# 1 Introduction

This guideline enshrines current clinical practice within the Stroke Department, for evaluation of "presumed cryptogenic stroke" (PCS). PCS is a diagnosis made during the hospital admission: and includes those with a confirmed diagnosis of cerebral infarct **AND** the following criteria:

- Age<55 years (some flexibility allowed for physiological age)
- Absence of Large Vessel Disease (LVD): Carotid atheroma <30% with no other atheromatous conditions (coronary or peripheral vascular disease)
- Mild or no Small Vessel Disease (SVD, Fazekas scale 1 or 0), on imaging
- Absence of significant traditional vascular risk factors (e.g. current smoker, ex-smoker with >20 pack year history); known diagnosis of hypertension, hypercholesterolaemia, diabetes mellitus, or known diagnosis of other recognised cause of stroke
- Need for further detailed investigations to ascertain aetiology & management strategy

This guideline does not include the general management of suspected stroke, for which separate guidance is in place, covering management of suspected or confirmed acute stroke and/or transient ischaemic attack (TIA) within the first 72 hours of symptom-onset.

## 1.1 Scope

This document is intended for use by medical staff within the Department of Stroke Medicine, under the guidance of a Consultant Stroke Physician, and is **not for general use** by non-specialists (who should consult a Stroke Physician to co-ordinate specialised investigations for PCS).

## 1.2 Consultation

Version 1 of the guideline was circulated to all Consultant Stroke Physicians and other stake-holders (Haematology and Cardiology) for review and comments on draft iterations over a six-month period.

Version 2 was drafted in 2023 and circulated to stake-holders for comment. Updates include: addition of monogenic SVD section (evidence review); update on hyperhomocysteinaemia (ASA guidelines, evidence review)

## 1.3 Education and training implications

Clinical staff are not required to develop novel skills in order to implement this guideline. The guideline is intended to provide a structure to the routine investigative work-up in the search for an underlying cause for an unexplained cerebral infarct. Where there are clinical pointers to a specific condition, earlier investigation towards exploring those specific diagnoses is advised. Most of these are undertaken and arranged from outpatient clinics run by Stroke Consultants. However, on occasion, these tests are requested from inpatient wards, and thus the need for awareness by junior doctors on the stroke wards. The guidelines will be advertised at Stroke Educational and Governance events and be made available on INsite for easy access.

# 2 Outline

## 2.1 Contents

## 2.2 Figures & Tables

# 3 General management of acute stroke

## 3.1 Definition

Overall, stroke is divided into two main types:

- Cerebral infarct / Ischaemic stroke occurs when a blood clot blocks an artery that carries blood to the brain.
- Primary intracerebral haemorrhage (PICH) is defined as non-traumatic spontaneous bleeding into the brain tissue – *excluded from this guideline*.

Other forms of brain injury: Subdural, extradural, subarachnoid, and trauma-induced intracerebral bleeding, cerebral trauma and diffuse axonal injury are also *excluded from this guideline*.

Transient symptoms of stroke without brain imaging evidence of infarction may satisfy the diagnostic criteria of Transient Ischaemic Attack (TIA), which can be considered as a milder equivalent to cerebral infarct for purposes of this guideline, by a Stroke Consultant.

The aetiopathology of cerebral infarct can be differentiated by the TOAST Classification [Adams HP et al. Stroke 1993; 24:35-41] into the following five types (see Figure **1** below):

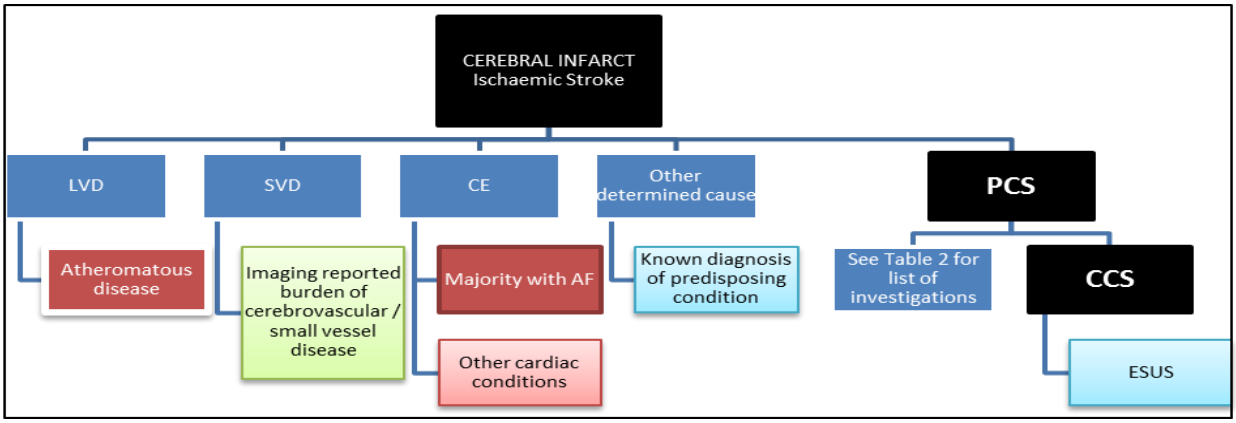
1. Large vessel disease – LVD
2. Small vessel disease – SVD
3. Cardioembolic stroke – CE
4. Stroke of other determined aetiology – usually a known diagnosis of an underlying cardiac condition, lupus or other predisposing condition
5. Cryptogenic stroke – CS

CS is a presumed diagnosis (PCS) pending investigational workup. PCS eventually gets split into

i. ***Confirmed* cryptogenic stroke** (CCS) – no cause found after detailed investigations (see flowchart)
   - ***ESUS (or "cryptogenic embolism"):*** Subcategorised if satisfies criteria for "embolic stroke" on imaging (about 2/3rds of all CS)

ii. ***Reclassified*** into 1-4 above after appropriate investigation

Figure 1: Aetio-pathophysiological classification of Ischaemic stroke (modified TOAST Criteria) [Adams HP et al. Stroke 1993; 24: 35-41]



More recently an alternative descriptive term “Embolic Stroke of Uncertain Source” (ESUS, also termed “cryptogenic embolism”) has been proposed for use when CCS is felt to be embolic (e.g. cortical syndromes – TACS/PACS, cortical infarction, multiple cortical infarcts in multiple vascular territories). A more comprehensive search for an embolic source is indicated in this uncommon patient group.

This guideline applies to category **5 (i) Presumed Cryptogenic Stroke**, where structured evaluation may lead to reclassification to one of the other categories (LVD, SVD, CE, other determined aetiology), confirmation of the presumed diagnosis (CCS) +/- sub-classification as ESUS. This guideline promotes a structured approach to a minimum work up advised for PCS. The order of investigation is based on the likelihood of finding a condition, in the absence of any clinical pointers. Should there be any clinical pointers, it is important that the suggested diagnosis is considered first.

