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Electrocardiogram (ECG) for the Prediction of Incident Atrial Fibrillation: An Overview

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Abstract

Electrocardiograms (ECGs) have been employed to medically evaluate participants in population-based studies, and ECG-derived predictors have been reported for incident atrial fibrillation (AF). Here, we reviewed the status of ECG in predicting new-onset AF. We surveyed population-based studies and revealed ECG variables to be risk factors for incident AF. When available, the predictive values of each ECG risk marker were calculated.

Both the atrium-related and ventricle-related ECG variables were risk factors for incident AF, with significant hazard risks (HRs) even after multivariate adjustments. The risk factors included P-wave indices (maximum P-wave duration, its dispersion or variation and P-wave morphology) and premature atrial contractions (PACs) or runs. In addition, left ventricular hypertrophy (LVH), ST-T abnormalities, intraventricular conduction delay, QTc interval and premature ventricular contractions (PVCs) or runs were a risk of incident AF. An HR of greater than 2.0 was observed in the upper 5th percentile of the P-wave durations, P-wave durations greater than 130 ms, P-wave morpholyg, PACs (PVCs) or runs, LVH, QTc and left anterior fascicular blocks. The sensitivity , specificity and the positive and negative predictive values were 3.6-53.8%, 61.7-97.9%, 2.9-61.7% and 77.4-97.7%, respectively.

ECG variables are risk factors for incident AF. The correlation between the ECG-derived AF predictors, especially P-wave indices, and underlying diseases and the effects of the reversal of the ECG-derived predictors on incident AF by treatment of comorbidities require further study.

Introduction

Atrial fibrillation (AF) is a common arrhythmia, and the number of patients with AF is increasing in many developed countries. AF is associated with increased morbidity and mortality [1], and the prediction of AF development is expected to improve both health and clinical outcomes at the population level. Thus far, demographic and clinical variables have been extensively studied, and some have been shown to be risk factors for AF development [2]-[6].

Electrocardiograms (ECGs) are essential to diagnose AF and are used in population-based health examinations because of their ease of use and low cost. Recent advancements in high-quality signal acquisition and the availability of automated hardware ECG setups have facilitated the use of ECGs in mass examinations, and many ECG-derived markers have been confirmed as risk factors for incident AF. Here, we reviewed community-based cohorts that have confirmed ECG-derived risks for AF development.

Key Words

New atrial fibrillation, ECG-derived predictor, P-wave indices, atrial remodeling.

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Studies treating incident AF

Mainly, studies treating incident AF in community-based cohorts were collected from the literature. Small studies of less than 100 participants were not included, except for those measuring P-wave duration or dispersion by signal averaged ECGs (SAECGs). SAECGs may present more accurate P-wave durations or dispersions in spite of the difficulty of using them in population-based examinations.

AF was diagnosed using ECG and Holter monitors. New AF was diagnosed when the participants had no AF at baseline ECG but had AF on an ECG during the follow-up period. Then, we included some paroxysmal AF (PAF), whereas some cases of PAF might have been undetected if the sinus rhythm had resumed.

Most ECG variables were automatically measured by the hardware ECG set-up, but some were confirmed by cardiologists in most studies.

Atrium-related ECG-derived predictors [Table 1]

P-rate (heart rate) and P-wave indices and PR intervals are considered to represent alterations of electrophysiological and/or structural remodeling of the atrium in association with or without demographic and clinical variables that are risk factors for incident AF. The appearance of premature atria contractions (PACs) or runs may trigger AF and can be another risk for incident AF.

P-rate

Bradycardia is known to be associated with AF, especially in

Table 1: Atrium-related ECG-derived predictors for new-onset AF

Author (Rf. No.)	Number of participants	FU time		Annual incidence	ECG finding	HR (95% CI, P-value)
P-wave duration						
Perez [13] Perez [13]	42,751	5.3 yrs		0.45%	>120 ms	1.6 (1.3-1.8, P<0.0001)
					per 20 ms	1.1 4 (1.02-1.27, P=0.022)
Soliman[14]	15,429	6.97 yrs	0.11%	>120 ms		1.94 (1.66-2.28) Model 1 1.79 (1.51-2.14) Model 2
				Upper 5%		5.23 (3.33-8.22) Model 1 4.07 (2.55 - 6.51) Model 2
Magnani[15]	1,550	15.8 yrs	1.46%	1.46%	Upper 5%	2.51 (1.13-5.57)
					per 1 SD	1.1 (0.90-1.47, P=0.27)
Nielsen[28]	285,933	6.7 yrs		0.49%	>89 ms	1.60 (1.41–1.81 P<0.001)
					100-105 ms	1.00
					112-119 ms	1.22
					120-129 ms	1.50
					≥130	2.06
P-wave dispersion						
Perez [13]					>80 ms	1.95 (1.7-2.3, P<0.0001)
					SD of P duration >35	1.7 (1.3-2.1, P<0.0001)
P-morphology						
Soliman[14]					95th% of PTFV1	1.23 (1.04-1.46)
Magnani[16]					PTFV1 >0.04 V•s	1.56 (1.24-2.00)
Enriquez[35]	122	30 mo		46.7%	P duration ≥120 ms	2.9 (1.02-8.6, P<0.04)
					Biphasic P in II,I II, aVF	
Abn. P axis						
Perez [13]					>95th%	1.21 (0.69-2.12, P<0.0001)
					>74° and <24°	1.52 (1.05-2.21, P>0.0001
PAC/runs						
Watanabe [51]	63,368	10 yrs		0.14%	Standard ECG, ≥1/10 sec	2.89 (1.80-3.35)
Perez [13]					Presence	2.1 (1.6-2.7, P<0.0001)
Murakoshi [52]	63,197	14 yrs		0.105%	Presence	4.87 (6.61-6.57) for men 3.87 (2.69-5.57) for women
Acharya[56]	1,357	7.5 yrs		11.4%	≥100/day	2.97 (1.85-4.80)
					couplets ≥50/day	3.11
					bigeminy	3.67
					3 PACs run ≥20 /day	2.94
					runs (≥10 beats/run)	1.73
PR interval						
Perez [13]					>200 ms	1.3 (1.1-1.6, P=0.003)
Nielsen[69]	288,181	6.7 yrs		3.8%	≥196 ms men	1.30 (1.17-1.44)
					≥204 ms women	1.18 (1.06-1.530)
					<129 ms men	1.09 (0.92-1.29) ‡
					<121 ms women	1. 32 (1.12-1.56)
Alonso[25]	262,288	5 yrs		6.8%	per 30 ms	1.03 (0.85-1.26, <0.0001) to 1.22 (1.01-1.42, 0.027)
Macfarlane[68]	5,680	3.2 yrs		9.4%	per 30 ms	1.19 (1.09-1.30, P<0.0001)

PAC: premature atrial contraction. FU: follow-up. HR: hazard risk. mo: months. yrs: years. Ref. No.: reference number.

athletes, but heart rate was not a significant predictor for incident AF after multivariable analysis [2],[5].

P-wave duration

The P-wave duration represents the time required for a sinus impulse to propagate from the sinus node to the entire atrium. A prolonged P-wave duration correlates with a slowed conduction velocity within the atria [7],[8], and fragmented local electrograms suggest the presence of fibrosis [9],[10]. P-wave duration (ms) was measured from the P-wave onset to its offset, and the maximum P-wave duration, defined as the longest duration observed on a standard 12-lead ECG, is most often used to predict incident AF in population-based studies and can be an intermediate ECG phenotype of AF [11],[12]. Perez [13] analyzed the data of 42,751 patients who were followed for 5 .3 years. New AF developed in 1,050 patients at an annual rate of 0.45%/yr. After correcting for age and sex, the maximum P-wave duration of >120 ms was predictive of AF, with a hazard ratio (HR) of 1.6

(95% confidence interval (CI): 1.3-1.8, P <0.0001). The ARIC study (15,429 participants), which had an annual rate of AF development of 0.11%/yr ([14]), and the Framingham Heart Study (FHS) (1,550 participants aged ≥60 years), which had an annual rate of AF development of 0.46%/yr ([15]), showed similar results. The HR per 20 ms or per 1 SD of the P-wave duration was also significant [13],[16]. In studies with smaller sample sizes, P-wave duration was a predictor of PAF in patients without [17],[21] or with heart diseases [22],[24].

