

Electrocardiographic Preexcitation and Risk of Cardiovascular Morbidity and Mortality

Results From the Copenhagen ECG Study

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Background—The majority of available data on the clinical course of patients with ventricular preexcitation in the ECG originates from tertiary centers. We aimed to investigate long-term outcomes in individuals from a primary care population with electrocardiographic preexcitation.

Methods and Results—Digital ECGs from 328 638 primary care patients were collected during 2001 to 2011. We identified 310 individuals with preexcitation (age range, 8–85 years). Data on medication, comorbidity, and outcomes were collected from Danish nationwide registries. The median follow-up time was 7.4 years (quartiles, 4.6–10.3 years). Compared with the remainder of the population, patients with preexcitation had higher adjusted hazards of atrial fibrillation (hazard ratio [HR], 3.12; 95% confidence interval [CI], 2.07–4.70) and heart failure (HR, 2.11; 95% CI, 1.27–3.50). Subgroup analysis on accessory pathway location revealed a higher adjusted hazard of heart failure for a right anteroseptal accessory pathway (HR, 5.88; 95% CI, 2.63–13.1). There was no evidence of a higher hazard of death among individuals with preexcitation when looking across all age groups (HR, 1.07; 95% CI, 0.68–1.68). However, a statistically significant ($P=0.01$) interaction analysis (<65 versus ≥ 65 years) indicated a higher hazard of death for patients with preexcitation ≥ 65 years (HR, 1.85; 95% CI, 1.07–3.18).

Conclusions—In this large ECG study, individuals with preexcitation had higher hazards of atrial fibrillation and heart failure. The higher hazard of heart failure seemed to be driven by a right anteroseptal accessory pathway. Among elderly people, we found a statistically significant association between preexcitation and a higher hazard of death. (*Circ Arrhythm Electrophysiol.* 2017;10:e004778. DOI: 10.1161/CIRCEP.116.004778.)

Key Words: atrial fibrillation ■ death ■ electrocardiography ■ heart failure ■ Wolff-Parkinson-White syndrome

The Wolf-Parkinson-White (WPW) syndrome is a clinical entity characterized by the presence of ≥ 1 accessory pathways between the atria and the ventricles pre-disposing patients to arrhythmias. Anterograde conduction through the accessory pathway leads to preexcitation of the ventricles and a delta wave in the ECG. The prevalence of preexcitation in the general population has been estimated to be 1 to 3 in 1000 individuals.^{1,2} Atrial fibrillation (AF) in patients with preexcitation is of particular concern because of the risk of rapid anterograde conduction through the accessory pathway ultimately resulting in ventricular fibrillation and potentially sudden cardiac death.^{3,4} Although ablation is considered curative with respect to accessory pathway-induced tachycardia and sudden death, recent studies have reported a persistent higher risk of AF after ablation.^{5,6} In addition, several casuistic reports of

patients with WPW have reported left ventricular dysfunction without indication of sustained tachyarrhythmia.^{7,8}

The majority of available data on the clinical course of patients with WPW originates from tertiary centers with inherited limitations, such as referral bias. A few studies have examined the natural history of preexcitation in individuals from the general population.^{9–12} However, to our knowledge, no studies comparing subjects with preexcitation versus no preexcitation have been conducted on individuals from the general population. Accordingly, there is a lack of information in the literature on preexcitation in the general population, and a recent editorial emphasized the need of a large prospective ECG database to determine the natural history of preexcitation.¹³

We investigated the prevalence of preexcitation in the ECG and its relationship to age and sex in a large ECG database

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WHAT IS KNOWN

- Patients with ventricular preexcitation have a higher risk of developing supraventricular arrhythmias, including atrial fibrillation. Albeit small, patients with ventricular preexcitation (especially the young) have a higher risk of sudden cardiac death because of the risk of rapid anterograde conduction through the accessory pathway.
- Several casuistic reports of patients with ventricular preexcitation have reported left ventricular dysfunction without indication of sustained tachyarrhythmia, especially for patients with a right-sided septal location of the accessory pathway.
- Most available data on the clinical outcomes from patients with Wolf–Parkinson–White syndrome have been reported from tertiary medical centers.

