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REVIEW

The Future of Ischemic Stroke Diagnosis and a Review of Underrecognized Ischemic Stroke Etiologies

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Abstract

Accurate ischemic stroke etiologic determination and diagnosis form the foundation of excellent cerebrovascular care as from it stems initiation of the appropriate secondary prevention strategy as well as appropriate patient education regarding specific risk factors for that subtype. Recurrent stroke rates are highest among those patients who receive an incorrect initial stroke diagnosis. Patient distrust and patient reported depression are also higher. The cause of the ischemic stroke also informs predicted patient outcomes and the anticipated recovery trajectory. Finally, determining the accurate cause of the ischemic stroke provides the patient the opportunity to enroll in appropriate research studies studying mechanism, or targeting treatment approaches for that particular disease process. Advances in ischemic stroke research, imaging techniques, biomarkers, and the ability to rapidly perform genetic sequencing over the past decade have shown that classifying patients into large etiologic buckets may not always be appropriate and may represent one reason why some patients are labeled as cryptogenic, or for whom an underlying etiology is never found. Aside from the more traditional stroke mechanisms, there is new research emerging regarding clinical findings that are not normative, but the contributions to ischemic stroke are unclear. In this article, we first review the essential steps to accurate ischemic stroke etiologic classification and then transition to a discussion of embolic stroke of undetermined source (ESUS) and other new entities that have been postulated as causal in ischemic stroke (i.e., genetics and subclinical atherosclerosis). We also discuss the limitations that are inherent in the current ischemic stroke diagnostic algorithms and finally review the most recent studies regarding more uncommon diagnoses and the future of stroke diagnostics and classification.

Keywords Ischemic stroke · Stroke diagnosis · Embolic stroke of unknown source · Stroke etiology

Stroke Diagnosis

The foundational components of an accurate stroke diagnosis still center around a patient history and physical exam. It usually follows a diagnostic battery of tests that enable safe and yet complete evaluation of vascular risk factors that are felt to likely be causal in a particular patient's case. Some tests are more routinely ordered in stroke care and may even comprise an electronic stroke admission order set, while others are more nuanced and either due to cost, or risk should not be ordered routinely on all patients.

The American Heart Association (AHA) 2021 guidelines describe a diagnostic algorithm and testing strategy that should take place immediately after a patient presents with stroke to assist with diagnosis [1]. After the initial decisions regarding acute reperfusion therapy are made, an electrocardiogram, an echocardiogram (update to the new guidelines), basic laboratory tests (complete blood panel, troponin, prothrombin time, partial thromboplastin time, hemoglobin A1C, creatinine, and a lipid panel), and vascular imaging with considerations for the location of the stroke (anterior versus posterior circulation) are recommended. Depending on the age of the patient and other medical risk factors, genetic stroke syndromes, infectious etiologies, and more advanced cardiac imaging or prolonged cardiac monitoring are recommended. The guidelines appropriately state that the diagnostic yield of certain tests, or how the stroke mechanism will be informed by the results of any one test, will vary based on the individual patient, citing the specific example of the low yield of hypercoagulable testing among those 50 years and older [2].

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Once testing results are obtained, the physician needs an algorithm by which to determine the importance of each result and how you place them in context of the known patient's stroke risk factors when determining causality. Various tools have been developed by which strokes are categorized, with the most familiar being the TOAST classification system [3]. Established in 1993, this system described stroke as secondary to large artery atherosclerosis, cardioembolism, small vessel occlusion (lacunar stroke), stroke of other determined etiology, and stroke of underdetermined etiology (cryptogenic) based on certain risk factors and imaging findings. Since then, the Causative Classification of Stroke System (CCS) [4] and the Atherosclerosis-SVD-Cardiac Causes-Other Causes-Dissection (ASCOD) algorithms [5, 6] attempt to even further characterize and subdivide stroke, with a hope of improving precision. The TOAST classification system attempts to assign a *single* cause of the stroke, while the CCS and ASCOD suggest what is the *most likely* cause of the stroke with increasing number of different stroke phenotypes described in the newer algorithms. The predictive validity of the etiologic stroke classification systems has been compared, with one group suggesting the CCS generated more distinct subtypes than TOAST or ASCOD [7]. The best diagnostic algorithms to date and in the future will be those that are easy to use, incorporate the newest evidence-based medicine, and are valid and reliable.

Regardless of what classification scheme is chosen by the physician, there is always going to be some degree of uncertainty when making a diagnosis. All diagnostic tests, even when correctly applied, have limits with regard to test-specific sensitivity and specificity, with a tradeoff between the two. In the TOAST classification system for example, a group that suggests more uncertainty is that of stroke of undetermined etiology category (i.e., cryptogenic) which includes those strokes for whom the etiology is truly unknown, those for whom a diagnostic algorithm is never completed, and those with more than two possible causes. In the ASCOD system, uncertainty is expressed by a grade of 2, which is assigned when a particular disease is present, but the causal link to stroke is uncertain.

