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SPECIAL REPORT

ESC Working Group on e-Cardiology Position Paper: accuracy and reliability of electrocardiogram monitoring in the detection of atrial fibrillation in cryptogenic stroke patients

In collaboration with the Council on Stroke, the European Heart Rhythm Association, and the Digital Health Committee

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The role of subclinical atrial fibrillation as a cause of cryptogenic stroke is unambiguously established. Long-term electrocardiogram (ECG) monitoring remains the sole method for determining its presence following a negative initial workup. This position paper of the European Society of Cardiology Working Group on e-Cardiology first presents the definition, epidemiology, and clinical impact of cryptogenic ischaemic stroke, as well as its aetiopathogenic association with occult atrial fibrillation. Then, classification methods for ischaemic stroke will be discussed, along with their value in providing meaningful guidance for further diagnostic efforts, given disappointing findings of studies based on the embolic stroke of unknown significance construct. Patient selection criteria for long-term ECG monitoring, crucial for determining pre-test probability of subclinical atrial fibrillation, will also be discussed. Subsequently, the two major classes of long-term ECG monitoring tools (non-invasive and invasive) will be

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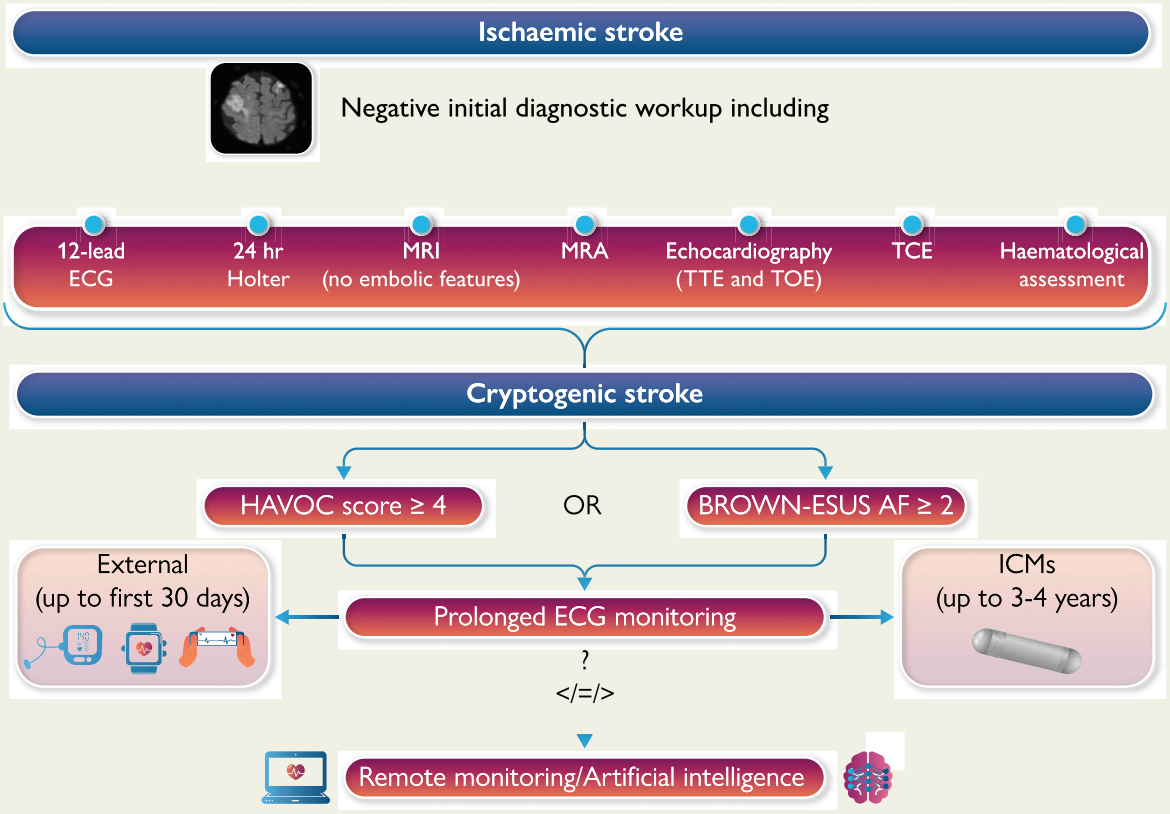
presented, with a discussion of each method's pitfalls and related algorithms to improve diagnostic yield and accuracy. Although novel mobile health (mHealth) devices, including smartphones and smartwatches, have dramatically increased atrial fibrillation detection post ischaemic stroke, the latest evidence appears to favour implantable cardiac monitors as the modality of choice; however, the answer to whether they should constitute the *initial* diagnostic choice for *all* cryptogenic stroke patients remains elusive. Finally, institutional and organizational issues, such as reimbursement, responsibility for patient management, data ownership, and handling will be briefly touched upon, despite the fact that guidance remains scarce and widespread clinical application and experience are the most likely sources for definite answers.

Graphical Abstract



Diagnostic algorithm in cryptogenic stroke. For HAVOC and BROWN ESUS-AF scores, see *Table 2*. ECG, electrocardiogram; ICM, implantable cardiac monitor; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; TCE, transcranial echocardiography; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography.

Keywords Cryptogenic stroke • Atrial fibrillation detection • ECG monitoring • mHealth • Implantable cardiac monitors • Remote monitoring • Cardiac rhythm monitoring

Introduction

Cryptogenic strokes (CSs) represent almost one-third of all ischaemic strokes (ISs). Detection of previously unknown but underlying atrial fibrillation (AF) has important implications for the secondary prevention of IS in the CS population.[1] Prolonged cardiac rhythm monitoring is appropriate in patients with CS and transient ischaemic attack (TIA) who have a negative baseline diagnostic workup including both in-patient telemetry and at least 24-h outpatient Holter monitoring.[2] Long-term monitoring devices have the potential to substantially increase the probability of AF detection in patients with CS, thereby allowing for timely initiation of anticoagulation therapy that may confer the greatest benefit in terms of recurrent stroke prevention in these patients.[1] Since the efficacy of anticoagulation for secondary stroke prevention is only established for patients with confirmed AF,[3,4] long-term electrocardiogram (ECG) monitoring tools that are commonly used for paroxysmal AF detection should be scrutinized for the accuracy and reliability of their detection algorithms.

Mobile Cardiac Outpatient Telemetry (MCOT) and External Loop Recorders (ELRs) are ambulatory non-invasive diagnostic tools that are commonly used for long-term ECG monitoring in CS patients. Novel mobile Health (mHealth) options for long-term ECG

monitoring are promising non-invasive tools, but their reliability and accuracy in this context are yet to be established. Implantable cardiac monitors (ICMs) have documented the highest yield in detecting paroxysmal AF in patients with CS since they prolong substantially the duration of cardiac monitoring (up to ≥3 years). Although ICMs have high sensitivity, their use is significantly hampered by high false-positive (FP) rates, necessitating the use of artificial intelligence (AI) or other techniques to improve the detection algorithms.[5] Improving the accuracy of ICMs is essential for the implementation of this costly technology in IS patients.

Aim and scope

Current international recommendations underline the role of prolonged ECG monitoring in the optimal diagnostic workup in patients with CS.[6,7] Detection of AF by either non-invasive or invasive ECG monitoring tools is essential for the appropriate selection of CS patients with a clear indication for anticoagulation in the context of secondary stroke prevention. Therefore, the accuracy and reliability of these ECG monitoring tools are prerequisites for the appropriate management of patients who have suffered a CS.

