Handheld ECG Tracking of in-hOspital Atrial Fibrillation (HECTO-AF): A Randomized Controlled Trial

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Research Article

Keywords: atrial fibrillation, ECG handheld device, prevention, screening, stroke

DOI: https://doi.org/10.21203/rs.3.rs-115978/v1

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Abstract

Background. Atrial fibrillation (AF) is frequent and causes substantial morbidity through AF-related strokes. Given the increasing prevalence of AF, screening methods are of interest given the potential to initiate timely appropriate anticoagulation. The HECTO-AF trial aims to determine the efficacy of AF screening with a single-lead electrocardiogram (ECG) handheld device in naive in-hospital patients.

Methods. The HECTO-AF is a single-centre, open label, randomized controlled trial. Patients admitted to the general medicine ward of the University and Hospital Fribourg without previous diagnosis of AF were invited to participate in a screening program with a 1:1 allocation to either the screening group with intermittent single-lead handheld ECG recordings vs. a control group undergoing detection of AF as per routine clinical practice. Primary outcome was prevalence of newly diagnosed AF. Enrollment was terminated for poor patient recruitment and apparent futility before a sufficient sample for powered efficacy comparisons was enrolled.

Results. A total 804 patients were included of whom 381 were allocated to the intervention and 423 to the control group. Mean age was 65±16 and 464 (58%) were male. Median CHA2DS2-VASc score was 3 (13% heart failure, 57% hypertension, 19% diabetes mellitus, 14% prior stroke/transient ischemic attack, 29% arterial disease) and all CHA2DS2-VASc risk factors were equally distributed between groups. Seven patients (1.8%) were diagnosed with AF in the intervention group versus 3 (0.7%) in the control group (p-value=0.20).

Conclusion. There was a trend towards a higher AF detection in the intervention group, but a definitive conclusion cannot be drawn due to the early termination of the present study. Systematic screening for AF in the hospital setting is resource-consuming, and of uncertain clinical benefit. The interpretation of single-lead handheld ECG is challenging and may result in inaccurate AF diagnosis.

Trial registration. ClinicalTrials.gov, ID: NCT03197090.

Introduction

Atrial fibrillation (AF) affects over 5 million people in Europe, with projected estimates up to 14 million by 2060 making it the most common arrhythmia. (1) AF patients have a two-fold increase in mortality and a five-fold increase in risk of stroke compared with the general population. (2) It is estimated that one third of AF patients will be hospitalized at least once a year due to worsening heart failure or cardioembolic events. (3) Asymptomatic or "silent" AF is present in close to 33% of patients and conveys a risk of stroke identical to symptomatic patients. (2) There is evidence that even short episodes of silent AF (of at least 6 minutes) have an increased thromboembolic risk. (4)

The 2016 European Society of Cardiology (ESC) guidelines encourage opportunistic AF screening programs in at-risk populations by pulse palpation. (5) To date there is insufficient evidence for a systematic screening strategy. (6) However, a number of randomised controlled trials have investigated the effectiveness of routine screening for AF in outpatients using different devices. Among them, is the Zenicor single-lead electrocardiogram (ECG) recording device which appropriately detects AF with a sensitivity of 96%, and a specificity of 92%. (7) Data on AF screening strategies and clinical benefit in hospitalized patients are lacking.

We therefore sought to determine the efficacy of systematic screening strategy for silent-AF using a single-lead ECG handheld device versus routine clinical practice in patients hospitalized in the General Internal Medicine Department at the Hospital and University of Fribourg.

Methods

In this single centre, open label, randomized controlled trial, we randomly assigned patients in a 1:1 ratio to a systematic screening strategy using the Zenicor (Medical Systems AB) single-lead handheld ECG recording device vs. a control group with standard clinical care. The study methods and design have been published previously. (8) The study was conducted in accordance with the Declaration of Helsinki and was approved by the regional ethics committee (ClinicalTrials.gov, ID: NCT03197090, first registration on 23/06/2017). All patients provided written, informed consent for participation.

All patients 18 years or older admitted to the general internal medicine ward were eligible. Patients with known or previously documented AF, patients with cardiac pacemakers or implantable cardioverter-defibrillators, length of stay <48 hours, life expectancy <6 months and those unable to provide written-informed consent, were excluded (Fig. 1).

