# Etiologic workup in cases of cryptogenic stroke: a systematic review of international clinical practice guidelines

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# Abstract

## Background and purpose

Identifying the etiology of acute ischemic stroke is essential for effective secondary prevention. However, in at least one third of ischemic strokes, existing investigative protocols fail to determine the underlying cause. Establishing etiology is complicated by variation in clinical practice, often reflecting preferences of treating clinicians and variable availability of investigative techniques. In this review, we systematically assess the extent to which there exists consensus, disagreement, and gaps in clinical practice recommendations on etiologic workup in acute ischemic stroke.

## Methods

We identified clinical practice guidelines (CPGs)/consensus statements through searches of four electronic databases, and hand-searching of websites/reference lists. Two reviewers independently assessed reports for eligibility. We extracted data on report characteristics and recommendations relating to etiologic workup in acute ischemic stroke, and in cases of cryptogenic stroke. Quality was assessed using the AGREE II tool (Appraisal of Guidelines for Research & Evaluation). Recommendations were synthesised according to a published algorithm for diagnostic evaluation in cryptogenic stroke.

## Results

We retrieved sixteen CPGs and seven consensus statements addressing acute stroke management (n=12), atrial fibrillation (n=5), imaging (n=5), and secondary prevention (n=1). Five reports were of overall high quality. For all patients, guidelines recommended routine brain imaging, non-invasive vascular imaging, a 12-lead electrocardiogram (ECG), and routine blood tests/laboratory investigations. Additionally, ECG monitoring (>24 hours) was recommended for patients with suspected embolic stroke, and echocardiography for patients with suspected cardiac source. Three reports recommended investigations for rarer causes of stroke. None of the reports provided guidance on the extent of investigation needed prior to classifying a stroke as ‘cryptogenic’.

## Conclusions

While consensus exists surrounding ‘standard’ etiologic workup, there is little agreement on more advanced investigations for rarer causes of acute ischemic stroke. This gap in guidance, and in the underpinning evidence, demonstrates missed opportunities to better understand and protect against ongoing stroke risk.

## Systematic review registration

PROSPERO Registration: <https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=127822>; Unique Identifier: CRD42019127822

# Introduction

In at least one third of acute ischemic strokes, investigative protocols fail to establish the exact etiology1, 2. Etiologic workup in such cases of ‘cryptogenic’ stroke, or stroke of unknown origin, is complicated by the varied emphasis of clinicians on establishing underlying cause due to the lack of evidence-based secondary prevention strategies3-5, and variable availability of different investigative techniques. Recent efforts to facilitate trials of secondary prevention strategies have resulted in the development of the ESUS construct (‘embolic stroke of unknown source’), which describes the subgroup of non-lacunar cryptogenic ischemic strokes in which embolism is considered the likely mechanism6. Two trials of non-vitamin K antagonist oral anticoagulants (NOACs) in ESUS populations however failed to show a reduction in recurrent stroke when compared to aspirin7, 8, with one trial showing possible harm with an excess of bleeding7. This may be due to unidentified heterogeneity even within the ESUS subgroup, resulting in the inclusion of patients who were unlikely to benefit from anticoagulation as a secondary prevention strategy9. These trials have demonstrated that one size does not fit all and further highlighted the importance of systematic and evidence-based investigation of cryptogenic stroke to facilitate the development and implementation of personalised secondary prevention strategies. In this review, we employ Saver’s (2016)10 algorithm for etiologic workup in cryptogenic stroke to systematically assess the extent to which there exists consensus, disagreement, and gaps in clinical practice recommendations on etiologic workup in acute ischemic stroke. The review findings highlight priorities for future research to inform more standardised approaches to evaluating cryptogenic stroke.

# Methods

The review was designed in accordance with the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) guidance. A PRISMA checklist is provided in Appendix A in the online supplement (please see <https://www.ahajournals.org/journal/str>). The protocol was prospectively registered on PROSPERO: CRD42019127822.

## Eligibility criteria

Clinical practice guidelines (CPGs) were included if they: (i) were endorsed by a national and/or international organisation (e.g. governmental, charitable, professional practice), (ii) included recommendations about etiologic workup in acute ischemic stroke, (iii) were published from January 2009 onwards (to ensure only the most up-to-date guidelines were included), and (iv) were available in English. During our searches, we also identified scientific statements and consensus documents. Although these reports used less robust methods to search for and synthesise the underpinning evidence, the content was sufficiently relevant to the objectives of the review to merit inclusion. For transparency, recommendations from these publications are presented separately throughout.

