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Etiologic Workup in Cases of Cryptogenic Stroke
A Systematic Review of International Clinical Practice Guidelines

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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/consensus statements through searches of 4 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 synthesized according to a published algorithm for diagnostic evaluation in cryptogenic stroke.

Results—We retrieved 16 clinical practice guidelines and 7 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, noninvasive vascular imaging, a 12-lead 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 before 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.

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Key Words: atrial fibrillation ■ diagnosis ■ neuroimaging ■ secondary prevention ■ stroke

In at least one third of acute ischemic strokes, investigative protocols fail to establish the exact etiology.[1,2] 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 because of the lack of evidence-based secondary prevention strategies[3–5] and variable availability of different investigative techniques. Recent efforts to facilitate trials of secondary prevention strategies have resulted in the development of the embolic strokes of undetermined source construct (ESUS), which describes the subgroup of nonlacunar cryptogenic ischemic strokes in which embolism is considered the likely mechanism.[6] Two trials of non–vitamin K antagonist oral anticoagulants in ESUS populations however failed to show a reduction in recurrent stroke when compared with aspirin,[7,8] with one trial showing possible harm with an excess of bleeding.[7] This may be because

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of unidentified heterogeneity even within the ESUS subgroup, resulting in the inclusion of patients who were unlikely to benefit from anticoagulation as a secondary prevention strategy.[9] 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 personalized secondary prevention strategies. In this review, we use Saver's[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 standardized approaches to evaluating cryptogenic stroke.

Methods

The review was designed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis guidance. A Preferred Reporting Items for Systematic Review and Meta-Analysis checklist is provided in Appendix A in the Data Supplement. The protocol was prospectively registered on PROSPERO: CRD42019127822.

Eligibility Criteria

Clinical practice guidelines (CPGs) were included if they (1) were endorsed by a national and/or international organization (eg, governmental, charitable, professional practice), (2) included recommendations about etiologic workup in acute ischemic stroke, (3) were published from January 2009 onwards (to ensure only the most up-to-date guidelines were included), and (4) 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 synthesize 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 4 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); The American Academy of Neurology (www.aan.com/); The World Stroke Organisation (www.world-stroke.org); and Open Grey (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 Data Supplement. Two reviewers (Drs McMahon and Bangee) 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 before being finalized. 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; organization; 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 AGREE II tool (Appraisal of Guidelines for Research and Evaluation II[11]) was used to assess and illustrate the quality of the included publications. This tool includes 6 quality domains: scope and purpose; stakeholder involvement; rigor of development; clarity and presentation; applicability; and editorial independence. Each guideline was independently assessed by 4 appraisers from the review team (Dr McMahon, Dr Bangee, Dr Bray, Dr Gibson, R.F. Georgiou, Dr Benedetto, Dr Lane) 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 SD from the mean item score.[13] A domain was considered to be adequately addressed if scoring was ≥60%.[13–16] The data extraction and quality appraisal forms are provided in Appendix C in the Data Supplement.

Synthesis

All recommendations describing etiologic workup in acute ischemic stroke were collated in a spreadsheet and synthesized according to Saver's[10] algorithm for etiologic workup in cryptogenic stroke. Additional informal commentary was similarly collated in a spreadsheet and content analysis performed. These stages of refining and synthesizing 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 114 full texts for eligibility, of which 23 were included in the review (Figure). A full list of excluded records with reasons is provided in Appendix D in the Data Supplement.

Characteristics and Quality of the Included Guidelines/Statements

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

There were 16 CPGs[17–32] and 7 organizational statements or consensus documents.[33–39] 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 organizations (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 onwards.[17–26,33] Two guidelines disclosed industry support in the production of the guidelines.[30,31]

The mean quality appraisal scores of 4 reviewers for each domain of the AGREE II are shown in Table 2, where green indicates domains which were adequately addressed (ie, ≥60%). For completeness, we also appraised the included consensus statements, which, as expected, scored less favorably than the CPGs. Almost all documents adequately addressed Domain 4 (clarity of presentation), which was the highest scoring domain followed by Domain 1 (scope and 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 5 domains.[17,19,20,22,28]

