ORIGINAL ARTICLE

Automatic Holter electrocardiogram analysis in ischaemic stroke patients to detect paroxysmal atrial fibrillation: ready to replace physicians?

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Background and purpose: The detection of paroxysmal atrial fibrillation (pAF) in patients presenting with ischaemic stroke shifts secondary stroke prevention to oral anticoagulation. In order to deal with the time- and resource-consuming manual analysis of prolonged electrocardiogram (ECG)-monitoring data, we investigated the effectiveness of pAF detection with an automated algorithm (AA) in comparison to a manual analysis with software support within the IDEAS study [study analysis (SA)].

Methods: We used the dataset of the prospective IDEAS cohort of patients with acute ischaemic stroke/transient ischaemic attack presenting in sinus rhythm undergoing prolonged 72-h Holter ECG with central adjudication of atrial fibrillation (AF). This adjudicated diagnosis of AF was compared with a commercially available AA. Discordant results with respect to the diagnosis of pAF were resolved by an additional cardiological reference confirmation.

Results: Paroxysmal AF was finally diagnosed in 62 patients (5.9%) in the cohort ($n = 1043$). AA more often diagnosed pAF ($n = 60$, 5.8%) as compared with SA ($n = 47$, 4.5%). Due to a high sensitivity (96.8%) and negative predictive value (99.8%), AA was able to identify patients without pAF, whereas abnormal findings in AA required manual review (specificity 96%; positive predictive value 60.6%). SA exhibited a lower sensitivity (75.8%) and negative predictive value (98.5%), and showed a specificity and positive predictive value of 100%. Agreement between the two methods classified by kappa coefficient was moderate (0.591).

Conclusion: Automated determination of 'absence of pAF' could be used to reduce the manual review workload associated with review of prolonged Holter ECG recordings.

Introduction

Atrial fibrillation (AF) as a common cause of ischaemic stroke is associated with increased mortality and disability following various ischaemic stroke aetiologies [1]. The prevalence of AF will further increase as a consequence of the ageing population [2] and increased application of prolonged electrocardiogram (ECG) monitoring following ischaemic stroke [3].

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However, the number of patients undergoing prolonged monitoring episodes after ischaemic stroke is still low [4,5] and has to be optimized to seize the primary and secondary preventive effect of oral anticoagulative drugs in the case of paroxysmal AF (pAF) detection [6]. In addition, the detection of AF is time sensitive, as a retrospective analysis showed an increased risk of recurrent stroke in patients with delayed diagnosis of AF [7], calling for a contemporary and thorough analysis of ECG data.

However, all efforts to increase the detection rates of AF after ischaemic stroke also increase the workload in ECG analysis and interpretation [8]. One approach to reducing the workload might be to select patients for prolonged monitoring periods in the case of limited resources, unless current guidelines still advise monitoring for at least 72 h in every stroke patient [9] or even longer in patients with cryptogenic stroke [10]. Therefore, we recently proposed a scoring system [2], calculating the risk for pAF detection within 72-h Holter ECG, developed to motivate patients and physicians to tolerate and initiate prolonged Holter monitoring. In addition, the score might be used to select patients for prolonged monitoring periods in the case of limited resources. Another approach to facilitating the implementation of prolonged monitoring times into clinical routine [4] might be a reduction in the resource-consuming analysis of ECG data. A recent study proposes the application of an artificial intelligence algorithm on 12-lead ECG in sinus rhythm to identify individuals with a high likelihood of AF and thereby increases the diagnostic yield of AF [11].

Aims

Here we assess whether ECG data analysis by a fully automated algorithm (AA) [8] is similar to the current practice of manual analysis with software support [study analysis (SA)] within a prospective multicentre study [12] with regard to pAF detection in prolonged 72-h Holter ECG.