## Search strategy and guideline selection

We searched four electronic databases (MEDLINE, Health Management Information Consortium (HMIC), Embase, and CINAHL) from their inception to the 4th of March 2019 using a combination of Medical Subject Headings and keywords. As CPGs are often not indexed by electronic databases, we also systematically searched for guidelines on relevant websites including, but not limited to, the Guidelines International Network ([www.g-i-n.net](http://www.g-i-n.net)); The American Academy of Neurology ([www.aan.com/](http://www.aan.com/)); The World Stroke Organisation ([www.world-stroke.org](http://www.world-stroke.org)); and Open Grey ([www.opengrey.eu/](http://www.opengrey.eu/)). Additionally, we reviewed the reference lists of included CPGs to identify relevant guidelines. The final list of CPGs/consensus statements was reviewed by all authors to confirm that no relevant documents, of which the team were already aware, had been omitted. The complete search strategy is provided in Appendix B in the online supplement, (please see <https://www.ahajournals.org/journal/str>). Two reviewers (NMcM/MB) independently screened all retrieved citations for eligibility. Full texts of potentially relevant citations were obtained and independently assessed by both reviewers. Uncertainty was resolved through discussions with the review group.

## Data collection and quality appraisal

A bespoke data extraction form was piloted prior to being finalised. For each guideline, one reviewer extracted all relevant information using this form which was then fully checked by a second reviewer for completeness and accuracy. We extracted the following information: authors; organisation; year of publication; country/region; development approach, evidence-assessment scales, and approach to producing recommendations; funding and disclosures; any content relating to the level of etiologic workup required in acute ischemic stroke. Relevant supplementary material cited in the guidelines was also retrieved and used to inform data extraction and quality appraisal.

The Appraisal of Guidelines Research and Evaluation II11 (AGREE II) tool was used to assess and illustrate the quality of the included publications. This tool includes six quality domains: scope and purpose; stakeholder involvement; rigor of development; clarity and presentation; applicability; and editorial independence. Each guideline was independently assessed by four appraisers from the review team (NMcM/MB/EB/JG/RG/VB/DL) and a quality score calculated for each domain as per the AGREE II formula.12 In line with similar reviews, we assessed agreement for each domain item and collectively reviewed items where appraisers scores were >1.5 standard deviations (SD) from the mean item score13. A domain was considered to be adequately addressed if scoring ≥60%13-16. The data extraction and quality appraisal forms are provided in Appendix C in the online supplement, (please see <https://www.ahajournals.org/journal/str>).

## Synthesis

All recommendations describing etiologic workup in acute ischemic stroke were collated in a spreadsheet and synthesised according to Saver’s (2016) algorithm for etiologic workup in cryptogenic stroke10. Additional informal commentary was similarly collated in a spreadsheet and content analysis performed. These stages of refining and synthesising the data were regularly discussed with the review team, particularly practising clinicians, to determine the consistency and appropriateness of the process and decision-making.

# Results

The electronic search strategy retrieved a total of 8442 citations. After the removal of duplicates and pre-2009 publications, 4566 were screened on title and abstract. We assessed 124 full texts for eligibility, of which 23 were included in the review (Figure 1. PRISMA flow diagram). A full list of excluded records with reasons is provided in Appendix D in the online supplement, (please see <https://www.ahajournals.org/journal/str>).

<Insert Figure 1. PRISMA flow diagram about here>

## Characteristics and quality of the included guidelines/statements

An overview of the included guidelines/statements is provided in Table 1.

<Insert Table 1 about here>

There were sixteen clinical practice guidelines17-32, and seven organisational statements or consensus documents33-39. Most publications came from American (n=5)18, 23, 35, 38, 39, European (n=3)25, 33, 36, 37, Canadian (n=3)19, 20, 27, and British organisations (n=3)17, 24, 28. Topics included acute stroke management (n=12)17-19, 22, 24, 26, 29-32, 34, 38, atrial fibrillation and tachyarrhythmias (n=5)21, 25, 27, 28, 33, imaging in acute stroke (n=5)23, 35-37, 39, and secondary prevention (n=1)20. Just under half (n=11) were published from 2016 onwards17-26, 33. Two guidelines disclosed industry support in the production of the guidelines30, 31.

