Screen-detected atrial fibrillation predicts mortality in elderly subjects

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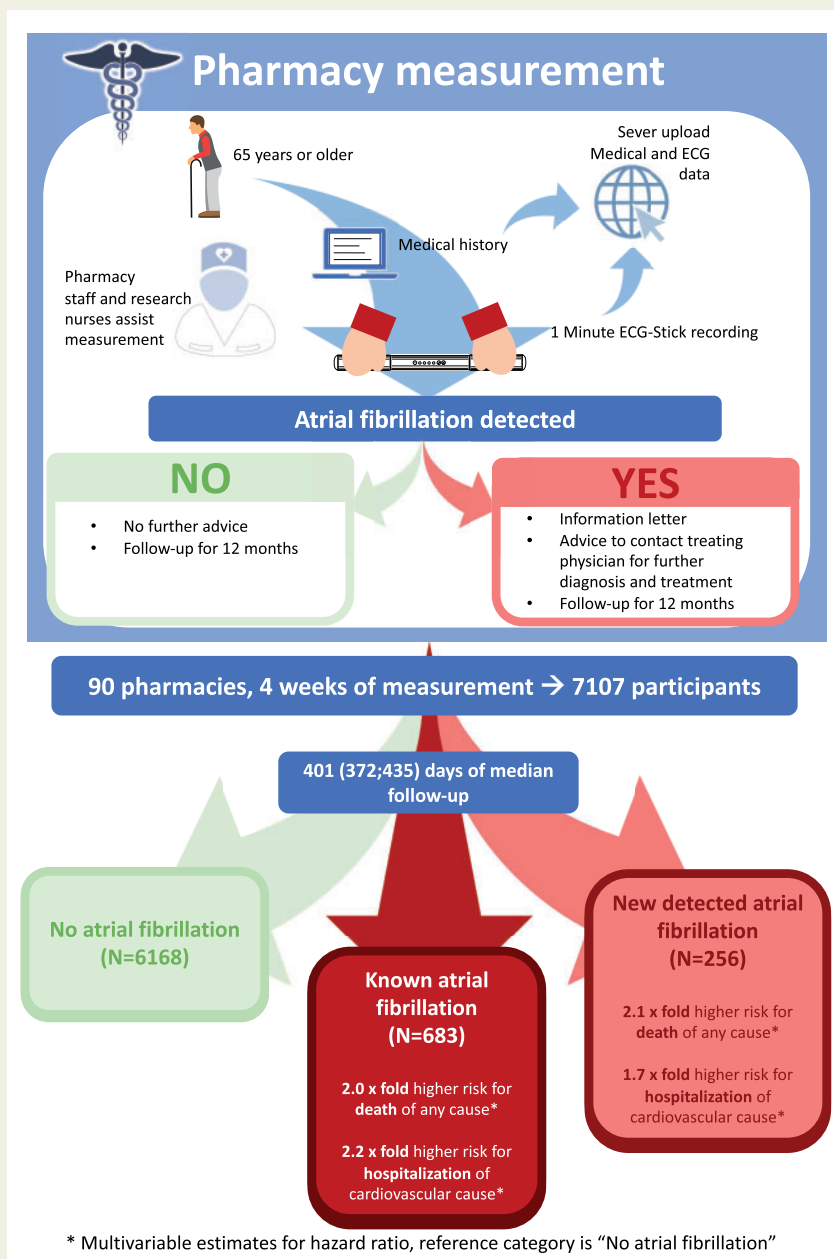|	
Aims	Current guidelines recommend opportunistic screening for atrial fibrillation (AF) but the prognosis of individuals is unclear. The aim of this investigation is to determine prevalence and 1-year outcome of individuals with screen-detected AF.
Methods and results	We performed a prospective, pharmacy-based single time point AF screening study in 7107 elderly citizens (≥65 years) using a hand-held, single-lead electrocardiogram (ECG) device. Prevalence of AF was assessed, and data on all-cause death and hospitalization for cardiovascular (CV) causes were collected over a median follow-up of 401 (372; 435) days. Mean age of participants was 74 ± 5.9 years, with 58% ($N = 4130$) of female sex. Automated heart rhythm analyses identified AF in 432 (6.1%) participants, with newly diagnosed AF in 3.6% of all subjects. During follow-up, 62 participants (0.9%) died and 390 (6.0%) were hospitalized for CV causes. Total mortality was 2.3% in participants with a screen-detected AF and 0.8% in subjects with a normal ECG [hazard ratio (HR) 2.94; 95% confidence interval (CI) 1.49–5.78; $P = 0.002$]; hospitalization for CV causes occurred in 10.6% and 5.5%, respectively (HR 2.08; 95% CI 1.52–2.84; $P < 0.001$). Compared with subjects without a history of AF at baseline and a normal ECG, participants with newly diagnosed or known AF had a significantly higher mortality risk with HRs of 2.64 (95% CI 1.05–6.66; $P = 0.04$) and 2.68 (95% CI 1.44–4.97; $P = 0.002$), respectively. After multivariable adjustment, screen-detected AF remained a significant predictor of death or hospitalization for CV causes.
Conclusion	Pharmacy-based, automated AF screening in elderly citizens identified subjects with unknown AF and an excess mortality risk over the next year.

