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Prognostic significance of first-degree atrioventricular block in a large Asian population: a prospective cohort study

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ABSTRACT

Objective To investigate the prognostic significance of first-degree atrioventricular block (AVB) in Asian populations.

Design and setting Participants (N=9634) from the Northeast China Rural Cardiovascular Health Study were included. The first-degree AVB was defined as PR (from the beginning of the P wave to the beginning of the QRS complex on an electrocardiogram) interval >200 ms, and primary composite outcome (all events) included new onset cardiovascular disease (CVD) and mortality. Cox regression and restricted cubic spline were used to identify the associations of PR interval or first-degree AVB with end points. Furthermore, the relationship between new-onset CVD and mortality and first-degree AVB was separately evaluated. The value of first-degree AVB for predicting adverse events was evaluated by reclassification and discrimination analyses.

Results During a median of 4.65 years follow-up, 524 participants developed CVD and 371 died. Compared with participants with PR ≤200 ms, those with first-degree AVB had an increased risk of all events (HR: 1.84; 95% CI 1.18 to 2.88). Furthermore, first-degree AVB was predictive of incident CVD (1.96, 1.18 to 3.23) and stroke (2.22, 1.27 to 3.90) after adjusting for conventional risk. These statistically significant associations remained unchanged after further stratification by potential confounding factors. Discrimination and reclassification analyses suggested that first-degree AVB addition could improve the conventional model for predicting adverse outcomes within 4 years.

Conclusions Our results indicated that first-degree AVB was an independent risk factor for adverse events, suggesting that it should not be considered as inconsequential factor in general population. These results have potential clinical value for identifying individuals at high risk for adverse outcomes.

Strengths and limitations of this study

- ► This study was a large prospective study for the general population, and sufficient confounding factors were collected.
- ► The Marquette Universal System for Electrocardiography, not manual ECG measurements, was used to accurately measure the PR intervals.
- ► The number of events was limited because of the short follow-up time.

INTRODUCTION

The PR interval is measured from the beginning of the P wave to the beginning of the QRS complex on an ECG, which reflects the total conduction time from atrial to ventricular depolarisation. In general, first-degree atrioventricular block (AVB) is defined as PR interval prolongation >200 ms, which is frequently encountered in clinical practice.[1 2] Previous studies, which overwhelmingly focused on young and healthy men, indicate that first-degree AVB appears to be a benign condition.[3–5] In view of this, the current authoritative guidelines suggest that specific treatment is not required, unless there are symptoms and/or the PR interval is >300 ms.[1 6]

Currently, the prognostic significance of first-degree AVB is controversial. Results from the Framingham study indicated that PR interval prolongation in the general population was significantly associated with atrial fibrillation (AF), pacemaker implantation and mortality.[2] In individuals with hypertension,[7 8] or coronary heart disease (CHD)[9 10] and in elderly individuals,[11 12] the PR interval prolongation was associated with in more severe adverse outcomes, although the definition of this ECG pattern was largely varied across studies. In contrast, the third National Health and Nutrition Examination Survey and the Finnish Social Insurance Institution's CHD Study indicated that PR interval prolongation was associated with a benign prognosis in general population.[13 14] Thus, previous studies in Western general populations have indicated conflicting associations between first-degree AVB and cardiovascular outcomes. Considering racial differences, black people were more likely to have PR interval prolongation compared with white people,[15] the prognostic impact of PR interval prolongation in Asian populations is largely unexplored.[7 16 17] Moreover, almost

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all previous studies used manual ECG measurements to determine PR intervals, which can lead to measurement bias.

This study was based on follow-up data from 9634 participants from the Northeast China Rural Cardiovascular Health Study (NCRCHS), who were followed-up for a median of 4.65 years. The Marquette Universal System for Electrocardiography was used to accurately measure the PR intervals to identify the prognostic significance of first-degree AVB. This was the largest study conducted to investigate the relationship between first-degree AVB and adverse outcomes in an Asian general population. To our knowledge, this study was also the first to elucidate the prognostic significance of PR interval prolongation in Chinese population.

