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Guidelines

Scientific statement from the French neurovascular and cardiac societies for improved detection of atrial fibrillation after ischaemic stroke and transient ischaemic attack☆

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ABSTRACT

Atrial fibrillation (AF) is the primary cause of ischaemic stroke and transient ischaemic attack (TIA). AF is associated with a high risk of recurrence, which can be reduced using optimal prevention strategies, mainly anticoagulant therapy. The availability of effective prophylaxis justifies the need for a significant, coordinated and thorough transdisciplinary effort to screen for AF associated with stroke. A recent French national survey, initiated and supported by the Société française neurovasculaire (SFNV) and the Société française de cardiologie (SFC), revealed many shortcomings, such as the absence or inadequacy of telemetry equipment in more than half of stroke units, insufficient and highly variable access to monitoring tools, delays in performing screening tests, heterogeneous access to advanced or connected ambulatory monitoring techniques, and a lack of dedicated human resources. The present scientific document has been prepared on the initiative of the SFNV and the SFC with the aim of helping to address the current shortcomings and gaps, to promote efficient and cost-effective AF detection, and to improve and, where possible, homogenize the quality of practice in AF screening among stroke units and outpatient post-stroke care networks. The working group, composed of cardiologists and vascular neurologists who are experts in the field and are nominated by their peers, reviewed the literature to propose statements, which were discussed in successive cycles, and maintained, either by consensus or by vote, as appropriate. The text was then submitted to the SFNV and SFC board members for review. This scientific statement document argues for the widespread development of patient pathways to enable the most efficient AF screening after stroke. This assessment should be carried out by a multidisciplinary team, including expert cardiologists and vascular neurologists.

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1. Abbreviations

AF	atrial fibrillation
AFL	atrial flutter
AHRE	atrial high-rate episodes
ASCOD	atherosclerosis, small vessel disease, cardiac pathology, other cause, or dissection
AT	atrial tachycardia
BNP	B-type natriuretic peptide
CHA_2DS_2-VASc	Congestive heart failure, Hypertension, Age ≥ 75 years (2 points), Diabetes, Stroke (2 points) – Vascular disease, Age 65–74, Sex category (female)
CIED	cardiac implantable electronic device
DOAC	direct oral anticoagulant
ECG	electrocardiogram
ELR	external loop recorder
ESUS	embolic ischaemic stroke of undetermined source
HR	hazard ratio
ILR	implantable loop recorder
LA	left atrial
LAVI	left atrial volume index
NIHSS	National Institutes of Health Stroke Scale
NT-proBNP	N-terminal pro-B-type natriuretic peptide
OR	odds ratio
PAC	premature atrial complexes
SFC	Société française de cardiologie
SFNV	Société française neurovasculaire
TIA	transient ischaemic attack
VKA	vitamin K antagonist

2. Introduction

The prevention and management of stroke and atrial fibrillation (AF) are two major priorities for public health. The conditions are closely related, with an "epidemic" growth incidence in Western countries linked to the ageing population. Despite the established progress in prevention and management of these two diseases, it is estimated that one in three people reaching age 55 years will experience AF, and one in four people after the age of 25 will experience a stroke during their lifetime [1,2].

AF is often asymptomatic, justifying opportunistic screening in at-risk populations; it is the primary cause of ischaemic stroke and transient ischaemic attack (TIA) and is associated with a threefold increased risk of recurrence. Recurrence can, however, be reduced by the use of optimal prevention, including anticoagulant treatments [1,3]. The availability of effective thromboprophylaxis justifies the need for a significant, coordinated and thorough transdisciplinary effort around AF screening associated with stroke [2]. In parallel, various new technologies and tools for prolonged monitoring, such as implantable loop recorders (ILR), have gradually enriched the available screening techniques, but the development of this strategy appears hampered by difficulties in access and implementation for practitioners in charge of stroke patients.

In this context, a French national survey was conducted between 2020 and 2022 across the mainland and overseas, covering the entire territory. The survey was initiated and endorsed by the Société française neurovasculaire (SFNV) and the Société française de cardiologie (SFC). The aim was to create a snapshot of practices, beliefs and available means, as well as identifying gaps in provision and the organization of care related to AF screening in patients with ischaemic stroke or TIA treated in French stroke units [4,5]. The survey revealed, through a significant participation of neurologists/stroke units, a major interest in screening with the use of advanced investigations in stroke units and outpatient post-stroke care networks, quality access to morphological explorations, and a desire to develop or improve monitoring in stroke units and post-stroke care departments. Nevertheless, the survey primarily revealed many shortcomings, such as lack of or insufficient telemetry equipment in more than half of the stroke units, insufficient and highly variable access to monitoring tools, long delays in obtaining screening tests, heterogeneous access to advanced or connected outpatient monitoring techniques and a lack of dedicated human resources.

The huge discrepancies between routine practices in French stroke-care organization and current evidence-based guidelines [1,2], and the extensive heterogeneity in access to and use of resources for AF screening, led to a call to propose good practice recommendations, and to promote a French national strategy to improve and raise awareness of AF detection after ischaemic stroke/TIA, particularly through enhanced collaboration between neurologists and cardiologists.

3. Methods

This document was drafted at the initiative of the SFNV and the SFC and was designed and driven to help address current deficiencies and gaps, to promote efficient and cost-effective AF detection when required, and to improve and homogenize, when possible, quality of practice in AF screening in stroke units and outpatient post-stroke care networks.

The method used to draft these recommendations was based initially on the constitution of a working group in 2021, composed of four cardiologists and four vascular neurologist experts in the field (nominated by their peers). A review of the literature was carried out and the main lines of discussion and key clinical questions were defined by consensus. Each statement was debated in successive cycles and retained whether by consensus or after a vote (acceptance if ≥ 75% of the votes were in favour of the proposal) when facing conflicting opinions.

The working group then submitted the text to the SFNV and SFC board members for review and finalization. As this document is based on expert opinion, formal recommendations with grades and classes are not provided.

3.1. Epidemiological preamble and context justifying the recommendations

3.1.1. Epidemiological context

Stroke is the leading cause of acquired disability worldwide, and it is estimated that 1 in 4 adults after the age of 25 years will experience a stroke during their lifetime [6]. AF is also very common after the age of 60 (one in three people after the age of 55 will have a stroke), is a major cause of ischaemic stroke/TIA (fourfold higher risk vs. people without AF). AF is currently the leading cause of ischaemic stroke/TIA in Western countries. Its frequency and embolic risk increase considerably with age and presence of cardiovascular risk factors [1]. The prevalence of AF following ischaemic stroke can reach 39% [7–10]; half of the cases are diagnosed on admission on the basis of the medical history or initial electrocardiogram (ECG) [10], and will become chronic (paroxysmal or permanent AF) in > 90% [8]. The epidemiology of AF explains that its prevalence in ischaemic stroke increases with age, reaching almost 50% over age 80 years [11–13].

After an ischaemic stroke/TIA, the presence of AF (≥ 30 s) exposes the patient to an annual risk of recurrence, assessed by the CHA_2DS_2-VASc score (Congestive heart failure, Hypertension, Age 75 years [2 points], Diabetes, Stroke [2 points] – Vascular disease, Age 65–74, Sex category [female]), ranging from 2.2–12.2% [14]. Up to 80% of ischaemic stroke/TIA associated with AF are esti-

mated to be due to cardiac embolism secondary to AF. However, AF detection is challenging, because most patients with ischaemic stroke/TIA have paroxysmal and asymptomatic AF [1,8,15], which highlights the need to use accurate AF-detection strategies. Such health organization is difficult and is slow to put into practice, raising concerns about unmet goals in AF detection after stroke in Western countries [16].

The antithrombotic strategy for secondary prevention is based on long-term anticoagulation. A meta-analysis showed that the relative risk reduction of recurrence was 64% for warfarin versus only 22% for aspirin [17]. Randomized trials (RE-LY [Randomized Evaluation of Long-term anticoagulant therapy with dabigatran etexilate] [18], ROCKET-AF [Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation] [19] and ARISTOTLE [Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation] [20]) compared the efficacy and safety of the direct oral anticoagulants (DOAC; dabigatran, rivaroxaban and apixaban) to warfarin in patients with non-valvular AF. These studies showed non-inferiority of efficacy with a significant reduction in bleeding risk for DOAC versus warfarin, resulting in a 70–80% reduction in stroke risk compared with aspirin. Thus, with a better benefit/risk balance, the prescription of DOAC is preferred to vitamin K antagonists (VKA) in secondary prevention of ischaemic stroke/TIA associated with non-valvular AF [1,3,21] and is approved by European Medicines Agency and endorsed by European and American guidelines [1,3,21].

The detection of undiagnosed AF on admission accounts for half of AF associated with ischaemic stroke/TIA [2]. Tracking unknown AF in ischaemic stroke/TIA patients using both early (in-hospital) and longer-term cardiac monitoring improves AF detection by a factor five- to sixfold [10,22–29]. Meta-analysis of various optimized AF-detection protocols showed that approximately 50% of AF detections occur during the in-hospital acute stroke phase within the first days to weeks after ischaemic stroke and the remaining 50% during the weeks to years following stroke using ambulatory long-term monitoring ECG. The number of ischaemic stroke/TIA patients needed to be screened for AF detection is approximatively 8 after 1 month [22] and 4 at 3 years [10,23,24]. Modern and innovative high-tech tools such as smart-watches [30] or artificial intelligence-assisted ECG analysis [31] open a new era for improved AF detection but have not been applied selectively to stroke patients to date.

