Title: Orthogonal P-wave morphology, conventional P-wave indices, and the risk of atrial fibrillation in the general population using data from the Finnish Hospital Discharge Register

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Condensed abstract

The risk of AF (documented during hospitalization for any reason), associated with sinus P-wave parameters linked to atrial fibrosis, was assessed in the general population. 3rd degree interatrial block and Type 3 orthogonal P-wave morphology were associated with the risk of AF. Type 1 P waves <110ms indicated low risk.

Abstract

Aims: Identifying subjects at high and low risk of atrial fibrillation (AF) is of interest. This study aims to assess the risk of AF associated with electrocardiographic (ECG) markers linked to atrial fibrosis: P-wave prolongation, 3rd degree interatrial block (3degIAB), P terminal force in lead V_1 (PTF), and orthogonal P-wave morphology.

Methods: P-wave parameters were assessed in a representative Finnish population sample aged ≥30 years (n=7217, 46.0% male, mean age 51.4 years). Subjects (n=5489) with a readable ECG including the orthogonal leads, sinus rhythm, and a predefined orthogonal P-wave morphology type (positive in leads X and Y and either negative [Type1] or -/+ biphasic [Type 2] in lead Z; Type 3 defined as positive in lead X and +/- biphasic in lead Y), were followed 10 years from the baseline examinations (performed 1978-80). Subjects discharged with AF diagnosis after any-cause hospitalization (n=124) were defined as having developed AF. 3degIAB was defined as P-wave ≥120ms and the presence of ≥2 +/- biphasic P waves in the inferior leads. Hazard ratios (HR) and confidence intervals (CI) were assessed with Cox models.

Results: 3degIAB (n=103, HR 3.18, 95% CI 1.66–6.13, p=0.001) and Type 3 morphology (n=216, HR 3.01, 95% CI 1.66–5.45, p<0.001) were independently associated with the risk of hospitalization with AF. Subjects with P-wave <110ms and Type 1 morphology (n=2074) were at low risk (HR 0.46, 95% CI 0.26–0.83, p=0.006), compared to the rest of the subjects.

Conclusion: P-wave parameters associate with the risk of hospitalization with AF.

Key Words: Atrial Fibrillation, Electrocardiography, P Wave, Interatrial Block, P Terminal Force

What's New?

- This is the first study to assess the prevalence of different orthogonal P-wave morphologies and their association with the risk of atrial fibrillation (documented during hospitalization for any reason) in the general population.
- Type 3 orthogonal P-wave morphology was independently associated with the risk of hospitalization with AF also in the general population.
- Subjects presenting with P waves of Type 1 orthogonal morphology and <110ms in duration were at low risk of being hospitalized with atrial fibrillation.

Introduction

The prevalence of atrial fibrillation (AF) is increasing throughout the Western world, but a substantial portion of the risk of AF and the risk of stroke in AF patients remains unexplained by the established risk factors. Multiple risk factors of AF, such as ischemia, diseases leading to increased atrial wall stretch, and systemic inflammation, lead to atrial injury, inflammation, and fibrosis. These changes in the atrial walls contribute in formation of a prothrombotic and proarrhythmogenic milieu. Indeed, atrial fibrosis correlates with AF burden and persistence. Thus, the quantification of atrial fibrosis might be of value in assessment of ones risk of AF and possibly even the risk of stroke.(1,2)

The electrocardiogram (ECG) is an affordable and noninvasive tool that enables the estimation of atrial conduction properties which correlate with fibrosis. P-wave prolongation is a marker of atrial conduction slowing and AF risk, and increases in AF risk have been documented even in subjects with P-wave duration 110-119ms, which has been previously considered normal.(3-6) It was recently shown in AF patients in sinus rhythm that the duration of amplified P wave correlates with the amount of left atrial low-voltage substrate, indicative of fibrofatty remodeling, and amplified P wave duration ≥150ms accurately identified AF patients with low-voltage substrate.(7) Third degree interatrial block is characterized by P-wave duration ≥120ms and +/- biphasic P waves in the inferior leads of the ECG and frequently coexists with atrial arrhythmias, especially AF, constituting the Bayés' syndrome.(8-10) Recent data indicate the presence of a dose-response-relationship between the number of inferior ECG leads exhibiting biphasic P waves and clinical outcome.(11) Also, ECG signs of left atrial abnormality, such as a marked negative P terminal force (PTF) in lead V_1 may be associated with impaired interatrial conduction or elevated left atrial pressure, and is associated with the risk of AF.(5,12) However, these ECG abnormalities are often

absent in a large portion of subjects prone to developing AF. Nevertheless, the assessment of interatrial conduction in greater detail provides further insights into atrial properties. Electroanatomic endocardial mapping data in patients without marked left atrial enlargement suggests that P-wave morphology is strongly related to the route involved in interatrial propagation of depolarization wave and the earliest left atrial breakthrough site.(13) Upright positive P waves in right precordial leads observed predominantly in young and healthy were associated with preserved conduction over the posterior interatrial connections in the vicinity of oval fossa and right pulmonary veins while backward activation of the left atrium through the Bachmann's bundle without contribution of posterior connections was observed in patients exhibiting pronounced terminal negative deflection in right precordial leads. Damage also in the Bachmann's bundle results in advanced interatrial block, in which interatrial conduction occurs through muscular connections near the coronary sinus resulting in upward depolarization of the left atrium and biphasic +/- P waves in inferior leads of the standard ECG and lead Y of the orthogonal lead system.(5) Recently, an endocardial electroanatomic mapping study, in AF patients, reported that sinus P-wave morphology correlates with left atrial low-voltage substrate and patients with extensive left atrial damage may lack the biphasic +/- P morphology in the inferior leads, and instead present with a severely prolonged low-amplitude P wave.(14) The aim of this study was to assess the prevalence of different interatrial conduction patterns in the general population and to test whether they can be used in AF risk stratification.