Methods

Study population

This analysis included individual patient data from the IDEAS study [12], a prospective, multicentre observational study, investigating prolonged 72-h Holter ECG monitoring following ischaemic stroke. A total of 1043 patients with available ECG, raw data and clinical information were evaluated within this analysis. The detailed screening and exclusion numbers of patients are depicted in Fig. 1 following the Standards for Reporting Diagnostic (STARD) accuracy studies guidelines [13]. In order to ensure comparable treatment standards within the study cohort, only centres with a certified stroke unit, with regard to strictly defined standards and regular external audits, participated in this study. Main exclusion criteria were as follows: patients under 18 years of age, patients with known AF, documented AF on admission, patients with a pacemaker with an atrial lead and patients with life expectancy below 1 year. The full study protocol can be accessed upon request from the corresponding author. The primary study results have recently been published [12].

We report the diagnostic accuracy of the AA for ECG analysis (SRA clinic®, Apoplex Medical Technologies GmbH, Pirmasens, Germany) with regard to detection of pAF and used the STARD accuracy studies checklist [13](for details see Table S1).

Standard protocol approval and patient consent

All patients or their legal representatives gave written informed consent to participate in the study. The study was in line with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of the Ärztekammer Westfalen-Lippe (AZ2009-363-fS) and by all local ethics boards.

Data collection

A standardized questionnaire was used to evaluate baseline characteristics of the included patients. Within this questionnaire a detailed medical history and clinical parameters regarding stroke severity, as measured by the modified Rankin Scale and National Institutes of Health Stroke Scale (NIHSS), were rated by video-trained physicians.

Electrocardiogram analysis

Within this multicentre cohort, we evaluated AA compared with the original SA with regard to pAF detection. All patients underwent 72-h Holter ECG monitoring, started within 12 h after hospital admission, with utilization of a commercially available three-lead Holter monitoring device (Lifecard CF, Spacelabs Healthcare, Issaquah, WA, USA). The manual analysis with software support (SA) was performed within the IDEAS study and was conceptualized as follows. All ECG recordings were subject to physician-based analysis in a central core laboratory situated at the Institut für Klinisch-Kardiovaskuläre Forschung (IKKF GmbH, Munich, Germany) by two independent investigators blinded to individual patient data using the