The documentation of AF is a mandatory prerequisite to start anticoagulants after an ischaemic stroke/TIA [1,3,21]. Indeed, the strategy of treating with empirical anticoagulant therapy for embolic ischaemic stroke of undetermined source (ESUS) without documentation of AF has not been demonstrated and is not therefore recommended [21,32]. ESUS is an entity that combines cryptogenic ischaemic stroke/TIA and strokes related to embolic sources not documented by the specific minimum work-up. This includes cardioembolic sources with minor embolic risk, covert AF, cancers, aortic or non-stenotic atheroma, and paradoxical emboli or other unknown embolic sources [33]. Of these, paroxysmal AF may dominate the other embolic causes and, therefore, patients may benefit from DOAC. According to the literature, ESUS account for approximately 17% of ischaemic strokes, with an annual recurrence risk on aspirin of 4–5% [34,35]. The NAVIGATE-ESUS (New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source) [34] and RESPECT-ESUS (Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate versus Acetylsalicylic Acid in Patients with Embolic Stroke of Undetermined Source) [35] trials failed to demonstrate the superiority of rivaroxaban and dabigatran over aspirin in secondary prevention of ESUS. The ATTICUS (Apixaban for Treatment of Embolic Stroke of Undetermined Source) [36] trials tested the superiority of apixaban in a population of ESUS at high risk of paroxysmal AF by enriching the inclusion criteria with markers of atrial cardiomyopathy. Despite a 25% prevalence of AF in the ATTICUS trial, this study did not show superiority of apixaban over aspirin [36–38]. Recently, a randomized trial was stopped prematurely for safety concerns and failed to show any benefit of edoxaban over placebo in stroke prevention in patients with atrial high-rate episodes (AHRE) detected by ILR in patients aged $\geq$ 65 years with a median CHA_2DS_2-VASc sore of 4, of whom approximately 10% had previous ischaemic stroke or TIA. The incidence of stroke was low (1% per patient-year) in both groups [39]. These results led to some interrogation about the potential lower embolic risk for AF when it is found long after the stroke on an implantable ECG monitor [10]. However, another more recently published randomized trial, ARTESIA, showed for the first time that among patients (mean [standard deviation] age 76.8 ± 7.6 years, mean CHA_2DS_2-VASc score 3.9 ± 1.1 and 9% with a previous stroke/TIA or systemic embolism) with subclinical AF (lasting 6 min to 24 h) that a DOAC (apixaban) resulted in a lower risk of stroke or systemic embolism than aspirin but a higher risk of major bleeding [40].

Although the value of anticoagulation for these patients remains to be demonstrated [41], it is still recommended after documentation of AF following cryptogenic ischaemic stroke/TIA or ESUS, based on randomized clinical trials that included patients with AF detected by conventional techniques [1,38].

The optimization of AF detection is driven by arguments related to the secondary prevention strategy of an ischaemic stroke/TIA:

- firstly, antiplatelet therapy initiated after cryptogenic ischaemic stroke/TIA does not provide optimal risk reduction of recurrent stroke in the case of covert AF [17]. The risk of recurrence of ischaemic stroke/TIA of cardioembolic origin on antiplatelet therapy is high [42];
- secondly, AF is responsible for more severe ischaemic stroke, affecting mortality and functional prognosis due to a higher rate of proximal arterial occlusions [43]. The advent of mechanical thrombectomy has changed the prognosis of these patients, reinforcing the importance of recurrence prevention;
- thirdly, the strategy of treating with empirical anticoagulant therapy for ESUS without documentation of AF has not been demonstrated and is not therefore recommended.

3.1.2. *Definition of atrial fibrillation*

AF is a supraventricular tachyarrhythmia with uncoordinated atrial electrical activation and consequent ineffective atrial contraction. The electrocardiographic features of AF are irregular R-R intervals, absence of distinct P waves and irregular atrial activations. The diagnosis of AF needs to be documented by an ECG tracing. A 12-lead ECG showing AF throughout the tracing or a single-lead tracing (Holter monitoring, cardiac monitor, wearable, etc.) showing at least 30 s of arrhythmia diagnoses clinical AF. The term valvular/non-valvular AF is no longer recommended [1]. Instead, the underlying heart disease, if any, and the comorbidities of the AF should be accurately described.

Apart from clinical AF, which is diagnosed on an ECG tracing, the term subclinical AF is used when AF is documented by the stored electrograms of implanted devices (pacemakers, defibrillators, ILR) even though it does not cause symptoms and has not been diagnosed on an ECG. After a specialist confirms the diagnosis by interpreting the tracings, the term “subclinical AF” is used (Table 1). Even if not completely synonymous, the terms AHRE and subclinical AF are frequently used interchangeably. AHRE are defined as episodes of atrial tachycardia with an atrial rate exceeding

Table 1
Definitions and types of atrial fibrillation [1,44].

Type	Definition
Clinical AF	Symptomatic "overt" or asymptomatic "silent" AF that is documented by surface ECG. The minimum duration of an ECG tracing of AF required to establish the diagnosis of clinical AF is ≥ 30 s or a 12-lead ECG
AHRE	Events fulfilling programmed or specified criteria for AHRE that are detected by CIED with an atrial lead. They need to be visually inspected for confirmation of an atrial arrhythmia
Subclinical AF	Refers to individuals without symptoms attributable to AF, in whom clinical AF is NOT previously detected (that is, there is no surface ECG tracing of AF) Subclinical AF includes AHRE confirmed to be AF, AFL or AT, or AF episodes detected by insertable cardiac monitor or wearable monitor and visually confirmed

AF: atrial fibrillation; AFL: atrial flutter; AHRE: atrial high-rate episode; AT: atrial tachycardia; CIED: cardiac implantable electronic device; ECG: electrocardiogram.

a programmed value (180 bpm most frequently) for a certain duration (5 min most commonly) and detected through the capability of continuous monitoring and data storage of cardiac implantable electronic devices with atrial sensing, occurring in patients with no history of clinical AF or AF-related symptoms, and with no AF on routine 12-lead ECG.

From recent studies, it appears that the risk of ischaemic stroke associated with subclinical AF is lower than with clinical AF, being slightly above 1% per patient-year in patients with AHRE and receiving placebo or aspirin versus 3% per patient-year in patients with clinical AF treated with aspirin [39,45,46]. A small benefit of oral anticoagulation has been shown over standard care in patients detected as having subclinical AF with intermittent self-ECG screening [47]. On the other hand, screening with an ILR and treating with anticoagulants in case of subclinical AF detection did not show benefit [48].

3.1.3. Summary of national surveys on AF detection after stroke

Between September and November 2020, French vascular neurologists were asked by the SFNV to participate in a national survey to evaluate, using structured online questionnaires, their practice for AF screening in stroke units. The results of this survey are summarized in Table 2. The survey was repeated in September 2022 to assess whether practices had changed.

The results of the 2020 survey were presented to neurologists and cardiologists [4,5]; 67% of the 140 heads of stroke units and 33% of neurologists involved in a stroke units activity responded across all French regions. The three main clinical characteristics associated with highly suspected AF were: TIA/ischaemic stroke recurrence on antiplatelet therapy (97%), patient age (if > 60 years; 74%) and proximal occlusion of a major cerebral artery (72%). Clinical severity (National Institutes of Health Stroke Scale [NIHSS] score) and the CHA_2DS_2-VASc embolic risk score influenced only a minority.

The results that led practitioners to suspect, and particularly to check for, AF were brain imaging showing several simultaneously involved vascular territories (100%), presence of a stroke sequela in another vascular territory (98%), moderate-to-severe LA dilatation (96%) and the presence of non-sustained bursts (< 30 s) of supraventricular tachycardia on continuous cardiac recording (94%). High plasma B-type natriuretic peptide (BNP)/NT-proBNP (N-terminal pro-B-type natriuretic peptide) or the presence of supraventricular hyperexcitability (supraventricular extrasystoles > 1000/24 h) on the 24-h Holter influenced a minority.

As regards the availability of cardiac rhythm screening during hospitalization, continuous cardiac monitoring was considered necessary by 90% of neurologists, but only one-third had continuous cardiac monitoring (outside the intensive care unit). Screening for AF in-hospital was also based, to varying degrees depending on the centre, on the initial and repeated ECG (29%) and the 24-h Holter ECG (70%). For TIA patients, > 75% of neurologists have introduced continuous monitoring for 24 h (during hospitalization) and 8% for a few hours.

Ambulatory cardiac monitoring was considered of major interest or mandatory by all vascular neurologists. When the 24-h Holter was initially normal and AF was strongly suspected, additional prolonged monitoring was suggested. Three-quarters of neurologists requested non-invasive ambulatory monitoring for at least 7 days, and more than half requested ILR. The accessibility of ambulatory monitoring modalities was classified as follows: fairly easy for 24/48-h Holter ECG (85%) but after a delay of 1 week to 1 month post-stroke in 70% of stroke units; fairly easy for ILR (68%); fairly difficult/impossible for 3–7-day Holter ECG (51%), 8–21 day Holter ECG (75%), or connected devices (99%). The main barriers to developing monitoring capacity in stroke units were: lack of staff (80%), effective networking with cardiologists (56%) and familiarity with techniques (42%); and cost of technical equipment (44%). A very high proportion of neurologists (96.5%) felt it necessary to set up cooperation protocols with cardiologists to help select patients for monitoring.

