HHS Public Access
Author manuscript
Am J Cardiol. Author manuscript; available in PMC 2021 May 01.

Factors Modifying the Risk of Atrial Fibrillation Associated with Atrial Premature Complexes in Patients with Hypertension

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Abstract

Patients with hypertension who develop atrial premature complexes (APCs) are at a particularly high risk for atrial fibrillation (AF). We sought to identify medications and modifiable risk factors that could reduce the risk of AF imposed by presence of APCs in such a high risk group. This analysis included 4,331 participants with treated hypertension from the REGARDS study who were free of AF and cardiovascular disease at the time of enrollment (2003–2007). APCs were detected in 8.2% (n=356) of the participants at baseline. During a median follow-up of 9.4 years, 9.9% (n=429) of the participants developed AF. Participants with APCs, compared to those without, were more than twice as likely to develop AF (Odds ratio (95% confidence interval): 2.36(1.75, 3.19)). This association was significantly weaker in statin users than non-users (Odds ratio (95% confidence interval):1.42(0.81,2.48) vs. 3.01(2.11,4.32), respectively; *interaction p-value*= 0.02), and in angiotensin-II receptor blocker users than non-users (Odds ratio (95% confidence interval):1.31(0.66,2.61) vs. 2.78(1.99,3.89), respectively; *interaction p-value= 0.05*). Borderline weaker associations between APCs and AF were also observed in alpha-blocker users than non-users, non-diabetics than diabetics, and in those with systolic blood pressure level 130–

139 mmHg compared to those with other systolic blood pressure levels. No significant effect modifications were observed by use of other medications or by presence of other cardiovascular risk factors. In conclusion, the significant AF risk associated with APCs in patients with hypertension could potentially be reduced by treatment with angiotensin-II receptor blockers and statins along with lowering blood pressure and management of diabetes.

Keywords

Premature Atrial Complexes; Atrial fibrillation; Hypertension; Effect Modification

Atrial premature complexes (APCs) play a critical role in the pathogenesis of atrial fibrillation (AF) by acting as a trigger for AF in the presence of the appropriate substrate (1). In a previous report from the Reasons for Geographic and Racial Differences in Stroke (REGARDS), presence of APCs on routine resting electrocardiogram was associated with a 92% increased risk of AF (2). Also, high blood pressure is an established risk factor for AF, explaining more than one-fifth of AF cases (3). Hence, patients with hypertension who develop APCs are exposed to two major AF risk factors; high blood pressure and APCs. Identifying factors that could potentially modify the risk of AF associated with APCs in patients with hypertension will inform AF prevention in such a high-risk group. In particular, since there are multiple therapeutic options for treatment of hypertension, some of which may also affect APCs, it would be helpful to know if certain therapies or combinations are associated with a higher or lower incidence of AF. In this analysis from the REGARDS study, we examined the effect modification of several classes of blood pressure lowering medications as well as modifiable cardiovascular risk factors on the association between baseline APCs and incident AF among REGARDS participants who had hypertension requiring medical treatment.

Methods

The REGARDS study is a longitudinal cohort study aimed to investigate the regional and racial disparities in stroke mortality (4). Between January 2003 to October 2007, 30,239 participants were recruited from the continental United States, oversampling blacks and residents of the Southeastern stroke belt region (North Carolina, South Carolina, Georgia, Alabama, Mississippi, Tennessee, Arkansas, and Louisiana]. Demographic information and medical history data were collected via a computer-assisted telephone interview followed by an in-home physical examination which included blood pressure measurement, electrocardiogram recording, and blood draw. Verbal consent was obtained initially on the telephone then written informed consent was obtained during the in-home physical exam.

After 9.4 years (median) of the first in-home visit, 15,521 participants completed a similar second in-home follow-up examination. Out of the REGARDS participants who completed both in-home visits, we applied the following exclusions to the baseline data: no hypertension, hypertension not requiring medical treatment, missing blood pressure measurements data, missing blood pressure medications data, prevalent baseline AF, prevalent cardiovascular disease (coronary heart disease, heart failure and stroke), missing baseline APCs. We also excluded those with missing incident AF data. Figure 1 outlines the

inclusions and exclusions criteria we applied to reach our REGARDS subsample we used in this analysis.

Blood pressure was obtained with an aneroid sphygmomanometer using appropriate cuff size after the participant had been seated for 5 minutes with both feet on the floor. Using the mean of two blood pressure measurements, hypertension was defined as systolic blood pressure 140 mmHg, diastolic blood pressure 90 mmHg, or self-reported use of blood pressure lowering medications.

During the baseline in-home visit, the names of all prescription medications including blood pressure lowering medications were recorded from the pharmacy label. The following classes of blood pressure lowering medications were later determined from the medications inventory: angiotensin-converting enzyme inhibitors, aldosterone antagonists, alpha-blockers, angiotensin-II receptor blockers, beta-blockers, calcium channel blockers, central agonists, diuretics, or direct vasodilators. Participants who reported not taking or had no blood pressure lowering medications in the inventory were defined as not taking blood pressure lowering medications.

