

Searching for Atrial Fibrillation Post-Stroke: A White Paper of the AF-SCREEN International Collaboration

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Running title: Searching for post-stroke atrial fibrillation

Brief summary: Searching for atrial fibrillation post-stroke and subsequent anticoagulation is important for reducing recurrent stroke risk.

Word count: 7497

ABSTRACT (word count 349)

Cardiac thromboembolism attributed to atrial fibrillation (AF) is responsible for up to one third of ischemic strokes. Stroke may be the first manifestation of previously undetected AF. Given the efficacy of oral anticoagulants (OAC) in preventing AF-related ischemic strokes, strategies of searching for AF post-stroke using ECG monitoring followed by OAC treatment, have been proposed to prevent recurrent cardioembolic strokes. This white paper by experts from the AF-SCREEN International Collaboration summarizes existing evidence and knowledge gaps on searching for AF post-stroke using ECG monitoring.

New AF can be detected by routine plus intensive ECG monitoring in approximately one quarter of patients with ischemic stroke. It may be causal, a bystander, or neurogenically-induced by the stroke. AF post-stroke is a risk factor for thromboembolism and a strong marker for atrial myopathy.

After acute ischemic stroke, patients should undergo 72 hours of electrocardiographic monitoring to detect AF. The diagnosis requires an ECG of sufficient quality for confirmation by a health professional with ECG rhythm expertise. AF detection rate is a function of monitoring duration and quality of analysis, AF episode definition, interval from stroke to monitoring commencement, and patient characteristics including old age, certain ECG alterations, and stroke type. Markers of atrial myopathy (e.g. imaging, atrial ectopy, natriuretic peptides) may increase AF yield from monitoring, and could be used to guide patient selection for more intensive/prolonged post-stroke ECG monitoring. Atrial myopathy without detected AF is not currently sufficient to initiate OAC.

The concept of ESUS (Embolic Stroke of Unknown Source) is not proven to identify stroke patients benefitting from empiric OAC treatment. However, some ESUS sub-groups (e.g. advanced age, atrial enlargement) might benefit more from Non-Vitamin K-dependent OAC (NOAC) therapy than aspirin. Fulfilling ESUS criteria is neither an indication for empiric NOAC treatment nor for withholding prolonged ECG monitoring for AF.

Clinically diagnosed AF after stroke/transient ischemic attack (TIA) is associated with significantly increased risk of recurrent stroke or systemic embolism, in particular with additional stroke risk factors, and requires OAC rather than antiplatelet therapy. The minimum subclinical AF duration required on ECG monitoring post-stroke/TIA to recommend OAC therapy is debated.

Key words: Atrial fibrillation, post-stroke, search, screening, monitoring, oral anticoagulation, atrial myopathy.

Non-standard Abbreviations and Acronyms	
AF	atrial fibrillation
AHRE	atrial high-rate episodes
CIED	cardiac implantable electronic devices
DWI	diffusion weighted imaging
ESUS	embolic stroke of undetermined source
ICER	incremental cost-effectiveness ratio
ICM	implantable cardiac monitor
MCOT	mobile cardiac outpatient telemetry
MRT	magnetic resonance imaging
NOAC	non-vitamin K antagonist oral anticoagulant
NT-proBNP	N-terminal pro B-type natriuretic peptide
OAC	oral anticoagulation
PACs	premature atrial contractions
QALY	quality adjusted life years
RCT	randomized controlled trial
TEE	transesophageal echocardiography
TIA	transient ischemic attack

Atrial Fibrillation-related stroke: scope of the health problem

Cardiac thromboembolism attributed to atrial fibrillation (AF) is responsible for up to one third of ischemic strokes. The proportion increases with age,¹⁻³ with an apparent secular trend to increasing prevalence.⁴ AF-related strokes are more frequently fatal or disabling, and have a higher risk of institutionalization, than ischemic strokes from other causes.^{3,4} Patients with AF-related strokes are older, and more likely women than those experiencing strokes without AF.⁴

For between 11.5 and 24% of all patients with ischemic stroke or transient ischemic attack (TIA), the stroke/TIA is the first clinical documentation of AF. It is uncovered either on the admission electrocardiogram (ECG), or by ECG monitoring after stroke.^{5,6} In addition, the majority of AF-related strokes can be prevented by oral anticoagulation (OAC). These observations have been the rationale behind calls to search for undetected AF after stroke as well as before stroke to prevent a recurrent or first ischemic stroke.⁷ After the occurrence of ischemic stroke, the need to search for AF becomes even more obvious to start optimal secondary prevention. Direct evidence on the benefits of OAC initiation in patients with post-stroke AF diagnosis is limited.⁸ On the other hand, prior stroke in patients who are found to have clinical AF is one of the most powerful predictors of a recurrent stroke and has been incorporated in the CHA₂DS₂-VASc (congestive heart failure, hypertension, age category, diabetes, stroke/TIA/systemic embolism history, sex, vascular disease history) score with two points.

Searching for unknown AF post-stroke requires a defined process of using ECG monitoring of variable intensity and duration. An overview of post-stroke AF monitoring studies is provided in **Supplemental Table 1**. Variations in the proportion of newly identified AF after stroke are related to timing, duration, and method of ECG monitoring, patient selection^{5,6} and the probability of AF being detected before stroke, which has likely increased in recent years.⁴ In AF-free patients who presented with a stroke or transient ischemic attack (TIA), a stepwise approach to searching for AF using resting ECG, followed by Holter monitoring, and later, 7-day external loop recorders, the AF detection rate was 14.8%.⁹ The estimated overall yield of AF detection across heterogeneous studies will result in a new AF diagnosis in 23.7% (95% confidence interval 17.2-31.0) of

all post-stroke patients,⁵ 11.5% (95% confidence interval, 8.9%-14.3%) in a smaller earlier meta-analysis.⁶ The heterogeneity of these data is obvious, highlighting the evolving nature of the information available to guide patient selection and ECG monitoring intensity in survivors of a stroke.

In the following white paper, we summarize existing evidence and knowledge gaps on post-stroke AF monitoring compiled by experts in the field. Key points do not represent guidelines or formal recommendations, but provide consensus formulations of the AF-SCREEN International Collaboration that may help with a better understanding of the complex situation and uncertainties about searching for AF post-stroke and provide support for decision-making in clinical practice. There is no uniformly used term for searching for AF post-stroke by ECG monitoring, but it is different from population screening in asymptomatic individuals. To call it screening for AF may therefore not be appropriate. Prior reviews and meta-analyses applied the terms “diagnosis”, “monitoring” and “detection” of AF.^{5,6,10} The AF-SCREEN International Collaboration proposes the term “searching for AF” in secondary prevention. This implies an active, targeted process, requiring a post-stroke “AF search” and “electrocardiographic monitoring”.⁷ These latter terms will therefore be used in the white paper.