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Graphical Abstract

Pharmacy measurement

65 years or older

Pharmacy staff and research nurses assist measurement

Medical history

Sever upload Medical and ECG data

1 Minute ECG-Stick recording

Atrial fibrillation detected

NO
- No further advice
- Follow-up for 12 months

YES
- Information letter
- Advice to contact treating physician for further diagnosis and treatment
- Follow-up for 12 months

90 pharmacies, 4 weeks of measurement → 7107 participants

401 (372;435) days of median follow-up

No atrial fibrillation (N=6168)

Known atrial fibrillation (N=683)

2.0 x fold higher risk for **death** of any cause*

2.2 x fold higher risk for **hospitalization** of cardiovascular cause*

New detected atrial fibrillation (N=256)

2.1 x fold higher risk for **death** of any cause*

1.7 x fold higher risk for **hospitalization** of cardiovascular cause*

* Multivariable estimates for hazard ratio, reference category is "No atrial fibrillation"

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia with an estimated prevalence of about 3% in adults, with a significant increase for people aged 65 years or older.[1] Atrial fibrillation is independently associated with an increased risk of all-cause mortality, as well as an about five-fold increased risk of stroke throughout all ages.[2] In recent decades, there has been an increase in the general disease burden and in AF-associated health problems with significant impact on public health. Treatment with oral anticoagulants (OACs)

in patients with AF and risk factors has been shown to substantially improve the prognosis for both, stroke and mortality.[3] Still, prevention of sequelae and death in AF patients remains a significant clinical problem, mainly because of undertreatment and undiagnosed subjects especially those with subclinical AF.[1]

Screening for AF in a hospital or outpatient environment may improve the prognosis in at-risk populations and is currently recommended by various guidelines.[1] The prevalence of AF detected in these healthcare provider-related screening approaches mainly depends on the population screened as well as the intensity of

What's new?

- We identified individuals with actionable atrial fibrillation (AF) (known and newly diagnosed) by a single time point large-scale pharmacy screening in elderly citizens (≥65 years).
- Heart rhythm was determined in a blinded way independent from any electrocardiogram recorded by expert rating. We found an acceptable proportion of false-ratings by the automated algorithm. This has never been shown in such a large prospective AF screening approach and provides higher confidence for the found data.
- Individuals with screen-detected AF (known and newly diagnosed) face an excess mortality risk and risk for hospitalization compared to subjects with normal heart rhythm while screening.
- With our thoroughly collected data, we provide the indispensable input for the planning of upcoming randomized controlled trials.

Terminology

screen-detected AF	AF detected by the automated, 1-min single-lead ECG (SL-ECG)
known AF	Participants reporting a history of AF, independent of automated SL-ECG finding
new AF	Participants without a history of AF and diagnosis of screen-detected AF
no AF	Participants without a history of AF, nor screen-detected AF

screening.[4–8] Recently available smartphones, hand-held, or wearable devices provided promising results as consumer-led or healthcare provider driven AF screening tool.[8] Therefore, the number of subjects with screen-detected AF outside of professional medical contact is expected to increase over the next years.[9] However, the prognosis of newly detected AF has been inferred from studies of incidentally detected AF registries,[10] retrospective studies,[11] or from the detection of subclinical AF using continuous recordings from implanted devices or patches.[12] There have been no studies to date to determine the prognosis of subjects with newly diagnosed AF in a prospective population-based single time point screening approach outside a primary medical contact. For population-based screening, community pharmacies provide easy access throughout rural and urban areas all over the world, and in western societies, 90% of the general population visits community pharmacies at least once per year.[13]

We performed a pharmacy-based, automated, 1-min single-lead electrocardiogram (SL-ECG) AF screening study in elderly citizens. Our primary objective was to determine the prevalence of AF in elderly pharmacy customers in a single time point, 1 min, hand-held SL-ECG screening approach. The secondary objective was to determine the incidence of clinical endpoints (mortality and morbidity) in those with newly detected AF compared to no AF after 1 year of follow-up.

Methods

Study population

In this pharmacy-based AF screening study, all individuals aged ≥65 years were invited to participate when entering a pharmacy in the region of Aachen, Germany. The 4-week screening period was performed in January and February 2017 in 90 pharmacies.

Written informed consent was obtained from all participants in the pharmacy. The study was approved by the ethics review board of the University Hospital RWTH Aachen (Registration number: EK306/16, date: 25 October 2016; Clinical trials gov.: NCT 03004859). The study met the ethical principles of the Declaration of Helsinki, the guidelines of Good Clinical Practice, and current legal requirements.

Study design

After informed consent, a brief, self-reported medical history was taken, followed by a 1-min ECG recording by trained pharmacy staff using a hand-held, SL-ECG device (MyDiagnostick®; Applied Biomedical Systems BV, Maastricht, the Netherlands)[14] with automated heart rhythm analysis. The device employed in our study records a 1-min ECG tracing (Supplementary material online, *Figure S1*). Subjects were allocated to a specific protocol depending whether the automated SL-ECG device found AF or not and followed up for 1 year (*Figures 1* and *2*, Supplementary material online, *Figure S2*).

Definition and validation of atrial fibrillation

For primary outcome analysis, AF detected by the automated, 1-min SL-ECG in the pharmacy were considered as screen-detected AF. Patients without AF detection by the automated, 1-min SL-ECG were considered as normal SL-ECG.