Standard resting electrocardiograms were recorded during the baseline and the 2nd in-home visits and were sent to the Epidemiological Cardiology Research Center at Wake Forest School of Medicine (Winston- Salem, North Carolina) for processing and reading. Incident AF was ascertained during the 2nd in-home visit using two methods: 1) from the study electrocardiograms; and 2) self-reported history of a previous physician diagnosis of AF (5).

All covariates were collected from the first in-home visit (baseline). Data on age, sex, race, income, smoking status, alcohol drinking, and physical activity were self-reported. Use of regular aspirin was based on self-report, while statins and anti-hypertensive medications were based on pill-bottle review. Body mass index was calculated from height and weight. Electrocardiographic left ventricular hypertrophy was defined by Sokolow-Lyon criteria. Diabetes mellitus was defined as fasting glucose 126 mg/dL, non-fasting glucose 200 mg/dL, or taking medications to control blood sugar. Dyslipidemia was defined as total cholesterol 240 mg/dl, low-density lipoprotein cholesterol 160 mg/dl, high-density lipoprotein cholesterol 40 mg/dl or the participant was on cholesterol-lowering medication. Chronic kidney disease was defined as an estimated glomerular filtration rate <60 ml/min per 1.73 m^2.

Baseline characteristics of the participants were tabulated and compared between those with and without APCs using Student's *t* test for continuous variables and *Chi* square for categorical variables. We conducted two main sets of analyses:

First, we examined the association between baseline APCs and incident AF. The purpose of this step in the analysis was to ensure that the previously reported relationship between APCs and AF is generalizable to our unique study population composed entirely of participants with treated hypertension. We used logistic regression models to examine the association between APCs at baseline (first in-home visit) with incident AF during follow-up (second in-home visit). The following models were constructed with incremental adjustments: Model 1 (Socio-demographics): age, sex, race, region of residence, and

income; Model 2 (Behavioral factors): Model 1 plus smoking, alcohol drinking, physical activity; Model 3 (cardiovascular risk factors): Model 2 plus dyslipidemia, diabetes, obesity, chronic kidney disease; Model 4 (Markers of hypertension severity) Model 3 plus systolic blood pressure, number of blood pressure medications, and left ventricular hypertrophy; Model 5 (Medications): Model 4 plus statin use and regular use of aspirin; Model 6 (Inflammatory markers): Model 5 plus high sensitivity C-reactive protein. A 2-sided value of p<0.05 was considered significant.

Second, we examined the effect modification of the association between APCs and AF. The goal was to identify subgroups of participants who would get more benefit (or harm) by their exposure to different medications or by having different characteristics (6). Effect modification was tested using the following subgroups: use of angiotensin-converting enzyme inhibitors, use of alpha blockers, use of angiotensin-II receptor blockers, use of beta-blockers, use of calcium channel blockers, use of diuretics, use of statins, use of aspirin, age (65 years and >65 years), sex, race (black and white), smoking status (current, past, and never), alcohol drinking (current, past, and never), physical activity (0, 1–3, and 4 times/week), dyslipidemia, chronic kidney disease, left ventricular hypertrophy, number of blood pressure lowering medications (1, 2 and 3 medications), systolic blood pressure levels (<120 mmHg, 120–129 mmHg, 130–139 mmHg, and >140 mmHg), obesity (obese, overweight, and normal), diabetes, and high sensitivity C-reactive protein (3.0 mg/L and >3.0 mg/L). Due to the small number of participants receiving direct vasodilators, we did not test effect modification by the use of direct vasodilators. In each subgroup, logistic regression analysis was used to calculate the AF odds ratio and 95% confidence interval associated with the presence (vs. absence) of baseline APCs. Unless the variable is the stratifying variable, models were adjusted for age, sex, race, region of residence, income, smoking, alcohol drinking, physical activity, dyslipidemia, diabetes, obesity, chronic kidney disease, systolic blood pressure, number of blood pressure medications, left ventricular hypertrophy, statins use, use of regular aspirin, and high sensitivity C-reactive protein. Potential interaction was examined by including a product term of each variable with the APCs and comparing the models with and without the product terms using the likelihood ratio test. Significant effect modification was considered present if *interaction p-value* is <0.05. Because using a more relaxed p-value for interaction is an increasingly acceptable approach (7), and since prior REGARDS publications used p-value of 0.10 to indicate significant interaction (8), we also used *interaction p-value* <.15 to indicate a "borderline significant" interaction. All analyses were conducted using SAS 9.4 [SAS Institute, Cary, NC].