The sensitivity, specificity and positive and negative predictive values for a P-wave duration ≥120 ms were 53.8%, 61.7%, 49.0% and 97.3%, respectively [25], and they were 7.2%, 94.5%, 34.6% and 76.4%, respectively, for a P-wave duration above the 95th percentile [16].

In studies with smaller sample sizes (n=50 to 371), a shorter P-wave duration was associated with AF development [26],[27]. In the Copenhagen ECG study, 285,933 participants were followed for 6.7 years [28]. The ECGs were digitally analyzed with clinically validated software (Marquette 12SL algorithm, General Electric Co., Fairfield, CT). AF developed at a rate of 0.49%/yr in this study. Compared to subjects who had a P-wave duration of 100-105 ms, both shorter and longer P-wave durations were associated with an increased risk of AF development [Table 1].

Using SAECG, the filtered P-wave duration (FPD) ≥125 ms as well as the root mean square value of the last 20 ms (RMS20) of ≤3.3 μV were independent predictors for incident AF [29],[32].

P-wave dispersion and variation

P-wave dispersion (PWD) is defined as the difference between the longest and shortest P-wave durations across 12-leads of the surface ECG. Although a precise electrophysiological role for AF development is only speculative, a P-wave dispersion of >80 ms was associated with an AF history ([13],[15]-[18],[26],[30],[33]) or new AF detection on Holter ECG recordings [23]. The sensitivity, specificity and positive and negative predictive values for a P-wave dispersion above the 95th percentile were 3.6%, 94.5%, 16.7% and 76.4%, respectively [15]. The standard deviation (SD) of the P-wave duration across 12 leads >35 ms was another risk factor for incident AF [13].

P-wave morphology and P-wave axis

P-wave duration ≥120 ms with and without inversion of the terminal part of the P-wave was defined as an inter-atrial block (IAB) [34], and an advanced IAB was defined as a P-wave duration ≥120 ms, with a biphasic morphology in the inferior leads shown to represent a block in the Bachman bundle with caudo-cranial activation of the left atrium. Association of an IAB with new onset of AF or recurrence of AF after cardioversion has been observed [35]-[38]. Following cavo-tricuspid isthmus ablation in 122 patients with typical flutter and no history of AF (mean age 63 years), advanced IAB was observed in 23% [35]. After a mean follow-up of 30 months, 46.7% developed new-onset AF. The incidence of AF was significantly higher in patients with advanced IAB than in those without: 71.4% vs. 39.4% (P=0.003) and a risk of new AF ([Table 1]). A recent meta-analysis included 18,204 patients (mean age 56±13, 48% male) with a mean follow-up period of 15.1 years [39]; advanced IAB was a significant predictor of new-onset AF with a pooled HR of 2.58 (95% CI: 1.35 to 4.96; P< 0.01), but the risk of new-onset AF for partial IAB (=P-wave duration ≥120 msec) did not reach statistical significance (HR: 1.42, 95% CI: 0.85 to 2.34; P=0.18).

The P-wave terminal force (μV•ms) was determined as the product of the negative P-wave deflection in the lead V1 (μV) and the duration (ms) from the onset of the negative deflection to its nadir (PTFV1). PTFV1 is considered to represent a volume or pressure overload of the left atrium [40], inter-atrial conduction delay [7] and fibrosis of the left ventricle as measured by MRI [41]. PTFV1 >0.04 mV•s and the upper 5th percentile of PTFV1 are risk factors for developing AF ([13],[14],[52]). Notching or deflection of the P-wave [30], P-pulmonale [43], the area of the initial portion of the P-wave [14] and pre-specified P-wave morphology were risk factors for incident AF [32]. The P-wave axis represents the electrical wave front propagation and the geometry of the atria, and it is altered under a volume or pressure overload of the atrium. A P-wave axis outside of 24°-74° [13] or <74° in the frontal plane was another risk factor for new AF [43].

Premature atrial contractions

The prevalence of PACs increases with advancing age and comorbidities, and PAC becomes a risk factor for AF. PAC may originate within pulmonary veins and precipitate PAF [44]. Prevention is difficult when it progresses to chronic AF [45]-[49], and catheter ablation is the only effective therapeutic modality thus far [50]. Watanabe analyzed data from a mass examination of a general population of 63,386 participants aged ≥50 years in the Niigata Preventive Medicine Study [51]. During a 10-year follow-up, new AF developed at a rate of 0.14%/yr. The presence of PACs in 10-second recordings of standard 12-lead ECGs was associated with AF, with an odds ratio (OR) of 2.89 (1.80-3.35). This result was confirmed later by Perez [13] and Murakoshi [52].

In Holter ECGs, supraventricular tachyarrhythmias have been shown to be a predictor of incident AF [53]-[59]. Frequent PACs, defined as ≥100 beats /day [56]-[57], ≥30 beats/hr [58] or PACs ≥102 beats/day [59], were a risk factor for incident AF. It has been found that subclinical atrial tachyarrhythmias detected by implanted devices within 3 months are a predictor of clinical AF, with an HR of 5.56 (95% CI: 3.78-8.17, P<0.001) [60]. The CHADS2 score and the count of PACs can predict incident AF independently and synergistically [59]. PACs have been shown to aid the detection of AF in patients with cryptogenic stroke or transient ischemic attack who had no AF at baseline [61]-[68].

The sensitivity was in the range of 4.1-29.0%, with a high specificity of >90%. The positive and negative predictive values ranged from 2.9-9.1% and 88.7-97.7%, respectively ([13],[51],[52]).

PR interval

The PR interval (ms) was defined by automatic measurement from the onset of the P-wave to the initiation of the QRS segment. It is composed of atrial conduction, conduction through the atrio-ventricular node and the His-Purkinje system, and it is affected by autonomic tones. A PR interval >200 ms or PR interval of ≥95th percentile (≥196 ms for women and ≥204 ms for men) was a risk factor for incident AF ([3],[66]-[71]). A significant HR was obtained for a 30-ms increment of the PR intervals [3],[25]. In a subgroup of patients with P-pulmonale (n=591), a PQ interval >150 ms was associated with a higher HR of 6.89 (95% CI: 2.39-29.15, P<0.0001) [43]. A short PR interval (≤121 ms for women and ≤129 ms for men) [69] or PR interval variation (maximum PR interval minus minimum PR interval) >36.5 ms [71] was another risk for AF development.

The sensitivity, specificity and positive and negative predictive values were 7.5%, 95.8%, 5.2% and 77.4%, respectively, for PR intervals >95th percentile in FHS [15] and were 13.2%, 90.1%, 4.8% and 96.6%, respectively, for PR intervals >200 ms compared with those ≤200 ms [25].

However, there was a study showing that a prolonged PR interval was not associated with increased incident AF and that a PR interval >200 ms could normalize to ≤200 ms in 30% of patients during follow-up [72]. The underlying mechanism of how a prolonged PR interval induces AF is not well understood.

Ventricle-related ECG-derived predictors ([Table 2])

Left ventricular hypertrophy (LVH), premature ventricular contraction (PVC) or non-sustained ventricular tachycardia (NSVT), ST-T abnormalities and the QT (QTc) interval or bundle branch block (BBB) have been examined in large studies.

LVH

LVH is usually diagnosed from ECG criteria, and ECG-derived LVH has been used in mass examinations [73],[74]. The Sokolow-Lyon, Romhilt-Estes, Cornell voltage criteria or Minnesota code were used. LVH reduces the compliance of the left ventricle and imposes a pressure overload on the atrium, leading to dilatation and remodeling.

