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ORIGINAL RESEARCH

Excessive Supraventricular Ectopic Activity in Patients With Acute Ischemic Stroke Is Associated With Atrial Fibrillation Detection Within 24 Months After Stroke: A Predefined Analysis of the MonDAFIS Study

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BACKGROUND: Excessive supraventricular ectopic activity (ESVEA) is regarded as a risk marker for later atrial fibrillation (AF) detection.

METHODS AND RESULTS: The investigator-initiated, prospective, open, multicenter MonDAFIS (Impact of Standardized Monitoring for Detection of Atrial Fibrillation in Ischemic Stroke) study randomized 3465 patients with acute ischemic stroke without known AF 1:1 to usual diagnostic procedures for AF detection or additive Holter monitoring in hospital for up to 7 days, analyzed in a core laboratory. Secondary study objectives include the comparison of recurrent stroke, myocardial infarction, major bleeding, and all-cause death within 24 months in patients with ESVEA (defined as ectopic supraventricular beats ≥480/day or atrial runs of 10–29 seconds or both) versus patients with newly diagnosed AF versus patients without ESVEA or AF (non-ESVEA/AF), randomized to the intervention group. Overall, 1435 (84.8%) of 1714 patients randomized to the intervention group had analyzable study ECG monitoring of at least 48 hours' duration within the first 72 hours of monitoring. ESVEA was detected in 363 (25.3%) patients, while AF was first detected in 48 (3.3%) patients. Within 24 months, AF was newly detected in 67 (18.5%) patients with ESVEA versus 60 (5.9%) patients without ESVEA/AF- (P<0.001). The composite outcome at 24 months was not different between patients with ESVEA and patients without ESVEA/AF (15.2% versus 12.6%; P=0.242). All-cause death was numerically higher in patients with ESVEA (6.6% versus 3.2%), but failed statistical significance (P=0.433) in multivariate analysis (including age, heart failure, stroke severity, and creatinine at baseline).

CONCLUSIONS: ESVEA in the acute phase of ischemic stroke or transient ischemic attack is associated with AF detection during follow-up and therefore may be used to select patients for prolonged ECG monitoring.

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Key Words: atrial fibrillation ■ atrial run ■ death ■ ECG ■ stroke ■ supraventricular ectopy

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CLINICAL PERSPECTIVE

What Is New?

- This predefined analysis of the prospective multicenter MonDAFIS (Impact of Standardized Monitoring for Detection of Atrial Fibrillation in Ischemic Stroke) study shows that a standardized, core laboratory–based analysis of 72-hour Holter monitoring identifies excessive supraventricular ectopic activity (ESVEA) in 1 of 4 patients with acute ischemic stroke or transient ischemic attack.
- Notably, stroke recurrence rate and death over a 24-month period after the index stroke or transient ischemic attack was not increased in patients with ESVEA, if compared with study patients without ESVEA or atrial fibrillation within the first 72 hours of Holter monitoring.

What Are the Clinical Implications?

- As ESVEA in the acute phase of ischemic stroke or transient ischemic attack was associated with AF detection during follow-up, the presence of ESVEA inhospital may be used to select patients for prolonged ECG monitoring after discharge.

Nonstandard Abbreviations and Acronyms

ESVEA	excessive supraventricular ectopic activity
Find-AF 2	Intensive Rhythm Monitoring to Decrease Ischemic Stroke and Systemic Embolism
MonDAFIS	Impact of Standardized Monitoring for Detection of Atrial Fibrillation in Ischemic Stroke

Detection of atrial fibrillation (AF) in patients with ischemic stroke and subsequent initiation of oral anticoagulation instead of aspirin use is important in stroke prevention, as there is no proven benefit of oral anticoagulation in patients with stroke without AF.[1] Prolonged ECG monitoring in patients with stroke detects a first episode of AF in up to 1 of 3 patients with stroke, depending on patient selection, quality of ECG analysis, and duration of ECG recording.[2] Nevertheless, paroxysmal forms of AF are often missed in clinical practice, and the optimal duration of ECG monitoring after stroke is unclear in terms of cost effectiveness and secondary stroke prevention.[3,4] Currently, European Society of Cardiology guidelines and several position papers recommend a minimum duration of 72 hours of (cumulative) ECG recording in patients with acute ischemic stroke or transient ischemic attack (TIA).[2,3,5] The European Stroke Organization recommends "prolonged cardiac monitoring instead of 24 hours monitoring" and adds an expert consensus statement to monitor for AF for >48 hours.[6] Based on expert consensus, prolonged ECG monitoring is recommended in selected patients at "high risk" of AF, focusing on patients' age as well as laboratory, echocardiography, or ECG findings, such as atrial runs or excessive supraventricular beats.[2,3] However, the most recent European Stroke Organization guideline states that "blood, echocardiographic, ECG, or brain imaging biomarkers" should not be used to exclude patients from long-term ECG monitoring.[6] Considering that diagnostic resources are limited worldwide and the identification of stroke survivors at high risk of recurrent stroke is desirable, there is a need to select patients at risk of AF for prolonged monitoring after ischemic stroke or TIA.[2,3]