## 3.2 Diagnostic evaluation of PCS

### 3.2.1 Confirm diagnosis of cerebral infarct

a. **Definite** diagnosis of
    i. Ischaemic stroke (as evidenced by brain imaging & clinical presentation) or
    ii. Transient Ischaemic Attack – typical history, with exclusion of other potential cause, PCS evaluation may be deemed appropriate by Stroke Consultant
b. Evaluation should include:
    i. Identification of known condition predisposing patient to cerebral infarction
    ii. History of other thrombo-embolic phenomena is supportive
    iii. FH to identify familial predisposition to VTE
    iv. Screen for symptoms/signs suggestive of lupus and vasculitis

### 3.2.2 Confirm absence of other TOAST subtypes

#### *3.2.2.1 Early indicators (inpatient)*

SMALL VESSEL DISEASE: No/mild burden of small vessel disease equivalent to Fazekas 0 or 1. Both CT head or MRI brain are considered adequate for quantifying vascular burden.
LARGE VESSEL DISEASE: Carotid Doppler shows no significant disease (i.e. <~30% stenotic disease) AND no other atherosclerotic disease (coronary or peripheral arteries)
CARDIOEMBOLIC DISEASE: Screen for AF (admission ECG, daily pulse rhythm checks, and a low threshold for repeated ECGs), and cardiac monitoring on the stroke unit.

*Inpatient cardiac Holter monitoring* is recommended if high Consultant clinical suspicion of PAF, as suggested by one of: (criteria discussed with Cardiologists)
(a) frequent atrial ectopics
(b) atrial enlargement - left (p wave >3mm height) or right (p>3mm width)
(c) multiple embolic events

***Inpatient Trans-Thoracic Echocardiogram*** (TTE) is recommended ~~should be undertaken urgently~~ where there is high suspicion of:
a) endocarditis – *subacute illness preceding stroke, features of infection with no clear source, typical organism on blood culture and potential cardiac substrate (new murmur or prior valve replacement). NOTE: Duckett-Jones Criteria and clinical stigmata rarely helpful in guiding investigative workup*)
b) mural thrombus (higher risk if transmural myocardial infarction in last 3 months, can occur with chronic *regional wall motion abnormalities* - RWMA)
c) stroke in the context of AF on optimal anticoagulation (to exclude mural thrombus, consider alternative anticoagulation and, in select situations, referral for left atrial appendage occlusion).
Where clinical suspicion of any of the above remains high, an ***inpatient Trans-Oesophageal Echocardiogram*** (TOE) should be organised via the Cardiology Specialist on call.
PS. Ideally a Stroke Consultant should discuss directly with a Cardiology Consultant undertaking Echo (Dr Jeffrey Khoo, Dr Derek Chin or Dr Rajesh Chelliah), if needing to facilitate clinical care or if there are undue delays.

Inpatient tests may sometimes be appropriate for logistical reasons (in elderly frail patients). Please consider if the test results are going to influence immediate management decisions. In most cases, an outpatient evaluation is adequate.

#### *3.2.2.2 Subsequent indicators (post-discharge)*

3.2.2.2.1 CARDIOEMBOLIC DISEASE
24/48-hour cardiac monitoring is the initial test of choice to be undertaken as an outpatient (see indications for inpatient testing above), followed by prolonged monitoring (7 day monitoring should be considered where suspicion of PAF remains high). Note: Prolonged monitoring can be requested by referral to Cardiology. The HAVOC score can serve as an aid ~~be used~~ to estimate the likelihood of detecting PAF (see section 5.5).

Monitoring is required to screen for *significant cardiac arrhythmia* (chiefly paroxysmal atrial fibrillation or flutter), and *significant ventricular ectopic burden* (which may point to subclinical coronary artery disease; consider echocardiography, beta blocker e.g. bisoprolol, and Cardiology input).

TTE is an appropriate initial test to screen for significant emboligenic substrate (left-sided valvular disease, RWMA, or other rarer diagnoses e.g. atrial myxoma, endocarditis).

Where appropriate, TOE should be considered to identify aortic atheroma (*occult atherosclerosis is the commonest underlying cause found in presumed cryptogenic stroke; NOTE: CT Angiogram preferred first line modality*), or to characterise a potential shunt identified on a TCD Bubble test (refer to PFO MDT, GH).

TCD Bubble test is the recommended initial screening test for a right-to-left shunt (commonly a PFO) – see TCD Bubble Request form. This is not an urgent test or an inpatient test, and is normally

available as an outpatient. In rare circumstances, it may be possible to administer contrast alongside an inpatient bedside Echo – please consult Dr Mistri for availability.

Table 1: Consensus recommendations for Echocardiography (with UHL Cardiologists: Sandilands & Khoo)

| | **TTE as initial test** | **TOE (after TTE)** |
|---|---|---|
| NOTE: TOE is not easily available, thus a TTE is the first line investigation to be undertaken in all patients<br>INPATIENT testing is only required in select situations (see 3.2.2.1) | | |
| **INPATIENT** | Prior or suspected cardiac disease should prompt consideration of mural thrombus in the following groups:<br>i. Recent myocardial infarction (MI) <3 months - especially transmural i.e. Q waves on ECG<br>ii. Previous MI with features of decompensation (suggesting RWMA)<br>iii. Hypotension &/or CCF<br>iv. AF on anticoagulation (to look for mural thrombus and consider alternative anticoagulation).<br>v. Clinical suspicion of endocarditis, or high risk based on presence of artificial valve | i. Suspicion of intracardiac thrombus<br>ii. Patients with AF sustaining an embolic event, whilst on Anticoagulation (after a TTE)<br>iii. Recent multiple systemic embolic episodes<br>iv. Patients with a mechanical heart valve |
| **OUTPATIENT** | Systemic embolism (includes embolic stroke) and no identified cerebrovascular disease<br><br>Patient factors<br>TOE may be contraindicated (e.g. oesophageal stricture, unstable hemodynamic status) or TOE may be declined by patient<br><br>**NOTE**: Patients with AF & embolic stroke do not routinely need an Echocardiogram if the decision to anticoagulate has already been made; however an Echo is strongly recommended for those with stroke occurring whilst on anticoagulation for AF | Patients <45 years without known cardiovascular disease (i.e. no history or features of CAD or valvular disease) – can be used to evaluate subclinical atherosclerosis e.g. aortic arch atheroma<br><br>NOTE: CT Angiogram – Arch to Circle of Willis would be the preferred first line investigation for seeking large vessel atheroma; with TOE as second line where an angiogram is not feasible (e.g. CKD) |

### 3.2.3 Other Defined Aetiology

The standard set of tests to identify rarer conditions associated with stroke fall under the following four broad categories:

1. Arterial dissection
2. Autoimmune disease
3. Thrombophilic disease
4. Genetic conditions

#### *3.2.3.1 Arterial dissection*

3.2.3.1.1 Clinical pointers

Young patient with paucity of vascular risk factors
History of neck trauma or extreme movement temporally associated with onset
*Head / neck pain 60-90% (20% report a thunderclap headache)
*Horner's Syndrome 25% - can be isolated
NOTE: Bilateral dissection is common (thus bilateral symptoms are suggestive; and should not be considered functional by default, at initial presentation).