Results

This analysis included 4,331 participants with treated hypertension (mean age 64.6 years, 59.5% women, 45.8% blacks) who were free of cardiovascular disease and AF at baseline. APCs were detected in 8.2% (n=356) of the study participants at baseline. Participants with APCs were more likely to be older, men, have a history of chronic kidney disease, and have higher levels of systolic blood pressure. Baseline characteristics of the study participants, overall and stratified by presence of APCs, are detailed in Table 1.

During a median follow-up of 9.4 years, 429 (9.9%) of the participants developed AF. More participants with baseline APCs developed AF during follow-up compared to those without baseline APCs (*p-value* <0.001). In a multivariable logistic regression model adjusted for socio-demographics, behavioral risk factors, cardiovascular risk factors, markers of hypertension severity, medications and inflammatory markers, presence (vs. absence) of baseline APCs was associated with more than double the odds of incident AF (*p-value <0.001*) (Table 2).

We observed a significant effect modification for the association between presence of APCs and AF by angiotensin-II receptor blockers use and statin use, i.e., the risk of AF associated with APCs was significantly weaker in the ARB users than non-users (*interaction p-value* =0.05), and in statin users than non-users (*interaction p-value*= 0.02). When the study participants were stratified by concomitant use of angiotensin-II receptor blockers and statins, the risk of AF associated with APCs showed a dose-response relationship i.e., the risk of AF associated with APCs was weakest in those using both statins and angiotensin-II receptor blockers, strongest in those not using either medications, and somewhere in the middle in those using only one of the medications (*interaction p-value 0.043*). Borderline significant effect modification was also observed by alpha-blocker use (i.e., borderline significant weaker risk of AF in alpha-blocker users than non-users; interaction p-value= 0.12). On the other hand, no significant effect modifications were observed by other medications (angiotensin-converting enzyme inhibitors, beta-blockers, calcium channel blockers, diuretics, and aspirin) (Figure 2)

Borderline significant effect modifications were observed by diabetes (i.e., borderline significant higher risk of AF in those with than without diabetes; *interaction p-value=0.13*), and systolic blood pressure levels (i.e., borderline significant weaker risk of AF in those with systolic blood pressure 130–139 mmHg compared to those with other systolic blood pressure levels; *interaction p-value 0.14*). On the other hand, no significant effect modifications were observed by cardiovascular risk factors, or other participant characteristics (Figure 3).

Discussion

About 46% of the United States adults are estimated to have high blood pressure, and up to 6.1 million suffer from AF (9). In our study, which was limited to a subset of REGARDS participants with hypertension, presence of APCs was associated with 1.36 higher odds of AF. This compares to only 0.92 higher odds of AF associated with presence of APCs reported among all REGARDS participants (2), which underscore the additive AF risk imposed by APCs on patients with hypertension.

The strong and entangled triangular associations between high blood pressure, AF and APCs highlight the clinical and public health importance of prevention of AF in those with hypertension who have APCs. Our analysis revealed two significant effect modifiers of the association between APCs and AF: use of angiotensin-II receptor blockers and use of statins. The antiarrhythmic effect of angiotensin-II receptor blockers may be attributed to the favorable impact of angiotensin-II receptor blockers on left atrial pressure stretch, improved

left ventricular hemodynamics, and prevention of atrial fibrosis (10). Although angiotensin-converting enzyme inhibitors share these properties with angiotensin-II receptor blockers via controlling the renin-angiotensin system and reducing blood pressure, we did not observe significant effect modification by angiotensin-converting enzyme inhibitors similar to angiotensin-II receptor blockers. It is possible that differences in the mechanisms by which angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers control the renin-angiotensin system enable more favorable impact of angiotensin-II receptor blockers on AF risk. Unlike angiotensin-II receptor blockers, angiotensin-converting enzyme inhibitors increase bradykinin bioavailability by reducing its degradation in the process of reducing angiotensin II (11). Although bradykinin adds to the cardiovascular benefits of angiotensin-converting enzyme inhibitors by enhancing tissue plasminogen activator and inhibiting platelet aggregation (12, 13), it also increases oxidative stress and inflammation (14–16) which are involved in the AF pathogenesis (17). The balance between these contradictory actions of bradykinin, which probably vary across populations, may explain the conflicting reports on the effect of angiotensin-converting enzyme inhibitors in prevention of AF in hypertensive individuals (18–24). This is unlike the reports on the angiotensin-II receptor blockers which have been more consistent in showing benefit compared to other blood pressure lowering medications (21–25).

The antioxidant and anti-inflammatory effects of statins led to the hypothesis that this class of lipid-lowering medications could be promising in AF prevention. However, prior reports found evidence for the benefit only after cardiac surgery (26–28). In our study, we observed an additive effect modification in a dose-response fashion with concomitant use of statins and angiotensin-II receptor blockers. This is probably due to the combined antioxidant and anti-inflammatory effect from both medications.