Additionally, how to handle an individual risk factor that may span multiple stroke etiologies, or when two tests suggest competing diagnoses, is another important consideration. Among 16,954 participants in the National Institute of Neurological Disorders and Stroke (NINDS) Stroke Genetics Network Study, there was about a 50% discordance between the presence of a phenotypic characteristic (an abnormal test finding) and the causative subtype (ultimate cause determined after considering multiple aspects of the patient) of the stroke [8]. This emphasizes that identification of an abnormality in the workup of a stroke patient does not necessarily imply stroke causality and that there is extensive heterogeneity in the etiologic contributions to ischemic stroke. As a result, there has been an increasing desire and awareness of the potential importance of expanding the diagnostic algorithm for stroke, apart from the more traditional stroke mechanisms alone. There has been an emergence of new phenotypic descriptions, such as embolic stroke of undetermined source (ESUS) or the Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) for those with small vessel disease, which will help to move the field of stroke classification, and diagnosis into the second half of the twenty-first century [9, 10]. The overarching aim of this manuscript is to review the most up-to-date literature regarding the latest concepts in ischemic stroke diagnosis, particularly with regard to embolic stroke of unknown source, as well as review some of the less common causes of stroke that must be considered prior to labeling a patient cryptogenic, or cause unknown. While not a formal systematic review, the literature chosen as the foundation of this manuscript represents the latest science in each of the topic areas.

Embolic Stroke of Undetermined Source

As previously mentioned, patients with cryptogenic stroke may be labeled as such because they have a workup that was not completed, multiple causes to their stroke, or a stroke that is actually of unknown etiology in that the case is fully investigated and a cause is not found (Table 1). The landmark paper by Hart et al. in 2014 described an entity called embolic stroke of undetermined source (ESUS) which was defined as non-lacunar brain infarcts without proximal arterial stenosis or an apparent cardioembolic source [9]. Since that time, there have been more potential sources of ESUS described, with the largest proportion of ESUS-related emboli thought to arise from the heart [11, 12]. Subclinical atrial fibrillation, or covert atrial fibrillation, asymptomatic left ventricular disease, valvular heart disease, a patent foramen ovale, subclinical atherosclerotic plaques, and finally a state of atrial cardiopathy are all cardiac-related conditions that might contribute to ESUS [12–16]. Marantic endocarditis or embolic arising from cancer involving cardiac structures will be discussed in another section.

Atrial fibrillation is the number one cause of cardioembolic stroke, and subclinical atrial fibrillation is an important contributor to ESUS [17, 18]. Over the past 10 years, multiple studies have supported that the longer that you monitor a patient for atrial fibrillation, the more likely you are to detect AF with a reported hazard ratio for detection of AF in the implantable cardiac device group vs conventional monitoring of 7.3 reported in the CRYSTAL-AF trial over 12 months of monitoring [19]. Notably, the majority of AF episodes that were detected in CRYSTAL-AF were asymptomatic. The EMBRACE trial showed that ambulatory 30-day ECG monitoring improved the detection of subclinical AF

Table 1 Comparison of cryptogenic versus embolic stroke of unknown source diagnostic criteria

Stroke subtype	Definition
Stroke of undetermined etiology ("cryptogenic")	TOAST trial [3] • Two or more causes of ischemic stroke identified OR • Complete, negative evaluation OR • Incomplete evaluation of potential stroke causes
Embolic stroke of undetermined source (ESUS)	Ischemic stroke identified by cerebral imaging that is • Not lacunar (subcortical infarct in the distribution of a penetrating cerebral artery that is ≤ 1.5 cm on CT or ≤ 2 cm on MRI diffusion weighted image) • Without intracranial or extracranial atherosclerosis in the area of the stroke that is ≥ 50% luminal stenosis of the artery • Without a major cardioembolic source of embolism (i.e., atrial fibrillation and intracardiac thrombus) • Not secondary to another more likely specific cause of stroke (i.e., vessel dissection, vasculitis, and arteritis)

fivefold and doubled the rates of initiation of appropriate anticoagulation for secondary prevention when compared to ECG alone [20, 21]. The importance of prolonged cardiac monitoring in patients with an embolic appearing stroke cannot be overemphasized and should be included in the diagnostic algorithm.

