**REVIEW**

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# Expert opinion paper on atrial fibrillation detection after ischemic stroke

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## Abstract

This expert opinion paper on atrial fibrillation detection after ischemic stroke includes a statement of the "Heart and Brain" consortium of the German Cardiac Society and the German Stroke Society. This paper was endorsed by the Stroke Unit-Commission of the German Stroke Society and the German Atrial Fibrillation NETwork. In patients with ischemic stroke, detection of atrial fibrillation should usually lead to a change in secondary stroke prevention, since oral anticoagulation is superior to antiplatelet drugs. The detection of previously undiagnosed atrial fibrillation can be improved in patients with ischemic stroke to optimize stroke prevention. This paper summarizes the present knowledge on atrial fibrillation detection after ischemic stroke. We propose an interdisciplinary standard for a "structured analysis of ECG monitoring" on the stroke unit as well as a staged diagnostic scheme for the detection of atrial fibrillation. Since the optimal duration and mode of ECG monitoring has not yet been finally established, this paper is intended to give advice to physicians who are involved in stroke care. In line with the nature of an expert opinion paper, labeling of classes of recommendations is not provided, since many statements are based on the expert opinion, reported case series and clinical experience. Therefore, this paper is not intended as a guideline.

**Keywords** Acute ischemic stroke · Atrial fibrillation · ECG monitoring · Stroke unit

## Introduction

Stroke is the fourth most common cause of death and the leading cause for comorbidities in Germany. More than 260,000 stroke cases occur annually in Germany alone [1, 2]. About 15–20% of these strokes are due to atrial fibrillation (AF). AF is prevalent in about 2% of the German population and known to increase the risk of ischemic stroke four-to five-fold [3, 4]. Due to a high risk of stroke recurrence and a higher stroke case fatality, patients with AF show a poorer prognosis compared to stroke patients without the rhythm disorder [5]. In a relevant proportion of patients with AF, the rhythm disorder occurs intermittently and often is

asymptomatic. This observation also applies to the majority of stroke patients who are diagnosed with AF for the first time in the post stroke course [6]. The detection of AF after ischemic stroke is relevant due to the following reasons:

- Stroke patients with (undetected) AF have a comparatively high risk of recurrence of ischemic stroke if they remain untreated [5, 7]
- Strokes that affect specific areas of the brain (e.g., insular cortex) may possibly predict the onset of AF [8, 9] as similarly described for myocardial infarction, infection or certain metabolic disorders [10].
- AF, which has been detected for the first time in the acute phase of stroke, will also be documented at later stages [11].
- The diagnosis of AF is relevant for secondary prevention of ischemic stroke [4], even if the documentation of AF

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does not automatically imply a cardio-embolic cause of stroke [12–14]. Oral anticoagulants are effective in the secondary prevention of ischemic stroke in patients with AF and achieve a relative risk reduction of up to 70–80% compared to placebo [15, 16].

- Effective oral anticoagulation at the time of ischemic stroke is associated with a reduction in stroke severity and mortality in AF patients [17, 18].

## Current guidelines and recommendations

In stroke patients the duration of ECG monitoring [19, 20], the quality of the evaluation [21, 22] and patient selection [23, 24] correlate with the frequency of detected AF. ECG monitoring for at least 24 h in patients with ischemic stroke was recommended in 2010 [24]. In addition to a 12-lead resting ECG on admission and continuous ECG monitoring in the stroke unit, the guidelines of the German Neurological Society and European [25, 26] Stroke Organization (ESO) [27] recommend a long-term ECG registration in stroke patients with high suspicion of asymptomatic, paroxysmal AF. Specific information on the duration of ECG monitoring in the acute phase is not given. The US guideline recommends ECG monitoring for 30 days (class IIa, level C) in patients with cryptogenic stroke within the last 6 months [28]. The 2016 AF guidelines by the European Society of Cardiology (ESC) recommend ECG monitoring for at least 72 h for stroke patients and for patients with a transient ischemic attack (TIA) without known AF (Class I, Level B) [4]. In addition to an ECG monitoring with a central monitoring unit, the German Stroke Society (DSG) certification criteria recommend the use of Holter ECGs, a written standard for the application of the Holter monitoring as well as an extended diagnostic concept for patients with cryptogenic stroke [29]. Besides structured rhythm rounds on the stroke unit and the use of specific detection software for monitoring systems, reference is made to the implantation of event recorders.