Our analysis also revealed three borderline effect modifiers for the AF risk associated with APCs: Systolic blood pressure levels, diabetes and use of alpha-blockers. The borderline lower AF risk associated with APCs in the subgroup with systolic blood pressure 130–139 mmHg compared to other systolic blood pressure subgroups underscores the role of controlling systolic blood pressure to normal levels. A post-hoc analysis from the Losartan Intervention for Endpoint Reduction in Hypertension study showed that the greatest reduction in AF risk occurred in those who achieved optimal systolic blood pressure levels compared to those with systolic blood pressure   142 mmHg (25). The borderline significant higher risk of AF associated with APCs in diabetes may be related to the added AF risk from diabetes through other mechanisms such as atrial fibrosis which provides a substrate for APCs to initiate AF. Higher levels of glycosylated hemoglobin have been linked to AF risk (29), and diabetes has been shown to be a risk factor for AF (30). Finally, we also found a favorable borderline effect-modification by alpha-blockers. It is unclear whether this is a chance finding, a result of a unique action by alpha-blocker, or the possibility that alpha-blocker was prescribed to healthier participants at a lower risk for AF.

Management of hypertension coexisting with cardiovascular disease such as heart failure or coronary heart disease is typically dictated by the management of these coexisting conditions. On the other hand, there is no consensus approach to the reduction of AF risk associated with APCs in hypertension without cardiovascular disease. Our study provides

insights into how to deal with this common clinical situation in two ways. First, our findings suggest that the relationship between APCs and AF is modifiable in principle, as evident by the heterogeneity among the subgroups. This opens the door for exploring the modifiable factors that could favorably impact the relationship between APCs and AF. Second, our study went further and provided details about a few potential effect modifiers. Pending further investigations in efficacy clinical trials, our results suggest that angiotensin-II receptor blockers and statins, along with control of blood pressure and management of diabetes may have a favorable modifying effect on the AF risk associated with APCs concomitantly occurring with hypertension.

Our study has limitations. Although we used two methods for AF ascertainment (study scheduled electrocardiograms and self-reported history of a previous physician diagnosis), it remains possible that some AF cases such as paroxysmal/intermittent AF were not detected. By design, REGARDS study enrolled only white and black participants and we excluded participants with baseline cardiovascular disease; hence, our results may not apply to certain groups. Although we accounted for the severity of hypertension by adjusting for the number of blood pressure medications, we did not account for the length of time of hypertension which leaves room for residual confounding. Also, we did not adjust for medication discontinuation or changes over time. Despite these limitations, this is the first report from a large population-based study addressing factors modifying the risk of AF associated with APCs in individuals suffering from hypertension.

ACKNOWLEDGMENT-

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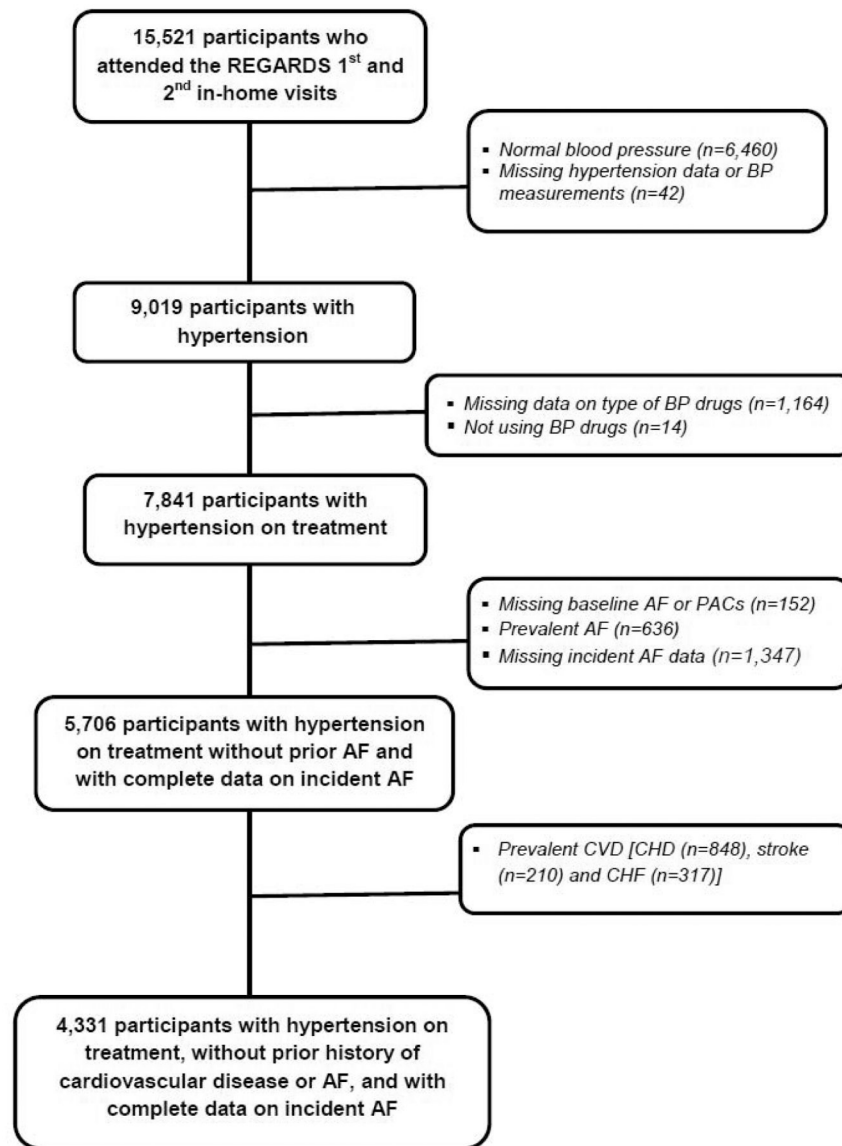
Figure 1.
Flow Diagram Outlining the Inclusion and Exclusion Criteria

