Long-term Outcomes in Individuals With Prolonged PR Interval or First-Degree Atrioventricular Block

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Context Prolongation of the electrocardiographic PR interval, known as first-degree atrioventricular block when the PR interval exceeds 200 milliseconds, is frequently encountered in clinical practice.

Objective To determine the clinical significance of PR prolongation in ambulatory individuals.

Design, Setting, and Participants Prospective, community-based cohort including 7575 individuals from the Framingham Heart Study (mean age, 47 years; 54% women) who underwent routine 12-lead electrocardiography. The study cohort underwent prospective follow-up through 2007 from baseline examinations in 1968-1974. Multivariable-adjusted Cox proportional hazards models were used to examine the associations of PR interval with the incidence of arrhythmic events and death.

Main Outcome Measures Incident atrial fibrillation (AF), pacemaker implantation, and all-cause mortality.

Results During follow-up, 481 participants developed AF, 124 required pacemaker implantation, and 1739 died. At the baseline examination, 124 individuals had PR intervals longer than 200 milliseconds. For those with PR intervals longer than 200 milliseconds compared with those with PR intervals of 200 milliseconds or shorter, incidence rates per 10 000 person-years were 140 (95% confidence interval [CI], 95-208) vs 36 (95% CI, 32-39) for AF, 59 (95% CI, 40-87) vs 6 (95% CI, 5-7) for pacemaker implantation, and 334 (95% CI, 260-428) vs 129 (95% CI, 123-135) for all-cause mortality. Corresponding absolute risk increases were 1.04% (AF), 0.53% (pacemaker implantation), and 2.05% (all-cause mortality) per year. In multivariable analyses, each 20-millisecond increment in PR was associated with an adjusted hazard ratio (HR) of 1.11 (95% CI, 1.02-1.22; $P=.02$) for AF, 1.22 (95% CI, 1.14-1.30; $P<.001$) for pacemaker implantation, and 1.08 (95% CI, 1.02-1.13; $P=.005$) for all-cause mortality. Individuals with first-degree atrioventricular block had a 2-fold adjusted risk of AF (HR, 2.06; 95% CI, 1.36-3.12; $P<.001$), 3-fold adjusted risk of pacemaker implantation (HR, 2.89; 95% CI, 1.83-4.57; $P<.001$), and 1.4-fold adjusted risk of all-cause mortality (HR, 1.44, 95% CI, 1.09-1.91; $P=.01$).

Conclusion Prolongation of the PR interval is associated with increased risks of AF, pacemaker implantation, and all-cause mortality.

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PROLONGATION OF THE ELECTROcardiographic PR interval, conventionally known as first-degree atrioventricular block (AVB) when the PR interval exceeds 200 milliseconds, is frequently encountered in clinical practice.[1-4] The PR interval is determined by the conduction time from the sinus node to the ventricles and thus integrates information about a number of sites in the conduction system of the heart. First-degree AVB may result from conduction delay in the atrium, atrioventricular node, and/or His-Purkinje system. The atrioventricular node is the site most commonly involved in adults, although more than 1 site of conduction delay is often present.[5]

The known causes of first-degree AVB are numerous and include ischemic heart disease, degenerative conduction system disease, congenital heart disease, connective tissue disease, inflammatory diseases, and medications. However, in ambulatory individuals, first-degree AVB typically occurs in the absence of acute cardiovascular disease.[1,4] The clinical significance of first-degree AVB in this setting is unclear. Several prior studies suggest that first-degree AVB has a benign prognosis, although these studies were based on young, healthy men in the military.[1,6] Data from more representative cohorts are limited, although one study in middle-aged men suggested that first-degree AVB may be associated with a higher risk of coronary heart disease.[2]

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To investigate the prognosis associated with first-degree AVB, we prospectively examined the associations of electrocardiographic PR interval with arrhythmic events and all-cause mortality in the community-based Framingham Heart Study. Advantages of this study population include its large size, inclusion of both sexes, use of a reproducible electrocardiographic measurement protocol, and the availability of multiple decades of follow-up data.

