvre to assess for RLS and grade the shunting.²¹ Test sensitivity was shown to improve with the Valsalva manoeuvre.³⁶ It is unlikely to be a high-risk PFO if there is minimal or no shunt on c-TCD after the Valsalva manoeuvre.³⁷ As TEE is particularly helpful in establishing the anatomy of the PFO and its adjacent structures, it continues to be the gold standard for PFO diagnosis.²⁸

Each modality has its advantages and limitations.³² These are listed in Table III along with the sensitivity and specificity of different modalities for RLS and PFO detection.³⁸⁻⁴⁰

HSC/HSO experts advised that a skilled operator conduct a c-TEE for PFO detection and PFO closure assessment.⁹ Some modalities are not widely available in all acute stroke settings, especially in Malaysia. Asian-Pacific experts suggested using the best available modalities that the operator is trained in and most experienced in.²⁰

The consensus among Malaysian expert panels regarding the preferred screening and diagnostic strategy has been summarised in Table IV.

PATIENTS SELECTION FOR PFO CLOSURE

To answer which patients can benefit from PFO closure, we need to carefully evaluate the inclusion criteria of the clinical trials that demonstrated the superiority or efficacy of PFO closure over the control groups.

In the earlier randomised control trials published in 2012 (CLOSURE) and 2013 (PC and RESPECT), PFO closure failed to show a significant reduction in stroke recurrence compared to antithrombotic medication alone in a cryptogenic stroke patient with PFO less than 60 years old.^{13,14,17} The main reasons for the trial failure were probably due to the lack of high-risk PFO patient inclusion, unclear methods of confirmation of cryptogenic stroke, and a short follow-up period for a low annual risk of recurrent stroke among the

study population.⁴¹ Subsequently, from 2017 onwards, trials that included high-risk PFO patients (CLOSE, REDUCE, and DEFENSE-PFO trials) or prolonged the follow-up period (RESPECT follow-up trial), showed a significant reduction in stroke recurrence among the patients who had undergone PFO closure compared with the medical therapy group.^{15,16,18,19} The DEFENSE-PFO is the only trial that recruited subjects above 60 years old; the others were mostly below 60 years old. Thus, the trial outcome might not be generalised for all.

Approximately 50% of all young patients with ischaemic stroke have a PFO.⁴² PFO is more common in younger cryptogenic stroke patients and is more likely to be pathogenic than in older patients.³⁴ The European Society of Cardiology (ESC) stated that when the patients are young and have no other risk factors, PFO is more likely to be pathogenic.²³ The guidelines from the American Heart Association/American Stroke Association (AHA/ASA) and the American Academy of Neurology (AAN) recommended PFO closure in patients younger than 60 years with an embolic-appearing infarct and no other mechanism of stroke identified.^{21,24} AAN additionally mentioned that such recommendation may be following a discussion of the potential benefits of reducing stroke recurrence and the risks of complications from the procedures.²¹

The Risk of Paradoxical Embolism (RoPE) scores can also be considered before deciding on PFO closure. The RoPE score is an assessment tool to determine the probability that a PFO is related to a cryptogenic stroke.⁴³ Table V shows the scoring for the RoPE score. A higher score indicates a higher probability that a PFO is associated with a cryptogenic stroke. A score of above 7 indicates a causative risk of above 72%. However, the risk of recurrent stroke decreases with increasing RoPE scores. The estimated 2-year stroke/TIA recurrence rates decreased from 20% in the lowest RoPE score to 2% in the highest. Therefore, it cannot be solely used to determine which individuals with PFO-related strokes may benefit from closure. The RoPE score does not consider the PFO's high-risk anatomic or physiological aspects and should be used in conjunction with other factors.³⁴

Kuijpers et al. (44) suggested the closure of a PFO in cryptogenic stroke patients with a RoPE score of more than eight and at least one clinical risk factor.⁴⁴ The Asian-Pacific region experts stated that PFO closure should be considered in patients with a RoPE score of six or more and may be