This position paper provides guidance towards the best use of both non-invasive and invasive long-term ECG monitoring tools for the detection of paroxysmal AF, focusing on the current limitations in the use of these tools in patients with CS. It aspires to constitute both a benchmark to address the issues of accuracy and reliability in the detection of paroxysmal AF with long-term ECG monitoring tools and a framework for directing future research and policy in relation to the use of long-term ECG monitoring tools for cardiovascular disease prevention.

CS: definition, prevalence, and clinical impact

CS is estimated to represent 20–40% of all ISs,[8–11] with an annual incidence of 300 000 cases in Europe and North America.[12] The term 'cryptogenic' indicates the absence of an identified aetiology and therefore comprises a heterogeneous group of patients in terms of risk profile, comorbidities, outcome, and potential treatment options. The frequently observed inability to identify the underlying mechanism of an IS explains the incorporation of CS as a separate category in various classification systems (*Table 1*). More specifically, the complete definition of CS according to TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria underscores the heterogeneity in combining three different patient subgroups:

(i) no identifiable stroke aetiology because of incomplete (or missing) diagnostic assessment, or
(ii) no identifiable reason of IS despite appropriate diagnostic workup, or
(iii) inability to establish a distinct aetiology due to the presence of other competing stroke mechanisms.[13]

Accordingly, the prevalence of CS among IS patients is inversely related to the extent of diagnostic workup, while the reproducibility of CS diagnosis is the lowest among IS subtypes.[12,14] Moreover, classification of strokes as cryptogenic offers little information in terms of treatment guidance or even trial design, since it groups together heterogeneous IS cases with propensity for different underlying stroke mechanisms.[13] The main underlying mechanism of the majority of CS may be cerebral embolism, as corroborated by angiographic findings and thrombus composition.[15] Stroke severity in CS is lower than in other subtypes of IS in terms of neurological or functional assessment on admission [median National Institutes of Health Stroke Scale (NIHSS) Score 5 [16] as opposed to a score of 14 in carotid/vertebrobasilar stroke[17]], as well as in terms of mortality.[18] CS appears to represent the most common stroke subtype in IS patients aged ≤ 45 years.[19]

In the 2019 SARS-CoV-2 pandemic, it appears that CS incidence increased four-fold due to coagulation disorders,[20] cardiac involvement, and endothelial dysfunction that have been associated with COVID-19.[21]

Given that the term CS indicates the inability to identify a specific stroke mechanism by initial definition, CS should be viewed as a *working* diagnosis until efforts of diagnostic workup succeed in identifying a specific underlying aetiology. Although it is difficult to advocate on the appropriate time window of CS evaluation to find the underlying aetiology, we should consider a CS patient being in the evaluation phase if ≤1 year from stroke/TIA onset.

Embolic Stroke of Undetermined Source

The pathophysiology of stroke significantly affects response to treatment, especially in terms of recurrence prevention (with platelet-rich thrombus formation inhibition achieved better with antiplatelets and erythrocyte-fibrin-rich thrombus formation inhibition achieved with anticoagulants) and cost–benefit ratio. As mentioned, most CS are embolic in origin[22,23]—thus, the concept of Embolic Stroke of Undetermined Source (ESUS) as a subset of CS was put forward[12] (*Table 1*).

Based on a recent review,[16] ESUS frequency averages 17% of ISs with an annual recurrence rate of ∼4.5%. Despite the temptation to consider this entity coterminous with subclinical AF-related stroke, several alternative sources of emboli and clinical phenotype clusters exist[24–26] (valvular, atrial, ventricular, arterial, venous—paradoxical embolism, thrombophilia-related and cancer-related), each with a different embolus composition,[12,27] and thus different response to treatment (8% of emboli in ESUS patients are platelet-rich[28]). In fact, two-thirds of ESUS patients under prolonged (3 years) rhythm monitoring with an ICM never exhibited AF.[29] The stroke risk of AF-free ESUS patients (usually younger and with clinically milder symptoms)[16] could be attributed to the underlying atrial cardiomyopathy.[24,30–34] In turn, in AF patients, this framework would explain both the inconsistent findings in the temporal association between fibrillatory rhythm and stroke,[35–38] as well as the incidence of stroke with subclinical AF [including atrial high-rate episodes (AHREs)[6,15]]. Finally, ESUS patients may still have non-embolic stroke mechanisms.[39] The emerging therapeutic strategies may include anticoagulation in cases of ESUS with pathologies associated with erythrocyte-rich thrombi, and low-dose anticoagulation plus aspirin in ESUS associated with atherosclerosis.[27] These concepts need validation.

Table 1 Main classification schemes for ischaemic stroke aetiology

Classification	Discrete aetiologies/features
TOAST(Trial of ORG 10172 in Acute Stroke Treatment)	1. Large artery atherosclerosis—Clinical and brain imaging findings of >50% stenosis (including occlusion) of a major brain or branch cortical artery. Invasive angiography was the gold standard but due to (potentially disabling/lethal) complications has been replaced with either duplex ultrasonography (most widely available) or CT/MR angiography. Alternatively, lesions with a diameter >15 mm in brain CT/20 mm in brain MRI are potentially of large vessel atherosclerotic origin. Known peripheral artery disease/carotid bruit support the diagnosis. 2. Cardioembolism—Requires presence of at least one major (such as mechanical prosthetic valve/atrial fibrillation) or medium (such as a patent foramen ovale) risk cardiac source of emboli. Involvement of more than one vascular territory or other systemic thromboembolism (such as pulmonary embolus) support the diagnosis. 3. Small vessel occlusion leads to lacunar infarcts with either normal brain imaging or with lesions involving deeper cerebral structures, most often with diameters <15mmin brain CT/20 mm in brain MRI. Patients clinically exhibit one of the five classic lacunar syndromes. Presence of comorbidities, such as hypertension and/or diabetes mellitus support the diagnosis. 4. Other determined aetiology—Includes rarer causes of stroke, such as cases of known thrombophilia, arterial dissection, central nervous system vasculitis and others. 5. Cryptogenic stroke (CS)—An umbrella term including: • strokes of undetermined aetiology following an extensive diagnostic workup, • strokes of undetermined aetiology after a cursory evaluation • strokes with >1 potential cause Of note, no minimum diagnostic workup is recommended prior to classification of a stroke as cryptogenic.
CCS	1. Cardio-aortic (embolic) 2. Large artery atherosclerosis 3. Small artery atherosclerosis 4. Other cause 5. Cryptogenic CCS constitutes essentially an update of the TOAST classification, using updated estimates of stroke risks associated with specific pathologies or clinical or imaging parameters known to be more commonly associated with particular stroke mechanisms, in order to assign the most likely phenotype.
ASCOD	• A: Atherosclerosis • S: Small vessel disease • C: Cardiac pathology • O: Other • D: Dissection Each category is further characterized by a number, denoting degree of certainty regarding association between disease and stroke. • 1: Disease present and a potential cause • 2: Disease present, uncertain causality • 3: Disease present, unlikely causality • 0: Disease absent • 9: Insufficient workup to grade association. Each patient receives a grade for more than one categories and more than one grades for the same category, e.g. A1A3S2C1O0D0. Detailed required workup and associated diagnoses are included for scoring each category.

ASCOD, Atherosclerosis—Small vessel disease—Cardiac pathology—Other causes—Dissection; CCS, Causal Classification of Stroke; CT, computed tomography; MRI, magnetic resonance imaging; TOAST, Trial of ORG 10172 (danaparoid) in Acute Stroke Treatment.

