Cardioembolic Stroke

Hooman Kamel, Jeff S. Healey

Abstract: **Cardiac embolism accounts for an increasing proportion of ischemic strokes and might multiply several-fold during the next decades. However, research points to several potential strategies to stem this expected rise in cardioembolic stroke. First, although one-third of strokes are of unclear cause, it is increasingly accepted that many of these cryptogenic strokes arise from a distant embolism rather than in situ cerebrovascular disease, leading to the recent formulation of embolic stroke of undetermined source as a distinct target for investigation. Second, recent clinical trials have indicated that embolic stroke of undetermined source may often stem from subclinical atrial fibrillation, which can be diagnosed with prolonged heart rhythm monitoring. Third, emerging evidence indicates that a thrombogenic atrial substrate can lead to atrial thromboembolism even in the absence of atrial fibrillation. Such an atrial cardiomyopathy may explain many cases of embolic stroke of undetermined source, and oral anticoagulant drugs may prove to reduce stroke risk from atrial cardiomyopathy given its parallels to atrial fibrillation. Non–vitamin K antagonist oral anticoagulant drugs have recently expanded therapeutic options for preventing cardioembolic stroke and are currently being tested for stroke prevention in patients with embolic stroke of undetermined source, including specifically those with atrial cardiomyopathy. Fourth, increasing appreciation of thrombogenic atrial substrate and the common coexistence of cardiac and extracardiac stroke risk factors suggest benefits from global vascular risk factor management in addition to anticoagulation. Finally, improved imaging of ventricular thrombus plus the availability of non–vitamin K antagonist oral anticoagulant drugs may lead to better prevention of stroke from acute myocardial infarction and heart failure. (*Circ Res*. 2017;120:514-526. DOI: 10.1161/CIRCRESAHA.116.308407.)**

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Twenty-six million people worldwide experience a stroke each year, making it the second-leading cause of mortality and a leading cause of long-term disability.[1] One-third of strokes represent intracerebral or subarachnoid hemorrhage, whereas two-thirds represent cerebral ischemia.[1] Ischemic stroke can result from a variety of causes, such as atherosclerosis of the cerebral circulation, occlusion of cerebral small vessels, and cardiac embolism.[2] Of these causes, cardioembolic

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From the Clinical and Translational Neuroscience Unit, Feil Family Brain and Mind Research Institute (H.K.) and Department of Neurology, Weill Cornell Medicine, New York, NY (H.K.); and Department of Medicine and Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada (J.S.H.).

Correspondence to Hooman Kamel, MD, Clinical and Translational Neuroscience Unit, Weill Cornell Medicine, 407 East 61st St, New York, NY 10065. E-mail hok9010@med.cornell.edu

Nonstandard Abbreviations and Acronyms	
AF	atrial fibrillation
CI	confidence interval
ESUS	embolic stroke of undetermined source
MI	myocardial infarction
NOAC	non–vitamin K antagonist oral anticoagulant
PFO	patent foramen ovale

stroke has significance for 2 reasons. First, cardiac embolism causes more severe strokes than other ischemic stroke subtypes.[3] Second, as treatment of hypertension and dyslipidemia improves, cardiac embolism has accounted for an increasing share of strokes in high-income countries, such as Canada.[4] Despite a decrease in the overall incidence of stroke, cardioembolic strokes have tripled during the past few decades and may triple again by 2050 based on projections from the United Kingdom.[5] Given demographic changes and increasing life expectancy, risk factors for cardiac embolism may become more common in low- and middle-income countries as well.[6] Conversely, oral anticoagulant therapy can prevent ≈70% of strokes in patients with the most common cardioembolic risk factor, namely atrial fibrillation (AF).[7] This leads to hope that randomized trials and translational research of therapies for other forms of cardioembolic stroke may substantially reduce stroke incidence worldwide.

Risk Factors for Cardioembolic Stroke

Atrial Fibrillation

AF is a disorder of heart rhythm that affects 33 million people worldwide.[6] AF is associated with a 3- to 5-fold increased risk of stroke.[8] The prevalence of AF increases sharply from 0.1% among adults aged <55 years to almost 10% among those aged >80 years.[9] The number of patients with AF may double and the number of AF-related strokes may triple in the next few decades based on projections from high-income countries, such as the United States.[9]

Systolic Heart Failure

Heart failure affects ≈26 million people worldwide.[10] Although hospitalizations for heart failure are decreasing in high-income countries,[11] this condition accounts for ≈2% of primary hospital discharge diagnoses, making it the most common reason for hospital admission.[12] Regional stasis, a hypercoagulable state, and likely undiagnosed AF seem to predispose heart failure patients to cardiac thrombus.[13,14] As a result, these patients face at least a 3-fold higher risk of stroke than the general population.[15]

Recent Myocardial Infarction

Acute myocardial infarction (MI) is a long-established risk factor for ischemic stroke. In case series from the 1980s, 2.5% of patients experienced a stroke within 4 weeks of acute MI,[16] well above the background incidence during that time.[17] The association seems causal because thrombi are often seen overlying areas of ventricular dyskinesis.[18] Furthermore, percutaneous coronary intervention for acute MI carries its own risk of stroke, ≈0.1% in modern series.[19] Rates of stroke after acute MI are decreasing over time, perhaps because of acute reperfusion therapy, widespread use of antithrombotic medications, and improved long-term secondary prevention therapies.[20]

Patent Foramen Ovale

Patent foramen ovale (PFO) affects ≈25% of the general population[21] and may serve as a passageway for paradoxical embolism from the venous to arterial circulation. Patients with an unexplained ischemic stroke more often have a PFO than those with known stroke causes.[22–24] However, in a large study of patients with recent stroke, the presence of a PFO was not associated with a higher risk of stroke recurrence.[22] In a population-based study of stroke-free individuals, the presence of a PFO was not significantly associated with either clinically overt stroke[25] or subclinical brain infarction on magnetic resonance imaging.[26] Furthermore, among patients whose strokes appeared most attributable to a PFO, rates of stroke recurrence were low compared with overall recurrence rates.[27,28] Although PFO may be a common stroke risk factor, it is not a strong one, except perhaps in young stroke patients (<50 years).