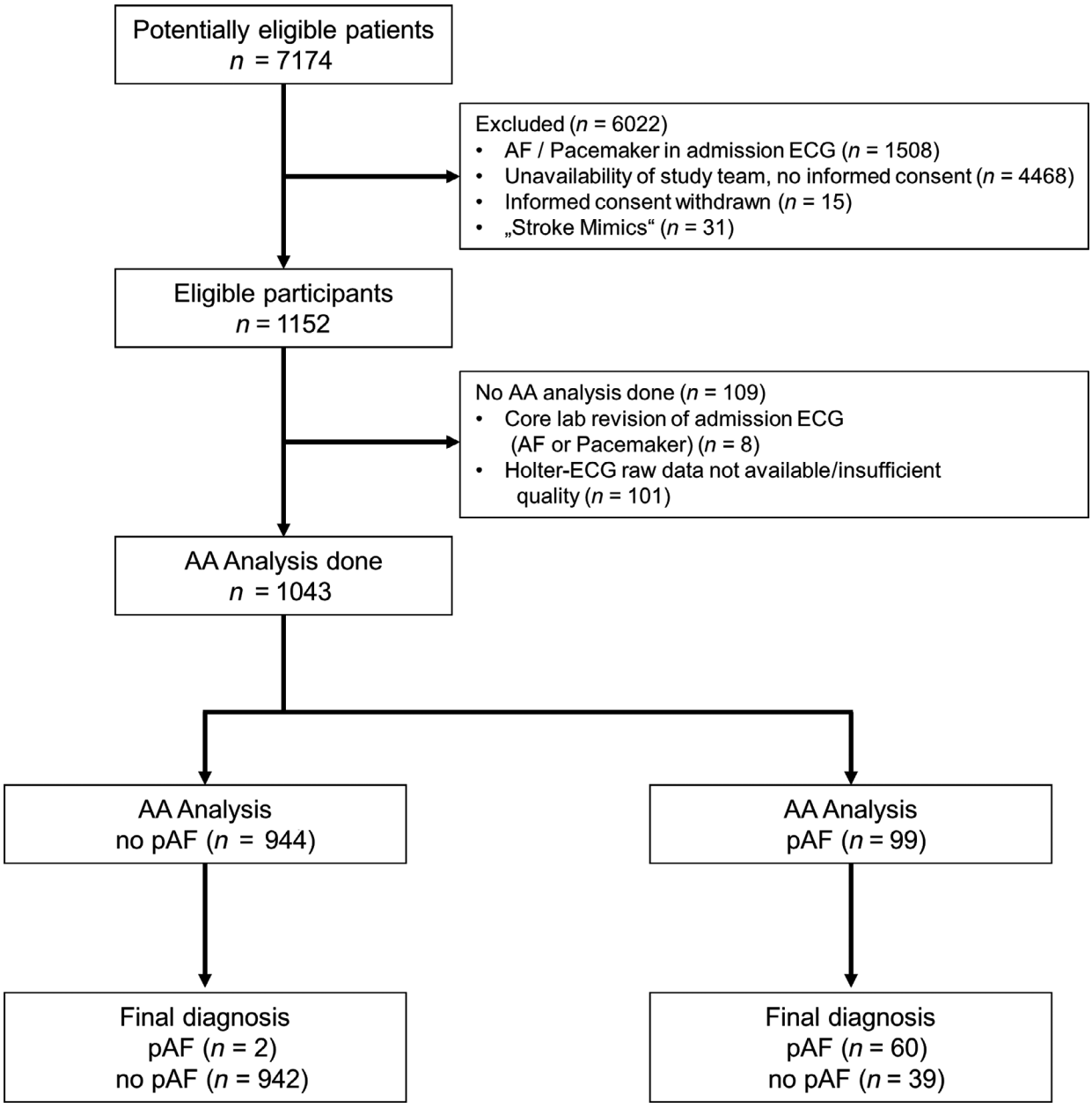

Figure 1 Selection of patients included in the study with regard to availability of automated algorithm (AA). AF, atrial fibrillation; ECG, electrocardiogram; pAF, paroxysmal atrial fibrillation.

Pathfinder® analysis software (version 8.701, Spacelabs Healthcare GmbH, Nürnberg, Germany). In the case of suspected AF, the diagnosis was subsequently evaluated by an independent electrophysiologist (P.K.) for final confirmation (i.e. positive SA result).

For further validation of the SA Holter ECG analysis, 100 randomly selected Holter ECG recordings were re-evaluated by another independent investigator (R.W.), blinded to patient characteristics and the results of previous ECG analysis.

Detection of pAF by SA within the IDEAS study was compared with an AA, which analysed the same copied ECG dataset with the commercially available software SRAclinic® (version 2.9.1, Apoplex Medical Technologies). The developing company kindly provided the software without influence on analysis and data interpretation. In short, the AA creates a report as to whether pAF is detectable due to a proprietary time-series analysis of multiple mathematical imputations, especially the R–R interval. The final result

consists of a report in which the detection of AF is indicated [8,14]. In the case of conflicting results between SA and AA with regard to the occurrence of pAF, the ECG data underwent re-evaluation, by a cardiologist experienced in atrial arrhythmias (B.L.), with commercially available ECG data analysis software (Pathfinder Digital®, version 1.9.0.9484, Spacelabs, Snoqualmie, WA, USA). All investigators involved in the analysis of ECG raw data were blinded to results of stroke-unit telemetry, evaluation results of other methods and clinical characteristics of the patients.

Definition of variables

In line with current guidelines [9], AF was defined as a period of an absolute arrhythmia, lasting at least 30 s, without detectable p-waves. Moreover, absolute irregular R–R intervals and no repetitive ECG pattern were criteria for definition of AF. With regard to cardiovascular risk factors, arterial hypertension was defined as treatment with antihypertensive drugs or either systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg. For calculation of the CHA_2DS_2-VASc score [15], each patient's medical history was obtained from the individualized study case report forms.

