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Electrocardiographic Morphology-Voltage-P-Wave-Duration (MVP) Score to Select Patients for Continuous Atrial Fibrillation Screening to Prevent Stroke

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Morphology-voltage-P-wave-duration (MVP) score combining P-wave duration (PWD), P-wave voltage in lead I (PWVI), and interatrial block (IAB) has been demonstrated to predict atrial fibrillation (AF). Therefore, this study aimed to examine MVP score and its P-wave components as potential predictors of AF screening effects on stroke prevention. This was a secondary analysis of the LOOP Study (*Atrial Fibrillation detected by Continuous ECG Monitoring using Implantable Loop Recorder to prevent Stroke in High-risk Individuals*) which randomized older persons (aged 70 to 90 years) with additional stroke risk factors to either continuous monitoring with implantable loop recorder and anticoagulation upon detection of AF episodes ≥6 minutes (the intervention group), or usual care. A total of 5,759 participants were included in the present analysis, where PWD, PWVI, and IAB were determined through a computerized analysis of 12-lead electrocardiogram and further employed to calculate baseline MVP score (0 to 6) for each participant. In total, 305 (5.3%) had stroke or systemic embolism during follow-up, with a higher risk in the group with MVP score 5 to 6 than those having score 0 to 2 (hazard ratio (HR) 1.54 [95% confidence interval (CI) 1.01 to 2.35]). This risk increase was mainly upheld by participants with IAB (HR 1.62 [95% CI 1.11 to 2.36] for IAB vs no IAB) and with longer PWD (HR 1.37 [95% CI 1.07 to 1.75] for >110 vs ≤110 ms). Compared with usual care, implantable loop recorder screening did not significantly reduce the risk of stroke or systemic embolism in any MVP risk categories (HR 0.80 [95% CI 0.60 to 1.08] for MVP score 0 to 2, 0.54 [95% CI 0.16 to 1.85] for MVP score 3 to 4, and 0.89 [95% CI 0.35 to 2.25] for MVP score 5 to 6; $p_{interaction}$ = 0.78). In conclusion, a higher MVP score was associated with an increased stroke risk, but it did not demonstrate an association with effects of AF screening on stroke prevention. These findings should be considered hypothesis-generating and warrant further study. **(Am J Cardiol 2023;205:457−464)**

Keywords: atrial fibrillation, electrocardiogram, screening, stroke, P-wave

Atrial fibrillation (AF), as the most common sustained cardiac arrhythmia, is a well-known risk factor for stroke.[1,2] Due toadvancing technology for heart rhythm monitoring and growing evidence on high prevalence of asymptomatic AF,[3,4] a substantial interest has arisen in screening for AF. However, data on health benefits from

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See page 463 for Declaration of Competing Interest.

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AF screening and the optimal screening strategies are scarce.[4,5] Morphology-Voltage-P-wave-duration (MVP) risk score that combines 3 P-wave parameters is a newly proposed risk stratification tool and has demonstrated to predict AF in different patient populations.[6–8] Indeed, many measured parameters from the P-wave in a 12-lead electrocardiogram (ECG) have been identified and proved their value in AF prediction previously.[9–15] Therefore, this risk score might also be useful in risk-stratifying for AF screening and subsequent preventive treatment. In this study, we sought to examine the MVP risk score and its P-wave components for prediction of AF and stroke as well as AF screening effects.

Methods

The LOOP study (*Atrial Fibrillation detected by Continuous ECG Monitoring using Implantable Loop Recorder to prevent Stroke in High-risk Individuals*) was a randomized, controlled trial to assess AF screening by long-term continuous ECG monitoring using implantable loop recorder (ILR). The trial was registered at *Clinical-Trials.gov* (identifier: NCT02036450) and approved by the local scientific ethics committee (H-4-2013-025) and Danish Data Protection Agency. All study participants gave oral and written informed consent at enrolment. Details of the study design and methods have been published previously.[16,17] In short, AF-naïve persons aged ≥70 years and with ≥1 additional stroke risk factor — hypertension, diabetes mellitus, heart failure, or previous stroke — were recruited from the general population and randomized in a ratio 1:3 to ILR screening or usual care. The participant recruitment was done at 4 centers in Denmark between January 31, 2014 and May 17, 2016. Upon inclusion, a standard 12-lead ECG was digitally recorded in all participants at rest. In the ILR group, any new-onset AF episodes lasting ≥6 minutes were adjudicated by at least 2 cardiologists independently and oral anticoagulation was recommended upon confirmation of AF diagnosis. In the control group, data on AF diagnosis were extracted from the medical records.