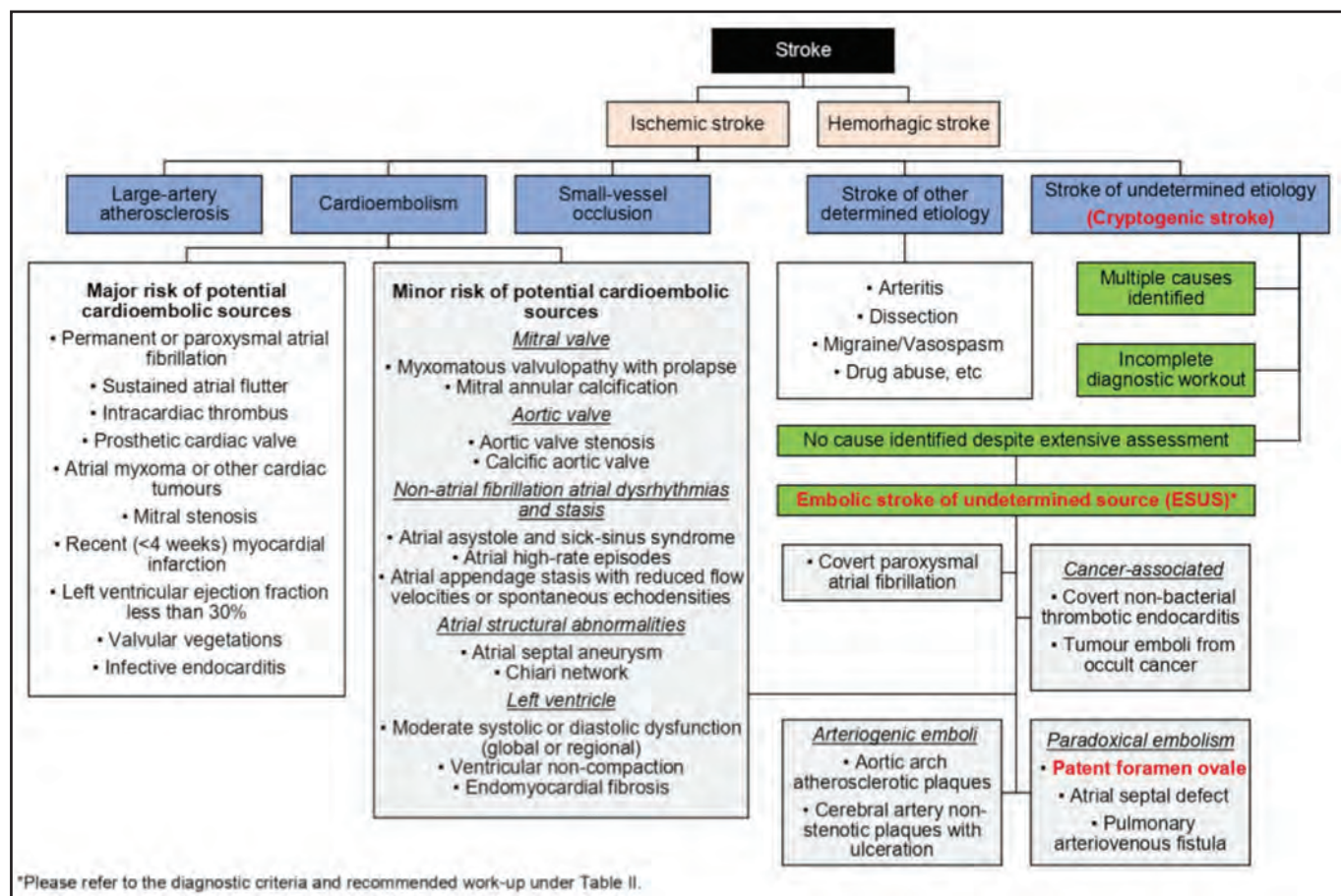


Fig. 1: Classification of stroke and the potential causes of ESUS

considered in patients with a score of less than six.²⁰ The recent review by Elzanaty et al. (45) mentioned that in patients aged 60 or younger with recent cryptogenic stroke with PFO, guideline recommendations consider the need for PFO closure on a case-by-case basis and individual risk factors.⁴⁵