LVH was a risk factor for AF development during a 10-year follow-up period in Japanese people [51] (OR: 1.43; 95% CI: 1.13-1.80). This was confirmed by subsequent studies ([13],[25],[67],[68]). The ECG-derived LVH measure of the Sokolow-Lyon voltage product had a risk similar to that of the cardiac magnetic resonance-derived LVH: 1.83 (95% CI: 1.06-3.14) and 2.04 (95% CI: 1.15-3.62), respectively [75]. The calculated sensitivity, specificity and positive and negative predictive values for LVH were 5.1-11.5%, 94.7-97.9%, 5.2-8.3% and 97%, respectively ([13], [15], [25]).

PVC and runs

Watanabe [51] and later, Perez [13], showed that the presence of a PVC on surface ECG recordings during examination was associated with incident AF. Any PVCs recorded for 2 minutes were risk factors for incident AF [76]. In studies from Taiwan [77],[78], non-sustained

Table 2: Ventricle-related ECG-derived predictors for new-onset AF.

Author (Rf. No.)	Number of participants	FU time	Annual incidence	ECG finding	HR (95% CI, P-value)
LVH					
Watanabe(51)				Sokolow-Lyon	1.43 (1.13-1.80)
Perez[13]				**Romhilt-Estes**	**1.3 (1.0-1.7, P=0046)**
Chrispin[75]	4942			Sokolow-Lyon	1.83 (1.06-3.14)
Alonso[25]					1.04 (0.99-1.10) to 2.96 (1.08-8.01)
Macfarlane[68]	117			Minnesota code, definite	2.51 (1.13-5.57)
	138			probable	1.1 (0.90-1.47, P=0.27)
	709			possible	1.35 (1.08-1.70, 0.010)
PVC/runs					
Watanabe[51]				presence	3.49 (2.40-5.08)
Perez[13]				presence	1.5(1.2-1.9, P=0.004)
Agarwal[76]	14,783	15-17yrs		**presence in 2 min**	1.56 (1.30-1.87)
Lin[77]	3751	10.1 yrs	0.68	multiform NSVT	1.546 (1.058-2.258)
Lin[78]	3367	10.1 yrs	0.68	NSVT (≥3 PVCs)	**1.716(1.243-2.368)**
ST-T abn					
Watanabe[51]				without LVH	1.89 (1.34-2.13)
Macfarlane[68]				Minnesota code 5-1/5-2	1.7 6(1.41-2.21, P<0.0001)
BBB					
Perez[13]				LBBB	1.7(1.2-2.5, P<0.0001)
Watanabe[51]				LBBB	0.96 (-)
				RBBB	0.84 (-)1.17(1.08-1.27, P<0.001)
				QRS width per 20 ms	1.17(1.08-1.27, P<0.001)
Macfarlane[68]	4,696	12.3 yrs	2.16%	LAFB	2.1 (1.1- 3.9, P=0.023)
QTc					
Macfarlane[68]				per 30 ms increment	1.31(1.20-1.42, P<0.0001)
Mandyam[83]	14,538		0.51%	per 10 ms increment	1.11(1.07-1.14, P<0.001)
				≥460ms (women)/≥450 ms (men)	1.99 (1.37-2.89, P<0.001)
Nielsen[84]				≤372 ms	1.45 (1.14-1.84; P=0.002)
				≥458 ms	2.32 (1.52- 3.54, P<0.001)
Nguyen[55]				≥460 ms (women) or≥450 ms (men)	2.5 (1.4-4.3, P=0.002)

From the pooled data of the Framingham study, the ARIC study3) and the Cardiovascular Health study40) for derivation and the Rotterdam study41) for validation in CHARGE-AF Consortium.25) BBB: bundle branch block or hemi-block. FU: follow-up. HR: hazard risk. LAFB: left anterior fascicular block. LBBB: left bundle branch block. LVH: left ventricular hypertrophy. NSVT: non-sustained ventricular tachycardia ≥3 beats. RBBB: right bundle branch block. PVC: ventricular premature contraction. Ref. No.: reference number. ST-T abn. : ST-T abnormality

ventricular tachycardia was a risk for new-onset AF.

ST-T abnormalities

ST-T abnormalities reflect the presence of hypertrophy, fibrosis or conduction abnormalities of the ventricle and ischemia of the ventricle, and these conditions can lead to diastolic dysfunction of the ventricle and atrial remodeling. In the general population, Watanabe [51] showed that ST-T abnormalities unrelated to LVH were risk factors for new-onset AF, and this was confirmed by the PROSPER study [68].

Bundle branch block (BBB)

Perez [13] has shown that left BBB (LBBB) is a risk factor for AF development, but neither right BBB nor left BBB was a risk factor for new-onset AF in the Niigata Preventive Medicine study [51]. In the PROSPER study [68], widening of the QRS complex was a risk factor for incident AF. A left anterior fascicular block (LAFB) was a risk for AF development [55], but cases with LAFB were found in only 2.3% of the 1,664 participants [79].

QT interval

An inherited abnormality of the QT interval is known to be associated with a high incidence of AF ([80]-[82]), and its pathogenesis is related to the ion channelopathy of the atrium. QT intervals were corrected by either the Bazett, Framingham study, Hodges or Fridericia formula. A QTc ≥460 ms for women or QTc ≥450 ms for men was a risk factor for incident AF in the ARIC studies [83]. The risk of incident AF increases for every 40 ms [62] or 10 ms [1]increment of QTc. A QTc interval lower than the first percentile (≤372 ms) was also associated with a significant HR for incident AF compared with that in reference individuals (411 to 419 ms) [84].

Discussion

In population-based studies, some ECG-derived variables are risk factors for AF development. P wave abnormality, such as prolongation of the P-wave width, its dispersion, and morphology, and the presence of PACs/runs are the ECG phenotype of electrical remodeling of the left atrium and triggers for AF initiation, respectively. The ECG markers of the ventricle were also predictors for incident AF. Most of these ECG predictors are associated with low sensitivity and low positive predictive values, which leads to difficulty in identifying patients who are likely to develop AF. However, the high negative sensitivity can be used to identify those who are unlikely to develop AF.The ECG-derived risk findings can be a result of the underlying diseases that cause remodeling of the ventricle and the atrium.

Measurements of ECG-derived variables

The ECG-derived predictors for incident AF can be easily and simply obtained in a population-based study and measured automatically by recent ECG hardware setups, with the exception of P-wave index measurements. P-wave durations were initially measured manually and more recently by a computer-assisted system, but it may still require confirmation by cardiologists. P-wave dispersion is defined as the difference between the longest and the shortest P-wave durations across 12-leads, but its electrophysiological significance and role in AF development need to be clarified. P-wave durations may be measured precisely using SAECG, but its use is impractical for screening mass examinations.

ECG-based LVH is associated with incident AF, and it can be measured easily and automatically. However, it is known that the ventricular mass is more accurately determined by echocardiography [85] or magnetic resonance imaging [86], although the use of such techniques is apparently limited in population-based screening. The number and runs of PACs and PVCs can be counted precisely, but we were unable to locate their origin from the surface ECG alone. The majority of PACs that trigger paroxysmal AF is known to occur within the pulmonary vein [44]. Of other ECG variables, the QT interval has been shown to be a risk for new-onset AF, but it was corrected differently by the formulas of Bazett, Framingham, Hodges and Fridercia. Uniformed measurements may be desired in screening candidates for incident AF in a population-based study .

Clinical risk variables and ECG-derived risks

There are well-known clinical predictors for new-onset AF (age, gender, hypertension, obesity, diabetes mellitus and heart failure) ([1]-[6],[79]), and all of these variables induce electrical and structural remodeling of the atrium and the ventricle. With advancing age, the heart increases in weight, ventricular wall thickness and valve circumferences, and the myocardium contains increased fat, collagen, elastin and lipofuscin [14]; these abnormalities all involve the LA. The age-related LA remodeling is accelerated by comorbidities, such as hypertension, diabetes mellitus or obesity. On the surface ECG, the maximal P-wave duration, P-wave dispersion and standard deviation of P-wave duration were observed to correlate with advancing age ([87]-[89]). LV dysfunction imposes a pressure overload on the left atrium and leads to electrical and structural remodeling of the atrium. P-wave durations showed a correlation with diastolic dimensions, ejection fractions and diastolic functions of LV ([28], [72]-[74]) and interstitial fibrosis as determined by MRI [75].