WHAT THE STUDY ADDS

- Patients from a primary care population with ventricular preexcitation have a higher risk of incident atrial fibrillation and heart failure. The higher risk of heart failure seemed to be driven by patients with a right anteroseptal location of their accessory pathway.
- Across all age groups, patients with ventricular preexcitation did not have a higher risk of death from all causes. However, a statistically significant interaction analysis indicated a higher risk of death for patients with ventricular preexcitation ≥ 65 years.

consisting of individuals from a primary care population. In addition, we evaluated the association between preexcitation and the hazard of AF, heart failure (HF), and death from all causes. Such knowledge could contribute to a more informed basis for clinical decision making about the management of patients with preexcitation.

Methods

Study Population

The majority of general practitioners in Copenhagen, Denmark, refer their patients to the Copenhagen General Practitioners' Laboratory (CGPL) for clinical tests, such as ECG recordings. This study is part of the Copenhagen ECG study that includes all patients who had an ECG recorded at the CGPL during 2001 to 2011, as described in details previously.¹⁴ Individuals were excluded if they had an ablation procedure of an accessory pathway before inclusion, surgery for WPW, a diagnosis of congenital heart disease, a pacemaker or implantable cardioverter-defibrillator implanted, or in case they had an ECG with findings inconsistent with interpretation of the presence of preexcitation as noted in Electrocardiography section.

According to Danish law, no approval from an ethics committee is needed in a registry-based study without any active participation from study subjects. The use of deidentified registry data was approved by the Danish Data Protection Agency (record number 2007-58-0015).

Electrocardiography

All ECGs recorded at CGPL were obtained on subjects at rest and in supine position. Recordings were stored in the MUSE Cardiology Information System (GE Healthcare, Wauwatosa, WI) and processed using version 21 of the Marquette 12SL algorithm.¹⁴ With the use

of the 12SL algorithm, we excluded ECGs with rhythms other than sinus rhythm, heart rate <30 or >120 beats per minute, second and third degree AV-blocks, multiple premature ventricular complexes, multiple premature atrial complexes, junctional rhythms, and pace spikes.¹⁴ After exclusions, we identified all ECGs with a 12SL algorithm statement of WPW ECG pattern. In addition, at CGPL, trained technicians have manually described all ECGs, and in case of abnormal findings, ECGs were passed to an expert consultant in cardiology for further evaluation. By searching for WPW, delta wave, and preexcitation in these manual descriptions, we were able to identify ECGs with manually identified WPW ECG pattern. All ECGs identified with a suspicion of preexcitation, whether by the computerized algorithm or by manual evaluation, were carefully evaluated for preexcitation (any delta wave) by a second manual rater (MWS).¹⁵ In cases of doubt, consensus was reached by consulting a third manual rater (JBN). For all ECGs with preexcitation, the most likely location of the accessory pathways was determined using the algorithm provided by Fox et al.¹⁶ By applying this algorithm, locations of the accessory pathway were determined and classified as right lateral, left lateral, right anteroseptal, or posteroseptal, as well as an undetermined location, which largely represents patients with multiple accessory pathways or patients with a fasciculoventricular pathway.¹⁶ We chose this algorithm because identification of broader areas of accessory pathway location may be less prone to errors than algorithms designed to a more precise location.¹⁶ Two manual raters (MWS and JG) independently identified the most likely location of the accessory pathway. In case of discrepancy, a third manual rater (JHS) made the final decision. All manual ECG interpretations were conducted on deidentified ECGs, and hence, all raters were blinded to clinical characteristics and outcomes.

Baseline Variables and Follow-Up

In Denmark, it is possible to follow individuals with respect to death, emigration, the use of prescription medication and any hospital, outpatient clinic, or emergency room discharge diagnosis with the use of nationwide healthcare registries, and a unique personal identification number. In this way, we identified subjects with the following baseline characteristics: hypertension, AF, HF, and valvular heart disease. We constructed a modified Charlson comorbidity index in which we excluded *International Classification of Diseases* codes for HF, as this covariate was adjusted for separately. Using the modified Charlson comorbidity index, we were able to adjust for several comorbidities, including myocardial infarction, diabetes mellitus, various cancer diseases, hepatic diseases, pulmonary diseases, and vascular diseases ([Data Supplement](#)).¹⁷ Hypertension was defined from discharge diagnosis or as being present if a subject before inclusion was treated simultaneously with at least 2 kinds of antihypertensive drugs. AF and HF were defined from discharge diagnoses.^{18,19} Valvular heart disease was defined from discharge diagnoses and procedure codes.¹⁹ A hospital, outpatient clinic, or emergency room discharge diagnosis of AF and HF, as well as death from all causes, were the end points of interest. Details about the duration of AF or type (paroxysmal, persistent, and permanent) were not available in the registries used. The pathogenesis of HF is not known. Accordingly, the end point HF should be interpreted as HF of any cause. Information on the identification of covariates and clinical outcomes in the Danish registries are provided in the [Data Supplement](#).