Subgroups		Participants/Events (n)	Odds Ratio (95% CI)†	Interaction p-value
ACE-Is	Yes	1512/155	2.72 (1.70, 4.36)	.41
	No	2819/274	2.19 (1.48, 3.24)	
Alpha blockers	Yes	271/36	1.26 (0.32, 5.04)	.12
	No	4060/393	2.51 (1.84, 3.41)	
ARBs	Yes	1053/97	1.31 (0.66, 2.61)	.05
	No	3278/332	2.78 (1.99, 3.89)	
Beta blockers	Yes	1257/164	2.59 (1.47, 4.54)	.93
	No	3074/265	2.44 (1.70, 3.50)	
CCB	Yes	1307/128	2.73 (1.60, 4.67)	.48
	No	3024/301	2.26 (1.57, 3.25)	
Diuretics	Yes	2185/196	2.12 (1.34, 3.34)	.65
	No	2146/233	2.56 (1.73, 3.82)	
Statins	Yes	1516/154	1.42 (0.81, 2.48)	.022
	No	2815/275	3.01 (2.11, 4.32)	
Aspirin	Yes	1999/218	2.25 (1.47, 3.45)	.82
	No	2331/211	2.33 (1.53, 3.56)	
Statins & ARBs	Both	387/41	0.92 (0.27, 3.17)	.043
	Statin only	1129/113	1.71 (0.90, 3.24)	
	ARBs only	666/56	1.76 (0.72, 4.28)	
	Neither	2149/219	3.44 (2.30, 5.14)	
BP medications (n)	1	1991/198	2.73 (1.77, 4.20)	.44
	2	1553/136	2.35 (1.39, 3.97)	
	≥3	787/95	1.61 (0.78, 3.30)	

0.5 1.0 2.0 4.0

Figure 2: Effect Modification of the Association between APCs and AF by Cardiovascular Medications

APCs= premature atrial complexes; AF= atrial fibrillation; CCBs= Calcium channel blockers; ARBs= angiotensin II receptor blockers; ACE-Is= Angiotensin-converting enzyme inhibitors; BP= blood pressure

†Model adjusted for age, sex, race, region of residence, income, smoking, alcohol drinking, physical activity, dyslipidemia, diabetes, obesity, chronic kidney disease, SBP, number of blood pressure medications, left ventricular hypertrophy, statin use, regular aspirin use, and high sensitivity C-reactive protein, unless the variable is the stratifying variable.

