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Electrocardiographic markers of subclinical atrial fibrillation detected by implantable loop recorder: insights from the LOOP Study

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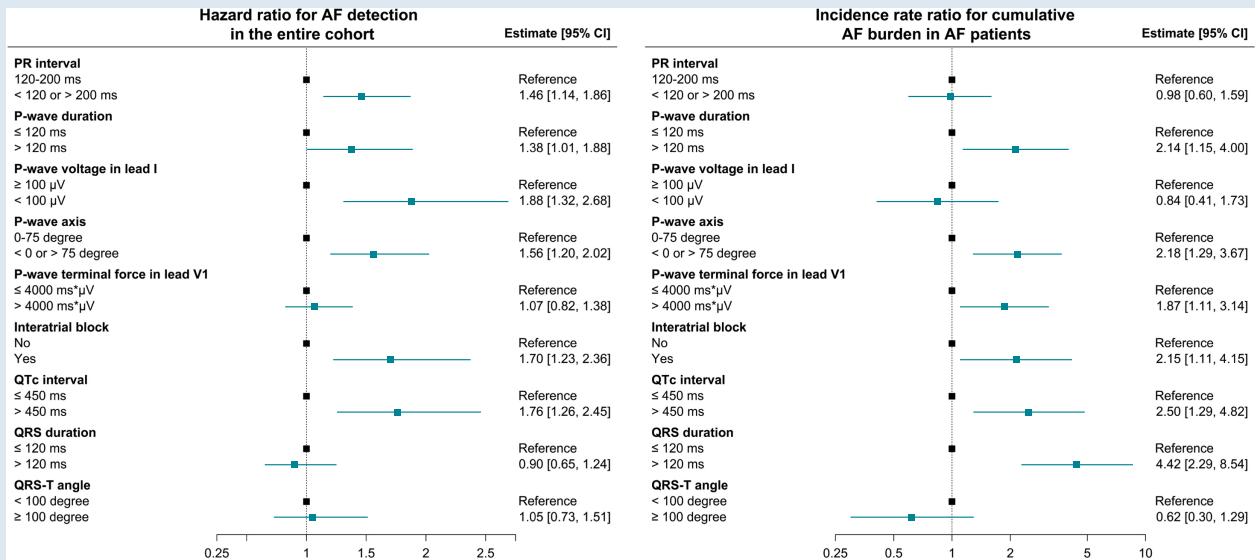|	
Aims	Insights into subclinical atrial fibrillation (AF) development are warranted to inform the strategies of screening and subsequent clinical management upon AF detection. Hence, this study sought to characterize the onset and progression of subclinical AF with respect to 12-lead electrocardiogram (ECG) parameters.
Methods and results	We included AF-naïve individuals aged 70–90 years with additional stroke risk factors who underwent implantable loop recorder (ILR) monitoring in the LOOP Study. Using data from daily ILR recordings and the computerized analysis of baseline ECG, we studied empirically selected ECG parameters for AF detection ($\geq$6 min), cumulative AF burden, long-lasting AF ($\geq$24 h), and AF progression. Of 1370 individuals included, 419 (30.6%) developed AF during follow-up, with a mean cumulative AF burden of 1.5% [95% CI: 1.2–1.8]. Several P-wave-related and ventricular ECG parameters were associated with new-onset AF and with cumulative AF burden in AF patients. P-wave duration (PWD), P-wave terminal force in Lead V_1, and interatrial block (IAB) further demonstrated significant associations with long-lasting AF. Among AF patients, we observed an overall reduction in cumulative AF burden over time (IRR 0.70 [95% CI: 0.51–0.96]), whereas IAB was related to an increased risk of progression to AF $\geq$24 h (HR 1.86 [95% CI: 1.02–3.39]). Further spline analysis also revealed longer PWD to be associated with this progression in AF duration.
Conclusion	We identified several ECG parameters associated with new-onset subclinical AF detected by ILR. Especially PWD and IAB were robustly related to the onset and the burden of AF as well as progression over time.

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Graphical Abstract

Hazard ratio for AF detection in the entire cohort		Estimate [95% CI]
PR interval		
120-200 ms		Reference
< 120 or > 200 ms		1.46 [1.14, 1.86]
P-wave duration		
≤ 120 ms		Reference
> 120 ms		1.38 [1.01, 1.88]
P-wave voltage in lead I		
≥ 100 μV		Reference
< 100 μV		1.88 [1.32, 2.68]
P-wave axis		
0-75 degree		Reference
< 0 or > 75 degree		1.56 [1.20, 2.02]
P-wave terminal force in lead V1		
≤ 4000 ms*μV		Reference
> 4000 ms*μV		1.07 [0.82, 1.38]
Interatrial block		
No		Reference
Yes		1.70 [1.23, 2.36]
QTc interval		
≤ 450 ms		Reference
> 450 ms		1.76 [1.26, 2.45]
QRS duration		
≤ 120 ms		Reference
> 120 ms		0.90 [0.65, 1.24]
QRS-T angle		
< 100 degree		Reference
≥ 100 degree		1.05 [0.73, 1.51]

Incidence rate ratio for cumulative AF burden in AF patients		Estimate [95% CI]
PR interval		
120-200 ms		Reference
< 120 or > 200 ms		0.98 [0.60, 1.59]
P-wave duration		
≤ 120 ms		Reference
> 120 ms		2.14 [1.15, 4.00]
P-wave voltage in lead I		
≥ 100 μV		Reference
< 100 μV		0.84 [0.41, 1.73]
P-wave axis		
0-75 degree		Reference
< 0 or > 75 degree		2.18 [1.29, 3.67]
P-wave terminal force in lead V1		
≤ 4000 ms*μV		Reference
> 4000 ms*μV		1.87 [1.11, 3.14]
Interatrial block		
No		Reference
Yes		2.15 [1.11, 4.15]
QTc interval		
≤ 450 ms		Reference
> 450 ms		2.50 [1.29, 4.82]
QRS duration		
≤ 120 ms		Reference
> 120 ms		4.42 [2.29, 8.54]
QRS-T angle		
< 100 degree		Reference
≥ 100 degree		0.62 [0.30, 1.29]

Keywords   Atrial fibrillation • Electrocardiography • *P*-wave • Cardiac arrhythmias • Stroke

What's new?