METHODS

Study Sample

The design and selection criteria of the original and offspring cohorts of the Framingham Heart Study have been described previously.[7,8] The baseline examinations for the present investigation were the 11th biennial examination of the original cohort (1968-1971; n=2955 attendees) and the first offspring cohort examination (1971-1974; n=5124). Of the 8079 attendees at the index examinations, we excluded 504 individuals (6.2%) for the following reasons, in hierarchical fashion: inadequate electrocardiogram for measurement of PR interval (n=81), younger than 20 years (n=243), history of atrial fibrillation (AF) or prevalent AF at the examination (n=29), use of antiarrhythmic agents or cardiac glycosides or a history of pacemaker implantation (n=86), and missing covariate data (n=65). After these exclusions, 7575 participants (4089 women) remained eligible. All participants provided written informed consent, and the study protocol was approved by the institutional review board at Boston University Medical Center.

Examination and Electrocardiography

All attendees underwent a routine physical examination, anthropometry, standard 12-lead electrocardiography recorded at a paper speed of 25 mm/s, and laboratory assessment of cardiovascular disease risk factors. At the 11th original cohort examination and the first offspring cohort examination, electrocardiographic measurements were made digitally by eResearchTechnology Inc (Philadelphia, PA; previously Premier Worldwide Diagnostics Ltd). The PR intervals were measured to the nearest millisecond by trained technicians using digital calipers and a magnifying tablet. A single lead (lead II) was used, and 2 measurements were averaged, with a mean coefficient of variation of 3.9%. The PR interval was defined as the interval from the onset of the P wave (junction between the T-P isoelectric line and the beginning of the P-wave deflection) to the end of the PR segment (junction with the QRS complex). At subsequent examinations of the original cohort (every 2 years) and offspring cohort (approximately every 4 years), 12-lead electrocardiography was repeated, and intervals were measured by physician investigators.

Follow-up and Outcome Events

All Framingham Heart Study participants are under surveillance for death and cardiovascular events (including myocardial infarction, coronary insufficiency, stroke, and heart failure), as detailed elsewhere.[9] Additionally, we routinely ascertain information on 2 arrhythmia-related end points: AF and pacemaker implantation. Information about cardiovascular and arrhythmic events was obtained by review of medical histories, physical examinations at the Framingham Heart Study, and hospitalization and personal physician records, including electrocardiograms. A panel of 3 experienced investigators reviewed pertinent medical records for all suspected new events. A cardiologist evaluated all electrocardiograms demonstrating suspected AF or atrial flutter. A diagnosis of AF was made when the following electrocardiographic features were noted: absence of P waves, presence of coarse or fine fibrillatory waves, and irregular RR intervals. Atrial flutter was defined according to standard criteria[10] and combined with AF in all analyses.

Statistical Analyses

We constructed multivariable Cox proportional hazards regression models to examine the associations of PR interval with the occurrence of arrhythmic events and all-cause mortality on follow-up. All models were stratified by sex and prevalent cardiovascular disease status (indicated by a history of myocardial infarction, coronary insufficiency, stroke, or heart failure). Follow-up was censored after 20 years to reduce the influence of competing risk factors. We then tested for proportionality of hazards for each end point (AF, pacemaker implantation, and all-cause mortality) by fitting a multiplicative interaction term of follow-up time and PR interval. Proportionality of hazards was confirmed for AF and all-cause mortality but not for pacemaker implantation. Therefore, we used a single 20-year follow-up period in the longitudinal analyses of AF and all-cause mortality as end points.

For the end point of pacemaker implantation, we used the method of pooling repeated observations[11] to assess the prediction of pacemaker events over consecutive 12-year intervals, a period over which the hazards of pacemaker placement were proportional. Cox models were constructed for each 12-year follow-up interval, and participants became eligible to reenter the analyses if they remained free of events and met the exclusion criteria at each index visit. Original and offspring cohort participants attended a total of 17 206 person-examinations during up to 35 years of follow-up. In analyses of incident pacemaker implantation only, we used the physician-coded PR interval rather than the interval measured from the digital calipers, because the latter was available at only a single set of examinations.

We analyzed the PR interval, first as a continuous variable and then as a categorical variable, using the clinical definition of first-degree AVB (PR interval >200 milliseconds). In the multivariable models, we adjusted for age, heart rate, hypertension, body mass index, ratio of total to high-density lipoprotein cholesterol, smoking, and diabetes. For the AF analysis, we included the following additional covariates: valve disease (≥ grade 3/6 systolic murmur or any dia-

stolic murmur; yes/no), electrocardiographic left ventricular hypertrophy,[12] and presence or absence of atrial premature beats on a 10-second rhythm strip.[13-15] Additional adjustment for QRS interval was performed for models of time to pacemaker implantation.