Pathophysiology of stroke in atrial fibrillation

AF occurs when electrophysiological triggers act on a vulnerable atrial substrate,¹¹ e.g. an atrial myopathy determined by genetic, age-, lifestyle- and disease-related dysfunction. Atrial myopathy can be a manifestation of a more general cardiomyopathy.¹² Once AF begins, it leads to further atrial remodeling, thus worsening atrial cardiomyopathy.¹¹ It is well established that fibrillation of the atria causes blood stasis, endothelial dysfunction, hypercoagulability, systemic in-

flammation, and thus an increased risk of thromboembolism,¹³ Change in rhythm from AF to sinus, whether spontaneous or through cardioversion, temporarily increases the risk of cardioembolic stroke.^{14,15}

There are alternative hypotheses for AF occurrence after stroke. In one, AF may just be an innocent bystander. Given the shared cardiovascular risk factors, in particular older age, stroke and AF may coincide in patients with concurrent small and large vessel atherosclerosis in the brain and cervico-cranial vasculature.^{16,17} In those cases, AF may be just a co-morbidity. This hypothesis is supported by the finding that in about 15% of all strokes with prevalent AF, the stroke etiology does not appear to be secondary to AF,¹⁸ and maintenance of sinus rhythm by a rhythm control strategy does not necessarily show a strong reduction in stroke rate.¹⁹ Whether or not maintenance of sinus rhythm by a rhythm control strategy in AF is associated with a reduction in stroke rate, has not been proven by a prospective randomized controlled trial.¹⁹ Similarly, about 10% of patients with lacunar stroke (i.e. ischemic stroke due to small vessel disease) also have AF.^{20,16} In a second hypothesis, the stroke itself causes AF by affecting central autonomic pathways, possibly when the insula, frontal regions, or the brainstem are affected. However, recent data show no clear relationship between specific acute infarct location and post-stroke AF, even after adjusting for infarct size.²¹ Nevertheless, short, self-limiting AF episodes are observed after hemorrhagic strokes, which are unlikely to have a cardioembolic cause.²²

In young, fit patients with structurally normal hearts and AF, but no other additional stroke risk factors, the risk of stroke is only mildly increased,²² indicating that AF alone is not a strong enough risk factor to warrant treatment with anticoagulation. In paroxysmal subclinical AF detected by implanted devices, the temporal relationship between AF episodes and first-ever stroke is weak in most cases,²³⁻²⁵ and stroke rates are lower than in patients with clinically detected AF, although there is a temporal relationship within 5 days of AF shown in one study.¹⁵ The *TRENDS* and *ASSERT* studies demonstrate that ischemic stroke might occur without episodes of atrial tachyarrhythmias or AF in the past 30 days, and in many cases within the 6 months prior to the stroke. AF is often detected only after the occurrence of stroke. However, there does appear to

be a relationship between the load or burden of subclinical AF and stroke: AF burden >5.5 hours/day or episodes lasting >24 hours are associated with higher first-ever stroke risk.^{24,25,26}

Whether this relationship holds true for AF detected after stroke is not fully understood.

Markers of abnormal atrial tissue substrate and electrical changes are associated with stroke, particularly embolic stroke.^{27,28} This observation indicates that AF may not be the sole or even necessary cause for thromboembolism. Many of the atrial tissue changes predisposing to AF-structural dilatation, myocyte and endothelial dysfunction, fibrosis, and inflammation plausibly play a role in thrombus formation. Thus, left atrial thromboembolism likely involves a complex interplay of systemic cardiovascular risk factors, atrial tissue substrate, and arrhythmia (**Figure 1**). AF may be a strong marker of atrial myopathy.²⁴ An exact quantitation of atrial myopathy is not yet available in routine clinical practice. Once AF occurs, it further increases thromboembolic risk by impairing atrial contractile function and blood flow and worsening the underlying atrial myopathy. It has remained difficult to clearly characterize atrial myopathy or define if it is part of a more generalized cardiomyopathy, partially related to the complex and heterogeneous etiology of AF. In a 2016 consensus paper, atrial cardiomyopathy was defined as “any complex of structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically-relevant manifestations” which applies to AF and stroke.²⁹

For all these reasons, the mechanistic relationship between AF and stroke requires a more complex theoretical framework. Potential clinical consequences are that it may be possible to tailor the intensity and duration of post-stroke AF search by assessing atrial substrate, e.g. by echocardiography,³⁰ electrocardiography, cardiac magnetic resonance imaging, computed tomography, or blood biomarkers³¹ to understand atrial structure and function, degree of fibrosis, and cardiac stress. Furthermore, assessment of atrial myopathy may complement a post-stroke AF search when investigating stroke etiology and determining treatments for secondary stroke prevention.³² In the future, it might even be possible to titrate the intensity of antithrombotic therapy based on the severity of atrial myopathy, but this represents a key knowledge gap requiring further research. To date, the prescription of oral anticoagulants post-stroke remains dependent on

documentation of AF in daily practice, and the causal chain of Virchow's triad and left atrial thrombus formation, the most common reason for stroke in AF.

Key points 1 and 2

1. Atrial fibrillation is a risk factor for thromboembolism and a strong marker for atrial myopathy. In cases of ischemic stroke of uncertain cause, signs of atrial myopathy can be used to inform decisions on the intensity or duration of monitoring for AF.
2. Signs of atrial myopathy without detected AF are not currently sufficient to initiate OAC.

Definitions: Atrial arrhythmias and AF

AF is currently defined as an irregularly irregular rhythm without clear P waves on a surface ECG with a duration arbitrarily designated at ≥ 30 sec or a standard 12-lead ECG.³³ Whereas computerized ECG interpretation may support pre-selection of abnormal electrocardiograms, the AF diagnosis should be made/confirmed by a health professional experienced in ECG reading. Shorter episodes have been termed supraventricular or atrial runs, atrial tachycardia, or micro AF, depending on the rate.³⁴ The surface ECG can be recorded by standard 12-lead electrocardiography, by precordial or limb leads, by hand-held lead 1 rhythm strips, or by wearable devices such as Holter monitors or skin adhesive patches. For implanted cardiac devices that have an atrial lead, AF is detected as atrial high rate episodes (AHREs) but must be confirmed as being truly AF by inspection of intracardiac electrograms. Similarly, implantable cardiac monitors (ICMs) produce a single lead ECG to diagnose AF which must be examined to confirm the diagnosis. Because many of the episodes detected by continuous recorders are silent, these have been termed subclinical AF.³⁵

Key Point 3

3. The diagnosis of AF on post-stroke monitoring requires documentation by an ECG of sufficient quality to allow confirmation by a health professional with expertise in ECG rhythm interpretation.

Definitions: Stroke types and transient ischemic attack (TIA) potentially related to AF, and management implications

Cryptogenic stroke

Stroke is defined as neurologic dysfunction caused by focal brain, spinal cord or retinal ischemia with symptoms typically lasting >24 hours.³⁶ The term “cryptogenic stroke” is defined as a stroke for which no probable cause is found, after a thorough diagnostic work-up.³⁷ The definition was later modified in the *TOAST* trial,³⁸ as a brain infarction that is either not attributable to a source of definite cardio-embolism, large artery atherosclerosis, small artery disease nor a defined rare cause of brain infarction in patients with competing stroke etiologies. Unfortunately, the term also includes strokes in patients with incomplete vascular, cardiac, and serologic workup as well as patients with competing causes of stroke. AF monitoring has been performed inconsistently in cryptogenic stroke.

