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Continuous Stroke Unit Electrocardiographic Monitoring Versus 24-Hour Holter Electrocardiography for Detection of Paroxysmal Atrial Fibrillation After Stroke

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Background and Purpose—Cardioembolism in paroxysmal atrial fibrillation (pxAF) is a frequent cause of ischemic stroke. Sensitive detection of pxAF after stroke is crucial for adequate secondary stroke prevention; the optimal diagnostic modality to detect pxAF on stroke units is unknown. We compared 24-hour Holter electrocardiography (ECG) with continuous stroke unit ECG monitoring (CEM) for pxAF detection.

Methods—Patients with acute ischemic stroke or transient ischemic attack were prospectively enrolled. After a 12-channel ECG on admission, all patients received 24-hour Holter ECG and CEM. Additionally, ECG monitoring data underwent automated analysis using dedicated software to identify pxAF. Patients with a history of atrial fibrillation or with atrial fibrillation on the admission ECG were excluded.

Results—Four hundred ninety-six patients (median age, 69 years; 61.5% male) fulfilled all inclusion criteria (ischemic stroke: 80.4%; transient ischemic attack: 19.6%). Median stroke unit stay lasted 88.8 hours (interquartile range, 65.0–122.0). ECG data for automated CEM analysis were available for a median time of 64.0 hours (43.0–89.8). Paroxysmal AF was documented in 41 of 496 patients (8.3%). Of these, Holter detected pxAF in 34.1%; CEM in 65.9%; and automated CEM in 92.7%. CEM and automated CEM detected significantly more patients with pxAF than Holter ($P < 0.001$), and automated CEM detected more patients than CEM ($P < 0.001$).

Conclusions—Automated analysis of CEM improves pxAF detection in patients with stroke on stroke units compared with 24-hour Holter ECG. The comparative usefulness of prolonged or repetitive Holter ECG recordings requires further evaluation. (*Stroke*. 2012;43:00-00.)

Key Words: acute ischemic stroke ■ atrial fibrillation ■ ECG ■ Holter ECG ■ stroke unit ■ transient ischemic attack

Stroke prevention is a key medical challenge worldwide.¹ Atrial fibrillation (AF) causes at least 20% of all ischemic strokes; these strokes have a higher mortality and are frequently more disabling compared to other etiologies.^{2–4} Ischemic strokes caused by AF can be effectively prevented by oral anticoagulation.^{5,6} However, because AF is often asymptomatic^{7–9} and only paroxysmally present, it can easily escape diagnosis (“silent AF”^{10,11}). Reportedly, delayed detection of AF is common in patients with stroke.¹² Paroxysmal AF (pxAF) carries the same risk of cardioembolism as persistent

AF,^{13–15} and cardiogenic embolism due to undetected pxAF is probably responsible for a substantial part of cryptogenic ischemic strokes.^{16–18} Consequently, efforts to improve the detection of pxAF after a stroke are of great importance.¹⁹

There is considerable uncertainty how patients with stroke/transient ischemic attack (TIA) should be evaluated for the presence of pxAF.^{10,16,17,20} Available evidence suggests that pxAF frequently evades standard 12-channel electrocardiography (ECG) and 24-hour Holter ECG recordings.^{18,21,22} Prolonged or repetitive Holter monitoring, repeated ECGs,

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event or loop recorders, and mobile telemetry devices can increase the likelihood of AF detection after stroke.^{18,21–26} Adequately powered prospective studies comparing these modalities are lacking.

According to current guidelines, patients with stroke should be treated on dedicated stroke units. Besides recording a 12-channel ECG on admission, it is recommended to monitor the ECG continuously for at least the first 24 hours to detect rhythm disorders.^{16,17} Continuous ECG monitoring (CEM) may help to recognize pxAf.^{27,28} An automated analysis of ECG data to reveal pxAf^{29,30} could further increase detection rates. However, the diagnostic value of CEM has not been appropriately studied, particularly not in comparison to the more widely used 24-hour Holter ECG.^{17,27,28}

The aim of this study was to evaluate CEM for the detection of pxAf in patients with acute stroke and TIA. We tested whether CEM detects more pxAf than a 24-hour Holter ECG and whether automated processing of ECG data derived from CEM (aCEM) using dedicated software further increases the rate of pxAf detection.