In this secondary analysis, we included the LOOP participants with available 12-lead surface ECG at baseline and further excluded those who had an ECG with non-sinus rhythm or other findings unsuitable for measurement of P-wave parameters — including ectopic atrial rhythm, junctional rhythm, ventricular rhythm, undetermined rhythm, second-degree and third-degree atrioventricular block, and delta-wave — using the Marquette 12SL ECG Analysis Program (version 23). To estimate an overall MVP ECG risk score for each participant at baseline, point allocation (0 to 2) was conducted based on the P-wave morphology in the inferior leads, and the voltage and duration of the P-wave from 12-lead ECG; Table 1. The information about P-wave duration (PWD), P-wave voltage in lead I (PWVI), and interatrial block (IAB) was extracted from the computerized analysis of baseline 12-lead ECGs (see Supplementary Methods for more details). The MVP score ranges from 0 to 6, where 0 to 2 is classified as low AF risk, 3 to 4 as intermediate AF risk, and 5 to 6 as high AF risk.[6]

The primary outcome in the present study was a composite of stroke or systemic embolism (SE), whereas the secondary outcomes were (1) ischemic stroke, (2) the composite of stroke, SE, or cardiovascular death, and (3) AF diagnosis. The adjudication of stroke, SE, and death was conducted by a blinded clinical endpoint committee as previously described.[17]

Table 1
Morphology-Voltage-P-wave-duration (MVP) risk score

Variable	Value	Score
P-wave duration	<120 ms	0
	120–140 ms	1
	>140 ms	2
P-wave voltage in lead I	>200 μV	0
	100–200 μV	1
	<100 μV	2
P-wave morphology in inferior leads	no interatrial block	0
	partial interatrial block	1
	interatrial block	2

The P-wave parameters were assessed using data from baseline 12-lead electrocardiogram. Interatrial block was defined as P-wave duration ≥120 ms combined with the presence of biphasic P-wave (positive-negative) in any inferior lead, whereas partial interatrial block was defined as P-wave duration ≥120 ms with monophasic positive P-waves in inferior leads.

For statistical analysis, the study participants were divided into different prespecified groups according to MVP risk scores (0 to 2 vs 3 to 4 vs 5 to 6), PWD (<120 vs 120 to 140 vs >140 ms), PWVI (<100 vs 100 to 200 vs >200 μV), and IAB patterns at baseline (no IAB vs partial IAB vs IAB), separately. Baseline characteristics are presented as mean with standard deviation (SD) for continuous variables and frequency with percentage for categorical variables. The distributions were compared by Student *t* test and chi-square test, respectively.

For the study outcomes, crude event rates were calculated as annual incidence rates with Poisson regression and are presented as events per 100 person-years with (95% confidence interval), whereas cumulative incidences are plotted using the Aalen-Johansen estimator with death as a competing event. The associations of outcomes with MVP score and its P-wave components were investigated using multivariate cause-specific Cox regression models — adjusted for gender, age, body mass index, weekly alcohol consumption, smoking pack years, and baseline co-morbidities (hypertension, diabetes mellitus, previous stroke, heart failure, valvular heart disease, chronic ischemic heart disease, and peripheral artery disease) — and are presented as hazard ratio (HR) with (95% confidence interval). PWD and PWVI were further assessed as continuous variables using restricted cubic spline regression in the multivariate Cox models, where the relative risks were estimated with the 5th percentile as reference.

The effects of ILR screening vs usual care were evaluated according to MVP score, PWD, PWVI, and IAB in cause-specific Cox regression models, whereas the interactions between randomization and the respective parameters were tested by adding an interaction term into the models. The ILR screening effects were also examined according to PWD and PWVI as continuous variables using restricted cubic spline regression to estimate separate effects on the log hazards of the outcomes

Table 2
Overview of baseline characteristics according to Morphology-Voltage-P-wave-duration (MVP) risk group

