Stroke

SPECIAL REPORT

Atrial Fibrillation Detection and Load: Knowledge Gaps Related to Stroke Prevention

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ABSTRACT: Atrial fibrillation is a major cause of ischemic stroke. Technological advances now support prolonged cardiac rhythm monitoring using either surface electrodes or insertable cardiac monitors. Four major randomized controlled trials show that prolonged cardiac monitoring detects subclinical paroxysmal atrial fibrillation in 9% to 16% of patients with ischemic stroke, including in patients with potential alternative causes such as large artery disease or small vessel occlusion; however, the optimal monitoring strategy, including the target patient population and the monitoring device (whether to use an event monitor, insertable cardiac monitor, or stepped approach) has not been well defined. Furthermore, the clinical significance of very short duration paroxysmal atrial fibrillation remains controversial. The relevance of the duration of monitoring, burden of device-detected atrial fibrillation, and its proximity to the acute ischemic stroke will require more research to define the most effective methods for stroke prevention in this patient population.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: anticoagulation ■ atrial fibrillation ■ left atrial appendage closure ■ stroke

Atrial fibrillation (AF) is a well-established risk factor for ischemic stroke. On admission for an acute ischemic stroke, 18% of patients with ischemic stroke have a history of AF[1] and another 7.7% are newly diagnosed with previously unrecognized AF based on ECG in the emergency department.[2]

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Even after a thorough evaluation including brain and vascular imaging, ECG, routine cardiac rhythm monitoring, and hypercoagulability testing as needed, the cause of ischemic stroke in 20% of cases is uncertain.[3] The concept of the embolic stroke of underdetermined source (ESUS) was developed to identify the subset of cryptogenic ischemic strokes that are likely be caused by embolism from a proximal source, including the heart.[4]

AF is insidious because it can be paroxysmal and asymptomatic; thus, it cannot be confidently excluded it as a cause of ESUS even when it fails to be detected by shorter term monitoring for 24 or 48 hours. A series of landmark trials evaluating prolonged cardiac monitoring (PCM) found that the frequency of previously undiagnosed asymptomatic paroxysmal AF is much higher than previously recognized.[5–8]

Clearly, the more one listens, the more one hears, but the clinician has many outstanding questions. In which patients should we listen? For how long? With what technologies? Then, what should be done after the testing? What burden of AF is sufficient to cause an ESUS event? Mechanistically, is AF detected poststroke the same as prestroke AF and does it carry the same risks for subsequent embolism? What type, burden, and setting of subclinical AF should justify anticoagulation or left atrial appendage (LAA) closure? Does it matter whether it caused the initial stroke or not, if the goal is to prevent future strokes? Are there biomarkers in addition to the burden of AF that can help predict embolic risk and inform treatment decisions?

The 2021 Roundtable of Academia and Industry for Stroke Prevention meeting invited experts in stroke,

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cardiology, and the pharmaceutical and device industries to discuss opportunities to improve the secondary prevention of stroke, including stroke related to AF. We review current knowledge on detection of AF in ESUS, with a focus on the type and duration of cardiac monitoring, the association of AF burden with stroke risk, and treatment decisions including anticoagulation. Based on discussions and consensus at the Roundtable of Academia and Industry for Stroke Prevention meeting, we will draw interim conclusions from the available data, identify gaps in knowledge, and offer suggestions for a future research agenda.

CARDIAC MONITORING TO DETECT AF AFTER ISCHEMIC STROKE

Cardiac rhythm monitoring for screening for AF is one of the mainstays of the diagnostic workup of patients with ischemic stroke and transient ischemic attack (TIA). A wide range of technologies are available for evaluating the heart rhythm poststroke. However, to date, there has not been an established PCM strategy that leads to a significant reduction in the risk of recurrent stroke, with the caveat that randomized controlled trials (RCTs) were powered to detect differences in AF rates rather than ischemic stroke rates.[9] AF screening can be conducted for varying durations, ranging from 24 hours to 3 years, using noninvasive or invasive technologies (Figure [A]).