Randomization was performed as soon as written consent was provided, using a computer-generated allocation sequence (www.randomizer.org) and concealment until assignment. Research nurses generated the random allocation sequence, enrolled participants and assigned the patients to the study groups according to the previously generated randomization sequence. There was no blinding.

ECG recording

Patients included in the Zenicor group were instructed to use the handheld ECG recorder for intermittent ECG recordings. Recordings were planned twice daily under supervision of specially trained nurses. Patients had to apply their thumbs over the captors of the device during 30-seconds to yield a single-lead ECG recording which was stored, and subsequently transmitted to a central server for analysis. In the control group, 12-lead ECG were
performed and interpreted by the treating physicians as per standard clinical care (i.e. in case of palpitations, chest pain, suspicion of arrhythmia during physical examination).

**ECG analysis**

All single-lead ECGs were stored in a web-based interface analysis system (Zenicor-ECG Doctor System) and independently reviewed on the same day by the investigators to assess the presence of AF (Fig. 2). A 12-lead ECG was performed in all cases of suspected AF in the Zenicor group. Additional recordings, including 24–48 h Holter monitoring or 7-day R-Test were performed in case of uncertainty. Finally, two cardiologists reviewed every case of suspected new AF.

**Outcomes**

The primary outcome was the incidence of new-onset AF defined as a 30-s recording of irregular rhythm without p waves. Each patient with newly diagnosed AF was treated according to the 2016 ESC guidelines on the management of atrial fibrillation (i.e. regarding anticoagulation, rhythm and/or rate control therapy). Additional workup including 12-lead ECG, laboratory investigations, and further cardiological workup such as echocardiography, were organized as per guidelines.

**Statistics**

We calculated that a total of 1600 patients would yield a power of 80% to detect superiority with an estimated event rate of 3% in the Zenicor group and 1% in the control group, allowing a 9% loss to follow-up. The trial was interrupted at interim analysis after 50% of patients were enrolled (n = 804), due to poor patient recruitment and limited resources. The premature interruption of the trial was responsible for patient number differences between groups. The inclusion of 804 patients yields a power of 53% for the presumed event rate of 3% and 1% respectively. Because of the potential for type I error due to incomplete patient enrollment, the reported analyses should be interpreted as exploratory.

Categorical variables are reported as counts and percentages; continuous variables are reported as means and SD. Normality was assessed by visual inspection of histograms and computation of Q-Q plots. Continuous variables were analysed using the Student t test or the Wilcoxon rank-sum test according to their distribution. Categorical variables were compared using chi-square or Fisher exact test as appropriate. All statistical analyses were performed using dedicated software (Stata 14, College Station, Texas) at a 2-tailed significance level of alpha = 0.05.

**Results**

**Participation**

From March 2018 and August 2019, 3261 patients were screened for eligibility of which 806 (25%) underwent randomization. 2 patients were excluded from the analysis because of AF on 12-lead ECGs at admission. 381 patients were assigned to intermittent single-lead handheld ECG recordings, and 423 patients to routine clinical practice. Patient flow-chart is depicted in Fig. 1.