	Low risk (n = 5130)	Intermediate risk (n = 346)	High risk (n = 283)	Total (n = 5759)	p-value
Male sex (%)	2,606 (50.8)	211 (61.0)	191 (67.5)	3,008 (52.2)	< 0.001
Age, years (standard deviation)	74.6 (4.1)	75.2 (4.4)	75.4 (4.3)	74.7 (4.1)	< 0.001
Alcohol consumption, standard units per week (standard deviation)	7 (8)	9.7 (9.2)	9.1 (9.1)	7.2 (8.1)	< 0.001
Smoking pack years (standard deviation)	16.7 (23.2)	17.3 (23)	19.3 (24.7)	16.9 (23.2)	0.17
Body mass index, kg/m^2 (standard deviation)	27.6 (4.5)	27.6 (4.6)	28.8 (4.6)	27.6 (4.5)	< 0.001
CHA_2DS_2-VASc score (standard deviation)	3.8 (1.2)	3.7 (1.3)	3.7 (1.3)	3.8 (1.2)	0.71
Co-morbidities (%)					
Hypertension	4,636 (90.4)	323 (93.4)	257 (90.8)	5,216 (90.6)	0.18
Diabetes mellitus	1,473 (28.7)	73 (21.1)	79 (27.9)	1,625 (28.2)	0.010
Congestive heart failure	222 (4.3)	12 (3.5)	14 (4.9)	248 (4.3)	0.64
Previous stroke	901 (17.6)	61 (17.6)	48 (17.0)	1,010 (17.5)	0.97
Chronic ischemic heart disease	659 (12.8)	42 (12.1)	45 (15.9)	746 (13.0)	0.30
Valvular heart disease	206 (4.0)	15 (4.3)	11 (3.9)	232 (4.0)	0.95
Peripheral artery disease	134 (2.6)	16 (4.6)	3 (1.1)	153 (2.7)	0.02
Concomitant medications (%)					
Beta-blockers	1,282 (25.0)	91 (26.3)	71 (25.1)	1,444 (25.1)	0.86
Calcium channel blockers	1,914 (37.3)	122 (35.3)	109 (38.5)	2,145 (37.2)	0.67
Non-dihydropyridine calcium channel blocker	116 (2.3)	7 (2.0)	10 (3.5)	133 (2.3)	0.36
Digitalis	5 (0.1)	0 (0.0)	2 (0.7)	7 (0.1)	0.01
Renin-angiotensin system inhibitors	3,391 (66.1)	226 (65.3)	196 (69.3)	3,813 (66.2)	0.52
Diuretics	1,716 (33.5)	103 (29.8)	87 (30.7)	1,906 (33.1)	0.26
Platelet inhibitors	2,484 (48.4)	154 (44.5)	143 (50.5)	2,781 (48.3)	0.27
Statins	3,008 (58.6)	187 (54.0)	157 (55.5)	3,352 (58.2)	0.16
Insulins	415 (8.1)	18 (5.2)	24 (8.5)	457 (7.9)	0.15
Non-insulin antidiabetic drugs	1,108 (21.6)	57 (16.5)	53 (18.7)	1,218 (21.1)	0.05
ECG parameters					
P-wave duration, ms (standard deviation)	89.8 (19.6)	125.7 (5.1)	128.2 (7.6)	93.9 (21.9)	< 0.001
P-wave voltage in lead I, μV (standard deviation)	62.6 (37.8)	82.5 (34.3)	67.1 (26)	64 (37.4)	< 0.001
Interatrial block (%)					< 0.001
No interatrial block	5,130 (100.0)	0 (0.0)	0 (0.0)	5,130 (89.1)	
Partial interatrial block	0 (0.0)	278 (80.3)	4 (1.4)	282 (4.9)	
Interatrial block	0 (0.0)	68 (19.7)	279 (98.6)	347 (6.0)	

Risk category assignment was based on estimated MVP score at baseline, where score 0 to 2 classified as low risk, 3 to 4 as intermediate risk, and 5 to 6 as high risk. Interatrial block was defined as P-wave duration ≥120 ms combined with the presence of biphasic P-wave (positive-negative) in any inferior lead, whereas partial interatrial block was defined as P-wave duration ≥120 ms with monophasic positive P-waves in inferior leads.

Missing observations: alcohol consumption, n = 3; body mass index, n = 1.

in each randomization group. The analyses for screening effects were performed in accordance with the intention-to-treat principle.

Scaled Schoenfeld residuals were applied to assess the Cox proportional-hazard assumption, and any variables violating this were treated with stratification to allow different baseline hazards. All data analyses were conducted using R version 4.1.0 (The R Foundation for Statistical Computing, Vienna, Austria). The statistical significance was set at a 2-sided p value ≤0.05.

Results

Of all LOOP study participants (n = 6,004), 245 (4.1%) were excluded from this secondary analysis due to missing baseline ECG (n = 40) or ECG with findings unsuitable for measurement (n = 205). The final study population comprised 5,759 participants, with a mean follow-up time of 5.2 years (SD, 1.1). Most of them (89.1%) had an MVP risk score of 1 to 2, whereas no participant was assigned a score of 0 (Supplementary Figure 1). Baseline characteristics according to AF risk categories based on MVP score are listed in Table 2. Participants with higher MVP score were slightly older, more likely to be male, and had a higher weekly alcohol consumption and a higher body mass index. There was no difference in mean CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years [2 points], diabetes, stroke/thromboembolism [2 points], vascular disease, age 65-74 years, gender category [female]) score across these 3 risk categories, and the same was true for most baseline cardiovascular co-morbidities.