METHODS

Participants

The NCRCHS is a community-based prospective cohort study carried out in rural areas of Northeast China.[18 19] 11 956 participants aged ≥35 years were prospectively recruited from Liaoning province in 2013. In 2015 and 2017, participants were invited to attend follow-up visits, and 10 700 consented and were eligible for the follow-up study. A total of 10 349 participants (96.7%) completed at least one follow-up visit. In current analyses, we further excluded participants (n=715) for the following reasons: missing or unreadable electrocardiograms (n=221), history of AF or current AF at baseline or inadequate electrocardiograms for measurement of PR interval (n=133), use of antiarrhythmic agents or cardiac glycosides (n=5), QRS interval ≥120 ms (n=193) and missing covariate data (n=163) (figure 1). Eventually, data from 9634 (93.1%) participants were available for analysis.

Data collection (including electrocardiograms)

At baseline, detailed information on demographic characteristics, lifestyle, medical history and medication history in the past 2 weeks was obtained using a standardised questionnaire. Self-reported history of stroke and CHD was confirmed based on medical records. Participants who self-reported a certain disease such as stroke, CHD and diabetes were asked whether they had taken prescription medication for this disease in the past 2 weeks. Body mass index was calculated by dividing weight in kilograms by height in metres squared. Blood pressure was assessed three times using a standardised automatic electronic sphygmomanometer, with participants seated after at least 5 min of rest. Hypertension was defined as systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic blood pressure (DBP) ≥90 mm Hg and/or use of antihypertensive medications in the past 2 weeks.[20] Dietary patterns have been described and diet score was calculated (range 0–6) in previous study.[21] Blood samples were collected in the morning after at least 12 hours of overnight fasting. Current drinking was defined more than one drink a day for women and more than two drinks a day for the man in the past year.[22] Biochemical parameters, including fasting blood glucose (FBG), triglyceride, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol and serum creatinine, were analysed enzymatically. Diabetes mellitus was defined as FBG ≥7 mmol/L and/or self-reported diagnosis that was previously determined by a physician.[23] Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[24] Echocardiograms were obtained using Doppler echocardiography with a 3.0-MHz transducer. Echocardiogram analyses were performed by at least two independent doctors specialised in echocardiography. Left ventricular ejection fraction (LVEF) was calculated as follows: (end diastolic volume—end systolic volume)/end diastolic volume. The E/A ratio was defined as the mitral early to late diastolic flow velocity ratio.

After a rest for at least half an hour, twelve-lead electrocardiograms (resting, 10 s) were recorded at the time of enrolment for each participant using an MAC 5500 (GE Healthcare). The electrocardiograms were automatically analysed by the MUSE Cardiology Information System V.7.0.0 (GE Healthcare). Electrocardiogram-based diagnoses (including AF) were confirmed by at least two independent cardiologists. The third cardiologist was required to make final judgement if the two cardiologists disagreed. AF was diagnosed based on ECG findings and/or previous diagnosis by a physician.

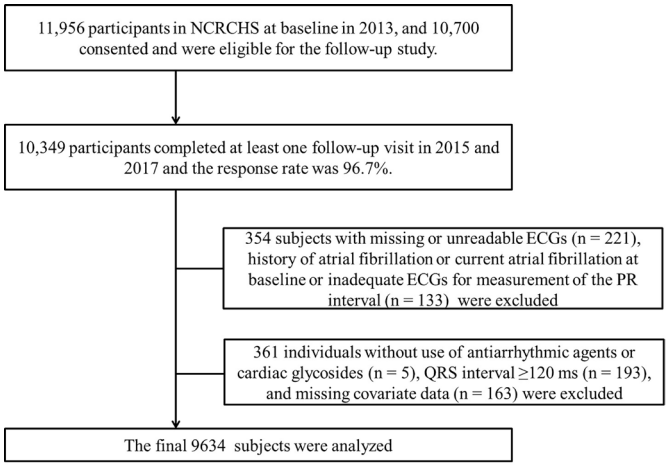

Figure 1 Study flowchart. NCRCHS, Northeast China Rural Cardiovascular Health Study.