## State of the art for the detection of AF after ischemic stroke

To date, the results of four randomized studies on the efficacy of prolonged ECG monitoring in acute stroke have been presented in patients with ischemic strokes previously classified as cryptogenic (Table 1) [30–33]. These studies have demonstrated that different monitoring methods can increase the detection rate of AF and increase the number of consecutively anticoagulated stroke patients. The AF detection rate is correlated with the duration of ECG monitoring and decreases over the monitoring period [33]. However, the number of patients or the duration of follow-up of these randomized trials was not powered to demonstrate that prolonged ECG monitoring results in a reduction in clinical endpoints. Currently, the relevance of prolonged inpatient non-invasive ECG monitoring after acute ischemic stroke or TIA is investigated in Germany as part of the multi-center randomized MonDAFIS study [34]. Several prospective cohort studies have shown that the detection of AF after ischemic stroke does not only depend on the duration of the monitoring but also on the time of ECG monitoring relative to the index stroke and patient selection (Table 1). Due to the heterogeneity of the patient cohorts, the ECG monitoring methods, the AF definition used and the duration of the monitoring, published meta-analyses only are of limited value [35]. Nevertheless, they demonstrate that the detection rate of AF is higher in selected compared to unselected stroke cohorts [22]. Optimal AF detection will continue to have relevance in the future, since the first phase III study on systematic anticoagulation after embolic stroke of unknown source (ESUS) was stopped due to futility (NAVIGATE ESUS, NCT02313909). Another phase III study is ongoing (RESPECT ESUS, NCT02239120). Interestingly, a relevant subset of ESUS patients demonstrates a first episode of AF during long-term monitoring [35].

**Table 1** Comparison of baseline characteristics and results of four randomized studies on prolonged ECG monitoring after ischemic stroke [36]

| Study [references] | Type of monitoring | n | Age (mean ± SD) [inclusion criterion] | Enrollment window | AF detection (number needed to screen) |
|---|---|---|---|---|---|
| Higgins et al. [30] | 7-day Holter ECG | 100 | 66 ± 12 a [≥ 18 a] | < 7 days | 18 vs. 2% after 14 days (6) |
| EMBRACE [32] | 30-day event recorder vs. 24-h Holter ECG | 572 | 73 ± 9 a [≥ 55 a] | < 6 months | 16.1 vs. 3.2% after 30 days (8) |
| CRYSTAL-AF [31] | Implantable loop recorder vs. routine care | 441 | 61 ± 11 a [≥ 40 a] | < 3 months | 8.9 vs. 1.4% after 180 days (14)<br>12.4 vs. 2.0% after 1 year (10)<br>30.0 vs. 3.0% after 3 years (4) |
| FIND AF$_{randomised}$ [33] | 10-day ECG on admission, after 3 and 6 months vs. routine care | 402 | 73 ± 7 a [≥ 60 a] | ≤ 7 days | 13.5 vs. 4.5% after 180 days (11)<br>13.5 vs. 6.1% after 1 year (14) |

## Definition of AF and relevance of the type of AF

According to experts, the diagnosis "AF" requires an episode of at least 30 s of atrial arrhythmia with missing P-waves. Shorter episodes (< 30 s) should not be called AF, but "atrial run" or increased supraventricular ectopia. The 30-s duration is also mentioned in the ESC guidelines [4]. However, this definition has not been prospectively validated and is based on consensus and frequently used in clinical trials. In up to 44% of all patients with acute ischemic stroke, "atrial runs" are found in the acute phase [30, 37] and the prognostic relevance has not been conclusively clarified. According to the authors, the current data suggest that the duration of clinically detected AF episodes has rather a minor relevance for the risk of stroke [38, 39]. A meta-analysis of prospective studies on the (primary) prevention of ischemic stroke postulated a slightly higher risk of stroke in patients with persistent or permanent AF compared to patients with paroxysmal AF [40]. A retrospective analysis of the ASSERT study in pacemaker patients also suggests that the risk of stroke only increases when atrial tachycardia persists for at least 24 h [41]. A correlation of AF type with the risk of stroke has not been proven for the secondary prevention of stroke. It should not influence therapeutic decisions on anticoagulation. In particular, since in a relevant proportion of patients the clinical classification of AF type cannot be done correctly, because continuous monitoring data are not readily available in all patients.

## Quality standards of ECG monitoring

So far, few studies on the systematic evaluation of ECG monitoring on the stroke unit are available [20, 21]. A survey on the detection of AF from 2014 involving 171 operators of a certified German stroke unit participated, illustrates several possibilities for optimizing ECG diagnostics in daily clinical practice [42]. Therefore, the authors consider it important to have standards of a high-quality "rhythm visit" that also includes involvement of cardiologists. It should be ensured that recorded ECG data should be analyzed in a standardized manner at least once daily by trained and experienced staff [21]. In this context automated analysis is helpful, however, requires a "manual" validation of the ECG findings and a medical diagnosis [20, 21, 43]. Besides detecting AF and atrial flutter, potentially life-threatening arrhythmias have to be considered. Stroke unit derived ECG data should be recorded for off-line analysis. A standardized diagnostic scheme can improve rhythm monitoring [21].