In the secondary outcome analysis, all participants were allocated in new groups according to history of AF and automated SL-ECG measurement at the pharmacy measurement. Participants reporting a history of AF were considered as 'known AF' independent of the automated SL-ECG result. Participants without a history of AF and diagnosis of screen-detected AF were allocated to 'new AF'. Participants without a history of AF and no signal of AF in SL-ECG were allocated to the group 'no AF'.

Screen-detected AF identified by the SL-ECG device was validated in a four-level recorded ECG analysis (Supplementary material online, *Figure S3*). Atrial fibrillation was defined as an episode of arrhythmia for at least 30 s in absence of p-waves in the 1-min SL-ECG device recording according to the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement.[15] In 1.1% ($n = 77$), the SL-ECG recording was uninterpretable and was not considered for the sensitivity validation analysis.

Follow-up

Participants with screen-detected AF had a follow-up after 70 (62; 78) days (median; interquartile range) and all participants after 401 (372; 435) days (*Figure 2*, Supplementary material online, *Figure S2*). At both follow-up timepoints (8 weeks and 12 months), data for all-cause mortality, hospitalization for cardiovascular (CV) cause, and health service-related data were collected. No further medical advice was given additional to the information each patient received at the pharmacy measurement.

Follow-up (at 8 weeks and 12 months) was performed by phone-call, printed questionnaire, or personal visit at the discretion of the participant. Furthermore, at 8-week follow-up all data for all patients with screen-detected AF were cross-checked with the treating physician by printed questionnaire or personal visit at the discretion of the physician. In case of hospitalization for CV causes or death of any cause all information was gathered by chart review, printed discharge letter and if applicable, medical records, obituaries, or death certificates. Hospitalization for CV cause

Figure 1 Study design.
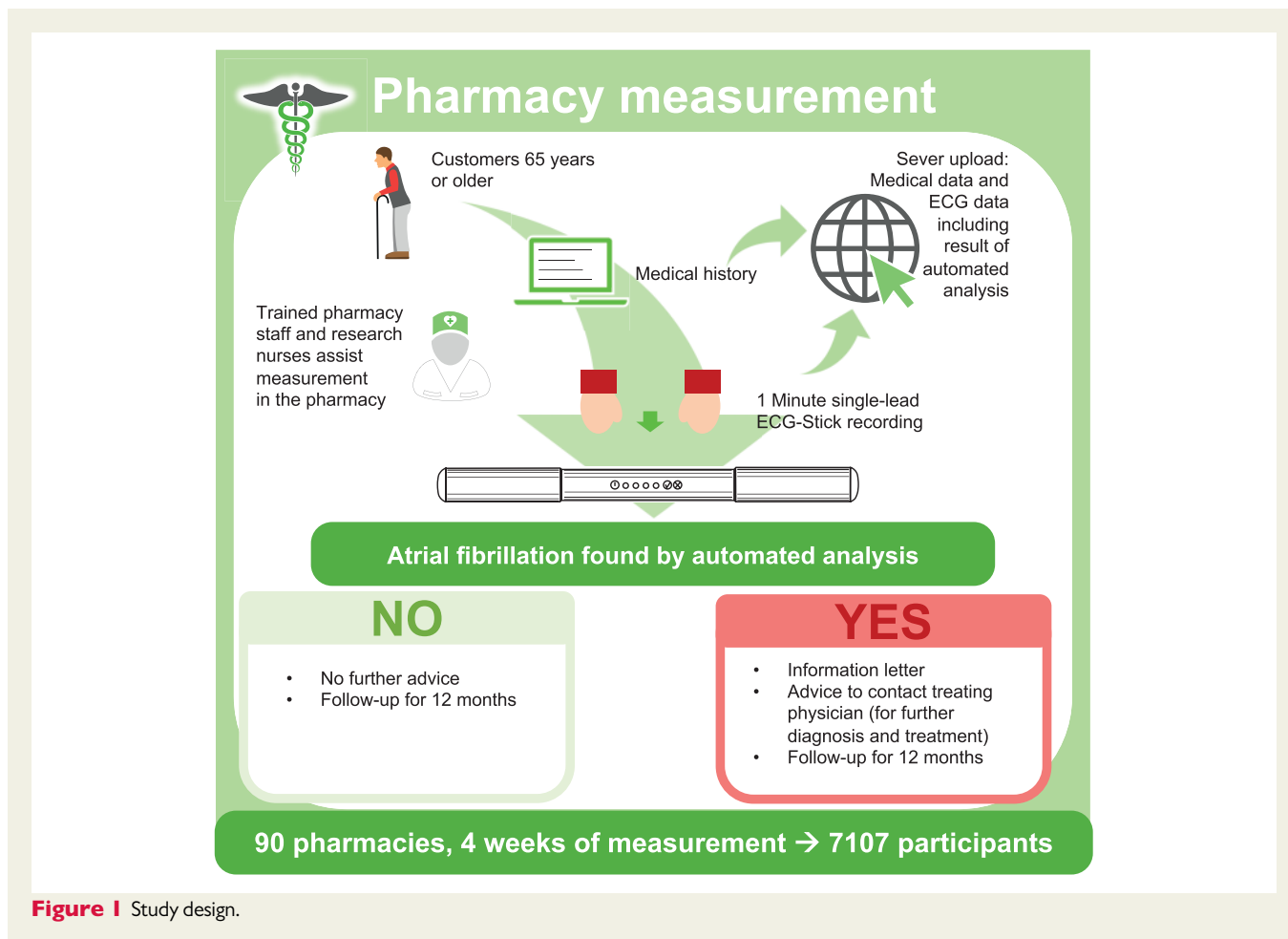
was defined as any situation which leads to hospital admission and primarily originates from the heart or related vascular system which includes but is not restricted to ischaemic, arrhythmic, heart failure, and thrombo-embolic events.