- Both *P*-wave-related and ventricular parameters from 12-lead electrocardiogram were associated with the cumulative burden of new-onset atrial fibrillation (AF) detected by long-term continuous monitoring.
- Individuals with shorter and longer *P*-wave duration (PWD), with greater *P*-wave terminal force in Lead V_1, and with interatrial block (IAB) were at increased risk of long-lasting AF.
- Individuals with device-detected AF tended to experience an overall reduction in cumulative AF burden over time.
- Longer PWD and IAB were associated with progression to longer AF duration.

Introduction

Atrial fibrillation (AF) is a well-known and treatable risk factor for stroke but often remains asymptomatic and thus undiagnosed.[1–4] This has stimulated a substantial interest in screening for subclinical AF. Mounting evidence further indicates that a greater burden of subclinical AF is associated with increased stroke risk.[1–5] Therefore, insights into the onset and the progression of subclinical AF are warranted to inform screening strategy and to guide subsequent clinical management.

The pathogenesis of AF is thought to be closely related to structural and functional changes in the atria that are encompassed in a newly proposed entity, the so-called atrial cardiomyopathy.[6] These changes would be reflected in electrical abnormalities and can, therefore, be detected by a standard 12-lead electrocardiogram (ECG). Indeed, various ECG parameters have already been demonstrated to predict clinical AF in large epidemiological studies.[6–17] There is also a growing body of evidence on the applicability of artificial intelligence (AI) algorithm based on sinus rhythm ECGs in AF risk prediction, and a recent study further showed that AI-based risk stratification could help to increase the yield for AF detection by screening.[6,18] However, data on the underlying relationships between ECG parameters and subclinical or screen-detected AF are sparse. In this *post hoc* analysis of the LOOP Study (*Atrial Fibrillation detected by Continuous ECG Monitoring using Implantable Loop Recorder to prevent Stroke in High-risk Individuals*), we aimed to identify 12-lead ECG parameters associated with the onset and progression of subclinical AF detected by long-term continuous monitoring.

Methods

Study design

The LOOP Study was a randomized, controlled trial to investigate continuous AF screening with an implantable loop recorder (ILR; Reveal LINQ, Medtronic). The trial was registered at Clinical-Trials.gov (NCT02036450) and approved by the Regional Scientific Ethics Committee for the Capital Region of Denmark (H-4-2013-025). Oral and written informed consents were obtained from all participants. A detailed description of the trial design and the primary reporting of the LOOP Study have been published previously.[19,20] In brief, AF-naïve individuals aged 70–90 years and with any history of hypertension, diabetes, stroke, or heart failure were randomized to either ILR monitoring or usual care. At baseline, all participants underwent a 12-lead ECG. For ILR participants, continuous ECG monitoring was performed via the device during follow-up and automated remote transmissions were reviewed daily by an experienced physician. Any new-onset ILR-detected AF episode lasting ≥6 min was independently evaluated by at least two senior cardiologists, while subsequent ILR-detected AF ≥24 h was adjudicated by at least one experienced physician.

In the present analysis, we included the LOOP participants with available ILR recordings and with a baseline 12-lead ECG suitable for the measurement of ECG parameters.

Electrocardiogram measurement

All digital 12-lead ECGs were processed by the Marquette 12SL ECG Analysis Program (version 23) to obtain relevant ECG measurements

(see *Supplementary Methods* for more details). Using this analysis program, we excluded the ECGs with non-sinus rhythm or other findings unsuitable for the measurement of ECG parameters, including ectopic atrial rhythm, junctional rhythm, ventricular rhythm, undetermined rhythm, second- and third-degree atrioventricular block, and delta-wave.

We assessed the following ECG parameters as potential AF predictors: PR interval (abnormal interval defined as <120 or >200 ms); P-wave duration (*PWD*, abnormal duration defined as >120 ms); P-wave voltage in Lead I (*PWV*, abnormal voltage defined as <100 µV); P-wave axis (*PWA*, abnormal axis defined as axis deviation outside the range 0–75°); P-wave terminal force in Lead V$_1$ (*PTF*, abnormal terminal force defined as >4000 ms × µV); the presence of interatrial block (*IAB*, defined as PWD ≥120 ms combined with biphasic P-wave in any inferior lead); heart rate-corrected QT (*QTc*) interval (abnormal interval defined as >450 ms); QRS duration (abnormal duration defined as >120 ms); and QRS-T angle (abnormal angle defined as ≥100°).

Outcomes and follow-up

The primary outcome was time to first AF detection (≥6 min). Secondary outcomes were: (i) time to first long-lasting AF episode ≥24 h; (ii) cumulative AF burden—defined as cumulative duration of all ILR-detected AF episodes ≥6 min from the first adjudicated episode, divided by the total monitoring duration; (iii) time from first AF detection to first AF episode ≥24 h; and (iv) progression in cumulative AF burden over time. Cumulative AF burden progression was assessed in the timespan starting from the first adjudicated AF episode to censoring, which was divided into two equal periods. Hence, the progression in cumulative AF burden was estimated by comparing cumulative AF duration in the first half-period with the second half. The study participants were right-censored at end of device service or death, whichever came first.

Statistical analysis

For baseline characteristics, continuous variables are presented as mean with standard deviation (SD), whereas categorical variables are presented as frequency with proportion. The distributions are compared by *t*-test and χ^2 test, respectively.

The risks of AF detection (≥6 min) and AF episode ≥24 h were assessed with the time-to-first-event principle. Crude event rates were calculated with Poisson regression and are presented as events per 100 person-years [95% confidence interval (CI)]. The relative risks were determined in the multivariate, cause-specific Cox regression models accounting for death as competing risk and are presented as hazard ratio (HR) [95% CI]. Additionally, to enhance the statistical power and to provide more flexibility in our analyses, ECG parameters were also evaluated as continuous variables using the restricted cubic spline regression, where HR was estimated with the median value as the reference for each of the relevant parameters. The Cox proportional-hazards assumption was tested with scaled Schoenfeld residuals and no violations were detected.

Crude rates of cumulative AF burden were calculated in the negative binomial regression model using cumulative AF duration (in minutes) as count data and the total monitoring time (in minutes) as offset and are presented as percentage [95% CI]. The relative risks according to the ECG parameters were estimated as incidence rate ratio (IRR) for cumulative AF duration in the multivariate negative binomial model using the total monitoring time (offset) to adjust for interindividual differences in the monitoring duration. Moreover, progression in cumulative AF burden over time was assessed in the multivariate generalized linear mixed model with negative binomial distribution for cumulative AF duration (in minutes) in each half-period as the outcome variable and the corresponding monitoring duration (in minutes) as the offset.

