

# First-degree atrioventricular block is associated with heart failure and death in persons with stable coronary artery disease: data from the Heart and Soul Study

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## Aims

First-degree atrioventricular block (AVB) has traditionally been considered a benign electrocardiographic finding in healthy individuals. However, the clinical significance of first-degree AVB has not been evaluated in patients with stable coronary heart disease. We investigated whether first-degree AVB is associated with heart failure (HF) and mortality in a prospective cohort study of outpatients with stable coronary artery disease (CAD).

## Methods and results

We measured the P–R interval in 938 patients with stable CAD and classified them into those with (P–R interval  $\geq 220$  ms) and without (P–R interval  $< 220$  ms) first-degree AVB. Hazard ratios (HRs) and 95% confidence intervals were calculated for HF hospitalization and all-cause mortality. During 5 years of follow-up, there were 123 hospitalizations for HF and 285 deaths. Compared with patients who had normal atrioventricular conduction, those with first-degree AVB were at increased risk for HF hospitalization (age-adjusted HR 2.33; 95% CI 1.49–3.65;  $P = 0.0002$ ), mortality [age-adjusted HR 1.58; 95% CI (1.13–2.20);  $P = 0.008$ ], cardiovascular (CV) mortality [age-adjusted HR 2.33; 95% CI (1.28–4.22);  $P = 0.005$ ], and the combined endpoint of HF hospitalization or CV mortality (age-adjusted HR 2.43; 95% CI 1.64–3.61;  $P \leq 0.0001$ ). These associations persisted after multivariable adjustment for heart rate, medication use, ischaemic burden, and QRS duration. Adjustment for left ventricular systolic and diastolic function partially attenuated the effect, but first-degree AVB remained associated with the combined endpoint of HF or CV death (HR 1.61, CI 1.02–2.54;  $P = 0.04$ ).

## Conclusion

In a large cohort of patients with stable coronary artery disease, first-degree AVB is associated with HF and death.

## Keywords

Stable coronary artery disease • Atrioventricular block • Heart failure

## Introduction

The P–R interval measures the time from the onset of atrial depolarization to the onset of ventricular depolarization.<sup>1</sup> This interval sums the time taken for the sequential conduction of electrical impulses from the sino-atrial node through the atrium, atrioventricular (AV) node, His Bundle, and early fascicular system until the initiation of septal depolarization. Consequently, there are numerous potential causes of P–R prolongation including intra-atrial conduction defects, increased vagal tone leading to

increased AV nodal delay, conduction disease in the AV node, conduction disease in the His-Bundle, and the presence of anti-arrhythmic medications.

Prior studies have indicated that first-degree atrioventricular block (AVB) is a benign finding with no prognostic significance in healthy patients at low risk for cardiovascular events.<sup>2–4</sup> However, a growing body of literature has emerged that challenges our established conceptions of apparently ‘benign’ echocardiogram (ECG) findings such as right bundle branch block, repolarization abnormalities, and T-wave morphology.<sup>5–10</sup> Notably, a P–R

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interval  $>300$  ms and sudden increases in AV delay have been proposed as a cause of heart failure (HF) symptoms.<sup>11,12</sup> Accordingly, symptoms or haemodynamic abnormalities attributable to first degree AVB have been accepted by the American College of Cardiology, the American Heart Association, and the Heart Rhythm Society as indications for permanent pacemaker implantation.<sup>13</sup> Furthermore, the demographic trend of population ageing is likely to increase the prevalence of abnormal ECGs<sup>14,15</sup> and the incidence of cardiovascular events.<sup>16</sup>

Recently, the Framingham group reported that first-degree AVB portended an increased risk for atrial fibrillation, pacemaker implantation, and all-cause mortality among community-dwelling adults.<sup>17</sup> However, the prognostic effects of AVB have not been evaluated in patients with established coronary artery disease (CAD). Therefore, we tested the hypothesis that first-degree AVB is associated with HF, cardiovascular (CV) mortality, and all-cause mortality in a prospective cohort study of patients with stable CAD.