Aortic Arch Atheroma

Approximately 45% of individuals aged ≥45 years harbor atherosclerotic plaque in their aorta,[29] and this has been associated with stroke.[30] Large, ulcerated, noncalcified, or mobile atheromas, which occur in ≈8% of the population,[29] have been particularly linked with stroke.[31] Few population-based studies have assessed the relationship between aortic atheroma and incident stroke,[29] and those few may have been underpowered to detect an association.[32] In clinical practice, aortic atheromas may be an under-recognized cause of stroke because the imaging modalities required to detect them, such as transesophageal echocardiography, are not routinely performed in stroke patients.[33] Early reports suggested a high rate of stroke recurrence (12% per year) in patients with aortic arch atheromas,[34] but a more recent trial found a much lower rate (<3% per year),[35] suggesting that secular trends in the treatment of atherosclerotic risk factors may be reducing the contribution of aortic atherosclerosis to the burden of stroke.

Prosthetic Heart Valves

The prevalence of moderate-to-severe valvular heart disease is ≈2.5% in the general population and 12% in those aged ≥75 years.[36] The standard treatment for many of these valvular conditions is surgical or endovascular valve replacement.[37] Approximately 0.1% of individuals aged ≥65 years undergo aortic valve replacement per year in the United States.[38] A meta-analysis of studies published between 1985 and 1992 found that patients with a mechanical valve faced a 4.0% annual risk of stroke, which decreased with the use of oral anticoagulation to 0.8% for aortic valves and 1.3% for mitral valves.[39] Bioprosthetic valves seem to confer a lower risk of stroke than mechanical valves, especially over the long term.[40] Although stroke risk has decreased over time, thromboembolic complications remain a significant cause of morbidity and mortality.[41] The risk of stroke seems similar regardless of the use of traditional surgical aortic valve replacement or transcatheter aortic valve replacement.[42]

Infective Endocarditis

Infective endocarditis affects ≈1 per 10 000 individuals in high-income settings.[43] It is a relatively uncommon stroke risk factor, but the magnitude of association between infective endocarditis and stroke greatly exceeds that of more common stroke risk factors. Approximately 1 in 5 cases of endocarditis are complicated by stroke,[44] and multiple studies have found a >20-fold relative increase in stroke risk in the month after a diagnosis of bacteremia[45] or infective endocarditis.[46]

Other Causes

There are several rare causes of embolism, such as papillary fibroelastoma, myxoma, and mitral calcification. Each accounts for <1% of cardioembolic strokes.[47]

Diagnostic Criteria for Cardioembolic Stroke

Although the factors above place patients at an increased risk of cardioembolic stroke, these patients also experience other types of ischemic stroke because of shared risk factors. How can one distinguish a cardioembolic stroke from other etiologic subtypes of ischemic stroke?

Clinical Presentation

Classically, cardioembolic strokes present with the sudden onset of neurological deficits that are maximal at onset, whereas strokes caused by small-vessel occlusion (also known as lacunar strokes) or large artery atherosclerosis may have a more stuttering course.[48] Cardiac embolism often lodges in distal arteries supplying the cerebral cortex while small-vessel occlusion affects subcortical tissue,[49] so cardioembolic stroke can be differentiated from lacunar stroke by cortical signs, such as aphasia or visual field deficits.[2] However, clinical characteristics alone cannot reliably classify the underlying cause of ischemic stroke.[48] Thus, accurate classification also requires integration of neuroimaging, cardiac, and vascular evaluation.

Neuroimaging Profile

The neuroimaging profile of cardiac embolism was established by studying patterns of cerebral infarction in patients with a high-risk cardiac condition and no other obvious cause of stroke. The vast majority of these cardioembolic strokes involve lesions in a cortical territory.[50] In contrast, lacunar stroke is by definition restricted to a subcortical location.[51] About half of cardioembolic strokes involve multiple cerebral arterial territories (ie, both internal cerebral arteries or 1 internal cerebral artery as well as the basilar artery),[50] which distinguishes cardiac embolism from artery-to-artery embolism because of large artery atherosclerosis in the cerebral circulation.[2] In the acute phase, vascular imaging of the intracranial circulation, such as with computed tomographic or magnetic resonance angiography, often reveals an abrupt vessel cutoff without significant atherosclerotic narrowing of the upstream vessel.[52]

Table. High-Risk Sources of Cardiac Embolism

Mechanical prosthetic valve
Atrial fibrillation or flutter
Left atrial or ventricular thrombus
Recent myocardial infarction (<4 wk)
Dilated cardiomyopathy
Infective endocarditis
Regional left ventricular akinesis
Atrial myxoma
Rheumatic heart disease
Patent foramen ovale with thrombus in situ