Excessive supraventricular ectopic activity (ESVEA; summarizing the presence of excessive ectopic supraventricular beats or atrial runs of <30 seconds' duration) is regarded as a marker of atrial cardiomyopathy[7] and was reported to be associated with higher rates of later detected AF in middle-aged to older people[8–11] and in selected patients with ischemic stroke.[12–16] While ESVEA occurs in 7% to 15% of middle-aged to older people,[10,11] ESVEA can be found in up to 40% of all patients with acute ischemic stroke, depending on the ESVEA definition used.[14,17,18] While ESVEA was associated with stroke or death in a meta-analysis of longitudinal studies that did not focus on patients with stroke,[15,18] robust data on the relevance of ESVEA detected in the acute phase of ischemic stroke or TIA on clinical end points are sparse.[15]

The aim of this preplanned analysis of the randomized, multicenter MonDAFIS (Impact of Standardized Monitoring for Detection of Atrial Fibrillation in Ischemic Stroke) study was to investigate whether the presence of ESVEA in the acute phase of ischemic stroke or TIA is associated with the detection of AF and the occurrence of recurrent stroke, myocardial infarction, major bleeding, or all-cause death in patients with stroke without known AF at randomization during a 2-year follow-up period.[19]

METHODS

We followed the Strengthening the Reporting of Observational Studies in Epidemiology statement–checklist for reporting the results of this subanalysis of the MonDAFIS study. Data will be made available on reasonable request (see Data Sharing section for details).

Data Sharing

Deidentified participant data with corresponding data dictionary of the data underlying the current manuscript will be made available on reasonable request to the corresponding author. The data will be shared to external researchers for scientific noncommercial purposes with investigator support after approval of the proposal by the MonDAFIS study steering committee, including a signed data access agreement.

Study Design

The MonDAFIS study was an investigator-initiated, prospective, 1:1 randomized, multicenter study sponsored by the Charité–Universitätsmedizin Berlin, Germany, and supported by an unrestricted research grant from Bayer Vital GmbH, Germany, to the Charité. The study design as well as the primary results were published previously.[19,20] The MonDAFIS study received primary approval from the Institutional Ethics Committee of the Charité–Universitätsmedizin Berlin. All participating study centers provided approval from their respective institutional ethics committees. All study patients gave written informed consent. The steering committee members developed the protocol and were responsible for study conduct and study analyses as well as drafting and editing of the article and its final contents. An independent data safety monitoring board assessed study conduct and safety outcomes. A critical event committee adjudicated all serious adverse events of special interest (including recurrent stroke, myocardial infarction, major bleeding, all-cause death) blinded to study randomization.

Study Population

Men or women aged ≥18 years were eligible for study enrollment if they had an index stroke, defined as ischemic stroke[21] or TIA (with new-onset neurological deficit present and documented by a neurologist on hospital admission or TIA with documented acute ischemic lesion[s] on brain imaging). Moreover, study patients had to be admitted to a certified stroke unit within 72 hours after stroke onset. Study ECG recording in the intervention group had to be started as soon as possible (but not later than 24 hours) after stroke unit admission. Patients were excluded if AF was known before stroke or detected by 12-lead ECG on hospital admission or by stroke unit monitoring before enrollment. Furthermore, patients were not eligible for study inclusion if prestroke life expectancy was assumed to be <1 year, if poststroke life expectancy was assumed to be <1 month, if patients were participating in an interventional study, if the patient was pregnant or breastfeeding, if there was a preexisting indication for long-term oral anticoagulation, or if the patient had an implanted device with the ability to record AF.[19]

Study Intervention

Within 2014 and 2017, 3470 patients with stroke were enrolled in 37 study sites in Germany running a certified stroke unit, and 3465 study patients were randomized 1:1 to either undergo additional continuous Holter-ECG recording until hospital discharge or for a maximum of 7 days in hospital (intervention group) on top of standard of care or to standard of care alone (control group). The complete randomized data set included 3431 patients with 1714 patients in the intervention group and 1717 patients in the control group (see Haeusler et al[20] for details). Study ECG recording was performed in parallel to standard care using the portable LIFECARD CF recorder (SPACELABS HEALTHCARE, Nuremberg, Germany). Study ECGs were transmitted to the cardiology core laboratory at the Institute of Cardiovascular Sciences, University of Birmingham (Birmingham, UK) and reviewed by trained physiologists and physicians blinded to clinical data. The reports included the presence or absence of AF, atrial flutter, atrioventricular block, or ventricular tachycardia; minimal, maximal, and mean heart rate; number of atrial and ventricular ectopic beats per day; number and duration of the longest atrial run per day; and longest pause and number of pauses. Additional ECG monitoring after hospital discharge was neither intended nor strictly recommended nor restricted and was performed at the discretion of the treating physicians. Follow-up was carried out in a blinded fashion with regard to randomization by a standardized telephone interview conducted by trained personnel at the Center for Stroke Research Berlin (Berlin, Germany) (Figure 1).[19]