Embolic stroke of undetermined source (ESUS)

ESUS is a new term coined in 2014 to provide a more specific definition of a cryptogenic stroke by excluding patients with competing causes or incomplete diagnostic evaluation. ESUS is defined as a non-lacunar brain infarction confirmed by imaging, without hemodynamically relevant stenosis ($\geq 50\%$ lumen diameter reduction) of supply arteries, and without an apparent cardioembolic source as determined by echocardiography and ≥ 24 hour ECG monitoring.^{39,40} The reported frequency of ESUS ranges between 9% and 25% of all ischemic strokes, averaging 17%.³⁹ Pa-

tients with ESUS are generally younger and have a lower prevalence of cardiovascular risk factors than patients with non-ESUS ischemic strokes.³⁹ The average ischemic stroke recurrence rate after ESUS is 4.5% per year, which is comparable to non-ESUS ischemic strokes.^{39,41} According to current guidelines, antiplatelet therapy is recommended for secondary stroke prevention in the majority of ESUS patients.³⁹

The ESUS concept has been criticized for including patients with short ECG monitoring duration, thereby potentially encompassing many patients with unknown AF.³⁹ Unfortunately, even in an industrialized country such as Canada, 24 hour Holter ECG monitoring for AF is completed routinely in only a minority of stroke patients.⁴² As a result of the short duration of ECG monitoring, AF is detected in only 2-3% of patients following cryptogenic stroke in clinical practice.^{43,44} Studies using prolonged continuous cardiac monitoring have detected AF in 23-30% of ESUS patients during follow-up,^{41,45} showing that paroxysmal (typically asymptomatic) AF remains undetected in a significant proportion of post-stroke patients. Again, data for this estimate are heterogeneous and not sufficient for a robust number, but it is clear that searching longer, harder and using more sophisticated monitoring will increase detection rates.⁵ Given the high prevalence of asymptomatic paroxysmal AF after ESUS and the established benefits of OAC⁴⁶ for the prevention of AF-related cardio-embolic stroke, several clinical trials have been conducted to determine if the use of a NOAC was more effective than aspirin to prevent recurrent stroke, testing the hypothesis that the presumed embolic etiology of ESUS would respond favorably to OAC compared to aspirin for prevention of recurrent stroke.⁴⁷⁻⁴⁹ A corollary was that if a significant proportion of ESUS is related to asymptomatic paroxysmal AF undetected by a 24 hour Holter recording, then recurrent strokes should respond in the same way.

The two largest trials, *NAVIGATE ESUS* (Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients with Recent Embolic Stroke of Undetermined Source) and *RE-SPECT ESUS* (Dabigatran Etexilate for Secondary Stroke Prevention in Patients with Embolic Stroke of Undetermined Source) studies,^{50,51} did not show a reduction in recurrent stroke among all ESUS patients treated empirically with NOAC compared to aspirin.

NAVIGATE ESUS used a lower daily rivaroxaban dose (15 mg OD) than the 20 mg OD dose that is effective in stroke prevention in patients with AF and normal renal function. This may lead to the assumption that recurrent strokes in ESUS patients could have been prevented better by using the standard dose of rivaroxaban. However, using the standard dose of rivaroxaban would not have lowered the observed bleeding rate. One might argue that the prevalence of undetected AF in the trial was rather low or the risk of ischemic stroke associated with subclinical AF was comparably low. However, analyses are ongoing to explore subgroups of ESUS patients, in whom a strategy of empiric anticoagulation may be beneficial. A post-hoc analysis from *NAVIGATE ESUS* suggests that patients with an enlarged left atrium (estimated as left atrial diameter >4.6 cm, approximately 10% of trial patients) had less recurrent ischemic stroke on Rivaroxaban compared with aspirin, but this will require prospective confirmation. While it is plausible that patients with markedly enlarged left atria would be at greatest risk of having or developing AF, it is also postulated that an enlarged left atrium and abnormal left atrial substrate may predispose to atrial thromboembolism in the absence of AF. This concept is being prospectively tested in the *ARCA-DIA* (AtRial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke) trial, which is enrolling patients with ESUS and either left atrial enlargement, abnormally high P-wave terminal force in ECG lead V₁, or elevated NT-ProBNP.⁴⁹

In the *RE-SPECT ESUS* trial there was a trend in favor of Dabigatran compared to acetylsalicylic acid for secondary stroke prevention that developed after 1 year of follow-up, but this was a post-hoc exploratory analysis.⁵² In a pre-specified secondary analysis, patients older than 75 years appeared to derive greater protection against recurrent stroke with Dabigatran (many taking the lower dose of 110 mg BD) vs. acetylsalicylic acid. However, the overall negative results for the primary outcomes of both, *NAVIGATE ESUS* and *RE-SPECT ESUS*, may reflect the heterogeneity of underlying embolic sources and composition of emboli (arterial, cardiogenic, or paradoxical),⁵⁰ only some of which would benefit from OAC, plus a relatively short average duration of

treatment and follow-up in those trials. Better phenotyping may be required to identify subgroups of patients who may benefit from OAC.

The concept of ESUS may thus need a revision and specification of defined subtypes. Anticoagulation may be effective in selected patients without AF but with other evidence of atrial myopathy, although randomized trial evidence for this is currently lacking.⁴⁹ Even if AF detected during post-stroke monitoring after ESUS was not the cause for the index stroke, its detection should influence the anti-thrombotic strategy for prevention of recurrent stroke.

Key points 4 and 5

4. The concept of ESUS has not been proven to identify stroke patients benefitting from OAC. However, there may be ESUS sub-groups (e.g. advanced age, significant atrial enlargement) that could benefit more from NOAC therapy than from aspirin.
5. Fulfilling ESUS criteria is neither an indication for NOAC treatment nor for withholding prolonged ECG monitoring.

Transient ischemic attack (TIA)

A TIA is defined as a transient episode of neurologic dysfunction caused by focal brain, spinal cord or retinal ischemia without acute infarction according to brain imaging, with symptoms typically lasting <24 hours. The updated TIA definition encompasses the absence of infarction on brain imaging, as approximately one third of TIA patients-according to clinical criteria-have MRI-detected diffusion weighted imaging (DWI) lesions, indicating ischemic stroke.⁵³ The diagnosis of TIA is difficult to validate and TIAs are probably over-diagnosed in clinical practice. TIA has rarely been used as an individual inclusion criterion or study endpoint in AF randomized trials, limiting available evidence regarding TIA in particular. Based on a pooled analysis of the *Dutch TIA Trial* and Dutch participants of the *European Atrial Fibrillation Trial*, the risk of vascular events or mortality after TIA or minor stroke is higher in AF patients compared to TIA patients without AF at enrolment with an adjusted hazard ratio of 1.94, 95% confidence interval 1.47-2.55 for first

stroke.⁵⁴ According to a meta-analysis of the randomized European Atrial Fibrillation trial and the *Stroke Prevention in Atrial Fibrillation III Trial*, the annualized rate of recurrent ischemic stroke was more than halved using a vitamin K-antagonist compared to aspirin in TIA patients with AF.⁵⁵ Compared to AF patients with ischemic stroke (N=551), the annualized rate of recurrent ischemic stroke was lower in AF patients with TIA (N=222) before enrolment (7% vs. 11% using aspirin and 3% vs. 4% using anticoagulation, respectively). To date, there is no gold standard of ECG monitoring post-TIA and the precise yield of prolonged monitoring is unknown. Among patients with TIA or minor stroke in the multicenter TIA registry.org project, 9.6% had an AF diagnosis at discharge and about 13% had AF after five years of follow-up.⁵⁶ The proportion of patients with AF increases steeply with age, with a prevalence of over 30% in patients age 85 years or older.⁵⁷ A systematic review and meta-analysis revealed a higher rate of AF in selected TIA patients (including older patients, intensified testing for arrhythmias before enrolment, or presumed cardioembolic/cryptogenic cause), and after prolonged duration of continuous ECG recordings.^{33,44,58} While a substantial under-diagnosis of AF in TIA patients may lead to suboptimal secondary stroke prevention in high risk patients, caution is needed to avoid unnecessary ECG monitoring in patients with non-specific symptoms mimicking TIA.