Methods

Study population and baseline examinations

The study population consists of participants of the Mini-Finland Health Survey, conducted 1978–80. A detailed report of the study protocol has been published elsewhere.(15,16) Briefly, a representative sample of 8000 Finnish subjects, above the age of 30, received an invitation to the study, and 7217 subjects took part in health examinations. The participants answered questionnaires about their health habits, known diseases, medications, and symptoms suggestive of cardiovascular disease, and the questionnaires were revised during health interviews, conducted by nurses. Age and sex were obtained from the Finnish Population Register. Height and weight were measured directly by study personnel. Blood pressure was measured twice using a manual sphygmomanometer after 40 minutes of completing questionnaires and the latter systolic and diastolic readings were used in the present study. Blood and urine samples were obtained, and posterior-anterior and lateral chest radiographs were taken. Diabetes was defined as fasting glucose > 11.0mmol/l in a single measurement or > 6.7mmol/l in two separate measurements or use of a glucose lowering medication. The participants presenting with symptoms or findings suggestive of cardiovascular disease (angina pectoris, myocardial infarction [MI], or congestive heart failure [CHF]) later received an invitation to clinical examination by survey doctor, during which the validity of diagnoses was ascertained using data collected during the survey, and also previous medical records, if available. However, no data regarding history of AF were collected. Thus, subjects with previously documented AF episode could not be excluded. The exact definitions of these diagnoses are presented in the Supplemental Methods. Smoking was defined as “current” if the participant had smoked regularly for a minimum of one year preceding the study visit. Subjects with an available ECG of sufficient quality for P-wave assessment, including the orthogonal leads, were included in the analyses of the present study (n=6217). Furthermore, the subjects whose orthogonal P-wave

morphology did not correspond to a predefined category (n=728) were excluded from models assessing the risk of clinical end-points due to the heterogeneity of this group. The Mini-Finland Health Survey preceded the current legislation on ethics in medical research. All participants were fully informed about the study, they participated in the study voluntarily, and the use of the information for medical research was explained to them. Agreeing to participate in the baseline health examination was taken to indicate informed consent. The participants were free to unconditionally withdraw their consent at any time, in which case their data were deleted. The study protocol and the practice of the subject's voluntary participation indicating informed consent were approved by the Institutional Review Board (IRB 00007085) of National Institute for Health and Welfare.

Electrocardiographic measurements

An ECG consisting of the standard 12 leads and a vectorcardiogram "Frank X, Y, and Z leads"(17) was registered by trained personnel, three leads at a time, with the subject resting in supine position with Olli 308 ECG registering device (KONE Oy). The paper speed was 50mm/s and calibration of 10mm/mV was used. Special attention was paid to the placement of electrodes. The V4 and V6 electrodes served as Frank C- and A-electrodes, respectively, and Frank H, M, I, and E electrodes were placed separately on the skin of the subject.(15) The ECGs of study participants were stored in paper format for decades and due to the use of an inkjet printer during the recording of electrocardiograms they remained in excellent condition. During years 2013–2016 the electrocardiograms were scanned, the ECG signals were traced into a digital format using a custom software with trained personnel inspecting the process, and editing the tracings, if necessary. Later, ECG measurements including basic intervals, amplitudes, and axes of the major waveforms were made by A.E., A.Ho., and A.Ha. from digital median beats using a custom software. The details of the digitizing and digital measuring of the ECGs have been published elsewhere.(18) The presence of bundle branch blocks and intraventricular conduction defect (IVCD) were later ascertained

manually by A.E. Due to the ECG tracings being only 3-5 seconds long in the standard 12 leads, and the signal-to-noise ratio being at times low, the presence of sinus rhythm (initial P-wave positivity in leads I and aVF), P-wave duration (<110ms, 110-119ms, and ≥120ms), the biphasicity of the P waves in leads II, aVF, and III, and the depth and width of a possible PTF in lead V1 were later manually assessed by A.E. from the paper ECGs. Third degree interatrial block was defined as P-wave duration ≥120ms and at least two +/- biphasic P waves in leads II, aVF, and III. As the optimal method for the quantification of PTF is not known, we tested both the original duration-depth-product, and also a binary PTF variable, which was classified as pathological when the terminal negative deflection of the P wave in lead V1 was ≥0.1mV deep and ≥40ms wide. Heart rate was measured from the ECG tracing containing the orthogonal leads.

Orthogonal P-wave morphology

The predominant interatrial conduction route was assessed by P-wave analysis using the orthogonal leads.(13,17) The electroanatomical basis for this assessment is presented in Figure 1. During the initial digital ECG measurements, the orthogonal P-wave morphology was registered manually, or in case of low signal quality, borderline morphology, or fluctuating morphology filed for a more detailed assessment to be performed later. After the initial measurements, an automated algorithm developed by J.C., F.H., and P.P. was used to automatically assess the orthogonal P-wave morphology from the digital median beats calculated from tracings of leads X, Y, and Z.(19) After this phase, the ECGs in which the orthogonal P-wave morphology was not initially classified, or was classified differently by the user and the algorithm were checked, the probable reason for this discordance was documented, and the final P-wave morphology was decided. In borderline cases between P-wave types the algorithm was generally trusted. All ECG measurements were made blinded to the outcome of the subjects.

Follow-up data

After the baseline examinations, the subjects were followed 10 years from the Causes of Death register for death, and The Finnish Hospital Discharge Register for AF (follow-up data was available until December 31th, 2011). The Finnish Hospital Discharge register includes the dates of hospital admission and discharge, and up to four coded discharge diagnoses of all inpatient episodes in Finland at an individual level. A subject was defined as having developed AF, the primary end-point of this study, if one of the discharge diagnoses of an inpatient episode was AF, regardless of whether AF was the principal cause for the hospitalization.