Methods

Patients

Consecutive patients with TIA and ischemic stroke who had been admitted to our stroke unit were prospectively screened for enrollment into this single-center study. To be included into the final analysis, the following prespecified criteria had to be fulfilled: (1) age ≥ 18 years; (2) confirmation of stroke/TIA diagnosis by a stroke neurologist; (3) no previously known AF in the medical history; (4) no AF on the admission ECG; (5) presence of a 24-hour Holter ECG with a minimum data acquisition period of ≥ 18 hours; (6) duration of CEM ≥ 24 hours; and (7) availability of ECG data for aCEM analysis ≥ 24 hours.

The independent ethics committee of the Medical Faculty of the University Heidelberg, Heidelberg, Germany, approved the study protocol. Written informed consent was obtained from the patient or his or her legal representative.

ECG Procedures to Detect pxAf

Cardiac workup for AF detection encompassed a baseline 12-channel ECG on arrival (ELI 350; Mortara Instruments). Holter ECG was performed on the stroke unit within the first 48 hours after admission (H12+; Mortara Instruments). Holter data were analyzed by a blinded cardiologist supported by the H-SCRIBE software (Version 4.0; Mortara Instruments).

CEM was started immediately after admission using the Infinity-Delta monitoring system (Draeger, Lübeck, Germany). This monitoring system includes different rhythm alarms: (1) flat ECG; (2) ventricular fibrillation; (3) couplets or bigeminy; and (4) preset upper and lower heart rate thresholds (120/min and 40/min). Dedicated software for AF detection is not included in this system. CEM required physical wire connection to the monitor. Whenever AF was suspected from the monitor trace by the stroke unit staff, a 12-channel ECG was performed and reviewed by a cardiologist. The stroke unit personnel had been advised to document any episode suspicious of AF.

Additionally, CEM data were analyzed automatically (aCEM). Monitor ECG data were sent to a computer where an unsupervised automated AF episode detection algorithm was applied using the SRAclinic software (Apoplex Medical Technologies, Pirmasens, Germany). This software uses an algorithm that detects QRS complexes of the ECG data and then classifies them as being of atrial or ventricular origin and finally creates a list of R-R-intervals. To detect episodes of AF, the software performs a time series analysis of

multiple mathematical parameters that are typical for an absolute arrhythmia during AF.³⁰ Based on this analysis, the system creates a report on whether episodes of AF are present. In all cases in which the software reported AF, ECG source data were reviewed in detail to confirm or falsify these reports by 2 investigators (T.R., C.R.). An independent external institute, blinded to all clinical data, additionally verified aCEM data. Using the SmartHolter24 system (Version 1.8; Schmidt GmbH), 2 investigators (P.K., E.A.) reviewed all ECG source data derived from the automated monitoring system of patients with presumed pxAf (ie, cases with positive AF reports from aCEM and at least one episode of sinus rhythm during the hospital stay) and an equal number of randomly selected ECG source data derived from the automated monitoring system.

Persistent AF was diagnosed in patients without evidence of sinus rhythm in any ECG performed. AF was classified as paroxysmal in all cases in which sinus rhythm and at least one episode of AF, lasting for >30 seconds,^{11,31} was documented during hospitalization. Additionally, basic demographic variables and risk factors, including CHADS₂ scores, were registered. All nurses and physicians involved in the care of patients were unaware of results generated by aCEM. Employees of Apoplex Medical Technologies had no access to any clinical data.

Statistical Analysis

For basic demographic variables and ECG results, descriptive data analysis was performed. Descriptive data are presented as median and interquartile ranges. To test group differences, nonparametric tests were applied. The pxAf detection rate of different methods of AF was compared using the McNemar test. To test possible influences of β -blockers and cardiac pacemakers on aCEM results, a Cochran-Mantel-Haenszel test was applied. A probability value of <0.05 was considered significant. For detailed sample size calculation, see the online-only Data Supplement biometrical methods. Data analysis was conducted using the Statistical Package for the Social Sciences (SPSS 19.0) and BiAS (9.11).

Results

Patients

In total, 832 patients with ischemic stroke and TIA were admitted to our stroke unit between March /2010 and January 2011; 496 of 832 patients (59.6%) fulfilled all criteria for entering data analysis (compare with Figure 1: recruitment synopsis).