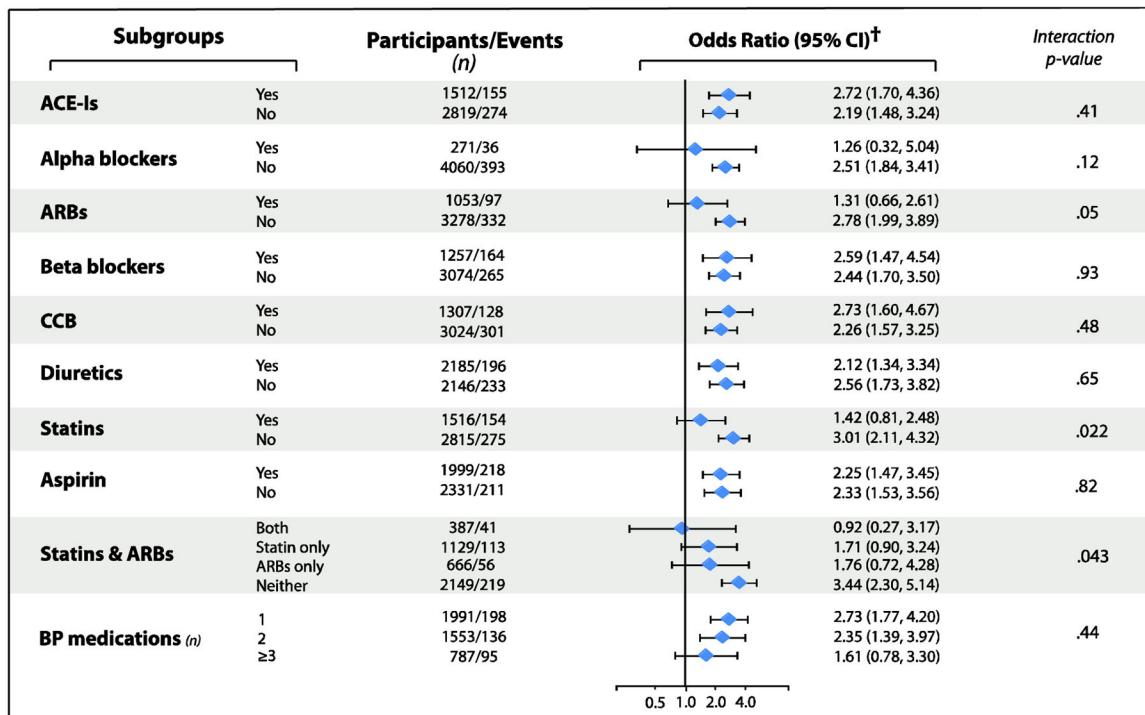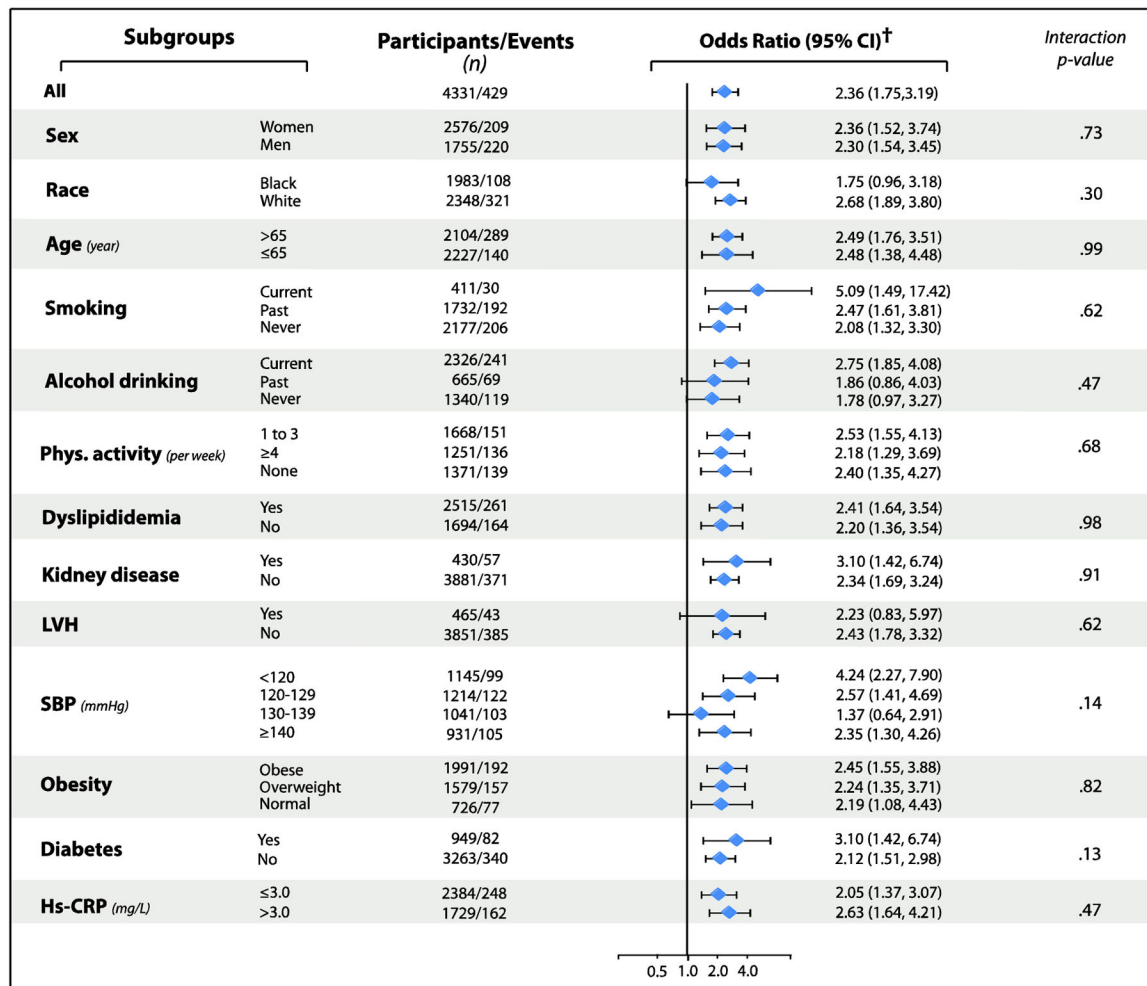| Subgroups		Participants/Events (n)	Odds Ratio (95% CI)†	Interaction p-value
All		4331/429	2.36 (1.75,3.19)	
Sex	Women	2576/209	2.36 (1.52, 3.74)	.73
	Men	1755/220	2.30 (1.54, 3.45)	
Race	Black	1983/108	1.75 (0.96, 3.18)	.30
	White	2348/321	2.68 (1.89, 3.80)	
Age (year)	>65	2104/289	2.49 (1.76, 3.51)	.99
	≤65	2227/140	2.48 (1.38, 4.48)	
Smoking	Current	411/30	5.09 (1.49, 17.42)	.62
	Past	1732/192	2.47 (1.61, 3.81)	
	Never	2177/206	2.08 (1.32, 3.30)	
Alcohol drinking	Current	2326/241	2.75 (1.85, 4.08)	.47
	Past	665/69	1.86 (0.86, 4.03)	
	Never	1340/119	1.78 (0.97, 3.27)	
Phys. activity (per week)	1 to 3	1668/151	2.53 (1.55, 4.13)	.68