Current views on the selection of patients for poststroke PCM vary. One argument is that AF screening should be used in patients with ESUS because if paroxysmal AF is diagnosed, it can be considered a likely cause of stroke. It has also been proposed that finding paroxysmal AF may still be relevant even if other potential causes for the stroke are identified, because of the potential for AF to cause another event. In the STROKE-AF trial (Stroke of Known Cause and Underlying AF), patients with stroke thought to be caused by large and small artery disease mechanisms were randomized to implantable cardiac monitoring (ICM) versus noninvasive standard of care. AF was diagnosed after 12 months in 12.1% of participants in the ICM arm versus 1.8% in the standard of care group (hazard ratio, 7.4 [95% CI, 2.6–21.3]; $P<0.001$).[8] The AF diagnostic yield at 12 months of 12.1% in the ICM group of STROKE-AF is strikingly similar to the 12.4% reported for cryptogenic strokes in the CRYSTAL-AF trial (Cryptogenic Stroke and Underlying AF).[5] Although the characteristics of the populations of the 2 trials are not comparable, the similarities in AF detection rates in patients with cryptogenic strokes and strokes of noncardioembolic etiologies suggest that some of the AF diagnosed by PCM may not be the cause of the stroke but may reflect shared risk factors for both AF and stroke, such as older age and hypertension. Additionally, the STROKE-AF trial lacked a control group of participants with a similar cardiovascular risk factor profile who had not had a stroke. As such, it remains unknown if the rate of AF detection in the trial simply represents the background subclinical AF prevalence for both patients with or without stroke. The REVEAL-AF single-arm trial of ICM in patients with $CHADS_2$ score of 3 or higher, 20% of whom had a history of stroke, found that 29.3% had 1 more AF episodes lasting 6 minutes or more.[10] In the ASSERT-II (Prevalence of Sub-Clinical Atrial Fibrillation Using an Implantable Cardiac Monitor II) single-arm trial of ICM for mean 16.3 months in patients with CHA_2DS_2-VASc of 2 or higher or AF risk factors, the proportion with AF episodes lasting 5 minutes or more did not differ between patients with or without a prior history of stroke, TIA, or systemic embolism (detected in 39.4% per year compared with 30.3%, $P=0.32$).[11]

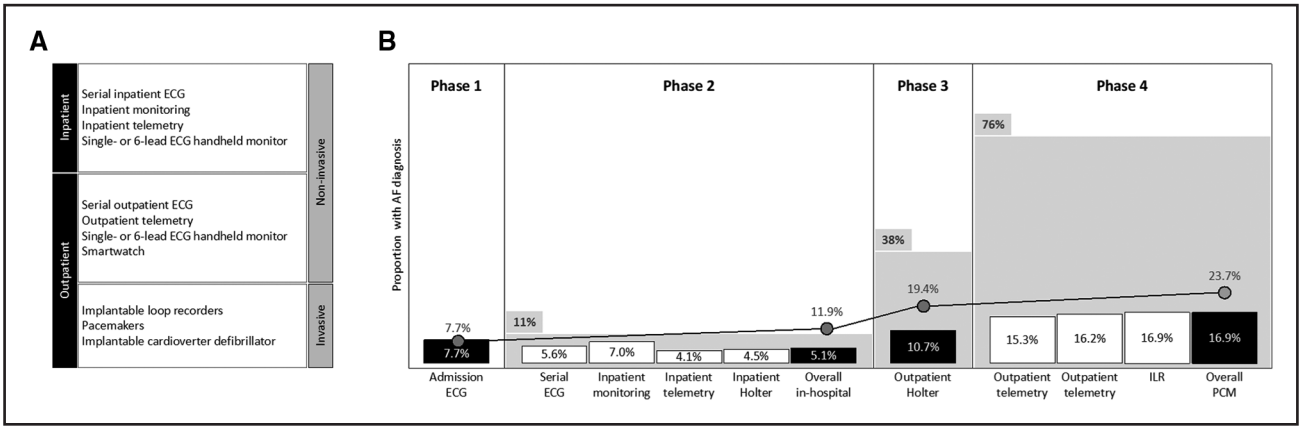

Figure. Available cardiac rhythm monitoring technologies and their incremental diagnostic yield.
A, Classification of cardiac rhythm technologies based on the setting in which they are used and their invasiveness. **B**, Model of a 4-phase sequential cardiac monitoring strategy based on a meta-analysis of 50 studies.[2] White bars: AF diagnostic yield of each technology. Black bars: summary measure for each phase. Dark gray circles: incremental diagnostic yield after applying each phase. Light gray background: proportion of studies restricted to cryptogenic strokes in the meta-analyses for each phase. ILR indicates implantable loop recorder; and PCM, prolonged cardiac monitoring.