The multivariate models were adjusted for sex, age, baseline comorbidities (including hypertension, diabetes, previous stroke, heart failure, valvular heart disease, ischaemic heart disease, and peripheral artery disease), baseline antiarrhythmic treatment (including beta-blockers and non-dihydropyridine calcium channel blockers), QRS duration, P_{end}-Q interval (only for P-wave parameters except PR interval), and left ventricular hypertrophy (only for ventricular ECG parameters); see *Supplementary Methods* for definitions of these ECG covariates. The generalized linear mixed model was additionally adjusted for time from ILR implantation to the first adjudicated AF episode. The statistical analysis was performed using R (version 4.1.0) and a two-sided *P*-values ≤0.05 defined the statistical significance.

Table 1 Overview of baseline characteristics

	The study population (*n* = 1370)
Male sex (%)	731 (53.4)
Age, years (SD)	74.7 (4.1)
Alcohol consumption, standard units per week (SD)	7.4 (8)
Smoking pack years (SD)	16.7 (22.9)
Body-mass index, kg/m^2 (SD)	27.8 (4.6)
CHA$_2$DS$_2$-VASc score (SD)	3.7 (1.2)
Comorbidities (%)	
Hypertension arterialis	1254 (91.5)
Diabetes mellitus	382 (27.9)
Congestive heart failure	57 (4.2)
Previous stroke	236 (17.2)
Chronic ischaemic heart disease	157 (11.5)
Valvular heart disease	59 (4.3)
Peripheral artery disease	34 (2.5)
Concomitant medications (%)	
Beta-blockers	319 (23.3)
Calcium channel blockers	512 (37.4)
Non-dihydropyridine calcium channel blocker	40 (2.9)
Renin-angiotensin system inhibitors	898 (65.5)
Diuretics	449 (32.8)
Statins	802 (58.5)
Insulins	111 (8.1)
Other antidiabetic drugs	297 (21.7)
ECG parameters	
PR interval, ms (SD)	170.7 (31.7)
P-wave duration, ms (SD)	94.5 (21.8)
P-wave voltage in Lead I, µV (SD)	65.7 (36.1)
P-wave axis, degree (SD)	47.3 (24)
P-wave terminal force in Lead V$_1$, ms × µV (SD)	1813.4 (2248.7)
Interatrial block (%)	91 (6.7)
QTc interval, ms (SD)	421.2 (22.2)
QRS duration, ms (SD)	92.3 (19)
QRS-T angle, degree (SD)	42.4 (35.4)

Interatrial block was defined as *P*-wave duration ≥120 ms combined with the presence of biphasic P-wave (positive–negative) in any inferior lead. QTc interval was estimated using the Framingham formula.
Missing observations: PR interval, *n* = 3; *P*-wave duration, *n* = 4; *P*-wave voltage in Lead I, *n* = 7; *P*-wave axis, *n* = 28, *P*-wave terminal force in Lead V$_1$, *n* = 7; interatrial block, *n* = 7.
Abbreviations: AF, atrial fibrillation; ECG, electrocardiogram; QTc, heart rate-corrected QT interval; SD, standard deviation.

Results

In the LOOP Study, 1420 (94.6%) of the 1501 participants assigned to the ILR group had received an ILR. Among them, 9 (0.6%) were excluded from the present analysis due to un-retrievable ILR recordings and further 41 (2.9%) were excluded due to missing baseline ECG or ECG with findings unsuitable for measurement. The final study
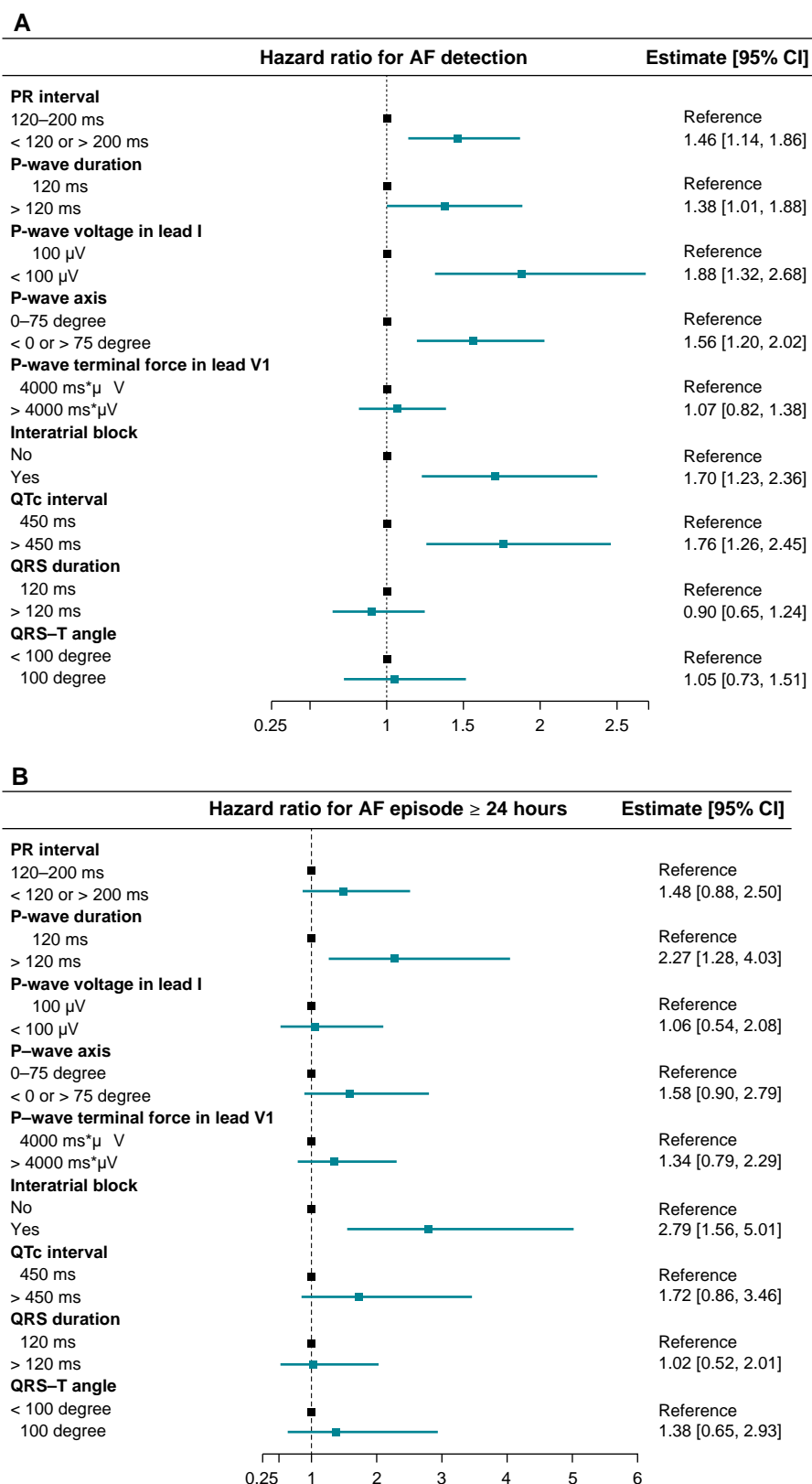
Figure 1 Hazard ratio for detection of any AF and for first AF episode ≥24 h. The figure shows the relative risk of AF detection (*A*) and AF episode ≥24 h (*B*) according to dichotomized ECG parameters. Interatrial block was defined as *P*-wave duration ≥120 ms combined with biphasic (positive–negative) *P*-wave in any inferior lead. QTc interval was estimated using the Framingham formula. Hazard ratios were determined in multivariate Cox models with death as competing risk. Abbreviations: AF, atrial fibrillation; CI, confidence interval; ECG, electrocardiogram; QTc, heart rate-corrected QT interval.