## Duration of ECG monitoring after ischemic stroke

Due to limited resources and economic constraints, it is not possible (for stroke units) to immediately expand the diagnostic standard of cardiac arrhythmia diagnostics at scale. From the authors' point of view and the Stroke Unit Commission of the German Stroke Society this requires appropriate structural adjustments in the respective specialty departments. There is consensus among the authors that a baseline ECG monitoring after ischemic stroke should be performed, ideally for at least 72 h to increase the likelihood of detecting AF, which was also recommended by the current ESC guidelines [4]. It seems to be irrelevant whether this monitoring is done entirely by telemetry on the stroke unit or by Holter ECG, as long as a high-quality, standardized evaluation of the ECG is ensured [21]. No distinction should be made between patients with (confirmed) ischemic stroke and those with TIA if relevant differential diagnoses of TIA are unlikely. In case of a shorter inpatient length of stay an outpatient continuation of ECG monitoring is recommended for TIA patients to reach 72 h in total. In addition, ECG monitoring should be performed even if a non-cardio-embolic cause of ischemic stroke is suspected. A diagnosis of AF is also relevant for the secondary prevention of these patients, which has to be multifactorial [44]. Even in the presence of absolute contraindications for permanent oral anticoagulation ECG monitoring in the acute phase of ischemic stroke is recommended. Besides the occurrence of other relevant cardiac arrhythmias, interventional occlusion of the left atrial appendage may be considered in certain patients upon detection of AF [4]. The costs, the decreasing compliance in non-invasive monitoring procedures and the probability of AF detection have to be weighed for ECG monitoring beyond 72 h. Currently, a continuous ECG monitoring of 30 days, as recommended by the US guidelines for stroke patients with cryptogenic stroke [28], is not regularly feasible in clinical practice. A number of clinical, ECG and echocardiographic parameters have been described (Table 2) that increase the probability to detect a first episode of AF after ischemic stroke. The current evidence is presented in the following.

### Relevance of clinical parameters to predict AF

The strongest predictor of AF is age [45, 46]. Therefore, patient age should be considered for the cumulative duration of ECG monitoring (see Table 2). At present, the use of published risk scores including classical cardiovascular risk factors to tailor ECG monitoring after ischemic stroke or TIA does not seem to be efficient.

**Table 2** Consensus recommendation on the possible relevance of clinical, imaging or electrocardiographic parameters for a first episode of AF after ischemic stroke [36]

| | Probability of a first episode of AF after stroke | |
| --- | --- | --- |
| | Probability comparatively low | Probability comparatively high |
| Patient age | < 60 years | ≥ 75 years |
| Supraventricular extrasystole | < 120/24 h | ≥ 480/24 h |
| Longest "atrial run" | < 5 beats | ≥ 20 beats |
| BNP or | < 50 pg/ml | > 100 pg/ml |
| Nt-proBNP | < 200 pg/ml | > 400 pg/ml |
| Left atrial diameter | < 40 mm | > 45 mm |
| Stroke etiology | Lacunar stroke; other definite cause of stroke | Arterio-arterial embolism; cryptogenic stroke or ESUS; cardiac cause other than AF |

BNP B-type natriuretic peptide, Nt-proBNP Nt-pro B-type natriuretic peptide, ESUS embolic stroke of undetermined source

## Relevance of brain imaging to predict AF

Multilocular lesion patterns affecting various cerebral vascular territories suggest a cardio-embolic origin or an embolic source in the aortic artery [47, 48]. Thus, prolonged ECG monitoring may be considered in these stroke patients (Table 2). However, the detection of a first episode of AF did not correlate with brain lesion pattern in the CRYSTAL-AF study (Table 1) [49]. Of note, about 10% of all patients with a "lacunar" stroke have AF [13, 14]. Thus, standardized (baseline) ECG monitoring is also indicated in patients with "lacunar" stroke, although the likelihood of detecting AF for the first time is lower than in patients with non-lacunar infarction [49]. Furthermore, some brain lesions (e.g., in the right insular region) have shown to induce autonomous imbalance and may thus mediate the occurrence of AF [8, 9]. The question whether AF detected after stroke is the cause or consequence of the stroke may not be conclusively answered in individual cases.