Statistical analyses

The general linear model was used to compare the age- and sex-adjusted means of continuous variables and the prevalence of categorical variables between the P-wave morphology groups. ANOVA and Chi-square test were used to assess the differences in the means of continuous variables and the prevalence of categorical variables in other between-group comparisons. The Cox proportional hazards model was used to assess the risk of hospitalization with AF diagnosis in subjects presenting with different P-wave morphologies. The covariates were chosen based on previously established associations with the risk of AF. Age, body mass index, and systolic blood pressure were used as continuous variables, and sex, diabetes, congestive heart failure, previous myocardial infarction, coronary heart disease, the use of antihypertensive medication, the use of β-blocker medication, smoking, and the presence of LVH were used as categorical variables. The value of P-wave parameters in risk stratification was assessed by calculating the change in C statistic, continuous net reclassification improvement (NRI), and integrated discrimination improvement (IDI). The survival models and reclassification models were truncated at 10 years because P-wave morphology changes over time, and thus it is not reasonable to assume proportional hazards over a follow-up of decades. All p values are two-sided and 0.05 serves as the alpha level.

Statistical analyses were performed with IBM® SPSS® Statistics, Version 22.0, and R, version 3.1.2, (http://www.Rproject.com packages survC1 and survIDINRI). A.E. had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

Results

Orthogonal P-wave morphology classification

There were 6217 subjects with an available ECG of sufficient quality for P-wave assessment, with the orthogonal leads registered. The most common reasons for exclusion were P and U waves overlapping in such a way that reliable P-wave measurements were not possible (n=238), low ECG signal quality (n=235), missing data (n=127), missing ECG (n=100), AF or atrial flutter (n=98), or no orthogonal ECG leads recorded (n=93). The complete list of reasons for exclusion is presented in the Supplemental Table 1. Of the 6217 subjects (46.3% male, mean age 50.3 years) included in the study, 3674 (59.1%) presented with type 1 P waves, 1599 (25.7%) presented with type 2 P waves, and 216 (3.5%) presented with type 3 P waves. In 728 subjects (11.7%), the P-wave morphology either fluctuated (n=32), was indicative of non-sinus rhythm (initial negativity in leads I or aVF, n=71), or did not correspond to any of the predefined morphologies (n=625, most of these subjects had minor initial negativity in lead X). Due to the heterogeneity of P waves in this group, also these subjects (n=728) were excluded from the analyses. During the initial classification, 73.8% of P waves were interpreted similarly by user and the algorithm. The most common reason for the orthogonal P-wave morphology classification being not performed initially by the user, or being discordant between the user and the algorithm, was borderline morphology. This occurred in 22.9% of cases, and 77.5% of these cases were borderline cases between P-wave Types 1 and 2. In 3.3% of subjects the reason for discordance was either erroneous initial manual interpretation (n=40), baseline artefacts affecting automated analysis (n=53), atrial ectopic beats affecting automated analysis (n=39), falsely set P-wave onset or end affecting automated analysis (n=62), or U wave affecting automated analysis (n=7, in these cases the manual analysis could be made with certainty). Overall, during the final classification, the interpretation of the algorithm was plausible in 6056 cases (97.4%), and overruled in 161 cases (2.6%).

Characteristics of subjects with different P-wave morphologies

The age- and sex-adjusted baseline characteristics of subjects presenting with different P-wave morphologies are presented in Table 1. The most distinct difference between the P-wave morphology groups was that subjects presenting with Type 2 and Type 3 P waves were markedly older than subjects with Type 1 P waves and subjects whose P-wave morphology did not belong to a pre-specified group. Subjects whose P waves did not correspond to any of the pre-specified morphologies were more likely to be female, but no other striking differences were observed when they were compared to the rest of the population (data shown in the Supplemental Table 2). As expected based on electrophysiological similarities, a marked PTF was relatively prevalent in subjects with Type 2 P waves, and a 3rd degree interatrial block was most commonly observed among subjects with Type 3 P waves. The prevalence of different P-wave morphologies according to sex differed (Chi-Square $p<0.001$). The prevalence of different P-wave morphologies according to age decile in males and females are presented in Supplemental Figures 1 and 2, respectively. The proportions of different P-wave duration–P-wave morphology combinations according to age decile are presented in Figure 2.

P-wave duration, PTF, III degree interatrial block, and the risk of hospitalization with AF

Overall, 124 subjects were hospitalized with AF among subjects with a defined orthogonal P-wave morphology, during the follow-up. The prevalence of P-wave abnormalities among these subjects is illustrated in Figure 3. The exact numbers of subjects with and without hospitalization with AF during the follow-up presenting with P-wave abnormalities, and the hazard ratios for hospitalization with AF associated with these abnormalities, in 10-year follow-up, are presented in Table 2. PTF, P-wave duration ≥120ms and 3rd degree IAB were associated with the risk of hospitalization with AF, but after multivariate adjustments only P-wave duration ≥120ms, and 3rd degree IAB remained

independent predictors of the risk of hospitalization with AF. Furthermore, P-wave duration ≥120ms without the presence of 3rd degree IAB was not independently associated with the risk of hospitalization with AF.

Orthogonal P-wave morphology and the risk of hospitalization with AF

Type 2 P waves were associated with the risk of hospitalization with AF univariately, and in an age- and sex-adjusted model, but the association diminished with further adjustments. Type 3 P waves were associated with the risk of hospitalization with AF also in the multivariate adjusted model. The hazard ratios are presented in Table 2. As Type 2 P waves and Type 3 P waves are somewhat similar electrophysiologically as P waves with a marked PTF and 3rd degree IAB, respectively, an additional analysis was conducted after exclusion of subjects with either of these conditions. However, the results remained practically alike. The results of these analyses are presented in the Supplemental Table 3. Survival curves free of hospitalization with AF according to the presence of different P-wave abnormalities are presented in Figure 4.