Table 2 AF characteristics according to ECG parameters among 419 AF patients

		Cumulative AF burden, % [95% CI]	Number of AF episodes (SD)	Mean episode duration, hour (SD)	Maximum episode duration, hour (SD)	Any episode ≥24 h (%)
PR interval	120–200 ms (n = 332)	1.5 [1.2–1.9]	80.5 (209.3)	6.9 (21.3)	72.4 (321.7)	63 (19.0)
	<120 or >200 ms (n = 85)	1.6 [1.0–2.4]	118.5 (167.8)	5.6 (18.6)	54.4 (248.8)	17 (20.0)
P-wave duration	≤120 ms (n = 368)	1.4 [1.1–1.7]	82.9 (190.1)	5.8 (19.3)	64.2 (309.2)	65 (17.7)
	>120 ms (n = 48)	2.4 [1.4–4.4]	130.8 (276.6)	13.2 (29)	105 (303.2)	15 (31.2)
P-wave voltage in Lead I	≥100 μV (n = 34)	2.2 [1.1–4.5]	51.1 (95)	9.4 (20.5)	132.9 (465)	9 (26.5)
	<100 μV (n = 380)	1.5 [1.2–1.8]	90.9 (208.1)	6.5 (20.8)	63.5 (291.4)	71 (18.7)
P-wave axis	0–75° (n = 332)	1.5 [1.2–1.9]	77.4 (192.3)	7.1 (22.4)	63.8 (287)	63 (19.0)
	<0° or >75° (n = 77)	1.8 [1.1–2.8]	142.2 (242.9)	5.5 (12.6)	94.6 (399.4)	15 (19.5)
P-wave terminal force in Lead V$_1$	≤4000 ms × μV (n = 340)	1.5 [1.2–1.9]	92.7 (214.7)	6.2 (20.4)	58.6 (268.5)	62 (18.2)
	>4000 ms × μV (n = 74)	1.7 [1.0–2.7]	64.3 (122.2)	8.8 (22.6)	118.1 (450.4)	18 (24.3)
IAB	No (n = 374)	1.4 [1.1–1.7]	83.2 (189.2)	5.9 (19.3)	64 (306.9)	66 (17.6)
	Yes (n = 42)	2.6 [1.4–4.8]	135.3 (291.9)	13.9 (30.1)	112.1 (322.2)	14 (33.3)
QTc interval	≤450 ms (n = 367)	1.4 [1.1–1.7]	75.8 (163)	6.4 (19.9)	67.5 (311.3)	71 (19.3)
	>450 ms (n = 52)	2.3 [1.3–4.0]	188.4 (375.6)	8.3 (25.5)	75.1 (280.7)	9 (17.3)
QRS duration	≤120 ms (n = 376)	1.4 [1.1–1.7]	90.3 (211.4)	6.4 (20.1)	62.6 (298.7)	73 (19.4)
	>120 ms (n = 43)	2.6 [1.4–4.8]	84.8 (132.5)	8.6 (25.5)	119.3 (374.5)	7 (16.3)
QRS-T angle	<100° (n = 383)	1.6 [1.3–1.9]	90.9 (209)	6.8 (21.3)	69.2 (312.7)	73 (19.1)
	≥100° (n = 36)	1 [0.5–1.9]	77.7 (151.1)	5.3 (13)	59.9 (245.9)	7 (19.4)

Crude cumulative AF burden was calculated as cumulative AF duration in the negative binomial model with the total monitoring duration as offset. IAB was defined as P-wave duration ≥120 ms combined with the presence of biphasic P-wave (positive–negative) in any inferior lead. QTc interval was estimated using the Framingham formula.
Missing observations: PR interval, n = 2; P-wave duration, n = 3; P-wave voltage in Lead I, n = 5; P-wave axis, n = 10, P-wave terminal force in Lead V$_1$, n = 5; IAB, n = 3.
Abbreviations: AF, atrial fibrillation; CI, confidence interval; ECG, electrocardiogram; IAB, interatrial block; QTc, heart rate-corrected QT interval; SD, standard deviation.

population consisted of 1370 participants, with a mean ILR monitoring time of 3.19 years (SD, 0.52). *Table 1* summarizes the baseline characteristics. The study participants had a mean age of 74.7 (SD, 4.1) years and 53.4% of them were male. For baseline medications, a total of 354 (25.8%) participants received treatment with either beta-blockers or non-dihydropyridine calcium channel blockers. IAB was observed in 91 (6.7%) participants: 67 (6.4%) among the participants without beta-blocker treatment vs. 24 (7.5%) among those treated with beta-blockers. During follow-up, 419 (30.6%) developed AF and 14 (1.0%) died. The baseline prevalence of IAB was 10.1% among the participants who developed AF during follow-up and 5.2% among those who did not.