Gaps in knowledge

- It is imperative to improve the delineation of the underlying pathophysiology in IS as it significantly affects response to treatment. Better discrimination between embolic and non-embolic IS pathophysiology—more specifically the magnitude of association between embolic stroke and red (erythrocyte-rich) thrombus, and non-embolic stroke and white

(platelet-rich) thrombus, as well as the extent of overlap could impact long-term follow-up, mainly in terms of recurrence prevention. However, mechanical thrombectomy and histological evaluation of removed thrombus has currently limited place in clinical practice, as many stroke patients are not eligible for mechanical thrombectomy treatment.

- The necessary diagnostic workup for the ESUS patients with regard to anticoagulation treatment (e.g. direct imaging of thrombus to determine composition and age[40]) has not been yet determined.

The role of AF in CS

AF is the most common cardiac arrhythmia, barring extrasystoles, and is one of the most common cardiovascular conditions. Up to 1–2% of the population worldwide has AF and the incidence rises to over 10% at age >80 years. About one in three incident ISs are associated with AF.[41–43] Several studies have found age, prior stroke, hypertension, diabetes mellitus, and congestive heart failure as independent risk factors for stroke in a population suffering from AF.[44] Other recently identified factors are peripheral vascular disease, coronary artery disease, complex aortic plaque, and renal failure.[45–49] Also, although not taken into consideration by current guidelines,[6] the risk of stroke appears to increase as patients progress from paroxysmal to permanent AF.[50,51]

Strokes associated with AF are usually more severe, often fatal, or leaving the patient with permanent disability[6,52]: 30-day mortality of AF-related stroke is 22%, compared with 10% for non-AF-related stroke; 1-year mortality after AF-related stroke is 37%, compared with 20% for non-AF-related stroke.[53] Furthermore, 1-year stroke recurrences are higher after AF-related stroke (6.9%), compared with non-AF-related stroke (4.7%).[54] In addition, the length of hospital stay is longer for patients with AF-related strokes.[55] Targeted strategies to improve AF diagnosis may provide a substantial benefit to reduce the rates of stroke and of severe disabling stroke at a population level. Detection of previously unknown, but underlying AF has important implications for primary and secondary prevention of stroke.

Routine clinical workup to detect AF in CS patients

Detection of AF is critical because it determines the post-stroke management strategy. Careful consideration must be given to investigations as there are several modalities available. Every stroke patient requires routine workup including an ECG and in-hospital continuous telemetry for at least the first 24 h after stroke onset.[56] AF, if transient, infrequent, and largely asymptomatic, may be undetected on routine monitoring. Prolonged monitoring should be performed if an arrhythmic cause of stroke is suspected.[57] Studies have shown that longer durations of monitoring are likely to obtain the highest diagnostic yield.[58,59] Although the optimal monitoring method and duration of monitoring is debated,[60,61] both randomized control studies[2,62] and meta-analyses[1,63] advocate for the superiority of ICMs to any other monitoring tool for the AF detection in CS patients and the secondary prevention of IS. Nevertheless, the available options for prolonged cardiac rhythm monitoring are as follows:

(1) Serial ECGs (including those acquired though mobile health—mHealth—capable devices)
(2) External loop recorders (event-triggered)[64]
(3) Wearable photoplethysmographic (PPG)-based monitoring devices[65]
(4) ICMs [2,62,66,67]

Ideally, the treating physician and patient jointly decide which form of monitoring is most suitable, taking into account the risk of AF, the burden on the patient and the risk of complications.

Long-term ECG monitoring in CS: patient selection

Although ICMs proved to be cost-effective diagnostic tools for the prevention of recurrent stroke in CS patients,[68,69] pre-selection of CS patients with the highest AF probability is still crucial. Several risk markers have been documented and some risk-stratification scores have been proposed.[39,70–80] The HAVOC score is a clinical score ranging between 0 and 14 points.[79] Increasing HAVOC scores (≥4 points) has been internally and externally validated to predict higher yield of AF detection among CS patients.[81] The BROWN ESUS-AF score combines age and left atrial enlargement detected on echocardiography to stratify CS patients with high risk of occult AF.[80] The score ranges between 0 and 4, has satisfactory internal validation but still requires adequate external validation. Both of these scores can be applied during the diagnostic workup of CS patients either during hospitalization or at the outpatient setting (*Table 2*).

Finally, there are three important considerations when selecting CS for prolonged cardiac rhythm monitoring.

- First, the diagnostic workup for uncovering the aetiopathogenic mechanism of cerebral ischaemia should be both comprehensive and complete to exclude alternative causes of acute cerebral ischaemia (extra- or intra-cranial symptomatic atherosclerosis, small vessel disease, patent foramen ovale-associated stroke, arterial dissection, etc.)[82,83] before referring patients for prolonged cardiac rhythm monitoring.
- Second, it is realistic to favourably recommend prolonged cardiac rhythm monitoring even to patients with contraindications to oral anticoagulation, if paroxysmal AF is detected, due to the advent of left atrial apex occlusion devices. Of course, short life expectancy (<1 year) should be considered as a contraindication to prolonged cardiac rhythm monitoring.
- Third, the proposed risk-stratification scores do not include biomarkers (e.g. cardiac natriuretic peptides) that may further refine the selection of appropriate CS patients for prolonged cardiac rhythm monitoring.[84–86] The results of the NOR-FIB study are anticipated shortly.[87]

Gaps in knowledge

- Although longer more intensive ECG monitoring to detect AF in CS patients is desirable, the optimal duration of monitoring is unclear. It is however difficult to make any causal assumption regarding AF episodes detected very long after the index stroke.

Table 2 Overview of risk-stratification scores for detection of paroxysmal atrial fibrillation in patients with cryptogenic stroke

Risk-stratification score	Components	Range	Proposed cut-off for prolonged cardiac monitoring
HAVOC[79]	• Hypertension: 2 points • Age≥75 years: 2 points • Valvular heart disease: 2 points • Vascular disease (peripheral): 1 point • Obesity (BMI > 30 kg/m^2): 1 point • Congestive heart failure: 4 points • Coronary artery disease: 2 points	0–14 points	≥4
BROWN ESUS-AF[80]	• Age 65–74 years: 1 point • Age≥75 years: 2 points • Moderate/severe left atrial enlargement[a] (left atrial volume index > 34 mL/m^2): 2 points	0–4 points	≥2

[a]Detected on transthoracic echocardiography.

- Optimal implementation of clinical risk scores, such as HAVOC and BROWN ESUS-AF, regarding selection of CS patients who should undergo prolonged ECG monitoring is still lacking.
- Contribution of biomarkers in further refining the selection of CS patients for prolonged cardiac rhythm monitoring is currently unclear.

Non-invasive diagnostic tools for long-term ECG monitoring

Ambulatory non-invasive diagnostic tools: efficacy, risk factors, and algorithms

It is well-known that absence of AF symptoms should not be considered absence of AF. In fact, several clinical trials have demonstrated that long-term ambulatory ECG monitoring can increase the efficacy of AF detection, and up to 50% of patients may be asymptomatic during some AF episodes.[88–90]

Over the past two decades, several academic and industrial institutions have developed and launched innovative monitors for long-term ECG recording.[61] Owing to improvements in ECG electrodes durability and battery duration that overcome previous limitations, long-term ambulatory ECG monitoring (7–30 days), with acceptable quality of ECG signal,[91–94] is becoming a common clinical practice to unmask potential arrhythmia episodes and ultimately to help prevent strokes. Nevertheless, external ECG monitoring is typically not practical for more than 30 days due to patient adherence.