In hypertension, the conduction time is prolonged ([90]-[92]), and the P-wave duration is prolonged in the surface ECG [18],[93]. Furthermore, P-wave indices can be a marker of target organ damage [94]. P-wave indices are abnormal in type 2 diabetes ([95],[96]) and obesity ([93]) compared to those in healthy control individuals.

Reversal of ECG-derived risks

Treatment of hypertension induces reversed remodeling of the heart [97]. With the use of angiotensin-2 receptor blockers or angiotensin converting enzyme inhibitors, prolonged P-wave durations or dispersions were observed to normalize ([98]-[102]), but this was not the case with calcium channel blockers [99].

These findings are compatible with the results of our experiments. In spontaneously hypertensive rats (SHRs), olmesartan (OM), an angiotensin 2 type 1 receptor blocker, reversed hypertrophy and fibrosis of the atrium more effectively than azelnidipine, a calcium channel blocker [103]. OM decreased atrial oxidative stress and activation of Rac1. The structural remodeling of the atrium was prevented by OM and a mineral corticoid antagonist eplerenone in Dahl salt-sensitive rats [104]. They induced an attenuation of oxidative stress and an attenuation of the Rac1-oxidative stress/inflammatory axis. The regression was associated with prevention of AF induction by electrical stimulation [104].

Through intensified treatment of blood pressure in patients with type 2 diabetes mellitus, a composite endpoint of new AF and prolonged P-wave indices and incident abnormal P-waves were shown to decrease (P=0.02 for both) in the ACCORD Blood Pressure Trials [105].

A significant decrease of P-wave duration or dispersion was observed in patients with loss of their original weight ([106],[107]). Severely obese patients (n=40) who underwent bariatric surgery showed a significant decrease of P-wave dispersion after surgery [108]. Treatment of underlying diseases can correct the abnormal P-wave

indices, but their prophylactic efficacy for incident AF is yet to be determined.

Limitations

In the population-based studies, AF was diagnosed on ECGs recorded for approximately 10 seconds, and this may lead to the under diagnosis of PAF. The correlation between the ECG-derived predictors and clinical predictors for incident AF was studied in a small number of patients. It is unknown whether the reversal of ECG risk variables can prevent new-onset AF. Future study of a larger number of participants is needed. Recently, a genetic analysis has highlighted candidate genes or SNPs associated with AF development [109], but their relevance to ECG-derived predictors remains unknown.

Conclusions

ECG-derived variables have been confirmed as a risk for incident AF from large population-based studies. The correlation between these markers with underlying disease or clinical predictors of incident AF needs to be shown in a study with a larger number of participants. Whether AF can be prevented by treatment of comorbidities requires prospective study.

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References

1. Benjamin E J, WolfP A, D'AgostinoR B, SilbershatzH, KannelW B, LevyD. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation. 1998;98 (10):946–52.
2. Feinleib M, KannelW B, GarrisonR J, McNamaraP M, CastelliW P. The Framingham Offspring Study. Design and preliminary data. Prev Med. 1975;4 (4):518–25.
3. Chamberlain Alanna M, AgarwalSunil K, FolsomAaron R, SolimanElsayed Z, ChamblessLloyd E, CrowRichard, AmbroseMarietta, AlonsoAlvaro. A clinical risk score for atrial fibrillation in a biracial prospective cohort (from the Atherosclerosis Risk in Communities [ARIC] study). Am. J. Cardiol. 2011;107 (1):85–91.
4. Fried L P, BorhaniN O, EnrightP, FurbergC D, GardinJ M, KronmalR A, KullerL H, ManolioT A, MittelmarkM B, NewmanA. The Cardiovascular Health Study: design and rationale. Ann Epidemiol. 1991;1 (3):263–76.
5. Hofman Albert, BretelerMonique M B, van DuijnCornelia M, JanssenHarry L A, KrestinGabriel P, KuipersErnst J, StrickerBruno H Ch, TiemeierHenning, UitterlindenAndré G, VingerlingJohannes R, WittemanJacqueline C M. The Rotterdam Study: 2010 objectives and design update. Eur. J. Epidemiol. 2009;24 (9):553–72.
6. Watanabe Hiroshi, TanabeNaohito, WatanabeToru, DarbarDawood, RodenDan M, SasakiShigeru, AizawaYoshifusa. Metabolic syndrome and risk of development of atrial fibrillation: the Niigata preventive medicine study. Circulation. 2008;117 (10):1255–60.
7. Josephson M E, KastorJ A, MorganrothJ. Electrocardiographic left atrial enlargement. Electrophysiologic, echocardiographic and hemodynamic correlates. Am. J. Cardiol. 1977;39 (7):967–71.
8. Xia Yunlong, HertervigEva, KongstadOle, LjungströmErik, PlatonovPyotr, PyotrPlatonov, HolmMagnus, OlssonBertil, YuanShiwen. Deterioration of interatrial conduction in patients with paroxysmal atrial fibrillation: electroanatomic mapping of the right atrium and coronary sinus. Heart Rhythm. 2004;1 (5):548–53.
9. Spach M S, DolberP C. Relating extracellular potentials and their derivatives to anisotropic propagation at a microscopic level in human cardiac muscle. Evidence for electrical uncoupling of side-to-side fiber connections with increasing age. Circ. Res. 1986;58 (3):356–71.
10. Kistler Peter M, SandersPrashanthan, FynnSimon P, StevensonIrene H, SpenceSteven J, VohraJitendra K, SparksPaul B, KalmanJonathan M. Electrophysiologic and electroanatomic changes in the human atrium associated with age. J. Am. Coll. Cardiol. 2004;44 (1):109–16.
11. Mines G R. On dynamic equilibrium in the heart. J. Physiol. (Lond.). 1913;46 (4-5):349–83.
12. Nattel Stanley. New ideas about atrial fibrillation 50 years on. Nature. 2002;415 (6868):219–26.
13. Perez Marco V, DeweyFrederick E, MarcusRachel, AshleyEuan A, Al-AhmadAmin A, WangPaul J, FroelicherVictor F. Electrocardiographic predictors of atrial fibrillation. Am. Heart J. 2009;158 (4):622–8.
14. Soliman Elsayed Z, PrineasRonald J, CaseL Douglas, ZhangZhu-ming, GoffDavid C. Ethnic distribution of ECG predictors of atrial fibrillation and its impact on understanding the ethnic distribution of ischemic stroke in the Atherosclerosis Risk in Communities (ARIC) study. Stroke. 2009;40 (4):1204–11.
15. Magnani Jared W, JohnsonVictor M, SullivanLisa M, GorodeskiEiran Z, SchnabelRenate B, LubitzSteven A, LevyDaniel, EllinorPatrick T, BenjaminEmelia J. P wave duration and risk of longitudinal atrial fibrillation in persons ≥ 60 years old (from the Framingham Heart Study). Am. J. Cardiol. 2011;107 (6):917–921.e1.
16. Magnani Jared W, ZhuLei, LopezFaye, PencinaMichael J, AgarwalSunil K, SolimanElsayed Z, BenjaminEmelia J, AlonsoAlvaro. P-wave indices and atrial fibrillation: cross-cohort assessments from the Framingham Heart Study (FHS) and Atherosclerosis Risk in Communities (ARIC) study. Am. Heart J. 2015;169 (1):53–61.e1.
17. Dilaveris P E, GialafosE J, SiderisS K, TheopistouA M, AndrikopoulosG K, KyriakidisM, GialafosJ E, ToutouzasP K. Simple electrocardiographic markers for the prediction of paroxysmal idiopathic atrial fibrillation. Am. Heart J. 1998;135 (5 Pt 1):733–8.
18. Aytemir Kudret, AmasyaliBasri, AbaliGulcan, KoseSedat, KilicAyhan, OnalanOrhan, TokgozogluLale, KabakciGiray, OzkutluHilmi, NazliNasih, IsikErsoy, OtoAli. The signal-averaged P-wave duration is longer in hypertensive patients with history of paroxysmal atrial fibrillation as compared to those without. Int. J. Cardiol. 2005;103 (1):37–40.
19. Andrikopoulos G K, DilaverisP E, RichterD J, GialafosE J, SynetosA G, GialafosJ E. Increased variance of P wave duration on the electrocardiogram distinguishes patients with idiopathic paroxysmal atrial fibrillation. Pacing Clin Electrophysiol. 2000;23 (7):1127–32.
20. Yoshizawa Tomoharu, NiwanoShinichi, NiwanoHiroe, IgarashiTazuru, FujiishiTamami, IshizueNaruya, OikawaJun, SatohAkira, KurokawaSayaka, HatakeyamaYuko, FukayaHidehira, AkoJunya. Prediction of new onset atrial fibrillation through P wave analysis in 12 lead ECG. Int Heart J. 2014;55 (5):422–7.
21. De Bacquer Dirk, WillekensJulie, De BackerGuy. Long-term prognostic value of p-wave characteristics for the development of atrial fibrillation in subjects aged 55 to 74 years at baseline. Am. J. Cardiol. 2007;100 (5):850–4.
22. Girasis Chrysafios, VassilikosVassilios, EfthimiadisGeorgios K, PapadopoulouStella-Lida, DakosGeorgios, DalamagaEmmanuela G, ChouvardaIoanna, GiannakoulasGeorgios, KamperidisVassilios, ParaskevaidisStylianos, MaglaverasNicos, KarvounisHaralambos I, ParcharidisGeorgios E, StyliadisIoannis H. Patients with hypertrophic cardiomyopathy at risk for paroxysmal atrial fibrillation: advanced echocardiographic evaluation of the left atrium combined with non-invasive P-wave analysis. Eur Heart J Cardiovasc Imaging. 2013;14 (5):425–34.
23. Dilaveris P E, GialafosE J, ChrissosD, AndrikopoulosG K, RichterD J,