Cortical infarction is mostly due to embolism, but it is still possible that the subcortical infarct or lacunar stroke can be embolic.²³ Lacunar infarcts are a subtype of ischaemic stroke that occurs in small, deep-penetrating arteries of the brain. Up to 25% of all ischaemic strokes are due to a lacunar infarct.⁴⁶ Since lacunar strokes are unlikely due to a distant embolic source, PFO closure may be appropriate in young patients with a lacunar stroke plus a PFO if other risk factors for cerebral small vessel disease and atrial fibrillation (AF) have been ruled out.⁴⁶ However, the Asian-Pacific experts do not recommend PFO closure in a lacunar stroke.²⁰ Moreover, lacunar stroke was one of the trial exclusion criteria.^{15,19} According to AAN, PFO closure, however, may be recommended for younger patients (e.g., 30 years old) with a single, small, deep stroke (1.5 cm) with the presence of a large shunt and no vascular risk factors that would lead to intrinsic small-vessel diseases, such as hypertension, diabetes or hyperlipidaemia.²¹

As mentioned earlier, trials that included high-risk PFO patients showed a favourable outcome with PFO closure. High-risk PFO is defined as PFO with atrial septal aneurysm

(ASA), a condition characterised by hypermobility of the inter-atrial septum (phasic septal excursion into either atrium ≥ 10 mm), or PFO size (maximum separation of the septum primum from the secundum) ≥ 2 mm.¹⁵ Besides that, a prominent Eustachian valve and large (≥ 20 microbubbles) right-to-left shunt were also anatomical characteristics of high-risk PFO.⁴² The European Society of Cardiology (ESC) stated that ASA and PFO size are linked to the association between PFO and cryptogenic stroke.²³ The presence of ASA was related to stroke recurrence in PFO-associated stroke patients but not in large PFO patients.⁴⁷ In contrast, AAN suggested that patients with a large shunt may benefit from PFO closure, but ASA without a large PFO is questionable.²¹ In a recent review, PFO patients with ASA likely have a stronger link to the risk of recurrent stroke.⁴⁸ A large PFO and ASA do not necessarily indicate a significant risk factor for a recurrent stroke, but they may indicate that the PFO is likely very pathogenic and may benefit from closure.³⁴ Patients with a RoPE score ≥ 7 with high-risk PFO may be good candidates for PFO closure.²⁶

The Patent Foramen Ovale - Associated Stroke Causal Likelihood (PASCAL) classification system combines RoPE score and PFO features to assess patients who will benefit from PFO closure to prevent recurrent stroke.⁴⁹ As shown in Table VI, PASCAL classifies patients into three categories based on their causal relatedness: unlikely, possible, and probable.