Of 5,759 participants included, 305 (5.3%) had stroke/SE during follow-up. When comparing AF risk categories in the entire study cohort, the event rate of the primary outcome was numerically higher in the intermediate-risk group (1.11 [0.68 to 1.71] per 100 person-years) and the high-risk group (1.67 [1.07 to 2.49] per 100 person-years) than in the low-risk group (1.00 [0.88 to 1.13] per 100 person-years), but only the risk increase in the high-risk group reached the statistical significance (HR 1.54 [1.01 to 2.35]); Figure 1. Similar observations were made for the secondary outcome of ischemic stroke, with a significantly higher event rate in

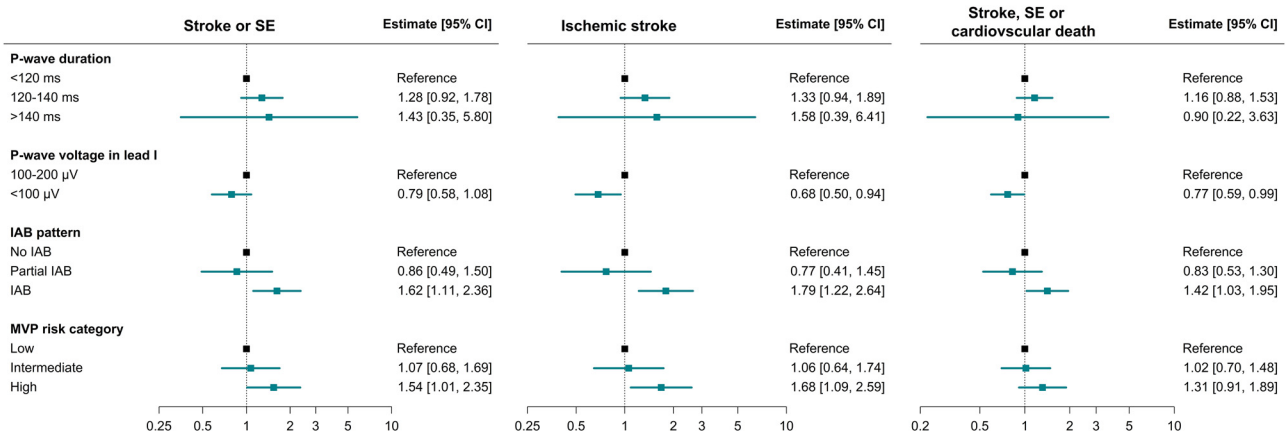

Figure 1. Hazard ratios of clinical outcomes according to MVP score and P-wave parameters. The figure shows the relative risks of stroke/SE, ischemic stroke, and stroke/SE/cardiovascular death according to P-wave duration, P-wave voltage in lead I, IAB, and MVP risk categories. Hazard ratios were determined in multivariate cause-specific Cox regression models adjusted for gender, age, body mass index, alcohol consumption, smoking pack years, hypertension, diabetes mellitus, previous stroke, heart failure, valvular heart disease, ischemic heart disease, and peripheral artery disease. MVP scores 0 to 2 were classified as low risk, 3 to 4 as intermediate risk and 5 to 6 as high risk. IAB was defined as P-wave duration ≥120 ms combined with the presence of biphasic P-wave (positive-negative) in any inferior lead, whereas partial IAB was defined as P-wave duration ≥120 ms with monophasic positive P-waves in inferior leads. For P-wave voltage in lead I no participant had a voltage >200 µV.
CI = confidence interval; IAB = interatrial block; MVP score = Morphology-Voltage-P-wave-duration score; SE = systemic embolism.

the high-risk group than in the low-risk group (HR 1.68 [1.09 to 2.59]). The event rates for the composite endpoint of stroke/SE/cardiovascular death were non-significantly increased in the intermediate-risk and high-risk group. The event rates and HRs of the clinical outcomes are listed in Table 3, whereas the cumulative incidences are plotted in Supplementary Figure 2.

Among the P-wave components of the MVP risk score, the presence of IAB was consistently associated with significantly increased risks of stroke/SE (HR 1.62 [1.11 to 2.36]), ischemic stroke (HR 1.79 [1.22 to 2.64]), and stroke/SE/cardiovascular death (HR 1.42 [1.03 to 1.95]) in the entire cohort, compared with no IAB; Figure 1. For P-wave voltage, participants with PWVI <100 µV were at significantly lower risks of ischemic stroke and stroke/SE/cardiovascular death than those with higher PWVI (HR 0.68 [0.50 to 0.94] and 0.77 [0.59 to 0.99], respectively). The same association patterns were present when PWVI was assessed as a continuous variable; Figure 2. For PWD, the risk increases of stroke/SE, ischemic stroke, and stroke/SE/cardiovascular death were nonsignificant in participants with PWD of 120 to 140 ms and with PWD >140 ms, compared with those having a duration <120 ms. When examined as a continuous variable, the risks of stroke/SE and ischemic stroke clearly demonstrated a positive correlation with PWD, as illustrated in Figure 2. Further exploration with a cutoff of PWD >110 ms revealed significantly higher risks of stroke/SE (HR 1.37 [1.07 to 1.75]) and ischemic stroke (HR 1.39 [1.06 to 1.81]) than those with shorter durations; Supplementary Table 1.