Statistical analysis

Data are presented as median (interquartile range) or *n* (%) if not indicated otherwise. For univariate analysis, Student's *t*-test, Mann–Whitney *U*-test, chi-squared test or Fisher's exact test was used where appropriate. Diagnostic accuracy of the compared ECG analysis methods was assessed by sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and rate of false-positive and false-negative test results. Inter-rater reliability analysis to assess consistency between SA and AA was performed using κ statistic. Agreement between the two methods was qualified as fair (κ, 0.21–0.40), moderate (κ, 0.41–0.60), substantial (κ, 0.61–0.80) or almost perfect (κ, 0.81–0.99). $P < 0.05$ was rated as statistically significant. Patients with missing ECG raw data were excluded from this analysis (for details see Fig. 1), which is in line with and mandatory with respect to the STARD guidelines [13]. Statistical analysis was performed using SPSS (version 23, IBM, Armonk, NY, USA) and MedCalc Statistical Software (version 18.11.3, MedCalc Software, Ostend, Belgium).

Data availability statement

Deidentified patient data, analysis plan and study protocol will be available for 5 years after first publication of the article upon request from the corresponding author for collaboration purposes and meta-analysis.

Results

Between May 2010 and January 2011, a total of 7174 patients were assessed for eligibility; out of 1152 eligible patients, 1043 were included in this analysis. Figure 1 shows the flow of patients through the study. The mean age of participants was 66.9 (SD 13.1) years, stroke severity at admission to hospital revealed a median NIHSS score of 2 (interquartile range 0–4) and pAF was finally detected in 62 of 1043 (5.9%) patients. The occurrence of pAF was more frequent in both older patients (pAF 76.0 ± 10.6 vs. no AF 66.3 ± 13.1, $P < 0.001$) and patients presenting with symptoms of ischaemic stroke (pAF 88.7% vs. no AF 75.2%, $P = 0.016$) compared with transient ischaemic attack (pAF 11.3% vs. no AF 24.8%, $P = 0.016$). Patients with diagnosis of pAF within 72-h Holter ECG presented with more severe clinical deficits as rated by NIHSS score [pAF 4 (1–8) vs. no AF 2 (0–4), $P = 0.001$] and modified Rankin Scale score (≥2 at admission; pAF 48.4% vs. no AF 32.9%, $P = 0.007$). With regard to acute stroke treatment and aetiology of the index stroke, patients with a diagnosis of pAF were more likely to receive intravenous thrombolysis (pAF 32.3% vs. no AF 9.8%, $P < 0.001$) and presented with enlarged left atrial diameters as assessed by transthoracic/transoesophageal echocardiography [pAF 46 mm (43–47) vs. no AF 43 mm (41–45), $P = 0.006$], respectively. In addition, the CHA_2DS_2-VASc score was higher in the proportion of patients with AF [pAF 6 (5–6) vs. no AF 4 (3–5), $P < 0.001$]. Detailed patient characteristics are shown in Table 1.

Logistic regression analysis, including all variables that were unbalanced at univariate level ($P < 0.1$), revealed the following patient characteristics to be associated with diagnosis of AF within 72-h Holter ECG: increased age [odds ratio (OR), 1.057; 95% confidence intervals (CI), 1.015–1.101, $P = 0.008$], more severe clinical deficits at admission as measured by the NIHSS score (OR, 1.083; 95% CI, 1.012–1.160, $P = 0.021$) and acute stroke treatment with intravenous thrombolysis (OR, 3.132; 95% CI, 1.605–6.112, $P < 0.001$) (for details see Table 2). Left atrial diameter was not considered for multivariate analysis due to low numbers of available values ($n = 190$).