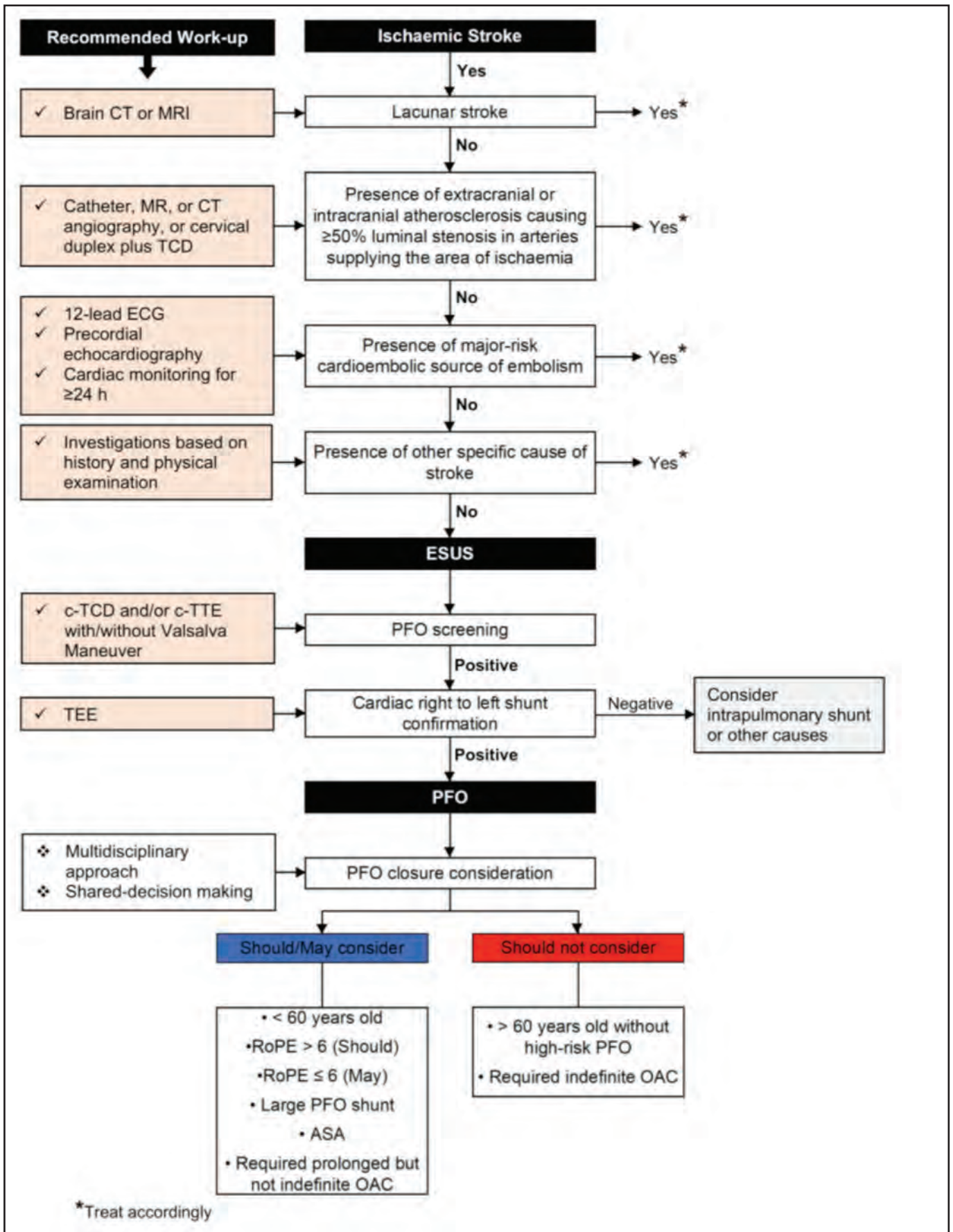


Fig. 2: Diagnostic approaches of PFO in cryptogenic stroke

About 15% of patients in the PASCAL "unlikely" classification without high-risk PFOs and vascular risk factors, did not benefit from PFO closure. However, 90% relative risk reduction was noted for PASCAL "probable" patients with high-risk PFO and a high RoPE score after PFO closure.⁴⁹ Therefore, the PASCAL classification system should guide clinicians during the individualised decision-making for PFO closure patient selection.

PFO Closure in Patients More Than 60 Years

More randomised trials to assess the safety and efficacy of PFO closure in people over 60 years old are needed to provide recommendations for these. For patients over 60 years of age, Asian-Pacific experts suggested that PFO closure may be suitable if they are in biologically good condition and have strong indications of PFO causality in the embolic stroke mechanism, e.g., significant right-to-left shunt and ASA.²⁰ The ANN and Thaler et al. (50) suggested we may offer PFO closure if they have very limited vascular risk factors and thorough evaluation has ruled out other mechanisms of stroke, including AF.^{21,50} Even though elderly patients are more prone to additional stroke risks and may be excluded for PFO closure, they may still be at risk of venous thromboembolism and right-to-left shunt in the presence of a PFO.²⁶ However, the benefit of PFO closure in elderly patients, especially those with competing stroke mechanisms, is still unknown.

The risk of stroke in PFO patients is much higher in the older age group.⁵¹ However, the risk of adverse events during PFO closure is also considerably higher (10.9%) in this age group.⁵² The expert panellists from the Hellenic Stroke Organisation and the Working Group for Stroke of the Hellenic Society of Cardiology (HSO/HSC) are against the PFO closure in extreme age groups (<18 and >60 years) and may be considered on a case-by-case basis following a thorough examination.⁹ According to Asian-Pacific expert panels, PFO closure should not be performed in patients over 60 who do not have a high-risk PFO.²⁰ It should not be inferred that PFO closure will benefit older patients with high-risk PFO because a prior study found that stroke recurrence rates in high-risk PFO patients > 60 years who underwent PFO closure were not significantly different from those who received medical therapy alone.⁵³