Statistical analysis

Baseline characteristics of participants were tabulated using standard descriptive statistics for continuous and categorical data. Kaplan–Meier survival estimates were plotted for time to death and cumulative incidences for time to hospitalization. Cox proportional-hazards models were used to estimate hazard ratios (HRs) for time to death from any cause and time to hospitalization for CV causes between subjects with or without screen-detected AF. Subjects with missing follow-up data were excluded from the main analysis (Supplementary material online, *Figure S4*). The proportional hazards assumption was graphically checked using the log-minus-log transformation of the survival curve. Multivariable models included the following dichotomous independent variables: history of congestive heart failure, hypertension, diabetes, vascular disease, stroke/TIA, as well as age >75 years and male sex. Non-significant variables ($P \geq 0.05$) were removed from the models presented (*Table 3*, Supplementary material online, *Tables S2 and S3*).

In order to evaluate the robustness of the main analysis, sensitivity analyses were performed assuming constant failure rates for subjects with missing follow-up (Supplementary material online, *Tables S4 and S5*). Estimates were calculated from 1000 imputations in each scenario. To check the possible influence of ascertainment bias, additional analysis using follow-up information only from the 12-month follow-up visits was

also performed (Supplementary material online, *Tables S6 and S7*). Analyses were carried out using R version 3.3.2. (www.R-project.org). Additional packages 'survival' and 'plyr' were used.

Role of funding source

Results

Baseline characteristics

During the screening period of 4 weeks, 7107 participants with an automated SL-ECG analysis were enrolled in the study. Mean age of participants was 74 ± 5.9 years with 58% women. Mean CHA_2DS_2-VASc score was 3.3 ± 1.4 and 6% reported a therapy with OACs. In total, 683 (9.6%) of all subjects reported a history of AF, but only 44% of these reported taking OAC. Overall, automated SL-ECG analyses revealed screen-detected AF in 432 (6.1%) participants (*Figure 2*) with 176 of them reporting a history of AF, thus leading to newly diagnosed AF in 256 (3.6%) subjects by single time point pharmacy-based screening. Compared to participants with a normal signal in the automated SL-ECG analysis, subjects with screen-detected AF were older (77 ± 6.2 vs. 74 ± 5.8 years), reported more often a history of heart failure
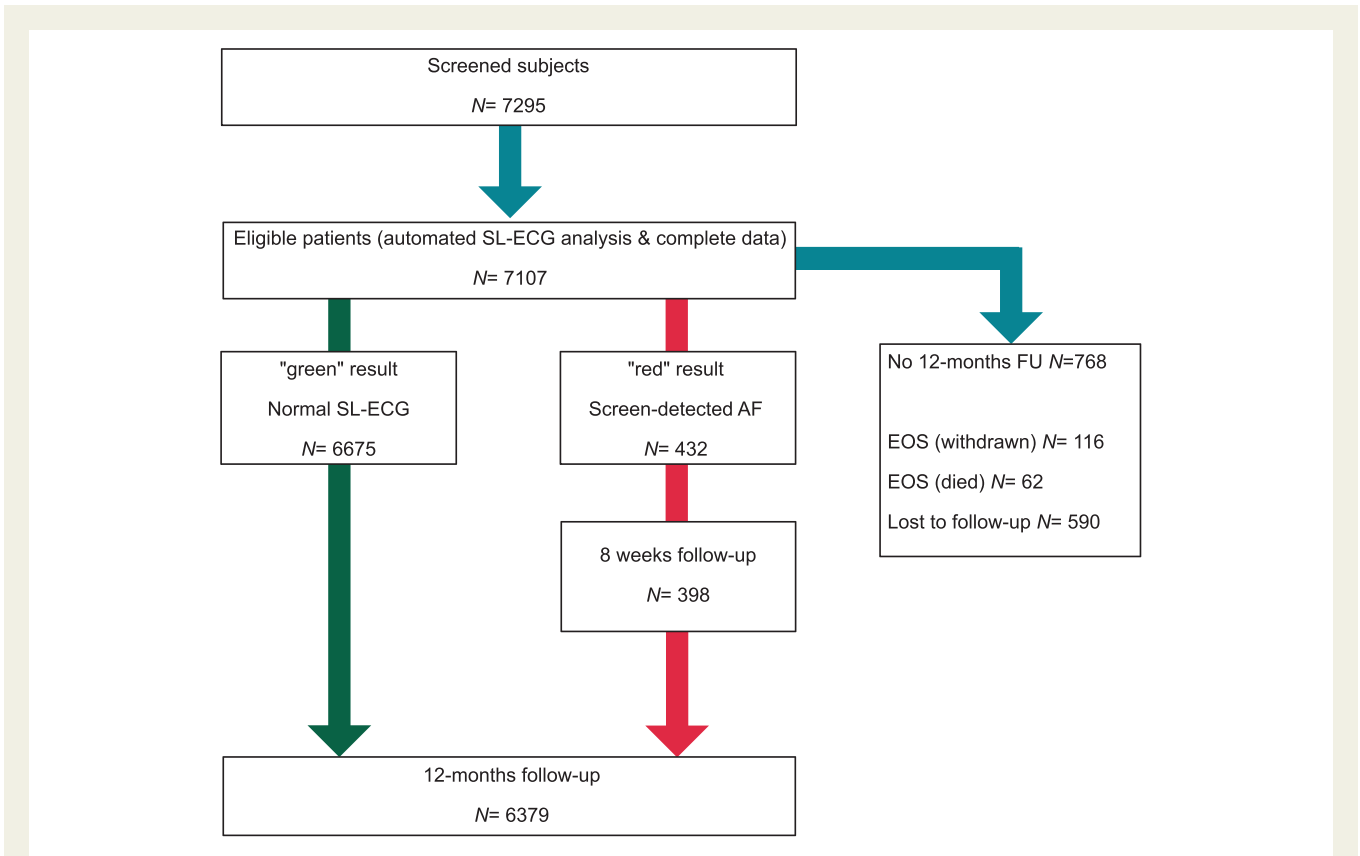
Figure 2 Flow chart of participants in the study. A total of 7295 subjects were screened in the study. We found 7107 patients eligible to participate in the study with correct age, automated SL-ECG analyses, and completed self-reported baseline characteristics. All subjects with screen-detected AF were contacted 8 weeks after index measurement. All participants were contacted after at least 12 months to obtain detailed medical information. The 8-week and 12-month follow-up consist of a telephone questionnaire in which information on medical history, AF and cardiovascular-related events after the pharmacy measurement were obtained (Supplementary material online, *Figure S2*). In case the participants could not be reached, could not answer, or in case of patient death all information were obtained from treating physicians and first degree relatives. All fatality cases were confirmed by treating physicians, medical records, first degree relatives, obituaries, and death certificates. AF, atrial fibrillation; FU, follow-up; EOS, end of study.