Because β-blockers and calcium channel blockers can affect cardiac conduction times, we performed analyses with and without participants who were taking these nodal-blocking medications at baseline (concurrent with the PR interval measurement). For the pacemaker analyses, this exclusion was applied at the beginning of every 12-year follow-up interval. For the analyses of AF and all-cause mortality, we accounted for use of β-blockers or calcium channel blockers subsequent to the baseline examination by incorporating time-dependent covariates in secondary analyses.

Secondary analyses were also performed excluding participants with QRS intervals of 120 milliseconds or longer, adjusting for interim myocardial infarction or heart failure as time-dependent covariates and censoring participants with baseline or subsequent myocardial infarction or heart failure at the time of development of the event. Because right ventricular pacing has been associated with incident AF,[16] we also performed analyses adjusting for interim pacemaker placement as a time-dependent covariate in models predicting AF. Lastly, we assessed whether prolongation of the PR interval predicted future coronary heart disease events, defined as myocardial infarction or coronary insufficiency.[2]

All statistical analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, North Carolina)[17]; a 2-sided $P<.05$ was considered statistically significant.

RESULTS

Study Sample

Baseline characteristics of the 7575 study participants (mean age, 47 years; 54% women) are shown in TABLE 1. One-third of individuals had hypertension, and only 2% had a previous history of myocardial infarction or heart failure. The median PR interval was 149 milliseconds, and 124 participants had PR intervals longer than 200 milliseconds at the baseline examination.

Table 1. Baseline Characteristics

Characteristic	All (N = 7575)	Baseline PR Interval >200 ms (n = 124)	Baseline PR Interval ≤200 ms (n = 7451)
Age, mean (SD), y	47 (15)	55 (16)	46 (15)
Women, No. (%)	4089 (54)	34 (27)	4055 (54)
Body mass index, mean (SD)[a]	25.8 (4.3)	26.6 (3.4)	25.8 (4.3)
Cigarette smoking, No. (%)	3417 (45)	52 (42)	3365 (45)
Hypertension, No. (%)	2462 (33)	53 (43)	2409 (32)
Diabetes mellitus, No. (%)	661 (9)	24 (19)	637 (9)
Ratio of total to HDL cholesterol, mean (SD)	4.4 (1.6)	4.6 (1.7)	4.4 (1.6)
Valve disease, No. (%)	432 (6)	14 (11)	418 (6)
Prior MI or CHF, No. (%)	169 (2)	12 (10)	157 (2)
Heart rate, mean (SD), beats/min	76 (14)	65 (12)	76 (14)
Electrocardiographic LVH, No. (%)	69 (1)	2 (2)	67 (1)
Atrial premature beats, No. (%)[b]	76 (1)	1 (1)	75 (1)
QRS interval, mean (SD) ms	87 (10)	93 (16)	87 (10)
PR interval, mean (SD) ms	151 (20)	216 (15)	150 (19)
PR interval, median (IQR) ms	149 (137-163)	211 (205-221)	149 (137-162)

Abbreviations: CHF, congestive heart failure; HDL, high-density lipoprotein; IQR, interquartile range; LVH, left ventricular hypertrophy; MI, myocardial infarction.
[a] Calculated as weight in kilograms divided by height in meters squared.
[b] Defined based on a 10-second rhythm strip.

PR Prolongation and Incident Events

During the follow-up period, 481 participants developed AF, 124 participants required implantation of a pacemaker, and 1739 participants died. Among 102 individuals in whom the indication for pacemaker placement was documented, 36% were for high-grade AVB and 53% were for sinus node dysfunction. The cumulative incidence of arrhythmic and mortality events, according to the baseline PR interval, is shown in the FIGURE. Crude incidence rates of AF, pacemaker implantation, and all-cause mortality among participants having a baseline PR interval longer than 200 milliseconds, compared with those having PR intervals of 200 milliseconds or shorter, are shown in TABLE 2. Individuals having baseline first-degree AVB, compared with those having a normal PR interval, had unadjusted hazard ratios (HRs) of 4.26 (95% confidence interval [CI], 2.85-6.38) for AF (absolute risk increase, 1.04% per person-year), 10.26 (95% CI, 6.66-15.82) for pacemaker implantation (absolute risk increase, 0.53%), and 2.72 (95% CI, 2.11-3.51) for all-cause mortality (absolute risk increase, 2.05%) (TABLE 3). Based on the absolute risk increases for the outcomes associated with PR interval prolongation, the numbers needed to harm were 96 for AF, 189 for pacemaker implantation, and 49 for all-cause mortality.