An overview of AA diagnostic accuracy is given in Table 3. In short, AA detected pAF in 99 patients, yielding a sensitivity of 96.8% (95% CI, 88.8–99.6%) and a specificity of 96% (95% CI, 94.6–97.2%) due to a rate of 39 false-positive (PPV 60.6%) and 2 false-

Table 1 Baseline characteristics of the study population

Variable	No AF	pAF	*P*-value
n	981	62	
Male sex	547 (55.8%)	27 (43.5%)	0.061
Age (years)	66.3 ± 13.1	76.0 ± 10.6	<0.001
BMI (kg/m^2)	26.5 (24.5–29.4)	27.2 (24.1–31.6)	0.620
History of stroke	170 (17.3%)	12 (19.4%)	0.684
History of TIA	81 (8.3%)	5 (8.1%)	0.595
Arterial hypertension	602 (61.4%)	44 (71.0%)	0.133
Diabetes mellitus	193 (19.7%)	18 (29.0%)	0.077
Coronary artery disease	163 (16.6%)	13 (21.0%)	0.375
Cardiac heart failure	56 (5.7%)	7 (11.3%)	0.074
Hyperlipidaemia	345 (35.7%)	22 (36.7%)	0.877
Current/former tobacco use	492 (50.9%)	25 (40.3%)	0.105
CHA_2DS_2-VASc score	4 (3–5)	6 (5–6)	<0.001
NIHSS score at admission	2 (0–4)	4 (1–8)	0.001
mRS score ≥ 2 at admission	313 (32.9%)	30 (48.4%)	0.007
LAD (mm)	43 (41–45)	46 (43–47)	0.006
i.v. thrombolysis	95 (9.8%)	20 (32.3%)	<0.001
Qualifying event Stroke (vs.TIA)	738 (75.2%)	55 (88.7%)	0.016

Data are given as *n* (%), mean ± SD and median (range). AF, atrial fibrillation; BMI, body mass index; i.v., intravenous; LAD, left atrial diameter; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; pAF, paroxysmal atrial fibrillation; TIA, transient ischaemic attack.

Table 2 Multiple logistic regression analysis results for detection of paroxysmal atrial fibrillation

Variable	OR	95% CI	*P*-value
Age	1.057	1.015–1.101	0.008
NIHSS score	1.083	1.012–1.160	0.021
i.v. thrombolysis	3.132	1.605–6.112	0.001

Corrected for sex, age, diabetes mellitus, cardiac failure, CHA_2DS_2-VASc score, National Institutes of Health Stroke Scale (NIHSS) score, intravenous (i.v.) thrombolysis, stroke and modified Rankin Scale score ≥ 2. CI, confidence intervals; OR, odds ratio.

negative results. In contrast, SA detected pAF in 47 patients. SA reached both a specificity and a PPV of 100%. AA reached an NPV of 99.8 (95% CI, 99.2–99.9%) and the NPV in SA was 98.5% (95% CI, 97.7–99.9%). Area under the curve (AUC) for AA (AUC, 0.964; 95% CI, 0.951–0.974, $P < 0.001$) to detect pAF was significantly higher compared with SA (AUC, 0.879; 95% CI, 0.858–0.898, $P < 0.001$; for AUC difference between AA and SA, $P = 0.006$). Kappa statistics to assess inter-rater reliability

Table 3 Detection rates of paroxysmal atrial fibrillation and test effectiveness of different analysis procedures

	SA	95% CI	AA	95% CI
Correctly diagnosed cases	47 (73.8%)		60 (96.7%)	
False positive	0		39	
False negative	15		2	
Sensitivity	75.8	63.3–85.8	96.8	88.8–99.6
Specificity	100.0	99.6–100	96.0	94.6–97.2
PPV	100		60.6	53.0–67.7
NPV	98.5	97.7–99.0	99.8	99.2–99.9
AUC	0.879	0.858–0.898	0.964	0.951–0.974

AA, automated algorithm; AUC, area under the curve; CI, confidence intervals; NPV, negative predictive value; PPV, positive predictive value; SA, study analysis. Data are given as *n* (%).

revealed a moderate agreement with $\kappa = 0.591$ (95% CI, 0.496–0.687, $P < 0.001$) (for details see Table 4).