The judgement and definition of clinical outcomes

For all participants, all available clinical information or mortality was collected and all materials were independently reviewed and adjudicated by an end point assessment committee. Stroke was defined as rapidly developing signs of focal or global cerebral function disturbance lasting >24 hour (unless interrupted by surgery or death) with no apparent non-vascular cause.[25] Haemorrhagic stroke was defined as stroke with subarachnoid or intracerebral haemorrhage, and ischaemic stroke

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was defined as stroke with thrombosis or embolism. Transient ischaemic attack and chronic cerebral vascular disease were excluded. CHD was defined as a diagnosis of angina requiring hospitalisation, myocardial infarction requiring hospitalisation, CHD-related mortality or any revascularisation procedure.[26] Deaths were diagnosed through direct contact with family members and hospital records. Cardiovascular disease (CVD)-related mortality was diagnosed based on death certificates, autopsy reports, medical record abstractions or information obtained from family members.

CVD during the follow-up period was defined as new-onset stroke or CHD. Primary composite outcome designated 'all events' was defined as CVD and all-cause mortality during the follow-up period.

Statistical analysis

Continuous variables were reported as means and SD, or medians and quartiles. Categorical variables were reported as frequencies and percentages. Differences between categories were evaluated using the t test, Mann-Whitney U test or the χ^2 test, as appropriate. Kaplan-Meier curves were used to evaluate the cumulative incidence for adverse events, and log-rank test was used to compare differences. Cox proportional hazards models were sequentially conducted to identify the associations of PR interval with adverse outcomes (reported as HRs and 95% CIs). According to the clinical definition of first-degree AVB (PR interval >200 ms),[1] PR interval was analysed as a binary variable. We constructed the following models: model 1, adjusted for age, sex, body mass index, heart rate, current smoking, current drinking, SBP, beta-blocker treatment, calcium blocker treatment, diabetes, history of CVD, TC, HDL-C, triglyceride and eGFR; model 2, further adjusted for left ventricular systolic and diastolic function (LVEF and E/A ratio) after excluding participants without ECG date.

In the sensitivity analysis, Cox proportional hazards models were used based on the variables adjusted in model 2. As beta-blockers and calcium channel blockers can affect cardiac conduction times, participants who took these drugs at baseline would be excluded (n=376). Further sensitivity analyses were conducted according to baseline CVD status (history of CHD or stroke), that is, the regression analyses were independently conducted before and after the exclusion of baseline CVD history (n=708). Additionally, the interaction between first-degree AVB and sex was evaluated for each endpoint. The dose–response curves were drawn using a restricted cubic spline approach based on Cox proportional hazards models, in which PR interval served as a continuous variable.

To evaluate the improvement in risk prediction for adverse outcomes by adding first-degree AVB to the conventional model (including age, sex, body mass index, heart rate, current smoking, current drinking, SBP, beta-blocker treatment, calcium blocker treatment, diabetes, history of CVD, TC, HDL-C, triglyceride, eGFR, LVEF and E/A ratio), the integrated discrimination improvement (IDI) and net reclassification improvement (NRI) for adverse outcome prediction models were calculated, respectively.

The dose–response curves for relationships between PR interval and the risks of adverse outcomes were plotted using EmpowerStats software (http://www.empowerstats.com, X&Y Solutions, Boston, MA), and the reclassification and discrimination analyses were calculated using statistical software packages R (http://www.R-project.org, The R Foundation). The other statistical analyses were performed using SPSS V.22.0 software package and p values <0.05 were considered to be statistically significant.

Patient and public involvement statement

The patients were not actively involved during the design and conduct of this study. The patients and the general public will be informed of the study results through peer-reviewed journals.