Statistical Analysis

Follow-up began on the day of the first ECG recording (index ECG) and ended in case of the event of interest, death, emigration, or at December 31, 2013, whichever occurred first. Separate analyses were performed for outcomes AF, HF, and death from all causes. Analyses of AF also excluded individuals with a history of AF ($n=4913$) or a history of treatment with class I or III antiarrhythmics or digoxin at baseline ($n=4315$). Analysis of HF also excluded patients with a diagnosis of HF at inclusion ($n=5243$). Time-on-study was used as timescale in all survival analyses. Cause-specific Cox regression was used to assess the association of preexcitation on the index ECG with the hazards of AF, HF, and death from all causes during follow-up.

We also conducted analyses in which the preexcitation population was divided into subgroups based on accessory pathway location. In these analyses, we excluded individuals with an undetermined location ($n=9$) because of low statistical power for this subgroup. In all analyses, the reference group was individuals without preexcitation.

Several sensitivity analyses were conducted. First, all association analyses were repeated with censoring for ablation of an accessory pathway during follow-up. Second, we tested for any significant interaction between preexcitation and the occurrences of possible WPW syndrome-related events (syncope, palpitations, AF, or supra-ventricular tachycardia) on the hazard of death. This interaction was tested by introducing the presence of possible WPW syndrome-related events as a time-updated variable. Third, to quantify the possibility of surveillance bias of individuals with preexcitation on the ECG, we conducted separate analyses with prescriptions of oral antidiabetic medication and statins, as well as a diagnosis of aortic stenosis as outcomes. For these analyses, we additionally excluded individuals who already had the event of interest at baseline. Finally, we tested for any statistically significant interaction between preexcitation and age (<65 versus ≥ 65 years) on the hazard of AF, HF, and death using the likelihood ratio test.

All Cox models were adjusted for age at inclusion as a linear variable and stratified for the following risk factors that were obtained at baseline: sex, hypertension, history of HF (except for the analysis of HF as outcome), valvular heart disease, and a modified Charlson comorbidity index (0, 1, or ≥ 2 points). Because of the stratification procedure, no proportional hazard assumption was made, except for the effect of preexcitation and age. The latter was checked and accepted using a stopped Cox model.²⁰

Age-adjusted cumulative incidence curves for the outcomes of AF and HF were plotted based on the method of Fine and Gray.²¹ For death from all causes, age-adjusted survival curves were plotted based on Cox regression.

A 2-sided $P < 0.05$ was considered statistically significant. All analyses were conducted with the use of Stata 14.0 software package (StataCorp LP, College Station, TX).

Results

Study Population

The greater region of Copenhagen currently has a population of 1.18 million citizens. Among them, 343 607 individuals ($\approx 29\%$) had at least 1 ECG recorded at CGPL during the 11-year study period. Of these individuals, 328 638 ($\approx 96\%$) were eligible for inclusion. A total of 310 had preexcitation on their index ECG (age range, 8–85 years), corresponding to an overall prevalence of 0.9 per 1000 individuals. Baseline characteristics of the study population are presented in Table 1. Compared with the remaining population, the preexcitation population was generally younger, predominantly male, and had less comorbidity. Median time from inclusion to end of follow-up was 7.4 years (Q1–Q3, 4.6–10.3 years). Of the 310 individuals with preexcitation on index ECG, 73 individuals underwent an ablation procedure for WPW during follow-up. Age- and sex-specific prevalences of preexcitation are provided in Figure 1. The distribution of accessory pathway location is presented in Table 2.

Overall Risk of AF, HF, and Death

For the AF analysis, 319 410 individuals were eligible for inclusion and 16 842 individuals were diagnosed with incident AF during follow-up, of which 23 had preexcitation on the index ECG. The preexcitation population had an adjusted hazard ratio (HR) of 3.12 (95% confidence interval [CI], 2.07–4.70) for AF compared with the remainder of the population

