Published in final edited form as:

Am J Cardiol. 2016 June 1; 117(11): 1755–1759. doi:10.1016/j.amjcard.2016.03.013.

Electrocardiographic Advanced Inter-Atrial Block and Atrial Fibrillation Risk in the General Population

Wesley T. O'Neal, MD, MPH[1], **Zhu-Ming Zhang, MD, MPH**[2], **Laura R. Loehr, MD, PhD**[3], **Lin Y. Chen, MD, MS**[4], **Alvaro Alonso, MD, PhD**[5], and **Elsayed Z. Soliman, MD, MS**[2]

[1]Department of Medicine, Wake Forest School of Medicine, Winston-Salem, NC USA

[2]Epidemiological Cardiology Research Center, Department of Epidemiology and Prevention, Wake Forest School of Medicine, Winston-Salem, NC

[3]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC

[4]Cardiovascular Division, Department of Medicine, University of Minnesota, Minneapolis, MN

[5]Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN

Abstract

Although advanced inter-atrial block (aIAB) is an established electrocardiographic phenotype, its prevalence, incidence, and prognostic significance in the general population are unclear. We examined the prevalence, incidence, and prognostic significance of aIAB in 14,625 (mean age=54±5.8 years; 26% black; 55% female) participants from the Atherosclerosis Risk In Communities (ARIC) study. aIAB was detected from digital electrocardiograms recorded during 4 study visits (1987–1989, 1990–1992, 1993–1995, and 1996–1998). Risk factors for the development of aIAB were examined using multivariable Poisson regression models with robust variance estimates. Cox regression was used to compute hazard ratios (HR) and 95% confidence intervals (CI) for the association between aIAB, as a time-dependent variable, and atrial fibrillation (AF). AF was ascertained from study electrocardiogram data, hospital discharge records, and death certificates thorough 2010. A total of 69 (0.5%) participants had aIAB at baseline and 193 (1.3%) developed aIAB during follow-up. The incidence rate for aIAB was 2.27 (95%CI=1.97, 2.61) per 1000 person-years. Risk factors for aIAB development included age, male sex, white race, antihypertensive medication use, low-density lipoprotein cholesterol, body mass index, and systolic blood pressure. In a Cox regression analysis adjusted for socio-demographics, cardiovascular risk factors, and potential confounders, aIAB was associated with an increased risk for AF (HR=3.09, 95%CI=2.51, 3.79). In conclusion, aIAB is not uncommon in the general population. Risk factors for developing aIAB are similar to those for AF and the presence of aIAB is associated with an increased risk for AF.

Correspondence to: Wesley T. O'Neal, MD, Wake Forest School of Medicine, Department of Internal Medicine, Medical Center Blvd, Winston-Salem NC 27101, ; Email: woneal@wakehealth.edu

CONFLICTS OF INTEREST

The authors report no conflicts of interest.

Keywords

inter-atrial block; atrial fibrillation; epidemiology

INTRODUCTION

Advanced inter-atrial block (aIAB) exists when a delay of conduction occurs over the Bachmann bundle.[1] It manifests on the 12-lead electrocardiogram (ECG) as a prolonged P-wave with biphasic morphology (±) in the inferior leads. Although aIAB is an established electrocardiographic phenotype, its prevalence, incidence, and prognostic significance in the general population are unclear. Previous reports from patient-based populations have shown that aIAB is associated with an increased risk for paroxysmal supraventricular tachyarrhythmias.[2,3] The presence of aIAB also was shown to be an independent predictor of new-onset atrial fibrillation (AF) in patients with heart failure and among patients with atrial flutter.[4,5] Additionally, aIAB has been associated with a higher risk of AF recurrence after pharmacological cardioversion to normal sinus rhythm.[6] To date, the association between aIAB and AF has not been examined in prospective population-based studies. Therefore, the purpose of this analysis was to examine the prevalence and incidence of aIAB as well as the association between aIAB and AF in the Atherosclerosis Risk In Communities (ARIC) study, a community-based prospective cohort study.