Two recording modalities are currently available for long-term surface ECG monitoring. *First*, continuous ECG recording up to 30 days, generally performed by wearable devices using leadless electrodes, utilizing either patch or belt or vest with embedded electrodes. *Second*, long-term ECG recording by an external loop recorder (ELR), which is an event recorder utilizing standard lead-wired electrodes, continuously recording the ECG signals, but memorizing only short ECG periods following pre-established triggers. An algorithm is continuously analysing the input signal to detect potential events and then triggers the recording function. Sensitivity and specificity of such real-time algorithms is crucial to ensure the balance between prolonging battery life and not losing relevant segments. This became especially important following the publication of the *IEC 60601-2-47:2012—Medical electrical equipment—Part 2-47: Particular requirements for the basic safety and essential performance of ambulatory electrocardiographic systems* where the requirements for AF detection are well-defined.

Traditionally, algorithms based on the statistical analysis of RR intervals have been used to differentiate normal sinus rhythm from arrhythmia events.[95] However, they present important limitations to discriminate between AF and other arrhythmic or noisy events.[96] Moreover, such algorithms based on RR irregularity may miss stroke-related rhythms like atrial flutter which presents fixed conduction patterns. In addition, R-wave detection in high-noise signals continues to be a challenging problem and specific algorithms for long-term recordings are being developed.[97]

Most recent long-term recording systems allow for continuous storage, usually by having periodic upload of data to on-line services. The use of the entire ECG signal to detect AF requires higher computational resources and may not be available for real-time use; nevertheless, off-line analysis is becoming as (or even more) clinically relevant than real-time analysis. High-quality algorithms to automatically label ECGs of several days or weeks can reduce the human workload requirement. The combination of biomarkers extracted from ECG signals (e.g. power spectral density, entropy, etc.) and AI algorithms [e.g. machine learning, deep neural networks (DNNs)] is an area of work and constant improvement[98] (*Figure 1*).

Novel mHealth options for long-term ECG monitoring

Mobile health, or 'mHealth' is a component of Digital Health, defined by the World Health Organization as 'medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, and other wireless devices'.[99] One of the main

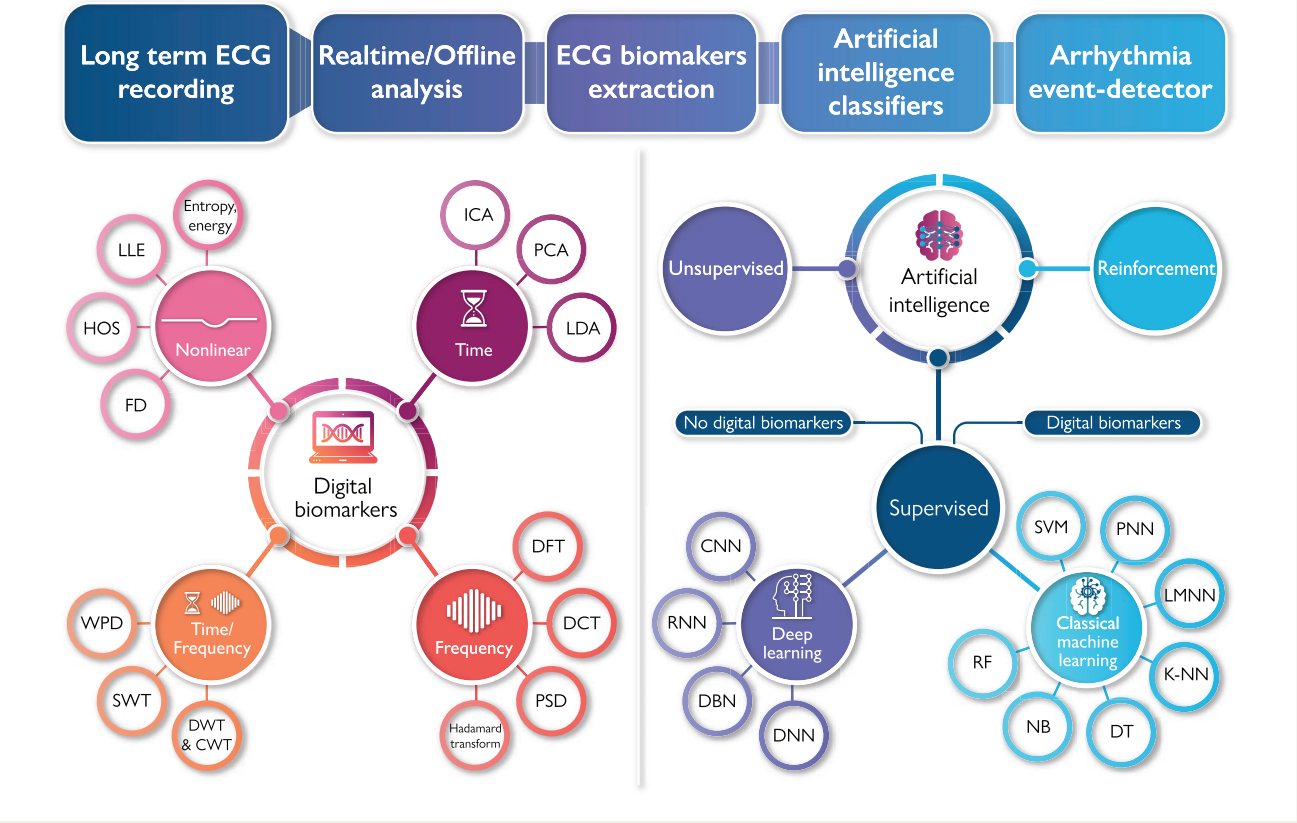


Figure 1 Flowchart of AF detection and summary of automated AF detection methods from ECG signals (modified from[98]). AF, atrial fibrillation; CNN, convolutional neural network; CWT, continuous wavelet transform; DBN, deep belief network; DCT, discrete cosine transform; DFT, discrete Fourier transform; DNN, deep neural network; DT, decision tree; DWT, discrete wavelet transform; ECG, electrocardiographic; FD, fractal dimension; HOS, higher order spectra; ICA, independent component analysis; K-NN, K-Nearest Neighbour; LDA, linear discriminant analysis; LLE, largest Lyapunov exponent; LMNN, Levenberg–Marquardt neural network; NB, Naive Bayes; PCA, principal component analysis; PNN, probabilistic neural network; PSD, power spectral density; RF, Random Forest; RNN, recurrent neural network; SVM, support vector machine; SWT, stationary wavelet transform; WPD, wavelet packet decomposition.

applications of mHealth is arrhythmia monitoring that can be performed either by ECG-based, or non-ECG-based devices.[99] mHealth devices generally have an embedded capability for data transmission, may have the possibility of monitoring other parameters simultaneously with the ECG or heartbeat, and may be linked to machine learning analyses.