RESULTS

Characteristics of study population

Data from 9634 (93.1%) participants were available for analysis (table 1). Of the 9634 NCRCHS participants included in the analysis (mean age: 53.53±10.39; men: 45.2%), 126 (1.3%) had first-degree AVB. Baseline clinical characteristics by first-degree AVB status are shown in table 1. Compared with the participants without first-degree AVB, those with first-degree AVB were more likely to be elder, men, drinkers and hypertension; have higher body mass index, SBP, DBP and TC and have lower eGFR and E/A ratio (all p<0.05).

The associations between first-degree AVB and adverse outcomes

During follow-up, a median of 4.65 years (quartile: 4.36–4.92), 710 participants developed primary composite outcome (CVD or all-cause mortality) and 524 participants of them developed CVD (new-onset stroke or CHD). Furthermore, 371 participants died, 182 of whom died due to CVD-related causes (49.1% of all-cause mortality). The cumulative incidences of primary composite outcome, CVD and stroke were significantly higher in participants with first-degree AVB than in participants without first-degree AVB. However, there was no significant statistical difference in mortality and CHD (figure 2).

We further explored the associations between first-degree AVB and adverse outcomes, as indicated by the unadjusted and adjusted regression models. As shown in table 2, after adjusting for age, sex, body mass index, heart rate, current smoking, current drinking, TC, HDL-C, triglyceride, eGFR, SBP, beta-blocker treatment, calcium blocker treatment, diabetes and history of CVD, first-degree AVB was an independent risk factor for all events (HR: 1.80, 95% CI 1.16 to 2.79), CVD (HR: 1.84, 95% CI 1.11 to 3.03) and stroke (HR: 2.10, 95% CI 1.20 to 3.67). The conclusions remain consistent after further

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Table 1 Baseline characteristics of the study sample

Variable	Without first-degree AVB (N=9508)	With first-degree AVB (N=126)	P value
PR interval (ms)	151.17±18.26	213.78±13.40	<0.001
Age (years)	53.49±10.38	56.16±10.96	0.004
Male (n (%))	4272 (44.9)	85 (67.5)	<0.001
Current smoking (n (%))	3340 (35.1)	48 (38.1)	0.488
Current drinking (n (%))	2112 (22.2)	40 (31.7)	0.011
body mass index (kg/m^2)	24.82±3.69	25.74±3.71	0.006
SBP (mm Hg)	141.81±23.38	147.54±23.56	0.006
DBP (mm Hg)	82.05±11.67	84.90±12.73	0.006
FBG (mmol/L)	5.54 [5.15–6.02)	5.51 [5.21–6.17)	0.517
TC (mmol/L)	5.23±1.08	5.42±1.48	0.049
LDL-C (mmol/L)	2.94±0.83	3.09±0.86	0.058
HDL-C (mmol/L)	1.42±0.39	1.36±0.38	0.099
Triglyceride (mmol/L)	1.22 [0.86–1.86)	1.31 [1.00–2.24)	0.072
eGFR (mL/min per 1.73 m^2)	93.82±15.22	89.51±16.80	0.005
Heart rate (bpm)	71.91±12.22	70.10±13.59	0.139
LVEF (%)	62.82±3.88	62.12±4.68	0.106
E/A ratio	0.89 [0.72–1.28)	0.80 [0.66–1.16)	0.001
Hypertension (n (%))	4774 (50.2)	79 (62.7)	0.005
Diabetes (n (%))	951 (10.0)	17 (13.5)	0.195
History of CVD (n (%))	700 (7.4)	8 (6.3)	0.665
Hypertension drugs use (n (%))	1366 (14.4)	36 (28.6)	<0.001
Beta-blocker (n (%))	52 (0.5)	0 (0)	1.0
Dihydropyridine calcium blocker (n (%))	329 (3.5)	9 (7.1)	0.047
Diabetes drugs use (n (%))	335 (3.5)	8 (6.3)	0.089
Exercise regularly (n (%))	1954 (20.6)	31 (24.6)	0.264
Diet score (<3 vs≥3) (n (%))	4793 (50.4)	56 (44.4)	0.183

Data are presented as mean±SD, median (upper and lower quartiles), or n (%), as appropriate.
AVB, atrioventricular block; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; E/A ratio, the mitral early to late diastolic flow velocity ratio; SBP, systolic blood pressure; TC, total cholesterol.

adjustment for left ventricular systolic and diastolic function (all events: HR: 1.84, 95% CI 1.18 to 2.88; CVD: HR: 1.96, 95% CI 1.18 to 3.23 and stroke: HR: 2.22, 95% CI 1.27 to 3.90). However, our results failed to show any significant associations between first-degree AVB and risk of mortality or CHD.