During follow-up, AF was diagnosed in 446 (30.8%) of 1448 participants in the ILR group and 505 (11.7%) of 4,311 participants in the control group. In the ILR group, participants with MVP score 5 to 6 were more likely to develop AF than those with score 0 to 2 (HR 1.82 [1.31 to 2.53]). When considering each of the P-wave components separately, PWD >140 ms, PWVI <100 µV, and the presence of IAB were all associated with increased AF risk in the ILR group (HR 6.08 [2.44 to 15.12], 1.96 [1.39 to 2.76] and 1.70 [1.25 to 2.31], respectively). Similar trends were present in the control group; Supplementary Table 2. To further assess AF as a potential mediator for the associations of the clinical outcomes with MVP risk categories and its P-wave components, a sensitivity analysis was performed by treating incident AF as a competing event during follow-up. As presented in Supplementary Table 1 and Supplementary Table 3, these associations remained of similar magnitude in the multivariate Cox model when censoring for AF.

Figure 3 depicts the screening effects according to the MVP risk score and its P-wave components. There were no significant interactions between ILR screening effects and MVP risk categories, PWD categories, PWVI categories, or IAB patterns; $p_{interaction}>0.05$ for all. ILR screening did not significantly reduce the risks of stroke/SE, ischemic stroke, and stroke/SE/cardiovascular death in any participant groups regardless of MVP risk score, PWD, PWVI, or the presence of IAB. Similar results were obtained when PWD and PWVI were analyzed as continuous variables; Supplementary Figure 3.

Discussion

This is the first study to assess ECG parameters for prediction of AF screening effects on stroke prevention. In an older population with additional stroke risk factors, our study yielded 2 main findings: (1) higher MVP ECG risk score, longer PWD, and the presence of IAB in 12-lead standard ECG were associated with increased risks of AF and stroke, whereas subjects with lower PWVI — despite a higher risk of AF development — were at lower stroke risk; and (2) neither MVP risk score nor its P-wave components separately could predict effects of ILR screening for subclinical AF.

Table 3
Event rates and hazard ratios of clinical outcomes according to Morphology-Voltage-P-wave-duration (MVP) risk score and its components

	P-wave duration			P-wave voltage in lead I			Interatrial block			MVP risk categories		
	Event rate	Hazard ratio		Event rate	Hazard ratio		Event rate	Hazard ratio		Event rate	Hazard ratio
Stroke or systemic embolism	<120 ms 1.00 [0.88-1.13]	Reference	>200 μV	NA*	NA*	No interatrial block	1.00 [0.88-1.13]	Reference	Low risk	1.00 [0.88-1.13]	Reference
	120-140 ms 1.35 [0.97-1.82]	1.28 [0.92-1.78]	100-200 μV	1.17 [0.86-1.55]	Reference	Partial interatrial block	0.88 [0.47-1.50]	0.86 [0.49-1.50]	Intermediate risk	1.11 [0.68-1.71]	1.07 [0.68-1.69]
	>140 ms 1.68 [0.20-6.06]	1.43 [0.35-5.80]	<100 μV	1.02 [0.90-1.15]	0.79 [0.58-1.08]	Interatrial block	1.76 [1.20-2.50]	1.62 [1.11-2.36]	High risk	1.67 [1.07-2.49]	1.54 [1.01-2.35]
Ischemic stroke	<120 ms 0.86 [0.75-0.98]	Reference	>200 μV	NA*	NA*	No interatrial block	0.86 [0.75-0.98]	Reference	Low risk	0.86 [0.75-0.98]	Reference
	120-140 ms 1.22 [0.86-1.67]	1.33 [0.94-1.89]	100-200 μV	1.12 [0.82-1.49]	Reference	Partial interatrial block	0.68 [0.32-1.24]	0.77 [0.41-1.45]	Intermediate risk	0.94 [0.55-1.51]	1.06 [0.64-1.74]
	>140 ms 1.68 [0.20-6.06]	1.58 [0.39-6.41]	<100 μV	0.87 [0.75-0.99]	0.68 [0.50-0.94]	Interatrial block	1.70 [1.15-2.43]	1.79 [1.22-2.64]	High risk	1.60 [1.02-2.40]	1.68 [1.09-2.59]
Stroke, systemic embolism, or cardiovascular death	<120 ms 1.52 [1.37-1.67]	Reference	>200 μV	NA*	NA*	No interatrial block	1.52 [1.37-1.67]	Reference	Low risk	1.52 [1.37-1.67]	Reference
	120-140 ms 1.92 [1.47-2.48]	1.16 [0.88-1.53]	100-200 μV	1.73 [1.35-2.18]	Reference	Partial interatrial block	1.35 [0.83-2.09]	0.83 [0.53-1.30]	Intermediate risk	1.66 [1.12-2.37]	1.02 [0.70-1.48]
	>140 ms 1.68 [0.20-6.06]	0.90 [0.22-3.63]	<100 μV	1.53 [1.38-1.69]	0.77 [0.59-0.99]	Interatrial block	2.39 [1.72-3.22]	1.42 [1.03-1.95]	High risk	2.23 [1.52-3.15]	1.31 [0.91-1.89]

* None of our participants had a *P*-wave voltage in lead I >200 μV at baseline

Event rates [95% confidence interval] were calculated and are presented in events per 100 person-years, whereas hazard ratios [95% confidence interval] were determined in Cox regression model adjusted for gender, age, body mass index, alcohol consumption, smoking pack years, hypertension, diabetes mellitus, previous stroke, heart failure, valvular heart disease, ischemic heart disease, and peripheral artery disease.