Median age of patients was 69 years (57–77), 61.5% were male, 80.4% had an ischemic stroke, and 19.6% a TIA. Median initial National Institutes of Health Stroke Scale score in patients with ischemic stroke was 3.0 (1–7); median time between onset of symptoms and start of CEM on the stroke unit was 7.5 hours (3.5–25.0). Median duration of the stroke unit stay was 88.8 hours (65.0–122.0). Data derived from continuous ECG monitoring were available for a median time of 64.0 hours (43.0–89.8). In 406 of 496 patients (81.9%), Holter ECG was started within the first 24 hours after ward admission; the median time interval between ward admission and start of Holter ECG was 14.9 hours (5.8–22.9).

Basic demographic variables and the duration of the different ECG recordings are presented in Table 1. Characteristics of these patients are compared with those excluded from data analysis in online-only Data Supplement Table I.

Total AF Burden and Association to Basic Demographic Variables

In total, AF was newly documented during the stroke unit stay in 68 of 496 patients (13.7%). Persistent AF was present

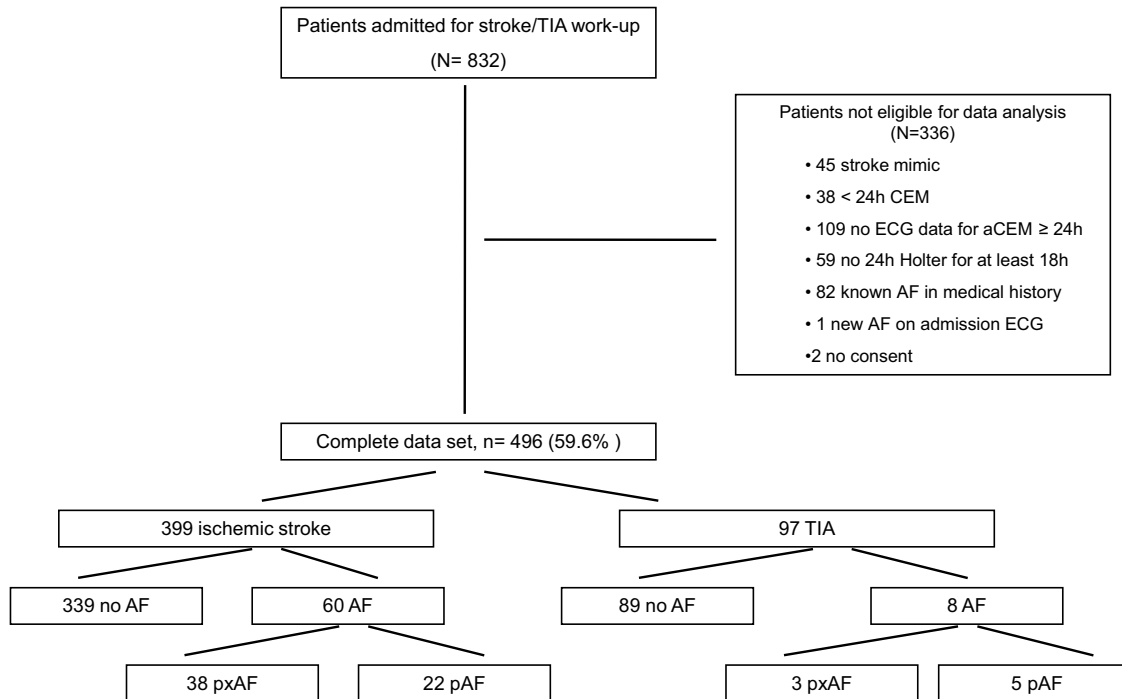


Figure 1. Patient recruitment and AF burden of the population including AF subtypes. CEM indicates continuous ECG bedside monitoring; AF, atrial fibrillation; pxAF, paroxysmal atrial fibrillation; pAF, persistent atrial fibrillation; TIA, transient ischemic attack; h, hours.

in 27 (5.4%). Paroxysmal AF was identified in 41 of 68 by at least one method (60.3% of all patients with AF; compare with Figure 1). Thus, the overall rate of newly documented pxAF was 8.3% (41 of 496) in the study population. The

Table 1. Demographic Data, Basic Risk Factors, and Duration of the Different ECG Recordings of the Cohort