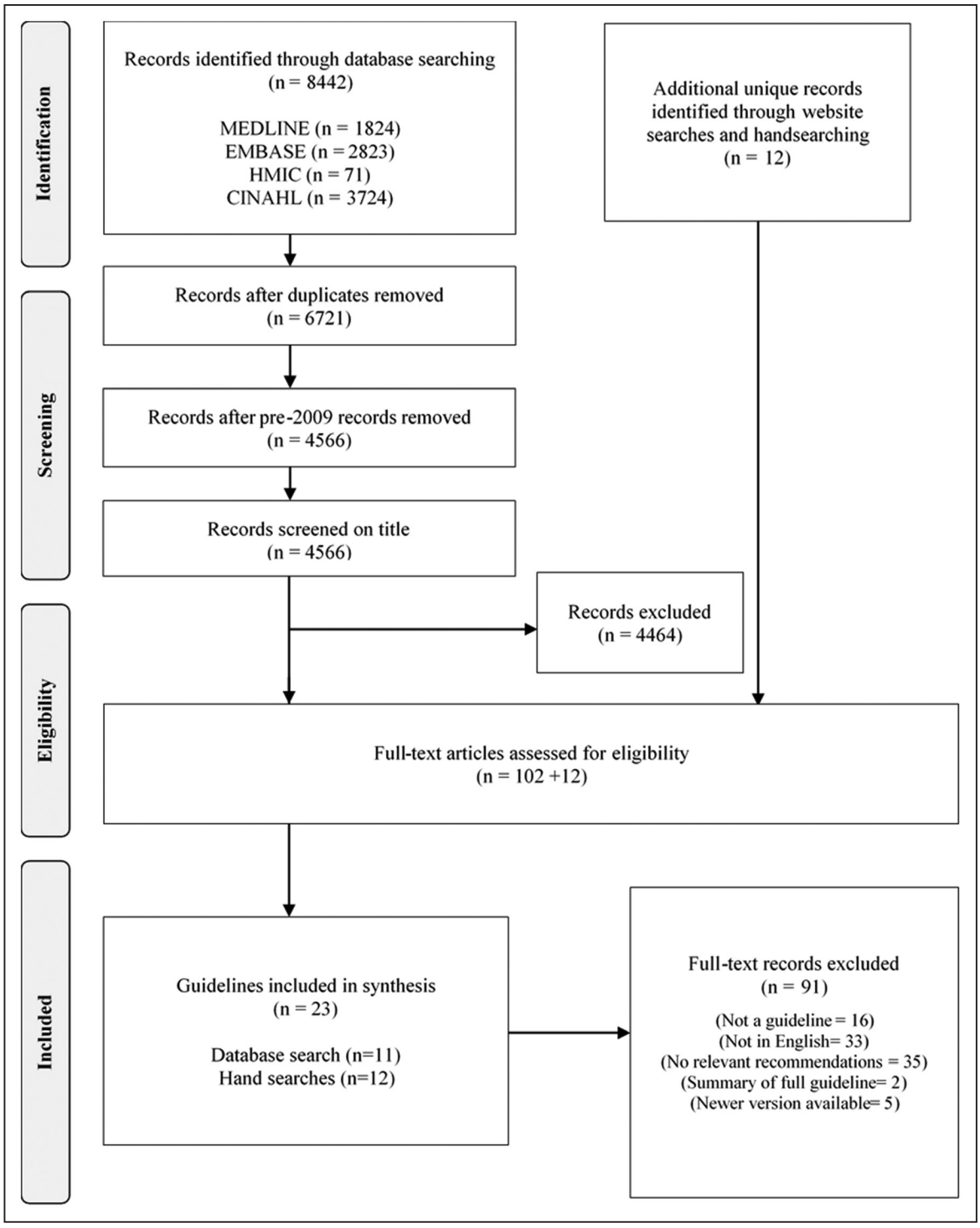

Figure. PRISMA flow diagram. HMIC indicates Health Management Information Consortium.

Establishing Stroke Etiology

Of the guidelines/statements specific to acute stroke management (n=12), 7 explicitly highlighted the importance of establishing stroke etiology[19,22,24,30–32,34] (Table I in the Data Supplement). Two made recommendations on additional investigations to be performed for ESUS patients,[19,22] with a further 4 reports providing recommendations on tests that should be considered in selected patients where cause has not been established through standard workup.[24,30,31,34]

Reflective of Saver's algorithm,[10] we organized recommendations into 6 categories of investigation: (1) brain imaging, (2) vascular imaging, (3) cardiac rhythm, (4) cardiac structure, (5) laboratory, and (6) other investigations (Table 3). Full details of all guideline recommendations with respect to these 6 categories of investigations are provided in Tables II through VII in the Data Supplement, while a summary of the recommendations for diagnostic workup in acute ischemic stroke can be found in Table 3. For reference purposes, the

Table 1. Characteristics of Included Guidelines and Consensus Statements

Country/Region	Organization	Lead Author (Year)	Title	Development Approach
Clinical practice guidelines				
United Kingdom	National Institute for Health and Care Excellence	National Institute for Health and Care Excellence (2019)[17]	Stroke and transient ischemic attack in over 16s: diagnosis and initial management (NG128)	Systematic search GRADE framework
United States	American Heart Association/American Stroke Association	Powers et al (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 et al (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 et al (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 et al (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	Stroke Foundation (2017)[22]	Clinical Guidelines for Stroke Management 2017	Systematic search GRADE framework
United States	American Society of Echocardiography (ASE)	Saric et al (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
United Kingdom	Royal College of Physicians	Intercollegiate Stroke Working Party (2016)[24]	National Clinical Guideline for Stroke	Systematic search
Europe	European Society of Cardiology	Kirchhof et al (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	Ministry of Public Health (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 et al (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
United Kingdom	National Institute for Health and Care Excellence	National Institute for Health and Care Excellence (2014)[28]	Atrial fibrillation: management (CG180)	Systematic search GRADE framework

(*Continued*)