Table 1. Baseline Characteristics of the Study Population

Characteristics	No Preexcitation	Preexcitation
Total count, n (%)	328 328 (99.9)	310 (0.09)
Age, y, median (Q1–Q3)	54 (41–66)	43 (30–56)
Women, n (%)	180 287 (55)	134 (43)
Medical history, n (%)		
Hypertension	61 390 (19)	32 (10)
Heart failure	5242 (2)	<4 (<1.3)*
Valvular heart disease	1764 (0.5)	<4 (<1.3)*
Atrial fibrillation	4909 (1)	4 (1)
Charlson comorbidity index		
0 point	256 910 (78)	251 (81)
1 points	38 643 (12)	35 (11)
≥ 2 points	32 775 (10)	24 (8)
ECG variables		
PR interval, ms, median (Q1–Q3)	156 (142–172)	118 (106–128)
QRS duration, ms, median (Q1–Q3)	92 (86–100)	122 (110–136)
QTc _{Bazett} † interval, ms, median (Q1–Q3)	426 (410–443)	448 (428–467)
Heart rate, bpm, median (Q1–Q3)	69 (62–79)	68 (61–77)

bpm indicates beats per minute.

*Because of the Act on Processing of Personal Data, we are not allowed to report any number <4 observations.

†QTc_{Bazett}=QT interval corrected for heart rate using Bazett formula.

(Table 3). When censoring for ablation during follow-up, the adjusted HR increased to 3.43 (95% CI, 2.28–5.16). No statistically significant interaction between preexcitation and age on the hazard of AF was observed ($P=0.55$).

For the HF analysis, 323 395 individuals were eligible for inclusion. During follow-up, 15 593 individuals were diagnosed with HF, of which 15 had preexcitation on the index ECG. Mean age at onset of HF was 57 years in individuals with preexcitation compared with 75 years in individuals without preexcitation. The preexcitation population had an adjusted HR of HF of 2.11 (95% CI, 1.27–3.50) compared with the remainder of the population (Table 3). When censoring for ablation during follow-up, the adjusted HR increased to 2.29 (95% CI, 1.38–3.81). No statistically significant interaction between preexcitation and age on the hazard of HF was observed ($P=0.22$).

During follow-up, there were a total of 51 453 deaths, of which 19 occurred among individuals with preexcitation on the index ECG. Of these 19 deaths, 4 were classified as having a cardiovascular cause, all of which occurred in patients >75 years of age. Individuals with preexcitation on index ECG had an adjusted HR of death from all causes of 1.07 (95% CI, 0.68–1.68) compared with individuals without preexcitation (Table 3). No meaningful change in the association was seen when censoring for ablation during follow-up (HR, 1.18; 95% CI, 0.75–1.85). No statistically significant interaction was seen

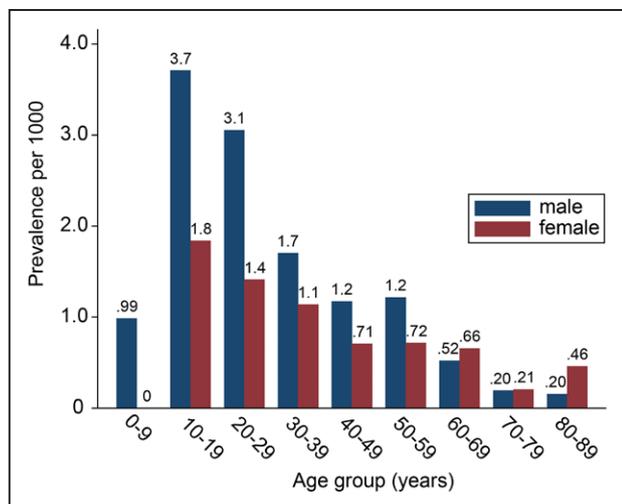


Figure 1. Prevalence of preexcitation on the index ECG in relation to 10-year age groups and sex.

between possible WPW syndrome-related events (AF, supra-ventricular tachycardia, palpitations, and syncope) during follow-up and preexcitation on the hazard of death ($P=0.35$). There was a statistically significant interaction between preexcitation and age on the hazard of death ($P=0.01$) with an HR of 0.55 (95% CI, 0.25–1.23) for those <65 years of age and an HR of 1.85 (95% CI, 1.07–3.18) for those ≥ 65 years of age. Age-adjusted cumulative incidences of AF and HF, as well as the age-adjusted survival curve for death from all causes, are shown in Figure 2.