To examine the combined effect of orthogonal P-wave morphology and P-wave duration, the subjects in each orthogonal P-wave morphology group were divided according to P-wave duration to those with P duration <110ms, those with P duration 110-119ms and those with P duration ≥120ms. The results of the association of orthogonal P-wave morphology and P-wave duration and risk of hospitalization with AF are presented in Table 3. In this model, subjects with longer P-wave durations were at increased risk for hospitalization with AF, compared to subjects presenting with Type 1 P waves with duration <110ms. Also subjects presenting with Type 2 or 3 P waves <110ms were at increased risk of hospitalization with AF, compared to subjects with Type 1 P waves <110ms. On the other hand, subjects with Type 1 P waves with duration <110ms were at low risk of hospitalization with AF when compared to rest of subjects with a defined P morphology (univariate

HR 0.21, 95% CI 0.12–0.36, p<0.001, multivariate-adjusted HR 0.46, 95% CI 0.26–0.83, p=0.006). The absolute risk of hospitalization with AF among subjects presenting with Type 1 P wave with duration <110ms was low: there were no hospitalizations with AF during the first year of follow-up in this group, and only five cases during the first five years of follow-up. When the orthogonal P morphology – duration variables were added to the multivariate adjusted Cox model the C index improved from 0.815 to 0.832 (change 0.017, 95% CI 0.001–0.033), IDI was 0.012 (95% CI 0.006–0.051), and continuous NRI was 0.220 (95% CI 0.048–0.357). In the Cox model with orthogonal P-wave duration-morphology variables, risk estimates were higher in 60.4% of subjects who were hospitalized with AF, and risk estimates were lower in 38% of subjects who were not hospitalized with AF.

Discussion

The main finding of the present study is that orthogonal P-wave morphology can be used in assessing the risk of hospitalization with AF in the general population. Type 3 morphology was associated with an increased risk of hospitalization with AF, whereas subjects presenting with P waves <110ms long with Type 1 morphology were at very low risk for hospitalization with AF. We also replicated previous findings regarding the increased risk of AF among subjects with 3rd degree IAB. The statistical model which included conventional risk factors and P-wave morphology-duration variables yielded excellent discrimination (C-index 0.832).

This was the first study to assess the utility of orthogonal P-wave morphology in the general population. Previously established electrocardiographic markers of AF risk, 3rd degree IAB and a marked P-wave prolongation, identify subjects at high risk of AF. However, the use of orthogonal P-wave morphology identified more subjects with a high risk of being diagnosed with AF in an inpatient setting, and also groups of subjects with intermediate and low risk.

Subjects presenting with 3rd degree interatrial block, Type 3 P waves, and P-wave duration ≥120ms were at high risk of hospitalization with AF (absolute risk >5% in 10 years) in the present study. This highlights that if subjects with any of these P-wave attributes presents with palpitations, at least AF should be searched. New technologies, such as smartwatches and mobile phone applications that turn a smartphone to an AF screening device, may prove useful in this setting. As 3rd degree interatrial block is frequently seen in subjects with a high $CHADS_2VA_2Sc$ score, and is also associated with the risk of stroke, it has been discussed that future studies should assess whether subjects presenting with 3rd degree interatrial block would benefit of anticoagulation.(20)

These findings warrant further research in specific patient populations. AF-related cardioembolism is a common etiology of stroke, but AF is detected with conventional methods, such as in-hospital rhythm monitoring and Holter recordings, in only a small subset of patients with stroke and AF paroxysms. The assessment of P-wave morphology, among other risk factors of AF and AF-related stroke, could be used to identify stroke patients who would, and who would not, benefit of intensive diagnostic workup for the detection of AF, for example with implantable loop recorders. On the other hand, it should be studied whether Holter monitorings or loop recorder implantations could be omitted in patients with cryptogenic stroke presenting with a completely benign P morphology.

PTF was not an independent predictor of hospitalization with AF in this study. This was a somewhat unexpected finding, but it could be explained by the relatively small and low-risk population. In addition, the present study had a more thorough adjustment for potential confounding factors, including congestive heart failure, than earlier studies.(12)

Unexpectedly, in the analyses in which the P-wave morphology groups were divided according to P-wave duration, Type 2 and Type 3 P waves with duration 110-119ms did not predict hospitalization with AF. This was both in the age- and sex-adjusted, and multivariate adjusted models. This may be explained by the slightly older age and a larger burden of comorbidities explaining the AF events among these subjects.

The amount of subjects in whom the P-wave morphology did not correspond to any of the pre-defined morphologies in this study was relatively large. However, this group seemed to be relatively similar to the rest of the population. Thus, this causes only minor concern regarding to the generalizability of the results to general population samples. The major cause for non-pre-defined

morphology was initial negativity in lead X. A part of this phenomenon could be explained by the acquisition of XYZ leads directly from skin. Indeed, comparison was performed between the XYZ leads recorded directly from skin, and XYZ leads obtained with inverse Dower transform from the standard 12 ECG leads, and some of the initial X negativity was not present with the inverse Dower transform.

The strengths of this study include a large and representative population and comprehensive baseline examinations including a clinical examination and ascertainment of diagnoses by a survey doctor. Still, no data regarding AF events before the baseline examinations were systematically collected. Thus, AF events preceding the baseline examinations may have caused atrial inflammation and injury, leading to P-wave abnormalities in some of the subjects. However, it is reasonable to assume that this was rare, as most documented AF events occurred quite late in the follow-up. An important limitation of this study is that only AF documented in an inpatient setting was captured during the follow-up. AF patients ending up hospitalized may not be a representative sample of the whole AF patient population. Thus, the P-wave abnormalities indicative of high AF risk in the present study should not be assumed to similarly predict all AF events in population. Another weakness of this study is the lack of echocardiographic parameters, especially those assessing left atrial size, systolic and diastolic function of the left ventricle, and left-sided valvular function. Of note, the population studied was predominantly Caucasian origin, and these results must be interpreted with caution in other populations. Also, the algorithm used in the assessment of left atrial breakthrough site was originally validated using orthogonal leads computed from a standard 12-lead ECG, with inverse Dower transform, whereas in this study the orthogonal leads were recorded directly from the skin of the subject. Having modern digital ECG signals of high quality would have allowed for the detection of lower voltage waveforms, which would have improved the accuracy of P-wave assessment.