Multivariable Analyses

Table 3 displays the results of the multivariable Cox proportional hazards models for PR interval. After adjustment for conventional risk factors, the PR interval was a significant predictor of all 3 outcomes. Each 1-SD increment in the PR interval (20 milliseconds) was associated with adjusted HRs of 1.11 (95% CI, 1.02-1.22; $P=.02$) for AF, 1.22 (95% CI, 1.14-1.30; $P<.001$) for pacemaker implantation, and 1.08 (95% CI, 1.02-1.13; $P=.005$) for all-cause mortality. Similar results were observed when individuals taking nodal-blocking medications were excluded from the analyses.

Figure. Cumulative Unadjusted Incidence of Atrial Fibrillation, Pacemaker Implantation, and All-Cause Mortality Among Individuals With Baseline PR Interval Above or Below the Median (149 milliseconds)

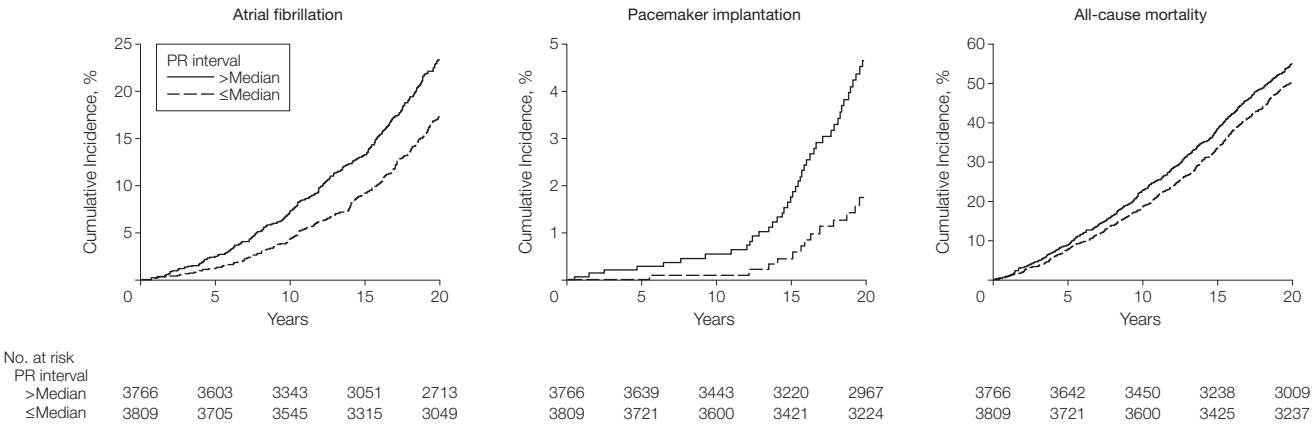

Table 2. Incidence of Atrial Fibrillation, Pacemaker Implantation, and All-Cause Mortality[a]

End Point	Incidence Rate per 10 000 Person-Years (95% CI)	
	PR Interval >200 ms	PR Interval ≤200 ms
Atrial fibrillation	140 (95-208)	36 (32-39)
Pacemaker implantation	59 (40-87)	6 (5-7)
All-cause mortality	334 (260-428)	129 (123-135)

Abbreviation: CI, confidence interval.
[a] Among the 7451 individuals with PR intervals of 200 milliseconds or shorter, 456 developed atrial fibrillation, 98 required pacemaker implantation, and 1677 died; among the 124 individuals with PR intervals longer than 200 milliseconds, 25 developed atrial fibrillation, 26 required pacemaker implantation, and 62 died. Data for pacemaker implantation are based on pooled observations from sequential 12-year follow-up periods.

Analyses were repeated using the clinical definition of first-degree AVB (PR interval >200 vs ≤200 milliseconds) (TABLE 4). Defined in this manner, PR prolongation was associated with multivariable-adjusted HRs of 2.06 (95% CI, 1.36-3.12; $P<.001$) for AF, 2.89 (95% CI, 1.83-4.57; $P<.001$) for pacemaker implantation, and 1.44 (95% CI, 1.09-1.91; $P=.01$) for all-cause mortality.