LazakiE, GialafosJ E. Detection of hypertensive patients at risk for paroxysmal atrial fibrillation during sinus rhythm by computer-assisted P wave analysis. J. Hypertens. 1999;17 (10):1463–70.

24. Altunkeser Bülent B, OzdemirKurtuluş, GökHasan, TemizhanAhmet, TokaçMehmet, KarabağTurgut. Can P wave parameters obtained from 12-lead surface electrocardiogram be a predictor for atrial fibrillation in patients who have structural heart disease?. Angiology. 2003;54 (4):475–9.
25. Alonso Alvaro, KrijtheBouwe P, AspelundThor, StepasKatherine A, PencinaMichael J, MoserCarlee B, SinnerMoritz F, SotoodehniaNona, FontesJoão D, JanssensA Cecile J W, KronmalRichard A, MagnaniJared W, WittemanJacqueline C, ChamberlainAlanna M, LubitzSteven A, SchnabelRenate B, AgarwalSunil K, McManusDavid D, EllinorPatrick T, LarsonMartin G, BurkeGregory L, LaunerLenore J, HofmanAlbert, LevyDaniel, GottdienerJohn S, KääbStefan, CouperDavid, HarrisTamara B, SolimanElsayed Z, StrickerBruno H C, GudnasonVilmundur, HeckbertSusan R, BenjaminEmelia J. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. J Am Heart Assoc. 2013;2 (2):–.
26. Ivanov A P, DedovD V. [Evaluation of the risk of atrial fibrillation using disperse analysis of P in ECG]. Klin Med (Mosk). 2007;85 (2):30–2.
27. Chang Ian C Y, AustinErin, KrishnanBalaji, BendittDavid G, QuayChwee N, LingLieng H, ChenLin Y. Shorter minimum p-wave duration is associated with paroxysmal lone atrial fibrillation. J Electrocardiol. 2013;47 (1):106–12.
28. Nielsen Jonas B, KühlJørgen T, PietersenAdrian, GraffClaus, LindBent, StruijkJohannes J, OlesenMorten S, SinnerMoritz F, BachmannTroels N, HaunsøStig, NordestgaardBørge G, EllinorPatrick T, SvendsenJesper H, KofoedKlaus F, KøberLars, HolstAnders G. P-wave duration and the risk of atrial fibrillation: Results from the Copenhagen ECG Study. Heart Rhythm. 2015;12 (9):1887–95.
29. Guidera S A, SteinbergJ S. The signal-averaged P wave duration: a rapid and noninvasive marker of risk of atrial fibrillation. J. Am. Coll. Cardiol. 1993;21 (7):1645–51.
30. Budeus Marco, HennersdorfMarcus, FelixOliver, ReimertKlaus, PeringsChristian, WienekeHeinrich, ErbelRaimund, SackStefan. Prediction of atrial fibrillation in patients with cardiac dysfunctions: P wave signal-averaged ECG and chemoreflexsensitivity in atrial fibrillation. Europace. 2007;9 (8):601–7.
31. Dixen Ulrik, LarsenMette Vang, RavnLasse, ParnerJan, JensenGorm B. Signal-averaged P wave duration and the long-term risk of permanent atrial fibrillation. Scand. Cardiovasc. J. 2008;42 (1):31–7.
32. Holmqvist Fredrik, PlatonovPyotr G, McNittScott, PolonskySlava, CarlsonJonas, ZarebaWojciech, MossArthur J. Abnormal P-wave morphology is a predictor of atrial fibrillation development and cardiac death in MADIT II patients. Ann Noninvasive Electrocardiol. 2010;15 (1):63–72.
33. Tükek T, AkkayaV, AtilganD, DemirelE, OzcanM, GüvenO, KorkutF. Effect of left atrial size and function on P-wave dispersion: a study in patients with paroxysmal atrial fibrillation. Clin Cardiol. 2001;24 (10):676–80.
34. Bayes de Luna A, Fort de RibotR, TrillaE, JuliaJ, GarciaJ, SadurniJ, RibaJ, SaguesF. Electrocardiographic and vectorcardiographic study of interatrial conduction disturbances with left atrial retrograde activation. J Electrocardiol. 1985;18 (1):1–13.
35. Enriquez Andres, SarriasAxel, VilluendasRoger, AliFariha Sadiq, CondeDiego, HopmanWilma M, RedfearnDamian P, MichaelKevin, SimpsonChristopher, De LunaAntoni Bayés, Bayés-GenísAntoni, BaranchukAdrian. New-onset atrial fibrillation after cavotricuspid isthmus ablation: identification of advanced interatrial block is key. Europace. 2015;17 (8):1289–93.
36. Sadiq Ali Fariha, EnriquezAndres, CondeDiego, RedfearnDamian, MichaelKevin, SimpsonChristopher, AbdollahHoshiar, Bayés de LunaAntoni, HopmanWilma, BaranchukAdrian. Advanced Interatrial Block Predicts New Onset Atrial Fibrillation in Patients with Severe Heart Failure and Cardiac Resynchronization Therapy. Ann Noninvasive Electrocardiol. 2015;20 (6):586–91.
37. Martínez-Sellés Manuel, Massó-van RoesselAlbert, Álvarez-GarcíaJesús, García de la VillaBernardo, Cruz-JentoftAlfonso J, VidánMaría Teresa, López DíazJavier, Felix RedondoFrancisco Javier, Durán GuerreroJuan Manuel, Bayes-GenisAntoni, Bayes de LunaAntonio. Interatrial block and atrial arrhythmias in centenarians: Prevalence, associations, and clinical implications. Heart Rhythm. 2016;13 (3):645–51.
38. Enriquez Andres, CondeDiego, HopmanWilma, MondragonIgnacio, ChialePablo A, de LunaAntoni Bayés, BaranchukAdrian. Advanced interatrial block is associated with recurrence of atrial fibrillation post pharmacological cardioversion. Cardiovasc Ther. 2014;32 (2):52–6.
39. Tse Gary, WongCheuk Wai, GongMengqi, WongWing Tak, BazoukisGeorge, WongSunny Hei, LiGuangping, WuWilliam K K, TseLap Ah, LampropoulosKonstantinos, XiaYunlong, LiuTong, BaranchukAdrian. Predictive value of inter-atrial block for new onset or recurrent atrial fibrillation: A systematic review and meta-analysis. Int. J. Cardiol. 2018;250 ():152–156.
40. Morris J J, Estes E H, Whalen R E, Thompson H K, Mcintosh H D. P-wave analysis in valvular heart disease. Circulation. 1964;29 ():242–52.
41. Tiffany Win Theingi, Ambale VenkateshBharath, VolpeGustavo J, MewtonNathan, RizziPatricia, SharmaRavi K, StraussDavid G, LimaJoao A, TereshchenkoLarisa G. Associations of electrocardiographic P-wave characteristics with left atrial function, and diffuse left ventricular fibrosis defined by cardiac magnetic resonance: The PRIMERI Study. Heart Rhythm. 2015;12 (1):155–62.
42. Ishida Katsuya, HayashiHideki, MiyamotoAkashi, SugimotoYoshihisa, ItoMakoto, MurakamiYoshitaka, HorieMinoru. P wave and the development of atrial fibrillation. Heart Rhythm. 2010;7 (3):289–94.
43. Hayashi Hideki, MiyamotoAkashi, KawaguchiTamiro, NaikiNobu, XueJoel Q, MatsumotoTetsuya, MurakamiYoshitaka, HorieMinoru. P-pulmonale and the development of atrial fibrillation. Circ. J. 2014;78 (2):329–37.
44. Haïssaguerre M, JaïsP, ShahD C, TakahashiA, HociniM, QuiniouG, GarrigueS, Le MourouxA, Le MétayerP, ClémentyJ. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N. Engl. J. Med. 1998;339 (10):659–66.
45. Ohe T, MatsuhisaM, KamakuraS, YamadaJ, SatoI, NakajimaK, ShimomuraK. Relation between the widening of the fragmented atrial activity zone and atrial fibrillation. Am. J. Cardiol. 1983;52 (10):1219–22.
46. Wijffels M C, KirchhofC J, DorlandR, AllessieM A. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation. 1995;92 (7):1954–68.
47. Tsang Teresa S M, BarnesMarion E, MiyasakaYoko, ChaStephen S, BaileyKent R, VerzosaGrace C, SewardJames B, GershBernard J. Obesity as a risk factor for the progression of paroxysmal to permanent atrial fibrillation: a longitudinal cohort study of 21 years. Eur. Heart J. 2008;29 (18):2227–33.
48. Pappone Carlo, RadinovicAndrea, MangusoFrancesco, VicedominiGabriele, CiconteGiuseppe, SacchiStefania, MazzonePatrizio, PaglinoGabriele, GullettaSimone, SalaSimone, SantinelliVincenzo. Atrial fibrillation progression and management: a 5-year prospective follow-up study. Heart Rhythm. 2008;5 (11):1501–7.
49. Aizawa Yoshifusa, YagiharaNobue, IzumkiDaisuke, HanawaHaruo, KodamaMakoto, SatohMasahito, TanabeYasuhiko, TsudaTakashi, AbeAkira, SakaiKazuyuki, MatsubaraTaku, SuzukiKeisuke, TagawaMinoru, SugiuraHirotaka, MasaniFumiaki, MorikawaMasatsugu. The time course of paroxysmal atrial fibrillation and its implications: an analysis from a snapshot. Int. J. Cardiol. 2013;168 (3):2867–8.
50. Cappato Riccardo, CalkinsHugh, ChenShih-Ann, DaviesWyn, IesakaYoshito, KalmanJonathan, KimYou-Ho, KleinGeorge, PackerDouglas, SkanesAllan. Worldwide survey on the methods, efficacy, and safety of catheter ablation for