Key point 6

6. Clinically diagnosed AF after stroke and TIA is associated with significantly increased risk of stroke or systemic embolism, particularly in the presence of additional stroke risk factors. Patients with a recent cerebrovascular event and an episode of post-stroke AF have not been specifically included in randomized trials, but the AF-SCREEN expert consensus is that OAC therapy (either well-controlled vitamin K antagonist or NOAC) is generally preferred for new AF detected by ECG monitoring after stroke or TIA.

Whom to monitor post-stroke

While the minimum recommended monitoring has traditionally been a 24 hour Holter ECG,^{59,60} the requirement for more prolonged ECG monitoring for all patients is under consideration. In unselected survivors of stroke or TIA, 72-hour Holter monitoring was feasible and detected an

additional 1.8% of patients with paroxysmal AF compared to 2.6% in the first 24 hours.⁶¹ During a median of 64.0 hours, continuous automated stroke unit ECG monitoring detected 92.7% of paroxysmal AF cases compared to only 34.1% in 24-hour Holter recordings after ischemic stroke/TIA.⁶² Therefore, an extension to 72 hours of continuous rhythm monitoring appears to be justified and “short-term ECG recording followed by continuous ECG monitoring for at least 72 hours” is recommended by current ESC guidelines “in patients with TIA or ischemic stroke” (Class I, Level B).⁶³ However, higher costs incurred by prolonged monitoring and the need of logistics for out-patient follow-up have hampered broad application despite demonstration of long-term cost-effectiveness.⁶⁴ In particular, in many resource-limited regions, prolonged ECG monitoring may not be feasible, though at least a single time point ECG is feasible and should become a minimal standard.

Key point 7

7. Patients with ischemic stroke or TIA should have continuous ECG monitoring post-stroke for at least 72 hours.

For selection of patients to undergo more intensive monitoring, a number of factors have been proposed. Most rely on either enrichment of AF yield during monitoring, or increase in likelihood that any AF discovered is associated with recurrent stroke. Descriptors include age, demographics, simple clinical risk factors such as heart failure, stroke severity, and ECG, imaging or blood biomarkers, but the most appropriate clinical approach has yet to be precisely defined.

Co-existing cardiovascular risk factors, and prediction of new AF post-stroke

Old age and heart failure are the most powerful predictors of new AF after ischemic stroke.⁶⁵⁻⁶⁸ The CHA₂DS₂-VASc score and most of its individual components are related to post-stroke AF diagnosis.^{66,69} Prediction of AF detection post-stroke is made more difficult because some risk factors associated with incident AF, such as diabetes, are more closely associated with non-

cardioembolic ischemic stroke,⁷⁰ so diabetes may actually be associated with a lower risk of finding AF after ischemic stroke.⁶⁶ In addition, patients with diabetes may undergo closer clinical scrutiny, so AF may be detected prior to stroke, contributing to the inverse association.⁷⁰ Similarly, smoking, which is strongly associated with non-AF ischemic stroke, exhibits an inverse relationship with post-stroke AF.^{66,68} Some other characteristics including mitral valve disease or a pacemaker or defibrillator implantation may also increase the likelihood of finding AF.⁶⁶ On the other hand, factors that are more specific for AF as a cause for stroke, such as frequent atrial premature beats, heart failure, B-type natriuretic peptide, and left atrial size or strain, are more likely to be consistent predictors of AF in diverse populations and settings, as they may reflect the atrial myopathy proposed to underlie both AF and cardioembolism.

In clinical practice, a decision to recommend prolonged post-stroke ECG monitoring is not based on any established clinical scores, although some have been proposed as being predictive of incident AF.⁷¹ **Supplemental Table 2** outlines predictors for AF in the post-stroke setting. The studies were performed in populations with stroke and without prior known AF. The data presented for the study by Friberg et al. have been re-analyzed to include only new cases of AF diagnosed after the stroke event. **Figure 2** is a suggested schema for improving post-stroke AF monitoring. Indicators of an elevated post-stroke AF detection rate after stroke are summarized in **Table 1**.

Brain imaging

A multi-focal pattern of ischemic brain lesions, a wedge-shaped cortical/subcortical pattern, or secondary hemorrhagic transformation on brain imaging, may suggest an embolic origin from the heart or the aortic arch.⁷² In contrast to hemorrhagic stroke, which has no underlying brain ischemia, secondary hemorrhagic transformation of an ischemic stroke occurs after reperfusion, and is more frequently observed in patients with AF. However, in a post-hoc analysis of the *CRYSTAL AF* study, the detection of a first episode of AF did not correlate with brain lesion pattern.¹⁷ Although the likelihood of AF detection is comparatively low in patients with a lacunar stroke type,

about 10% of patients with presumed lacunar stroke have AF.¹⁶ This is sufficient to recommend a minimum duration of post-stroke ECG monitoring in such patients.

Cardiac imaging

Left atrial enlargement,^{73,74} valvular abnormalities (particularly rheumatic mitral valve stenosis or severe mitral and tricuspid valve insufficiency), as well as spontaneous echo contrast or solid thrombi in the atrium may be predictive of the development of AF post-stroke.²⁰ In addition, left atrial volume index in combination with atrial function has been demonstrated to be predictive for detection of AF,⁷⁵ as has low atrial strain, which provides independent risk stratification for development of new AF over clinical markers.³⁰ It remains to be established whether the morphology of the left atrial appendage itself, which has been related to thromboembolic risk, is a relevant predictor of AF detection after stroke.⁷⁶

ECG

The presence of atrial runs (lasting <30 sec) and excessive supraventricular ectopic activity are associated with an increased probability of AF detection after stroke.^{33,73} Atrial runs also increase the risk of recurrent stroke.⁷⁷ An algorithm for ECG monitoring has been proposed based on the presence of frequent or infrequent atrial premature beats.³³ P wave characteristics including P wave axis, duration, terminal force, and dispersion, may be predictors of intermittent AF.^{78,79}

Biomarkers

The predictive value of N-terminal pro B-type natriuretic peptide or B-type natriuretic peptide measurement for AF detection has been highlighted in several stroke cohorts.^{80,81} In addition, elevated C-reactive protein as well as troponin levels are related to AF detection rate after stroke.²⁰ These biomarkers are non-specific predictors, being elevated in various comorbidities (cardiac and non-cardiac) and are predictive of various cardiovascular and non-cardiovascular outcomes.

Key point 8

8. Cardiac imaging markers, excessive atrial ectopy and blood biomarkers including natriuretic peptides which are suggestive of atrial myopathy, increase the yield of AF detection, and could be used to guide the selection of patients for more intensive or prolonged post-stroke ECG monitoring.