Participation was lower for the survey carried out in September 2022 compared with 2020: 35.7% of heads of stroke units and 28.4% of neurologists involved in a stroke unit activity responded. Bearing in mind the possible bias linked to the low response rate, it appears that neurologists are more in favour of advanced tests and, in particular, the early implantation of ILR. These ILR are preferred to non-invasive monitoring. In cases of strong suspicion of AF, there appears to be an increase in the proportion of neurologists requesting early implantation of an ILR (78% in 2022). There was also an increase in the number of patients implanted per year and earlier implantation (including during hospitalization or on discharge from hospital). As far as tests are concerned, access to the 24-h Hol-

Table 2
Summary of the strengths and weaknesses of AF screening in France following the 2020 French. National surveys.

Strengths	Weaknesses
Significant and representative participation Covering two-thirds of all stroke units All French regions Hospitals and private clinics	Monitoring tools are heterogeneous and judged insufficient in most stroke units
The search for AF after an ischaemic stroke/TIA: – Is central to the practices and concerns of the stroke units – Is considered of major interest or necessary and homogeneous – Calls for extensive and cumulative use of the monitoring resources	In-hospital continuous cardiac monitoring (outside the intensive care unit): – Insufficiently covers estimated needs – Often difficult to implement due to lack of resources
Availability of cardiac morphological explorations is mostly good and fairly homogeneous	Access to ambulatory cardiac monitoring is highly variable and generally difficult to obtain. Main barriers to developing monitoring capacity in stroke units were lack of: – Staff – Familiarity with techniques – Cost of technical equipment
ILR seems to be preferred to non-invasive prolonged monitoring	Access to ILR is highly variable

AF: atrial fibrillation; ILR: insertable loop recorder; TIA: transient ischaemic attack.

ter ECG appeared to be easier. However, there was no change in the clinical and laboratory criteria for AF screening.

As a conclusion, these surveys show the need to define areas for improvement and to promote the development of AF detection (patient selection, tools and prioritization of tests) after ischaemic stroke/TIA in France, through a close partnership between neurologists and cardiologists and institutional support.

4. Left atrial cardiomyopathy and risk of stroke

4.1. Definition of left atrial cardiomyopathy

Statement 1
Atrial cardiomyopathy is a pathophysiological concept of an abnormal atrial substrate and function, defined as atrial dilation, impaired myocyte function and fibrosis, and postulated to form a nidus for embolism. Earlier LACM and later AF could be the causes of stroke.
AF: atrial fibrillation; LACM: left atrial cardiomyopathy.

A temporal relationship between subclinical AF/AHRE and the development of atrial appendage thrombus has never been demonstrated.

The expert group defined LA cardiomyopathy (LACM) as "any complex of structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically relevant manifestations" [49].

Diagnostic criteria of LACM are usually derived from predictors for the occurrence of AF, even though pre-existing AF may also trigger atrial remodelling. Multiple vascular risk factors, such as ageing, hypertension, diabetes, obesity and obstructive sleep apnoea, are associated with a pro-inflammatory milieu and an increased risk for stroke can undermine the atrial substrate, cause atrial cardiomyopathy and subsequently increase the risk of AF and thromboembolism. By contrast, AF in turn leads to further worsening of atrial cardiomyopathy and thromboembolism. Indeed, AF and atrial cardiomyopathy have bidirectional interactions, with one predisposing to the other, and share common risk factors.

The NAVIGATE-ESUS trial [34], RE-SPECT ESUS trial [35] and the ATTICUS trial [50] did not confirm the hypothesis that anticoagulant therapy would decrease the risk of stroke in patients presenting with an ESUS and not included on the basis of criteria for LACM. The ARCADIA trial was designed to answer this question [51]. LACM was defined as at least one of the following biomarkers: P-wave terminal force > 5000 μV × ms in ECG lead V1, serum NT-proBNP > 250 pg/mL and LA diameter index ≥ 3 cm/m^2 on echocardiogram [51].Apixaban did not show significant reduction in recurrent stroke risk compared with Aspirin.

The potential markers of atrial cardiomyopathy used in a general population study included LA volume index ≥ 34 mL/m^2, ≥ 500 premature atrial complexes/24 h, P-wave duration > 120 ms or P-wave terminal force in V1 > 4000 ms*μV [52].

In the recently proposed classification of AF from the American College of Cardiology/American Heart Association, the term "pre-AF" has been launched for describing a very early stage of the arrhythmia disease, which may progress to AF. This condition includes most of the anomalies of LACM [53].

4.2. How to diagnose left atrial cardiomyopathy

4.2.1. ECG tracings and monitoring

Statement 2
A 12-lead ECG should be systematically recorded after a stroke/TIA (on admission) to detect AF and its main risk factors on ECG being acute or chronic cardiomyopathy, left ventricular hypertrophy and LACM.
AF: atrial fibrillation; ECG: electrocardiogram; LACM: left atrial cardiomyopathy marker; TIA: transient ischaemic attack.

Statement 3
LACM should be suspected in the presence of ECG LA dilatation criteria and confronted to other diagnostic tools, in the presence of an enlarged P-wave (duration ≥ 120 ms).
ECG: electrocardiogram; LA: left atrial; LACM: left atrial cardiomyopathy marker.

4.2.1.1. ECG tracing. The presence of a P-wave duration ≥ 120 ms and an advanced interatrial block is associated with a higher likelihood for subsequent cardioembolic stroke [54]. The prevalence of potential atrial cardiomyopathy markers among ESUS, non-cardioembolic and cardioembolic stroke patients, has been determined in a systematic review [55]. Increased P-wave terminal force in lead V1 was more prevalent in ESUS versus non-cardioembolic stroke (odds ratio [OR]: 2.26, 95% confidence interval [95% CI]: 1.40–3.66). However, cut-off values remain debatable.

Statement 4

- Frequent PAC (PACs > 30/h or > 500/24 h) identify patients likely to develop AF, which leads to an increased risk of incident AF, stroke and death. PAC are predictors of enlarged LA and reduced LA peak contractile strain.
- AF burden increases significantly with a higher burden of PAC, and is significantly correlated with an increase in incidental AF and thromboembolic risk.
- The prescription of oral anticoagulants in patients detected with subclinical AF/frequent PAC did not exhibit a clear benefit of the initiation of oral anticoagulant therapy.

AF: atrial fibrillation; LA: left atrial; PAC: premature atrial complexes.

4.2.1.2. ECG monitoring and Holter ECG. Holter ECG may also provide evidence of LACM. Increased atrial ectopy is frequently associated with traditional risk factors for cardiovascular disease [56]. The presence of frequent premature atrial complexes (PAC) identifies patients likely to develop AF, which leads to an increased risk of stroke [57]. Frequent PAC may be a marker for LACM since excessive PAC in patients with an ischaemic stroke/TIA correlate with LA remodelling, which may be directly related to the

development of AF and to an increased risk of stroke. LA volume index (LAVI) was larger in the frequent PAC versus the control group (26.6 ± 7.8 vs. 24.6 ± 8.8 mL/m^2; $P < 0.05$).

Longer-lasting AF episodes may cause AF-induced LACM. The presence of subclinical AF, particularly a higher burden, is significantly correlated with an increased thromboembolic risk [58]. Therefore, subclinical AF may be an early manifestation of LACM with increased risk of stroke and not the underlying cause of thromboembolic events. Chen et al. [59] demonstrated that all durations of AHRE detected by pacemaker (> 30 s to 24 h) were associated with subsequent cardiovascular and cerebrovascular events. The presence of subclinical AF/AHRE, and particularly a higher burden of subclinical AF/AHRE, is significantly associated with an increased risk of thromboembolic events. Direct causality has not been established.

Regarding subclinical AF, the recently published Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial High Rate Episodes 6 (NOAH-AFNET 6) trial found that oral anticoagulation in patients with AHRE (a surrogate of subclinical AF) increases bleeding without reducing a composite outcome of stroke, systemic embolism or cardiovascular death [39]. The results of NOAH-AFNET 6 clearly suggest ECG documentation of AF before initiation of oral anticoagulation.

4.2.2. Echocardiography

Statement 5

- LA volume index is more precise and therefore more suitable for estimating atrial size.
- Increased LA volume index (two-dimensional echo, ≥ 34 mL/m^2; three-dimensional echo, ≥ 46 mL/m^2) has been described as a potential early marker of AF, AF burden, recurrence of AF after ablation and ischaemic stroke.

AF: atrial fibrillation; LA: left atrial; PAC: premature atrial complexes.

4.2.2.1. Transthoracic echocardiography. The anatomical and functional remodelling of cardiac structures has been investigated in patients with AHRE, subclinical AF and clinical AF [60]. LA structural and functional remodelling could be considered as surrogate imaging markers for stroke risk assessment in patients with AF. Estimation of LA volume has evolved as the preferred measurement of atrial size. On the other hand, a 15% reduction of initial LA volume is considered to mirror the degree of reverse remodelling [61–63].