However, not all ESUS patients are under-diagnosed, or clinically silent AF patients, and whether or not AF is best defined as a binary entity has been called into question [22]. First, when comparing patient populations between ESUS and known AF-related cardioembolic mechanisms, there are differences. For example, the NIHSS of ESUS patients tends to be lower than cardioembolic stroke (average of 13 versus 5) and they also tend to be younger at the time of stroke onset compared to cardioembolic AF strokes [23, 24]. The average frequency of ESUS strokes compared to other stroke subtypes is about 20% with a reported recurrent stroke rate of 4.5% per year. The majority of ESUS patients are treated with antiplatelets, while AF strokes are treated with anticoagulation [13]. Additionally, the timing and direct causality of AF alone with regard to ischemic stroke have conflicting evidence. For example, in the Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and Atrial Fibrillation Reduction Pacing Trial (ASSERT) trial, only 8% of patients had subclinical AF detected within 30 days preceding the stroke, with a median interval of 339 days to an AF event before the stroke, suggesting that AF did not always closely precede the time of the stroke [25, 26]. This has also been supported in other studies [27]. Another important concept is the burden of AF, or how much AF is necessary to lead to embolization and thereby stroke. In the Registry of Atrial Tachycardia and Atrial Fibrillation Episodes (RATE) study, patients with pacemakers who had an AF episode of greater than 20 s were more likely to have an incident stroke, but there was no difference between those without AF and those with AF less than 20 s in duration [28]. It is therefore feasible that an increased burden of AF may lead to increased thrombosis through changes in the left atrium more than the rhythm alone.

For this and other reasons, the concept of atrial cardiopathy was introduced, which captures the idea that the fibrillating atrium is only one sign of left atrial dysfunction and that other changes in hemodynamics, atrial shape, and left atrial fibrosis might all contribute to an embolic stroke, with the clot arising from the left atrium [29]. This may happen in the setting of atrial fibrillation, or it may happen apart from atrial fibrillation, with an independent pathway between this state of atrial dysfunction and ischemic stroke [30–32]. There has been an explosion of work in the area of the important of left atrial size and function. Left atrial diameter is strongly correlated with risk of ischemic stroke; abnormalities in P-wave duration, P-wave area, and P-wave terminal force have been associated with embolic stroke and left atrial appendage morphology; and even number of left atrial lobes has been associated with thrombus [30, 33]. It becomes apparent that there are likely multiple mechanisms converging to lead to a state of pathology of the left atrium, which leads to embolization based on the propensity to thrombus which is characterized by both structure and function of the left atrium [14, 16].

Younger patients represent a particularly important group of patients that are likely impacted by ESUS; as among 3,331 patients aged 15–49 years old in a young stroke registry, the etiology remained undetermined in approximately 40% [34]. Those who suffer a stroke younger in life have a longer life span and therefore longer duration of disability post-stroke and are more likely to experience complications, such as seizures or dementia [35, 36]. Following ESUS patients overtime to understand their risk of post-stroke dementia will be important, as measures of atrial dysfunction have also been associated with poor cognition [37]. Recently, several transthoracic echocardiographic measures that were suggestive of worse LA function were significantly associated with

an increased risk of dementia [38]. A formal definition of atrial cardiopathy based on three different biomarkers of left atrial size and function was also associated with dementia in a large US cohort of older adults [39]. Whether or not this leads to an additive effect above and beyond cognitive impairment that might be anticipated post-stroke is unknown.

Regarding treatment for ESUS, the optimal therapy is still not established. Given the overlap with atrial fibrillation and the thought that there might be similar mechanisms, anticoagulation rather than antiplatelet therapy was postulated as the best possible therapy [9]. Two recent randomized controlled trials compared direct oral anticoagulants (DOACs) to aspirin for secondary stroke prevention among those who had an ESUS stroke. Using first rivaroxaban and then dabigatran, these two studies failed to show a difference between the two treatment strategies [24, 40]. A major weakness that has been cited for these two trials is the relatively loose inclusion criteria, or specifically whether or not ESUS was appropriately defined. The most recent trial was completed, apixaban for treatment of embolic stroke of undetermined source (ATTICUS), compared apixaban to aspirin and also included a more "enriched" ESUS population in that the patients had to have at least one risk factor to include an enlarged left atrium, spontaneous echo contrast, a slow left atrial appendage velocity, a patent foramen ovale, or an elevated CHADS2VASC score [41]. They also did not show a difference in the primary endpoint, which was a little different than the other trials in that they did not look at recurrent stroke, but rather at new ischemic lesions present on 12-month follow-up brain MRI. Encouragingly, there was no difference in any of the safety endpoints between the apixaban or aspirin arm while prior trials had suggested an increased risk of bleeding on the DOAC. They did find that AF was relatively common in the population, with approximately 28% of the ESUS group developing AF in the prolonged monitoring arm.