Outcomes

The primary study outcome was the proportional number of study patients alive and on oral anticoagulation at 12 months after the index stroke. Secondary outcomes of the MonDAFIS study included (1) the proportional number of study patients with newly detected AF in hospital using a standardized prolonged ECG monitoring compared with usual stroke unit diagnostic procedures alone; and (2) the proportional number of the composite end point including recurrent stroke, myocardial infarction, major bleeding, and all-cause death within 6, 12, and 24 months after the index stroke/TIA of patients randomized to the intervention group or control group. Furthermore, corresponding proportions for these outcomes should be compared within the intervention group between the following subgroups: (1) sinus rhythm; (2) nonpermanent AF in hospital; (3) paroxysmal short atrial tachycardia (lasting <30 seconds); and (4) ESVEA in hospital.[19]

AF was defined as an absolute arrhythmia with loss of p wave activity and irregular R-R intervals lasting ≥30 seconds.[22] Paroxysmal atrial tachycardia was

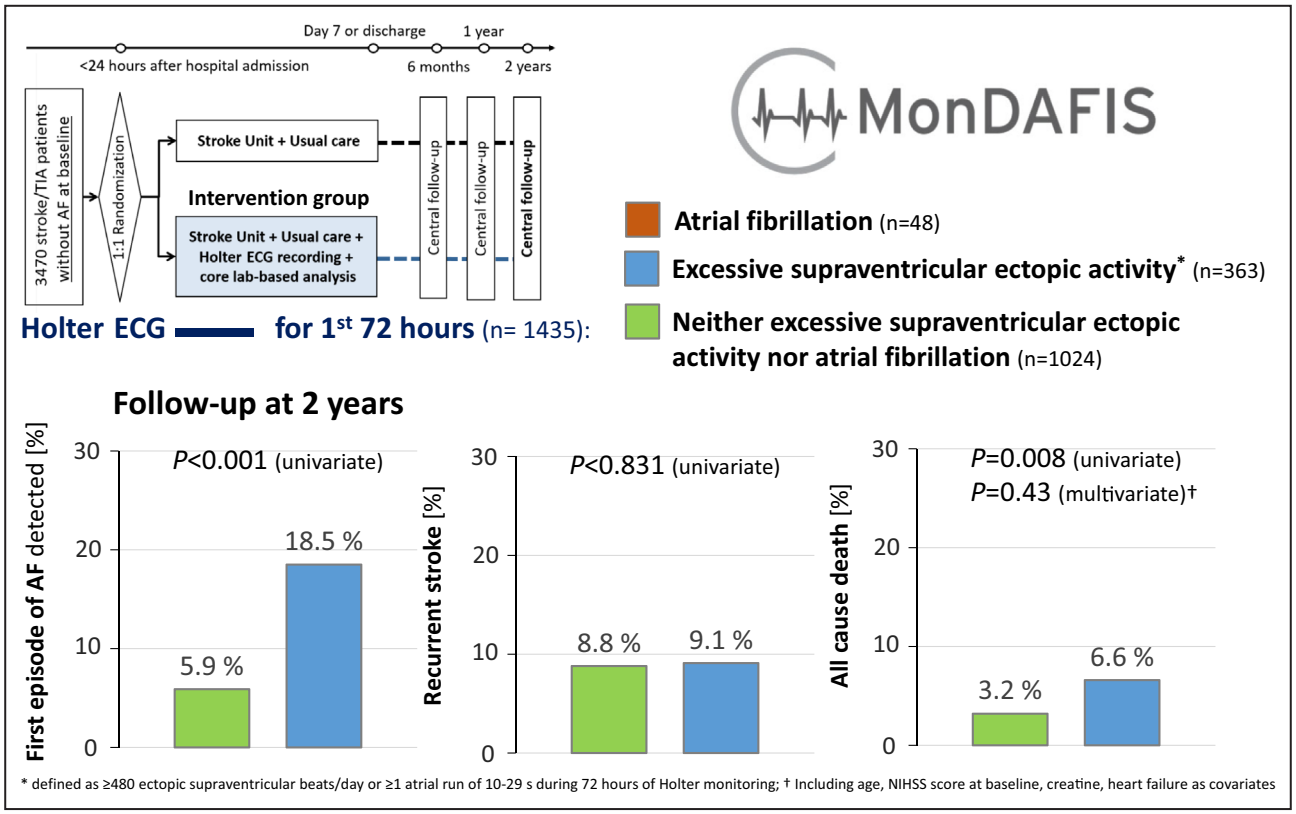

Figure 1. Study design and prevalence of predefined clinical end points within 24 months after the index stroke according to the presence or absence of excessive supraventricular ectopic activity in the absence of AF.
AF indicates atrial fibrillation; MonDAFIS, Impact of Standardized Monitoring for Detection of Atrial Fibrillation in Ischemic Stroke; NIHSS, National Institutes of Health Stroke Scale; and TIA, transient ischemic attack.

predefined by the MonDAFIS steering committee as a regular or irregular run of consecutive supraventricular ectopic beats lasting ≥10 but <30 seconds. ESVEA activity was defined as the presence of at least 1 supraventricular ectopic run lasting ≥10 but <30 seconds and/or ≥480 supraventricular ectopic beats per 24 hours on at least 1 day during study ECG recording for 72 hours after enrollment.