	Total (n=496)
Age, y (median, IQR)	69; 57–77
Male sex	61.5%
Manifest stroke	80.4%
TIA	19.6%
Prior stroke or TIA	22.2%
Hypertension	78.8%
Diabetes	24.6%
Hypercholesterolemia	40.1%
CHADS ₂ score, median (IQR)*	3.0 (3–4)
Extracranial internal carotid artery stenosis >70%†	14.5%
Cardiac pacemaker	2.2%
Interval between symptom-onset and beginning of CEM, h, median (IQR)	7.5 (3.5–25)
Duration of stroke unit stay, h, median (IQR)	88.8 (65.0–122.0)
Effective duration of CEM, h, median (IQR)	64.0 (43.0–89.8)
Duration of Holter ECG, h, median (IQR)	24 (23–24)
Ward admission until starting Holter ECG, h, median (IQR)	14.9 (5.8–22.9)

ECG indicates electrocardiography; IQR, interquartile range; TIA, transient ischemic attack; CEM, continuous bedside ECG monitoring.

*For patients with atrial fibrillation.

†European Carotid Surgery Trial criteria (available carotid ultrasound: n=488).

median time until first detection of pxAF after admission during aCEM was 30.5 hours (6.8–55.1; compare with also online-only Data Supplement Figure I).

Patients with AF (median age, 75 years) were older compared with patients without AF (median age, 68 years; $P<0.001$). Median age did not differ between patients with paroxysmal (75 years) and persistent AF (74 years; $P=0.691$). No association between sex and AF subtype was evident (persistent AF male: 12, pxAF male: 23; $P=0.619$). In patients with newly detected AF, ischemic stroke was more frequent than TIA (ischemic stroke: 60, TIA: 8; $P<0.001$). Strokes in patients with AF were more severe (median National Institutes of Health Stroke Scale score, 9; 5–18) compared with strokes without AF (median National Institutes of Health Stroke Scale score, 3; 1–5; $P<0.001$). Stroke severity did not differ between paroxysmal and persistent AF (median National Institutes of Health Stroke Scale score in persistent AF, 9.5, median National Institutes of Health Stroke Scale score in pxAF, 8; $P=0.950$).

Cervicocranial ultrasound measurements to assess carotid stenosis were available in 488 of 496 patients (98.4%). In patients with a carotid stenosis $\geq 70\%$ according to European Carotid Surgery Trial (ECST) criteria (72 of 488), AF was present in 9 of 72 (14.8%; persistent AF: 2, pxAF: 7). In patients without stenosis (n=416), AF was present in 57 (13.7%; persistent AF: 24, pxAF: 33). No association between presence of carotid stenosis and AF was present ($P=0.478$).

Yield of Different Methods for Detection of pxAF

Holter detected pxAF in 34.1%; CEM in 65.9%; and aCEM in 92.7%. Accordingly, CEM and aCEM detected significantly more patients with pxAF than Holter ($P<0.001$), and

Table 2. Detection of Paroxysmal AF by Different Methods, Excluding Patients With Previously Known AF and/or Detection of AF in the Admission ECG

	24-H Holter ECG	CEM	aCEM
Absolute no. of detected cases	14	27	38
Relative frequency, n=41	34.1%	65.9%	92.7%
absolute frequency, n=496	2.8	5.4	7.7
	24-H Holter ECG Versus CEM	CEM Versus aCEM	24-H Holter ECG Versus aCEM
Difference of percentages of detected cases, n=41	31.7%	26.8%	58.5%
Difference of percentages of detected cases, n=496	2.6%	2.2%	4.8%
McNemar test	0.004	<0.001	<0.001

Total no. of detected pxAF=41. Upper part: detection rates. Lower part: differences of methods to detect pxAF. AF indicates atrial fibrillation; ECG, 12-channel electrocardiogram; CEM, continuous bedside ECG monitoring; aCEM, automated CEM; pxAF, paroxysmal atrial fibrillation.

aCEM detected more patients than CEM ($P<0.001$). One patient was detected with Holter but not with CEM or aCEM; this patient was not connected to the monitor during the pxAF episode. Table 2 summarizes the data for the different methods for detection of pxAF.

Figure 2 illustrates the proportional yield of applied ECG methods to reveal pxAF. Online-only Data Supplement Table II and online-only Data Supplement Figure II present the data for the entire population including patients with known AF before hospitalization and with AF detection already on the admission ECG.

As a consequence of AF detection, 31 of 41 patients (75.6%) with newly detected pxAF were started on oral anticoagulants.