Secondary Analyses

Results were unchanged in secondary analyses for each end point that excluded individuals with QRS intervals of 120 milliseconds or longer. Additionally, there was no evidence for a sex interaction with PR interval for any of the outcomes ($P>.20$ for interaction). There was also no significant change in outcomes or risk estimates when analyses were stratified by original vs offspring cohort.

Because myocardial infarction, heart failure, and pacemaker implantation could be predisposing factors for AF, we repeated the analyses for AF with adjustment for these interim events; the association with PR interval remained significant. Similarly, adjustment for interim myocardial infarction or heart failure in the cross-sectional pooling analyses did not attenuate the relation between PR interval and risk of pacemaker placement. The relation of PR interval with incident AF and all-cause mortality remained significant after adjusting for exposure to nodal-blocking medications as a time-dependent covariate.

The relation between prolonged PR interval and all 3 outcomes remained significant after excluding individuals with prevalent myocardial infarction or heart failure at baseline and censoring those developing these events during follow-up. Furthermore, there was no relation between baseline PR interval and incidence of coronary heart disease events in multivariable-adjusted analyses.

Progression of Conduction Disease

Among individuals with first-degree AVB at the initial examination (n=124), a majority returned for at least 1 subsequent examination and had an interpretable follow-up electrocardiogram (n=98). Of this group, 13 developed further PR interval prolongation (increase by >40 milliseconds), and 26 developed higher-grade conduction abnormalities (4 with second-degree AVB, 14 with incomplete bundle-branch block, and 8 with complete bundle-branch block).

Among individuals with a normal PR interval at the baseline examination, 161 (3%) developed first-degree AVB by the follow-up examination 12 years later. These individuals had higher multivariable-adjusted hazards for AF (HR, 1.53; 95% CI, 1.05-2.24; $P=.03$) and pacemaker implantation (HR, 2.65; 95% CI, 1.60-4.37; $P<.001$) but not all-cause mortality.

COMMENT

In summary, our results suggest that individuals with first-degree AVB are at substantially increased risk of future AF (approximately 2-fold) and pacemaker implantation (approximately 3-fold) and moderately increased risk of all-cause mortality, compared with individuals without first-degree AVB. The validity of these findings is supported by the large, community-based sample, the routine surveillance of all participants for cardiovascular outcomes, and the long period of follow-up.

These observations challenge the longstanding perception that PR interval prolongation or first-degree AVB has a benign prognosis.[1,3,4,6,18] Notably, pre-

vious longitudinal studies relating PR interval to prognosis have been almost exclusively restricted to young or middle-aged men,[1,3,4,6] with the 2 largest studies based on healthy air force pilots recruited in the World War II era.[1,6] A subsequent study based on several international cohorts (Seven Countries Study) found an association between first-degree AVB and coronary heart disease but with very few incident events and using unadjusted analyses.[2] To our knowledge, the present study is the first investigation based on a contemporary, community-based cohort, with standardized assessment of baseline risk factors and outcomes, including arrhythmic end points.

Although PR prolongation can occur in association with overt cardiovascular disease, residual confounding by prevalent cardiovascular disease is an unlikely explanation for our findings. Participants who attended the routine Framingham Heart Study examinations were generally healthy, and the proportion with existing cardiovascular diagnoses or treatment with medications known to affect the conduction system was low. The results were not changed by exclusion of individuals with prevalent cardiovascular disease or by comprehensive adjustment for risk factors and interim cardiovascular events. In addition, the excess hazard associated with prolonged PR interval was strongest for arrhythmic events (AF and pacemaker implantation), which provides further support for the specificity of our findings.