3.2.3.1.2 Imaging

Initial non contrast CT scan may reveal a cerebral infarct
CT angiography is easily available and provides good image resolution, making it the preferred modality (however specificity is low, as luminal abnormalities may be due to atheroma or dissection).
MR angiography has high specificity for diagnosis of dissection (blood in vessel wall); however possible dissection is not an indication for out-of-hours MRI (no impact on initial management), nor does it impact on the initial management strategy.
CTA/MRA should be organised after discussion with a Consultant, with further discussion at the NeuroRadiology meeting (as appropriate).

3.2.3.1.3 Management

The largest clinical study of arterial dissection [*CADISS Lancet Neurology 2015; 14: 361-7*] was unable to provide a definitive answer as to the best management options, due to inadequate sample size. Both antiplatelets and anticoagulants are thus clinically used for stroke prevention in the context of arterial dissection. Antiplatelets may be a reasonable strategy in the presence of no infarct or a single isolated infarct, whilst dual antiplatelets or anticoagulants may be preferred in the face or recurrent embolism (symptomatic or imaging) – subject to responsible Consultant opinion. There is no evidence to support a defined duration of treatment, interventional or surgical intervention at present (May 2018).

Repeat angiographic imaging should be considered at about 6 months to support duration of antithrombotic treatment (antiplatelet or anticoagulant), by establishing resolution or persistence of luminal abnormalities. If angiography is normal, cessation of anti-thrombotic may be appropriate. Where there is persistent luminal abnormality, prolonged anti-thrombotic use may be appropriate. An individualised management strategy is required under guidance of a Stroke Physician keeping in

mind other co-morbidities (*Consensus statements following UHL Stroke Consultant body discussion – October 2019*).

***Autoimmune disease***

3.2.3.1.4 Clinical pointers

Known history of autoimmune disease

Clinical stigmata of vasculitis

a) Neurologic features (may be difficult to isolate from stroke related neurology)
   (i) Mononeuritis multiplex – damage of >=2 named nerves (typically "foot drop")
   (ii) Polyneuropathy – distal, symmetric
   (iii) Radiculopathy &/or plexopathy (nerve root or plexus distribution)
b) Non-neurologic features
   (i) Constitutional: fever, malaise, weight loss
   (ii) Skin: Palpable non-blanching purpura or skin ulcers
   (iii) ENT: Allergic rhinitis / nasal polyps
   (iv) GI: Intestinal angina (polyarteritis nodosa)
   (v) Large vessel: absent / asymmetrical pulses, bruits on large vessel auscultation

Often have headaches, personality changes, fluctuating consciousness, meningism

Urine dip test (proteinuria, haematuria, casts)

Positive antibodies on autoimmune testing (ANA, ANCA, Myeloma, Syphilis, HIV)

3.2.3.1.5 Imaging

If suspected, angiography or biopsy may be indicated.

Biopsy is usually taken from suspected organ involved (skin, kidney, lung, nerve, rarely brain)

3.2.3.1.6 Management

Important to **differentiate primary systemic vasculitis from secondary causes** (e.g. inflammatory conditions like SLE; a variety of infections; neoplasia and drug-related) to direct management

Patients with vasculitis should ideally be managed by a multi-disciplinary team, including a Rheumatologist. Steroids are the mainstay of initial treatment on the Stroke Unit, with ongoing management in liaison with a Rheumatologist depending on concomitant disease.

***3.2.3.2 Thrombophilic disease***

3.2.3.2.1 Arterial thrombophilia

PCS evaluation should include a basic set of "arterial thrombophilia" testing (including lupus screen, and cardiolipin antibody) - see **Table 2** & Flowchart). The value of homocysteine testing is uncertain.

3.2.3.2.2 Venous thrombophilia

An extended set of thrombophilia tests should be considered if there is coexistent DVT or pulmonary embolism, or a right-to-left shunt (with potential paradoxical embolism) is demonstrated (including *prothrombotic factors*: Factor V Leiden, Prothrombin 20210A and *deficiency of antithrombotic factors*: Protein C & S, ATIII - see **Table 2** & Flowchart).

3.2.3.2.3 Antiphospholipid syndrome

Basic screening for antiphospholipid syndrome includes blood tests for lupus anticoagulant screen, cardiolipin antibody and β2 glycoprotein (if not already done for arterial thrombophilia testing).

**NOTE: Lupus anticoagulant carries a much higher risk than cardiolipin antibody.**

If ANA screen is positive, then specific antibody testing should be undertaken (ENA screen, dsDNA & β2 glycoprotein), with additional Haematologist input as required – refer to supporting documents for further information.

3.2.3.2.4 Hyperhomocysteinemia

The updated ASA guidelines question the efficacy of vitamin supplementation for stroke prevention in those with elevated homocysteine levels. In the absence of definitive evidence, it is not clear whether homocysteine testing adds any value.

Should consultants wish to undertake testing: Homocysteine levels should be taken (with concomitant B12 and folate samples). B12/folate deficiency can raise homocysteine levels. Elevated homocysteine levels should be repeated in the fasting state (if not undertaken in the fasting state already) and can be treated with B12 & folate supplements – refer to Table 2 for further information and supporting documents.

### *3.2.3.3 Genetic conditions*

If considering any genetic testing, the patient should be referred on to the Clinical Genetics Team, to ensure appropriate pre-test counselling and prompt follow up, and to avoid inappropriate and costly investigations.

The exception is Fabry's Disease, where a specific kit for free testing is available. Details are included in supporting documents, under Appendices. Testing to be undertaken via Chemical Pathology to ensure appropriate recording and follow up of requests within hospital systems.