Associations between PR interval and adverse outcomes

Our finding remained unchanged after the conduction of sensitivity analysis. First, after the exclusion of participants taking beta-blockers or calcium-channel blockers, participants with first-degree AVB still had a higher risk of adverse outcomes as compared with those without first-degree AVB (all events: HR: 1.88, 95% CI 1.16 to 3.035; CVD: HR: 2.21, 95% CI 1.32 to 3.72 and stroke: HR: 2.47, 95% CI 1.38 to 4.44). Second, stratified analysis by baseline CVD status shows that even if participants with CVD at baseline had been excluded, the relationships between first-degree AVB and adverse outcomes remained statistically significant. Third, we analysed the interaction between first-degree AVB and sex for each end point. Interestingly, although the prevalence of first-degree AVB in males was higher than women, there were no significant interactions (p>0.05) (online supplemental file 1). Furthermore, using PR interval as a continuous variable (per SD increase) in the Cox proportional hazards models, there were no significant independent associations between PR interval and all events, CVD or stroke. The dose–response relationships assessed using a restricted cubic spline approach suggested that the relationships between PR interval and risks of adverse outcomes were non-linear; risks of adverse outcomes began to increase considerably from a PR interval of approximately 150 ms (figure 3).

Reclassification and discrimination statistics for adverse outcomes within 4 years by first-degree AVB

Finally, we evaluated whether adding first-degree AVB to the conventional model could improve prediction performance. Fortunately, the IDI value and NRI value

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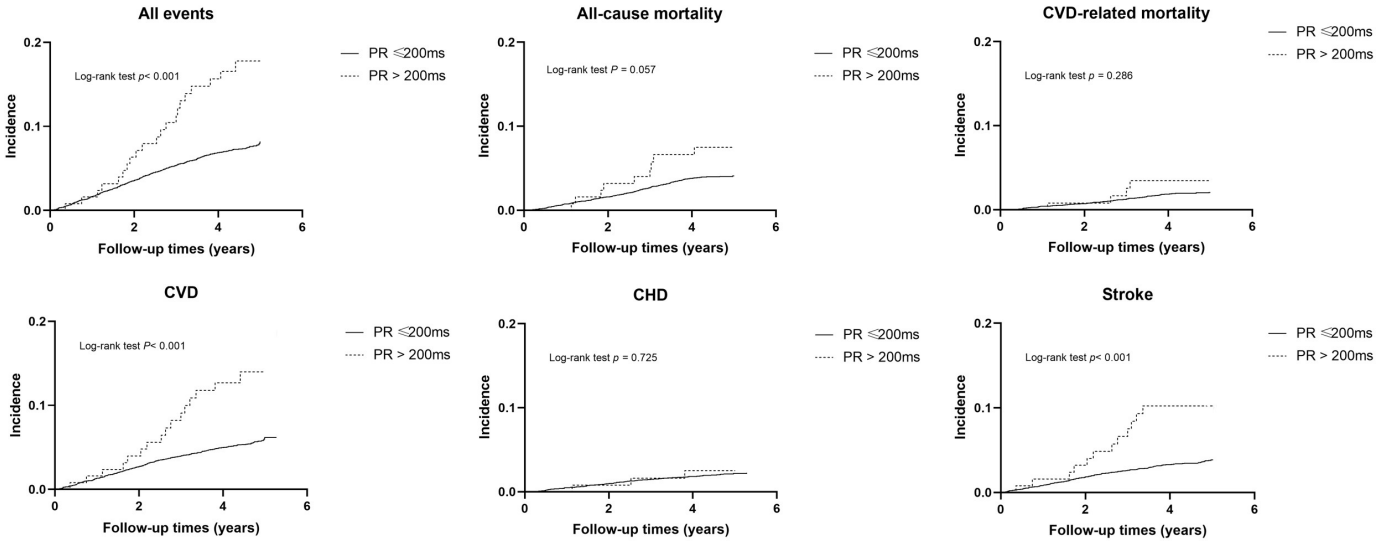