In conclusion, orthogonal P-wave morphology can be used to identify subjects at high and low risk for hospitalization with AF in the general population. However, more research is needed before it can be used to guide clinical decision-making in specific patient populations.

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Tables

Table 1. Age and sex adjusted baseline characteristics of subjects according to orthogonal P-wave type

	Type 1 (n=3674)	Type 2 (n=1599)	Type 3 (n=216)	Other morphologies (n=728)	p
Males, %*	48.6	46.4	47.2	34.9	<0.001
Age, years†	47.2 (12.3, 46.8–47.6)	56.7 (13.2, 56.1–57.3)	56.8 (14.5, 55.1–58.5)	49.5 (14.6, 48.6–50.5)	<0.001
Systolic blood pressure, mmHg	141 (20, 140–141)	146 (25, 145–147)	142 (24, 139–144)	142 (24, 140–143)	<0.001
Diastolic blood pressure, mmHg	86 (11, 86–86)	88 (12, 88–89)	87 (12, 86–89)	85 (11, 84–86)	<0.001
Body mass index, kg/m²	25.5 (3.8, 25.4–25.6)	27.0 (4.2, 26.8–27.2)	26.0 (3.8, 25.5–26.6)	25.0 (4.0, 24.7–25.2)	<0.001
Serum cholesterol, mmol/l	6.96 (1.33, 6.92–7.00)	6.97 (1.36, 6.91–7.04)	6.88 (1.36, 6.70–7.05)	6.89 (1.43, 6.80–6.99)	0.445
Serum HDL-cholesterol, mmol/l	1.71 (0.40, 1.70–1.73)	1.67 (0.42, 1.65–1.69)	1.69 (0.37, 1.62–1.74)	1.74 (0.41, 1.71–1.77)	0.001
Heart rate, bpm	66.4 (12.0, 66.0–66.8)	67.2 (12.6, 66.6–67.8)	63.8 (11.2, 62.2–65.4)	68.1 (11.9, 67.2–69.0)	<0.001
Current smoker, %	25.0	23.4	19.0	24.6	0.146
Diabetes, %	3.8	6.1	6.3	4.5	0.002
Angina pectoris, %	8.6	10.1	11.7	8.3	0.125
Previous myocardial infarction, %	3.1	3.7	5.9	3.4	0.164
Congestive heart failure, %	6.4	8.3	10.0	7.7	0.017
Antihypertensive medication‡, %	12.2	18.1	14.2	11.4	<0.001
β-blocker, %	6.1	8.0	4.2	5.7	0.022

Digitalis medication, %	6.2	7.6	8.1	7.4	0.191
P duration ≥120ms, %	11.6	16.0	29.2	13.7	<0.001
Pathological P terminal force§, %	2.2	11.7	0.4	6.8	<0.001
Third degree interatrial block, %	0.6	0.9	31.0	0.9	<0.001
LBBB, %	0.2	0.5	1.7	0.3	0.004
IVCD, %	1.1	0.9	2.1	1.3	0.385
LVH (Sokolow-Lyon), %	13.1	14.4	15.5	10.6	0.062
LVH (Cornell voltage), %	8.8	13.9	10.9	7.7	<0.001

Continuous variables are presented as mean (SD, 95% CI). *Adjusted for age. †Adjusted for sex. ‡Including β-blockers used to control hypertension. §Amplitude ≥0.1mV and duration ≥40ms.

Table 2. Different P-wave parameters and the risk of hospitalization with AF

	Number of subjects with event / n (%)	Unadjusted HR	Age and sex adjusted HR	Multivariate-adjusted* HR
P terminal force, depth-duration-product, mm·s				
<0.04	88/4669 (1.9 %)	1 (reference)	1 (reference)	1 (reference)
0.04–0.059	23/591 (3.9 %)	2.23 (1.41–3.53, p=0.001)	1.24 (0.77–1.98, p=0.371)	1.10 (0.68–1.76, p=0.709)
≥0.06	13/229 (5.7 %)	3.70 (2.06–6.62, p<0.001)	1.67 (0.92–3.04, p=0.094)	1.29 (0.70–2.37, p=0.413)
P terminal force, depth ≥0.1mV and duration ≥40ms				
No PTF	110/5218 (2.1 %)	1 (reference)	1 (reference)	1 (reference)
PTF	14/271 (5.2 %)	2.88 (1.65–5.02, p<0.001)	1.59 (0.91–2.80, p=0.107)	1.34 (0.75–2.37, p=0.321)
P-wave duration, ms				
<110	41/2813 (1.5 %)	1 (reference)	1 (reference)	1 (reference)
110–119	40/1924 (2.1 %)	1.47 (0.95–2.27, p=0.083)	1.03 (0.66–1.60, p=0.891)	0.93 (0.60–1.45, p=0.748)
≥120	43/752 (5.7 %)	4.43 (2.89–6.80, p<0.001)	2.17 (1.39–3.37, p=0.001)	1.67 (1.06–2.64, p=0.027)
Interatrial block				