The mean quality appraisal scores of four reviewers for each domain of the AGREE II are shown in Table 2, where green indicates domains which were adequately addressed (i.e. ≥60%). For completeness, we also appraised the included consensus statements, which, as expected, scored less favourably than the CPGs. Almost all documents adequately addressed Domain 4 (clarity of presentation), which was the highest scoring domain followed by Domain 1 (scope & purpose). Applicability (Domain 5) scored most poorly, with this domain also noted to have the poorest agreement across raters. Five reports were of high quality overall, scoring ≥ 60% across all five domains17, 19, 20, 22, 28.

<Insert Table 2 about here

## Establishing stroke etiology

Of the guidelines/statements specific to acute stroke management (n=12), seven explicitly highlighted the importance of establishing stroke etiology19, 22, 24, 30-32, 34 (Table I in the online supplement, <https://www.ahajournals.org/journal/str>). Two made recommendations on additional investigations to be performed for ESUS patients19, 22, with a further four reports providing recommendations on tests which should be considered in selected patients where cause has not been established through standard workup24, 30, 31, 34.

Reflective of Saver’s algorithm10, we organised recommendations into six categories of investigation: (i) brain imaging, (ii) vascular imaging, (iii) cardiac rhythm, (iv) cardiac structure, (v) laboratory and (vi) other investigations (Table 3). Full details of all guideline recommendations with respect to these six categories of investigationsare provided in Tables II-VII in the online supplement, please see <https://www.ahajournals.org/journal/str>), whilst a summary of the recommendations for diagnostic workup in acute ischemic stroke can be found in Table 3. For reference purposes, the different evidence assessment scales, and class of recommendations used in the included guidelines can also be found in Appendix E. For all patients with suspected acute stroke, guidelines recommend that they routinely undergo brain imaging, non-invasive vascular imaging, a 12-lead ECG, and routine blood tests/laboratory investigations. Recommendations on additional investigations included ECG monitoring for more than 24-hours for patients being investigated for embolic stroke (extended if atrial fibrillation is not detected but a cardioembolic source is suspected), and echocardiography for patients where etiology has not been established but a cardiac source is suspected. Three guidelines provided recommendations of further investigations for more unusual causes of stroke. These investigations included serology for Chagas’ disease and syphilis29, and, in younger people specifically, evaluation of autoimmune diseases, prothrombotic states (e.g. antiphospholipid syndrome)24, 29, Fabry disease24, and thrombophilia26, 29.

< Insert Table 3 about here>

While cryptogenic stroke was often discussed in the context of established classification systems (notably TOAST21, 23, 25-27, 37), none of the included guidelines/statements went beyond the TOAST categories to specifically identify when a stroke should be classified as cryptogenic (Tables VIII in the online supplement, please see <https://www.ahajournals.org/journal/str>). More recently published guidelines using the ESUS construct included recommendations on prolonged cardiac monitoring, but lacked guidance on investigating other stroke mechanisms, and the extent to which investigation which should be undertaken to establish stroke cause.

# Discussion

We have presented a systematic assessment of recommendations from international CPGs and consensus statements detailing etiologic workup in acute ischemic stroke. The review demonstrates that clear consensus exists on investigations which should be routinely performed for all acute ischemic stroke patients (‘standard evaluation’10), but highlights the lack of consistency and detail on additional investigations for patients in whom a cause is not identified through standard evaluation. While recently published high quality guidelines employing the ESUS construct included recommendations for advanced evaluation focusing on prolonged ECG monitoring (i.e. > 24hours), they do not yet provide guidance on the optimum or desired duration of monitoring. Indeed, the most recent update of the American Heart Association/American Stroke Association Guidelines for the Early Management of Acute Ischemic Stroke, published following the completion of this review, further reiterate that the effectiveness of prolonged cardiac monitoring for the purposes of guiding secondary prevention remains uncertain40. Additionally, as ESUS represents only a subgroup of cryptogenic stroke, guidance is still lacking for those patients where the stroke mechanism is not embolic. Indeed, consideration of more unusual causes of stroke was limited to just three reports, all of which were published in 2016 or earlier 24, 26, 29. It was therefore not possible to identify a standardised evaluation approach from current guidelines, suggesting that practice variability in investigating cryptogenic stroke is inevitable. Practice variability is likely to be further compounded by the limited attention paid to the applicability of recommendations across included reports, a limitation of CPGs often highlighted in published reviews13, 14.