Figure 2 Unadjusted Kaplan-Meier curves for incident adverse events stratified by PR interval. CHD, coronary heart disease; CVD, cardiovascular disease.

suggested that the model after addition of first-degree AVB led to a significant improvement in predicting primary composite outcome, CVD and stroke within 4 years. Adding first-degree AVB to model improved NRI (0.0213, 95% CI 0.0099 to 0.0340; p<0.05) and IDI (0.0015, p=0.0259) for primary composite outcome. Meanwhile, the value of NRI suggested that first-degree AVB could significantly improve the prediction of CVD (0.0241, 95% CI 0.0095 to 0.0417; p<0.05), although IDI was borderline significant (0.0011, p=0.0733) (table 3).

DISCUSSION

Our study provides strong clinical evidence on the adverse prognostic significance of first-degree AVB, and the results confirm that this previously reported conclusion applies to the general population in China. This study demonstrated that first-degree AVB was positively associated with risk of primary composite outcome, especially CVD and stroke, and the association was independent from conventional risk factors even left ventricular systolic and diastolic function. Sensitivity analysis showed that when stratified by potential confounding factors (beta-blocker/calcium-channel blocker use and baseline CVD status), the statistical associations remained unchanged. Furthermore, adding first-degree AVB to conventional model could improve the capacity of risk prediction for adverse outcomes. Our results have potential applications in risk stratification and

Table 2 Associations between first-degree AVB and risks of adverse outcomes

Outcome	Unadjusted HR (95% CI)	P value	Model 1 HR (95% CI)	P value	Model 2 HR (95% CI)	P value
All events	2.39 (1.55 to 3.69)	<0.001	1.80 (1.16 to 2.79)	0.008	1.84 (1.18 to 2.88)	0.008
Mortality						
All-cause mortality	1.88 (0.97 to 3.65)	0.061	1.38 (0.71 to 2.69)	0.340	1.36 (0.67 to 2.75)	0.398
CVD-related mortality	1.71 (0.63 to 4.59)	0.291	1.15 (0.42 to 3.12)	0.785	1.26 (0.46 to 3.43)	0.657
CVD						
Total	2.48 (1.51 to 4.08)	<0.001	1.84 (1.11 to 3.03)	0.017	1.96 (1.18 to 3.23)	0.009
CHD	1.23 (0.39 to 3.84)	0.725	0.98 (0.31 to 3.13)	0.984	1.03 (0.32 to 3.29)	0.964
Stroke	2.96 (1.69 to 5.18)	<0.001	2.10 (1.20 to 3.67)	0.010	2.22 (1.27 to 3.90)	0.005

Model 1: Adjusted for age, sex, body mass index, heart rate, current smoking, current drinking, TC, HDL-C, triglyceride, eGFR, SBP, beta-blocker and calcium blocker treatment, diabetes, and history of CVD. Model 2: model 1+adjusted for left ventricular systolic and diastolic function (LVEF and E/A ratio).
AVB, atrioventricular block; CHD, coronary heart disease ; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; E/A ratio, the mitral early to late diastolic flow velocity ratio; SBP, systolic blood pressure; TC, total cholesterol.