The risk of atrial fibrillation

The time-to-first-event analysis revealed that abnormal PR interval, PWD, PWV, PWA, and QTc interval as well as the presence of IAB were associated with an increased risk of AF detection (HR 1.46 [1.14–1.86], 1.38 [1.01–1.88], 1.88 [1.32–2.68], 1.56 [1.20–2.02], 1.76 [1.26–2.45], and 1.70 [1.23–2.36], respectively; *Figure 1A*). For long-lasting AF, 83 participants experienced AF episodes ≥24 h during follow-up. Only abnormal PWD and IAB were significantly associated with the risk of AF episodes ≥24 h (HR 2.27 [1.28–4.03] and 2.79 [1.56–5.01], respectively; *Figure 1B*). Event rates and HRs according to dichotomized ECG parameters are listed in Supplementary material online, *Table S1*.

Supplementary material online, *Figures S1 and S2* illustrate the restricted cubic spline analysis assessing ECG parameters as continuous variables. For AF detection, the risk appeared to be higher in patients with longer PR interval, lower PWV, and longer QTc interval. PWD demonstrated a U-shaped relationship with AF detection and AF episode ≥24 h, where the incidences were increased both for shorter and longer durations. Albeit no significant association with AF risk, greater PTF did confer a higher risk of AF duration ≥24 h. Further exploration with a cut-off of PTF >6000 ms × μV revealed a remarkably increased risk of AF episode ≥24 h, as indicated by HR 2.28 [1.11–4.67].

Cumulative atrial fibrillation burden among atrial fibrillation patients

Among the 419 patients who developed AF during follow-up, the total number of AF episodes was 38,579, with a mean cumulative AF burden of 1.5% [1.2–1.8%]. The average time from ILR implantation to the first adjudicated AF episode was 1.01 (SD, 0.98) years. *Table 2* presents AF characteristics according to ECG parameters. Among the ECG parameters assessed in the present study, abnormal PWD, PWA, PTF, QTc interval, and QRS duration as well as the presence of IAB were related to a significant increase in cumulative AF burden (*Figure 2*).

Atrial fibrillation progression among atrial fibrillation patients

Among 419 AF patients, an overall reduction in cumulative AF burden was seen in the second half-period compared with the first half of the timespan from the first adjudicated AF episode to censoring (IRR 0.70 [0.51–0.96]). No significant interactions were detected between the ECG parameters and the development in cumulative AF burden over time (see Supplementary material online, *Table S2*).
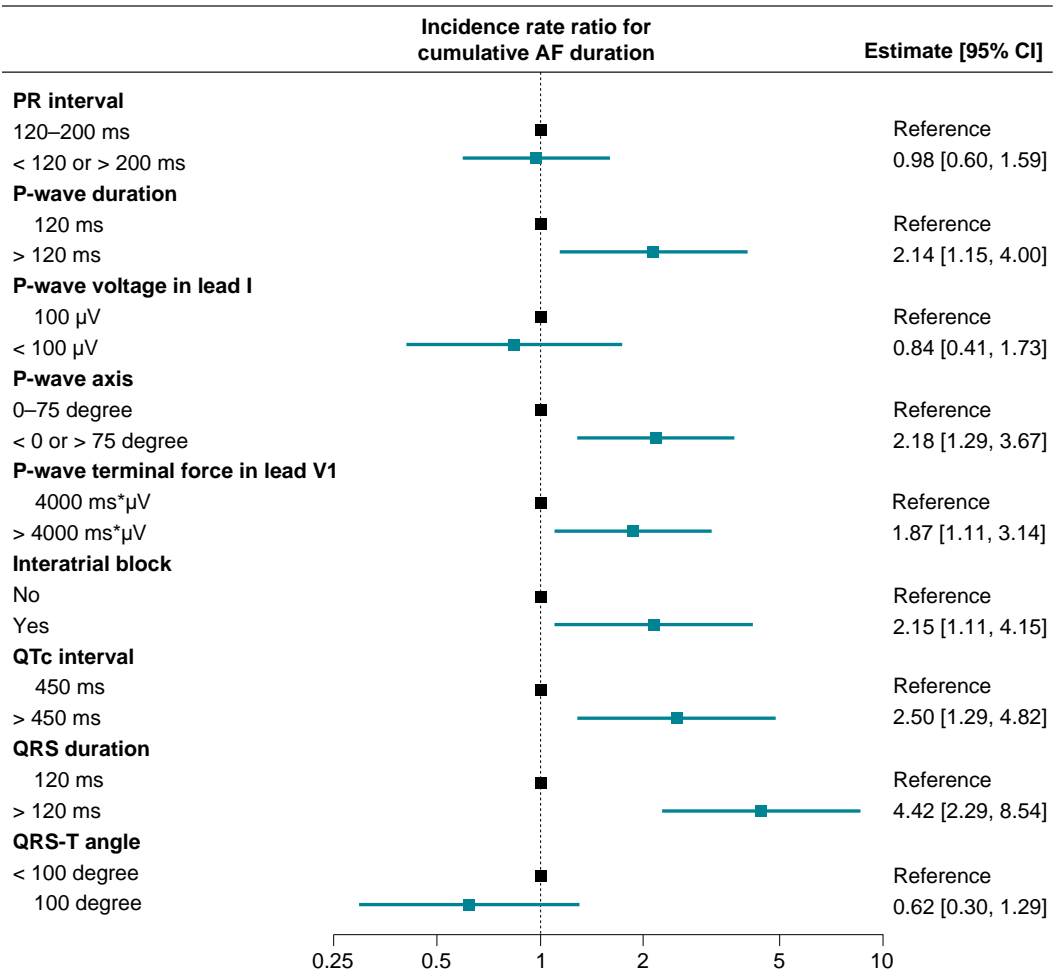
Figure 2 Incidence rate ratio for cumulative AF burden among 419 AF patients. The figure shows the incidence rate ratio for cumulative AF burden according to dichotomized ECG parameters among 419 patients who developed AF. The interatrial block was defined as *P*-wave duration ≥120 ms combined with biphasic (positive–negative) *P*-wave in any inferior lead. QTc interval was estimated using the Framingham formula. Incidence rate ratios were determined in multivariate negative binomial regression models. Abbreviations: AF, atrial fibrillation; CI, confidence interval; ECG, electrocardiogram; QTc, heart rate-corrected QT interval.