**Patient characteristics**

Baseline characteristics are summarized in Table 1. Mean age was 65 ± 16 years and 464 (58%) were male. Median CHA2DS2-VASc score was 3 of which: 13% heart failure, 57% hypertension, 19% diabetes mellitus, 14% prior stroke/transient ischemic attack, and 29% vascular disease (including myocardial infarction, peripheral artery disease, and complex aortic plaque). CHA2DS2-VASc risk factors were equally distributed between groups. All main diagnoses were well balanced between the groups (Table 2). The most common primary diagnosis was malignancy (14%). Moreover, 34 patients (8%) were hospitalised due to an ischaemic stroke in the Zenicor group vs. 24 patients (6%) in the control group (p = 0.08).
| Baseline patient characteristics | Zenicor (n = 381) | Control group (n = 423) | p-value |
|----------------------------------|-------------------|-------------------------|---------|
| Male                             | 216 (57)          | 248 (59)                | 0.62    |
| Age, yrs                         | 66.16 ± 14.79     | 64.57 ± 17.03           | 0.56    |
| Hypertension                     | 219 (57)          | 229 (54)                | 0.35    |
| Diabetes mellitus                | 71 (19)           | 78 (18)                 | 1.00    |
| Dyslipidemia                     | 145 (38)          | 134 (31)                | 0.06    |
| Smoker or previous smoker        | 175 (46)          | 177 (42)                | 0.26    |
| Positive family history for cardiovascular disease | 66 (17) | 81 (19) | 0.52 |
| Ischemic heart disease           | 72 (19)           | 69 (16)                 | 0.35    |
| Congestive heart failure         | 48 (13)           | 49 (12)                 | 0.67    |
| Previous stroke                  | 55 (14)           | 52 (12)                 | 0.40    |
| Vascular disease (MI, peripheral artery disease, complex aortic plaque) | 112 (29) | 119 (28) | 0.70 |
| Age (>75 years)                  | 215 (33)          | 135 (32)                | 0.82    |
| CHA<sub>2</sub>DS<sub>2</sub>-VASc risk score (categorical) | | | |
| 0–1                              | 121 (32)          | 141 (33)                | 0.65    |
| 2–4                              | 181 (48)          | 203 (48)                | 0.94    |
| >4                               | 79 (21)           | 79 (19)                 | 0.48    |
| CHA<sub>2</sub>DS<sub>2</sub>-VASc risk score (quantitative) | 2.80 ± 1.93 | 2.69 ± 1.89 | 0.52 |
| Medication predisposing to bleeding (aspirin, clopidogrel, NSAID) | 224 (59) | 226 (53) | 0.14 |
| Length of hospitalisation, days  |                  |                        |         |
| Mean ± SD                        | 10 ± 7            | 10 ± 8                  | 0.78    |
| Median (IQR)                     | 8(6–12)           | 8 (6–11)                |         |

Values are mean ± SD or n (%)
Table 2
Main diagnosis during hospitalization

| Diagnosis                                | Zenicor (n = 381) | Control (n = 423) | p-value |
|------------------------------------------|-------------------|-------------------|---------|
| Heart failure                            | 19 (5)            | 21 (5)            | 1.00    |
| Ischaemic heart disease                  | 22 (6)            | 16 (4)            | 0.19    |
| Pneumonia                                | 31 (8)            | 43 (10)           | 0.33    |
| Chronic obstructive pulmonary disease    | 12 (3)            | 8 (2)             | 0.27    |
| Pulmonary embolism                       | 15 (4)            | 6 (1)             | 0.28    |
| Other lung disease                       | 16 (4)            | 14 (3)            | 0.58    |
| Ischemic stroke or TIA                   | 34 (8)            | 24 (6)            | 0.08    |
| Gastrointestinal bleed                   | 11 (3)            | 12 (3)            | 1.00    |
| Malignancy                               | 47 (12)           | 65 (15)           | 0.22    |
| Minor trauma                             | 21 (5)            | 22 (5)            | 0.88    |
| Vascular disease                         | 6 (2)             | 6 (1)             | 1.00    |
| Infection/sepsis                         | 39 (10)           | 60 (14)           | 0.11    |
| Kidney failure                           | 8 (2)             | 5 (1)             | 0.40    |
| Miscellaneous                            | 100 (26)          | 121 (29)          | 0.48    |
| Values are n (%)                         |                   |                   |         |

TIA - transient ischemic attack

Atrial fibrillation screening in the Zenicor group

Systematic single-lead ECG screening was performed in 381 patients. Although single-lead ECG were scheduled twice daily, compliance with study protocol was incomplete. Median number of ECG recordings per individual was 6 (IQR 3–10), over a median screening period of 6 days (IQR 4–10). A total of 3015 records were made using the Zenicor device. The time required for the screening strategy was 1 hour per patient for identification of inclusion/exclusion criteria, explanation of device use and recording of one-lead ECGs. The time required for post-recording interpretation of the ECG was variable (between 1 and 5 minutes per ECG), requiring single-lead ECG review 7 days a week.