**Table 2: List of investigations for PCS to identify 'Other defined aetiologies'. Refer to flowchart in supporting documents for proposed timeline (in the absence of any clinical pointers)**

| Arterial Dissection | Autoimmune disease | Thrombophilic disease | Genetic conditions |
|---|---|---|---|
| Appropriate angiographic imaging in discussion with NeuroRadiologist – usually CT or MR Angiogram | **Basic antibody testing**<br>Vasculitis screen (ANA, ANCA)<br>Myeloma screen<br>Syphilis & HIV screen | **Basic arterial thrombophilia screen**<br>I. Lupus anticoagulant screen, Anti-Cardiolipin antibody & β2 glycoprotein 1<br>II. +/- Homocysteine level (ideally fasting if feasible)<br>(if elevated, repeat in fasting state, with B12 and folate) | If there is FH of young stroke, or other genetic conditions, then REFER to a Clinical Geneticist. |
| Consider referral to Clinical Genetics if considering underlying cause like Marfans etc | If ANA is positive<br>i) consider false + and drug induced ANA+<br>ii) Repeat in 6 weeks to confirm<br>iii) **If persistently +,** | **Extended venous thrombophilia screen**<br>**INDICATIONS**<br>(i) Suspected right to left shunt<br>(ii) h/o recurrent VTE or presence of a right-to-left shunt (e.g. PFO)<br>(iii) Multiple unprovoked VTE – | Screening for Fabry's disease for all under 55 with CCS (see Section 0: Supporting documents) |

| | | | |
|---|---|---|---|
| | undertake<br><br>**Extended antibody testing** (ENA panel, dsDNA, β2 glycoprotein 1)<br><br>**NOTE: overlap with thrombophilia screen** | *please check if already had tests done.*<br>**WHAT TESTS TO DO**<br>**PROTHROMBOTIC FACTORS**<br>Activated Protein C, Activated Factor Xa, P20210A mutation<br>**DEFICIENCY OF ANTICLOTTING FACTORS**<br>Protein C & S, ATIII, FV Leiden | |

### 3.2.4 Cryptogenic Stroke

a. Not elderly, usually <55 years of age
b. Usually no significant smoking history
c. Absence of significant hypertension OR hypercholesterolaemia
d. Not diabetic
e. No h/o previous vascular disease (coronary, cerebro, carotid, renal, peripheral)

#### *3.2.4.1 Presumed - PCS*

**The presence of any clinical pointers towards a specific condition should prompt testing for that condition.**

When initial evaluation during the initial presentation of stroke/TIA reveals no overt cause for stroke, the working diagnosis of presumed cryptogenic stroke is appropriate. A search for less common causes should be undertaken in a structured format to identify "other determined cause" or to confirm cryptogenic stroke, as per Figure 2.

#### *3.2.4.2 Confirmed - CCS*

When detailed investigations reveal no cause for the stroke, then the diagnosis of cryptogenic stroke can be deemed to be "confirmed".

Fabry's testing should have been undertaken in the under 50 age group.
Consideration should have been given to prolonged cardiac monitoring.

## 3.3 Initial Management

The emergency management of acute stroke in people who receive a subsequent diagnosis of ESUS is not disparate from standard management and the UHL guidelines for acute stroke / TIA should be followed.

### 3.3.1 Neuroradiological study

#### *3.3.1.1 CT scan*

The initial scan for people presenting with a suspected stroke is usually a CT scan, because it is rapid, readily available, and has high negative predictive value for haemorrhage. A "venous" infarct may be noted secondary to venous sinus thrombosis (and should prompt an urgent CT Venogram, as this influences the initial treatment). Please refer to UHL Guideline for Stroke & TIA.

#### *3.3.1.2 MRI scan*

Most people with paucity of vascular risk factors are likely to benefit from an MRI brain scan to categorically rule out vascular (small vessel) disease, and to identify mimics not evident on CT scan (e.g. demyelinating plaques). An MRI should only be requested **after** discussion with the Consultant given limited MRI resources, and documenting the Consultants name on the request. The IPFD (inpatient for discharge) process is eminently suitable for urgent OP MRI arrangements. **Where an urgent inpatient scan may alter the immediate management**, please discuss with a NeuroRadiologist.

**NOTE**: Where capacity allows, the TIA clinic may be able to facilitate a basic MRI (basic diagnostic MRI including FLAIR). More complex MRI with additional sequences e.g. dissection or TOF MRA or contrast cannot be accessed via the TIA clinic. Pre-requisites: Consultant approval; ambulatory patient (in own clothing); completed paper request form, completed MRI questionnaire, no suspicion of dissection.

### 3.3.2 Other investigations

Perform the standard set of blood tests (**see NC > Stroke folder > First/Initial Stroke Presentation**). A 12-lead ECG is required. Request a chest x-ray if an indication is present. Secondary investigations will be guided by consultant review.

#### *3.3.2.1 People taking anticoagulant medication*

The two time critical investigations at presentation are:

a) **CT brain** to confirm or rule out bleed and
b) **Blood tests**: Full coagulation profile (INR for warfarinised patients) and renal profile (with CrCl calculation for DOAC patients). Use near-patient INR, where available to facilitate immediate decisions.

**Most thrombophilia testing is unreliable in the presence of an anticoagulant.**

Bloods for Anti Cardiolipin antibody can be undertaken acutely after a stroke if there is a high suspicion and management is likely to be altered. A standard wait of 6 weeks "off anticoagulation" AND after a thrombotic event is required before definitive testing can be undertaken; this delay is not mandated following a TIA.

## 3.4 Specific management

Identification of a specific cause for stroke (other determined cause) enables targeted management of that specific condition. This should be undertaken in consultation with appropriate specialists e.g. Haematology, Rheumatology, Cardiology, Clinical Genetics.

Specific management has been cited in section 3.2.3 for various conditions, with further information on specific conditions in Section 5: Supporting documents.

In addition, there is an internal department document with collated information on patients diagnosed with rare underlying causes of stroke. This is accessible to the Stroke Consultant body for reference.

# 4 Appendices

## 4.1 Monitoring and Audit Criteria

**Table 3: Monitoring and audit criteria for guideline**

| Key Performance Indicator | Target | Issuing body | Body reference | UHL guideline reference | Method of Assessment | Frequency | Lead |
|---|---|---|---|---|---|---|---|
| Appropriate requests for MRI Brain | | | | 3.3.1.2 | Audit | Every 2-3 years | UHL Acute Stroke working group<br><br>Head of service for stroke medicine<br><br>Delegated to Stroke Audit Lead |
| Appropriate requests for autoimmune disease and thrombophilia screening | | | | 0<br>3.2.3.2 | | | |
| Appropriate requests for TCD Bubble Test | | | | 3.2.2.2.1 | | | |
| Appropriate cardiac testing | | | | 3.2.2.2.13.<br>2.2.2.1 | | | |

Performance targets described herein are aimed to have been achieved within one year of the release of the guideline. The responsibility rests with the Stroke Audit Lead.