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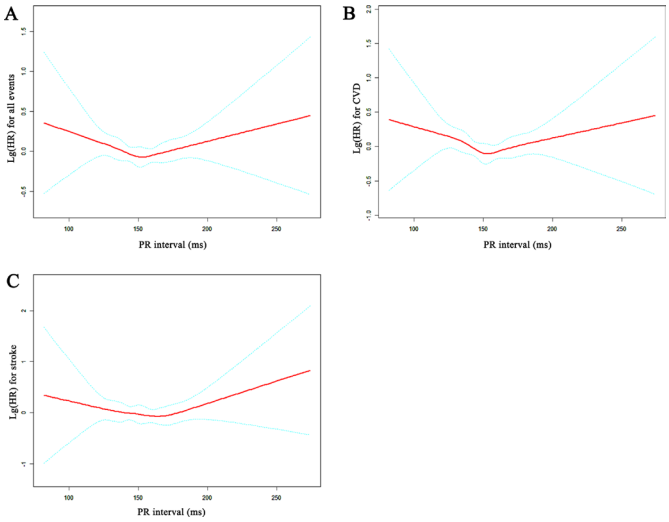

Figure 3 Associations between PR interval and adverse outcomes based on a restricted cubic spline approach. (A: all events, B: CVD, C: stroke). CVD, cardiovascular disease.

for identifying individuals at high risk for adverse outcomes.

The adverse prognostic significance of first-degree AVB might be explained by the following mechanisms. First, previous studies show that a prolonged PR interval could be a marker of other cardiovascular changes, resulting from ageing and elevated blood pressure values that are associated with adverse outcomes.[2 27] First-degree AVB in young individuals is mainly caused by prolonged conduction in the AV node due to enhanced vagal activity, which in light of the results from the previous study, may be related to significantly improved survival (decreased overall mortality).[28] However, in the elderly, electrical and structural remodelling, such as atrial fibrosis as well as calcification and fibrosis of the conduction system, may have an important impact on the development of prolonged PR interval.[29] Additionally, electrophysiological studies have suggested that the refractory and conduction times of atrium will increase with ageing.[30 31] Hypertension may promote increase in intracardiac pressures, causing structural remodelling and changes in atrial electrical function.[7 11] This explanation seems to be supported by the results of our study because we observed that participants with first-degree AVB were older and more likely to have hypertension compared with the normal PR interval group. Second, the PR interval prolongation may be a sign of the increased likelihood of arrhythmia. Although atrioventricular node delay is the most common cause of first-degree AVB, AVB sometimes occurs because of intra-atrial conduction defects. Both interatrial block and first-degree AVB have been identified as significant independent risk factors for AF.[32 33] A recent long-term follow-up study in patients with Brugada syndrome also suggested that first-degree AVB was an independent predictor of malignant arrhythmia.[34]

To our knowledge, the associations between first-degree AVB and adverse outcomes have rarely been reported in the general population. An early US study conducted in the 1960s indicated that there was no excess incidence of CVD or mortality among participants with PR interval >220 ms.[5] Subsequently, the results from the Finnish Social Insurance Institution's CHD Study of 10 957 participants aged 30–59 years confirmed the benign prognosis of the ECG pattern, as PR interval >200 ms was not associated with all-cause mortality, CVD-related mortality or additional hospitalisations for heart failure, CHD, AF or stroke.[14] Additionally, in the Japanese National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged, PR interval prolongation (≥220 ms) was not associated with

Table 3 Reclassification and discrimination statistics for adverse outcomes within 4 years by first-degree AVB

Outcome	Model	NRI (95% CI)	IDI	
			Estimate	P
All events				
Conventional		Reference	Reference	
Conventional + first-degree AVB		0.0213 (0.0099 to 0.0340)*	0.0015	0.0259
Cardiovascular disease				
Conventional		Reference	Reference	
Conventional + first-degree AVB		0.0241 (0.0095 to 0.0417)*	0.0011	0.0733
Stroke				
Conventional		Reference	Reference	
Conventional + first-degree AVB		0.0276 (0.0104 to 0.0486)*	0.0018	0.0484

Conventional model: including age, sex, body mass index, heart rate, current smoking, current drinking, TC, HDL-C, triglyceride, eGFR, SBP, beta-blocker and calcium blocker treatment, diabetes, and history of CVD, left ventricular systolic and diastolic function (LVEF and E/A ratio).
*P<0.05.
AVB, atrioventricular block; CVD, cardiovascular disease; E/A ratio, the mitral early to late diastolic flow velocity ratio; eGFR, estimated glomerular filtration rate ; eGFR, estimated glomerular filtration rate; HDL-C, high density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; IDI, integrated discrimination index; LVEF, left ventricular ejection fraction; NRI, net reclassification index; SBP, systolic blood pressure; TC, total cholesterol.