In a meta-analysis, LA diameter was independently associated with ischaemic stroke as both a categorical variable (hazard ratio [HR]: 1.39, 95% CI: 1.06–1.82) and a continuous variable (HR: 1.20, 95% CI: 1.06–1.35). In a systematic review [55], LAVI (OR: 1.04, 95% CI: 1.02–1.06) and LA diameter (OR: 3.41, 95%: CI 1.35–8.61) were higher in ESUS versus non-cardioembolic stroke.

In a subanalysis of the LOOP study investigating LA fibrosis by four-dimensional echocardiography, an association of minimal LA volume, LA emptying fractions, and LA reservoir strain with LA late gadolinium enhancement measured by cardiac magnetic resonance imaging was observed. LA emptying fractions had the strongest effect on predicting high LA late gadolinium enhancement and therefore LA fibrosis [64]. Speckle-tracking echocardiography has the ability to study atrial functional remodelling. Abnormal atrial strain may represent an earlier stage of atrial cardiomyopathy and is a predictor of new-onset AF even in patients with normal LA volumes [65] and is associated with atrial fibrosis [66].

Statement 6

Abnormal LA strain may represent an earlier stage of atrial cardiomyopathy and is a predictor of new-onset AF even in patients with normal LA volumes.

AF: atrial fibrillation; LA: left atrial.

A correlation between delayed-enhancement and reduced LA function has been demonstrated by speckle-tracking echocardiography. An inverse effect between the extent of LA wall fibrosis measured by delayed-enhancement magnetic resonance imaging and LA strain and strain rate in speckle-tracking echocardiography was reported [67].

Peak LA longitudinal and peak atrial contractile strain were significantly reduced in patients with AHRE > 6 min versus < 6 min. LA volumes were increased in patients with AHRE > 6 h versus < 6 h. No obvious LA volume differences were observed when comparing those with AHRE < 6 min to those with AHRE lasting ≥ 6 min up to 6 h. LA total/active ejection fraction and peak LA longitudinal/peak atrial contractile strain were significantly impaired with AHRE > 6 h versus < 6 min. Thus, impaired LA strain is an important correlate of subclinical atrial arrhythmias, even after adjustment for conventional measures of LA structure and function [68]. This study suggests that AHRE duration is associated with cumulative AHRE burden (> 5%, 8 days/year) [69].

The incidence of subclinical AF was 19% in an analysis of data from 11 studies (2081 patients). Both peak LA longitudinal strain and peak atrial contractile strain were significantly lower in patients with newly diagnosed AF. According to the diagnostic accuracy, peak LA longitudinal strain < 20% presents 71% (95% CI: 47–87%) sensitivity and 71% (95% CI: 60–81%) specificity for the diagnosis of subclinical AF, assuming a prevalence of 20%. The corresponding values for peak atrial contractile strain < 11% are 83% (95% CI: 57–94%) and 78% (95% CI: 56–91%) [70]. In another meta-analysis, LA reservoir strain independently predicted the risk of incident ischaemic stroke (HR: 0.88, 95% CI: 0.84–0.93) [71]. LA longitudinal reservoir strain identified patients at higher risk for atrial thrombogenesis. LA global longitudinal strain < 19.1% is a potent predictor for LA appendage (LAA)-thrombus in patients in sinus rhythm (area under the curve: 0.79, 95% CI: 0.66–0.93; sensitivity 77.8% and specificity 67.1%) and < 13.9% in AF (area under the curve: 0.74, 95% CI: 0.59–0.88; sensitivity 70.6% and specificity 80.0%) and is well correlated to the LAA peak emptying flow velocity [72]. The combined diagnostic value of LA longitudinal reservoir strain threshold and amplified P-wave duration threshold (165 ms) yielded an even better diagnostic performance (96% sensitivity for detection of LAA thrombus).

Transthoracic echocardiography should systematically include measurement of the LA volume and, whenever possible, the global strain of the left atrium and its three components (reservoir, conduit, contraction). These parameters are complementary and characterize atrial dysfunction described in atrial cardiomyopathy.

Statement 7

- Transoesophageal echocardiography is a powerful diagnostic tool in the search for cardiovascular embolism in patients with cryptogenic stoke.
- LAA morphology should be described, because the non-chicken wing morphology is associated with an increased risk of thromboembolism.
- A thrombogenic milieu, defined as LA/LAA thrombus or spontaneous echocardiographic contrast, low flow emptying and filling velocities, has been described in patients with AF and in stroke patients. Whether these abnormalities are relevant in atrial cardiomyopathy is unknown.

AF: atrial fibrillation; LA: left atrial; LAA: left atrial appendage.

4.2.2.2. Transoesophageal echocardiography. LA appendage morphology and (dys)function is highly variable and is considered a major source of thromboembolism in patients with AF. The presence of LAA thrombus or LA/LAA spontaneous echocardiographic contrast is associated with increased long-term thromboembolic risk and all-cause death [73] and with LAA dilation and low LAA velocities [74]. LAA anatomical parameters, including LAA volume, LAA depth, short and long axes of LAA neck, and numbers of lobes, are diagnostic tools for risk stratification for thromboembolism in patients with AF [75]. Several studies on the associations between LAA volume and stroke risk have shown that AF patients with a history of ischaemic stroke/TIA tend to exhibit a larger LAA volume [76]. However, the specific cardiac phase for defining the LAA volume was not clearly defined, being end-systolic versus end-diastolic volume, and the threshold value is unknown [77]. Patients with LAA thrombus had a higher amount of LA fibrosis compared to patients without thrombus [78]. LA fibrosis was higher in patients with versus those without spontaneous echo contrast (116). In addition, patients with high atrial fibrosis were more likely to have both thrombus and spontaneous echo contrast in the LAA [78]. Reduced LA/LAA flow dynamics and increased LA size are risk factors for the occurrence of thrombus and spontaneous echo contrast [79]. Decreased LAA velocities have been strongly associated with increased grades of severity of LAA/LA spontaneous echocardiography contrast and thromboembolic events [80]. A study correlated LAA flow with LAA morphology in patients with AF: LAA flow velocity was higher in patients with chicken wing than in those with cactus and cauliflower (but not in those with windsock [$P = 0.102$] morphology) [81].

4.2.3. Cardiac magnetic resonance imaging

Statement 8

- Cardiac magnetic resonance is a validated tool for evaluation of LA morphology and size (volumes).
- Delayed-enhancement magnetic resonance imaging is the reference method to diagnose the extent of LV and LA fibrosis, an independent predictor of cerebrovascular events. However, reference values are lacking and deserve further investigations before its use in clinical practice.

AF: atrial fibrillation; LA: left atrial; LV: left ventricle.

Cardiac magnetic resonance is an alternative imaging modality for LA characterization, particularly in patients unable to undergo transoesophageal echocardiography due to oesophageal pathology and computed tomography scanning due to advanced renal insufficiency, severe iodine contrast allergy or iodine contrast shortage. Cardiac magnetic resonance outperforms standard transthoracic echocardiography for quantification of LA volume [82].

LA fibrosis in delayed-enhancement magnetic resonance imaging is an independent predictor of cerebrovascular events and significantly increased the predictive power of the CHA_2DS_2-VASc score [83].

Impaired LA function and LA enlargement were associated with the burden of PAC/h on extended ambulatory electrocardiographic monitoring [84].

Four-dimensional flow magnetic resonance imaging yields 3-dimensional volume sets over time (4-dimensional) and enables precise quantitative evaluation of cardiovascular blood flows [85]. AF patients present with lower LA mean velocities and more often LA stasis compared with controls; a correlation was described between LA blood flow indices, age and LA volume, but not with left ventricular ejection fraction [86].

4.2.4. Cardiac computed tomography

Statement 9

Cardiac computed tomography can determine LA volumes, LAA anatomy and size, including the presence of a thrombus and is the reference diagnostic tool to characterize LAA morphology (chicken versus non-chicken wing).

LA: left atrial; LAA: left atrial appendage.

Cardiac computed tomography provides accuracy similar to that of transoesophageal echocardiography for the detection of LA thrombus. Unlike transoesophageal echocardiography, for which the reference standards were postmortem and operative findings, cardiac computed tomography has been validated only by comparison with transoesophageal echocardiography [87]. Non-chicken wing LAA morphology increases the risk of thromboembolism compared with chicken wing morphology (OR: 10.1, 95% CI: 1.25–79.7; $P = 0.019$) in patients with a $CHADS_2$ (Cardiac failure, Hypertension, Age, Diabetes, Stroke [Doubled]) score of 0 to 1 [88,89]. These results were confirmed in a meta-analysis [90].

Non-chicken wing morphology of the LA appendage was more frequent in ESUS compared with non-cardioembolic patients [55].

Patients with AHRE $\geq$ 6 min had worse remodelling features of LA structure and function than those with AHREs < 6 min and without AHRE. Multivariable analysis showed that reduced LAA/AA Hounsfield unit ratio is an independent predictor for the development of AHRE $\geq$ 6 min in the next 6 months.