## 4.2 Legal Liability Guideline Statement

Guidelines or Procedures issued and approved by the Trust are considered to represent best practice. Staff may only exceptionally depart from any relevant Trust guidelines or Procedures and always only providing that such departure is confined to the specific needs of individual circumstances. In healthcare delivery such departure shall only be undertaken where, in the judgement of the responsible healthcare professional, it is fully appropriate and justifiable - such decision to be fully recorded in the patient's notes.

## 4.3 Key References


1. National Clinical Guideline for Stroke 5th Edition 2016 – Intercollegiate Stroke Working Party (available online at www.rcplondon.ac.uk)
2. Kernan et al 2014 Stroke - AHA/ASA Guidelines for Prevention of Stroke in patients with ischaemic stroke or TIA (available online at ahajournals.org)
3. ASA Cryptogenic Stroke Initiative (available online at www.stroke.org)
4. Yaghi S, Elkind MS. Cryptogenic stroke: A diagnostic challenge. Neurol Clin Pract. 2014; 4:386-393.
5. University Hospitals of Leicester NHS Trust. Acute Stroke & TIA Management Guidelines for the first 72 hours of symptom-onset. Version 3.0 (April 2019)

## 4.4 Key Words

Stroke; Ischaemic; Haemorrhagic; Haemorrhage; Transient Ischaemic Attack; TIA; Cryptogenic; ESUS

## 4.5 Equality Impact Assessment

The Trust recognises the diversity of the local community it serves. Our aim therefore is to provide a safe environment free from discrimination and treat all individuals fairly with dignity and appropriately according to their needs.

As part of its development, this guideline and its impact on equality have been reviewed and no detriment was identified.

## 4.6 Process for Version Control, Document Archiving and Review

This document will be uploaded onto SharePoint and available for access by Staff through INsite. It will be stored and archived through this system.

The next guideline review date is scheduled for November 2022. Dr Mistri, on behalf of the UHL stroke working group, will be responsible for review and updating of the document.

# 5 Supporting documents

## 5.1 Unusual causes of stroke: symptoms, tests and management

### 5.1.1 ANTI PHOSPHOLIPID SYNDROME (APS)

*International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS) [Miyakis et al J Thromb Haemost; 4: 295-306]*

| | |
|---|---|
| Symptoms | **Clinical criteria** for diagnosis<br>1. ***Vascular thrombosis*** (1 or more episodes of confirmed thrombosis – arterial, venous or small vessel)<br>2. ***Pregnancy morbidity*** (miscarriage in first 10 weeks, foetal death, eclampsia or pre-eclampsia in 10-34 weeks of gestation)<br>Other clinical features (not in diagnostic criteria): Migraine with aura, livedo reticularis, thrombocytopenia, heart valve abnormalities, seizures, chorea and nephropathy. |
| Tests | Basic set of screening tests: lupus screen, cardiolipin antibody<br>Extended set of tests: specific antibodies: ENA panel, dsDNA, β2Glycoprotein)<br>**Laboratory criteria** for diagnosis<br>1. ***Lupus anticoagulant*** [x2, 12 weeks apart]<br>2. ***Anticardiolipin antibody*** (IgG or IgM ACL >40 units) [x2, 12 weeks apart]<br>3. ***Anti β2 glycoprotein*** ELISA IgG or IgM >90$^{th}$ centile) [x2, 12 weeks apart]<br>Most tests cannot be undertaken in the context of a thrombotic event (DVT, PE, cerebral infarct), and a minimum 6 week delay is recommended.<br>NOTE: Cardiolipin antibody test may be undertaken early in the setting of acute stroke, if there is a high degree of suspicion at Consultant level. |
| Management | Initial positives tests should be repeated after an interval of 12 weeks (and often become negative, so should not be over-interpreted)<br>Persistently positive antibody tests are suggestive of the diagnosis (requires 1 clinical and 1 lab criteria for diagnosis)<br>a) Standard antiplatelet therapy is reasonable for cryptogenic stroke with antiphospholipid antibodies [ASA Guidelines]<br>b) Anticoagulation (warfarin INR 2-3) is *reasonable* if the criteria for APS are met (arterial/venous occlusive disease in multiple organs, pregnancy morbidity (early miscarriages (<10w) and livedo reticularis [ASA Guidelines]<br>**NOTE**: no significant benefit seen in RCT [WARSS]<br>c) Joint care with a Haemostasis & Thrombosis Haematologist is recommended.<br>NOTE: Direct oral anticoagulants are contraindicated in patients with APS, due to an increased risk of thrombotic events noted in the TRAPS Study (Pengo V, et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. Blood 2018; 132: 1365–71). |

### 5.1.2 CADASIL (prototype monogenic SVD)

***Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts & Leucoencephalopathy***

| | |
|---|---|
| Symptoms | Prevalence estimated at <5 per 100,000<br>Stereotypical presentation of migraine with aura, small subcortical strokes, or cognitive impairment in middle-aged patients (typically age 40-60 years)<br>FH of stroke or dementia, consanguinity<br>Typical vascular risk factors appear to increase stroke risk (smoking, HT)<br>Typical subcortical pattern of cognitive impairment |
| Tests | Brain MRI – extensive white matter changes. **Confluent bilateral anterior temporal pole** T2 hyperintensities are highly suggestive (sensitivity & specificity ~90%). External capsule and callosal involvement is common (but can occur with other differentials).<br>**Molecular genetic analysis** for NOTCH3 mutations is the gold standard. Where genetic testing is negative and clinical suspicion is strong, skin biopsy should be considered to look for GOM (granular osmiophilic material, in close relation to vascular smooth muscle cells) on electron microscopy (neuropathological hallmark: 100% specificity). |
| Management | There are **no evidence-based interventions** or effective treatments for CADASIL.<br>One trial showed that Donepezil had no significant impact on cognition.<br>There are no studies of antiplatelets, thrombolysis relatively contraindicated in acute small vessel disease strokes (LACS).<br>Standard management of stroke focussed on vascular risk factors is reasonable, noting a high prevalence of microbleeds (suggesting that the risk of bleeding may be increased).<br>**Genetic counselling** (via Clinical Genetics) should be offered to support:<br>a) All diagnosed patients<br>b) Family members offered predictive testing<br>c) Family planning |
| Differential diagnoses to consider | • **Multiple sclerosis** – Optic nerve & spinal cord involvement, CSF oligoclonal bands<br>• **CARASIL** (HTRA1 gene mutations) – extra-neurological findings (early onset spondylosis and early onset alopecia), no GOM on skin biopsy<br>• **Other hereditary leucoencephalopathies** e.g.<br>o MELAS (stroke-like episodes: headache, N&V, encephalopathy, focal onset seizures and focal neurological deficits; myopathy (ptosis, CMX, weakness), diabetes & lactic acidosis<br>o Krabbe disease<br>o Fabry disease (see specific section)<br>o CARASAL (extensive subcortical and brainstem hyperintensity)<br>o hereditary diffuse leukoencephalopathy with axonal spheroids |