Hypotheses of the Present Analysis

We hypothesized that the presence of ESVEA during study-related ECG recording of 72 hours (as recommended by the European Society of Cardiology guideline[5]) with ≥48 hours of analyzable ECG recording (as recommended by the European Stroke Organization guideline[6]) correlates with:

1. AF detection during 24 months of follow-up;
2. the composite end point (recurrent stroke, myocardial infarction, major bleeding, or all-cause death) during 24 months of follow-up;
3. all-cause death during 24 months of follow-up, if compared with patients without ESVEA or AF during study ECG recording within 72 hours.

Statistical Analysis

Descriptive statistics are given as mean±SD for normally distributed variables or median with interquartile range for nonnormally distributed variables and as frequencies for categorical variables. Univariate differences regarding baseline characteristics and study end points during follow-up between patients with ESVEA activity and (1) patients with AF in hospital as well as (2) patients without AF or ESVEA in hospital were evaluated using the Wilcoxon rank-sum test or Fisher's exact test as appropriate. Risk of the composite end point and all-cause death within 24 months after the index stroke was estimated by the Kaplan–Meier-method for each subgroup. Log-rank tests were calculated to compare hazard functions between subgroups. Hazard ratios from Cox proportional hazard models adjusted for baseline covariates (patients' age, National Institutes of Health Stroke Scale score on admission, creatinine value at baseline, heart failure) were calculated for the composite endpoint, all-cause death and recurrent stroke. The proportional hazards assumption for Cox models was evaluated graphically by Schoenfeld residual plots and log–log plots of survival time. No multiplicity adjustments were planned for

secondary outcomes. Therefore, *P* values from univariate analyses must be considered exploratory.

RESULTS

Study Cohort

In the intervention group (n=1735), study patients who had withdrawn informed consent and requested data deletion, patients with lack of any data after randomization, and patients without analyzable study ECG recording (n=42) were excluded. Subsequently, 1693 patients were available for analysis (Table S1). Of those, 258 patients had <48 hours of analyzable ECG recording within the first 72 hours after starting study-related Holter ECG monitoring. Therefore, 1435 (82.7%) of 1735 patients randomized to the intervention group were considered for the analysis of the predefined secondary end point of the MonDAFIS study (Figure S1[20]). The mean age of these 1435 patients was 66.4 years, 40.0% were women, and 19.2% had a prior ischemic stroke or TIA before enrollment. The median National Institutes of Health Stroke score (ranges from 0 to 42, with higher scores indicating more severe neurological deficits[23]) on admission was 2 points, and 393 (27.4%) patients had a TIA as the qualifying event (Table 1, Table S1). The assumed cause of the index stroke at hospital discharge was cryptogenic stroke (30.7%), large-artery atherosclerosis (27.1%), small-artery occlusion (25.9%), cardioembolism (12.5%), or other determined cause (2.9%). Brain imaging and echocardiographic findings are listed in Table S2.

Study ECG Findings

Within the first 72 hours of study-related Holter ECG recording, the total duration of analyzable study ECG recording was 48 to 60 hours in 113 (7.9%) of 1435 patients, and 60 to 72 hours in 1322 (92.1%) patients. A first episode of AF was detected within 72 hours of ECG monitoring in 48 (3.3%) of 1435 patients. ESVEA according to the predefined study definition was found in 363 (25.3%) patients without AF, including 78 (5.4%) patients with at least 1 supraventricular ectopic run of 10 to 29 seconds and 312 (21.7%) patients with ≥480 ectopic supraventricular beats per day on at least 1 day within 72 hours of ECG monitoring (Figure 1). Overall, 1024 (71.4%) of 1435 patients had no AF and did not fulfill the ESVEA criteria. During the total in-hospital stay but after the first 72 hours of ECG monitoring, a first episode of AF was detected in 23 patients with ESVEA and 14 patients without ESVEA/AF.