METHODS

The ARIC study prospectively enrolled 15,792 community-dwelling men and women between 45 and 64 years of age. Four field centers across the United States (Washington County, MD; Forsyth County, NC; Jackson, MS; suburban Minneapolis, MN) recruited participants between 1987 and 1989. Participants returned for 4 follow-up examinations (1990–1992, 1993–1995, 1996–1998, and 2011–2013), and continue to be followed via annual telephone calls to ascertain study end points. Endpoints are further ascertained from examination of lists of hospital discharges that include any cardiovascular diagnoses from hospitals in the study communities. The study was approved by the institutional review boards at all participating universities and all participants provided written informed consent at the time of study enrollment.

For this analysis, we excluded participants with AF (n=37), those with missing baseline covariates (n=783), and participants with missing follow-up data (n=384). Additionally, the few ARIC participants with race other than black or white were excluded, including the small number of black participants from Washington County and Minneapolis.

Digital 12-lead ECGs were obtained at baseline and at subsequent follow-up examinations using MAC PC ECG machines (Marquette Electronics, Milwaukee, WI). All ECGs were inspected for technical errors and adequate quality at the Epidemiology Coordinating and Research Centre at the University of Alberta (Edmonton, Alberta, Canada) during the initial phases of the study and at the Epidemiological Cardiology Research Center at the Wake Forest School of Medicine (Winston-Salem, North Carolina, USA) during later phases. aIAB manifests on the 12-lead ECG with a P-wave duration ≥120 ms and biphasic (positive

negative) morphology in leads II, III and AV_F.[1] Prevalent aIAB was identified using baseline ECG data and incident aIAB cases were detected during the first 3 follow-up study visits (1990–1992, 1993–1995, and 1996–1998).

Cases of AF were identified from study visit ECGs, review of hospital discharge diagnoses, and death certificates.[7] A cardiologist visually confirmed all AF cases automatically detected from the study ECGs.[8] Information on hospitalizations during follow-up was obtained from annual follow-up calls and surveillance of local hospitals, with hospital discharge diagnosis codes collected by trained abstractors. AF during follow-up was defined by *International Classification of Diseases, 9th Revision* codes 427.31 or 427.32. AF cases detected in the same hospitalization as open cardiac surgery were not included since these were considered transient.[9]

Age, sex, and race were self-reported. Tobacco use was defined as current or former cigarette smoking. Diabetes was defined as a fasting glucose level ≥126 mg/dL (or non-fasting glucose ≥200 mg/dL), a physician diagnosis of diabetes, or the use of diabetes medications. Systolic blood pressure was obtained from each participant using sphygmomanometers to measure 3 readings in the upright position after 5 minutes of rest. The average of the last 2 blood pressure measurements was used as the final reading. Antihypertensive medication use was self-reported. Body mass index was defined as the weight in kilograms divided by the square of the height in meters. Low-density lipoprotein cholesterol levels were calculated indirectly using cholesterol values assayed from serum samples obtained at the baseline study visit. Prevalent heart failure was defined as present if participants reported taking heart failure medications or if participants met all 3 of the Gothenburg criteria.[10] Prevalent coronary heart disease was defined by self-reported history of physician-diagnosed myocardial infarction, coronary artery bypass surgery, coronary angioplasty, or electrocardiographic evidence of myocardial infarction.

Categorical variables were reported as frequency and percentage while continuous variables were recorded as mean ± standard deviation. Baseline characteristics were examined by stratifying participants by the presence of the following: prevalent aIAB, incident aIAB, and no aIAB. Differences between groups were tested using the chi-square test for categorical variables and the analysis of variance procedure for continuous variables.