PFO Closure in Patient Requiring Oral Anticoagulant (OAC)

Some patients may be on long-term oral anticoagulation (OAC) due to suspected or confirmed hypercoagulabilities such as thrombophilia, unprovoked deep venous thrombosis, or unprovoked pulmonary embolism. If a stroke patient with PFO with such a condition is considered for PFO closure, the clinician should inform the patient that the benefit of PFO closure in conjunction with anticoagulation is uncertain.^{21,34} The Asian-Pacific expert panels suggested that PFO closure may be considered in patients with evidence of thrombi or emboli and a need for prolonged but not indefinite OAC, such as those with deep venous thrombosis.²⁰ However, PFO closure should not be performed in patients who have comorbidities that requires an indefinite OAC since it is likely to cause more harm than benefit, in addition to the danger of OAC-related bleeding.²⁰

Multidisciplinary Approach

During the decision-making process for PFO closure, the probability of the PFO being a cause for ESUS and the risk of recurrence of a person must be considered.²³ PFO features need to be assessed before deciding on PFO closure.²³ A trained, experienced clinician should evaluate the degree of shunting and anatomic aspects of a PFO and whether it is suitable for closure. Clinicians should also ensure no additional factors may affect the procedure's risk and should be competent to handle the post-closure management.²¹

Shared decision-making is an integral part of patient-centered care. Clinicians should explain the available treatment options, provide risk, and benefit information, understand their concerns, and assist them in making decisions. The decision for PFO closure or medical therapy in ESUS patients with a PFO should be made jointly by the patient, a neurologist, and a cardiologist.^{9,24,34,54}

Indications for PFO closure should be in accordance with the updated international guidelines and consensus statements.²⁰ The consensus among Malaysian expert panels regarding the patient selection for PFO closure has been summarised in Table VII. (*Note that PASCAL classification can be considered during patient selection for PFO closure.)

Figure 2 illustrates the Malaysian experts' suggested diagnostic approaches of PFO in ESUS.

TIMING OF PFO CLOSURE IN ESUS

Experts from the Asian-Pacific region suggested that ESUS with evidence of significant PFO should be closed as soon as possible.²⁰ However, no duration was specifically mentioned. In addition, they suggested that late PFO closure (> 1 year) may be performed in ESUS patients with evidence of high-risk PFO and no new risk factors since the stroke.²⁰ However, there is no evidence from clinical trials to support this recommendation. Most of the clinical trials that supported PFO closure included patients who had a recent stroke within 6 or 9 months.^{15,16,18,19} The French Neurovascular Society and the French Society of Cardiology (FNS/FSC) have recommended PFO closure in patients with recent (\leq 6 months) ischaemic stroke. However, this time frame can be extended if AF detection is required for a longer duration.⁵⁵

The consensus among Malaysian expert panels regarding the timing of PFO closure in ESUS has been summarised in Table VIII.

POST-CLOSURE TREATMENT AND FOLLOW-UP

No procedure is risk-free, and PFO closure is no exception; not only is it invasive, but PFO closure may also be accompanied by complications such as thrombus formation on the device and the development of AF following the procedure.

PFO closure device implantation increased thromboembolism risk by 1-2%.⁴¹ In addition, the risk of AF was substantially higher in PFO closure than in medical therapy, ranging from 2.9% to 6.6%, based on the previous clinical trial data.⁵⁰ According to a meta-analysis of AF rates

after PFO closure, AF developed in 3.7 patients per 100 patient-years of follow-up. The risk of AF was greatest in the first 45 days after the procedure, and PFO closure increased the odds of having AF by 5.3 times over medical therapy.⁵⁶ Therefore, it is appropriate to administer dual antiplatelet therapy (DAPT) after PFO closure. Furthermore, PFO closure with medical therapy has been considered more cost-effective than medical therapy alone.⁴⁵