Primary outcome

The overall incidence of newly detected AF was 1.4% (n = 10) over the 17 months inclusion period. A total of 7 AF episodes were detected in the Zenicor group versus 3 AF events in the control group (1.8% vs 0.7%, p-value = 0.20).

Management of newly detected AF

Oral anticoagulation was initiated in 7 newly detected AF patients with a median CHA₂DS₂-VASc score of 3 (1–4), of which 4 in the Zenicor group, and 3 in the control group. Amongst the 3 non-anticoagulated patients in the Zenicor group (median HAS-BLED score of 2.5 (1.5-4), OAC therapy was withheld because of risk of fall, risk of bleeding, and advanced malignancy. History and follow-up of patients with newly detected AF is summarized in Table 3.
Table 3
Clinical characteristics of patients with newly detected atrial fibrillation

| Patient Age | AF detection group | Main diagnosis | Possible trigger factor | Time to detection (days) | OAC | Type of AF | CHA2DS2-VASc/HAS-BLED | Relevant FUP | Time to FUP (months) |
|-------------|-------------------|---------------|------------------------|--------------------------|-----|-----------|------------------------|-------------|---------------------|
| 82 years-old women | control | interstitial pneumonia | unknown | 7 | yes | paroxysmal | 4/2 | Ischemic stroke after OAC interruption (reason for interruption unknown) | 12 |
| 83 years-old women | control | lumbar trauma | hyperthyroidism | 7 | yes | paroxysmal | 4/2 | No known AF recurrence | 6 |
| 80 years-old women | control | kidney failure | unknown | 5 | yes | paroxysmal | 6/4 | No known AF recurrence | 7 |
| 50 years-old man | zenicor | skin infection | infection | 1 | yes (for planned electrical cardioversion, but not long term)* | paroxysmal | 0/0 | No known AF recurrence | 12 |
| 74 years-old man | zenicor | pneumonia | unknown | 2 | yes | paroxysmal | 1/2 | No known AF recurrence | 8 |
| 78 years-old man | zenicor | gastrointestinal bleeding | bleeding | 0 | yes (after resolution of gastrointestinal bleeding) | paroxysmal | 3/3 | Death from septic shock | 5 |
| 74 years-old man | zenicor | malignancy | mild hypokalaemia, severe hypomagnesemia | 1 | no, advanced malignancy | paroxysmal | 1/3 | Death from malignancy | 1 |
| 90 years-old man | zenicor | cholecystitis | infection, mild hypokalaemia | 9 | no, high risk of fall | paroxysmal | 3/3 | Pulmonary embolism requiring OAC | 1 |
| 88 years-old women | zenicor | TIA | n/a | 1 | yes | paroxysmal | 7/5 | AF recurrence | 24 |
| 68 years-old man | zenicor | malignancy | mild hypomagnesemia | 0 | no, bleeding risk (oesophageal cancer) | paroxysmal | 2/2 | No known AF recurrence | 12 |

OAC, oral anticoagulation; TIA, transient ischemic attack; FUP, follow-up

* instead, patient had spontaneous cardioversion and anticoagulation was stopped at 1 month in the absence of AF recurrence after 24-hours Holter

Harms and misdiagnosis of AF
A total of 4 patients in the Zenicor group were initially considered to have AF, but were subsequently reclassified as no AF by two independent cardiologists. None of the latter were started on OAC as two were already anticoagulated for other indications (mesenteric venous thrombosis, pulmonary embolism), and two refused anticoagulation. All patients were correctly reclassified in the final analysis.

Discussion
The HECTO-AF trial was designed to determine whether a systematic screening strategy using daily recordings with a single-lead handheld ECG device increases the detection rate of AF compared to standard clinical practice in the hospital setting. The main findings of the HECTO-AF randomized trial are: a) the overall incidence of newly detected AF was 1.4% b) in the systematic screening group, a total of 7 AF episodes were...
detected of which 4 (57%) were started on OAC c) the systematic screening for AF in the hospital setting is resource-consuming, and of uncertain clinical benefit.