This review has highlighted the need for well-designed primary research to identify an optimal pathway to expedite the identification of rare and very rare stroke etiologies in a timely and cost-effective manner. A significant challenge to further clinically-based research is however the rarity of these causes. Additionally, as treating healthcare professionals are deeply engaged in dealing with the consequences of the current stroke, advanced etiologic workup often takes a back seat. While the TOAST classification acts as a useful starting point, it is evident that further research is needed to underpin and guide investigation in clinical practice. However, due to the lack of individualized secondary prevention strategies, such research should include economic analysis to compare the costs, risks and benefits of less or more exhaustive approaches, while also exploring variation in stroke subtype by race and ethnicity, along with genetic differences. Importantly, the perspectives of stroke survivors and family members are paramount and should guide future research and implementation, enabling a personalised approach for each individual based not only on their clinical presentation, but also on their values, needs and preferences.

# Conclusion

Current clinical practice guidelines on the etiologic workup of acute ischemic stroke are of variable quality, but largely reach consensus about appropriate ‘standard’ investigations. There is, however, little agreement and a lack of underpinning evidence for more advanced or specialised investigations for rarer causes of stroke. This lack of evidence and consensus, along with poor applicability of many of the existing guidelines, is likely to contribute to variability of access to investigations, inappropriate use of costly and specialised resources and skills, along with delays or lack of diagnosis of etiologies. Unless addressed, this gap in knowledge will continue to result in missed opportunities to identify and implement necessary secondary prevention measures and provide high quality clinical and psychological advice and support to stroke survivors and their families in relation to ongoing stroke risk.