P duration <120ms	81/4737 (1.7 %)	1 (reference)	1 (reference)	1 (reference)
P duration ≥120ms, no III degree IAB	32/649 (4.9 %)	3.18 (2.11–4.78, p<0.001)	1.88 (1.24–2.84, p=0.003)	1.51 (0.99–2.32, p=0.057)
III degree interatrial block	11/103 (10.7 %)	7.62 (4.06–14.31, p<0.001)	3.70 (1.94–7.04, p<0.001)	3.18 (1.66–6.13, p=0.001)
Orthogonal P-wave morphology				
Type 1	52/3674 (1.4 %)	1 (reference)	1 (reference)	1 (reference)
Type 2	57/1599 (3.6 %)	2.76 (1.90–4.02, p<0.001)	1.63 (1.10–2.41, p=0.015)	1.35 (0.90–2.01, p=0.148)
Type 3	15/216 (6.9 %)	5.57 (3.14–9.89, p<0.001)	3.26 (1.81–5.86, p<0.001)	3.01 (1.66–5.45, p<0.001)

* Adjusted for age, sex, diabetes, congestive heart failure, previous myocardial infarction, coronary heart disease, systolic blood pressure, body mass index, antihypertensive medication, β-blocker, smoking, and LVH (Sokolow-Lyon).

Table 3. Orthogonal P-wave morphology, P-wave duration, and the risk of hospitalization with AF

	Number of subjects with event / n (%)	Unadjusted HR	Age and sex adjusted HR	Multivariate adjusted HR*
Type 1, <110ms	15/2074 (0.7 %)	1 (reference)	1 (reference)	1 (reference)
Type 1, 110-119ms	22/1232 (1.8 %)	2.52 (1.31–4.86, p=0.006)	1.85 (0.96–3.58, p=0.067)	1.69 (0.97–3.28, p=0.118)
Type 1, ≥120ms	15/368 (4.1 %)	5.98 (2.92–12.23, p<0.001)	3.04 (1.47–6.29, p=0.003)	2.49 (1.19–5.18, p=0.015)
Type 2, <110ms	22/661 (3.3 %)	4.91 (2.55–9.47, p<0.001)	2.99 (1.53–5.82, p=0.001)	2.59 (1.32–5.09, p=0.001)
Type 2, 110-119ms	15/625 (2.4 %)	3.65 (1.79–7.47, p<0.001)	1.72 (0.83–3.59, p=0.146)	1.35 (0.64–2.85, p=0.424)
Type 2, ≥120ms	20/313 (6.4 %)	10.96 (5.61–21.41, p<0.001)	4.25 (2.12–8.50, p<0.001)	2.77 (1.35–5.71, p=0.006)
Type 3, <110ms	4/78 (5.1 %)	7.66 (2.54–23.09, p<0.001)	5.35 (1.77–16.16, p=0.003)	5.43 (1.79–16.44, p=0.003)
Type 3, 110-119ms	3/67 (4.5 %)	6.81 (1.97–23.51, p=0.002)	3.34 (0.96–11.65, p=0.059)	2.87 (0.82–10.08, p=0.100)
Type 3, ≥120ms	8/71 (11.3 %)	20.27 (8.59–24.83, p<0.001)	7.41 (3.06–17.96, p<0.001)	5.82 (2.36–14.38, p<0.001)

*Adjusted for age, sex, diabetes, congestive heart failure, previous myocardial infarction, coronary heart disease, systolic blood pressure, body mass index, antihypertensive medication, β-blocker, smoking, and LVH (Sokolow-Lyon).

Figure Legends

Figure 1 legend: The main atrial depolarization vectors underlying the three defined P-wave morphologies are presented in schematic illustrations of human atria in the top row (anterior view) and the second row (superior view). The three lowest rows present P waves from leads X, Y, and Z, with P-wave onsets and ends marked by red lines. Atrial depolarization begins in the sinus node (SN) and the depolarization propagates anteriorly, downwards, and leftwards in the right atrium leading to a positive initial deflection in the P-wave in leads X and Y, and a negative initial deflection in lead Z. Type 1 P morphology (Column A) is associated with interatrial propagation of activation wavefront through posterior fibers near the foramen ovale (FO), leading to left atrial depolarization directed forward resulting a negative terminal portion in lead Z. Type 2 P morphology (Column B) is associated with the interatrial conduction occurring exclusively through the anteriorly and superiorly located Bachmann's bundle (BB), which leads to inferiorly and posteriorly directed left atrial depolarization, resulting in a positive terminal portion of the P wave in lead Z. Type 3 P morphology (Column C) results from left atrial breakthrough occurring near the coronary sinus (CS), without involvement of the BB in the interatrial conduction, as in the case of advanced interatrial block, which results in the left atrial activation directed upwards leading to a negative terminal portion of the P wave in lead Y.(13)

Figure 2 legend. The proportions of different P-wave duration–P wave morphology combinations according to age decile

Figure 3 legend. The prevalence of orthogonal P-wave morphologies (A), PTF (B), and IAB (C) among subjects who were hospitalized with AF during the follow-up (n=124). The exact no. of subjects are presented in Table 2.

Figure 4 legend. Kaplan-Meier curves for survival free of hospitalization with AF according to orthogonal P-wave morphology (A), PTF (B), and IAB (C).

Figures

Figure 1.