Automated CEM Results

In total, aCEM reported the presence of AF in 78 of 496 patients. AF was confirmed by review of CEM in 64 of 78 cases (ie, aCEM yielded 14 false-positive results). All patients with persistent AF were detected correctly by the system. Automated CEM failed to detect pxAF in 3 of 41 patients. The presence of a cardiac pacemaker had an impact on false-negative results of aCEM ($P=0.026$), whereas co-medication with β -blockers did not influence aCEM results ($P=0.682$).

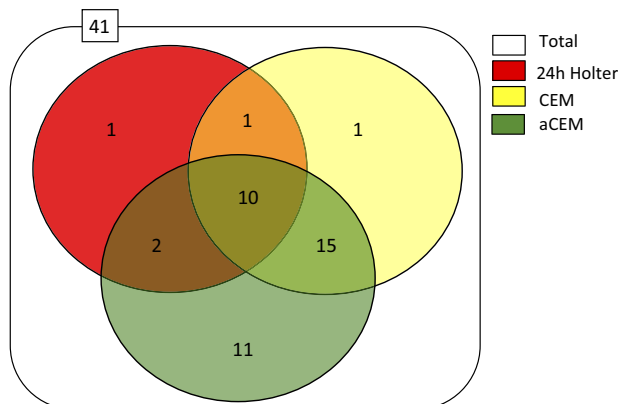


Figure 2. Venn diagram to illustrate the detection of pxAF by the different ECG methods (compare with also Table 2). pxAF indicates paroxysmal atrial fibrillation; ECG, electrocardiographic.

Discussion

The major new finding of our study is that continuous ECG monitoring, a standard procedure on stroke units anyway, is more efficacious for detection of pxAF than a 24-hour Holter ECG, particularly when combined with automated analysis software aimed at detecting AF.

A number of studies have evaluated different techniques for detection of AF after stroke but comparison of their findings is hampered by different study designs. According to a review by Liao and coworkers²¹ and a more recent study,²² routine 24-hour Holter detects approximately 5% of new pxAF. In the present study, 2.8% of new pxAF was revealed by Holter ECG. Extending the duration of Holter monitoring may increase the likelihood of detecting AF after stroke.²¹ This is supported by Stahrenberg and coworkers²² who reported that Holter ECG for up to 7 days detected pxAF in 12.5% of patients with stroke. However, prolonged Holter recording is time-consuming for medical staff and uncomfortable for patients.

In contrast, bedside ECG monitoring uses the available infrastructure and is part of treatment standards on stroke units.^{16,17} Although recent guidelines already recommend the use of ECG monitoring,^{16,17} the actual evidence supporting its usefulness to detect pxAF is sparse. Hidalgo and coworkers²⁷ detected pxAF in 3.4% of patients with acute stroke during a mean CEM period of 45.6 hours but results of admission ECG and 24-hour Holter ECGs were not reported. In a previous study of our group,²⁹ CEM appeared to be advantageous in comparison to 24-hour Holter. However, findings may have been biased due to nonconsecutive enrollment and start of Holter at an undefined time after admission. Furthermore, our previous study did not use aCEM to analyze continuous ECG monitoring data. More recently, a reading algorithm for CEM data was reported to assist in detecting AF but no comparison to Holter was performed.²⁷ Our study shows that stroke unit ECG monitoring can improve the pxAF detection rate compared with a 24-hour Holter ECG. However, pxAF diagnosis based on CEM requires special attention and training by the ward staff and extrapolation of our results to all stroke units might be limited. An alternative approach is to store and analyze ECG data derived from CEM automatically (aCEM). Our study suggests that this approach

leads to a considerable increase of pxAf detection. However, competent ECG readers must verify positive aCEM results on source ECG traces, because false-positive results can occur. Importantly, the absolute detection rate of CEM and particularly aCEM significantly exceeded that of 24-hour Holter ECGs (2.2% and 4.8%, respectively). In contrast, the detection of previously undiagnosed pxAf exclusively by 24-hour Holter ECG was marginal (n=1). This patient was not connected to the monitor during the pxAf episode. Indeed, a limitation of CEM is that CEM monitoring on our unit requires physical wire connection to the monitor and patients have to be disconnected from the monitor to undergo examinations and therapy (ie, MRI brain scanning, physiotherapy), which reduces the actual ECG data acquisition period (ie, mean availability of ECG data: 64.0 hours versus mean stroke unit stay: 88.8 hours). Nevertheless, a 24-hour Holter ECG in addition to CEM appears unnecessary in the vast majority of patients on a stroke unit in the setting of in-hospital stroke unit diagnostic workup for pxAf.