Within the first 72 hours of study-related ECG monitoring, the prevalence of patients with ESVEA (23.7%) and patients without ESVEA/AF (72.9%) was similar in 1693 patients (including all patients with analyzable

Table 1. Baseline Characteristics of Study Patients Randomized to the Intervention Group With At Least 48 Hours of Study ECG Recording Within the First 72 Hours of Study-Related ECG Recording

	All study patients, n=1435	Patients with ESVEA, n=363	Patients with AF, n=48	*P* value (ESVEA vs AF)	Patients without ESVEA/AF, n=1024	*P* value (ESVEA vs non-ESVEA/AF)
Age, y, mean±SD	66.4±12.7	72.3±10.5	75.5±8.53	0.045	63.9±12.7	<0.001
Female sex, n (%)	574 (40.0)	159 (43.8)	21 (43.8)	>0.999	394 (38.5)	0.081
Index event: Transient ischemic attack, n (%)	393 (27.4)	91 (25.1)	10 (20.8)	0.596	292 (28.6)	0.219
CHA_2DS_2-VASc score, median (IQR)	4 [3–6]	5 [4–6]	5 [5–6]	0.019	4 [3–5]	<0.001
Congestive heart failure, n (%)	41 (2.9)	16 (4.4)	2 (4.3)	>0.999	23 (2.3)	0.041
Hypertension, n (%)	1114 (77.9)	299 (82.4)	40 (85.1)	0.838	775 (76.0)	0.013
Diabetes, n (%)	396 (27.7)	97 (26.7)	19 (40.4)	0.059	280 (27.4)	0.837
Previous stroke or transient ischemic attack, n (%)	275 (19.2)	81 (22.3)	12 (25.5)	0.584	182 (17.8)	0.073
Vascular disease, n (%)	130 (9.1)	30 (8.3)	7 (14.9)	0.171	93 (9.1)	0.669
NIHSS* score on admission, median (IQR)	2 (1–4)	3 (1–4)	2 (1–5)	0.983	2 (1–4)	0.019
Modified Rankin Scale† score before admission, median (IQR)	0 (0–0)	0 (0–0)	0 (0–1)	0.311	0 (0–0)	0.099
Modified Rankin Scale† score on admission, median (IQR)	2 (1–3)	2 (1–3)	2 (1–3)	0.378	2 (1–3)	0.003
Creatinine on admission, mg/dL, median (IQR)	0.91 (0.77–1.09)	0.94 (0.80–1.12)	1.03 (0.84–1.29)	0.050	0.90 (0.76–1.06)	0.033
Heart failure, n (%)	188 (13.1)	62 (17.1)	13 (27.1)	0.106	113 (11.0)	0.004

Patient cohort was stratified according to the presence of ESVEA, a first episode of (AF or sinus rhythm (without ESVEA or AF). AF indicates atrial fibrillation; ESVEA, excessive supraventricular ectopic activity; IQR, interquartile range; and NIHSS, National Institutes of Health Stroke Scale.

*NIHSS score ranges from 0 to 42 points, with higher scores indicating more severe neurological deficits.

†Modified Rankin Scale ranges from 0 to 6, indicating degree of disability in daily activities after stroke, 0 indicating no deficit, 6 indicating death.

study-ECG recording; Table S1) versus 1435 patients of the main analysis (Table 1).

Factors Influencing the Presence of ESVEA Within 72 Hours After Starting Study ECG Monitoring

Compared with patients without ESVEA/AF, patients with ESVEA were older and had a higher median CHA_2DS_2-VASc score on admission, while stroke severity, type of the index stroke, and sex distribution were similar. There were no differences regarding age, sex, CHA_2DS_2-VASc score, stroke severity, and type of index stroke between patients with ESVEA and patients with a first episode of AF within 72 hours of ECG monitoring (Table 1).

Follow-Up Data

At 24 months after enrollment, 67 (18.5%) of 363 patients with ESVEA versus 60 (5.9%) of 1024 patients without ESVEA/AF (according to baseline definition) had been diagnosed with AF (P<0.001; Table 2). At this time point, 68 (18.7%) patients with ESVEA versus 77 (7.5%) patients without ESVEA/AF were on oral anticoagulation (P<0.001), while the percentage of patients on antiarrhythmic drugs was similar. The rate of oral anticoagulation (18.7% versus 72.9%; P<0.001) was statistically significantly lower in patients with ESVEA versus patients with AF (Table 2). The main reasons for prescribing oral anticoagulation in patients with ESVEA in the absence of AF at 12 months were patent foramen ovale (n=6), left atrial thrombus (n=5), pulmonary embolism (n=2), or deep venous thrombosis (n=2).

The composite of recurrent stroke, myocardial infarction, major bleeding, and all-cause death at 24 months did not differ statistically significantly between patients with ESVEA versus patients without ESVEA/AF (15.2% versus 12.6%; P=0.242) or patients with ESVEA versus patients with AF (15.2% versus 14.6%; P>0.999; Figure 2A). In fact, none of the single components of this combined clinical end point was statistically significantly different between patients with ESVEA and patients with AF (Table 2). The risk of all-cause death was similar in patients with ESVEA and patients with AF (6.6% versus 6.2%; P>0.999; Figure 2B) but higher in patients with ESVEA than in patients without ESVEA/AF (6.6% versus 3.2%; P=0.008; unadjusted hazard ratio [HR], 1.93) according to univariate analysis (Figure 1). After multivariate adjustment, patients´ age (P<0.001), National Institutes of Health Stroke Scale score on hospital admission (P=0.001) and creatinine on admission (P=0.011) remained significant regarding the risk of all-cause death, while ESVEA (adjusted HR, 1.26; P=0.433) and heart failure (P=0.563) were not (Table 3). Multivariate analyses for recurrent stroke (unadjusted HR, 1.06; P=0.787; adjusted HR, 1.00; P=0.988; Table S3) and the composite of recurrent stroke, myocardial infarction, major bleeding, and all-cause death (unadjusted HR, 1.25; P=0.204; adjusted