4.2.5. Biomarkers

Statement 10

- Circulating biomarkers (NT-proBNP, BNP, troponins) can provide evidence of inflammatory and fibrosis in the atrium.
- Elevated BNP (> 100 pg/mL) and NT-proBNP (> 400 pg/mL) may be useful for defining LA remodelling and dysfunction and predict AF incidence.

BNP: B-type natriuretic peptide; LA: left atrial; LAA: left atrial appendage; NT-proBNP: N-terminal pro-B-type natriuretic peptide.

N-terminal pro-B-type natriuretic peptide (NT-proBNP) showed a strong correlation with echocardiographic parameters of

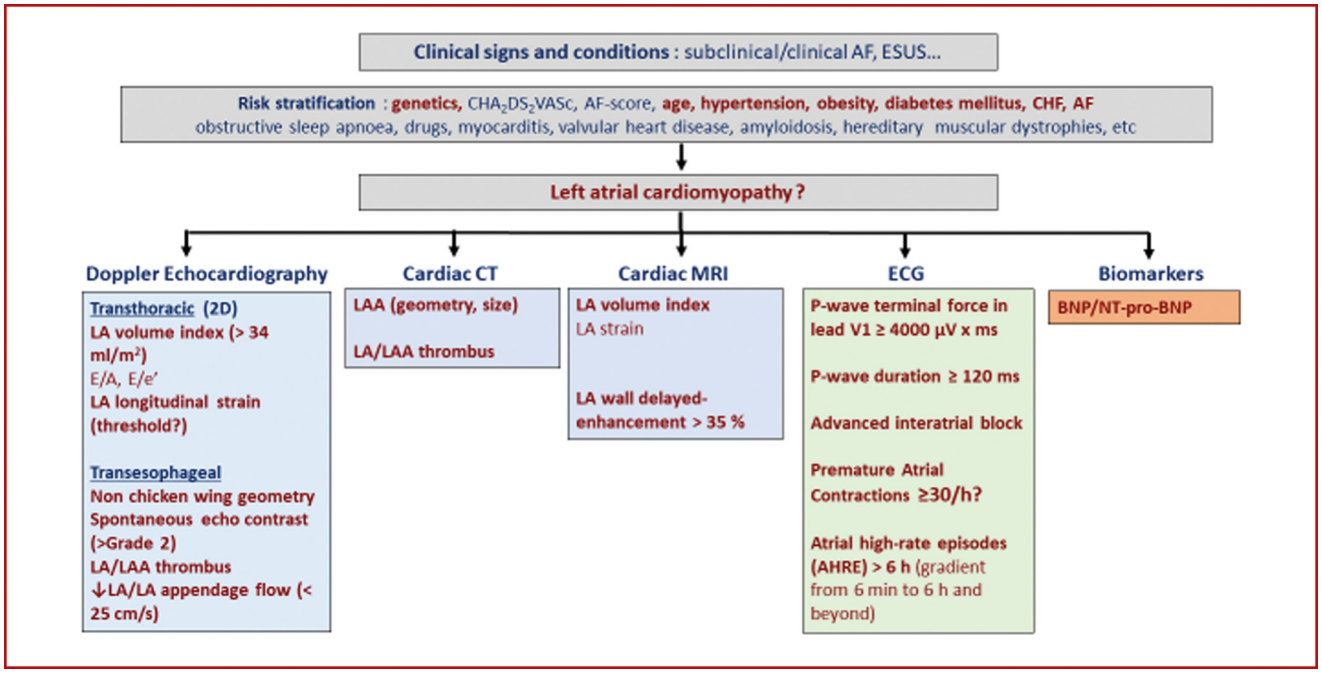

Fig. 1. Proposal for a diagnostic algorithm for atrial cardiomyopathy. 2D: 2-dimentional; AF: atrial fibrillation; AHRE: atrial high-rate episodes; BNP: B-type natriuretic peptide; CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age ≥ 75 years (2 points), Diabetes, Stroke (2 points) – Vascular disease, Age 65–74, Sex category (female); CHF: congestive heart failure; CT: computed tomography; ECG: electrocardiogram; ESUS: embolic stroke of undetermined source; LA: left atrium/left atrial; LAA: left atrial appendage; MRI: magnetic resonance imaging; NT-proBNP: N-terminal pro-B-type natriuretic peptide.

LA remodelling and dysfunction, and was a significant but weak predictor of AF [91] and is associated with AF burden [92]. In the systematic review [55], the prevalence of NT-proBNP > 250 pg/mL did not differ among ESUS versus non-cardioembolic stroke (OR: 0.73, 95% CI: 0.39–1.35). In another meta-analysis, NT-proBNP was associated with incident ischaemic stroke risk, both as a categorical variable (HR: 2.37, 95% CI: 1.61–3.50) and a continuous variable (HR: 1.42, 95% CI: 1.19–1.70) [71].

In anticoagulated patients with AF, the biomarker-based ABC stroke score is more accurate than the CHA_2DS_2-VASc and ATRIA stroke scores [93].

A proposed diagnostic algorithm for atrial cardiomyopathy is presented in Fig. 1.

5. Criteria for selecting patients to be monitored

Thorough AF screening will concern mainly patients whose ischaemic stroke/TIA has not been linked to any embolic source determined by a well-conducted aetiological assessment. However, it may also be proposed to patients whose suspected aetiology has led to the introduction of antiplatelet therapy as long-term secondary prevention and who have a high probability of occult AF. Indeed, as the risk factors for AF are common to those for atheromatous disease, mixed causes of ischaemic stroke/TIA are not uncommon [1,94]. Indeed, the Stroke of Known Cause and Underlying Atrial Fibrillation (STROKE-AF) study reported 11.7% of AF in a cohort of ischaemic stroke patients classified as atheromatous [95].

5.1. Cryptogenic embolic ischaemic stroke/TIA patients

Concluding that there is no identified embolic cause after an ischaemic stroke/TIA is not without difficulties. The definition of a cryptogenic ischaemic stroke/TIA is subject to different interpretations due to disagreements and gaps in recommendations regarding the aetiological work-up, heterogeneity in clinical practice and accessibility of investigations, the questionable causal relationship between the causative disease and the ischaemic stroke/TIA and the aetiological classification used (causal or phenotypic).

After an ischaemic stroke/TIA, the aim of the aetiological assessment is to identify the cause of the ischaemic event and guide an individualized "best of care" secondary prevention strategy. The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) causative classification [96] classifies patients into one of five broad categories: large-vessel atherosclerosis, cardioembolic, small-vessel disease, other identified causes, and undetermined cause (i.e. two or more identified causes, negative work-up, and incomplete work-up). Because mixed causes are not uncommon, and the imputability of a cause is not always established with certainty, the phenotypic aetiological approach proposed in the ASCOD (atherosclerosis, small vessel disease, cardiac pathology, other cause, or dissection) classification is preferred [97]. Each major aetiological category is assigned a causality grade according to established criteria (i.e. potentially causal, uncertain causality and unlikely causality). The cryptogenic classification of ischaemic stroke/TIA will be concluded by a neurovascular physician on the basis of the established phenotype. Cryptogenic ischaemic stroke/TIA may occur in up to one-third of young patients [98]. It implies the absence of an identified cause of stroke despite a well-conducted aetiological work-up. As the absence of a cause depends on the aetiological approach taken, the absence of a minimum aetiological work-up to qualify a cryptogenic ischaemic stroke/TIA is a limitation of this definition. It raises the problem of misuse of cryptogenic qualification in the case of an incomplete negative work-up. Secondary prevention of cryptogenic ischaemic stroke/TIA is based by default on long-term antiplatelet therapy, a strategy that is insufficiently protective in certain situations, particularly in the presence of occult AF [17].

Table 3
Aetiological work-up proposal to define ischaemic stroke/TIA as cryptogenic after standard and advanced evaluation.