How to monitor: methods and clinical significance of detected AF

Monitoring methods for AF vary according to the device used for ECG recording, quality of ECG signal, number of leads available, duration and interval of monitoring, time of commencement of recording post-stroke, invasiveness of the procedure, and methodology and software for rhythm analysis (**Supplemental Table 1**). Technological advances have produced novel devices which may improve the feasibility, patient comfort, and cost-effectiveness of monitoring for AF. In **Figure 3** a wide spectrum of devices and methods for AF search are illustrated from blood pressure monitors and handheld devices that can be used by a health care provider or in a patient-activated intermittent rhythm monitoring strategy, to wearable, non-adhesive dry-electrode belts, adhesive patch devices and implantable loop recorders which provide continuous ECG recordings of variable durations. A full exposition of available monitoring devices is beyond the scope of this white paper, and is available in a recent review by Zungsontiporn and Link.¹⁰

Oscillometric devices to measure blood pressure, or smartphone photoplethysmographic methods permit the detection of an irregular pulse using proprietary algorithms. To confirm a diagnosis of AF however, these devices require an ECG rhythm strip, which is currently a significant limitation. Similarly, smart-watches and fitness trackers are capable of determining AF from pulse irregularity, and have a similar limitation. Some smart-watch apps can monitor pulse regularity continuously when the watch is being worn, and even notify the patient if possible AF is detected. If an ECG is built into the device (e.g. Kardia Band and Apple Watch Series 4), a patient-activated rhythm strip can also be recorded when a warning is sent by the watch. If the devices do not

provide a confirmatory ECG rhythm strip, an additional ECG is required for AF confirmation as was the case in the Apple Heart Study.⁸² Due to the increasing availability of smartphones and smart-watches even in post-stroke patients they may become an attractive alternative to classical ECG rhythm monitoring for prolonged AF search. For smartphone-based or other handheld devices providing an ECG rhythm strip recording by health professionals or even by patient-activated intermittent recordings, the feasibility has been shown,⁸³ however, the validity of algorithms, the accuracy of AF detection and non-inferiority compared to classical devices for prolonged ECG monitoring needs to be demonstrated for smart-watch ECG techniques in studies post-stroke. Low-noise high-quality signals are necessary for the automated algorithms to perform well, which is critical, in particular, when devices are used in elderly post-stroke patients with neurological deficits. Therefore, the place of smart-watches with or without inbuilt ECGs in the post-stroke setting remains to be determined.

Supplemental Table 1 gives an overview of studies in post-stroke populations with different monitoring methods and the yield of AF. Direct comparison between the methods is difficult for the following reasons:

- i. Post-stroke AF prevalence in certain subgroups (e.g. cryptogenic stroke, ESUS, large artery atherosclerosis, non-AF cardiac source) may be higher than in others (e.g. lacunar stroke) and selection of subgroups will have an impact on AF detection rate.
- ii. Greater efforts made to detect AF during hospitalization after acute ischemic stroke, will lower the yield of new AF on ECG monitoring post-discharge.⁸⁴
- iii. The earlier AF monitoring starts after stroke onset, the higher the yield of a first episode of AF.
- iv. The longer and more continuous the monitoring post discharge, the higher the yield of new AF.
- v. Quality of ECG analysis relates to AF detection rates.

For post-stroke AF search, a combination of different approaches, e.g. non-invasive cumulative 72-hour monitoring in all patients, and more prolonged monitoring in patients with increased risk

of AF, has been proposed.²⁰ Some studies have used a staged approach to monitoring, with initial resting ECG, followed by Holter monitoring in AF-free individuals, and then an ICM if these are negative. Other approaches use a longer duration of intermittent patient-activated or even nurse-activated monitoring, which may represent a compromise.⁸³ AF can be detected in up to one quarter of patients after stroke if all the phases of ECG surveillance are included.⁵

Extended continuous or intermittent monitoring other than 24-hour Holter recordings

The *Find-AF* randomized trial⁸⁵ analyzed stroke patients aged 60 years or older presenting with sinus rhythm and without history of AF randomly assigned to standard care (at least 24 h of rhythm monitoring), or 10-day Holter ECG at baseline, 3 months and 6 months after the index stroke, with the second and third Holter being performed in 68% and 65% of patients without prior AF diagnosis who remained in the study. The overall value of this monitoring method was similar across the whole spectrum of stroke etiology, with 14% new AF vs. 5% in the control arm at 6 months. During extended follow-up between 6-36 months, the control arm almost caught up, with significantly more new AF cases compared to the intervention arm, indicating that short term monitoring detects AF cases that would otherwise be diagnosed later.⁸⁶ Guideline adherence, with 24 hour Holter monitoring performed as usual care in 91.4% of the control arm, was very high compared to other studies. A trend for stroke risk reduction was observed with the intensified monitoring strategy. A large-scale randomized study based on this protocol is planned, with recurrent stroke as the endpoint.

Outpatient cardiac telemetry

Mobile cardiac outpatient telemetry (MCOT) was designed for arrhythmia monitoring in patients out of the hospital setting. New or silent AF discovered by short-term outpatient monitoring ranges from 0-24% over a variable length of follow-up **Supplemental Table 1**. The definition of “an episode of AF” in some of these studies is as short as 5-30 sec in duration which is below the currently accepted definition of AF duration although recent observational studies indicate that the risk of clinical AF is high among subjects with AF episodes <30s (micro-AF).³⁴ A common

observation in these studies was that a significant proportion did not complete the recommended monitoring course.

ICM, long-term wearable devices, and intermittent recordings

ICMs usually detect AF by analyzing the irregularity and incoherence of successive R-R intervals. Consequently, ICMs require a minimum amount of time, typically 2 minutes, over which rhythm evidence is accrued and analyzed. Data from several studies using ICMs after cryptogenic stroke are presented in **Supplemental Table 1**. AF incidence ranges from 16-33.7% depending on the definition of episode duration, the duration of monitoring, and the amount of monitoring performed prior to device implantation.

Two pivotal randomized studies explored long-term monitoring vs. shorter term monitoring after cryptogenic stroke; *CRYSTAL-AF*⁴³ compared ICM vs. standard of care in 441 patients (aged 40 years and older) within 90 days of cryptogenic stroke, and *EMBRACE*⁴⁴ studied a 30 day wearable monitor vs. a repeat 24-hour Holter in 572 patients (aged 55 years and older) with a cryptogenic stroke or TIA within the last six months.³³ Both studies showed that long-term monitoring is significantly more sensitive than standard arrhythmia monitoring for AF identification.

In the *CRYSTAL-AF* study,⁴³ AF defined as >30 sec was detected in 8.9%, 12.4%, and 30.0% in the ICM arm and 1.4%, 2.0%, and 3.0% in the “standard of care” monitoring arm at 6, 12, and 36 months, respectively.⁴³ At the 12 month’s analysis, the median time from randomization to AF detection in the ICM arm was 84 days, with 79% of these episodes asymptomatic. At 36 months, AF was detected in 30.0% in the ICM patients vs. 3.0% of the control group.⁴³ Ambulatory monitoring in the control arms of *CRYSTAL-AF* was at the discretion of the treating physician and resulted in very limited ECG rhythm monitoring: less than 30% of patients received conventional ECGs, and less than 10% received 24-hour Holter monitoring.