Kaplan-Meier estimates were used to compute the cumulative incidence of aIAB. Prevalent aIAB cases were excluded in the analysis to examine incident aIAB. Follow-up time was defined as the time between the baseline visit until aIAB development, loss to follow-up, death, or the end of study visit 4 (1996–1998). To examine risk factors for aIAB development, we examined the association between baseline characteristics, obtained from study visit 1, and incident aIAB using multivariable Poisson regression with robust variance estimates to compute relative risk (RR) and 95% confidence intervals (CI).[11] Models were adjusted as follows: Model 1 adjusted for demographics (age, sex, and race) and Model 2 adjusted for variables in Model 1 plus body mass index, systolic blood pressure, use of blood pressure lowering medication, smoking, diabetes, low-density lipoprotein cholesterol, coronary heart disease, and heart failure.

Kaplan-Meier estimates also were used to examine the cumulative incidence of AF by the presence of aIAB as a time-dependent variable. The first 3 follow-up study visits were used to identify more aIAB cases due to the limited number of cases present in the baseline study visit. Follow-up was defined as the time between aIAB detection until AF development, loss to follow-up, death or end of follow-up (December 31, 2010). The period between the baseline visit and aIAB diagnosis was considered as non-aIAB follow-up. Cox regression was used to compute hazard ratios (HR) and 95% CIs for the association between aIAB as a time-dependent variable and AF. Multivariable models were constructed with baseline characteristics, obtained from study visit 1, as follows: Model 1 adjusted for age, sex, and race; Model 2 adjusted for Model 1 covariates plus body mass index, systolic blood pressure, use of blood pressure lowering medication, smoking, diabetes, low-density lipoprotein cholesterol, coronary heart disease, and heart failure. Statistical significance was defined as $p < 0.05$. SAS version 9.4 (Cary, NC) was used for all analyses.

RESULTS

A total of 14,625 (mean age=54±5.8 years; 26% black; 55% female) participants were included in the final analysis. A total of 69 (0.5%) participants had aIAB at baseline and 193 (1.3%) cases of aIAB were detected on subsequent study ECGs (mean follow-up=5.9 years). Baseline characteristics stratified by prevalent aIAB, incident aIAB, and no aIAB are shown in Table 1. Participants with aIAB were more likely to be older, male, and white, and to have diabetes, coronary heart disease, and heart failure compared with those without aIAB. They also were more likely to smoke, to take antihypertensive medications, and to have higher values for body mass index and systolic blood pressure.

The crude incidence rate for aIAB was 2.27 (95%CI=1.97, 2.61) cases per 1000 person-years. Table 2 shows the unadjusted and adjusted risk factors for aIAB development. As shown, age, male sex, white race, antihypertensive medication use, low-density lipoprotein cholesterol, body mass index, and systolic blood pressure were significantly associated with aIAB development.

Over a mean follow-up of 18.6 years, a total of 1,929 (13%) AF cases were identified. A higher incidence rate (per 1000 person-years) of AF was observed among those with aIAB (29.8, 95%CI=24.5, 36.3) compared with those without IAB (6.8, 95%CI=6.5, 7.1). The unadjusted cumulative incidence of AF by aIAB is shown in Figure 1. After adjustment for demographics and potential confounders, aIAB was associated with an increased risk of AF (Table 3).

DISCUSSION

In this analysis from ARIC, we have shown that aIAB is not uncommon in the general population and identified several risk factors associated with its development. Several of the risk factors identified are known to be associated with AF.[12,13] Additionally, we have shown that aIAB is associated with the development of AF.

The prevalence of aIAB is reported to be around ~1% in patients with valvular heart disease and several small studies have reported a higher prevalence of aIAB in persons with heart

failure, AF, and typical atrial flutter.[4–6,14] The higher prevalence in the aforementioned studies likely is due to the populations examined (e.g., those with structural heart disease). In contrast, we observed a lower prevalence in the ARIC study, as this community-based population is not limited to participants with cardiovascular disease. Interestingly, coronary heart disease and heart failure were not associated with an increased risk of aIAB development. However, it is probable that our study was underpowered to detect associations between these risk factors and aIAB.