The most likely explanation for its superiority is that CEM monitored cardiac rhythm for a longer time than 24-hour Holter.

Efforts to detect pxAf after cryptogenic stroke and TIA should clearly not be limited to the stroke unit. Event loop recorders and cardiac event recorders revealed pxAf in 5.7%²⁵ and 7.7%²⁶ of patients with stroke, respectively. The ongoing Cryptogenic Stroke and underlying Atrial Fibrillation (CRYSTAL-AF) study evaluates the diagnostic yield of long-term ECG monitoring after cryptogenic stroke using a subcutaneously implanted device.¹⁸

Our study has additional limitations. Performance at a single center and analysis only of patients with defined inclusion criteria (ie, no consecutive enrollment for the analyzed population) may have introduced biases of our results. Another limitation is the lack of a subanalysis concerning the presence of lacunar stroke. Moreover, no subanalysis on how timing of Holter affected results was performed and we cannot exclude that repetitive or prolonged 24-hour Holter recordings may have yielded a comparable rate of pxAf.

In conclusion, the present study suggests that continuous ECG monitoring may replace 24-hour Holter ECG as the routine diagnostic procedure for the detection of pxAf on stroke units. The usefulness of prolonged or repetitive Holter ECG recordings, in particular in the outpatient setting, requires further investigation.

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SUPPLEMENTAL MATERIAL

Supplemental Methods:

Sample size was calculated prior to study initiation to examine whether the detection rate of pxAf can be significantly enlarged by ECG monitoring (CEM) compared to 24h-Holter ECGs in addition to the admission 12-channel ECG. Based on published data¹, we estimated that pxAf would be detected in 6% of stroke and TIA patients by admission ECG plus 24h Holter. Sample size was calculated to detect an increase of pxAf detection of $\geq 3\%$ by CEM. A sample size of 562 subjects was required to show that CEM detects pxAf more often than Holter ECG with a power of 80% and an alpha error of 5% (two-sided).

Supplemental Tables

Supplemental Table 1: Comparison between patients that were included and those that were excluded from the final data analysis (detailed description of inclusion/exclusion criteria cp. methods). Note: Not all excluded patients received all diagnostic techniques to detect AF; this group further includes patients with known AF prior to admission and with AF on the admission ECG. (IQR: interquartile range, TIA: transient ischemic attack, NIHSS: National Institute of Health Stroke Scale Score). *: presented for patients with AF

	Included patients (n=496)	Excluded patients (n=336)	p value
Age (median, IQR)	69; 57-77	72; 61-80	p=0.01
Male	51.5%	57.4%	p=0.242
Diagnosis	Stroke: 80.4% TIA: 19.6%	Stroke: 69.0% TIA: 31.0%	p=0.006
NIHSS in stroke patients (median, IQR)	3.0; 1-7	5.0; 2-12	p<0.001
Atrial fibrillation	13.7%	33.4%	p<0.001
Persistent AF	5.4%	25.3%	p<0.001
Paroxysmal AF	8.3%	8.0%	p=0.898
Hypertension	78.8%	78.3%	p=0.848
Diabetes	24.6%	20.8%	p=0.206
Hypercholesterolemia	40.1%	43.2%	p=0.383
CHADS ₂ (median, IQR)*	4.0; 3-5	4.0; 4-5	p=0.259