Finally, the ongoing AtRial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke (ARCADIA) trial is enrolling patients with ESUS who have evidence of study defined atrial cardiopathy using P-wave terminal force, serum NT-proBNP, and left atrial diameter to either apixaban or aspirin and following them for recurrent stroke events [42]. Given that the current stroke treatment is not clear for this group of patients, the default treatment has become antiplatelet therapy. Hopefully with future trial results and an acceleration of technology and biomarkers by which to define a state of atrial dysfunction, apart from atrial fibrillation alone, the secondary stroke prevention strategy will become clearer, and the question if a subset would benefit from anticoagulation will be answered.

Stroke Genetics

Stroke is a multifaceted disease, and the growing field of stroke genetics and epigenetics may help improve sensitivity and specificity of some already recognized stroke risk factors and biomarkers that may overlap between different stroke etiologies to arrive at one diagnosis. Those performing research in this field believe that an understanding of the influence of various genes on the microbiome, metabolome, proteome, transcriptome, and epigenome will provide insight into mechanisms of disease and hopefully provide insight into stroke mechanisms formally labeled cryptogenic.

For example, while a healthy diet, physical exercise, and appropriate medications are important to the prevention of all stroke, why some patients respond to lifestyle interventions or some drugs more than others is not well understood. There may be a genetic predisposition to thrombosis that makes one patient more susceptible to stroke than another with the same "level" of vascular risk. Determining whether this is the case is not easy in clinical stroke practice as genetic batteries can be expensive, and even if a mutation is identified, it may not lead to any meaningful change in clinical care.

There are however some cerebrovascular diseases that are associated with a single, primary gene mutation, and they most commonly involve diseases of the small vessels. These entities should be familiar to the practicing cerebrovascular neurologist, particularly when patients present with a traditional phenotype which may be missed unless a detailed family history is taken. A classic example is a mutation of the NOTCH3 gene, which is causal in CADASIL (cerebral autosomal dominant arteriopathy with leukoencephalopathy and stroke). The traditional clinical description is a patient with migraine with aura, mood disturbances, subcortical ischemic infarcts, apathy, and cognitive impairment. While this entity has been described for over a decade, more recent work has demonstrated that even in CADASIL, there are mutations that can lead to less severe phenotypes, with the description of the original disease perhaps being one of the most severe manifestations of disease [43].

Others include but are not limited to cerebral autosomal recessive arteriopathy with leukoencephalopathy and stroke or CARASIL (HTRA1 gene), PADMAL (COL4A1 gene), or Fabry disease (GLA mutation). CARASIL is often thought of as a recessive form of CADASIL with a similar clinical presentation; however, the cognitive impairment usually begins earlier and can also be accompanied by gait disturbance, back pain, and alopecia [44]. Pontine autosomal dominant microangiopathy and leukoencephalopathy (PADMALs) is dominantly inherited

and characteristically presents with severe lacunar infarcts and leukoaraiosis of the pons leading to severe dysphagia, spastic gait, and eventual paraparesis and progression to anarthria [45].

Fabry disease is a lysosomal storage disorder which impacts many different organ systems, but it is important to remember that it can involve the central nervous system, usually with development in adulthood of a higher risk of transient ischemic attacks or ischemic stroke or development of white matter hyperintensities. Recognition of this x-linked disease is imperative as there are FDA-approved enzyme replacement therapies to mitigate disease progression [46]. Mutations in high-temperature requirement A serine peptidase 1, or HTRA1, have been associated with stroke at a young age with white matter changes that are similar to those of CARASIL and represent a growing area of interest in defining the family of conditions related to mutations in this gene [47]. While a full review of Ehlers-Danlos syndrome (EDS) is outside of the scope of this article, it is also imperative to mention type 4, or the vascular type, as management often requires a multidisciplinary team, including a cerebrovascular neurologist. It is believed to result from a pathologic variant of the COL3A1 gene which encodes type III procollagen, which is imperative to the structure of the vessel wall. As a result, these patients are at increased risk for vessel dissection, although not all dissections are symptomatic. Suggestions regarding lifestyle modification to decrease risk of vessel rupture and trauma are the only recommended preventative strategy.

Monogenic causes of cerebrovascular diseases are more likely to be causally related to stroke when the clinical onset of symptoms occurs at a younger age, the patient has no or few vascular risk factors, and there is a history of other affected members in the family. Sickle cell disease, or a specific variant in the hemoglobin beta globin chain HBB, located on chromosome 11 is one example (Table 2). However, a monogenic cause should also be suspected if the clinical picture is suggestive, even without a family history, as genetic cases can present as sporadic cases.