The association between aIAB and atrial arrhythmias has been reported. A study of 16 patients with aIAB and 22 controls showed that patients with aIAB and retrograde activation of the left atrium have a much higher incidence of paroxysmal supraventricular tachyarrhythmias.[2,3] aIAB also is associated with an increased risk for new-onset AF in patients with severely reduced ejection fraction who undergo cardiac resynchronization therapy and among patients with typical atrial flutter who receive cavotricuspid isthmus ablation.[4,5] Additionally, aIAB has been associated with an increased risk of AF recurrence after successful pharmacologic cardioversion to normal sinus rhythm.[6] Our findings extend prior literature by linking aIAB with AF in a population-based cohort not limited to persons who are high risk for AF development (e.g., heart failure). Given that several risk factors identified for aIAB development also are associated with AF, both conditions possibly are linked through shared comorbid conditions.[12,13]

The ECG pattern of aIAB is due to blockade of the electrical impulse in the upper and middle part of the inter-atrial septum in the Bachman bundle.[1] The left atrium is then depolarized by retrograde activation via muscle connections near the coronary sinus. This abnormal conduction disrupts normal electrical activation and predisposes to the development of arrhythmias by modifying atrial refractory periods.[15] Additionally, abnormal activation leads to premature beats that serve as inciting events for supraventricular arrhythmias. These abnormal properties often are observed among persons with risk factors for myocardial fibrosis and abnormal cardiac remodeling (e.g., advanced age, hypertension). This provides a likely explanation for the identified aIAB risk factors as these conditions are commonly associated with atrial remodeling. Similarly, these mechanisms provide a plausible link between aIAB and AF due to the fact that those with aIAB have the necessary substrate to maintain the irregularly irregular rhythm of AF.

It is worth mentioning that blacks were less likely to develop aIAB compared with whites. Similar observations have been reported regarding AF risk.[16] Although blacks are more likely to have an increased number of AF risk factors (e.g., hypertension, smoking), they are less likely to have cardiac remodeling. This is supported by data showing that blacks have smaller left atrial diameters compared with whites.[17] Therefore, the lower aIAB risk among blacks would coincide with the decreased prevalence of AF observed in the general population.

The current study should be interpreted in the context of several limitations. Incident AF cases were ascertained from hospitalization discharge records and death certificates which possibly resulted in misclassification. However, these codes have adequate positive predictive value for the identification of AF events in ARIC.[7] Additionally, paroxysmal AF

cases potentially were missed due to the time-dependent nature of such events. Furthermore, we included several covariates in our multivariable models that likely influenced the development of AF. Similar to other epidemiologic studies, we acknowledge that residual confounding remains a possibility.

In conclusion, aIAB is not an uncommon electrocardiographic finding in the ARIC study. Several risk factors for aIAB were identified that coincide with conditions associated with AF development and provide a plausible link for the observed association between aIAB and AF. Our findings also suggest that aIAB is a useful marker to identify persons who are high risk for developing AF.

Acknowledgments

The authors thank the staff and participants of the ARIC study for their important contributions.

FUNDING

The Atherosclerosis Risk in Communities study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C).

