Neurologists have played a key role in understanding the causal relationship between atrial fibrillation (AF) and stroke since the frequent coincidence of embolic stroke and AF was reported in the 1970s. Since then, the Framingham Heart Study and other observational studies have reported strong epidemiologic associations between nonvalvular AF and stroke. Randomized trials of warfarin vs aspirin demonstrated the benefits in preventing a first or recurrent stroke in people with longstanding AF; these benefits were extended to those with paroxysmal AF. Trials of direct oral anticoagulants demonstrated greater safety than warfarin, with similar efficacy. For many vascular neurologists, AF is regarded as an old, if important, success story in stroke prevention. One may wonder, what more could there be to say about AF and stroke?

The past decade, however, has witnessed a resurgence in understanding of the relationship of AF to stroke. First, occult AF has been recognized as an important contributor to unexplained strokes, generating enthusiasm among cardiac electrophysiologists and engineers to find ways to identify AF in stroke survivors. Second, the model of the mechanisms by which AF leads to stroke has been reconsidered, leading to the concept of atrial cardiopathy. Third, observational studies have led to the exciting hypothesis that atrial cardiopathy itself, even in the absence of AF, may be a risk factor for stroke. Finally, clinical trials are now beginning to provide evidence that treatment of atrial cardiopathy may reduce the risk of stroke, ushering in a potential second era in our understanding of the relationship of disorders of the atria to stroke risk.

**Unexplained Stroke and Occult Atrial Fibrillation**

After thorough evaluation, 30% to 40% of ischemic strokes may be considered of unknown cause. Initially, strokes of unknown cause were referred to as cryptogenic strokes, indicating the mystery inherent in their origins. The original definition of cryptogenic stroke allowed inclusion of people with multiple potential causes of stroke, as well as those who underwent incomplete investigation. The more precise category, *embolic stroke of undetermined source* (ESUS), has since been widely adopted. The advantage of the ESUS definition is that it requires that the person with stroke undergo a full etiologic evaluation, including exclusion of 1) small deep infarcts in the distribution of penetrating cerebral vessels; 2) intracranial or extracranial stenosis through vascular imaging; 3) a definite cardioembolic source through transthoracic echocardiography, electrocardiography (ECG), and at least 24 hours of cardiac monitoring; 4) other well-defined if unusual causes of stroke such as vasculitis, hypercoagulability, or dissection. The appearance of these infarcts, generally affecting the territory of major branches or distal end vessels of the cerebral arterial tree, suggests a distant embolic source.

Occult paroxysmal AF (PAF) is among potential mechanisms of ESUS and is important to identify because it is known that oral anticoagulants substantially reduce the risk of stroke in persons with AF. Because AF may be asymptomatic, intermittent, and infrequent, many individuals may not have a history of AF or evidence of it during a brief hospital stay at the time of stroke. In fact, 25% of those with AF do not know they have the disorder until a thromboembolic event occurs. Similarly, a history of palpitations or tachycardia is not helpful in establishing a diagnosis of AF, because most people with such symptoms are in sinus rhythm or other type of benign dysrhythmia when these symptoms occur. Thus, some form of additional cardiac monitoring is usually employed to detect occult, or difficult to find, AF after stroke. In the old days, Holter monitoring was done for 24 to a maximum of 72 hours to search for PAF. Now, however, 30-day external cardiac monitors or implanted cardiac monitors that can be worn for up to 3 years may be used.
In 2 randomized controlled trials, outpatient cardiac monitoring after cryptogenic stroke was shown to increase detection of AF beyond that accomplished with standard monitoring approaches. The EMBRACE trial showed that 30 days of continuous monitoring with an external device was superior to the standard 24 hours of continuous monitoring. The CRYSTAL-AF trial demonstrated the benefit of using an implanted cardiac monitoring device that can capture PAF for up to 3 years after implantation, compared to standard monitoring. Although these trials were designed with discovery of AF, rather than clinical outcome events, as their primary outcome, finding AF had clinical implications. More than 95% of those with AF detected were placed on oral anticoagulation therapy for secondary stroke prevention. In CRYSTAL-AF, moreover, the stroke rate at 1 year was lower in participants randomly assigned to the implantable cardiac monitor (ICM) compared with those assigned to conventional monitoring (7.1% vs 9.1%, P > .05), although the result did not reach statistical significance. Because the trials did not have a reduction in clinical outcome events as primary outcomes, recommendations to perform 30 days of cardiac monitoring or to insert ICMs in patients with unexplained strokes have not yet been incorporated into clinical practice guidelines with the highest level of evidence. Because the studies have not yet compared 30 days of monitoring to a longer time window, such as 3 years, the duration of monitoring remains uncertain. Secondary prevention guidelines recommend that 30 days of cardiac monitoring be considered.