Whether skipping shorter-duration monitoring and applying longer-duration monitoring soon after stroke to reduce diagnostic delays and increase the AF diagnostic yield is controversial. Evidence from observational studies suggests that most AF paroxysms occur early after stroke onset; however, it is unknown if very early AF paroxysms are markers of longer-term AF persistence or stroke recurrence. In a retrospective single-center study including ischemic stroke patients monitored immediately after being admitted until the discharge date, 71% of AF paroxysms occurred within the first 3 days.[12] In most cases, the AF reverted spontaneously to sinus rhythm and did not recur during the hospitalization. In this study, initiating cardiac monitoring after the third day of admission would have resulted in a substantially higher number of missed episodes of AF. In contrast, a more recent meta-analysis of 28 ICM studies did not find an association between AF detection rates and time elapsed from a stroke to initiation of monitoring.[13] A strategy of cardiac rhythm monitoring modeled in 4 sequential phases of increasing duration and enhanced patient selection (eg, a larger proportion of patients with cryptogenic strokes) found that AF can be newly diagnosed in 23.7% of patients with a cerebrovascular event and no history of AF (Figure [B]).[2] This sequential strategy may, however, result in delays in AF diagnosis. In an analysis of administrative claims data, the use of external monitors before the insertion of an ICM was associated with a median delay of 142 days in the time to AF diagnosis compared with ICM insertion without prior external monitoring.[14] An RCT conducted among unselected patients with an ischemic stroke or TIA with <7-day baseline cardiac monitoring showed higher AF detection rates at 12 months with ICMs than for 30-day external loop recorders (15.3% versus 4.7%; risk ratio, 3.29 [95% CI, 1.45–7.42]; *P*=0.003).[7] Based on these data, skipping external loop recorders seems reasonable from the perspective of diagnostic yield. Although the early use of ICMs may reduce the time to AF diagnosis and increase AF detection rates, it remains unknown if a direct-ICM strategy may result in lower stroke recurrence rates or lower cost.

The use of commercially available wearable technologies with AF detection by artificial intelligence algorithms, including mobile phone and smart watch applications are interesting approaches that could play a role in screening strategies in the future.[15] However, additional research is needed to establish their accuracy and reliability for detecting AF after ischemic stroke, and many of wearable devices are not approved by the US FDA to make medical diagnoses. Relying on these technologies for AF detection is currently not advised.

Substantial evidence indicates that a longer duration of cardiac rhythm monitoring results in higher AF detection rates and increased use of oral anticoagulants.[9,16] The intensity of cardiac monitoring varies depending on local availability, cost, and stroke physicians' preferences.[17–20] Most clinical guidelines recommend at least 24 hours of cardiac monitoring[21–24] suggesting longer-term monitoring for selected patients with ESUS but without recommending a specific duration.[21–23]

The main question that remains unanswered regarding AF screening poststroke is whether a longer duration of monitoring reduces the risk of stroke recurrence and other vascular events (eg, decompensated heart failure, decompensated AF, and acute myocardial infarction).[9,25] Meta-analyses of RCTs conducted in patients with stroke showed that PCM did not result in fewer recurrent cerebrovascular events despite higher rates of both AF detection and the use of oral anticoagulants.[16,26] A likely explanation is that none of the abovementioned vascular outcomes was the primary end point in the RCTs included in the meta-analyses (Table). Therefore, these trials did not directly assess the effect of PCM on vascular outcomes. Additionally, it has been proposed that PCM may result in the detection of low-burden and, therefore, lower-risk AF (see the section on AF burden).[9,28] However, another meta-analysis that added the LOOP trial (Atrial Fibrillation Detected by Continuous ECG Monitoring) which randomized patients with a stroke risk factor but no history of stroke to either ICM or standard care,[29] to the data from 6 RCTs in patients with ischemic stroke found that PCM was associated with reduced risk for future stroke (risk ratio, 0.76 [95% CI, 0.59–0.96).[30]