Risk category assignment was based on estimated MVP score at baseline, where score 0 to 2 classified as low risk, 3 to 4 as intermediate risk, and 5 to 6 as high risk. Interatrial block was defined as P-wave duration ≥120 ms combined with the presence of biphasic P wave (positive-negative) in any inferior lead, whereas partial interatrial block was defined as P-wave duration ≥120 ms with monophasic positive P waves in inferior leads.

There is mounting evidence that subclinical AF also confers an increased stroke risk,[3,18] but data confirming health benefits from AF screening are scarce.[4,5] Only 2 randomized clinical trials have so far examined AF screening for stroke prevention. The primary analysis of the LOOP study showed a nonsignificant reduction in stroke risk by ILR screening,[16] whereas the STROKESTOP (Systematic ECG Screening for Atrial Fibrillation Among 75 Year Old Subjects in the Region of Stockholm and Halland, Sweden) study assessing intermittent ECG screening for 2 weeks in a general population reported a marginal reduction of the composite endpoint of stroke, major bleedings, and death, without significant effects on any of these outcomes separately.[19] Still, large knowledge gaps exist within this research field, especially when it comes to identifying those to screen. In this regard, 12-lead surface ECG could potentially be of great value to guide clinical decision-making, as ECG parameters are easily accessible and more importantly, alterations of many of these parameters have been linked to an increased risk of AF development.[10−15]

MVP ECG risk score is a newly proposed risk stratification tool encompassing the presence of IAB, the voltage, and the duration of P-wave in 12-lead ECG to assess AF risk.[6] Of these, PWD and IAB are well-documented risk markers for AF in large epidemiological cohorts,[11−14] while PWVI is a relatively new P-wave parameter where low voltage had been demonstrated to be associated with both new-onset AF in patients with ischemic heart disease and with AF recurrence in patients who underwent ablation.[9,10] In line herewith, an association was found between MVP score and AF risk in earlier studies.[6−8] Indeed, our study also confirms that participants with higher MVP scores were at higher risk of AF development, which could potentially explain the increased stroke risk in these participants. This increase in stroke risk further appeared to be upheld by those with IAB and with longer PWD in baseline 12-lead ECG, supporting previous research that linked PWD and IAB to ischemic stroke.[12,13,20] However, an interesting observation from our study was the lower stroke risk in participants with reduced PWVI despite a significantly higher AF risk. A low PWVI in standard ECG is believed to indicate compromised interatrial conduction through Bachmann's bundle — the same mechanism proposed to underlie IAB, as a previous study by Park et al[9] reported displacement of interatrial conduction in AF patients with low PWVI using electro-anatomical mapping. Therefore, reduced PWVI was hypothesized to also be a risk marker for ischemic stroke. Nevertheless, our rather contradictory results point toward a limitation of using PWVI for risk stratification to AF screening. Indeed, P-wave voltage may also reflect myocardial mass in atria beyond the electrical conduction and notably, a previous study demonstrated right atrial enlargement in AF patients to be independently associated with cardiovascular events including stroke.[21] Thus, this could be a reason for the discrepancy between AF and stroke risk with respect to PWVI, but further studies are needed to provide more insights into the pathophysiological mechanisms for PWVI alteration.

Albeit the significant associations with both AF and ischemic stroke, the effects of ILR screening on stroke prevention did not change with MVP risk scores, PWD, or