References

1. Bayes de Luna A, Platonov P, Cosio FG, Cygankiewicz I, Pastore C, Baranowski R, Bayes-Genis A, Guindo J, Vinolas X, Garcia-Niebla J, Barbosa R, Stern S, Spodick D. Interatrial blocks. A separate entity from left atrial enlargement: a consensus report. J Electrocardiol. 2012; 45:445–451. [PubMed: 22920783]
2. Bayes de Luna A, Cladellas M, Oter R, Torner P, Guindo J, Marti V, Rivera I, Iturralde P. Interatrial conduction block and retrograde activation of the left atrium and paroxysmal supraventricular tachyarrhythmia. Eur Heart J. 1988; 9:1112–1118. [PubMed: 3208776]
3. Bayes de Luna A, Guindo J, Vinolas X, Martinez-Rubio A, Oter R, Bayes-Genis A. Third-degree inter-atrial block and supraventricular tachyarrhythmias. Europace. 1999; 1:43–46. [PubMed: 11220539]
4. Enriquez A, Sarrias A, Villuendas R, Ali FS, Conde D, Hopman WM, Redfearn DP, Michael K, Simpson C, De Luna AB, Bayes-Genis A, Baranchuk A. New-onset atrial fibrillation after cavotricuspid isthmus ablation: identification of advanced interatrial block is key. Europace. 2015; 17:1289–1293. [PubMed: 25672984]
5. Sadiq Ali F, Enriquez A, Conde D, Redfearn D, Michael K, Simpson C, Abdollah H, Bayes de Luna A, Hopman W, Baranchuk A. Advanced Interatrial Block Predicts New Onset Atrial Fibrillation in Patients with Severe Heart Failure and Cardiac Resynchronization Therapy. Ann Noninvasive Electrocardiol. 2015; 20:586–591. [PubMed: 25639950]
6. Enriquez A, Conde D, Hopman W, Mondragon I, Chiale PA, de Luna AB, Baranchuk A. Advanced interatrial block is associated with recurrence of atrial fibrillation post pharmacological cardioversion. Cardiovasc Ther. 2014; 32:52–56. [PubMed: 24417765]
7. Alonso A, Agarwal SK, Soliman EZ, Ambrose M, Chamberlain AM, Prineas RJ, Folsom AR. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. Am Heart J. 2009; 158:111–117. [PubMed: 19540400]
8. Soliman EZ, Prineas RJ, Case LD, Zhang ZM, Goff DC Jr. Ethnic distribution of ECG predictors of atrial fibrillation and its impact on understanding the ethnic distribution of ischemic stroke in the Atherosclerosis Risk in Communities (ARIC) study. Stroke. 2009; 40:1204–1211. [PubMed: 19213946]

9. Epstein AE, Alexander JC, Gutterman DD, Maisel W, Wharton JM. Anticoagulation: American College of Chest Physicians guidelines for the prevention and management of postoperative atrial fibrillation after cardiac surgery. Chest. 2005; 128:24S–27S. [PubMed: 16167661]
10. Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE. Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). Am J Cardiol. 2008; 101:1016–1022. [PubMed: 18359324]
11. Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol. 2004; 159:702–706. [PubMed: 15033648]
12. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study JAMA. 1994; 271:840–844. [PubMed: 8114238]
13. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. Am J Med. 1995; 98:476–484. [PubMed: 7733127]
14. Bayes de Luna A, Fort de Ribot R, Trilla E, Julia J, Garcia J, Sadurni J, Riba J, Sagues F. Electrocardiographic and vectorcardiographic study of interatrial conduction disturbances with left atrial retrograde activation. J Electrocardiol. 1985; 18:1–13. [PubMed: 3156200]
15. Daubert JC, Pavin D, Jauvert G, Mabo P. Intra- and interatrial conduction delay: implications for cardiac pacing. Pacing Clin Electrophysiol. 2004; 27:507–525. [PubMed: 15078407]
16. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA. 2001; 285:2370–2375. [PubMed: 11343485]
17. Marcus GM, Olgin JE, Whooley M, Vittinghoff E, Stone KL, Mehra R, Hulley SB, Schiller NB. Racial differences in atrial fibrillation prevalence and left atrial size. Am J Med. 2010; 123:375 e371–377. [PubMed: 20227049]