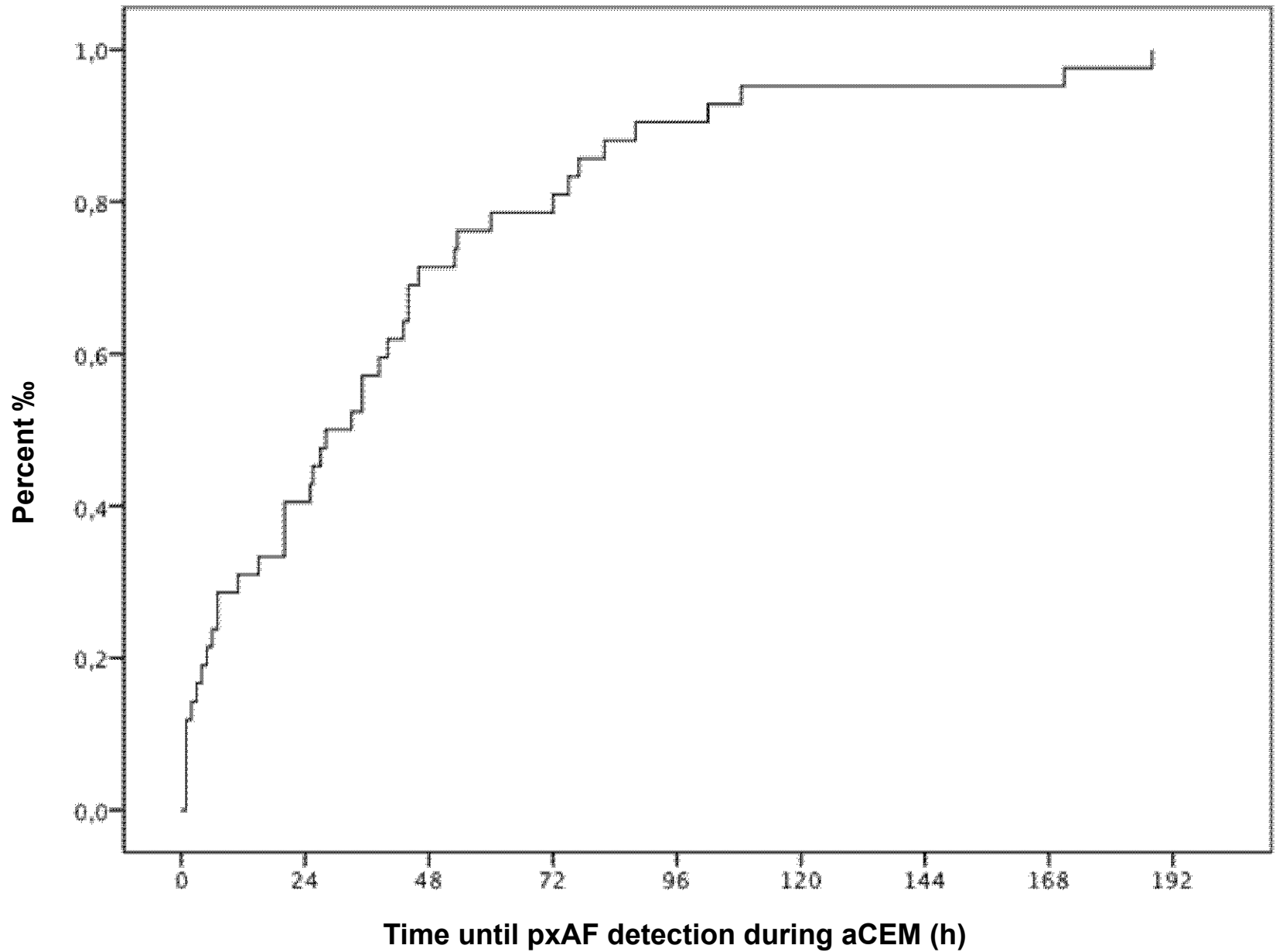
Supplemental table 2: Detection of paroxysmal AF by different methods. Patients with known AF prior to admission and with AF detection on the admission ECG are included. Total number of detected cases in the cohort: 57.

Upper part: Detection rates

Lower part: Differences of methods to detect pxAf.

(A: admission ECG; B: admission ECG + 24h Holter ECG; C: admission ECG + CEM; D: admission ECG + aCEM; No: Number, ECG: 12 channel electrocardiogram, CEM: continuous bedside ECG monitoring, aCEM: automated CEM)

	A	B	C	D
No of detected cases	16	31	40	55
Relative frequency, n=57	28.1%	54.4%	70.2%	96.5%
	A vs. B	B vs. C	C vs. D	B vs. D
Difference of percentages of detected cases, n=579	2.6%	1.6%	2.6%	4.2%
McNemar Test	<0.001	0.02	<0.001	<0.001