### 5.1.3 HAEMATOLOGICAL CONDITIONS ASSOCIATED WITH STROKE

| | |
|---|---|
| Symptoms | Any clinical pointers towards a prothrombotic condition (prior thrombo-embolism and/or first degree family history), or a bleeding condition (prior bleeding, especially if recurrent). The past medical history may note prior haematological conditions. Critically ill patients may have coagulopathy including disseminated intravascular coagulation. |
| Tests | Abnormally low or high blood counts, and/or abnormal cells on blood picture may suggest the presence of haematological conditions. A full coagulation profile and haemolysis screen including MCV, LDH and beta-2 microglobulin should be considered. |
| Management | Targeted at specific condition, with specialist haematological input |

| 5.1.4 PATENT FORAMEN OVALE | |
|---|---|
| Symptoms | Platypnoea-orthodeoxia (rare) – drop in oxygen saturation on sitting up<br>Recurrent migraine especially with aura is a supportive feature<br>Consider PFO in the setting of recurrent embolic events |
| Tests | A contrast enhanced TCD Bubble Test is the first line screening test.<br>If there is already a suspicion of PFO based on TT Echo or other imaging, the next step is referral to Cardiology for a contrast TOE (or alternative modality)<br>If PFO +: additional venous thrombophilia tests should be considered (paradoxical embolism) |
| Management | Use ROPE Score to quantify PFO-attributable stroke risk (see TCD Bubble Request form)<br>Refer to Brain-Heart MDT if TCD Bubble suggests right-to-left shunt (e.g. PFO) to refine risk assessment and consider PFO closure. |

| 5.1.5 FABRY'S DISEASE | |
|---|---|
| Symptoms | Young adults 18-50 years, about 1% of all stroke<br>GLA gene variant resulting in deficiency or absence of α-galactosidase A.<br>PMH of Fabry's disease; or FH of Fabry's disease (or dialysis <55 yrs)<br>Peripheral neuropathy, proteinuria, hearing or visual impairment (corneal clouding)<br>Typical features of "classic" Fabry's disease:<br>a) **Angiokeratoma** – small reddish papules, "swimming trunk" distribution<br>b) **Cataracts**: Bilateral posterior 'Fabry' cataracts<br>c) **Acroparaesthesia** (neuropathic pain in about 2/3rds)<br>d) **Hypohidrosis** (heat intolerance) |
| Tests | MRI may show increased signal in posterior thalamus (pulvinar sign) and basilar artery dolichoectasia<br>Specialist blood test (tested externally at ***Lysosomal Storage Disorders Unit, Royal Free London NHS Foundation Trust***, via Chemical Pathology)<br>(i) MALES: Enzyme test, if + > Gene test and Lyso-Gb3 test<br>(ii) FEMALES: Gene test, if + > Lyso-Gb3 test (confirmatory test) |
| Management | Referral to specialist centre ***(QE Birmingham, 0121 627 2000)***<br>a) Enzyme replacement<br>b) Testing of family members (as appropriate)<br>c) Other management e.g. painful neuropathy |

## 5.1.6 HYPERHOMOCYSTEINEMIA

Hyperhomocysteinemia is associated with a doubling of stroke risk, and people with elevated homocysteine levels (>9.5 µmol/L in men; and >8.5 µmol/L in women) have a 10% risk of recurrent stroke at 10 years. However, there is no clear RCT evidence to support vitamin therapy [VISP Study, Toole JAMA 2004;291:565–575]. Consequently, there is no clear guidance as to whether or not homocysteine levels should be tested.

The latest ASA guidance [Kleindorfer Stroke 2021; 52: e364–e467] states that "*in patients with ischemic stroke or TIA with hyperhomocysteinemia, supplementation with folate, vitamin B6, and vitamin B12 is not effective for preventing subsequent stroke*". However, this has been challenged [Spence Stroke. 2022; 53: 2702–2708]. It is essential that testing or any treatment involves full discussion with the patient/legal representative expressing the uncertainty in the evidence base.
Should a decision be made to test, the recommendations below are based on expert consensus guidance. Ongoing follow up under the Stroke clinician is advised.

| | |
|---|---|
| Symptoms | Childhood presentations have the typical features: Marfanoid habitus, lens dislocation<br>Other rarer features: malar flush, livedo reticularis, mental retardation, myopia, glaucoma<br>PMH of other unprovoked thromboembolism (50% have an embolic event before age 30)<br>Adults may have no typical features |
| Tests | Screening Homocysteine level (with B12 & folate) – ideally fasting<br>Confirmatory Homocysteine level (with B12 & folate) – MUST be fasting |
| Management | The evidence base for stroke prevention in the setting of elevated homocysteine levels remains uncertain. Any decisions should be made at consultant level.<br>1. Traditional vascular risk factors should be treated appropriately.<br>2. B12 & folate deficiency should be corrected with supplements<br>3. B Complex vitamin supplements for all<br>4. Use Cyanacobalamin (B12) 400 microgram and folate 5mg daily<br><br>*Recommended target for homocysteine level is < 15 or 25% reduction from baseline*<br>*Repeat levels at ~6 weeks, 3 months and every 6-12 months if target not reached*<br><br>If target reached: continue treatment for 3 months with aim of reducing to twice weekly supplements if it stays <15<br>If target not reached, escalate treatment: Escalation options<br>a) consider adding pyridoxine ($B_6$) 10mg daily<br>b) consider trimethylglycine (<u>betaine</u>) 750 mg twice daily – can be up titrated<br>Ensure that traditional vascular risk factors are optimally controlled. |