Vascular and Cardiac Evaluation

An ischemic stroke cannot be assigned a subtype without a vascular evaluation to rule out large artery plaque and a cardiac evaluation to identify a high-risk cardiac condition (Table).[2] To determine the cause of stroke, almost all stroke specialists worldwide perform vascular imaging of the extracranial (cervical) carotid arteries to rule out carotid stenosis and a 12-lead ECG to rule out AF or recent MI.[33] About 70% perform vascular imaging of the intracranial cerebral circulation to rule out intracranial plaque and transthoracic echocardiography to rule out high-risk sources of cardiac thrombus.[33] Only 20% perform transesophageal echocardiography, ≈50% perform inpatient cardiac telemetry or 24-hour Holter monitoring to rule out AF, and only ≈20% perform prolonged (>24 hours) heart rhythm monitoring.[33] Although the minimum cardiac and vascular evaluation required to establish the underlying cause of ischemic stroke remains subject to debate,[47] the presence of a typical clinical presentation and neuroimaging profile, positive evidence of a high-risk cardiac source, and the exclusion of a large artery plaque suffice to establish a diagnosis of cardioembolic stroke.

Stroke Subtype Classification Systems

This definition of cardioembolic stroke is enshrined in several classification systems for determining the subtype of ischemic stroke. The TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification provides nonoverlapping definitions for cardiac embolism, small-vessel occlusion, and large artery atherosclerosis.[2] Two more recent classification systems, the CCS (Causative Classification of Stroke)[53] scheme and the ASCOD (Atherosclerosis, Small-vessel disease, Cardiac pathology, Other causes, or Dissection)[54] scheme, acknowledge that multiple potential risk factors can coexist and make it difficult to determine the one underlying cause of stroke, so these scores assign a degree of probability to all potential mechanisms. This offers a more nuanced assessment of potential underlying causes, which might aid global vascular risk factor management in a given patient. Conversely, the TOAST system forces a clearer formulation regarding the underlying cause of stroke, which may be helpful for research classification and clinical decision making (eg, decisions about carotid endarterectomy or anticoagulation). The 3 classification systems largely agree on the list of cardiac conditions that present a high risk for embolism (Table).

Cardioembolic Stroke, Cryptogenic Stroke, and Embolic Stroke of Undetermined Source

Strokes that do not clearly meet the criteria for an established subtype are classified as cryptogenic strokes or strokes of undetermined source.[2,53] About one-third of ischemic strokes

remain cryptogenic after the standard evaluations outlined above.[55] The clinical and neuroimaging characteristics of cryptogenic strokes often suggest a distant embolic source rather than in situ cerebral small-vessel occlusion, which has led to the recent formulation of an entity called embolic stroke of undetermined source (ESUS).[47] A designation of ESUS requires a transthoracic echocardiogram, 24 hours of continuous heart rhythm monitoring, vascular imaging of the cervical and intracranial arteries supplying the brain, and exclusion of other well-defined but rare causes, such as vasculitis or arterial dissection.[47]

Comparisons between ESUS and cryptogenic stroke are hindered by varying definitions of cryptogenic stroke. The ASCOD classification does not recognize cryptogenic stroke because all patients are assigned a combination of scores representing the underlying severity of large artery atherosclerosis, small-vessel disease, and cardiac disease[54]; a typical ESUS patient would have a low ASCOD score for small-vessel disease and medium scores for atherosclerosis or cardiac pathology. In the TOAST classification, a patient lacking a basic evaluation (eg, because of early death after stroke) is diagnosed with a cryptogenic stroke[2]; it is likely that many of these cases would not have qualified as ESUS because even a basic evaluation would have identified an obvious source, such as carotid stenosis or AF. The proposed definition of ESUS[47] most closely aligns with the CCS classification's definition of cryptogenic stroke,[53] which requires unrevealing cardiac evaluation and imaging of the entire cerebral circulation.

Several potential causes of embolism may underlie ESUS. Some cases may represent artery-to-artery embolism from large artery atherosclerotic plaques in the cerebral circulation that go unrecognized because they do not cause significant stenosis of the arterial lumen. Current stroke classification systems mostly require ≥50% luminal stenosis to invoke large artery disease.[54,56] However, recent evidence suggests that vulnerable atherosclerotic plaque can rupture and cause downstream artery-to-artery embolism without necessarily causing luminal stenosis,[57,58] and these currently unrecognized plaques may explain some ESUS cases. The other likely underlying source of ESUS is the heart. Indirect evidence at the time of stroke suggests that many cryptogenic strokes arise from cardiac embolism,[59] and long-term follow-up of cryptogenic stroke patients with continuous heart rhythm monitoring often reveals paroxysmal AF that was not apparent at the time of stroke.[60,61]

Together, these considerations suggest an imperfect but substantial overlap among cryptogenic stroke, ESUS, and cardioembolic stroke (Figure 1). Cryptogenic stroke can be used to refer to a stroke with incomplete evaluation. However, if cryptogenic stroke is stringently defined, it essentially equals ESUS. Throughout the remainder of this article, this formulation of cryptogenic stroke—synonymous with ESUS—will be used. Cryptogenic stroke and cardioembolic stroke are not synonymous because some cases of cryptogenic stroke likely reflect nonstenosing large artery atherosclerosis, but the overlap between cryptogenic and cardioembolic stroke is substantial because many cases of cryptogenic stroke likely reflect undiagnosed paroxysmal AF.[60,61] In addition, emerging evidence suggests that some seemingly cryptogenic strokes originate in the left atrium even though AF is not present.[62]

AF, Other Atrial Dysrhythmias, and Thrombogenic Atrial Substrate

Subclinical AF

Clinically apparent AF has been associated with a 3- to 5-fold higher risk of ischemic stroke.[8,63] These findings reflected AF detected on a routine ambulatory 12-lead ECG, so most trials