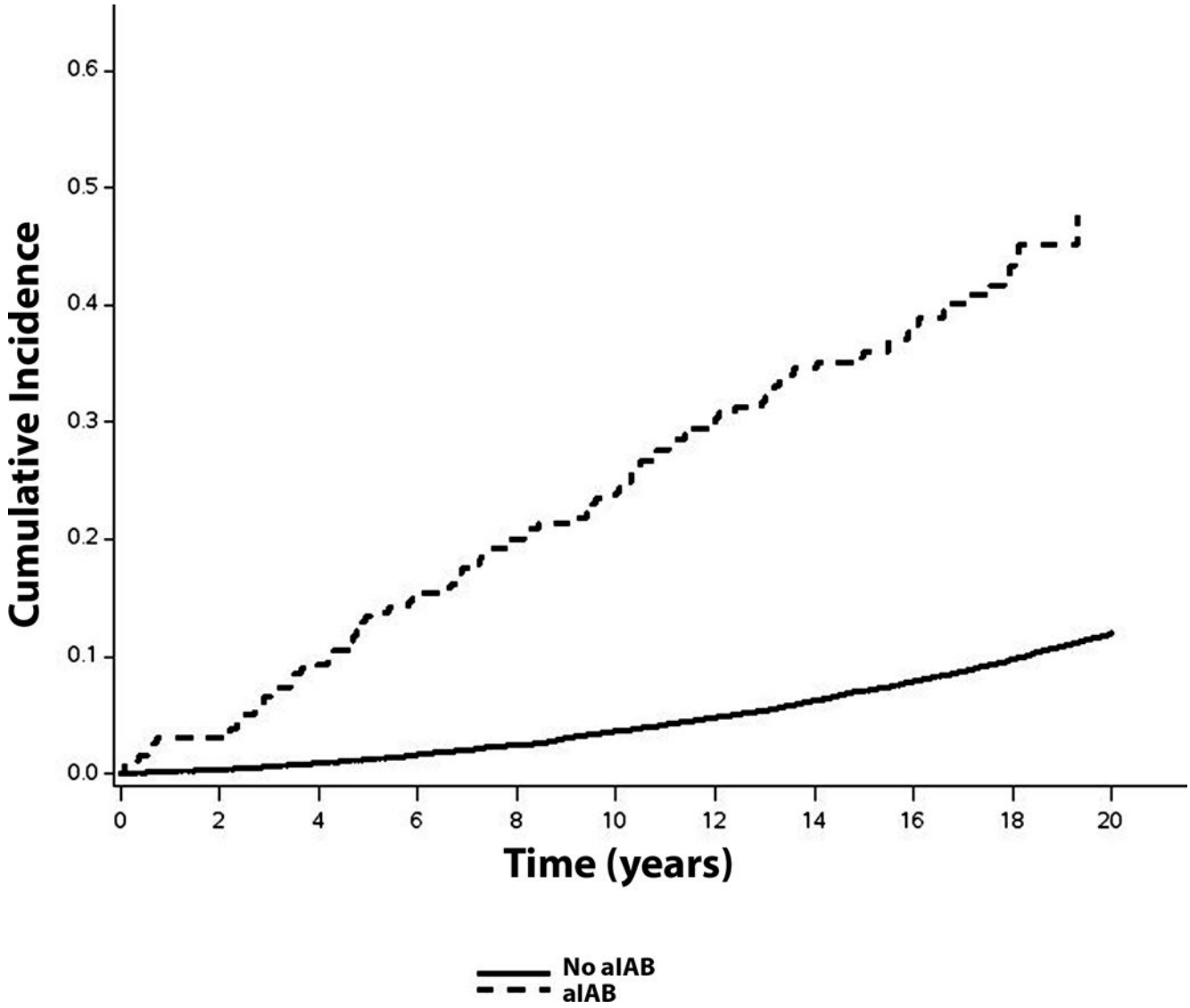

Figure 1. Cumulative Incidence of Atrial Fibrillation by Advanced Inter-Atrial Block

* Cumulative incidence curves at statistically different (log-rank p<0.0001).