In the *EMBRACE* study⁴⁴ unlike *CRYSTAL-AF*, trans-esophageal echocardiography or intracranial vascular imaging was not required as part of the stroke work-up. The primary endpoint (detection of AF ≥30 sec within 90 days) was met in 16.1% and 3.2% of patients in the event recorder

vs. control arms, respectively, with AF ≥ 2.5 minutes (secondary endpoint) in 9.9% and 2.5% respectively, indicating that a third of the episodes detected were very brief.

The duration or burden of episodes of subclinical AF relevant for an elevated stroke risk is currently debated, and may need to be corrected for the duration of the monitoring period. From studies of implanted devices in patients without a prior stroke, a dose-response association exists between AF duration or burden and the subsequent risk of stroke,^{26,87} but there is a significant dynamic process of transition from lower to higher AF burden, determined principally by the burden of first-detected AF episodes.⁸⁸ The implications of high vs. low burden of AF detected by continuous monitoring may differ in patients after stroke. In the absence of evidence, there is consensus among experts to treat as significant any episode of AF ≥ 30 sec detected by continuous monitoring post-stroke, and prescribe anticoagulant prophylaxis. However, the finding of similar yield of new AF on ICMs in patients with no stroke history (*ASSERT II*, *REVEAL-AF*, and *PREDATE-AF*)^{24,89-91} to that seen in *CRYSTAL-AF* post-cryptogenic stroke, requires some rethinking of the implications of prolonged continuous ECG monitoring post-stroke, and whether the threshold of AF burden for basing a therapeutic decision differs between the two populations.

Key point 9

9. The AF detection rate after cryptogenic stroke is a function of length of monitoring, the definition of duration of AF which constitutes an episode, the interval from the index stroke to the start of monitoring, the type of stroke, and patient characteristics.

Management changes when AF is detected post-stroke

The *EMBRACE* and *CRYSTAL-AF* trials indicate that AF detection changes the treatment from antiplatelet to OAC therapy in most patients with cryptogenic stroke: OAC use increased from 5-10% to almost 97% following AF detection,^{43,44} although this may not apply to healthcare settings outside trials. An important limitation of the *CRYSTAL-AF* and *EMBRACE* trials is that they were not designed to demonstrate an improvement in post-stroke outcome from prescription of OAC

to patients with detected AF, but rather, set up to determine AF detection rate with prolonged or continuous monitoring. In *Find-AF* randomized, all patients with detected AF were switched from antiplatelet to OAC therapy, and one year after randomization, 97% remained on anticoagulation.⁸⁵ Evidence is limited whether OAC rather than antiplatelet therapy in patients with post-stroke AF reduces the risk of recurrent ischemic stroke, but expert consensus is that OAC therapy is indicated for any documented AF episode lasting >30 seconds. The results of the ongoing Impact of standardized MONitoring for Detection of Atrial Fibrillation in Ischemic Stroke (*Mon-DAFIS*) study will add further evidence, although recurrent stroke is not the primary outcome measure in this study.⁸⁴

In patients with AF detected during monitoring and an absolute contraindication to oral anticoagulation, left atrial appendage occluders could be considered. While their role and benefit in secondary stroke prevention is not defined, multiple randomized trials are ongoing.

Potential harms of monitoring

There are several reasons why monitoring for AF post-stroke might potentially cause harm. **Supplemental Table 3** summarizes potential reasons for harms and possible methods to counteract each harm. Most harms result from overtreatment with OAC and the potentially fatal side-effects of OAC-related bleeding. As in clinical AF in patients without prior stroke, a risk-benefit assessment of OAC should be considered for each patient. This certainly favors anticoagulation when sexless CHA₂DS₂VA score is ≥ 2 . Because the CHA₂DS₂VASc score gives 2 points for a prior stroke or TIA, the net clinical benefit would be expected to be positive for patients with prior stroke or TIA, and AF, as all have a score of at least 2.

Another harm is that AF monitoring procedures and additional medical work-up could result in unnecessary further tests and use of healthcare resource. To reduce these potential harms, the population that should undergo monitoring, particularly more intensive continuous monitoring,

should be carefully defined, and continuous quality control of the monitoring procedures instituted. Appropriate patient information about potential discomfort with ECG monitoring, and emphasizing the need for anticoagulation in case of AF detection, is necessary at the time of initiating monitoring. If AF was missed during monitoring or the ECG misinterpreted, patients with AF may not seek medical attention if AF becomes symptomatic, because the negative monitoring could provide a false sense of security. If the harms of untreated AF detected during monitoring or the benefit of AF treatment have been overestimated, this would also distort the risk-benefit of monitoring for post-stroke AF. Data from a large UK dataset of 5,555 ambulatory asymptomatic patients with incidentally detected AF (of whom 9.2% had prior stroke) suggest that the risk of stroke at 3 years is similar to that of symptomatic or hospitalized patients with AF, providing the rationale for clinical monitoring in specific settings, such as post-stroke, with prescription of oral anticoagulation in patients with AF detected during monitoring.⁹²

Patient perspective

While patients in general are strongly supportive of detection of AF post-stroke, consideration needs to be given to comfort of the chosen detection strategy, as well as to subsequent potential referral and treatment recommendations if AF is detected. Although ambulatory Holter ECG monitoring is widely available, poor patient compliance can occur, due in part to the bulky size and wired connections to leads. This is a particular issue if Holter recordings are continued over a number of days. Skin preparation for ECG monitoring can be abrasive and irritating, and adhesives can cause allergic reactions, again more of an issue for wearable recorders used over a number of days. In a systematic review of patient preference for monitoring, it was noted that any chosen monitoring device should be compact, and simple to operate and maintain.⁹³ The monitoring devices should not affect daily behavior such as showering. Although patient preference for treatment is of paramount importance, patient involvement in choice of monitoring strategy rarely occurs, yet this may be a key factor in patient compliance.

Health-economic assessments

In the absence of randomized trial evidence, all health-economic studies rely on assumptions of benefit of OAC treatment for AF discovered post-stroke. This is the main caveat of cost-effectiveness calculations.

A meta-analysis of four studies⁹⁴ of prolonged Holter monitoring (2-21 days) following routine post-stroke telemetry, found an incidence of detected AF 4.9-7.7% and a calculated incremental cost-effectiveness ratio (ICER) of \$13,000 per quality adjusted life years (QUALY) gained by identifying patients who benefit from anticoagulation. A comparison of 24-hour Holter with 7-day Holter found that the longer period was associated with greater cost-benefit (ICER €8,354/QUALY).⁹⁵ Pre-screening with transthoracic echocardiography added no additional cost-benefit. Intermittent ECG monitoring using a hand-held device for 10 sec twice daily for 30 days was found more cost effective (ICER €6,458/QUALY) than 24 hour Holter monitoring.⁹⁶

Although longer duration of continuous monitoring increases AF detection, cost-effectiveness needs to balance this against the increased cost of the devices, implantation, and device monitoring, and the possibility that short episodes detected late after stroke on continuous recordings do not carry the same risk. In a cost-effectiveness analysis of the *EMBRACE* trial, a strategy of 30 day non-invasive monitoring appeared cost-effective with an ICER of \$2,000/QUALY compared with an additional 24-hour Holter. The 7-day or 14-day ECG monitoring was cost saving and more effective than an additional 24-hour Holter in this analysis.⁹⁷ The *CRYSTAL-AF* study⁴³ comparing an ICM against usual standard of care (ECG and 24-hour Holter monitoring) found an ICER of £17,175 per QUALY.⁹⁸ The *CRYSTAL-AF* analysis assumed a number needed to implant to prevent one stroke of about 20, which may be optimistic, and does not take into account the low use of conventional or Holter recorders in the control arm. It is notable that both *NAVIGATE ESUS* and *EMBRACE* analyses recruited patients on average more than one month from stroke onset. It is arguable that less prolonged, less expensive monitoring techniques may have more easily detected patients at an earlier time point where cardioembolic risk from the AF may be higher, and this would impact health-economic comparisons of different ECG monitoring strategies.