- *ECG-based mHealth devices* can perform single or multi-lead intermittent or continuous ECG recordings of variable durations for arrhythmia monitoring with different clinical indications.[61,99,100] Traditional wearable ECG monitors, based on belts or vests with embedded electrodes, allow continuous monitoring for multiple weeks and multiple leads recording, and they have been used for evaluating palpitations, syncope, and CS.[94,101] Several patches are currently available, consisting of light, small, waterproof, energy-efficient recorders, continuously recording single or dual leads, capable of wireless data transfer, minimally interrupting daily life, and able to automatically detect AF.[102–104] Intermittent recorders, generally based on smartphone or smartwatch technology, can perform brief (generally 30 s) 1- to 6-lead ECG recordings activated by the user with applications for clinical diagnoses of AF in individuals at high risk[105,106] or for fitness purposes.[99] In selected populations with high pre-test probability of AF (e.g. recent CS/TIA), even opportunistic use of smartphone-based ECG recorders may lead to an almost fivefold increased probability for the detection of AF (9.5 vs. 2.0%) at 30 days post-event.[107]
- *Non-ECG-based mHealth devices* are based on HR sensors (inertial, optical) embedded into specific medical devices as well as in consumer electronics (smartphones, virtual reality headsets) used ubiquitously in daily life, and may improve the ability to monitor heart rhythm and detect AF. The miniaturization of PPG sensors has expanded their application to new wearables, such as smartwatches or even rings, by which, thanks to the power of machine learning, AF can be accurately detected.[65,108–110] A high positive predictive value of the PPG algorithm, ranging from 84 to 98%, has been reported.[65,108] However, these devices pre-dominantly pick up AF during times of physical inactivity and that they do not detect episodes of AF lasting only minutes. Nevertheless, the clinical acceptance of PPG-based heart rate and rhythm monitoring is rapidly growing as demonstrated in the recent TeleCheck-AF study

that arose from the 2019 SARS-CoV-2 pandemic.[111] There is an ongoing interest in population screening for AF aiming not only to define the appropriate non-invasive tool to screen for AF but also to prevent stroke.[65,108,109,112] To evaluate for AF in the CS population, an ambulatory non-invasive diagnostic tool should be light, small, waterproof, energy-efficient, reliable, and mainly cost-effective.

Gaps in knowledge

- Optimal ambulatory non-invasive diagnostic tool for the detection of AF in the CS population is not known and more research is needed.
- Accurate and efficient signal analysis approaches (e.g. RR interval vs. complete ECG signal analysis) need to be established.
- AI algorithms, needed to improve the accuracy of prolonged ambulatory non-invasive ECG recording, should be determined.
- Numerous mHealth options for long-term ECG monitoring are rising on the market, but reliability and accuracy of each device for the detection of paroxysmal AF in CS patients should be established before consideration for inclusion in clinical practice.
- Studies on broader population groups to evaluate sensitivity and specificity of such technologies compared with conventional clinical evaluation are limited.

Invasive diagnostic tools for long-term ECG monitoring

Pacemakers—implantable cardioverter defibrillators

Cardiovascular implantable electronic devices (CIEDs) are rhythm management devices limited to patients with specific medical conditions, needing this specific therapy. CIEDs with an atrial lead may record AHREs, which are assumed to be a surrogate for AF. Methodology and optimal programming of AHRE detection are critical for correct AF detection. FP AF detection using AHREs may result from near-field P-wave oversensing or far-field R-wave oversensing, runs of pre-mature atrial complexes, electrical interference, myopotentials, or repetitive non-re-entrant ventriculoatrial synchrony[113] and trigger inappropriate initiation of anticoagulation, associated with considerable risk of bleeding. On the other hand, brief AF episodes that last for a shorter period of time than that required for the AHRE detection according to manufacturer-specific algorithms would be missed.

The likelihood of AHRE being an equivalent of a clinical AF is higher the longer is the duration of AHRE episodes. For AHREs episodes defined as atrial rate >190/min lasting >6 min, the positive predictive value for AF was 82.7%[114] and increased to 93.2, 96.7, and 98.2% when the threshold duration was prolonged to 30 min, 6 h, and 24 h, respectively. Electrogram review is unlikely to improve the diagnostic accuracy of AHRE longer than 6 h, however, it may be useful in the evaluation of shorter episodes.[115] Accurate detection of AF by CIEDs using AHREs requires several criteria to be fulfilled[116] (*Table 3*). In patients with device-detected (subclinical) AF (i.e. AHRE) the risk of IS is related to the duration of the AHRE episodes.

Table 3 Optimization criteria for AHRE detection by CIEDs (modified from Tomson and Passman[113])

A. Implantation issues
• Atrial lead type and position (preferably passive vs. active fixation pacing lead; appendage vs. low septum)
• Maximize A to V signal ratio (to avoid false positives)
• Choice of closely spaced atrial bipolar leads (e.g. 5 mm interelectrode distance to avoid far-field signal recording)
B. Optimal programming of atrial sensing
• Appropriate high atrial sensitivity without noise detection (e.g. 0.1–0.5 mV)
• Short PVARP (to avoid false negatives)
• Long PVAB (e.g. >25 ms to avoid false positives)
C. Optimal specificity for AF
• Long AHRE duration (≥5 min)
• High atrial rate (≥175 b.p.m.)
• AHREs visual validation (when >5 min and <6 h)
• Avoid competition atrial pacing or RNRVAS

AF, atrial fibrillation; AHRE, atrial high-rate episode; PVAB, post-ventricular atrial blanking; PVARP, post-ventricular atrial refractory period; RNRVAS, repetitive non-re-entrant ventricular atrial synchrony.

he ASSERT study, the IS risk was mostly observed in patients with AHRE exceeding 24 h.[117] An interaction between AF duration and CHA_2DS_2-VASc score on stroke risk has previously been reported.[118] The clinical relevance of shorter AHRE episodes is addressed in the ongoing NOAH-AFNET6[119] and ARTESiA[120] trials.

Therefore, in patients with an implanted pacemaker/defibrillator, regular device interrogation should be performed to search for AF or subclinical atrial tachyarrhythmias, associated with a significantly increased risk of IS or systemic embolism.[35,121] Current guidelines advocate ECG verification of device-detected AF before considering anticoagulation. However, in the absence of such confirmation, it is recommended to regularly (re)assess the thromboembolic risk (CHA_2DS_2-VASc score) and AHRE burden and consider starting anticoagulation when the risk and burden increase over time.[6]

Implantable cardiac monitors

- The use of ICMs in CS patients

ICMs record and store ECG tracings based on the loop recording technique. ICMs have a battery life from 3 to 5 years and can be regularly interrogated through remote monitoring (RM) (*Table 4*). ICMs were initially used to document infrequent tachy- or bradyarrhythmia events in the workup of unexplained syncope and palpitations,[122] and later in the investigation of episodes of paroxysmal AF in CS,[2,60,123,124] or after transcatheter AF ablation.[100] In contrast to ambulatory ECG monitoring, that can detect AF episodes lasting at least 30 s, ICMs can detect AF episodes lasting at least 2 min (*Table 4*). The positive predictive value of ICMs to detect AF may range from 16.6% for AF episodes lasting <2 min to 87.6% for those AF episodes with a duration >30 min.[125]

Several studies with implantable loop recorders (ILR) or ICM demonstrated that about 25–30% of CS patients had AF documented over 3 years of follow-up[2,60,123,124] Nowadays, both randomized

Table 4 **Characteristics, advantages, and disadvantages of different external ambulatory ECG monitoring vs. ILR or cardiac monitor strategies in CS patients**