Discussion

Within the IDEAS study population, algorithm-based analysis (AA) of 72-h Holter ECG monitoring increased the diagnostic yield of pAF after ischaemic stroke from 4.5% to 5.8% compared with manual analysis with software support (SA). AA-based ECG analysis had a good NPV (only missing 2/62 patients with pAF). Despite the reduced precision of AA as compared with SA (with a PPV of 60.6% leading to the necessity of additional cardiologist assessment in all detected cases of pAF detection after AA), this approach could increase the currently low rates of prolonged ECG monitoring in routine clinical practice [4] by reducing the time- and resource-consuming analysis of conventional ECG analysis due to the acceptably low NPV and high sensitivity.

Our results are in line with previously published data assessing software-based pAF detection in stroke patients [8,16,17] showing both a high sensitivity and

Table 4 Agreement between study analysis (SA) and automated algorithm (AA)

	AA	
	No AF	pAF
SA		
No AF	942	54
pAF	2	45

AF, atrial fibrillation; pAF, paroxysmal atrial fibrillation. κ = 0.591, $P < 0.001$; 95% confidence intervals, 0.496–0.687.

NPV of this automated tool. The value of automated analysis of telemetry data, which is accessible in a majority of acute stroke patients but may potentially be associated with a reduced ECG quality, has yet to be elucidated. The broad applicability of the algorithm-based analysis approach within aetiological stroke unit workup needs further studies to assess its diagnostic accuracy on telemetry ECG data in direct comparison to 72-h Holter ECG.

The strengths of our study are the large sample size, data collection within a prospective multicentre stroke study and the validation of discordant results between SA and AA as well as in all cases of detected pAF in a core laboratory by an experienced cardiologist. However, not all ECG raw data of patients included in the IDEAS study were available for the current analysis, which might represent a selection bias.

Our study suggests automated ECG analysis by AA as a pAF screening tool to deal with increasing ECG data. Due to the high NPV and sensitivity compared with staff-based analysis methods, the AA might be able to increase the diagnostic yield of pAF in everyday stroke care. In this scenario, only the verification of positive AA results would have to be assigned to experienced ECG readers in order to prevent false-positive results potentially leading to consecutive oral anticoagulation. The presented approach could serve as a screening tool in pAF detection and might thereby increase the low rate of prolonged ECG monitoring in current practice by reduction of the manual ECG analysis workload.

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Disclosure of conflicts of interest

P.K. reports grants from several industry partners during the conduct of the study [grants and non-financial support from the European Union, British Heart Foundation, Leducq Foundation, Medical Research Council (UK), German Centre for Heart Research and several drug and device companies that are active in AF] and has received honoraria from several such companies outside the submitted work. In addition, P.K. has a patent: P.K. is listed as inventor on two patents held by the University of Birmingham (Atrial Fibrillation Therapy WO 2015140571, Markers for Atrial Fibrillation WO 2016012783). R.W. reports grants from Sanofi during the conduct of the study, personal fees from Bayer, Berlin Chemie and Bristol-Myers-Squibb, grants and personal fees from Boehringer Ingelheim, personal fees from CVRx, grants from Bundesministerium für Bildung und Forschung and Deutsche Forschungsgemeinschaft, personal fees from Daiichi Sankyo and Gilead, grants and personal fees from Medtronic, personal fees from Novartis, Pfizer and Servier, and grants from the European Union outside the submitted work. K.G. reports personal fees and non-financial support from Bayer AG, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo and Pfizer outside the submitted work. T.U. reports personal fees from Merck Serono and Pfizer, and grants from Else Kröner-Fresenius Stiftung outside the submitted work. The other authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1 Standards for Reporting of Diagnostic (STARD) accuracy studies checklist.

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