AF BURDEN

AF can be permanent or intermittent, that is, paroxysmal. These 2 forms of AF are considered equivalent ischemic stroke risk factors. Additionally, current treatment guidelines do not consider this a distinction regarding the use of anticoagulation after presumed AF-related stroke.[21] The risk of an initial or recurrent stroke seems to be lower in patients with paroxysmal AF as compared with patients with permanent AF.[31,32] This was observed in 3 large clinical trials of the newer oral anticoagulants, apixaban, edoxaban, and rivaroxaban and has also been seen in large clinical registries.[31]

The paroxysmal AF detected after stroke can be of quite variable duration, but a duration of at least 30 seconds is considered necessary to accurately identify AF. This definition is based on consensus but does not predict clinically meaningful AF patterns.[33] Some clinicians may accept durations of <30 seconds as sufficient evidence to support the identification of paroxysmal AF. The amount of AF detected during cardiac rhythm monitoring has been termed AF burden.[34] The most straightforward and likely relevant definition of AF burden is to derive a percentage of the time in AF during cardiac monitoring by dividing the amount of time of AF by the total monitoring time.[31] Other parameters of potential significance in the monitoring of AF include the sum of the duration of all AF

Table. Rate of AF Detection in Clinical Trials of Prolonged (14 Days or More) Cardiac Monitoring in Patients With Recent Ischemic Stroke

Trial	Intervention	Duration of long-term monitor (d)	Required AF duration	AF rate (%)	Ischemic events (no.)
CRYSTAL-AF	ICM	180	>30 s	8.9	11
	24-h holter or telemetry	--	>30 s	1.4	18
EMBRACE	30-d event recorder	30	>30 s	16.1	NR
	24-h holter	--	>30 s	3.2	NR
Find-$AF_{RANDOMIZED}$	10-d holter repeated thrice	30	>30 s	14	5
	24-h holter	--	>30 s	5	9
PER-DIEM	ICM	180	>120 s	15.3	5
	External loop recorder	30	>120 s	4.7	8
STROKE-AF	ICM	365	>120 s	12.1	16
	Usual care	--	>30 s	1.8	23

CRYSTAL-AF indicates Cryptogenic Stroke and Underlying AF trial[5]; EMBRACE, 30-Day Cardiac Event Monitor Belt for Recording Atrial Fibrillation after a Cerebral Ischemic Event[6]; FIND-AF, Finding Atrial Fibrillation in Stroke - Evaluation of Enhanced and Prolonged Holter Monitoring[27]; ICM, insertable cardiac monitor; NR, not reported; PER-DIEM, Post-Embolic Rhythm Detection With Implantable vs External Monitoring[7]; and STROKE-AF, Rate of Atrial Fibrillation Through 12 mo in Patients With Recent Ischemic Stroke of Presumed Known Origin.[8]

episodes and the longest episode of AF. The initial studies of AF burden came from patients with cardiac implanted electronic devices such as automated defibrillators. More recently, with the increasingly widespread use of ICMs, studies are emerging in patients with a different pattern of underlying cardiovascular disorders and risk factors.[31] Generally, patients with data derived from cardiac implanted electronic devices are sicker than those with ICM-derived data because of their underlying differences in comorbidities. As such, results from cardiac implanted electronic devices may not be generalizable to other populations such as patients with stroke. Furthermore, data derived from cardiac implanted electronic device monitoring tend to show a higher AF burden and risk of stroke as compared with ICM-derived data.[31] Paroxysmal AF and AF burden are associated with the presence of other factors such as age, left atrial enlargement, increased levels of cardiac natriuretic peptides, and frequent premature atrial complexes. An elevated cardiac troponin level may also be associated with an increased rate of paroxysmal AF detection after stroke.[9] The presence or absence of such factors may therefore predict patients more or less likely to have paroxysmal AF after an ischemic stroke.