Risk of AF, HF, and Death in Relation to Accessory Pathway Location

All locations were associated with a higher hazard of AF with exception of right anteroseptal location, which was only borderline statistically significant (Table 3). For HF as outcome, only a right anteroseptal accessory pathway location was associated with a higher hazard (HR, 5.88; 95% CI, 2.63–13.1; Table 3). All pathway-specific analyses with death as outcome were nonsignificant, although a right anteroseptal location was borderline statistically significant (HR, 2.14; 95% CI, 0.96–4.77; Table 3). Age-adjusted cumulative incidence of AF and HF, as well as the age-adjusted survival curve for death from all causes, stratified by accessory pathway location are shown in Figure 3.

Evaluation of Possible Surveillance Bias

The preexcitation population had adjusted HRs of oral antidiabetic medication and statins of 0.95 (95% CI, 0.59–1.53) and 0.85 (95% CI, 0.64–1.14), respectively. No individuals in the preexcitation population were diagnosed with aortic stenosis during follow-up.

Discussion

Using a large contemporary primary care population, we found higher hazards of AF and HF for individuals with preexcitation. When looking into the presumed anatomic location of the accessory pathway, we found that the association between preexcitation and the hazard of HF seemed to be

driven by right anteroseptal accessory pathways. We did not find evidence for an association between preexcitation in the ECG and a higher risk of death when looking across all age groups. However, a borderline statistically significant interaction analysis indicated a higher risk of death for the elderly with preexcitation.

We found the overall prevalence of preexcitation on ECG to be 0.9 per 1000 individuals, and the peak prevalence was seen in the second decade for both male and female (Figure 1). This is in accordance with previous findings from other large-scale general population studies including both children and adults, who have reported prevalences ranging from 1 to 3 per 1000 individuals.^{1,2} Also in line with previous reports,^{16,22} left lateral and posteroseptal locations of accessory pathways were the most common subtypes in our study (Table 2).

We observed a higher hazard of AF among individuals with preexcitation. This finding is consistent with previous studies of both symptomatic and asymptomatic cohorts,^{5,6,23} some of which have also reported that the risk of AF persists despite ablation.^{5,6} This post-ablation higher risk of AF combined with the fact that we found the hazard of AF to be consistent across the different anatomic locations of the accessory pathway might indicate that the higher hazard of AF is because of a common underlying substrate for both AF and preexcitation and not preexcitation itself.⁶ Accordingly, these data suggest that clinicians may consider monitoring patients with ventricular preexcitation closely for the occurrence of AF, regardless of ablation status.

Several casuistic reports and echocardiographic studies have described left ventricular dysfunction in patients with WPW, also in the absence of sustained tachyarrhythmias.^{7,8} This is consistent with our novel finding of a higher hazard of HF in the preexcitation population. Two mechanisms could account for the higher hazard of HF: tachycardia-induced cardiomyopathy²⁴ and ventricular dyssynchrony because of abnormal ventricular activation.⁸ As shown in this study and others, preexcitation is associated with a higher hazard of supraventricular tachycardia,²⁵ and this could lead to tachycardia-induced cardiomyopathy.²⁴ Although this condition is often reversible, these patients may end up with an HF diagnosis at discharge. Ventricular dysfunction because of abnormal ventricular activation may depend on accessory pathway location and has primarily been observed for right-sided septal accessory pathways causing abnormal interventricular septal wall motion.⁸ In line with this, we observed a significantly higher hazard of HF for a right anteroseptal pathway location but not for other locations. Interestingly, left ventricular

Table 2. Distribution of Accessory Pathway Location

Location	Frequency on ECG, n (%)
Left lateral	123 (39.7)
Posteroseptal	107 (34.5)
Right anteroseptal	45 (14.5)
Right lateral	26 (8.4)
Undetermined	9 (2.9)
Total	310

Table 3. Risk of Atrial Fibrillation, Heart Failure, and Death From All Causes

Characteristics	Atrial Fibrillation		Heart Failure		Death From All Causes	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
Preexcitation vs no preexcitation						
Preexcitation	3.12 (2.07–4.70)	<0.001	2.11 (1.27–3.50)	0.004	1.07 (0.68–1.68)	0.768
Accessory pathway location vs no preexcitation						
Posteroseptal	2.56 (1.22–5.38)	0.013	1.15 (0.37–3.57)	0.806	0.31 (0.08–1.24)	0.099
Left lateral	3.09 (1.61–5.95)	0.001	1.05 (0.34–3.27)	0.928	1.33 (0.69–2.56)	0.392
Right anteroseptal	2.94 (0.95–9.11)	0.062	5.88 (2.63–13.1)	<0.001	2.14 (0.96–4.76)	0.062
Right lateral	5.27 (1.70–16.4)	0.004	3.63 (0.91–14.5)	0.068	1.31 (0.33–5.23)	0.704