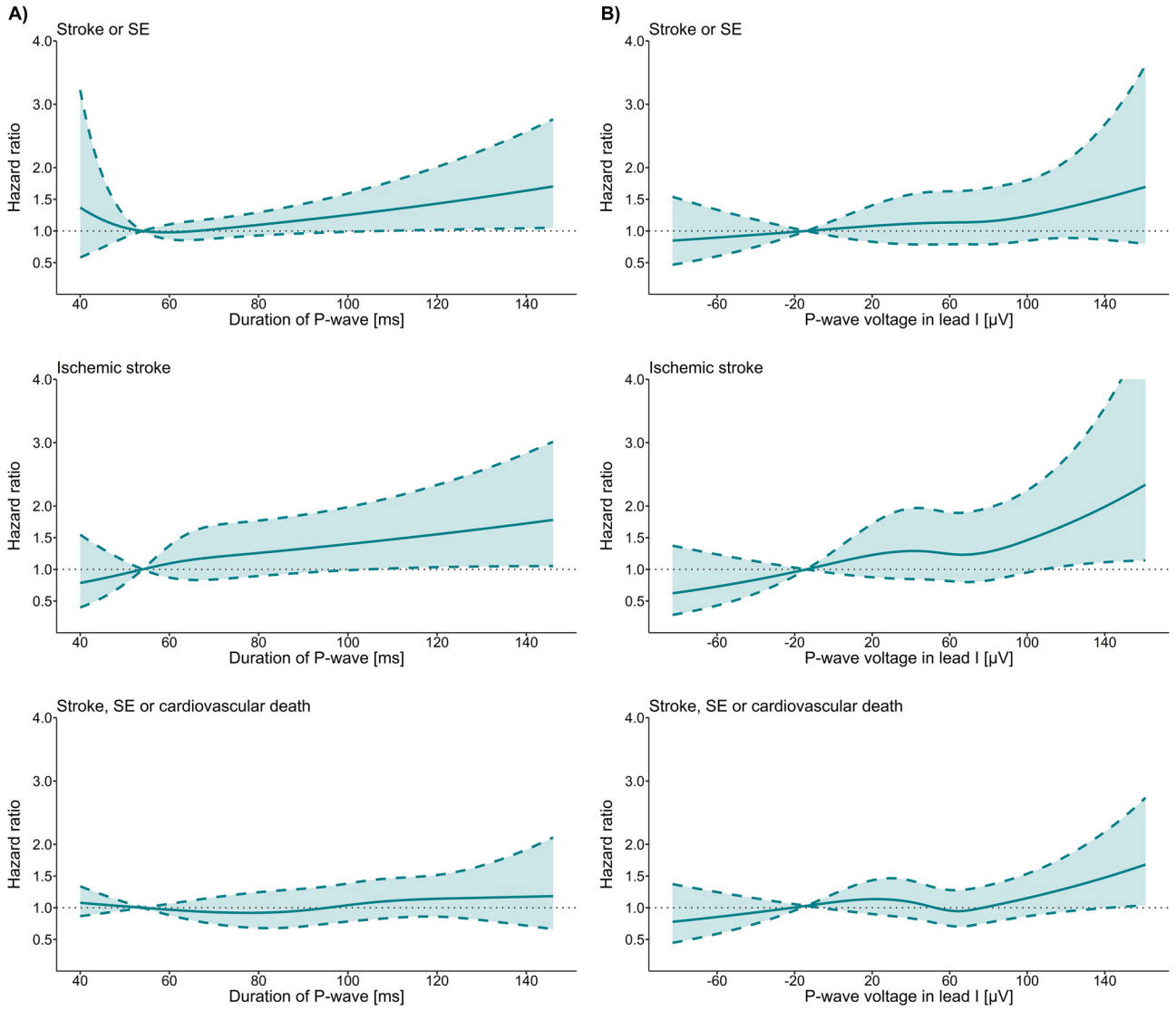

Figure 2. The associations of clinical outcomes with P-wave duration and voltage. The figure shows the risks of stroke/SE, ischemic stroke, and stroke/SE/cardiovascular death as a function of P-wave duration (*A*) and P-wave voltage in lead I (*B*), respectively. Hazard ratios were estimated with the fifth percentile as reference, in multivariate cause-specific Cox regression models adjusted for gender, age, body mass index, alcohol consumption, smoking pack years, hypertension, diabetes mellitus, previous stroke, heart failure, valvular heart disease, ischemic heart disease, and peripheral artery disease. The dashed lines represent 95% confidence intervals.
SE = systemic embolism.

IAB patterns in the present study. As in the main reporting of the LOOP Study,[16] the screening effects were also neutral in participants with higher MVP risk scores, with longer PWD, and with IAB. The lack of response on AF screening despite higher stroke rate could be explained partly by our findings that the associations of ischemic stroke with MVP score and its P-wave components were seemingly not mediated by incident AF. Indeed, if the P-wave parameters were not risk markers for specifically AF-related stroke, these would neither be useful for identifying persons more likely to benefit from AF screening. This is arguably consistent with a previous finding by Ahlberg et al[22] showing a stronger genetic association of left atrial size with cardioembolic stroke than with AF. Our results further support the notion of atrial cardiomyopathy representing atrial remodeling that manifests in electrical, contractile and/or structural changes and acting as the major driver for both AF development and cardioembolic stroke.[4,23] In this context, PWD alterations and the presence of IAB in 12-lead ECG could be potential markers of atrial cardiomyopathy that might predispose to ischemic stroke even in the absence of AF. This could speculatively have diluted the effects of AF screening and subsequent preventive treatment in our study. Nonetheless, the precise definition of atrial cardiomyopathy and the confirmation of its necessity for medical treatment is still warranted and require more evidence from prospective trials.[4,23]