Diagnostic evaluation	Aim/target	Timing to be carried out and optimal duration after ischaemic stroke/TIA	When to be considered?
12-lead ECG	To screen for AF	As soon as possible, can be usefully repeated	Must be systematic
Brain MRI (preferably) and/or CT	Stroke or TIA confirmation and ischaemic/haemorrhagic acute and chronic tissue injury phenotyping and distribution (lacunar/territorial/junctional or combined; uni/multiterritorial distribution; acute/subacute or chronic injuries)	As soon as possible can be usefully repeated	Must be systematic
Cervical and transcranial ultrasonography and/or cervical and intracranial MRI or CT angiography	Anterior and posterior arterial cervical and intracranial circulation exploration for diagnosis of an arterial stenosis (atheromatous, arterial dissection, inflammatory stenosis, arteritis, Moya-Moya disease, carotid web or other vasculopathies)	As soon as possible	Must be systematic
Transcranial Doppler with embolus/contrast detection	Detection of right-to-left shunt	Initial or secondary evaluation	Patients with cryptogenic stroke in whom PFO closure would be contemplated
Blood tests including complete blood count, prothrombin time, partial thromboplastin time, glucose, glycated haemoglobin, creatinine, hepatic function, lipid profile	To detect coagulopathy and stroke risk factors	As soon as possible	Must be systematic
Specific blood tests including BNP/NT-proBNP, troponins	Detection of LACM or left cardiac dysfunction	As soon as possible	Suspicion of cardiomyopathy/cardioembolic source
Specific blood tests including inherited or acquired hypercoagulable state, bloodstream or cerebral spinal fluid infection or inflammation, infections or inflammation that can cause CNS vasculitis, drug use, and genetic tests for Inherited diseases Venous hypercoagulability test (right-to-left shunt)	Identify contributors to or relevant risk factors for stroke	Initial or secondary evaluation	Systematic if cryptogenic ischaemic stroke/TIA < 55 years-old and restricted to specific situation if cryptogenic ischaemic stroke/TIA > 55 year-old
Cardiac transthoracic 2D-echocardiography (TTE) with and without contrast and LA size and morphology assessment	Evaluate possible cardiac source of embolism	As soon as possible	Must be systematic
TTE with and without contrast and LA size and morphology assessment	Evaluate possible cardiac source of embolism	Initial or secondary evaluation	Systematic in cryptogenic ischaemic stroke/TIA after first-line evaluations or in case suboptimal TTE
Cardiac CT or cardiac MRI	Evaluate possible cardiac source of embolism or associated cardiomyopathy	Initial (if TTE or TOE contra-indicated or unavailable), secondary or tertiary evaluation	Cryptogenic ischaemic stroke/TIA or high suspicion of cardiac source of embolism
Cardiac in-hospital telemetry	To screen for intermittent AF	As soon as possible	Must be systematic
Cardiac mobile outpatient ELR	To screen for intermittent AF	As soon as possible if required	Cryptogenic ischaemic stroke/TIA or high suspicion of AF or suspicion of cardiac source embolism
ILR	To screen for intermittent AF	As soon as possible if required	Cryptogenic ischaemic stroke/TIA or high suspicion of AF or suspicion of cardiac source embolism
Holter ECG 72 h	To screen for intermittent AF	As soon as possible if required	Consider as a substitution or complement if unavailability of telemetry or ELR or ILR
Body CT scan	To screen for visceral thromboembolism or active cancer	Initial or secondary evaluation	Consider if high probability of active cancer or major source of proximal embolism

BNP: B-type natriuretic peptide; CT: computed tomography; ECG: electrocardiogram; ELR: external loop recorder; ILR: implantable loop recording; LA: left atrium; LACM: left atrial cardiomyopathy; MRI: magnetic resonance imaging; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PFO: patent foramen ovale; TIA: transient ischaemic attack; TOE: transoesophageal echocardiography; TTE: transthoracic echocardiography.

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The cryptogenic qualification of an ischaemic stroke/TIA should be determined by a physician competent in neurovascular pathology after a thorough aetiological evaluation has been carried out, preferably according to the ASCOD classification.
ASCOD: atherosclerosis, small vessel disease, cardiac pathology, other cause, or dissection; TIA: transient ischaemic attack.

In 2014, Hart et al. proposed the pragmatic concept of ESUS to describe an ischaemic stroke/TIA of embolic origin for which the source is not known despite a minimal standard assessment [33]. This is a construct whose purpose was to conduct therapeutic trials comparing DOAC and aspirin in secondary prevention in a group of patients presumed to benefit more from DOAC than from antiplatelet therapy [34–36,99]. Although cryptogenic ischaemic stroke/TIA implies, like ESUS, the absence of an overt embolic cause, the two concepts are not synonymous. ESUS is an entity that combines cryptogenic ischaemic stroke/TIA with those related to embolic

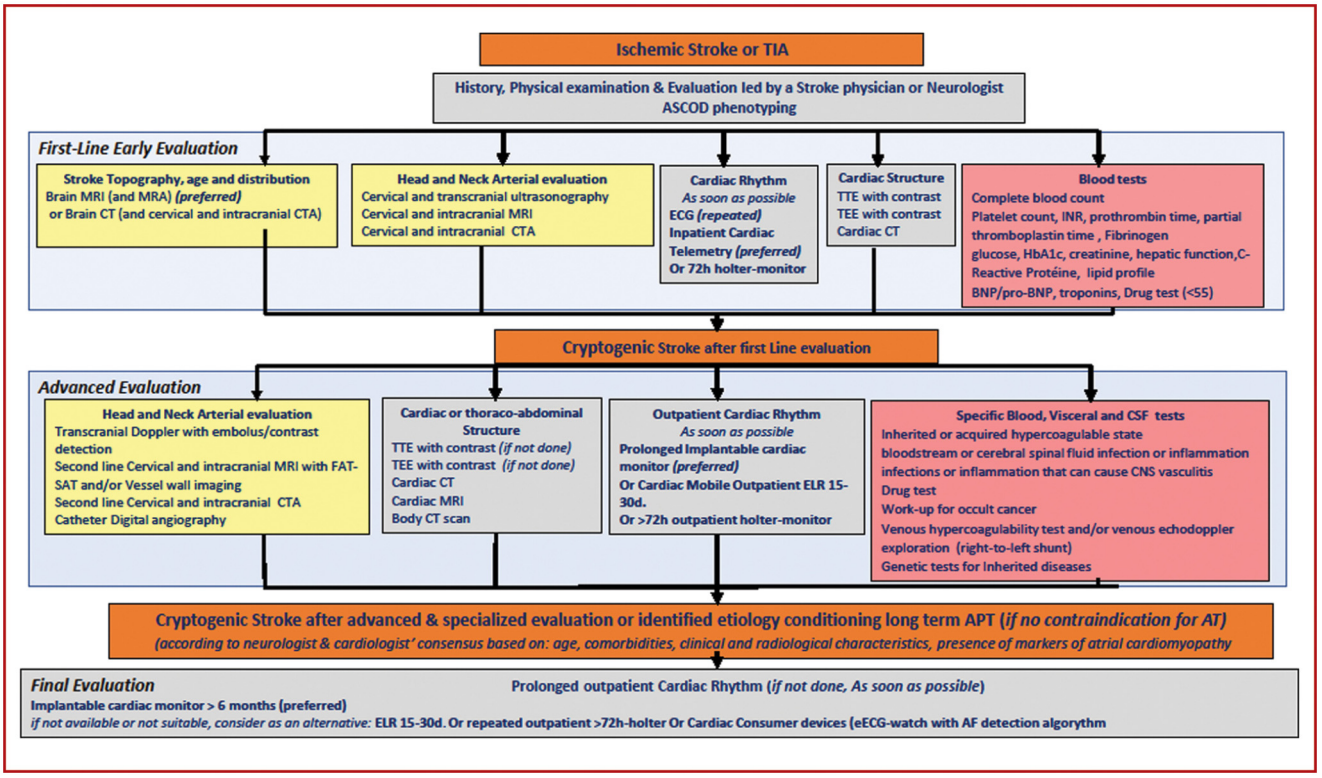

Fig. 2. Proposed algorithm for identification and diagnostic evaluation of patients with cryptogenic ischaemic stroke/TIA and stratification of cardiac rhythm monitoring for AF screening. APT: antiplatelet therapy; ASCOD: atherosclerosis, small vessel disease, cardiac pathology, other cause, or dissection; AT: anticoagulant therapy; BNP: B-type natriuretic peptide; CNS: central nervous system; CSF: cerebrospinal fluid; CT: computed tomography; CTA: computed tomography angiography; ECG: electrocardiogram; ECG: 12-lead electrocardiogram; ELR: external loop recorder; FAT-SAT: fat saturation; HbA1c: glycated haemoglobin; MRI: magnetic resonance imaging; TIA: transient ischaemic attack; TOE: transoesophageal echocardiography; TTE: transthoracic echocardiography.

sources not documented by the specified minimal but "submaximal" work-up (i.e. cardioembolic sources with minor emboligenic risk, unrecognized paroxysmal AF, active cancers, aortic or non-stenotic atheroma and paradoxical emboli). The working group proposes a complete work-up to help clinicians in the diagnosis of cryptogenic stroke/TIA (Table 3), based on current guidelines and the ASCOD classification and a decision-support tree to help to stratify evaluations for AF diagnosis (Fig. 2).

Statement 12

The ESUS qualification of an ischaemic stroke/TIA should not be assimilated to the cryptogenic qualification due to the minimalist aetiological assessment required by this concept. We therefore discourage the use of the ESUS qualification in favour of the cryptogenic qualification based on a more thorough initial or secondary assessment, as proposed in Fig. 2.

ESUS: Embolic stroke of undetermined source; TIA: transient ischaemic attack.

5.2. Ischaemic stroke/TIA patients at high risk of AF

The risk of paroxysmal AF after ischaemic stroke/TIA can be assessed through two approaches that should be combined: a patient-based characteristics phenotypic analysis and an ischaemic stroke/TIA phenotypic-based characterization.