Even if testing for some of the more common genetic causes of stroke is negative, it may still represent a monogenetic presentation of a cerebrovascular disease yet to be identified as currently over 80% of patients referred for genetic testing with cerebrovascular disease of a highly suggestive genetic etiology do not have a pathologic mutation identified [48]. Aggregate data at the international level and

Table 2 Ischemic stroke in the adult with sickle cell disease

Epidemiology	• Estimated ischemic stroke rate for adults 35–65 years of age was 7.4 person-years among 69, 586 hospitalization for sickle cell disease complications (1998–2007), which was three times higher than reported rates for African Americans of similar age[a]
Risk factors	• Traditional stroke risk factors, such as hypertension, type 2 diabetes, hyperlipidemia, renal disease, and atrial fibrillation, all are associated with increased risk of stroke in sickle cell disease adults as compared to children[b] • Stenotic vasculopathy, vaso-occlusive crisis, acute chest syndrome, and fat embolism have been cited as sickle cell specific causes of ischemic stroke[c]
Treatment	• There are no randomized trials, but adults with sickle cell disease should be considered for intravenous rtPA based on the traditional inclusion and exclusion criteria[d] • There is limited data looking at the benefits and risks of endovascular therapy in acute ischemic stroke in sickle cell and should be considered carefully due to the increased prevalence of cerebral vasculopathy in these patients[e]
Exchange transfusion	• The stroke prevention (STOP) prevention trial in children showed that those with elevated transcranial Doppler ultrasound measures had a decreased risk of stroke when undergoing exchange transfusion, which some have extrapolated to adults[f] • There are no studies however evaluating the effectiveness of preventing ischemic stroke in adults with exchange transfusion but should be considered for acute therapy in the adult at time of an ischemic stroke with the aim to reduce sickle percentage to < 30%[d]
Risk factor reduction	• Treatment of co-occurring vascular risk factors remains important, especially in the older adult, with no clear evidence regarding antiplatelet therapy in this population for secondary stroke prevention[d,e]

[a]Strouse JJ, Jordan LC, Lanzkron S, Casella JF. The excess burden of stroke in hospitalized adults with sickle cell disease. American journal of hematology 2009 Sep;84(9):548–552

[b]Strouse JJ, Lanzkron S, Urrutia V. The epidemiology, evaluation and treatment of stroke in adults with sickle cell disease. Expert Review of Hematology 2011 Dec 1,;4(6):597–606

[c]Gueguen A, Mahevas M, Nzouakou R, Hosseini H, Habibi A, Bachir D, et al. Sickle-cell disease stroke throughout life: a retrospective study in an adult referral center. American journal of hematology 2014 Mar;89(3):267–272

[d]Alakbarzade V, Maduakor C, Khan U, et al. Cerebrovascular disease in sickle cell disease. Practical Neurology 2023;23:131–138

[e]DeBaun MR, Jordan LC, King AA, et al. American Society of Hematology 2020 guidelines for sickle cell disease: prevention, diagnosis, and treatment of cerebrovascular disease in children and adults. Blood Adv 2020;4:1554–88

[f]Adams RJ, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med 1998;339:5–11

longitudinal studies allowing for careful tracking of rates of progression, and clinical characteristics of rare genetic disease, may help determine more monogenic causes of disease, which will hopefully lead to targeted treatment strategies in the future.

Another area that has grown over the past decade in stroke genetics is that of a polygenic risk score, whereby patients with multiple variants that may individually contribute a small risk are combined enabling the ability to quantify genetic predisposition to vascular conditions, such as stroke or hypertension [49]. Through the generation of a "meta-genomic risk score" by a weighted sum of allele counts, a clinical risk score can be created with one study suggesting a hazard ratio of 1.26 when testing the score in the UK biobank of 395,393 participants with over 3,000 stroke events [50]. Further validation of such scores is ongoing with the hopes that these could eventually be universally applied across different race and sex groups and thereby help in the stroke diagnostic algorithm.

Subclinical Extracranial Carotid Artery Disease

Extracranial carotid artery disease is a well-recognized mechanism of large artery atherosclerosis and resulting stroke, with established guidelines regarding the need for carotid artery surgery for patients with ischemic stroke meeting certain artery stenosis criteria [51]. Clinical trials are underway regarding whether or not surgery is indicated for those with a high degree of stenosis but have asymptomatic carotid artery disease [52].

There is already a well-known association between degree of carotid stenosis and stroke risk [53], but advances in the imaging field over the past 5 years and further understanding of the flow dynamics of these atherosclerotic lesions that do not currently meet surgical criteria over the next decade will inevitably lead to improved determination of stroke etiology by providing evidence of causality and treatment strategies. As a result, this is an area to carefully consider as potentially causal when stroke etiology is not certain.