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CVD-related or all-cause mortality.[16] In contrast, Cheng *et al* found that first-degree AVB (PR interval >200 ms) was significantly associated with adverse outcomes (AF, pacemaker implantation and all-cause mortality) in the Framingham study, which was only positive finding in general population so far.[2] Although data on heart failure, AF and pacemaker implantation were not systematically collected in our study, our results also supported this previous findings obtained in Framingham study, regarding the adverse prognostic significance of first-degree AVB in the general population. Besides, several previous studies assessed the relationship between this ECG pattern and adverse outcomes, but none evaluated reclassification. Our results furtherly confirmed that adding first-degree AVB to conventional model could improve the capacity of risk prediction for adverse outcomes within 4 years in general population.

At present study, the significant, independent association between first-degree AVB and all-cause mortality were not found, which was inconsistent with the results of Framingham study. The effect of racial differences can be an important reason underlying the differences in mortality results observed between our study and the Framingham study. Meanwhile, we noticed that the number of end point events of mortality was scarce due to the limited follow-up period. These may have affected the accuracy of our results. In further exploration, we found that the association between first-degree AVB and CVD was inconsistent in our study (only increasing risk for stroke but not CHD). Our conclusions are in line with the findings of a study of a Japanese urban population.[17] The Japanese study included 5425 participants aged 30–83 years, and first-degree AVB (PR ≥220 ms) was not associated with CHD. As mentioned, the strong association between first-degree AVB and AF has been reported,[33] and AF is a known risk factor for stroke. Therefore, there are ample reasons to infer that the association between first-degree AVB and CVD is largely attributable to AF. Additionally, we found that the independent relationships (involving all events and CVD) were not maintained when PR interval was used as a continuous variable, which is different from the results of the Framingham study.[2 35] The reason is not clear but, according to the restricted cubic spline results, the effect of the PR interval on each endpoint was nonlinear. This provides a good explanation for the difference between the results for when PR interval was used as a binary or continuous variable. Simultaneously, it also validated previous findings that shorter PR interval was a predictor of adverse outcomes.[36 37]

The strengths of our study involve the fact that it is a large prospective study that used a general population cohort, accurate PR interval measurements were taken, and there was adequate adjustment for confounding factors. However, there are several limitations in our study. First, when a restrictive definition was used to define first-degree AVB (PR >220 ms), the number of participants with this ECG pattern was only 30, which would have limited our subsequent multivariate analysis. Second, we grouped stroke and CHD into one category (CVD) and grouped CVD and mortality into primary composite outcome due to the limited number of events because of the short follow-up time. However, the actual results might vary according to each outcome. Third, although we hypothesised that the relationships between first-degree AVB and end point events were partly attributable to AF, the study was not designed to examine AF risk factors, and data on the incidence of AF were not collected during follow-up. Lastly, although a previous study suggested that some participants with a prolonged PR interval can recover,[14] we did not perform ECG examination during the follow-up period. Meanwhile, as foresaid, detailed information on heart failure, cardiac rhythm, and pacemaker implantation, CHA_2DS_2-VAS_C score, other situations that could increase PR interval such as number of athletes and presence of collagen vascular disease were not systematically collected in our study. Further large-sample prospective studies are needed to further confirm the results.

CONCLUSIONS

Our results indicated that first-degree AVB is an independent risk factor for adverse outcomes. Adding first-degree AVB to conventional risk factors significantly improved risk prediction for adverse outcome in general population, suggesting that first-degree AVB should not be considered as inconsequential factor in general population. These findings have potential clinical value for identifying individuals at high risk for adverse outcomes.

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