## Methods

### Participants

The Heart and Soul Study is a prospective cohort study investigating the influence of psychosocial factors on cardiovascular events in outpatients with stable CAD. The enrolment process for the Heart and Soul Study has been previously described.<sup>18</sup> Eligible participants were recruited from outpatient clinics in the San Francisco Bay Area if they met at least one of the following inclusion criteria: (i) history of myocardial infarction, (ii) angiographic evidence of at least 50% stenosis by area in at least one coronary artery, (iii) evidence of exercise-induced ischaemia by treadmill electrocardiogram or stress nuclear perfusion imaging, or (iv) history of coronary revascularization. Individuals were excluded if they had a history of myocardial infarction in the past 6 months, deemed themselves unable to walk one block, or if they were planning to move out of the local area within 3 years.

The study protocol was approved by the following Institutional Review Boards: the University of California San Francisco Committee on Human Research, the Research and Development Committee at the San Francisco VA Medical Center, the Medical Human Subjects Committee at Stanford University, the Human Subjects Committee at the VA Palo Alto Health Care System, and the Data governance Board of the Community Health Network of San Francisco. All participants provided written informed consent. Between September 2000 and December 2002, a total of 1024 participants enrolled in the study.

### Electrocardiographic measurements

Each patient underwent a single EKG that was done at the time of enrolment. The P–R interval was determined manually by two independent and blinded internal medicine physicians using a 7 $\times$  scale loupe. Using Minnesota Code Criteria<sup>19</sup> each physician classified the AV conduction as normal, first-degree AV block (P–R interval  $\geq 0.22$ , recorded as a dichotomous variable), Mobitz I block, Mobitz II block, third-degree block or indeterminable. The P–R interval was initially transcribed from the computer interpretation of the ECG. Any discrepancies were resolved by consensus or (if necessary) by a third internal medicine physician. Of the 1024 enrolled patients, 82 did not undergo electrocardiography, and a further 4 participants with second- or third-degree heart block or indeterminable AV conduction were excluded from the analysis, leaving 938 participants in

the final study sample. There were no significant differences in age, gender, or ethnicity between individuals who did and did not undergo electrocardiography.

### Echocardiographic measurements

All patients underwent complete resting two-dimensional echocardiography and Doppler examination using an Acuson Sequoia ultrasound system (Siemens Medical Solutions, Mountain View, CA, USA) with a 3.5-MHz transducer. Standard parasternal short-axis and apical two- and four-chamber views were obtained and planimetric to determine left atrial volume as well as end-diastolic and end-systolic volumes. Left ventricular end-diastolic and end-systolic volumes were calculated using the biplane method of discs (modified Simpson's rule) in the apical four- and two-chamber views, as recommended by the American Society of Echocardiography.<sup>20</sup> The left ventricular ejection fraction (LVEF) was calculated as (end diastolic volume – end systolic volume)/end diastolic volume. Diastolic dysfunction was defined as pseudonormal or restrictive based on the mitral Doppler inflow pattern.<sup>21</sup>

We performed a symptom-limited, graded exercise treadmill test according to Standard Bruce protocol. To achieve maximal heart rate, participants who were unable to continue the Standard Bruce protocol were switched to lower settings on the treadmill and encouraged to exercise for as long as possible. At peak exercise, parasternal long-axis and short-axis as well as apical two-chamber and four-chamber views were used to detect the development of left ventricular wall motion abnormalities. Inducible ischaemia was defined as the presence of new wall motion abnormalities at peak exercise that were not present at rest.

### Other measurements

Baseline demographics, age, sex, and self-reported ethnicity were recorded. Cardiovascular co-morbidities, including hypertension, diabetes, hyperlipidaemia, and smoking status, were determined by self-report of medical history. Medication use was determined by having participants bring bottles to the study appointment during which study personnel recorded all medications. Participants were weighed, and height was measured without shoes. Body mass index (BMI) was calculated (kilogram per metre square). Medications were categorized using Epocrates Rx (San Mateo, CA, USA). Fasting serum samples were used to measure C-reactive protein.

### Outcomes

We conducted annual telephone interviews with participants or their proxies regarding recent emergency room visits, hospitalizations, or death. For any reported event, medical records, death certificates, and coroner's reports were reviewed by two independent and blinded adjudicators. If the adjudicators agreed on the outcome classification, their classification was binding. If they disagreed, a third blinded adjudicator reviewed the event and determined the outcome classification. Patients were censored at the time of first event, or last contact, whichever came first.