During follow-up, one (0.2%) of the 419 AF patients debuted with AF episode ≥24 h. Among the remaining 418 patients with shorter AF at first detection, the presence of IAB was associated with progression to AF duration ≥24 h in the time-to-first-event analysis using the date of first AF episode as index (HR 1.86 [1.02–3.39]; *Figure 3*). Additionally, with ECG parameters treated as continuous variables, also longer PWD demonstrated a significant association with this progression in AF episode duration (*Figure 4*).

Discussion

This *post hoc* analysis of the LOOP Study investigated the relationships between ECG parameters and new-onset AF detected by long-term continuous monitoring in elderly individuals with additional stroke risk factors. The key findings were (i) several ECG parameters—mainly those related to *P*-wave—were associated with new-onset AF; (ii) both shorter and longer PWD, greater PTF, and the presence of IAB demonstrated associations with an increased risk of long-lasting AF; (iii) abnormal PWD, PWA, PTF, QTc interval, and QRS duration as well as the

presence of IAB were associated with higher cumulative AF burden; and (iv) longer PWD and IAB were related to an increased risk of AF progression.

Atrial fibrillation detection

Previous research has identified various ECG parameters as predictors of incident AF as well as AF recurrence after ablation.[6–17,21,22] Especially the use of *P*-wave parameters has been suggested by the recent consensus document from the International Society of Electrocardiology for detection of pathological changes in atria and thereby AF risk stratification.[6] Indded, through an AI-based algorithm, a non-randomized, interventional trial also confirmed the utility of sinus rhythm ECG features in the selection of patients with high AF risk for screening.[18] In line herewith, our study found several ECG parameters to be associated with new-onset ILR-detected AF, with abnormal PWV showing the most remarkable association (*Figure 1A*). This inverse correlation between PWV and AF is supported by a retrospective study of patients undergoing AF ablation wherein Park *et al.*[7] observed a higher incidence of AF recurrence
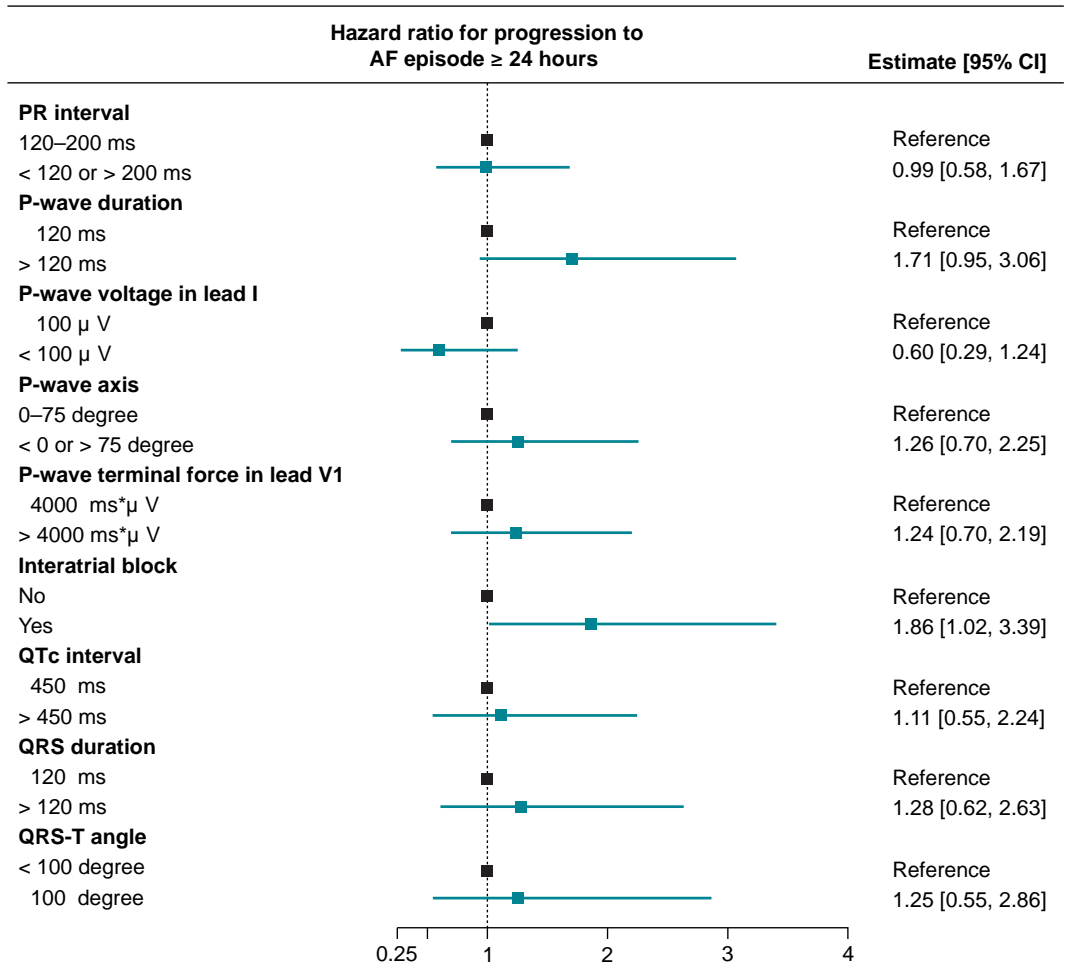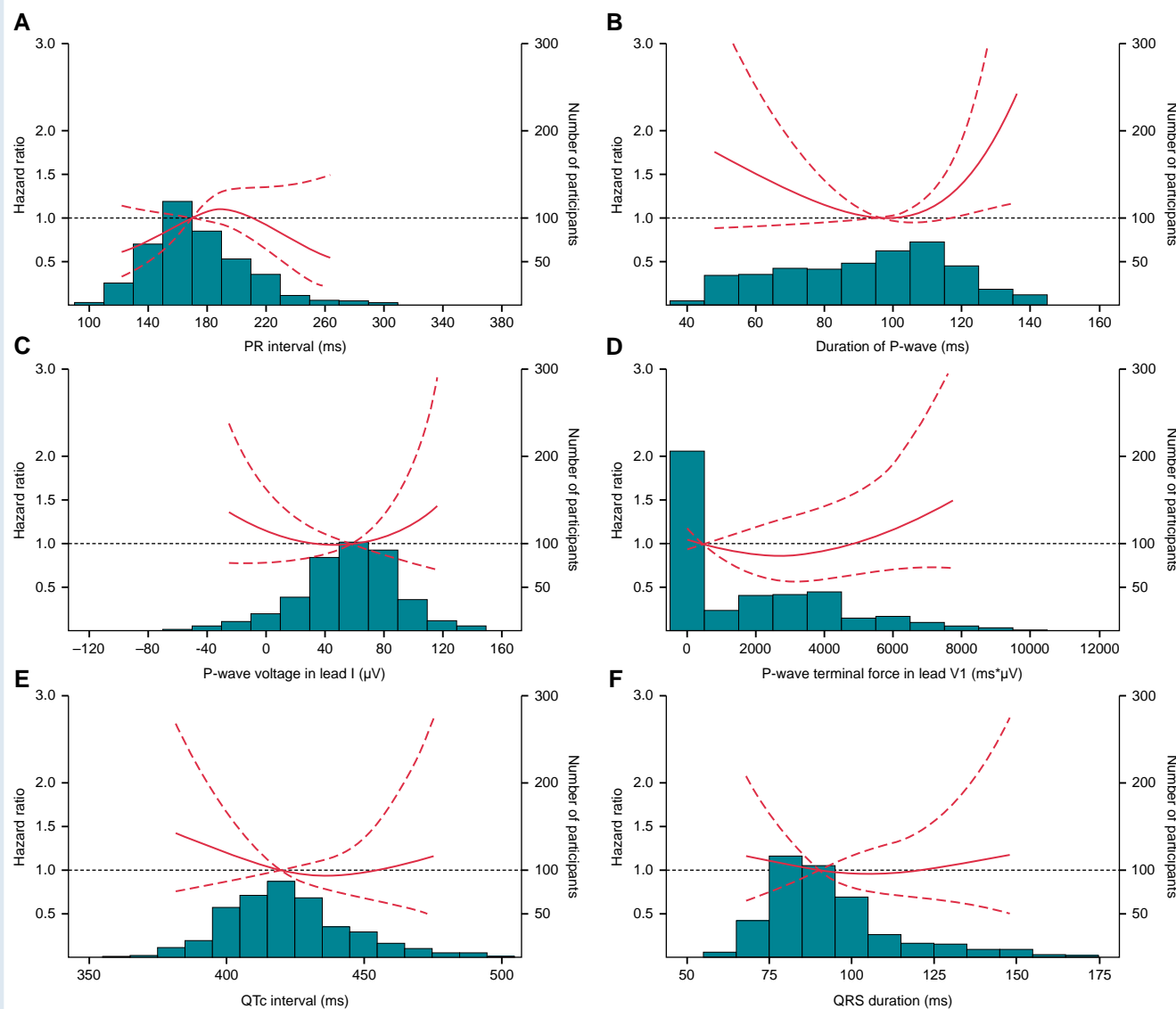
Figure 3 Hazard ratio for progression to AF episode ≥24 h. The figure shows the risk of AF progression to the first episode ≥24 h according to dichotomized ECG parameters, among 418 patients debuted with shorter AF duration. The interatrial block was defined as P-wave duration ≥120 ms combined with biphasic (positive–negative) P-wave in any inferior lead. QTc interval was estimated using the Framingham formula. Hazard ratios were determined in a multivariate Cox model with death as competing risk. Abbreviations: AF, atrial fibrillation; CI, confidence interval; ECG, electrocardiogram; QTc, heart rate-corrected QT interval.