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# Tables

## Table 1. Characteristics of included guidelines and consensus statements

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Country/ region** | **Organisation** | **Lead author (year)** | **Title** | **Development approach** |
| **Clinical practice guidelines** | | | | |
| UK | National Institute for Health and Care Excellence | n/a (2019)17 | Stroke and transient ischaemic attack in over 16s: diagnosis and initial management (NG128) | Systematic search.  GRADE framework. |
| USA | American Heart Association/ American Stroke Association | Powers (2018)18 | 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association | Systematic search. |
| Canada | Acute Stroke Management Best Practice Writing Group, and the Canadian Stroke Best Practices and Quality Advisory Committees; in collaboration with the Canadian Stroke Consortium and the Canadian Association of Emergency Physicians | Boulanger (2018)19 | Canadian Stroke Best Practice Recommendations for Acute Stroke Management: Prehospital, Emergency Department, and Acute Inpatient Stroke Care, 6th Edition, Update 2018 | Systematic search .  Framework adapted from the Practice Guideline Evaluation and Adaptation Cycle. |
| Canada | Heart and Stroke Foundation Canadian Stroke Best Practice Committees | Wein (2018)20 | Canadian stroke best practice recommendations: Secondary prevention of stroke, sixth edition practice guidelines, update 2017 | Systematic search.  Framework adapted from the Practice Guideline Evaluation and Adaptation Cycle. |
| Korea | Korean Heart Rhythm Society (KHRS) Committee | Joung (2018)21 | 2018 Korean Guideline of Atrial Fibrillation Management | Systematic search.  Based on recent data of the Korean population and the recent guidelines of the European Society of Cardiology, European Association for Cardio-Thoracic Surgery, American Heart Association, and Asia Pacific Heart Rhythm Society. |
| Australia | Stroke Foundation/ Australian Department of Health | n/a (2017)22 | Clinical Guidelines for Stroke Management 2017 | Systematic search.  GRADE framework. |
| USA | American Society of Echocardiography (ASE) | Saric (2016)23 | Guidelines for the Use of Echocardiography in the Evaluation of a Cardiac Source of Embolism | Based on an extensive literature review including all other relevant guidelines from the ASE and other national and international medical societies. |
| UK | Royal College of Physicians | Intercollegiate Stroke Working Party (2016)24 | National Clinical Guideline for Stroke | Systematic search. |
| Europe | European Society of Cardiology | Kirchhof (2016)25 | 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS | Based on a comprehensive review of the published evidence for management (including diagnosis, treatment, prevention and rehabilitation) of a given condition. |
| Qatar | Ministry of Public Health | n/a (2016)26 | Clinical Guidelines for the State of Qatar: The diagnosis and management of Stroke and transient ischemic attack | Systematic search. |
| Canada | Canadian Cardiovascular Society | Verma (2014)27 | 2014 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation | Based on a thorough consideration of medical literature and the best available evidence and clinical experience. |
| UK | National Institute for Health and Care Excellence | n/a (2014)28 | Atrial fibrillation: management (CG180) | Systematic search.  GRADE framework. |
| Brazil | Brazilian Academy of Neurology | Oliveira-Filho (2012)29 | Guidelines for acute ischemic stroke treatment - part I | Members from Brazilian stroke society participated in web-based discussion forum with pre-defined themes, followed by a formal onsite meeting. |
| Malaysia | Ministry of Health Malaysia, Academy of Medicine Malaysia, Malaysian Society of Neurosciences | n/a (2012)30 | Management Of Ischaemic Stroke (2nd Edition) | A standard methodology based on a systematic review of current evidence was used to look at the literature. |
| South Africa | South African Stroke Society (SASS) and the SASS Writing Committee | Bryer (2010)31 | South African guideline for management of ischaemic stroke and transient ischaemic attack 2010: a guideline from the South African Stroke Society (SASS) and the SASS Writing Committee. | Authors were nominated by consensus to write chapters of the Guideline. Submissions were first discussed in a meeting of the Stroke Guideline Writing Committee. |
| Singapore | Ministry of Health | n/a (2009)32 | Stroke and Transient Ischaemic Attacks. Assessment, Investigation, Immediate Management and Secondary Prevention. | Based on the Scottish Intercollegiate Guidelines Network’s Clinical Practice Guidelines on the Management of Patients with Stroke. These guidelines were reviewed and modified to meet local needs. |
| **Scientific statements and consensus documents** | | | | |
| Europe | European Heart Rhythm Association | Gorenek (2017)33 | Device-detected subclinical atrial tachyarrhythmias: definition, implications and management—an European Heart Rhythm Association (EHRA) consensus document, endorsed by Heart RhythmSociety (HRS), Asia Pacific Heart Rhythm Society (APHRS) and Sociedad Latinoamericana de Estimulacióín Cardíaca y Electrofisiología (SOLEACE) | This is evidence-based, and derived primarily from published data. |
| India | Indian Stroke Association | Prasad (2014)34 | Recommendations for the Early Management of Acute Ischemic Stroke: A Consensus Statement for Healthcare Professionals from the Indian Stroke Association | Systematic literature reviews, clinical and epidemiology study publications, and clinical and public health guidelines were used to summarize the existing evidence and indicate gaps in the current knowledge and, when appropriate, formulate the recommendations. |
| USA | American Society of Neuroradiology | Wintermark (2013)35 | Imaging Recommendations for Acute Stroke and Transient Ischemic Attack Patients: A Joint Statement by the American Society of Neuroradiology, the American College of Radiology and the Society of NeuroInterventional Surgery | Based on a review of the evidence in the literature on the utility of various imaging techniques in acute stroke and TIA patients. |
| Europe | European Federation of Neurological Societies – | Irimia (2011)36 | Use of imaging in cerebrovascular disease | A comprehensive literature review using the MEDLINE database search the period 1965 – 2009. Relevant literature in English, including existing guidelines, meta-analyses, systematic reviews, randomized controlled trials, and observational studies have been critically assessed. |
| Europe | European Association of Echocardiography (EAE) | Pepi (2010)37 | Recommendations for echocardiography use in the diagnosis and management of cardiac sources of embolism | Based on a literature review conducted using Medline (PubMed) for peer-reviewed publications and focuses on the studies published mainly in the last 10 years. |
| USA | American Heart Association | Summers (2009)38 | Comprehensive Overview of Nursing and Interdisciplinary Care of the Acute Ischemic Stroke Patient: A Scientific Statement From the American Heart Association | No systematic search reported |
| USA | American Heart Association | Latchaw (2009)39 | Recommendations for Imaging of Acute Ischemic Stroke: A Scientific Statement From the American Heart Association | The review has been confined to literature in English and includes all relevant articles but focuses on the literature from 2000 to 2006, with some more recent. |