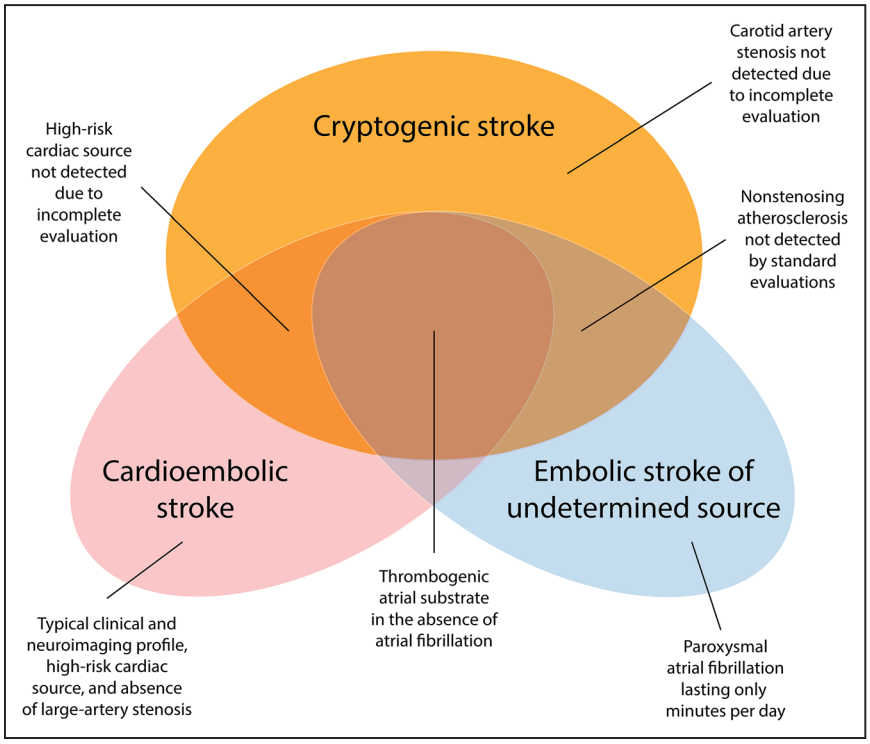

Figure 1. Overlap among cryptogenic stroke, embolic stroke of undetermined source, and cardioembolic stroke.

of antithrombotic therapy in AF have required 2 or more separate episodes of AF, with at least 1 documented by 12-lead ECG.[64] However, implantable cardiac devices, such as pacemakers and defibrillators, increasingly lead to the detection of brief, isolated episodes of asymptomatic AF. To ascertain the significance of these dysrhythmias, the ASSERT study (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial) enrolled 2580 patients with a recently implanted pacemaker or defibrillator, at least 1 stroke risk factor, and no previous AF. Patients with a single episode of AF lasting ≥6 minutes during the first 3 months after device implantation experienced a 2.5-fold higher hazard of stroke during an average 2.5 years of follow-up.[65]

Secondary AF

Cases of AF that newly appear during certain medical or surgical disease states have long been categorized as secondary AF and considered to be temporary conditions without long-term implications for stroke risk. For example, guidelines have traditionally made no recommendations about long-term monitoring or treatment for new-onset perioperative AF or AF occurring in the setting of acute medical disease, such as hyperthyroidism or pulmonary embolism.[66] More current guidelines have cautioned that "sparse data support the notion that patients with AF … in the setting of … these potentially 'reversible' conditions are, in fact, cured of AF after effective treatment or elimination of the condition."[67] Indeed, new-onset AF during hospitalization for sepsis has been associated with long-term stroke risk among those who survived to hospital discharge.[68] Similarly, new-onset perioperative AF is associated with a heightened long-term risk of stroke, especially among patients undergoing noncardiac surgery.[69] These findings were expanded by an analysis from the Framingham cohort in which participants with secondary AF had a similar risk of stroke as those with spontaneous AF.[70] It is, therefore, becoming increasingly clear that patients who develop AF during an acute illness are not freed of the typical AF-related thromboembolic risk even if the AF seemingly terminates after the resolution of their primary illness.

Temporal Relationship Between AF and Stroke

The prevailing mechanistic explanation for the association between AF and stroke has been that fibrillation of the left atrium causes stasis of blood, which encourages the development of thrombus, which then embolizes to the brain.[71] However, it is difficult to explain on this basis the reported association with stroke for a single 6-minute episode of device-detected AF, a 20-beat run of atrial tachycardia,[72] or a transient bout of AF during sepsis or the postoperative period, especially when these studies censored patients once AF was clinically detected.[65,69] It is even more difficult to explain recent in-depth findings from the ASSERT study on the temporal relationship between AF and stroke. Among patients in this study who had both AF and stroke, 31% had no evidence of AF during a median 8 months of continuous heart rhythm monitoring before the stroke and only manifested AF for the first time after the stroke.[73]

AF Precursors and Stroke Risk

If in some cases stroke precedes AF, what is the relationship between stroke and supraventricular rhythm disorders that do not qualify as AF but often serve as precursors to AF? For example, the frequency of premature atrial contractions predicts the subsequent development of AF.[74] Two prospective, community-based cohort studies have documented an association between excessive premature atrial contractions and the risk of ischemic stroke, even after censoring those who developed clinically apparent AF.[75,76] Similarly, paroxysmal supraventricular tachycardia has been associated with a 2-fold higher risk of ischemic stroke in AF-free patients aged ≥65 years, a population in which this tachyarrhythmia often reflects injury to the atrioventricular node and atrial myocardium from age and concomitant vascular disease.[77]