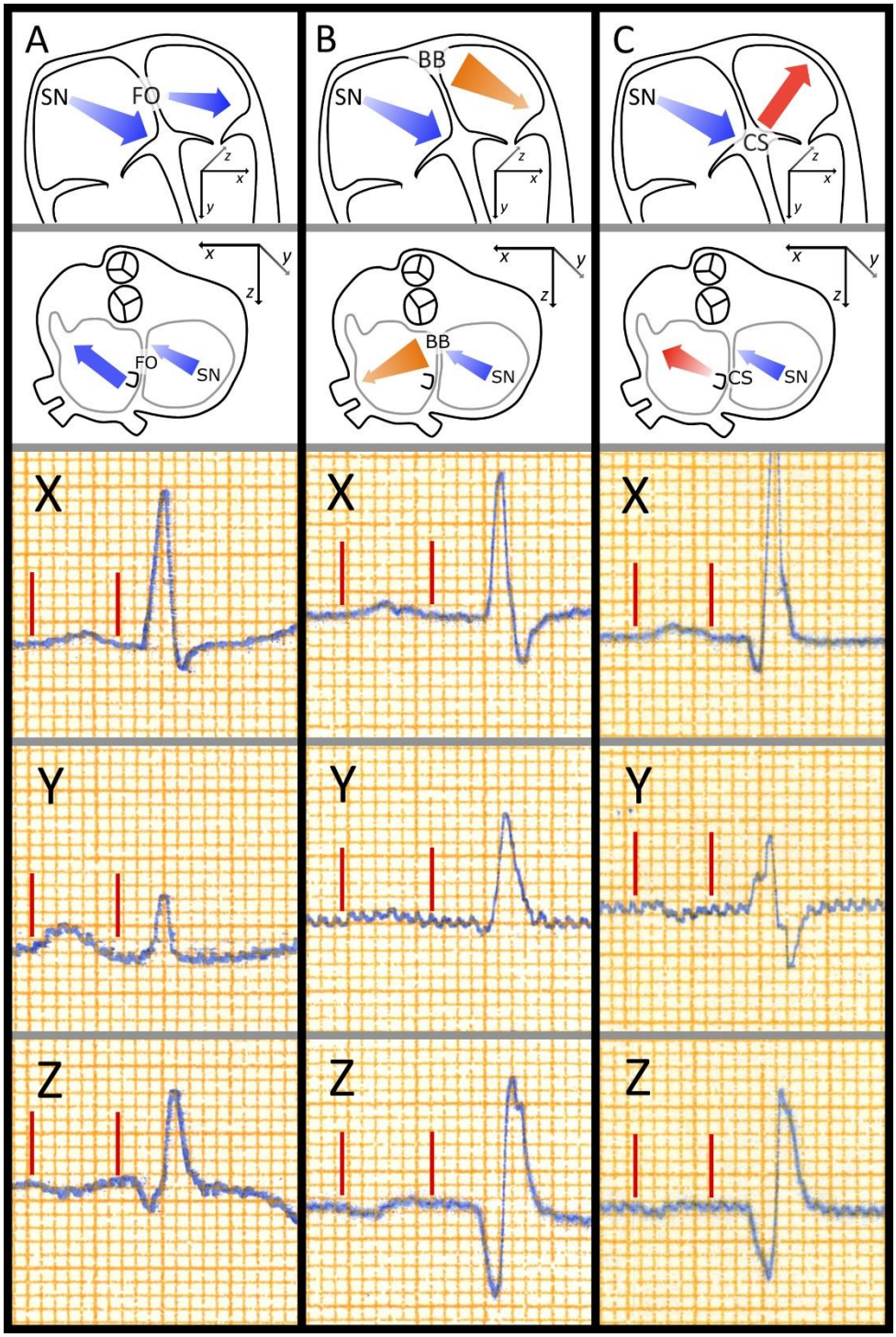


Figure 2.

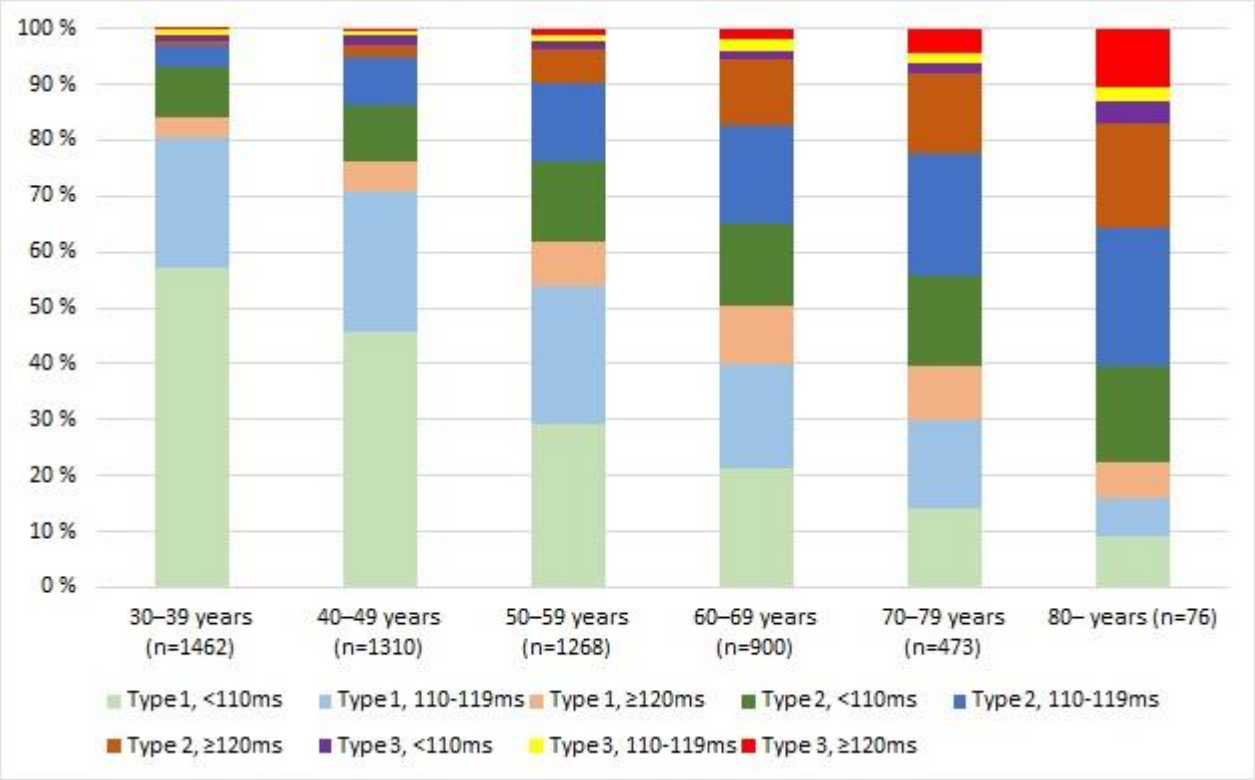


Figure 3.