The Carotid Plaque Imaging in Acute Stroke (CAPIAS) study demonstrated that there is a higher prevalence of ipsilateral versus contralateral complicated carotid artery plaques among those with cryptogenic stroke [54]. They also showed a higher prevalence of complicated ipsilateral plaque among those with cryptogenic stroke when compared to strokes of other etiologies, with the anticipated exception of large artery atherosclerosis [53]. Updated results from the initial study reported a twofold increase of recurrent ischemic stroke or TIA with an ipsilateral complicated plaque compared to those without plaque, and interestingly, the effect was more pronounced in those with a prior cryptogenic stroke (hazard ratio of 5.6). Others have reported similar findings with the ESUS Global Registry, finding that 79% of patients had nonstenotic plaques in the cervical carotid arteries [55].

The CAPIAS study took advantage of more advanced imaging techniques to characterize plaque morphologies that were felt to be particularly vulnerable to thrombosis [56, 57]. Plaques that are echolucent, have a lipid-rich core, have a large volume or thickness, have evidence of spontaneous embolization (non-calcified), or are irregular have been associated with higher risk of stroke. A vast array of imaging modalities to include CT, MRI, advanced ultrasound, and now PET each have unique findings that can help characterize a plaque as high risk. Neovascularization which can be seen with contrast on CT or MRI, or microbubbles in the delayed phase on ultrasound, all suggests that the plaque might be unstable and therefore more likely to embolize. PET imaging is allowing for evaluation of plaque inflammation, with recent work by Camps-Renom et al. describing the SCAIL score which uses degree of carotid stenosis and PET FDG tracer uptake to assign points to the carotid lesion [58]. The group demonstrated an increase in stroke risk per 1-point SCAIL score increase.

The treatment of "asymptomatic" carotid artery disease is an area of great interest with no current evidence for either endarterectomy or stenting when it is found. The US Prevention Services Task Force recently reaffirmed their statement that patients without a history of stroke or TIA should not undergo screening for asymptomatic carotid artery disease [59]. However, secondary prevention after stroke among those with stenosis less than 50% (moderate stenosis) is less clear or if the plaque appears to be high risk on imaging and is in the distribution of the ischemic stroke but does not meet current intervention criteria. This issue is even more muddled in the modern era of more advanced medical treatments, such as statin medications, given that the carotid intervention trials were performed prior to widespread use of these drugs.

The SPARCL trial, which is over a decade old, demonstrated a 33% reduction in stroke among those whose LDL cholesterol was lowered to a target goal of 70 mg/dL compared to the placebo arm (130 mg/dL) [60]. The JUPITER trial which also lowered cholesterol to a goal of 70 mg/dL on rosuvastatin demonstrated a 48% reduction in stroke [61]. The advent of PCSK9 inhibitors adds to the arsenal of the treating physician taking care of stroke patients who may not be able to tolerate statin medications secondary to side effects [62]. The addition of evolocumab to a statin drug decreased the risk of stroke approximately 25% in the FOURIER trial [62]. While physicians await for the results of the ongoing clinical carotid intervention trials, aggressive risk factor management, patient dietary counseling, and initiation

of high-dose statin therapy in those who have already had stroke are certainly warranted.

There is no current data comparing antiplatelet dosing strategies among those with carotid stenosis, but best practice suggests treatment with aspirin. There is no evidence to suggest that anticoagulation is superior to aspirin among those with ESUS and carotid atherosclerosis [63].

Although the treatment strategy for subclinical extracranial atherosclerosis is still being defined, it may therefore be that atherosclerosis that does not currently meet criteria for surgical intervention has a stronger causal role in strokes of unknown cause than previously thought. The continued advancement of imaging will help us look beyond the degree of stenosis and identify those plaques with high-risk features that are likely causal and would warrant intervention.

Cancer and Stroke

In ischemic stroke patients, the prevalence of prior cancer has been cited as high as 16% when compared to the general population, and up to 10% of newly diagnosed ischemic patients may have comorbid cancer at the time of the stroke diagnosis, with increasing work dedicated to techniques and tools to determine whether the cancer is causal [64, 65]. Stroke risk is felt to be highest soon after the cancer diagnosis, with a reported time of decreased risk after initiation of cancer treatment, but then, another upturn with increased stroke risk months after treatment is initiated [66–68].

There are several possible reasons why cancer may lead to stroke. It may be the result of a mechanism caused by the cancer that then contributes to stroke (i.e., inflammation), traditional vascular risk factors that lead to both (i.e., smoking), or as a result of a hypercoagulable state triggered by the presence of cancer. Cancer can lead to abnormalities in the coagulation system at any point along the coagulation cascade, either increasing risk of clot formation and thereby ischemic stroke or leading to platelet dysfunction, and thereby a hemorrhagic stroke, or intracranial hemorrhage [69]. Clonal hematopoiesis of indetermined potential (CHIP), which is present in some hematologic malignancies, has also been cited as contributing to cardiovascular disease risk through accelerated atherosclerosis, increased risk of thrombosis, and early onset of heart failure [70]. A recent study among the Women's Health Initiative cohort (7,426 stroke events) suggested that this was significantly associated with an accelerated risk of stroke (adjusted hazard ratio 1.25), with the effect mainly driven by association with hemorrhagic stroke [71].