## Relevance of cardiac imaging to predict AF

Structural and functional changes of the heart and neighboring structures that indicate an increased risk of AF can be detected by echocardiography. Valvular abnormalities, in particular rheumatic mitral valve stenosis or severe mitral and tricuspid valve insufficiency are predictive for AF. Transesophageal echocardiography provides a higher resolution for the imaging of atrial structures (e.g., atrial appendage) and atheroma load of the thoracic aorta [50] compared to transthoracic echocardiography. Spontaneous echo contrast and solid thrombi in the atrium can be predictors of AF. Whether the morphology of the atrial appendage correlates with thrombogenicity is currently under investigation [51]. The possible role of left atrial deformation characteristics measured by tissue Doppler as left atrial strain [52, 53] after ischemic stroke needs confirmation. The size of the left atrium measured by transthoracic echocardiography

can be considered as a predictor of paroxysmal AF [54], and therefore, can be considered for the decision on a prolonged ECG monitoring after ischemic stroke (Table 2). However, a normal left atrium does not exclude the prevalence of AF. In addition, the combination of left atrial volume index and atrial function appear to have a predictive value for the detection of AF [55, 56]. Nevertheless, validation is necessary in larger stroke cohorts. Currently, the importance of magnetic resonance imaging or computed tomography is examined in dedicated studies [57]. Both methods have increasingly better spatial and temporal resolution for the functional characterization of the heart.

## Relevance of biomarkers to predict AF

Based on pathophysiological concepts of AF development, several biomarkers have been in the focus of interest: biomarkers of atrial dilatation and impaired cardiac function (natriuretic peptides), myocyte damage (troponins), markers of inflammation (interleukin-6, C-reactive protein), procoagulatory pathways (D-dimer), vascular damage (interleukin-6, C-reactive protein, glomerular filtration rate, cystatin C, markers of endothelial function), or impaired hemodynamics (natriuretic peptides, glomerular filtration rate, cystatin C) [9, 58, 59]. For most of the listed biomarkers, convincing data from large prospective studies are missing. The acute phase reactant C-reactive protein and the natriuretic peptides N-terminal pro B-type natriuretic peptide (Nt-proBNP) and B-type natriuretic peptide (BNP) are most promising for the detection of AF [60, 61] and should be considered for a prolonged ECG monitoring after ischemic stroke (Table 2). For natriuretic peptides, validation data in stroke cohorts are available [62–64]. Despite an increase in natriuretic peptides in the acute phase of a stroke, it can be assumed that BNP values of > 100 pg/mL and Nt-proBNP values > 400 pg/mL have a predictive value for the occurrence of AF in stroke patients [62]. A retrospective analysis of the WARSS study for stroke patients without known AF

showed a benefit of oral anticoagulation by warfarin compared to secondary prevention by acetylsalicylic acid in case of elevated Nt-proBNP [65].

## Relevance of ECG parameters to predict AF

Increased excessive supraventricular ectopic activity (ESVEA) over 24 h or the detection of supraventricular tachycardia (atrial run) lasting less than 30 s may indicate an increased risk of AF and should be considered for the cumulative duration of ECG monitoring (Table 2). In the Copenhagen Holter Study [66] patients with ESVEA had a significantly higher risk of stroke and clinically manifest AF. Stroke patients with ESVEA also show AF more frequently later on [67]. However, there is a lack of reliable standard values for the acute phase of stroke. A retrospective analysis of the EMBRACE study (Table 1) also showed that the detection of frequent atrial extra beats in stroke patients was associated with an increased probability of AF detection [68].

## Consensus recommendation on stratification for prolonged ECG monitoring

Following baseline ECG monitoring, ideally of 72 h, the authors suggest that AF risk estimation should be considered using the parameters listed in Table 2 to pragmatically specify the duration of prolonged ECG monitoring (also see Fig. 1). The decision on prolonged ECG monitoring should be based on a written standard procedure as required by the current certification criteria of the German Stroke Unit Commission [29].