In practice, it is likely that decisions about how long to monitor patients will depend on individualized characteristics. A reasonable clinician may limit monitoring to several weeks in a younger, otherwise healthy stroke patient who has no evidence of structural heart disease and lengthen monitoring or have a device implanted in a person with a history of heart disease and evidence of ectopy on initial shorter-term monitoring. This approach would be consistent with data suggesting that the likelihood of detecting AF can be predicted by patient history and ECG indices (eg, a prolonged PR interval) or biomarkers (eg, brain natriuretic peptide [BNP]).

**Atrial Cardiopathy in Context of Atrial Fibrillation**

Traditionally, AF was presumed to cause embolic stroke based on the pathophysiology represented by Virchow’s famous triad: stasis, coagulability, and endothelial injury or dysfunction. According to the interpretation of this paradigm, fibrillation of the atrium and lack of effective atrial contraction lead to stasis, permitting blood clots to form in the left atrium or the left atrial appendage (LAA). Blood clots then embolize to the brain or systemic circulation, causing ischemic stroke and peripheral emboli. In this model, it is stasis in the fibrillating atrium—often referred to as a bag of worms—for the characteristic appearance of the wiggling atrial walls—that creates the risk of stroke.

Recent evidence, however, challenges this simple logic (Table 1). Studies among large numbers of people with implanted cardiac devices followed over time, for example, provide evidence that brief, asymptomatic runs of PAF occur commonly and that even very brief asymptomatic runs of AF may be associated with an increased risk of ischemic stroke. There is also a temporal disassociation between when AF occurs and embolic stroke. People can have ischemic strokes when they are not in AF, and often weeks removed from the occurrence of AF. In the ASSERT and TRENDS studies, only 8% to 28% of patients were in AF in the 30 days prior to their stroke. A clear temporal association is generally considered a critical factor in ascribing causality to a relationship; thus, the absence of a temporal association between AF and stroke suggests that the fibrillating atrium itself may not be the direct cause of stroke in most people with AF.

The evidence that AF may be a marker of stroke risk, rather than its proximate cause, has been reviewed elsewhere and is briefly summarized here. Cardiac conduc- tion abnormalities other than AF (eg, paroxysmal supraventricular tachycardia and excessive supraventricular ectopic activity) have been associated with a doubling of stroke risk. There may also be a disconnection between surface ECG evidence of AF and atrial contraction patterns, such that echocardiographic evidence of atrial contraction and flow patterns typical of AF may occur despite electrical normal sinus rhythm on ECG. Polymorphisms in genes associated with AF, moreover, may also be associated with stroke even before evidence of AF can be seen on ECG.

<table>
<thead>
<tr>
<th>Classic mechanisms (“Virchow’s triad”)</th>
<th>Stasis</th>
<th>Endothelial dysfunction</th>
<th>Thrombophilia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other potential mechanisms involving left atrium</td>
<td>Myocardial fibrosis</td>
<td>Impaired myocyte function</td>
<td>Chamber dilatation</td>
</tr>
<tr>
<td>Left atrial appendage characteristics potentially associated with thromboembolic risk</td>
<td>Morphology (nonchicken wing morphologies such as cauliflower, cactus, windsock)</td>
<td>Increased size</td>
<td>Number of lobes</td>
</tr>
</tbody>
</table>

**TABLE 1. MECHANISMS OF ATRIAL DYSFUNCTION AND THROMBOEMBOLISM**

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a. Event Monitor Belt for Recording Paroxysmal Atrial Fibrillation After a Cerebral Ischemic Event (NCT00846924)
b. Cryptogenic Stroke and Underlying Atrial Fibrillation (NCT00924638)
c. Prevalence of Subclinical Atrial Fibrillation in Elderly Patients With Hypertension, Detected Using an External Loop Recorder (NCT02401854)
d. A Prospective Study of the Clinical Significance of Atrial Arrhythmias Detected by Implanted Device Diagnostics (NCT00279981)
Among cardiologists, it is also generally acknowledged that the LAA, not the fibrillating atrium itself, is the most common site for thrombus formation. When present, thrombi in persons with AF are found in the LAA in more than 90% of cases. Features of the LAA, including shape, size, and number of lobes may play a role in determining embolic potential. In a retrospective analysis of 932 people with AF, cactus, windsock, and cauliflower LAA morphologies were associated with a higher stroke risk than chicken wing morphology. Although uncertainty persists, it is possible that among those with AF, increased trabeculations and lobules found in nonchicken-wing morphologies contribute to likelihood of thrombus formation.