5.2.1. Patient-based characteristics associated with AF after ischaemic stroke/TIA

Common cardiovascular risk factors, thromboembolic risk factors for AF, increasing age (≥ 75 years) and the presence of atheromatous disease are predictors of AF after ischaemic stroke/TIA and are included in the CHA_2DS_2-VASc score [1,43,100,101]. Several reviews of the literature have listed the main features predictive of occult AF after a stroke [25,37,102–104]. These include electrocardiographic, ultrasound and cardiac biomarkers. Dilatation of the left atrium (> 46 mm or > 34 mL/m^2) [105–109], elevated plasma BNP (> 100 pg/mL) or NT-proBNP (> 400 pg/mL) [110–113] levels, which are readily available, have been particularly studied for their value in predicting AF after ischaemic stroke/TIA. Other parameters reported as independently associated with AF detection or prediction after ischaemic stroke/TIA among observational cohorts or randomized trials are: excessive supraventricular extrasystole , paroxysmal atrial tachycardia (≥ 20 beats and < 30 s) [22,114–122], ECG showing PR prolonged interval (> 200 ms; HR 1.3 per 10 ms [1.2–1.4]) [121,123], P-wave terminal force in lead V1 ≥ 4000 μV × ms, P-wave duration ≥ 120 ms [124] or use of an artificial intelligence-guided screening for AF using ECG [125].

5.2.2. Stroke characteristics associated with AF after ischaemic stroke/TIA

The clinical severity of ischaemic stroke as assessed by the NIHSS score (> 5–8), is predictive of AF after ischaemic stroke, in association with the greater frequency of large artery occlusions or larger ischaemic strokes [43,126]. Multiterritorial distribution with preferential cortical or watershed territories of ischaemic lesions [127] and coexisting ischaemic brain injuries of different ages or a combination of both are also highly suggestive of a high-risk cardioembolic source of ischaemic stroke/TIA. Although not clearly proven to date, a high annualized rate of recurrent TIA/ischaemic stroke (≥ 10% per year), particularly when occurring despite appro-

priate antiplatelet therapy, may also be suggestive of a high-rate cardioembolic pattern.

Together, most of these parameters form the basis of many composite scores, such as STAF, SURF, HAVOC, AS5F and CHA_2DS_2-VASc, aimed at predicting AF after ischaemic stroke and guiding the diagnostic strategy for occult AF [101,106,128–130]. Developed over a decade ago, these composite scores have not been incorporated into clinical practice to guide diagnostic strategy due to insufficient sensitivity and specificity. This is due to several methodological biases in their construction, such as the lack of high diagnostic yield tools to diagnose AF at the time the scores were built or heterogeneity of the populations included for score derivation.

On the other hand, it seems that the profile of ischaemic stroke/TIA patients with AF diagnosed remotely from the ischaemic event by an ILR is not the same as those whose AF is more easily diagnosed during acute ischaemic stroke/TIA hospitalization [10,41,131]. This new clinical entity, assimilated to an earlier stage of arrhythmic pathology, could lead to ischaemic stroke/TIA with less severe consequences [1,10,41,131]. Snyman et al. showed that clinical severity did not discriminate patients with AF from the others in an ESUS population (median NIHSS 4) in which nearly 23% of AF was diagnosed by an implantable cardiac monitor [131]. Age and LA dilatation were predictors of diagnosed AF [131]. Similarly, enrichment of inclusion criteria with markers of atrial cardiomyopathy (i.e. LA dilatation > 45 mm of diameter, spontaneous LA contrast, AHRE) in the ATTICUS study [36], which tested the superiority of apixaban over aspirin in an ESUS population, detected nearly 25% of new AF cases with an ILR. This rate was much higher than in the previous NAVIGATE-ESUS and RESPECT-ESUS studies, which observed rates of 3.4% and 7.5%, respectively, but without the systematic use of ILR. In RESPECT-ESUS, age and NT-proBNP were independently associated with the occurrence of AF in this ESUS population [35].

Statement 13

Patients at high risk of developing AF after an ischaemic stroke/TIA can be considered according to the following criteria:

- Clinical and radiological characteristics:
  - Presence of any AF symptom: recurrent unexplained palpitations, transient dyspnoea, paroxysmal chest pain.
  - Older age (≥ 75 years).
  - Cardiovascular risk factors (CHA_2DS_2-VASc ≥ 4 and severe sleep apnoea syndrome, moderate to severe chronic renal failure).
  - Cardioembolic phenotype: clinical severity (higher admission NIHSS), proximal cerebral artery occlusion or large stroke, ischaemic stroke in different vascular territories simultaneously or of different ages, ischaemic stroke exclusively or preferentially distributed in the cortical and/or junctional regions, presence of other visceral (non-cerebral) ischaemic injury.
  - Recurrence(s) of embolic ischaemic stroke/TIA on antiplatelet therapy especially < 5 years after the index ischaemic stroke/TIA or an annualized risk of recurrence > 10% per year.
- Presence of markers of atrial cardiomyopathy (see section 4).

CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age ≥ 75 years (2 points), Diabetes, Stroke (2 points) – Vascular disease, Age 65–74, Sex category (female); NIHSS: National Institutes of Health Stroke Scale; TIA: transient ischaemic attack.

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Patients may be offered optimized AF detection by the means of prolonged cardiac rhythm monitoring:

- Embolic ischaemic stroke/TIA classified as "cryptogenic" by stroke physician after appropriate aetiological work-up.
- Ischaemic stroke/TIA at high risk of AF in patients whose aetiology has led to the introduction of a long-term antiplatelet therapy. This should be proposed according to neurologists' and cardiologists' consensus.

AF: atrial fibrillation; TIA: transient ischaemic attack.

6. When and how to detect atrial fibrillation

6.1. How to detect atrial fibrillation

In the acute phase of an ischaemic stroke or TIA, in patients without a history of AF, it is recommended [1] (class I, level of evidence B) to perform ECG monitoring for at least the first 24 h, followed by continuous ECG monitoring for at least 72 h whenever possible [1]. For some patients at risk of developing AF (e.g. elderly, with cardiovascular risk factors or comorbidities, with indices of LA remodelling, high C_2HEST score, or in case of cryptogenic stroke with stroke characteristics suggestive of an embolic stroke) additional prolonged ECG monitoring using external ECG monitors or implantable cardiac monitors should be considered to detect paroxysmal AF (European Society of Cardiology 2020 guidelines; class IIa, level of evidence B) [1].

At least 25% of all ischaemic stroke/TIA are estimated to be due to AF. The intermittent and very often asymptomatic nature of this arrhythmia makes its detection difficult, although it is crucial for anticoagulation decision. Here, we will review the available methods of detecting AF after ischaemic stroke/TIA beyond the initial ECG, which detects between 2% and 4% of new AF cases [15]. The expert committee will advise on these screening methods. The main characteristics and advantages/disadvantages of current available recorders used for AF screening after cryptogenic stroke/TIA are summarized in Tables 4 and 5.

6.1.1. In-hospital telemetry

In-hospital telemetry is used between 24 h and 76 h and has a median (quartile 1, quartile 3) yield of 6.3% (5.8%, 8.7%) for detecting new AF. Rizos et al. compared the value of a median 64-h telemetry recording with a 24-h Holter recording in a population of 496 consecutive patients admitted to a neurovascular unit. The Holter detected AF in 2.8% and telemetry in 5.4% of cases [132]. Despite its imperfect cost-effectiveness, its non-invasive nature and ease of implementation make telemetry a recommended method in neurovascular units. Telemetric recording should be set up as soon as the patient is admitted to the neurovascular unit or emergency department and at best last throughout the stay in this unit, ideally for a minimum duration of ≥ 72 h. However, a recent French survey showed that telemetry was not available in all neurovascular units [4].

Statement 15

Telemetric recording should be set up as soon as the patient is admitted to the neurovascular unit or emergency department and at best last throughout the stay in this unit.

Table 4
Characteristics of the main recorders that can be used in France for AF screening after cryptogenic stroke/TIA.

Device	Operation	Technology	Patient discomfort	Installation	Reading	Reimbursement
Conventional Holter and patches	Continuous recording of all heart beats in multiple leads	Small wearable device connected to electrodes by wires (conventional Holter) or to a large electrode (patch)	Minimal (if extended)	Nurse in a cardiological environment	Time consuming (proportional to duration)	For 24 h only, no matter how long it is
External loop ECG recorder	Events stored by the device according to programming (cut-off heart rate) or triggered by the patient	Small wearable device connected to electrodes by wires	Moderate (extended)	Nurse in a cardiological environment	Events to be adjudicated Time consuming (proportional to duration)	No specific reimburse-ment, coded by assimilation as a 24-h Holter
Implantable loop ECG monitor	Events stored by the device according to programming (cut-off heart rate) or triggered by the patient	Very small device (1.2–5 cm^3; 2.5–10 g) implanted subcutaneously in the left prepectoral region	Low: implanted device	Physician (or nurse by delegation). Outpatient setting	Remote (not reimbursed) and face-to-face follow-up Events to be adjudicated Time consuming	Device and implantation: reimbursed Remote monitoring: not reimbursed
Consumer devices	Photoplethysmography and/or single-lead ECG	Semicontinuous photo-plethysmography measurement of heart rate possible, with alarm (AF detection) ECG requires patient manipulation	No (should be worn all time)	Not applicable	ECG tracings to be adjudicated	No

AF: atrial fibrillation; ECG: electrocardiogram; TIA: transient ischaemic attack.

Table 5
Comparative description of the main recorders that can be used in France for AF screening after cryptogenic stroke/TIA.