Table 2. Study End Points of Study Patients Randomized to the Intervention Group With At Least 48 Hours of Study ECG Recording Within the First 72 Hours of Study-Related ECG Recording

	All study patients, n=1435	Patients with ESVEA, n=363	Patients with AF, n=48	*P* value (ESVEA vs AF)	Patients without ESVEA/AF, n=1024	*P* value (ESVEA vs non-ESVEA/AF)
Detection of a first episode of AF						
Until 6-mo follow-up, n (%)	132 (9.2)	47 (12.9)	48 (100.0)	NA	37 (3.6)	<0.001
Until 12-mo follow-up, n (%)	148 (10.3)	54 (14.9)	48 (100.0)	*NA*	46 (4.5)	<0.001
Until 24-mo follow-up, n (%)	175 (12.2)	67 (18.5)	48 (100.0)	*NA*	60 (5.9)	<0.001
Oral anticoagulation at 6 mo, n (%)	170 (11.8)	65 (17.9)	38 (79.2)	<0.001	67 (6.5)	<0.001
At 12 mo, n (%)	174 (12.1)	67 (18.5)	36 (75.0)	<0.001	71 (6.9)	<0.001
At 24 mo, n (%)	180 (12.5)	68 (18.7)	35 (72.9)	<0.001	77 (7.5)	<0.001
Antiarrhythmic drug(s) at 12 mo, n (%)	531 (37.0)	140 (38.6)	28 (58.3)	0.012	363 (35.4)	0.309
Recurrent stroke, myocardial infarction, major bleeding, or all-cause death at 6 mo, n (%)	99 (6.9)	33 (9.1)	5 (10.4)	0.790	61 (6.0)	0.051
At 12 mo, n (%)	132 (9.2)	39 (10.7)	6 (12.5)	0.630	87 (8.5)	0.203
At 24 mo, n (%)	191 (13.3)	55 (15.2)	7 (14.6)	>0.999	129 (12.6)	0.242
Recurrent stroke at 24 mo, n (%)	126 (8.8)	33 (9.1)	3 (6.2)	0.785	90 (8.8)	0.831
Myocardial infarction at 24 mo, n (%)	20 (1.4)	4 (1.1)	2 (4.2)	0.148	14 (1.4)	>0.999
Major bleed at 24 mo, n (%)	17 (1.2)	7 (1.9)	2 (4.2)	0.283	8 (0.8)	0.080
All-cause death at 24 mo, n (%)	60 (4.2)	24 (6.6)	3 (6.2)	>0.999	33 (3.2)	0.008

Patient cohort was stratified according to the presence of ESVEA, a first episode of AF or sinus rhythm (without ESVEA or AF). AF indicates atrial fibrillation; and ESVEA, excessive supraventricular ectopic activity.