human atrial fibrillation. Circulation. 2005;111 (9):1100–5.
51. Watanabe Hiroshi, TanabeNaohito, MakiyamaYashiro, ChopraSameer S, OkuraYuji, SuzukiHiroshi, MatsuiKazumitsu, WatanabeToru, KurashinaYoshiaki, AizawaYoshifusa. ST-segment abnormalities and premature complexes are predictors of new-onset atrial fibrillation: the Niigata preventive medicine study. Am. Heart J. 2006;152 (4):731–5.
52. Murakoshi Nobuyuki, XuDongZhu, SairenchiToshimi, IgarashiMiyako, IrieFujiko, TomizawaTakuji, TadaHiroshi, SekiguchiYukio, YamagishiKazumasa, IsoHiroyasu, YamaguchiIwao, OtaHitoshi, AonumaKazutaka. Prognostic impact of supraventricular premature complexes in community-based health checkups: the Ibaraki Prefectural Health Study. Eur. Heart J. 2015;36 (3):170–8.
53. Thong Tran, McNamesJames, AboyMateo, GoldsteinBrahm. Prediction of paroxysmal atrial fibrillation by analysis of atrial premature complexes. IEEE Trans Biomed Eng. 2004;51 (4):561–9.
54. Johnson Linda S B, JuhlinTord, Juul-MöllerSteen, HedbladBo, NilssonPeter M, EngströmGunnar. A prospective study of supraventricular activity and incidence of atrial fibrillation. Heart Rhythm. 2015;12 (9):1898–904.
55. Nguyen Kaylin T, VittinghoffEric, DewlandThomas A, MandyamMala C, SteinPhyllis K, SolimanElsayed Z, HeckbertSusan R, MarcusGregory M. Electrocardiographic Predictors of Incident Atrial Fibrillation. Am. J. Cardiol. 2016;118 (5):714–9.
56. Acharya Tushar, TringaliSteven, BhullarManminder, NalbandyanMarta, IlineniVishnu Karthik, CarbajalEnrique, DeedwaniaPrakash. Frequent Atrial Premature Complexes and Their Association With Risk of Atrial Fibrillation. Am. J. Cardiol. 2015;116 (12):1852–7.
57. Chong Boon-Hor, PongVincent, LamKwok-Fai, LiuShasha, ZuoMing-Liang, LauYuk-Fai, LauChu-Pak, TseHung-Fat, SiuChung-Wah. Frequent premature atrial complexes predict new occurrence of atrial fibrillation and adverse cardiovascular events. Europace. 2012;14 (7):942–7.
58. Binici Zeynep, IntzilakisTheodoros, NielsenOlav Wendelboe, KøberLars, SajadiehAhmad. Excessive supraventricular ectopic activity and increased risk of atrial fibrillation and stroke. Circulation. 2010;121 (17):1904–11.
59. Suzuki Shinya, SagaraKoichi, OtsukaTakayuki, KanoHiroto, MatsunoShunsuke, TakaiHideaki, UejimaTokuhisa, OikawaYuji, KoikeAkira, NagashimaKazuyuki, KirigayaHajime, YajimaJunji, TanabeHiroaki, SawadaHitoshi, AizawaTadanori, YamashitaTakeshi. Usefulness of frequent supraventricular extrasystoles and a high CHADS2 score to predict first-time appearance of atrial fibrillation. Am. J. Cardiol. 2013;111 (11):1602–7.
60. Healey Jeff S, ConnollyStuart J, GoldMichael R, IsraelCarsten W, Van GelderIsabelle C, CapucciAlessandro, LauC P, FainEric, YangSean, BailleulChristophe, MorilloCarlos A, CarlsonMark, ThemelesEllison, KaufmanElizabeth S, HohnloserStefan H. Subclinical atrial fibrillation and the risk of stroke. N. Engl. J. Med. 2012;366 (2):120–9.
61. Wallmann Dieter, TüllerDavid, WustmannKerstin, MeierPascal, IseneggerJörg, ArnoldMarcel, MattleHeinrich P, DelacrétazEtienne. Frequent atrial premature beats predict paroxysmal atrial fibrillation in stroke patients: an opportunity for a new diagnostic strategy. Stroke. 2007;38 (8):2292–4.
62. Weber-Krüger Mark, GröschelKlaus, MendeMeinhard, SeegersJoachim, LahnoRosine, HaaseBeatrice, NiehausCord-Friedrich, EdelmannFrank, HasenfußGerd, WachterRolf, StahrenbergRaoul. Excessive supraventricular ectopic activity is indicative of paroxysmal atrial fibrillation in patients with cerebral ischemia. PLoS ONE. 2013;8 (6):–.
63. Kochhäuser Simon, DecheringDirk G, DittrichRalf, ReinkeFlorian, RitterMartin A, RamtinShahram, DuningThomas, FrommeyerGerrit, EckardtLars. Supraventricular premature beats and short atrial runs predict atrial fibrillation in continuously monitored patients with cryptogenic stroke. Stroke. 2014;45 (3):884–6.
64. Gladstone David J, DorianPaul, SpringMelanie, PanzovVal, MamdaniMuhammad, HealeyJeff S, ThorpeKevin E. Atrial premature beats predict atrial fibrillation in cryptogenic stroke: results from the EMBRACE trial. Stroke. 2015;46 (4):936–41.
65. Larsen Bjørn Strøier, KumarathuraiPreman, FalkenbergJulie, NielsenOlav W, SajadiehAhmad. Excessive Atrial Ectopy and Short Atrial Runs Increase the Risk of Stroke Beyond Incident Atrial Fibrillation. J. Am. Coll. Cardiol. 2015;66 (3):232–241.
66. Cheng Susan, KeyesMichelle J, LarsonMartin G, McCabeElizabeth L, Newton-ChehChristopher, LevyDaniel, BenjaminEmelia J, VasanRamachandran S, WangThomas J. Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block. JAMA. 2009;301 (24):2571–7.
67. Schnabel Renate B, SullivanLisa M, LevyDaniel, PencinaMichael J, MassaroJoseph M, D'AgostinoRalph B, Newton-ChehChristopher, YamamotoJennifer F, MagnaniJared W, TadrosThomas M, KannelWilliam B, WangThomas J, EllinorPatrick T, WolfPhilip A, VasanRamachandran S, BenjaminEmelia J. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. Lancet. 2009;373 (9665):739–45.
68. Macfarlane Peter W, MurrayHeather, SattarNaveed, StottDavid J, FordIan, BuckleyBrendan, JukemaJ Wouter, WestendorpRudi G J, ShepherdJames. The incidence and risk factors for new onset atrial fibrillation in the PROSPER study. Europace. 2011;13 (5):634–9.
69. Nielsen Jonas Bille, PietersenAdrian, GraffClaus, LindBent, StruijkJohannes Jan, OlesenMorten Salling, HaunsøStig, GerdsThomas Aalexander, EllinorPatrick Thomas, KøberLars, SvendsenJesper Hastrup, HolstAnders Gaarsdal. Risk of atrial fibrillation as a function of the electrocardiographic PR interval: results from the Copenhagen ECG Study. Heart Rhythm. 2013;10 (9):1249–56.
70. Magnani Jared W, WangNa, NelsonKerrie P, ConnellyStephanie, DeoRajat, RodondiNicolas, SchelbertErik B, GarciaMelissa E, PhillipsCaroline L, ShlipakMichael G, HarrisTamara B, EllinorPatrick T, BenjaminEmelia J. Electrocardiographic PR interval and adverse outcomes in older adults: the Health, Aging, and Body Composition study. Circ Arrhythm Electrophysiol. 2013;6 (1):84–90.
71. Chun Kwang Jin, HwangJin Kyung, ParkSeung-Jung, OnYoung Keun, KimJune Soo, ParkKyoung-Min. Electrical PR Interval Variation Predicts New Occurrence of Atrial Fibrillation in Patients With Frequent Premature Atrial Contractions. Medicine (Baltimore). 2016;95 (14):–.
72. Aro Aapo L, AnttonenOlli, KerolaTuomas, JunttilaM Juhani, TikkanenJani T, RissanenHarri A, ReunanenAntti, HuikuriHeikki V. Prognostic significance of prolonged PR interval in the general population. Eur. Heart J. 2014;35 (2):123–9.
73. Romhilt D W, EstesE H. A point-score system for the ECG diagnosis of left ventricular hypertrophy. Am. Heart J. 1968;75 (6):752–8.
74. Benjamin E J, LevyD, VaziriS M, D'AgostinoR B, BelangerA J, WolfP A. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA. 1994;271 (11):840–4.
75. Chrispin Jonathan, JainAditya, SolimanElsayed Z, GuallarEliseo, AlonsoAlvaro, HeckbertSusan R, BluemkeDavid A, LimaJoão A C, NazarianSaman. Association of electrocardiographic and imaging surrogates of left ventricular hypertrophy with incident atrial fibrillation: MESA (Multi-Ethnic Study of Atherosclerosis). J. Am. Coll. Cardiol. 2014;63 (19):2007–13.
76. Agarwal Sunil K, HeissGerardo, RautaharjuPentti M, ShaharEyal, MassingMark W, SimpsonRoss J. Premature ventricular complexes and the risk of incident stroke: the Atherosclerosis Risk In Communities (ARIC) Study. Stroke. 2010;41 (4):588–93.
77. Lin Chin-Yu, ChangShih-Lin, LinYenn-Jiang, LoLi-Wei, ChungFa-Po, ChenYun-Yu, ChaoTze-Fan, HuYu-Feng, TuanTa-Chuan, LiaoJo-Nan, HuangYen-Chang, ChangYaoting, ChiouChuen-Wang, ChenShih-Ann. Long-term outcome of multiform premature ventricular complexes in structurally normal heart. Int. J. Cardiol. 2015;180 ():80–5.
78. Lin Chin-Yu, ChangShih-Lin, ChungFa-Po, ChenYun-Yu, LinYenn-Jiang,