Device	Type of recording	Duration of the recording	Duration of collected episodes	Can be used in post-stroke	Cost	Benefits	Disadvantages
Conventional Holter and patches	Continuous	24 h to 7–14 days	Any duration	Yes	Moderate	Non-invasive	Availability Tedious reading
External event recorder	Intermittent: automatically triggered or when symptoms occur	Up to 28 days	> 30 s	Yes	Moderate	Non-invasive	Availability Tedious reading Compliance
Implantable loop ECG monitor	Intermittent: automatically triggered or when symptoms occur	At least 2 years, up to 5 years	> 30 s or > 2 min depending on the model	Yes	High	Duration of the monitoring	Invasive Demanding (adjudication) Remote monitoring non-reimbursed
Consumer devices	Photoplethysmography and/or single-lead ECG	Photoplethysmography:– intermittent or semi-permanent ECG: 30 s episodes		Depends on motor and cognitive functions	Endorsed by the patient	Non-invasive	Workload (no reimbursement for the adjudication of the tracings) May be difficult to use after stroke

AF: atrial fibrillation; ECG: electrocardiogram; TIA: transient ischaemic attack.

6.1.2. Continuous ECG recording by Holter

Continuous ECG recording by the Holter method has a median (quartile 1, quartile 3) diagnostic yield of 3.9% (2.0%, 6.2%). The earlier the recording is started and the longer its duration, the higher its diagnostic yield. The FIND-AF randomized study randomized 398 patients over 60 years with an ischaemic stroke of less than 7 days into an intensive monitoring group (10 days of Holter at baseline, repeated at 3 and 6 months) and a conventional monitoring group (at least 24 h of Holter). At 6 months, the detection of AF > 30 s was 14% in the intensive monitoring group and only 5% in the other group [27]. These results confirm those obtained by the FIND-AF observational study of 281 patients admitted for ischaemic stroke. A 7-day recording, started early, was far superior (12.5% AF detection) to a 24 or 48-h recording at any time (4.5% or 6.4%, respectively) [133].

Apart from its low diagnostic yield, one of the limitations of Holter recording is its availability and the cumbersome nature of its interpretation, which in France is carried out, by law, by cardiologists. A French single-centre pilot study, carried out in a university hospital, showed that a 72-h recorder was available 96 ± 52 days after the ischaemic stroke/TIA and required 8.8 ± 1.1 min of nurse time and 8.1 ± 5.0 min of cardiologist time for its installation and interpretation. For a 7-day recording, the times for availability, insertion and interpretation were, respectively, 130 ± 124 days, 17.2 ± 1.5 min and 16.4 ± 3.5 min [134]. Systems using artificial intelligence to facilitate their interpretation could partly com-

pensate for these cumbersome requirements, which are hardly compatible with routine practice [135].

Statement 16
24-h Holter ECG recording has low diagnostic yield and a particularly low negative predictive value. For optimal diagnostic yield, Holter ECG should be started as early as possible, ideally during index hospitalization and extended or repeated for at least 72 h.
ECG: electrocardiogram.

6.1.3. External loop recorders

With external loop recorders, the median diagnostic yield of a 30-day recording period, estimated from three studies involving 536 patients, is on average 11.5% (7–20%). The randomized EMBRACE study compared the 30-day event recorder with 24-h Holter monitoring in 572 patients over age 55 years with an unexplained ischaemic stroke/TIA in the previous 6 months. At 30 days, the detection rates for AF lasting > 30 seconds were 16.1% in the 30-day recorder group and 3.2% in the Holter group [22]. The main limitation of this method lies in patient compliance and the cumbersome nature of the interpretation: in EMBRACE, the recording was implemented on average 75 days after the stroke and could only be completed in 60% of cases due to patient compliance [22].

Similarly, ambulatory telemetry, used in the other countries, has a diagnostic yield of 5–24% for recordings of 21–30 days. Patient compliance is also a limitation for this method, being only 80% at 14 days and 62% at 21 days [136]. This method is not currently available in France.

Statement 17
External loop recorders extend the duration of monitoring in a non-invasive way and can therefore be recommended.

6.1.4. Implantable loop recorder

The ILR is the gold standard. The Cryptogenic Stroke and Underlying AF (CRYSTAL AF) study, which included 441 patients with a cryptogenic ischaemic stroke/TIA < 90 days before, compared ILR with conventional AF screening, which was left to the discretion of the investigators. At 1 and at 36 months, the AF detection rates were 12.4% and 30.0%, respectively, in the ILR group, compared with 2% and 3% in the conventional group. Median time to detection was 84 days in the ILR group [23].

One of the limitations of ILR is its low positive predictive value for the diagnosis of AF, estimated at between 54% and 66% depending on the studies. As a result, episodes have to be adjudicated systematically, which leads to a significant workload. For example, when 1049 patients are followed for 90 days with an ILR, 16,505 episodes > 2 min are transmitted [137], indicating how artificial intelligence can be proposed to facilitate the interpretation. In a recent study, for 1500 episodes of AF recorded in 425 patients, use of an artificial intelligence algorithm reduced the number of false positives in the detection of AF by 66.4% in a cohort of cryptogenic strokes [138]. To date, artificial intelligence is not available in ILR marketed in France, except in the very recent Linq II™ monitor (Medtronic, Mineapolis), which is not yet reimbursed.

The Post-Embolic Rhythm Detection with Implantable vs. External Monitoring (PER DIEM) randomized trial compared ILR with a 30-day external recorder within 6 months of an ischaemic stroke in 300 patients. At 1 year, AF was detected in 15.3% of cases in the ILR group and 4.7% of cases in the other group [29]. External recording before ILR implantation does not appear to be necessary either, as AF is most often detected after the first month following the ischaemic stroke [139]. The medicoeconomic yield of ILR implantation is favourable in the US healthcare system, particularly when implanted before a 7-day Holter recording [139].

Recently, the Gapless Electrocardiogram-Monitoring in Stroke at High Risk of Atrial Fibrillation (GEMS-AF) study showed that ECG monitoring without interruption increases detection rates of AF after ischaemic stroke. In 110 patients, during 6 months of follow-up, AF was newly diagnosed in 15.5% using an ILR compared to 0.9% with 24–72-h Holter ECG. Two-thirds of new AF diagnoses were made within the first 30 days of monitoring, underlining the importance of uninterrupted ECG-monitoring [140].

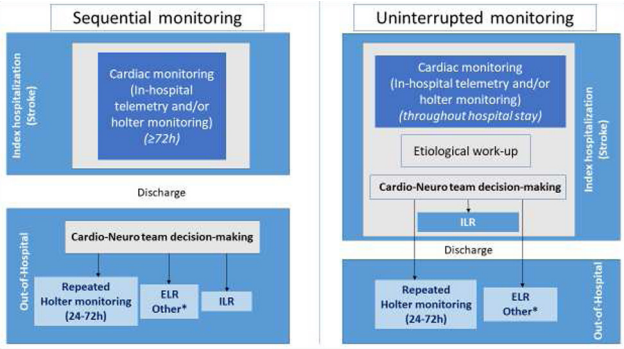
Statement 18
ILR is the reference method for the detection of AF after cryptogenic ischaemic stroke/TIA. Its diagnostic yield, linked to the possibility of continuous recording for a very long time, is threefold higher than that of an external 30-day recorder. Early and first-line implantation after ischaemic stroke, rather than after prolonged or repeated external recording, may be the more efficient option.
AF: atrial fibrillation; TIA: transient ischaemic attack.

Consumer devices such as some connected intermittent smartwatch-ECG, semicontinuous photoplethysmogram or mobile phones allow AF research by photoplethysmography, either automatically or on demand [141,142]. Other devices allow for on-demand single-shot ECG tracing [142]. The cost-effectiveness of these technologies for AF detection after cryptogenic stroke compared with 7-day Holter or ILR is being investigated in Remote Monitoring of AF Recurrence using mHealth Technology (REMOTE AF) and Mobile phones in cryptogenic strOke patients Bringing sIngle Lead ECGs for Atrial Fibrillation detection (MOBILE-AF) [141].

Statement 19
The contribution of patient wearable devices (such as an intermittent smartwatch-ECG and semicontinuous photoplethysmogram) in the search for AF after cryptogenic stroke/TIA seems to be a promising complementary strategy, but its predictive and comparative value compared with existing medical technologies is not currently known. Consequently, it might be advised as a complementary tool according to patient preference or specific situations.

7. Conclusion

Ischaemic stroke/TIA is a major cause of disability in our society. Screening for AF after the event is crucial. Although major gaps still exist in the evidence regarding the optimal strategy for detecting AF and the optimal management after detection of AF in this setting, this scientific statement argues for the widespread development of patient pathways to enable the most efficient assessment. This assessment should be carried out by a multidisciplinary team, including expert cardiologists and vascular neurologists. The procedures implemented by the team will depend on local human and technical resources, but should tend towards what the panel considers optimal, as shown in the Central Illustration. Protocols should be clearly stated and revised as necessary, especially as scientific knowledge evolves.



Central Illustration. Proposal for atrial fibrillation screening after ischaemic stroke/TIA. Depending on local organization the monitoring may be sequential of uninterrupted. The Task Force recommends uninterrupted monitoring when feasible. ELR: external loop recorder; ILR: implantable loop recorder; TIA: transient ischaemic attack. * Consumer devices may become an alternative in the future.

Disclosure of interest

The authors declare that they have no competing interest.

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