No. at risk

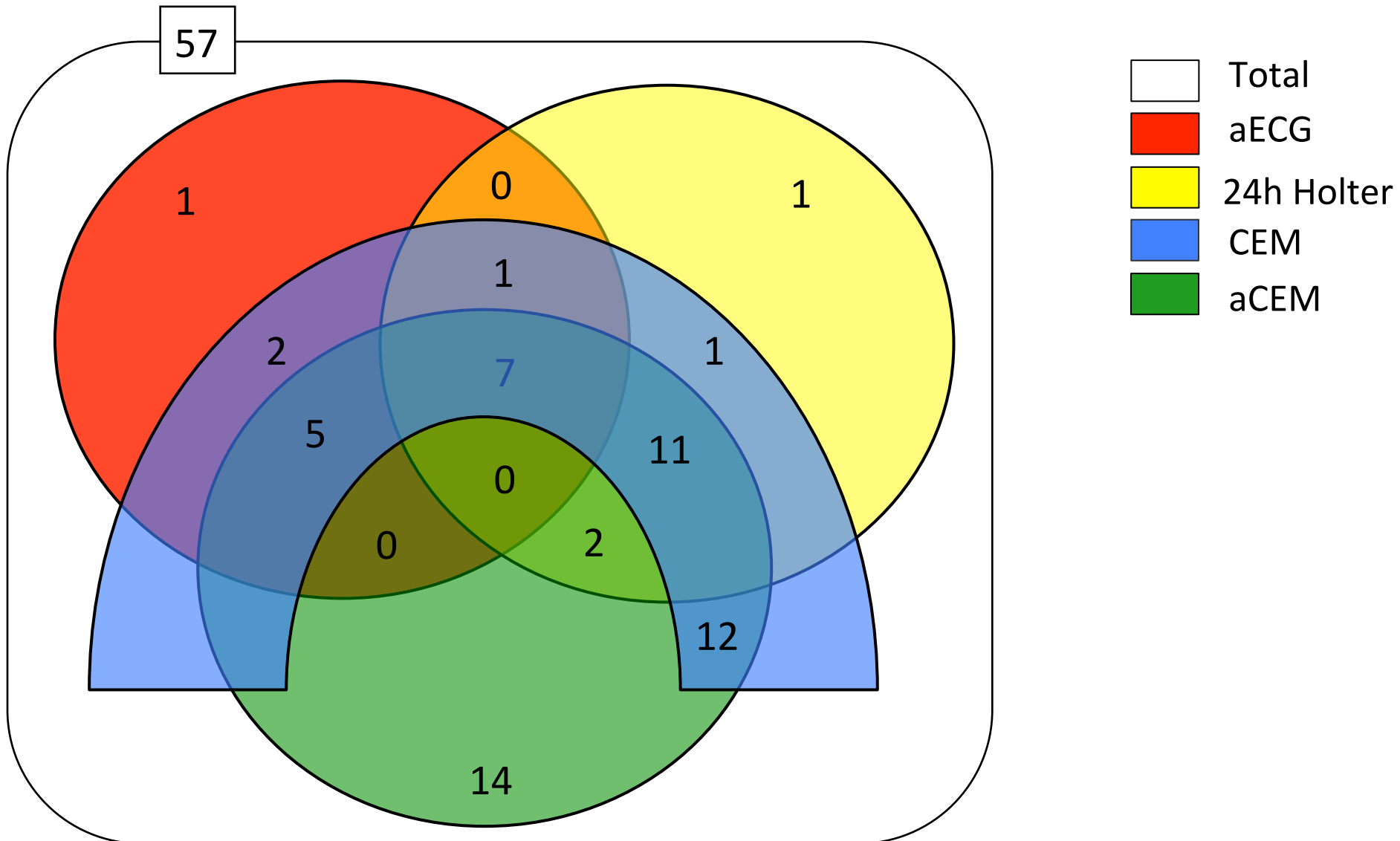
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Supplemental Figure 1:

Time until first detection of pxAf after admission during aCEM (automated continuous ECG monitoring, pxAf: paroxysmal atrial fibrillation).

Supplemental Figure 2:

Detection of pxAf by the different ECG methods including patients with known AF prior to hospitalization and with AF detection already on the admission ECG.



Supplemental references

1. Liao J, Khalid Z, Scallan C, Morillo C, O'Donnell M. Noninvasive cardiac monitoring for detecting paroxysmal atrial fibrillation or flutter after acute ischemic stroke: a systematic review. *Stroke*. 2007;38:2935.