Relationships Between AF, Atrial and Systemic Substrate, and Stroke

Age, male sex, hypertension, diabetes mellitus, valvular heart disease, congestive heart failure, coronary heart disease, chronic kidney disease, inflammatory disorders, sleep apnea, and tobacco use have all been established as risk factors for both AF[78] and stroke.[79] Furthermore, patients with AF often have aortic arch atheromas,[80] which are associated with an increased risk of stroke in this population.[81] Because these atheromas are not routinely ruled out via transesophageal echocardiography after stroke,[33] particularly when another cause such as AF is apparent, the association between AF and stroke may partially reflect embolism from undetected aortic arch lesions. However, even seemingly thorough adjustment for shared risk factors still reveals an independent association between AF and stroke.[82] Not only is there a clear association between AF and stroke in general, but a particular association between AF and strokes with typical neuroimaging patterns of cardiac embolism.[83,84] Although some proportion of the association between AF and stroke may be because of shared systemic risk factors, these risk factors cannot entirely explain the association between AF and stroke.

It may be that other atrial factors besides AF can result in thromboembolism, and in some cases, AF may be a lagging marker of these other thrombogenic atrial abnormalities. AF often occurs in the setting of atrial abnormalities, such as endothelial dysfunction,[85] fibrosis,[86] impaired myocyte function,[87] chamber dilatation,[88] and mechanical dysfunction in the left atrial appendage.[89] These abnormalities of atrial substrate have recently been associated with stroke risk independently of AF. P-wave terminal force in ECG lead V_1, an accepted marker of left atrial abnormalities, such as fibrosis, elevated filling pressures, and dilatation,[90–92] has been associated with incident stroke independently of AF in several different longitudinal cohort studies.[93–95] Similarly, echocardiographic measures of left atrial size and contractile function have been associated with stroke independently of AF.[96–101] Furthermore, these markers of abnormal atrial substrate seem to signal a specific risk of atrial thromboembolism rather than general vascular risk because ECG-defined left atrial abnormality is associated specifically with cryptogenic or embolic stroke subtypes and not with in situ cerebral small-vessel occlusion.[94,95]

Thrombogenic Atrial Substrate

On the basis of the findings discussed above, it is likely that the relationship between AF and stroke is more complex than

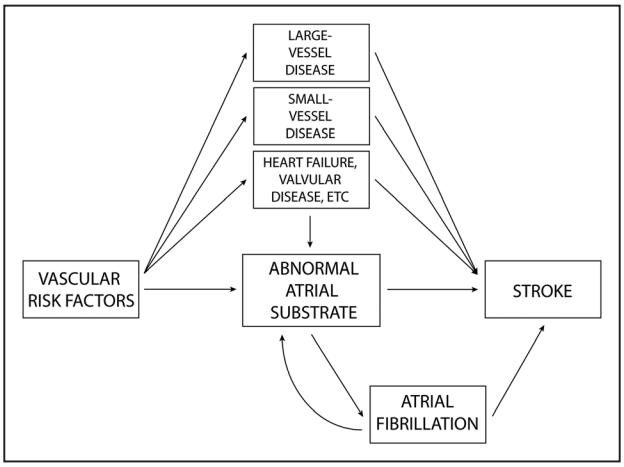

Figure 2. Relationship among systemic risk factors, atrial substrate, atrial fibrillation (AF), and stroke. Aging and systemic vascular risk factors lead to an abnormal atrial substrate, or atrial cardiomyopathy, that can itself result in both AF and thromboembolism. Once AF develops, it directly worsens atrial contractile function and secondarily worsens the underlying atrial cardiomyopathy via structural remodeling, both of which further increase thromboembolic risk. At the same time, the systemic vascular risk factors that give rise to atrial cardiomyopathy and AF also increase stroke risk via nonatrial mechanisms, such as large artery atherosclerosis, systolic heart failure, and cerebral small-vessel disease.

currently appreciated. The available evidence is not consistent with AF as a necessary and sufficient cause of stroke. Instead, it seems that AF, atrial substrate, and systemic substrate interact in complex ways in the pathway leading to stroke.[62] Aging and systemic vascular risk factors lead to an abnormal atrial substrate, or atrial cardiomyopathy, that can itself result in both AF and thromboembolism. Once AF develops, it directly worsens atrial contractile function and secondarily worsens the underlying atrial cardiomyopathy via structural remodeling, both of which further increase thromboembolic risk. This would explain why there seems to be an increase in stroke risk soon after the onset of AF[102] and why stroke risk seems to increase in proportion to the burden of AF.[103–105] At the same time, the systemic vascular risk factors that give rise to atrial cardiomyopathy and AF also increase stroke risk via nonatrial mechanisms, such as large artery atherosclerosis, systolic heart failure, and cerebral small-vessel disease (Figure 2).

Such an interaction among AF, thrombogenic atrial substrate, and systemic vascular substrate would explain the lack of temporal synchrony between AF and stroke. It would explain why vascular risk factors so strongly modify the association between AF and stroke. Patients with a single episode of subclinical AF and >2 vascular risk factors face a 4-fold higher risk of stroke,[65] whereas AF in young and otherwise healthy patients does not seem to significantly increase stroke risk.[106] Lastly, a thrombogenic atrial substrate would explain many strokes that are currently considered cryptogenic. Many cryptogenic stroke patients do not manifest AF until months or years after the stroke, and 70% do not manifest AF at all even after 3 years of continuous heart rhythm monitoring.[61] It seems likely that some of these cryptogenic strokes arose from the left atrium even though AF was not (yet) apparent.