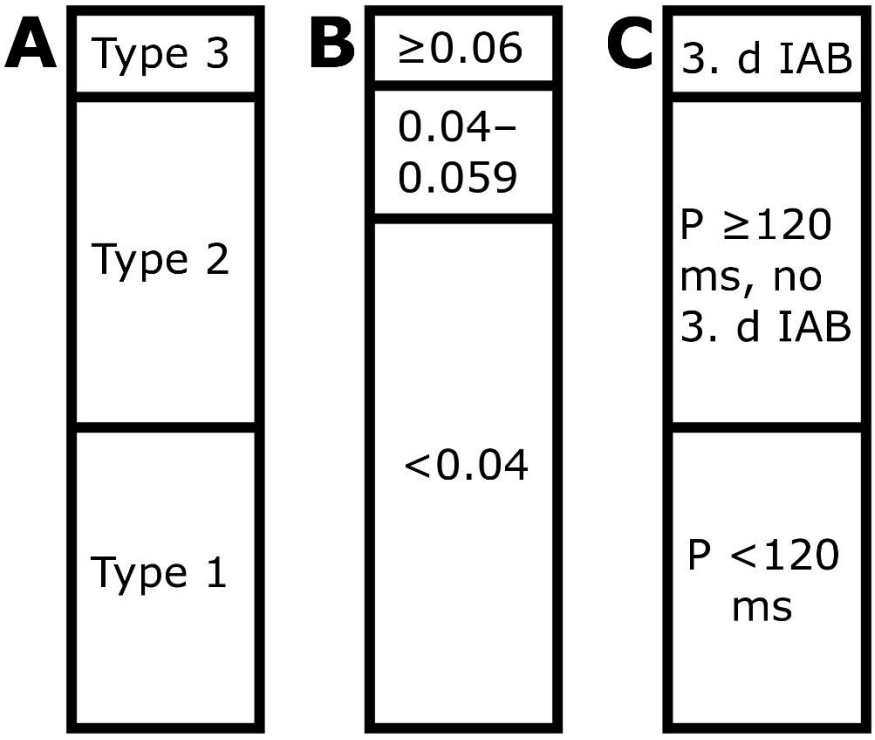
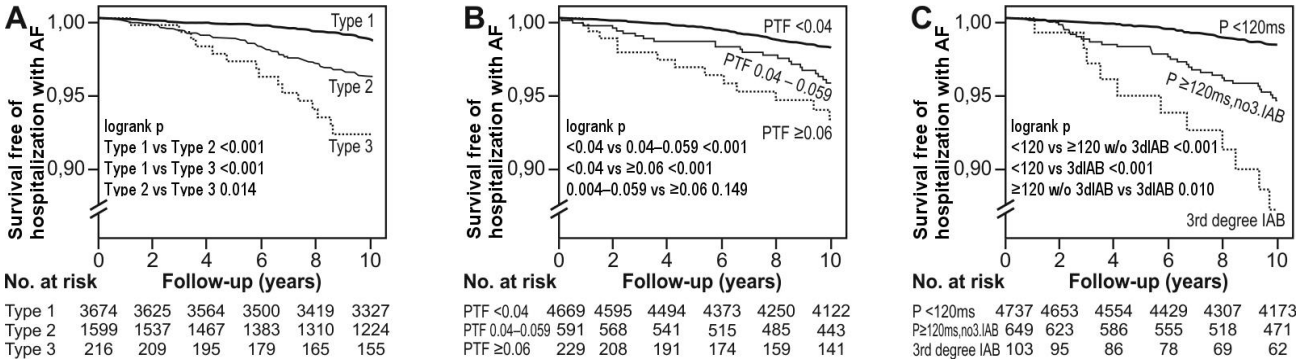


Figure 4.


A
Survival free of hospitalization with AF
1,00
0,95
0,90
Type 1
Type 2
Type 3
logrank p
Type 1 vs Type 2 <0.001
Type 1 vs Type 3 <0.001
Type 2 vs Type 3 0.014
0 2 4 6 8 10
No. at risk
Follow-up (years)
Type 1 3674 3625 3564 3500 3419 3327
Type 2 1599 1537 1467 1383 1310 1224
Type 3 216 209 195 179 165 155
B
Survival free of hospitalization with AF
1,00
0,95
0,90
PTF <0.04
PTF 0.04 – 0.059
PTF ≥0.06
logrank p
<0.04 vs 0.04–0.059 <0.001
<0.04 vs ≥0.06 <0.001
0.004–0.059 vs ≥0.06 0.149
0 2 4 6 8 10
No. at risk
Follow-up (years)
PTF <0.04 4669 4595 4494 4373 4250 4122
PTF 0.04–0.059 591 568 541 515 485 443
PTF ≥0.06 229 208 191 174 159 141
C
Survival free of hospitalization with AF
1,00
0,95
0,90
P <120ms
P ≥120ms,no3.IAB
3rd degree IAB
logrank p
<120 vs ≥120 w/o 3dIAB <0.001
<120 vs 3dIAB <0.001
≥120 w/o 3dIAB vs 3dIAB 0.010
0 2 4 6 8 10
No. at risk
Follow-up (years)
P <120ms 4737 4653 4554 4429 4307 4173
P≥120ms,no3.IAB 649 623 586 555 518 471
3rd degree IAB 103 95 86 78 69 62