## 5.1.7 NEUROSYPHILIS

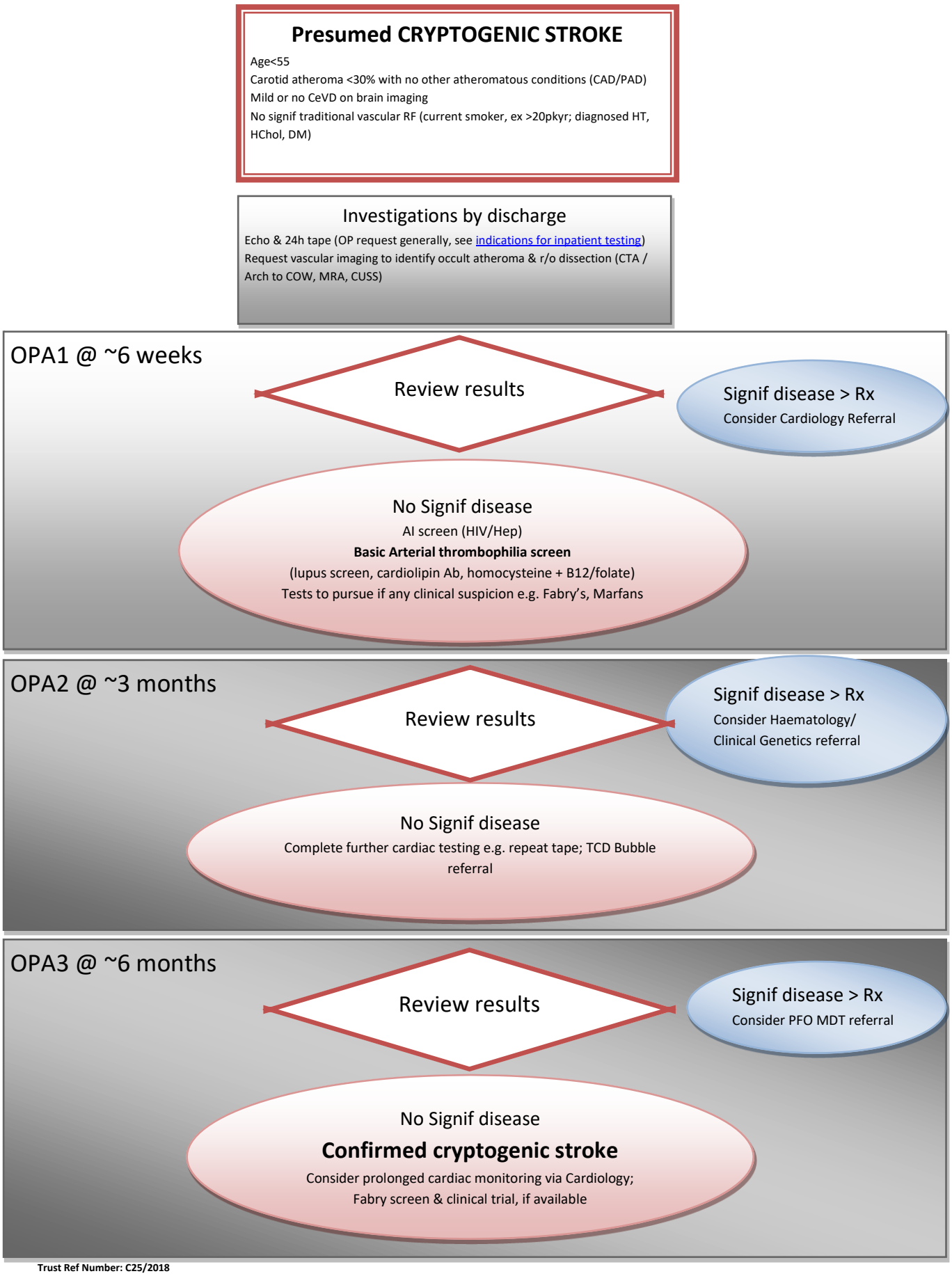
| | |
|---|---|
| Symptoms | Age 25-50 years<br>Progressive neurological symptoms<br>History of syphilis or HIV positive<br>Migration from a high-risk syphilis region (SE Asia, Sub-Saharan Africa, Latin America, Caribbean) |
| Tests | Syphilis serology – 95% positive RPR<br>CSF analysis is required for a diagnosis of neurosyphilis (high protein, oligoclonal bands directed to T pallidum antigen)<br>Neuroimaging suggestive of arteritis (CTA / other angiogram) |
| Management | Penicillin G (or ceftriaxone) – as guided by infectious diseases |

| 5.1.8 TAKAYASU DISEASE | |
|---|---|
| Symptoms | Young women<br>Constitutional symptoms (anorexia, weight loss, malaise)<br>Claudication<br>Asymmetrical pulse or BP, absent femoral pulse |
| Tests | Raised ESR (Plasma viscosity used in UHL)<br>CRP is usually raised<br>Elevated Gamma Globulin and WBC<br>MR Angiography & Echo should be undertaken |
| Management | Abnormal aortic dilatation or AV Regurgitation necessitates strict BP control<br>Corticosteroids +/- immunosuppressants<br>The role of anticoagulation is unclear<br>Vascular Referral guided by vascular anatomy on Angiography/Doppler (Aneurysm, AVR or renovascular hypertension, carotid stenosis, subclavian steal syndrome) |

| 5.1.9 TEMPORAL ARTERITIS (in consultation with Opthalm/Rheum – see relevant UHL guideline – Suspected TA) | |
|---|---|
| Symptoms | Headache<br>Symptoms of or known Polymyalgia rheumatica<br>HIGH RISK FEATURES NEEDING REFERRAL TO EYE CASUALTY: Jaw / tongue ***claudication***,<br>**visual symptoms** (ischaemic optic neuropathy)<br>Constitutional symptoms (anorexia, weight loss, malaise), **scalp necrosis** |
| Tests | **80% have raised ESR (Plasma viscosity** used in UHL)<br>CRP is sensitive and usually raised in TA (i.e. a normal CRP makes TA unlikely – high negative predictive value)<br>A combination of raised ESR & CRP reportedly has a sensitivity of 100%<br>**Normal blood tests do not negate the diagnosis in the presence of high clinical suspicion**<br>A third have deranged LFT |
| Management | Contact Rheumatology on call, for Temporal Artery Biopsy<br>Contact Eye Casualty (phone 6867) if eye symptoms are present<br><br>A stat dose of Prednisolone should be administered<br>In the presence of visual loss, IV Methylprednisolone may be considered, in consultation with an Ophthalmologist |

## 5.2 Flowchart for UHL Guidelines: Evaluation of Presumed Cryptogenic Stroke

**(in the absence of clinical pointers to a specific condition)**



## 5.3 Crib sheet for detailed history and examination in the setting of PCS

Complete prior to confirming diagnosis of CCS

| History | Record any findings |
|---|---|
| *Symptom screen*<br>Alopecia, scalp necrosis<br>Lens dislocation<br>Mouth ulcers<br>Jaw or tongue claudication<br>Visual loss (suggestive of ischaemic optic neuropathy)<br>Rashes<br>Joint swelling<br>Acroparaesthesia (+/- neuropathic pain)<br>Claudication<br>Heat intolerance / hypohidrosis<br>Constitutional symptoms: anorexia, weight loss, malaise | |
| *PMH*<br>Rheumatic heart disease<br>Malignancy<br>Seizure disorder<br>Spinal problems<br>HIV<br>Syphilis (or migration from a high-risk region SE Asia, Sub-Saharan Africa, Latin America, Caribbean)<br>PMR<br>Premature bilateral cataract<br>High burden of migraine with aura<br>Pregnancy morbidity (miscarriage, foetal death, eclampsia or pre-eclampsia)<br>Prior unprovoked thrombo-embolism (venous, arterial or small vessel) | |
| **Examination** | |
| Fundoscopy for retinal tortuosities<br>Malar rash<br>Livedo reticularis<br>Angiokeratoma<br>Detailed peripheral pulse examination (absent pulses, claudication) | |
| **Investigations** | |
| Elevated CRP, PV (not explained by infection)<br>High or low blood cell counts<br>Blood picture abnormalities | |