(13% vs. 4%) or stroke/TIA (13% vs. 6%), and had a higher CHA$_2$DS$_2$-VASc score (3.6 ± 1.5 vs. 3.3 ± 1.4). Baseline characteristics are shown in *Table 1*.

Electrocardiogram validation

All ECGs were evaluated and validated as described above. Expert ECG evaluation identified AF in 5% (n = 367) of all participants. Following expert validation, there were 76 false-negative and 70 false-positive results in automated SL-ECG analyses.

Follow-up based on results of automated SL-ECG analyses

Long-term follow-up was achieved in 6379 (90%) of the 7107 enrolled participants. Among these, 62 deaths (0.9%) occurred during a median follow-up of 401 (372; 435) days, with 52 deaths in the 6129 subjects without AF in the automated SL-ECG analysis (0.8%) and 10 deaths in the 432 participants screen-detected AF (2.3%). Compared with participants without AF, subjects with screen-detected AF had a significantly higher mortality risk during 1-year follow-up with an HR

of 2.94 [95% confidence interval (CI) 1.49–5.78; P = 0.002] (*Figure 3A*).

During follow-up, 390 participants were hospitalized at least once for CV causes. Incidence of hospitalization was 5.5% in participants with a normal SL-ECG and 10.6% in subjects with AF at pharmacy screening. Compared to participants with a normal SL-ECG, those with screen-detected AF exhibited an HR for CV hospitalization for 2.08 (95% CI 1.52–2.84; P < 0.001) (*Figure 3B*). Sensitivity analyses using expert validated SL-ECGs revealed similar results (Supplementary material online, *Figure S5*). The incidence of stroke was low in both groups with 0.4% in subjects with a normal SL-ECG and 0.7% in participants with screen-detected AF.

Follow-up based on automated SL-ECG analyses and history of atrial fibrillation at baseline

A total of 683 participants reported a history of AF at study entry; in 26% (176/683), the ECG device identified ongoing AF, while 507 participants had a normal SL-ECG. All participants were allocated to

Table 1 Baseline characteristics of study participants by pharmacy-based AF-screening

	Total (*n* = 7107)	SL-ECG normal (*n* = 6675)	Screen-detected AF (*n* = 432)
Age (years), mean ± SD	74 ± 5.9	74 ± 5.8	77 ± 6.2
Female sex, *n* (%)	4130 (58%)	3943 (59%)	187 (43%)
BMI (kg/m^2), mean ± SD	27 ± 4.7	27 ± 4.7	26 ± 4.7
Congestive heart failure, *n* (%)	338 (5%)	283 (4%)	55 (13%)
Hypertension, *n* (%)	4184 (59%)	3897 (58%)	287 (66%)
Diabetes mellitus, *n* (%)	952 (13%)	888 (13%)	64 (15%)
Previous stroke/TIA, *n* (%)	465 (7%)	409 (6%)	56 (13%)
Vascular disease, *n* (%)	881 (12%)	808 (12%)	73 (17%)
CHA_2DS_2-VASc score, mean ± SD	3.3 ± 1.4	3.3 ± 1.4	3.6 ± 1.5
OAC treatment, *n* (%)	447 (6%)	292 (4%)	155 (36%)

BMI, body mass index; OAC, oral anticoagulation; SD, standard deviation.

three groups based on the reported history of AF and the automated SL-ECG results (known AF, new AF, or no AF). Subjects with known or new AF were older, had a higher CHA_2DS_2-VASc score and were more often treated with OAC compared to subjects in the no AF group (Supplementary material online, *Table S1*).