Rational for AF screening

The European Society of Cardiology Guidelines recommend opportunistic screening of AF using pulse palpation based on a randomised controlled trial which found 1.64% incidence of new AF in patients > 75 years-old.(9) Recently a number of studies have assessed the effect of systematic screening on the detection of AF, with the idea that even brief (30 seconds or longer) episodes of AF detected during a limited period are clinically relevant. Four randomized controlled trials (RCTs) have compared screening programs to routine care. The Screening for Atrial Fibrillation in the Elderly (SAFE) trial including 14'802 patients demonstrated that active screening for AF (invitation for a 12-lead ECG) was more effective than routine care (pulse palpation and ECG in case of pulse irregularity). This study conducted in 50 primary care centres in England found a detection rate of new AF of 1.63% a year in the intervention group vs. 1.04% in the control group (difference 0.59%, 95% CI: 0.20–0.98).(10) Another RCT comparing opportunistic pulse palpation to systematic screening with 12-lead ECG in outpatient primary care, reported, in 3'001 patients, a greater AF detection rate in the intervention group (4.5% vs. 1.3%, OR, 3.7, 95% CI: 2.2–1.6).(11) In the REHEARSE-AF Study which randomized patients with CHA2DS2-VASc score ≥ 2 and ≥ 65 years old, to an AliveCor Kardia monitoring vs. routine care, in 1’001 patients, showed a statistically significant increase in detection of AF in the monitoring arm over a 12-month period (3.8% vs. 0.9%, HR, 3.9; 95% IC: 1.4–10.4; P = 0.007).(12) Finally, the STROKESTOP trial (Systematic ECG screening for Atrial Fibrillation Among) has reported a prevalence of AF of 3% in 7'625 outpatients from Sweden undergoing a 2-week intermittent recording using the Zencor device.(13)

More recently, there has been a paradigm shift in clinical trial design with the Apple Heart Study, in which photoplethysmography was used to detect irregularity in 419'297 participants wearing the Apple Watch.(14) Of these, 2'161 participants (0.52%) received a notification of pulse irregularity, and were assessed for the necessity to wear a 7-day ECG patch. Of those notified and wearing the ECG-patch, 153 patients were diagnosed with AF (0.036% of the total population). It must be stressed that Apple Watch-like devices attract younger populations with uncertainty about the clinical value of detecting AF in low-risk individuals.

The place of AF screening is widely debated, and despite meta-analyses pointing to an apparent benefit in patients > 40 years-old,(15) a recent US Preventive Services Task Force (USPSTF) has concluded that the evidence on the benefits for AF screening with ECG is insufficient.(16)

Screening for atrial fibrillation in the hospital setting

HECTO-AF is the first randomized study to assess a systematic screening strategy using a handheld device in the hospital setting. The incidence of newly diagnosed AF episodes (1.8%, n = 7) in the Zencor group was lower than expected in hospitalized patients compared to outpatients. Factors that could explain a lower detection rate in the internal medicine ward include a younger population, short hospitalisation stay (median 6 days) resulting in shorter screening periods as compared with the two-weeks in the STROKESTOP trial. All patients were considered to have paroxysmal AF, none required neither rhythm nor rate control.

Recording and interpretation of ECGs

Single-lead ECG recordings were performed at rest under direct supervision of nurses to ensure optimal quality. Nonetheless, single-lead ECG quality was variable, and in some situations uninterpretable. Poor quality has been described due to the electric disturbance caused by movements, or high thumb pressures during recordings.(7) Overall, and after review by expert cardiologists, initial AF misdiagnosis was considered in 4 patients. 12-lead ECGs were performed in all cases of suspected AF in the Zencor group. The most common reason for discrepancy between single-lead ECG and 12-lead ECG was the presence of atrial or ventricular premature beats.

As mentioned, a previous study in patients with known AF, calculated ECG Zencor sensitivity at 96% and specificity 92% which points towards AF overdiagnosis.(7) It must be stressed however, that this was done in a context of 10-second recordings and not 30 seconds. Our trial results also indicated potential AF overdiagnosis. Although our aim was not to test for sensitivity, nor specificity we hypothesise that they may have differed from previous reports.