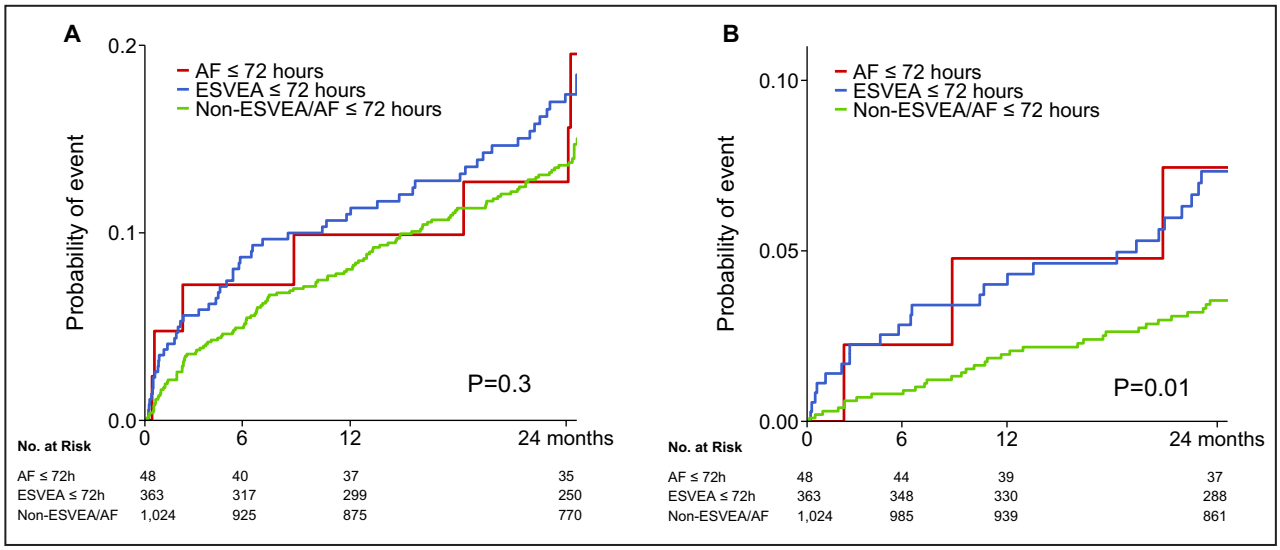

Figure 2. Prevalence of predefined clinical end points during follow-up.
Risk of recurrent stroke, myocardial infarction, major bleeding, or all-cause death (**A**) or all-cause death (**B**) within 24 months after the index stroke according to the presence of atrial fibrillation in-hospital (red), the presence of (blue) or absence (green) of ESVEA in the absence of AF within 72 hours of study ECG monitoring in hospital. *P* values are from univariate log-rank tests. AF indicates atrial fibrillation; and ESVEA, excessive supraventricular ectopic activity.

HR, 1.04; *P*=0.847; Table S4) confirmed the results of the univariate analysis comparing patients with ESVEA versus patients without ESVEA/AF.

At 6 and 12 months after randomization, outcomes were comparable when comparing patients with ESVEA with patients without ESVEA/AF (Table 2). Compared with patients without ESVEA/AF, patients with ESVEA had a higher rate of oral anticoagulation at 6 months (17.9% versus 6.5%; *P*<0.001), and 12 months (18.5% versus 6.9%; *P*<0.001). Compared with patients with AF, patients with ESVEA had a lower rate of oral anticoagulation at 6 months (17.9% versus 79.2%; *P*<0.001), and 12 months (18.5% versus 75.0%; *P*<0.001).

Table 3. Multivariate Survival Analysis Regarding All-Cause Death Within 24 Months After Ischemic Stroke or Transient Ischemic Attack Comparing Patients With ESVEA to Patients Without ESVEA and Without AF According to Baseline Classification

Variable	HR	95% CI	*P* value
ESVEA	1.26	(0.71–2.23)	0.433
Age	1.07	(1.04–1.10)	<0.001
NIHSS* score on admission	1.12	(1.04–1.20)	0.001
Creatinine	1.42	(1.08–1.85)	0.011
Heart failure	0.79	(0.35–1.77)	0.563

AF indicates atrial fibrillation; ESVEA, excessive supraventricular ectopic activity; HR, hazard ratio; and NIHSS, National Institutes of Health Stroke Scale.

*NIHSS score ranges from 0 to 42 points, with higher scores indicating more severe neurological deficits.

Compared with patients with ESVEA/AF or patients with stroke with a first episode of AF during the first 72 hours of ECG monitoring, the rate of recurrent stroke, major bleeding, myocardial infarction, or death did not differ significantly in patients with ESVEA at 6 months or 12 months after the index stroke or TIA (Table 2). Comparing patients with ESVEA to patients without ESVEA/AF, the rate of the composite clinical outcome was numerically higher in patients with ESVEA at 6 months (9.1% versus 6.0%; *P*=0.051) and 12 months (10.7% versus 8.5%; *P*=0.203), failing statistical significance.

DISCUSSION

This predefined analysis of a large multicenter study provides important insights for daily clinical practice in patients with ESVEA during the acute phase of ischemic stroke or TIA. The pragmatic approach of ESVEA detection, based on the first 72 hours of ECG recording in-hospital, is in line with the present recommendations for ECG monitoring after stroke in the European Society of Cardiology guideline[5] and the European Stroke Organization guideline.[6] As reported in previous studies with different definitions of rhythm irregularity burden,[13,14,17,24] ESVEA was found in ≈25% of all stroke patients randomized to the intervention group of the MonDAFIS study.

An important finding of our analysis is that ESVEA detected in the acute phase of stroke or TIA is a risk marker for AF detection during follow-up, when compared with patients without ESVEA. In the past, ESVEA

has been described as risk marker for later AF detection in patients with stroke,[13,14,25–27] but respective data derived from much smaller stroke cohorts are inconsistent.[15,24,26]

The multicenter MonDAFIS study demonstrated that core laboratory–based analysis of ECG recordings for the presence of ESVEA is feasible with short intervals for reporting ECG findings to local investigators.[20] Therefore, a recommendation to consider or not to consider ambulatory prolonged ECG monitoring in the individual patient with stroke can be inserted in the doctor's letter at discharge in the vast majority of hospitalized patients. This recommendation may be based on risk scores for AF detection, like the Atrial Fibrillation in Embolic Stroke of Undetermined Source score[17] or on ESVEA detection in patients without embolic stroke of undetermined source.