Hospitalization for HF was defined as a minimum one-night hospital stay for a clinical syndrome comprising at least two of the following: paroxysmal nocturnal dyspnoea, orthopnoea, elevated jugular venous pressure, pulmonary rales, third heart sound, and cardiomegaly or pulmonary oedema on chest roentgenography. These clinical signs and symptoms must have represented a clear change from the baseline clinical status of the participant and must have been accompanied by either failing cardiac output as determined by peripheral hypoperfusion (in the absence of other causes such as sepsis or dehydration) or

**Table 1** Baseline characteristics of participants by the presence or absence of first-degree AVB

	Normal (PR <220 ms) n = 851	First-degree AVB (PR ≥220 ms) n = 87	P-value
Age	65 ± 11	73 ± 10	<0.0001
Men (%)	686 (81)	79 (91)	0.02
Caucasian (%)	491 (58)	59 (68)	0.07
BMI (kg/m <sup>2</sup> )	28.4 ± 5.3	28.1 ± 4.3	0.64
History of diabetes (%)	222 (26)	28 (32)	0.23
History of hypertension (%)	600 (71)	64 (74)	0.58
History of myocardial infarction (%)	454 (54)	49 (56)	0.64
History of HF (%)	134 (16)	22 (26)	0.02
History of revascularization (%)	497 (59)	56 (64)	0.30
Smoking (%)	179 (21)	10 (11)	0.03
Statin use (%)	546 (64)	64 (74)	0.08
Beta-blocker use (%)	495 (58)	53 (61)	0.62
Digoxin use (%)	42 (5)	6 (7)	0.43
Aspirin use (%)	678 (80)	70 (80)	0.86
ACE-I or ARB use (%)	419 (49)	48 (55)	0.29
Resting heart rate (b.p.m.)	67.8 ± 12.0	65.3 ± 10.8	0.06
Inducible ischaemia (%)	173 (22)	25 (31)	0.07
Log C-reactive protein	0.69 ± 1.34	0.70 ± 1.19	0.97
LV ejection fraction (%)	62.2 ± 9.4	59.3 ± 11.0	0.008
Diastolic dysfunction (%)	89 (11)	13 (17)	0.14
QRS ≥100 ms (%)	141 (17)	24 (28)	0.01
Arrhythmia or pacemaker implantation during follow-up	70 (8)	15 (17)	0.005

peripheral or pulmonary oedema requiring intravenous diuretics, inotropes, or vasodilators. All-cause mortality was determined by review of death certificates. CV death was defined as a death, occurring during the same hospitalization in which an acute MI was documented, or death occurring within 1 h of the onset of terminal symptoms not explained by other aetiologies. Arrhythmia or pacemaker implantation during follow-up was defined as a severe cardiac dysrhythmia requiring external defibrillation, ablation, pacemaker, or AICD placement.

### Statistical analysis

Differences in baseline characteristics were compared with the use of analysis of variance for continuous variables, and the  $\chi^2$  test for dichotomous variables, as appropriate. We used Cox proportional hazards models to examine the association between first-degree AVB and cardiovascular outcomes (time to first event), and verified the proportionality assumptions of all models. Using the Cox models, we plotted age-adjusted survival curves for survival free from HF hospitalization and mortality. For the multivariable models, covariates were chosen *a priori* using visual inspection of directed acyclic graphs based on their likely confounding effects.<sup>22</sup> Multivariable adjustment was performed for known demographic characteristics (age, gender, ethnicity), vagal tone (as indicated by the resting heart rate), medication use, cardiac function [LVEF (analysed as a continuous variable), diastolic dysfunction, history of HF], and intraventricular conduction disease (QRS duration ≥100 ms). The threshold for statistical significance was a two-sided alpha of 0.05. We explored potential effect modification of the association of first-degree AVB with adverse outcomes by age and LVEF. There were too few women in the first-degree AVB group to adequately evaluate for an interaction between

first-degree AVB, gender, and the outcomes of HF, CV mortality, and all-cause mortality. Participants were censored at date of first event or last contact, whichever came first. Outcome ascertainment was complete in 99% of participants. Statistical analysis was performed using SAS software version 9.1 (SAS Institute, Inc.). The authors take responsibility for the integrity of the data. All authors had full access to the data, and have read and agree to the manuscript as written.