in patients with lower PWV, along with displaced interatrial conduction. Given the axis of Lead I running in parallel to Bachmann's bundle, a reduction of PWV might, therefore, represent impaired conduction in Bachmann's region, similarly to the proposed mechanism underlying IAB that has been linked to incident AF in previous studies.[15,21,22] For PWD and PR interval, Nielsen et al.[11,17] demonstrated a U-shaped relationship between both parameters and incident AF in the Copenhagen ECG Study of nearly 300 000 subjects. Our data portrayed a similar trend for PWD, but not for PR interval which was related to AF detection only in the longer range (see Supplementary material online, Figure S1). However, it could be speculated that a heritability of shortened PR interval predisposing to enhanced AF susceptibility[23] might potentially also have led to early AF diagnosis and thereby exclusion from the LOOP Study. It is also possible that a larger sample size and thus greater statistical power were needed to identify such an AF risk increment for shortened PR interval, considering that the community-based Framingham Heart Study neither showed an association of AF with PR shortening.[9] These two explanations might also apply to the inconsistency between our results and that of the Copenhagen ECG study with

respect to QTc interval. Indeed, Nielsen et al.[12] reported QTc interval to confer a higher risk of clinical AF both in the shorter and the longer range, whereas our study did not detect a significantly increased AF rate for shortened QTc interval (Figure 1A and Supplementary material online, Figure S1) in agreement with an analysis of three US population-based cohorts.[8] However, these inconsistent findings also indicate the complexity of the associations between ECG parameters and AF, and hence, more evidence is needed to establish the clinically relevant reference values for the respective parameters.[6]

Atrial fibrillation burden

One of the main issues in AF screening raised by the recent position paper from the European Heart Rhythm Association is the lack of a practical, cost-effective screening strategy.[1] Indeed, we have learned from the primary reporting of the LOOP Study that not all AF are worth being screened for. There is a need for risk stratification tools to better identify the high-risk subpopulation more likely to benefit from AF screening. In the present study, we attempted to investigate 12-lead

Figure 4 The relationships between ECG parameters as a continuous variable and the risk of progression to AF episode ≥24 h. The figure shows the risk of AF progression to the first episode ≥24 h as a function of PR interval (*A*), *P*-wave duration (*B*), *P*-wave voltage in Lead I (*C*), *P*-wave terminal force in Lead V$_1$ (*D*), QTc interval estimated using the Framingham formula (*E*), and QRS duration (*F*) among 418 patients debuted with shorter AF duration, superimposed on a histogram of the distribution of each of the ECG parameters. Hazard ratios were estimated by using the respective medians as the references in multivariate Cox models with death as a competing risk. The dashed lines represent 95% confidence intervals. Abbreviations: AF, atrial fibrillation; ECG, electrocardiogram; QTc, heart rate-corrected QT interval.