Additional mechanisms of stroke among cancer patients include marantic endocarditis, or seeding of the cardiac valves with sterile vegetations, which could lead to embolic appearing stroke [72]. Large, solid tumors might cause compression, or invasion, of essential arterial vessels. These patients are also at increased risk for deep venous thrombosis, which may result in a paradoxical embolism [73]. Cancer patients are also immunosuppressed, which may increase risk of infection, such as fungal infections or varicella zoster, which can also result in stroke.

In a large Korean cohort with cryptogenic stroke, colorectal cancer, lung cancer, and pancreatic cancer were found to have the highest association with stroke, but certainly other cancer types, such as breast cancer or prostate cancer which are more common in the population at large, have also been cited as associated with increased risk of stroke [74, 75].

Treatment of the cancer can actually also increase stroke risk. Invasive procedures, such as surgical operations for tumor removal, may result in direct vascular injury or vessel occlusion and lead to stroke. Radiation therapy may lead to fibrosis, and scaring of the vasculature, and thereby stroke, particularly among those who are childhood survivors of cancer [76, 77]. Chemotherapy has also been linked to an increased risk of stroke through a variety of mechanisms. In a large study of nearly 20,000 cancer patients, chemotherapy increased the risk of stroke, but that association was no longer present after the association was adjusted for cancer status (for example, advanced cancer) [78]. Chemotherapy agents are not all the same, with the risk of stroke linked to the specific drug and its mechanism of action. For example, the vascular endothelial growth factor (VEGF) inhibitors appear to cause more arterial clots, rather than venous embolism [79], while L-asparaginase depletes protein C and protein S, thereby increasing risk of venous thromboembolism. Immune checkpoint inhibitors are used for many different cancer indications, with rapid expansion in use, and have a relatively strong risk of stroke (about 2% per year) with some suggestion that concurrent statin medication use may attenuate this risk among those who can tolerate these medications while undergoing treatment [80].

When considering the diagnostic workup for cancer-associated stroke, laboratory values, such as D-dimer levels, can be helpful, especially when there is an ESUS mechanism suspected, or multifocal embolic pattern on brain imaging [81, 82]. A full-body computer tomography imaging (CT) to look for evidence of malignancy can be diagnostic, as can a PET scan with a high level of suspicion. Selvik et al. created a score based on elevated D-dimer levels, low hemoglobin levels, and a history of smoking to define the risk of stroke among those with stroke of unknown etiology, citing the probability of active cancer as causal to be 53% if a patient had all three [83]. Transcranial Doppler micro-emboli were found to be more likely in a small group of patients with cancer and stroke, compared to those with stroke alone or cancer alone [67]. While a detailed discussion of these entities is outside of the scope of this article, certain imaging patterns

that suggest either reversible cerebral vasoconstrictive syndrome (RCVS), or posterior reversible encephalopathy syndrome (PRES), which indicate cerebral ischemia, can be caused by either neoplastic syndromes, or chemotherapy agents, such as rituximab.

While the relationship between the presence of cancer, concurrent vascular risk factors, and causality of stroke is complex, an awareness of the potential mechanisms of injury at all treatment stages and aggressive control of traditional vascular risk factors among patients with cancer is important.

"Silent" Infarction and Imaging Findings of Potential Ischemia

While different than a clinical stroke in initial presentation, the incidental finding of "silent" strokes is still an important entity to consider when discussing stroke etiology and diagnosis. There is a growing awareness that silent infarction is not actually silent or even asymptomatic but is rather associated with future clinical stroke and cognitive decline. Various words have been used to describe these lesions, such as covert brain infarcts, white matter hyperintensity, leukoaraiosis, lacunar strokes, or lacunes. Wardlaw et al. attempted to distinguish these entities by developing the STRIVE principles, which state that terms and definitions should reflect the imaging characteristics of these lesions and that using the same language is essential in defining and studying the same entity [10]. For example, a lacune should be descriptive of a hole in the brain, rather than associated with small vessel disease (lacunar stroke) and can actually be caused by embolic disease [84].