Definitions	Modalities of recording	Duration of recording	Type of electrodes	Number of leads	Clinical indications	Advantages	Limitations
External event recorders *or* Smartphone-based event recorders	Intermittent external event recorders Trans-telephonic transmission	Up to 30 s *(multiple recordings)*	Build-in electrodes to be applied directly on the chest (or held by both hands)	1–6 leads	-Rhythm monitoring for symptomatic arrhythmias only *(palpitations)* -Scheduled screening for the detection of silent AF	-Non-invasive -Easy to use -Low cost -Readily available *(can be directly provided to the patient at hospital discharge after CS)* -Possibility of timely reaction to AF detection *(in case of trans-telephonic transmission)*	-Frequent artefacts -Require expert validation of automatic interpretation -Require call-centre for RM with off-line or on-line analysis *(in case of trans-telephonic transmission)*
Patch ECG monitors	Continuous external recorders with or without wireless data transmission	Up to 14 days	Adhesive patches with built-in recording systems	1 or 2 leads	-Rhythm monitoring for symptomatic and asymptomatic PAF -Detection other arrhythmias besides AF (PSVT/VT/pauses) -Can detect AF episodes lasting >30 s -Provide AF burden	-Provide AF burden -Good patient compliance -Easy to use -Relatively low cost -Readily available *(can be directly provided to the patient at hospital discharge after CS)*	-Frequent artefacts -Require off-line analysis with expert validation of automatic interpretation
External loop recorders (ELR)	Intermittent external patient- or auto-triggered recorders	4–8 weeks	Adhesive disposable wired electrodes	1 or 2 leads	-Rhythm monitoring for symptomatic and asymptomatic PAF -Detection other arrhythmias besides AF (PSVT/VT/pauses) -Can detect AF episodes lasting >30 s	-Easy to use -Relatively low cost -Readily available *(can be directly provided to the patient at hospital discharge after CS)*	-Unpredictable patient compliance -Require off-line analysis with expert validation of automatic interpretation -Discontinuous recording (not providing AF burden)

Continued

Table 4 ***Continued***

Definitions	Modalities of recording	Duration of recording	Type of electrodes	Number of leads	Clinical indications	Advantages	Limitations
Multiday Holter recorders	Continuous multi-lead external recorders	(a) 1–7 days (b) 7–21 days	(a) Adhesive disposable wired electrodes (b) Wireless embedded electrodes in vests or belts	(a) 3–12 leads (b) 1–3 leads	-Rhythm monitoring for symptomatic and asymptomatic PAF -Detection other arrhythmias besides AF (PSVT/VT/pauses) -AF burden	-Easy to use -Relatively low cost -Readily available *(can be directly started in patients at hospital discharge after CS)* -*Provide arrhythmic* burden	-Unpredictable patient compliance -Require off-line analysis with expert validation of automatic interpretation
Mobile cardiac outpatient telemetry (MCOT)	External real-time continuous cardiac tele-monitoring systems	Real-time streaming to call-centres	(a) Adhesive disposable wired electrodes (b) Wireless electrodes embedded in a patch, necklace pendant or a chest belt carrier	(a) 1–3 leads (b) 1 lead	-Rhythm monitoring for symptomatic and asymptomatic PAF -Possibility to detect other arrhythmias besides AF (PSVT/VT/pauses) -Provide AF burden	-Easy to use -Readily available *(can be directly started in patients at hospital discharge after CS)* -RM allows timely reaction to AF detection	-MCOT monitors not widely available outside the US -Require call-centres for RM and on-line analysis -Relatively high cost
Implantable loop recorders (ILRs) or Implantable cardiac monitors (ICMs)	Intermittent recorders (patient- or auto-trigger activation) with remote monitoring (RM)	Up to 5 years	Build-in electrodes	1 lead	-Rhythm monitoring for symptomatic and asymptomatic PAF -Possibility to detect other arrhythmias besides AF (PSVT/VT/pauses) -Provide AF burden	-Long-term of monitoring (up to 5 years) -Remote monitoring with timely reaction to AF detection -Provide information about AF (number of episodes, duration, burden, ventricular rates) -Possibility to detect other rhythm disturbances besides AF (PSVT/VT/pauses)	-Relatively high cost -Require RM facilities (without reimbursement fares in many Countries) -Not-so-easy to be implanted in patients before discharge from the hospital -Cannot detect AF lasting <2 min -Low positive predictive value for short AF episodes -High false-positive AF detection, requiring visual validation of automatic AF detected episodes

AF, atrial fibrillation; CS, cryptogenic stroke; ELRs, external loop recorders; ILRs, implantable loop recorders; ICM, implantable cardiac monitor; MCOT, mobile cardiovascular outpatient telemetry (only available in United States); RM, remote monitoring; PAF, paroxysmal atrial fibrillation; PSVT, paroxysmal supraventricular tachycardia; VT, ventricular tachycardia.

control studies[2,62] and meta-analyses[1,63] advocate for the superiority of ICMs to any other monitoring tool for the AF detection in CS patients and the secondary prevention of IS. However, one still unresolved issue is whether ambulatory ECG monitoring should be performed first in all CS patients, followed by an ICM in case of non-diagnostic yield, or ICM should be implanted routinely in all patients immediately after a CS.[123]

Ambulatory ECG monitoring is less invasive, less expensive, and can be easily started directly after CS before hospital discharge; however, the likelihood of AF detection in the first month post-CS is low (about 5–10%)[61,64] (*Table 4*). As the diagnostic yield of 30 days of ambulatory ECG monitoring is likely to be limited, there is a rationale for proceeding directly to ICM implantation prior to hospital discharge in all CS patients, as the likelihood of detecting AF during longer follow-up increases, with the added benefit of careful long-term monitoring of CS patients.[123]. Furthermore, in CS patients, ICMs have also detected an unexpectedly high rate of bradyarrhythmias (5–10%), mostly clinically asymptomatic, thus contributing to better detection and treatment of other cardiac arrhythmias, besides AF.[124] Moreover, the recurrence rate of stroke was lower in patients who had an ICM, because of a higher likelihood of AF detection and anticoagulation initiation after a CS or TIA compared with conventional cardiac rhythm monitoring.[126]

Algorithms to increase accuracy and reliability of AF by ICMs: pitfalls and methods to overcome them

ICMs have high accuracy in detecting AF and determining its burden using irregularity of RR intervals. However, due to the extracardiac location of the ICMs and limitations in the accuracy of diagnostic algorithms, remote ICM transmissions require a careful and detailed review by electrophysiology staff to adjudicate for the presence of FP episodes. Timely review of these data is essential to identify clinically important arrhythmias and to allow for prompt intervention and requires significant resources from the device clinic.[127] Incidence of FP during RM with nominal settings on ICMs is substantial, ranging from 46 to 86% depending on the indication for implantation.[128] FP transmissions in the category of tachycardia and AF are due to a multitude of reasons, including atrial and ventricular ectopy, oversensing of P and T waves, and extracardiac noise signals. All ICM manufacturers have devised algorithms for the elimination of such episodes, and it appears that AI algorithms substantially improve diagnostic accuracy, especially increasing positive predictive value for shorter duration AF episodes (where misdiagnosis due to ectopy is frequent).[125]