CI indicates confidence interval; and HR, hazard ratio.

dysfunction because of abnormal ventricular activation has been found to be fully reversible in pediatric patients, either spontaneously, due to loss of preexcitation, or by ablation.²⁶ However, whether left ventricular dysfunction, and thereby potentially HF, as a result of preexcitation is fully reversible in adult patients remains elusive. A recent study using ECG-gated cardiac computed tomography on adult patients with WPW suggested irreversible myocardial damage reflecting long-term effects of dyskinesia.²⁷ This finding might favor early ablation, even before onset of HF-related and tachyarrhythmia-related symptoms, if the location of the accessory pathway is right anteroseptal.

We observed a higher risk of death among elderly patients (≥ 65 years) with preexcitation. Although these results should be interpreted with great caution because of relatively low statistical power for the 2 subgroups, our finding is in line with a recent study indicating that tachycardia is poorly tolerated among individuals with preexcitation ≥ 60 years compared with those < 60 years.²⁸ With this finding, combined with the fact that the burden of AF is known to increase with age, it seems biologically plausible that the elderly patients are those most vulnerable to preexcitation. Further studies are needed to determine whether this novel finding should affect clinical decision making.

Regarding the location of the accessory pathway, we found that a right anteroseptal accessory pathway location was borderline significantly associated with a higher hazard of death from all causes. A likely explanation may be found in the higher hazard of HF for this subtype. We found no significant

interaction between preexcitation and events potentially related to this on the hazard of death. This suggests that there is no difference in the risk of death from all causes between asymptomatic and symptomatic preexcitations in this study. We were, however, limited by only having data on symptoms leading to hospitalization.

Limitations

Despite an ECG cohort of $> 300\,000$ individuals and the largest preexcitation cohort from the primary sector, this study has important limitations.

The study relied on administrative registries regarding data on morbidity and mortality, and for some of the registry diagnoses, we do not know the validity. However, we are confident about the diagnoses most central to our analysis. The registry-based definition of AF has recently been found to have a positive predictive value of 93% for ECG-documented AF by review of patient records.²⁹ Our registry-based definition of HF has been found to have a positive predictive value of 81% and a specificity of 99% by evaluating patients with a registered diagnosis of HF with echocardiogram and physical examination.¹⁸

The indication of the general practitioners referral of an individual to ECG at CGPL is unknown, and some degree of selection bias has obviously occurred. However, we have previously shown that the mortality rate in the ECG study population is similar to an age- and sex-matched background population.¹⁴ Moreover, the prevalence of preexcitation that we report is in accordance with previous reports.^{1,2}

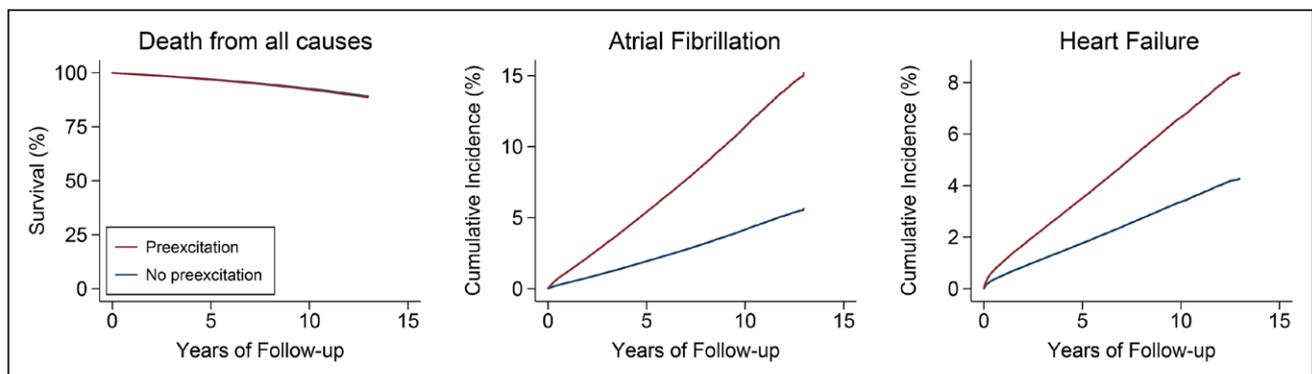


Figure 2. Age-adjusted cumulative incidence curves for the outcomes of atrial fibrillation and heart failure based on the method of Fine and Gray and age-adjusted survival curves for death from all causes based on Cox regression.