Current guideline recommendations

ECG monitoring for AF is recommended in national and international guidelines on post-stroke care (**Supplemental Table 4**). Apart from a baseline ECG, guidelines remain vague regarding length and type of monitoring and direction as to which patients should undergo more intensified monitoring. The broadest indication for monitoring is given by the 2016 European Society of Cardiology AF guidelines that recommend AF monitoring for 72 hours in all patients with ischemic stroke without known AF. The American Heart Association guidelines state that for patients with TIA or ischemic stroke and AF detected by ECG at the time or within 24 months preceding the presentation, oral anticoagulation begun within 3 months is deemed superior to aspirin for the prevention of vascular death, stroke, myocardial infarction, and systemic embolism, and is therefore recommended. The recommendation is based on 225 patients of whom 78% had persistent/permanent AF and 22% paroxysmal AF. For eligibility, AF had to be documented on ECG at admission, or in the case of paroxysmal AF, within the previous 24 months.⁹⁹ The guidelines designate class IB level of evidence. The Canadian stroke best practice recommendations suggest prolonged ECG monitoring for at least fourteen days in selected patients with ischemic stroke/TIA of undetermined source in whom a cardio-embolic mechanism is suspected and who would be amenable to OAC. They assign an evidence level A. In general, guidelines focus on the detection of AF rather than the yield of AF from the monitoring technique. The American College of Chest Physicians 2018 anti-thrombotic AF guidelines have no specific recommendation but discuss continued cardiac evaluation (e.g. prolonged rhythm monitoring) for patients with ESUS. The Australian Heart Foundation and Cardiac Society of Australia and New Zealand 2018 guideline recommends that for patients with ESUS, longer term ECG monitoring (external or implantable) should be used, while the 2019 AHA/ACC/AHA update of the 2014 guideline states that ICM implantation is reasonable to optimize detection of silent AF, in patients with cryptogenic stroke in whom external ambulatory monitoring is inconclusive.

Conclusions

In the absence of a prior history of the arrhythmia, AF can be detected by ECG monitoring in approximately one quarter of all patients with acute ischemic stroke by routine monitoring followed by an intensified or prolonged AF search. It may be the cause of the index stroke, a bystander, particularly in older patients with high cardiovascular comorbidity and risk factor burden; or a neurogenically induced, secondary consequence of stroke. Atrial myopathy may play a role in thromboembolic risk and is an indicator of increased post-stroke AF detection rate on ECG monitoring. Monitoring for AF post-stroke/TIA requires an ECG-based diagnosis. A minimum duration of 72 hours of cumulative ECG recording should follow ischemic strokes in patients who do not have a prior AF diagnosis. Longer periods of continuous monitoring will detect more AF cases, and a number of factors could be used to determine selection of patients for more intensive monitoring. Whether the duration or burden of AF increases the risk of recurrent stroke is debated and is a key knowledge gap (Table 2); nevertheless, OAC treatment is often prescribed for any AF episode ≥ 30 seconds. Currently, there is no evidence supporting initiation of OAC therapy in patients with markers of atrial myopathy or with cryptogenic stroke or ESUS. The diagnosis of AF post-stroke should lead to changes in clinical work-up, and usually, institution of OAC therapy. There are a number of knowledge gaps summarized in **Table 2**. In particular, further evidence is needed to establish risk-stratified ECG monitoring strategies that are safe, effective, and cost-effective.

Acknowledgements

The AF-SCREEN International Collaboration, founded in September 2015, involves over 160 physicians, nurses and allied health professionals, epidemiologists, health economists and patient groups from 36 countries. Its major goal is to promote evidence generation and collection, on screening for unknown or under-treated AF in order to reduce stroke and mortality worldwide. It supports the implementation of AF monitoring programs adapted to country-specific needs. We thank Daniel Engler, MSc for his support with the formatting and proofreading of the manuscript.

Sources of Funding

AF-SCREEN received funding for holding its meeting from: Bayer HealthCare, Bristol-Myers Squibb/Pfizer, Daiichi Sankyo, Medtronic, C-SPIN (Canadian Stroke Prevention Intervention Network), Zenicor and iRhythm. The sponsors played no role in setting the agenda or the program for the meeting and played no role in this document.

Disclosures

Dr Schnabel reports research support from the European Research Council under the European Union's Horizon 2020 research and innovation program (grant agreement no. 648131) and German Ministry of Research and Education (BMBF 01ZX1408A) and German Centre for Cardiovascular Research (DZHK e.V.) (81Z1710103). Dr. Haeusler reports research support from Bayer and Sanofi-Aventis and receive lecture fees /advisory board fees from Sanofi-Aventis, Pfizer, Bristol-Myers-Squibb, Boehringer Ingelheim, Daiichi Sankyo, Biotronik and Medtronic. Dr Healey reports research support and lecture fees from BMS, Pfizer, Medtronic, Abbott and Boston Scientific and Servier. Dr Freedman reports grants to the institution, personal fees and non-financial support from Bayer, grants to the institution, personal fees and non-financial support from BMS/Pfizer, personal fees and non-financial support from Daiichi-Sankyo, non-financial support from Alivecor outside the submitted work. Dr Boriani reports lecture fees from Biotronik, Boehringer Ingelheim, Boston and Medtronic. Dr. Brandes reports research support and lecture fees from Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead, MSD, Odense University Hospital, Pfizer. Dr. Bustamante and Dr. Montaner Villalonga report research support from Juan Rodes research contract from Instituto de Salud Carlos III (JR16/00008), the AFRICAT study research support from Fundació la Marató de TV3 in the research call "La Marató 2014: malalties del cor" (201528-30-31-3). Dr. Casadei reports research support from ROCHE Diagnostics (assays free of charge), British Heart Foundation, UK National Institute for Health Research Oxford Biomedical Research Centre and European Union Horizon 2020. Dr. Crijns reports research support from Medtronic (<100.000€ / year), idem from Daiichi-Sankyo, BMS/Pfizer, Boehringer, Bayer (all <50.000€ / year), idem from Netherlands Heart Foundation grant CVON 2014-9. Dr