White matter hyperintensities (WMH) are frequently encountered incidentally after brain MRI imaging has been obtained for another indication, such as headache, and may even result in a referral to a vascular neurologist to discuss its implications. WMH appear hyperintense on FLAIR/T2 weighted MRI and are usually symmetric, involving the white matter tracks throughout the bilateral hemispheres, but can also involve the brainstem and sometimes occur in deep grey matter. What exactly composes the area of white matter change remains a point of discussion with axonal damage, loss of oligodendrocytes, demyelination, and impaired blood–brain barrier all being postulated as potential mechanisms [85]. One study enrolling 999 participants for MRI found that a greater amount of WMH indicated a higher risk of ischemic stroke, vascular-related death, and all-cause death in the years following the MRI, and a confluent WMH pattern was associated with the highest risk of death, compared to other WMH patterns [86].

Hypertension has been strongly linked to WMH; however, blood pressure targets for these patients are unclear. White et al. conducted the INFINITY trial for those with MRI white matter hyperintensity and systolic hypertension. They found that the increase in baseline WMH volume was smaller in the intensive group compared to the standard treatment group; however, there was no difference in cognitive outcomes. In a meta-analysis, however, there was a suggestion that with intensive blood pressure lowering, WMH decreased overtime compared to standard therapeutic targets for antihypertensive agents. Regarding the guidelines, there is currently no recommendation to target blood pressures less than 140/90 in these patients with the European Stroke Association citing insufficient evidence [87].

When a covert, isolated lesion is discovered on imaging, it is usually secondary to small vessel disease with approximately 83% representing true lacunar disease and about 17% attributed to embolic disease [88, 89]. Risk factors for covert brain infarcts largely overlap with risk factors for symptomatic stroke. Those that have been strongly linked include older age, hypertension, metabolic syndrome, carotid artery disease, and chronic kidney disease, but this list is not exhaustive, and many others such as tobacco use are also likely related [90, 91].

The American Heart Association guidelines recommend preventative care for these patients that are in line with primary prevention of ischemic stroke to include a healthy diet, physical activity, measuring blood pressure, and body mass index, checking the patient's pulse at the clinic visit and possibly getting an electrocardiogram to check for atrial fibrillation [1]. Carotid artery imaging or an echocardiogram could be "considered" per these guidelines, but the evidence is not strong for these recommendations.

Regarding use of antiplatelet therapy for either WMH, or covert small vessel disease, the 2021 European Stroke Guidelines recommend against the use of antiplatelet drugs, stating that such therapy may actually be harmful in older patients (> 70 years old) if there is no other indication for this therapy [87]. However, it is important to note that this patient population will likely have other small vessel risk factors, such coronary artery disease, that may necessitate initiation of antiplatelet therapy.

There remain gaps in knowledge in this area, such as the following: does the stroke risk vary per the covert infarct brain mechanism and locations? Are there some patients with WMH who should be treated with aspirin, or other antithrombotic medications, or statin medications, even without other vascular risk factors? For now, counseling with patients and their families regarding what these imaging findings mean, and do not mean, as they can be surprising and upsetting to some patients is a good start, as is using the opportunity to ensure all primary prevention strategies are being followed.

Conclusions and the Future

Accurate, complete, and reliable ways to determine the cause of an ischemic stroke are paramount in providing excellent patient care. Achieving diagnostic excellence is perhaps one of the most important skills that a physician can have, particularly when caring for patients with a disease that will likely have long-term ramifications, such as stroke. Patients that have the initial cause of the stroke undiagnosed, or incorrectly diagnosed, are at increased risk for a recurrent event. If there is one thing that should be understood from this review, it is that stroke is a disparate disease, and while lumping characteristics together help in the diagnostic pathway and with treatment decisions, each patient represents an individual with a unique set of vascular risk factors that should be carefully considered.

Diagnosis is also a process, and each iterative step could be an important one, with the benefits and harms of each test to the patient weighed. As technology and imaging techniques have advanced, so has the ability to consider conditions, such as genetic contributions to potential thrombotic risk, that were previously unattainable. However, no one patient could or should go through all of the possible tests to arrive at a diagnosis, especially if the information garnered is not helpful, or even costly, either financially or in terms of opportunity/time lost for the patient, or their family.

Causative classification systems have expanded over the past 5 years, and new and improved description of entities, such as ESUS or the STRIVE criteria, should help tease apart patients who may have been inappropriately lumped with another, more general disease process. The hope is that this will prevent loss of important individual information when they are collapsed into an inappropriate category of causative disease, or even worse, left undiagnosed, or harmed by an inferior treatment choice. Important also to consider is that there are limitations inherent in any diagnostic strategy, and identification of an abnormality in a stroke workup does not mean that it is causal to the patient's presenting stroke event. The stroke diagnosis that is the most accurate is the one that leads to the best, most superior treatment and prevention pathway.

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Required Author Form Disclosure form provided by the author are available with the online version of this article.

Declarations

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