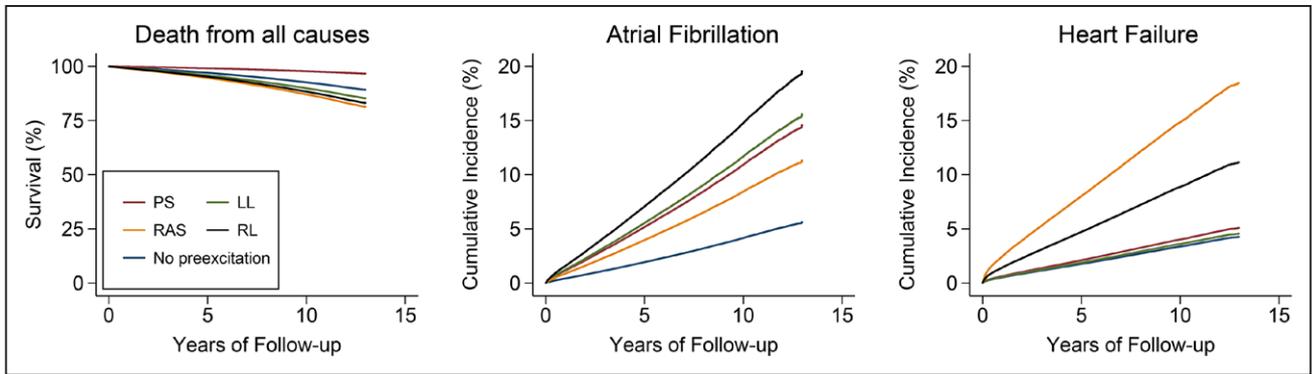


Figure 3. Age-adjusted cumulative incidence curves for the outcomes of atrial fibrillation and heart failure based on the method of Fine and Gray and age-adjusted survival curves for death from all causes based on Cox regression, stratified by location of the accessory pathway. LL indicates left lateral; PS, posteroseptal; RAS, right anteroseptal; and RL, right lateral.

There is a possibility of surveillance bias, meaning that patients with preexcitation may be examined more thoroughly compared with individuals without preexcitation. Because there is no biologically plausible link between treatment with antidiabetic medication or statins and preexcitation, any higher hazard for the preexcitation population could be interpreted as surveillance bias. We did not find evidence of a higher prescription rate of the medications among individuals with preexcitation. In addition, no individuals in the preexcitation population were diagnosed with aortic stenosis during follow-up, indicating that surveillance was not a major issue in this study.

Given the relatively high median age of 43 years (Q1–Q3, 30–56 years) in our study population, there is a risk of survival bias, meaning that individuals with the highest risk of death because of ventricular preexcitation could potentially have died before entering the study. Accordingly, the interpretation of the present results should be narrowed to an adult preexcitation population.

Conclusions

In a large primary care population, we found that individuals with preexcitation had significantly higher hazards of AF and HF compared with the remainder of the population. The higher hazard of HF seemed to be driven by a right anteroseptal location of the accessory pathway. We observed a statistically significant association between preexcitation and a higher risk of death in elderly patients. Further studies are required to determine the mechanism and consequences of these novel findings.

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Electrocardiographic Preexcitation and Risk of Cardiovascular Morbidity and Mortality: Results From the Copenhagen ECG Study

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SUPPLEMENTAL MATERIAL

Supplemental Table 1. Modified* Charlson Co-morbidity Index

All Charlson conditions	Weights	ICD-10 code
Myocardial infarction	1	I21-I23
Peripheral vascular disease	1	I70- I74, I77
Cerebrovascular disease	1	I60- I69, G45, G46
Dementia	1	F00-F03, F05.1, G30
Chronic pulmonary disease	1	J40- J47, J60- J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3
Connective tissue disease	1	M05, M06, M08, M09, M30-M36, D86
Ulcer disease	1	K22.1, K25-K28
Mild liver disease	1	B18, K70.0-K70.3, K70.9, K71, K73, K74, K76.0
Diabetes mellitus	1	E10.0, E10.1, E10.9, E11.0, E11.1, E11.9
Diabetes mellitus with complications	2	E10.2-E10.8, E11.2-E11.8
Hemiplegia	2	G81, G82
Moderate/severe renal disease	2	I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61
Any tumor	2	C00-C75
Leukemia	1	C91-C95
Lymphoma	1	C81-C85, C88, C90, C96
Metastatic solid tumor	3	C76-C80
Moderate/severe liver disease	3	B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85
AIDS	6	B21-B24