aIAB=advanced inter-atrial block

Table 1

Characteristics by Prevalent aIAB, Incident aIAB, and No aIAB (N=14,625)*

Characteristics	Advanced Inter-Atrial Block			P-value†
	Prevalent (n=69)	Incident (n=193)	Absent (n=14,363)	
Age, mean ± SD (years)	59 ± 4.9	57 ± 5.5	54 ± 5.7	<0.0001
Male	45 (65%)	121 (63%)	6,377 (44%)	<0.0001
Black	23 (33%)	35 (18%)	3,771 (18%)	0.016
Smoking	42 (61%)	122 (63%)	8,383 (58%)	0.37
Diabetes mellitus	19 (28%)	27 (14%)	1,593 (11%)	<0.0001
LDL cholesterol, mean ± SD (mg/dl)	143 ± 35	147 ± 38	137 ± 39	0.47
Body mass index, mean ± SD (kg/m^2)	30 ± 4.8	29 ± 5.5	28 ± 5.3	<0.0001
Systolic blood pressure, mean ± SD (mm Hg)	132 ± 23	129 ± 19	121 ± 19	<0.0001
Antihypertensive medications	44 (64%)	108 (56%)	4,229 (29%)	<0.0001
Coronary heart disease	13 (19%)	18 (9.3%)	658 (4.6%)	<0.0001
Heart failure	8 (12%)	18 (9.3%)	630 (4.4%)	<0.0001

*Prevalent aIAB were cases present during visit 1. Incident aIAB cases were identified during visits 2, 3, and 4.

†Statistical significance for categorical data was tested using the chi-square procedure and continuous data was tested using the analysis of variance procedure.

aIAB=advanced inter-atrial block; LDL=low-density lipoprotein; SD=standard deviation.

Table 2

Risk Factors for Advanced Inter-Atrial Block (N=14,556)

Characteristics	Unadjusted RR (95%CI)	P-value	Adjusted* RR (95%CI)	P-value
Age (per 10-year increase)	2.71 (2.09, 3.54)	<0.0001	2.09 (1.57, 2.77)	<0.0001
Male	2.08 (1.56, 2.78)	<0.0001	2.11 (1.55, 2.87)	<0.0001
Black	0.63 (0.43, 0.90)	0.012	0.48 (0.33, 0.69)	0.0001
Smoking	1.22 (0.91, 1.63)	0.18	1.02 (0.76, 1.38)	0.88
Diabetes	1.30 (0.87, 1.94)	0.20	0.75 (0.48, 1.16)	0.19
LDL cholesterol (per 10 mg/dl increase)	1.06 (1.03, 1.09)	0.0001	1.04 (1.01, 1.08)	0.019
Body mass index (per 5 kg/m^2 increase)	1.30 (1.19, 1.43)	<0.0001	1.31 (1.15, 1.48)	<0.0001
Systolic blood pressure (per 10 mm Hg increase)	1.21 (1.15, 1.27)	<0.0001	1.14 (1.06, 1.22)	0.0003
Antihypertensive medications	2.99 (2.26, 3.97)	<0.0001	2.41 (1.75, 3.30)	<0.0001
Coronary heart disease	2.11 (1.31, 3.41)	0.0022	0.91 (0.55, 1.52)	0.73
Heart failure	2.21 (1.37, 3.56)	0.0012	1.21 (0.72, 2.03)	0.47

*Adjusted for age, sex, race, body mass index, systolic blood pressure, smoking, diabetes, LDL cholesterol, coronary heart disease, and heart failure.

CI=confidence interval; LDL=low-density lipoprotein; RR=relative risk.

Table 3

Risk of Atrial Fibrillation associated with Advanced Inter-Atrial Block

	AF Cases	Person-years	Incidence per 1000 person-years (CI)	Model 1* HR (95%CI)	P-value	Model 2† HR (95%CI)	P-value
No aIAB	1,829	268,860	6.8 (6.5, 7.1)	Ref	–	Ref	–
aIAB	100	3,355	29.8 (24.5, 36.3)	3.80 (3.10, 4.66)	<0.0001	3.09 (2.51, 3.79)	<0.0001

*Adjusted for age, sex, and race.

†Adjusted for Model 1 covariates plus body mass index, systolic blood pressure, smoking, diabetes, LDL cholesterol, coronary heart disease, and heart failure.

aIAB=advanced inter-atrial block; CI=confidence interval; HR=hazard ratio; LDL=low-density lipoprotein.