Other acquired abnormalities of the left atrium may also provide a milieu for thrombus formation by promoting stasis, endothelial dysfunction, and hypercoagulability. Left atrial enlargement (LAE), for example, has been associated with spontaneous echocardiographic contrast, considered an echocardiographic marker of a prothrombotic tendency, and frank thrombus formation. Endothelial dysfunction and hypercoagulability may also occur in diseased atria prior to the occurrence of frank stasis or atrial fibrillation. Myocardial fibrosis, representing the progressive accumulation of fibrotic tissue within the myocardium, for example, is thought to be the fundamental cause of AF and may increase risk of cardiac embolism independent of AF. Fibrosis occurs with aging and inflammatory conditions such as systemic infections and autoimmune disorders and may also occur with lower-grade or subclinical inflammatory states (eg, coronary artery disease). Atrial fibrosis may precede AF or be present even in the absence of development of AF.

These data suggest that ECG-defined AF does not provide the sole mechanism of embolic events in people with evidence of atrial dysfunction. Other mechanisms, such as other atrial arrhythmias, genetic factors, atrial enlargement, fibrosis, inflammation, or coagulation disturbances in patients with an underlying abnormal atrial substrate may provide an explanation of embolic stroke even in the absence of AF. The ECG hallmark of AF may instead be another marker of an underlying risk of embolic stroke associated with atrial dysfunction, rather than the specific cause. The traditional concept of the fibrillating atrium as the bag of worms predisposing to stroke may need to be rethought.

**Atrial Cardiopathy and Stroke**

There is no consensus on how to define atrial cardiopathy. Left atrial dysfunction occurs along a continuum, from normal to severely diseased, and at some point along this continuum, the risk of thromboembolic events begins to increase. There are several potential biomarkers indicative of atrial cardiopathy, including structural, electrophysiologic, imaging, and serum biomarkers (Table 2).

Left atrial enlargement (LAE) is associated with incident ischemic stroke risk after adjusting for several confounders including AF in population-based studies. In a study of 655 people with AF in northern Manhattan who were followed for a median of 4 years, moderate to severe LAE independently predicted recurrent stroke risk and, in particular, predicted strokes considered likely related to embolism (adjusted HR 2.83, 95% CI 1.03-7.81). On standard ECG, P-wave terminal force in lead V1 (PTFV1) is a marker of atrial dysfunction and risk of ischemic stroke. Electrical conduction through the atria is reflected by PTFV1. Increased PTFV1 predicts incident AF and ischemic stroke risk independently of AF. A case-cohort analysis in the Northern Manhattan Study also found an association between PTFV1 and incident ischemic stroke (adjusted HR 1.20, 95% CI 1.0-1.39) and particularly stroke of embolic subtypes (adjusted HR 1.31, 95% CI 1.08-1.58). More than

### Table 2. Biomarkers Associated with Atrial Cardiopathy and Stroke Risk

<table>
<thead>
<tr>
<th>Category of biomarker</th>
<th>Specific examples</th>
</tr>
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<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>Permanent atrial fibrillation, Persistent atrial fibrillation, Paroxysmal atrial fibrillation (PAF)</td>
</tr>
<tr>
<td></td>
<td>“Occult” (difficult to diagnose, infrequent intermittent paroxysmal atrial fibrillation)</td>
</tr>
<tr>
<td>Atrial ectopy</td>
<td>Excessive supraventricular ectopic activity (ESVEA), Paroxysmal supraventricular tachycardia, Prolonged PR interval, Increase P-wave terminal force in lead V1 (PTFV1)</td>
</tr>
<tr>
<td>Atrial structural abnormality</td>
<td>Left atrial enlargement (LAE), Left atrial appendage morphological variations, Myocardial fibrosis (cardiac magnetic resonance imaging evidence of delayed enhancement)</td>
</tr>
<tr>
<td>Atrial functional abnormality</td>
<td>Reduced left atrial appendage flow velocity</td>
</tr>
<tr>
<td>Serum biomarkers</td>
<td>N-terminal pro B-type natriuretic peptide (NT-proBNP), High-sensitivity cardiac troponin T (cTnT)</td>
</tr>
<tr>
<td>Thrombotic potential</td>
<td>Spontaneous echocardiographic contrast</td>
</tr>
<tr>
<td>Genetics</td>
<td>Genes associated with atrial fibrillation</td>
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</table>
a 200 ms prolongation of the PR interval on ECG is another possible biomarker of atrial disease.19