### Results

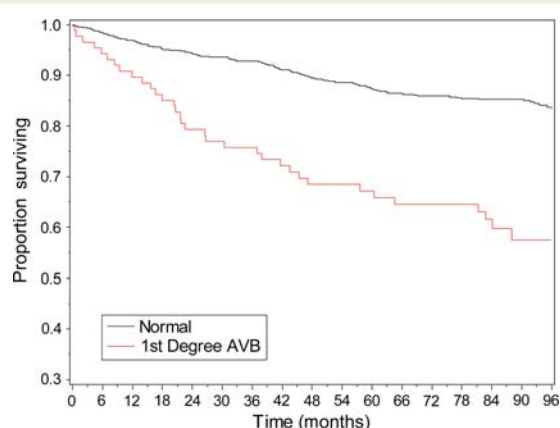
Of the 938 participants, 87 (9.3%) had first-degree AVB. When compared with participants who did not have first-degree AVB, those with first-degree AVB were older, more likely to be male, had a higher prevalence of HF history, and were less likely to smoke (Table 1). They also had a lower ejection fraction and were more likely to have inducible ischaemia. Finally patients with first-degree AVB were significantly more likely to have a QRS interval ≥100 ms and to have an arrhythmia or pacemaker implantation during the follow-up period.

During a mean follow-up of 6.2 ± 2.2 years, there were 285 deaths and 123 hospitalizations for HF exacerbations (Table 2). In the group with first-degree AVB, there were significantly more hospitalizations for HF, CV mortality, all-cause mortality, and the combined endpoint of HF hospitalization or CV mortality. Figure 1 demonstrates a Kaplan–Meier curve for the combined endpoint of freedom from HF hospitalization or CV death with a P-value between the two groups of <0.0001.

**Table 2** Number (%) of outcomes by the presence or absence of first-degree AVB

	Normal (n = 851)	First-degree AVB (n = 87)	P-value
HF hospitalization	97 (11)	26 (29)	<0.0001
CV death	52 (6)	15 (17)	0.0001
All-cause mortality	243 (29)	42 (48)	0.0002
HF or CV death	122 (14)	34 (39)	<0.0001

CV, cardiovascular; HF, heart failure.



Time (months)	Number at risk										P-value
	0	12	24	36	48	60	72	84	96		
Normal	848	813	778	741	684	626	580	445	177		<0.0001
1 <sup>st</sup> Degree AVB	87	78	68	62	54	51	47	35	10		

**Figure 1** Kaplan–Meier curve for the combined endpoint of freedom from heart failure hospitalization or cardiovascular mortality by the presence or absence of first-degree AVB.

In age-adjusted models, first-degree AVB was associated with a greater than two-fold increase in the risks of HF hospitalization and CV mortality [HR 2.33; 95% CI 1.49–3.65;  $P = 0.0002$  and HR 2.33; 95% CI (1.28–4.22);  $P = 0.005$ , respectively] and >50% risk of all-cause mortality [age-adjusted HR 1.58; 95% CI (1.13–2.20);  $P = 0.008$ ] CV mortality (age-adjusted) (Table 3). Figure 2 is an age-adjusted survival curve for the endpoint of freedom from HF hospitalization or CV death. These associations persisted after multivariable adjustment for demographics using age as a continuous variable (Model 1), baseline resting heart rate and medication use (Model 2), prolonged QRS duration (Model 3), and inducible ischaemia (Model 4). The association between first-degree AVB and HF appeared to be partly attenuated by lower LVEF and history of HF (Model 5); however, first-degree AVB remained associated with the combined endpoint of HF hospitalization or CV mortality in multivariate models. First-degree AVB also remained associated with all CV events after adjustment for interim arrhythmia or pacemaker implantation.