Compared with subjects without a history of AF and a normal SL-ECG (no AF group), participants with newly diagnosed AF had a significantly higher mortality risk with an HR of 2.64 (95% CI 1.05–6.66; *P* = 0.04) during follow-up. Similarly, subjects with known AF exhibited an elevated risk of death compared to subjects without AF (HR 2.68; 95% CI 1.44–4.97; *P* = 0.002). In addition, the risk of hospitalization for CV causes was significantly higher in participants with new AF (HR 1.94; 95% CI 1.25–2.99; *P* = 0.003) or known AF (HR 2.92; 95% CI 2.29–3.72; *P* < 0.001) compared to subjects without AF. Risk of death or hospitalization did not significantly differ between subjects with new or known AF. Kaplan–Meier curves for death and hospitalization are shown in *Figures 3C* and *D*.

Results of univariable estimates of HRs for death and hospitalization are shown in *Table 2*. After adjustment for significant factors in a multivariable analysis, screen-detected AF remained a significant predictor of death (HR 2.17; 95% CI 1.09–4.29; *P* = 0.03, adjusted for: age >75 years, diabetes mellitus, and male gender) or CV hospitalization (HR 1.61; 95% CI 1.17–2.22; *P* = 0.004, adjusted for: congestive heart failure, age >75 years, vascular disease, male gender) compared to subjects with a normal SL-ECG (*Table 3*). In addition, multivariable models including differing covariates indicate that the presence of AF (newly detected by screening or known) at study entry remained a significant predictor of both, death and hospitalization compared with subjects without AF (Supplementary material online, *Tables* S2 *and S3*). Sensitivity analyses demonstrated only partial attenuation of association estimates thus confirming the robustness of the data (Supplementary material online, *Tables S4–S7*). The respective incident rates for death and hospitalization are shown in Supplementary material online, *Table S8* .

Discussion

This large-scale pharmacy-based screening study in elderly subjects demonstrates that a single time point, hand-held, automated, 1-min

SL-ECG can robustly identify subjects with unknown AF who face an increased 1-year risk of all-cause mortality and CV hospitalization. To our knowledge, this is the first AF screening study reporting not only prevalence of newly diagnosed AF but also providing long-term data on mortality and hospitalization in an elderly population of 7107 pharmacy customers.

Our study enrolled subjects ≥65 years of age. The rate of 3.6% of newly diagnosed AF in our study needs to be compared with other AF screening studies using a single or multiple time point approach. In a systematic review, Lowres *et al.*[7] reported a rate of 1.4% individuals with newly diagnosed AF in 18 189 subjects ≥65 years of age using single time point ECG, or pulse palpation followed by ECG in those with an irregular pulse. Perez *et al.*[8] reported a yield of 3.1.% for subjects 65 years or older in a large-scale longitudinal assessment for AF in 419 297 participants. Chan and Choy[6] found a prevalence of 0.8% in adults above the age of 18 years, increasing up to 5% in subjects older than 80 years employing a smart-phone based single time point SL-ECG. Thus, the rate of new AF in our study ranges at the upper boundary of reported prevalences of newly detected AF for population-based screening.

The reported performance of available SL-ECG devices for automated AF detection is often based on retrospective or super-selected cohorts with a high prevalence of AF.[14] These approaches potentially yield a too high sensitivity and may not reflect prospective performance of current AF detection technology. To identify a false automated heart rhythm annotation we performed ECG expert validation of heart rhythm of any recorded SL-ECG. Concerning automated AF detection, the utilized ECG-stick performed favourably compared with other prospective studies.[16,17] As we report data of one of the biggest validated prospective cohorts so far, our rate of 18% (*N* = 76) false-negatives and 1% false-positives (*N* = 70) may allow higher confidence in expected frequency for population-based approaches.