Serum biomarkers indicative of cardiac dysfunction, and particularly of atrial dysfunction, have been associated with stroke risk, even in people without known AF. For example, N-terminal probrain natriuretic peptide (NT-proBNP), is released by the myocardium in response to stretch, increases in heart failure, structural heart disease, AF, and other situations of ventricular strain.20 Concentrations of NT-proBNP predict cardiovascular events, including incident AF, detection of AF after stroke, subclinical cerebrovascular disease, and cardioembolic stroke. 21

A limited number of studies have simultaneously explored multiple biomarkers of atrial cardiopathy. In the Cardiovascular Health Study, among 3,723 participants free of both stroke and AF at baseline, PTFV1 (HR per 1,000 mcV*m 1.04; 95% CI 1.00-1.08), NT-proBNP (HR per doubling of NT-proBNP 1.09; 95% CI 1.03-1.16), and incident AF (HR 2.04; 95% CI, 1.67-2.48) were each independently associated with incident stroke. Left atrial dimension was not associated with stroke risk independently of these other markers.22 These findings suggest that ECG and serum biomarkers may be early correlates of atrial cardiopathy, occurring even prior to structural changes in the atrium.

Clinical Implications

Emerging evidence suggests that atrial cardiopathy without evidence of AF may be optimally treated with anticoagulants to prevent recurrent stroke, just as is currently standard for people with AF. Among participants in the WARSS study, which was a multicenter randomized trial of anticoagulation with warfarin vs aspirin for secondary prevention of stroke among people with strokes of noncardioembolic mechanism, blood samples were stored for future ancillary analyses. Although the primary result of the trial was that there was no evidence of benefit of anticoagulation over aspirin among all patients enrolled in the trial, there was evidence of a benefit among those with elevations in NT-proBNP. Among participants who had NT-proBNP levels of 750 pg/ml or more, treatment with warfarin was associated with a reduced risk of stroke or death at 2 years when compared with treatment with aspirin (P=.021). Similarly, in a secondary analysis of the NAVIGATE-ESUS trial, there was evidence that anticoagulation was of greater benefit than aspirin among those with moderate to severe left atrial enlargement.23 These results, although post hoc, provide a rationale for conducting a clinical trial testing anticoagulation vs standard of care antiplatelet therapy among people with ESUS and atrial cardiopathy.24

Future Directions

Recently, the National Institute of Neurological Disorders and Stroke (NINDS) provided support for the ARCADIA trial, with a primary objective to test the hypothesis that the direct-acting oral anticoagulant apixaban is superior to aspirin for the prevention of recurrent stroke in people with ESUS and atrial cardiopathy, but without known AF. The secondary objective is to test the hypothesis that relative efficacy of apixaban over aspirin increases with the severity of atrial cardiopathy. The trial is being conducted through the NINDS StrokeNet and is also supported by Bristol Meyers Squibb-Pfizer and Roche. In ARCADIA, 1,100 people with ESUS and atrial cardiopathy will be randomly assigned to receive either apixaban 5 mg twice daily (or a dose of 2.5 mg twice daily to those who meet criteria for a reduced dose) or to aspirin 81 mg daily. All participants must have standard diagnostic testing to exclude small vessel strokes, large artery stenosis, and definite source of cardioembolism, including AF. Then, in a second step prior to randomization, participants undergo testing for 1 of 3 biomarkers of atrial cardiopathy:

- PTFV1 >5,000 μV*ms on 12-lead ECG;
- Serum NT-proBNP >250 pg/ml;
- Left atrial diameter index ≥3 cm/m² on echocardiogram (severe left atrial enlargement).

The primary efficacy endpoint of ARCADIA is recurrent stroke of any type (ischemic, hemorrhagic, or of undetermined type). The secondary efficacy endpoints are: a) composite of recurrent ischemic stroke or systemic embolism, and b) composite of recurrent stroke of any type or death from any cause. Safety will also be assessed.

Although the level of each biomarker most appropriate for making a determination of atrial cardiopathy remains uncertain, the use of several biomarkers, relatively low thresholds, and requirement that only 1 criterion be met should facilitate testing of the secondary ARCADIA hypothesis that atrial cardiopathy represents a spectrum of illness, with different levels of severity. Ideally, this will provide clinicians with the information needed to balance the risks and benefits of anticoagulation in patients with atrial cardiopathy.

Conclusion

Atrial cardiopathy may be among the mechanisms of unexplained stroke, and people with evidence of atrial cardiopathy constitute a group in whom clinical trials are warranted to test anticoagulation versus antiplatelet therapy to reduce stroke recurrence risk. More studies are needed, however, to determine both the degree of overlap between atrial cardiopathy biomarkers and to establish which ones, alone or in combination, are most useful in predicting the risk of stroke and response to anticoagulation therapy.25

(Continued on page 46)


Disclosure
MSVE has disclosures at www.practicalneurology.com