## Discussion

In this large prospective cohort study of patients with stable CAD, we found that P–R prolongation (>220 ms) is associated with an increased risk of HF and CV death. This association appeared to be partly explained by lower LVEF, a more restrictive filling pattern on ECG, and a history of HF in patients with first-degree AVB. Our findings extend the recent findings from the Framingham cohort<sup>17</sup> to patients with coronary heart disease, and provide the first evidence that first-degree AVB is associated with HF. The novel outcome of HF hospitalization and the extensive adjustment for confounding effect of LVEF, diastolic dysfunction, and ischaemic burden add new perspectives on the prognostic impact of first-degree AVB.

**Table 3** Association of first-degree AV block with adverse cardiovascular outcomes

Model	HF (hospitalization)		CV mortality		All-cause mortality		HF or CV death	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age adjusted	2.33 (1.49–3.65)	0.0002	2.33 (1.28–4.22)	0.005	1.58 (1.13–2.20)	0.008	2.43 (1.64–3.61)	<0.0001
Model 1	2.29 (1.46–3.60)	0.0003	2.23 (1.23–4.04)	0.009	1.53 (1.09–2.14)	0.01	2.38 (1.60–3.54)	<0.0001
Model 2	2.21 (1.40–3.50)	0.0007	2.20 (1.21–4.00)	0.01	1.53 (1.09–2.15)	0.02	2.31 (1.55–3.46)	<0.0001
Model 3	2.18 (1.39–3.43)	0.0007	2.22 (1.22–4.03)	0.009	1.48 (1.06–2.08)	0.02	2.30 (1.55–3.43)	<0.0001
Model 4	2.58 (1.59–4.18)	0.0001	2.61 (1.37–4.97)	0.003	1.67 (1.17–2.37)	0.005	2.61 (1.70–3.99)	<.0001
Model 5	1.55 (0.92–2.61)	0.10	1.73 (0.90–3.35)	0.10	1.24 (0.85–1.82)	0.27	1.61 (1.02–2.54)	0.04
Model 6	2.07 (1.31–3.25)	0.002	2.07 (1.14–3.78)	0.02	1.42 (1.01–1.99)	0.04	2.19 (1.48–3.26)	0.0001
Model 7	2.02 (1.24–3.31)	0.005	2.29 (1.18–4.45)	0.01	1.49 (1.04–2.14)	0.03	2.09 (1.36–3.23)	0.0008

Model 1 = age, gender, ethnicity (white), smoking.

Model 2 = Model 1 + resting heart rate, beta-blocker use, digoxin use.

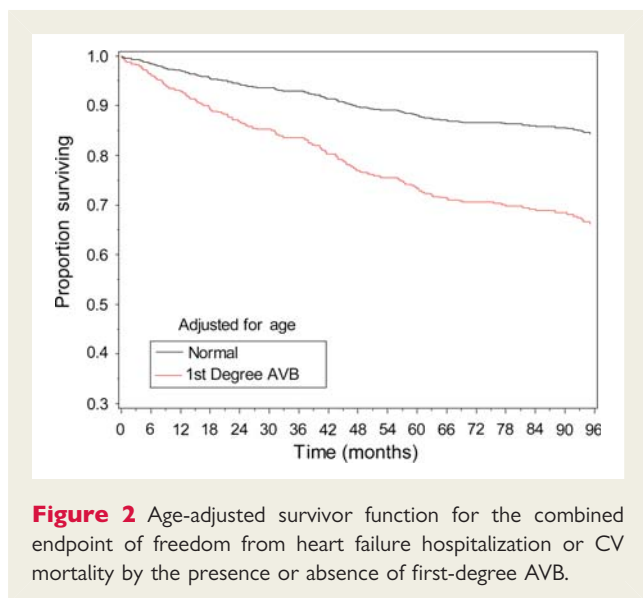
Model 3 = Model 1 + QRS duration >100 ms.

Model 4 = Model 1 + inducible ischaemia.

Model 5 = Model 1 + LVEF (continuous), diastolic dysfunction, h/o heart failure.

Model 6 = Model 1 + arrhythmia or pacemaker implantation during follow-up.

Model 7 = Model 1 + history of heart failure, LVEF, inducible ischaemia and arrhythmia or pacemaker implantation.



**Figure 2** Age-adjusted survivor function for the combined endpoint of freedom from heart failure hospitalization or CV mortality by the presence or absence of first-degree AVB.