Therapy to Prevent Cardioembolic Stroke

The risk factors and diagnostic criteria discussed above are vital for informing therapeutic strategies for preventing cardioembolic stroke.

Atrial Fibrillation

Vitamin K Antagonists Versus Antiplatelet Drugs

The mainstay of preventive therapy for cardioembolic stroke is anticoagulation. AF is the most common risk factor for cardioembolic stroke, and in 8 trials involving ≈10 000 patients with chronic nonvalvular AF and no previous stroke, adjusted-dose warfarin therapy significantly decreased the risk of ischemic stroke compared with aspirin (odds ratio, 0.53; 95% confidence interval [CI], 0.41–0.68).[7] Although warfarin significantly increased the risk of intracranial hemorrhage (odds ratio, 1.98; 95% CI, 1.20–3.28), it significantly reduced the more clinically relevant composite end point of ischemic or hemorrhagic stroke (odds ratio, 0.68; 95% CI, 0.54–0.85).[7]

Non–Vitamin K Antagonists

Since 2008, oral anticoagulant drugs other than vitamin K antagonists have been available. Non–vitamin K antagonist oral anticoagulants (NOACs) work as either direct thrombin inhibitors (dabigatran) or inhibitors of factor Xa (rivaroxaban, apixaban, and edoxaban). In randomized trials involving patients with AF, these drugs performed similar to warfarin in regard to ischemic stroke risk (risk ratio [RR], 0.92; 95% CI, 0.83–1.02) while significantly reducing the risk of hemorrhagic stroke (RR, 0.49; 95% CI, 0.38–0.64), resulting in a net reduction in overall stroke risk (RR, 0.81; 95% CI, 0.73–0.91) and mortality (RR, 0.90; 95% CI, 0.85–0.95).[107] Among AF patients considered unsuitable for vitamin K antagonists, apixaban significantly reduced the risk of ischemic stroke (hazard ratio, 0.37; 95% CI, 0.25–0.55) without a significant increase in hemorrhagic stroke (hazard ratio, 0.67; 95% CI, 0.24–1.88) compared with aspirin.[108]

Compared with warfarin, these newer anticoagulants offer the advantages of a fixed dose with no need for frequent laboratory monitoring of therapeutic effect. These agents initially lacked therapies to reverse their anticoagulant effect in cases of major bleeding, but a reversal agent (idarucizumab) was recently approved for dabigatran[109] and approval of a reversal agent for the factor Xa inhibitors (andexanet) seems likely soon.[110] NOACs also cost more than vitamin K antagonists, such as warfarin, but analyses incorporating the costs of laboratory monitoring and the downstream costs of strokes and hemorrhages indicate that these newer agents are reasonably cost-effective for both primary[111] and secondary[112] stroke prevention.

Knowledge Gaps Regarding Antithrombotic Therapy

Several evidence gaps complicate the application of the guidelines above to routine clinical practice. First, what counts as low risk in regard to stroke? There remains considerable controversy about the relative and absolute risks of stroke in patients with AF who have few or no concomitant risk factors.[106,113,114]

Second, what counts as AF? The randomized trials discussed above enrolled patients with clinically apparent AF,

patients who had at least 2 episodes of AF and who had a sufficient burden of AF for it to be captured on a routine 12-lead ECG. It remains unclear whether patients with subclinical AF would similarly benefit from anticoagulation for stroke prevention. To address this question, the ARTESiA trial (Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation; NCT01938248) and NOAH trial (Non-Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes; NCT02618577) are enrolling patients without overt AF but with device-detected episodes of AF lasting ≥6 minutes. These trials of NOAC versus aspirin therapy are expected to be completed in 2019.

Third, might anticoagulation reduce stroke risk in patients with abnormal atrial substrate but no evidence of AF? Post hoc analyses of at least one randomized trial support this hypothesis.[115] More information will be forthcoming from several randomized trials enrolling patients with cryptogenic stroke. The NAVIGATE ESUS (Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source; NCT02313909) and RE-SPECT ESUS (Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate vs. Acetylsalicylic Acid in Patients With Embolic Stroke of Undetermined Source; NCT02239120)[116] trials are randomly assigning patients with cryptogenic stroke to therapy with a NOAC or aspirin. These trials do not selectively enroll patients based on markers of a potential cardioembolic source and allow the inclusion of patients with ≤6 minutes per day of AF on poststroke heart rhythm monitoring. Therefore, if positive, the relative benefits of anticoagulation will be unclear with regard to the different potential stroke mechanisms underlying cryptogenic stroke: subclinical AF, atrial cardiomyopathy and no AF, and nonstenosing large artery atherosclerosis and no atrial dysfunction. The ATTICUS trial (Apixaban for Treatment of Embolic Stroke of Undetermined Source; NCT02427126) of apixaban or aspirin will enroll patients with cryptogenic stroke and at least one marker suggestive of an underlying cardioembolic source. The outcome will be new infarcts on follow-up magnetic resonance imaging rather than the traditional end point of clinically overt stroke. The ARCADIA trial (Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke; clinicaltrials.gov registration pending) will enroll patients with cryptogenic stroke and at least one marker of atrial cardiomyopathy, randomly assign them to apixaban or aspirin, and assess the primary outcome of recurrent stroke.