ECG parameters for the burden of new-onset subclinical AF, as numerous studies have ascertained a dose–response relationship between AF burden and stroke risk.[2–5] Given the fact that widely varying definitions of AF burden have been applied in previous research,[2,5,24] the burden of ILR-detected AF was, therefore, examined in our study both as the risk of continuous AF episode ≥24 h and as the cumulative AF duration divided by the total monitoring duration.

For the risk of long-lasting AF, we demonstrated PWD and IAB to be associated with AF episodes ≥24 h, with PWD exhibiting a similar *U*-shaped association pattern as for AF detection (*Figure 1B* and Supplementary material online, *Figure S2*). More interestingly, although greater PTF was not related to higher incidence of AF detection, it did appear to be associated with an increased risk of AF duration ≥24 h.

However, the statistical significance was not reached at the pre-specified cut-off of >4000 ms × μV, but first at >6000 ms × μV. This seemingly accords with results from a large epidemiological study in Finland showing an increased AF risk only in subjects with PTF >6000 ms × μV, but not those with 4000–6000 ms × μV.[10]

With AF burden assessed as the percentage of the total monitoring time, the mean cumulative burden among AF patients was estimated to be 1.5% [1.2–1.8%] in the present study, which was lower than the previously reported 3.0% among paroxysmal AF patients with cardiac implantable electronic device (CIED).[25] However, this difference comes as no surprise, since our study population exclusively comprised AF-naïve subjects at baseline, with an average time of 1.01 (SD, 0.98) years to first AF detection among AF patients. Our study reported

several ECG parameters to be significantly associated with cumulative AF burden, with abnormal QRS duration showing the largest increase (*Figure 2*). This is in alignment with Aeschbacher *et al.*[13] who found an association between longer QRS and increased risk of clinical AF in the Atherosclerosis Risk in Communities Study. Given the lacking associations between QRS duration and the risks of AF detection and long-lasting AF, our results may suggest that individuals with longer QRS duration tend to experience more short-lasting AF episodes. However, further studies are needed to elucidate the clinical impact of a high cumulative AF burden in the absence of long-lasting episodes.

Atrial fibrillation progression

For the development of ILR-detected AF, we observed an overall reduction of cumulative AF burden over time in AF patients (see Supplementary material online, *Table S2*). This is in line with a previous sub-analysis of the ILR participants by Diederichsen *et al.*[26] showing a cumulative burden reduction over time, even when censoring for initiation of AF ablation, Direct-Current cardioversion, or the initiation of Class I/III antiarrhythmics. These results may thus imply that subclinical AF is a disease of highly heterogeneous nature, with the majority emerging only transiently and diminishing over time spontaneously afterwards. Therefore, it is particularly important to identify in advance the patients who tend to experience persistence and even progression of their subclinical AF. Indeed, these patients would be more prone to AF-related complications and may constitute the appropriate patient population more likely to benefit from AF treatment including anticoagulation. In our study, although no ECG parameters succeeded in predicting the course of cumulative AF burden over time, we found PWD and IAB to be significantly associated with progression from shorter AF episode to ≥24 h (*Figures 3* and *4*). These findings are indeed consistent with the observed trend towards persistent cumulative AF burden over time in AF patients with PWD >120 ms and IAB, albeit no statistical significance was reached (see Supplementary material online, *Table S2*). More importantly, both parameters demonstrated significant associations with this progression in AF episode duration, independent of conventional risk factors such as sex and comorbidities which have been linked to transition to longer AF duration in previous studies of CIED patients.[27] Therefore, these *P*-wave parameters may potentially also contribute to better risk characterization of patients with known AF for further intensification of management strategies, as the conventional comorbidity-based risk stratification tools have shown to predict the residual stroke risk in these patients receiving guideline-directed AF treatment.[28] Moreover, it is noteworthy that only patients with longer PWD were at increased risk of transition to longer AF duration in our study. The lack of significant association with *P*-wave shortening could be partly due to the insufficient power of this study and partly due to the predominantly short-term effect of shorter PWD on AF as observed in the Copenhagen ECG Study.[17]

Perspectives

According to current guidelines from the European Society of Cardiology, opportunistic AF screening is recommended in patients aged ≥65 years.[2] However, with a number of 110 needed to screen for AF detection in the general population, this strategy does not seem to be realistic and cost-effective.[1] Therefore, better risk stratification tools to define the high-risk patient population for AF screening are urgently demanded to optimize the cost-effectiveness and inform screening strategy. In this regard, the easily accessible 12-lead ECG may be useful, as particularly *P*-wave parameters are found to be risk factors for incident AF and AF-related complications such as stroke, heart failure, dementia, and death.[6] Indeed, our study suggests several ECG parameters to be associated with the onset and the cumulative burden of subclinical AF. PWD and IAB have further been demonstrated to be effective at identifying individuals with a higher risk of long-

lasting AF and AF progression. This might imply that these two *P*-wave parameters could serve as early risk markers of atrial cardiomyopathy that acts as the underlying cause of AF and cardioembolic stroke.[1,2,6] However, further studies are needed to assess whether these parameters could predict the benefits of subclinical AF detection and treatment.[6]

Limitations

Our study has several limitations. First, our study might be underpowered to detect small, but relevant associations between ECG parameters and subclinical AF, although the study has a very well-characterized population with adjudicated outcomes. Secondly, the participant recruitment outside the hospital setting, which is highly relevant for screening, could have introduced healthy user bias, and further, these results might not be extrapolated outside the Caucasian population. Thirdly, we do not have data on the anatomy, function, and fibrosis of the atria which are also associated with subclinical AF. However, we were able to adjust for several baseline cardiovascular comorbidities and risk factors that may be closely related to the atrial morphology.

Conclusions

Several ECG parameters were associated with new-onset subclinical AF detected by ILR, and especially *P*-wave parameters demonstrated robust associations with both the onset, the burden and the progression of AF over time. Hence, *P*-wave parameters may help to identify patients more prone to AF-related complications and thus more likely to benefit from screening. However, further studies are needed to assess whether ECG parameters could predict the benefits of subclinical AF detection and treatment.

Supplementary material

Supplementary material is available at *Europace* online.

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Data availability

The data underlying this article cannot be shared publicly for ethical reasons, but the methodology will be shared on reasonable request to the corresponding author (J.H.S.).

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