Several potential mechanisms may account for the association of first-degree AVB with HF and death. First, the increased risk of HF hospitalization might be due, in part, to atrioventricular dyssynchrony in patients with first-degree AVB,<sup>23–26</sup> described by Kim *et al.*<sup>12</sup> as the pseudo-pacemaker syndrome. In a subset of patients, the onset of atrial depolarization occurs just after the previous ventricular contraction, such that blood is forced against a closed AV valve and pulses retrogradely into the vena cavae and pulmonary veins. This could adversely affect ventricular filling pressures contributing to a clinical exacerbation of HF. Indeed, symptomatic or haemodynamically significant first-degree AVB is now recognized as a class IIb indication for pacemaker implantation by the ACC/AHA/HRS.<sup>13</sup>

Second, the increased risk of cardiovascular and all-cause mortality observed in persons with first-degree AVB may be due to an increased propensity for malignant arrhythmias. We examined surface ECGs only, and thus were unable to accurately localize the lesion in the conduction system. The most common cause of a prolonged P–R interval is AV nodal delay<sup>27</sup> which is estimated to be secondary to intra-atrial conduction defects 3% of the time.<sup>28</sup> Neither of these aetiologies of first-degree AVB has been associated with increased mortality. In contrast, prior invasive electrophysiological studies have suggested that prolonged His-ventricular conduction in patients with known bundle branch block is associated with increased rates of HF and progression to higher degree AVB.<sup>29</sup> Furthermore, Hisian and infra-Hisian conduction delay are associated with increased mortality in patients with established cardiac disease.<sup>30–33</sup> There are, however, no reliable data on the incidence of P–R prolongation secondary to Hisian or infra-Hisian conduction disease in persons with stable coronary artery disease.<sup>34,35</sup> Infra-Hisian disease is often discussed in the context of Mobitz type 2 second-degree AVB or third-degree AVB. However, it remains possible that such disease is an under-recognized cause of first-degree AVB.

Third, first-degree AVB in persons with stable CAD may reflect a more diffuse distribution of ischaemic heart disease, such as

ischaemic territories that may affect the conduction system and thus may be more fatal. In particular, the association of first-degree AVB with prior inferior myocardial infarction and with acute atrial ischaemia may be of relevance. Rather than being an independent predictor of HF and death, first-degree AV block may be a general marker of more severe underlying disease.

Finally, it is possible that right ventricular pacing may have influenced prognosis by increasing the risk of HF and death. However, first-degree AVB remained strongly associated with CV events even after adjustment for interim arrhythmia or pacemaker implantation during the follow-up period. Regardless of the causal pathway, our findings suggest that first-degree AVB should not be ignored as a benign ECG finding but instead should alert the provider that the patient may be at higher risk for subsequent HF or death.

The main strengths of the present study include large sample size, virtually complete outcome ascertainment, and comprehensive adjustment for potential confounding factors including demographic data, resting heart rate, medication use, inducible ischaemia, ventricular conduction disease, and cardiac function. However, there are several limitations which must be considered in the interpretation of our findings. First, we cannot completely exclude the possibility of residual confounding of the association between first-degree AVB and adverse cardiovascular outcomes by unmeasured variables. For example, we did not measure myocardial fibrosis by cardiac magnetic resonance, which may account for at least some of the prognostic significance of first-degree AVB. Second, the predominance of males in our study population limits generalizability to women. Third, we did not perform invasive electrophysiological studies to determine the relative contribution of each component of the P–R interval.<sup>27–29</sup> Fourth, we could not investigate the effect of alternative definitions for first-degree AV block since the P–R interval was not ascertained as a continuous variable.

In conclusion, we report new data suggesting that first-degree AVB is associated with HF and CV mortality in persons with stable CAD. The individual outcomes of HF and CV mortality were partially—but not entirely—explained by worse systolic and diastolic function as well as a personal history of HF in patients with first-degree AVB. Clearly these findings require replication in other cohorts before any implications for clinical risk-stratification and treatment can be considered. However, our results suggest that a prolonged P–R interval may not be as benign as previously thought. In patients with known CAD, the presence of first-degree AVB may identify those at higher risk for HF and death and may warrant more intense surveillance, follow-up, and preventive measures.

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**Conflict of interest:** none declared.

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