	≥4	1251/136	2.18 (1.29, 3.69)	
	None	1371/139	2.40 (1.35, 4.27)	
Dyslipididemia	Yes	2515/261	2.41 (1.64, 3.54)	.98
	No	1694/164	2.20 (1.36, 3.54)	
Kidney disease	Yes	430/57	3.10 (1.42, 6.74)	.91
	No	3881/371	2.34 (1.69, 3.24)	
LVH	Yes	465/43	2.23 (0.83, 5.97)	.62
	No	3851/385	2.43 (1.78, 3.32)	
SBP (mmHg)	<120	1145/99	4.24 (2.27, 7.90)	.14
	120-129	1214/122	2.57 (1.41, 4.69)	
	130-139	1041/103	1.37 (0.64, 2.91)	
	≥140	931/105	2.35 (1.30, 4.26)	
Obesity	Obese	1991/192	2.45 (1.55, 3.88)	.82
	Overweight	1579/157	2.24 (1.35, 3.71)	
	Normal	726/77	2.19 (1.08, 4.43)	
Diabetes	Yes	949/82	3.10 (1.42, 6.74)	.13
	No	3263/340	2.12 (1.51, 2.98)	
Hs-CRP (mg/L)	≤3.0	2384/248	2.05 (1.37, 3.07)	.47
	>3.0	1729/162	2.63 (1.64, 4.21)	