There are several potential explanations for the observed association of a longer PR interval with adverse outcomes. Chronic PR prolongation could be a precursor to more severe degrees of conduction block. Because there are few "hard" clinical end points related to the conduction system, we examined the rate of pacemaker implantation as a surrogate for advanced conduction system disease. The risk of pacemaker implantation was strongly associated with the PR interval, despite adjustment for age, cardiovascular risk factors, and QRS interval. Although Mymin et al[6] reported a low incidence of second- and third-degree AVB in young air force pilots with first-degree AVB, the generalizability of their sample to unselected populations is uncertain. Air force pilots may be similar to conditioned athletes, in whom first-degree AVB is caused by enhanced vagal tone[19,20] and typically disappears on long-term follow-up.[21]

Prolongation of the PR interval also could be a marker of other changes in the cardiovascular system that contribute to a worse prognosis or represent advanced "physiologic" age. Autonomic as well as structural cardiac abnormalities may lead to prolongation of the PR interval.[22] For instance, responses to catecholaminergic or inotropic stimuli are blunted with advanced age.[23,24] Fibrosis and calcification of the cardiac skeleton after age 40 years was described by Lev,[25] and an early

Table 3. PR Interval and Risks of Atrial Fibrillation, Pacemaker Implantation, and All-Cause Mortality[a]

	HR (95% CI)[b]							
	All				No Nodal-Blocking Medications			
End Point	Unadjusted	*P* Value	Multivariable-Adjusted	*P* Value	Unadjusted	*P* Value	Multivariable-Adjusted	*P* Value
Atrial fibrillation[c]	1.38 (1.27-1.50)	<.001	1.11 (1.02-1.22)	.02	1.39 (1.28-1.52)	<.001	1.12 (1.02-1.23)	.02
Pacemaker implantation[d]	1.43 (1.37-1.50)	<.001	1.22 (1.14-1.30)	<.001	1.88 (1.68-2.09)	<.001	1.37 (1.20-1.57)	<.001
All-cause mortality[e]	1.27 (1.22-1.33)	<.001	1.08 (1.02-1.13)	.005	1.27 (1.21-1.34)	<.001	1.08 (1.02-1.14)	.009

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Number of events in the sample included 481 for atrial fibrillation, 124 for pacemaker implantation, and 1739 for all-cause mortality.
[b] Hazard ratios represent risk per 1-SD increment in PR interval (20 milliseconds). All models are stratified by sex and cardiovascular disease status and further adjusted for age, heart rate, body mass index, hypertension, smoking, diabetes, and ratio of total to high-density lipoprotein cholesterol.
[c] Additional covariates included atrial premature beats, valve disease, and electrocardiographic left ventricular hypertrophy.
[d] Included QRS duration as an additional covariate.
[e] Included the main covariates listed above and no additional covariates.

Table 4. First-Degree Atrioventricular Block and Risks of Atrial Fibrillation, Pacemaker Implantation, and All-Cause Mortality[a]

	HR (95% CI)							
	All				No Nodal-Blocking Medications			
End Point	Unadjusted	*P* Value	Multivariable-Adjusted	*P* Value	Unadjusted	*P* Value	Multivariable-Adjusted	*P* Value
Atrial fibrillation[b]	4.26 (2.85-6.38)	<.001	2.06 (1.36-3.12)	<.001	4.91 (3.23-7.48)	<.001	2.36 (1.53-3.64)	<.001
Pacemaker implantation[c]	10.26 (6.66-15.82)	<.001	2.89 (1.83-4.57)	<.001	13.30 (7.76-22.80)	<.001	4.32 (2.46-7.59)	<.001
All-cause mortality[d]	2.72 (2.11-3.51)	<.001	1.44 (1.09-1.91)	.01	2.86 (2.18-3.76)	<.001	1.48 (1.10-1.99)	.01

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Number of events in the sample included 481 for atrial fibrillation, 124 for pacemaker implantation, and 1739 for all-cause mortality. All models are stratified by sex and cardiovascular disease status and further adjusted for age, heart rate, body mass index, hypertension, smoking, diabetes, and ratio of total to high-density lipoprotein cholesterol.
[b] Additional covariates included atrial premature beats, valve disease, and electrocardiographic left ventricular hypertrophy.
[c] Included QRS interval as an additional covariate.
[d] Included the main covariates listed above and no additional covariates.

electrocardiographic manifestation may be PR interval prolongation. As such, the observed association between PR interval and mortality may be related to progressive alterations in the conduction system, cardiac structure, or both.