The present study has several limitations. First, the results of this secondary analysis should be considered solely as hypothesis-generating. Second, the sample size

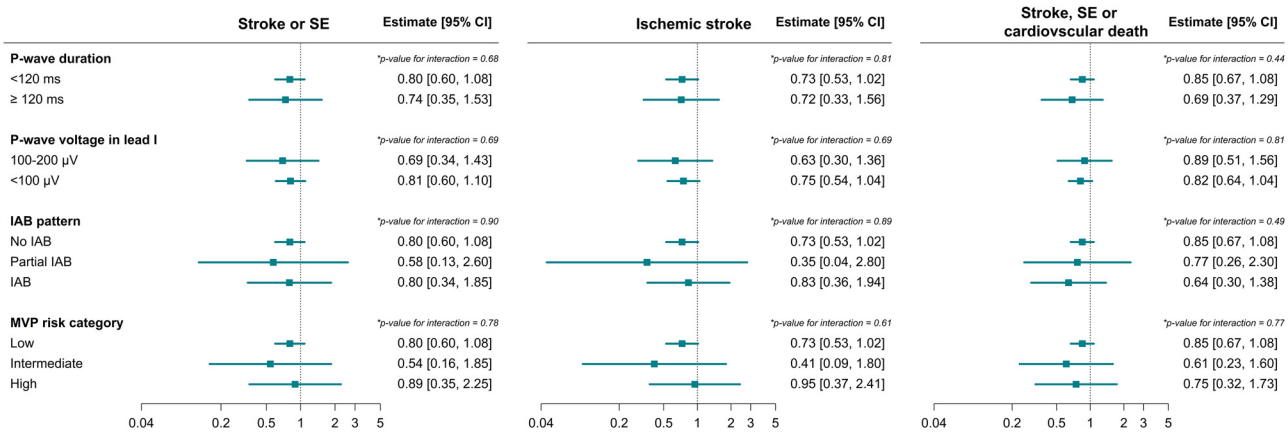

Figure 3. Screening effects according to MVP risk score and P-wave parameters. The figure shows the relative risks of stroke/SE, ischemic stroke, and stroke/SE/cardiovascular death for ILR screening vs usual care (control), stratified by P-wave duration, P-wave voltage in lead I, IAB, and MVP risk score, respectively. Hazard ratios were determined in cause-specific Cox regression models, where p values for interaction were estimated by adding an interaction term between randomization assignment and the respective parameter. MVP scores 0 to 2 were classified as low risk, 3 to 4 as intermediate risk and 5 to 6 as high risk. IAB was defined as P-wave duration ≥120 ms combined with the presence of biphasic P-wave (positive-negative) in any inferior lead, whereas partial IAB was defined as P-wave duration ≥120 ms with monophasic positive P-waves in inferior leads. For P-wave duration, the 2 upper categories were merged due to very low event number and hereby infinite hazard ratio coefficient in the participant category with a duration >140 ms. For P-wave voltage in lead I no participant had a voltage >200 µV.
CI = confidence interval; IAB = interatrial block; ILR = implantable loop recorder; MVP score = Morphology-Voltage-P-wave-duration score; SE = systemic embolism.

might have limited the power of our study to detect those small associations. Third, the participant recruitment from outside the hospital setting could have led to healthy user bias. Fourth, our study population comprised older persons aged 70 to 90 years and of mainly Caucasian ethnicity, which might have limited the applicability of our findings to other age groups and other ethnicities.

In conclusion, in an older population with additional stroke risk factors, both the P-wave parameters and the combined MVP risk score assessed from 12-lead ECG were associated with ischemic stroke, but these did not demonstrate an association with effects of AF screening on stroke prevention. Indeed, their associations with ischemic stroke were not mediated by incident AF, which might be a reason for the failure to predict screening effects. These findings should be considered hypothesis-generating and warrant further study.

Declaration of Competing Interest

Jesper Hastrup Svendsen reports to be a member of Medtronic advisory boards and to have received speaker honoraria and research grants from Medtronic in relation to this work and outside this work. Søren Diederichsen reports being a part-time employee of VitalBeats and adviser at Bristol-Myers Squibb/Pfizer, not related to this work. Derk Krieger reports to be a Medtronic Focus Group member. Jonas Bille Nielsen reports being an employee of Regeneron Pharmaceuticals outside this work. Axel Brandes reports research grants from The Region of Southern Denmark and The Region of Zealand, The Canadian Institutes of Health Research, and Theravance, speaker honoraria from Bayer, Boehringer Ingelheim, and Bristol-Myers Squibb, and a travel grant from Biotronik not related to this work. Lars Køber reports speaker honoraria from Novo, AstraZeneca, Novartis, and Boehringer, not related to this work. The other authors have no competing interests to declare.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2023.08.042.

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