EACTS: European Association for Cardio-Thoracic Surgery

GRADE: Grading of Recommendations Assessment, Development and Evaluation

TIA: Transient Ischaemic Attack

## Table 2. AGREE II appraisal of included studies (Domain adequately addressed if green: ≥60%)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Guideline** | **Domain 1: Scope & Purpose** | **Domain 2: Stakeholder involvement** | **Domain 3: Rigour of development** | **Domain 4: Clarity of presentation** | **Domain 5: Applicability** | **Domain 6: Editorial independence** |
| **Clinical practice guidelines** | | | | | | |
| National Institute for Health and Care Excellence (2019)17 | 88 | 99 | 90 | 86 | 78 | 77 |
| Powers (2018)18 | 88 | 50 | 74 | 99 | 25 | 52 |
| Boulanger (2018)19 | 74 | 94 | 70 | 90 | 74 | 92 |
| Wein (2018)20 | 60 | 90 | 71 | 69 | 71 | 85 |
| Joung (2018)21 | 56 | 11 | 32 | 81 | 9 | 56 |
| Stroke Foundation/Australian Department of Health (2017)22 | 100 | 94 | 91 | 93 | 81 | 100 |
| Saric (2016)23 | 71 | 15 | 24 | 63 | 9 | 38 |
| Intercollegiate Stroke Working Party (2016)24 | 86 | 67 | 60 | 88 | 57 | 94 |
| Kirchhof (2016)25 | 58 | 33 | 67 | 89 | 33 | 65 |
| Ministry of Public Health (2016) [Qatar]26 | 65 | 49 | 31 | 81 | 8 | 73 |
| Verma (2014)27 | 50 | 42 | 10 | 82 | 35 | 40 |
| National Institute for Health and Care Excellence (2014)28 | 88 | 94 | 91 | 89 | 90 | 79 |
| Oliveira-Filho (2012)29 | 43 | 26 | 9 | 57 | 7 | 17 |
| Ministry of Health Malaysia, Academy of Medicine Malaysia, Malaysian Society of Neurosciences (2012)30 | 94 | 56 | 41 | 89 | 61 | 23 |
| Bryer (2010)31 | 50 | 47 | 28 | 83 | 53 | 73 |
| Ministry of Health (2009) [Singapore]32 | 60 | 69 | 20 | 83 | 20 | 4 |
| **Scientific statements and consensus documents** | | | | | | |
| Gorenek (2017)33 | 65 | 32 | 31 | 85 | 15 | 52 |
| Prasad (2014)34 | 72 | 32 | 9 | 75 | 23 | 8 |
| Wintermark (2013)35 | 54 | 11 | 13 | 54 | 32 | 6 |
| Irimia (2011)36 | 75 | 44 | 38 | 76 | 13 | 31 |
| Pepi (2010)37 | 65 | 4 | 30 | 79 | 9 | 21 |
| Summers (2009)38 | 50 | 32 | 20 | 85 | 13 | 46 |
| Latchaw (2009)39 | 60 | 8 | 38 | 75 | 13 | 46 |

≥60% shown in green

**Table 3. Overview of recommendations for diagnostic workup in acute ischemic stroke**

|  |  |  |
| --- | --- | --- |
| **Type of investigation** | **Patient group** | **Investigative technique** |
| Brain imaging | All patients | Non-contrast CT as soon as possible  MRI is superior to CT scan in terms of diagnostic sensitivity and identifying the etiology of the stroke |
| Vascular imaging | All patients (and especially those who are potentially eligible for endovascular treatment) | CTA or MRA from aortic arch to vertex  Or doppler ultrasound, or carotid duplex ultrasound  TCD is the only imaging technique that allows detection of circulating emboli |
| Cardiac rhythm  Cardiac rhythm  Cardiac rhythm | All patients  For patients being investigated for an acute embolic ischemic stroke or TIA  For patients being investigated for an acute embolic ischemic stroke or TIA of undetermined source whose initial short-term ECG monitoring does not reveal atrial fibrillation but a cardioembolic mechanism is suspected | 12-lead ECG  24-hour ECG monitoring  Prolonged ECG monitoring (at least two weeks19, 20; undetermined length21, 22, 24, 25, 27) |
| Cardiac structure | For patients where a stroke mechanism has not been identified and a cardiac source is suspected | Echocardiography (2D or transesophageal) |
| Laboratory and other investigations | All patients  Young patients | Hematology (complete blood count)  Electrolytes  Coagulation (aPTT, INR)  Renal function (creatinine, e-glomerular filtration rate)  Random glucose  Troponin  Evaluation of autoimmune diseases, arteritis, homocysteine levels, coagulopathy, screening for thrombophilia and genetic profile24, 26, 29 |

aPTT: activated partial thromboplastin time

CT: computerised tomography

CTA: computed tomography angiography

ECG: electrocardiogram

INR: international normalized ratio

MRA: magnetic resonance angiography

TCD: transcranial doppler

TIA: transient ischemic attack