The most surprising finding in our study is the fact that a single time point, pharmacy-based, automated, 1-min SL-ECG AF screening identifies elderly subjects with an excess mortality risk over the next year. Patients with identified AF are older and have more comorbidities. But even after multiple adjustment for various risk factors (including congestive heart failure, hypertension, age > 75, diabetes
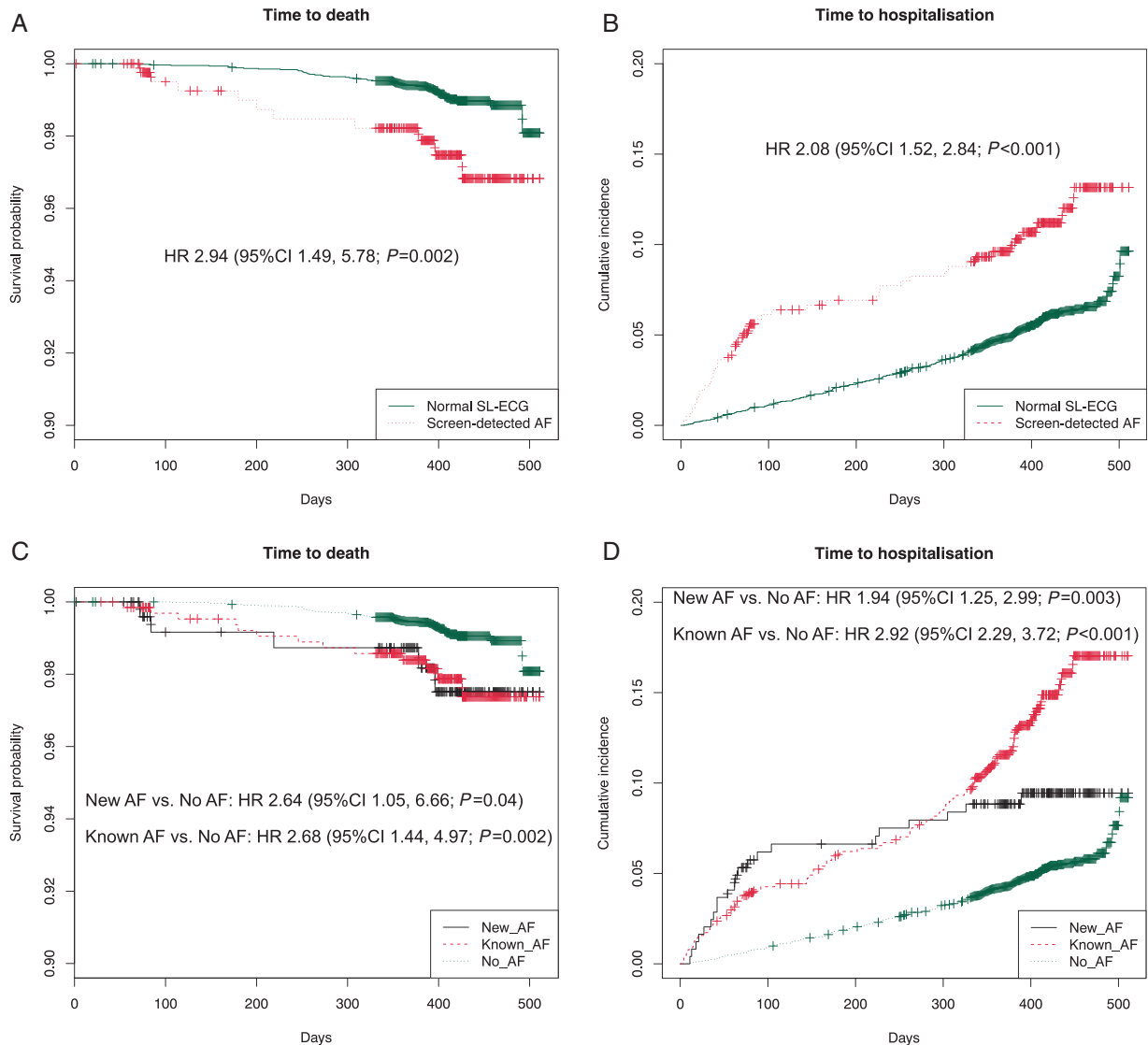
Figure 3 One year outcome of subjects with and without atrial fibrillation. (*A* and *B*) Time to death or hospitalization in participants with screen-detected AF (red line) vs. participants with a normal SL-ECG (green line). (*A*) Kaplan–Meier curves for survival. (*B*) Cumulative incidences of hospitalization for cardiovascular causes. For time to death 6552 subjects with 62 events were analysed. For time to hospitalization 6504 subjects with 390 events were analysed. (*C* and *D*) Time to death or hospitalization in participants with no AF (green line), newly detected AF (black line), as well as known AF (red line) based on history of AF at baseline and results of the automated SL-ECG analysis. (*C*) Kaplan–Meier curves for survival. (*D*) Cumulative incidences for hospitalization for cardiovascular causes. For time to death 6552 subjects with 62 events were analysed. For time to hospitalization 6504 subjects with 390 events were analysed.

mellitus, peripheral artery disease, history of stroke/TIA, gender, and OAC treatment at baseline), AF detected by the automated SL-ECG algorithm is associated with a two- to three-fold increased risk of death. Moreover, our sensitivity analysis after expert validation of all SL-ECGs corroborated this finding.

None of the population-based AF screening studies published so far has reported data on the prognosis of subjects with newly diagnosed AF. Results derived from healthcare records[18] or registries[10,11] showed an increased overall mortality risk in patients with newly diagnosed asymptomatic AF but there are no previous data in a population with screen-detected new AF. Thus, our study extends the

current knowledge by suggesting that detection of AF in a single time point, 1-min SL-ECG screening test can identify patients with a high mortality risk over the next year. Since our data cannot provide any detailed information on therapeutic measures after AF diagnosis, future studies are needed to evaluate appropriate diagnostic or therapeutic approaches to limit the risk in this patient group ideally in a randomized controlled approach. Interestingly, there was no difference in the risk of death or hospitalization for CV causes between participants with new or known AF even though those with known AF had a higher prevalence of congestive heart failure, previous stroke/TIA, vascular disease, as well as a higher CHA_2DS_2-VASc

Table 2 Univariable estimates of hazard ratio for death and hospitalization

	HR	95% CI low	95% CI high	*P*-value
Hazard ratio for death of any cause				
Screen-detecded AF[a]	2.94	1.49	5.78	0.002
New AF[b,c]	2.64	1.05	6.66	0.04
Known AF[b,c]	2.68	1.44	4.97	0.002
Known or new AF[c]	2.67	1.54	4.61	<0.001
Congestive heart failure	1.79	0.72	4.46	0.213
Hypertension	1.48	0.87	2.53	0.146
Age >75 years	2.96	1.71	5.12	<0.001
Diabetes mellitus	2.91	1.70	5.12	<0.001
Vascular disease	1.10	0.52	2.32	0.798
Previous stroke/TIA	1.81	0.82	3.96	0.141
Gender male	2.71	1.60	4.59	<0.001
Hazard ratio for hospitalization for cardiovascular cause				
Screen-detected AF[a]	2.08	1.52	2.84	<0.001
New AF[b,c]	1.94	1.25	2.99	0.003
Known AF[b,c]	2.92	2.29	3.72	<0.001
Known or new AF[c]	2.65	2.12	3.30	<0.001
Congestive heart failure	2.33	1.67	3.24	<0.001
Hypertension	1.32	1.07	1.63	0.009
Age >75 years	1.68	1.38	2.06	<0.001
Diabetes mellitus	1.21	0.92	1.59	0.177
Vascular disease	2.08	1.63	2.65	<0.001
Previous stroke/TIA	1.68	1.22	2.33	0.002
Gender male	1.67	1.37	2.04	<0.001