The sample sizes in previous stroke cohorts were too small to assess an impact of arrhythmias on mortality rate.[13,14,24–26] Another major novel finding of our analysis is that the detection of ESVEA in the acute phase of stroke or TIA was not associated with all-cause death within 24 months of the index stroke according to multivariate analysis compared with patients without a first episode of AF or no ESVEA above the described cutoff at baseline. Interestingly, the mortality rate in patients with ESVEA was similar to patients with a first episode of AF within 72 hours of ECG monitoring in hospital (Figure 2B).

Of note, a recent analysis of the MonDAFIS study revealed that discontinuation of β blockers during the 24-month follow-up period was associated with a higher mortality rate in the control group than in the intervention group (adjusted HR, 11 [95% CI, 2.4–50]).[28] Whether prolonged ambulatory ECG monitoring in patients with stroke with ESVEA has the potential to reduce the death rate during follow-up needs to be investigated in future trials. The ongoing multicenter Find-AF 2 (Intensive Rhythm Monitoring to Decrease Ischemic Stroke and Systemic Embolism; NCT04371055) study aims to provide evidence of individual atrial ectopy for risk stratification before randomization of in 5200 patients with cryptogenic stroke to prolonged ECG monitoring or usual care. The primary end point of the Find-AF 2 trial is recurrence of stroke or systemic embolism, and all-cause death is one of the secondary outcome measures ().

The combined end point (recurrent stroke, myocardial infarction, major bleeding, or all-cause death) did not differ in patients with ESVEA compared with patients without ESVEA/AF or patients with AF (Figure 2A). Of note, the rate of recurrent stroke was not statistically significantly increased in patients with ESVEA compared with patients without ESVEA/AF in MonDAFIS, which contrasts with a previous meta-analysis that included 7 stroke studies[29] but is in line with a recent meta-analysis including 4 stroke studies.[15] Interestingly, meta-analyses focusing on participants without stroke reported an association of ESVEA detection at baseline with first-ever ischemic stroke after including 11 or 5 longitudinal studies, respectively.[15,18]

According to its definition, ESVEA is not classified as paroxysmal AF and is therefore not an indication for prescribing oral anticoagulation.[5] Surprisingly, in MonDAFIS, the rate of anticoagulation in patients with ESVEA was almost the same at 6, 12, and 24 months (18%–19%), whereas the detection of AF increased steadily at 6 months (13%), 12 months (15%), and 24 months after stroke (18.5%). Reasons documented for prescribing oral anticoagulation in patients with ESVEA in the absence of AF were patent foramen ovale, left atrial thrombus, pulmonary embolism, or deep venous thrombosis. Antiarrhythmic drug use was not statistically significantly different in patients with ESVEA versus patients without ESVEA/AF but, not surprisingly, was more frequent in patients with AF versus patients without ESVEA.

Despite the large sample size, cardiology core laboratory evaluation, and standardized assessment and validation of clinical end points by a Critical Event Committee,[20] some limitations should be noted. First, the incidence of AF during follow-up might be underestimated, as the pragmatic MonDAFIS trial did not use standardized ECG follow-up and excluded patients with implantable loop recorders at baseline. However, standardized ambulatory ECG follow-up is not established in the routine care in patients with stroke worldwide, as also demonstrated in the control groups of previous controlled trials randomizing patients with cryptogenic stroke to implantable loop recorders versus standard of care.[2,30] Furthermore, unblinding of patients and treating clinicians regarding the study intervention may have resulted in ascertainment bias of ECG-based diagnostic measures. Second, we do not have detailed information on the cause of death in MonDAFIS, as autopsy is performed rather rarely in Germany. Third, the inclusion of patients able to provide informed consent in study sites conducting several stroke studies at the same time might have resulted in a selection bias. As patients with missing data in covariates were omitted from multivariate analyses, there is a resulting potential bias for missing not at random data. Fourth, although MonDAFIS is the largest randomized study on AF detection after stroke so far, it was not powered to observe a reduction of clinical outcomes in patients with ESVEA versus patients without ESVEA/AF. Furthermore, there was no standardized cardiac rhythm monitoring after hospital discharge in the MonDAFIS cohort, limiting our ability to collect data on AF detection. Fifth, as brain magnetic resonance imaging was not an inclusion criterion, corresponding brain lesions might have been missed in study patients

with clinical TIA "documented by a neurologist" not undergoing magnetic resonance imaging. Therefore, we decided not to classify patients with TIA "with documented acute ischemic lesion(s) on brain imaging" as ischemic stroke. Sixth, an experienced staff is needed to precisely assess the number ectopic supraventricular beats and presence of atrial runs.

CONCLUSIONS

This predefined analysis of the MonDAFIS study shows that a standardized, core laboratory–based analysis of 72-hour Holter monitoring identifies ESVEA in 1 of 4 patients with acute ischemic stroke or TIA. Compared with patients without ESVEA/AF, ESVEA detected in the acute phase of stroke was associated with later AF detection. Therefore, ESVEA may guide prolonged ECG monitoring after hospital discharge. Of note, the stroke recurrence rate and death over a 24-month period after the index stroke/TIA was not increased in patients with ESVEA, if compared with patients without ESVEA/AF.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S4
Figure S1

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