For patients with paroxysmal AF, there seems to be a relationship between AF burden and stroke risk. The higher the AF burden the greater the stroke risk. Stroke risk may not only be related to AF burden but also to vascular risk factors, including hypertension and diabetes.[35] When PCM is performed and paroxysmal AF is detected, an important but unresolved question remains: what is the threshold of paroxysmal AF that is associated with an increased risk for ischemic stroke recurrence? Based on the ASSERT study (Prevalence of Sub-Clinical Atrial Fibrillation Using an Implantable Cardiac Monitor) and others, AF episodes lasting between 6 minutes and 24 hours have a questionable and variable risk of stroke.[36,37] Vascular risk factor burden may modify the relationship between AF burden and risk of future stroke, with 1 study finding that AF episodes lasting 6 minutes to 24 hours were only associated with higher stroke risk when the CHA_2DS_2-VASc score was 3 or higher.[37] AF episodes lasting <6 minutes have a lower risk of stroke and systemic embolism.[38] Furthermore, the SOS AF project (Stroke Prevention Strategies Based on Atrial Fibrillation Information From Implanted Devices) that included data from 10016 patients with cardiac implanted electronic devices indicated that the annual risk of stroke in patients with an AF burden that ranged from >5 minutes to <23 hours was very low, ranging from 0.08% to 0.34% per year; 82% were not taking anticoagulation.[39]

An important question that has emerged as a consequence of a wider use of ICMs is whether short episodes of AF detected after stroke after up to 3 years of cardiac rhythm monitoring have the same risk of stroke as AFs diagnosed on short-term monitors or ECGs before the occurrence of a stroke.[9] The AF detected after stroke concept proposes that AF paroxysms in stroke patients are usually short lasting,[9] and patients with AF detected after stroke have a lower prevalence of risk factors, cardiovascular comorbidities, and structural heart disease than those with previously known AF.[28] This is further reinforced by recent evidence suggesting that the self-termination of AF detected during hospitalization for acute ischemic stroke is associated with a lower risk of 10-year mortality, stroke recurrence, and major adverse cardiovascular events, although outpatient PCM to detect later recurrence was not done in this study.[40] In the last decade, most of the focus on patient selection has been placed on predicting an elevated risk of AF detection. There is growing consensus that high-risk phenotypes of patients with stroke who may benefit from anticoagulation once AF is diagnosed on PCM should be established.[9] Future research is needed to characterize these high-risk phenotypes based on the combination of

different AF burden, vascular risk factors, and prevalence of structural heart disease.

Knowing the burden of AF and the duration of monitoring is key when analyzing the data of observational studies and RCTs evaluating the benefit of oral anticoagulants in patients with AF detected after stroke. The AF-related risk of stroke in studies in which the arrhythmia is diagnosed on admission ECGs or short-term in-hospital monitoring may be considered higher than that of studies in which short paroxysms of AF are detected on 2- or 3-year ICMs. In a study based on an administrative data in which patients with ischemic stroke received a new diagnosis of AF based on admission ECGs and in-hospital cardiac monitoring, the use of oral anticoagulants was independently associated with a 16% reduction in the risk of recurrent ischemic stroke.[41] To date, there are no studies evaluating the role anticoagulation for the prevention of recurrent events in patients with stroke with ICM-detected AF. The FIND-AF2 trial (Intensive Rhythm Monitoring to Decrease Ischemic Stroke and Systemic Embolism; clinicaltrials.gov, unique identifier: NCT04371055) is currently evaluating whether a risk-based approach to PCM (external monitoring or ICM versus standard of care) can reduce stroke recurrence.

AF BURDEN THRESHOLD FOR ANTICOAGULATON OR LAA CLOSURE

AF Burden and Risk of Ischemic Stroke and Systemic Embolism

In patients with AF, a meta-analysis of 12 studies including nearly 100 000 patients showed an increased risk of thromboembolism in patients with nonparoxysmal versus paroxysmal AF (adjusted hazard ratio [HR], 1.38 [95% CI, 1.19–1.61]; $P<0.001$).[32] The lower risk of thromboembolism with paroxysmal AF compared with persistent or permanent AF was also demonstrated in a study of 4115 AF patients from Japan among oral anticoagulation users (adjusted HR, 0.59 [95% CI, 0.35–0.93]; $P=0.03$ and among non oral anticoagulation users: adjusted HR, 0.45 [95% CI, 0.27–0.75]; $P<0.01$).[42]