Other Preventive Therapies

Besides anticoagulation, other strategies offer promise for reducing the risk of cardiac embolism in patients with AF. First, evidence that most AF-related emboli originate in the left atrial appendage[117] has led to surgical and transcatheter techniques for obliterating the appendage in an effort to reduce stroke risk. The PROTECT AF randomized trial (WATCHMAN Left Atrial Appendage System for Embolic PROTECTion in Patients With Atrial Fibrillation) compared the risk of stroke with standard warfarin therapy versus implantation of the Watchman left atrial appendage closure device. The noninferiority margin was met at the initial analysis[118] and the device proved more effective than warfarin after 4 years of follow-up,[119] leading to recent regulatory approval of the device. However, uncertainties remain. Although the device significantly reduced the risk of any stroke (RR, 0.68; 95% CI, 0.72–3.68), this was driven entirely by a remarkable reduction in hemorrhagic stroke (RR, 0.15; 95% CI, 0.03–0.49), whereas there was no apparent reduction in ischemic stroke risk (RR, 1.26; 95% CI, 0.72–3.28). It is unclear how left atrial appendage closure would compare against NOACs, which have a significantly lower risk of hemorrhagic stroke than warfarin. Given this uncertainty, current guidelines cautiously recommend the use of these devices only in patients at high risk of ischemic stroke and an absolute contraindication to anticoagulation.[120–122] However, PROTECT AF did not include patients with contraindications to long-term anticoagulation.

When medical therapy fails to prevent AF symptoms, such as palpitations, dyspnea, and lightheadedness, catheter ablation therapies can be used to reduce the occurrence of AF and maintain normal sinus rhythm.[123] In randomized clinical trials, antiarrhythmic drugs have not decreased stroke risk,[124] despite leading to a substantially higher rate of normal sinus rhythm,[124,125] suggesting that maintenance of normal rhythm alone does not prevent stroke. Most strokes in these trials occurred after cessation of anticoagulant therapy,[126] suggesting that anticoagulant therapy continues to provide protection against thromboembolism even after the dysrhythmia has apparently resolved. This may be because antiarrhythmic drugs rarely completely obliterate the dysrhythmia or because even successful termination of AF does not eliminate the underlying thrombogenic atrial substrate. For now, guidelines recommend against cessation of anticoagulant therapy after catheter AF ablation.[122] It remains unclear whether more effective AF termination via catheter-based ablation might serve as a useful adjunct to anticoagulation for reducing stroke risk in AF.

A recent analysis demonstrated a significant reduction in left atrial size and AF recurrence in patients who underwent intensive vascular risk factor management after catheter ablation of AF compared with those who received usual care.[127] Therefore, future trials may be warranted to assess whether treatment of atrial substrate reduces the risk of stroke. In addition, if AF is a downstream marker of vascular risk factors that may separately result in nonatrial stroke mechanisms, such as carotid atherosclerosis or cerebral small-vessel disease, then a comprehensive approach to stroke prevention in patients with AF should explore and emphasize intensive management of all vascular risk factors rather than just focusing on recommendations regarding anticoagulant therapy. As of yet, few data are available on the effects of intensive vascular risk factor management on stroke risk in AF, and the topic of global vascular risk factor management is not emphasized as an important consideration in current consensus guidelines.[67]

Systolic Heart Failure

Several randomized clinical trials have compared warfarin versus antiplatelet therapy in patients with a reduced ejection fraction. No significant differences were found in their primary cardiovascular composite end points,[128–130] but warfarin resulted in a significant reduction in overall stroke in the

WATCH (Warfarin and Antiplatelet Therapy in Chronic Heart Failure) trial[130] and ischemic stroke in the WARCEF (Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction) trial.[128] However, anticoagulation is not recommended for primary stroke prevention, given low absolute risks and the increased bleeding risk associated with anticoagulation.[121] For heart failure patients with previous stroke, indirect evidence from WARCEF does support a role for anticoagulation, especially with an ejection fraction <15%.[131]

Patent Foramen Ovale

No evidence supports a benefit of antithrombotic treatment or PFO closure in patients with a PFO and no previous stroke or transient ischemic attack. Therapies to prevent recurrent stroke in patients with PFO will be discussed in a separate section of this Compendium (see section on Cryptogenic Stroke).

Aortic Arch Atheroma

Similarly, no evidence exists to guide specific primary stroke prevention in patients with aortic arch atheroma. However, given their manifest atherosclerotic disease, these patients stand to benefit from general recommendations about primary prevention of stroke.[121] Data on therapies to prevent recurrent stroke in patients with aortic atherosclerosis[35] will be discussed in a separate section of this Compendium (see section on Cryptogenic Stroke).

Prosthetic Heart Valves

Few data from randomized clinical trials exist to guide therapy for stroke prevention in patients with prosthetic heart valves. On the basis of the available observational data, guidelines provide detailed recommendations for vitamin K antagonist therapy according to the type and position of the replaced valve.[121] The RE-ALIGN trial (Dabigatran Etexilate in Patients With Mechanical Heart Valves), a phase 2 randomized trial of dabigatran versus warfarin in patients with AF and recent implantation of mechanical aortic or mitral valves, was stopped early because of a higher rate of stroke and bleeding with dabigatran.[132]

Recent MI

Multiple randomized clinical trials performed several decades ago found that anticoagulant therapy lowered the risk of ischemic stroke after acute MI compared with antiplatelet therapy.[16] These trials were performed before the widespread use of coronary stents and dual antiplatelet therapy, and it is becoming increasingly clear that triple antithrombotic therapy with an anticoagulant drug and 2 antiplatelet drugs results in extremely high rates of bleeding. Therefore, current professional guidelines state that anticoagulant therapy is reasonable for patients with ST elevation MI who have evidence of left ventricular mural thrombus, but only a weak recommendation is given for anticoagulation in patients with anterior apical akinesis or dyskinesis but no evidence of thrombus.[133] However, standard echocardiographic assessment misses many cases of left ventricular mural thrombus seen by cardiac magnetic resonance imaging.[134] Furthermore, therapeutic options besides triple therapy with warfarin, aspirin, and clopidogrel, such as a combination of a low-dose NOAC and a single antiplatelet agent, have not been rigorously evaluated in patients with ST elevation MI and mural thrombus. It therefore remains unclear whether better algorithms for detecting post-MI mural thrombus[135] and newer therapeutic strategies can reduce the risk of stroke after acute MI.