## Ambulatory ECG monitoring after ischemic stroke

Guidelines recommend ECG monitoring after the acute phase of stroke [27, 28]. This appears to be feasible in practice but is often performed only to a limited extent [7, 31, 33]. A focused and standardized communication between the neurology acute clinic and the outpatient clinicians seems important for the practical implementation of a continued ECG monitoring. Systematic analyses are lacking. It is not conclusively clarified which device and technique could ensure a cost-efficient ambulatory ECG monitoring after ischemic stroke or TIA. Apart from the ECG, pulse palpitation is an established method of rhythm monitoring which can easily be taught to patients and their caregivers. The procedure achieves relatively high sensitivity and specificity for the detection of AF [69].
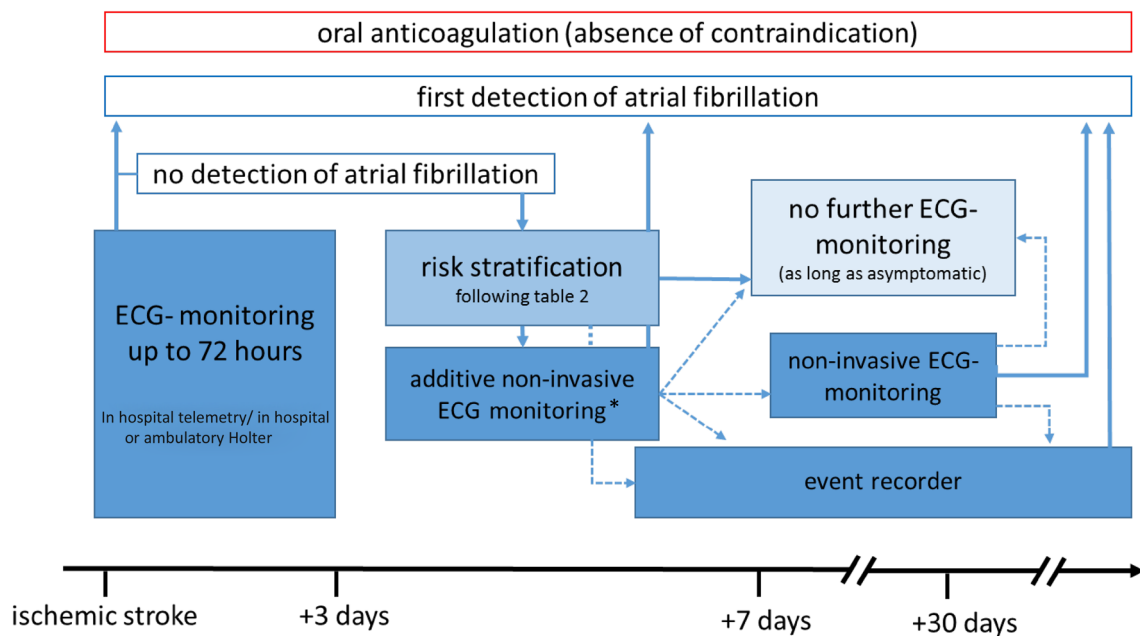


**Fig. 1** Staged diagnostic scheme for the duration of (post-) inpatient ECG monitoring after acute ischemic stroke as suggested by the authors [36]. Dashed lines indicate that it may be considered, asterisk indicates if feasible

## Which stroke patients should receive continuous ECG monitoring?

A comparatively small monocentric study showed that the consideration of the cardiovascular risk profile as well as specific ECG and echocardiographic parameters could increase the post-discharge detection rate of AF in stroke patients by an implanted event recorder [23]. Therefore, stroke patients with specific risk factors for AF should receive prolonged ECG monitoring. Non-invasive ECG monitoring should be based on practicability and should ideally last for at least 7 days. The compliance for longer non-invasive monitoring decreases significantly [32]. Therefore, the majority of the authors suggest the implantation of event recorders in stroke patients without AF identified during prolonged non-invasive ECG monitoring, but high probability of AF (Table 2).

## Reimbursement of extended ECG monitoring

Currently, the reimbursement of post discharge ECG monitoring constitutes a relevant socio-economic problem. To date, health insurance companies have not reimbursed the costs for non-invasive ECG monitoring adequately. Extended monitoring appears to be a cost-effective measure, although information varies. In the US a quality-adjusted life year using a 30-day ECG monitor costs 2,000 USD in the US [70], while using a 7-day long-term ECG in Germany costs approximately 3,900 EUR [71], and £ 13,296 when using an implanted event recorder in the Crystal AF Study (Table 1) [72]. In Germany, the implantation of event recorders in stroke patients has been financed so far by a corresponding increase of the DRG during the hospital stay. However, an ambulatory implantation is not always reimbursed, neither is the interpretation of the ECG data recorded over years.

## Summary

As part of the diagnostic work-up after an ischemic stroke, a timely ECG diagnosis to detect previously undiagnosed AF is essential. Due to an extended and high-quality ECG monitoring and patient selection based on clinical, laboratory, echocardiographic and electrographic parameters the likelihood of non-permanent AF detection and thus the efficiency of ECG monitoring can be improved.

## Compliance with ethical standards

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