Although no data supported the optimal DAPT duration, most guidelines and consensus recommended DAPT for up to 6 months, followed by a single antiplatelet agent.^{9,23,41} Experts from FNS/FSC and the Asian-Pacific region suggested DAPT for up to 3 months, followed by a single APT.^{20,55} Uncertainty remains on the length of time that a single APT should be continued. Still, some suggest that it may be continued for up to 5 years.^{23,41,55} However, the decision to continue APT should be made by an expert clinician, such as a neurologist, based on the overall risks and benefits for the patient.^{20,23} Low-dose aspirin and clopidogrel were the common choices of APT.^{9,55}

Other long-term complications that may occur after PFO closure include the presence of residual shunt, scar tissue development, endocarditis, pericardial effusion, and the risk of aortic root dilation and erosion.^{41,45} About 2.6% of patients may develop uncommon long-term complications following PFO closure.²³ If complications are suspected, imaging such as echocardiography should be performed.^{20,55}

There were no clear guidelines for the timing and frequency of follow-up evaluations following the PFO closure. About 19.5% of post-closure patients had residual shunt at four months, which dropped to 8.4% at 11 months and 2.8% with a persistent mild shunt at two years during follow-up.⁵⁷ The ESC suggested c-TCO after six months post-closure to assess for the residual shunt and annually in the presence of a residual shunt.²³ FNS/FSC experts recommended 12-lead ECG and c-TTE at 1 and 12 months.⁵⁵ Asian-Pacific experts recommended more frequent imaging follow-ups every three months and advised re-evaluating the DAPT decision if a residual shunt was seen.²⁰ Long-term antithrombotic medication should be considered after discussion with cardiologists and neurologists for people with residual shunt who are at risk for recurrent stroke. In the event of a recurrent stroke, the patient's compliance with antithrombotic treatment must be verified, and additional causes must be investigated.²⁰

The meta-analysis of AF following PFO closure revealed that older patients have a considerably increased risk of developing AF after closure.⁵⁶ Higher risk groups were hence justifiable for more regular follow-up.²⁰ CHA₂DS₂-VASc score can be used to determine the higher-risk group. Nevertheless, the patient's needs and resource availability must be considered when determining the frequency of monitoring. The consensus among the Malaysian expert panels regarding the post-closure treatment and follow-up has been summarised in Table IX.

MEDICAL THERAPY IF PFO IS NOT CLOSED DESPITE AN INDICATION FOR CLOSURE

In certain instances, a patient may decline PFO closure

despite being indicated for PFO closure. If this occurs, medical therapy such as antiplatelet or anticoagulant can be considered.²¹

Antiplatelet medications, such as aspirin, and anticoagulants, such as rivaroxaban, dabigatran, and warfarin, are the treatments of choice for patients, although the superiority of one over another has never been conclusively proven. In the RESPECT ESUS trial, although dabigatran did not significantly lower the risk of recurrent stroke in the general population, it did demonstrate a stroke reduction specifically in older stroke patients compared to aspirin.⁵⁸ Even though there were no differences in stroke recurrence rates between aspirin and rivaroxaban in the NAVIGATE ESUS trial, the risk of bleeding was significantly higher in the rivaroxaban group.⁵⁹ Therefore, the choice of medical therapy should be on a case-by-case basis. Patients with additional risk factors such as a large shunt or ASA, those with multiple infarcts, the presence of deep vein thrombosis, and the elderly may benefit from anticoagulant therapy.²⁹ Otherwise, antiplatelet therapy was reasonable to consider as the first choice for ESUS patients who were not considered for PFO closure if there was no other justification for anticoagulation.^{9,29,44,54,60}

The consensus among Malaysian expert panels regarding the medical therapy if PFO is not closed despite an indication for closure has been summarised in Table X.

CREATING AWARENESS ABOUT PFO CLOSURE IN ESUS

Creating awareness among Malaysian clinicians regarding the management of PFO in ESUS patients is crucial. This will help clinicians in performing adequate PFO and ESUS screenings and initiating early therapy.

Malaysian experts supported the industry's role in sponsoring training and education initiatives at general neurology meetings and events. Introducing PFO management in ESUS via online training and national forums could raise awareness. Providing technicians with screening training should enhance their ability to diagnose PFO.

Continuous medical education (CME) at the hospital might be useful to keep the clinician up to date on the latest PFO management in ESUS.