The Reveal XT performance trial (XPECT, Medtronic) showed that an ICM can accurately quantify AF burden and is very sensitive to identify asymptomatic patients with AF.[127] The AF detection algorithm in this ICM looks for incoherence in an RR interval time series[127,128] and absence of evidence of a single P-wave between two R-waves to detect AF.[5,129] In order to reduce rates of FP AF episodes, the ICM algorithm was further improved by computing a P-wave evidence score that quantifies P-waves in the absence of noisy baseline or flutter waves. However, intermittent ineffectiveness of P-sense during prolonged duration of sinus arrhythmia or runs of ectopy may still lead to detection of inappropriate episodes (*Figure 2*). This intermittent ineffectiveness of the P-sense algorithm can be caused by P-wave amplitude fluctuation, baseline noise, rapid rates, or long P-R intervals. The Reveal LINQ usability study verified the ability of the adaptive P-sense algorithm to reduce false episodes by 49% and false duration by 66% without significantly reducing true episodes and true duration.[130] In addition, the enhanced algorithm appropriately detected close to 99% of total AF duration and over 99.8% of total sinus or non-AF rhythm duration. However, despite currently available ICM programming options, designed to maximize positive predictive value in each population, FP AF episodes remain common. An AI-based solution may significantly reduce the time and effort needed to adjudicate these FP events. In a recent study, application of a DNN filter reduced by up to two thirds these FP episodes with only a trivial reduction in loss of true-positive AF episodes.[125]

The Confirm Rx™ (Abbot) algorithm must fulfil three criteria to detect an episode of AF: *regularity* (based on a Markov chain model), *variance* (large) and (sudden) *onset*.[131] Recently, a P-wave discriminator has been added with the objective to reduce FP alarms, activated upon base algorithm triggering. The *P*-wave detection algorithm analyses the EGM signal prior to the trigger and rejects the initial detection if consistent P-waves are found. A recent prospective randomized clinical trial comparing Reveal LINQ and Confirm Rx reported that AF FP rate was high in both ICMs (48% in Reveal LINQ and 62% in Confirm Rx).[131] Adjudication of the FP AF events concluded that pre-mature beats are the most common reason for a FP result, followed by double-counting of *P*-wave, *T*-wave, and noise.

The Biomonitor III model (Biotronik) detects AF based on continuous checking of RR variability.[132] Intervals with RR variability above a defined threshold trigger the AF suspicious phase, during which the system will evaluate whether AF is present. There is also a bigeminy and extrasystole rejection function that detects patterns of (periodically occurring) extrasystoles and prevents erroneous AF diagnosis. The relatively longer dipole offers some benefit regarding P-wave detection and in a relevant study a mean R-wave amplitude around 1 mV and a high percentage of patients with visible P-wave on the subcutaneous ECG (65 and 68% in the standard and axillary subgroups, respectively), was reported.[133] However, even with this technology, high AF FP rates were recently reported.[134]

Since most FP AF episodes were due to the presence of ventricular ectopy and not to undersensing of sinus rhythm, further research should be focused on filtering and detection of ectopic beat morphology. From a physician standpoint, current nominal programming seems to be overly conservative, and custom programming with AF detection enhancements based on indication and patient characteristics may result in a reduction of the number of FPs. Custom programming may include turning off some clinically irrelevant arrhythmia detections or extending the duration of arrhythmia detections to improve specificity. Finally, it should be once more emphasized that performance of AF detection algorithms in ICMs depends heavily on the pre-test probability of the population, incidence rate of AF, duration of monitoring, and type of AF.

Gaps in knowledge

- Randomized-controlled trials are needed to better define the risk (CHA_2DS_2-VASc score) and AHRE burden thresholds that

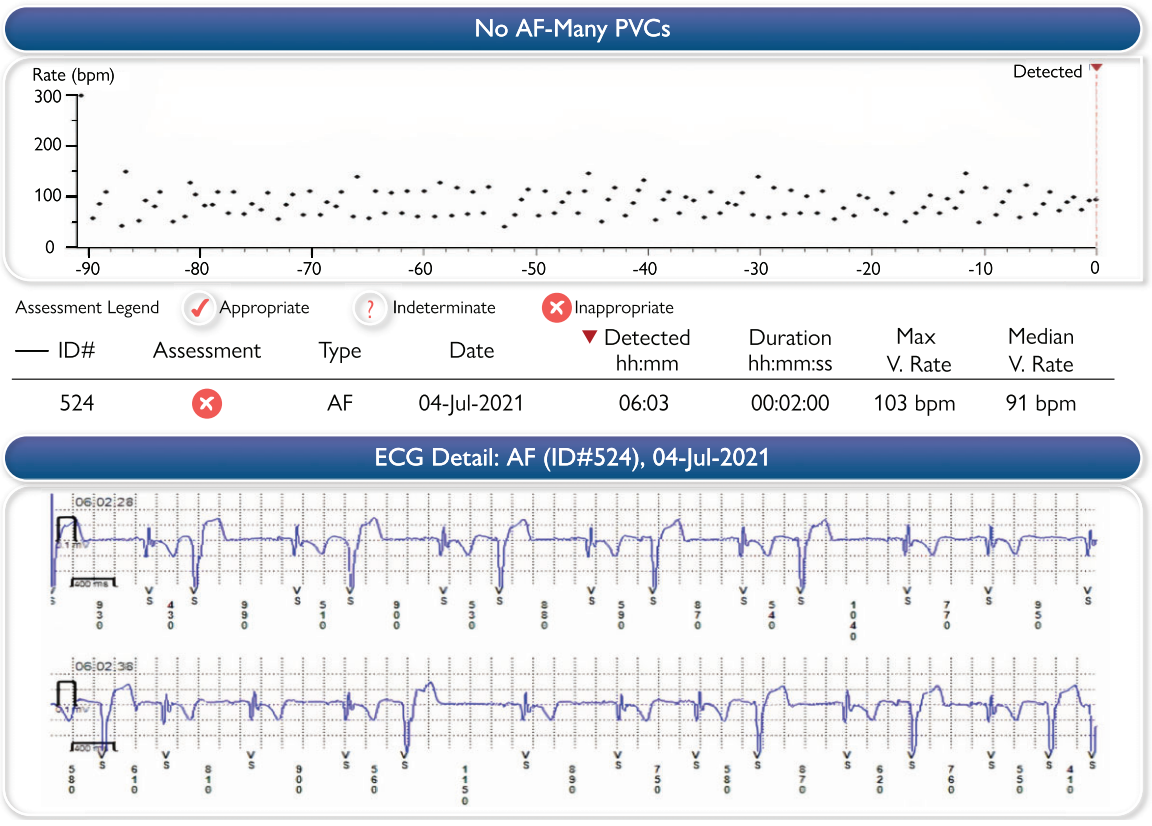


Figure 2 False-positive AF detection by an ICM. Failure of the P-wave sensing algorithm due to both concealment by PVCs and ectopic atrial activity, the latter leading to divergent *P*-wave morphology, not registering as such with the algorithm. Note the significant RR interval variability in the tachogram above. AF, atrial fibrillation; ICM, implantable cardiac monitor; PVC, pre-mature ventricular contraction.

warrant starting anticoagulation in patients implanted with a pacemaker or an implantable cardioverter defibrillator.

- ICMs are highly promising tools for long-term cardiac rhythm monitoring and management of CS patients; however, additional refinement of the AF detection algorithm is needed to reduce the incidence of FP signals.
- Data on accuracy and relative cost-effectiveness of non-invasive ambulatory ECG monitoring and ICM-first approaches in detecting subclinical AF post-CS are lacking.

Interpretation and handling of long-term ECG monitoring data in CS patients

According to the current European Society of Cardiology (ESC) guidelines, in all patients after stroke without previously known AF, a 24-h Holter ECG recording is recommended, followed by at least 72-h ECG monitoring, if possible [Class I, Level of evidence (LOE) B]. Also, long-term monitoring, based on non-invasive recorders or ICMs should be considered in selected stroke patients (Class IIa, LOE B).[6] 24-h or 72-h ECG recordings are mostly performed during hospitalization and their interpretation and handling is in line with hospital routine. Nonetheless, such approach allows to identify only 20–25% of all AF cases.[64] Therefore, one can expect that long-term ECG monitoring with the use of either ICMs or non-invasive long-term recording systems (patches, vests, belts) will, in time, become a clinical routine available for all, rather than selected, IS patients. Such an approach, if applied routinely, will require advanced large data processing capacity and effective algorithms for data interpretation.