**Diagnostic code for congestive heart failure (I50) is excluded as this covariate was adjusted for separately.*

Supplemental Table 2. Identification of covariates and outcomes

Conditions	ICD-10 code, procedure, and operation codes
Hypertension	I10, I15
Heart failure	I50
Valvular heart disease	ICD10; I05, I06, I34, I35 Procedure and operation codes; KFK, KFM
Atrial fibrillation	I48
Ablation for accessory pathway	BFFB1
Syncope	R55.9
Supraventricular tachycardia	I47.1, I47.8
Palpitations	R00.2
Aortic stenosis	I350, I352

Supplemental Table 3. Identification of covariates and outcomes from drugs

Indication	Drugs (ATC code)
Hypertension	Alpha blockers: C02A, C02B, C02C, Non-loop diuretics: C02L, C02DA, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09BA, C09DA, C09XA52, Vasodilators: C02DB, C02DD, C02DG, C04, C05, Beta-blockers: C07, Calcium blockers: C07F, C08, C09BB, C09DB, ACE-inhibitors: C09
Diabetes	Oral antidiabetics: A10B
Statin	C10A

Hypertension was defined from discharge diagnosis or as being present if a subject prior to inclusion was treated simultaneously with at least two kinds of antihypertensive drugs

Circulation: Arritmia y electrofisiología

Preexcitación electrocardiográfica y riesgo de morbimortalidad cardiovascular

Resultados del estudio de ECG de Copenhague

Este gran estudio de ECG investigó los resultados a largo plazo en individuos con preexcitación electrocardiográfica de una población que había recibido atención primaria. Los pacientes con preexcitación ventricular tuvieron mayor riesgo de fibrilación atrial e insuficiencia cardíaca, con el mayor riesgo de insuficiencia cardíaca entre los pacientes con una vía anteroseptal derecha. Aunque el riesgo total de muerte en aquellos con preexcitación no aumentó, ocurrió una diferencia entre los grupos de edades, en donde los pacientes > 65 años de edad y con preexcitación tenían mayor riesgo de muerte que el resto de la población de atención primaria.

ANTECEDENTES: La mayoría de los datos disponibles en la evolución clínica de los pacientes con preexcitación ventricular en el ECG proceden de centros de atención terciaria. Nuestro objetivo fue investigar resultados a largo plazo en individuos de una población de atención primaria con preexcitación electrocardiográfica.

MÉTODOS Y RESULTADOS: Los ECG digitales de 328 638 pacientes se recopilaron durante el período de 2001 a 2011. Identificamos 310 individuos con preexcitación (rango etario, 8-85 años). Los datos sobre la medicación, las enfermedades concomitantes y los resultados se recopilaron de los registros nacionales daneses. El seguimiento medio fue de 7.4 años (cuartiles, 4.6-10.3 años). En comparación con el resto de la población, los pacientes con preexcitación tuvieron mayores riesgos ajustados de fibrilación atrial (*hazard ratio* [HR], 3,12; intervalo de confianza [IC] 95%, 2,07-4,70) y de insuficiencia cardíaca (HR, 2,11; IC 95%, 1,27-3,50). El análisis de subgrupo de la ubicación de la vía accesoria reveló un mayor riesgo ajustado de insuficiencia cardíaca para una vía accesoria anteroseptal derecha (HR, 5,88; IC 95%, 2,63-13,1). No hubo pruebas de un mayor riesgo de muerte entre los individuos con preexcitación al observar todos los grupos etarios (HR, 1,07; IC 95%, 0,68-1,68). No obstante, un análisis de interacción (< 65 *versus* ≥ 65 años) estadísticamente significativo ($P = 0,01$) indicó mayor riesgo de muerte para los pacientes con preexcitación ≥ 65 años (HR, 1,85; IC 95%, 1,07-3,18).

CONCLUSIONES: En este estudio de ECG de gran magnitud, los individuos con preexcitación tuvieron mayor riesgo de fibrilación atrial e insuficiencia cardíaca. El mayor riesgo de insuficiencia cardíaca parecía estar impulsado por una vía accesoria anteroseptal derecha. Entre los ancianos, encontramos una asociación estadísticamente significativa entre la preexcitación y un mayor riesgo de muerte.

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