Paroxysmal AF, however, is associated with a higher risk of thromboembolism when compared with no AF. For example, the ASSERT trial enrolled 2580 patients aged 65 years or older with hypertension but without known AF in whom a cardiac device (defibrillator or pacemaker) was implanted and with follow-up for mean duration of 2.5 years.[43] In ASSERT, 10.1% of patients were found to have subclinical episodes of atrial tachyarrhythmias of 6 minutes or longer by 3 months, and these episodes were associated with an increased risk of ischemic stroke or systemic embolism (adjusted HR, 2.50 [95% CI, 1.28–4.89]; $P=0.008$).[43] A post hoc analysis of ASSERT showed that only subclinical AF lasting for >24 hours was associated with increased risk of ischemic stroke or systemic embolism (adjusted HR, 3.24 [95% CI, 1.51–6.95]; $P=0.003$), whereas the risk of ischemic stroke or systemic embolism was not higher in patients with subclinical AF episodes lasting for 6 minutes to 6 hours (adjusted HR [95% CI, 0.83 0.11–6.01]; $P=0.851$) nor in those with subclinical AF episodes lasting for 6 to 24 hours (adjusted HR, 2.54 [95% CI, 0.35–18.55]; $P=0.357$).[44] A pooled analysis of 3 prospective studies suggested that 1 hour or more of device-detected AF was associated with increased risk of ischemic stroke and systemic embolism (adjusted HR, 2.11 [95% CI, 1.22–3.64]; $P=0.008$).[39] Furthermore, the RATE study (Registry of Atrial Tachycardia and Atrial Fibrillation Episodes) including 5379 patients with cardiac pacemakers showed that episodes of AF lasting <20 seconds were not associated with increased risk of stroke or TIA (adjusted HR, 0.87 [95% CI, 0.58–1.31]) but episodes lasting 20 seconds or longer were associated with increased risk of stroke or TIA (adjusted HR, 1.51 [95% CI, 1.03–2.21]).[45]

Therefore, although paroxysmal AF is associated with a higher risk of ischemic stroke and systemic embolism as compared with people without detected AF, the burden threshold for this risk remains unknown. Caution should be exhibited as the burden of AF is dynamic and can increase over time and that brief episodes of AF can progress to more persistent episodes and pose a higher risk of ischemic stroke and systemic embolism over time.

AF Burden Threshold for Anticoagulation Benefit

There are data to support anticoagulation in patients with paroxysmal AF. For example, a pooled analysis of 6 RCTs (4052 patients with AF) in which patients were treated with vitamin K antagonists or aspirin found that a benefit of vitamin K antagonist was present in patients with paroxysmal AF.[46] Although 27% of patients enrolled in the AVERROES trial (Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) had paroxysmal AF and were treated with either apixaban or aspirin, no subgroup analysis was performed to determine whether the reduction in ischemic stroke and systemic embolism with apixaban was maintained in patients with paroxysmal AF. Furthermore, analysis of the ACTIVE-A (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Event) and AVERROES trial data showed that the risk of ischemic stroke and systemic embolism in patients with paroxysmal AF was a nontrivial 2.1% per year.[47]

In patients with ischemic stroke and subclinical AF detected on a cardiac monitoring device, the burden of AF associated with a high risk of recurrence that would be reduced with anticoagulation remains uncertain. The CRYSTAL-AF trial randomized patients 40 years or older with cryptogenic stroke to standard of care

cardiac monitoring versus ICM.[5] CRYSTAL-AF showed increased AF detection with ICM by 12 months (HR, 7.3 [95% CI, 2.6–20.8]; *P*<0.001); although it was not powered to demonstrate differences in risk of recurrent ischemic stroke or TIA the rate was numerically, not significantly, smaller in patients randomized to ICM (5.2% versus 8.6%, *P*>0.1). The maximum AF duration per day was <1 hour in ≈27% and >12 hours in 46% of patients.

Although there is increasing evidence that subclinical paroxysmal AF lasting at least 1 hour carries a higher risk of ischemic stroke and although some experts suggest anticoagulation if at least 30 seconds of subclinical AF on cardiac monitoring is detected, the burden of AF-related stroke that would be reduced with targeted treatments such as anticoagulation or LAA closure remains unknown. The ongoing ARTESiA trial (Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation; clinicaltrials.gov, unique identifier: NCT01938248) is investigating the safety and efficacy of apixaban versus aspirin for preventing ischemic stroke or systemic embolism in patients with device-detected subclinical AF lasting between 6 minutes and 24 hours. Similarly, the NOAH-AFNET 6 trial (Non-Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes Atrial Fibrillation Network 6; clinicaltrials.gov, unique identifier: NCT02618577) randomized patients with more than 6 minutes of subclinical device-detected AF and a $CHADS_2$-VASc score of 2 or more to edoxaban versus aspirin and followed them for the primary composite end point of stroke, systemic embolism, or cardiovascular death; the trial was terminated in September 2022 for futility, but the results have not yet been published. Although these trials are not restricted to patients with cryptogenic stroke, they will provide some information about the duration of AF that would portend an increased risk of ischemic stroke with aspirin treatment, which might be reduced with oral anticoagulation.