Potential harms of AF misdiagnosis

A recent meta-analysis suggests that there is a lack of data regarding potential harms of AF screening versus no screening.(15) Indeed, AF misdiagnosis can lead to the initiation of unnecessary treatment with potential complications, and unwarranted tests. We strived to reduce this harm by requiring confirmation of every suspected AF single-lead recording by two senior cardiologists. Additional 24-hours Holter monitoring were necessary in 4 patients from the Zencor group (57%) with suspected AF. None of them detected a recurrence of AF.

Treatment of AF and initiation of OAC treatment in the acute setting

There is a lack of evidence on the benefit of anticoagulation initiation in newly diagnosed AF in the acute setting. Prior studies have shown that AF in sepsis is associated with higher in-hospital and 5-year stroke risk when compared with patients with no AF.(17) Gundlund et al.(18) found a greater recurrence of AF among patients with infection-related AF and twice the risk of thromboembolic events compared to infections without AF at one
year’s follow-up. Conversely, a retrospective study (19) did not demonstrate a lower risk of ischemic stroke following anticoagulation in patients with
new-onset AF associated with sepsis, acute pulmonary disease and myocardial infarction. Meanwhile, anticoagulant use was associated with a
higher risk of bleeding in patients with acute pulmonary disease (6.8 vs. 11.8%, p < 0.05). In our study, anticoagulation was not started in 3 (43%)
patients in the intervention group because of bleeding risk. Overall, the uncertainty of initiating long-term OAC in the acute setting, limits the indication
for systematic AF screening in the hospital setting. Finally, AF was paroxysmal in all patients, and none required rhythm nor rate control therapy on
the long term.

**Limitations**

The most important study limitation was the lack of statistical power caused by prematurely discontinuing patient enrollment. Bias may have
occurred due to fluctuations of AF detection during the study. The time to inclusion was not standardized for each patient and may have led to
underdetection of AF in patients with very short hospital stays. There was a potential selection bias as only patients capable of performing a proper
single-lead handheld recording were eligible. Therefore, the most vulnerable and fragile patients who may have been at even higher risk of AF were
excluded. This may have underestimated the overall AF rate, but the benefit of introducing OAC in this population is debatable. In some cases, the
presence of artefacts has limited the interpretation of ECG. The sensitivity and specificity as well as positive and negative predictive values in the in-
hospital setting were not assessed as no systematic simultaneous 12-lead ECG were performed with each one-lead ECG. Finally, this was a
monocentric study with results that may not be applicable to a more general population.

**Conclusion**

There was a trend towards a higher AF detection in the intervention group, but a definitive conclusion cannot be drawn because of the insufficient
statistical power of the present study. A systematic screening program with daily single-lead handheld ECG recordings is resource-consuming and did
not detect a significantly higher number of AF episodes compared to routine clinical practice. The interpretation of single-lead handheld ECG is
challenging and may result in inaccurate AF diagnosis. The long-term benefit of oral anticoagulation in patients with accurate detection of AF during
acute illness is uncertain.

**Abbreviations**

AF - atrial fibrillation
ECG - electrocardiogram
FUP- follow-up
HECTO-AF - Handheld ECG Tracking of in-hospital Atrial Fibrillation
IQR - interquartile range
NSAID - nonsteroidal anti-inflammatory drug
OAC - oral anticoagulation
SD - standard deviation
TIA - transient ischemic attack

**Declarations**

**Ethics approval and consent to participate.** The study protocol was approved by the Cantonal Research Ethics Committee, Vaud and was in
accordance with standards set forth by the Declaration of Helsinki. All participants provided their informed consent.

**Consent for publication.** Not applicable.

**Availability of data and materials.** The datasets used and/or analysed for the current study are available from the corresponding author on
reasonable request.

**Competing interests.** There are no conflicts of interest with any of the authors.

**Funding.** The trial is supported by an unrestricted grant from Fond Scientifique Cardiovasculaire Fribourg.

**Authors’ contributions.** M.M and S.C conceived the original idea and planned the study. Y.F. contributed to the implementation of the research and
data management. S.S. contributed to the study design, analysed the data and wrote the manuscript with support from D.A. S.P and M.M. D.A. et S.P.
contributed to data analysis. S.C. supervised the project.
Acknowledgements. The authors would like to thank the nursing staff of the Department of Internal Medicine, University and Hospital of Fribourg.

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