CI, confidence interval; HR, hazard ratio; TIA, transient ischaemic attack.
[a]Automated SL-ECG analysis; reference category is 'Normal SL-ECG'.
[b]Estimates are calculated from the same model.
[c]Reference category is 'No AF'.

Table 3 Multivariable estimates of hazard ratio for death and hospitalization

	HR	95% CI low	95% CI high	*P*-value
Hazard ratio for death of any cause				
Screen-detected AF[a,b]	2.17	1.09	4.29	0.03
New AF[b,c,d]	2.11	0.83	5.35	0.12
Known AF[b,c,d]	2.00	1.07	3.74	0.03
Known or new AF[b,d]	2.03	1.17	3.54	0.01
Hazard ratio for hospitalization for cardiovascular cause				
Screen-detected AF[a,e]	1.61	1.17	2.22	0.004
New AF[c,d,e]	1.67	1.08	2.59	0.02
Known AF[c,d,e]	2.24	1.74	2.88	<0.001
Known or new AF[d,e]	2.09	1.65	2.63	<0.001

CI, confidence interval; HR, hazard ratio.
[a]Automated SL-ECG analysis; reference category is 'Normal SL-ECG'.
[b]Adjusted for age >75, diabetes, gender male.
[c]Estimates are calculated from the same model.
[d]Reference category is 'No AF'.
[e]Adjusted for congestive HF, age >75, vascular disease, gender male.

score. This lack of a difference in risk between participants with new or known AF could potentially be explained by a higher proportion of paroxysmal AF cases in the group with known history of AF, because the probability of paroxysmal AF detection might be low in single time point measurement, while the new AF cases for the same reason were likely to be mostly persistent AF.

The overall OAC treatment rate in known AF was relatively low (44%), whilst the reverse held in newly detected AF (11%). For both patients groups, screening identified 'actionable AF' in a significant number of individuals. The relatively high rate of anticoagulation in the group with newly detected AF may indicate underreporting of already known AF by the study participants, or the presence of other OAC indications like venous thromboembolism or artificial heart valves. The latter was not recorded and is an inherent limitation of a pragmatic trial in pharmacies. With respect to stroke, our data show a numerical increase in the hospitalization rate for stroke in patients with screen-detected AF but the number of events is too low to draw firm conclusions.

Limitations and strengths of our study

Our study has some limitations. First, our study is a population-based AF screening approach in local pharmacies which may present a selection bias. In addition, the study-design does not include a control group—a limitation that needs to be taken into consideration when interpreting the data.

Nevertheless, previous studies used a comparable screening settings[19,20] showing that this approach is feasible, cost-effective, and allows to be easily replicated in any community-pharmacy worldwide. Second, follow-up was available in 90% of all subjects potentially causing a reporting bias for the outcomes analysed. However, our follow-up proportion ranges in upper region of reported pragmatic studies and sensitivity analyses assuming no relationship between SL-ECG results and outcome among subjects with missing data, and suggested only partial attenuation of association estimates. Moreover, the results are stable in various sensitivity analyses as well as after various multivariate adjudication. Third, ascertainment bias due to differential efforts to follow-up subjects may have affected the results, but the additional sensitivity analyses using only 12-month follow-up data, which was collected in the same manner in all subjects, suggest that a substantial bias is unlikely. Fourth, all baseline as well as all outcome data are participant- or relative-reported which may in particular have an impact on the endpoint of hospitalization for CV causes. Still, fatality cases were confirmed by treating physicians, medical records, first degree relatives, obituaries, and death certificates. Finally, our study demonstrates data only on the association of screen-detected new AF with increased mortality but cannot provide further insight into potential mechanisms. Several factors such as frailty, undertreatment, or socio-economic background may contribute to our findings but future work has to elucidate the underlying causes for the increased mortality risk observed.

The strength and novelty of our study is to provide robust prospective data for the first time on relation between screen-detected AF and outcome in a large-scale study. Additionally, we identified by this approach actionable AF for newly diagnosed patients as well as for patients with a history of AF. The outcome data as well as our data on actionable AF could be used for the planning of future studies. Moreover, the screening method used, employing a hand-held

ECG stick with a result available after 1 min, is broadly applicable and very well suited for rapid and cost-effective identification of high-risk patients in public healthcare settings like pharmacies.

Conclusions

Based on our data, the results of this pragmatic large-scale study suggest that a pharmacy-based, automated, 1-min SL-ECG screening in elderly citizens can identify subjects with unknown AF who face an increased risk of mortality and CV hospitalization over the next year.

Supplementary material

Supplementary material is available at *Europace* online.

Data availability

Full access to data (raw and derived) can be granted for reasonable request to the corresponding author.

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