INFLUENCE OF OTHER BIOMARKERS ON TREATMENT DECISIONS FOR OCCULT AF

Biomarkers of cardiac dysfunction and more specifically atrial dysfunction have been shown to be associated with ischemic stroke risk in patients with AF. These include serum, ECG, and imaging biomarkers and will be discussed in more details below. While these biomarkers relate to higher stroke risk, it is important to note that their impact on therapeutic clinical decision-making remains unclear.

Serum Biomarkers

High-sensitivity cardiac troponin and NT-proBNP (N-terminal probrain natriuretic peptide) are biomarkers of myocardial injury and wall stress, respectively. Analysis of the RE-LY trial (Randomized Evaluation of Long-Term Anticoagulation Therapy) data showed an increased risk of stroke with the highest versus lowest quartiles of high-sensitivity cardiac troponin (adjusted HR, 1.99 [95% CI, 1.17–3.39]; *P*=0.004) as well as NT-proBNP (adjusted HR, 2.40 [95% CI, 1.41–4.07]; *P*=0.0014).[48]

ECG Biomarkers

Increased P-wave terminal force in lead V1 on 12-lead ECG is a biomarker of left atrial dysfunction. In patients with paroxysmal AF, increased P-wave terminal force in lead V1 is associated with increased stroke risk (adjusted HR, 1.84 [95% CI, 1.33–2.55]).[49]

Imaging Biomarkers

Imaging biomarkers of left atrial and LAA dysfunction have been shown to predict stroke risk in patients with AF. For example, left atrial enlargement (LA diameter >45 mm) was associated with stroke risk in a study from Japan including nearly 2700 patients with AF after adjusting for $CHADS_2$-VASc score and oral anticoagulation use (adjusted HR, 1.74 [95% CI, 1.25–2.42]; *P*<0.001).[50] Furthermore, the LAA is the source of the majority of thrombi in patients with AF[51] and biomarkers of LAA dysfunction predicted stroke risk in patients with AF. Two studies demonstrated an increased risk of stroke and systemic embolism in patients with low peak LAA flow velocity (<20 cm/s; RR 2.6, *P*=0.02)[52] and in patients with spontaneous echocardiographic contrast (OR, 3.5; *P*=0.03), both identified on transesophageal echocardiogram.[53] Another promising biomarker is the morphology of the LAA; studies found an increased odds of stroke in nonchicken wing morphologies[54,55] as well as the high risk morphology (LAA-H) based on a new classification system.[56] Finally, atrial fibrosis detected on cardiac magnetic resonance imaging (MRI) with late gadolinium enhancement is thought to be the underlying substrate for AF development. One study showed that in patients with AF, stage IV left atrial fibrosis (compared with stage I) on cardiac MRI with late gadolinium enhancement is associated with stroke or TIA risk (adjusted HR, 3.94 [95% CI, 1.72–8.98]).[57] Another study showed an association between left atrial fibrosis detected on cardiac MRI with late gadolinium enhancement and ischemic stroke.[58] Studies investigating LAA biomarkers are limited by sample size or retrospective nature and thus larger prospective studies are needed to test the utility of these biomarkers particularly when compared with other well-established atrial or general cardiac biomarkers.

Using Biomarkers to Risk Stratify Patients With Brief Asymptomatic Subclinical AF

Studies testing these biomarkers have been utilized in patients with clinical AF and thus there are very limited

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data on the predictive ability of such biomarkers in patients with paroxysmal occult atrial fibrillation. Post hoc analyses of studies investigating ischemic stroke risk in patients with AF could test the utility of these biomarkers in improving risk stratification when added to AF burden.

CONSIDERATIONS FOR A FUTURE RESEARCH AGENDA

With so many unanswered questions, there is clearly a need for additional research on the differential diagnostic yield, cost effectiveness, and clinical effectiveness of different strategies for diagnosing subclinical paroxysmal atrial fibrillation and managing associated stroke risk.