Long-term follow-up of stroke patients with a PFO among the Malaysian population may help to establish better management approaches for secondary stroke prevention in our local setting. Further research and developing a standardised national registry on PFO management in Malaysia may aid in this endeavour.

The Malaysian expert panels suggested raising awareness regarding PFO closure in ESUS by implementing the strategies outlined in Table XI.

CONCLUSION

The role of PFO in ESUS is not well understood due to many uncertainties in this condition, and it is often under-recognised in Malaysia. It is essential to identify PFO and

other aetiologies of ESUS in stroke patients and promptly refer them to appropriate clinicians with expertise and facilities. The list of public hospitals and institutions currently offering PFO closure services in Malaysia can be found in Appendix B. Multidisciplinary involvement and action are needed to determine the diagnosis and prognosis of the patient. A shared decision-making process would help determine the patient's optimal management. Even though the most effective management for this condition has not yet been established, continuous efforts should be made to improve clinicians' awareness of this condition and begin the necessary screening and treatment. Data on PFO studies continues to evolve and, as such, the consensus recommendation currently put forward by Malaysian experts may evolve too in the future. Therefore, this consensus should provide an overview of how ESUS patients with PFO should be managed locally in Malaysia until robust evidence from more clinical trials emerges in the future.

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CONFLICT OF INTEREST

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Appendix A

Malaysian PFO-Stroke Working Group Experts

Neurologists

Dr. Ahmad Shahir Mawardi
Hospital Kuala Lumpur
Kuala Lumpur

Dr. Ang Chong Lip
KPJ Ipoh Specialist Centre
Ipoh, Perak

Dr. Asha Prerna
Loh Guan Lye Specialist Centre
George Town, Pulau Pinang

Dr. Chai Chiun Hian
KPJ Kuching Specialist Hospital
Kuching, Sarawak

Dr. Chia Yuen Kang
Hospital Queen Elizabeth
Kota Kinabalu, Sabah

Dr. Hiew Fu Liong
Sunway Medical Centre
Petaling Jaya, Selangor

Assoc. Prof. Dr. Hoo Fan Kee
Hospital Pengajar Universiti Putra Malaysia,
Universiti Putra Malaysia (UPM)
Serdang, Selangor

Dr. Hor Jyh Yung
Hospital Pulau Pinang
George Town, Pulau Pinang

Dr. Irene Looi
Hospital Seberang Jaya
Seberang Jaya, Pulau Pinang

Dr. Khairul Azmi Ibrahim
Hospital Sultanah Nur Zahirah
Kuala Terengganu, Terengganu

Dr. Law Wan Chung
Hospital Umum Sarawak
Kuching, Sarawak

Dr. Linda Then Yee Yen
Hospital Umum Sarawak
Kuching, Sarawak

Dr. Loo Lay Khoon
Hospital Seberang Jaya
Seberang Jaya, Pulau Pinang

Dr. Mohd Azman M Aris
Hospital Melaka
Bandar Melaka, Melaka

Dr. Ong Beng Hooi
Kedah Medical Centre
Alor Setar, Kedah

Dr. Rishikesan Kuppusamy
Pantai Hospital Kuala Lumpur
Bangsar, Kuala Lumpur

Dr. Rose Izura Abdul Hamid
Hospital Raja Perempuan Zainab II
Kota Bharu, Kelantan

Dr. Sally Tee Sow Kuan
Pantai Hospital Kuala Lumpur
Bangsar, Kuala Lumpur

Dr. Sapiah Sapuan
Hospital Sungai Buloh
Sungai Buloh, Selangor

Dr. Sathindren T. Santhirathelagan
Gleneagles Hospital Penang
George Town, Pulau Pinang

Dr. Shanthi Viswanathan Shanthakumar
Hospital Kuala Lumpur
Kuala Lumpur

Dr. Sim Bee Fung
Gleneagles Hospital Penang
George Town, Pulau Pinang

Dr. Sim Siew Hung
Borneo Medical Center
Kuching, Sarawak

Dr. Siva Seeta Ramaiah
Subang Jaya Medical Centre
Subang Jaya, Selangor

Dr. Stefanie Hung Kar Yan
Hospital Tengku Ampuan Rahimah
Klang, Selangor

Dr. Tan Kenny
Loh Guan Lye Specialist Centre
George Town, Pulau Pinang

Dr. Teh Pei Chiek
Hospital Tuanku Ja'afar
Seremban, Negeri Sembilan

Dr. Wan Asyraf Wan Zaidi
Hospital Canselor Tuanku Muhriz,
Universiti Kebangsaan Malaysia (UKM)
Kuala Lumpur