Table 1. Continued

Country/Region	Organization	Lead Author (Year)	Title	Development Approach
Brazil	Brazilian Academy of Neurology	Oliveira-Filho et al (2012)[29]	Guidelines for Acute Ischemic Stroke Treatment—Part I	Members from Brazilian Stroke Society participated in web-based discussion forum with predefined themes, followed by a formal onsite meeting
Malaysia	Ministry of Health Malaysia, Academy of Medicine Malaysia, Malaysian Society of Neurosciences	Malaysian Society of Neurosciences (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 et al (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	Ministry of Health. Stroke and Transient Ischaemic Attacks Assessment, Investigation, Immediate Management and Secondary Prevention (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 et al (2017)[33]	Device-detected subclinical atrial tachyarrhythmias: definition, implications and management—an European Heart Rhythm Association (EHRA) consensus document, endorsed by Heart Rhythm Society (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 et al (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
United States	American Society of Neuroradiology	Wintermark et al (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 et al (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

(*Continued*)

Table 1. Continued

Country/Region	Organization	Lead Author (Year)	Title	Development Approach
Europe	European Association of Echocardiography (EAE)	Pepi et al (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 y
United States	American Heart Association	Summers et al (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
United States	American Heart Association	Latchaw et al (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 2000–2006, with some more recent

GRADE indicates Grading of Recommendations Assessment, Development and Evaluation; EACTS, European Association for Cardio-Thoracic Surgery; and TIA, transient ischemic attack.

different evidence assessment scales and class of recommendations used in the included guidelines can also be found in Appendix E in the Data Supplement. For all patients with suspected acute stroke, guidelines recommend that they routinely undergo brain imaging, noninvasive vascular imaging, a 12-lead ECG, and routine blood tests/laboratory investigations. Recommendations on additional investigations included ECG monitoring for >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 syphilis[29] and, in younger people specifically, evaluation of autoimmune diseases, prothrombotic states (eg, antiphospholipid syndrome),[24,29] Fabry disease,[24] and thrombophilia.[26,29]

While cryptogenic stroke was often discussed in the context of established classification systems (notably TOAST [Trial of ORG 10172 in Acute Stroke Treatment][21,23,25–27,37]), 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 Data Supplement). 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 investigations 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 using the ESUS construct included recommendations for advanced evaluation focusing on prolonged ECG monitoring (ie, >24 hours), 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 reiterates that the effectiveness of prolonged cardiac monitoring for the purposes of guiding secondary prevention remains uncertain.[40] 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 3 reports, all of which were published in 2016 or earlier.[24,26,29] It was therefore not possible to identify a standardized 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 reviews.[13,14]

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, because of 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

Table 2. AGREE II Appraisal of Included Studies

Guideline	Domain 1: Scope and Purpose	Domain 2: Stakeholder Involvement	Domain 3: Rigor 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 et al (2018)[18]	88	50	74	99	25	52
Boulanger et al (2018)[19]	74	94	70	90	74	92
Wein et al (2018)[20]	60	90	71	69	71	85
Joung et al (2018)[21]	56	11	32	81	9	56
Stroke Foundation/Australian Department of Health (2017)[22]	100	94	91	93	81	100
Saric et al (2016)[23]	71	15	24	63	9	38
Intercollegiate Stroke Working Party (2016)[24]	86	67	60	88	57	94
Kirchhof et al (2016)[25]	58	33	67	89	33	65
Ministry of Public Health (2016) [Qatar][26]	65	49	31	81	8	73
Verma et al (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 et al (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 et al (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 et al (2017)[33]	65	32	31	85	15	52
Prasad et al (2014)[34]	72	32	9	75	23	8
Wintermark et al (2013)[35]	54	11	13	54	32	6
Irimia et al (2011)[36]	75	44	38	76	13	31
Pepi et al (2010)[37]	65	4	30	79	9	21
Summers et al (2009)[38]	50	32	20	85	13	46
Latchaw et al (2009)[39]	60	8	38	75	13	46

Domain adequately addressed if ≥60%. AGREE II indicates Appraisal of Guidelines for Research and Evaluation II.

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 personalized approach for each individual based not only on their clinical presentation but also on their values, needs, and preferences.

Conclusions

Current CPGs 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 specialized 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 specialized 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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Table 3. Overview of Recommendations for Diagnostic Workup in Acute Ischemic Stroke

Type of Investigation	Patient Group	Investigative Technique
Brain imaging	All patients	Noncontrast 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	All patients	12-lead ECG
Cardiac rhythm	For patients being investigated for an acute embolic ischemic stroke or TIA	24-hour ECG monitoring
Cardiac rhythm	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	Prolonged ECG monitoring (at least 2 weeks[19,20]; undetermined length[21,22,24,25,27])
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	Hematology (complete blood count)
	Young patients	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 profile[24,26,29]

2D indicates 2-dimensional; aPTT, activated partial thromboplastin time; CT, computerized tomography; CTA, computed tomography angiography; INR, international normalized ratio; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; TCD, transcranial doppler; and TIA, transient ischemic attack.

Ingelheim, and Daiichi-Sankyo. Dr Lip has Consulted for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo and has been a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally. Dr Al-Khalidi receives a salary from Medtronic Ltd, United Kingdom. The other authors report no conflicts.

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