Roundtable of Academia and Industry for Stroke Prevention attendees identified that it was critical to better define the relationship between AF burden and the risk for subsequent embolic ischemic stroke. Past trials of long-term cardiac monitoring have included sufficient numbers of patients to show differences in AF detection rate but without enough patients and long enough follow-up to confidently detect the rate of subsequent recurrent ischemic stroke in the subset in whom AF was detected. As shown in the Table, in the 5 major RCTs of PCM, the number of ischemic events per trial was very small (≤23 per trial). To better delineate the dose response between burden of subclinical AF duration and subsequent risk, larger studies of longer duration will be needed. One approach could be to implement large-scale, pragmatic cluster-randomized trials of various poststroke PCM strategies and follow patients for the primary composite end point of stroke, systemic embolism, or cardiovascular death. Furthermore, for the data to be applicable to patients with recent ischemic stroke, they should be collected in that setting. Much of the prior literature on AF burden and stroke has come from stroke-free patients with pacemakers, and it is possible that short-duration AF in that setting may be less consequential than similar duration AF shortly after ischemic stroke. Ideally, cohort studies would include brain and cardiac imaging, echocardiographic, and plasma biomarkers to test whether they can stratify risk. A challenge to the interpretation of such cohort studies is that detecting AF may prompt changes to the stroke prevention strategy, altering the natural history and necessitating statistical adjustment for their effects.

The most important question is whether long-term monitoring can be used to better treat patients with ischemic stroke to reduce the risk of recurrence. Among the Roundtable of Academia and Industry for Stroke Prevention clinician attendees, opinion regarding the minimum subclinical AF burden that should prompt consideration of anticoagulation or LAA closure varied widely. To resolve this controversy over very short-duration AF, an RCT would ideally be conducted. However, executing such a trial could be difficult because many individual clinicians have strong opinions and established practices. Some clinicians were uncomfortable with randomizing to antiplatelet treatment even when the AF burden was very low (eg, only a few minutes). However, a trial investigating the association between AF and stroke risk for AF episodes lasting 6 minutes to 24 hours or even considering AF burden as a continuous variable would potentially resolve this controversy over the minimum threshold for treatment. There was consensus that if such an RCT is conducted, both the means of detection and the subsequent treatment algorithm should be standardized as part of the trial protocol. One cannot judge the applicability of different treatment strategies when the detection method is unspecified or variable, and conversely, one cannot judge the clinical effectiveness of different monitoring strategies when the treatment of patients with subclinical AF is highly variable. Because RCTs may be lengthy and difficult to conduct, implementation studies of PCM are needed now to provide information on the AF load and the risk of recurrent stroke using different preventive approaches in patients who survived an ischemic stroke.

DISCUSSION

Long-term cardiac monitoring with either external devices or ILMs frequently reveals subclinical AF in patients with recent ischemic stroke. Consequently, the American Heart Association/American Stroke Association guidelines recommend that it is reasonable to perform long-term cardiac rhythm monitoring in patients with cryptogenic stroke who would be candidates for anticoagulation, without specifying the type of technology, duration of monitoring, or threshold for clinically relevant AF burden.[21]

Although the burden of subclinical AF is probably related to recurrent stroke risk, there are still many unresolved questions. Because of the absence of RCT data, management of patients with subclinical paroxysmal AF is currently based upon individualized clinician and patient preferences. Data from large cohorts of patients with recent ischemic stroke and subclinical paroxysmal AF of varying duration are needed to better define the relationship between AF burden and subsequent ischemic stroke risk, which could be the foundation for patient-centered discussions on the potential utility of anticoagulation or LAA closure. To provide guidelines based on high-quality evidence, RCTs comparing anticoagulation or LAA closure to antiplatelet therapy will be needed, with standardization of both the monitoring and subsequent treatment, but may be difficult to conduct efficiently given the potentially large sample sizes needed and the lack of personal equipoise on the part of some clinicians.

ARTICLE INFORMATION

Affiliations

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APPENDIX

The RAISE Consortium included members: Joseph Broderick, Alvin S. Das, Mitchell S.V. Elkind, Larry B. Goldstein, M. Edip Gurol, Hooman Kamel, John R. Morgan, Bruce Ovbiagele, Sean Savitz, Magdy Selim, and Manish Wadhwa who reviewed the manuscript and provided feedback.

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