Affix patient label here

## 5.4 Grid for cryptogenic stroke testing

| Stage of investigations | Test | Requested | On W/L | Resulted | Action |
|---|---|---|---|---|---|
| **Discharge** | **TTEcho** | | | | |
| | **24 hour monitor** | | | | |
| | **CT Angio (Arch>COW)** | | | | |
| | **MRI brain** | | | | |
| **6 week review** | **Basic Autoantibody Panel** | | | | |
| | **Basic Thrombophilia Panel (Arterial)** | | | | |
| | **TCD Bubble Test** (see specific form for pre-requisites) | | | | |
| **3 month review** | **Extended Thrombophilia Panel (Venous)** *(if indicated)* | | | | |
| | **Extended Autoantibody Panel** *(if indicated)* | | | | |
| | **Fabry screen** *(if indicated)* | | | | |
| **6 month review** | **Other tests** | | | | |

| **REFERRALS** *(✓, X, dates)* | **REQUIRED** | **Referred** | **On W/L** | **Outcome letter seen** | **Any further actions** |
|---|---|---|---|---|---|
| **Cardiology** | | | | | |
| **Brain-Heart MDT** (if TCD Bubble+) | | | | | |
| **Haematology** | | | | | |
| **Clinical Genetics** | | | | | |
| **Other** | | | | | |

***Strike off if test deemed not applicable**

## 5.5 HAVOC Score

This score can be used to estimate likelihood of identifying PAF and establish PAF detection strategy.
This is only a consensus guide and individualised clinical judgement is required.
NOTE: Does not apply to patients with known paroxysmal or persistent AF.

| Predictor | Score |
|---|---|
| Hypertension | 2 |
| Age ≥75 | 2 |
| Valve Disease | 2 |
| Vascular Disease (Peripheral) | 1 |
| Obesity | 1 |
| Congestive Heart Failure | 4 |
| Coronary Artery Disease | 2 |
| HAVOC Score | add for total score |

Table 4. HAVOC Score – variables and scoring (Kwong C et al. Cardiology 2017; 138(3):133-140)

| | CHARACTERISTICS | | | | CONSENSUS MONITORING STRATEGY | | |
|---|---|---|---|---|---|---|---|
| Score categories | Prevalence of score in population | Risk of AF | Predicted AF detection (%) | NPV | ECG | 24h tape (can repeat) | Long term monitoring |
| 0-4 | 80 | 2.5 | LOW | 0.97 | Admission Discharge | Consider | Not recommended |
| 5-9 | 15 | 12 | MEDIUM | | Admission Discharge | Recommended | Consider |
| 10-14 | 5 | 25 | HIGH | | Admission Discharge | Recommended | Recommended |

Table 5. HAVOC Score, associated risk and consensus monitoring strategy

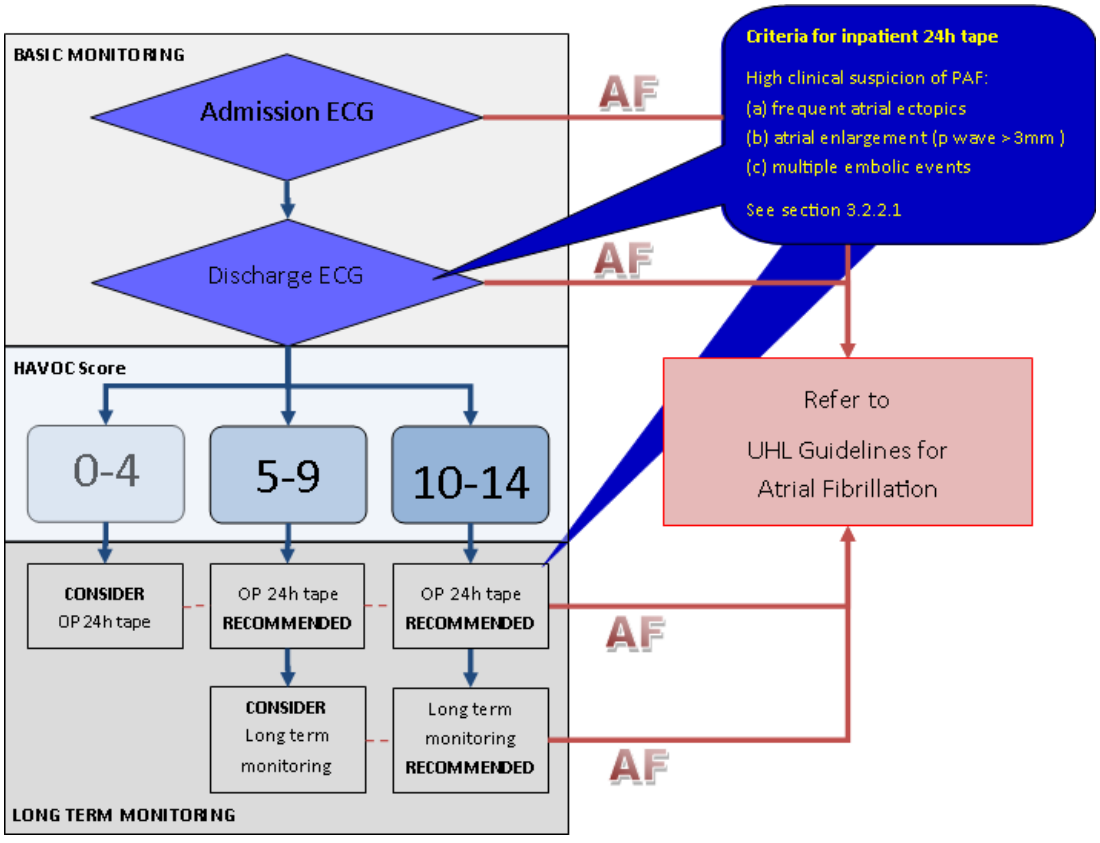



Figure 2. Consensus strategy for PAF screening using HAVOC Score