0.5 1.0 2.0 4.0

Figure 3: Effect Modification of the Association between APCs and AF by Cardiovascular Risk Factors

APCs= premature atrial complexes; AF= atrial fibrillation; Hs-CRP= High sensitivity C-reactive protein; LVH= Left ventricular hypertrophy; SBP= Systolic blood pressure

†Model adjusted for age, sex, race, region of residence, income, smoking, alcohol drinking, physical activity, dyslipidemia, diabetes, obesity, chronic kidney disease, systolic blood pressure, number of blood pressure medications, left ventricular hypertrophy, statin use, regular aspirin use, and hs-CPR, unless the variable is the stratifying variable.

Table 1

Baseline Characteristics

Characteristics	*All Participants*	Atrial Premature Complexes (APCs)		
mean ±SD or n (%)	*(n=4,331)*	*Absent (n=3975)*	*Present (n=356)*	*p-value*
Age *(years)*	64.6 ± 8.1	64.3 ± 8.0	67.7 ± 8.4	<0.001
Women	2576 (59.5%)	2391 (60.2%)	185 (52.0%)	0.003
Income *($)*				0.35
< 20,000	609 (14.1%)	547 (13.8%)	62 (17.4%)	
20,000–34,000	1018 (23.5%)	934 (23.5%)	118 (33.2%)	
35,000–74,000	1464 (33.8%)	1346 (33.9%)	56 (15.7%)	
$75,000 and above	784 (18.1%)	728 (18.3%)	36 (10.1%)	
Refused	456 (10.5%)	420 (10.6%)	52 (11.1%)	
Black	1983 (45.8%)	1830 (46.0%)	153 (43.0%)	0.27
Smoking				0.29
Current	411 (9.5%)	376 (9.5%)	35 (9.9%)	
Past	1732 (40.1%)	1577 (39.8%)	155 (43.7%)	
Alcohol drinking				0.41
Current	2326 (53.7%)	2143 (53.9%)	183 (51.4%)	
Past	665 (15.4%)	602 (15.1%)	63 (17.7%)	
Exercise *(times/week)*				0.36
1 to 3	1668 (38.9%)	1532 (38.9%)	136 (38.4%)	
>4	1251 (29.2%)	1137 (28.9%)	114 (32.2%)	
Dyslipidemia	2515 (59.8%)	2318 (59.9%)	197 (57.6%)	0.40
Diabetes mellitus	949 (22.5%)	870 (22.5%)	79 (22.8%)	0.89
High sensitivity C-reactive protein *(mg/dL)*	4.4±6.9	4.4±6.9	4.6±6.5	0.64
Body mass index *(kg/m²)*				0.37
>35	1991 (46.2%)	1832 (46.3%)	159 (44.8%)	
25–30	1579 (36.6%)	1456 (36.8%)	123 (34.75%)	
<25	17 (0.4%)	15 (0.4%)	2 (0.6%)	
Chronic kidney disease	430 (10.0%)	379 (9.6%)	51 (14.4%)	0.004
Left ventricular hypertrophy	465 (10.8%)	421 (10.6%)	44 (12.4%)	0.29
Number of Blood Pressure drugs				0.021
1	1991 (46.0%)	1831 (46.1%)	160 (44.9%)	
2	1553 (35.9%)	1426 (35.9%)	127 (35.7%)	
3	603 (13.9%)	554 (13.9%)	49 (13.8%)	
4	156 (3.6%)	141 (3.6%)	15 (4.2%)	
5	27 (0.6%)	23 (0.6%)	4 (1.1%)	
6	1 (0.0%)	0 (0.0%)	1 (0.3%)	
Systolic blood pressure *(mmHg)*	128.7 ± 15.3	128.5 ± 15.1	130.6 ± 17.6	0.015
Angiotensin-converting enzyme inhibitors	1512 (34.9%)	1379 (34.7%)	133 (37.4%)	0.31
Aldosterone receptor antagonists	56 (1.3%)	50 (1.3%)	6 (1.7%)	0.49
Alpha blockers	271 (6.4%)	237 (6.0%)	34 (9.6%)	0.007

Characteristics	All Participants	Atrial Premature Complexes (APCs)		
mean ±SD or n (%)	(n=4,331)	Absent (n=3975)	Present (n=356)	p-value
Angiotensin II receptor blockers	1053 (24.3%)	960 (24.2%)	93 (26.1%)	0.41
Beta-blockers	1257 (29–0%)	1166 (29.3%)	91 (25. 6%)	0.13
Calcium channel blockers	1307 (30.2%)	1193 (30.0%)	114 (32.0%)	0.43
Central agonists	12 (0.3%)	11 (0.3%)	2 (0.4%)	0.99
Diuretics	2185 (50.5%)	2014 (50.7%)	171 (48.0%)	0.34
Direct vasodilators	18 (0.4%)	14 (0.4%)	4 (1.1%)	0.030
Aspirin	1999 (46.2%)	1833 (46.1%)	166 (46.6%)	0.85
Statin	1516 (35.0%)	1409 (35.5%)	107 (30.1%)	0.041

Left ventricular hypertrophy was defined by Sokolow-Lyon criteria from ECG.

Diabetes mellitus was defined as fasting glucose 126 mg/dL, non-fasting glucose 200 mg/dL, or use of medications to control blood sugar.

Dyslipidemia was defined as total cholesterol >240 mg/dl, low-density lipoprotein >160 mg/dl, high-density lipoprotein <40 mg/dl or the participant was on cholesterol-lowering medication.

Chronic kidney disease was defined as an estimated glomerular filtration rate <60 ml/min per 1.73 m2.

Table 2:

Association between Baseline Atrial Premature Complexes and Incident Atrial Fibrillation

Baselin eAPCs	Participants (n) / AF (n %))	Model 1: Socio-demographics	Model 2: Model 1 + Behaviora 1 factors	Model 3: Model 2+ cardiovascular risk factors	Model 4: Model 3+ Markers of hypertension severity	Model 5: Model 4 + Medications	Model 6: Model 5+ Inflammatory markers
		Odds Ratio (95% Confidence Interval)					
Absent	3975/351(8.8 %)	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
Present	356/78 (21.9%)	2.43(1.83, 3.24)	2.45 (1.84, 3.27)	2.35(1.75, 3.15)	2.37(1.76, 3.18)	2.37(1.76, 3.18)	2.36 (1.75, 3.19)

APCs= atrial premature complexes; AF= atrial fibrillation

Socio-demographics: *Age, sex, race, region of residence, income*

Behavioral factors: *Smoking, alcohol drinking, physical activity*

Cardiovascular risk factors: *Dyslipidemia, diabetes mellitus, obesity, chronic kidney disease*

Markers of hypertension severity: *Systolic blood pressure, number of blood pressure medications, left ventricular hypertrophy*

Medications: *Statins use and regular aspirin*

Inflammatory markers: *High sensitivity C-reactive protein*