Finally, in line with the current ESC and AHA/ACC/HRS guidelines, physician review to confirm the adequacy of a definite diagnosis of AF is necessary.[135] Regardless of the final interpretation, two approaches of handling long-term ECG monitoring data are applied:

- Continuous or intermittent ECG monitoring with retrospective analysis of records[94,136,137] and
- Continuous or intermittent ECG monitoring with daily data transmission using GSM (Global System for Mobile telecommunications) technology and instantaneous analysis of transmitted data.[138] Daily evaluation of incoming reports may not be always feasible, but-weekly evaluation/review should be manageable.

In case of non-invasive systems, the possibility to shorten monitoring should a definite AF episode be detected and confirmed appears to be an advantage. For both approaches, invasive and non-invasive, 'real-time' data analysis accelerates initiation of appropriate

antithrombotic therapy and potentially reduces the risk of further thromboembolism.

The value of RM in the handling of CS patients

The role of RM of CIEDs, including pacemakers, implantable cardiac defibrillators, cardiac resynchronization therapy, and ICM, is well established in current clinical practice.[139] Several studies have demonstrated that RM optimizes clinic workflow and improves CIED monitoring and patient management by reducing in-hospital visits and social costs.[139,140]

RM has been shown to facilitate the early detection and quantification of AF episodes and arrhythmia burden, leading to a timely initiation of anticoagulation therapy for the prevention of IS.[141] Furthermore, early detection of AF by RM can reduce the likelihood of inappropriate ICD therapy, heart failure decompensation, and avoid loss of biventricular pacing, improving overall patient outcome.[141] Several studies have suggested the benefit of RM-mediated early notification and quantification of AF, reporting lower stroke rates or all-cause mortality in patients followed up with RM.[139,141,142] Specifically, in patients with pacemakers and implantable cardiac defibrillators, the RM follow-up outperformed standard follow-up regarding AF detection, since it detected AF several months earlier, especially in cases of asymptomatic episodes.[143] In patients with CS implanted with ICMs, RM has particularly important and crucial functions, namely preventing memory saturation whilst increasing diagnostic effectiveness.[2,60,123,139]

Patients implanted with ICMs for documenting AF after a CS represent a special problem, since the indication for the implant is generally established by neurologists, rather than by the cardiologists or electrophysiologists, who generally perform post-implant surveillance, so it is often unclear who is responsible for the clinical follow-up after implantation. Therefore, it is of the utmost importance that those patients are correctly informed about implant functions and are specifically referred to an RM unit for long-term surveillance.

There are very few data to guide anticoagulation strategies for AF detected by RM of CIEDs, and the risk/benefit ratio of initiating anticoagulation therapy in response to an AF event of any specific duration detected during RM remains uncertain. In general, the risk of thromboembolic events may be increased even by brief AF episodes (5-min AHREs), further increasing following longer episodes. A recent meta-analysis combining randomized and observational data suggested that prolonged cardiac rhythm monitoring is associated with decreased risk of recurrent stroke by 55% due to increased (approximately two-fold) anticoagulation initiation, related to higher AF detection rates in CS patients.[1] Thus, management of AF should be guided by current guidelines, regardless of detection method (by RM or other modality).[6,144]

Gaps in knowledge

- The optimal method for 'real-time' analysis of long-term invasive or non-invasive monitoring data remains to be defined.
- Standardization of the RM methods to detect AF in CS patients implanted with devices from different manufacturers should be achieved.
- Data on the rationale of long-term ECG monitoring in the presence of other competing IS causes are virtually non-existent.
- It is still unclear for how long patients should be monitored if no AF events are recorded, and at what point in time the incremental diagnostic value conferred by ECG monitoring is no longer cost/effective.
- Finally, the responsibility of monitoring physicians towards patients, especially regarding timely evaluation of data, remains largely undetermined, both institutionally, and legally.

Final suggestions/conclusion

Based on currently available evidence, that is presented in this position paper, several suggestions can be made (*Graphical Abstract*), although it is expected that widespread application of such approaches will lead to further guidance in the near future, improving patient care and outcomes.

- An extensive, multidisciplinary workup is advocated in all IS cases before a *working* diagnosis of CS is made.
- This workup should ideally include a 12-lead ECG, 72-h ECG telemetry followed by 24-h Holter monitoring, cerebral magnetic resonance imaging, cerebral magnetic resonance angiography, echocardiography (transthoracic or transoesophageal, depending on degree of suspicion for intracardiac right to left shunts), as well as haematological assessment in cases of patients aged $<$55 years.
- Use of the ESUS diagnostic construct is not suggested in terms of guiding anticoagulation following cryptogenic stroke.
- HAVOC and BROWN ESUS-AF risk scores should be used for determining CS patients at high probability for subclinical AF that will benefit from prolonged/long-term ECG monitoring.
- Additional parameters, such as number of atrial extrasystoles, left atrial size, and stroke features on imaging suggesting an embolic nature may be used as adjudicators for prolonged/long-term ECG monitoring in ambiguous cases.
- Both non-invasive and invasive ECG monitoring modalities could be used to improve the diagnostic yield for post-CS AF.
- mHealth devices proven to accurately diagnose AF with intermittent use (opportunistic or symptom-driven) may be utilized. Either ECG- or PPG-based wearable devices could be used, but the reliability and accuracy of each device for the detection of paroxysmal AF in CS patients should be established before consideration for inclusion in clinical practice.
- Invasive ECG monitoring through use of ICMs is superior to non-invasive alternatives in diagnosing AF in post-CS patients.
- Optimization and personalization of AF detection-related ICM parameters, in accordance with manufacturer standards, in order to increase diagnostic accuracy should be performed.
- In patients with rhythm management devices capable of atrial sensing, regular review for occurrence of AHREs is recommended.
- Adjusting AHRE diagnostic criteria to comply with current guidance is recommended.

- Pending outcomes of ongoing randomized-controlled clinical trials, initiation of anticoagulation post-AHRE detection should be in accordance with current AF guidelines.
- RM of patient data, whether from non-invasive or invasive monitoring modalities is strongly suggested to decrease workload, improve patient comfort, and expedite arrhythmia detection.
- RM should not guide anticoagulation discontinuation based on AF presence or absence.
- Protocols regarding data ownership, management, as well as responsibility and accountability towards patients must be introduced at an institutional, organisational, or systemic level.

In conclusion, CS represents a major subgroup (almost one-third) of IS, with subclinical AF underlying a significant proportion thereof. Timely AF detection and initiation of appropriate secondary IS prevention treatment (in most cases oral anticoagulation) is a sine qua non for improved patient outcomes. A thorough and multidisciplinary diagnostic evaluation process is necessary to exclude most other IS causes.

Modern modalities for prolonged and long-term ECG monitoring and rhythm assessment are a cornerstone of our armamentarium for AF detection. Both non-invasive (ECG- or PPG-based wearable devices) and invasive (ICMs and atrial leads in the case of CIED presence) monitoring tools provide considerable diagnostic yield that can be further improved through the use of refined signal processing algorithms and AI approaches.

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