Infective Endocarditis

Antithrombotic therapy is a mainstay of stroke prevention, but patients with infective endocarditis face a high risk of hemorrhagic stroke. There is a paucity of high-level evidence and therefore considerable controversy regarding starting or continuing antithrombotic therapy in this population.[136]

Acute Treatment of Cardioembolic Stroke

Despite the preventive treatments discussed above, many patients with cardiac disease will experience an ischemic stroke. Treatment options for acute ischemic stroke are thus discussed below.

At least 9 randomized clinical trials have assessed long-term neurological outcomes of patients treated with intravenous thrombolysis after acute ischemic stroke. A patient-level meta-analysis of these trials found that thrombolysis increased the rate of good neurological outcomes (defined as no residual disability) by 10% in absolute terms if given within 3 hours of stroke onset.[137] Thrombolysis within the 3- to 4.5-hour period after onset led to a less robust but still statistically significant benefit of 5% in absolute terms. However, cardioembolic stroke commonly occurs in settings that preclude or complicate the use of intravenous thrombolysis. Patients with cardiac disease can present with stroke, despite therapeutic levels of anticoagulation. Observational data support the long-standing recommendation to proceed with intravenous thrombolysis even given active vitamin K antagonist use as long as the international normalized ratio is <1.7.[138] Less is known about the use of thrombolysis in patients receiving NOAC therapy. Expert opinion recommends avoiding thrombolytic therapy unless it can be firmly established that the patient did not take a NOAC for at least 48 hours and has laboratory evidence of normal renal function and normal coagulation parameters.[139] Cardioembolic stroke can also occur in the setting of a recent surgery or invasive procedure, such as in patients with recent valve surgery or acute MI leading to percutaneous coronary intervention. A small number of case series indicate that although intravenous thrombolysis in this setting may lead to surgical site hemorrhage, such an occurrence does not seem to have a strong effect on long-term outcomes.[139] However, several larger studies have found a link between bleeding and worsened ischemia,[140,141] so caution must be exercised when deciding on the use of intravenous thrombolysis in postsurgical patients.

Many patients remain permanently disabled after a stroke even after treatment with intravenous thrombolysis. During the past several decades, this has spurred the development of catheter-based techniques for recanalizing intracranial arteries that remain occluded, despite intravenous thrombolysis. Several randomized clinical trials in the past few years have established that intra-arterial mechanical thrombectomy with the newest generation of catheters, which deploy retrievable stents, improves long-term neurological outcomes.[142] On the

basis of these results, the American Heart Association gives a Class I, Level of Evidence A recommendation to mechanical thrombectomy in patients who meet all of the following criteria:

1. Adult with no prestroke disability (modified Rankin Scale score ≤1);
2. Acute ischemic stroke from occlusion of the intracranial internal carotid artery or first segment of the middle cerebral artery;
3. National Institutes of Health Stroke Scale score ≥6;
4. ASPECTS CT imaging score ≥6;
5. Intravenous thrombolysis given within 4.5 hours of stroke onset; and
6. Groin puncture can occur within 6 hours of stroke onset.

Of relevance to patients with cardioembolic stroke in the setting of therapeutic anticoagulation or a recent invasive procedure, the guidelines state that in "… carefully selected patients with anterior circulation occlusion who have contraindications to intravenous r-tPA, endovascular therapy with stent retrievers completed within 6 hours of stroke onset is reasonable (Class IIa; Level of Evidence C)."

If anticoagulation is indicated to prevent stroke recurrence after a cardioembolic stroke, the timing of starting or resuming anticoagulation is uncertain. A meta-analysis of trials found no benefit overall and no identifiable subgroups that benefited from starting anticoagulant therapy within the first 2 weeks after stroke.[143] Given the relative equipoise, practice varies widely, with some clinicians starting anticoagulants within the first week to minimize recurrent embolization and others waiting several weeks to minimize the risk of hemorrhagic transformation of an acute infarct.

Future Directions

On the basis of demographic projections and secular trends in vascular risk factors, cardiac embolism will be an increasingly common cause of stroke. Therefore, future efforts to decrease the burden of stroke will require better prevention, detection, and treatment of cardiac risk factors. Especially important knowledge gaps that will need to be addressed include (1) the full relationship between AF, thrombogenic atrial substrate, and stroke; (2) optimal strategies for population-level screening and treatment of subclinical AF; and (3) optimal antithrombotic strategies for preventing cardiac embolism in the setting of heart failure and acute MI. Further advances in these areas will help continue the steady decrease in stroke incidence seen in high-income countries over the past several decades and help to start the process of decreasing stroke incidence in low- and middle-income countries.[144] Given that stroke is the second leading cause of death and a leading cause of disability worldwide,[1] such advances promise to make a significant contribution to global health.

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