Dr. Wong Sing Keat
Hospital Kuala Lumpur
Kuala Lumpur

Dr. Wong Yee Choon
Pantai Hospital Penang
Bayan Lepas, Pulau Pinang

Dr. Zariah Abdul Aziz
Hospital Sultanah Nur Zahirah
Kuala Terengganu, Terengganu

Cardiologists

Dr. Annamalar Muthu Muthuppalaniappan
Gleneagles Hospital Penang
George Town, Pulau Pinang

Dr. Liew Houg Bang
Hospital Queen Elizabeth II
Kota Kinabalu, Sabah

Dato' Dr. Muhamad Ali S K Abdul Kader
Hospital Pulau Pinang
George Town, Pulau Pinang

Dr. Saravanan Krishinan
Hospital Sultanah Bahiyah
Alor Setar, Kedah

Dato' Dr. Yap Yee Guan
Sunway Medical Centre
Petaling Jaya, Selangor

Paediatrics Cardiologist

Assoc. Prof. Dr. Abdul Rahim Wong
Universiti Sultan Zainal Abidin
Kuala Terengganu, Terengganu

Dr. Amir Hamzah Abd Rahman
Hospital Tengku Ampuan Afzan
Kuantan, Pahang

Dr. Geetha Kandavello
Institut Jantung Negara
Kuala Lumpur

Dr. Koh Ghee Tiong
Hospital Serdang
Kajang, Selangor

Dr. Leong Ming Chern
Institut Jantung Negara
Kuala Lumpur

Dr. Martin Wong Ngie Liong
Pusat Jantung Sarawak
Kota Samarahan, Sarawak

Dr. Mohammad Tamim Jamil
Hospital Pulau Pinang
George Town, Pulau Pinang

Dr. Mohd Rizal Mohd Zain
Hospital Universiti Sains Malaysia
Kubang Kerian, Kelantan

Dr. Siva Rao Muniandy
Hospital Queen Elizabeth II
Kota Kinabalu, Sabah
Geriatricians

Dr. Cheah Wee Kooi
Hospital Taiping
Taiping, Perak

Dr. Teh Hoon Lang
Hospital Sultanah Bahiyah
Alor Setar, Kedah

Internal Medicine Physicians

Dr. Abdul Hanif Khan Yusof Khan
Hospital Pengajar Universiti Putra Malaysia
Universiti Putra Malaysia (UPM)
Serdang, Selangor

Dr. Aznita Ibrahim
Hospital Sultan Abdul Halim
Sungai Petani, Kedah

Dr. Lee Aik Kheng
Hospital Pulau Pinang
George Town, Pulau Pinang

Dr. Neoh Kar Keong
Hospital Seberang Jaya
Seberang Jaya, Pulau Pinang

Dr. Zainura Che Isa
Hospital Sultan Abdul Halim
Sungai Petani, Kedah

Medical Officer

Dr. Stephenie Ann Albart
Clinical Research Centre
Hospital Seberang Jaya
Seberang Jaya, Pulau Pinang

Appendix B

List of public hospitals and institutes that are currently offering PFO closure services in Malaysia. (Last updated: 22.07.2022)

List of public hospitals/institutes offering PFO closure services	Location
Hospital Pulau Pinang	Georgetown, Penang
Hospital Queen Elizabeth II	Kota Kinabalu, Sabah
Hospital Raja Perempuan Zainab	Kota Bharu, Kelantan
Hospital Serdang	Serdang, Selangor
Hospital Universiti Sains Malaysia	Kota Bharu, Kelantan
Institut Jantung Negara	Kuala Lumpur
Pusat Jantung Sarawak	Kota Samarahan, Sarawak
Pusat Perubatan Universiti Malaya	Kuala Lumpur