LoLi-Wei, HuYu-Feng, TuanTa-Chuan, ChaoTze-Fan, LiaoJo-Nan, ChangYao-Ting, LinChung-Hsing, AllamsettySuresh, WaliaRohit, TeAbigail Louise D, YamadaShinya, ChiangShuo-Ju, TsaoHsuan-Ming, ChenShih-Ann. Long-Term Outcome of Non-Sustained Ventricular Tachycardia in Structurally Normal Hearts. PLoS ONE. 2016;11 (8):–.

79. Mandyam Mala C, SolimanElsayed Z, HeckbertSusan R, VittinghoffEric, MarcusGregory M. Long-term outcomes of left anterior fascicular block in the absence of overt cardiovascular disease. JAMA. 2013;309 (15):1587–8.
80. Giustetto Carla, SchimpfRainer, MazzantiAndrea, ScroccoChiara, MauryPhilippe, AnttonenOlli, ProbstVincent, BlancJean-Jacques, SbragiaPascal, DalmassoPaola, BorggrefeMartin, GaitaFiorenzo. Long-term follow-up of patients with short QT syndrome. J. Am. Coll. Cardiol. 2011;58 (6):587–95.
81. Johnson Jonathan N, TesterDavid J, PerryJames, SalisburyBenjamin A, ReedCarol R, AckermanMichael J. Prevalence of early-onset atrial fibrillation in congenital long QT syndrome. Heart Rhythm. 2008;5 (5):704–9.
82. Enriquez Andres, AntzelevitchCharles, BismahVerdah, BaranchukAdrian. Atrial fibrillation in inherited cardiac channelopathies: From mechanisms to management. Heart Rhythm. 2016;13 (9):1878–84.
83. Mandyam Mala C, SolimanElsayed Z, AlonsoAlvaro, DewlandThomas A, HeckbertSusan R, VittinghoffEric, CummingsSteven R, EllinorPatrick T, ChaitmanBernard R, StockeKaren, ApplegateWilliam B, ArkingDan E, ButlerJaved, LoehrLaura R, MagnaniJared W, MurphyRachel A, SatterfieldSuzanne, NewmanAnne B, MarcusGregory M. The QT interval and risk of incident atrial fibrillation. Heart Rhythm. 2013;10 (10):1562–8.
84. Nielsen Jonas Bille, GraffClaus, PietersenAdrian, LindBent, StruijkJohannes Jan, OlesenMorten Salling, HaunsøStig, GerdsThomas Alexander, SvendsenJesper Hastrup, KøberLars, HolstAnders Gaarsdal. J-shaped association between QTc interval duration and the risk of atrial fibrillation: results from the Copenhagen ECG study. J. Am. Coll. Cardiol. 2013;61 (25):2557–64.
85. Devereux R B, KorenM J, de SimoneG, OkinP M, KligfieldP. Methods for detection of left ventricular hypertrophy: application to hypertensive heart disease. Eur. Heart J. 1993;14 Suppl D ():8–15.
86. Hundley W Gregory, BluemkeDavid A, FinnJ Paul, FlammScott D, FogelMark A, FriedrichMatthias G, HoVincent B, Jerosch-HeroldMichael, KramerChristopher M, ManningWarren J, PatelManesh, PohostGerald M, StillmanArthur E, WhiteRichard D, WoodardPamela K. ACCF/ACR/AHA/NASCI/SCMR 2010 expert consensus document on cardiovascular magnetic resonance: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. Circulation. 2010;121 (22):2462–508.
87. Magnani Jared W, JohnsonVictor M, SullivanLisa M, LubitzSteven A, SchnabelRenate B, EllinorPatrick T, BenjaminEmelia J. P-wave indices: derivation of reference values from the Framingham Heart Study. Ann Noninvasive Electrocardiol. 2010;15 (4):344–52.
88. Yildirim Nesligül, TulmacMurat, SimsekVedat, Tolga DogruMehmet, EbincHaksun, GuzelMurat, CelikYunus, EserOzer. Atrial electromechanical coupling interval and P-wave dispersion in healthy elderly. Aging Clin Exp Res. 2012;24 (3):265–9.
89. Babaev A A, VlokaM E, SadurskiR, SteinbergJ S. Influence of age on atrial activation as measured by the P-wave signal-averaged electrocardiogram. Am. J. Cardiol. 2000;86 (6):692–5, A9.
90. Yildirim Nesligül, SimsekVedat, TulmacMurat, EbincHaksun, DogruMehmet Tolga, AlpCaglar, AgraliÖzkan, CelikYunus, EserOzer, DemirVahit, SimsekFadime. Atrial electromechanical coupling interval and P-wave dispersion in patients with white coat hypertension. Clin. Exp. Hypertens. 2012;34 (5):350–6.
91. Madu E C, BaughD S, GbadeboT D, DhalaA, CardosoS. Effect of ethnicity and hypertension on atrial conduction: evaluation with high-resolution P-wave signal averaging. Clin Cardiol. 2001;24 (9):597–602.
92. Emiroglu Mehmet Yunus, BulutMustafa, SahinMüslim, AcarGurkan, AkcakoyunMustafa, KarginRamazan, KayancicekHidayet, KarapinarHekim, AungSoe Moe. Assessment of atrial conduction time in patients with essential hypertension. J Electrocardiol. 2011;44 (2):251–6.