Doehner reports research support from EU (Horizon2020), German Ministry of Education and Research, German Center for Cardiovascular Research, Vifor Pharma, ZS Pharma and received lecture fees and advisory honoraria from Aimediq, Bayer, Boehringer Ingelheim, Medtronic, Pfizer, Sanofi-Aventis, Sphingotec, Vifor Pharma. Dr. Fauchier reports lecture fees from Bayer, BMS/Pfizer, Boehringer Ingelheim, Medtronic, Novartis. Dr. Friberg reports research support for epidemiological research/drug safety studies payed for by Bayer, Boehringer Ingelheim, Bristol Myers-Squibb, Pfizer and Sanofi. Dr Gladstone reports research support by a Mid-Career Clinician Scientist Award from the Heart & Stroke Foundation of Canada, and Sunnybrook Department of Medicine and is PI of the EMBRACE and SCREEN-AF trials, Medical Monitor for ARCADIA trial; Site PI and Co-Chair of a NAVIGATE ESUS trial subgroup analysis working group. Dr. Goto reports research support from Sanofi, Pfizer, Ono, MEXT/JSPS KAKENHI 17K19669 and partly by 18H01726 and the Nakatani Foundation. Dr. Hobbs reports occasional funding for speaking or consulting. Dr Johnson reports research support from governmental funding within the Swedish National Health Service and by the Swedish Heart and Lung Foundation. Dr. Kamel reports research support from the NIH/NINDS (grants R01NS097443, U01NS095869, U01NS106513) and serves as a steering committee member of Medtronic's Stroke AF trial, receives in-kind study drug from BMS-Pfizer and in-kind study assays for the ARCADIA trial, and has served on an advisory board for Roivant Sciences. Dr. Kirchhof reports research support from the European Union (grant agreement number 633193 (CATCH ME)), British Heart Foundation (FS/13/43/30324), Medical Research Council (UK), Leducq Foundation, German Centre for Cardiovascular Research and several drug and device companies active in atrial fibrillation and has received honoraria from several such companies. He is listed as an inventor on two pending patents (WO 2015140571 and WO 2016012783) filed by the University of Birmingham. Dr Korompoki reports advisory board fees from Pfizer and lecture fees from Amgen, Bayer, Pfizer. Dr Lip reports lecture fees from Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo (No fees are directly received personally.) and is consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi-Sankyo. Dr. Neu-

beck reports fees for participation in meetings from Pfizer/BMS. Dr. Ntaios reports lecture fees/advisory board and research support from Amgen, Bayer, BMS/Pfizer, Boehringer- Ingelheim, Elpen, Galenica, Sanofi, Winmedica. Dr. Quinn reports research support from BMS/Pfizer Alliance and travel support or lecture fees from Bayer, BMS and Pfizer. Dr. Reiffel reports research support from Medtronic, Janssen and is consultant for Medtronic, J&J, Portola, Acesion, Incardia Therapeutics, Roivant. Dr. Ribeiro reports research support from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, Brazil; grants 465518/2014-1 and 310679/2016-8) and by the Fundação de Amparo à Pesquisa de Minas Gerais (FAPEMIG, Brazil; PPM-00428-17). Dr Rienstra and Dr van Gelder report research support from the Netherlands Cardiovascular Research Initiative: an initiative with support of the Dutch Heart Foundation, CVON 2014-9: Re-appraisal of Atrial Fibrillation: interaction between hyperCoagulability, Electrical remodeling, and Vascular destabilisation in the progression of AF (RACE V). Dr Rosenqvist reports consultancy and lecture fees from Medtronic, Zenicor, Bayer, Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb, and Abbott and support grants from Roche Diagnostics, Bristol-Myers Squibb, Sanofi, Boehringer Ingelheim, and Bayer. Dr Sinner reports research support from the European Commission's Horizon 2020 research and innovation program (grant agreement no. 633196 CATCH ME). Dr Wachter reports research support from BMBF (Bundesministerium für Bildung und Forschung) and Boehringer Ingelheim, he reports lecture fees (outside the submitted work) from Bureau Bayer, BMS, Boehringer Ingelheim, Daiichi, Medtronic, Pfizer. All other authors report no disclosures.

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Figure legends

Figure 1. Competing and synergistic mechanisms of atrial myopathy and atrial fibrillation in ischemic stroke.

Abbreviations: renin-angiotensin-aldosterone System, RAAS; transient ischemic attack, TIA.

Figure 2. Algorithm for intensified atrial fibrillation monitoring in ischemic stroke.

Legend: High atrial fibrillation risk refers to several indicators shown in **Table 1**. Dashed lines indicate that additional rhythm monitoring could be considered. The color shading correlates with the strength of evidence (least evidence in light blue color). Right hand arrow indicates the relationship between atrial fibrillation yield and time after stroke that monitoring is commenced.

Figure 3. Selection of devices across the bandwidth of techniques currently available for atrial fibrillation search. ICM stands for implanted cardiac monitor.

An exact quantitation of atrial myopathy is not yet available in routine clinical practice.

Table 1. Broadly available indicators for a higher probability of atrial fibrillation detection after ischemic stroke (adapted from²⁰). Patients with high risk of atrial fibrillation (**Figure 2**) may have several of these characteristics.

Clinical characteristics
Older age, ≥ 75 years
Cardiovascular risk factors, in particular heart failure, hypertension
Signs of atrial myopathy ^{33,72,73}
Left atrial diameter > 46 mm
Supraventricular extrasystole $\geq 480/24$ hours
Atrial tachycardia ≥ 20 beats
Biomarkers ^{74,75}
BNP > 100 pg/ml
NT-proBNP > 400 pg/ml
Stroke etiology
Arterio-arterial embolism; cryptogenic or ESUS; cardiac cause other than atrial fibrillation
Abbreviations: B-type natriuretic peptide, BNP; embolic stroke of undetermined source, ESUS; N-terminal pro B-type natriuretic peptide, NT-proBNP.

Table 2. Key knowledge gaps about searching for atrial fibrillation post-stroke.

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- Pathophysiological role of AF detected post-stroke: how to determine whether this is a cause of the index stroke, or a bystander, and its association with recurrent cardioembolism.
 - Determine threshold of AF burden post-stroke relative to ECG monitoring intensity and duration, associated with an increased risk of recurrent cardioembolic stroke requiring anticoagulation, and the relationship of increased risk with timing of ECG monitoring commencement after stroke.
 - Determine the persistence and recurrence rate of paroxysmal AF first detected in the acute phase of stroke.
 - Define whether atrial myopathy/cardiomyopathy increases recurrent stroke risk independent of AF. This requires definition, quantitation, and validation of atrial myopathy markers, e.g. atrial enlargement, atrial ectopy or p wave morphology, functional imaging, and elevation in blood biomarkers such as NT-proBNP. Test use of these markers prospectively to tailor type, intensity and duration of ECG monitoring for AF detection, and effect of empiric antithrombotic treatment (as in the *ARCADIA* study).
 - Identify predictors of post-stroke AF that could be used to tailor intensified monitoring.
 - Identify ESUS subgroups with increased cardio-embolic risk likely to benefit from empiric OAC treatment without ECG monitoring for AF, and test prospectively.
 - Define the most effective method, intensity and duration of rhythm monitoring after ischemic stroke to detect clinically relevant AF.
 - Define and validate the most cost-efficient method for post-stroke AF monitoring in a variety of health care systems including those with limited resources and limited access to vitamin K antagonist monitoring and NOACs.
 - Develop pathways and structures for widespread implementation of searching for AF in stroke units and in post-stroke care tailored to country-specific resources and requirements.
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Abbreviations: AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke, *ARCADIA*; atrial fibrillation, AF; non-vitamin K antagonist oral anticoagulant, NOAC; N-terminal pro B-type natriuretic peptide, NT-proBNP; oral anticoagulation, OAC.