Other potential explanations may specifically account for the association of longer PR interval with AF risk. Although first-degree AVB usually involves conduction delay in the atrioventricular node, it is frequently accompanied by abnormalities in other parts of the conduction system as well. Prior studies have raised the possibility that slowed intra-atrial or interatrial conduction may directly increase the risk of AF,[26-31] and increased atrial conduction time or intra-atrial block may be manifested by prolongation of the PR interval. In addition, a prolonged PR interval results in delayed and ineffective mitral valve closure and diastolic mitral regurgitation,[32] especially when the PR interval exceeds 230 milliseconds.[33] An association between continuous PR interval and AF risk has been reported in a separate study using Framingham data to construct a clinical risk score for AF.[34] The current study extends this observation by examining a longer follow-up interval, quantifying the risk associated with first-degree AVB, and demonstrating that the association is not attributable to interim cardiovascular events, pacemaker implantation, or use of nodal-blocking medications. Further research is warranted to investigate the possible mechanisms underlying the relation of PR prolongation with AF.

Several limitations of our study merit comment. The PR interval typically shows a circadian variation[35] and may change over time.[6] However, such misclassification would likely be random and would result in a conservative bias. Furthermore, study participants typically underwent electrocardiography in the morning on arrival at the clinic. Investigators have also reported that longitudinal changes in individuals with a prolonged PR interval are typically small (<40 milliseconds).[4] Median PR, QRS, and RR intervals in our study were somewhat shorter than those reported recently in another large ambulatory cohort.[36] These differences could be attributable to the fact that manual measurements of paper recordings may deliver shorter electrocardiographic interval values compared with algorithms used to assess digital recordings. Thus, modern cutpoints for determining first-degree AVB could be slightly longer than that used for this analysis. Also, the somewhat higher heart rate in the Framingham participants could be the result of shorter supine rest periods prior to acquisition of the electrocardiogram, compared with the prior report, which was based on individuals enrolled in pharmaceutical trials. The Framingham protocol should more closely approximate standard clinical practice.

The proportion of individuals with baseline first-degree AVB who have progression of conduction system abnormalities on electrocardiography may be an underestimate, because individuals who did not return for follow-up examinations could have had a higher incidence of conduction disease progression. Although congenital abnormalities such as ostium primum atrial septal defects can cause PR lengthening, the low prevalence of such disorders in the community suggests that they are unlikely to contribute to our findings. Prolongation of the PR interval may be attributable to delayed conduction at different locations in the upper and lower conduction system and also may be a result of different underlying pathologies. Since the PR interval was measured from the surface electrocardiogram as opposed to an intracardiac recording, the relative contributions of delay at different conduction sites could not be assessed. As well, we did not have a measure of sinus node function apart from the heart rate, which we adjusted for in all of the multivariable analyses. The small number of individuals with first-degree AVB in the setting of nodal-blocking medications prevented us from specifically examining medication-related PR prolongation. Indeed, the association of PR prolongation with adverse outcomes in untreated individuals does not imply that PR prolongation from nodal blockade leads to increased risk.

Our analyses of pacemaker implantation were based on multiple index examinations to maintain proportionality of the hazards. For these analyses, we used the physician-coded PR interval rather than that measured using digital calipers. Reduced measurement precision would likely bias the association of PR interval with pacemaker placement toward the null. Furthermore, the use of physician-coded PR intervals most closely approximates standard clinical practice.

For AF analyses, we were unable to adjust for alcohol exposure or incident thyroid disease, because data regarding these variables were not consistently obtained during the study period. The presence of valvular disease was based on murmurs detected by physical examination, since echocardiograms were not consistently available at the baseline examinations. Severe valvular disease is rare in the Framingham cohort.[37] We focused on all-cause mortality, because adjudication of cardiovascular or sudden death in our cohort does not distinguish between arrhythmic and nonarrhythmic causes. Although there was no evidence for effect modification by sex in analyses using an interaction term for sex, we cannot exclude the possibility of such an interaction. Lastly, our sample was predominantly white, potentially limiting the applicability of our results to other racial/ethnic groups.

In conclusion, our findings indicate that individuals with PR interval prolongation have an increased risk of future AF, need for pacemaker implantation, and all-cause mortality. These results suggest that the natural history of first-degree AVB is not as benign as previously believed. Additional studies are needed to determine appropriate follow-up for individuals found to have prolongation of the PR interval on a routine electrocardiogram.

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Author Contributions: Drs Wang and Larson had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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Acquisition of data: Cheng, Benjamin, Vasan, Wang.
Analysis and interpretation of data: Cheng, Keyes, Larson, McCabe, Newton-Cheh, Levy, Benjamin, Vasan, Wang.
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