93. Magnani Jared W, LopezFaye L, SolimanElsayed Z, MaclehoseRichard F, CrowRichard S, AlonsoAlvaro. P wave indices, obesity, and the metabolic syndrome: the atherosclerosis risk in communities study. Obesity (Silver Spring). 2012;20 (3):666–72.
94. Dagli Necati, KaracaIlgin, YavuzkirMustafa, BalinMehmet, ArslanNadi. Are maximum P wave duration and P wave dispersion a marker of target organ damage in the hypertensive population?. Clin Res Cardiol. 2008;97 (2):98–104.
95. Yazici Mehmet, OzdemirKurtulus, AltunkeserBulent B, KayrakMehmet, DuzenliM Akif, VatankuluM Akif, SoyluAhmet, UlgenMehmet S. The effect of diabetes mellitus on the P-wave dispersion. Circ. J. 2007;71 (6):880–3.
96. Bissinger Andrzej, GrycewiczTomasz, GrabowiczWlodzimierz, LubinskiAndrzej. The effect of diabetic autonomic neuropathy on P-wave duration, dispersion and atrial fibrillation. Arch Med Sci. 2011;7 (5):806–12.
97. Schmieder R E, MartusP, KlingbeilA. Reversal of left ventricular hypertrophy in essential hypertension. A meta-analysis of randomized double-blind studies. JAMA. 1996;275 (19):1507–13.
98. Celik Turgay, IyisoyAtila, KursakliogluHurkan, YilmazM Ilker, KoseSedat, KilicSelim, AmasyaliBasri, DemirkolSait, IsikErsoy. The comparative effects of telmisartan and ramipril on P-wave dispersion in hypertensive patients: a randomized clinical study. Clin Cardiol. 2005;28 (6):298–302.
99. Nomura Masahiro, KawanoTomohito, NakayasuKimiko, NakayaYutaka. The effects of losartan on signal-averaged P wave in patients with atrial fibrillation. Int. J. Cardiol. 2008;126 (1):21–7.
100. Ozben Beste, SumerkanMutlu, TanrikuluAzra Meryem, Papila-TopalNurdan, FakAli Serdar, ToprakAhmet. Perindopril decreases P wave dispersion in patients with stage 1 hypertension. J Renin Angiotensin Aldosterone Syst. 2009;10 (2):85–90.
101. Tuncer Mustafa, GunesYilmaz, GuntekinUnal, GumrukcuogluHasan Ali, EryonucuBeyhan. Short-term effects of cilazapril and atenolol on P-wave dispersion in patients with hypertension. Adv Ther. 2008;25 (2):99–105.
102. Sengul Cihan, CevikCihan, OzverenOlcay, OduncuVecih, SunbulAysegul, KılıcarslanFethi, SemizEnder, DindarIsmet. Telmisartan decreases atrial electromechanical delay in patients with newly diagnosed essential hypertension. J Electrocardiol. 2012;45 (2):123–8.
103. Okamura Kazuki, ItoMasahiro, TanakaKomei, ChinushiMasaomi, AdachiTakeshi, MitsumaWataru, HironoSatoru, NakazawaMikio, KodamaMakoto, AizawaYoshifusa. Comparative effects of olmesartan and azelnidipine on atrial structural remodeling in spontaneously hypertensive rats. Pharmacology. 2009;83 (6):360–6.
104. Kimura Shinpei, ItoMasahiro, TomitaMakoto, HoyanoMakoto, ObataHiroaki, DingLimin, ChinushiMasaomi, HanawaHaruo, KodamaMakoto, AizawaYoshifusa. Role of mineralocorticoid receptor on atrial structural remodeling and inducibility of atrial fibrillation in hypertensive rats. Hypertens. Res. 2011;34 (5):584–91.
105. Chen Lin Y, BiggerJ Thomas, HickeyKathleen T, ChenHaiying, Lopez-JimenezCarlos, BanerjiMary Ann, EvansGregory, FlegJerome L, PapademetriouVasilios, ThomasAbraham, WooVincent, SeaquistElizabeth R, SolimanElsayed Z. Effect of Intensive Blood Pressure Lowering on Incident Atrial Fibrillation and P-Wave Indices in the ACCORD Blood Pressure Trial. Am. J. Hypertens. 2015; ():–.
106. Duru Mehmet, SeyfeliErgun, KuvandikGuven, KayaHasan, YalcinFatih. Effect of weight loss on P wave dispersion in obese subjects. Obesity (Silver Spring). 2006;14 (8):1378–82.
107. Falchi Anna Giulia, GrecchiIlaria, MuggiaChiara, TinelliCarmine. Weight loss and P wave dispersion: a preliminary study. Obes Res Clin Pract. 2014;8 (6):e614–

7.

108. Russo Vincenzo, AmmendolaErnesto, De CrescenzoIlaria, DocimoLudovico, SantangeloLucio, CalabròRaffaele. Severe obesity and P-wave dispersion: the effect of surgically induced weight loss. Obes Surg. 2008;18 (1):90–6.

109. Mahida Saagar, EllinorPatrick T. New advances in the genetic basis of atrial fibrillation. J. Cardiovasc. Electrophysiol. 2012;23 (12):1400–6. [PubMed]Aksu Tolga, GulerTumer Erdem, YalinKivanc, GolcukSukriye Ebru, OzcanKazim Serhan, GulerNiyazi. A Novel Deep Inspiration Maneuver for Difficult Transseptal Puncture. Am. J. Cardiol. 2017;119 (3):428–433